National Institute for Health and Care Excellence

Final

Chronic heart failure in adults

Diagnosis and management

NG106

Full Guideline

September 2018

Final

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

Update information

Minor changes since publication
November 2021: We added a link to the NICE guideline on heart valve disease in recommendations 1.2.8, 1.2.15 and 1.4.2.

See www.nice.org.uk/guidance/ng106 for more information.

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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1 Guideline summary

1.1 Full list of recommendations

1. Take a careful and detailed history, and perform a clinical examination and tests to confirm the presence of heart failure. [2010]
2. Measure N-terminal pro-B-type natriuretic peptide [NT-proBNP] in people with suspected heart failure. [2018]
3. Because very high levels of NT-proBNP carry a poor prognosis, refer people with suspected heart failure and an NT-proBNP level above 2,000 ng/litre (236 pmol/litre) urgently, to have specialist assessment and transthoracic echocardiography within 2 weeks. [2018]
4. Refer people with suspected heart failure and an NT-proBNP level between 400 and 2,000 ng/litre (47 to 236 pmol/litre) to have specialist assessment and transthoracic echocardiography within 6 weeks. [2018]
5. Be aware that:
   - an NT-proBNP level less than 400 ng/litre (47 pmol/litre) in an untreated person makes a diagnosis of heart failure less likely
   - the level of serum natriuretic peptide does not differentiate between heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. [2018]
6. Review alternative causes for symptoms of heart failure in people with NT-proBNP levels below 400 ng/litre. If there is still concern that the symptoms might be related to heart failure, discuss with a physician with subspeciality training in heart failure. [2018]
7. Be aware that:
   - obesity, African or African-Caribbean family origin, or treatment with diuretics, angiotensin-converting enzyme(ACE) inhibitors , beta-blockers, angiotensin II receptor blockers (ARBs) or mineralcorticoid receptor antagonist (MRAs) can reduce levels of serum natriuretic peptides.
   - high levels of serum natriuretic peptides can have causes other than heart failure (for example, age over 70 years, left ventricular hypertrophy, ischaemia, tachycardia, right ventricular overload, hypoxaemia [including pulmonary embolism], renal dysfunction [eGFR less than 60 ml/minute/1.73 m^2], sepsis, chronic obstructive pulmonary disease, diabetes, or cirrhosis of the liver). [2010, amended 2018]
8. Perform transthoracic echocardiography to exclude important valve disease, assess the systolic (and diastolic) function of the (left) ventricle, and detect intracardiac shunts. [2003, amended 2018]
9. Transthoracic echocardiography should be performed on high-resolution equipment, by experienced operators trained to the relevant professional

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standards. Need and demand for these studies should not compromise quality. [2003, amended 2018]

10. Ensure that those reporting echocardiography are experienced in doing so. [2003]

11. Consider alternative methods of imaging the heart (for example, radionuclide angiography [multigated acquisition scanning], cardiac MRI or transoesophageal echocardiography) if a poor image is produced by transthoracic echocardiography. [2003, amended 2018]

12. Perform an ECG and consider the following tests to evaluate possible aggravating factors and/or alternative diagnoses:

    - chest X-ray
    - blood tests:

    renal function profile

    thyroid function profile

    liver function profile

    lipid profile

    glycosylated haemoglobin (HbA_{1c})

    full blood count

    - urinalysis
    - peak flow or spirometry. [2010, amended 2018]

13. Try to exclude other disorders that may present in a similar manner.[2003]

14. When a diagnosis of heart failure has been made, assess severity, aetiology, precipitating factors, type of cardiac dysfunction and correctable causes. [2010]

15. Refer people with heart failure caused by valve disease for specialist assessment and advice regarding follow-up. [2003]

16. Review the basis for a historical diagnosis of heart failure, and manage care in accordance with this guideline only if the diagnosis is confirmed. [2003]

17. If the diagnosis of heart failure is still suspected, but confirmation of the underlying cardiac abnormality has not occurred, then the person should have appropriate further investigation. [2003]

18. Do not routinely advise people with heart failure to restrict their sodium or fluid consumption. Ask about salt and fluid consumption and, if needed, advise as follows:

    - restricting fluids for people with dilutional hyponatraemia
    - reducing intake for people with high levels of salt and/or fluid consumption. Continue to review the need to restrict salt or fluid. [2018]

19. Advise people with heart failure to avoid salt substitutes that contain potassium. [2018]

20. Offer people with heart failure an annual vaccination against influenza. [2003]

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21. Offer people with heart failure vaccination against pneumococcal disease (only required once). [2003]
22. In women of childbearing potential who have heart failure, contraception and pregnancy should be discussed. If pregnancy is being considered or occurs, specialist advice should be sought. Subsequently, specialist care should be shared between the cardiologist and obstetrician.]2003]
23. Air travel will be possible for the majority of people with heart failure, depending on their clinical condition at the time of travel. [2003]
24. Large Goods Vehicle and Passenger Carrying Vehicle licence: physicians should be up to date with the latest Driver and Vehicle Licensing Agency guidelines. Check the website for regular updates [2003]
25. Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. [2003]
26. People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice. [2003, amended 2018]
27. Avoid verapamil, diltiazem and short-acting dihydropyridine agents in people who have heart failure with reduced ejection fraction. [2003, amended 2018]
28. Make the decision to prescribe amiodarone in consultation with a specialist. [2003]
29. Review the need to continue the amiodarone prescription at the 6-monthly clinical review. [2003, amended 2018]
30. Offer people taking amiodarone liver and thyroid function tests, and a review of side effects, as part of their routine 6-monthly clinical review. [2003, amended 2018]
31. For people who have heart failure and atrial fibrillation, follow the recommendations on anticoagulation in the NICE guideline on atrial fibrillation. Be aware of the effects of impaired renal and liver function on anticoagulant therapies. [2018]
32. In people with heart failure in sinus rhythm, anticoagulation should be considered for those with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus. [2003]
33. Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have heart failure with reduced ejection fraction. Use clinical judgement when deciding which drug to start first. [2010]
34. Do not offer ACE inhibitor therapy if there is a clinical suspicion of haemodynamically significant valve disease until the valve disease has been assessed by a specialist. [2003]
35. Do not withhold treatment with a beta-blocker solely because of age or the presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. [2010]

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36. Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every 2 weeks) until the target or maximum tolerated dose is reached. [2010]

37. Measure serum sodium and potassium and assess renal function before and 1 to 2 weeks after starting an ACE inhibitor, and after each dose increment.[2010,amended 2018]

38. Measure blood pressure before and after each dose increment of an ACE inhibitor. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]

39. Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2010, amended 2018]

40. Introduce beta-blockers in a 'start low, go slow' manner. Assess heart rate, and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. [2010, amended 2018]

41. Switch people whose condition is stable and who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. [2010]

42. Consider an angiotensin II receptor blocker (ARB) licensed for heart failure as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side effects with ACE inhibitors. [2010]

43. Measure serum sodium and potassium and assess renal function before and after starting an ARB and after each dose increment.[2010, amended 2018]

44. Measure blood pressure after each dose increment of an ARB. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]

45. Once the target or maximum tolerated dose of an ARB is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2010 amended 2018]

46. If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have heart failure with reduced ejection fraction. [2010]

47. Offer a mineralcorticoid receptor antagonist (MRA) in addition to an angiotensin-converting enzyme inhibitor (ACE) or ARB and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. [2018]

48. Measure serum sodium and potassium and assess renal function before and after starting an MRA and after each dose increment. [2018]

49. Measure blood pressure before and after each dose increment of MRA. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]

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50. Once the target, or maximum tolerated, dose of an MRA is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2018]

51. Ivabradine is recommended as an option for treating chronic heart failure for people:

- with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and
- who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and
- who are given ivabradine in combination with standard therapy including beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitor and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and

52. Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. [2012]

53. Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. [2012]

54. Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people

- With New York Heart Association (NYHA) class II to IV symptoms and
- With a left ventricular ejection fraction of 35% or less and
- Who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBS) [2016]

55. Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team members as defined in NICE's guideline on chronic heart failure in adults: diagnosis and management. [2016]

56. This guidance is not intended to affect the position of patients whose treatment with sacubitril valsartan was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. [2016]

Hydralazine in combination with nitrate

57. Seek specialist advice and consider offering hydralazine in combination with nitrate (especially if the person is of African or Caribbean family origin and has moderate to severe heart failure [NYHA class III/IV] with reduced ejection fraction).[2010]

Digoxin

For recommendations on digoxin for people with atrial fibrillation see the section on rate and rhythm control in the NICE guideline on atrial fibrillation

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58. Digoxin is recommended for worsening or severe heart failure with reduced ejection fraction despite first line treatment for heart failure. Seek specialist advice before initiating.[2010, amended 2018]

59. Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within 8–12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence[2003]

60. the serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. [2003]

61. For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR of 30 ml/min/1,73 m^2 or above: (estimated glomerular filtration rate) as follows.

    - Offer the treatment outlined in section 6.2.7 and
    - If the person's eGFR is 45 ml/min/1.73 m2 or below, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, mineralcorticoid receptor antagonists and digoxin. [2018]

62. For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR below 30 ml/min/1.73 m^2 the specialist heart failure MDT should consider liaising with a renal physician [2018]

63. Monitor the response to titration of medicines closely in people who have heart failure with reduced ejection fraction and chronic kidney disease, taking into account the increased risk of hyperkalaemia. [2018]

64. Do not routinely offer coronary revascularisation to people who have heart failure with reduced ejection fraction and coronary artery disease. [2018]

65. Specialist referral for transplantation should be considered for people with severe refractory symptoms or refractory cardiogenic shock [2003]

66. Offer people with heart failure a personalised, exercise-based cardiac rehabilitation programme, unless their condition is unstable. The programme:

    - should be preceded by an assessment to ensure that it is suitable for the person
    - should be provided in a format and setting (at home, in the community or in the hospital) that is easily accessible for the person
    - should include a psychological and educational component
    - may be incorporated within an existing cardiac rehabilitation programme
    - should be accompanied by information about support available from healthcare professionals when the person is doing the programme. [2018]

67. All people with chronic heart failure need monitoring. This monitoring should include:

    - a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status
    - a review of medication, including need for changes and possible side effects

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- an assessment of renal function. [2010, amended 2018]

68. More detailed monitoring will be needed if the person has significant comorbidity or if their condition has deteriorated since the previous review. [2003]

69. The frequency of monitoring should depend on the clinical status and stability of the person. The monitoring interval should be short (days to 2 weeks) if the clinical condition or medication has changed, but is needed at least 6-monthly for stable people with proven heart failure. [2003]

70. People with heart failure who wish to be involved in monitoring of their condition should be provided with sufficient education and support from their healthcare professional to do this, with clear guidelines as to what to do in the event of deterioration. [2003]

71. Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m^2. [2018]

72. The core specialist heart failure multidisciplinary team (MDT) should work in collaboration with the primary care team, and should include:

    - a lead physician with a subspecialty interest in heart failure (usually a consultant cardiologist) who is responsible for making the clinical diagnosis
    - a specialist heart failure nurse
    - a healthcare professional with expertise in specialist prescribing for heart failure.

    [2018]

73. The specialist heart failure MDT should directly involve, or refer people to, other services, including rehabilitation services, and tertiary and palliative care, as needed. [2018]

74. The specialist heart failure MDT should:

    - diagnose heart failure
    - give information to people newly diagnosed with heart failure (see section 9.4.6)
    - manage newly diagnosed, recently decompensated or advanced heart failure (NYHA [New York Heart Association] class III to IV) heart failure
    - optimise treatment
    - start new medicines that need specialist supervision
    - continue to manage care after an interventional procedure such as implantation of a cardioverter defibrillator or cardiac resynchronisation device
    - manage heart failure that is not responding to treatment. [2018]

75. The primary care team should carry out the following for people with heart failure at all times, including periods when the person is also receiving specialist heart failure from the MDT:

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- ensure effective communication links between different care settings and clinical services involved in the person's care
- lead a full review of the person's heart failure care, which may form part of a long-term conditions review
- recall the person at least every 6 months and update the summary and clinical record
- ensure that changes to the clinical record are understood and agreed by the person with heart failure and shared with the specialist heart failure MDT
- arrange access to specialist heart failure services if needed. [2018]

For recommendations on the diagnosis and management of acute heart failure see NICE's guideline on acute heart failure.

76. People with heart failure should generally be discharged from hospital only when their clinical condition is stable and the management plan is optimised. Timing of discharge should take into account the wishes of the person and their family or carer, and the level of care and support that can be provided in the community. [2003]

77. The primary care team working within the specialist heart failure MDT should take over routine management of heart failure as soon as it has been stabilised and its management optimised. [2018]

78. The specialist heart failure MDT should write a summary for each person with heart failure that includes:

- diagnosis and aetiology
- medicines prescribed, monitoring of medicines, when medicines should be reviewed and any support the person needs to take the medicines
- functional abilities and any social care needs
- social circumstances, including carers' needs. [2018]

79. The summary should form the basis of a care plan for each person, which should include.

- plans for managing the person's heart failure, including follow-up care, rehabilitation and access to social care
- symptoms to look out for in case of deterioration
- a process for any subsequent access to the specialist heart failure MDT if needed
- contact details for:

a named healthcare coordinator (usually a specialist heart failure nurse)

local heart failure specialist care providers, for urgent care or review

- additional sources of information for people with heart failure. [2018]

80. Give a copy of the care plan to the person with heart failure, ther family or carer if appropriate, and all health and social care professionals involved in their care. [2018]

81. When giving information to people with heart failure, follow the recommendations in the NICE guideline on patient experience in adult NHS services. [2018]

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82. Discuss the person's prognosis in a sensitive, open and honest manner. Be frank about the uncertainty in predicting the course of their heart failure. Revisit this discussion as the person's condition evolves. [2018]

83. Provide information whenever needed throughout the person's care. [2018]

84. Consider training in advanced communication skills for all healthcare professionals working with people who have heart failure. [2018]

85. The specialist heart failure MDT should offer people newly diagnosed with heart failure an extended first consultation, followed by a second consultation, to take place within 2 weeks if possible. At each consultation:

    - discuss the person's diagnosis and prognosis
    - explain heart failure terminology
    - discuss treatments
    - address the risk of sudden death, including any misconceptions about that risk
    - encourage the person and their family or carers to ask any questions they have. [2018]

86. Do not offer long-term home oxygen therapy for advanced heart failure. Be aware that long-term home oxygen therapy may be offered for comorbidities, such as for some people with chronic obstructive pulmonary disease (see section 1.2.5 on oxygen in the NICE guidline on chronic obstructive pulmonary disease in over 16s. [2018]

87. If it is thought that a person may be entering the last 2 to 3 days of life, follow the NICE guideline on care of dying adults in the last days of life. [2018]

See NICE's technology appraisal guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure.

88. When discussing implantation of a cardioverter defibrillator:

    - explain the risks, benefits and consequences of cardioverter defibrillator implantation, following the principles on shared decision making in the NICE guideline on patient experience in adult NHS services
    - ensure the person knows that the defibrillator can be deactivated without affecting any cardiac resynchronisation or pacing, and reactivated later
    - explain the circumstances in which deactivation might be offered
    - discuss and dispel common misconceptions about the function of the device and the consequences of deactivation
    - provide the person and, if they wish, their family or carers with written information covering the information discussed. [2018]

89. Review the benefits and potential harms of a cardioverter defibrillator remaining active in a person with heart failure:

    - at each 6-monthly review of their heart failure care
    - whenever their care goals change
    - as part of advance care planning if it is thought they are nearing the end of life. [2018]

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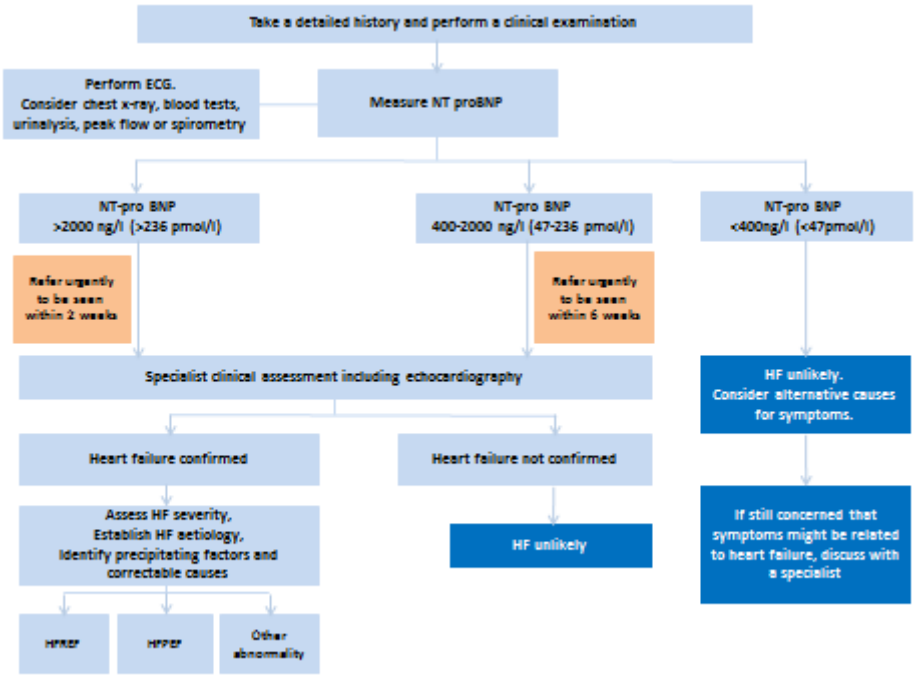
90. Do not use prognostic risk tools to determine whether to refer a person with heart failure to palliative care services. [2018]

91. If the symptoms of a person with heart failure are worsening despite optimal specialist treatment, discuss their palliative care needs with the specialist heart failure MDT and consider a needs assessment for palliative care. [2018]

92. People with heart failure and their families or carers should have access to professionals with palliative care skills within the heart failure team. [2003]

1.2 Diagnostic algorithm

Figure 1: Diagnostic algorithm



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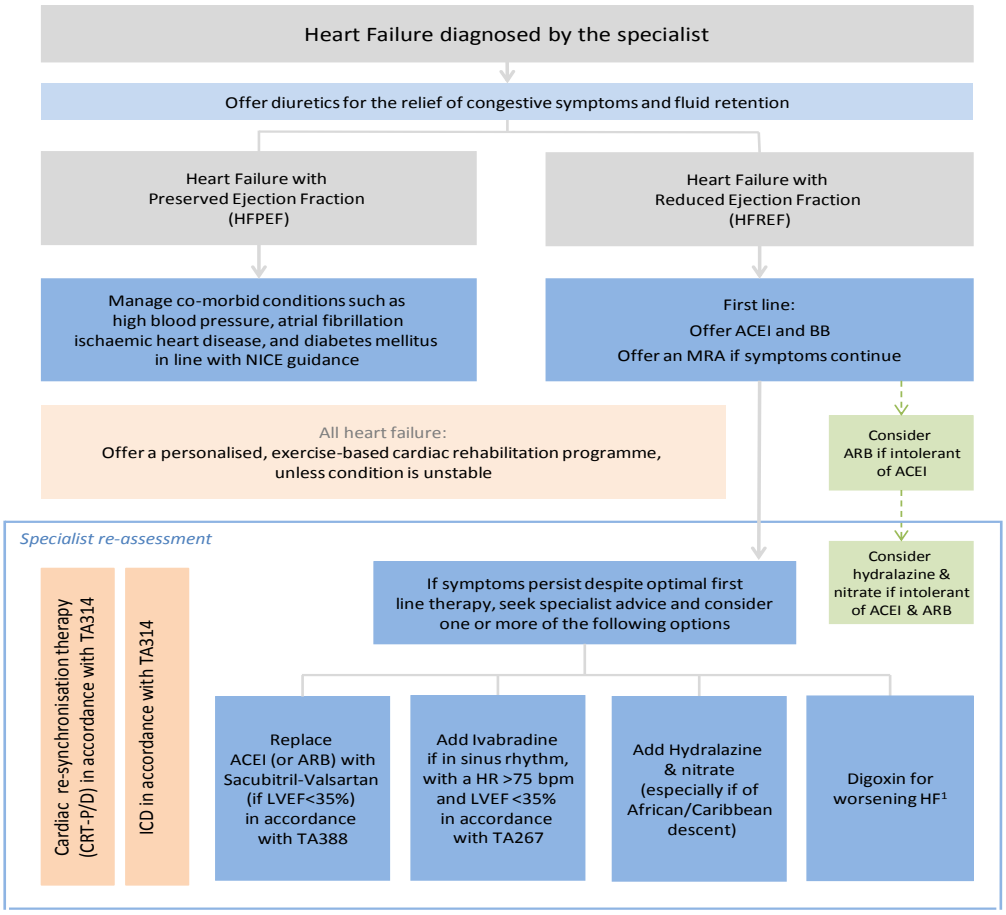
1.3 Therapeutic algorithm

Figure 2: Therapeutic algorithm



If the person's eGFR is 30-45 ml/min/1.73 m2, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, mineralocorticoid receptor antagonists, sacubitril valsartan, and digoxin.
If the person's eGFR is <30 ml/min/1.73 m2, consider liaising with a renal physician.

[1] *Please refer to CG180 for recommendations on the use of digoxin in patients with atrial fibrillation.*

For more information on drug treatment and monitoring see the NICE guideline on 'Chronic Heart Failure: assessment and management' (CGX).
Please refer to the NICE guidelines on 'chronic kidney disease' (CG182) and on 'acute kidney injury' (CG169).

1.4 Key research recommendations

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- What is the optimal NT-proBNP threshold for the diagnosis of heart failure in people with atrial fibrillation?
- What are the optimal NT-proBNP thresholds for diagnosing heart failure in people with IIIb, IV or V chronic kidney disease?
- What is the optimal threshold for NT-proBNP for the diagnosis of heart failure in people with suspected heart failure: 400 ng/ml or 125 ng/ml?
- What is the optimal imaging technique for the diagnosis of heart failure?

No recommendation

No recommendation

- In people with advanced heart failure and significant peripheral fluid overload, what is the clinical and cost effectiveness of oral, subcutaneous and intravenous diuretic therapy in the community?
- What is the most accurate prognostic risk toos in predicting 1 year mortality from heart failure at specific clinically relevant thresholds (for example, sensitivity, specificity, negative predictive value and positive predictive value at a threshold of 50% risk of mortality at 1 year)?

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2 Introduction

2.1 Diagnosis and definition of chronic heart failure

Heart failure is a common complex clinical syndrome of symptoms and signs caused by impairment of the heart's action as a pump supporting the circulation [11, 74, 337]. It is caused by structural or functional abnormalities of the heart. The demonstration of objective evidence of these cardiac abnormalities is necessary for the diagnosis of heart failure to be made. The symptoms most commonly encountered are breathlessness (exertional dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue, and oedema. Signs in heart failure could be due to pulmonary and systemic congestion, or the structural abnormalities either causing or caused by heart failure.

There is no single diagnostic test for heart failure, and diagnosis relies on clinical judgement based on a combination of history, physical examination and appropriate investigations. Patients may present acutely with heart failure[45] which is the subject of separate guidance (NICE Acute Heart Failure: diagnosis and management. Clinical Guideline 187) [234], or have a more insidious presentation. Most acute presentations are due to patients with chronic heart failure suffering an acute decompensation (≈65%), while the remainder are new presentations of acute heart failure (≈35%). Patients identified in the community with heart failure have breathlessness as their most common complaint. However, patients often consult their doctor with multiple non-specific symptoms such as fatigue, or with symptoms in the context of other long-term co-morbidities which can make the recognition of heart failure more challenging [45].

2.2 Clinical context

Around 920,000 people in the UK today have been diagnosed with heart failure [74]. Both the incidence and prevalence of heart failure increase steeply with age, with the average age at first diagnosis being 77 years. While around 1 in 35 people aged 65–74 years has heart failure, this increases to about 1 in 15 of those aged 75–84 years, and to just over 1 in 7 in those aged above 85 years. Less data exists about heart failure in younger age groups but there is increasing recognition that this condition affects a proportion of patients aged less than 65 years [371].

The prevalence of heart failure is rising overall despite improvements in care through a combination of improved survival of people with ischaemic heart disease, more effective treatments for heart failure, and the effects of population ageing [74]. The recent rise in the prevalence of heart failure with preserved left ventricular ejection fraction parallels the rise in the prevalence of obesity and allied co-morbidities of hypertension, and diabetes mellitus [166, 353]. The most common cause of heart failure in the UK is coronary artery disease. Other heart failure admissions are often associated with atrial fibrillation or heart valve disease as well with presentations of cardiomyopathies and myocarditis.

Heart failure commonly co-exists with other co-morbidities including hypertension, diabetes, ischaemic heart diseases, atrial fibrillation and chronic obstructive pulmonary disease [74]. The risk of heart failure is higher in men than in women in all age groups, but there are more women than men with heart failure due to population demographics. Heart failure is also more common in groups with higher indices of social deprivation. There are few reliable data for other ethnic groups but people of African or Afro-Caribbean origin are more likely to develop heart failure due to hypertension[58] rather than coronary artery disease, whereas those of Asian origin have a greater risk of developing heart failure due to coronary artery disease – often associated with obesity and diabetes mellitus[39].

The importance of heart failure was recognised by the All Party Parliamentary Group on Heart Disease Inquiry into Living with Heart Failure which issued 10 suggestions for improvement in care for patients with heart failure[9]. Heart failure accounts for a total of 1 million inpatient bed days – 2% of all NHS inpatient bed-days – and 5% of all emergency medical admissions to hospital. Hospital

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admissions due to heart failure are projected to rise by 50% over the next 25 years – largely due to ageing of the population. This is despite a progressive decline in the age-adjusted hospitalisation rates at 1-1.5% per annum since 1992-1993[235]. It is estimated that the total annual cost of heart failure to the NHS is around 2% of the total NHS budget: approximately 70% of this total is due to the costs of hospitalisation[9, 337]. Admissions tend to be protracted: The median length of stay is 6-9 days depending on the requirement for additional specialist cardiology management[235]. Readmissions are common: about 1 in 4 patients are readmitted in 3 months. Associated co-morbidities account for a substantial proportion of admissions of people with a diagnosis of heart failure[45]. The costs increase with disease severity, with the healthcare costs for patients with the most severe symptoms between 8 and 30 times greater than those with mild symptoms[35].

Patients on GP heart failure registers, representing prevalent cases of heart failure, continue to be at significant mortality risk, with a ten-year survival of 27% as compared to 75% in the age- and sex-matched general population in 2009[329]. The prognosis is poorer in patients with co-morbidities[329] and may be similar to patients with cancer[20]. On average, a GP will look after 30 patients with heart failure and suspect a new diagnosis of heart failure in, perhaps, 10 patients annually. Those who work in more deprived areas are likely to have more cases. The cost of GP consultations has been estimated at £50 million per year, with an additional £50 million for GP referrals to outpatient clinics. In addition, community-based drug therapy costs the NHS around £150 million per year.

The recent National UK Heart Failure audit of acute heart failure suggests continuing improvements in heart failure diagnosis and management. In-patient mortality has fallen from 15% in 2009 to 8.9% in 2016 leading to more patients requiring long-term care in the community[235]. Despite this 20% of patients are readmitted within 30 days of initial admission and 50% within one year though commonly due to non-heart failure causes[45].Younger patients do better, as do patients reviewed by specialist as opposed to general services. Rates of drug prescription have increased, but one-year mortality remains significant. The evidence suggests a trend of improved prognosis for heart failure in the last 10 years[74] but this is not found in all studies[331].

Patients indicate that their management of heart failure impacts beyond just the clinical management with effects on social relationships, emotional well-being and psychological status. As well as NHS costs, heart failure places a burden on other agencies such as social services and the benefits system, and of course on the patients with heart failure, their families and carers. For patients and their carers, the costs are more difficult to quantify, but the burden is both financial and via adverse effects on their quality of life. The financial costs of heart failure to the patient and family arise from prescription charges (in patients under the age of 60), attendance at GP surgeries and outpatient clinics, hospital stays, modifications to the home and loss of earnings due to absence from work or loss of employment thus leading to adverse pressures on the family. Quality of life is affected by the physical limitations imposed by the condition, the social limitations that follow from this and the emotional problems that may also arise[146]. These symptoms can be caused by the disease itself, by co-morbidities, or can result from the side effects of treatment. Pharmacological and non-pharmacological treatments can improve patients' quality of life, both in terms of physical functioning and well-being.

2.3 Definition of a specialist

The term "specialist" is applicable to a wide range of healthcare professionals; however, within the context of this guideline, the term specialist is used in relation to establishing the diagnosis of heart failure and more complex decisions on the management of heart failure and its multiple causes. Throughout this guideline the term "specialist" denotes a physician with sub-specialty interest in heart failure (often a consultant cardiologist) who leads a specialist multidisciplinary heart failure team of professionals with appropriate competencies from primary and secondary care (see chapter

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12). The team will involve, where necessary, other services (such as rehabilitation, other acute medical specialities, older person's care and palliative care) in the care of individual patients. Unless otherwise specified, within this guideline specialist assessment or management refers to assessment or management by this specialist multidisciplinary heart failure team. The team will decide who is the most appropriate team member to address any particular clinical problem.

2.4 Definitions used in the guideline

Initial research into heart failure concentrated on patients with heart failure due to impaired contraction of the left ventricle, also known as left ventricular systolic dysfunction (LVSD). Consequently, therapeutic interventions have primarily been tested in this group of patients. Over the last 20 years it has become evident that almost half the patients with clinical signs of heart failure do not have LVSD. This proportion is increasing [353]. Despite the prevalence of the latter group, there are far less diagnostic or intervention trials for this group, compared to those with LVSD. This distinction into two categories of heart failure have led to a classification system based on left ventricular ejection fraction.

The Guideline Development Group (GDG) agreed on the following definitions:

- Heart failure with reduced ejection fraction (HFREF)

This group of patients is characterised by heart failure with a left ventricular ejection fraction by echocardiography of less than 40%.

- Heart failure with preserved ejection fraction (HFPEF)

This group of patients with heart failure have a left ventricular ejection fraction greater than 50%,

  - no alternative cause for the syndrome,
  - the presence of a non-dilated left ventricle; evidence of structural remodelling (left ventricular hypertrophy or dilated left atrium); or diastolic dysfunction through imaging
  - and have abnormal biomarkers.

The GDG recognises that the two terms HFREF and HFPEF have several limitations. These include the variability of the left ventricular ejection fraction measured by different imaging modalities, and the lack of universal agreement on the threshold of ejection fraction at which these are defined or the exact definition of HFPEF. The GDG also recognised the proposal of another class as heart failure with mid-range ejection fraction (HFMREF). This proposal has not been fully clinically validated and remains the topic of further research [150, 354].

The GDG reviewed the available biomarkers for diagnosis of heart failure. Assays for both B-type natriuretic peptide (BNP) and NT-pro-BNP are commonly available. Other biomarkers have been identified but their utility is unclear. It considered that any marker chosen should be widely available, have an extensive evidence base, and good performance characteristics including high stability in patient samples given transfer times between primary care and central laboratory facilities. Though current practice favours the use of biomarkers for diagnosis rather than monitoring their future use cannot be predicted. Thus, the ability to interconvert between assays based on the same biomarker and the ability to clearly define baseline levels to allow long-term management by monitoring would be prudent to maintain. After consideration of the available assays[222], their performance and interference characteristics[248] and recent publications that inform the rest of the guideline the GDG decided that NT-proBNP should be the favoured biomarker as it was more commonly used, more stable, did not require additional laboratory specimens for ideal performance[248] and did not suffer from potential confounding of interpretation by novel therapies (e.g. sacubitril-valsartan)[303].

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2.5 Rationale for the update

This guideline is a partial update of NICE Guideline No 108: Chronic Heart Failure in adults – management (2010) [232]. The 2010 guidelines offered advice on best practice for the care of adult patients (aged 18 years or older) who have symptoms or a diagnosis of chronic heart failure. Since 2010, European[271] and North American[374] guidelines, based on new high-quality evidence from randomised controlled trials in diagnosis, treatment and monitoring have been published. A partial update of the existing NICE guideline is necessary to ensure that the recommendations take into account the new evidence available.

Diagnosis of heart failure depends on clinical symptoms and signs with imaging – usually echocardiography - and increasingly laboratory measured biomarkers such as natriuretic peptides (chapter 5). Technological progress has led to availability of further imaging technologies e.g. cardiac magnetic resonance imaging (chapter 5) and biomarkers which might be used in diagnosis or for monitoring the efficacy and titration of therapies (chapter 8).

The National Heart Failure audit highlights the roles that beta-blocker (chapter 6) and mineralocorticoid receptor antagonist (MRA) therapy (chapter 6) are playing in management of heart failure. The evidence base for these treatments has increased over the last 10 years. Despite the high prevalence of ischaemic heart disease in patients with heart failure the role of coronary intervention in patients with heart failure remains unclear (chapter 6). The high incidence of iron deficiency and anaemia in patients with heart failure has prompted trials of iron therapy in heart failure (chapter 6). Patients with co-morbidities have a worse prognosis and some co-morbidities such as atrial fibrillation (chapter 6) or chronic kidney disease can influence the management of heart failure (chapter 6).

Non-pharmacological interventions also have a substantial and under-recognised role to play in the management of heart failure. Evidence has accumulated for better outcomes in patients receiving care from cardiology services including specialist heart failure nurses (chapter 9) and in those able to access rehabilitation (chapter 7). The increasing move of complex care from hospital to primary care places a greater emphasis on communication and processes for transition of care (chapter 9) and the ability to manage symptomatic relief in community settings (chapter 10). Developments in information technology and in the use of telephone-based and direct telemonitoring technologies have the potential to further improve delivery of care (chapter 8) [241]. Heart failure is a progressive condition but access to palliative care services remains patchy, with unclear referral criteria (chapter 10), unclear policies on deactivation of implanted devices (chapter 10) and on the use of ancillary therapies such as diuretic regimes (chapter 10) or domiciliary oxygen (chapter 10).

2.6 Audience

The guideline update is intended for use by the following people or organisations:

- All healthcare professionals
- People with chronic heart failure and their carers
- Patient support groups
- Commissioning organisations
- Service providers

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3 Development of the guideline

3.1 What is a NICE guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. These may also include elements of social care or public health measures. We base our guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- A guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Guideline Centre (NGC).
- The NGC establishes a guideline committee.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NGC and NICE produce a number of versions of this guideline:

- The 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence.
- The 'NICE guideline' lists the recommendations.
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

3.2 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the NGC to produce the guideline.

The remit for this guideline is:

To develop a clinical guideline on the management of chronic heart failure in adults in primary and secondary care.

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3.3 Who developed this guideline?

A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members developed this guideline (see the list of guideline committee members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Guideline Centre (NGC) and thus supported the development of this guideline. The committee was convened by the NGC and chaired by Anthony Wierzbicki in accordance with guidance from NICE.

The group met approximately every 6 weeks during the development of the guideline. At the start of the guideline development process all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in appendix L.

Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information specialists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

3.3.1 What this guideline covers

Groups that will be covered

Adults (18 and over) with symptoms or a diagnosis of chronic heart failure (including heart failure with reduced ejection fraction and heart failure with preserved ejection fraction).

Areas from the published guideline that will be updated

- Diagnosing heart failure.
  - Role of circulating biomarkers (including natriuretic peptides).
  - Echocardiography and cardiac MRI.
- Managing chronic heart failure.
  - Initiation and sequencing of pharmacological therapies including:
    - Isosorbide/hydralazine.
    - Angiotensin-II receptor antagonists (ARBs).
    - Mineralocorticoid receptor antagonists
  - Fluid balance (optimum fluid and salt intake).
- Rehabilitation (including Home-based rehabilitation packages that include an exercise element).
- Monitoring heart failure.
  - Role of biomarkers (including natriuretic peptides).
  - Role of echocardiography.
  - Distance monitoring including telemonitoring.
  - Self-monitoring.
- Referral for invasive procedures:
  - Coronary revascularisation (including coronary artery bypass graft and angioplasty).

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- Referral and approach to care.
  - Heart failure multidisciplinary team.
  - Transfer of care between secondary and primary care services.
- Information and support.
  - Information and support on diagnosis and prognosis for people with chronic heart failure, their families and carers.
- Supportive and palliative care.
  - Domiciliary oxygen therapy.
  - Parenteral and intravenous diuretics.
  - Criteria for withdrawing treatment and device inactivation.

Areas not in the published guideline that will be included in the update

- How to manage chronic heart failure in different subgroups:
  - People with iron deficiency.
  - People with chronic kidney disease (estimated glomerular filtration rate [eGFR] less than 60 ml/min/1.73m^2 with or without markers of kidney damage).
  - People with chronic heart failure and secondary atrial fibrillation.
  - People aged over 75.
- Pharmacological therapies.
  - Beta-blockers in people with chronic heart failure and secondary atrial fibrillation.
- Palliative care.
  - Referral to palliative care.
  - Delivery of diuretics
- Monitoring heart failure.
  - Role of cardiac MRI.

For further details please refer to the scope in appendix L and the review questions in section 4.1.

3.3.2 What this guideline does not cover

Areas from the published guideline that will not be updated

- Symptoms and signs in diagnosing heart failure.
- Clinical review and monitoring of serum digoxin.
- Lifestyle.
  - Sexual activity, vaccination and air travel.

Areas from the published guideline that will be removed

- General.
  - Age.
  - Gender.
- Pharmacological agents.
  - Aspirin.

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  - Statins.
- Heart failure caused by valve disease.
- Management of depression and anxiety.
- Benefit of other therapies such as homeopathy, reflexology, hydrotherapy, crystal therapy and acupuncture.
- Referral for invasive procedures.
  - Implantable cardiac defibrillators.
- Valve surgery.
- Non-NHS agencies.
- Lifestyle.
  - Smoking and alcohol.

3.3.3 Relationships between the guideline and other NICE guidance

NICE guidance that will be updated by this guideline:

- Chronic heart failure in in adults: management (2010) NICE guidline CG108

NICE technology appraisals to be incorporated in this guidance:

- Ivabradine for treating chronic heart failure (2012) NICE technology appraisal guidance 267.
- Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (2016) NICE technology appraisal [TA388]

Related NICE technology appraisals:

- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (2014) NICE technology appraisal guidance [TA314]

Related NICE intervenetional procedures guidance

- Subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death [IPG603]

Related NICE guidelines:

- Medicines optimisation (2015) NICE guideline NG5
- Patient experience in adult NHS services (2012) NICE guideline CG138
- Medicines adherence (2009) NICE guideline CG76
- Acute heart failure: diagnosis and management (2014) Nice guideline [CG187]

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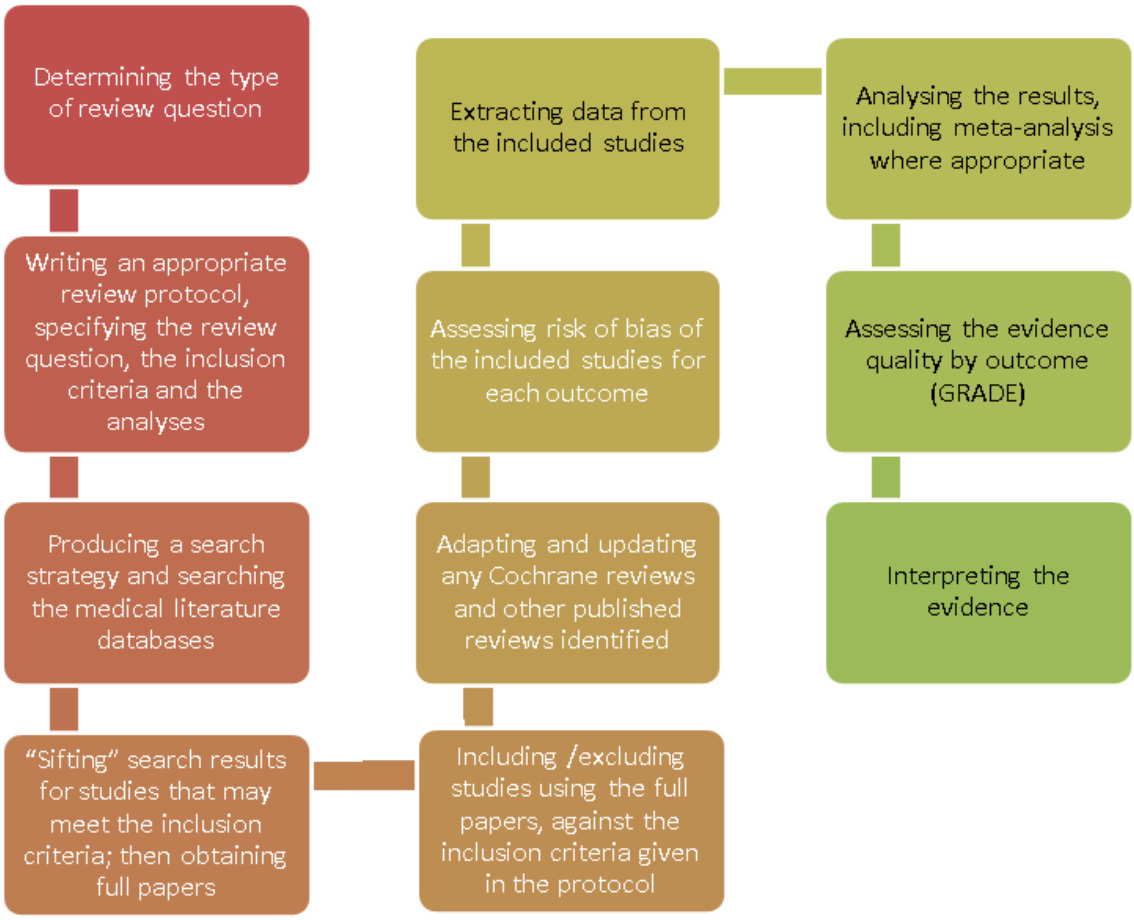
4 Methods

This chapter sets out in detail the methods used to review the evidence and to develop the recommendations that are presented in subsequent chapters of this guideline. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2014 version.[236]

Sections 4.1 to 4.3 describe the process used to identify and review clinical evidence (summarised in Figure 3), sections 4.2 and 4.4 describe the process used to identify and review the health economic evidence, and section 4.5 describes the process used to develop recommendations.

Figure 3: Step-by-step process of review of evidence in the guideline



4.1 Developing the review questions and outcomes

Review questions were developed using a PICO framework (population, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews; and using a framework of population, setting and context for qualitative reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the guideline committee. The review questions were drafted by the NGC technical team and refined and validated by the committee. The questions were based on the key clinical areas identified in the scope (appendix L).

A total of 26 review questions were identified.

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Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
5	Diagnostic	In people with suspected heart failure, what thresholds of pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?	Diagnostic accuracy of BNP and NT-proBNP: • 2x2 tables • Specificity • Sensitivity • PPV/NPV ROC curve or Area under Curve
5	Diagnostic RCT	In people with suspected heart failure, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?	Efficacy outcomes: • All-cause mortality • Quality of life • Unplanned hospitalisation Process outcomes: • Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results • Repeat testing / additional testing Secondary accuracy outcomes: Sensitivity / specificity and other test accuracy measures
5	Diagnostic	In people with suspected heart failure who also have atrial fibrillation, what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?	Diagnostic accuracy of BNP and NT-proBNP: • 2x2 tables • Specificity • Sensitivity • PPV/NPV ROC curve or Area under Curve
5	Diagnostic RCT	In people with suspected heart failure who also have atrial fibrillation, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?	Efficacy outcomes: • All-cause mortality • Quality of life • Unplanned hospitalisation Process outcomes: • Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results • Repeat testing / additional testing Secondary accuracy outcomes: Sensitivity / specificity and other test accuracy measures
5	Diagnostic	In people with suspected heart failure who also have chronic kidney disease,	Diagnostic accuracy of BNP and NT-proBNP:

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Chapter	Type of review	Review questions	Outcomes
		what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?	• 2x2 tables • Specificity • Sensitivity • PPV/NPV ROC curve or Area under Curve
5	Diagnostic RCT	In people with suspected heart failure who also have chronic kidney disease, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?	Efficacy outcomes: • All-cause mortality • Quality of life • Unplanned hospitalisation Process outcomes: • Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results • Repeat testing / additional testing Secondary accuracy outcomes: Sensitivity / specificity and other test accuracy measures
5	Intervention	In people with heart failure what is the clinical and cost effectiveness of cardiac MRI followed by the appropriate patient pathway?	Critical outcomes: • All-cause mortality (time to event) • Health-related quality of life at 12 months (continuous) • Unplanned hospitalisation (total number of events (rate ratio)) Important outcomes: • Adverse events related to test (non-specific fibrosis in the presence of renal dysfunction) • Reclassification of specific HF aetiology (including ability to classify previous unclassified patients) • Change in management • HF medication use • HF advanced therapy use, including disease specific therapies • Repeat testing / additional testing
6	Intervention	What is the clinical and cost effectiveness of salt and/or fluid restriction in people with heart failure?	Critical outcomes: • Quality of life at 12 months (Continuous) • Unplanned hospitalization (Count rate) Important outcomes: • Change in weight at 12 months

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Chapter	Type of review	Review questions	Outcomes
			(Continuous) • Change in oedema at 12 months (Continuous) • Change in sodium level (Continuous)(in the low baseline sodium strata only) • Adverse events - Renal function at 12 months (Dichotomous) • Adverse events - Hyperkalaemia at 12 months (Dichotomous)
6	Intervention	What is the clinical and cost effectiveness of beta-blockers in the management of chronic heart failure in people with heart failure with reduced ejection fraction (HFREF) and atrial fibrillation?	Critical outcomes: • All-cause mortality • Health-related quality of life • Unplanned hospitalisation Important outcomes: • Other adverse events (stroke, bradycardia, hypotension) • Improvement of NYHA class
6	Intervention	What is the clinical and cost effectiveness of mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction?	Critical outcomes: • All-cause mortality • Quality of life • Unplanned hospitalisation Important outcomes: • Improvement of NYHA class • Adverse events - Renal function • Adverse events – Gynaecomastia • Adverse events – Hypotension • Adverse events - Hyperkalaemia
6	Intervention	What is the clinical and cost effectiveness of adding a mineralocorticoid receptor antagonist to existing standard first line treatment in people with heart failure with reduced ejection fraction?	Critical outcomes: • All-cause mortality • Quality of life • Unplanned hospitalisation Important outcomes: • Improvement of NYHA class • Adverse events - Renal function • Adverse events – Gynaecomastia • Adverse events – Hypotension • Adverse events - Hyperkalaemia
6	Intervention	What is the clinical and cost effectiveness of iron supplementation in people with chronic heart failure and iron deficiency?	Critical outcomes: • Mortality • Quality of life • Unplanned hospitalisation Important outcomes: • Improvement in exercise

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Chapter	Type of review	Review questions	Outcomes
			tolerance • Change in haemoglobin in anaemic patients • Withdrawal due to adverse events/tolerability • Adverse events (hypertension, anaphylaxis/hypersensitivity, stroke, gastrointestinal)
6	Intervention	What is the clinical and cost effectiveness of pharmacological interventions for heart failure in people with heart failure who also have chronic kidney disease?	Critical outcomes: • All-cause mortality • Quality of life • Unplanned hospitalization Important outcomes: • Renal function • Adverse events - Bradycardia • Adverse events - Arrhythmic events • Adverse events - Progression to stage five kidney disease / unplanned dialysis • Adverse events - Hypotension • Adverse events - Hyperkalaemia
6	Intervention	What is the clinical and cost effectiveness of coronary revascularisation with coronary artery bypass grafting or angioplasty in people with heart failure?	Critical outcomes: • All-cause mortality at 30 days (Time to event) • All-cause mortality (Time to event) • Quality of life at 12 months (Continuous) • Unplanned hospitalisation at 12 months (Count rate) Important outcomes: • Additional revascularisation events at 24 months (Count rate) • Improvement of NYHA class at 12 months (Dichotomous) • Improvement in ejection fraction at 12 months (Dichotomous) • Adverse events - stroke at 12 months (Dichotomous)
7	Intervention	What is the clinical and cost effectiveness of home-based versus centre-based rehabilitation (that includes an exercise element) for people with heart failure (HF)?	Critical outcomes: • All-cause mortality • CV mortality • Health-related quality of life • All cause hospitalisation • HF-related hospitalisation Important outcomes:

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Chapter	Type of review	Review questions	Outcomes
			• Exercise capacity • Adverse events (withdrawal from the exercise programme) • Adherence (including maintenance of exercise/physical activity) • Health service use
8	Intervention	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure?	Critical outcomes: • Mortality (Time to event) • Quality of life at 12 months (Continuous) • Unplanned hospitalisation (all-cause) (Count rate) Important outcomes: • Adverse events - hypotension (Dichotomous) • Adverse events - hyperkalaemia (Dichotomous) • Adverse events - renal function (Continuous) • Adverse events - bradycardia (Dichotomous) • Adverse events - arrhythmic events (Dichotomous)
8	Intervention	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have CKD?	Critical outcomes: • Mortality (Time to event) • Quality of life at 12 months (Continuous) • Unplanned hospitalisation (all-cause) (Count rate) Important outcomes: • Adverse events - hypotension (Dichotomous) • Adverse events - hyperkalaemia (Dichotomous) • Adverse events - renal function (Continuous) • Adverse events - bradycardia (Dichotomous) • Adverse events - arrhythmic events (Dichotomous)
8	Intervention	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have atrial fibrillation?	Critical outcomes: • Mortality at during study (Time to event) • Quality of life at 12 months (Continuous) • Unplanned hospitalisation (all-cause) (Count rate) Important outcomes: • Adverse events - hypotension

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Chapter	Type of review	Review questions	Outcomes
			(Dichotomous) • Adverse events - hyperkalaemia (Dichotomous) • Adverse events - renal function (Continuous) • Adverse events - bradycardia (Dichotomous) • Adverse events - arrhythmic events (Dichotomous)
8	Intervention	What is the clinical and cost effectiveness of telemonitoring and self-monitoring using telephone technology, compared with usual care, in people with heart failure?	Critical outcomes: • All-cause mortality during study (dichotomous) • Quality of life during study (continuous) • All-cause hospitalisations during study (dichotomous) Important outcomes: • Adherence to intervention
9	Intervention	What competencies should be present in the multidisciplinary teams involved in the outpatient or community-based care of people with heart failure?	Critical outcomes: • All-cause mortality (Time to event) • Quality of life (Continuous) • Unplanned hospitalisation (Count rate) Important outcomes: • Medicine optimization and adherence • Dying in preferred place of death (for palliative care patients) • Adverse events – hypotension, hyperkalaemia, and renal function • Patient and carer experience
9	Qualitative	What are the experiences/preferences of staff and patients during transition between different heart failure care settings (including primary, secondary and community care)?	Thematic analysis- information synthesised into main review findings.
9	Qualitative	What are the information and support needs to be considered when communication a diagnosis and consequent prognosis, to people with heart failure, their families and carers?	Thematic analysis- information synthesised into main review findings.
10	Intervention	Which route of administration of diuretics (intravenous (IV), subcutaneous or oral) is most clinically and cost effective in people with advanced heart failure who are in the community, including patients receiving	Critical outcomes: • Quality of life • Unplanned hospitalization Important outcomes: • Change in dyspnoea

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Chapter	Type of review	Review questions	Outcomes
		palliative care?	• Weight change / change in oedema • Change in NYHA class • Patient and carer satisfaction • Time to death (survival) • Successful administration of intervention
10	Intervention	What is the effectiveness of domiciliary oxygen therapy in people with advanced heart failure?	Critical outcomes: • Quality of life at 2 weeks (Continuous) • Change in dyspnea at 2 weeks (Continuous) • Unplanned hospitalization at 4 weeks (Count rate) • Unplanned hospitalization at 4 weeks (number of bed days) • Patient and carer satisfaction 2 weeks (Continuous) Important outcomes: • Change in exercise capacity at 2 weeks (Continuous) • Change in NYHA class at 2 weeks (Continuous)
10	Qualitative	What criteria should determine when to discuss defibrillator deactivation?	Thematic analysis- information synthesised into main review findings.
10	Prognostic	In adults with heart failure, which validated risk tools best identify patients with heart failure who are at increased risk of mortality in the short term (up to 1 year)?In adults with heart failure, which validated risk tools best identify patients with heart failure who are at increased risk of mortality in the short term (up to 1 year)?	• Area under the ROC curve (AUC or c-statistic) • Sensitivity, specificity, negative predictive value, positive predictive value • Predicted risk versus observed risk (calibration) • Other outcomes e.g., D statistic, R^2 statistic and Brier score • Reclassification

4.2 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2014.[236] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed. All searches were conducted in Medline, Embase, and The Cochrane Library. Additional subject specific databases were used for the qualitative reviews: CINAHL and PsychINFO. All searches were updated on 06.12.17. No papers published after this date were considered.

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Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking committee members to highlight any additional studies. Searches were quality assured by a second information specialist before being run. The questions, the study types applied, the databases searched and the years covered can be found in appendix N.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- NHS Evidence Search (www.evidence.nhs.uk).
- Turning Research into Practice (TRIP (www.tripdatabase.com))
- Royal College of General Practitioners (www.rcgp.org.uk)

All references sent by stakeholders were considered. Searching for unpublished literature was not undertaken. The NGC and NICE do not have access to drug manufacturers' unpublished clinical trial results, so the clinical evidence considered by the committee for pharmaceutical interventions may be different from that considered by the MHRA and European Medicines Agency for the purposes of licensing and safety regulation.

4.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to heart failure in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA) with no date restrictions (NHS EED ceased to be updated after March 2015). Additionally, the search was run on Medline and Embase using a health economic filter, from September 2009, to ensure recent publications that had not yet been indexed by the economic databases were identified. The quality of life search was run on Medline and Embase using a quality of life filter, from January 2002. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed.

The health economic search strategies are included in appendix N. The general heart failure economic search was updated on 6 December 2017. No papers published after this date were considered.

4.3 Identifying and analysing evidence of effectiveness

Research fellows conducted the tasks listed below, which are described in further detail in the rest of this section:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in appendix A).

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- Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual.[236] Prognostic studies were critically appraised using NGC checklists. Qualitative studies were critically appraised using the GRADE CERQual approach for rating confidence in the body of evidence as a whole and using an NGC checklist for the methodological limitations section of the quality assessment.
- Extracted key information about interventional study methods and results using 'Evibase', NGC's purpose-built software. Evibase produces summary evidence tables, including critical appraisal ratings. Key information about non-interventional study methods and results was manually extracted onto standard evidence tables and critically appraised separately (evidence tables are included in appendix F).
- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
  - Randomised data were meta-analysed where appropriate and reported in GRADE profile tables.
  - Data from non-randomised studies were presented as a range of values in GRADE profile tables or meta-analysed if appropriate.
  - Prognostic data were meta-analysed where appropriate and reported in GRADE profile tables.
  - Diagnostic data studies were meta-analysed where appropriate or presented as a range of values in adapted GRADE profile tables
  - Qualitative data were synthesised across studies and presented as summary statements with accompanying GRADE CERQual ratings for each review finding.
- A sample of a minimum of 10% of the abstract lists of the first 3 sifts by new reviewers and those for complex review questions (for example, prognostic reviews) were double-sifted by a senior research fellow and any discrepancies were rectified. All of the evidence reviews were quality assured by a senior research fellow. This included checking:
  - papers were included or excluded appropriately
  - a sample of the data extractions
  - correct methods were used to synthesise data
  - a sample of the risk of bias assessments.

4.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in appendix A. Excluded studies by review question (with the reasons for their exclusion) are listed in appendix I. The committee was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- Adults (18 and older) with symptoms or a diagnosis of chronic heart failure (including heart failure with reduced ejection fraction and heart failure with preserved ejection fraction)

The key population exclusion criterion was:

- Diagnostic screening for heart failure in people who are asymptomatic.
- People with isolated right heart failure.
- Heart failure in people having chemotherapy.
- Heart failure in people having treatment for HIV.
- Heart failure in women who are pregnant.

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Conference abstracts were not included in any of the reviews. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

4.3.1.1 Saturation of qualitative studies

Data extraction in qualitative reviews is a thorough process and may require more time compared to intervention reviews. It is common practice to stop extracting data once saturation has been reached. This is the point when no new information emerges from studies that match the review protocol. The remaining identified studies are, however, not directly excluded from the review as they nevertheless fit the criteria defined in the review protocol. Any studies for which data were not extracted due to saturation having been reached, but that fit the inclusion criteria of the protocol, were listed in the table for studies 'identified but not included due to saturation' in the appendix for the qualitative evidence review.

4.3.2 Type of studies

Randomised trials, non-randomised intervention studies, and other observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. Crossover RCTs were not appropriate for any of the intervention reviews . In chronic conditions there is the possibility that the initial treatment permanently alters the disease or the process being investigated. The cardiac rehabilitation review was the exception where only data from the 1st period of cross-over trials was included, unless there was formal evidence of period effects in which case data from both 1st and 2nd periods was included.

If non-randomised intervention studies were considered appropriate for inclusion (for example, in prognostic risk tool and diagnostic reviews) the committee stated a priori in the protocol that either certain identified variables must be equivalent at baseline or else the analysis had to adjust for any baseline differences. If the study did not fulfil either criterion it was excluded. Please refer to the review protocols in appendix A for full details on the study design of studies selected for each review question.

For diagnostic review questions, diagnostic RCTs, cross-sectional studies and retrospective studies were included. For prognostic review questions, prospective and retrospective cohort studies were included. Case–control studies were not included.

Where data from non-randomised studies were included, the results for each outcome were presented separately for each study or meta-analysed if appropriate.

4.3.3 Methods of combining clinical studies

4.3.3.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted using Cochrane Review Manager (RevMan5)[283] software to combine the data given in all studies for each of the outcomes of interest for the review question.

For some questions stratification was used, and this is documented in the individual review question protocols (see appendix A). Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk, RR) for the binary outcomes, which included:

- All-cause mortality
- Cardiovascular mortality
- Unplanned hospitalisation
- HF related hospitalisation
- Adverse events (for example stroke, bradycardia, hypotension, arrhythmic events, hyperkalaemia)
- Change in NYHA class
- Change in management
- HF medication use
- HF advanced therapy use, including disease specific therapies
- Repeat testing or additional testing
- Additional revascularisation events
- Patient and carer satisfaction
- Successful administration of intervention
- Withdrawal due to adverse events/tolerability
- Medicine optimisation and adherence
- Dying in preferred place of death (for palliative care patients)
- Adherence to intervention
- Health service use

The absolute risk difference was also calculated using GRADEpro[138] software, using the median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events.

Continuous outcomes

Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes included:

- heath-related quality of life (HRQoL)
- Time to death
- Change in exercise capacity
- Improvement in exercise tolerance
- Change in haemoglobin in anaemic patients
- Improvement in ejection fraction
- Change in dyspnoea
- Weight change or change in oedema
- Change in sodium level

Where the studies within a single meta-analysis had different scales of measurement, standardised mean differences were used (providing all studies reported either change from baseline or final values rather than a mixture of both); each different measure in each study was 'normalised' to the

standard deviation value pooled between the intervention and comparator groups in that same study.

The means and standard deviations of continuous outcomes are required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals (95% CI) were reported, and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5[283] software. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if a p value was reported as 'p≤0.001', the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011) were applied.

4.3.3.1.1 Generic inverse variance

If a study reported only the summary statistic and 95% CI the generic-inverse variance method was used to enter data into RevMan5.[283] If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.[138] If multivariate analysis was used to derive the summary statistic but no adjusted control event rate was reported no absolute risk difference was calculated.

4.3.3.1.2 Heterogeneity

Statistical heterogeneity was assessed for each meta-analysis estimate by considering the chi-squared test for significance at $p<0.1$ or an I-squared (I^2) inconsistency statistic (with an I-squared value of more than 50% indicating significant heterogeneity) as well as the distribution of effects. Where significant heterogeneity was present, predefined subgrouping of studies was carried out as specified a priori in the review protocols (appendix A).

If the subgroup analysis resolved heterogeneity within all of the derived subgroups, then each of the derived subgroups were adopted as separate outcomes (providing at least 1 study remained in each subgroup. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Any subgroup differences were interpreted with caution as separating the groups breaks the study randomisation and as such is subject to uncontrolled confounding.

For some questions additional subgrouping was applied, and this is documented in the individual review question protocols (see appendix A). These additional subgrouping strategies were applied independently, so subunits of subgroups were not created, unlike the situation with strata. Other subgrouping strategies were only used if the age category subgroup was unable to explain heterogeneity, then these further subgrouping strategies were applied in order of priority. Again, once a subgrouping strategy was found to explain heterogeneity from all derived subgroups, further subgrouping strategies were not used.

If all predefined strategies of subgrouping were unable to explain statistical heterogeneity within each derived subgroup, then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence interval around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across more than 1 population. If, however, the committee considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were described narratively.

4.3.3.1.3 Complex analysis

Where studies had used a crossover design, paired continuous data were extracted where possible, and forest plots were generated in RevMan5[283] with the generic inverse variance function. When a crossover study had categorical data and the number of subjects with an event in both interventions

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was known, the standard error (of the log of the risk ratio) was calculated using the simplified Mantel-Haenszel method for paired outcomes. Forest plots were also generated in RevMan5[283] with the generic inverse variance function. If paired continuous or categorical data were not available from the crossover studies, the separate group data were analysed in the same way as data from parallel groups, on the basis that this approach would overestimate the confidence intervals and thus artificially reduce study weighting resulting in a conservative effect. Where a meta-analysis included a mixture of studies using both paired and parallel group approaches, all data were entered into RevMan5[283] using the generic inverse variance function.

4.3.3.2 Data synthesis for diagnostic test accuracy reviews

Two separate review protocols were produced to reflect the 2 different diagnostic study designs.

4.3.3.2.1 Diagnostic RCTs

Diagnostic RCTs (sometimes referred to as test and treat trials) are a randomised comparison of 2 diagnostic tests, with study outcomes being clinically important consequences of the diagnosis (patient-related outcome measures similar to those in intervention trials, such as mortality). Patients are randomised to receive test A or test B, followed by identical therapeutic interventions based on the results of the test (so someone with a positive result would receive the same treatment regardless of whether they were diagnosed by test A or test B). Downstream patient outcomes are then compared between the 2 groups. As treatment is the same in both arms of the trial, any differences in patient outcomes will reflect the accuracy of the tests in correctly establishing who does and does not have the condition. Data were synthesised using the same methods for intervention reviews (see section 4.3.3.1 above).

4.3.3.2.2 Diagnostic accuracy studies

For diagnostic test accuracy studies, a positive result on the index test was found if the patient had values of the measured quantity above or below a threshold value, and different thresholds could be used. The thresholds were prespecified by the committee including whether or not data could be pooled across a range of thresholds. Diagnostic test accuracy measures used in the analysis were: area under the receiver operating characteristics (ROC) curve (AUC), and, for different thresholds (if appropriate), sensitivity and specificity. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition. In practice this varies amongst studies. If a test has a high sensitivity then very few people with the condition will be missed (few false negatives). For example, a test with a sensitivity of 97% will only miss 3% of people with the condition. Conversely, if a test has a high specificity then few people without the condition would be incorrectly diagnosed (few false positives). For example, a test with a specificity of 97% will only incorrectly diagnose 3% of people who do not have the condition as positive. For this guideline, sensitivity or specificity was considered more important depending on the test threshold value being considered. For example at standard diagnostic thresholds of BNP and NT-proBNP sensitivity was prioritised as failing to diagnose people who have heart failure may delay the initiation of treatment and increase the risk of unplanned hospitalisations and mortality. While at much higher 'rule-in' thresholds specificity was prioritised as minimising false positives is more important in this context. Coupled forest plots of sensitivity and specificity with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5.[283] In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else were derived from raw data or calculated from the set of test accuracy statistics.

Diagnostic meta-analysis was conducted where appropriate, that is, when 3 or more studies were available per threshold. Test accuracy for the studies was pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random-effects approach in WinBUGS

software.[369] The advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the 2 statistics. Other advantages of this method have been described elsewhere.[282, 347, 348] The bivariate method uses logistic regression on the true positives, true negatives, false positives and false negatives reported in the studies. Overall sensitivity and specificity and confidence regions were plotted (using methods outlined by Novielli 2010.[284]) Pooled sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables. For scores with fewer than 3 studies, each study's sensitivity and the paired specificity were reported where possible.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots and pooled diagnostic meta-analysis plots.

The following criteria were used for evaluating AUCs:

- ≤0.50: worse than chance
- 0.50–0.60: very poor
- 0.61–0.70: poor
- 0.71–0.80: moderate
- 0.81–0.90: good
- 0.91–1.00: excellent or perfect test.

4.3.3.3 Data synthesis for risk prediction rules

Evidence reviews on risk prediction rules or risk prediction tool results were presented separately for discrimination and calibration. The discrimination data were analysed according to the principles of data synthesis for diagnostic accuracy studies as outlined in section 4.3.3.2.2. Calibration data such as r-squared (R^2), if reported, were presented separately to the discrimination data. The results were presented for each study separately along with the quality rating for the study and modified GRADE assessment.

4.3.3.4 Data synthesis for qualitative study reviews

The main findings for each included paper were identified and thematic analysis methods were used to synthesise this information into broad overarching themes which were summarised into the main review findings. The evidence was presented in the form of a narrative summary detailing the evidence from the relevant papers and how this informed the overall review finding plus a statement on the level of confidence for that review finding. Considerable limitations and issues around relevance were listed. A summary evidence table with the succinct summary statements for each review finding was produced including the associated quality assessment.

4.3.4 Appraising the quality of evidence by outcomes

4.3.4.1 Intervention reviews

The evidence for outcomes from the included RCTs and, where appropriate, non-randomised intervention studies, were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro[138]) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional or assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an overestimate of the effectiveness of that outcome.
Other issues	Sometimes randomisation may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be taken into account. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

4.3.4.1.1 Risk of bias

The main domains of bias for RCTs are listed in Table 3. Each outcome had its risk of bias assessed within each study first. For each study, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just 1 domain, the risk of bias was given a 'serious' rating of −1, but if there was risk of bias in 2 or more domains the risk of bias was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account the weighting of studies according to study precision. For example if the most precise studies tended to each have a score of −1 for that outcome, the overall score for that outcome would tend towards −1.

Table 3: Principle domains of bias in randomised controlled trials

Limitation	Explanation
Selection bias (sequence generation and allocation concealment)	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of: • knowledge of that participant's likely prognostic characteristics, and • a desire for one group to do better than the other.
Performance and	Patients, caregivers, those adjudicating or recording outcomes, and data analysts

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Limitation	Explanation
detection bias (lack of blinding of patients and healthcare professionals)	should not be aware of the arm to which patients are allocated. Knowledge of the group can influence: • the experience of the placebo effect • performance in outcome measures • the level of care and attention received, and • the methods of measurement or analysis all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of 10% between groups). Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules. • Use of unvalidated patient-reported outcome measures. • Lack of washout periods to avoid carry-over effects in crossover trials. • Recruitment bias in cluster-randomised trials.

4.3.4.1.2 Indirectness

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for the risk of bias, each outcome had its indirectness assessed within each study first. For each study, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just 1 source (for example in terms of population), indirectness was given a 'serious' rating of −1, but if there was indirectness in 2 or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome by taking into account study precision. For example, if the most precise studies tended to have an indirectness score of −1 each for that outcome, the overall score for that outcome would tend towards −1.

4.3.4.1.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in the underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (chi-squared $p<0.1$, or $I^2>50\%$), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of −1 if the I^2 was 50–74%, and a 'very serious' score of −2 if the I^2 was 75% or more.

If inconsistency could be explained based on prespecified subgroup analysis (that is, each subgroup had an $I^2<50\%$), the committee took this into account and considered whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory

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factors. In such a situation the quality of evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

4.3.4.1.4 Imprecision

The criteria applied for imprecision were based on the 95% CIs for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. If either end of the 95% CI of the overall estimate of effect crossed 1 of the MID lines, imprecision was regarded as serious and a 'serious' score of −1 was given. This was because the overall result, as represented by the span of the confidence interval, was consistent with 2 interpretations as defined by the MID (for example, both no clinically important effect and clinical benefit were possible interpretations). If both MID lines were crossed by either or both ends of the 95% CI then imprecision was regarded as very serious and a 'very serious' score of −2 was given. This was because the overall result was consistent with all 3 interpretations defined by the MID (no clinically important effect, clinical benefit and clinical harm). This is illustrated in Figure 4. As for inconsistency, since the imprecision score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

The position of the MID lines is ideally determined by values reported in the literature. 'Anchor-based' methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or 'anchoring' them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, a MID for an outcome could be defined by the minimum amount of change in that outcome necessary to make patients feel their quality of life had 'significantly improved'. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health. For binary variables, any MIDs reported in the literature will inevitably be based on expert consensus, as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, and so are not amenable to patient-centred 'anchor' methods.

The GC agreed to use these published values for quality of life scores: EQ-5D – 0.03 (from Sf-36 mapping),Kansas City – 5 (taken from literature) and SF-36 – 5 (taken from literature). The GC did not support the use of other MIDs as the measures were perceived as unreliable. The GC agreed that it was appropriate to use a reduction of 10 unplanned hospitilisation per 1000 as a clinically important benefit.

In the absence of values identified in the literature, the alternative approach to deciding on MID levels is the 'default' method, as follows:

- For categorical outcomes the MIDs were taken to be RRs of 0.75 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm.
- For mortality any change was considered to be clinically important and the imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect, that is whether the result was consistent with both benefit and harm.
- For continuous outcome variables the MID was taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. Hence the MID denoting the

minimum clinically significant benefit was positive for a 'positive' outcome (for example, a quality of life measure where a higher score denotes better health), and negative for a 'negative' outcome (for example, a visual analogue scale [VAS] pain score). Clinically significant harms will be the converse of these. If baseline values are unavailable, then half the median comparator group standard deviation of that variable will be taken as the MID.

- If standardised mean differences have been used, then the MID will be set at the absolute value of +0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the 2 groups, and are thus effectively expressed in units of 'numbers of standard deviations'. The 0.5 MID value in this context therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the committee. If the committee decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

Figure 4: Illustration of precise and imprecise outcomes based on the 95% CI of dichotomous outcomes in a forest plot (Note that all 3 results would be pooled estimates, and would not, in practice, be placed on the same forest plot)

4.3.4.1.5 Overall grading of the quality of clinical evidence

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores (0, −1 or −2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to −8 (the worst possible). However scores were capped at −3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. All RCTs started as High and the overall quality became Moderate, Low or Very Low if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in Table 4. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Non-randomised intervention studies started at Low, and so a score of −1 would be enough to take the grade to the lowest level of Very Low. Non-randomised intervention studies could, however, be upgraded if there was a large magnitude of effect or a dose-response gradient.

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.3.4.2 Prognostic reviews

Risk of bias and applicability of evidence for prognostic risk data were evaluated per study using the Prediction study Risk of Bias Assessment Tool (PROBAST) draft checklist. Risk of bias and applicability were evaluated using of these 5 domains:

- Patient selection
    - appropriate data sources, inclusion and exclusion criteria and comparability of baseline values in the participants

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- Predictors
    - Defined and assessed same way for all participants, blinding to outcome data,all relevant predictors analysed
- Outcome
    - Pre specified definition, predictors excluded from the outcome definition, outcome defined and determined in a similar way for all participants, blinding to predictor information
- Sample size and participant flow
    - Adequate number of outcome events, time interval between predictor assessment and outcome , appropriate missing data handling
- Analysis
    - non-binary predictors handled appropriately, univariable analysis avoided, model overfitting accounted for, complexities in the data (e.g. competing risks,) accounted for, assigned weights to predictors match the results from multivariable analysis, relevant performance measures are evaluated, e.g. calibration, discrimination, recalibrated if needed

If data were meta-analysed, the quality for pooled studies was presented. If the data were not pooled, then the quality rating was presented for each study.

4.3.4.2.1 Inconsistency

Inconsistency was assessed as for intervention studies.

4.3.4.2.2 Imprecision

Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was more than 20% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of more than 40%. Imprecision was not estimable where studies did not report confidence intervals.

4.3.4.2.3 Overall grading

Quality rating started at High for prospective and retrospective studies, and each major limitation brought the rating down by 1 increment to a minimum grade of Very Low, as explained for interventional reviews.

4.3.4.3 Diagnostic studies

Risk of bias and indirectness of evidence for diagnostic data were evaluated by study using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists (see appendix H in the NICE guidelines manual 2014[236]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Table 5: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions.):

- patient selection
- index test
- reference standard
- flow and timing.

Table 5: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions.

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods	Describe the index	Describe the	Describe any patients

Domain	Patient selection	Index test	Reference standard	Flow and timing
	of patient selection. Describe included patients (prior testing, presentation, intended use of index test and setting)	test and how it was conducted and interpreted	reference standard and how it was conducted and interpreted	who did not receive the index test(s) and/or reference standard or who were excluded from the 2×2 table (refer to flow diagram). Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/ unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case–control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias; (high/low/ unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability (high/low/ unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

4.3.4.3.1 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. Inconsistency was assessed by inspection of the sensitivity and specificity (based on the primary measure) using the point estimates and 95% CIs of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which it would be acceptable to recommend a test). For example, the committee might have set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas [(for example, 50–90% and 90–100%)] and by 2 increments if the individual studies varied across 3 areas [(for example, 0–50%, 50–90% and 90–100%)].

4.3.4.3.2 Imprecision

The judgement of precision was based on visual inspection of the confidence region around the summary sensitivity and specificity point from the diagnostic meta-analysis, if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted, imprecision was assessed according to the range of point estimates or, if only one study contributed to the evidence,

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the 95% CI around the single study. As a general rule (after discussion with the committee) a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

4.3.4.3.3 Overall grading

Quality rating started at High for prospective and retrospective cross-sectional studies, and each major limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by 1 increment to a minimum grade of Very Low, as explained for intervention reviews.

4.3.4.4 Qualitative reviews

Review findings from the included qualitative studies were evaluated and presented using the 'Confidence in the Evidence from Reviews of Qualitative Research' (CERQual) Approach developed by the GRADE-CERQual Project Group, a subgroup of the GRADE Working Group.

The CERQual Approach assesses the extent to which a review finding is a reasonable representation of the phenomenon of interest (the focus of the review question). Each review finding was assessed for each of the 4 quality elements listed and defined below in Table 6.

Table 6: Description of quality elements in GRADE-CERQual for qualitative studies

Quality element	Description
Methodological limitations	The extent of problems in the design or conduct of the included studies that could decrease the confidence that the review finding is a reasonable representation of the phenomenon of interest. Assessed at the study level using an NGC checklist.
Coherence	The extent to which the reviewer is able to identify a clear pattern across the studies included in the review.
Relevance	The extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol.
Adequacy	The degree of the confidence that the review finding is being supported by sufficient data. This is an overall determination of the richness (depth of analysis) and quantity of the evidence supporting a review finding or theme.

Details of how the 4 quality elements (methodological limitations, coherence, relevance and adequacy) were appraised for each review finding are given below.

4.3.4.4.1 Methodological limitations

Each review finding had its methodological limitations assessed within each study first using an NGC checklist. Based on the degree of methodological limitations studies were evaluated as having minor, moderate or severe limitations. The questions to be answered in the checklist below included:

- Was qualitative design an appropriate approach?
- Was the study approved by an ethics committee?
- Was the study clear in what it sought to do?
- Is the context clearly described?
- Is the role of the researcher clearly described?
- Are the research design and methods rigorous?
- Was the data collection rigorous?
- Was the data analysis rigorous?
- Are the data rich?
- Are the findings relevant to the aims of the study?

- Are the findings and conclusions convincing?

The overall assessment of the methodological limitations of the evidence was based on the primary studies contributing to the review finding. The relative contribution of each study to the overall review finding and of the type of methodological limitation(s) were taken into account when giving an overall rating.

4.3.4.4.2 Coherence

Coherence is the extent to which the reviewer is able to identify a clear pattern across the studies included in the review, and if there is variation present (contrasting or disconfirming data) whether this variation is explained by the contributing study authors. If a review finding in 1 study does not support the main finding and there is no plausible explanation for this variation, then the confidence that the main finding reasonably reflects the phenomenon of interest is decreased. Each review finding was given a rating of minor, moderate or major concerns about coherence.

4.3.4.4.3 Relevance

Relevance is the extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol. As such, relevance is dependent on the individual review and discussed with the guideline committee. Relevance is categorised in 3 ways: partial relevance, indirect relevance and no concerns about relevance.

4.3.4.4.4 Adequacy

The judgement of adequacy is based on the confidence of the finding being supported by sufficient data. This is an overall determination of the richness (depth of analysis) and quantity of the evidence supporting a review finding or theme. Rich data provide sufficient detail to gain an understanding of the theme or review finding, whereas thin data do not provide enough detail for an adequate understanding. Quantity of data is the second pillar of the assessment of adequacy. For review findings that are only supported by 1 study or data from only a small number of participants, the confidence that the review finding reasonable represents the phenomenon of interest might be decreased. As with richness of data, quantity of data is review dependent. Based on the overall judgement of adequacy, a rating of no concerns, minor concerns, or substantial concerns about adequacy was given.

4.3.4.4.5 Overall judgement of the level of confidence for a review finding

GRADE-CERQual is used to assess the body of evidence as a whole through a confidence rating representing the extent to which a review finding is a reasonable representation of the phenomenon of interest. The 4 components (methodological limitations, coherence, relevance and adequacy) are used in combination to form an overall judgement. GRADE-CERQual uses 4 levels of confidence: high, moderate, low and very low confidence. The significance of these overall ratings is explained in Table 7: Overall level of confidence for a review finding in GRADE-CERQual. Each review finding starts at a high level of confidence and is downgraded based on the concerns identified in any 1 or more of the 4 components. Quality assessment of qualitative reviews is a subjective judgement by the reviewer based on the concerns that have been noted. A detailed explanation of how such a judgement had been made was included in the narrative summary.

Table 7: Overall level of confidence for a review finding in GRADE-CERQual

Level	Description
High confidence	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest.
Moderate	It is likely that the review finding is a reasonable representation of the phenomenon of

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Level	Description
confidence	interest.
Low confidence	It is possible that the review finding is a reasonable representation of the phenomenon of interest.
Very low confidence	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

4.3.5 Publication bias

Funnel plots were constructed using RevMan5(RevMan5[283] software to assess against potential publication bias for outcomes containing more than 5 studies in intervention reviews (appendix F). This was taken into consideration when assessing the quality of the evidence.

4.3.6 Assessing clinical importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro[138] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The committee considered for most of the outcomes in the intervention reviews that if at least 100 more participants per 1000 (10%) achieved the outcome of interest in the intervention group compared to the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For the critical outcome of mortality any reduction represented a clinical benefit. For adverse events 50 events or more per 1000 (5%) represented clinical harm. For continuous outcomes if the mean difference was greater than the minimally important difference (MID) then this resented a clinical benefit or harm. For outcomes such as mortality any reduction or increase was considered to be clinically important.

This assessment was carried out by the committee for each critical outcome, and an evidence summary table was produced to compile the committee's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.3.7 Clinical evidence statements

Clinical evidence statements are summary statements that are included in each review chapter, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments).
- A description of the overall quality of the evidence (GRADE overall quality).

4.3.8 Appendix D-Practical notes

The 2010 guideline included practical recommendations which covered aspects of clinical management that were not included in the evidence reviewed but which the committee considered important. In updating the guideline the committee reviewed the information included within this

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appendix and agreed that where appropriate these practical notes should be absorbed into the treatment and monitoring recommendations.

4.4 Identifying and analysing evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical effectiveness and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost. However, the committee will also need to be increasingly confident in the cost effectiveness of a recommendation as the cost of implementation increases. Therefore, the committee may require more robust evidence on the effectiveness and cost effectiveness of any recommendations that are expected to have a substantial impact on resources; any uncertainties must be offset by a compelling argument in favour of the recommendation. The cost impact or savings potential of a recommendation should not be the sole reason for the committee's decision.[236]

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

4.4.1 Literature review

The health economists:

- Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using economic evaluations checklists as specified in the NICE guidelines manual.[236]
- Extracted key information about the studies' methods and results into health economic evidence tables (included in appendix G).
- Generated summaries of the evidence in NICE health economic evidence profile tables (included in the relevant chapter for each review question) – see below for details.

4.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 2001 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly

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applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see Table 8 below and the economic evaluation checklist (appendix H of the NICE guidelines manual[236]) and the health economics review protocol in appendix B.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the committee to inform the possible economic implications of the recommendations.

4.4.1.2 NICE health economic evidence profiles

NICE health economic evidence profile tables were used to summarise cost and cost-effectiveness estimates for the included health economic studies in each review chapter. The health economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual.[236] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base case analysis in the study, as well as information about the assessment of uncertainty in the analysis. See Table 8 for more details.

When a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[249]

Table 8: Content of NICE health economic evidence profile

Item	Description
Study	Surname of first author, date of study publication and country perspective with a reference to full information on the study.
Applicability	An assessment of applicability of the study to this guideline, the current NHS situation and NICE decision-making:[(a)] • Directly applicable – the study meets all applicability criteria, or fails to meet 1 or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet 1 or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study:[(a)] • Minor limitations – the study meets all quality criteria, or fails to meet 1 or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet 1 or more quality criteria, and this could change the conclusions about cost effectiveness. • Very serious limitations – the study fails to meet 1 or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Information about the design of the study and particular issues that should be considered when interpreting it.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with

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Item	Description
	one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects (usually in £ per QALY gained).
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in appendix H of the NICE guidelines manual[236]

4.4.2 Undertaking new health economic analysis

As well as reviewing the published health economic literature for each review question, as described above, new health economic analysis was undertaken by the health economist in selected areas. Priority areas for new analysis were agreed by the committee after formation of the review questions and consideration of the existing health economic evidence.

The committee identified determining a natriuretic peptide threshold for referral for echocardiography as the highest priority area for original health economic modelling. This was due to concerns that the current natriuretic peptide thresholds may be too high, resulting in delayed diagnosis, whilst also acknowledging that there could be significant increase in cost if the threshold were to be lowered and more patients were referred for echocardiography.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case for interventions with health outcomes in NHS settings.[236, 238]
- The committee was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NGC. The model methods were also peer-reviewed by Professor Martin Cowie because of his expertise in heart failure, knowledge of the literature and health economic modelling methodologies.

Full methods for the cost-effectiveness analysis of natriuretic peptide thresholds are described in appendix O.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money.[237] In general, an intervention was considered to be cost effective (given that the estimate was considered plausible) if either of the following criteria applied:

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

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If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[237]

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.4.4 In the absence of health economic evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

4.5 Developing recommendations

Over the course of the guideline development process, the committee was presented with:

- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables are in appendices F and G.
- Summaries of clinical and health economic evidence and quality (as presented in chapters 5-10).
- Forest plots and summary ROC curves (appendix E).
- A description of the methods and results of the cost-effectiveness analyses undertaken for the guideline (appendix O).

Recommendations were drafted on the basis of the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the committee took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the committee's values and preferences), and the confidence the committee had in the evidence (evidence quality). Secondly, the committee assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical and health economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the committee. The committee also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 4.5.1 below).

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The committee considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see section 9.2 in the NICE guidelines manual[236]).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

4.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

4.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited

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here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

4.5.5 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

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5 Diagnosing heart failure

The update to the heart failure guideline includes topics where new evidence has emerged since the publication in 2010. A review of new evidence published after 2010 was carried out in order to determine whether any changes to current recommendations where likely to be required. The decision on which topics to include in the update of the guideline was made following consultation of the scope.

The following topics were not within the scope of the update. For more information refer to the 2010 Guideline:

- Symptoms, signs and investigation.
- Natriuretic peptides versus echocardiography

See section 5.1 and 5.5 of 2010 guideline (Appendix R).

5.1 BNP and NT-proBNP in diagnosing heart failure

5.1.1 Introduction

The diagnosis of heart failure can be challenging because of the frequent overlap of the symptoms of breathlessness and fluid retention with other conditions, because the patient may already have a condition that produces similar symptoms, for example chronic obstructive pulmonary disease, and because the presence of co-morbidities may delay the diagnosis of heart failure. Furthermore, the demonstration of a structural or functional cardiac abnormality on imaging may not necessarily be the cause of the presenting symptoms. There is no single diagnostic test for heart failure, and the diagnosis relies on clinical judgement based on a combination of history, physical examination and appropriate investigations.

Biomarkers are substances measurable in the blood stream which can be used to diagnose and monitor disease. Natriuretic peptides are released from the myocardium in response to fluid overload. The two main natriuretic peptides used in clinical practice are amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP). The levels of natriuretic peptides correlate with prognosis in patients with heart failure and they may also be useful in patients with some other cardiovascular morbidities. The measurement of natriuretic peptides is recommended for the diagnosis of HF in previous NICE guidance. However, further evidence on the diagnostic efficiency of natriuretic peptides for heart failure in community settings has accumulated since that review, and the underlying prevalences of heart failure with reduced ejection fraction (HFREF) and with preserved ejection fraction (HFREF) are changing. The suggestion has been made that previous diagnostic threshold defined by natriuretic peptide levels may need to be revised. This question reviewed whether the diagnostic process for heart failure by the use of the appropriate combination of clinical signs, echocardiographic imaging and natriuretic peptide levels ought to be changed. Please note that natriuretic peptide levels have been reported in pg/ml throughout this review. However, the recommendations made have been converted to ng/L as this is more commonly recognised in practice (1pg/ml = 1ng/L).

5.1.2 Review question: In people with suspected heart failure, what thresholds of pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?

For full details see review protocol in appendix A.

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Table 9: Characteristics of review question

Population	People with suspected heart failure in a community or outpatient setting.
Target condition	Heart failure
Index test(s)	• NT-proBNP • BNP
Reference standard(s)	A clinical diagnosis based on the opinion of at least one cardiologist, considering symptoms (potentially with some signs) and objective evidence of cardiac dysfunction (either structural or functional).
Statistical measures	Diagnostic accuracy of BNP and NT-proBNP: • 2x2 tables • Specificity • Sensitivity • PPV/NPV • ROC curve or Area under Curve
Study design	Single gate studies (cohort/cross-sectional)

5.1.3 Review question: In people with suspected heart failure, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?

Table 10: PICO characteristics of review question

Population	People with suspected heart failure in a community or outpatient setting.
Index diagnostic test + treatment	NT-proBNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Comparator index diagnostic tests + treatment	BNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Outcomes	Efficacy outcomes: • All-cause mortality • Quality of life • Unplanned hospitalisation Process outcomes: • Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results • Repeat testing / additional testing Secondary accuracy outcomes: • Sensitivity / specificity and other test accuracy measures
Study design	Systematic Review RCT

5.1.4 Clinical evidence

A search was conducted for single gate studies assessing the diagnostic test accuracy of BNP or NT-proBNP to identify the presence of heart failure (as indicated by the reference standard) in people suspected of heart failure in a community or outpatient setting. A search was also conducted for diagnostic RCTs comparing outcomes in people tested with BNP versus NT-proBNP.

The search dates were limited to studies published from 2009 onwards, as this review was an update of a review within CG108 (the 2010 CHF guideline). The 2010 update included Mant 2009[212] . Mant

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2009 [212]conducted a meta-analysis of studies investigating the accuracy of BNP and/or NT-proBNP in diagnosing heart failure in a range of settings and populations, and using a range of reference standards. Only those studies from Mant 2009[212] that matched the current protocol were included in this review.

The 2010 update also included 8 studies[154,145,340,177,101,1,203,366] which used echocardiography as the reference standard, these papers have been excluded within the current update as the committee agreed that echocardiography was not an appropriate reference standard for the diagnosis of heart failure.

In total, 8 diagnostic accuracy studies were included in the review[79,173,243,245,330, 359,379,380] these are summarised in Table 11 below. Evidence from these studies is summarised in the clinical evidence summary. See also the study selection flow chart in Appendix C, sensitivity/specificity forest plots in Appendix E, study evidence tables in Appendix F and excluded studies list in Appendix I.

No diagnostic RCTs meeting the protocol were identified.

Table 11: Summary of studies included in the review

Study	Population	Target condition	Index test	Reference standard	Comments
Cowie 1997[79]	n=122 People with suspected heart failure Age range: 24-87 Gender (M:F): 59:63 UK	Heart failure	BNP	ESC criteria, assessed by panel of three cardiologists	
Kelder 2011[173]	n=200 People with suspected heart failure Age (mean SD): 70.2 (11.3) Gender (M:F): 59:133 The Netherlands	Heart failure	BNP NT-proBNP	ESC criteria and Heart Failure Society of America 2010 guideline, assessed by panel of cardiologist, pulmonologist and a GP.	Full diagnostic accuracy results not reported.
Nielsen 2003[243]	n=363 People complaining of dyspnoea of at	Heart failure	NT-proBNP	ESC criteria	Results stratified by age and sex. High risk of bias

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Study	Population	Target condition	Index test	Reference standard	Comments
	least 2 weeks duration. Not all participants were suspected to have heart failure, and a small number already had a clinical diagnosis of heart failure. Age (median; range): 65 (18-89) Gender (M:F): 178:169 Denmark				Serious indirectness
O'Shea 2012[245]	n=105 (74 people completed the study) People presenting with dyspnoea, or oedema and a "working diagnosis" of heart failure Age (median; range): 69 (47-85) Gender (M:F): 41:33 Ireland	Heart failure	BNP	Clinical assessment and objective evidence based on echocardiography, assessed by a single cardiologist	Very high risk of bias Serious indirectness
Taylor 2016[330]	n=304 People with symptoms suggestive of heart failure Age (mean SD): 73.9 (8.8)	Heart failure	NT-proBNP	ESC criteria, assessed by a panel of three cardiology specialists	

 ISBN: 978-1-4731-3093-7

Study	Population	Target condition	Index test	Reference standard	Comments
	Gender (M:F): 124:180 UK				
Verdu 2012[359]	n=220 People with suspected heart failure Age (mean SD): 73.2 (19.2) Gender (M:F): 76:144 Spain	Heart failure	NT-proBNP	ESC criteria, assessed by a single cardiologist	
Zaphiriou 2005[379]	n=306 People with suspected heart failure based on new symptoms Age (median; 90% range): 74 (52-87) Gender (M:F): 130:176 UK	Heart failure	BNP NT-proBNP	ESC criteria, assessed by a single cardiologist	
Zuber 2009[380]	n=384 People with suspected heart failure based on symptoms and clinical examination Age (mean SD): 65 (13) Gender (M:F): 245:139	Heart failure	BNP NT-proBNP	Presence of HF symptoms/signs and either: (a) an EF < 50%, according to the ESC criteria or (b) elevated LV filling pressure. Assessed by one of seven cardiologists.	Full diagnostic accuracy results not reported. Very high risk of bias Serious indirectness

 ISBN: 978-1-4731-3093-7

Study	Population	Target condition	Index test	Reference standard	Comments
	Switzerland				

 ISBN: 978-1-4731-3093-7

Table 12: Clinical evidence summary: diagnostic test accuracy for index test(s) BNP and NT-proBNP

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value (PPV) %	Negative Predictive Value (NPV) %	AUC (95% CI)
Plasma BNP								
BNP - 30 pg/mL	1	206	HIGH	95 (89 – 98)	35 (29 – 42)	43	93	0.84 (0.79 – 0.89)
BNP - 65 pg/mL	1	206	HIGH	87 (79 – 93)	57 (50 – 64)	51	90	0.84 (0.79 – 0.89)
BNP - 77 pg/mL	1	122	HIGH	97 (83 - 100)	84 (74 - 91)	70	98	0.96
BNP - 100 pg/mL	2[e]	406	HIGH	79 (70 – 87)	72 (65 – 78)	59	87	0.84 (0.79 – 0.89)
			Axsym	-	-	-	81	0.82 (0.73 – 0.90)
			Centaur	-	-	-	80	0.83 (0.76 - 0.91)
BNP - 178 pg/mL	1	105	VERY LOW[a,c,d] due to serious risk of bias, serious indirectness, serious imprecision	47 (33 – 62)	92 (74 – 99)	92	47	0.69 (0.57 – 0.79)
BNP - 400 pg/mL	1[e]	200	HIGH	10 (3 – 21)	100 (97 – 100)	100	72	0.82 (0.73 – 0.90)
			Axsym	6 (1 – 16)	100 (97 – 100)	100	72	0.83 (0.76 - 0.91)
			Centaur					
[Threshold data not accurately reported]	1	384	VERY LOW[a,c] due to serious risk of bias, serious indirectness	-	-	-	-	0.69
Plasma NT-proBNP								
NT-pro BNP Age specific thresholds (<50 years 50 pg/mL, 50-75 years 75 pg/mL, > 75 years 250 pg/mL)	1	220	HIGH	100 (93 – 100)	70 (63 – 77)	50	100	0.94 (0.91 – 0.97)
NT-pro BNP Women ≥ 50 years 67 pg/mL	1	363	LOW[a,c] due to serious risk of bias, serious indirectness	100 (90 - 100)	27 (19 - 37)	29	100	0.90 (0.84 – 0.97)

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value (PPV) %	Negative Predictive Value (NPV) %	AUC (95% CI)
NT-pro BNP Men ≥ 50 years 76 pg/mL	1	363	LOW[a,c] due to serious risk of bias, serious indirectness	100 (92 – 100)	60 (49 – 69)	53	97	0.93 (0.89 – 0.97)
NT-pro BNP Men ≥ 50 years 93 pg/mL	1	363	LOW[a,c] due to serious risk of bias, serious indirectness	96 (85 – 99)	67 (56 – 76)	57	97	0.93 (0.89 – 0.97)
NT-pro BNP 125 pg/mL	3	826	LOW[b,d] due to serious inconsistency, serious imprecision	Pooled[f:] 96 (72 – 100)	Pooled[f:] 48 (18 – 80)	Median: 44 Range: 38 – 48	Median: 97 Range: 87 – 100	Median: 0.85 Range: 0.74 – 0.94
NT-pro BNP Women ≥ 50 years 144 pg/mL	1	363	LOW[a,c] due to serious risk of bias, serious indirectness	94 (80 – 99)	69 (59 – 78)	48	97	0.90 (0.84 – 0.97)
NT-pro BNP Men ≥ 50 years 152 pg/mL	1	363	LOW[a,c] due to serious risk of bias, serious indirectness	89 (77 – 96)	79 (69 – 86)	66	94	0.93 (0.89 – 0.97)
NT-pro BNP 166 pg/mL	1	206	HIGH	96 (90 – 99)	43 (36 – 50)	47	96	0.85 (0.81 – 0.90)
NT-pro BNP Women ≥ 50 years 220 pg/mL	1	363	VERY LOW[a,c,d] due to serious risk of bias, serious indirectness, serious imprecision	91 (76 – 98)	84 (76 – 90)	64	97	0.90 (0.84 – 0.97)
NT-pro BNP 280 pg/mL	3	826	VERY LOW[b,d] due to serious inconsistency, very serious imprecision	Pooled[f:] 89 (41 – 99)	Pooled[f:] 75 (38 – 94)	Median: 55 Range: 47 – 72	Median: 92 Range: 83 – 100	Median: 0.85 Range: 0.74 – 0.94

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Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value (PPV) %	Negative Predictive Value (NPV) %	AUC (95% CI)
NT-pro BNP 400 pg/mL	3[g]	826[g]	VERY LOW[b,d] due to serious inconsistency, very serious imprecision	Pooled[f:] 79 (42 – 96)	Pooled[f:] 81 (49 – 95)	Median: 58 Range: 54 – 73	Median: 90 Range: 82 – 96	Median: 0.85 Range: 0.74 – 0.94
NT-pro BNP 2000 pg/mL	1	200	HIGH	2 (0 – 10)	100 (97 – 100)	100	71	0.86 (0.80 – 0.92)
[Threshold data not accurately reported]	1	384	VERY LOW[a,c] due to serious risk of bias, serious indirectness			-	-	0.74

The assessment was conducted with an emphasis on test sensitivity as this was identified by the GC as the primary measure in guiding decision making (except for the very high rule in thresholds of 400 ng/mL BNP and 2000 ng/mL NT-proBNP where specificity was the emphasis). The GC set the sensitivity threshold of 95% as an acceptable level to recommend a test.

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Inconsistency was assessed by inspection of the sensitivity/specificity plots. Particular attention was placed on the sensitivity threshold(s) set by the GC as an acceptable level to recommend a test. The evidence was:

- *downgraded by 1 increment if the individual study values varied across 2 areas, where values of individual studies are above/below 50%, or above/below the acceptable threshold 95%.*
- *downgraded by 2 increments if the individual study values varied across 3 areas, where values of individual studies are above/below 50%, and above/below the acceptable threshold 95%.*

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect.

(d) Imprecision was assessed based on inspection of the confidence region for sensitivity in the diagnostic meta-analysis. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

(e) One study reported the results of two BNP tests at this threshold: Axsym & Centaur (reported in that order in the table above).

(f) Pooled sensitivity/specificity from diagnostic meta-analysis.

(g) Three studies (n= 826) included in pooled analysis (one study only reported NPV and AUC and could not be pooled).

5.1.5 Economic evidence

5.1.5.1 Published literature

No economic evaluations were identified comparing NT-proBNP thresholds and BNP thresholds. One relevant economic evaluation was identified and included in this review. This is summarised in the health economic profile below (Table 13) and the health economic tables in Appendix G.

See also the economic article selection flow diagram in Appendix D.

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Table 13: Health economic evidence profile

Study	Applicability	Limitations	Other comments	Costs (c)	Effects (QALYs) (c)	Incremental cost (d)	Incremental effects (d)	Cost-effectiveness (d)	Uncertainty
Monahan 2017[226] [UK]	Directly applicable(a)	Potentially serious limitations (b)	• Cost-utility analysis (health outcome: QALYs) • Decision tree used to categorise patients according to diagnostic accuracy data[330] • Population: Primary care patients aged 55years or over presenting to GP with symptoms suggestive of HF recruited across 28 central England practices in the UK. • Interventions: 1. MICE clinical decision rule, upper cut-off 2. MICE clinical decision rule, lower cut-off 3. 2010 NICE guideline recommended strategy 4. Echo all 5. NT-proBNP	6. £119	6. 0.0000	Baseline			Probabilistic sensitivity analysis showed that the probability that Intervention 3 is the optimal strategy at £20,000/QALY is 99.9%. Intervention 3 remains the most cost effective strategy in a number of scenario analyses. However, when proportion of HF-REF is 50% intervention 5 is the most cost effective strategy. When proportion of HF-REF is 100% intervention 4 became the most cost effective strategy.
				1. £167	1. 0.0050	Dominated (3 has lower costs and greater effects)			
				3. £142	3. 0.0051	£23	0.0051	£4,400	
				2. £191	2. 0.0057	Extendedly dominated (the CIER for 5 vs 3 is higher than for 2 vs 3)			
				5. £196	5. 0.0059	£54	0.0008	£69,000	
				4. £241	4. 0.0063	£45	0.0004	£125,100	

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Study	Applicability	Limitations	Other comments	Costs (c)	Effects (QALYs) (c)	Incremental cost (d)	Incremental effects (d)	Cost-effectiveness (d)	Uncertainty
			threshold 125pg/ml 6. Do nothing • Lifetime horizon						

Abbreviations: ICER: incremental cost-effectiveness ratio; MICE: Male, Infarction, Crepitations, Edema; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Recent UK study from a NHS and PSS perspective.

(b) The analysis used diagnostic accuracy data where the level of NT-proBNP was used as a criterion in determining whether or not the patient had heart failure, therefore introducing incorporation bias to the diagnostic accuracy results. The committee were concerned that the hospitalisation rates applied in the model were overestimated compared to current clinical practice. The model does not report the outcomes for those who do not have heart failure and no assumptions have been reported for this population

(c) Incremental cost/QALYs compared to do nothing (intervention 6)

(d) Incremental cost/QALYs/cost effectiveness ratio compared to next most effect treatment option that is not ruled out by dominance or extended dominance. An option is ruled out by dominance when another option has higher QALYs and lower costs. An option is ruled out by extended dominance when it has a higher ICER than the next, more effective, option and so this option can never be the most cost effective. ICERs reported rounded to the nearest £100.

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5.1.5.2 Unit costs

The unit costs of BNP and NT-proBNP are provided below to aid committee discussion. Test costs were sought from a range of hospital trusts. Three sites provided unit cost information for BNP, and five sites provided unit cost information for NTproBNP. The average of these are reported below.

Table 14: Cost of natriuretic peptide tests

Test	Unit cost
BNP	£21.69
NT-proBNP	£26.07

5.1.5.3 New cost-effectiveness analysis

The committee identified this area as a priority for original economic analysis. The committee sought to determine whether natriuretic peptide testing is cost-effective and if so what the most cost-effective diagnostic threshold should to refer for echocardiography and specialist clinical assessment.

In recent years the European Society of Cardiology (ESC) has lowered their recommended natriuretic peptide thresholds from 100pg/ml for BNP and 400pg/ml for NT-proBNP to 35pg/ml (BNP) and 125pg/ml respectively, due to concern that previously recommended thresholds were too high.

The committee also raised concerns that the threshold recommended in the 2010 Chronic Heart Failure (CHF) guideline (which was in line with the previous ESC thresholds) may be too high, resulting in some patients with heart failure receiving a delayed diagnosis and either re-presenting to primary care at a later date with worsening symptoms or presenting to hospital due to a decompensation. Lowering the threshold could also allow for earlier diagnosis and a better prognosis of these patients. However, the committee also noted that lowering the threshold may greatly increase cost to the NHS due to the greater number of referrals for echocardiography and specialist clinical assessment, many of which are unlikely to lead to a diagnosis of heart failure and therefore the diagnosis of other possible underlying conditions could be delayed.

Therefore, original cost-effectiveness modelling was undertaken for this question. A summary is included here. Evidence statements summarising the results of the analysis can be found below. The full analysis can be found in Appendix O.

5.1.5.3.1 Methods

A cost-utility analysis was undertaken to determine the most cost effective threshold level of natriuretic peptide for referral from primary care for echocardiography and specialist clinical assessment. A decision tree with an attached Markov model was used to estimate lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective. The analysis was conducted in accordance with the NICE reference case unless otherwise stated including discounting at 3.5% for costs and QALYs.

The population entering the model are those presenting to primary care with signs and symptoms of heart failure, including breathlessness, fatigue or ankle swelling and upon clinical examination the general practitioner (GP) suspects that the patient has heart failure. The NICE 2010 Chronic Heart Failure guideline (CG108) recommendations state that patients with a previous history of myocardial infarction (MI) should be referred for echocardiography without a natriuretic peptide test. However, the committee decided that this was no longer appropriate as the definition of MI has changed over time and now includes many scenarios that differ from what was included in the Mant et al. 2009 HTA which formed the basis of the recommendation in the 2010 guideline[212]. People who first

present to an acute emergency setting were excluded as this population is covered by the Acute Heart Failure guideline (CG187).

The committee decided to exclude BNP testing from this analysis for the multiple reasons. The most important factor is that the clinical review demonstrates that NT-proBNP has a greater sensitivity over a range of thresholds compared to BNP. The committee emphasised the clinical importance of sensitivity over specificity as the test is used as a 'rule out' for heart failure. Secondly, on a practical level and since the test will be requested mainly by primary care and be sent to the laboratories with inherent delay in transport, NT-proBNP has a longer stability in blood samples than BNP (days versus 4-6 hours), therefore NT-proBNP is more appropriate for testing in primary care. Thirdly, although it is unlikely at this stage for a patient not diagnosed with heart failure to be on Sacubitril Valsartan which interferes with BNP physiology (TA388), natriuretic peptides can also be used for monitoring heart failure patients, therefore it would be more useful to have NT-proBNP as the baseline peptide in case monitoring was needed in a patient with heart failure who is subsequently treated with this new drug.

The following NT-proBNP thresholds were chosen as comparators:

- 400pg/ml – 2010 NICE recommended threshold and previous 2012 ESC threshold
- 125pg/ml – 2016 ESC threshold
- 280pg/ml – the optimal threshold found in one study included in clinical review[359], and also lies close to the middle of the other 2 thresholds.

As a reference, a diagnostic strategy was also included where no NT-proBNP test is undertaken and all patients with suspected heart failure are referred for echocardiography plus specialist clinical assessment.

The model is structured in 2 parts:

- A **decision tree** is used to calculate the proportion of the population that fall into one of a number of cohorts according to their underlying condition and test result. The decision tree calculates the proportion of patients who will receive a false negative (FN), false positive (FP), true negative (TN), or true positive (TP) NT-proBNP test result according to the sensitivity, specificity and prevalence data. Patients with a positive test result (levels above the chosen threshold) are then referred for echocardiography and specialist clinical assessment to determine if they have heart failure or not.
- A **Markov model** then evaluates patients' health and cost outcomes according to their cohort once the initial NT-proBNP test result is determined accounting for waiting times for diagnostic tests.

For more detailed explanation of the model structure, please refer to the technical report in Appendix O.

A number of assumptions were made when developing the model. The key assumptions are outlined below but are also discussed in more detail in Appendix O:

- Echocardiography plus specialist clinical assessment is 100% accurate.
- False negative patients are subsequently correctly diagnosed through 1 of 2 possible channels:
  - A patient is hospitalised due their undiagnosed heart failure and are diagnosed during admission
  - A patient re-presents to their GP within 6 months where the NT-proBNP test is repeated. The committee considered that after this we could assume that their NT-proBNP levels would be over 400pg/ml and therefore the patient would be referred for an echocardiogram and specialist clinical assessment and be correctly diagnosed.

- There is no mortality or morbidity benefit of treatment for HF-PEF patients.
- Heart failure for those with a NT-proBNP level < 400pg/ml will be less severe compared to those above the threshold and therefore mortality and hospitalisation rates will be lower than those reported in the literature. The cost and disutility consequences of missing these patients is therefore likely to be lower than for those with higher NT-proBNP levels.
- An individual's NT-proBNP level does not affect the rate of hospitalisation or mortality for other (non-HF) conditions.
- In heart failure patients with NT-proBNP levels <400pg/ml (treated or untreated) a hospitalisation causes their NT-proBNP levels to permanently be raised over 400pg/ml due to a worsening in their heart failure.
- Untreated heart failure patients (both HF-REF and HF-PEF) progress to having NT-proBNP levels >400pg/ml after 6 months if they have not already progressed due to hospitalisation. As HF-PEF patients are considered as untreated, all HF-PEF patients therefore progress to higher severity 6 months after first presentation.
- Treated low severity HF-REF patients who do not experience a hospitalisation progress to having NT-proBNP levels >400pg/ml 5 years after first presentation.
- The most common alternative diagnoses if a patient does not have heart failure are COPD, myocardial ischaemia, and obesity. The committee considered that the percentage of patients with these conditions would be 35% and 15%, and 50%, respectively.
- Patients do not have multiple-morbidities.

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. These are described in full in the technical report in Appendix O. All model inputs and assumptions were validated by the guideline committee.

Sensitivity analyses were also undertaken in areas of uncertainty to see how robust the model results are.

5.1.5.3.2 Results

The base-case results are presented below. For a full write up of the model results and sensitivity analyses see Appendix O.

In the base-case analysis 400pg/ml was found to be the most cost effective NT-proBNP threshold. Results are summarised below in Table 15 with regards to costs, QALYs and cost-effectiveness (net monetary benefit, and probability of cost effective at £20,000 per QALY threshold), and Table 16 with regards to ranking of the strategies.

A threshold of 400pg/ml produces both the highest incremental QALYs and the highest incremental cost versus echo all, and has the highest net monetary benefit at £20,000 per QALY and is therefore the most cost effective diagnostic threshold for referral to echocardiography. The probability of 400pg/ml being the most cost effective option at £20,000 per QALY is 77%.

Table 15: Base case analysis results (probabilistic analysis)

Diagnostic strategy	Mean per patient		NMB at £20,000 threshold	Probability most CE option at £20,000 per QALY
	Costs	QALYs		
Echo all	£ 1,682	4.894	£96,200	14%
NT-proBNP threshold: 125pg/ml	£ 2,080	4.960	£97,120	1%
NT-proBNP threshold: 280pg/ml	£ 2,297	5.004	£97,779	8%

Diagnostic strategy	Mean per patient		NMB at £20,000 threshold	Probability most CE option at £20,000 per QALY
	Costs	QALYs		
NT-proBNP threshold: 400pg/ml	£ 2,360	5.018	£97,990	77%

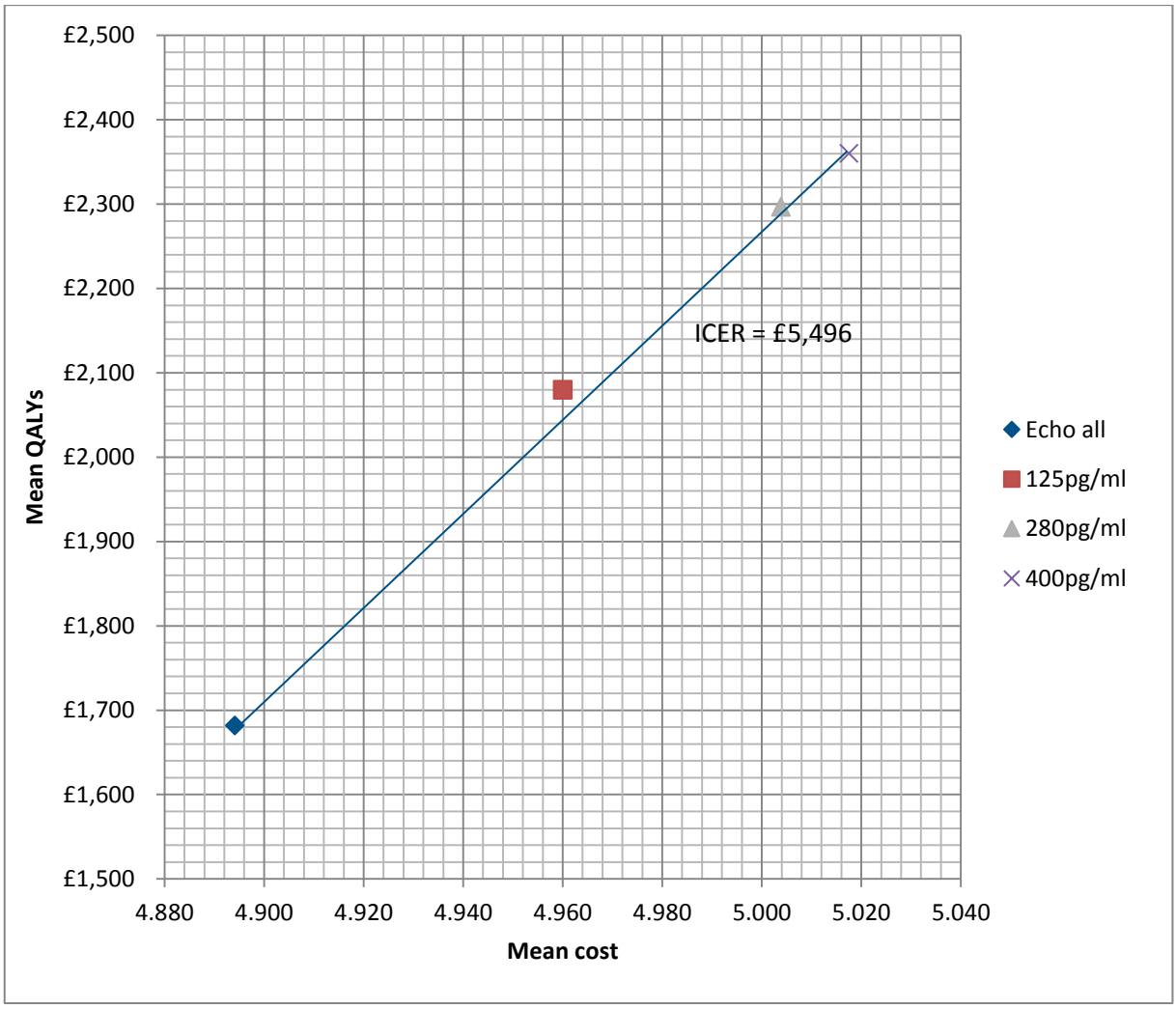
Abbreviations: CE = cost effective; QALYS: quality adjusted life years;.NMB: net monetary benefit.

Table 16: Base case analysis ranking results

Diagnostic strategy	Probability ranked 1	Probability ranked 2	Probability ranked 3	Probability ranked 4
Echo all	14%	1%	3%	82%
NT-proBNP threshold: 125pg/ml	1%	13%	82%	5%
NT-proBNP threshold: 280pg/ml	8%	78%	9%	5%
NT-proBNP threshold: 400pg/ml	77%	8%	6%	9%

The mean costs and QALYs from the probabilistic analysis have also been presented graphically on the cost-effectiveness plane in Figure 5. The cost-effectiveness ratio of 400pg/ml versus echo all is £5,496.

Figure 5: Base-case cost-effectiveness plane showing incremental costs and QALYs of each diagnostic strategy



The disaggregated costs and QALYs from the probabilistic base case analysis are summarised inTable 17, Table 18 and Table 19 below.

Table 17: Breakdown of diagnostic costs

Diagnostic strategy	Mean cost per patient to diagnose			Mean cost of echocardiography and specialist clinical assessment per patient
	Heart failure	COPD	Myocaridal ischaemia	
Echo all	£ 106	£ 309	£ 77	£ 235
NT-proBNP threshold: 125pg/ml	£ 148	£ 220	£ 69	£ 155
NT-proBNP threshold: 280pg/ml	£ 183	£ 160	£ 62	£ 98
NT-proBNP threshold: 400pg/ml	£ 200	£ 140	£ 60	£ 76

Table 18: Breakdown of management costs

Diagnostic strategy	Heart failure	COPD	Myocardial ischaemia
Echo all	£ 379	£ 651	£ 36

Diagnostic strategy	Heart failure	COPD	Myocardial ischaemia
NT-proBNP threshold: 125pg/ml	£ 334	£ 1,096	£ 131
NT-proBNP threshold: 280pg/ml	£ 276	£ 1,375	£ 190
NT-proBNP threshold: 400pg/ml	£243	£ 1,466	£ 210

Table 19: Breakdown of QALYs

Diagnostic strategy	Heart failure population	Non-heart failure population
Echo all	0.9978	3.8968
NT-proBNP threshold: 125pg/ml	0.9937	3.9668
NT-proBNP threshold: 280pg/ml	0.9935	4.0107
NT-proBNP threshold: 400pg/ml	0.9929	4.0251

Multiple sensitivity analyses were undertaken on the base case analysis including adjusting the proportion of HF-REF patients, extending the time to representation to the GP for false negatives, the prognostic differences for those with NT-proBNP levels above and below 400pg/ml, the composition of other conditions in the non-heart failure population, and the cost of NT-proBNP test. None of these led to a change in the optimal strategy.

In addition, two scenario analyses usingalternative diagnostic accuracy study data from Verdu et al. 2012 and Zaphiriou et al. 2005 were undertaken. It was considered important that these were also run probabilistically. However, when applying the ordinal logistic regression to the Verdu study data, the mean specificity values did not match the original study values. This was thought to be due to the fact that both 280pg/ml and 125pg/ml have a sensitivity of 1.00 and don't follow an order as such. Therefore the Verdu study was run both probabilistically (using the ordinal logistic regression model data) and deterministically (using the reported study data). The average estimates for the sensitivity and specificity values for Zaphiriou were consistent with the original data and were therefore only run probabilistically.The results of these analyses are presented in detail in Appendix O and summarised below.

In the scenario analysis based on Verdu et al. 2012 deterministic analysis, 280pg/ml was found to be the most cost effective NT-proBNP threshold. 280pg/ml dominates 400pg/ml with higher mean QALYs and a lower mean cost, and extendedly dominates 125pg/ml. The incremental cost effectiveness ratio of 280pg/ml compared to echo all is £5,952 per QALY gained.

In the scenario analysis based on Verdu et al. 2012 400pg/ml probabilistic anlaysis was found to be the most cost effective NT-proBNP threshold. A threshold of 400pg/ml produces both the highest incremental QALYs and the highest incremental cost versus echo all, and has the highest net monetary benefit at £20,000 per QALY and is therefore the most cost effective diagnostic threshold for referral to echocardiography. The cost-effectiveness ratio of 400pg/ml versus 280pg/ml is £9,842. The probability of 400pg/ml being the most cost effective option at £20,000 per QALY is 62%.

In the scenario analysis based on Zaphiriou et al. 2005 280pg/ml was found to be the most cost effective. 280pg/ml dominates (more effective and less costly) 400pg/ml. The cost-effectiveness ratio of 280pg/ml versus 125pg/ml is £15,088. The probability of 280pg/ml being the most cost effective option at £20,000 per QALY is 19%.

5.1.5.3.3 Limitations and interpretation

This analysis suggests that 400pg/ml is the most cost effective threshold for referring patients presenting to primary care with signs and symptoms of heart failure. Many uncertainties in the model structure, and assumptions were explored in sensitivity analyses.

The primary limitation of this model is that the diagnostic accuracy data was taken from one diagnostic accuracy study. This was due to the significant inconsistency in the results when a meta-analysis of three studies was undertaken. The committee discussed the diagnostic accuracy studies chosen for the meta-analysis at length to agree on chosing one of the studies for the base case analysis.

The committee were aware of the limitations of the diagnostic accuracy study by Taylor et al. 2016 chosen for the base case analysis. Particularly, the committee were concerned about the low proportion of HF-REF in the study, as they would have expected the proportion of HF-REF patients presenting to primary care to be higher.

The diagnostic accuracy study by Verdu et al. 2012 was not considered to be appropriate for the base case analysis as it was a Spanish study and not considered to be representative of current UK practice, and therefore generalisable to a UK population. The committee discussed that Zaphiriou was a UK study, however was conducted over ten years ago and again is unlikely to represent the current UK population presenting to primary care. Additionally, the criteria for diagnosing HF-PEF patients on echocardiography were not specifically defined as they are today.

The study by Taylor et al. 2016 were recruited from 28 practices across central England between 2011 and 2013. Therefore, this population was considered by the committee to be the most representative of current the population presenting to primary care in current UK practice. The committee raised concern about the low proportion of HF-REF patients identified in this study,. The committee considered that this may be due to study selection bias, as patients with severe symptoms, who are thought to be of high risk, are often not recruited into these types of clinical studies due to concern that there would be a delay in their treatment. The committee considered that the patients considered to be of high risk are more likely to have HF-REF than HF-PEF. However, the extent of possible selection bias is unknown. The committee acknowledged that the proportion of HF-REF patients in the heart failure population seems to be gradually declining, but still considered the proportion of HF-REF patients in the study to be low. The committee were concerned that this may bias the model results, as were there more clinical benefit to diagnosing heart failure the greater the benefit of earlier detection and therefore a lower NT-proBNP threshold. This effect was demonstrated in one of the sensitivity analyses (SA3): as the proportion of HF-REF in the model was increased, the cost effectiveness of 400pg/ml decreased – although the ICER was still well below the £20,000 threshold. The committee also acknowledged that were there clinically effective treatment for HF-PEF patients, then a lower NT-proBNP threshold is likely to be most cost effective.

Due to uncertainty around the diagnostic accuracy of the NT-proBNP test, two scenario analyses were undertaken to assess the diagnostic accuracy data and from two other study populations included in the clinical review.

A further limitation of the anlaysis is that when applying the ordinal logistic regression model to the Verdu data to enable the results to be run probabilistically, the mean sensitivity values were not consistent with the reported study values. Therefore the Verdu study was run both probabilistically (using the ordinal logistic regression model data) and deterministically (using the reported study data).

The inconsistency in the mean values from the regression model and those reported in the study was thought to be due to the fact that the sensitivity of 280pg/ml and 125pg/ml threshold were both 100%. Ordinal logisitic regression was thought to be the most suitable method to fit a distribution to

the diagnostic accuracy data to ensure that the sensitivity and specificity values maintained their order according to the threshold level for each run. Using this method one assumes that the model is predicting values that the data would show if you had a greater sample size.

The probabilistic analysis for Verdu found 400pg/ml to be the most cost effective NT-proBNP threshold, however when run deterministically using the reported study values 280pg/ml was found to be the most cost-effective threshold. This is likely to be due to the fact that this threshold had both the highest sensitivity and highest specificity.

The other scenario analyses (Zaphiriou) found 280pg/ml to be the most cost effective NT-proBNP threshold. The committee considered that the change in result from the Zaphiriou study was due to the high proportion of HF-REF patients in the population, supporting their previous hypothesis that the greater the proportion of heart failure likely to see benefits from treatment the more likely a lower threshold will be more cost effective.

Further limitations of the analysis are described in the full model write up in Appendix O.

Overall, this original analysis was considered to be directly applicable with potentially serious limitations.

5.1.6 Evidence statements

Clinical

Plasma BNP

Five studies explored the diagnostic test accuracy of plasma BNP for diagnosing chronic heart failure. The quality of the included evidence ranged from high to very low. Evidence was downgraded due to risk of bias and imprecision due to the range of the confidence interval around the point estimate. A number of studies were also downgraded due to indirectness as a result of the study population having a prevalence of CHF much higher than that of a representative sample or due to a lack of information regarding the reference standard used in the study. Two high quality studies (n=206 and n=122) reported a high sensitivity of plasma BNP at the thresholds 30pg/ml and 77pg/ml (95 (89-98) and 97 (83-100) respectively) which met the pre specified threshold of 95% set by the committee for possible recommendation. A further single study (n=200) reported a high specificity of 100 (97-100) at the threshold 400pg/ml. The committee placed an emphasis on specificity for the very high 'rule in' threshold of 400pg/ml of which this study met the specificity threshold. Very low quality evidence was found for plasma BNP at the threshold of 178pg/ml which reported a poor sensitivity of 47 (33-62). A further single study of very low quality reported an AUC 0.69. This study did not accurately report the threshold at which this accuracy data was collected.

Plasma NT-pro BNP

Six studies explored the diagnostic test accuracy of NT-pro BNP for diagnosing chronic heart failure. The quality of the included studies ranged from high to very low. Evidence was downgraded due to risk of bias and imprecision due to the range of the confidence interval around the point estimate. A single study was also downgraded due to indirectness as the study failed to include results for people under 50 years of age as the authors felt as though the prevalence of HF in this group was low. A single high quality study (n=220) reported a high sensitivity of 100 (93-100)% at a number of age specific thresholds (<50 years 50 pg/mL, 50-75 years 75 pg/mL, > 75 years 250 pg/mL). The majority of the evidence for NT-pro BNP was low quality. For women ≥50 years, a high sensitivity of 100 (90-100) was observed for a threshold of 67pg/ml which met the sensitivity threshold pre specified by the committee for possible recommendation. For the same group at thresholds of 144pg/ml and 220pg/ml the sensitivities were 94 (80-99) and 91 (76-98) respectively. For men ≥50 years, high sensitivities of 100 (92-100) and 96 (85-99) were observed at thresholds of 76mg/dl and 93mg/dl respectively. Both of which met the threshold set by the committee. A further single study of high

quality (n=206) reported a high sensitivity of 96 (90-99) at a threshold of 166pg/ml which again met the threshold set by the committee. At several thresholds, there was sufficient evidence to pool the diagnostic accuracy data. At the thresholds of 125pg/ml, 280pg/ml and 400pg/ml (3 studies; n=826) the sensitivities were 96 (72-100), 89 (41-99) and 79 (42-96) respectively. For the very high 'rule in 'threshold of 2000pg/ml the committee placed an emphasis on specificity. A single high quality study (n=200) reported a specificity of 100 (97-100) at this diagnostic threshold which met the threshold set by the committee for possible recommendation.

Economic

- One cost-utility anlaysis found the most cost effective diagnostic strategy for referring people with signs and symptoms of heart failure for echocardiography is to refer those with a history of myocardial infacrtion straight to echocardiography, and otherwise using an NT-proBNP threshold of 400pg/ml. This was compared to the MICE clinical decision rule (upper and lower thresholds), echo all, NT-proBNP threshold 125pg/ml and do nothing. It was cost effective compared to the do nothing strategy (ICER: £4,400 per QALY gained). This was assessed as diretly applicable with potentially serious limitations.
- An original cost-utility analysis found that 400pg/ml is the most effective NT-proBNP threshold to use for referring people presenting with signs and symptoms of heart failure for echocardiography compared to 280pg/ml, 125pg/ml and referring all patients straight for echocardiography. It was cost effective compared to referring all patients for echocardiography (ICER:£6,076 per QALY gained). This was assessed as directly applicable with potentially serious limitations.

5.2 BNP and NT-proBNP in diagnosing heart failure in people with atrial fibrillation

5.2.1 Review question: In people with suspected heart failure who also have atrial fibrillation, what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?

For full details see review protocol in Appendix A.

Table 20: Characteristics of review question

Population	People with atrial fibrillation and suspected heart failure in a community or outpatient setting.
Target condition	Heart failure
Index test(s)	• NT-proBNP • BNP
Reference standard(s)	A clinical diagnosis based on the opinion of at least one cardiologist, considering symptoms (potentially with some signs) and objective evidence of cardiac dysfunction (either structural or functional).
Statistical measures	Diagnostic accuracy of BNP and NT-proBNP: • 2x2 tables • Specificity • Sensitivity • PPV/NPV • ROC curve or Area under Curve

Study design	Single gate studies (cohort/cross-sectional)

5.2.2 Review question: In people with suspected heart failure who also have atrial fibrillation, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?

For full details see review protocol in Appendix A.

Table 21: PICO characteristics of review question

Population	People with atrial fibrillation and suspected heart failure in a community or outpatient setting.
Index diagnostic test + treatment	NT-proBNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Comparator index diagnostic tests + treatment	BNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Outcomes	Efficacy outcomes: • All-cause mortality • Quality of life • Unplanned hospitalisation Process outcomes: • Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results • Repeat testing / additional testing Secondary accuracy outcomes: • Sensitivity / specificity and other test accuracy measures
Study design	Systematic Review RCT

5.2.3 Clinical evidence

A search was conducted for single gate studies assessing the diagnostic test accuracy of BNP or NT-proBNP to identify the presence of heart failure (as indicated by the reference standard) in people with atrial fibrillation and suspected heart failure in a community or outpatient setting. A search was also conducted for diagnostic RCTs comparing outcomes in patients tested with BNP versus NT-proBNP.

No studies meeting either review protocol were identified. See also the study selection flow chart in Appendix C and excluded studies list in Appendix I.

5.2.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix D.

New cost-effectiveness analysis

Original economic analysis was planned for this question. However, due to a lack of diagnostic accuracy data for this cohort of patients modelling was not undertaken.

5.2.5 Evidence statements

Clinical

No clinical evidence was identified for this review question.

Economic

- No relevant economic evaluations were identified.

5.3 BNP and NT-proBNP in diagnosing heart failure in people with chronic kidney disease

5.3.1 Review question: In people with suspected heart failure who also have chronic kidney disease, what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?

For full details see review protocol in Appendix A.

Table 22: Characteristics of review question

Population	People with chronic kidney disease (excluding patients on dialysis) and suspected heart failure in a community or outpatient setting.
Target condition	Heart failure
Index test(s)	• NT-proBNP • BNP
Reference standard(s)	A clinical diagnosis based on the opinion of at least one cardiologist, considering symptoms (potentially with some signs) and objective evidence of cardiac dysfunction (either structural or functional).
Statistical measures	Diagnostic accuracy of BNP and NT-proBNP: • 2x2 tables • Specificity • Sensitivity • PPV/NPV • ROC curve or Area under Curve
Study design	Single gate studies (cohort/cross-sectional)

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5.3.2 Review question: In people with suspected heart failure who also have chronic kidney disease, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?

For full details see review protocol in Appendix A.

Table 23: PICO characteristics of review question

Population	People with chronic kidney disease (excluding patients on dialysis) and suspected heart failure in a community or outpatient setting.
Index diagnostic test + treatment	NT-proBNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Comparator index diagnostic tests + treatment	BNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Outcomes	Efficacy outcomes: • All-cause mortality • Quality of life • Unplanned hospitalisation Process outcomes: • Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results • Repeat testing / additional testing Secondary accuracy outcomes: • Sensitivity / specificity and other test accuracy measures
Study design	Systematic Review RCT

5.3.3 Clinical evidence

A search was conducted for single gate studies assessing the diagnostic test accuracy of BNP or NT-proBNP to identify the presence of heart failure (as indicated by the reference standard) in people with chronic kidney disease and suspected heart failure in a community or outpatient setting. A search was also conducted for diagnostic RCTs comparing outcomes in patients tested with BNP versus NT-proBNP.

One diagnostic accuracy study was included in the review[319, 375]; it is summarised in Table 24 below. The index test was BNP. The study was downgraded for serious indirectness as the reference standard did not fully match the protocol, but was included in the review in the absence of any direct evidence. Evidence from this study is summarised in the clinical evidence summary in Table 25 below. No diagnostic RCTs meeting the protocol were identified.

See also the study selection flow chart in Appendix C, sensitivity/specificity forest plots in Appendix E, study evidence tables in Appendix F and excluded studies list in Appendix I.

Table 24: Summary of studies included in the review

Study	Population	Target condition	Index test	Reference standard	Comments
Yang 2008[375]	n=182 Patients with CKD who visited	Heart failure	BNP	HF diagnosed based on history, radiological findings, and	Very high risk of bias Serious indirectness

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Study	Population	Target condition	Index test	Reference standard	Comments
	Nephrology Department with respiratory distress.			echocardiographic findings, which included clinical symptoms fulfilling Framingham's criteria, LVEF < 50% on echocardiography, and LV diameter at end-diastole greater than 5.5 cm. No mention of whether or not a cardiologist carried out this assessment.	Only the results of the subgroup of patients with CKD 3-4 have been extracted and reported in accordance with the protocol.

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Table 25: Clinical evidence summary: diagnostic test accuracy for index test(s) BNP and NT-proBNP

Index Test (Population, Target condition, Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value (PPV) %	Negative Predictive Value (NPV) %	AUC (95% CI)
Plasma BNP								
BNP CKD stages 3 &4; HF 410 pg/mL	1	111	VERY LOW[a,b,c] due to very serious risk of bias, serious indirectness, serious imprecision	81 (67 – 91)	90 (80 – 96)	86	87	0.94

The assessment was conducted with an emphasis on test sensitivity as this was identified by the GC as the primary measure in guiding decision making. The GC set the sensitivity threshold of 95% as an acceptable level to recommend a test.

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed according to the range of confidence intervals in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%

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5.3.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix D.

New cost-effectiveness analysis

Original economic analysis was planned for this question. However, due to a lack of diagnostic accuracy data for this cohort of patients modelling was not undertaken.

5.3.5 Evidence statements

Clinical

One study was identified which reported the diagnostic test accuracy of BNP for diagnosing HF in people with CKD. The study was rated as very low quality due to risk of bias, imprecision due to the range of the confidence interval around the point estimate and indirectness due a lack of information regarding the reference standard. The study reported a sensitivity and specificity of 81 (67-91) and 90 (80-96) respectively which did not meet the pre specified sensitivity of 95 which was set by the committee as a minimum threshold for possible recommendation.

Economic

- No relevant economic evaluations were identified.

5.3.6 Recommendations and link to evidence

Recommendations	**Measure N-terminal pro-B-type natriuretic peptide [NT-proBNP] in people with suspected heart failure. [2018]** **Because very high levels of NT-proBNP carry a poor prognosis, refer people with suspected heart failure and an NT-proBNP level above 2,000 ng/litre (236 pmol/litre) urgently, to have specialist assessment and transthoracic echocardiography within 2 weeks. [2018]** **Refer people with suspected heart failure and an NT-proBNP level between 400 and 2,000 ng/litre (47 to 236 pmol/litre) to have specialist assessment and transthoracic echocardiography within 6 weeks. [2018]** **Be aware that:** • **an NT-proBNP level less than 400 ng/litre (47 pmol/litre) in an untreated person makes a diagnosis of heart failure less likely** • **the level of serum natriuretic peptide does not differentiate between heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. [2018]** **Review alternative causes for symptoms of heart failure in people with NT-proBNP levels below 400 ng/litre. If there is still concern that the symptoms**

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	might be related to heart failure, discuss with a physician with a subspeciality interest in heart failure. [2018] **Be aware that:** • **obesity, African or African-Caribbean family origin, or treatment with diuretics, angiotensin-converting enzyme (ACE) inhibitors , beta-blockers, angiotensin II receptor blockers (ARBs) or mineralocorticoid receptor antagonist (MRAs) can reduce levels of serum natriuretic peptides** • **high levels of serum natriuretic peptides can have causes other than heart failure (for example, age over 70 years, left ventricular hypertrophy, ischaemia, tachycardia, right ventricular overload, hypoxaemia [including pulmonary embolism], renal dysfunction [eGFR less than 60 ml/minute/1.73 m^2], sepsis, chronic obstructive pulmonary disease, diabetes, or cirrhosis of the liver). [2010, amended 2018]**
Research recommendations	• **What is the optimal NT-proBNP threshold for the diagnosis of heart failure in people with atrial fibrillation?** • **What are the optimal NT-proBNP thresholds for diagnosing heart failure in people with IIIb, IV or V chronic kidney disease?** • **What is the optimal threshold for NT-proBNP for the diagnosis of heart failure in people with suspected heart failure: 400 ng/ml or 125 ng/ml?**
Relative values of different outcomes	The investigation into BNP and NT-proBNP in the diagnosis of heart failure was approached by considering both clinical effectiveness and diagnostic accuracy. Within each approach, evidence was sought separately for the general suspected heart failure population, as well as people with atrial fibrillation (AF) and suspected heart failure, and people with chronic kidney disease (CKD) and suspected heart failure. The analysis was broken down into three separate chapters for each population, each of which included two separate review questions. The clinical effectiveness reviews aimed to establish whether using NT-proBNP is more effective than using BNP in terms of improving patient outcomes, in each population. The committee agreed that the critical outcomes were all-cause mortality, quality of life and unplanned hospitalisations. In addition, a number of process outcomes were considered important, these were number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results, and the need for repeat or additional testing. Test accuracy measures would also be extracted if reported in clinical effectiveness studies. In the reviews focussing on the diagnostic accuracy of NT-proBNP and BNP at different thresholds in each population, sensitivity was considered the most critical outcome. This is because failing to diagnose people who have heart failure may delay the initiation of treatment and increase the risk of unplanned hospitalisations and mortality prior to an eventual diagnosis. A minimum threshold of 95% sensitivity was set for recommending the test.

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	Specificity was also considered important in order to avoid unnecessary referrals for echocardiography and specialist clinical assessment where heart failure was highly unlikely. Other accuracy statistics considered important were positive and negative predictive values and area under the curve (AUC), which provides an overall summary of the test performance. No evidence was identified for any of the clinical effectiveness outcomes for any of the reviews, including the process outcomes.
Quality of the clinical evidence	No RCTs were identified that compared a diagnostic strategy using NT-proBNP with a diagnostic strategy using BNP to establish the impact on patient outcomes, in any of the patient populations. **General suspected heart failure population** Eight diagnostic accuracy studies were included that evaluated the diagnostic accuracy of NT-proBNP and/or BNP at diagnosing heart failure in the general suspected heart failure population. The quality of the evidence ranged from high to very low. Common issues in in the studies were risk of bias due to unclear participant selection methods, high (or not reported) loss to follow up, extended length of time between BNP test and echo, and poor reporting of accuracy results. Some studies were also downgraded for indirectness of the population, where the prevalence of heart failure was much higher than would be expected in the target population indicating the populations may have been from different settings with a potential variation in the distribution of symptoms and severity. Various test thresholds were reported in the included studies. As the committee was interested in the relative accuracy of the tests at different thresholds, it was only appropriate to meta-analyse sensitivity and specificity data where multiple studies used the same test (NT-proBNP or BNP) and reported data at the same test threshold. While it was not possible to assess statistical heterogeneity for data that was not meta-analysed, upon viewing the forest plots, the committee agreed that there was clearly a high degree of inconsistency in the results across the thresholds. That is, the expected relationship between sensitivity and specificity and the test threshold was not clearly apparent. This suggested that the study populations or other features of the study design or quality were contributing to differences between test accuracy at different thresholds, rather than these differences necessarily reflecting true threshold-related differences in test accuracy. Sensitivity analyses using just the data assessed as low risk of bias were conducted, to see if this resolved the inconsistency in the results, but the inconsistency between studies remained. Given the committee's ability to establish the most appropriate test thresholds was limited by the thresholds reported by the included studies, the committee decided to contact study authors seeking additional data at the particular thresholds. The committee decided to limit this request to data on NT-proBNP rather than BNP for the multiple reasons: 1. The clinical review demonstrates that NT-proBNP has a greater sensitivity over a range of thresholds compared to BNP.

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The committee acknowledged the high sensitivity from one study conducted in 1997, but considered that the heart failure population has changed significantly since this study was conducted with a greater proportion of people with HF-PEF, which on a population level tend to have lower NT-proBNP levels than people with HF-REF . Therefore it is highly uncertain as to whether these results represent the diagnostic accuracy for BNP testing in current practice. Whereas, the majority of the high quality NT-proBNP studies are more recent studies and are more likely to be applicable to current practice.

Comparing thresholds between BNP and NT-proBNP is inherently difficult as there is no conversion algorithm between them. However, the Zaphiriou study (high quality study assessing both BNP and NT-proBNP) assessed the recommended industry cut-offs for each test. When comparing this data NT-proBNP thresholds have a consistently higher sensitivity than the BNP thresholds.

2. NT-proBNP has a longer stability in blood samples than BNP (days vs 4-6 hours), therefore NT-proBNP is more appropriate for testing in primary care.
3. Sacubitril Valsartan interferes with BNP physiology (TA388).

Natriuretic peptides can also be used for monitoring heart failure patients. Therefore, the committee considered it would be more useful to have NT-proBNP as the baseline peptide in case monitoring was needed in a patient with heart failure who is subsequently treated with this drug.

The test thresholds at which data was sought were 125pg/mL, 280 pg/mL and 400 pg/mL. The thresholds were selected based on the data already available in the included studies and to minimise the amount of additional data that needed to be collected, while still allowing for assessment of accuracy at key clinically relevant thresholds used in existing NICE guidelines and other international guidance.

The results of the requests for additional data meant that meta-analysis of three studies was possible at each of the above thresholds. Unfortunately, despite all three studies being of high quality and enrolling seemingly similar populations, the pooled data was of very low quality due to serious inconsistency and serious imprecision. For this reason, the committee had little confidence in the pooled estimates of sensitivity and specificity.

Suspected heart failure and CKD

One diagnostic accuracy study was included that evaluated the diagnostic accuracy of BNP at diagnosing heart failure in a population with CKD and respiratory distress. The reference standard used in the study was unclear and may not have fully matched the protocol, but the study was included in the review in the absence of any direct evidence. The evidence was graded very low quality due to very high risk of bias, serious indirectness and serious imprecision. Risk of bias was very high due to it being unclear how participants were selected, unclear whether the reference standard was applied blind to BNP results, and unclear whether any patients were lost to

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	follow up or missing from the analysis. Only the results of the subgroup of patients with CKD stages G3 to G4 were reported in accordance with the protocol. **Suspected heart failure and AF** No diagnostic accuracy studies meeting the protocol were identified. Six studies in an acute population or setting, and another study with a target condition of 'major structural heart disease', were identified. After discussion, the committee agreed that these studies should not be included in the review, despite the absence of any direct evidence, as they would not provide reliable evidence in the population of interest.
Trade-off between clinical benefits and harms	For the reasons outlined above, the committee's discussion of the clinical evidence focussed on NT-proBNP rather than BNP. **General suspected heart failure population** BNP and NT-proBNP are used as a triage test, with people whose results are above a certain threshold being referred for echocardiography and specialist clinical assessment, following which a definitive diagnosis can be made. The committee noted that the threshold for referral to echocardiography and specialist clinical assessment in the 2010 guideline was 400 pg/mL. The committee agreed that from a clinical perspective, a lower test threshold would mean fewer patients with heart failure would have their diagnoses missed or delayed, avoiding unnecessary hospitalisations and mortality. However, the committee recognised that if the test threshold was set lower than clinically necessary, many people may be unnecessarily referred for echocardiography and specialist clinical assessment. This could cause unnecessary worry for people and their families, as well as delaying diagnosis of an true underlying condition, and having resource and economic implications (discussed below). The committee considered the clinical evidence with the aim to determine which NT-proBNP threshold was most appropriate for identifying patients who should be referred for echocardiography and specialist clinical assessment, focussing on sensitivity of the test. The pooled sensitivity at a threshold of 125pg/mL was 96% (72%-100%), at a threshold of 280pg/mL was 89% (41%-89%), and at a threshold of 400pg/mL was 79% (42%-96%). The committee noted that the pooled evidence was very low quality due to inconsistency between the included studies and consequently very wide confidence intervals around the meta-analysed data. At a threshold of 400pg/mL, the committee also noted that specificity was likely to be much higher (82% (52%-95%)) compared with specificity at the lower thresholds (125pg/mL, 48% (19%-80%); 280pg/mL, 75% (38% - 94%)), which would reduce any clinical harms of over-referral. The committee discussed possible reasons for the inconsistency between the study results at length, and considered that the differences in sensitivity and specificity were likely to be due to heterogeneity in the study populations.

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The committee discussed the differences in setting between the studies as there was one Spanish study, one UK study that recruited patients between 2001 and 2003, and one recent UK study. The committee considered that across these settings the population presenting to primary care with signs and symptoms of heart failure could be different. The committee also noted that the proportions of HF-REF and HF-PEF across these studies were very different, supporting the hypothesis that the study populations were not similar.

The committee agreed that based on the clinical data alone, it was not possible to establish the threshold that provided the best overall trade-off between benefits and harms. The committee considered that an economic model was necessary to "trade-off" the benefits of a lower threshold against the potential increases in cost. For that reason, the most clinically and cost-effective threshold was identified as a priority for economic modelling.

Suspected heart failure and CKD

The committee discussed the evidence in a population of suspected heart failure and CKD. The committee noted that the only evidence available was for BNP at a threshold of 410 pg/mL. No evidence was available for NT-proBNP at any threshold.

The committee considered advice from a renal physician co-opted to the committee and the very low quality evidence, and agreed that there was no convincing rationale to have a different test threshold for people with CKD and suspected heart failure.

The committee noted that both advancing age and heart failure are associated with a gradual and progressive decline in renal function. In addition, the progression of heart failure and some treatments for heart failure lead to progressive deterioration of renal function. A decline in renal function is associated with increased fluid retention and a rise in the level of the serum natriuretic peptides, including NT-proBNP, even in the absence of heart failure. There is some evidence that the use of higher NT-proBNP thresholds would improve diagnostic accuracy for heart failure in people with significant deterioration of creatinine clearance.

Suspected heart failure and AF

No evidence was included in a population with suspected heart failure and AF. The committee agreed that in the absence of any evidence, there was no convincing rationale to have a different test threshold for people with AF and suspected heart failure. However the committee noted that atrial fibrillation can raise the level of serum natriuretic peptides, including NT-proBNP, even in the absence of heart failure. This is complicated further in heart failure with preserved ejection fraction, in which 2 echocardiographic diagnostic criteria become unreliable (the left atrial volume and the tissue Doppler imaging assessment of diastolic function). These factors contribute to the complexity of the diagnosis and have a potential impact on the usual thresholds for NT-proBNP in people who have atrial fibrillation. This has been recognised in several ongoing randomised controlled trials of heart failure,

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	which are using higher NT-proBNP thresholds for the diagnosis of heart failure in people with atrial fibrillation.
Trade-off between net clinical effects and costs	No economic evaluations were identified comparing NT-proBNP thresholds and BNP thresholds. Unit costs of BNP and NT-proBNP were presented to the committee for consideration. As previously discussed in the 'quality of the clinical evidence' section above, the committee agreed that NT-proBNP was a better test than BNP. They were therefore reassured that that the average cost difference between the two tests was only around £4. They discussed that there was some uncertainty in these estimates due to the limited sample size, although there was some overlap in costs where NT-proBNP was less expensive than BNP. The committee also mentioned that the purchase of new equipment for analysing NT-proBNP is not necessary as there are kits available for all main systems. Therefore the committee did not consider that there would be further cost implications beyond those reflected in the costs above. The committee were also aware that NT-proBNP is due to come off patent in the next couple of years and therefore expect the cost of NT-proBNP to decrease. Furthermore, the committee noted that as NT-proBNP overall had a higher sensitivity compared to BNP, there is potential for some offset of the current higher cost of NT-proBNP due to reduced number of false negative results for people being tested with NT-proBNP compared to BNP. A false negative result would either require re-testing, or could result in hospitalisation if an acute episode occurred prior to diagnosis. They therefore considered that taking into consideration the above that NT-proBNP and that the majority of labs now run NT-proBNP, some of them teaching hospitals which receive a high volume of tests, that only recommending NT-proBNP would not have a substantial resource impact for the NHS in England. One economic analysis was identified for this review assessing NT-proBNP thresholds. This study compared the MICE (Male, Infarction, Crepitations, (o)Edema) clinical decision rule using the upper NT-proBNP cut-off, the MICE clinical decision rule using the lower NT-proBNP cut-off, the 2010 NICE guideline recommended strategy (refer straight away for echocardiography if history of previous myocardial infarction (MI), otherwise refer for echocardiography if NT-proBNP>400pg/ml), NT-proBNP threshold of 125pg/ml, echocardiography for all, and do nothing. This analysis found that the 2010 NICE guideline strategy was the most cost effective approach for diagnosing heart failure in patients with suspected heart failure. This analysis was assessed as partially applicable with potentially serious limitations. The committee raised the following limitations of this economic evaluation. Firstly, this analysis used diagnostic accuracy data from the REFER study where the level of NT-proBNP had been used as a criterion in determining whether or not the patient had heart failure. The committee were concerned that this had introduced incorporation bias to the diagnostic accuracy results,

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potentially biasing the overall results of the model. The committee acknowledged that in practice the level of NT-proBNP is often used as part of the criteria for diagnosing heart failure but agreed that for our purposes in truly identifying the diagnostic accuracy of the test, this data was not considered to be suitable.

Secondly, the committee also noted that this analysis did not report any assumptions, costs or QALYs applied to the non-heart failure population in the model. The committee inferred from the results of the model that this population was not directly accounted for, and supposed that the model assumed there was no effect on this population of a differential diagnosis if they enter the diagnostic pathway for heart failure.

Thirdly, the committee stated that the definition of MI has changed over time and now includes many scenarios that differ from what was originally meant in the 2010 guideline, and as a result having a history of myocardial infarction (MI) should no longer be a criterion for early echocardiography. Therefore the NICE 2010 guideline diagnostic pathway was no longer considered to be an appropriate strategy to assess.

Due to the high clinical and economic importance of this question, an original cost-effectiveness analysis was therefore conducted for this question. The model sought to determine which NT-proBNP threshold is the most cost effective for diagnosing heart failure in patients presenting with signs and symptoms of heart failure. The comparators included were NT-proBNP thresholds of 400pg/ml, 280pg/ml and 125pg/ml, and echocardiography for all.

Due to the inconsistency in the pooled results and the very low quality of this data as discussed above, the committee did not consider it appropriate to use the pooled results of these thresholds for the base-case analysis. Therefore the committee decided to choose one diagnostic accuracy study for the base case analysis, and use the other two diagnostic studies to undertake scenario analyses adjusting the population characteristics as appropriate.

The committee chose to use the diagnostic accuracy data from the REFER study for the base case analysis; however the accuracy of this data was determined from a reference standard that did not include the level of NT-proBNP in part of the criteria for diagnosing heart failure therefore mitigating the effects of incorporation bias. In contrast to the study identified above, this analysis also incorporated the cost and QALY impact of misdiagnosis for a non-heart failure population. For more information on the model methods and data inputs please see Appendix O.

This original analysis found that an NT-proBNP threshold of 400pg/ml is the most cost effective strategy at a threshold of £20,000 per QALY gained (ICER: £5,496 compared to echo all) with a probability of 77% of being the most cost effective at the £20,000 threshold. This result was robust to multiple sensitivity analyses varying key input parameters and structural assumptions. This analysis was assessed as directly applicable with potentially serious

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limitations.

The committee discussed the breakdown of costs and QALYs across the strategies.

Contrary to the committees previous statement that sensitivity is the most critical outcome, the model suggests that the specificity of the test is most critical with regards to cost effectiveness. These results demonstrate that the model is being driven by the greater cost reductions and QALY benefits of diagnosing other conditions in the non-heart failure population earlier, rather than the cost reductions and QALY benefits of an earlier diagnosis of heart failure.

The committee noted that the QALYs accrued for the heart failure population are very similar across all of the strategies (difference of 0.01 QALYs between the 400pg/ml threshold (lowest QALYs for people with heart failure) and referring all patients for echocardiography (highest QALYs for people with heart failure). The committee was reassured to know that the difference was so small. However, acknowledged that this small difference is likely to be due to the low proportion of people with HF-REF in the model, and hence limited QALY gains from early treatment. Although the REFER study seemed the most appropriate study to choose for the base case analysis as it was the most recent UK study, the committee voiced concern about the very small proportion of HF-REF patients in the study population. The committee considered that this may be due to study selection bias, as patients with severe symptoms, who are thought to be of high risk, are often not recruited into these types of clinical studies due to concern that there would be a delay in their treatment. The committee considered that the patients considered to be of high risk are more likely to have HF-REF than HF-PEF. However, the extent of possible selection bias is unknown.

Due to uncertainty around the diagnostic accuracy of the NT-proBNP test, two scenario analyses were undertaken to assess the diagnostic accuracy data from two other studies included in the clinical review (Verdu et al. 2012 and Zaphiriou et al. 2005).

When applying the ordinal logistic regression model to the Verdu data to enable the results to be run probabilistically, the mean sensitivity values were not consistent with the reported study values. Therefore the Verdu study was run both probabilistically (using the ordinal logistic regression model data) and deterministically (using the reported study data).

The inconsistency in the mean values from the regression model and those reported in the study was thought to be due to the fact that the sensitivity of 280pg/ml and 125pg/ml threshold were both 100%. Ordinal logisitic regression was thought to be the most suitable method to fit a distribution to the diagnostic accuracy data to ensure that the sensitivity and specificity values maintained their order according to the threshold level for each run. Using this method one assumes that the model is predicting values that the data would show if you had a greater sample size.

The probabilistic analysis for Verdu supported the results of the base case analysis, showing that 400pg/ml was the most cost effective diagnostic

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strategy (ICER: £9,842 per QALY gained). The probability of this being the most cost effective strategy at the £20,000 per QALY gained threshold is 62%. The deterministic analysis for Verdu found 280pg/ml to be the most cost-effective diagnostic strategy (ICER: £5,952 per QALY gained). The was considered to be due to the fact that this threshold had both the highest sensitivity and highest specificity of all diagnostic strategies.

The other scenario analysis conducted using the data from Zaphiriou found that 280pg/ml was the most cost effective threshold (ICER:£15,088 per QALY gained compared to 125pg/ml). The probability of this being the most cost effective strategy at the £20,000 per QALY gained threshold is 19%. In this analysis the 400pg/ml threshold was dominated (more costly, less effective) by 280pg/ml, although the difference in QALYs between these two strategies was very small (0.003). This result was likely to be driven by the high proportion (76%) of HF-REF in the heart failure population for this study, as those with HF-REF receive a greater QALY benefit of being diagnosed and treated than those with HF-PEF.

The results of the scenario analyses were much more uncertain than those of the base case. This was considered to be due to the fact that the sensitivity and specificity values of the NT-proBNP across the thresholds are much closer compared to those in the base case diagnostic accuracy study. The committee also considered that the difference in the probabilistic and deterministic results of the Verdu study highlights the uncertainty in the results.

From the results of the economic analyses, the committee agreed to recommend that an NT-proBNP level of 400pg/ml be used to refer a patient for echocardiography when heart failure is suspected in a patient presenting with signs and symptoms of heart failure in primary care. The committee considered the base case analysis to be robust to changes in model assumptions and data inputs. However, they acknowledged the uncertainty that remains for this question due to the inconsistencies in the study populations and diagnostic accuracy data across the studies assessed in the model. However, the results of the scenario analyses using different diagnostic accuracy data from alternative studies were highly uncertain. Therefore, overall the committee agreed that there was currently not enough evidence to support reducing the threshold from 400pg/ml as recommended in the previous guideline.

Suspected heart failure and CKD or AF

No previously published economic evaluations were identified in these populations. Due to a lack of diagnostic accuracy data for the AF and CKD patients these cohorts were not included in the original economic analysis. However, as mentioned above the committee did not consider there to be a strong rationale to have a different test threshold for people with CKD and suspected heart failure.

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Other considerations	**General suspected heart failure population** The 2010 guideline considered a wider breadth of evidence than was considered in this review. This review protocol was limited to studies of patients presenting in a primary care or outpatient setting, on the basis that studies of patients in an acute setting now fall within the remit of the acute heart failure guideline. Studies in patients immediately post myocardial infarction (MI) were also excluded on the basis that they also more appropriately fall within the scope of the acute guideline. This review was also limited to patients presenting with signs or symptoms of heart failure, rather than the use of NT-proBNP to screen for heart failure in asymptomatic or high risk populations without signs or symptoms, as the aim of the review was to identify the most relevant evidence to the population of interest. In addition, this review protocol was limited to studies using a reference standard of echocardiography plus clinical assessment for the diagnosis of heart failure. The committee did not consider that echocardiography alone, or reduced ejection fraction on echocardiography, was an appropriate reference standard and studies using that reference standard were excluded from this review. The committee noted that patients can have reduced ejection fraction on echocardiography without having symptomatic heart failure, so echocardiography alone was not a sufficient reference standard. Further, patients with heart failure with preserved ejection fraction in particular could not be diagnosed with echocardiography alone as this diagnosis requires substantial clinical input and judgment. The committee also discussed the 2010 guideline recommendations that provide a different treatment pathway for patients with any previous MI (these patients were referred directly for echocardiography and specialist assessment, without prior natriuretic peptide testing). The committee noted that this was based on the MICE clinical decision rule developed by the Mant 2009 IPD, which included evidence that was outside the scope of this review (for example, it included studies in acute populations, and studies using a wider range of reference standards and target conditions than specified in this protocol). The committee agreed that this distinction between patients who had and had not had any previous MI was not supported by the latest clinical evidence in the population of interest to this review. The committee also noted that the definition of MI had changed over time. The committee agreed that the distinction between patients with and without previous MI should be removed from the diagnostic pathway. NT-proBNP testing should be done in all patients with suspected heart failure regardless of whether or not they have had a previous MI. The committee agreed to remove a recommendation from the 2010 guideline suggesting that a serum natriuretic peptide test should be considered when heart failure is still suspected after transthoracic Doppler 2D echocardiography has shown a preserved left ventricular ejection fraction. The committee recalled that this recommendation was made to inform an individual's prognosis from the NT-proBNP level. However, the

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committee noted that according to these recommendations, and the removal of the different diagnostic pathway for those with previous MI, all patients should receive an NT-proBNP level and therefore this recommendation was no longer necessary.

The committee also reiterated the importance that patients with very high NT-proBNP levels (>2,000pg/ml) receive an echocardiography promptly (within 2 weeks) due to the association of NT-proBNP levels and prognosis.

The committee noted that while an NT-proBNP threshold of 400 pg/mL was most cost-effective, some patients with test results below this threshold and even below 125pg/mL went on to be diagnosed with heart failure in the REFER trial. Therefore, it was important that healthcare professionals were aware that even in people with low NT-proBNP results, heart failure cannot definitively be ruled out. The committee noted that NT-proBNP levels were lower in populations of West African/Afro-Caribbeandescent and also in patients with morbid obesity. The committee agreed that in these patients, alternative causes for their symptoms should be reviewed, and if there is still concern that symptoms may be due to heart failure, this should be discussed with a heart failure specialist.

The committee considered that the changes to the recommendations would have limited impact on current practice in terms of the diagnostic pathway. However, laboratories that currently only do BNP testing would have to move to NT-proBNP testing and this may have an initial resource impact with regards to implementation.

Suspected heart failure and CKD

The committee agreed that studies in patients with CKD stage G5 or receiving dialysis were outside the scope of the review. This was on the basis that these patients would already be receiving specialist clinical review and assessment and were not relevant to a diagnostic pathway focussed primarily on patients presenting to primary care with heart failure symptoms.

The 2010 CHF guideline CG108 included echocardiography as a second reference standard, the committee discussed the clinical diagnosis of heart failure and agreed that echocardiography alone did not constitute a gold standard for diagnosis and that a definitive diagnosis should be based on the opinion of at least one cardiologist which considered symptoms and objective evidence of cardiac dysfunction (either structural or functional).

Due to the lack of evidence regarding the optimal threshold for NT-proBNP in either people with HF and atrial fibrillation or HF and CKD the committee agreed that further research in this area would be beneficial for future updates of this guideline.

In addition to this the committee agreed that a large study was needed to

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	provide more certainty with regards to which NT-proBNP threshold (400pg/ml or 125pg/ml) is more clinically and cost effective for the diagnosis of HF in people with suspected HF would also be of benefit for future guideline updates due to the limitations of current diagnostic accuracy studies. The committee agreed that the 400pg/ml and 125pg/ml thresholds would be of most interest as these are the two thresholds used in practice. 400pg/ml is used in the UK, and has previously been used elsewhere until recently. However, the European Society of Cardiology and the American Heart Association has reduced the threshold to 125pg/ml.

See section 5.4 of 2010 guideline (Appendix R): BNP2: Natriuretic peptides vs echocardiography.

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5.4 Recommendations for diagnosing heart failure

5.4.1 Symptoms, signs and investigations

1. **Take a careful and detailed history, and perform a clinical examination and tests to confirm the presence of heart failure. [2010]**

2. **Measure N-terminal pro-B-type natriuretic peptide [NT-proBNP] in people with suspected heart failure. [2018]**

3. **Because very high levels of NT-proBNP carry a poor prognosis, refer people with suspected heart failure and an NT-proBNP level above 2,000 ng/litre (236 pmol/litre) urgently, to have specialist assessment and transthoracic echocardiography within 2 weeks. [2018]**

4. **Refer people with suspected heart failure and an NT-proBNP level between 400 and 2,000 ng/litre (47 to 236 pmol/litre) to have specialist assessment and transthoracic echocardiography within 6 weeks. [2018]**

5. **Be aware that:**

- **an NT-proBNP level less than 400 ng/litre (47 pmol/litre) in an untreated person makes a diagnosis of heart failure less likely**
- **the level of serum natriuretic peptide does not differentiate between heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. [2018]**

6. **Review alternative causes for symptoms of heart failure in people with NT-proBNP levels below 400 ng/litre. If there is still concern that the symptoms might be related to heart failure, discuss with a physician with subspeciality training in heart failure. [2018]**

7. **Be aware that:**

- **obesity, African or African-Caribbean family origin, or treatment with diuretics, angiotensin-converting enzyme(ACE) inhibitors , beta-blockers, angiotensin II receptor blockers (ARBs) or mineralcorticoid receptor antagonist (MRAs) can reduce levels of serum natriuretic peptides.**
- **high levels of serum natriuretic peptides can have causes other than heart failure (for example, age over 70 years, left ventricular hypertrophy, ischaemia, tachycardia, right ventricular overload, hypoxaemia [including pulmonary embolism], renal dysfunction [eGFR less than 60 ml/minute/1.73 m^2], sepsis, chronic obstructive pulmonary disease, diabetes, or cirrhosis of the liver). [2010, amended 2018]**

8. **Perform transthoracic echocardiography to exclude important valve disease, assess the systolic (and diastolic) function of the (left) ventricle, and detect intracardiac shunts. [2003, amended 2018]**

9. **Transthoracic echocardiography should be performed on high-resolution equipment, by experienced operators trained to the relevant professional standards. Need and demand for these studies should not compromise quality. [2003, amended 2018]**

10. **Ensure that those reporting echocardiography are experienced in doing so. [2003]**

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11. Consider alternative methods of imaging the heart (for example, radionuclide angiography [multigated acquisition scanning], cardiac MRI or transoesophageal echocardiography) if a poor image is produced by transthoracic echocardiography. [2003, amended 2018]

12. Perform an ECG and consider the following tests to evaluate possible aggravating factors and/or alternative diagnoses:

- **chest X-ray**
- **blood tests:**

  renal function profile

  thyroid function profile

  liver function profile

  lipid profile

  glycosylated haemoglobin (HbA_{1c})

  full blood count
- **urinalysis**
- **peak flow or spirometry. [2010, amended 2018]**

13. Try to exclude other disorders that may present in a similar manner.[2003]

14. When a diagnosis of heart failure has been made, assess severity, aetiology, precipitating factors, type of cardiac dysfunction and correctable causes. [2010]

5.4.2 Heart failure caused by valve disease

15. Refer people with heart failure caused by valve disease for specialist assessment and advice regarding follow-up. [2003]

5.4.3 Reviewing existing diagnoses

16. Review the basis for a historical diagnosis of heart failure, and manage care in accordance with this guideline only if the diagnosis is confirmed. [2003]

17. If the diagnosis of heart failure is still suspected, but confirmation of the underlying cardiac abnormality has not occurred, then the person should have appropriate further investigation. [2003]

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5.5 Cardiac Magnetic Resonance Imaging (cMRI)

5.5.1 Introduction

Cardiac magnetic resonance imaging (cMRI) provides accurate and reproducible assessments of the systolic function of the ventricles, and some assessment of diastolic function of the ventricles. It is capable of studying the myocardial perfusion, infiltration and cardiac involvement by oedema, inflammation and scarring. cMRI provides an accurate assessment of the iron content of the myocardium. Using special sequences, cMRI is also capable of assessing ischaemia and scarring without the use of contrast media. cMRI is also capable of assessing valve lesions and shunts as well as measuring cardiac muscle mass and chamber volume. In chronic heart failure, cMRI is currently used in some centres for the assessment of left ventricular ejection fraction, the assessment of myocardial ischaemia, and for the detection and characterisation of myocardial scarring, inflammation or infiltration. There has been a rapid expansion in the number of cardiac magnetic resonance imaging (CMR) tests performed in the UK from 20597 in 2008 to 38485 in 2010 and yet there are no clear recommendations about its use. The role of cMRI in the diagnosis of chronic heart failure, in relation to other imaging techniques is unclear as is its place in the diagnostic pathway for patients with heart failure. This question addressed the clinical efficacy and cost effectiveness of cMRI compared to standard imaging technologies and whether all patients suspected of heart failure should undergo cMRI imaging or should it be used selectively in some patients?

5.5.2 Review question: In people with heart failure what is the clinical and cost effectiveness of cardiac MRI followed by the appropriate patient pathway?

For full details see review protocol in Appendix A.

Table 26: PICO characteristics of review question

Population	All people with HF in a community or outpatient setting.
Intervention/Comparators	• Echocardiography plus routine cardiac MRI • Echocardiography plus selective cardiac MRI • Echocardiography alone (all interventions will be compared against each other)
Outcomes	CRITICAL: • All-cause mortality (time to event) • Health-related quality of life at 12 months (continuous) • Unplanned hospitalisation (total number of events (rate ratio)) IMPORTANT: • Adverse events related to test (non-specific fibrosis in the presence of renal dysfunction) • Reclassification of specific HF aetiology (including ability to classify previous unclassified patients) • Change in management • HF medication use • HF advanced therapy use, including disease specific therapies • Repeat testing / additional testing
Study design	RCTs

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	Systematic reviews of RCTs

5.5.3 Clinical evidence

No relevant clinical studies comparing the effectiveness of different cardiac MRI (cMRI) imaging modalities with echocardiography (echo) were identified.

5.5.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in Appendix D.

Unit Costs

Table 27: Unit costs of cardiac MRI

Description	Unit cost	Source
Cardiac Magnetic Resonance Imaging Scan	£264(a)	NHS Reference costs 2014/15[242]
Simple Echocardiogram	£84	NHS Reference costs 2014/15[242]

(a) Weighted average of RD08Z, RD09Z, RD10Z.

5.5.5 Evidence statements

Clinical

No clinical evidence was identified.

Economic

No relevant economic evaluations were identified.

5.5.6 Recommendations and link to evidence

Recommendations	**No recommendation**
Research recommendations	• **What is the optimal imaging technique for the diagnosis of heart failure?**
Relative values of different outcomes	The committee considered the following outcomes to be critical for this review: all-cause mortality, quality of life, and all-cause hospitalisation. Data on all-cause mortality and hospitalisation were considered preferable to data limited to heart-failure related mortality and hospitalisations, primarily for consistency of methodology across the guideline, but also to take into account the potential adverse events associated with cardiac MRI or echocardiography. Adverse events related to the use of gadolinium in cardiac MRI – specifically non-specific fibrosis in the presence of renal dysfunction – were considered

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	to be important for decision-making. Given the nature of the review, namely to establish whether there was any benefit in using an additional diagnostic test, the committee also specified the following process outcomes as important for decision making: reclassification of specific heart failure aetiology, change in management, change in heart failure medication, advanced therapy use, and the need for repeat or additional testing.
Quality of the clinical evidence	No clinical evidence was found.
Trade-off between clinical benefits and harms	As no randomised controlled studies were found that addressed the review question, the committee was not able to make a recommendation on the clinical and cost effectiveness of cardiac MRI in heart failure. The committee decided to make a research recommendation to establish the added value of cardiac MRI (in terms of its clinical and cost effectiveness) in the clinical pathway of heart failure, for the reasons discussed below.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified evaluating the cost effectiveness of cardiac MRI (followed by the appropriate patient pathway) in patients with heart failure. The cost of a cardiac MRI and echocardiography was presented to the committee (£264 and £84 respectively); however, as there was no clinical evidence, the committee could not make a judgement on the cost-effectiveness of cardiac MRI. However, the committee agreed that due to the greater cost of cardiac MRI compared to echocardiography it was important that an assessment of the cost-effectiveness of cardiac MRI was included in the research recommendation.
Other considerations	The committee considered the use of cardiac MRI in heart failure to be an area of high priority for future research. While cardiac MRI is being increasingly used in heart failure in the UK, there remains large variation in practice across the country, and significant equality issues around access (for example, based on age and geography). There are also significant cost and resource implications. The committee discussed an existing clinical trial that is currently underway (OUTSMART[255]), which will compare outcomes in patients randomised to either routine cardiac MRI or selective (clinically driven) cardiac MRI. The trial is recruiting patients with heart failure and a working clinical diagnosis of non-ischaemic cardiomyopathy and patients with heart failure with preserved ejection fraction. The committee considered that the results of this trial would be very useful in answering the question posed in this review, but noted that it would not answer a number of the questions of interest, namely: • the clinical and cost effectiveness of adding cardiac MRI (either routinely or selectively) to echocardiography in all patients with HFREF For those reasons, notwithstanding the trial presently underway, the committee decided to make a research recommendation to establish the added value of cardiac MRI (in terms of its clinical and cost effectiveness) in all patients with heart failure. The committee also discussed the following proposed review question in the guideline scope: “What is the role of secondary imaging investigations in

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	diagnosing suspected amyloidosis?" The original objective of this question was to see if various imaging techniques (including cardiac MRI and bone scintigraphy using DPD tracing), when used following echocardiography, could identify a particular subset of people with HFPEF caused by amyloidosis. Amyloidosis accounts for around 5-13% of cases with HFPEF. The committee noted that during scoping for the guideline, it was thought that the amyloidosis question would complete the diagnostic picture, sitting alongside general recommendations on cardiac MRI imaging for HF. However, as no evidence was identified for the effectiveness of cardiac MRI in improving outcomes for HF patients, the committee decided that it would not be necessary for the guideline to specifically consider secondary imaging for a relatively narrow subset of patients with HFPEF. The committee noted that future research addressing the research recommendation – including the OUTSMART [255] trial – should answer the question on whether cardiac MRI in HF patients is clinically and cost-effective. Once this area of uncertainty is resolved for the general HF population, depending on the outcome of that research, it may then be appropriate to consider whether other forms of secondary imaging are effective in specific subpopulations of HF. If cardiac MRI were, in the future, to become a standard first line imaging technique for all HF patients, secondary imaging specific to amyloidosis may not be necessary (or may be used more judiciously in people with suspicious cardiac MRI results). However, until the effectiveness of cardiac MRI is known, the committee agreed that to conduct a review and make guideline recommendations specific to amyloidosis would be premature.

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6 Treating Heart Failure

The treatment of heart failure involves management of underlying causes and risk factors, treatment of symptoms and long-term pharmacological and non-pharmacological interventions for specific types of disease. The management of heart failure has evolved with increasing interest in preventative therapies which deal with conditions predisposing to heart failure such as ischaemic herat disease with attedant risk-factors such as smoking and diabetes, and the role of hypertension and obesity in exacerbation of heart failure especially if ejection fraction is preserved. Dietary factors such as salt (sodium intake), fatty acids, cholesterol and carbohydrates are involved in promoting the progression of hypertension, hyperlipidaemia, obesity and diabetes which all have implications for the management of heart failure. The management of these outside heart failure is the subject of separate guidance (see NICE CG 181; PH38) but these recommendations may not apply completely in patients with heart failure . As fluid overload is a common feature of heart failure sodium and fluid restriction has been advised and new evidence is available to be able to review whether this is efficacious.

The diagnosis of heart failure has implications for activities of daily life as well as affecting the ability to travel or drive. The presence of oedema and reduced activity found with heart failure prediposes to chest infections and thus this group of patients need to receive advice on vaccination for influenza.

6.1 Lifestyle

The update to the heart failure guideline includes topics where new evidence has emerged since the publication in 2010. A review of new evidence published after 2010 was carried out in order to determine whether any changes to current recommendations where likely to be required. The decision on which topics to include in the update of the guideline was made following consultation of the scope.

This section, with the exception of salt and fluid restriction, was not within the scope of the update. For more information on the following aspects of lifestyle please refer to appendix R in the 2003 guideline: vaccinations, sexual activity, air travel, driving

For guidance on alcohol and smoking cessation see 6.1.2.

6.1.1 Salt and fluid restriction

6.1.1.1 Introduction

Information provided to patients with heart failure usually includes advice to restrict salt and fluid intake. Patients often find this difficult to adhere to, and little is known as to whether or not adherence affects their overall condition, and helps prevent episodes of decompensation. There is a concern that advising fluid restriction in the elderly, whose fluid intake is often low, could potentially be harmful. There is currently variation in practice on what advice patients are given by health professionals and consequently confusion and uncertainty among patients about whether salt and fluid restriction is beneficial. Stakeholders identified this as a priority area for the guideline update, and the committee regarded this as an important aspect of patient care and education that required clarification.

6.1.1.2 Review question: What is the clinical and cost effectiveness of salt and/or fluid restriction in people with heart failure?

For full details see review protocol in Appendix A.

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Table 28: PICO characteristics of review question

Population	People diagnosed with heart failure according to the New York Heart Association (NYHA) class system (I-IV), who are being managed as outpatients or in the community. Where possible, results will be stratified based on the serum sodium level of patients at baseline.
Interventions / Comparisons	• Salt and/or fluid restriction programme – structured, protocol-driven programme to limit salt and/or fluid to certain levels. Programme may or may not be individualised. • General advice to limit salt and/or fluid intake • No advice to limit salt and/or fluid intake Interventions compared to each other
Outcomes	CRITICAL • Quality of life at 12 months (Continuous) • Unplanned hospitalization (Count rate) IMPORTANT • Change in weight at 12 months (Continuous) • Change in oedema at 12 months (Continuous) • Change in sodium level (Continuous)(in the low baseline sodium strata only) • Adverse events - Renal function at 12 months (Dichotomous) • Adverse events - Hyperkalaemia at 12 months (Dichotomous)
Study design	Systematic Review RCT

6.1.1.3 Clinical evidence

A search was conducted for randomised control trials looking at the effect of sodium (salt) and/or fluid restriction in people with heart failure being managed in the community. Two studies were included in the review[70, 281] these are summarised in Table 29. See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

Both studies are small, and refer to themselves as "pilot" studies. One study compared a moderate salt intake (2300mg/day sodium) with low salt intake (1500mg/day sodium) in people with HF and normal serum sodium. A further study compared an education programme with support to maintain fluid restriction at 1.5-2L (intervention) with general support unrelated to the fluid restriction (control) in people with HF who were already in a trial of an intrathoracic impedance monitoring device who had been hospitalised in the last six months.

Table 29: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Colin-Ramirez 2015[70]	Intervention 1: (n=19) Salt restriction programme with target of reducing salt to <1500mg/day Intervention 2: (n=19) Salt restriction programme with target of reducing salt to <2300mg/day	n=38 Adults with HFREF or HFPEF on optimally tolerated medical therapy with normal serum sodium Age median 66 Male/Female 20:18	• Quality of Life (KCCQ) – six months • Renal failure (Creatinine) – six months	Actual intake of salt in two groups (median): Intervention– 1398 (IQR 1090-2060), Control 1461 (1086-1765) All results reported using non-parametric summary scores. Significant inequality at

Study	Intervention and comparison	Population	Outcomes	Comments
		95% White ethnicity		baseline. BMI and oedema inadequately reported for extraction. Normal sodium status Pilot study.
Reilly 2015[281]	Intervention: (n=13) Fluid restriction with self-care programme to encourage fluid restriction to 1.5-2L Control: (n=12) Attention control received same fluid prescription and contacts, but interaction more general Both groups also encouraged to restrict salt to <2g/day	n=25 Adults with HF enrolled in a different trial. NYHA class II-IV Had previously been prescribed fluid regimen of 1.5-2L/day Age mean 63 Male/Female 14:11 80% White ethnicity, 20% African American	• EQ5D – visual analogue scale (VAS) – six months • Oedema – three months (extracted, but not analysed)	Actual fluid intake of two groups: intervention – mean 1703, control – 2021ml/day No baseline sodium levels given. Pilot study.

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Table 30: Clinical Evidence summary: Low sodium diet versus moderate sodium diet for heart failure

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Time frame is 6 months	
				Risk with Advice for moderate sodium diet	Risk difference with Advice for low sodium diet (95% CI)
Quality of Life Kansas City Cardiomyopathy Questionnaire. Scale from: 0 to 100. High is better	38 (1 study) 6 months	⨁⨁⊖⊖ LOW[a,b] due to risk of bias		The median quality of life in the control groups was 72.4 IQR (63.8-86.3)	The median quality of life in the intervention groups was 7.8 lower
Renal function Creatinine (umol/L)	38 (1 study) 6 months	⨁⨁⊖⊖ LOW[a,b,] due to risk of bias		The median renal function in the control groups was 106.5 IQR (78-114)	The median renal function in the intervention groups was 4 lower

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the evidence was at very high risk of bias.
(b) Imprecision cannot assessed due to reporting of median and inter-quartile range.

Table 31: Clinical evidence summary: Fluid restriction programme versus advice on fluid restriction for heart failure

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Time frame is 6 months	
				Risk with Advice on fluid restriction	Risk difference with Programme for fluid restriction (95% CI)
Quality of Life EQ5D - visual analogue scale. Scale from: 0 to 100. High is better.	21 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision		The mean quality of life at 6 months in the control groups was 70.5	The mean quality of life at 6 months in the intervention groups was 8.68 lower (24.96 lower to 7.6 higher)
Oedema Congestion score. Scale from: 0 to 5. High is worse.	23 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision		The mean congestion sore in the control groups was 1.18	The mean congestion score in the intervention groups was 0.07 higher (1.1 lower to 1.24 higher)

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(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 or 2 increments because the majority of evidence was from an indirect population (people were already enrolled in a intrathoracic impedance monitoring device trial).
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(d) Downgraded by 2 increments because the majority of evidence was from an indirect population (people were already enrolled in a intrathoracic impedance monitoring device trial) and was looking at congestion, which includes things other than oedema (the protocol outcome).

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6.1.1.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in Appendix D.

6.1.1.5 Evidence statements

Clinical

Two studies were identified for inclusion within the review. The quality of the evidence ranged from low to very low due to risk of bias, imprecision due to wide confidence intervals surrounding the effect estimate and indirectness of the study population. One study including 38 people with HFREF or HFPEF on optimally tolerated medical therapy with normal serum sodium compared a moderate salt intake (2300mg/day sodium) with low salt intake (1500mg/day sodium). In reality, participants in either arm reduced salt to a relatively similar extent (median difference 63mg/day). The outcome QoL (as measured by the KCCQ) showed a clinically important reduction in quality of life with the low sodium diet. The low sodium diet also showed no clinical effect on renal function. Imprecision could not be assessed for these outcomes as the study reported the results as median and interquartile range. The results of this pilot study were used to inform the larger SODIUM-HF trial, which is currently recruiting

The second study which included 25 people, who were already enrolled in a trial of an intrathoracic impedance monitoring device and who had been hospitalised within the previous 6 months, compared an education programme providing support to maintain fluid restriction at 1.5-2L (intervention) with general support unrelated to the fluid restriction (control). The outcome QoL (as measured by the EQ5D VAS) showed a clinically important reduction in quality of life with the fluid restriction programme (associated with wide confidence intervals around the effect estimate). The fluid restriction programme had no clinical effect on the outcome oedema (again associated with wide confidence).

Economic

- No relevant economic evaluations were identified.

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6.1.1.6 Recommendations and link to evidence

Recommendations	**Do not routinely advise people with heart failure to restrict their sodium or fluid consumption. Ask about salt and fluid consumption and, if needed, advise as follows:** • **restricting fluids for people with dilutional hyponatraemia** • **reducing intake for people with high levels of salt and/or fluid consumption.** **Continue to review the need to restrict salt or fluid. [2018]** **Advise people with heart failure to avoid salt substitutes that contain potassium. [2018]**
Relative values of different outcomes	The committee considered quality of life and unplanned hospitalisation to be the critical outcomes for this review. Data on all-cause hospitalisation were considered preferable to data limited to heart failure (HF) related hospitalisations, as such data take into account the broader unintended consequences of the interventions (for example, an increase in hospitalisations due to adverse events). Change in appetite, weight and oedema, as well as impact on renal function and hyperkalaemia, were considered to be important for decision-making. For patients with low sodium levels at baseline, change in serum sodium level was also considered an important outcome. While serum sodium level is often reported as an outcome in sodium restriction studies, it was not considered clinically relevant for HF patients with normal baseline sodium. Also, while studies often report actual reductions in sodium and/or fluid intake after the delivery of a restriction intervention, again this was not considered to be a key clinically important outcome. Given the nature of the interventions in this review, mortality was not included as an outcome. The committee was more interested in the impact on symptoms and hospitalisation. For the comparison of low sodium diet programme versus moderate sodium diet programme, the only evidence reported in a complete format enabling analysis was on quality of life and renal function. For the comparison of fluid restriction programme versus advice on fluid restriction, the only evidence was on quality of life and oedema. There was no evidence for any comparison on hospitalisation, change in weight, change in sodium level for patients with low baseline sodium, or hyperkalaemia.
Quality of the clinical evidence	The committee noted the paucity of evidence in this area, which was limited to 2 very small pilot studies looking at different comparisons. Low sodium programme versus moderate sodium programme: The evidence for both quality of life and renal function was graded low quality due to risk of bias (selection bias and performance bias). Imprecision could not be formally assessed due to reporting of the outcomes as median and interquartile range (IQR), but the committee noted the small size of the study. Fluid restriction programme versus general advice on fluid restriction:

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Recommendations	**Do not routinely advise people with heart failure to restrict their sodium or fluid consumption. Ask about salt and fluid consumption and, if needed, advise as follows:** • **restricting fluids for people with dilutional hyponatraemia** • **reducing intake for people with high levels of salt and/or fluid consumption.** **Continue to review the need to restrict salt or fluid. [2018]** **Advise people with heart failure to avoid salt substitutes that contain potassium. [2018]**
	The evidence for quality of life was graded very low quality due to risk of bias (selection bias and performance bias), indirectness (indirect population) and imprecision. The evidence for oedema was graded very low quality due to risk of bias (selection bias, performance bias and measurement bias), indirectness (indirect population and outcome) and imprecision. Other comparisons: There was no evidence on any of the following comparisons: • Salt restriction programme versus general advice to restrict salt. • Salt restriction programme versus no restriction/no advice. • Fluid restriction programme versus no restriction/no advice.
Trade-off between clinical benefits and harms	The committee discussed the evidence for a low sodium programme compared with a moderate sodium programme, which was based on a single small trial. The committee noted that patients' median intake of sodium at both baseline and at the end of the study was similar between the 2 groups (at the end of the study, low sodium – 1398 mg/day, moderate sodium – 1461 mg/day). Notwithstanding the similar reduction in sodium consumption in each group, quality of life in the low sodium group was lower than in the moderate sodium group. This suggested that the restrictive nature of the programme itself, independent of the actual reduction in sodium consumption achieved, had a negative impact on quality of life. There was no clinically important difference in renal function (measured by creatinine) between the low and moderate sodium programmes, which was to be expected given the similarity in the actual sodium levels consumed. The committee also discussed the evidence for a fluid restriction programme compared with general advice to restrict fluid, which again was based on a single small trial. The fluid restriction programme did appear to have a clinically important impact on actual levels of fluid consumed in each group, with the 'general advice' group consuming 300mL more per day on average than the 'restriction programme' group. Quality of life was lower in the restriction programme group than in the general advice group which was agreed to represent a clinically important reduction. The restriction programme did not appear to have any impact on oedema measured via a 'congestion score', though the committee placed little weight on this scale that has not been validated. In weighing up the possible benefits and harms of salt and fluid restriction, the committee acknowledged the quality of the evidence, which ranged from low to very low, and the uncertainty around the effect estimates. The absence of evidence on most of the outcomes was noted, in particular

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Recommendations	**Do not routinely advise people with heart failure to restrict their sodium or fluid consumption. Ask about salt and fluid consumption and, if needed, advise as follows:** • **restricting fluids for people with dilutional hyponatraemia** • **reducing intake for people with high levels of salt and/or fluid consumption.** **Continue to review the need to restrict salt or fluid. [2018]** **Advise people with heart failure to avoid salt substitutes that contain potassium. [2018]**
	hospitalisation, which was stated to be critical for decision making. Although there was only limited evidence and it was uncertain, the committee felt that the the possible negative impact of salt and fluid restriction programmes on patient experience and quality of life should not be ignored. Committee members agreed that the negative impact on quality of life was consistent with their experience in practice, particularly with older, frailer HF patients who often do not drink sufficient fluid, so any advice to restrict fluid further may risk serious dehydration in some patients. In the absence of any evidence of benefit, the committee decided that patients should not be routinely advised to restrict their salt and fluid consumption. The committee discussed whether it would be beneficial to cross-refer to existing healthy eating, cardiovascular risk management or hypertension NICE guidance in the recommendation, but agreed some of this guidance may, in fact, be dangerous to HF patients (for example, the use of sodium substitutes that contain potassium would put HF patients at higher risk of hyperkalaemia). The change in recommendations in standard drug treatments, will result in triple therapy with ACE inhibiter, beta-blocker and MRA becoming more common, and the risks of hyperkalaemia are significant if people are advised to switch from salt to potassium-containing salt substitutes (particularly if their baseline levels of salt intake are high, leading to high level of substitute consumption). A consensus recommendation was made that they should be avoided in the heart failure population, in the hope that this would facilitate communication between patients and professionals on this point. While healthcare professionals should not routinely advise patients to restrict salt or fluid, there may be specific clinical circumstances where restriction is appropriate. For example, both salt and fluid restriction may be beneficial in very severe or advanced heart failure (though should be used very carefully in older patients), and fluid restriction may be beneficial for hyponatremia. In addition, for patients consuming large quantities of sodium or fluid, reduction to normal levels of consumption may be beneficial (especially for hypertensive patients consuming a large amount of salt). Healthcare professionals should ask their patients about their levels of salt and fluid consumption in order to provide appropriate advice, and this should not be open-ended, but there should be opportunities to review whether the strategy was effective for the individual. The committee recognised the uncertainty in the evidence and the possibility

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Recommendations	**Do not routinely advise people with heart failure to restrict their sodium or fluid consumption. Ask about salt and fluid consumption and, if needed, advise as follows:** • **restricting fluids for people with dilutional hyponatraemia** • **reducing intake for people with high levels of salt and/or fluid consumption.** **Continue to review the need to restrict salt or fluid. [2018]** **Advise people with heart failure to avoid salt substitutes that contain potassium. [2018]**
	that future research may conclude that salt and/or fluid restriction is beneficial. In particular, the large RCT currently underway comparing a low sodium diet versus usual care (general advice to limit salt) (SODIUM-HF[346]). Given the importance of this issue to patients, the potential for significant negative impact on quality of life, and the absence of any randomised evidence of benefit, a 'do not routinely offer' recommendation was made, acknowledging that this review will be updated in the future if new evidence arises to change the recommendation. The need for further trials of fluid restriction was considered – either of advice about restriction, or based on actual restriction values.. While some further guidance on overall efficacy would clarify the population benefit, further research would be difficult to carry out, and would not change the conclusion that advice should be given on an individual basis according to intake and fluid balance in the individual.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified assessing the cost effectiveness of salt and/or fluid restriction programmes in people with heart failure. As described in the 'trade of between clinical benefits and harms' above, the committee considered that the harms of salt and fluid restriction, particularly in terms of quality of life, outweighed the benefits in most circumstances, and therefore decided that salt and fluid restriction should not be routinely offered. Current practice is highly variable, but many health professionals do advise people with heart failure to restrict their salt and fluid intake. The committee therefore considered that implementing a 'do not routinely offer' recommendation might improve quality of life for current heart failure patients and could also be cost saving due to reduced appointment time as most people will no longer require information and advice on how to restrict their intake of salt and fluid.
Other considerations	The committee are aware of a recently published large observational study[104] (with propensity matching on plausible confounders) on the impact of dietary sodium restriction on heart failure outcomes. The study included patients in an unrelated trial, categorising them into sodium restricted and unrestricted groups based on their sodium intake prior to death or hospitalisation. This study found that sodium restriction was associated with a statistically significant and clinically important increase in the risk of death or HF hospitalisation, and was not associated with improved quality of life, physical functioning, 6-min walk distance, or symptoms. The study concluded that "in symptomatic patients with chronic HF, sodium restriction may have a detrimental impact on outcome". While a randomised trial is needed to definitely address the role of sodium restriction in heart failure, the

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Recommendations	**Do not routinely advise people with heart failure to restrict their sodium or fluid consumption. Ask about salt and fluid consumption and, if needed, advise as follows:** • **restricting fluids for people with dilutional hyponatraemia** • **reducing intake for people with high levels of salt and/or fluid consumption.** **Continue to review the need to restrict salt or fluid. [2018]** **Advise people with heart failure to avoid salt substitutes that contain potassium. [2018]**
	committee considered that this non-randomised evidence provided further support for its recommendation to 'not routinely offer' sodium restriction until such randomised evidence is available. Current practice regarding salt and fluid restriction is highly variable, with some healthcare professionals advising patients to restrict intake and others not. The lay members indicated that salt and fluid restriction is the subject of much discussion in patient groups. Given it is one of a limited number of opportunities for self-management in HF, some patients may feel that it enables them to exercise some personal control over the course of what is an unpredictable and serious long term condition. However, the variation in practice and advice has led to confusion and uncertainty among patients about whether salt and fluid restriction is necessary or beneficial. The recommendation to not routinely advise salt and fluid restriction should operate to reduce variation in practice across the country, and ensure that any discussions between patients and healthcare professionals start from a consistent position. Where patients are currently attempting to restrict salt and/or fluid without specific clinical circumstances for doing so, healthcare professionals should discuss the uncertainty in the evidence with those patients as part of shared decision making. Patients may have been asked to restrict fluid intake during acute episodes, and not given information on when this is no longer indicated. The decision on whether to continue to restrict salt and/or fluid should take into account patient preferences.

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6.1.2 Recommendations on lifestyle

6.1.2.1 Smoking and alcohol

See NICE's guidance on smoking and tobacco and alcohol.

6.1.2.2 Salt and fluid restrictions

18. Do not routinely advise people with heart failure to restrict their sodium or fluid consumption. Ask about salt and fluid consumption and, if needed, advise as follows:

- **restricting fluids for people with dilutional hyponatraemia**
- **reducing intake for people with high levels of salt and/or fluid consumption.**

Continue to review the need to restrict salt or fluid. [2018]

19. Advise people with heart failure to avoid salt substitutes that contain potassium. [2018]

6.1.2.3 Vaccinations

20. Offer people with heart failure an annual vaccination against influenza. [2003]

21. Offer people with heart failure vaccination against pneumococcal disease (only required once). [2003]

6.1.2.4 Contraception and pregnancy

22. In women of childbearing potential who have heart failure, contraception and pregnancy should be discussed. If pregnancy is being considered or occurs, specialist advice should be sought. Subsequently, specialist care should be shared between the cardiologist and obstetrician.]2003]

6.1.2.5 Air travel

23. Air travel will be possible for the majority of people with heart failure, depending on their clinical condition at the time of travel. [2003]

6.1.2.6 Driving

24. Large Goods Vehicle and Passenger Carrying Vehicle licence: physicians should be up to date with the latest Driver and Vehicle Licensing Agency guidelines. Check the website for regular updates [2003]

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6.2 Pharmacological treatment

6.2.1 Introduction

A review of new evidence published after 2010 was carried out in order to determine whether any changes to current recommendations where likely to be required. The decision on which drugs to include in the update of the guideline was made following consultation of the scope.

Drugs reviewed in the update included:

- Mineralocorticoid receptor antagonists
- Beta-blockers in people with with CHF and atrial fibrillation
- Treating heart failure in people with chronic kidney disease
- Iron supplementation

As a consequence of updating the mineralocorticoid evidence, and the need to incorporate new NICE technology appraisal guidance for sacubitril valsartan and ivabradine within the treatment pathway, the initiation and sequencing of pharmacological therapies was considered and revised by the guideline committee.

The following agents were not considered in the update. For more information:

Refer to Appendix R, the 2010 Guideline:

- Angiotensin converting enzyme inhibitors (ACEI)
- Beta-blockers
- Hydralazine and nitrate combination
- Angiotensin-II receptor antagonists

Refer to Appendix R, the 2003 Guideline

- Amiodarone
- Anticoagulants
- Inotropic agents
- Calcium channel blockers
- Diuretics
- Digoxin

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6.2.2 Beta-blockers in people with heart failure and atrial fibrillation

6.2.2.1 Introduction

Since the early 1990s, there have been several randomised controlled trials which clearly demonstrated that beta-blockers can significantly reduce the morbidity and mortality of patients with HFREF. Beta-blockers have been recommended in NICE heart failure guidance since 2003.The prescription of beta-blockers in heart failure has become more common as recorded in successive large observational studies such as those from the UK National Heart Failure audit. This development has been associated with a progressive decline in the reported mortality of patients with HFREF over the past 10 years or so. However, in 2014 a high-profile individual patient data meta-analysis was published, which examined the role of beta-blockers in a specific sub-population of HREF patients who also have atrial fibrillation (AF). This paper failed to demonstrate the same mortality benefit of beta-blockers as had previously been seen in the overall HFREF population. Therefore it became important to review the guidance for the use of beta-blockers in this sub-population of patients.

6.2.2.2 Review question: What is the clinical and cost effectiveness of beta-blockers in the management of chronic heart failure in people with heart failure with reduced ejection fraction (HFREF) and atrial fibrillation?

For full details see review protocol in Appendix A.

Table 32: PICO characteristics of review question

Population	People diagnosed with HFREF with concomitant atrial fibrillation.
Intervention(s)	Beta-blockers: • bisoprolol (up to 10mg once daily) • carvedilol (up to 50mg twice daily) • nebivolol (licensed in stable mild to moderate heart failure in people over 70 years) (up to 10mg once daily) • metoprolol CR/XL(up to 200 mg once daily) In addition to usual care in CHF.
Comparison(s)	Placebo In addition to usual care in CHF.
Outcomes	CRITICAL • All-cause mortality • Health-related quality of life • Unplanned hospitalisation IMPORTANT • Other adverse events (stroke, bradycardia, hypotension) • Improvement of NYHA class
Study design	Systematic reviews of RCTs RCTs

6.2.2.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of beta-blockers versus placebo in addition to usual care in people with chronic heart failure and atrial fibrillation. One study

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was included in the review;[181] it is summarised in Table 33 below. See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

Kotecha 2014[181] is an individual patient data (IPD) meta-analysis which compiled subgroup data from 10 major beta-blocker mortality trials. The meta-analysis included 4 studies comparing carvedilol and placebo; 2 studies comparing metoprolol and placebo; 2 studies comparing bisoprolol and placebo; 1 study comparing nebivolol and placebo; and 1 study comparing bucindolol and placebo. The committee discussed the studies included within the IPD and agreed that:

- Bucindolol is not licensed for any indication in the UK (it does not have marketing authorisation), nor is it currently used in practice for HF-REF. This is due to a lack of trial data suggesting prognostic benefit of bucindolol in patients with HF-REF, with respect to all-cause mortality. In addition to this Bucindolol demonstrates pharmacogenetic differences in different ethnicities. Based on this, the committee concluded that results of trials using this beta-blocker should be excluded.
- Although the form of metoprolol (metroprolol succinate) used in MERIT-HF[349] is not available in the UK, an alternative form metoprolol tartrate is available and licensed for use in clinical practice (though it is not licensed for heart failure). The committee agreed that the 2 forms were likely to have a similar overall effect despite difference in pharmacokinetic properties (metoprolol succinate is longer acting and more bioavailable than tartrate). Overall, the committee agreed that studies using this beta-blocker were still considered relevant and should be included.

For the outcome all-cause mortality, the IPD presented the results of the individual trials separately. This allowed us to exclude the BEST trial[36], which used bucindolol, from our meta-analysis. For the other reported outcomes (heart-failure related hospitalisation and non-fatal stroke), only an overall summary statistic was reported in the IPD. For this reason, we contacted the study authors and obtained the overall effect estimates for these outcomes with the BEST trial excluded from the analysis (this was a pre-specified sensitivity analysis conducted by the authors that was not reported in the main paper). The data presented and analysed in this review therefore excludes the BEST trial.

Data could not be obtained for the studies CORPENICUS[251] (unable to obtain full text paper) and MERIT-HF[349](no extractable data). However data for these 2 studies was included in the IPD meta-analysis as published by Kotecha[181].

Table 33: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Kotecha 2014[181]	• Beta blockers (n = 1523) Bucindolol; bisoprolol; carvedilol; metoprolol; and, nebivolol • Placebo (n = 1543) Matching placebo was reported in 4 included trials: ANZ; BEST; CIBIS I; and, SENIORS.	Age, median years (IQR): Beta-blocker: 69 (60-75); placebo: 69 (61 – 74). % Female: beta-blocker: 18.9%; placebo: 19.8% LVEF, median (IQR): beta-blocker: 0.27 (0.21 – 0.33); placebo: 0.27 (0.22 – 0.33).	• All-cause mortality (time-to-event) • First heart-failure-related hospital admission (time-to-event) • Non-fatal stroke (time-to-event) All outcomes reported at 3.3 years	Studies included in the IPD: – ANZ – BEST – CAPRICORN – CIBIS I – CIBIS II – CORPENICUS – MDC – MERIT-HF – US-HF – SENIORS Pre-defined sensitivity analysis excluding the results of the BEST trial (bucindolol vs placebo)

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Study	Intervention and comparison	Population	Outcomes	Comments
		NYHA III: beta-blocker: 72.2%; placebo: 72.1% Only unconfounded head-to-head trials with recruitment of more than 300 people and a planned follow-up of more than 6 months were eligible for inclusion in the IPD.		was conducted by the authors of this IPD. These results were obtained directly from the authors and have been extracted in this review.

Table 34: Summary of studies included in the Kotecha 2014 IPD*

Study	Intervention and comparison	Inclusion criteria	Exclusion criteria
Bollano 1997 [43] ANZ	• Carvedilol (n=207) • Placebo (n=208)	• Chronic stable heart failure due to ischaemic heart disease (defined as a documented history of myocardial infarction, typical angina, an exercise electrocardiogram positive for ischaemia, or angiographic evidence of coronary disease) • LVEF by radionuclide ventriculography of less than 45% • current NYHA class II or III, or previous class II-IV	• current NYHA class IV • heart rate below 50 bpm; • sick sinus syndrome; • second degree or third-degree heart block; • blood pressure below 90 mmHg systolic or above 160/100 mm Hg; • treadmill exercise duration less than 2 min or more than 18 min (modified Naughton protocol); • coronary event or procedure (myocardial infarction, unstable angina, coronary-artery bypass surgery, or coronary angioplasty) within the previous 4 weeks; • primary myocardial or valvular disease; • current treatment with a β-blocker, β-agonist, or verapamil; • insulin-dependent diabetes mellitus; • chronic obstructive airways disease; • hepatic disease (serum

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Study	Intervention and comparison	Inclusion criteria	Exclusion criteria
			aminotransferase above three times normal); • renal impairment (serum creatinine >250 µmol/L); • or any other life-threatening non-cardiac disease.
Dargie 1999 [84], Lechat 2001[192] CIBIS II	• Bisoprolol (n=1327) • Placebo (n=1320)	• Ambulatory • aged 18 – 80 years • LVEF, measured within 6 weeks of randomisation, of 35% or less • NYHA class III and IV • diagnosis of chronic heart failure, made at least 3 months previously , with clinical stability during the preceding 6 weeks for heart failure or 3 months for acute myocardial infarction or unstable angina. • Cardiovascular therapy had to have been unchanged in the 2 weeks before randomisation • treatment with ACEI (if tolerated); use of digoxin was optional	• uncontrolled hypertension, myocardial infarction or unstable angina pectoris in the previous 3 months, percutaneous transluminal coronary angioplasty or coronary artery bypass graft in the previous 6 months • previous or scheduled heart transplant, atrioventricular block greater than first degree without a chronically implanted pacemaker, resting heart rate of less than 60 bpm, systolic blood pressure at rest of less than 100 mm Hg, renal failure (serum creatinine ≥300 µmol/L), • reversible obstructive lung disease • pre-exisintg or planned therapy with β-adrenoreceptor blockers
Dargie 2001[85] CAPRICORN	• Carvedilol (n = 975) • placebo (n=984) • 17 countries/168 centres	• People aged 18 years or older • stable, definite myocardial infarction occurring 3 – 21 days before randomization • LVEF ≤ 40% by two-dimensional echocardiography or by radionuclide or contrast ventriculography, or wall-motion-score index of 1.3 or less; • receipt of concurrent treatment with ACEI for at least 48 hours and stable dose for more than 24 h unless there was intolerance of ACEI • people with heart failure appropriately treated with diuretics and ACEI during the acute phase,	• Unstable angina, hypotension (systolic blood pressure <90 mm Hg), uncontrolled hypertension, bradycardia (heart rate <60 bpm), and unstable insulin-dependent diabetes mellitus • People with a continuing need for β-blockers for any indication other than heart failure were excluded, as were those requiring ongoing therapy with inhaled β2-agonists or steroids. • People who continue to require intravenous diuretics or inotropes, or those with uncontrolled heart failure
Domanski 1994 [99]	• Bisoprolol (n = 320)	• Aged between 18 and 75 years	• heart failure due to hypertrophic or restrictive

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Study	Intervention and comparison	Inclusion criteria	Exclusion criteria
CIBIS I	• Placebo (n=321)	• chronic heart failure with or without sinus rhythm, and dyspnea or fatigue corresponding to NYHA class III or IV • people had to be ambulatory and not awaiting cardiac transplantation • mandatory background medication was diuretic and vasodilator therapy. • LVEF < 40% (isotopic or angiographic performed within 4 weeks before randomization) • aetiology of heart failure was defined as (1) idiopathic dilated cardiomyopathy when no known cause of cardiomyopathy could be found, (2) ischaemia when typical history of coronary artery disease, history of myocardial infarction, or presence of significant (70%) coronary artery stenoses had been documented (3) hypertension when history of established hypertension or antihypertensive therapy was present, and (4)valvular heart disease; people with primary valvular disease (that had to be surgically repaired for at least 6 months) and people with nonischaemic dilated cardiomyopathy associated with a significant mitral valve insufficiency • clinical stability, defined as the absence of any episode of heart failure decompensation during the 6 week period before entry into the trial and the absence of major modification of heart failure therapy in the previous 3 weeks.	cardiomyopathy with predominant left ventricular diastolic dysfunction, heart failure secondary to mitral or aortic valve disease that was not surgically repaired or had been surgically repaired for less than 6 months, • patient with coronary heart disease awaiting bypass surgery or a recent history of myocardial infarction (less than 3 months) • people already on a heart transplantation waiting list • nonambulatory patient with disabling permanent dyspnea at rest • insulin-dependant diabetes • asthma • renal insufficiency (serum creatinine >300 µmol/L) • hypothyroidism or hyperthyroidism • people whose life expectancy was shortened by a severe illness such as malignant disease • resting heart rate <65 bpm or systolic blood pressure < 100 mm Hg or >160 mm Hg immediately before randomization.
Flather	• Nebivolol (n=1067)	• Aged ≥ 70 years	• new drug therapy for heart

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Study	Intervention and comparison	Inclusion criteria	Exclusion criteria
2005[119], Mulder 2012[230] SENIORS	• Placebo (n=1061)	• clinical history of chronic heart failure with at least one of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive heart failure or documented • LVEF ≤ 35% within the previous 6 months	failure in the 6 weeks prior to randomization • a change in cardiovascular drug therapy in the 2 weeks prior to randomization • heart failure due primarily to uncorrected valvular heart disease • contraindication or previous intolerance to beta-blockers (e.g. heart rate < 60 bpm or systolic blood pressure <90 mm Hg) • current use of beta-blockers • significant hepatic or renal dysfunction • cerebrovascular accidents within the previous 3 months • being on a waiting list for percutaneous coronary intervention or cardiac surgery or other major medical conditions that may have reduced survival during the period of the study
Packer 1996 [250], Joglar 2001[160] US-HF	• Carvedilol (n=696) • Placebo (n=398) Multicentre with varying treatment protocols.	• Symptomatic heart failure for at least three months • ejection fraction ≤35%, despite at least two months of treatment with diuretics and an ACE (if tolerated)	• A major cardiovascular event or a major surgical procedure within three months of entry into the study; • uncorrected, primary valvular disease; • active myocarditis; • sustained ventricular tachycardia or advanced heart block not controlled by antiarrhythmic intervention or a pacemaker; • systolic blood pressure of more than 160 or less than 85 mm Hg or diastolic blood pressure of more than 100 mm Hg; • a heart rate of less than 68 beats per minute; • clinically important hepatic or renal disease; or any condition other than heart failure that could limit exercise or survival. • people receiving calcium-channel blockers, α- or β-adrenergic agonists or class IC

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Study	Intervention and comparison	Inclusion criteria	Exclusion criteria
			or III antiarrhythmic agents were not enrolled. • people already receiving β-blockers
Waagstein 1993 [363] MDC	• Metoprolol (n=184) • Placebo (n=189)	• Symptomatic dilated cardiomyopathy and ejection fraction below <40% • aged 16-75 years • people were required to have achieved a state of compensated heart failure by means of conventional heart failure treatment, which could include digitalis, diuretics, ACEI and nitrates. • Systolic BP of ≥ 90 mm Hg and heart rate of ≥ 45 bpm	• treatment with β-blockers , calcium channel blockers, inotropic agents (except digitalis), or high doses of tricyclic antidepressant drugs • significant coronary artery disease shown by angiography (> 50% obstruction of a major epicardial vessel) • clinical or histological signs of ongoing myocarditis, • other life threatening diseases • chronic obstructive lung disease requiring β2-agonists • excessive alcohol consumption (> 700 g per week)

*Data could not be directly extracted for: CORPENICUS[251] which could not be accessed and MERIT-HF[349].

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Table 35: Clinical evidence summary: beta-blocker versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta-blockers (95% CI)
All-cause mortality	2666 (9 studies) 3.3 years	⨁⨁⨁⊖ MODERATE[b] due to imprecision	HR 1.02 (0.85 to 1.23)	157 per 1000[d]	3 more per 1000 (from 22 fewer to 32 more)
First heart-failure related hospital admission	2615 (1 study) 3.3 years	⨁⨁⨁⊖ MODERATE[a] due to indirectness	HR 0.93 (0.77 to 1.12)	149 per 1000[d]	10 fewer per 1000 (from 32 fewer to 16 more)
Fatal and non-fatal stroke at 3.3 years	2616 (1 study) 3.3 years	⨁⨁⊖⊖ LOW[b] due to imprecision	HR 1.11 (0.71 to 1.74)	[c]	[c]

(a) Downgraded by 1 increment due to indirectness of the outcome which only reported first heart-failure related hospital admission rather than all-cause.

(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both.

(c) Not estimable as only the summary statistic was reported by Kotecha 2014[181] and no additional information regarding the event rates were available from the original papers.

(d) Control group risk was calculated as a median from the data included within the original CIBIS-II[349], SENIORS [230]and US-HF[160] publications, as this could not be attained from the IPD.

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6.2.2.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in Appendix D.

Unit costs

In the absence of any economic analysis, unit costs for beta-blockers are presented in Table 36. Additional costs are likely to be incurred in the first year of beta-blocker initiation due to up-titration. These costs are presented in Table 37. The cost of heart failure hospitalisation and first year after stroke are also presented in Table 38 and Table 39 below.

Table 36: UK unit costs of Beta-blockers

Drug	mg/unit	Units/day	Units/pack	Cost/pack (£)	Cost/unit (£)	Cost/year (£)
Bisoprolol	1.25	1	28	0.97	0.03	13
	2.5	1	28	0.91	0.03	12
	3.75	1	28	1.25	0.04	16
	5	1	28	0.84	0.03	11
	7.5	1	28	4.32	0.15	56
	10	1	28	0.87	0.03	11
Carvedilol	3.125	2	28	0.98	0.04	26
	6.25	2	28	1.08	0.04	28
	12.5	2	28	1.10	0.04	29
	25	2 (under 85kg) 4 (over 85kg)	28	1.27	0.05	33 66
Nebivolol	2.5	0.5 1	28	46.26	1.65	302 603
	5	1	28	1.50	0.05	20
	10	1	28	3.96	0.14	52

Sources: NHS Drug Tariff, May 2016[240]; BNF May 2016[161]

Table 37: Additional first year costs for up-titration

Description	Unit cost	Source	Notes
Community nurse specialist appointment	£50 per hour	PSSRU2014/15 [80]	10-15 minute appointment occurring every 2 weeks until maximum tolerated dose achieved.
Electrocardiogram	£52.13 (a)	NHS Reference Costs 2014/15 [242]	Undertaken in first appointment, and may be repeated at later appointments if necessary.

(a) Cost to direct access diagnostic services.

Table 38: Cost of heart failure hospitalisation

Description	Unit cost	Source	Notes

Description	Unit cost	Source	Notes
Non-elective admission for Heart Failure or Shock	£2,768	NHS Reference Costs 2014/15 [242]	Cost weighted according to units of activity for each CC group.

First year NHS costs of stroke were calculated from the Sentinel National Audit Programme: cost and cost-effectiveness analysis (unpublished report to NHS England), May 2016[181]. Costs in the audit were reported by age, sex and type of stroke (ischaemic or haemorrhagic). Using the average age and percentage of females reported in Kotecha et al. 2014[181] and an assumption that 80% of cases were ischaemic stroke, and 20% haemorrhagic stroke (committee consensus) the weighted costs are presented below.

Table 39: First year costs of stroke

Initial NIHSS	Weighted average cost per patient (a)(b)
0	£7,866
1-4	£9,110
5-15	£14,914
16-20	£19,404
21-42	£15,789

(a) Assuming mean age = 69 costs are reported for the age group 65-74 years[181]and assuming 19% female population [181].
(b) Assuming 80% ischaemic stroke, 20% haemorrhagic stroke (committee consensus).

6.2.2.5 Evidence statements

Clinical

One study was identified for inclusion within the review. The study consisted of an IPD meta-analysis which included data from 9 trials. The trials compared the effectiveness of beta-blockers with placebo in addition to usual care in people with chronic heart failure and atrial fibrillation. The meta-analysis included 4 studies comparing carvedilol and placebo; 2 studies comparing metoprolol and placebo; 2 studies comparing bisoprolol and placebo and 1 study comparing nebivolol and placebo. All-cause mortality (9 studies; n=2666) was rated as moderate quality evidence, no clear effect was shown with the confidence interval ranging from a decrease and increase in all-cause mortality. First heart-failure related admission was rated as moderate quality evidence (due to the indirectness of the outcome which did not report all-cause admissions as per the protocol) and showed no clinically important effect of beta-blockers (1 study; n=2616). Fatal and non-fatal stroke (1 study; n=2616) was rated as low quality evidence due to imprecision (as the confidence intervals surrounding the point estimate were wide). An absolute effect for this outcome could not be calculated as only the summary statistic was reported by the authors of the study with no report of event rates.

No evidence was identified for the outcomes quality of life or improvement in NYHA class.

Economic

- No relevant economic evaluations were identified.

6.2.2.6 Recommendations and link to evidence

Recommendations	**No recommendation.**
Research recommendation	**What is the clinical and cost-effectiveness of beta blockers in patients with heart failure with reduced ejection fraction who are in atrial fibrillation?**

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Relative values of different outcomes	The committee considered the following outcomes as critical for this review: all-cause mortality, quality of life and all-cause hospitalisation. Data on all-cause mortality and all-cause hospitalisation were considered preferable to data limited to heart-failure related mortality and hospitalisations, as such data take into account the broader unintended consequences of the interventions (for example, an increase in mortality or hospitalisations due to adverse events). The committee agreed that cardiovascular mortality and heart failure related hospital admissions would be considered if the all-cause data was not available. The following outcomes were considered important: improvement of NYHA class and adverse events (stroke, bradycardia and hypotension). Overall, the committee considered that all-cause mortality was the most essential of the critical outcomes for decision making. No evidence was found for the following outcomes: quality of life, improvement of NYHA class, bradycardia and hypotension.
Quality of the clinical evidence	The only included study was an individual patient data meta-analysis (IPD). The quality of the evidence ranged from high to low quality across the outcomes. The committee agreed that all-cause mortality was the most essential of the critical outcomes. The quality of the evidence for this outcome was moderate due to imprecision of the confidence interval around the point estimate. For heart-failure related hospital admission the evidence was rated as moderate quality due to the indirectness of the outcome. This was due to the fact that this outcome would not capture those hospitalisations that may relate to the intervention but are not considered 'heart failure related'. For the adverse outcome of stroke, the quality of the evidence was rated as low due to wide confidence intervals surrounding the point estimate. Prior to commencing the review, the committee noted that only bisoprolol, carvedilol, and nebivolol were licensed for use in heart failure in the UK.
Trade-off between clinical benefits and harms	Evidence was found on the following outcomes: all-cause mortality, unplanned hospitalisation and stroke. The committee considered that all-cause mortality was the most essential of the critical outcomes for decision making and the discussion of the committee focussed on this outcome. In patients with HF-REF and atrial fibrillation, the meta-analysis showed a small increase in the number of deaths in the beta-blocker group, however, the committee were not confident in the evidence due to the wide confidence intervals around the absolute effect estimate, which ranged from a clinically important harm to a clinically important benefit of beta-blockers. Similarly, the data suggest a slight increase in the risk of stroke, but the committee was not confident in the effect estimate due to the very serious imprecision. Therefore, the committee was not confident that the evidence actually showed harm in those prescribed beta-blockers. The evidence did not show any clinically important reduction in the number of heart-failure hospitalisations in people taking beta-blockers. The committee also noted the indirectness of this outcome: the data does not take into account the broader unintended consequences of the intervention

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	such as adverse events leading to hospitalisation (for example, bradycardia). The committee noted that the uncertainty in the evidence is likely to be due to the fact that the analysis was a retrospective sub-group analysis. Due to this uncertainty the committee did not consider that they could make a recommendation for the use of beta-blockers in those with heart failure with reduced ejection fraction and atrial fibrillation. Therefore, the committee agreed to make a research recommendation for a prospective RCT to be undertaken to determine whether or not beta-blockers should be given to patients with HF-REF and AF.
Trade-off between net clinical effects and costs	No relevant economic studies were identified from the published literature. Unit costs of beta-blockers, the costs for heart-failure related hospitalisation and stroke were therefore presented to the committee for consideration of cost-effectiveness. The committee noted the high cost of low dose (2.5mg) Nebivolol, however, this beta-blocker is not commonly prescribed. If used, it is often a higher dosage that is split to gain the required dose; therefore this high cost is not always incurred. The committee discussed and agreed that an up-titration appointment would likely occur every 2 weeks and would most likely be in a community setting with a specialist nurse. The committee agreed a conservative appointment time of 30 minutes. The committee agreed to the chosen HRG codes for heart failure hospitalisation, and decided that a weighted average of these codes based on activity would be the most suitable as an average cost of heart failure hospitalisation. The committee stated that stroke events in patients with chronic heart failure and AF are likely to be of greater severity and therefore of higher cost. Given that the committee found that the clinical evidence for the use of beta-blockers compared with placebo for all outcomes was highly uncertain, the committee could not determine cost-effectiveness with any certainty, and therefore agreed to incorporate this in the research recommendation.
Other considerations	The committee decided only to review the evidence in the HF-REF and AF population, and not the HF-PEF and AF population, because there is no prognostic evidence for use of beta-blockers in HF-PEF. The committee were aware of the recent IPD published by Kotecha[180] which looked at the effect of baseline heart rate on mortality in a subgroup of people with AF treated with beta-blockers. The committee agreed that the previously reported IPD data by Kotecha[181] and the resulting data obtained directly from the trial authors was more appropriate for inclusion within the review as these summary statistics did not include the BEST trial of bucindolol versus placebo which is not licensed for any indication in the UK.

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6.2.3 Mineralocorticoid Receptor Antagonists in HFPEF

6.2.3.1 Introduction

Heart failure with preserved ejection fraction (HFpEF) is associated with myocardial stiffness and reduced ventricular filling. The mechanism for this is incompletely understood but cell hypertrophy and interstitial fibrosis can be found in myocardial biopsies of patients with HFpEF.

A number of drugs affecting parts of the renin-angiotensin pathway have been developed and shown to be effective in the treatment of heart failure with reduced ejection fraction (HFREF). Many have also been investigated in HFpEF but have not shown similar benefits so currently none of these drugs are recommended for treatment of patients with HFpEF. The mineralocorticoid aldosterone, the neurohormone produced as the final product of the renin-angiotensin system is known to promote myocyte hypertrophy and fibrosis. Inhibition through mineralocorticoid receptor antagonism has been hypothesised to counteract the underlying pathological process causing HFpEF. Spironolactone and eplerenone are mineralocorticoid receptors antagonists (MRAs) licensed for treatment of people with HFREF. New studies have investigated the role of MRAs in patients with HFpEF. The aim of this review was to examine the clinical and cost-effectiveness of MRAs in people with HFpEF.

6.2.3.2 Review question: What is the clinical and cost effectiveness of mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction?

For full details see review protocol in Appendix A.

Table 40: PICO characteristics of review question

Population	People diagnosed with heart failure with preserved ejection fraction (HFPEF).
Interventions	Mineralocorticoid receptor antagonist: • Spironolactone (up to 50mg/day) • Eplerenone (up to 50mg/day)
Comparison	Placebo
Outcomes	CRITICAL • All-cause mortality • Quality of life • Unplanned hospitalisation IMPORTANT • Improvement of NYHA class • Adverse events - Renal function • Adverse events – Gynaecomastia • Adverse events – Hypotension • Adverse events - Hyperkalaemia
Study design	Systematic Review RCT

6.2.3.3 Clinical evidence

A search was conducted for randomised controlled trials comparing the effectiveness of mineralocorticoid receptor antagonists with placebo in people with heart failure with preserved ejection fraction (HFPEF) on current standard first line treatment. Two studies (reported in 11 publications) were included in the review: Treatment Of Preserved Cardiac function heart failure with

an Aldosterone antagonist Trial (TOPCAT)[94, 199, 259, 265, 306-310] and Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF).[108, 109]. These are summarised in Table 41 below. See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

The previous guideline for chronic heart failure (CG108) included 8 studies.[5, 27, 110, 205, 264, 266-268] These studies have all been excluded within this review, because they no longer meet the review protocol. For further explanation please refer to the excluded clinical studies table (appendix I) and the Recommendations and link to evidence

Table 41: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Aldo-DHF Edelmann 2013[108, 109]	Intervention: Spironolactone (25 mg / day) Comparison: Placebo	n=422 People aged ≥ 50 years with chronic NYHA class II or III heart failure, preserved LVEF ≥ 50%, and evidence of diastolic dysfunction/atrial fibrillation. 72% on BB, 77% on ACEI or ARB.	• Mortality • Quality of life (SF-36 Physical Functioning, Minnesota Living with Heart Failure Questionnaire) • Hospitalisation • Adverse events (gynaecomastia, hyperkalaemia, renal function) • NYHA class	Length of follow up: 1 year. SF-36 global self-assessment, Patient Health Questionnaire – depression scale, and Hospital Anxiety and Depression Scale were also reported in study but have not been extracted as validated quality of life measures were also reported.
TOPCAT Pitt 2014[94, 199, 259, 265, 306-310]	Intervention: Spironolactone (15 – 45 mg / day) Comparison: Placebo	n=3445 People aged ≥ 50 years with symptomatic heart failure and LVEF ≥ 45%. 78% on BB, 84% on ACEI or ARB.	• Mortality • Quality of life (EQ5D-VAS, Kansas City Cardiomyopathy Questionnaire) • Hospitalisation • Adverse events (gynaecomastia, hyperkalaemia, renal function)	Length of follow up: 3.3 years. McMaster Overall Treatment Evaluation instrument was also used to assess quality of life but was not been extracted as validated quality of life measures were also reported.

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Table 42: Clinical evidence summary: Mineralocorticoid receptor antagonists versus placebo for heart failure with preserved ejection fraction

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Mineralocorticoid receptor antagonist (95% CI)
All-cause mortality (time to event)	3445 (1 study) 3.3 years	⊕⊕⊕⊖ MODERATE[a] due to imprecision	HR 0.91 (0.77 to 1.08)	159 per 1000	13 fewer per 1000 (from 34 fewer to 12 more)
All-cause mortality (dichotomous)	400 (1 study) 1 years	⊕⊖⊖⊖ VERY LOW[a, c] due to risk of bias, imprecision	Peto Odds Ratio 7.07 (0.14 to 356.74)	0 per 1000	[h]
Quality of life (Kansas City) Kansas City Cardiomyopathy Questionnaire. Scale from: 0 to 100.	2902 (1 study) 1 years	⊕⊕⊖⊖ LOW[c] due to risk of bias		[b]	The mean quality of life (kansas city) in the intervention groups was 1.35 higher (0.21 to 2.49 higher)
Quality of life (EQ-VAS) EQ-VAS[i]. Scale from: 0 to 100.	400 (1 study) time unclear[j]	⊕⊕⊖⊖ LOW[c] due to risk of bias		[b]	The mean quality of life (eq-vas) in the intervention group was 0.47 higher (0.27 lower to 1.21 higher)
Quality of life (MLWHF). Scale from: 0 to 105.	400 (1 study) 1 years	⊕⊕⊕⊖ MODERATE[c] due to risk of bias		The mean quality of life (minnesota) in the control groups was 21	The mean quality of life (minnesota) in the intervention groups was 0 higher (3.54 lower to 3.54 higher)
Quality of life (SF-36 Physical Functioning) SF-36 Physical Functioning scale	400 (1 study) 1 years	⊕⊕⊕⊖ MODERATE[c] due to risk of bias		The mean quality of life (sf-36 physical functioning) in the control groups was 66	The mean quality of life (sf-36 physical functioning) in the intervention groups was 2 lower (6.61 lower to 2.61 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Mineralocorticoid receptor antagonist (95% CI)
All-cause hospitalisation (count rate)	3445 (1 study) 3.3 years	⨁⨁⨁⨁ HIGH	Rate Ratio 0.94 (0.87 to 1.02)	200 events per 1000 person-years	12 fewer events per 1000 person-years (from 26 fewer to 4 more)
All-cause hospitalisation (dichotomous)	408 (1 study) 1 years	⨁⨁⨁⨀ MODERATE[a] due to imprecision	RR 1.2 (0.87 to 1.65)	245 per 1000	49 more per 1000 (from 32 fewer to 159 more)
Participants with NYHA class I status	400 (1 study) 1 years	⨁⨀⨀⨀ VERY LOW[a,c,e] due to risk of bias, indirectness, imprecision	RR 0.7 (0.29 to 1.7)	56 per 1000	17 fewer per 1000 (from 40 fewer to 39 more)
Hyperkalaemia serum potassium > or ≥ 5.5mm/L	3845 (2 studies) 1-3.3 years	⨁⨁⨁⨀ MODERATE[c] due to risk of bias	RR 2.04 (1.71 to 2.43)	83 per 1000	87 more per 1000 (from 59 more to 119 more)
Worsening renal function various[d]	3845 (2 studies) 1-3.3 years	⨁⨁⨁⨀ MODERATE[c] due to risk of bias	RR 1.53 (1.27 to 1.83)	145 per 1000	77 more per 1000 (from 39 more to 120 more)
Gynaecomastia various[f]	3845 (2 studies) 1-3.3 years	⨁⨁⨀⨀ LOW[c,e] due to risk of bias, indirectness	Peto Odds Ratio 5.23 (3.07 to 8.9)	4 per 1000	17 more per 1000 (from 8 more to 32 more)

(a) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

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(b) Unable to calculate as the control group risk was not reported.

(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias .

(d) TOPCAT used serum creatinine level ≥2 times the baseline value and above the upper limit of the normal range; ALDO-DHF used eGFR < 30mL/min/1.73m2, or eGFR decrease > 15mL/min/1.73m2 versus baseline.

(e) Downgraded by 1 increment because the study had indirect outcomes.

(f) TOPCAT: Breast tenderness or enlargement leading to study drug discontinuation; ALDO-DHF: "Gynaecomastia" (not defined)

(g) Unable to calculate as there were zero events in the control arm.

(h) Not the full EQ-5D, just the VAS component.

(i) Time outcome reported unclear. Study states that 'impacts of therapy on changes in [the scores] over time were examined using a repeated-measure analysis of covariance (using all follow-up time points (4, 12, 24, 36, 48 and 60 months))'.

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6.2.3.4 Economic evidence

Published literature

No relevant health economic studies were identified.

Unit costs

In the absence of any economic analysis, unit costs are presented in Table 43 below for consideration of cost effectiveness. Additional costs are likely to be incurred in the first year of initiation due to up-titration. These costs are presented in Table 44.

Table 43: Unit costs of Mineralcorticoid receptor antagonists

Drug	Mg/unit	Units/day	Units/pack	Cost/pack (£)	Cost/unit (£)	Cost/year (£)
Spironolactone	25	1	28	1.40	0.05	18
	50	1	28	3.16	0.11	41
Eplerenone	25	1	28	3.99	0.14	52
	50	1	28	5.10	0.18	66

Source: NHS Drug Tariff, May 2017[93, 239, 240]*,*

Table 44: Unit costs of up-titration

Description	Unit cost	Source
Nurse specialist appointment in community setting (a)	£91 per hour of client contact	PSSRU2014/15[80]
Phlebotomy (b)	£3	NHS Reference costs 2014/15[242]

(a) 30 minute appointment occurring every 4 weeks until maximum tolerated dose achieved.
(b) Direct access service (community).

In addition, the unit costs of all cause hospitalisation and acute kidney injury are presented in Table 45 below. The GC agreed that the cost of acute kidney injury treatment would be typical for a chronic heart failure population experiencing hyperkalaemia or worsening renal function.

Table 45: Unit costs of clinical outcomes

Description	Code	Unit cost	Source
All-cause hospitalisation (non-elective)	-	£2,930	NHS Reference costs 2014/15[242]
Acute kidney injury (with and without interventions)	LA07H-P	£2,337(a)	NHS Reference costs 2014/15[242]

(a) Weighted using the activity reported for each of the included HRG codes.

6.2.3.5 Evidence statements

Clinical

Two studies (reported in 11 publications), comparing MRAs with placebo in people with heart failure with preserved ejection fraction on current standard first line treatment, were identified for inclusion within the review. Both studies compared spironolactone with placebo. The quality of the evidence ranged from high to very low. Evidence was downgraded due to a number of contributory factors including risk of bias, imprecision due to wide confidence intervals surrounding the effect estimate

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and indirectness of the reported outcomes. All-cause mortality (n=3445) was rated as moderate quality with the confidence interval ranging from a decrease and increase in all-cause mortality hHigh quality evidence was found for all-cause hospitalisation (count rate) (n=3445), and showed a clinically important reduction with MRAs (associated with wide confidence intervals around the effect estimate). Moderate quality evidence was found for the outcomes QoL as measured by the MLWHF (n=400) and SF-36 physical functioning component (n=400), all-cause hospitalisation (dichotomous) (n=408), hyperkalaemia (n=3845) and worsening renal function (n=3845). For both the moderate quality QoL outcomes there was no clinical effect of MRAs. For the remaining moderate quality outcomes there was a clinically important increase in hospitalisations (associated with wide confidence intervals around the effect estimate), hyperkalaemia and worsening renal function with MRAs. The remaining outcomes were all rated as low or very low quality. These included all-cause mortality (dichotomous), QoL as measured by the KCCQ and EQ5D-VAS, number of participants with NYHA class I status and gynaecomastia. All of these outcomes showed no clinical effect of MRAs.

Economic

- No relevant economic evaluations were identified.

6.2.3.6 Recommendations and link to evidence

Research recommendation	No recommendation
Relative values of different outcomes	The committee considered the following outcomes to be critical for this review: all-cause mortality, quality of life, and all-cause hospitalisation. Data on all-cause mortality and hospitalisation were considered preferable to data limited to heart-failure related mortality and hospitalisations, as all-cause takes into account the broader unintended consequences of the interventions (for example, an increase in mortality or hospitalisations due to adverse events). Improvement of NYHA class and specified adverse events (hyperkalaemia, renal function, hypotension, and gynaecomastia) were also considered to be important for decision-making. Evidence was identified for all outcomes except for hypotension.
Quality of the clinical evidence	The evidence for the critical outcome of all-cause mortality (measured as time to event) was moderate quality, though the confidence intervals around the absolute effect were imprecise, ranging from 34 fewer deaths to 12 more deaths per 1000 individuals. Time to event data could not be extracted from the smaller included study, so dichotomous data was extracted instead, which was very low quality due to risk of bias and very serious imprecision (no events occurred in the placebo arm and only one event in the intervention arm). The evidence for the critical outcome of quality of life ranged from moderate to low quality due to risk of bias stemming from the reporting of the data. The evidence on all-cause hospitalisation (measured as a count rate – number of events) was high quality, while the evidence from the second smaller study was reported as number of participants with events and was moderate quality due to imprecision. The evidence was of moderate quality for the important outcomes of hyperkalaemia and worsening renal function (due to risk of bias caused by likely underestimation of the frequency of events) and was of low quality for

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Research recommendation	No recommendation
	gynaecomastia (due to risk of bias and indirectness again due to likely underestimation of the incidence of events). Evidence quality was very low for improvement in NYHA class (due to risk of bias, indirectness and imprecision), meaning that the committee placed little weight on this outcome in their decision making.
Trade-off between clinical benefits and harms	There was moderate quality evidence estimating 13 fewer deaths per 1000 patients and high quality evidence estimating12 fewer hospitalisations per 1000 patients per year in people taking mineralocorticoid receptor antagonists (MRAs). The committee noted that although the confidence intervals were mostly indicating beneft there was also indication of increased mortality and hospitalisation.. There was also moderate quality evidence (from a smaller study that did not report number of events) that suggested an increase in the number of patients hospitalised for any cause in the intervention group compared to the placebo group, though this evidence was imprecise. Based on the body of evidence, the committee concluded that it was unclear whether MRAs have a clinical benefit, a clinical harm, or no effect on mortality and hospitalisation in this population. The committee discussed the clinically important harm of MRAs on renal function (estimate of 77 more patients experiencing worsening renal function per 1000 in the intervention group) and hyperkalaemia (estimate of 87 more per 1000). They also noted the increased risk of gynaecomastia in patients taking spironolactone (estimate of 17 more per 1000), and that all of these effect estimates were subject to a high risk of bias likely to underestimate the effect. The committee also acknowledged that the use of MRAs had no clinically important impact on quality of life or NYHA class. The committee was aware that post hoc analyses of the principle trial (TOPCAT) suggested a considerable degree of heterogeneity within the population recruited and that MRAs might habe differential effcts in the different groups. Due to the uncertainties around any possible benefit of MRAs on mortality and hospitalisations in this population, a lack of alternative treatments and the clinically important risk of deteriorating renal function and hyperkalaemia, the committee was uncertain about the affect of MRAs in HFPEF but aware they were used in clinical practice. Therefore it was decided not to make a clinical recommendation on the use of MRAs in this population pending further evidence.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified for chronic heart failure patients with preserved ejection fraction and therefore unit costs were presented to the committee for consideration. This included annual drug costs: spironolactone (25mg: £18, 50mg: £41) and eplerenone (25mg: £52, 50mg: £66); dose up-titration, including 30 minute appointment with a specialist nurse (£45.50) and blood tests (£3), and the costs of all cause hospitalisation (£2,930) and acute kidney injury (£2,337). The committee noted that there could be potential cost savings from a reduced number of all cause hospitalisations for those treated with MRAs; however, as mentioned above, the clinical evidence for this outcome is uncertain. The committee also noted the greater number of acute kidney injury (AKI) events occurring in those treated with MRAs and agreed that the high cost of AKI would likely outweigh any potential cost savings from

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Research recommendation	No recommendation
	reduced hospitalisation. Due to the uncertainty on the clinical benefit of MRAs in this population, and the lack of published economic evaluations, the committee could not make a clear judgement on the cost-effectiveness of MRAs for those with chronic heart failure with preserved ejection fraction and therefore did not make a recommendation.
Other considerations	The majority of the evidence in this review was from the TOPCAT trial[265] – a large, high quality study comparing spironolactone with placebo in patients with heart failure with preserved ejection fraction. The main report of this study was published in 2014, but the committee was aware of the subsequent post-hoc analyses of this study investigating regional variation in the results[259]. The post-hoc analyses noted a substantial (~4 fold) difference in the primary composite outcome (time to cardiovascular death, aborted cardiac arrest, or hospitalisation for heart failure), as well as substantial differences in baseline characteristics, between patients randomised from Russia and Georgia compared with patients from the United States, Canada, Brazil and Argentina (the Americas). In the Americas, a substantial and clinically important reduction in the primary composite outcome was seen in patients with a phenotype more typical of HFPEF as defined in the UK. A similar difference was found across the other clinical outcomes recorded. In the post-hoc analysis, the study authors examined the baseline characteristics and responses to treatment in each region, and speculated that the clinical diagnostic criteria for heart failure with preserved ejection fraction were not uniformly interpreted or applied. It noted that the death rate of the cohort from Russia/Georgia was more reflective of the general population than of patients with heart failure. The authors concluded that 2 distinctly different populations were enrolled in the 2 regions. The authors acknowledged that the overall neutral finding of TOPCAT would generally be considered the most reliable result of the trial, and that their post-hoc analysis should not be considered definitive. However, they concluded that the findings from the post-hoc analysis "may be informative to those currently faced with clinical decisions for patients with heart failure with preserved ejection fraction with anticipated risk profiles similar to those enrolled in the Americas". The committee discussed the findings of the post-hoc analysis and agreed that, while interesting, it was not sufficient to support any recommendation to use MRAs in this population. Post-hoc subgroup analyses, while useful in hypothesis generation, are generally at high risk of bias and should always be interpreted with great caution. The previous guideline for chronic heart failure (CG108) included 8 studies which are referenced in the clinical review. These studies have all been excluded within this review as they no longer meet the review protocol. The committee discussed the current protocol for this review question and agreed that the previously included studies, which had a population of people with heart failure post myocardial infarction, were not appropriate for consideration within the review as these people represented a

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Research recommendation	No recommendation
	significantly different population. In addition to this the committee agreed that the minimum duration of follow-up for included studies should be 6 months to ensure an accurate clinical effect can be established. In addition to this the committee agreed that cross-over studies should be excluded to ensure that potential carryover effects are not confounding the outcome. The committee noted that a prospective randomised registry-based trial in HFPEF was due to start recruiting (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction (SPIRRIT) that would help answer the questions in this field.

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6.2.4 Mineralocorticoid Receptor Antagonists in HFREF

6.2.4.1 Introduction

The renin-angiotensin system and its products play a key role in the pathogenesis of heart failure. The final product of this pathway is the neurohormone aldosterone is involved in cardiac fibrosis, sodium retention and other pathways leading to deterioration in heart failure. Mineralocorticoid receptor antagonists (MRA) block the action of aldosterone leading to a potent diuretic effect and may also inhibit aldosterone-stimulated fibrosis in the myocardium. The two licensed MRAs are spironolactone and eplerenone.

Studies published since the last update of this guideline in 2010 have investigated whether MRA therapy would result in clinical benefits in the general population of patients with heart failure with reduced ejection fraction (HFREF) as opposed to those post-acute myocardial infarction or with highly symptomatic disease. Nonetheless, MRAs like other drugs affecting the renin-angiotensin-aldosterone pathway (including ACE-Is and ARBs) have the potential to induce adverse events including electrolyte disturbances (particularly hyperkaleaemia) and worsening renal dysfunction resulting in increased morbidity and hospitalisations. Concerns about their adverse effects and uncertainty about their benefits have reduced the uptake of these medications in clinical practice. The aim was to review the evidence for the clinical and cost-effectiveness of MRAs in people with HFREF.

6.2.4.2 Review question: What is the clinical and cost effectiveness of adding a mineralocorticoid receptor antagonist to existing standard first line treatment in people with heart failure with reduced ejection fraction?

For full details see review protocol in Appendix L.

Table 46: PICO characteristics of review question

Population	People diagnosed with heart failure with reduced ejection fraction (HFREF).
Interventions	Mineralocorticoid receptor antagonist: • Spironolactone (up to 50mg/day) • Eplerenone (up to 50mg/day)
Comparison	Placebo
Outcomes	CRITICAL • All-cause mortality • Quality of life • Unplanned hospitalisation IMPORTANT • Improvement of NYHA class • Adverse events - Renal function • Adverse events – Gynaecomastia • Adverse events – Hypotension • Adverse events - Hyperkalaemia
Study design	Systematic Review RCT

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6.2.4.3 Clinical evidence

A search was conducted for randomised controlled trials comparing the effectiveness of mineralocorticoid receptor antagonists with placebo in in people with heart failure with reduced ejection fraction (HFREF) on current standard first line treatment. Four studies (reported in 13 papers) were included in the review: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[71, 113, 132, 184, 287, 288, 377, 378], EMPHASIS-HF in Japanese patients (J-EMPHASIS-HF)[343], Randomized Aldactone Evaluation Study (RALES)[268, 350, 351] and Udelson 2010[345]. These are summarised in Table 47 below. Three of the included studies compared eplerenone with placebo and one study compared spironolactone with placebo. Evidence from these studies is summarised in the clinical evidence summary below (Table 48). See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

The majority of patients in the RALES study[268, 350, 351] were not taking beta-blockers as background medication, as the study was conducted prior to beta-blockers being mainstream first line treatment. Because of this, any evidence of a beneficial effect of adding MRAs to 'first line therapy' from this study would likely be overestimated. The evidence has therefore been downgraded for indirectness for the efficacy outcomes where the RALES study makes up the majority of the evidence.

The previous guideline for chronic heart failure (CG108) included 8 studies.[5, 27, 110, 205, 266, 268, 264, 267]. Seven of these studies[5, 27, 110, 205, 264, 266, 267] have been excluded within the current review, because they no longer meet the review protocol. For further explanation please refer to the excluded clinical studies table (appendix I) and the Recommendations and link to evidence.

Table 47: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
EMPHASIS-HF Zannad 2011[71, 113, 132, 184, 287, 288, 377, 378]	Intervention: Eplerenone (up to 50 mg / day) Comparison: Placebo	n=2737 People aged ≥ 55 years with NYHA class II heart failure and LVEF ≤ 30% (or ≤ 35% if also QRS duration >130msec), treatment with ACEI, ARB or both and a BB (unless contraindicated) at the recommended maximum dose. 87% on BB, 93% on ACEI and/or ARB. Patients were within 6 months of hospitalisation for CV reason (or high levels of BNP/NTpro-BNP).	• Mortality • Hospitalisation • Adverse events (renal function, hyperkalaemia, hypotension, gynaecomastia/breast pain)	Mild heart failure population. Trial was stopped prematurely according to pre-specified rules after a median follow-up period of 21 months.
J-EMPHASIS-HF	Intervention: Eplerenone (up to 50	n=221 People aged ≥ 55	• Mortality • Hospitalisation	EMPHASIS-HF trial in a Japanese population.

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Study	Intervention and comparison	Population	Outcomes	Comments
Tsutsui 2017[343]	mg / day) Comparison: Placebo	years with NYHA class II heart failure or higher, and LVEF ≤ 30% (or ≤ 35% if also QRS duration >130msec), treatment with ACE inhibitor, ARB, β-blocker, or diuretic. Patients were within 6 months of hospitalisation for CV reason (or high levels of BNP/NTpro-BNP).	• Adverse events (renal impairment, hyperkalaemia, hypotension, gynaecomastia)	Higher incidence of diabetes, angina pectoris and coronary artery bypass grafting in the placebo group. Maximum of 4 yrs intervention plus 1 year follow-up.
RALES Pitt 1999[268, 350, 351]	Intervention: Spironolactone (up to 50 mg / day) Control: Placebo	n=1663 People with NYHA class IV heart failure in previous six months (class III or IV at time of enrolment) and LVEF ≤ 35%, treatment with ACEI, loop diuretic and (in most cases) digoxin. 11% on BBs, 95% on ACEI.	• Mortality • Hospitalisation (for cardiac causes) • Change in NYHA class • Adverse events (renal function, gynaecomastia, hyperkalaemia)	Severe heart failure population. Most patients not on beta-blockers. Trial was stopped early based on the interim results and the 'advice of the data and safety monitoring board'. Trial had a mean follow-up period of 24 months. Trial included in 2010 guideline.
Udelson 2010[345]	Intervention: Eplerenone (50 mg / day) Control: Placebo	n=226 People aged ≥ 21 years with NYHA class II or III health failure and LVEF ≤ 35%, treatment with ACEI and/or ARB and BB (unless documented intolerance). 95% on BB, 97% ACEI and/or ARB.	• NYHA class • Adverse events (hyperkalaemia, renal function, hypotension)	Moderate severity heart failure population. Quality of life (Kansas City) results not extracted as only reported narratively (p value).

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Table 48: Clinical evidence summary: Mineralocorticoid receptor antagonists versus placebo for heart failure with reduced ejection fraction

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Mineralocorticoid receptor antagonist (95% CI)
All-cause mortality	4621 (3 studies) 1-2 years	⊕⊖⊖⊖ VERY LOW[a, b, c] due to inconsistency, indirectness, imprecision	HR 0.78 (0.61 to 1.00)	155 per 1000[d]	32 fewer per 1000 (from 57 fewer to 0 more)
All-cause hospitalisation	4400 (2 studies) 1.75-2 years	⊕⊖⊖⊖ VERY LOW[a, b,j] due to indirectness, imprecision, inconsistency	Rate Ratio 0.79 (0.71 to 0.87)	397 events per 1000 person-years[d]	83 fewer events per 1000 person years (from 52 fewer to 115 fewer)
Hospitalisation for any cause (dichotomous)	221 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW[b,e] due to risk of bias, imprecision	RR 0.77 (0.58 to 1.02)	527 per 1000	121 fewer per 1000 (from 221 fewer to 11 more)
Change in NYHA class - Improved	1456 (2 studies) 0.7-2 years	⊕⊖⊖⊖ VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision	RR 1.27 (1.1 to 1.46)	330 per 1000[f]	89 more per 1000 (from 33 more to 152 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Mineralocorticoid receptor antagonist (95% CI)
Hyperkalaemia various[g]	4786 (4 studies) 0.7-2 years	⊕⊕⊖⊖ LOW[e, h] due to risk of bias, inconsistency	RR 1.97 (1.18 to 3.27)	64 per 1000	62 more per 1000 (from 12 more to 145 more)
Renal function (change in creatinine (umol / L) - continuous)	2729 (1 study) 1.75 years	⊕⊕⊕⊖ MODERATE[e] due to risk of bias		The mean renal function (change in creatinine (umol / l) - continuous) in the control groups was 3.5 umol/L	The mean renal function (change in creatinine (umol / l) - continuous) in the intervention groups was 4.5 higher (1.94 to 7.06 higher)
Renal function (change in eGFR (ml/min/173m^2) - continuous)	2737 (1 study) 1.75 years	⊕⊕⊕⊖ MODERATE[e] due to risk of bias		The mean renal function (change in eGFR (ml/min/173m^2) - continuous) in the control groups was -1.29 ml/min/1.73 m^2	The mean renal function (change in eGFR (ml/min/173m^2) - continuous) in the intervention groups was 1.89 lower (3.26 to 0.52 lower)
Renal function (creatinine increased - dichotomous)	226 (1 study) 0.7 years	⊕⊖⊖⊖ VERY LOW[b, e] due to risk of bias, imprecision	RR 1.71 (0.65 to 4.46)	55 per 1000	39 more per 1000 (from 19 fewer to 190 more)
Renal function (30% reduction in eGFR (ml/min/1.73 m^2) from baseline)	1663 (1 study) 3 months	⊕⊕⊖⊖ MODERATE[e] due to risk of bias	RR 2.43 (1.82 to 3.24)	70 per 1000	100 more per 1000 (from 58 more to 157 more)
Renal impairment (not defined)	221 (1 study) 1 years	⊕⊖⊖⊖ VERY LOW[b,e] due to risk of bias, imprecision	RR 0.5 (0.18 to 1.4)	91 per 1000	46 fewer per 1000 (from 75 fewer to 36 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Mineralocorticoid receptor antagonist (95% CI)
Renal failure (not defined)	2729 (1 study) 1.75 years	⊕⊖⊖⊖ VERY LOW[b,e] due to risk of bias, imprecision	RR 0.93 (0.6 to 1.44)	30 per 1000	2 fewer per 1000 (from 12 fewer to 13 more)
Gynaecomastia - Spironolactone	1217 (1 study) 2 years	⊕⊕⊕⊖ MODERATE[e] due to risk of bias	RR 7 (3.36 to 14.57)	13 per 1000	78 more per 1000 (from 31 more to 177 more)
Gynaecomastia (or other breast disorders) - Eplerenone	2950 (2 studies) 1-1.75 years	⊕⊖⊖⊖ VERY LOW[b,e] due to risk of bias, imprecision	Peto odds ratio 0.72 (0.32 to 1.61)	5 per 1000	1 fewer per 1000 (from 3 fewer to 3 more)
Hypotension	3176 (3 studies) 0.7-1.75 years	⊕⊕⊖⊖ LOW[b,e] due to risk of bias, imprecision	RR 1.22 (0.84 to 1.78)	37 per 1000[f]	8 more per 1000 (from 6 fewer to 29 more)

(a) Downgraded by one increment as the majority of the evidence included an indirect population (not on beta-blockers).

(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

(c) Downgraded by 1 increment because: Heterogeneity, I2=63%, unexplained by subgroup analysis.

(d) Control group risk based on risk reported in EMPHASIS, as that population were on current first line treatment including beta-blockers.

(e) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(f) Control group risk based on risk reported in EMPHASIS, as it carries the vast majority of the weight in the meta-analysis.

(g) EMPHASIS - serum potassium > 5.5 mmol/L. RALES – serum potassium ≥ 5.5 mmol/L. Udelson 2010 - no definition. Tsutsui 2017 – no definition.

(h) Downgraded by 1 or 2 increments because: Heterogeneity, I2=79%, p=0.002, unexplained by subgroup analysis.

(i) Peto odds ratio due to zero events in one trial.j Downgraded by 1 increment because: Heterogeneity, I2=59%, unexplained by subgroup analysis.

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6.2.4.4 Economic evidence

Published literature

No economic evaluations were identified in the 2003 guideline (CG5). Two studies were included in the 2010 guideline update (CG108): one Irish cost-effectiveness study assessing the addition of spironolactone to optimal medical treatment based on the RALES trial for patients with severe heart failure (NYHA class III-IV) and LVSD,[334] which is included in this review and is summarised in the health economic profile below (Table 49) and the health economic evidence table in Appendix G; and one UK cost-effectiveness study assessing the addition of eplerenone to optimal medical treatment based on the EPHESUS trial for patients with heart failure and LVSD, post-acute myocardial infarction[107] which has been excluded from this review as this population is no longer included in the scope of this guideline. This population is now covered in the Acute Heart Failure guideline (CG187).

Five additional health economic studies were identified with the relevant comparison from the update searches. One study is included in this review, and is summarised in the health economic evidence profile below (Table 49) and the health economic evidence tables in Appendix G. [194] The other studies were selectively excluded due to the availability of more applicable evidence. [2, 3,21,332] These are listed in Appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix D.

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Table 49: Health economic evidence profile: Mineralocorticoid receptor antagonists versus placebo for heart failure with reduced ejection fraction

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Lee 2014 [194] (UK)	Directly applicable[(a)]	Potentially serious limitations[(b)]	• Discrete event simulation model using EMPHASIS-HF RCT trial data. • Two comparators: 1. Standard therapy (ACEi and BB) 2. Eplerenone (starting dose of 25mg daily increased to 50mg daily after 4 weeks) in addition to standard therapy. • Trial follow-up: 4 years • Lifetime time horizon modelled	£4,284	1.22	£3,520 per QALY gained	Eplerenone remained cost-effective after undertaking both deterministic and probabilistic sensitivity analysis. Two scenario analyses using EMPHASIS-HF data with no extrapolation and another using only a 2 year time horizon generated ICERs of £20,730 and £20,101 per QALY gained, respectively. In all other scenario analyses eplerenone remained cost-effective.
Tilson 2003 [107]	Partially applicable[(c)]	Potentially serious limitations[(d)]	• Cost effectiveness analysis reporting cost per life year gained • Two comparators: 1. Optimal medical management (might include diuretics, ACEi, digoxin, BB, or a combination of these) 2. Spironolactone added to optimal medical management • Time horizon: 10 years	NR	NR	£291/ LY gained[(e)]	Two-way sensitivity analysis – variation of probabilities of death (0.16, 0.21) and hospitalisation (0.21, 0.29): from £193/LY to £390/LY One-way sensitivity analysis – additional outpatient visits required to initiate medication for spironolactone group (1, 2, 4): from £291/LY to £710/LY One-way sensitivity analysis – cost of hospitalisation varied (£663; £5826): from £455/LY to spironolactone cohort dominates (it is more effective and less costly than) the placebo cohort.

Abbreviations: ACEi = Angiotensin-converting enzyme inhibitor; BB = Beta-blockers; CHF = chronic heart failure; ICER: incremental cost-effectiveness ratio; LYG =life year Gained; NYHA = New York Heart Association Classification; QALY: quality-adjusted life years; RALES = Randomised Aldactone Evaluation Study; RCT: randomised controlled trial.

(a) UK NHS perspective, however HRQoL is not reported directly from patients the trial analysis is based upon.

(b) The analysis is based on estimates of relative treatment effect and resource use from a single study, so does not reflect all available evidence in this area. There is cross-over between the trial arms. Utility values are not reported directly from patients of the EMPHASIS-HF trial. Potential bias due to the sponsor of the study.

(c) Analysis developed from an Irish perspective, a healthcare system reasonably comparable to the UK NHS; Population assessed limits the generalisation of results. There is also some uncertainty regarding the applicability of resource use and costs from the Irish NHS in 2003 to current NHS setting.

(d) Outcomes were not reported as QALYs; Incremental cost and incremental effect were not reported.

(e) Using the utility score proposed by Mant 2009[212] of 0.65 for patients with heart failure, we estimated the threshold in cost per LYG equivalent to the £20,000 per QALY gained, proposed by NICE, to be £13,000 per LYG.

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6.2.4.5 Evidence statements

Clinical

Four studies (reported in 13 publications), comparing MRAs with placebo in people with heart failure with reduced ejection fraction on current standard first line treatment, were identified for inclusion within the review. Three of the studies compared eplerenone with placebo and one study compared spironolactone with placebo. The quality of the evidence ranged from moderate to very low. Evidence was downgraded due to a number of contributory factors including risk of bias, imprecision due to wide confidence intervals surrounding the effect estimate and indirectness of the reported outcomes. Moderate quality evidence was found for the outcomes renal function as measured by a 30% reduction in eGFR from baseline (n=1663) and gynaecomastia as a result of spironolactone use (n=1217), and low quality evidence was found for the outcome hyperkalaemia (n=4786), all of which showed a clinically important harm with the use of MRAs. Moderate quality evidence was also found for the outcomes renal function as measured by change in creatinine (n=2729) and renal function as measured by change in eGFR (n=2737), both of which showed no clinically important effect with the use of MRAs. The outcomes all-cause mortality (n=4621), hospitalisation for any cause (dichotomous) (n=221) and all-cause hospitalisation (n=4400) were rated as very low quality for the first two and low quality for the latter, and showed a clinically important reduction in deaths with the use of MRAs (associated with wide confidence intervals around the effect estimate). The outcome change in NYHA class (n=1456) was rated very low quality and also showed a clinically important benefit with MRA use. Three of these outcomes (all-cause mortality, all-cause hospitalisation and Change in NYHA class – Improved) were downgraded for indirectness due to the fact that the majority of people included were not taking beta-blockers as concomitant medication. As a result of this, it is likely that any evidence of a beneficial effect of adding MRAs to 'first line therapy' may have been overestimated for these outcomes. Yet, the outcome hospitalisation for any cause (dichotomous) showed the same effect in a different population albeit with a much smaller sample size (n=221) (associated with wide confidence intervals around the effect estimate). The outcome renal impairment (not defined) (n=221) was of very low quality and showed a clinical benefit of MRA. The remaining outcomes, renal function as measured by increased creatinine (n=226), renal failure (n=2729), gynaecomastia (n=2950) and hypotension (n=3176) were all rated as low or very low quality and showed no clinical effect with MRAs.

Economic

- One cost-utility analysis found that eplerenone in addition to standard therapy is cost effective compared to standard therapy alone for those with heart failure with reduced ejection fraction (ICER: £3,520). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-effectiveness analysis found that spironolactone in addition to optimal medical management is more costly and more effective than optimal medical management alone. This was assessed as partially applicable with potentially serious limitations.

6.2.4.6 Recommendations and link to evidence

Recommendations	**Offer a mineralcorticoid receptor antagonist (MRA), in addition to an angiotensin-converting enzyme (ACE) inhibitor (or ARB) and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. [2018]** **Measure serum sodium and potassium and assess renal function before**

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	and after starting an MRA and after each dose increment.[2018] **Measure blood pressure before and after each dose increment of an MRA. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]** **Once the target, or maximum tolerated, dose of an MRA is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2018]**
Relative values of different outcomes	The committee considered the following outcomes to be critical for this review: all-cause mortality, quality of life, and all-cause hospitalisation. Data on all-cause mortality and hospitalisation were considered preferable to data limited to heart-failure related mortality and hospitalisations, as such data take into account the broader unintended consequences of the interventions (for example, an increase in mortality or hospitalisations due to adverse events). Improvement of NYHA class and specified adverse events (hyperkalaemia, renal function, hypotension, and gynaecomastia) were also considered to be important for decision-making. Evidence was identified for all outcomes except for quality of life. The evidence for eplerenone and spironolactone was analysed together for all outcomes except for gynaecomastia, where the 2 interventions were analysed separately due to gynaecomastia being a common adverse effect of spironolactone but an uncommon effect of eplerenone.
Quality of the clinical evidence	The evidence for the critical outcomes of all-cause mortality, all-cause hospitalisation and hospitalisation for any cause (dichotomous) was graded low to very low quality due to indirectness (the majority of the evidence was from a population not on beta-blockers), imprecision (based on the confidence intervals around the relative effect) and inconsistency (due to heterogeneity in the case of all-cause mortality caused by a study with a small sample size). However, the committee noted that for all-cause mortality and all-cause hospitalisation, the confidence intervals around the absolute effect were reasonably narrow and the committee was confident that in each case that there was a clinically important effect. The quality of the evidence for the important outcomes ranged from moderate to very low. For the adverse event of hyperkalaemia, the quality of the evidence was low, due to inconsistency and risk of bias which likely underestimated the incidence of hyperkalaemia (as the incidence of hyperkalaemia of 7 % was far exceeded by the rate of drug discontinuation of 17%). For deterioration in renal function, the quality of the evidence varied, with the majority of the evidence being of moderate quality, again due to risk of bias. The quality of the evidence for gynaecomastia was moderate for spironolactone due to risk of bias which likely underestimated the incidence of the event, and very low for eplerenone due to risk of bias and imprecision (though regarding the latter, the committee noted that there was no serious imprecision in the confidence intervals around the estimated absolute effect). The quality of the evidence for hypotension was low due to risk of bias and imprecision. The quality of evidence for change in NYHA class was very low due to risk of bias, indirectness and imprecision, and so it did not weigh heavily in decision making.

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Trade-off between clinical benefits and harms	The use of mineralocorticoid receptor antagonists (MRAs) led to a clinically important reduction in mortality and hospitalisations, and possibly an improvement in NYHA class. However, MRAs also led to a clinically important increase in the number of patients experiencing hyperkalaemia. There was also some evidence of worsening renal function and an increase in hypotension in patients using MRAs, though this evidence was mixed and mostly suggested a difference of insufficient magnitude to be clinically important. The use of spironolactone was associated with a clinically important increase in gynaecomastia. This was not the case for eplerenone, where the very low quality evidence suggested that there was no clinically important difference. The committee agreed that there was likely to be no clinically important difference between the eplerenone and placebo group. Overall, the beneficial effects of MRAs on mortality and hospitalisation outweighed the risk of hyperkalaemia and the possible impact on renal function. The committee acknowledged that the quality of the evidence on the risk of hyperkalaemia and renal function impairment was affected by the risk of bias, which may have led to an underestimation of the actual risk of hyperkalaemia/renal impairment in this population (as there was a proportion of participants who discontinued the study drug but remained in the study, and due to the strict inclusion criteria). The potential underestimation of these risks is confirmed by the results of other studies, which suggest a higher rate of these adverse events in patients using MRAs Juurlink 2004[164]. However, these risks can be managed by starting patients on appropriate doses, measuring patients' potassium levels and renal function at baseline and monitoring those levels regularly, and appropriate dose adjustment (see NICE Acute Kidney Injury guideline CG169). Patients with chronic renal impairment and hence the lowest eGFR appear to be those who have the most to gain in terms of mortality benefit. There is, however, a small cohort of patients who may experience a clinically significant deterioration in renal function and this highlights the need for baseline measurement and meticulous monitoring and follow-up by someone with specific expertise in managing heart failure and acute kidney injury. The committee acknowledged the evidence of an increased risk of gynaecomastia in patients taking spironolactone, but noted that the majority of patients did not experience this adverse event. Clinicians should consider switching to eplerenone in patients who experience gynaecomastia while taking spironolactone. Switching should be considered as part of shared decision making, as the value placed on avoiding gynaecomastia varies from patient to patient. Overall, the clinically important reduction in all-cause mortality and hospitalisation supported a recommendation to offer MRAs to all people with HFREF who remain symptomatic despite treatment with beta-blockers and ACE inhibitors. The committee also recommended baseline measurement and regular monitoring of patients' renal function and potassium levels, as well as drug interactions, and that clinicians seek specialist advice in the case of deterioration (rather than automatically discontinuing the MRA). The committee discussed the intervals at which patients taking MRAs should

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	be monitored and agreed that this should take place before starting an MRA, 1-2 weeks after commencing the medicine and after each dose increment. Once a person had reached their target or highest tolerated dose they should be monitored monthly for 3 months to ensure no adverse effects. After this, the committee agreed that 6 monthly monitoring was sufficient or when a person became acutely unwell. The importance of measuring blood pressure after each dose increment was also stressed by the committee as postural hypotension was a common cause of hospital admission in the elderly. For further explanation of the monitoring recommendations please see section 4.3.8 of the methodology section of the guideline and appendix D.
Trade-off between net clinical effects and costs	Two relevant economic analyses were identified that compared the additional use of mineralcorticoid receptor antagonists to optimal medical management. One UK economic evaluation assessed the addition of eplerenone to optimal medical management based on the EMPHASIS-HF trial included in the clinical review. This analysis found that the addition of eplerenone to optimal medical management was more effective and more costly than optimal medical management alone, with an ICER of £3,520 per QALY gained and was therefore considered to be cost effective. The committee noted that at the time of this analysis the cost of eplerenone was around £42, however, as this drug has recently come off patent its price has significantly decreased. Therefore, the ICER will now be much lower. One Irish economic evaluation assessed the addition of spironolactone to optimal medical management based on the RALES RCT included in the clinical review. This analysis was reviewed in the previous 2010 guideline update. This analysis found that the addition of spironolactone to optimal medical management was more effective and more costly than optimal medical management alone, with an additional cost of £291 per life year gained. The main limitation of this analysis is that it does not incorporate quality of life and could therefore not be assessed using the NICE cost per QALY threshold. However, in the 2010 guideline an equivalent threshold of £13,000 per life year gained was calculated based on a utility value of 0.65, as reported in a health technology assessment by Mant et al. 2009. The committee agreed to also adopt this threshold, and the addition of MRAs to optimal medical management was considered to be cost effective. The committee noted that costs are likely to have risen since this was last reported in the previous guideline, but agreed that this would not change the overall conclusion of the result. The committee noted the higher risk of renal dysfunction for people taking MRAs. Renal dysfunction was not included in the Irish study, but was included in the UK study model. The committee considered that the associated cost in the UK economic analysis may have been underestimated due to the definitions adopted to report renal dysfunction in the EMPHASIS-HF trial, and believed that a significant proportion of these patients are likely to have had acute kidney injury (AKI) which incurs a higher cost than that adopted in the economic analysis. However, due to the negative effects that MRAs have on renal function the committee decided to recommend that blood monitoring should be undertaken during uptitration in the first 3 months, and then 6 monthly thereafter. This frequency of monitoring was previously suggested in the 2010 CHF guideline (CG108) 'Appendix D – practical notes'. Uptitration monitoring was a requirement of the EMPHASIS-

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	HF clinical trial and therefore these costs were incorporated in the UK study. This consisted of 2 sets of blood tests and 2 hospital appointments with a consultant, and further monitoring costs were assumed to be the same as standard care. Although the committee recommend a couple more blood tests than were undertaken in the trial, this additional cost would be minor. In the Irish study, 1 extra outpatient visit for monitoring in the MRA arm compared to the standard care arm was assumed. The study also reports that even if 4 additional outpatient visits were assumed that spironolactone is still highly cost-effective. Taking this into consideration the committee agreed that MRAs would still remain highly cost-effective and therefore should be offered to chronic heart failure patients with reduced ejection who remain symptomatic on current first line therapy.
Other considerations	The committee considered that the introduction and continuation of MRAs, as with all pharmaceuticals in heart failure, should be part of shared decision making, and noted that this was already reflected in recommendation [85] in the communication' section of the chronic heart failure guidance. A lay committee member raised the issue of polypharmacy and whether, if a person's heart function improves significantly, one or more of medications could be discontinued. The clinical committee members acknowledged the understandable desire of patients to not take more medications than required and the burden of polypharmacy. There are no large-scale trials addressing this question so evidence in this regard is lacking. Healthcare professionals should ensure that patients are on appropriate polypharmacy while taking into account that the reduction or removal of particular medications, even in controlled heart failure, has empirically been noted to lead to deterioration of heart function and risk of arrhythmia. The decision to discontinue therapies should therefore be made on an individual patient basis, as part of shared decision with the patient as part of the wider multi-disciplinary team, with full discussion of potential risks and benefits and taking into account patient side-effects and symptoms. The committee discussed current practice regarding the prescribing of MRAs, and the potential impact of their recommendation. In the 2010 guideline, MRAs can be 'considered' as one of several second line treatment options, after specialist advice. The new recommendation is stronger than the previous recommendation on the use of MRAs ('offer' rather than 'consider') and the suggestion to seek specialist advice prior to introduction has been removed. This is due to the strengthening of the evidence base and the recognition of local variation in heart failure multidisciplinary teams. Further, it is in line with the recommendations in the Acute Heart Failure guideline (CG187), from which many patients are likely to transition to chronic management. In formulating the new recommendation, the committee discussed the patient population to whom the recommendation should apply. RALES required an entry ejection fraction (EF) of ≤ 35%, and EMPHASIS ≤ 30%. The committee agreed that this was critical to the studies' designs to ensure that the correct population was being studied, but that there is some variation about the measurement of ejection fraction. Accordingly MRAs should be offered to all people with HFREF, as the evidence indicated a beneficial effect across the disease severity spectrum and is likely to remain cost effective. The committee considered whether MRAs should be offered to all people

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	with HFREF who remain symptomatic on after the optimisation of beta-blocker and ACEi dose titration. The committee did not consider that the evidence supported the initiation of triple therapy immediately following diagnosis of HFREF, as the patient populations included in the review were all symptomatic on existing first line treatment. Furthermore, taking the technology appraisals into consideration, sacubitril valsartan and ivabradine recommendations were added as possible specialist treatments. The committee recognised that the strengthening of the recommendation to offer MRAs for this population could have a significant resource impact for the NHS due to increased prescribing volume. However, there was good economic evidence suggesting that the addition of MRAs for patients with heart failure with reduced ejection fraction in the community is cost-effective. Although spironolactone is currently cheaper than eplerenone the committee decided not to specify which drug should be prescribed and agreed that this should be the decision of the prescribing clinician while taking into account the pharmacological differences of the 2 medicines, as there has been no head to head comparison trial of the 2 drugs. The previous guideline for chronic heart failure (CG108) included 8 studies which are referenced in the clinical review. Seven of these studies have been excluded within the current review as they no longer meet the review protocol. The committee discussed the protocol for this review question and agreed that the previously included studies which had a population of people with heart failure post myocardial infarction were not appropriate for consideration within the review as these people represented a significantly different population. In addition to this the committee agreed that the minimum duration of follow-up for included studies should be 6 months and have a minimum sample size of 100 to ensure an accurate clinical effect can be established. In addition to this, the committee agreed that cross-over studies should be excluded to ensure that potential carryover effects are not confounding the outcome.

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6.2.5 Iron supplementation for iron deficiency in heart failure

6.2.5.1 Introduction

Iron deficiency (both with or without overt anaemia) commonly occurs in heart failure affecting between and a third and half[176] of patients, and appears to be related to disease severity[176] as well as being an independent predictor of mortality. Iron deficiency in heart failure has been an area of intense research since the last guideline update. One of the postulated mechanisms for iron deficiency in the context of heart failure is malabsorption and therefore the mode of delivery of iron supplementation (oral versus intravenous) has also been an area of investigation. There are currently no specific quality standards addressing this area.

6.2.5.2 Review question: What is the clinical and cost effectiveness of iron supplementation in people with chronic heart failure and iron deficiency?

For full details see review protocol in Appendix A.

Table 50: PICO characteristics of review question

Population	People with heart failure who also have iron deficiency (whether or not they are anaemic), are on optimal heart failure medical therapy and are in a community or outpatient setting
Interventions	• Intravenous iron • Oral iron
Comparisons	• Each other • Placebo
Outcomes	CRITICAL: • Mortality • Quality of life • Unplanned hospitalisation IMPORTANT: • Improvement in exercise tolerance • Change in haemoglobin in anaemic patients • Withdrawal due to adverse events/tolerability • Adverse events (hypertension, anaphylaxis/hypersensitivity, stroke, gastrointestinal)
Study design	• Systematic review of RCTs • RCT

6.2.5.3 Clinical evidence

A search was conducted for randomised trials investigating the effectiveness of intravenous (IV) or oral iron supplementation, compared with each other or placebo, for patients with heart failure (HF) who also have iron deficiency (ID).

Five studies were included in the review: FAIR-HF [17, 18, 72, 118, 139, 269], CONFIRM-HF[270], IRON-HF[31] and Toblli 2007[336], and IRONOUT HF[200]; these are summarised in Table 51 below. Four trials compared IV iron with placebo; of which 1 trial also included an oral iron arm. A further single study compared oral iron with placebo. Two of the trials were in patients with anaemia; the other 3 trials included both anaemic and non-anaemic patients.

Evidence from these studies is summarised in the clinical evidence summaries below (Table 52 toTable 54). See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

Table 51: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
CONFIRM-HF trial: Ponikowski 2015[270]	Intervention: Two injections (at baseline and week 6) of IV iron (ferric carboxymaltose) each equivalent to 500 or 1000 mg of iron, depending on weight and Hb. Maintenance injections of 500 mg iron at weeks 12, 24 and 36 if ID still present. Control: Matching placebo (saline solution)	N = 304 Stable ambulatory HF patients with ID • NYHA class II or III • LVEF ≤ 45% • Elevated NPs • Hb <15 g/dL at screening visit Study duration: 12 months	• Mortality • Quality of life (EQ-5D VAS, KCCQ) • Hospitalisation • Exercise tolerance • Discontinuation due to adverse events • Drug related vascular disorders • Drug related gastrointestinal disorders	
FAIR-HF trial: Anker 2009[18] (Anker 2009[17], Comin-colet 2013[72], Filippatos 2013[118], Gutzwiller 2013[139], Ponikowski 2015[269])	Intervention: Weekly injections of IV iron (ferric carboxymaltose) equivalent to 200 mg iron, until week 8 or week 12, depending on required iron-repletion dose. Maintenance injections every four weeks until week 24. Control: Matching placebo (saline solution)	N = 461 Ambulatory HF patients with ID • NYHA class II or III • LVEF ≤ 40% (class II) or ≤ 45% (class III) • Hb at screening between 95 - 135 g/L Study duration: 6 months	• Mortality • Quality of life (EQ-5D, EQ-5D VAS, KCCQ) • Hospitalisation • Exercise tolerance • Stroke • Gastrointestinal disorders	
IRON-HF trial: Beck-da-silva 2013[31] (Beck-da-silva 2007[32])	Intervention 1: Weekly infusions of IV iron (iron sucrose) equivalent to 200mg iron for 5 weeks, plus oral placebo Intervention 2: Oral iron (ferrous sulphate) 200 mg three times / day for 8 weeks, plus IV placebo (saline) Control: Placebo of both IV and oral preparations	N = 23 HF outpatients with ID • HF diagnosis ≥ 3 months • NHYA class II-IV • LVEF < 40% • Hb ≤12g/dL and ≥9g/dL Study duration: 3 months	• Mortality • Improvement in NYHA class (surrogate for quality of life)	Study terminated due to poor recruitment
IRONOUT HF trial: Lewis 2017[200]	Intervention: Oral iron. oral iron polysaccharide 150 mg twice daily for 16 weeks Control: Matching placebo	n=225 Stable HFREF outpatients with ID	• Mortality • Permanent study drug discontinuation • Adverse events • Serious adverse	Study reported several outcomes (peak VO_2, 6 minute walk test distance and

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Study	Intervention and comparison	Population	Outcomes	Comments
		• NYHA class II-IV • LVEF ≤40% • Hb between 9 and 15 g/dL (men) or 9 and 13.5 g/dL (women) Study duration: 16 weeks	events • Change in peak VO_2 • Change in 6 minute walk test distance • Change in KCCQ clinical summary score	KCCQ) as median and IQR
Toblli 2007[336] (Toblli 2015[335])	Intervention: Weekly infusions of IV iron (iron sucrose) equivalent to 200 mg iron for 5 weeks Control: Matching placebo (saline solution)	N = 60 HF outpatients with ID, anaemia and CKD • NYHA class II-IV • LVEF ≤ 35% • creatinine clearance ≤90 ml/min • Hb <12.5 g/dl for men and <11.5 g/dl for women	• Mortality • Quality of life (MLWHFQ) • HF hospitalisations • Exercise tolerance • Change in haemoglobin • Abdominal pain • Nausea • Systolic blood pressure	Originally, 40 patients recruited and analysis published. Additional 20 patients recruited subsequently and second analysis published on full dataset. Study duration: 6 months

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Table 52: Clinical evidence summary: IV iron versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Intravenous iron (95% CI)
Mortality	836 (4 studies) 3-12 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.86 (0.47 to 1.58)	59 per 1000	8 fewer per 1000 (from 31 fewer to 34 more)
Quality of life EQ5D. Scale from: 0 to 1.	459 (1 study) 5.5 months	⨁⨁⨁⨁ HIGH		The mean change in quality of life in the control groups was -0.01	The mean quality of life in the intervention groups was 0.08 higher (0.03 to 0.12 higher)
Quality of life EQ5D VAS. Scale from: 0 to 100.	679 (2 studies) 5.5-12 months	⨁⨁⊖⊖ LOW[a, b] due to risk of bias, imprecision		The mean change in quality of life in the control groups was 3.9	The mean quality of life in the intervention groups was 4.02 higher (1.52 to 6.52 higher)
Quality of life KCCQ. Scale from: 0 to 100.	679 (2 studies) 5.5-12 months	⨁⨁⊖⊖ LOW[a, b] due to risk of bias, imprecision		The mean change in quality of life in the control groups was 4.25	The mean quality of life in the intervention groups was 5.43 higher (2.84 to 8.02 higher)
Quality of life MLWHFQ . Scale from: 0 to 105.	40 (1 study) 6 months	⨁⨁⨁⨁ HIGH		The mean quality of life in the control groups was 59	The mean quality of life in the intervention groups was 18 lower (22.66 to 13.34 lower)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Intravenous iron (95% CI)
Improvement in NYHA class Data on improvement in NYHA has only been extracted where quality of life data is not reported in a trial.	16 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a, b, c] due to risk of bias, indirectness, imprecision	RR 1.2 (0.14 to 10.58)	167 per 1000	33 more per 1000 (from 144 fewer to 1000 more)
Hospitalisation due to HF	40 (1 study) 6 months	⨁⨁⊖⊖ LOW[a,c] due to risk of bias, indirectness	Peto Odds Ratio 0.11 (0.02 to 0.69)	250 per 1000	250 fewer per 1000 (from 450 fewer to 50 more)
Hospitalisation all cause	760 (2 studies) 6-12 months	⨁⨁⊖⊖ LOW[a, b] due to risk of bias, imprecision	Rate Ratio 0.66 (0.5 to 0.85)	Moderate[d]	
				383 per 1000	130 fewer per 1000 (from 57 fewer to 191 fewer)
Exercise tolerance 6MWT, distance	688 (3 studies) 5.5-12 months	⨁⨁⨁⊖ MODERATE [b] due to imprecision		The mean exercise tolerance in the control groups was 277 m	The mean exercise tolerance in the intervention groups was 39.5 higher (25.11 to 53.88 higher)
Haemoglobin in anaemic patients (anaemia defined as <12.5g/dL for men and <11.5g/dL for women)	60 (1 study) 6 months	⨁⨁⨁⨁ HIGH		The mean haemoglobin in anaemic patients in the control groups was 9.6 g/dL	The mean haemoglobin in anaemic patients in the intervention groups was 2.1 higher (1.8 to 2.4 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Intravenous iron (95% CI)
Discontinuation: adverse events	304 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 0.74 (0.38 to 1.42)	125 per 1000	32 fewer per 1000 (from 78 fewer to 52 more)
Ischaemic stroke	459 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	Peto Odds Ratio 4.52 (0.24 to 85.34)	0 per 1000	10 more per 1000 (from 10 fewer to 20 more)
Drug related vascular disorders (not defined)	304 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b, c] due to risk of bias, indirectness, imprecision	Peto Odds Ratio 1.00 (0.06 to 16.06)	7 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)
Gastrointestinal disorders (not defined)	459 (1 study) 6 months	⨁⨁⊖⊖ LOW[a, b] due to risk of bias, imprecision	RR 2.42 (0.94 to 6.23)	33 per 1000	47 more per 1000 (from 2 fewer to 173 more)
Drug related gastrointestinal disorders (not defined)	304 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	Peto Odds Ratio 7.44 (0.46 to 119.46)	0 per 1000	10 more per 1000 (from 10 fewer to 40 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Intravenous iron (95% CI)
Nausea	60 (1 study) 6 months	⨁⨁⊖⊖ LOW[b] due to imprecision	RR 1 (0.07 to 15.26)	33 per 1000	0 fewer per 1000 (from 31 fewer to 471 more)
Abdominal pain	60 (1 study) 6 months	⨁⨁⊖⊖ LOW[b] due to imprecision	Peto Odds Ratio 0.14 (0.00 to 6.82)	33 per 1000	30 fewer per 1000 (from 120 fewer to 50 more)
Systolic blood pressure	60 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[b] due to imprecision		The mean systolic blood pressure in the control groups was 134.5 mmHg	The mean systolic blood pressure in the intervention groups was 1.3 higher (1.95 lower to 4.55 higher)

(a) [a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias .
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MID.
(c) Downgraded by 1 increment as the outcome is indirect.
(d) Mean control group rate per 100 patient-years.

Table 53: Clinical evidence summary: oral iron versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Oral iron (95% CI)
Mortality	238 (2 study) 3 to 4 months	⨁⊖⊖⊖ VERY LOW[a, b,e] due to risk of bias, imprecision,	Peto Odds ratio 1.48 (0.25 to 8.66)	Moderate 17 per 1000	8 more per 1000 (from 13 fewer to 128 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Oral iron (95% CI)
		inconsistency			
Improvement in NYHA class Data on improvement in NYHA has only been extracted where quality of life data is not reported in a trial.	13 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[a, b, c] due to risk of bias, indirectness, imprecision	RR 5.14 (0.84 to 31.57)	Moderate 167 per 1000	690 more per 1000 (from 27 fewer to 1000 more)
Permanent study drug discontinuation	225 (1 study) 4 months	⊕⊕⊖⊖ LOW [b] due to imprecision	RR 0.91 (0.48 to 1.72)	149 per 1000	13 fewer per 1000 (from 78 fewer to 107 more)
Adverse events (not described)	225 (1 study) 4 months	⊕⊖⊖⊖ VERY LOW[a, b, c] due to risk of bias, indirectness, imprecision	RR 0.89 (0.63 to 1.25)	395 per 1000	43 fewer per 1000 (from 146 fewer to 99 more)
Serious adverse events (not described)	225 (1 study) 4 months	⊕⊖⊖⊖ VERY LOW[a, b, c] due to risk of bias, indirectness, imprecision	RR 1.13 (0.5 to 2.55	88 per 1000	11 more per 1000 (from 44 fewer to 136 more)
Change in peak VO_2 ml/kg/min	225 (1 study) 4 months	⊕⊕⊖⊖ LOW [a,d] due to risk of bias	-	The median change in peak VO_2 in the placebo group was 13.0 ml/kg/min IQR (10.2-15.9)	The median change in peak VO_2 in the oral iron group was 0.5ml/kg/min higher (IQR 11.7 to 16.3)
Change in 6-minute walk test distance (m)	225 (1 study) 4 months	⊕⊕⊖⊖ LOW[a,d] due to risk of bias	-	The median 6 minute walk test distance in	The median 6 minute walk test distance in the oral iron group was 31m lower

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Oral iron (95% CI)
				the placebo group was 397 IQR (299-472)	(IQR 315 to 456)
Change in KCCQ clinical summary score (Higher score indicates better outcome)	225 (1 study) 4 months	⨁⨁⊖⊖ LOW [a,d] due to risk of bias	-	The median KCCQ in the placebo group was 77.1 IQR (65.1-89.6)	The median KCCQ clinical summary score in the oral iron group was 3.6 higher (IQR 67.7 to 91.6)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias .
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs .
(c) Downgraded by 1 increment as the outcome is indirect.
(d) Unable to assess imprecision as study reported the results as median and IQR.
(e) Downgraded by 1 increment due to heterogeneity, I^2=51%.

Table 54: Clinical evidence summary: IV iron versus oral iron

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral iron	Risk difference with Intravenous iron (95% CI)
Mortality	17 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	Peto Odds Ratio 6.13 (0.33 to 112.36)	0 per 1000	200 more per 1000 (from 100 fewer to 500 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral iron	Risk difference with Intravenous iron (95% CI)
Improvement in NYHA class Data on improvement in NYHA has only been extracted where quality of life data is not reported in a trial.	17 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a, b,c] due to risk of bias, indirectness, imprecision	RR 0.23 (0.07 to 0.84)	857 per 1000	660 fewer per 1000 (from 137 fewer to 797 fewer)

(a) [a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias .
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Downgraded by 1 increment as the outcome is indirect.

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6.2.5.4 Economic evidence

Published literature

One health economic study was identified with the relevant comparison and has been included in this review[140]. This is summarised in the health economic evidence profile below (Table 55) and the health economic evidence table in Appendix G.

Four economic studies relating to this review question were identified but were selectively excluded due to the availability of more applicable evidence[73],[147],[201]. These are listed in Appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix D.

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Table 55: Health economic evidence profile: IV iron versus placebo

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Gutzwiller 2012 [140]	Directly applicable [(a)]	Potentially serious limitations [(b)]	• Within-trial analysis of FAIR-HF RCT [17, 18, 72, 118, 139, 269]. • Comparators: 1. No iron treatment 2. Iron repletion with ferric carboxymaltose IV bolus injection • 24 week follow-up	£149	0.037 QALYs	£3,977 per QALY gained	Probability Intervention 2 cost-effective (£20K/30K threshold): 99.66%/99.68% Univariate and probabilistic sensitivity analysis undertaken. Frequency and duration of hospitalisation, QALY difference, and cost of hospital day were the most influential parameters. None of the parameters tested resulted in an ICER above £20,000 per QALY gained.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) The FAIR-HF trial did not include British participants, but was mostly performed in European countries with a predominantly Caucasian population. This is unlikely to change the conclusions of cost-effectiveness.

(b) Short time horizon may not capture full costs and effects of the intervention. Lack of detailed medical resource use data. Within-trial analysis and so does not reflect full body of available evidence for all comparators; FAIR-HF is one of 4 studies comparing IV iron to no iron treatment.

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Unit costs

Relevant unit costs of oral and intravenous iron are provided below to aid consideration of cost effectiveness.

Oral iron

The cost of oral iron therapy was taken from the Drug Tariff, May 2016[240] with the number of tablets prescribed estimated from the Prescription Cost Analysis, July 2016.[143] Table 56 below, shows a weighted average of the 2 most commonly prescribed tablets.

Table 56: Cost of oral iron therapy

Drug	Tablets	Cost per tablet (£)	Tablets per day	Cost per month (£)
Ferrous Fumarate 210mg	16,398,736	0.04	3	3.80
Ferrous Sulfate 200mg	13,490,134	0.08	3	7.27
Weighted average				5.70

Intravenous iron

These costs were updated from the NICE clinical guideline entitled 'Anaemia management in people with chronic kidney disease (AMCKD) (NG8). In the AMCKD guideline, cost was estimated based on: drug cost, staff time, clinical space, administrator time, and transport. Detail regarding the sources and assumptions used for costing are outlined below.

Staff time was estimated by the committee members and the infusion time dependent on drug SPCs. Observation (30 minutes) is required for all regimens. It was assumed that a nurse would observe 2 patients concurrently. The cost of a band 6 nurse at a rate of £51 per hour was applied[80].

The following costs were taken from a published cost analysis for pre-dialysis patients conducted at Kings College Hospital, London[368]:

- Clinic space - £5 per patient-hour
- Clerical staff - £3.28 per visit
- Transporting a patient to hospital (assumed 10% patients will require this) - £45 for return visit

Disposables were assumed to cost £5 per visit (including cannula, needles, syringes, dressing, IV giving set and sodium chloride solution).

The unit costs of intravenous iron were estimated based on the doses reported in the trials included in the clinical review. These are summarised below and more detail is available in Table 57:

- FAIR-HF: min. dose (11x200mg) = £831, max. dose (15 x 200mg) = £1,133
- CONFIRM-HF: min (1x500mg/vial) = £131, max. dose (7x500mg/vial) = £916*
- IRON-HF: 5x200mg = £374
- Tobilli 2007: 5x200mg = £374

* please note that the cost of 1000mg vial has fallen and is now less costly than two 500mg vials. Therefore this cost may be slightly over-estimated if an initial dose of 1000mg was given rather than 500mg. All maintenance doses in the trial were 500mg.

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Table 57: Cost of IV iron therapy

	Regimen				Drug cost (£)		Nurse time per infusion, minutes			Nurse cost (£) (b)		Other (£)			Total (£)
Trial	Drug	Iron mg/ vial	Vials /visit	No. visits	Cost/ vial (a)	Total drug cost	Preparation	Infusion	Observation	Cost per visit	Total cost	Consumables	Transport	Admin time and clinic space	
FAIR-HF	Ferric Carboxy-maltose	100	2	11	16.24	357	15	2	30	26	244	55	50	79	831
	Ferric Carboxy-maltose	100	2	15	16.24	487	15	2	30	26	333	75	68	108	1133
CONFIRM-HF	Ferric Carboxy-maltose	500	1	1	81.18	81	15	15	30	32	32	5	5	8	131
	Ferric Carboxy-maltose	500	1	7	81.18	568	15	15	30	32	223	35	32	58	916
IRON-HF Tobilli2007	Iron Sucrose (infusion)	100	2	5	8.71	87	15	30	30	38	161	25	23	48	374

(a) BNF, May 2016[161]
(b) PSSRU 2015 [80]

6.2.5.5 Evidence statements

Clinical

Five studies were identified for inclusion within the review. Four trials compared IV iron with placebo; 1 of which also included an oral iron arm. A further single study compared oral iron with placebo. Two of the trials were in patients with anaemia; the other 3 trials included both anaemic and non-anaemic patients. The evidence ranged from high to very low quality. Evidence was downgraded for a number of reasons including risk of bias, imprecision due to wide confidence intervals surrounding the effect estimate and indirectness of the reported outcome.

For the comparison of IV iron with placebo a number of the outcomes were rated as high quality evidence . These included QoL (as measured by the EQ5D scale (n=459) and MLWHFQ (n=40)) and the haemoglobin level in people with anaemia (n=60). These outcomes all showed a clinically important symptomatic benefit of IV iron. Moderate quality evidence was found for the outcomes exercise tolerance (n=688) and systolic blood pressure (n=60) both of which suggested no clinical effect of IV iron. The remaining outcomes were all rated as low or very low quality evidence. Of these outcomes, , QoL (as measured by both the EQ5D VAS (n=679) and KCCQ scales (n=678)), hospitalisation (due to both HF (n=40) and all-cause (n=760)) all showed a clinically important benefit of IV iron (associated with wide confidence intervals around the effect estimate). The outcome ischaemic stroke (n=459) was also rated as very low quality evidence and suggested a clinical harm of IV iron, this was associated with wide confidence intervals around the effect estimate. The remaining outcomes which included mortality,improvement in NHYA class (data on improvement in NYHA has only been extracted where quality of life data is not reported in a trial), discontinuation due to adverse events, drug related vascular disorders, gastrointestinal disorders, nausea and abdominal pain failed to identify any clear clinical effect of IV iron.

For the comparison of oral iron with placebo, very low quality evidence was found for the outcomes mortality (n=238, 2 studies), improvement in NYHA class (n=13, study), adverse events (n=225, 1 study) and serious adverse events (n=225, 1 study). The evidence showed a clinically important increase in mortality and clinically important improvement in NHYA class with oral iron (both associated with wide confidence intervals around the effect estimate). Data on improvement in NYHA has only been extracted where quality of life data is not reported in a trial.The evidence for both adverse events and serious adverse events suggested no clinical effect of oral iron. This was also the case for permanent study drug discontinuation which was rated as low quality. The evidence for change in peak VO2, 6 minute walk test distance and KCCQ clinical summary score were reported by the study as median and IQR. Therefore, imprecision could not be assessed.

The comparison of IV iron with oral iron included the same outcomes (mortality and change in NYHA class) which were also rated as very low quality evidence (n=17 for both). Change in NYHA (data on improvement in NYHA has only been extracted where quality of life data is not reported in a trial), showed a clinical harm of IV iron when compared to oral iron (associated with wide confidence intervals around the effect estimate). Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

Economic

- One cost-utility analysis found that iron supplementation was cost-effective compared to no iron treatment for patients with heart failure and iron deficiency (ICER = £3,997 cost per QALY). This was assessed as directly applicable with potentially serious limitations.

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6.2.5.6 Recommendations and link to evidence

Recommendation	No recommendation
Relative values of different outcomes	The committee agreed that all-cause mortality, quality of life and unplanned hospitalisation were the most critical outcomes for decision making. The committee agreed that the impact of iron on improvement in exercise tolerance, change in haemoglobin in anaemic patients, withdrawal due to adverse events/tolerability and adverse events (including hypertension, anaphylaxis/hypersensitivity, stroke and gastrointestinal issues) were also important outcomes. The committee discussed the outcome change in haemoglobin and agreed that it was only relevant to capture this information in people who had low baseline haemoglobin levels (people with anaemia) as increasing haemoglobin levels in these people was likely to have a beneficial clinical effect. Conversely in people with normal haemoglobin levels, increasing this was less likely to have a clinical effect. The incidence of anaphylaxis/hypersensitivity was not reported in any of the included trials.
Quality of the clinical evidence	Four studies were identified that included an IV iron arm versus placebo; 2 small trials and 2 larger multi-centre trials. One of these studies also included an oral iron arm in addition to a further single study which looked at just oral iron versus placebo. IV iron versus placebo: For mortality, the evidence was rated very low quality due to risk of bias and imprecision. In addition to this the evidence for all-cause hospitalisation was graded as low quality for the same reasons. However, the committee noted that the confidence intervals around the absolute effect were reasonably narrow for this outcome, suggesting that the committee could have greater confidence in the result. Another study reported heart failure related hospitalisations (rather than all-cause); this outcome was downgraded for indirectness as the outcome may not have captured all of the potential hospitalisations relating to the intervention. The committee noted that quality of life measures reported by the studies, both general (EQ5D and EQ5D-VAS) and disease-specific scales (KCCQ and MLWHFQ), ranged from high quality to low quality. One study did not report quality of life, but reported change in NYHA class. This outcome was downgraded for indirectness as the committee agreed that the outcome would give some idea of overall improvement in the severity of HF symptoms. For the important outcomes, the quality of the evidence ranged from high to moderate. The outcome exercise tolerance, as measured by the 6-minute walk test, was rated as moderate quality due to imprecision and haemoglobin change in anaemic patients was rated as high quality. The committee noted that evidence regarding discontinuation and adverse events were graded as low and very low quality, often due to missing data

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	and imprecision. However, they were reassured that discontinuation and gastrointestinal disorder rates appeared low. Oral iron versus placebo: For mortality the evidence was rated as very low quality due to risk of bias, imprecision and inconsistency. The committee discussed the inconsistency of the results and noted that the single study showing a negative effect of oral iron was the larger of the 2 studies and weighted more heavily in the meta-analysis. The outcome improvement in NYHA class was also rated as very low quality due to risk of bias, indirectness (as this was interpreted as a surrogate for QoL as it implies an improvement in symptoms) and imprecision. The confidence intervals surrounding the effect estimate were wide which reduced the committee's ability to be confident in the results. The committee noted that evidence regarding discontinuation and adverse events and serious adverse events were graded as low and very low quality, often due to risk of bias and imprecision. Both of the adverse event outcomes were also downgraded for indirectness due to the lack of description regarding what these events consisted of, making it difficult for the committee to interpret this evidence. The committee agreed that discontinuation and adverse event rates with oral iron appeared low (difference against placebo was less than 50 per 1000 for all 3 outcomes). No evidence was identified for anaphylaxis or hypersensitivity. The evidence for peak VO2, 6 minute walk test distance and KCCQ clinical summary score were reported by the study as median and IQR. Therefore imprecision could not be assessed. It was noted that the populations in the included trials was not representative of the general HF population, being in general younger and having fewer comorbidities. The committee was unsure how the benefit seen in the trials would translate in the general HF population. It was also discussed whether the trials had been long enough to encompass the possible risks and benefits. In addition, the committee noted that the trials had only included people with reduced ejection fraction, so there was a lack of evidence in people with iron deficiency and HFPEF.
Trade-off between clinical benefits and harms	IV iron IV iron for people with HFREF and iron deficiency appeared to have a clinically important benefit on quality of life and haemoglobin levels (in people with anaemia). However, the impact on mortality was unclear. The committee noted that while the point estimate showed a clinically important reduction in deaths, the confidence intervals around the absolute effect were wide, reducing their confidence in the effect estimate. The effect estimate suggested a clinically important reduction in hospitalisations also (130 fewer hospitalisations per 1000 people); the committee agreed that this appeared to represent a marked decrease. There was no clinical effect shown on exercise tolerance. In terms of adverse effects, there was no evidence of potential gastro-intestinal disturbance (difference against placebo was less than 50 per 1000 for discontinuation). The committee also agreed that the impact on systolic

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blood pressure was not clinically significant. The committee was concerned by the apparent excess of ischaemic stroke in the IV iron arm, but noted that this was from only 2 occurrences in 1 study.

On the basis of these findings the committee was uncertain that the benefits of IV iron had been completely demonstrated. Although there was some high (and low quality) evidence on quality of life, the committee agreed that this was not enough to support a recommendation when taking into account the uncertainty of the evidence on the other outcomes. The GC noted quality of life was a secondary endpoint in the trials and hospitalisations are the main outcome the study was powered for. The committee decided that making a recommendation in this area was premature given the variation seen in outcomes and differences in administration protocols between current studies and preferred UK practice.They were aware of continuing studies in the field including Intravenous Iron Treatment in Patients With Heart Failure and Iron Deficiency (IRONMAN), Intravenous Iron in Patients With Systolic Heart Failure and Iron Deficiency to Improve Morbidity & Mortality (FAIR-HF2), and Randomized Placebo-controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency (HEART-FID). The latter two trials are using ferric carboxymaltose (FCM), however all IV formulations would be relevant and could be considered together unlike oral preparations where varaiations in bioavailability may be more of an issue.

Because of the potential to cause toxicity using iron therapy, there needs to be good evidence that a patient is iron deficient prior to being given IV iron. A small percentage of patients with HF have iron overload as the cause of their HF. There was also concern that because iron deficiency can be a symptom of other disorders, particularly gastro-intestinal tract cancer, there was the risk of missing other causes if the iron was replaced without further investigation.

The committee heard testimony from the co-optee renal physician who regularly oversees IV infusion on an outpatient basis for patients with anaemia and/or renal disease and regularly cares for people with heart failure. He reported that using a dosage regimen similar to CONFIRM-HF was generally well tolerated. It was suggested, however, that the population currently given IV iron, like the population included in the clinical trials, may not be reflective of the population treated for HF in practice, and that tolerability may be worse in 'typical' patients with HF who are on average older and have more comorbidities.

No evidence was found indicating whether repeat administration will always be necessary, nor the frequency of any such repeat administration. However, the co-optee confirmed that the experience from the chronic kidney disease (CKD) community is that they actively recall patients to repeat iron infusion, as reflected in the CKD and anaemia guidelines, and there is no expectation that patients would stop needing iron supplementation. It was felt this was also likely to be the case for people with HF and iron deficiency.

Oral iron

Oral iron for people with HFREF and iron deficiency appeared to show a clinically important increase in mortality. In terms of adverse events, there was no evidence of a clinically important effect. Oral iron appeared to show a clinically important improvement in NYHA class, which may be suggestive

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	of an overall improvement in the severity of CHF symptoms in these patients. However, the width of the confidence intervals reduced the committee's ability to interpret this result. Oral iron showed a marginal increase in peak VO2 max and a relative decrease in distance walked in the 6-minute walk test. However, these results were reported as median and interquartile range and therefore could not be assessed for imprecision. Similar to IV iron the committee agreed that due to the potential to cause toxicity using iron therapy, there needs to be good evidence that a patient is iron deficient prior to being given oral iron. In addition, the committee agreed that the cause of iron deficiency should be fully investigated to ensure that other causes could be elucidated before starting replacement therapy. The committee also noted that patient compliance with oral iron tended to be poor in clinical practice due to unpleasant gastrointestinal side effects. Overall, the committee agreed that there did not appear to be a benefit of oral iron in people with HFREF and iron deficiency and therefore decided not to make a recommendation regarding oral iron.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified that considered oral iron supplementation compared to no supplementation or IV iron supplementation compared to oral iron supplementation in people with HF and iron deficiency. One relevant economic evaluation was included in this review that considered IV iron supplementation compared to no iron supplementation for people with HF and iron deficiency. This was based on the FAIR-HF trial included in the clinical review. This economic evaluation found that IV iron supplementation increased costs and improved health (increased QALYs) compared with no iron supplementation with an incremental cost-effectiveness ratio of £3,977 per QALY gained. The probability that IV iron is cost effective at the £20,000 per QALY threshold was around 99%. The analysis only reflected the effectiveness evidence from 1 RCT of 4 included in the clinical review and was assessed as directly applicable with potentially serious limitations. The committee were concerned that the time horizon of this economic evaluation is short and therefore does not capture the longer term costs and effects of treatment. The trial with the longest follow-up included in the clinical review was CONFIRM-HF, which had a 12 month follow up. This trial implemented different dosing regimes of 500mg or 1000mg of iron given per visit compared to 200mg per visit as in the other included trials. Unit costs of IV iron were presented to the committee for consideration of the costs and cost effectiveness associated with different dosing regimes. The mean total dose in CONFIRM-HF trial was 1500mg over 1 year. The unit cost per milligram of iron is the same between the 100mg and 500mg vial sizes; however, the 500mg dosing regime (as in CONFIRM-HF) requires significantly fewer visits than the 200mg dosing regime and is therefore less costly. The committee also noted that such a regime is likely to be more acceptable to people due to the fewer number of visits. It was noted that this dosing regime is similar to current clinical practice in the NHS for people receiving IV iron therapy (for example, anaemic patients with CKD). The committee therefore considered the cost effectiveness of IV iron supplementation based on the clinical evidence of CONFIRM-HF with a different dosing regime and longer follow-up. The committee noted that all-

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	cause hospitalisation event rates in CONFIRM-HF were similar to those of FAIR-HF. CONFIRM-HF did not report the EQ-5D index, only the EQ-5D VAS which suggested that there was a benefit in quality of life. Comparing the EQ-5D VAS and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores from FAIR-HF and CONFIRM-HF the clinical review shows that there was a smaller quality of life gain in CONFIRM-HF than that found in FAIR-HF. The committee considered that the overall cost will be lower in CONFIRM-HF than FAIR-HF due to the reduced intervention cost and similar reduced hospitalisation rate to that of FAIR-HF and therefore considered that IV iron therapy administered according to the CONFIRM-HF dosing regime and over a 12 month period is likely to be cost-effective. Due to the lack of evidence on the effectiveness of IV iron after 12 months and whether to continue or stop supplementation, the committee were still concerned that 12 months was not a sufficient follow-up period to capture all costs and effects of iron supplementation. The unit costs of oral iron were also presented to the committee for consideration. The committee noted that although oral iron is much cheaper, as mentioned above, the clinical evidence suggests that there is no clinical benefit. In addition, the committee also discussed that there are also compliance issues in clinical practice and therefore there is not likely to be any benefit of oral iron to people with HF. The high cost of IV iron supplementation and the large population of people with HF requiring treatment would mean a positive recommendation for IV iron supplementation would have a large cost impact for the NHS. Considering this, the committee agreed that overall both the clinical and cost-effectiveness evidence was currently too uncertain to recommend that patients with iron deficiency should be treated with IV iron supplementation. The committee stated that trials currently underway should help to strengthen both the clinical and economic evidence to aid recommendations for IV iron supplementation in the future.
Other considerations	Iron deficiency is a common comorbidity with HF. It has been estimated that up to 30 to 50% of patients with NYHA class II-IV heart failure have iron deficiency, and that the prognosis for these patients is worse than for patients without iron deficiency. [176] Therefore any recommendations will have implications for a large number of people covered by this guideline. The studies of IV iron included those with and without low haemoglobin and this review did not distinguish between them, as it was the committee's intention to make recommendations that covered both anaemic and non-anaemic patients with iron deficiency. There are guidelines on treating iron deficiency anaemia in the general population, which recommend a trial of oral iron. However, the evidence included within this review does not suggest a clinical benefit of oral iron for people with HFREF and iron deficiency alone. The committee considered a number of points about the potential impacts of making a recommendation for the treatment of iron-deficiency in people with HF. Testing for iron deficiency; treating with oral iron; regimens of IV iron replacement (from provider and patient perspective); and ongoing clinical trials. The committee considered whether the potential benefits from iron replacement in people with iron-deficiency (with and without anaemia) was such that there should be a recommendation to test all people with HF for

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	iron-deficiency. There was consensus that iron studies were already done for everyone known to have anaemia (estimated at around 10% HF population), and that people with HF in a specialist clinic would generally also get iron studies, but that this left a large number who would currently not be tested. If any treatment recommendation were made, it would be important to raise awareness of iron-deficiency in HF amongst non-specialists in order to ensure equity of access to treatment. However, since this review has not looked at the effectiveness of *testing* for iron deficiency, the committee could only consider a recommendation that all people with HF be tested if there was robust evidence of both clinical and cost effectiveness of treating identified iron deficiency, particularly in those without anaemia. Since this was lacking, the committee felt that no such recommendations could be made, but felt that this could change in the future. It was discussed that despite general consensus that oral iron was largely ineffective and poorly tolerated, patients were sometimes offered oral iron in clinical practice, often by their GP. This clinical opinion was confirmed by the results from the IRONOUT-HF study which showed that oral iron did not have a clinical benefit in people with HFREF and iron deficiency. The committee considered the different regimens of IV iron in various trials and in the real-life situation. Practice tends to be moving from multiple long infusions to shorter injections to replace iron more quickly. The patient representatives expressed a preference for large infusion if this completely replaced their iron more quickly, as they felt this would quickly improve their quality of life. There was consensus that we should be moving towards a separate pathway for iron deficiency in HF, in a manner similar to the pathway for anaemia in CKD, and that this was likely to include IV iron. However, the committee considered that a general recommendation at this time would be a change in practice with an impact from both testing and treatment, without high quality evidence that this would be beneficial. It was felt that when further evidence was published in the future, this should be revisited. The committee was aware of the currently active IRONMAN trial (https://clinicaltrials.gov/ct2/show/NCT02642562), funded by the British Heart Foundation, that will look at longer time points. It was commented that this will be useful to find out whether the effect is simply on symptoms due to replacing iron, or whether it has an effect on HF pathophysiology (a feasible mechanism was offered involving myocyte iron use). It should also provide long term data on clinical effectiveness. The committee noted that the trials had only included people with reduced ejection fraction. It was decided that it would not be possible to generalise the evidence in these trials to people with HFPEF, as the patholophysiology differs, and therefore the balance of benefits and harms may be different. The committee were aware of a clinical trial which was currently active and included people with HFpEF. The FAIR-HFpEF trial (https://clinicaltrials.gov/ct2/show/NCT03074591) will look at the outcomes exercise capacity, QoL, NYHA functional class, mortality and HF related hospitalisations in people with heart failure with preserved ejection fraction and iron deficiency with and without anaemia randomised to either IV iron or placebo. Based on this, the committee decided not to recommend further research in the area.

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6.2.6 Pharmacological treatment for heart failure in people with heart failure and chronic kidney disease

6.2.6.1 Introduction

Chronic kidney disease (CKD), defined by a reduction in glomerular filtration rate (eGFR) to <60 ml/min/1.73 m^2 and/or persistent albuminuria, is a common and important comorbidity in people with heart failure that confers significant additional risks of mortality, hospitalisation and adverse drug reactions. People with severe CKD (eGFR<30 ml/min/1.73 m^2) have largely been excluded from key randomised controlled trials of heart failure pharmacotherapies, and the evidence base for such therapies in this important subgroup has therefore been lacking and clinical practice inconsistent

The presence of even mild or moderate CKD (eGFR 31-59 ml/min/1.73 m^2) can limit the ability to introduce and/or adequately up-titrate heart failure medications, many of which are potentially nephrotoxic and often reduced or discontinued in people with worsening renal function or acute kidney injury complicating intercurrent illness or concomitant drug therapy.

People with CKD are also more prone to develop adverse effects related to their heart failure medication including hyperkalaemia and hypotension as well as worsening renal function, which is often mild but may be significant in the long term and contribute to deteriorating renal function and worsening heart failure prognosis

As a result, there may be significant underutilisation of evidence-based pharmacotherapies in people with heart failure who also have CKD, particularly those with HFREF, who may be denied potentially life-saving disease-modifying medication. When considering the update of this guideline this topic was highlighted as an important area to review to establish if pharmacological interventions recommended for the general heart failure population were associated with similar clinical benefits, risks and cost effectiveness in people with heart failure who also have CKD.

6.2.6.2 Review question: What is the clinical and cost effectiveness of pharmacological interventions for heart failure in people with heart failure who also have chronic kidney disease?

For full details see review protocol in Appendix A.

Table 58: PICO characteristics of review question

Population	Adults with heart failure and chronic kidney disease (at least stage 3A / eGFR <60 mL/min), who are not on dialysis.
Interventions / Comparisons	• Angiotensin Converting Enzyme (ACE) inhibitor • Angiotensin Receptor Antagonist / Blocker (ARB) • Beta-Adrenergic Antagonia / Blocker (Beta-blocker) • Mineralocorticoid Receptor Antagonist (MRA) • Digoxin • Diuretics – loop and loop-related • Ivabradine and Sacubitril-Valsartan • Hydralazine-Nitrate Compared against each other (class versus class and within class comparisons), against the same drug at a different dose, or against placebo.
Outcomes	CRITICAL • All-cause mortality • Quality of life • Unplanned hospitalization IMPORTANT

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	• Renal function • Adverse events - Bradycardia • Adverse events - Arrhythmic events • Adverse events - Progression to stage five kidney disease / unplanned dialysis • Adverse events - Hypotension • Adverse events - Hyperkalaemia
Study design	Systematic Review RCT

6.2.6.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of medications for long-term treatment of heart failure (HF) in patients with both HF and chronic kidney disease of stage 3 or greater (CKD). Twelve studies were identified that met the inclusion criteria,[46, 60, 67, 69, 95, 113, 130, 179, 289, 311, 351, 361] all of which were sub-group analyses of randomised controlled trials of HF medication in the wider HF population. Trials of medication versus placebo were identified in the following drug classes: ACE-inhibitors[46], ARBs[95], beta-blockers[60, 67, 130], digoxin[311], ivabradine[361] and MRAs[113, 351]. In addition, there was a dose comparison for ACE inhibitors[289] and ARBs[179]. No evidence was found regarding the use of loop diuretics, sacubitril-valsartan or hydralazine/nitrate in people with HF and CKD. The critical outcomes of mortality and hospitalisation were frequently reported, but no studies reporting quality of life or change in NYHA class were identified.

The included studies are summarised in Table 59 below. Evidence from these studies is summarised in the clinical evidence summary below(Table 60 to 65). See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

Table 59: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
ATLAS trial, Ryden 2000[289] (Massie 2001[215] Cleland 1999[64])	Intervention 1: Angiotensin converting enzyme (ACE) inhibitors. Lisinopril 32.5-35mg per day Intervention 2: Angiotensin converting enzyme (ACE) inhibitors. Lisinopril 2.5-5mg per day Duration 4y average (median 46 months).	N=988 patients with CKD Post-hoc subgroup analysis of multicentre trial HF: NYHA class III or IV (or class II if admission for acute decompensation of heart failure in last 6 months) with ejection fraction ≤30%, who had received diuretics for at least 60 days CKD subgroup: Creatinine between 1.5 and 2.5 mg/dl, which equates to eGFR approx 45-26[a], therefore mostly stage	• Mortality • Hospitalisation • Hyperkalaemia	Recruitment 1992-94. 31% of patients in trial had CKD stage 3b+ Subgroup status: Ejection fraction: All reduced NYHA class: Mixed (mainly III) Industry funded

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Study	Intervention and comparison	Population	Outcomes	Comments
		3b		
CHARM-Overall trial: Desai 2007[95] (Pfeffer 2003[260])	Intervention 1: Angiotensin receptor antagonists. Candesartan up to 32mg (as tolerated) Intervention 2: Placebo Duration 3.2y average (range 2-4y).	N=154 patients with CKD Subgroup analysis, pre-specified but not stratified HF: symptomatic HF (NYHA II-IV) for at least four weeks CKD subgroup: Creatinine between 2 and 3 mg/dl, equating approximately to GFR 22-34[a], stage 3b-4	• Hospitalisation • Hyperkalaemia	Analysis of pooled results of three trials (looking at ARBs in different HF populations). 2% of patients in trials had CKD stage 3b+ Subgroup status: Ejection fraction: Mixed NYHA class: Mixed (II-IV) Industry funded
HEAAL trial: Konstam 2009[179]	Intervention 1: Angiotensin receptor antagonists. Losartan 150mg per day Intervention 2: Angiotensin receptor antagonists. Losartan 50mg daily Duration median 4.7y	N=945 patients with CKD Pre-specified subgroup analysis of multicentre study. HF: NYHA class II-IV, with LVEF≤40%, intolerant to ACE-inhibitors CKD subgroup: eGFR ~30[a]-60, class 3	• Hospitalisation	Recruitment dates not reported. 20% of patients in trial had CKD 3a+ Subgroup status: Ejection fraction: All reduced NYHA class: Mixed, most class II Funded by industry
SOLVD-treat trial: Bowling 2013[46] (Bohm 2014[42]; SOLVD investigators 1991 [316])	Intervention 1: Angiotensin converting enzyme (ACE) inhibitors. Enalapril 2.5 to 20mg/day Intervention 2: Placebo Duration Mean 41 months	N=1036 patients with CKD Post-hoc subgroup analysis of older trial[b] HF: LVEF <35% who were not currently receiving ACEIs CKD subgroup: eGFR~30[a]-60, class 3	• Mortality • Hospitalisation • Renal function • Hyperkalaemia	Recruited 1986-89. 40% of patients in trial had CKD (10% stage 3b+) Subgroup status: Ejection fraction: All reduced NYHA class: mixed Original study funded by industry, but this analysis was not
VAL-HeFT trial: Anand 2009[12] (Lesogor 2013[197]; Cohn 2001[68])	Intervention 1: Angiotensin receptor antagonists/blockers (ARB) Valsartan, target dose 160mg twice a day with creatinine and blood	N=2890 Post-hoc analysis of multicentre trial. HF: Stable, symptomatic HF, LVSD	• Mortality • Hospitalisation • Renal function • Renal failure • Hyperkalaemia	Recruitment dates NK. 58% of patients in trial had CKD stage 3a+ Subgroup status: Ejection fraction: All

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Study	Intervention and comparison	Population	Outcomes	Comments
	pressure monitoring Intervention 2: Placebo with creatinine and blood pressure monitoring Duration 2y average (mean 23 months, range 0-38 months)	on echo. On HF medication. CKD subgroup: eGFR~26[a]-59 (further subdivided by those with and without proteinuria) mostly stage 3, some early 4.		reduced NYHA class: Mixed Funded by industry
CIBIS-II trial: Castagno 2010 [60] (Dargie 1999 [84])	Intervention 1: Beta-blockers (BB). Bisoprolol dose increased progressively to 10mg daily according to tolerance. Intervention 2: Placebo. Duration 1.3y average (mean)	N = 1119 patients with CKD Subgroup analysis of older trial[b] HF: LVEF 35% or less. Symptoms corresponding to class III or IV of the New York Heart Association (NYHA). Stability during the preceding 6 weeks. Cardiovascular therapy stable 2weeks, including a diuretic and ACE inhibitor. CKD subgroup: Two strata • eGFR 45-59, stage 3a, n=669 • eGFR ~20[a]-45, stage 3b+, n=450	• Mortality • Hospitalisation	Recruitment dates not reported. 43% of patients in trial had CKD (17% stage 3b+) Subgroup status: Ejection fraction: All reduced NYHA class: Class III or IV Industry funded
MERIT-HF trial: Ghali 2009[130] (MERIT-HF group 1999[221])	Intervention 1: Beta-blockers (BB). Metoprolol CR/XL. target dose of 200mg daily. Intervention 2: Placebo. Duration 1 year	N=1469 patients with CKD Post-hoc subgroup analysis of older trial[b] HF: aged 40-80 y, HF class II-IV, ejection fraction <40% taking ACE-I unless not tolerated and diuretics. CKD subgroup: Two strata • eGFR 45 to 60, class 3a, n=976 • eGFR <45, class 3b+, n=493	• Mortality • Hospitalisation	Recruitment 1997-98. 37% of patients in trial had CKD (12% stage 3b+) Subgroup status: Ejection fraction: All reduced NYHA class: Mixed Funded by industry

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Study	Intervention and comparison	Population	Outcomes	Comments
SENIORS trial: Cohen-solal 2009[67] (Flather 2005[119])	Intervention 1: Beta-blockers (BB). Nebivolol initial target of 10mg once daily Intervention 2: Placebo. Duration mean 21 (SD 9) months.	N=704 patients with CKD Post-hoc subgroup analysis of multicentre trial of elderly patients HF: Aged 70 years or over. Documented heart failure of any severity, plus either: LVEF of <35% in last 6 months; or hospitalisation for decompensated HF in the previous year CKD subgroup: Tertile of study population with the poorest renal function, eGFR ~20[a]-55.5, mostly stage 3	• Mortality • Hospitalisation • Renal function • Bradycardia • Hypotension	Recruitment 2000-02. Divided into tertiles (33%) of renal function. Subgroups: Ejection fraction: Mixed NYHA class: Mixed Funded by industry
EMPHASIS-HF trial: Eschalier 2013[113] (Zannad 2011[377])	Intervention 1: Mineralocorticoid receptor antagonists (MRA). Eplerenone 50mg once daily, with potassium monitoring Intervention 2: Placebo, with potassium monitoring Duration ave 2y (median 21 months, range 0-60 months).	N=912 patients with CKD Pre-specified subgroup analysis of multicentre trial. HF: NYHA functional class II symptoms, age ≥55y, an EF≤30% (or 30-35% with QRS duration of >130 msec on electrocardiography), admission for cardiovascular reason within last six months (or BNP ≥250 pg/ml). Existing tx with ACE-I and/or ARB, and a B-blocker (unless contraindicated). CKD subgroup: eGFR 30-60, stage 3	• Hospitalisation • Renal function • Hyperkalaemia	Recruited 2006-10. 33% of patients in trial had CKD stage 3a+ Subgroup status: Ejection fraction: All reduced NYHA class: All patients class II Funded by industry
RALES trial: Vardeny 2012[351] (Pitt 1999[268], Vardeny 2014[350])	Intervention 1: Mineralocorticoid receptor antagonists (MRA). Spironolactone dose between 12.5-50mg	N=792 patients with CKD Post-hoc subgroup analysis of older trial[b]	• Mortality • Hospitalisation • Hyperkalaemia	Recruited 1995-96. 48% of patients in trial had CKD class 3a+

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Study	Intervention and comparison	Population	Outcomes	Comments
	per day according to response Intervention 2: Placebo Duration 2y	HF: HF for at least 6 weeks, NYHA class III-IV and had been NYHA IV at some point in the previous 6 months, were being treated with an ACE inhibitor (if tolerated) and a loop diuretic, LVEF <35% CKD subgroup: eGFR~26[a]-59,mostly class 3		Subgroup status: Ejection fraction: All reduced NYHA class: Class III or IV Funded by industry
SHIFT trial: Voors 2014[361] (Swedberg 2010[324])	Intervention 1: Ivabradine to a target dose of 7·5 mg twice daily according to heart rate Intervention 2: Placebo according to heart rate Duration Median 23 months.	N=1579 patients with CKD Pre-specified subgroup of multicentre trial HF: Adults in sinus rhythm ≥70 bpm. Stable symptomatic heart failure, admission for HF within the previous year, and an LVEF of ≤35% CKD subgroup: eGFR~30[a]-60, stage 3	• Renal function • Bradycardia • Hyperkalaemia	Recruitment 2006-10. 26% of patients in trial had CKD stage 3a+ Subgroup status: Ejection fraction: All reduced NYHA class: Mixed Funded by industry
DIG trial: Shlipak 2004[311] (DIG Group, 1997[97])	Intervention 1: Digoxin. An algorithm based on age, gender, weight and creatinine levels determined doses of digoxin. Intervention 2: Placebo Duration mean 3 years	N=3157 patients with CKD Subgroup analysis of multicentre North American trial HF: Stable heart failure and left ventricular ejection fraction <45% and were in sinus rhythm CKD subgroup: Two strata • eGFR 30-59, stage 3, n=2939 • eGFR ~20[a]-30, stage 4+, n=218	• Mortality • Hospitalisation	Recruited 1991-93. 46% of patients in trial had CKD (3% stage 4+) Subgroup status: Ejection fraction: All reduced NYHA class: Mixed

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(a) GFR approximated using creatinine level (umol/l) and average participant demographics using the abbreviated MDRD equation: 186 x (Creat / 88.4)$^{-1.154}$ x (mean age)$^{-0.203}$ x (0.742 x (proportion female%))

(b) Ten or more years elapsed between the publication of the main trial results and the publication of the reported sub-group analysis

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Table 60: Clinical evidence summary: ACE-inhibitor versus Placebo (CKD stages 3-4)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ACE-inhibitor
All-cause mortality - CKD stages 3-4	1036 (1 study) 41 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	HR 0.88 (0.73 to 1.06)	385 per 1000	37 fewer per 1000 (from 86 fewer to 18 more)
All-cause mortality - CKD stage 3b and 4 only	268 (1 study) 41 months	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	HR 0.76 (0.54 to 1.07)	396 per 1000	78 fewer per 1000 (from 158 fewer to 21 more)
All-cause hospitalisation	1036 (1 study)	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	HR 0.88 (0.73 to 1.06)	483 per 1000	43 fewer per 1000 (from 101 fewer to 20 more)
Renal function (change in serum creatinine umol/l)	967 (1 study) 12 months	⨁⨁⊖⊖ LOW[a] due to risk of bias		The mean change in serum creatinine (umol/l) in the control groups was -0.02 umol/l	The mean change in serum creatinine (umol/l) in the intervention groups was 0.06 higher (0.02 to 0.1 higher)
Hyperkalaemia	970 (1 study) 41 months	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.62 (0.58 to 4.5)	12 per 1000	7 more per 1000 (from 5 fewer to 42 more)

a Downgraded by 2 increments if the majority of the evidence was at very high risk of biasb Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 61: ACE-inhibitor high dose versus low dose (CKD stages 3b-4)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low dose	Risk difference with ACE-inhibitor high dose (CKD stages 3b-4) (95% CI)
All-cause mortality	988 (1 study) 46 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, indirectness	HR 1.02 (0.86 to 1.21)	Overall risk[a]	
				520 per 1000	7 more per 1000 (from 52 fewer to 69 more)
Mortality or Hospitalisation	988 (1 study) 46 months	⊕⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness	HR 1.02 (0.89 to 1.16)	Overall risk[a]	
				870 per 1000	5 more per 1000 (from 33 fewer to 36 more)
Renal dysfunction or hyperkalaemia	988 (1 study) 46 months	⊕⊖⊖⊖ VERY LOW[b,c,d,e] due to risk of bias, indirectness, imprecision	RR 1.27 (1.07 to 1.50)	318 per 1000	86 more per 1000 (from 22 more to 159 more)
Hypotension/Dizziness	988 (1 study) 46 months	⊕⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness	RR 1.56 (1.28 to 1.89)	237 per 1000	133 more per 1000 (from 66 more to 211 more)

a Data insufficient to calculate control group, overall risk for CKD group given
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment because the majority of evidence was from an indirect population (defined CKD in terms of creatinine, not eGFR)
d Downgraded by 1 increment because the outcome was compound, and could not extract protocol outcome
e Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 62: Angiotensin receptor antagonist (ARB) versus placebo (CKD class 3b-4)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ARB (95% CI)
All-cause mortality	2917 (1 study) 23 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	HR 1.01 (0.85 to 1.2)	237 per 1000	2 more per 1000 (from 32 fewer to 40 more)
Combined outcome: cardiovascular mortality or HF admission	154 (1 study) 3.2 years	⊕⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	HR 0.92 (0.79 to 1.07)	629 per 1000	31 fewer per 1000 (from 86 fewer to 25 more)
Morbid event (includes hospitalisation and death)	2917 (1 study) 23 months	⊕⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	HR 0.86 (0.74 to 1)	381 per 1000	43 fewer per 1000 (from 82 fewer to 0 more)
Renal function: change in eGFR	2179 (1 study) 23 months	⊕⊕⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision		The mean change in eGFR in the control groups was -1.2 ml/min	The mean in eGFR in the intervention groups was 3.6 lower (4.31 to 2.89 lower)
Renal failure - progression to dialysis	2911 (1 study) 3.2 years	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	Not estimable[d]	Not estimable[d]	Not estimable[d]
Hyperkalaemia	3065 (2 studies) 30 months	⊕⊕⊖⊖ LOW[a] due to risk of bias	RR 1.85 (1.4 to 2.43)	73 per 1000	62 more per 1000 (from 29 more to 104 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment due to indirectness, as compound outcome rather than numbers of admissions
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ARB (95% CI)
d Unable to calculate as there were zero events in both arms					

Table 63: ARB high dose versus low dose (CKD class 3a/b)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low dose	Risk difference with ARB high dose (95% CI)
Combined outcome: death or HF hospitalisation	945 (1 study) 4.7 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	HR 0.98 (0.85 to 1.13)	820 per 1000	6 fewer per 1000 (from 53 fewer to 36 more)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded 1 increment due to indirectness as outcome was compound rather than numbers of admissions					

Table 64: Beta-blocker versus placebo (CKD stages 3-4)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Beta-blocker (95% CI)
All-cause mortality - CKD class 3a	1645 (2 studies) 1.1 years	⨁⨁⊖⊖ LOW[b] due to risk of bias	HR 0.69 (0.51 to 0.91)	Estimate[a]	
				62 per 1000	19 fewer per 1000 (from 5 fewer to 30 fewer)
All-cause mortality - CKD class 3b-4	958	⨁⨁⊖⊖	HR 0.55	Estimate[a]	

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Beta-blocker (95% CI)
	(2 studies) 1.1 years	LOW[b] due to risk of bias	(0.32 to 0.94)	89 per 1000	39 fewer per 1000 (from 5 fewer to 60 fewer)
All-cause mortality - CKD class 3-4	704 (1 study) 1.8 years	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	HR 0.76 (0.56 to 1.03)	258 per 1000	55 fewer per 1000 (from 104 fewer to 7 more)
Death or hospitalisation - CKD class 3a	669 (1 study) 1.3 years	⊕⊖⊖⊖ VERY LOW[b,c,e] due to risk of bias, indirectness, imprecision	HR 0.72 (0.57 to 0.91)	Overall[d]	
				464 per 1000	102 fewer per 1000 (from 31 fewer to 165 fewer)
Death or hospitalisation - CKD class 3b-4	235 (1 study) 1.3 years	⊕⊖⊖⊖ VERY LOW[b,c,e] due to risk of bias, indirectness, imprecision	HR 0.82 (0.64 to 1.05)	Overall[d]	
				553 per 1000	70 fewer per 1000 (from 150 fewer to 18 more)
Hospitalisation (time to event) - CKD class 3a	870 (1 study) 1 years	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	HR 0.9 (0.73 to 1.11)	374 per 1000	30 fewer per 1000 (from 84 fewer to 31 more)
Hospitalisation (time to event) - CKD class 3b-4	341 (1 study) 1 years	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	HR 0.61 (0.47 to 0.79)	883 per 1000	153 fewer per 1000 (from 67 fewer to 248 fewer)
Hospitalisation for cardiovascular disorder - CKD class 3-4	704 (1 study) 1.8 years	⊕⊖⊖⊖ VERY LOW[b,c,f] due to risk of bias,	HR 0.93 (0.7 to 1.24)	292 per 1000	17 fewer per 1000 (from 77 fewer to 56 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Beta-blocker (95% CI)
		indirectness, imprecision			
HF hospitalisation - CKD class 3a	669 (1 study) 1.3 years	⊕⊖⊖⊖ VERY LOW[b,c,f] due to risk of bias, indirectness, imprecision	HR 0.66 (0.45 to 0.97)	Overall[d]	
				167 per 1000	53 fewer per 1000 (from 5 fewer to 88 fewer)
HF hospitalisation - CKD class 3b-4	450 (1 study) 1.3 years	⊕⊖⊖⊖ VERY LOW[b,c,f] due to risk of bias, indirectness, imprecision	HR 0.76 (0.51 to 1.13)	Overall[d]	
				220 per 1000	48 fewer per 1000 (from 101 fewer to 25 more)
Renal failure (not defined)	886 (1 study) 1.8 years	⊕⊕⊖⊖ LOW[b] due to risk of bias	Not estimable[g]	Not estimable[g]	Not estimable[g]
Bradycardia	886 (1 study) 1.8 years	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.35 (0.58 to 3.18)	20 per 1000	7 more per 1000 (from 8 fewer to 44 more)
Hypotension	886 (1 study) 1.8 years	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	Peto Odds Ratio 7.51 (0.47 to 120.22)	0 per 1000	0 more per 1000 (from 0 more to 10 more)[i]

a Control risk taken from MERIT-HF
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Data insufficient to calculate control risk. Overall risk given
e Downgraded by 1 increment due to indirectness as a compound outcome was reported rather than numbers of admissions

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Beta-blocker (95% CI)
f Downgraded by 1 increment due to indirectness as the outcome was reported as a subset of the protocol outcome all-cause hospitalisation g Unable to calculate as zero events in both arms i Absolute risk difference calculated using RevMan software					

Table 65: Digoxin versus placebo (CKD class 3-5)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Digoxin (95% CI)
All-cause mortality - CKD class 3a/b	2939 (1 study) 3 years	⨁⨁⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	HR 0.95 (0.85 to 1.06)	Overall[a]	
				380 per 1000	15 fewer per 1000 (from 46 fewer to 18 more)
All-cause mortality - CKD class 4-5	218 (1 study) 3 years	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	HR 0.93 (0.65 to 1.33)	Overall[a]	
				580 per 1000	26 fewer per 1000 (from 149 fewer to 105 more)
Death or Hospitalisation - CKD class 3a/b	2939 (1 study) 3 years	⨁⊖⊖⊖ VERY LOW [a,e] due to risk of bias, indirectness	HR 0.84 (0.76 to 0.93)	Low estimate[d]	
				380 per 1000	49 fewer per 1000 (from 21 fewer to 75 fewer)
Death or Hospitalisation - CKD class 4-5	218 (1 study) 3 years	⨁⊖⊖⊖ VERY LOW[b,c,e] due to risk of bias, indirectness, imprecision	HR 0.77 (0.55 to 1.08)	Low estimate[d]	
				580 per 1000	93 fewer per 1000 (from 201 fewer to 28 more)
a Data not sufficient to calculate control risk. Overall risk for given for participants with eGFR around 45 or below 34 respectively b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Digoxin (95% CI)
d Data not sufficient to calculate control risk. Mortality risk given per group as above (actual risk would be higher as includes hospitalisation) e Downgraded due to indirectness as composite outcome rather than protocol outcome					

Table 66: Ivabradine versus placebo (CKD class 3a/b)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Ivabradine (95% CI)
Renal function: change in eGFR	865 (1 study) 23 months	⨁⨁⊖⊖ LOW[a] due to risk of bias		The mean eGFR in control was 53.7 ml/min (SD 17.3)	The mean eGFR in the intervention groups was 0.2 higher (2 lower to 2.4 higher)
Renal failure	1579 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.95 (0.71 to 1.27)	106 per 1000	5 fewer per 1000 (from 31 fewer to 29 more)
Hyperkalaemia	1579 (1 study) 23 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.53 (0.28 to 1.01)	34 per 1000	16 fewer per 1000 (from 24 fewer to 0 more)
Bradycardia (symptomatic only)	1579 (1 study) 23 months	⨁⨁⊖⊖ LOW[a] due to risk of bias	RR 2.56 (1.39 to 4.72)	18 per 1000	27 more per 1000 (from 7 more to 65 more)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 67: MRA versus placebo (CKD class 3a/b)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MRA (95% CI)
All-cause mortality (RR)	792 (1 study) 2 years	⊕⊕⊖⊖ LOW[a,b,c] due to risk of bias (subgroup), imprecision	RR 0.69 (0.45 to 1.05)	119 per 1000	37 fewer per 1000 (from 66 fewer to 6 more)
Combined outcome: cardiovascular mortality or HF admission (RR)	912 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 0.71 (0.58 to 0.87)	345 per 1000	100 fewer per 1000 (from 45 fewer to 145 fewer)
HF hospitalisation (RR)	792 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW[a,c,e] due to risk of bias (subgroup), indirectness, imprecision	RR 0.7 (0.45 to 1.09)	109 per 1000	33 fewer per 1000 (from 60 fewer to 10 more)
Renal function change in eGFR	883 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision		The mean change in eGFR in the control groups was 4.15 ml/min (improvement)	The mean change in eGFR in the intervention groups was 2.11 less improvement (4.23 less to 0.01 more)
Hyperkalaemia	1675 (2 studies) 2 years	⊕⊕⊖⊖ LOW[a,f] due to risk of bias	RR 2.32 (1.37 to 3.91)	89 per 1000	118 more per 1000 (from 33 more to 260 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Reports mortality as relative risk, rather than protocol time to event but not downgraded
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Downgraded 1 increment for indirectness as reporting compound outcome rather than numbers of hospitalisations
e Downgraded 1 increment for indirectness as reporting only proportion having HF hospitalisations, not numbers of all cause hospitalisations
f Statistical heterogeneity, but not downgraded as both studies appear to show clinically important difference (harm). Subgroup analysis not done as not appropriate where only two studies.

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6.2.6.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in Appendix D.

6.2.6.5 Evidence statements

Clinical

Twelve studies were identified for inclusion within the review. The majority of the evidence was from subgroup analyses of trials in the general HFREF population. The studies included comparisons of different classes of medicine including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, digoxin, ivabradine and mineralocorticoid receptor antagonists with placebo in people with chronic kidney disease (specifically at least stage IIIa). Outcomes were analysed by disease severity, where this information was reported by the paper. Evidence was also found comparing high dose ARB with low dose ARB and high dose ACE-inhibitor with low dose ACE-inhibitor. The evidence ranged from low to very low quality with the majority being rated as very low quality. This was based on a number of contributory factors including risk of bias and imprecision due to wide confidence intervals. The studies frequently used a composite outcome of death or hospitalisation, which led to the evidence being downgraded for indirectness.

No evidence was identified for the outcomes QoL, arrhythmic events or progression to stage 5 kidney disease/unplanned dialysis. In addition to this no evidence was identified for the interventions of loop diuretics; sacubitril-valsartan; or hydralazine-nitrate versus placebo. Furthermore, no inter or intra class comparisons were identified.

ACE inhibitors:

For the comparison of ACE inhibitors versus placebo the evidence was rated as very low quality and suggested a clinically important reduction in hospitalisations with ACE inhibitors (n=1036) (associated with wide confidence intervals around the effect estimate).

For the outcomes renal function (n=967) and hyperkalemia (n=970) there was no clinical effect of ACE inhibitors. With high dose versus low dose ACE inhibitors all of the outcomes were again rated as very low quality. The outcomes renal dysfunction or hyperkalaemia (associated with wide confidence intervals around the effect estimate) and hypotension/dizziness all suggested a clinically important increase in events with high dose ACE inhibitors (n=988). Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

ARBs:

For the comparison of ARB versus placebo the evidence was rated from low to very low quality. The evidence suggested a clinically important increase in hyperkalemia (n=3065) with ARBs. The composite outcome of CV mortality and HF admission (n=154) suggested a clinically important reduction in events with ARBs. This was also the case for the outcome 'morbid events' which included hospitalisations and death (n=2917). For renal function there was no clinically important effect of ARBs on eGFR (n=2179) and zero events of renal failure or progression to dialysis were reported in a single study (n=2911). For the comparison of high dose ARBs with low dose the evidence was rated as very low quality and suggested a clinically important reduction in HF

hospitalisations (n=945). Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

BBs:

For the comparison of BBs versus placebo the majority of the evidence was rated as very low quality. The outcome all-cause mortality suggested a clinically important reduction in deaths for CKD class 3a (n=1645) and CKD class 3b-4 (n=958) with BBs. This was also the case for the composite outcome of death or hospitalisation (CKD class 3a (n=669) and hospitalisation alone (CKD class 3a (n=870) and CKD class 3b-4 (n=341)). There was also a clinically important reduction in HF hospitalisations for both CKD class 3a (n=669) and CKD class 3b-4 (n=450) with BBs. For the outcomes bradycardia and hypotension there was no clinical effect of BBs (n=886). Mortality in the CKD class 3-4 (n=704) and CKD class 3b-4 (n=235))did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

Digoxin:

For the comparison of digoxin versus placebo the majority of the evidence was rated as very low quality. Mortality in both CKD class 3a-b (n=2939) and CKD class 4-5 (n=218)did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.This was also the case for the composite outcome of death or hospitalisation which again showed a clinically important reduction in events with digoxin.

Ivabradine:

For the comparison of ivabradine versus placebo the evidence ranged from low to very low quality, and suggested no clinical effect of ivabradine on the outcomes renal function (n=865), renal failure (n=1579), hyperkalaemia (n=1579) and symptomatic bradycardia (n=1579).

MRAs:

For the comparison of MRA versus placebo the evidence ranged from low to very low quality. HF hospitalisations (n=792) suggested a clinically important reduction with MRAs. This was also the case for the combined outcome of cardiovascular mortality and HF admission (n=912) (associated with wide confidence intervals around the effect estimate). For the outcome hyperkalemia the evidence suggested a clinically important increase with MRAs (n=1675). Mortality (n=792) did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

Economic

- No relevant economic evaluations were identified.

6.2.6.6 Recommendations and link to evidence

Recommendations	**For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR of 30ml/min/1.73 m^2 or above:** • **Offer the treatment outlined in section 6.2.7 and** • **If the person's eGFR is 45ml/min/1.73 m^2 or below, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, mineralocorticoid receptor antagonists and digoxin. [2018]** **For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR below 30 ml/min/1.73 m^2, the**

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	specialist heart failure MDT should consider liaising with a renal physician. [2018] **Monitor the response to titration of medicines closely in people who have heart failure with reduced ejection fraction and chronic kidney disease, taking into account the increased risk of hyperkalaemia. [2018]**
Relative values of different outcomes	The committee agreed that all-cause mortality, all-cause unplanned hospitalisation and quality of life were the most critical outcomes for determining the efficacy and potential harms of heart failure medications in people with CKD. The committee agreed that the impact of heart failure medication on renal function, and adverse events of the medication (specifically, bradycardia, arrhythmia, hypotension and hyperkalaemia) were also important outcomes. No evidence was found on the effect of any of the medications on quality of life in people with HF and CKD.
Quality of the clinical evidence	The evidence found was exclusively from subgroup analyses (SGA) of trials in the general HFREF population. None of the subgroups had been pre-specified and stratified, which introduced a risk of bias. Four of the SGAs were published over 10 years after the overall trial was published. The baseline population characteristics of the intervention and control arms within each subgroup were often not published, preventing a proper assessment of the risk of selection bias. The analysis was sometimes given as summary statistics only, without details regarding the numbers in each group, which may also have resulted in bias. These factors combined, along with additional bias issues specific to the individual studies and outcomes, meant that all the evidence found had a high or very high risk of bias. The studies frequently used a composite outcome of death or hospitalisation, which led to the evidence being downgraded for indirectness, as it was not possible to assess the impact on each of these critical outcomes separately. A number of medications had no reported evidence with regards to the population with CKD: loop diuretics; sacubitril-valsartan; and hydralazine-nitrate. The only evidence found on hydralazine-nitrate was the African American Heart Failure Trial[327] which was excluded, as the possible CKD subgroup was referred to as having “history of chronic renal insufficiency” without further definition. Twelve SGAs were considered, 10 of which compared intervention to placebo and 2 that compared different doses of the same drug. There were no intra or inter class comparisons. Most trials considered the intervention on top of existing heart failure drugs (for the era in which the trial took place), except for when Angiotensin II Receptor Blocker (ARB) was considered as an alternative when Angiotensin Converting Enzyme Inhibitors (ACE-I) were not tolerated. Notwithstanding the limitations of the evidence base, the committee agreed that it was important to provide advice for this common subgroup of HFREF patients. Based on the evidence reviewed and the experience of the committee members, consensus was reached on the optimal treatment approach for patients with HFREF and CKD (see discussion below).
Trade-off between clinical benefits	The committee noted the new HFREF treatment algorithm in this guideline. First-line is double therapy with beta-blocker and ACE-I; or if ACE-I is not

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and harms	tolerated, an ARB. If still symptomatic, the addition of a Mineralocorticoid Receptor Antagonist (MRA) ("triple therapy"). Beta-blocker, ACE-I/ARB and MRA combined is referred to as "triple therapy". Further medication options after seeking specialist advice, might be sacubitril valsartan (in place of ACEi [or ARB]), digoxin, or ivabradine. For people with CKD stage III and HFREF, the evidence suggested that ACE-I are efficacious and do not result in excess renal complications (such as hyperkalaemia). The committee agreed that ACE-I should be used as part of first-line treatment, as in the general HFREF population. This approach accords with the current practice of regularly prescribing ACE-I in CKD to prevent adverse cardiovascular outcomes. However, people with both CKD and HFREF appear not to get the same increased benefit of a high dose ACEI-I seen in the general HFREF population, perhaps because of additional renal adverse effects related to the drug. The committee agreed that prescribers may wish to carefully consider the utility of titrating to the highest doses in this population, as a lower dose may be just as effective overall, when the potential harms are weighed against the benefits. The high absolute risk of hyperkalaemia was not felt to be a reason to withhold these effective drugs, but should lead to increased attention in monitoring. The evidence also suggested an overall benefit of beta-blockers as first-line treatment alongside ACE-I. This is aligned with practice, with beta-blockers being routinely prescribed in patients with HFREF and established kidney disease. The committee agreed that the evidence on MRA in the CKD/HFREF population also supported the adoption of the general recommendation that it should be prescribed if patients are still symptomatic on beta-blocker plus ACE-I. Just as for the general HFREF population, any further medication (beyond beta-blockers, ACE-I and MRA) for heart failure in people with CKD should be prescribed by, or in liaison with, a heart failure specialist. The committee noted that ARBs for people with CKD showed only limited benefit, based on the evidence reviewed. For digoxin, there was no safety evidence, and the committee expressed concern that the risk of complete heart block and digitalis' toxicity may be higher in those with CKD. As digoxin is primarily excreted by the kidneys, safe use of digoxin in people with CKD would include dose titration based on biochemistry and appropriate monitoring, such as the regimen used in the DIG trial [97]. The risk of hyperkalaemia is important in this group. Several studies showed high numbers of additional incidents of hyperkalaemia in the intervention arm. But the risk of hyperkalaemia in this group is not confined to the issue of these particular drugs, as the risk for patients with CKD is high even on placebo. In CKD stage IV, monitoring is already fairly intensive, so any incident hyperkalaemia should be identified and responded to quickly. For people with CKD stage III on heart failure medication, especially on triple therapy, the committee stressed the importance of monitoring of electrolytes and appropriate response to any deterioration. In general, the committee felt the evidence shows the efficacy and safety of specific drugs in this group of patients with renal impairment. Patients with HFREF and CKD stage IIIa or less should be offered standard double or triple therapy, with appropriate modifications to dosing and careful monitoring. The evidence in stage IIIb patients was more limited, and while this group

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	would also benefit from standard HFREF therapies, the evidence was not sufficient to support an 'offer' recommendation. Instead, the committee agreed that standard HFREF drugs should be considered in this group. In CKD stage IV, the side effects of all of these medications is likely to be increased. While there is not a substantial evidence base in this population, the committee agreed that standard HFREF treatment recommendations should generally be applied, subject to the consideration of individual risk factors and liaison with renal specialists as appropriate.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified specifically for patients with heart failure and chronic kidney disease. Unit costs were not presented to the committee as all of the drugs reviewed are already recommended for all patients with HFREF and have been shown to be cost-effective treatments The committee discussed the cost of monitoring that is required in patients with both HFREF *and* CKD. The cost of monitoring would primarily involve blood tests to assess serum sodium, potassium, creatinine and eGFR and are therefore likely to be consist of a biochemistry blood test which is a small cost. The committee stressed that close monitoring is even more important in patients with CKD to help prevent hyperkalaemia and possible acute kidney injuries, and therefore the cost of monitoring could be offset by the savings by reducing the potential adverse effects of heart failure treatment on kidney function. The committee stated that close monitoring of patients with HFREF and CKD is common in current practice as these patients are high risk and therefore did not consider that there would be a significant additional resource impact. Based on the balance of the clinical risks and benefits the committee considered that as these drugs are highly cost effective for HF-REF patients and the additional cost of monitoring would be low that these treatments would remain cost effective in patients with HFREF and CKD stages I to IIIb.
Other considerations	Most patients with heart failure will have some degree of renal impairment. Specialist renal care for people with co-morbid CKD and heart failure is unusual, as renal physicians generally take referrals only after stage IV, unless there are other kidney issues. The committee reported a lack of clarity about using ACE-I, ARB and MRA in patients with CKD where renal function is declining. They discussed that in these circumstances, total cessation of these medications may deprive patients of the beneficial effects on morbidity and mortality. Therefore, modification to the doses of these agents, or even temporary cessation of one or more agents, should be made based on individual patient circumstances, and guidance from renal physicians should be considered where necessary. Due to the lack of evidence identified in this review for those with more severe CKD the committee noted this as an area warranting further research attention. In particular, the committee considered it important to establish the safety and optimal dosing for people with HFREF and more severe CKD (stages IIIb or greater).

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6.2.7 All recommendations for the pharmacological treatment of heart failure

6.2.7.1 Diuretics

25. **Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. [2003]**

26. **People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice. [2003, amended 2018]**

6.2.7.2 Calcium-channel blockers

27. **Avoid verapamil, diltiazem and short-acting dihydropyridine agents in people who have heart failure with reduced ejection fraction. [2003, amended 2018]**

6.2.7.3 Amiodarone

28. **Make the decision to prescribe amiodarone in consultation with a specialist. [2003]**

29. **Review the need to continue the amiodarone prescription at the 6-monthly clinical review. [2003, amended 2018]**

30. **Offer people taking amiodarone liver and thyroid function tests, and a review of side effects, as part of their routine 6-monthly clinical review. [2003, amended 2018]**

6.2.7.4 Anticoagulants

31. **For people who have heart failure and atrial fibrillation, follow the recommendations on anticoagulation in the NICE guideline on atrial fibrillation. Be aware of the effects of impaired renal and liver function on anticoagulant therapies. [2018]**

32. **In people with heart failure in sinus rhythm, anticoagulation should be considered for those with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus. [2003]**

6.2.7.5 Contraception and pregnancy

In women of childbearing potential who have heart failure, contraception and pregnancy should be discussed. If pregnancy is being considered or occurs, specialist advice should be sought. Subsequently, specialist care should be shared between the cardiologist and obstetrician. [2003]

6.2.7.6 ACE inhibitors and beta-blockers

33. **Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have heart failure with reduced ejection fraction. Use clinical judgement when deciding which drug to start first. [2010]**

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34. **Do not offer ACE inhibitor therapy if there is a clinical suspicion of haemodynamically significant valve disease until the valve disease has been assessed by a specialist. [2003]**

35. **Do not withhold treatment with a beta-blocker solely because of age or the presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. [2010]**

6.2.7.6.1 Starting and monitoring ACE inhibitors

36. **Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every 2 weeks) until the target or maximum tolerated dose is reached. [2010]**

37. **Measure serum sodium and potassium and assess renal function before and 1 to 2 weeks after starting an ACE inhibitor, and after each dose increment.[2010,amended 2018]**

38. **Measure blood pressure before and after each dose increment of an ACE inhibitor. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]**

39. **Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2010, amended 2018]**

6.2.7.6.2 Starting and monitoring beta-blockers

40. **Introduce beta-blockers in a 'start low, go slow' manner. Assess heart rate, and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. [2010, amended 2018]**

41. **Switch people whose condition is stable and who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. [2010]**

6.2.7.7 Alternative treatments if ACE inhibitors are not tolerated

6.2.7.7.1 Angiotensin II receptor antagonists (ARBs)

42. **Consider an angiotensin II receptor blocker (ARB) licensed for heart failure as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side effects with ACE inhibitors. [2010]**

43. **Measure serum sodium and potassium and assess renal function before and after starting an ARB and after each dose increment.[2010, amended 2018]**

44. **Measure blood pressure after each dose increment of an ARB. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]**

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45. Once the target or maximum tolerated dose of an ARB is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2010 amended 2018]

6.2.7.7.2 Hydralazine in combination with nitrate

46. If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have heart failure with reduced ejection fraction. [2010]

6.2.7.8 Additional treatments if heart failure remains symptomatic or worsens

6.2.7.8.1 Mineralcorticoid receptor antagonists (MRAs)

47. Offer a mineralcorticoid receptor antagonist (MRA) in addition to an angiotensin-converting enzyme inhibitor (ACE) or ARB and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. [2018]

48. Measure serum sodium and potassium and assess renal function before and after starting an MRA and after each dose increment. [2018]

49. Measure blood pressure before and after each dose increment of MRA. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]

50. Once the target, or maximum tolerated, dose of an MRA is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2018]

6.2.7.8.2 Specialist treatment

Ivabradine

6.2.7.8.3 These recommendations are from Ivabradine for treating chronic heart failure (NICE technology appraisal guidance 267).

51. Ivabradine is recommended as an option for treating chronic heart failure for people:

- **with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and**
- **who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and**
- **who are given ivabradine in combination with standard therapy including beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitor and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and**
- **with a left ventricular ejection fraction of 35% or less. [2012]**

52. Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. [2012]

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53. Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. [2012]

Sacubitril valsartan

These recommendations are from Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (NICE technology appraisal guidance 388)[a].

54. Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people

- **With New York Heart Association (NYHA) class II to IV symptoms and**
- **With a left ventricular ejection fraction of 35% or less and**
- **Who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBS) [2016]**

55. Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team members as defined in NICE's guideline on chronic heart failure in adults: diagnosis and management. [2016]

56. This guidance is not intended to affect the position of patients whose treatment with sacubitril valsartan was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. [2016]

Hydralazine in combination with nitrate

57. Seek specialist advice and consider offering hydralazine in combination with nitrate (especially if the person is of African or Caribbean family origin and has moderate to severe heart failure [NYHA class III/IV] with reduced ejection fraction).[2010]

Digoxin

For recommendations on digoxin for people with atrial fibrillation see the section on rate and rhythm control in the NICE guideline on atrial fibrillation

58. Digoxin is recommended for worsening or severe heart failure with reduced ejection fraction despite first line treatment for heart failure[b]. Seek specialist advice before initiating.[2010, amended 2018]

59. Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within 8–12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence[2003]

b For recommendations on digoxin for people with atrial fibrillation see the section on rate and rhythm control in the NICE guideline on atrial fibrillation

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60. the serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. [2003]

6.2.7.9 Chronic kidney disease

61. For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR of 30 ml/min/1,73 m^2 or above: (estimated glomerular filtration rate) as follows.

- **Offer the treatment outlined in section 6.2.7 and**
- **If the person's eGFR is 45 ml/min/1.73 m2 or below, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, mineralcorticoid receptor antagonists and digoxin. [2018]**

62. For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR below 30 ml/min/1.73 $m^{2,}$ the specialist heart failure MDT should consider liaising with a renal physician [2018]

63. Monitor the response to titration of medicines closely in people who have heart failure with reduced ejection fraction and chronic kidney disease, taking into account the increased risk of hyperkalaemia. [2018]

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6.3 Invasive procedures

The update to the heart failure guideline includes topics where new evidence has emerged since the publication in 2010. A review of new evidence published after 2010 was carried out in order to determine whether any changes to current recommendations where likely to be required. The decision on which topics to include in the update of the guideline was made following consultation of the scope.

This section with the exception of coronary revascularisation was not within the scope of the update. For more information on the following aspects of invasive procedures such as cardac transplantation please refer to appendix R in the 2003 guideline.

6.3.1 Coronary revascularisation

6.3.1.1 Introduction

Coronary artery disease (CAD) and heart failure often coexist and a majority of people with heart failure and reduced ejection fraction (HFREF) in the UK will have an ischaemic aetiology[149]. Myocardial ischaemia is therefore often an important additional consideration in the management of people with heart failure. Concomitant severe CAD may warrant consideration for revascularisation with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) in view of uncontrolled angina despite medical therapy, evidence of substantial myocardial ischaemia and viability or while undergoing valve intervention. Thus it might appear logical that coronary revascularisation, undertaken either surgically with CABG, or percutaneously with angioplasty, might result in improved outcomes when compared with medical therapy alone. However, the presence of left ventricular systolic dysfunction (LVSD) significantly increases the risk of both surgical and percutaneous revascularisation [373]and, if severe, may contraindicate CABG surgery altogether.

Historically, however, there has only been anecdotal evidence of improvement in symptoms or left ventricular function following revascularisation in people with heart failure in the absence of the above special indications. Early randomised studies of coronary artery bypass grafting appeared to support revascularisation, whereby the patients who derived most benefit from surgical intervention were also those patients with impaired LV function, albeit in the context of selective randomisation. However, the landscape of cardiovascular management has changed through the prescription of newer drug therapies, routine acute angioplasty, changes in surgical interventions and the availability of device therapies such as implantable cardioverter defibrillators.

It is therefore unclear if people with HFREF and severe CAD should be routinely offered myocardial revascularisation with CABG or PCI. Current practice varies widely depending on local interest and expertise as well as individual patient characteristics. This review was carried out to evaluate the emerging evidence in the field since the previous guidance was published regarding the clinical and cost effectiveness of coronary revascularisation in people with heart failure.

6.3.1.2 Review question: What is the clinical and cost effectiveness of coronary revascularisation with coronary artery bypass grafting or angioplasty in people with heart failure?

For full details see review protocol in Appendix A.

Table 68: PICO characteristics of review question

Population	People diagnosed with heart failure with reduced ejection fraction (HFREF).
Intervention	Coronary artery bypass graft surgery (CABG) CABG + ventricular reconstruction Percutaneous coronary intervention (PCI)

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Comparison	Medical management
Outcomes	CRITICAL • All-cause mortality at 30 days (Time to event) • All-cause mortality (Time to event) • Quality of life at 12 months (Continuous) • Unplanned hospitalisation at 12 months (Count rate) IMPORTANT • Additional revascularisation events at 24 months (Count rate) • Improvement of NYHA class at 12 months (Dichotomous) • Improvement in ejection fraction at 12 months (Dichotomous) • Adverse events - stroke at 12 months (Dichotomous)
Study design	Systematic Review RCT

6.3.1.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of coronary revascularisation (CABG, CABG + ventricular reconstruction or PCI) with medical management in people with heart failure and reduced ejection fraction. Two studies (reported in 14 publications) were included in the review: HEART[65] and STICH(ES)[44, 59, 98, 115, 162, 206, 213, 253, 254, 321, 356-358]. These are summarised in Table 69 below. HEART compared an invasive strategy (angiography followed by PCI or CABG at the clinician's discretion) with medical management; STICH compared CABG and medical management.

Evidence from these studies is summarised in the clinical evidence summaries below (Table 70 and Table 71). See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

Two studies were included within the 2003 CHF guideline.[24, 75] and referred to narratively. These studies have been excluded within the current update as they no longer match the review protocol. For further explanation please see the excluded studies table (appendix I) and the Recommendations and link to evidence.

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Table 69: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
HEART 2010[65]	CABG plus medical therapy n = 30 PCI plus medical therapy n = 15 Medical therapy n = 64	Age, median (IQR): CABG/PCI- 65 (58 – 70); medical therapy – 69 (60 – 74). %Male: CABG/PCI – 94; medical therapy – 93. NYHA class, n: I CABG/PCI - 13; medical therapy - 11; II CABG/PCI – 28; medical therapy - 36; III/IV CABG/PCI – 28; medical therapy – 22.	• All-cause mortality; Dichotomous • Quality of life – EQ5D; Mean difference between the groups reported only. • Quality of life - Minnesota Living With Heart Failure Questionnaire; Mean difference between the groups reported only.	Median follow-up of 4.9 years. Only 138 of the planned 800 patients were enrolled because of withdrawal of funding due to slow recruitment and because the larger STICH trial became available.
STICH(ES)[44, 59, 98, 115, 162, 206, 213, 253, 254, 321, 356-358]	CABG plus medical therapy n = 610 Medical therapy n = 602	Age year, median (IQR): CABG – 60 (54-60); medical therapy – 59 (53-67). %Male: CABG – 88; medical therapy – 88. NYHA class, n: I CABG – 65, medical therapy – 74; II – IV CABG – 545; medical therapy – 528.	• All-cause mortality at 30 days and 5 years • Quality of life – Kansas City Cardiomyopathy Questionnaire. Adjusted mean difference • Quality of life – EQ-5D (health state index); Adjusted mean difference • Quality of life – SF-12 (Physical); Adjusted mean difference • Quality of life – SF-12 (Mental); Adjusted mean difference • All-cause hospitalisations	Median follow-up of 9.8 years. The use of implantable defibrillators was encouraged as part of standard medical therapy. Data was adjusted for patients for repeated assessments of quality of life.

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Study	Intervention and comparison	Population	Outcomes	Comments
			• Stroke • Subsequent procedures – CABG • Subsequent procedures – PCI • No. in NYHA Class I	

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6.3.1.3.1 CABG versus medical therapy

Table 70: Clinical evidence summary: CABG + Medical therapy versus medical therapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical therapy	Risk difference with CABG (95% CI)
All-cause mortality	1212 (1 study) 9.8 years	⊕⊕⊖⊖ MODERATE[a] due to risk of bias	HR 0.80 (0.7 to 0.93)	661 per 1000	82 fewer per 1000 (from 27 fewer to 130 fewer)
All-cause mortality at 30 days	1212 (1 study) 30 days	⊕⊕⊕⊖ MODERATE[a] due to risk of bias	HR 3.12 (1.33 to 7.32)	12 per 1000	24 more per 1000 (from 4 more to 70 more)
Quality of life - EQ-5D Scale from: 0 to 1.	1212 (1 study) 12 months	⊕⊕⊖⊖ LOW[a,b] due to risk of bias, imprecision		The mean quality of life – EQ-5D at 12 months in the control groups was 0.776	The mean quality of life – EQ-5D at 12 months in the intervention groups was 0.05 higher (0.02 to 0.09 higher)
Quality of life - EQ5D-VAS Scale from: 0 to 100	1212 (1 study) 12 months	⊕⊕⊕⊖ MODERATE[a] due to risk of bias		The mean quality of life - EQ5D-VAS in the control groups was 65.4	The mean quality of life - EQ5D-VAS in the intervention groups was 5.9 higher (3.2 to 8.5 higher)
Quality of life – KCCQ (quality of life domain) Scale from: 0 to 100.	1212 (1 study) 12 months	⊕⊕⊕⊖ MODERATE [a] due to risk of bias		The mean quality of life - KCCQ at 12 months in the control groups was 65.6	The mean quality of life - KCCQ at 12 months in the intervention groups was 8.8 higher (5.4 to 12.2 higher)
Quality of life - SF-12 (Physical component)	1212 (1 study) 12 months	⊕⊕⊕⊖ MODERATE[a] due to risk of bias		The mean quality of life – SF-12 (physical component) at 12 months in the control groups was 40	The mean quality of life – SF-12 (physical component) at 12 months in the intervention groups was 1.5 higher

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical therapy	Risk difference with CABG (95% CI)
					(0.5 to 2.5 higher)
Quality of life - SF-12 (Mental Component)	1212 (1 study) 12 months	⊕⊕⊕⊖ MODERATE[a] due to risk of bias		The mean quality of life – SF-12(mental component) at 12 months in the control groups was 50.3	The mean quality of life – SF-12 (mental component) at 12 months in the intervention groups was 2.2 higher (0.5 to 3.9 higher)
All-cause hospitalisations	1212 (1 study) 4.7 years	⊕⊕⊕⊖ MODERATE[b] due to imprecision	RR 0.84 (0.75 to 0.94)	565 per 1000	90 fewer per 1000 (from 34 fewer to 141 fewer)
Subsequent procedures - CABG	1212 (1 study) 4.7 years	⊕⊕⊕⊖ MODERATE[a] due to risk of bias	Peto Odds Ratio 0.12 (0.08 to 0.17)	166 per 1000	146 fewer per 1000 (from 138 fewer to 153 fewer)
Subsequent procedures - PCI	1212 (1 study) 4.7 years	⊕⊕⊖⊖ LOW[a,b] due to risk of bias, imprecision	RR 0.69 (0.43 to 1.13)	61 per 1000	19 fewer per 1000 (from 35 fewer to 8 more)
NYHA class I	1212 (1 study) 4.7 years	⊕⊕⊖⊖ LOW[b,c] due to imprecision, indirectness	RR 1.22 (1.06 to 1.41)	342 per 1000	75 more per 1000 (from 21 more to 140 more)
Stroke	1212 (1 study) 9.8 years	⊕⊕⊖⊖ LOW[a,b] due to risk of	RR 1.13 (0.76 to 1.69)	68 per 1000	9 more per 1000 (from 16 fewer to 47 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical therapy	Risk difference with CABG (95% CI)
		bias, imprecision			

(a) Downgraded by 1 increment if majority of the evidence was rated high risk of bias, downgraded by 2 increments if majority of the evidence was rated very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID, downgraded by 2 increments if the confidence interval crossed both MIDs.
(c) Downgraded by 1 increment due to indirectness of the outcome (protocol outcome – improvement in NYHA class; extracted outcome no. in NYHA class I).

6.3.1.3.2 Invasive strategy (angiography with intent to revascularise (with CABG or PCI) versus medical therapy

Table 71: Clinical evidence summary: Invasive strategy + medical therapy versus medical therapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical therapy	Risk difference with invasive strategy (95% CI)
All-cause mortality	136 (1 study) 4.9 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.04 (0.67 to 1.61	368 per 1000	15 more per 1000 (from 121 fewer to 224 more)
Quality of life - EQ-5D Scale from: 0 to 1.	136 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		[c]	The mean quality of life – EQ-5D at 6 months in the intervention groups was 0.02 lower (0.14 lower to 0.10 higher)
Quality of life - MLWHF Scale from: 0 to 105.	136 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		[c]	The mean quality of life - MLWHF at 6 months in the intervention groups was 3.9 lower (11.35 lower to 3.55 higher)

(a) Downgraded by 1 increment if majority of the evidence was rated high risk of bias, downgraded by 2 increments if majority of the evidence was rated very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID, downgraded by 2 increments if the confidence interval crossed both MIDs.
(c) Unable to calculate as the study only reported the overall mean difference.

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6.3.1.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in Appendix D.

Unit costs

The unit cost of the revascularisation procedures are shown in Table 72 below. The unit cost of all-cause hospitalisation is also provided in Table 73.

Table 72: Cost of revascularisation procedures

Procedure	Code	Average cost	Source
Coronary Artery Bypass Graft (without ventricular reconstruction)	ED26A Complex Coronary Artery Bypass Graft (CC score 10+)	£17,714	NHS reference costs 2014/15[242]
Percutaneous Coronary Intervention	EY41A-B Standard Percutaneous Transluminal Coronary Angioplasty (CC score 8-12+)	£4,928 (a)	NHS reference costs 2014/15[242]

(a) Weighted cost using the activity reported for each of the included HRG codes.

Table 73: Unit costs of all-cause hospitalisation

Description	Unit cost	Source
All-cause hospitalisation (non-elective)	£2,930	NHS Reference costs 2014/15[242]

6.3.1.5 Evidence statements

Clinical

Two studies (reported in 14 publications) were identified for inclusion within the review: The evidence compared both an invasive strategy (angiography followed by PCI or CABG at the clinician's discretion) with medical management and CABG (plus medical management) with medical management alone.

The evidence for the outcomes from one study (n=1212) comparing CABG (plus medical management) with medical management alone ranged from moderate to very low. This was due to a risk of bias and imprecision as a result of wide confidence intervals around the effect estimate. A single outcome (NYHA class I) was downgraded due to indirectness of the outcome. The outcome reported was the number of people in NYHA class I at the specified follow-up point of 4.7 years rather than the protocol outcome which was improvement in NYHA class. QoL as measured by the EQ-5D, EQ-5D VAS and KCCQ; all-cause hospitalisation and the need for subsequent procedures (CABG and PCI) showed clinically important benefit from CABG (plus medical management). The outcomes QoL (SF-12) and stroke showed no clinically important effect of CABG (plus medical management). All-cause mortality at 30 days showed a clinically important harm of CABG (plus medical management), while at the extended follow-up period of 9.8 years there was evidence of a

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clinical benefit of CABG (plus medical management). No evidence was found for the outcome improvement in ejection fraction.

The evidence for the outcomes from one study (n=136) comparing an invasive strategy (angiography followed by PCI or CABG at the clinician's discretion) with medical management were all rated as very low. This was due to a risk of bias and imprecision as a result of wide confidence intervals around the effect estimate. Evidence for the outcome all-cause mortality showed a clinically important harm of the invasive strategy (associated with wide confidence intervals around the effect estimate) while evidence for the outcome QoL as measured by the EQ-5D and MLWHF showed no clinically important effect.

No evidence was found for improvement in ejection fraction.

Economic

- No relevant economic evaluations were identified.

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6.3.1.6 Recommendations and link to evidence

Recommendations	**Do not routinely offer coronary revascularisation to people who have heart failure with reduced ejection fraction and coronary artery disease. [2018]**
Relative values of different outcomes	The committee considered the following outcomes to be critical for this review: all-cause mortality (over study duration), all-cause mortality (at 30 days), quality of life, and all-cause hospitalisation. Data on all-cause mortality and hospitalisation were considered preferable to data limited to heart failure-related mortality and hospitalisations, as such data take into account the broader unintended consequences of the interventions (for example, an increase in mortality or hospitalisations due to adverse events or surgical complications). Improvement in ejection fraction and NYHA class, as well as additional revascularisation events and stroke, were also considered to be important for decision-making. For the comparison of CABG versus medical therapy, there was evidence on all outcomes except for improvement in ejection fraction. For the comparison of an invasive strategy versus medical therapy, there was only evidence for all-cause mortality (over study duration) and quality of life.
Quality of the clinical evidence	*CABG versus medical therapy:* The evidence for the outcome of all-cause mortality over the duration of the study was graded low quality due to risk of bias (differential cross-over rates in the intervention and control groups) and imprecision (based on the wide confidence intervals around the relative effect). However, the committee noted that the sensitivity analysis performed by the study authors suggested that the high rate of cross-over might have underestimated the beneficial effect of CABG on mortality, and also noted that the confidence intervals around the absolute effect were reasonably narrow and showed a clinically important benefit. The outcome of all-cause mortality at 30 days was graded moderate quality due to risk of bias (the cross-over rate being higher than the event rate). The evidence for the various quality of life measures were of moderate quality due to risk of bias (attrition). For all-cause hospitalisations, the evidence was graded moderate quality due to imprecision based on the wide confidence intervals around the relative risk estimate, but the committee noted that the confidence intervals around the absolute effect were reasonably narrow and showed a clinically important benefit. The evidence for subsequent CABG procedures was of moderate quality due to risk of bias (attrition), and for both subsequent PCI procedures and stroke was of low quality due to risk of bias (attrition) and imprecision. Finally, the evidence for improvement in NYHA class was graded as low quality due to imprecision and indirectness (the study only reported numbers in class I NYHA at the end of the trial rather than all of those whose NYHA class improved). *Invasive strategy versus medical therapy:* The evidence for all outcomes was of very low quality. For mortality over the duration of the study, the evidence had very serious imprecision and high risk of bias (unbalanced baseline characteristics between the groups). The quality of life evidence was downgraded for imprecision and risk of bias (lack of blinding). The committee noted that the trial upon which this evidence

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Recommendations	Do not routinely offer coronary revascularisation to people who have heart failure with reduced ejection fraction and coronary artery disease. [2018]
	was based, HEART,[65] enrolled only 138 of the planned 800 patients and was thus underpowered. *Other comparisons:* There was no other evidence comparing PCI with medical therapy, or CABG plus ventricular reconstruction with medical therapy.
Trade-off between clinical benefits and harms	The committee discussed the evidence for an invasive strategy (angiography with intent to revascularise (with CABG or PCI)) versus medical therapy. The evidence on mortality suggested a possible clinical harm of an invasive strategy, but the committee was not confident in this evidence due to the very wide confidence intervals around the absolute risk difference (which range from clinically important benefit to clinically important harm) and the risk of bias. An invasive strategy appeared not to have a clinically important impact on quality of life, but again, the committee placed little weight on this evidence due to its very low quality. The committee discussed the evidence for CABG plus medical therapy, compared to medical therapy alone, and noted that CABG led to clinically important reductions in all-cause mortality and all-cause hospitalisations. The committee noted that this clinically important reduction in mortality was only evident at the extended follow-up period of 9.8 years, with 30 day mortality in patients receiving CABG being substantially higher than those receiving medical therapy alone (estimate of 24 more per 1000, ranging from 4 more to 70 more). CABG was also associated with clinically important improvements in NYHA class and quality of life measured with EQ5D and the Kansas City Cardiomyopathy Questionnaire, though a smaller, not clinically important difference was found using the SF-12. These were notable given the invasive nature of the CABG procedure and the extended recovery period. Randomisation to receive CABG also led to fewer subsequent CABG and PCI procedures compared with patients randomised to medical therapy alone, though for subsequent PCI procedures the evidence was imprecise. For stroke, there appeared to be no clinically important difference between the groups, though the confidence intervals ranged from a clinically important benefit to a clinically important harm and so the committee was not confident in the effect estimate. In weighing up the benefits and harms of revascularisation, the evidence suggested that overall and in the long term, CABG led to improvements in critical outcomes for the people enrolled in the trial, albeit with substantial 30 day mortality. However, the committee had 2 serious concerns about the applicability of the evidence to modern clinical management of heart failure patients in the UK. The committee considered that the evidence for CABG was not generalisable to the majority of heart failure with reduced ejection fraction (HFREF) patients. The committee noted the evidence was based on a single trial (STICH(ES)[355]) and that the characteristics of the patients in that trial were not representative of the HFREF population in the UK community. In particular, the committee noted the relatively young average age (60 in the CABG arm and 59 in the medical therapy arm). In contrast, the majority of ischemic HFREF patients in the UK are over 70 years of age, and older

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Recommendations	Do not routinely offer coronary revascularisation to people who have heart failure with reduced ejection fraction and coronary artery disease. [2018]
	patients tend to be frailer and would likely do less well following major surgery such as CABG. [149] After agreeing that CABG should not be routinely offered to typical HFREF patients, the committee discussed whether CABG would be appropriate for patients who present with risk profiles similar to the cohort assessed in STICH(ES). However, the committee was not convinced that the prognostic benefit demonstrated in STICH(ES) would be seen in modern practice. This was primarily because of the relatively small proportion of patients in the trial with Implantable Cardioverter Defibrillators (ICDs), which are now recommended for patients with heart failure and EF ≤35%.[c] The committee suggested that a higher rate of ICD usage may have improved the outcomes in the medical therapy arm. For the reasons above, the committee was not convinced that CABG would demonstrate the same beneficial effect in the current UK ischaemic HFREF population, and any possible benefit could be outweighed by an increased risk of serious adverse events during or post-surgery. In light of their concerns about generalisability and applicability of the evidence on CABG to the general HFREF population, the committee decided that CABG should not be routinely offered to patients with HFREF. However, the committee recognised that a proportion of patients with ischemic HFREF may derive substantial benefit from CABG in the long term. In particular, people with more severe coronary artery disease and in whom viability has been established may be more likely to obtain a greater benefit from CABG than the average benefit demonstrated in the STICH(ES) trial although the sub-study looking for an influence of viability on the surgical outcome was unable to confirm this. For HFREF patients with extensive coronary disease, who have a surgical risk profile similar to the patients enrolled in the STICH(ES) trial, clinicians may wish to discuss the evidence on CABG as part of shared decision making regarding treatment options. That this is an area of significant uncertainty should be openly discussed with patients. In any shared-decision making with patients about CABG, a thorough discussion about the potential risks and benefits will be essential to enable informed consent. This discussion should go beyond the immediate post-surgery risks. In particular, clinicians should address any misconception that so long as a patient 'pulls through' the surgery, their heart failure will necessarily be 'fixed', as some patients will have an excellent symptomatic response and others far less. It should be emphasised that where benefit accrues from CABG this only occurs after more than 5 years, and that to date it is difficult to identify which individuals will do well. The committee noted that in the UK, PCI is used more commonly than CABG for revascularisation, due to a lower rate of complications and shorter recovery period. However, the committee recognised that in heart failure, there is no RCT evidence on the effectiveness of PCI. A UK study of PCI in patients with HFREF (EF < 30%), extensive coronary disease and viable myocardium (in ≥ 30% of dysfunction segments) is currently underway

[c] See TA314 *Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure*

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Recommendations	Do not routinely offer coronary revascularisation to people who have heart failure with reduced ejection fraction and coronary artery disease. [2018]
	(REVIVED [175]). When considering the totality of the evidence for revascularisation, the committee decided that neither CABG nor PCI should be routinely offered to patients with HFREF. This was based on the absence of RCT level evidence supporting the use of PCI in HFREF, and the concerns regarding the applicability of the evidence on CABG in HFREF.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified assessing the cost-effectiveness of coronary revascularisation in a heart failure population; therefore the unit costs of CABG and PCI were presented to the committee for consideration of cost effectiveness alongside the clinical evidence. The committee discussed that a CABG in people with heart failure would be complex and associated with a prolonged length of stay in both the intensive care unit (ICU) and inpatient ward. The average length of stay reported in the STICH trial was 9 days. Taking these factors into account the committee agreed that the average unit cost for CABG would be at the higher end of the scale in people with heart failure of £17,714 [NHS reference cost HRG ED26A]. The committee also highlighted that additional costs would be incurred prior to a person receiving CABG due to the high cost imaging (perfusion cardiac MRI and/or an invasive angiography) required to determine the location and extent of revascularisation required and the feasibility of the procedure, further increasing costs. As mentioned in the 'trade-off between clinical benefits and harms' section above, the population in the STICH(ES) trial is younger than the typical heart failure population. The committee discussed that there is an increased risk of mortality and complications of surgery with age and therefore agreed that CABG is unlikely to benefit the typical HF-REF population. Due to the high costs of the procedure, as well as the likely incurrence of additional costs of complications, the committee agreed that CABG is highly unlikely to be cost effective in the current UK heart failure population. The committee were uncertain about the cost effectiveness of CABG in a population that reflects those included in the STICH(ES) trial. The committee discussed that due to the higher uptake of ICDs nowadays, especially in younger patients, the survival benefit of CABG compared to those receiving medical therapy alone found in STICH(ES) could be negated and the average QALY gain could be low. However, the true effect of this is uncertain. The committee agreed that in exceptional cases CABG may be cost effective for a small proportion of people (the committee estimate less than 1%) with ischaemia and with characteristics similar to those in the STICH trial. The committee discussed that CABG should be decided on a case by case basis, resembling current clinical practice, and therefore agreed on a do not routinely offer recommendation. The cost of a PCI is much lower than CABG at £4,928. However, as there was no clinical evidence for PCI alone, the committee could not determine the cost-effectiveness of PCI. The committee were aware that the cost-effectiveness of PCI will be assessed in a health technology assessment alongside the REVIVE trial and therefore did not consider it important to make a research recommendation in this area.

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Recommendations	Do not routinely offer coronary revascularisation to people who have heart failure with reduced ejection fraction and coronary artery disease. [2018]
Other considerations	The committee discussed current practice regarding coronary revascularisation for HFREF in the UK, and the potential impact of their recommendation. In the 2010 guideline, the recommendation was that coronary revascularisation *should not be routinely considered*. This was based on an evidence review conducted for the 2003 guideline, and the review was not updated in 2010. The new recommendation clarifies that coronary revascularisation should not be *routinely offered* to patients with HFREF without angina, but allows clinicians to use their professional judgement to *consider* whether coronary revascularisation may be appropriate for each patient on a case by case basis. The committee considered that the new recommendation would be unlikely to have a significant resource impact as they do not consider that it will change current practice. The 2003 CHF guideline made reference to 2 papers narratively regarding this review question. These studies have been excluded within the current review as they were carried out previous to 2001 when new guidance regarding the use of beta-blockers for the management of HF were introduced. The committee agreed that this change in management was likely to have had an effect on treatment strategies overall and therefore only wished to consider studies carried out after 2001.

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6.3.2 Recommendations for invasive procedures

6.3.2.1 Implantable cardioverter defibrillators and cardiac resynchronisation therapy

See NICE's technology appraisal guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure

6.3.2.2 Coronary revascularisation

64. Do not routinely offer coronary revascularisation to people who have heart failure with reduced ejection fraction and coronary artery disease. [2018]

6.3.2.3 Cardiac transplantation

65. Specialist referral for transplantation should be considered for people with severe refractory symptoms or refractory cardiogenic shock [2003]

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7 Rehabilitation in chronic heart failure

The update to the heart failure guideline includes topics where new evidence has emerged since the publication in 2010. A review of new evidence published after 2010 was carried out in order to determine whether any changes to current recommendations where likely to be required. The decision on which topics to include in the update of the guideline was made following consultation of the scope.

In this section new evidence on home versus centre based cardiac rehabilitation was reviewed.

7.1 Home-based versus centre-based rehabilitation

7.1.1 Introduction

The importance of rehabilitation therapy has been recognised for many years in the management of patients post-myocardial infarction. Many patients with heart failure, especially those with heart failure with reduced ejection fraction (HFREF) have an underlying basis in myocardial iscahemia and previous myocardial events. A number of studies have investigated whether rehabilitation techniques deliver similar benefits in patients with heart failure to those achieved in patients after a myoacrdila infarct. The organisation of heart failure services is evolving to favour home and community-based interventions as opposed to hospital-based provision. There are known inequalities in access to hospital-based rehabilitation services across the UK. This question investigated whether home-based rehabilitation services could deliver similar outcomes to hospital-based rehabilitation services.

7.1.2 Review question: What is the clinical and cost effectiveness of home-based versus centre-based rehabilitation (that includes an exercise element) for people with heart failure (HF)?

For full details see review protocol in appendix A.

Table 74: PICO characteristics of review question

Population	People diagnosed with HF
Intervention	Home-based cardiac rehabilitation (CR) service. Programme must be structured, with clear objectives for the participants, and include a monitoring component. Programmes will be included whether they are based solely on exercise or include such as education and/or psychological support other intervention elements (comprehensive cardiac rehabilitation). No minimum duration of intervention.
Comparison	Centre-based CR service (including community based rehabilitation service and hospital based rehabilitation service). Programme must be structured, with clear objectives for the participants, and include a monitoring component. Programmes will be included whether they are based solely on exercise or include other intervention elements such as education and/or psychological support (‘comprehensive CR’).
Outcomes	CRITICAL • All-cause mortality • CV mortality • Health-related quality of life • All cause hospitalisation • HF-related hospitalisation IMPORTANT • Exercise capacity

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	• Adverse events (withdrawal from the exercise programme) • Adherence (including maintenance of exercise/physical activity) • Health service use
Study design	RCTs (individual or cluster level, including parallel group, cross-over or quasi-randomised designs).

7.1.3 Clinical evidence

The following review was conducted by the University of Exeter Medical School Cochrane Cardiac Rehabilitation group as part of a second update to the Cochrane systematic review 'Home versus centre-based Cardiac Rehabilitation'[13] in accordance with NGC methodology.

A search was conducted for randomised trials directly comparing home- with centre-based cardiac rehabilitation for people with heart failure.

Five randomised trials (8 publications) were included in the review;[76-78, 86, 151, 168, 262, 263] these are summarised in Table 75 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 76. See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

All of the studies compared home-based exercise training (which included aerobic circuit training and walking) with centre-based (which included aerobic circuit training, treadmill walking and cycling).

Summary of included studies

Table 75: Summary of RCTs included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Cowie 2012[78] (Cowie 2011[77], Cowie 2014[76])	Intervention: aerobic circuit (guided by DVD and booklet), 2 weekly phone calls by a physiotherapist; no other treatments reported • Frequency: twice per week • Duration: 1 hour • Intensity: 40-60% heart rate reserve or Borg 12-13, Control: As home but supervised (led by physiotherapist) and hospital-based; no other treatments	n = 60 Age (range): 65.8 (35-85) years Gender: 85% male NYHA class II and III: 100% Mean ejection fraction: NR (systolic dysfunction) Family origin not reported Single centre UK	• Mortality • QoL(SF-36) • QoL(MLWHF) • Exercise capacity (ISWT) Adherence	Maximum duration of follow-up: 2 months The study reported median values only for the outcome QoL (MLWHF), therefore it has not been included in the analysis
Daskapan 2005[86]	Intervention: Outdoor Walking &	n = 29	• Mortality • Exercise capacity	Maximum duration of follow-up:

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Study	Intervention and comparison	Population	Outcomes	Comments
	weekly phone calls provided; no other treatments reported • Frequency: 3 sessions per week • Duration: 45 minutes • Intensity: up to 60% peak heart rate (RPE 12-16) Control: As home but supervised laboratory based (treadmill walking)	Age (mean±SD): Intervention: 49±11 Control: 52±8 Gender: 73% male NYHA class II and III: 100% Mean ejection fraction: 36% Family origin not reported Single centre Turkey	(VO_{2max}) • Adherence	3 months Data obtained on mortality by personal contact
Hwang 2017[151]	Intervention: Aerobic and strength training exercises delivered via a synchronous videoconferencing platform across the internet. Participants were provided with additional home exercises to be undertaken three times per week. Educational topics were delivered as electronic slide presentations with a 15 minute interaction period held prior to the exercise session to discuss this. • Frequency: 2 sessions per week • Duration: 60 minutes • Intensity: RPE 9-13 (commencing at very light and progressing to somewhat hard). Exercise prescription was tailored to the participants goal. Control: As home-based	n=53 Age (mean±SD): 68±14 Gender: 79% male NYHA class II-III: 87% LVEF (mean±SD): 36±16 Family origin: 92% Caucasian 2 centres Australia	• Mortality • Exercise capacity: ○ 6 minute walk distance ○ 10m walk test (comfortable and fast) • QoL (EQ-5D) • QoL (MLWHFQ) • Adherence	Maximum duration of follow-up: 24 weeks

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Study	Intervention and comparison	Population	Outcomes	Comments
	telerehabilitation but centre-based led by physiotherapists			
Karapolat 2009[168]	Intervention: Walking with pedometer, weekly phone calls provided; breathing and flexibility exercises • Frequency: 3 sessions per week • Duration: 45-60 minutes • Intensity: 60-70% heart rate reserve, level 13-15 on the Borg scale Control: As home but supervised treadmill walking in rehabilitation centre with breathing and flexibility exercises	N = 74 Age (mean±SD): Intervention: 44.05±11.49 Control: 45.16±13.58 Gender (% male): Intervention: 62% Control: 66% NYHA class II-III: 100% Mean ejection fraction: Not reported Family origin not reported Single centre Turkey	• Mortality • Exercise capacity (VO_{2max}) • Adherence	Maximum duration of follow-up: 2 months
Piotrowicz 2010[262] (Piotrowicz 2015[263])	Intervention: Continuous walking on level ground and an education programme detailing how to measure HR, BP and body weight; how to evaluate signs and symptoms. All participants received psychological support. The home based group received an EHO 3 device and a mobile phone. Before beginning a training session, participants used the mobile phone to answer symptom based questions. A resting ECG was transmitted to the monitoring centre in order to establish that exercise was	n = 152 Age (mean): 58.1±10.2 years Gender: Intervention: 89% male Control: 95% male NYHA class II-III: 100% Mean ejection fraction: Home group: 30.2±8.2 Centre group: 30.8±6.7 Family origin not reported Single centre Poland	• Mortality • QoL(SF-36) • Exercise capacity (6MWT) • Exercise capacity (VO_{2max}) • Adherence	Maximum duration of follow-up: 2 months

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Study	Intervention and comparison	Population	Outcomes	Comments
	safe to continue. • Frequency:3 sessions per week • Duration: 20-45 minutes • Intensity: Individually tailored Control: As home but supervised in an outpatient setting, with interval training using a cycle ergonometer			

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Table 76: Clinical evidence summary: Home-based exercise training versus centre-based exercise training

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with centre-based exercise training	Risk difference with home-based exercise training (95% CI)
All-cause mortality	335 (5 studies) 2 to 6 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto odds ratio 1.01 (0.23 to 4.48)	24 per 1000	0 more per 1000 (from 18 fewer to 82 more)
Quality of life - SF-36 Physical component summary (PCS)	161 (2 studies) 2 to 3 months	⨁⨁⊖⊖ LOW[a] due to risk of bias		The mean SF-36 PCS in the centre-based exercise training groups was 42.6	The mean SF-36 PCS in the home-based exercise training groups was 0.56 lower (5.45 lower to 4.33 higher)
Quality of life - SF-36 Mental component summary (MCS)	161 (2 studies) 2 to 3 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision		The mean SF-36 MCS in the centre-based exercise training groups was 33.4	The mean SF-36 MCS in the home-based exercise training group was 0.72 higher (5.74 lower to 7.18 higher)
Quality of life – EQ-5D utility	49 (1 study) 6 months	⨁⨁⨁⨁ HIGH		[f]	The mean EQ-5D utility in the home-based exercise training group was 0.06 lower (0.16 lower to 0.04 higher)
Quality of life - MLWHFQ	49 (1 study) 6 months	⨁⨁⨁⊖ MODERATE [b] due to imprecision		[f]	The mean MLWHFQ in the home-based exercise training group was 4 lower (17 lower to 9 higher)
Exercise capacity - ISWT	30 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean exercise capacity - ISWT in the centre-based exercise training groups was 312	The mean exercise capacity - ISWT in the home-based exercise training group was 6 higher (104.42 lower to 116.22 higher)
Exercise capacity -	201	⨁⨁⨁⊖		[e]	The mean exercise capacity – 6MWT in

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with centre-based exercise training	Risk difference with home-based exercise training (95% CI)
6MWT	(2 studies) 2 months	MODERATE[a] due to risk of bias			the home-based exercise training groups was 0 82 higher (23.52 lower to 25.16 higher)
Exercise Capacity VO2max	221 (3 studies) 2 to 3 months	⨁⨁⨁⨀ LOW[a] due to risk of bias		The mean exercise capacity VO2max in the centre-based exercise training groups was 61.73	The mean exercise capacity VO2max in the home-based exercise training groups was 0.09 higher (1.27 lower to 1.46 higher)
Exercise capacity – 10 metre walk test (fast)	49 (1 study) 6 months	⨁⨁⨁⨁ HIGH		[6]	The mean exercise capacity – 10 metre walk test (fast) in the intervention group was 1.0 higher (0.9 to 1.1 higher)
Completers	295 (4 studies) 2 to 3 months	⨁⨁⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.18 (1.07 to 1.3)	781 per 1000	141 more per 1000 (from 55 more to 234 more)
Adherence to intervention (Cowie 2012)[d]	30 (1 study) 2 months	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.92 (0.62 to 1.36)	800 per 1000	64 fewer per 1000 (from 304 fewer to 288 more)
Adherence to intervention (Daskapan 2005)[d]	29 (1 study) 3 months	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.19 (0.88 to 1.61)	786 per 1000	149 more per 1000 (from 94 fewer to 479 more)
Adherence to intervention (Karapolat 2009)[d]	74 (1 study) 2 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 0.97 (0.82 to 1.15)	892 per 1000	27 fewer per 1000 (from 161 fewer to 134 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with centre-based exercise training	Risk difference with home-based exercise training (95% CI)
Adherence to intervention (Piotriwicz 2010)[d]	152 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.27 (1.13 to 1.43)	787 per 1000	212 more per 1000 (from 102 more to 338 more)
Adherence to intervention (Hwang 2017)	49 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[b] due to imprecision		[f]	The mean adherence to intervention in the intervention group was 6 higher (2 to 10 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Heterogeneity, I2=54%, downgraded by 1 increment.
(d) The outcome data for adherence to intervention was not meta-analysed as there was a significant degree of variation in the methods of obtaining this information across studies.
(e) Unable to estimate as one of the studies included in the meta-analysis only reported the mean difference. The outcome has therefore been analysed using generic inverse variance.
(f) Unable to calculate as the study only reported a mean difference.

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7.1.4 Economic evidence

Published literature

One health economic study was identified with the relevant comparison and has been included in this review.[76] This is summarised in the health economic evidence profile below (**Table 77**) and the health economic evidence table in appendix G.

See also the health economic study selection flow chart in appendix D.

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Table 77: Health economic evidence profile: Hospital vs home rehabilitation

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Cowie 2014 [76] [UK]	Partially applicable[(a)]	Very serious limitations [(b)]	• Comparative costing from UK NHS perspective • Population: people with heart failure on optimised medication dosages, clinically stable for one month. • Two comparators: 1. Hospital training 2. Home training • Follow-up: 5 years	2-1: £480 (c)	n/a	n/a	None.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years.

(a) Does not include any health outcomes.

(b) Small sample size, which has significant impact on cost per patient for the home training group. The baseline patient characteristics are not typical with a very high proportion of males. Furthermore, the usual care group nearly 10 years younger than hospital group suggesting there is selection bias. No discounting was undertaken.

(c) An additional comparator of usual care was also included in the study. Both hospital training and home training were cost saving compared to usual care. For further detail see full evidence table in appendix G.

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7.1.5 Evidence statements

Clinical

Five studies (8 publications) were identified for inclusion within the review. All of the studies compared home-based exercise training with centre-based exercise training supervised by a healthcare professional. The included evidence ranged from high to very low quality. Outcomes were downgraded due to a high or very high risk of bias, imprecision due to wide confidence intervals surrounding the point estimate and inconsistency due to heterogeneity between the effect estimates for meta analysed outcomes. Five studies reported the outcome all-cause mortality (n=335) which showed no clear clinical effect of home-based exercise training with the confidence interval ranging from a decrease and increase in all-cause mortality.. For the outcome QoL (as measured by the SF-36), 2 studies (n=161) showed that there was no clinically important effect of home-based exercise training on either the physical or mental component summaries. A further single study (n=49) also showed no clinical effect of home-based exercise training on either the EQ-5D utility score or the MLWHFQ. This was also the case for exercise capacity as measured by the 6 minute walk test (n=201), the incremental shuttle walk test (n=161), VO2max (n=221) and the 10 metre walk test (fast) (n=49). The outcome, number of people completing the exercise programmes (n=295) showed a clinically important benefit of home-based exercise training. For adherence to the intervention the outcome data reported by each study was not meta-analysed due to considerable variation in the manner in which it was reported across studies. The direction and magnitude of effect varied between studies with both a clinical benefit and clinical harm being shown. None of the studies reported the outcome hospitalisations (both all-cause and HF-related), cardiovascular mortality and health service use.

Economic

- One comparative cost analysis found that home training was more costly than hospital training for delivering rehabilitation (cost difference: £480 per patient). This analysis was assessed as partially applicable with very serious limitations.

7.1.6 Recommendations and link to evidence

Recommendations	**Offer people with heart failure a personalised, exercise-based cardiac rehabilitation programme, unless their condition is unstable. The programme:** • **should be preceded by an assessment to ensure that it is suitable for the person** • **should be provided in a format and setting (at home, in the community or in the hospital) that is easily accessible for the person** • **should include a psychological and educational component** • **may be incorporated within an existing cardiac rehabilitation programme** • **should be accompanied by information about support available from healthcare professionals when the person is doing the programme. [2018]**
Relative values of different outcomes	The committee considered all-cause mortality, quality of life and all-cause hospitalisation to be the critical outcomes for this review. Data on all-cause mortality and hospitalisation were considered preferable to data limited to heart failure (HF)

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	or cardiovascular related hospitalisations and mortality, as such data take into account the broader unintended consequences of the interventions (for example, an increase in hospitalisations due to adverse events). Cardiovascular mortality, heart-failure related hospitalisation, exercise capacity, health service use, and withdrawal from/adherence to the programme, were considered to be important for decision-making. No evidence was identified for the outcomes cardiovascular mortality, health-service use and hospitalisation (both all-cause and HF-related).
Quality of the clinical evidence	Five studies were identified for inclusion within the review. For the critical outcome of mortality the evidence was rated as very low quality due to risk of bias and imprecision as a result of wide confidence intervals surrounding the point estimate. For quality of life, which was also a critical outcome, the quality of the evidence ranged from high to very low depending on the scale used for measurement. The SF-36 physical component summary and mental component summary were rated as low and very low quality respectively. This was again due to risk of bias, imprecision and heterogeneity in the results reported by the studies. For the EQ-5D utility score the evidence was rated as high quality; for the MLWHFQ the evidence was rated as moderate quality, due to imprecision. Several measures of exercise capacity were reported by the studies; these included the incremental shuttle walk test (ISWT), the 6 minute walk test (6MWT), VO_2 max and the 10 metre walk test (fast). The quality of these outcomes ranged from very low to high quality, with outcomes being downgraded for risk of bias and imprecision. All of the included studies reported adherence to the intervention, which ranged in quality from moderate to very low. The outcome data reported by each study was not meta-analysed due to the significant degree of variation in the methods of obtaining this information across studies. The committee also noted that the subjective nature of the adherence data, when self-reported by people in a home-based exercise programme, meant that it was potentially less reliable. The majority of trials poorly reported details of sequence generation, concealment of the random allocation sequence and blinding of outcome assessment; contributing to the overall high risk of bias in the body of evidence for all outcomes. Losses to follow-up, which varied widely across studies, also contributed to the risk of bias for some outcomes.
Trade-off between clinical benefits and harms	There was no consistent evidence of a clinically important difference in exercise capacity between home-based and centre-based rehabilitation when quantified via the ISWT, 6MWT, VO_2 max and 10 metre walk test (fast). A similar result was seen for quality of life, with no consistent evidence of a clinically important difference between home and centre-based rehabilitation. This was also the case for adherence, with no consistent clinical benefit being observed. The committee noted that this evidence was more challenging to interpret as variation in the way this data was reported across studies prohibited the meta-analysis of these results. In addition to this the committee noted that self-reported adherence by participants enrolled in a home-based exercise programme were likely to be less reliable due to the subjective nature of the reporting. Similarly, no clinically important difference in mortality was seen between the groups, although this estimate was seriously imprecise, with confidence intervals ranging from a clinically important reduction to a clinically important increase in deaths in the home-based groups. Based on the clinical evidence reviewed, the committee agreed that home- and centre-based forms of cardiac rehabilitation seem to be similarly effective for patients with heart failure. The committee noted that the body of evidence was small (5 trials of 335 patients) and the majority of outcomes were at high risk of bias. The patient populations included in the trials were also much younger than the typical heart failure patients

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in the UK. However, the committee agreed that this was common in rehabilitation trials and wasn't specific to home versus centre-based trials. The committee acknowledged that the findings of this review which suggested that no clear difference could be demonstrated between home- and centre-based programmes. The committee also noted that findings in younger populations might also not translate to more typical older patient populations. The committee was also conscious that the critical outcome of hospitalisation was not reported by any of the included studies.

The evidence on patient completion suggested a clinically important increase in completion rates in the home-based groups compared to the centre-based groups. For some patients, the burden of travelling to a centre for rehabilitation and/or dislike of exercising in a group setting may be a substantial barrier to participation in centre-based programmes. For these patients, home-based rehabilitation may be a more attractive and achievable option. Similarly, a patient representative expressed his view that the main concern of many younger patients with heart failure is to learn and understand their limits with professional supervision, to enable them to then exercise safely and comfortably alone.

The committee expressed its concern about the continuing low uptake of rehabilitation since the previous guideline[52] and agreed that there may be inequalities in the ability to access rehabilitation, especially for older, frailer patients with heart failure. The committee agreed that the delivery of home-based rehabilitation may increase access and uptake, which is a major priority in the management of heart failure. The committee considered that even a modest increase had the potential to result in a marked improvement in patient outcomes at the population level.

The committee also discussed the potential downsides of a home-based programme, including:

- the loss of face-to-face support and encouragement from health professionals and peers, especially compared with a group programme;
- increased feeling of isolation for some patients;
- the potential for reduced adherence among some patients, and for patients to experience technological and comprehension barriers to full participation, which may not be picked up in patient self-reports.

On balance, the committee agreed that choice of participating in a more traditional and supervised centre-based programme or a home-based programme should ideally reflect the preference of the individual patient. The committee therefore decided to maintain the current recommendation to offer cardiac rehabilitation to heart failure patients, but removed the limitations on the mode of delivery. The committee agreed that the setting and format of the programme should facilitate the person's ability to access the programme.

The committee noted that several comprehensive, evidence-based, home-delivered cardiac rehabilitation programmes are currently available. These programmes typically involve an overarching self-help manual outlining the programme, and include an exercise training element (such as open air walking or indoor exercises using a DVD), as well as educational (for example, medications, symptom monitoring and help-seeking) and psychological (for example, managing stress and anxiety) components. The programmes are overseen by a trained healthcare professional who patients can contact for further advice.

The specific home-based programmes in the included studies were as follows:

- three studies were based on outdoor walking training, with the addition of flexibility and breathing exercises (1 study), and the addition of telephone conversations with a psychologist (1 study);
- one study was based on a DVD of functional aerobic exercises interspersed with active recovery.

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	All home-based programmes in the included studies were accompanied by tele-monitoring and written information, and some programmes included the use of heart rate monitors and pedometers. One programme utilised remote monitoring equipment (an EHO 6 device enabling the recording and transmission of an ECG via a mobile phone). The committee discussed how a home-based programme would be delivered and how professional support would be accessed in the NHS context. The committee did not expect a home-based programme would involve regular face-to-face contact with health professionals and agreed the use of expensive equipment would not be required. The committee agreed that, regardless of the programme delivery format or setting, all patients should be assessed by a trained healthcare professional prior to commencement, in order to: • ensure that the person can safely participate in exercise-based cardiac rehabilitation; • tailor an appropriate programme for the patient. In addition, professional support should be available to patients throughout both centre and home-based programmes and patients should be advised on how to access that support.
Trade-off between net clinical effects and costs	One relevant economic evaluation was identified and included in this review that compared home-based rehabilitation to hospital-based rehabilitation for people with heart failure. This was a 5 year follow-up comparative costing of patients who participated in a trial by Cowie et al. 2011 included in the clinical review. The study found home-based rehabilitation to be more costly compared to hospital-based rehabilitation. When discussing this paper, the committee considered that the estimated intervention cost of home-based rehabilitation would be lower in current practice. In the study, the cost of DVD production to deliver the home-based intervention was divided by the number of patients in the study arm (n=15) to give the average cost per patient. In practice with a much larger population size, the committee considered that home-based rehabilitation would be less costly than hospital-based rehabilitation as the fixed cost of producing a DVD would be divided over a greater number of patients, and the marginal cost of providing each additional DVD would be minimal. The estimated intervention cost of hospital-based rehabilitation is unlikely to differ in current practice. The committee also noted that the admission costs were higher in the home-based rehabilitation group in this study. However, the committee considered this to be highly uncertain due to the small sample size of the study, and therefore did not put much weight on this finding. Although there was no clinical evidence for hospitalisations, the committee considered that home-based rehabilitation would have similar hospitalisation rates as hospital-based rehabilitation, and therefore admission costs would not differ greatly between the 2 interventions. The committee were concerned with the small sample size of this study (n=30), that there was a large age difference of patients in each arm, and that no health outcomes were reported, and therefore this study was assessed as partially applicable with very serious limitations. Due to the limited quality of economic evidence, the committee considered the current cost of hospital-based rehabilitation. According to NHS reference costs the cost of 'Rehabilitation for Acute Myocardial Infarction or Other Cardiac Disorders' (VC38Z)' is £238. The committee also mentioned that these patients are likely to require transport, further increasing the cost of this intervention. The other interventions for home-based rehabilitation programmes identified in the clinical review consisted of outdoor walking and weekly telephone calls to healthcare staff. The committee considered that this would require limited NHS resource if such

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	programmes were implemented. Overall, the committee did not consider that home-based rehabilitation would be more costly than hospital/community rehabilitation as health professionals are not required to visit patients in their homes, and in some instances could be less costly. The lack of uptake of rehabilitation since the previous guideline has meant that the cost savings previously predicted due to reductions in hospitalisations have not come to fruition. Although there is no clinical evidence for hospitalisations the committee considered that home-based rehabilitation would have the same effect in reducing hospitalisations as hospital or centre based rehabilitation. Therefore the cost savings of rehabilitation are more likely to be met if home based rehabilitation is made available to aid in increasing the uptake of rehabilitation. The committee mentioned that in some areas hospital/centre-based rehabilitation is not available due to the significant up-front cost required to initiate the service. The committee agreed that initiating home-based rehabilitation programmes is unlikely to incur as high a cost, particularly if existing cardiac rehabilitation programmes are already in place, and considered that this recommendation would aid in reducing barriers to access. Due to the considerations above, the committee decided that home-based rehabilitation should be available for heart failure patients to increase uptake of rehabilitation and facilitate the previously predicted cost-savings.
Other considerations	The committee noted that access to cardiac rehabilitation for heart failure patients is currently highly variable and uptake nationally remains low. The committee's recommendation should address some of the underlying issues by improving access, equity, participation and adherence. The CHF Quality standard (QS9 2016, statement number 7) identified the need for choice of venues and measures such as providing transport when offering rehabilitation programmes to ensure equality of access for all the heart failure population. This update has added to the 2010 recommendations on rehabilitation while recognising the importance of programmes including a psychological and educational component and that the programme may be incorporated within an existing cardiac rehabilitation programme. The committee also noted the recommendations in the Patient experience in adult NHS services guideline that advocates an individualised approach to healthcare services tailored to patient needs and circumstances. All patients in the trials had HF with reduced ejection fraction (HFREF). However, as the 2010 recommendation to offer cardiac rehabilitation applied to all patients with heart failure, the committee saw no reason to limit the updated recommendation following this evidence review.

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8 Monitoring

The update to the heart failure guideline includes topics where new evidence has emerged since the publication in 2010. A review of new evidence published after 2010 was carried out in order to determine whether any changes to current recommendations where likely to be required. The decision on which topics to include in the update of the guideline was made following consultation of the scope.

This section includes monitoring using repeated biomarker measurement or imaging, and telemonitoring and self monitoring. Other topics were not within the scope of the update. For more information refer to Appendix R, the 2003 guideline:

1. Clinical review. For more information please refer to Section 8.1 of the 2003 Guideline [22].
2. Therapeutic drug monitoring of serum digoxin concentrations. For more information please refer to Section 8.4 of the 2003 Guideline [22]

8.1 Monitoring using repeated biomarker measurement or imaging for management of chronic heart failure

8.1.1 Introduction

Clinicians treating patients with HF use a combination of symptoms (e.g degree of breathlessness) and examination findings (e.g. heart rate, blood pressure) to make decisions about treatment changes. Biomarkers are substances measurable in the blood stream which can be used to diagnose and monitor disease. Natriuretic peptides are released from the myocardium in response to fluid overload. The two main natriuretic peptides used in clinical practice are amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP). The measurement of natriuretic peptides is recommended for the diagnosis of HF but their role in the on-going management (i.e monitoring of heart failure) remains a topic of active research and there is uncertainty about the optimum diagnostic thresholds for natriuretic peptides. Troponin is released in response to myocardial injury and is important in the diagnosis of myocardial infarction but it's role in HF is unclear. Co-existing conditions such as chronic kidney disease (CKD) and atrial fibrillation (AF) can affect the level of biomarkers in the bloodstream and this may influence their utility in diagnosis and monitoring of heart failure. Similarly imaging techniques for HF such as cardiac MRI and echocardiography which can be used to assess the structure and functional status of the heart could be used for similar purposes.

A number of evidence-based treatments for heart failure reduce hospital admissions and increase survival, particularly for patients with heart failure with reduced ejection fraction (HFREF). Typically these trials use fixed doses and thus their recommendations apply to the average population rather than any particular individual. Objective tests such as measurement of biomarkers and imaging could potentially also be used to inform management decisions and optimise treatment for individuals. The aim of this review was to examine the clinical and cost-effectiveness of biomarker measurement or imaging in the management of patients with HF.

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8.1.2 Review question: What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure?

For full details see review protocol in Appendix A.

Table 78: PICO characteristics of review question

Population	People diagnosed with heart failure in a community or outpatient setting. • Age under 75 years • Aged 75 years and over
Interventions	Biomarker monitoring: serial (protocol-driven) measurements of circulating biomarker concentration: • NT-proBNP (alone) • BNP (alone) • Troponin (alone) • Combination of 2 biomarkers • Combination of all 3 biomarkers Imaging monitoring: serial (protocol-driven) cardiac MRI Imaging monitoring: serial (protocol-driven) echocardiography
Comparisons	Each other Usual care: Clinical monitoring (protocol-driven) Usual care: Clinical monitoring (not protocol-driven)
Outcomes	CRITICAL • Mortality (Time to event) • Quality of life at 12 months (Continuous) • Unplanned hospitalisation (all-cause) (Count rate) IMPORTANT • Adverse events - hypotension (Dichotomous) • Adverse events - hyperkalaemia (Dichotomous) • Adverse events - renal function (Continuous) • Adverse events - bradycardia (Dichotomous) Adverse events - arrhythmic events (Dichotomous)
Study design	Systematic reviews of RCTs RCTs

8.1.3 Clinical evidence

A search was conducted for randomised trials and systematic reviews of randomised trials comparing the effectiveness of monitoring with repeated biomarker measurement (BNP, NT-proBNP or troponin) or repeated cardiac imaging (echocardiography or cardiac MRI), compared to usual care without repeated measurement or imaging.

Fourteen primary studies (28 publications);[16, 34, 37, 38, 54, 55, 114, 152, 159, 163, 169, 171, 172, 185, 188, 189, 210, 211, 256, 261, 273,, #3450, 292, 293, 299, 312, 338] were included in the review, as well as three systematic reviews (4 publications);[219,, #3362,, #2818,, #2829] providing additional information on some of the primary studies these are summarised in Table 79 and Table 80 below. See also the study selection flow chart in

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Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

All of the 14 studies involved repeated BNP or NT-proBNP (together called NP) biomarker testing. No relevant studies comparing usual care with troponin or combinations of different biomarkers were identified. No relevant studies comparing usual care with routine cardiac imaging were identified. The majority of the trials only included patients with HFREF as this is where the evidence base is for most of the treatments for HF.Treatment algorithms varied in the NP monitoring arm, some treated to an absolute NP target; others set a personal target based on percentage drop of NP levels; others did not aim to reduce NP levels, but used serial measurements to detect increases thought to represent deterioration and acted accordingly. The comparator arm involved treatment guided by protocol driven clinical monitoring in thirteen of fourteen studies. The comparator arm of one study and a third arm of two studies appeared to comprise of "usual care" that did not have a formal protocol for guiding treatment (described hereafter as "no protocol"). The results are presented separately for the "clinical monitoring" and "no protocol" comparison arms because it was felt that any form of guided treatment was likely to have an effect on outcomes.

The NP guided and clinically guided treatment arms were based in a specialist clinic in thirteen out of fourteen studies. The exception took place in primary care under general practitioners who had received training on how to use the monitoring protocols. One of the "no protocol" arms took place in a specialist clinic, and two were in primary care with no extra training.

Study details and results were taken from the first available source in the following hierarchy. The choice of source was based on utilising the advantages of individual patient data analysis while being able to present results for each study separately, stratified by age, wherever possible:

- individual patient-level data (IPD) from the meta-analysis in an NIHR funded HTA (Pufulete 2017[273])
- aggregate data from the same meta-analysis (Pufulete 2017[273]) based on the Troughton 2014[338] IPD meta-analysis
- IPD data from analysis of the Troughton 2014 meta-analysis[55, 338]
- aggregate data from a Cochrane meta-analysis (McLellan 2016[219])
- individual study reports

A single study was included in the 2010 update (CG108) of this question[30]. This paper has been excluded in the current review as it no longer matches the protocol. For further explanation please see the Recommendations and link to evidence.

Table 79: Summary of systematic reviews included in the review

Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Primary studies included
McLellan, 2016[219] **Cochrane systematic review**	NP guided therapy versus Usual care (review refers to as "Health plan" alone) Range of intervention times: 1-54 months	n=3660 age 62-80	Anguita 2010, BATTLESCARRED, Berger 2010, Christchurch pilot, NorthStar, OPTIMA, PRIMA, PROTECT, Shochat 2012, SIGNAL-HF, STARS-BNP, TIME-CHF, UPSTEP
Pufulete 2017[273] **NIHR HTA**	NP guided therapy versus Usual care (review refers to as "Symptom-guided therapy")	n=3101 Stratified by age (under 75 and 75 or over) analysis	As IPD: Anguita 2010, NorthStar, Shochat 2012, UPSTEP

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Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Primary studies included
	Range of intervention times: 3-36 months	available	As aggregate data: BATTLESCARRED, Berger 2010, Christchurch pilot, PRIMA, PROTECT, Shochat 2012, SIGNAL-HF, STARS-BNP, TIME-CHF
Troughton 2014[338] (Brunner-la rocca 2015[55]) "Troughton" review	NP-guided therapy versus Usual care (review refers to as "Clinically-guided therapy") Range of intervention times: 3-24 months	n=2431 Subgroups for age, and others including CKD	As IPD: BATTLESCARRED, Berger 2010 (labelled "Vienna"), Christchurch pilot, PRIMA, PROTECT, SIGNAL-HF, TIME-CHF, UPSTEP

NP: natriuretic peptides including BNP and NT-proBNP

Table 80: Summary of primary studies included in the review

Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Outcomes	Comments
Anguita 2010[16]	NP monitoring: Therapy increased to target (BNP level < 100 pg/mL), 18 months n=30 Clinical monitoring: Therapy intensified to reach target (congestion score and Framingham score <2), 18 months n=30	Age mean: 69(10) Recently hospitalised and NYHA II/III LVEF<40%: 51%	HTA IPD: • Mortality by age • All-cause admission by age	Recruited on discharge 2006-8
BATTLESCARRED trial: Lainchbury 2009[189] (Lainchbury 2006[188])	NP monitoring: Therapy increased to achieve clinical and NP target (congestion score<2 plus NT-proBNP<1300pg/ml), 36 months n=121 Clinical monitoring: Therapy increased to meet target (Framingham score <2), 36 months n=121 No protocol: Discharged to primary care n=122	Age > 18 mean: 74 Recently hospitalised HF-admission LVEF<40%: 63% Elevated NP (NT-proBNP > 50 pmol/L)	HTA aggregate: • Mortality by age Troughton IPD: • HF admission Study papers: • Quality of life • renal function, "no monitoring" arm	Recruited from hospital 2001-6

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Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Outcomes	Comments
Berger 2010[34] (Adlbrecht 2011[4])	NP monitoring: Therapy intensified to meet or maintain target (NT-proBNP <2200pg/l), 15 months n=92 Clinical monitoring: Therapy intensified at clinician's discretion according to clinical assessment n=96 No protocol: Discharged to primary care n=90	Age mean: 71(12) Recently hospitalised with NYHA class III/IV and cardiothoracic ratio > 0.5 or LVEF < 40%	HTA aggregate: • Mortality by age Troughton IPD: • HF admission Study papers: "No monitoring" arm	Recruited from hospital 2003-4
Christchurch pilot Troughton 2000[339]	NP monitoring: Treatment intensified to reach target (NT-proBNP 1700pg/ml), 15 months n=33 Clinical monitoring: Therapy increased to reach target (Framingham score <2), 15 months n=36	Age mean: 70(10) LVEF < 40%, NYHA class II-IV Treatment with at least ACEi and loop diuretic	HTA aggregate: • Mortality by age Study papers: • All-cause admission • Hypotension • Renal function	Recruited in hospital or HF clinic 1998-9
GUIDE-IT trial: Felker 2017[116]	NP monitoring: titrate HF therapy to target an NT-proBNP level of < 1000 pg/mL, 12-24 months n=446 Clinical monitoring: Therapy intensified at clinician discretion according to clinical assessment based on 2013 AHA/ACC guideline, 12-24 months n=448	Age median (IQR): NP monitoring: 62 (51-70), clinical monitoring: 64 (54-72) LVEF < 40%, history of HF event within the prior 12 months and an NT-proBNP level of more than 2000 pg/mL or BNP of more than 400 pg/mL within the prior 30 days	• All-cause mortality • HF hospitalisations (count rate) • Symptomatic hypotension • Symptomatic bradycardia • Hyperkalaemia • Worsening renal function	Recruited at 45 sites in the US and Canada 2013-2016 The study was prematurely discontinued due to lack of efficacy (based on statistical significance) of evidence for the biomarker-guided treatment group compared

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Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Outcomes	Comments
				with clinical monitoring
Northstar trial: Schou 2010[299]	NP monitoring: Further investigation and treatment if NT-proBNP increased >30%, 30 months n=199 Clinical monitoring: Therapy intensified at clinician discretion according to clinical assessment, 30 months n=208	Age ≥ 18 years, mean: 73(8) LVEF ≤ 45 % Elevated NP (NT-proBNP≥1000pg/ml) despite education on CHF and optimal ACE/ARB and BB therapy	HTA IPD: • Mortality by age • all-cause admission by age	Recruited from HF clinics 2005-9
OPTIMA trial: Krupika 2010[185]	NP monitoring: Therapy intensified according to clinical status and serial BNP levels, 2 years n=26 Clinical monitoring: Therapy was intensified according to clinical status, 2 years n=26	Age limits 18-90, mean: 70 Recently hospitalised, NYHA III/IV and LVEF≤45%	HTA: None Study papers: • Mortality by age • all-cause admission by age	No information on recruitment
PRIMA trial: Eurlings[114]	NP monitoring: therapy increased to reach or maintain target (NT-proBNP at the lowest level recorded at discharge or two weeks following), 24 months n=174 Clinical monitoring: Therapy increased at clinician's discretion according to clinical assessment, 24 months n=171	Age mean: 72(12) Recently hospitalised HF-admission, mainly NYHA III, LVEF<40%: 73% Elevated NPs (NT-proBNP levels at admission ≥ 1700 pg/mL) that respond to treatment (decrease ≥ 10% at discharge)	HTA aggregate: • Mortality by age Troughton IPD: • HF admission	Recruited from hospital 2004-7
PROTECT trial: Januzzi 2011[159] (Weiner 2013[367], Mallick 2016[211], Ibrahim 2017[152], Bhardwaj 2010[37], Bhardwaj 2012[38]))	NP monitoring: Therapy intensified to reach target (NT-proBNP≥1000pg/ml), 6-12 months n=75 Clinical monitoring: Therapy intensified at clinician discretion according to clinical assessment, 6-12 months	Age ≥ 21 years, mean: 63(14) NYHA class II-IV, LVEF ≤ 40%, destabilisation in last 6/12 (attended hospital or clinic for worsening HF)	HTA: Nil Troughton IPD: • HF hospitalisation Study papers: • Quality of life • Hypotension	Recruited 2006-10

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Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Outcomes	Comments
	n=76		• renal failure • atrial fibrillation • ventricular arrhythmia	
Shochat 2012[312]	NP monitoring: Therapy increased if NT-proBNP increased >30%, 11 months n=60 No protocol: No treatment algorithm reported, 11 months n=60	Age mean: 73(8) NYHA I/II/III/IV n=1/55/41/16	HTA IPD: • Mortality by age • all-cause admission by age	Recruited 2007-10
SIGNAL-HF trial: Persson 2010[256]	NP monitoring (in primary care): Treatment increased to achieve target (NT-proBNP reduction of 50% from baseline), 9 months n=127 Clinical monitoring (in primary care): Therapy increased at clinician's discretion according to clinical assessment, 9 months n=125	Age mean: 78(7) NYHA class II-IV, LVEF < 50%, stable in primary care Elevated NPs (NT-proBNP levels males > 800, females > 1000 ng/L)	HTA aggregate: • Mortality by age Troughton IPD: • HF admission Study papers: • Quality of life	Recruited from primary care 2006-9
STARS-BNP trial: Jourdain 2007[163]	NP monitoring: Therapy intensified to reach target (BNP<100pg/ml), 15 months n=110 Clinical monitoring: Therapy intensified at clinician discretion according to clinical assessment, 15 months n=110	Age > 18 years NYHA class II/III, LVEF < 45% No admission or change of medication in last month, optimal medical treatment with diuretics, ACEi/ARB and BB	HTA aggregate: • Mortality by age Troughton IPD: • HF admission Study papers: • Renal function	Recruited from clinics
TIME-CHF trial: Maeder 2013[210] (Pfisterer 2009[261], Brunner-la rocca 2006[54], Sanders-van wijk 2013[293], Sanders-van wijk 2014[292], Kaufmann 2015[172])	NP monitoring: Therapy intensified to reach BNP target (400og/ml for <75y, 800pg/ml for ≥75y), 18 months n=251 with rEF, 59 with pEF Clinical monitoring: Therapy intensified to reach target (NYHA ≤ II), 18 months n=248 with rEF, 64 with pEF	Age ≥ 60 years, mean: HFREF: 76 HFpEF: 80 NYHA class ≥ II with current therapy, HF admission in the last year, elevated NPs (NT-proBNP of ≥400pg/mL if < 75y or ≥800 pg/mL if ≥ 75y)	HTA aggregate: • Mortality by age • all-cause admission by age Study papers: • Quality of life • Hypotension • Bradycardia • renal failure • hyperkalaemia	Recruited from multiple centres in Switzerland and Germany 2003-4

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Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Outcomes	Comments
		Stratified by LVEF status		
UPSTEP trial: Karlstrom 2011[169] (Karlstrom 2016[171], Karlstrom 2015[170])	NP monitoring: Therapy increased towards guideline-target doses to reach BNP target (150pg/ml in <75, 300pg/ml in ≥75), 12 months n=140 Clinical monitoring: Therapy intensified at clinician's discretion according to clinical assessment n=128	Age > 18 years, mean: 71(10) LVEF < 40%, NYHA class II-IV, worsening HF (requiring hospitalisation and/or IV support) Elevated BNP (>150ng/L for those aged < 75 years and > 300 ng/L for those aged > 75 years) despite standard treatment with ACEi/ARB and BB	HTA IPD: • All-cause admission by age Study papers: • Quality of life	Recruited 2006-9

ACEi/ARB: Angiotensin converting enzyme inhibitor and/or Aldosterone receptor blocker, BB: Beta-blocker, IV: Intravenous therapy, NP: natriuretic peptides including BNP and NT-proBNP

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Table 81: Clinical evidence summary: NP monitoring versus clinical monitoring

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Clinical monitoring	Risk difference with NP monitoring (95% CI)
Mortality (HR) - Age <75 years	1234 (9 studies) 6-36 months	⊕⊕⊖⊖ LOW[b,c,g] due to risk of bias, imprecision	HR 0.74 (0.55 to 1)	Estimate[a]	
				248 per 1000	58 fewer per 1000 (from 103 fewer to 0 more)
Mortality (HR) - Age 75 and over	1254 (9 studies) 6-36 months	⊕⊕⊖⊖ LOW[b,c,g] due to risk of bias, imprecision	HR 1.22 (0.81 to 1.85)	Estimate[a]	
				353 per 1000	59 more per 1000 (from 56 fewer to 200 more)
Mortality (RR) - All ages	946 (2 studies) 1-2 years	⊕⊕⊖⊖ LOW[b,c] due to risk of bias, imprecision	RR 0.88 (0.65 to 1.18)	144 per 1000	17 fewer per 1000 (from 50 fewer to 26 more)
All-cause hospitalisation (HR) - Age <75 years	572 (4 studies) 6-36 months	⊕⊕⊕⊖ MODERATE[c] due to imprecision	HR 0.81 (0.66 to 0.99)	Estimate[e]	
				696 per 1000	77 fewer per 1000 (from 4 fewer to 152 fewer)
All-cause hospitalisation (HR) - Age 75 and over	598 (4 studies) 6-36 months	⊕⊕⊕⊖ MODERATE[c] due to imprecision	HR 1.03 (0.84 to 1.27)	Estimate[e]	
				699 per 1000	11 more per 1000 (from 64 fewer to 83 more)
All-cause hospitalisation (RR) - All ages	220 (1 study) 15 months	⊕⊕⊖⊖ LOW[b,c] due to risk of bias, imprecision	RR 0.87 (0.67 to 1.12)	546 per 1000	71 fewer per 1000 (from 180 fewer to 66 more)
All-cause hospitalisation (Rate Ratio) - All ages	69 (1 study) 9 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	Rate Ratio 0.74 (0.4 to 1.37)	694 events per 1000 person-years	181 fewer events per 1000 person years (from 417 fewer to 257 more)
HF hospitalisation (HR) - All ages	1515 (5 studies) 6-36 months	⊕⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias,	HR 0.78 (0.61 to 0.99)	Estimate[f]	
				245 per 1000	48 fewer per 1000 (from 2 fewer to 87 fewer)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Clinical monitoring	Risk difference with NP monitoring (95% CI)
		indirectness, imprecision			
HF hospitalisation (RR) - All ages	52 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RR 0.46 (0.21 to 1.03)	500 per 1000	270 fewer HF per 1000 (from 395 fewer to 15 more)
HF hospitalisation (Rate Ratio) – All ages	894 (1 study) 1-2 years	⊕⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	Rate ratio 1.26 (1.08 to 1.48)	618 events per 1000 person years	161 more events per 1000 person years (from 49 more to 297 more)
Quality of life MLWHFQ final	462 (2 studies) 12 months	⊕⊕⊕⊖ MODERATE[b] due to risk of bias		The mean quality of life (MLWHFQ) in the control groups was 26.75	The mean quality of life(MLWHFQ) in the intervention groups was 1.4 higher (2.23 lower to 5.02 higher)
Quality of life - KCCQ change	250 (1 study) 9 months	⊕⊕⊖⊖ LOW[b] due to risk of bias		The mean quality of life (KCCQ) in the control groups was 6.2	The mean quality of life (KCCQ)in the intervention groups was 2.6 lower (7.19 lower to 1.99 higher)
Quality of life SF36 physical final	418 (2 studies) 12 months	⊕⊖⊖⊖ VERY LOW [b,i] due to risk of bias, inconsistency		The mean quality of life (SF36 physical) in the control groups was 38.2	The mean quality of life (SF36 physical) in the intervention groups was 0.33 lower (5.13 lower to 4.47 higher)
Quality of life SF36 mental final	418 (2 studies) 12 months	⊕⊕⊕⊖ MODERATE[b] due to risk of bias		The mean quality of life (SF36 mental) in the control groups was 48.7	The mean quality of life (SF36 mental) in the intervention groups was 0.06 higher (1.9 lower to 2.02 higher)
Renal function - All ages eGFR, creatinine clearance	654 (4 studies)	⊕⊕⊕⊖ MODERATE[b]		The mean eGFR in the control group was	The mean eGFR in the intervention groups was 0.76 ml/min lower

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Clinical monitoring	Risk difference with NP monitoring (95% CI)
and creatinine level	6-12 months	due to risk of bias		51ml/min	(3.8 lower to 2.09 higher)[h]
Creatinine rise >30%	220 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.78 (0.3 to 2.01)	82 per 1000	18 fewer per 1000 (from 57 fewer to 83 more)
Acute Kidney Injury - Age <75 years	210 (1 study) 18 months	⨁⨁⊖⊖ LOW[c] due to imprecision	RR 1.08 (0.7 to 1.66)	275 per 1000	22 more per 1000 (from 82 fewer to 181 more)
Acute Kidney Injury - Age 75 and over	289 (1 study) 18 months	⨁⨁⊖⊖ LOW[c] due to imprecision	RR 0.88 (0.62 to 1.24)	329 per 1000	39 fewer per 1000 (from 125 fewer to 79 more)
Acute Kidney Injury - All ages	151 (1 study) 10 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.32 (0.3 to 5.68)	40 per 1000	13 more per 1000 (from 28 fewer to 187 more)
Worsening renal function – All ages	894 (1 study) 12-24 months	⨁⨁⊖⊖ LOW[b,c] due to imprecision	RR 1.79 (0.80 to 4.00)	20 per 1000	16 more per 1000 (from 4 fewer to 60 more)
Hyperkalaemia - Age <75 years	210 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.26 (0.68 to 2.32)	147 per 1000	38 more per 1000 (from 47 fewer to 194 more)
Hyperkalaemia - Age 75 and over	289 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.99 (0.66 to 1.50)	240 per 1000	2 fewer per 1000 (from 82 fewer to 120 more)
Hyperkalaemia – All ages	894 (1 study) 12-24 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.84 (0.69 to 4.94)	13 per 1000	11 more per 1000 (from 4 fewer to 53 more)
Hypotension - Age <75 years	210 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.19 (0.86 to 1.66)	373 per 1000	71 more per 1000 (from 52 fewer to 246 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Clinical monitoring	Risk difference with NP monitoring (95% CI)
Hypotension - Age 75 and over	289 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.58 (1.17 to 2.13)	301 per 1000	175 more per 1000 (from 51 more to 341 more)
Hypotension - All ages	1114 (3 studies) 10-24 months	⨁⨁⊖⊖ LOW[b] due to risk of bias	Peto odds ratio 3.08 (1.34 to 7.07)	11 per 1000	22 more per 1000 (from 4 more to 65 more)
Bradycardia - Age <75 years	210 (1 study) 18 months	⨁⨁⊖⊖ LOW[c] due to imprecision	RR 1.53 (0.66 to 3.55)	78 per 1000	42 more per 1000 (from 27 fewer to 200 more)
Bradycardia - Age 75 and over	289 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.19 (0.66 to 2.14)	123 per 1000	23 more per 1000 (from 42 fewer to 141 more)
Symptomatic bradycardia – All ages	894 (1 study) 12-24 months	⨁⨁⨁⊖ MODERATE[b] due to risk of bias	-	[j]	[j]
Significant Ventricular Arrhythmia - All ages	151 (1 study) 10 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.73 (0.53 to 5.66)	53 per 1000	39 more per 1000 (from 25 fewer to 249 more)
New Atrial Fibrillation - All ages	151 (1 study) 10 months	⨁⨁⊖⊖ LOW[c] due to imprecision	RR 0.39 (0.08 to 1.97)	67 per 1000	41 fewer per 1000 (from 61 fewer to 64 more)

a The age-specific control risk was calculated from TIME-CHF and BATTLESCARRED
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Downgraded by 1 increment because due to indirectness of the outcome
e The age-specific control risk was taken from TIME-CHF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Clinical monitoring	Risk difference with NP monitoring (95% CI)

f The control rate refers to the overall control risk in the Troughton meta-analysis (11 studies)

g Heterogeneity could not be formally assessed due to use of pooled data, which comprised seven of the nine included studies for the outcome. The paper reporting the pooled data did not report any statistics related to heterogeneity

h Scores estimated using a standardised mean difference of -0.04 (-0.2 to 0.11)

i Downgraded by 2 increment as point estimates were inconsistent with little overlap of confidence intervals, not enough studies to perform sub-group analysis, I^2=81%

j Unable to estimate as zero events in both arms of the trial

Table 82: Clinical evidence summary: NP monitoring v no monitoring protocol

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No monitoring (primary or secondary care)	Risk difference with NP monitoring (95% CI)
Mortality (HR) - Age <75 years	70 (1 study) 11 months	⨁⨁⊖⊖ LOW[b] due to risk of bias	HR 0.11 (0.01 to 0.86)	Estimate[a]	
				312 per 1000	272 fewer per 1000 (from 37 fewer to 309 fewer)
Mortality (HR) - Age 75 and over	50 (1 study) 11 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	HR 1.48 (0.35 to 6.26)	Estimate[a]	
				345 per 1000	120 more per 1000 (from 207 fewer to 584 more)
Mortality (RR) - Age <75 years	122 (1 study) 12 months	⨁⨁⨁⊖ MODERATE[c] due to imprecision	RR 0.5 (0.25 to 1)	312 per 1000	156 fewer per 1000 (from 234 fewer to 0 more)
Mortality (RR) - Age 75 and over	121 (1 study) 12 months	⨁⨁⨁⊖ MODERATE[c] due to imprecision	RR 1.43 (0.92 to 2.2)	345 per 1000	148 more per 1000 (from 28 fewer to 414 more)
Mortality (RR) - All ages	182 (1 study)	⨁⨁⨁⨁ HIGH	RR 0.56 (0.35 to	389 per 1000	171 fewer per 1000 (from 43 fewer to 253 fewer)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No monitoring (primary or secondary care)	Risk difference with NP monitoring (95% CI)
	12 months		0.89)		
All-cause hospitalisation (HR) - Age <75 years	50 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	HR 1.08 (0.55 to 2.12)	Estimate[d]	
				696 per 1000	28 more per 1000 (from 215 fewer to 224 more)
All-cause hospitalisation (HR) - Age 75 and over	70 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	HR 1.66 (0.81 to 3.4)	Estimate[d]	
				699 per 1000	165 more per 1000 (from 77 fewer to 284 more)
HF hospitalisation (RR) - Age <75 years	122 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[c,e] due to indirectness, imprecision	RR 0.82 (0.49 to 1.37)	359 per 1000	65 fewer per 1000 (from 183 fewer to 133 more)
HF hospitalisation (RR) - Age 75 and over	121 (1 study) 12 months	⨁⨁⊖⊖ LOW[c,e] due to indirectness, imprecision	RR 1.38 (0.86 to 2.23)	310 per 1000	118 more per 1000 (from 43 fewer to 382 more)
HF hospitalisation (RR) - All ages	182 (1 study) 12 months	⨁⨁⨁⊖ MODERATE[e] due to indirectness	RR 0.46 (0.32 to 0.67)	611 per 1000	330 fewer per 1000 (from 202 fewer to 416 fewer)

a Age-specific control rate taken from BATTLESCARRED usual care group
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Age-specific control rate taken from TIME-CHF clinically guided group (no usual care control available)
e Downgraded by one increment because the outcome was an indirect indicator of the protocol outcome

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8.1.4 Economic evidence

Published literature

No economic evaluations were identified in the 2003 guideline (CG5). One previously published economic evaluation was included in the 2010 guideline update (CG108) which assessed NP guided monitoring to usual care based on a clinical trial by Troughton et al. 2000[339]. However, a US Medicare perspective was taken and therefore this study has been excluded from this review in line with the protocol. An original economic analysis was conducted for this question in the 2010 guideline. An update of this analysis with the addition of new clinical evidence has been included in this review.[191] A further two health economic evaluations were identified with the relevant comparison and have been included in this review.[223] These are summarised in the health economic evidence profile below (Table 83) and the health economic evidence tables in Appendix G.

See also the health economic study selection flow chart in Appendix D.

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Table 83: Health economic evidence profile: NP guided therapy versus usual care

Study	Applicability	Limitations	Other comments	Costs	Effects	Inc. cost	Inc. effects	Cost-effectiveness	Uncertainty
Laramée 2013[191] [UK]	Directly applicable[(a)]	Minor Limitations [(b)]	• Cost-utility analysis, Monte Carlo simulation model • Comparators: 1. Usual care in the community 2. Specialist clinical assessment 3. Specialist natriuretic peptide monitoring • Lifetime horizon modelled • Population split into multiple sub-groups:						
			○ Patients with CHF and LVSD	1. n/a	1. n/a	-	-	-	-
				2. £12,869	2. 4.85	Baseline			Probability cost-effective (£20K threshold): 99.08%
				3. £13,972	3. 5.19	£1,103	0.34	£3,304 per QALY gained	
			○ Patients with CHF and LVSD aged <75 years	1. n/a	1. n/a	-	-	-	-
				2. NR	2. NR	Baseline			Probability cost-effective (£20K threshold): 97.92%
				3. NR	3. NR	NR	NR	£2,871 per QALY gained	
			○ Patients with CHF and LVSD aged ≥75 years	1. n/a	1. n/a	-			-
				2. NR	2. NR	Baseline			Probability cost-effective (£20K threshold): 67.50%
				3. NR	3. NR	NR	NR	£5,392 per QALY gained	

Study	Applicability	Limitations	Other comments	Costs	Effects	Inc. cost	Inc. effects	Cost-effectiveness	Uncertainty
			○ Patients with CHF of any cause	1. £7,360	1. 4.17	Baseline			
				2. £8,113	2. 4.26	£753	0.09	£8,471 per QALY gained	Probability cost-effective (£20K threshold): 99.86%
				3. £8,414	3. 4.28	£301	0.02	£14,694 per QALY gained	Probability cost-effective (£20K threshold): 84.18%
			○ Patients with CHF of any cause aged ≤75 years	1. NR	1. NR	Baseline			-
				2. NR	2. NR	NR	NR	Extendedly dominated	-
				3. NR	3. NR	NR	NR	£2,517 per QALY gained	Probability Intervention 3 cost-effective (£20K threshold): 98.10%
			○ Patients with CHF of any cause aged >75 years	1. NR	1. NR	Baseline			Probability cost-effective (£20K threshold): 50.26%
				2. NR	2. NR	NR	NR	£11,508 per QALY gained	
				3. NR	3. NR	NR	NR	Dominated.	-
Moertl 2012 [223] [Austria]	Partially applicable[(c)]	Potentially Serious Limitations [(d)]	• Cost-utility analysis, Markov model • Comparators: 1. Usual care in community 2. Nurse-led MDT 3. NT-proBNP guided intensive management • 20 year time horizon	1. £29,661	1. 2.36	Dominated (3 is less costly and more effective)			-
				2. £31,750	2. 3.04	Dominated (3 is less costly and more effective)			-
				3. £28,876	3. 3.20	Baseline			Probability cost-effective (£20K threshold): NR

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Study	Applicability	Limitations	Other comments	Costs	Effects	Inc. cost	Inc. effects	Cost-effectiveness	Uncertainty
			modelled						
Pufulete 2017[273] (Mohiuddin 2016[224]) [UK]	Directly applicable[(e)]	Minor Limitations [(f)]	• Cost-utility analysis, Markov model • Comparators: 1. Specialist-led clinically-guided therapy 2. Specialist-led BNP-guided therapy • Lifetime horizon modelled • Population split into multiple sub-groups:						
			○ All HF patients aged <75 years	-	-	2-1: £6,638	2-1: 0.66	£10,057 per QALY gained	Probability cost-effective (£20K threshold): 99%
			○ HF-REF patients aged <75 years	-	-	2-1: £5,388	2-1: 0.55	£9,840 per QALY gained	Probability cost-effective (£20K threshold): NR
			○ HF-PEF patients aged <75 years	-	-	2-1: £3,403	2-1: 0.37	£9,066 per QALY gained	Probability cost-effective (£20K threshold): 75%
			○ All HF patients ≥75 years	-	-	2-1: saves £291	2-1: 0.03	2 dominates 1 (less costly, more effective)	Probability cost-effective (£20K threshold): NR
			○ HF-REF patients ≥75 years	-	-	2-1: £1,583	2-1: 0.19	£8,123 per QALY gained	Probability cost-effective (£20K threshold): 88%

Abbreviations: BNP: brain natriuretic peptide; CHF: chronic heart failure; ICER: incremental cost-effectiveness ratio; HF; heart failure; LVSD; left ventricular systolic dysfunction; MDT: multidisciplinary team; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Preference weights of EQ-5D scores were based on subjects region of origin, not necessarily UK tariff (31% US, 52% Western Europe, 14% Latin America). Disease progression not captured in the model.

(b) Austrian payer perspective. EQ-5D not used to capture quality of life - utility scores converted from MLWHF questionnaire using previously published algorithm. Costs and effects discounted at 5%.

(c) Cost of GP visits and drug costs were not collected and not included in the analysis of the clinical trial phase.

(d) None

(e) Disease progression not captured in the model.

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8.1.5 Evidence statements

Clinical

Seventeen studies, comparing repeated biomarker measurement (BNP or NT-proBNP) with usual care (either protocol driven or not protocol driven and without repeated measurement) in people with heart failure were identified for inclusion within the review. The quality of the evidence ranged from moderate to very low. Evidence was downgraded for a number of reasons including risk of bias, imprecision due to wide confidence intervals surrounding the effect estimate, indirectness of the reported outcomes, and inconsistency due to heterogeneity in the effect estimates reported by the studies. Outcomes were stratified by age (<75 years and ≥75 years) where the study had reported this.

NP monitoring versus clinical monitoring

All ages:

Moderate quality evidence was found for the outcomes QoL as measured by the MLWHFQ (n=462) and the SF-36 mental component summary (n=418) both of which suggested no clinical effect of NP monitoring. Further moderate quality evidence was found for the outcome renal function as measured by eGFR, creatinine clearance and creatinine level (n=654) which also suggested no clinical effect of NP monitoring. Low quality evidence was found for the outcomes mortality (n=946) and hospitalisations (RR)(n=220), there was a reduction in hosptilisations suggesting a clinical benefit of NP monitoring (associated with wide confidence intervals around the effect estimate). Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

Low quality evidence was also found for the outcomes QoL as measured by the KCCQ (n=250), worsening renal function (n=849), hypotension (n=1114) and atrial fibrillation (n=151) all of which showed no clinical effect of NP monitoring. Very low quality evidence was found for the outcome hospitalisations reported as rate ratio (n=69) which suggested a clinically important decrease with NP monitoring. Further very low quality evidence was found for the outcome HF hospitalisation. When reported as a hazard ratio (n=1515) and risk ratio (n=52) the outcome showed a clinically important reduction with NP monitoring monitoring (associated with wide confidence intervals around the effect estimate). When reported as a rate ratio (n=894) the evidence suggested a clinically important increase in the number of HF hospitalisations with NP monitoring. For the outcomes creatinine rise >30% (n=220), acute kidney injury (n=151), hyperkalaemia (n=894), and significant ventricular arrhythmia (n=151) there was no suggestion of a clinically important effect on these outcomes.

Age <75 years:

Moderate quality evidence was found for the outcome hospitalisation (n=572) which suggested a clinically important reduction with NP monitoring. Low quality evidence was found for the outcomes mortality (n=1234) which suggested a clinically important reduction in deaths with NP monitoring. Further low quality evidence was found for the outcomes acute kidney injury (n=210) and bradycardia (n=210) both of which suggested no clinical effect of NP monitoring. Very low quality evidence was found for the outcome hyperkalaemia (n=210) which suggested no clinical effect of NP monitoring, and hypotension (n=210) which suggested a clinical harm with NP monitoring.

Age ≥ 75 years:

Moderate to very low quality evidence was found for the outcomes hospitalisations (n=598), mortality (n=1254), hyperkalaemia (n=289) and hypotension (n=289) . Hospitalisations and hyperkalaemia suggested a clinically important increase with NP monitoring (all associated with wide

confidence intervals around the effect estimate). For the outcomes acute kidney injury and bradycardia (n=289) low to very low quality evidence was found which suggested no clinical effect of NP monitoring. Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

NP monitoring versus no monitoring protocol

All ages:

High quality evidence was found for the outcome mortality (n=182), and moderate quality evidence for HF hospitalisations (n=182) both of which suggested a clinically important reduction in deaths with NP monitoring.

Age <75 years:

Moderate to very low quality evidence was found for the outcome mortality reported as a hazard ratio (n=70) and a risk ratio (n=122) both of which suggested a clinically important reduction in the number of deaths with NP monitoring. Very low quality evidence was found for the outcomes all-cause hospitalisation (n=50) and HF hospitalisation (n=122). For the outcome all-cause hospitalisation there was a clinically important increase with NP monitoring. However for HF hospitalisations the evidence suggested a clinically important reduction with NP monitoring.

Age ≥ 75 years:

Moderate to very low quality evidence was found for the outcomes mortality reported as a hazard ratio (n=50) and a risk ratio (n=121) both of which did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.Very low quality evidence was also found for the outcomes all-cause hospitalisation (n=70) and HF hospitalisation (n=121) both of which suggested a clinically important increase with NP monitoring..

No relevant studies comparing usual care with troponin or combinations of different biomarkers were identified. No relevant studies comparing usual care with routine cardiac imaging were identified.

Economic

- One cost–utility analysis found that:
  - in patients with CHF and LVSD specialist natriuretic peptide monitoring was cost effective compared to specialist clinical assessment (ICER: £3,304 per QALY gained).
    - in patients under the age of 75 with CHF and LVSD specialist natriuretic peptide monitoring was cost effective compared to specialist clinical assessment (ICER: £2,871 per QALY gained).
    - in patients over the age of 75 with CHF and LVSD specialist natriuretic peptide monitoring was cost effective compared to specialist clinical assessment (ICER: £5,392 per QALY gained).
  - in patients with CHF of any cause specialist natriuretic peptide monitoring was cost effective compared to specialist clinical assessment and usual care in the community (ICER: £14,694 per QALY gained compared to specialist clinical assessment).
    - in patients under the age of 75 with CHF of any cause specialist natriuretic peptide monitoring was cost effective compared to specialist clinical assessment and usual care in the community (ICER: £2,517 per QALY gained compared to usual care in the community). Specialist clinical assessment was extendedly dominated.

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  - in patients over the age of 75 with CHF of any cause specialist clinical assessment was cost effective compared to specialist natriuretic peptide monitoring and usual care in the community (ICER: £11,508 per QALY gained compared to usual care in the community). Specialist natriuretic peptide monitoring was dominated by specialist clinical assessment.

  This analysis was assessed as directly applicable with minor limitations.

- One cost-utility analysis found that NT-proBNP guided intensive management was dominant (more effective and less costly) compared to nurse-led MDT management and usual care in the community. This was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that:
  - in heart failure patients (any cause) under the age of 75 specialist-led BNP guided therapy was cost effective (ICER: £10,057 per QALY gained) compared to specialist-led clinically-guided therapy;
  - in heart failure patients (any cause) over the age of 75 specialist-led BNP guided therapy dominated (less costly, more effective) specialist-led clinically-guided therapy;
  - in HF-REF patients under the age of 75 specialist-led BNP guided therapy was cost effective (ICER: £9,840 per QALY gained) compared to specialist-led clinically-guided therapy;
  - in HF-REF patients over the age of 75 specialist-led BNP guided therapy was cost effective (ICER: £8,123 per QALY gained) compared to specialist-led clinically-guided therapy;
  - in HF-PEF patients under the age of 75 specialist-led BNP guided therapy was cost effective (ICER: £9,066 per QALY gained) compared to specialist-led clinically-guided therapy.

  This was assessed as directly applicable with minor limitations.

8.2 Monitoring using repeated biomarker measurement or imaging for management of chronic heart failure in people who also have chronic kidney disease

8.2.1 Introduction

Biomarkers are substances measurable in the blood stream which can be used to diagnose and monitor disease. Chronic kidney disease (CKD) develops when damage to the kidney results in reduced function. The extent of this damage can be approximated by blood tests to estimate glomerular filtration rate (GFR) from the kinetics of a stable excreted substance e.g. creatinine and a urine test to detect renal leakage of protein- usually albumin. The management of CKD is covered by NICE guideline CG182.

Natriuretic peptides and troponin are raised in patients with HF and could potentially be used to guide treatment. However renal function can affect the level of biomarkers in the blood principally by affecting their clearance and this effect could influence their interpretation of biomarker results by clinicians. Imaging with echocardiography or cardiac MRI could be an alternative method of monitoring.

The aim of this section of the review is to examine the clinical and cost-effectiveness of biomarker measurement or imaging in the management of heart failure in patients with CKD.

8.2.2 Review question: What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have CKD?

For full details see review protocol in Appendix A.

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Table 84: PICO characteristics of review question

Population	People diagnosed with heart failure in a community or outpatient setting who also have chronic kidney disease • Aged under 75 years • Aged 75 and over.
Interventions	Biomarker monitoring: serial (protocol-driven) measurements of circulating biomarker concentration: • NT-proBNP (alone) • BNP (alone) • Troponin (alone) • Combination of 2 biomarkers • Combination of all 3 biomarkers Imaging monitoring: serial (protocol-driven) cardiac MRI Imaging monitoring: serial (protocol-driven) echocardiography
Comparisons	Each other Usual care: Clinical monitoring (protocol-driven) • Usual care: Clinical monitoring (not protocol-driven)
Outcomes	CRITICAL • Mortality (Time to event) • Quality of life at 12 months (Continuous) • Unplanned hospitalisation (all-cause) (Count rate) IMPORTANT • Adverse events - hypotension (Dichotomous) • Adverse events - hyperkalaemia (Dichotomous) • Adverse events - renal function (Continuous) • Adverse events - bradycardia (Dichotomous) • Adverse events - arrhythmic events (Dichotomous)
Study design	Systematic reviews of RCTs RCTs

8.2.3 Clinical evidence

A search was conducted for randomised trials and systematic reviews of randomised trials comparing the effectiveness of monitoring with repeated biomarker measurement (BNP, NT-proBNP or troponin) or repeated cardiac imaging (echocardiography or cardiac MRI), compared to usual care without repeated measurement or imaging, that had a population or subgroup with chronic kidney disease.

Subgroup analyses in one primary study [114] and one systematic review [55, 338], including an individual patient data meta-analysis of seven studies, were included in the review. These are summarised in Table 85 and Table 86, and the clinical evidence is summarised in Table 87. See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

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All of the studies involved repeated BNP or NT-proBNP (together called NP) biomarker testing. Treatment algorithms varied, with some treating to an absolute target, others aiming for a personal target best on percentage drop of levels. These were compared against clinical monitoring in the other study arm.

No relevant studies comparing usual care with routine cardiac imaging, troponin, or combinations of different biomarkers were identified.

Table 85: Summary of systematic review included in the review

Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Included data
Troughton 2014[338] (Brunner-la rocca 2015[55]) "Troughton IPD"	NP-guided therapy vs Clinically-guided therapy (3-24 months)	n=1147 Stratified by LVEF status. Age mean (SD): HFREF 72.6 (10.7) HFpEF 77.2 (9.3)	Studies included in IPD: BATTLESCARRED, Berger 2010, Christchurch pilot, PRIMA, PROTECT, SIGNAL-HF, TIME-CHF*, UPSTEP *the HFpEF arm of TIME-CHF is included in Brunner La Rocca, but not the original meta-analysis

ACEi/ARB: Angiotensin converting enzyme inhibitor and/or Aldosterone receptor blocker, BB: Beta-blocker, IV: Intravenous therapy, NP: natriuretic peptides including BNP and NT-proBNP

Table 86: Summary of primary studies included in the review

Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Outcomes	Comments
BATTLESCARRED trial: Lainchbury 2009[189] (Lainchbury 2006[188])	NP monitoring: Therapy increased to achieve clinical and NP target (congestion score<2 plus NT-proBNP<1300pg/ml), 36 months n=121 Clinical monitoring: Therapy increased to meet target (Framingham score <2), 36 months n=121 No protocol: Discharged to primary care n=122	Age > 18 mean: 74 HF-admission LVEF<40%: 63% Elevated NP (NT-proBNP > 50 pmol/L)	Troughton IPD: • Mortality	Recruited from hospital 2001-6

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Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Outcomes	Comments
Berger 2010[34] (Adlbrecht 2011[4])	NP monitoring: Therapy intensified to meet or maintain target (NT-proBNP <2200pg/l), 15 months n=92 Clinical monitoring: Therapy intensified at clinician's discretion according to clinical assessment n=96 No protocol: Discharged to primary care n=90	Age mean: 71(12) Recently hospitalised with NYHA class III/IV and cardiothoracic ratio > 0.5 or LVEF < 40%	Troughton IPD: • Mortality	Recruited from hospital 2003-4
Christchurch pilot Troughton 2000[339]	NP monitoring: Treatment intensified to reach target (NT-proBNP 1700pg/ml), 15 months n=33 Clinical monitoring: Therapy increased to reach target (Framingham score <2) n=36	Age mean: 70(10) LVEF < 40%, NYHA class II-IV Treatment with at least ACEi and loop diuretic	Troughton IPD: • Mortality	Recruited in hospital or HF clinic 1998-9
PRIMA trial: Eurlings 2010[114]	NP monitoring: therapy increased to reach or maintain target (NT-proBNP at the lowest level recorded at discharge or two weeks following), 24 months n=174 Clinical monitoring: Therapy increased at clinician's discretion according to clinical assessment, 24 months n=171	Age mean: 72(12) Recent HF-admission, mainly NYHA III, LVEF<40%: 73% Elevated NPs (NT-proBNP levels at admission ≥ 1700 pg/mL) that respond to treatment (decrease ≥ 10% at discharge)	Troughton IPD: • Mortality Primary paper: • Admissions (as days in hospital)	Recruited from hospital 2004-7
PROTECT trial: Januzzi 2011[159] (Weiner 2013[367], Mallick 2016[211], Ibrahim 2017[152], Bhardwaj 2010[37])	NP monitoring: Therapy intensified to reach target (NT-proBNP≥1000pg/ml), 6-12 months n=75 Clinical monitoring: Therapy intensified at clinician discretion according to clinical assessment, 6-12 months n=76	Age ≥ 21 years, mean: 63(14) NYHA class II-IV, LVEF ≤ 40%, destabilisation in last 6/12 (attended hospital or clinic for worsening HF)	Troughton IPD: • Mortality	Recruited 2006-10

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Study	Intervention and comparison (in HF clinic unless stated otherwise)	Population	Outcomes	Comments
SIGNAL-HF trial: Persson 2010[256]	NP monitoring (in primary care): Treatment increased to achieve target (NT-proBNP reduction of 50% from baseline), 9 months n=127 Clinical monitoring (in primary care): Therapy increased at clinician's discretion according to clinical assessment, 9 months n=125	Age mean: 78(7) NYHA class II-IV, LVEF < 50%, stable in primary care Elevated NPs (NT-proBNP levels males > 800, females > 1000 ng/L)	Troughton IPD: • Mortality	Recruited from primary care 2006-9
TIME-CHF trial: Maeder 2013[210] (Pfisterer 2009[261], Brunner-la rocca 2006[54], Sanders-van wijk 2013[293], Sanders-van wijk 2014[292], Kaufmann 2015[172])	NP monitoring: Therapy intensified to reach BNP target (400og/ml for <75y, 800pg/ml for ≥75y), 18 months n=251 with rEF, 59 with pEF Clinically monitoring: Therapy intensified to reach target (NYHA ≤ II), 18 months n=248 with rEF, 64 with pEF	Age ≥ 60 years, mean:76 in HFREF: 76 HFpEF: 80 NYHA class ≥ II with current therapy, HF admission in the last year, elevated NPs (NT-proBNP of ≥400pg/mL if < 75y or ≥800 pg/mL if ≥ 75y) Stratified by LVEF status	Troughton IPD: • Mortality*	Recruited from multiple centres in Switzerland and Germany 2003-4

ACEi/ARB: Angiotensin converting enzyme inhibitor and/or Aldosterone receptor blocker, BB: Beta-blocker, IV: Intravenous therapy, NP: natriuretic peptides including BNP and NT-proBNP

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Table 87: Clinical evidence summary: NP monitoring versus clinical monitoring in people who also have chronic kidney disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Clinical monitoring	Risk difference with NP monitoring (95% CI)
All-cause mortality	1147 (8 studies) 9.5-36 months	⨁⊖⊖⊖ VERY LOW [b,c,e] due to risk of bias, imprecision, inconsistency	HR 0.9 (0.71 to 1.13)	Approximate[a]	
				275 deaths per 1000	9 more deaths per 1000 (from 105 fewer to 172 more)
All-cause hospitalisation (days in hospital)	163 (1 study)	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, imprecision, indirectness		The mean all-cause hospitalisation (days in hospital) in the control group was 6.54 days in hospital	The mean all-cause hospitalisation (days in hospital) in the intervention groups was 0.38 higher (2.81 lower to 3.57 higher)

a Control group risk not available, approximated from risk for both arms combined, will under-estimate effect
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Downgraded by 1 increment for indirectness as proxy for the protocol outcome of rate ratio of all-cause admissions
e Downgraded by 1 increment as point estimates were inconsistent, not enough studies to perform subgroup analysis, I^2=73%

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8.2.4 Economic evidence

Published literature

No previously published economic evidence was identified for this question in the review.

See also the health economic study selection flow chart in Appendix D.

8.2.5 Evidence statements

Clinical

Subgroup analyses in one primary study and one systematic review (which included an IPD meta-analysis of seven studies) were identified for inclusion within the review. All of the included studies compared repeated biomarker measurement (BNP or NT-proBNP) with clinical monitoring in people with HF who also have CKD. The quality of the evidence was very low as a result of risk of bias, imprecision due to wide confidence intervals surrounding the effect estimate, indirectness of the outcome and inconsistency due to heterogeneity in the results reported by individual studies. Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.The outcome all-cause hospitalisations (as measured by days in hospital) suggested no clinical effect of NP monitoring.

Economic

- No economic evaluations were identified.

8.3 Monitoring using repeated biomarker measurement or imaging for management of chronic heart failure in people who also have atrial fibrillation

8.3.1 Introduction

Atrial fibrillation (AF) is an abnormal heart rhythm affecting 2-3% of the adult population but is more common in patients with HF. Patients may be aware of palpitations, fatigue or breathlessness although many are asymptomatic. AF may be detected on examination, with an irregular pulse, and confirmed by ECG. The treatment of AF includes rate and rhythm control as well as anticoagulation to reduce the stroke risk. The management of AF is covered by NICE guideline CG180.

Biomarkers are substances measurable in the blood stream which can be used to diagnose and monitor disease. Natriuretic peptides are released from the myocardium in response to fluid overload. The two main natriuretic peptides used in clinical practice are amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP). Troponin is released in response to myocardial injury. Natriuretic peptides and troponin are raised in patients with HF and could potentially be used to guide treatment however AF can affect the level of these biomarkers by affecting their physiology of their secretion into the blood and also potentially affect their clearance thus affecting the ability of clinicians to interpret their results. Imaging with echocardiography or cardiac MRI could be an alternative method of monitoring.

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The aim of this section of the review is to examine the clinical and cost-effectiveness of biomarker measurement or imaging in the management of heart failure in patients with AF.

8.3.2 Review question: What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have atrial fibrillation?

For full details see review protocol in Appendix A.

Table 88: PICO characteristics of review question

Population	People diagnosed with heart failure in a community or outpatient setting who also have atrial fibrillation • Aged under 75 years • Aged 75 and over.
Interventions	Biomarker monitoring: serial (protocol-driven) measurements of circulating biomarker concentration: • NT-proBNP (alone) • BNP (alone) • Troponin (alone) • Combination of 2 biomarkers • Combination of all 3 biomarkers Imaging monitoring: serial (protocol-driven) cardiac MRI Imaging monitoring: serial (protocol-driven) echocardiography
Comparisons	Each other Usual care: Clinical monitoring (protocol-driven) • Usual care: Clinical monitoring (not protocol-driven)
Outcomes	CRITICAL • Mortality at during study (Time to event) • Quality of life at 12 months (Continuous) • Unplanned hospitalisation (all-cause) (Count rate) IMPORTANT • Adverse events - hypotension (Dichotomous) • Adverse events - hyperkalaemia (Dichotomous) • Adverse events - renal function (Continuous) • Adverse events - bradycardia (Dichotomous) • Adverse events - arrhythmic events (Dichotomous)
Study design	Systematic reviews of RCTs RCTs

8.3.3 Clinical evidence

A search was conducted for randomised trials and systematic reviews of randomised trials comparing the effectiveness of monitoring with repeated biomarker measurement (BNP, NT-proBNP or troponin) or repeated cardiac imaging (echocardiography or cardiac MRI), compared to usual care without repeated measurement or imaging, that had a population or subgroup with atrial fibrillation.

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No relevant studies were identified.

8.3.4 Economic evidence

Published literature

No previously published economic evidence was identified for this question in the review.

See also the health economic study selection flow chart in Appendix D.

8.3.5 Evidence statements

Clinical

No relevant clinical evidence was identified for inclusion within this review.

Economic

No economic evaluations were identified.

8.3.6 Recommendations and link to evidence

Recommendations	**Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2. [2018]**
Relative values of different outcomes	The critical outcomes were identified as mortality, all-cause hospitalisations and quality of life. Important outcomes were adverse events that could be related to treatment: bradycardia, hypotension, impaired renal function, hyperkalaemia, arrhythmic events. The committee sought evidence that stratified the results by age, as it was expected that older people (on average) may not respond as well to more intensive treatment regimes.
Quality of the clinical evidence	**Natriuretic peptide monitoring** General heart failure population: The review identified multiple existing meta-analyses that pooled data from a number of heterogeneous trials investigating the effect of natriuretic peptide (NP) guided therapy. The use of individual patient data (IPD) in two of the existing meta-analyses provided a higher quality source of evidence than using the data reported by each individual study, and so this review utilised data from the existing IPD meta-analyses where possible. The trials included in the existing meta-analyses differed in patient population, baseline medication, NP guided protocol and control arm protocol. The review was unable to formally assess heterogeneity of the results split by age due to reliance on aggregate data from one of the existing meta-analyses, but the low levels of heterogeneity in the overall (not age-stratified) results gave the committee some confidence that considering the trials together was a valid approach.

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Recommendations	**Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2. [2018]**
	An assessment of possible sources of bias showed that the randomisation and allocation concealment was either unclear or inadequate in many studies. The level of missing data was also not clear for some of the included studies, and there was limited detail in the existing meta-analyses on how the authors minimised the effects of missing data. Together these factors led to a high risk of bias assessment for many of the outcomes, including the mortality and quality of life evidence. The assessment showed generally low risk of bias in the subset of studies that contributed to the age-stratified all-cause hospitalisation data. The confidence intervals around most of the effect estimates were relatively wide, which further reduced the overall GRADE quality rating for all outcomes (with the exception of quality of life and renal function) and reduced the committee's confidence in the evidence. In particular, adverse events were not consistently reported, with many results based on only one trial, resulting in particularly large confidence intervals around the estimates of effect for those data. Heart failure and chronic kidney disease: Subgroup analyses of patients with chronic kidney disease (CKD) were available from one primary study and one of the existing meta-analyses mentioned above. These analyses provided evidence for all-cause mortality (eight studies) and all-cause hospitalisation (one study). For the all-cause hospitalisation data, the committee noted that of the 2021 patients included in the existing meta-analyses for whom an eGFR was calculated, 57% had an eGFR of ≤ 60ml/min/1.73m^2 and were therefore categorised as having CKD, so the subgroup was large and robust. All of the evidence was at serious or very serious risk of bias due to insufficient information about randomisation and/or allocation concealment, and insufficient information about the planning or categorisation of the CKD subgroup analyses. All of the evidence was also imprecise, with wide confidence intervals around the effect estimates, which reduced certainty in the results. The evidence for mortality was inconsistent due to the heterogeneity between effect estimates in those with HFREF and HFpEF. The hospitalisation evidence was also rated as indirect, as the reported data were number of days in hospital rather than the preferred measure of number of hospitalisation events or hospitalised patients. Heart failure and atrial fibrillation: No studies reported on the use of NP monitoring in patients with heart failure and atrial fibrillation (AF). **Monitoring using other biomarkers or repeated cardiac imaging (echocardiography or cardiac MRI)** No studies comparing usual care with monitoring with troponin or combinations of different biomarkers, repeated echocardiography, or cardiac

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Recommendations	**Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2. [2018]**
	MRI were identified.
Trade-off between clinical benefits and harms	**Natriuretic peptide monitoring** General heart failure population *Age and comorbidities* In people under 75 years of age, NP monitoring was associated with a clinically important reduction in deaths (58 fewer per thousand (from 103 fewer to 0 fewer)) and admissions (68 fewer per thousand (from 136 fewer to 4 more)) without a substantial increase in the incidence of adverse events. The committee felt that, while there was some uncertainty in this evidence, it was likely that some people under 75 years of age would benefit from NP monitoring in clinical practice. The committee agreed that the evidence supported a recommendation to consider NP monitoring in patients under 75 years of age. The evidence suggested that in people aged 75 and older, NP monitoring may result in clinically significant increase in numbers of deaths and admissions, with an average of 59 extra deaths per thousand (from 56 fewer to 200 more) and 24 extra admissions (from 47 fewer to 91 more). In terms of adverse events, there was a suggestion that people aged 75 years and older receiving NP monitoring may be more likely to develop hyperkalaemia and hypotension, although there was no clinically significant difference in the incidence of renal failure. However, the committee emphasised the very wide confidence intervals around all of these estimates of effect, which in many cases ranged from a clinically important benefit to a clinically important harm. The committee agreed that while there was no clear evidence of benefit in people aged 75 and over, there was also no clear evidence of harm. Because of the uncertainty around the impact of NP monitoring in people 75 years of age and older, the committee decided to make no recommendation for this age group. The committee discussed at length the stratification of the recommendation by age, including the biological plausibility of the finding that NP monitoring had a differential effect depending on age. The committee suggested that the metabolism of NPs may change with age, and this could make NP monitoring less useful in older patients. The committee also agreed that age could be a surrogate for comorbidity, and this could explain the benefit of a more aggressive NP monitoring strategy in younger people (i.e. with fewer comorbidities). Supporting this hypothesis, one of the existing meta-analyses conducted a post-hoc analysis suggesting that the reduced mortality associated with NP monitoring was primarily seen in patients without previous cerebrovascular accident/transient ischemic attack, diabetes or COPD, and that the benefit of NP monitoring was absent in patients with any one of those comorbidities [55]. Peripheral vascular disease was also found to be a relevant comorbidity explaining some of the association between the treatment affect and age. However, the authors of that analysis emphasise that these potential reasons for the lower effectiveness of more intensified therapy (NP monitoring) “must remain speculative” and should be “best regarded as hypothesis generating” until confirmed by further prospective

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Recommendations	**Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2. [2018]**
	studies. Based on the above, the committee discussed whether the existence of comorbidities could be substituted for age in the recommendation, in terms of the population in which NP monitoring may be suitable. The committee decided against this given the "speculative" nature of the finding that comorbidities rather than age *per se* explained the differential results in different age groups, and the uncertainty about which comorbidities were most relevant. The committee agreed that as the evidence reviewed clearly showed an age-effect above and below 75 years, it was appropriate to stratify the recommendation by this factor. However, it was unanimously agreed that age should not be an absolute barrier to (or indication for) NP monitoring, and that a person's general health and the presence of comorbidities should always be considered on a case by case basis when considering NP monitoring. *Role and scope of NP monitoring* The committee discussed the heterogeneous nature of the NP-guided treatment protocols used in the included studies. Some studies treated to an absolute NP target; others set a personal target based on percentage drop in NP levels; and others did not aim to reduce NP levels, but used serial measurements to detect increases thought to represent deterioration and acted accordingly. The variation in the NP-guided treatment protocols made it difficult for the committee to specify a particular model of NP monitoring, but the committee agreed that the greatest benefit of NP monitoring would be as part of a treatment optimisation protocol. The reduction in deaths and hospitalisation would be most significant for people in higher risk categories, such as those who are newly diagnosed or have had a recent deterioration, and require medication titration. An NP guided treatment protocol should not, however, override clinical assessment and judgement. It was not proposed that NP levels be routinely measured in stable patients on optimised medication, as such patients would likely gain little from the intervention. *Type of NP measured* The committee noted that across the included studies, both BNP and NT-proBNP monitoring was utilised. The committee agreed however that NT-proBNP should be the preferred NP for monitoring for two key reasons. Firstly, one of the recommended drugs for treating heart failure interferes with BNP physiology (Sacubitril valsartan - TA388). Secondly, concerns were raised by the committee about the stability of BNP samples. BNP is stable in a blood sample for only 4-6 hours while NT-proBNP is stable for days. In order to address the stability issue, BNP can be collected in different sample tubes (EDTA or fluoride-citrate); however this often requires more blood samples to be taken and therefore makes the process more complex and open to error as well as being more resource intensive. Samples for NT-proBNP testing can be collected in standard serum tube with the rest of the

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Recommendations	**Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2. [2018]**
	likely requests. Because NT-proBNP testing is likely to produce more reliable results than BNP testing, the committee agreed that where NP monitoring is conducted, NT-proBNP should be the peptide measured. *Impact of ejection fraction* The committee then discussed whether the recommendation should be limited to people with heart failure with reduced (HFREF), rather than preserved (HFpEF), ejection fraction. Although the results of the review were not formally split into HFREF and HFpEF, the committee acknowledged that a substantial majority of the patients in the included studies had HFREF. Because the committee agreed that NP monitoring would have greatest benefit as part of a treatment optimisation protocol, and there was no evidence for long term prognostic benefit from pharmaceutical treatment in HFPEF, it was unlikely that patients with HFPEF would receive significant benefit from NP monitoring. This aligned with subgroup analyses reported in the existing meta-analyses, [279] [55] which showed that the mortality and all-cause hospitalisation benefit of NP monitoring was found in HFREF but not HFPEF patients. For these reasons, the committee decided that the recommendation should be limited to people with HFREF. <u>People with heart failure and chronic kidney disease</u> The committee considered the evidence regarding the use of NP-guided treatment strategies in patients with HF and CKD and agreed that although there was suggestion of a clinically important increase in deaths (9 more (from 105 fewer to 172 more)) these results were imprecise making it difficult for the committee to have confidence in the results. In addition to this there was inconsistency in the results reported for people with HFREF and HFpEF which further reduced the committees confidence in the results. Regardless of this the committee agreed that the evidence may be suggestive of a clinically significant increase in deaths with NP monitoring and therefore people with HF and CKD should be monitored by a specialist. The committee noted the findings of the separate review of pharmaceutical treatment for HF in people with both HF and CKD, which generally concluded that most patients with CKD should be offered the same treatment options as patients without CKD. The committee noted that while the patients with CKD in the original trials made up more than half the total number of participants, many of the included studies excluded patients with severe renal disease with the majority of patients included in the trials having an eGFR of ≤ 60ml/min/1.73m^2. Therefore, the results cannot be extrapolated to patients with more severe CKD. <u>People with heart failure and atrial fibrillation</u> The committee discussed NP monitoring in patients with HF and AF. In the absence of evidence in this subgroup, and given the effect of AF itself on NP levels the committee agreed that no recommendation could be made on this topic.

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Recommendations	**Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2. [2018]**
	Monitoring using other biomarkers or repeated cardiac imaging (echocardiography or cardiac MRI) Given the absence of evidence on the clinical effectiveness of monitoring using other troponin, combinations of biomarkers, or repeated cardiac imaging, the committee agreed to make no recommendation in these areas. The committee acknowledged its related research recommendation on the added value of cardiac MRI in the diagnosis of heart failure and its aetiology, and considered that further research in that area would be necessary before developing an evidence base for the use of cardiac imaging as a monitoring tool.
Trade-off between net clinical effects and costs	Three economic evaluations (two from a UK perspective and one from an Austrian perspective) were identified and included in this review comparing NP monitoring to usual care. The Austrian cost-utility analysis assessed patients with heart failure who had recently been discharged after a heart failure hospitalisation. The study compared usual care by a primary care physician as well as usual care by a nurse-led multidisciplinary team (MDT) to intensive NP monitoring. Mortality and hospitalisation rates were taken from Berger et al. 2010 identified in the clinical review. [34] This economic evaluation suggests that NP monitoring is more effective and less costly and therefore dominates both usual care in the community and the nurse-led MDT. The committee did not put much weight on the results of this study as the relative effect of NP monitoring was taken from only one of 13 studies included in the clinical review and therefore is unlikely to reflect the best estimate of the effect of NP monitoring, and was also not from a UK perspective. This study was assessed as being partially applicable with potentially serious limitations. One UK cost-utility analysis compared usual care in the community and/or usual care through specialist clinical assessment to natriuretic peptide monitoring. The model assessed two population groups: patients with chronic heart failure due to LVSD, and patients with heart failure from any cause, and also presented results stratified by age. This study found that NP monitoring is cost effective for patients with chronic heart failure and LVSD at any age compared to specialist management [ICER: £3,304 per QALY gained]. The probability that NP monitoring is cost effective at the £20,000 threshold was 99%. Similar results were found for patients with CHF and LVSD <75 years old [ICER: £2,871 per QALY gained] with a 98% probability of being cost effective at the £20,000 threshold. NP monitoring was also found to be cost effective in patients with CHF and LVSD ≥75 years old [ICER: £5,392 per QALY gained], however this is uncertain as there is only a 68% probability that NP monitoring is cost effective at the £20,000 threshold. The committee noted that a larger proportion of the population were less than 75 years old in these trials, so the result for any age could be driven by this group. This study also found that NP monitoring is cost effective compared to both usual care in the community and usual care by a specialist for patients with CHF of any cause at any age [ICER: £14,694 per QALY gained comparing

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Recommendations	**Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2. [2018]**
	NP monitoring to specialist management]. The probability that NP monitoring is cost effective at the £20,000 threshold is 84%. NP monitoring is also found to be cost effective for the two age sub-groups (75 and under, and greater than 75), but again reflected the results found for those with CHF and LVSD, with greater uncertainty in the result for those older than 75 (50% probability cost effective at £20,000 threshold) than those under 75 (98% probability cost effective at £20,000 threshold). The committee noted that the majority of patients in the trials used for the analysis had HF-REF. The committee noted that this analysis only included 4 of 13 studies included in the clinical review and therefore may not reflect the most recent clinical evidence. This study was assessed as directly applicable with minor limitations. One UK cost-utility analysis compared specialist-led clinically guided therapy to specialist led NP-guided therapy in patients with heart failure who had recently been discharged from hospital following an acute episode. All heart failure patients and HF-REF patients were sub-grouped by age (less than 75 years old, 75 and older) whereas only HF-PEF patients less than 75 years of age were assessed. IPD data was used to estimate the relative effect of NP guided care on all-cause mortality and all-cause hospitalisations reported by Brunner le Rocca et al. 2006.[55] The study found NP monitoring to be cost effective for all sub-groups, and even dominated specialist-led clinically-guided therapy in all heart failure patients over 75. The study also reported incremental net monetary benefit results with 95% confidence intervals. These results suggest there is uncertainty in the cost effectiveness of NP monitoring for HF-PEF patients less than 75 years of age and both all heart failure and HF-REF patients over 75 years of age, with 95% confidence intervals ranging from negative to positive. The study also carried out a sensitivity analysis using IPD meta-analysis data from a more recent health technology assessment, in which this economic evaluation was developed. However, this was only assessed for HF-REF patients less than 75 years old. The results of this suggest that NP monitoring is cost effective compared to clinically-guided therapy, however this is more uncertain than the base-case results as the 95% confidence intervals of the incremental net monetary benefit now range from negative to positive. The committee discussed that the base-case results in this study may not reflect the best estimate of the relative effect of NP monitoring and suggested that the recent IPD meta-analysis data was more reflective of the clinical evidence presented in the review for this guideline. This study was assessed as being directly applicable with minor limitations. As previously mentioned, the committee agreed not to recommend NP monitoring for HFPEF patients due to the lack effective pharmacological treatments available for these patients and most of the studies did not include this population. The committee also considered that the clinical and cost effectiveness evidence for NP monitoring in heart failure patients over 75 years of age was too uncertain to make a recommendation for these patients. However, the committee considered that NP monitoring is likely to be cost

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Recommendations	**Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2. [2018]**
	effective for HFREF patients under the age of 75. The committee noted the variety of monitoring protocols used in the RCTs, and raised some concern about the potential range in cost of the intervention depending on the frequency of monitoring. The most recent cost-effectiveness analysis assumed NP testing every 3 months, but that this would cease after 18 months. The committee considered that this was a reasonable average, but also recognised that due to the low ICERs that even if the average frequency of monitoring were to be slightly higher that it would still be cost effective. Due to the uncertainty of the cost effectiveness of NP monitoring when the IPD data is used and the potential variation in cost of NP monitoring the committee decided to make a consider recommendation for people under the age of 75 with HF-REF . No economic evaluations were identified for those with heart failure and CKD or AF. As mentioned in the 'Trade-off between clinical benefits and harms' section above the committee did not consider that those with heart failure with CKD should not be monitored using NP due to concern of increased risk of death, but instead be monitored by a specialist. There was no clinical evidence identified for the heart failure plus atrial fibrillation population and therefore the committee could not assess the cost effectiveness of NP monitoring in this population and no recommendation was made for this group.
Other considerations	A single study was included in the 2010 update (CG108) of this question[30]. The committee agreed that this study should now be excluded as it no longer met the review protocol. This was due to the decision to impose a study duration threshold of a minimum of 6 months. The committee agreed that due to the chronic nature of the condition, this length of follow-up was necessary in order to be able to make appropriate recommendations. The committee discussed current practice regarding BNP measurement. It was agreed that usual practice is to measure BNP at the point of diagnosis. Repeated measurement is usually done only for specific populations (for example, people awaiting transplant), and by some specialist centres. It was felt that this recommendation, although not substantially different from the previous recommendation, may increase the uptake of NP monitoring in younger, newly diagnosed HFREF patients.

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8.4 Telemonitoring and self-monitoring

8.4.1 Introduction

Telemonitoring and self –monitoring in people with heart failure has been a area of interest not only amongst clinicians in primary and community care, but also with commissioners of services. The main drive for its use has been the perception that these interventions could reduce the need for face-to-face contact with patients, and promote self care. The 2010 guidelines did not make any recommendations for its implementation due to the difficulty in interpreting whether the differences shown in the outcomes were due to the monitoring intervention or the additional access provided to specialist care. Current use of these methods of monitoring patients remains patchy throughout the country Telemonitoring techonology has developed since publication of the last guideline, and the publication of further reviews and studies prompted the question of the clinical and cost effectiveness of telemonitoring to be revisited.

8.4.2 Review question: What is the clinical and cost effectiveness of telemonitoring and self-monitoring compared with usual care, in people with heart failure?

For full details see review protocol in appendix A.

Table 89: PICO characteristics of review question

Population	People with heart failure in a community or outpatient setting. The results will be presented separately in each of the following strata: • recently discharged patients • patients recruited in the community
Interventions	• Structured telephone support – monitoring or self-care management or both delivered using simple telephone technology • Telemonitoring – digital/broadband/satellite/wireless or Bluetooth transmission of physiological or other non-invasive data Interventions needed to be scheduled, as opposed to offering telephone follow-up on an 'as needed' basis. Intervention must have been initiated by a healthcare professional (medical, nursing, social work, pharmacist) and delivered to people with heart failure living in the community as the only aftercare intervention, without protocol-driven home visits or intensified clinic follow-up. The intervention has to be targeted at the person and intended to address their concerns and problems, not those of caregivers. The participant must not have been visited at home by a specialised heart failure healthcare professional or study personnel for the purpose of education or clinical assessment other than as an initiation visit to set up equipment. The results for telemonitoring and structured telephone support will be presented separately.
Comparators	• Usual care 'Usual care' consists of standard post-discharge care without intensified attendance at cardiology clinics or clinic-based heart failure disease management programme, or home visiting as described above. Studies will be excluded if there was any previous exposure to telemonitoring or structured telephone support for the usual care or intervention arms prior to the start of the study.
Outcomes	CRITICAL • All-cause mortality during study (dichotomous) • Quality of life during study (continuous) • All-cause hospitalisations during study (dichotomous)

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	IMPORTANT • Adherence to intervention
Study design	Systematic reviews of RCTs RCTs

8.4.3 Clinical evidence

This review was conducted as an update to an existing Cochrane review which included randomised trials comparing the effectiveness of telemonitoring and structured telephone support versus usual care[153]. Forty one studies were included in the Cochrane review;[15, 19, 23, 25, 28, 33, 40, 41, 48, 57, 61, 66, 88, 89, 92, 96, 100, 125, 128, 129, 131, 134, 178, 183, 190, 204, 228, 275, 276, 285, 286, 297, 305, 314, 317, 344, 360, 362, 364, 372, 376] these are summarised in Table 90 and Table 91 below.

A search was conducted from the publication date onwards in order to update the review, which led to a further five studies being identified for inclusion. These studies [7, 81, 247, 291, 320] are summarised in Table 92 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 93, Table 94 and Table 95). See also the study selection flow chart in Appendix C, forest plots in Appendix E, study evidence tables in Appendix F, GRADE tables in Appendix H and excluded studies list in Appendix I.

A HTA report[252] published in 2013, which reviewed the effectiveness of structured telephone support and telemonitoring in people recently admitted for an exacerbation of heart failure, was also identified. The Cochrane review was prioritised for update over this review as it included a broader population, was more recently published and included RCT level data only.

The previous chronic heart failure guideline [CG108] included eight studies.[19, 66, 82, 83, 131, 301, 317, 364] Three of these studies [82, 83, 301] were subsequently excluded by the Cochrane review as the intervention arms included home visits or were targeted at the caregiver as well as the person with heart failure. In addition to this two RCTs included in the Cochrane review [48, 376] on structured telephone support did not have any extractable data and were therefore excluded in this review.

The studies included within the Cochrane review were incorporated into our guideline in the following ways:

- Data has been analysed separately for patients who have recently been admitted to hospital and for patients recruited within the community. Where the study has not reported this information, we have included a mixed strata as these papers potentially represent a combination of recently admitted and community dwelling people.
- The outcomes quality of life and adherence to intervention were reported narratively by the Cochrane review. For the current review, quality of life and adherence data have only been included when reported by the study in an extractable format.
- Risk of bias assessment per study was directly adopted for the outcomes all-cause mortality and all-cause hospitalisation. The outcome quality of life was downgraded where studies reported final values with no baseline scores or where the intervention and comparison scores were not matched at baseline.

Two of the included studies reported multiple intervention arm[66, 228] Data from these studies was separated out into the two interventions of interest (structured telephone support and telemonitoring).

Funnel plots were constructed by the Cochrane authors to assess for potential publication bias (appendix F) for the outcomes all-cause mortality and all-cause hospitalisation. This was taken into consideration when assessing the quality of the evidence for strata containing more than 5 studies.

Table 90: Summary of studies included in the Cochrane review[153] – Structured telephone support

Study	Intervention and comparison	Population	Outcomes	Comments
Angermann 2012 (INH)[15]	Intervention: Structured telephone support Comparator: Usual care	n=715 People with HF ≥ 18 years of age, hospitalised with signs and symptoms of decompensated HF Mean age: 68.6 years M/F (%): 71/29 Germany	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: recent admission
Baker 2011[23]	Intervention: Structured telephone support Comparator: Usual care	n=605 People with HF from general and internal medicine and cardiology clinics Mean age: 60.7 years M/F (%): 52/58 USA	• All-cause mortality • Quality of life	• Strata: recent admission • Quality of life downgraded for risk of bias as all scores were not matched at baseline and final values were reported.
Barth 2001[28]	Intervention: Structured telephone support Comparator: Usual care	n=34 People discharged from acute care to home with a primary diagnosis of HF Mean age: 75 years M/F (%): 47/53 USA	• All-cause mortality	• Strata: recent admission
Bento 2009[33]	Intervention: Structured telephone support	n=40 People with a	• All-cause mortality • All-cause	• Strata: community

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Study	Intervention and comparison	Population	Outcomes	Comments
	Comparator: Usual care	diagnosis of HF and NYHA class I-IV, treated at a HF outpatient clinic with telephone access Mean age: Intervention: 54 years Control: 61 years M/F (%): 70/30 Brazil	hospitalisation	
Capomolla 2004[57]	Intervention: Structured telephone support Comparator: Usual care	n=133 People discharged from specialist HF units to home Mean age: 57 years M/F (%): 88/12 Italy	• All-cause mortality	• Strata: recent admission
Chaudhry 2010 (Tele-HF)[61]	Intervention 1: Structured telephone support Comparator: Usual care	n=1653 People who had recently been hospitalised for HF Median age: 61 years M/F (%): 58/42 USA	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission
Cleland 2005 (TENS-HMS)[66]	Intervention 1: Structured telephone support Intervention 2: Telemonitoring Comparator: Usual care	n=426 People with a recent admission for HF and LVEF<40% Mean age: 67 years M/F (%): 77/23	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission

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Study	Intervention and comparison	Population	Outcomes	Comments
		Germany, Netherlands, UK		
DeBusk 2004[89]	Intervention: Structured telephone support Comparator: Usual care	n=462 People hospitalised with a provisional diagnosis of HF from Kaiser Permanente Mean age: 72 years M/F (%): 51/49 USA	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission
DeWalt 2006[96]	Intervention: Structured telephone support Comparator: Usual care	n=127 People with confirmed HF Mean age: 62.5 years M/F (%): 47/53 USA	• All-cause mortality • Quality of life	• Strata: community
Domingues 2011[100]	Intervention: Structured telephone support Comparator: Usual care	n=120 People with HF, with a LVEF≤45% Mean age: 63 years M/F (%): 68/32 Brazil	• All-cause mortality • All-cause hospitalisation •	• Strata: recent admission
Galbreath 2004[125]	Intervention: Structured telephone support Comparator: Usual care	n=1069 People with symptoms of HF and documented systolic or diastolic dysfunction Mean age: 71 years M/F(%): 71/29	• All-cause mortality	• Strata: community
Gattis 1999 (PHARM)[128]	Intervention: Structured telephone	n=181	• All-cause mortality	• Strata: community

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Study	Intervention and comparison	Population	Outcomes	Comments
	support Comparator: Usual care	People with HF being evaluated in cardiology clinic Mean age: 67 years M/F(%): 68/32 USA	• All-cause hospitalisation	
GESICA 2005 (DIAL)[129]	Intervention: Structured telephone support Comparator: Usual care	n=1518 Outpatients with stable HF Mean age: 65 years M/F(%): 71/29 Argentina	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: community
Krum 2013 (CHAT)[183]	Intervention: Structured telephone support Comparator: Usual care	n=405 People with a recent hospital discharge due to a primary diagnosis of HF Mean age: 73 years M/F(%): 61/39 Australia	• All-cause mortality • All-cause hospitalisation	• Strata: community
Laramee 2003[190]	Intervention: Structured telephone support Comparator: Usual care	n=287 People admitted to hospital with primary or secondary diagnosis of HF Mean age: 71 years M/F(%): 54/46 USA	• All-cause mortality • All-cause hospitalisation • Adherence to intervention	• Strata: recent admission • Adherence to intervention downgraded for risk of bias as the scale used was not validated.
Mortara 2009 (HHH)[228]	Intervention 1: Structured telephone support Intervention 2:	n=461 People with HF NYHA class II-IV and	• All-cause mortality • All-cause hospitalisation	• Strata: mixed

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Study	Intervention and comparison	Population	Outcomes	Comments
	Telemonitoring Comparator: Usual care	LVEF≤40% Mean age: 60 years M/F(%): 85/15 UK, Poland, Italy		
Rainville 1999[275]	Intervention: Structured telephone support Comparator: Usual care	n=38 People aged ≥50 years discharged from hospital with HF Mean age: 70 years M/F(%): 50/50 USA	• All-cause mortality	• Strata: recent admission
Ramachandran 2007[276]	Intervention: Structured telephone support Comparator: Usual care	n=50 People attending a HF clinic with symptoms of HF and LVEF <40% Mean age: 44.5 years M/F(%): 78/22 India	• Quality of life	• Strata: mixed
Riegel 2002[286]	Intervention: Structured telephone support Comparator: Usual care	n=358 People discharged from hospital with HF Mean age: 74 years M/F(%): 49/51 USA	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission
Riegel 2006[285]	Intervention: Structured telephone support Comparator: Usual care	n=135 Hispanic people hospitalised for HF Mean age: 72 years	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: recent admission

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Study	Intervention and comparison	Population	Outcomes	Comments
		M/F(%): 46/54 USA		
Sisk 2006[314]	Intervention: Structured telephone support Comparator: Usual care	n=406 non-Hispanic and Hispanic people with documented systolic dysfunction Mean age: 59 years M/F(%): 54/46 USA	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: community
Tsuyuki 2004[344]	Intervention: Structured telephone support Comparator: Usual care	n=276 People discharged from hospital with HF Mean age: 72 years M/F(%): 58/42 Canada	• All-cause mortality	• Strata: recent admission
Wakefield 2008[364]	Intervention: Structured telephone support Comparator: Usual care	n=148 People hospitalised for HF exacerbation Mean age: 69 years M/F(%): 99/1 USA	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission

Table 91: Summary of studies included in the Cochrane review[153] - Telemonitoring

Study	Intervention and comparison	Population	Outcomes	Comments
Antonicelli 2008[19]	Intervention: Telemonitoring Comparator: Usual Care	n=57 People hospitalised for worsening symptoms and	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: recent admission • Quality of life downgraded for risk of bias as all scores were not matched at

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Study	Intervention and comparison	Population	Outcomes	Comments
		signs of HF Mean age: 78 years M/F (%): 78/22 Italy		baseline and final values were reported.
Balk 2008[25]	Intervention: Telemonitoring Comparator: Usual care	n=214 People with HF and NYHA class I-IV Mean age: 66 years M/F (%): 70/30 The Netherlands	• All-cause mortality	• Strata: mixed
Biannic 2012[40]	Intervention: Telemonitoring Comparator: Usual care	n=73 Elderly people with severe HF recently hospitalised for HF Mean age: Intervention: 76 Control: 77 M/F (%): Intervention: 79/21 Control: 77/23 France	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: recent admission
Blum 2014 (MCCD)[41]	Intervention: Telemonitoring Comparator: Usual care	n=204 People with HF who have been admitted to hospital within the past year Mean age: 72 years M/F (%): 71/29 USA	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: mixed • Quality of life downgraded for risk of bias as all scores were not matched at baseline and final values were reported.
Cleland 2005 (TENS-HMS)[66]	Intervention 1: Structured telephone support Intervention 2:	n=426 People with a	• All-cause mortality • All-cause	• Strata: recent admission

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Study	Intervention and comparison	Population	Outcomes	Comments
	Telemonitoring Comparator: Usual care	recent admission for HF and LVEF<40% Mean age: 67 years M/F (%): 77/23 Germany, Netherlands, UK	hospitalisation	
De Lusignan 2001[88]	Intervention: Telemonitoring Comparator: Usual care	n=20 People with HF confirmed by a cardiologist, identified from the database of an academic general practice Mean age: 75 years Gender not reported UK	• All-cause mortality	• Strata: mixed
Dendale 2012 (TEMA-HF1)[92]	Intervention: Telemonitoring Comparator: Usual care	n=160 People hospitalised with HF Mean age: 76 years M/F (%): 65/35 Belgium	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission
Giordano 2009[131]	Intervention: Telemonitoring Comparator: Usual care	n=460 People with confirmed HF with LVEF<40% and at least 1 hospitalisation for acute HF in the prior year Mean age: 57 years M/F(%): 85/15	• All-cause mortality • All-cause hospitalisation	• Unable to obtain full text paper. Included in mixed strata

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Study	Intervention and comparison	Population	Outcomes	Comments
		Italy		
Goldberg 2003 (WHARF)[134]	Intervention: Telemonitoring Comparator: Usual care	n=280 People hospitalised with NYHA class III-IV, with a LVEF < 35% Mean age: 59 years M/F(%): 68/32 USA	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: recent admission
Koehler 2011 (TIM-HF)[178]	Intervention: Telemonitoring Comparator: Usual care	n=710 People with HF in NYHA class II or III with an LVEF of 35% Mean age: 66.9 years M/F(%): 80/20 Germany	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: mixed • Quality of life downgraded for risk of bias as final scores were reported by the study with no report of baseline scores.
Lyngå 2012 (WISH)[204]	Intervention: Telemonitoring Comparator: Usual care	n=344 People who were hospitalised for HF with NYHA class III-IV Mean age: 73.9 years M/F(%): 75/25 Sweden	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission
Mortara 2009 (HHH)[228]	Intervention 1: Structured telephone support Intervention 2: Telemonitoring Comparator: Usual care	n=461 People with HF NYHA class II-IV and LVEF≤40% Mean age: 60 years M/F(%): 85/15	• All-cause mortality • All-cause hospitalisation	• Strata: mixed

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Study	Intervention and comparison	Population	Outcomes	Comments
		UK, Poland, Italy		
Scherr 2009 (MOBITEL)[297]	Intervention: Telemonitoring Comparator: Usual care	n=108 People with HF hospitalised for >24 hours within 4 weeks prior to the study Median age (IQR): Control: 67 (61-72) Intervention: 65 (62-72) M/F(%): Control: 72/28 Intervention: 74/26 Austria	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission
Seto 2012[305]	Intervention: Telemonitoring Comparator: Usual care	n=100 Ambulatory people diagnosed with HF Mean age: 55.1 years M/F(%): 82/18 Canada	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: mixed
Soran 2008[317]	Intervention: Telemonitoring Comparator: Usual care	n=315 People with a diagnosis of HF secondary to systolic dysfunction Mean age: 76 years M/F(%): 35/65 USA	• All-cause mortality • All-cause hospitalisation	• Strata: Mixed
Villani 2014 (ICAROS)[360]	Intervention: Telemonitoring Comparator: Usual care	n=80 People with HF with >2 hospitalisations in the last 6 months and at high risk of	• All-cause mortality	• Strata: recent admission

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Study	Intervention and comparison	Population	Outcomes	Comments
		early re-hospitalisation Mean age: 72 years M/F(%): 73.7/26.3 Italy		
Vuorinen 2014[362]	Intervention: Telemonitoring Comparator: Usual care	n=94 People with systolic HF Mean age: 58 years M/F(%): 83/17 Finland	• All-cause mortality	• Strata: mixed
Woodend 2008[372]	Intervention: Telemonitoring Comparator: Usual care	n=121 People with symptomatic HF (NYHA Class II or greater) Mean age: 68 years M/F(%): 74/26 Canada	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission

Table 92: Summary of studies included in the update of the Cochrane review

Study	Intervention and comparison	Population	Outcomes	Comments
Al-Sutari 2017[7]	Intervention: Structured telephone support Comparator: Usual care	n=144 People with heart failure (LVEF<40% and NYHA class II or III) who attended the cardiac clinic of an educational hospital Mean age: 64.78 (9.9) M/F(%): 60/40	• All-cause mortality • All-cause hospitalisation	• Strata: community

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Study	Intervention and comparison	Population	Outcomes	Comments
		Jordan		
Dang 2017[81]	Intervention: Structured telephone support Comparator: Usual care	n=61 People living in the community with a diagnosis of HF Mean age: 55.3 M/F(%): 64/36 USA	• Quality of life	• Strata: community
Ong 2016[247]	Intervention: Structured telephone support + telemonitoring Comparator: Usual care	n=1437 People admitted to hospital as inpatients or on observation being treated for decompensated HF Median age (IQR): Intervention: 73 (62-84) Comparator: 74 (63-82) M/F(%): Intervention: 53/47 Comparator: 53/47 USA	• All-cause mortality • All-cause hospitalisation • Quality of life	• Strata: recent admission • Quality of life downgraded for risk of bias as final scores were reported by the study with no report of baseline scores.
Sales 2014[291]	Intervention: Structured telephone support Comparator: Usual care	n=317 People with clinical signs and symptoms of HF Mean age: 72.6 M/F(%): 58/79 USA	• All-cause mortality • All-cause hospitalisation	• Strata: recent admission
Stavrianopoulos 2016[320]	Intervention: Structured telephone support Comparator: Usual care	n=50 People with HF Age 50-60 years: 11 Age >60: 39	• Quality of life	• Strata: mixed

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Study	Intervention and comparison	Population	Outcomes	Comments
		M/F(%): 68/32 Greece		

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Table 93: Clinical evidence summary: Structured telephone support versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with structured telephone support (95% CI)
Recent admission					
All-cause mortality	5359 (14 studies) 3 to 24 months	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, imprecision, publication bias	RR 0.84 (0.72 to 0.98)	114 per 1000	18 fewer per 1000 (from 2 fewer to 32 fewer)
All-cause hospitalisation	4549 (11 studies) 3 to 24 months	⨁⨁⨀⨀ LOW[1] due to risk of bias, publication bias	RR 1 (0.94 to 1.07	433 per 1000	0 fewer per 1000 (from 26 fewer to 30 more)
Quality of life (SF-36 Physical health component) Better indicated by higher	715 (1 study) 180 days	⨁⨁⨁⨀ MODERATE[1] due to risk of bias		The mean QoL in the control groups was 1.3	The mean QoL in the intervention groups was 1.5 higher (0.04 to 2.96 higher)
Quality of life (SF-36 Physical functioning component) Better indicated by higher	715 (1 study) 180 days	⨁⨁⨁⨀ MODERATE[1] due to risk of bias		The mean QoL in the control groups was 1.8	The mean QoL in the intervention groups was 4.1 higher (0.4 to 7.8 higher)
Quality of life (MLWHFQ) Better indicated by lower	134 (1 studies) 6 months	⨁⨁⨀⨀ LOW[2] imprecision		The mean QoL in the control groups was 12.9	The mean QoL in the intervention groups was 0.80 lower (6.48 lower to 4.88 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with structured telephone support (95% CI)
Quality of life (EQ-5D) Better indicated by higher	134 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[2] due to imprecision		The mean QoL in the control group was 0.78	The mean QoL in the intervention group was 0.04 higher (0.03 lower to 0.11 higher)
Quality of life (HFSS) Better indicated by higher	605 (1 study) 30 days	⨁⨁⊖⊖ LOW[1] due to risk of bias		The mean QoL in the control groups was 64.1	The mean QoL in the intervention groups was 1.2 higher (2.4 lower to 4.8 higher)
Adherence to intervention (weight self daily) Better indicated by higher	287 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean adherence to intervention in the control groups was 3.2	The mean adherence to intervention in the intervention groups was 1.5 higher (0.62 to 2.38 higher)
Adherence to intervention (check ankles and feet for swelling) Better indicated by higher	287 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean adherence to intervention in the control groups was 4.5	The mean adherence to intervention in the intervention groups was 0.4 higher (0.15 to 0.65 higher)
Adherence to intervention (follow fluid recommendations) Better indicated by higher	287 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean adherence to intervention in the control groups was 4.6	The mean adherence to intervention in the intervention groups was 0.4 higher (0.13 to 0.67 higher)
Adherence to intervention (follow low-salt diet)	287 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias,		The mean adherence to intervention in the control groups was	The mean adherence to intervention in the intervention groups was 0.3 higher

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with structured telephone support (95% CI)
Better indicated by higher		imprecision		4.6	(0.12 to 0.48 higher)
Adherence to intervention (take medication) Better indicated by higher	287 (1 study) 3 months	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean adherence to intervention in the control groups was 4.9	The mean adherence to intervention in the intervention groups was 0.1 higher (0.04 lower to 0.24 higher)
Community					
All-cause mortality	4495 (9 studies) 3 to 24 months	⨁⨁⨀⨀ LOW[2,3] due to imprecision, publication bias	RR 0.88 (0.73 to 1.05)	103 per 1000	12 fewer per 1000 (from 28 fewer to 5 more)
All-cause hospitalisation	2694 (6 studies) 3 to 24 months	⨁⨁⨀⨀ LOW[2,3] due to imprecision, publication bias	RR 0.81 (0.73 to 0.89)	498 per 1000	76 fewer per 1000 (from 44 fewer to 107 fewer)
Quality of life (MLWHFQ) Better indicated by lower	2103 (4 studies) 3 to 24 months	⨁⨁⨁⨁ HIGH		[4]	The mean QoL in the intervention groups was 4.28 lower (6.43 to 2.14 lower)
Quality of life (HDS) Better indicated by lower	52 (1 study) 3 months	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision		The mean QoL in the control groups was 1.03	The mean QoL in the intervention groups was 1.11 lower (1.97 to 0.25 lower)
Mixed					
All-cause mortality	254	⨁⨀⨀⨀	RR 1.32	56 per 1000	18 more per 1000

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with structured telephone support (95% CI)
	(1 study) 11.6 months	VERY LOW[1,2] due to risk of bias, imprecision	(0.51 to 3.44)		(from 28 fewer to 137 more)
All-cause hospitalisation	254 (1 study) 11.6 months	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.21 (0.84 to 1.72)	300 per 1000	63 more per 1000 (from 48 fewer to 216 more)
Quality of life (MLWHFQ) Better indicated by lower	50 (1 study) 16 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean QoL in the control groups was 1.4	The mean QoL in the intervention groups was 20.76 lower (23.78 to 17.74 lower)
Quality of life (KCCQ HRQoL) Better indicated by higher	50 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean QoL in the control groups was 63.4	The mean QoL in the intervention groups was 12.9 higher (1.96 to 23.84 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Funnel plots constructed by the Cochrane authors showed asymmetry and the potential of a strong publication bias in the studies included within the review
4 Unable to calculate as studies reported MD and were analysed using the generic inverse variance method

Table 94: Clinical evidence summary: Telemonitoring versus usual care

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

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	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with Usual care	Risk difference with telemonitoring (95% CI)
Recent admission					
All-cause mortality	1480 (9 studies) 3 to 24 months	⊕⊕⊖⊖ LOW[1,3] due to risk of bias, publication bias	RR 0.56 (0.42 to 0.74)	147 per 1000	65 fewer per 1000 (from 38 fewer to 85 fewer)
All-cause hospitalisation	1400 (8 studies) 3 to 24 months	⊕⊖⊖⊖ VERY LOW[1,2,3,4] due to risk of bias, imprecision, publication bias, inconsistency	RR 0.81 (0.66 to 0.98)	611 per 1000	116 fewer per 1000 (from 12 fewer to 208 fewer)
Quality of life (SF-12 Physical) Better indicated by higher	280 (1 study) 6 months	⊕⊕⊕⊕ HIGH		The mean QoL in the control groups was 4.3	The mean QoL in the intervention groups was 2.4 higher (0.15 lower to 4.95 higher)
Quality of life (SF-12 Mental) Better indicated by higher	280 (1 study) 6 months	⊕⊕⊕⊕ HIGH		The mean QoL in the control groups was 5.2	The mean QoL in the intervention groups was 0.7 higher (2.1 lower to 3.5 higher)
Quality of life (HDS) Better indicated by lower	280 (1 study) 6 months	⊕⊕⊕⊕ HIGH		The mean QoL in the control groups was 5.5	The mean QoL in the intervention groups was 0.7 lower (2.7 lower to 1.3 higher)
Quality of life (MLWHFQ) Better indicated by lower	353 (2 studies) 3 to 6	⊕⊕⊕⊖ MODERATE[1] due to risk of bias		[6]	The mean QoL in the intervention groups was 3.01 lower

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with telemonitoring (95% CI)
	months				(6.88 lower to 0.87 higher)
Quality of life (SF-36 Mental component summary) Better indicated by higher	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean QoL in the control groups was 48	The mean QoL in the intervention groups was 5 higher (0.52 lower to 10.52 higher)
Quality of life (SF-36 Physical component summary) Better indicated by higher	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean QoL in the control groups was 39	The mean QoL in the intervention groups was 0 higher (5.71 lower to 5.71 higher)
Community					
All-cause mortality	20 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.67 (0.14 to 3.17)	300 per 1000	99 fewer per 1000 (from 258 fewer to 651 more)
Mixed					
All-cause mortality	2360 (8 studies) 3 to 24 months	⨁⨁⊖⊖ LOW[1,3] due to risk of bias, publication bias	RR 0.96 (0.79 to 1.16)	137 per 1000	5 fewer per 1000 (from 29 fewer to 22 more)
All-cause hospitalisation	2052 (6 studies) 3 to 24	⨁⨁⊖⊖ LOW[3,5] publication bias,	RR 1.02 (0.88 to 1.18)	449 per 1000	9 more per 1000 (from 54 fewer to 81 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with telemonitoring (95% CI)
	months	inconsistency			
Quality of life (SF-36 Physical functioning component) Better indicated by higher	710 (1 study) 24 months	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean QoL in the control groups was 51.7	The mean QoL in the intervention groups was 2.1 higher (1.89 to 2.31 higher)
Quality of life (MLWHFQ) Better indicated by lower	285 (2 studies) 6 to 12 months	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision		The mean QoL in the control groups was 32.6	The QoL in the intervention groups was 5.98 lower (11.37 to 0.58 lower)
Quality of life (SF-36 Mental component summary) Better indicated by higher	203 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision		The mean QoL in the control groups was 55	The mean QoL in the intervention groups was 3 lower (5.76 to 0.24 lower)
Quality of life (SF-36 Physical component summary) Better indicated by higher	203 (1 study) 12 months	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean QoL in the control groups was 38	The mean QoL in the intervention groups was 0 higher (2.89 lower to 2.89 higher)

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2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Funnel plots constructed by the Cochrane authors showed asymmetry and the potential of a strong publication bias in the studies included within the review

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with telemonitoring (95% CI)
4 Heterogeneity, I^2=83%, unexplained by subgroup analysis for age, year of publication and intensity of intervention 5 Heterogeneity, I^2=55%, unexplained by subgroup analysis for age 6 Unable to calculate as studies reported MD and were analysed using the generic inverse variance method.					

Table 95: Clinical evidence summary: Telemonitoring + structured telephone support versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with structured telephone support and telemonitoring (95% CI)
Recent admission					
All-cause mortality	1437 (1 study) 180 days	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.7 (0.56 to 0.89)	199 per 1000	60 fewer per 1000 (from 22 fewer to 88 fewer)
All-cause hospitalisation	1437 (1 study) 180 days	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 1.03 (0.93 to 1.15)	492 per 1000	15 more per 1000 (from 34 fewer to 74 more)
Quality of life (MLHWFQ) Better indicated by lower	1437 (1 study) 180 days	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		[3]	The mean QoL in the intervention groups was 4.13 lower (7.6 to 0.66 lower)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with structured telephone support and telemonitoring (95% CI)
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 Unable to calculate as studies reported MD and were analysed using the generic inverse variance method					

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8.4.4 Economic evidence

No relevant economic evidence was identified in the 2003 guideline (CG5). Two studies were included in the 2010 guideline update (CG108): one UK cost-consequence analysis comparing remote monitoring to usual care using data collected during the Home-HF study,[83] and one Italian cost-consequence analysis comparing home-based telecardiology and usual care based on a prospective cohort study.[296]. However, these studies were excluded from this review. The UK study was excluded from this review as the intervention was not considered to be applicable, whereas the Italian study was excluded due to methodological limitations. This is listed in appendix I, with reasons for exclusion given.

Four additional health economic studies were identified in this update. One additional health economic study was identified with the relevant comparison and has been included in this review.[252, 333] This is summarised in the health economic evidence profile below (Table 96) and the health economic evidence table in appendix G. Two economic studies relating to this review question were identified but were excluded due to methodological limitations.[92, 315] One study was identified but selectively excluded as, the committee judged that other available evidence was of greater applicability and methodological quality, and therefore this study was selectively excluded. [360] These are listed in appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in appendix D.

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Table 96: Health economic evidence profile: Structured telephone support vs telemonitoring vs usual care

Study	Applicability	Limitations	Other comments	Costs (a)	Effects (a)	Incremental cost (b)	Incremental effects (b)	Cost effectiveness (b)	Uncertainty
Pandor 2013[252] [Thokala 2013[333]]	Directly applicable [(c)]	Potentially serious limitations [(d)]	• Cost-utility analysis • Comparators: 1. Usual care 2. Structured telephone support – human to machine interface 3. Structured telephone support – human to human interface 4. Home telemonitoring • Clinical data determined from a NMA of RCT data • Lifetime horizon – 6 month intervention, after which receive usual care.	1. £8,478	1. 2.4137	Baseline			Prob. CE: 0% at 20k threshold
				2. £9,060	2. 2.4128	Dominated (1 has lower costs and greater effects)			Prob. CE: 5% at 20k threshold
				3. £9,635	3. 2.5306	Extendedly dominated (the ICER for 3 vs 1 is higher (£9,897) than for 4 vs 1)			Prob. CE: 12% at 20k threshold
				4. £9,650	4. 2.5908	£1,172	0.1771	£6,616 per QALY gained	Prob. CE: 83% at 20k threshold

Abbreviations: CE: cost effective; ICER: Incremental Cost Effectiveness Ratio; NMA: network meta-analysis; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Cost/effect in order of least to most costly intervention.

(b) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(c) Assesses structured telephone support with human to machine contact and human to human contact separately.

(d) May not reflect full body of available evidence: two additional studies were included in the NMA used to determine treatment effect that were not included in the clinical review of this guideline, and five more recent studies included in the guideline review that were not included in the NMA. Utility decrement of heart failure hospitalisation considered to be overestimated.

8.4.5 Evidence statements

Clinical

Overall 41 studies were included in the review. The committee discussed the potential influence of publication bias on the direction and magnitude of the study results. Funnel plots , showed publication bias which was taken into consideration when assessing the quality of the evidence. Outcomes were also downgraded if risk of bias was present or if there was imprecision due to wide confidence intervals.

Structured telephone support

The studies contained within the following strata compared structured telephone support to usual care. There was a high degree of heterogeneity between the interventions with both the intensity and focus varying from study to study.

Recent admission

This strata included studies with populations comprising of people who have recently been admitted to hospital (n=5359). For the outcome all-cause mortality, 14 studies (n=5359) were included. The quality of the evidence was low and showed a clinically important reduction in deaths. The outcome all-cause hospitalisations contained 11 studies (n=4549), was rated low quality and showed no clinical effect. For the outcome QoL the majority of the evidence was rated as moderate quality. A number of different scales were used (MLWHF, EQ-5D and SF-36). The effect estimates were based on single studies and ranged from showing a clinically important improvement in QoL to no clinical difference. A single study (n=287) reported the outcome adherence to intervention. This evidence was very low quality and showed no clinical effect.

Community

This strata included studies with populations comprising of people who were recruited within the community. For the outcome all-cause mortality, 9 studies (n=4495) were included. The quality of the evidence was low and did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.The outcome all-cause hospitalisations contained 6 studies (n=2694), was rated low quality and showed a clinically important reduction in hospitalisations. For the outcome QoL the quality of the evidence ranged from high to very low quality depending on the scale being used. High quality evidence was obtained for 4 studies (n=2103) using the MLWHF score which showed no clinically important effect. For the scores (HDS and HFSS) there was a clinically important improvement in QoL and no clinical effect observed respectively.

Mixed

This strata included studies which did not specify which population were included. They therefore potentially represent a mixture of both people who have had a recent admission to hospital and those who were recruited within the community. For the outcome all-cause mortality, 1 study was included (n=254). The quality of the evidence was very low and did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.The outcome all-cause hospitalisations contained the same study and was rated low quality, and also showed a clinically important increase in hospitalisations (again associated with wide confidence). For the outcome QoL a single study (n=50) rated as very low quality showed a clinically important improvement in QoL using both the MLWHF and KCCQ HRQoL scales.

Telemonitoring

The studies contained within the following strata compared telemonitoring to usual care. There was also a high degree of heterogeneity between the interventions with technology used, interface and level of data acquisition varying from study to study.

Recent admission

For the outcome all-cause mortality, 9 studies (n=1480) were included. The evidence was low quality and showed a clinically important reduction in deaths. The outcome all-cause hospitalisation contained 8 studies (n=1400) was very low quality and showed a clinically important reduction in hospitalisations. This outcome displayed a significant level of heterogeneity (I^2=83%), unexplained by subgroup analysis for age, year of publication and intensity of intervention which was taken into consideration when judging the quality of the evidence. For the outcome QoL the evidence ranged from high to very low quality. High quality evidence (1 study, n=280) was found for the scales SF-12 and HDS, which both showed no clinical effect. Very low quality evidence was found for the SF-36 scale (1 study, n=57), the mental component summary showed a clinically important improvement in QoL, while the physical component showed no clinical effect.

Community

For this strata a single study (n=20) reported all-cause mortality alone. The evidence was very low quality and did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

Mixed

For the outcome all-cause mortality, 8 studies (n=2360) were included. The evidence was low quality and did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.. The outcome all-cause hospitalisation contained 6 studies (n=2052) was also low quality and showed no clinical effect. This outcome was also subject to heterogeneity (I^2=55%), unexplained by subgroup analysis for age which was taken into consideration when judging the quality of the evidence. For the outcome QoL the evidence ranged from low to very low quality. Depending on the scale used the clinical outcome varied. For the physical functioning component of the SF-36 there was evidence of a clinically important improvement in QoL. However, for the mental component summary there was evidence of a clinically important reduction in QoL. For the scale MLWHF there was no evidence of a clinical effect.

Telemonitoring + structured telephone support

Recent admission

A single study (n=1437) looked at the effect of telemonitoring in addition to structured telephone support. For the outcome all-cause mortality (low quality) there was evidence of a clinically important reduction in deaths. For the outcome all-cause hospitalisations (moderate quality) there was evidence of a clinically important increase in hospitalisations. For the outcome QoL (low quality) the MLWHF showed no clinical effect.

Economic

- One cost–utility analysis found that home telemonitoring was cost effective compared to usual care, structured telephone support (human-to-machine interface), and structured telephone support (human-to-human interface) for managing heart failure (ICER: £6,616 per QALY gained compared to usual care). It also found that usual care was dominant (less costly and more effective) compared to structured telephone (human-to-machine interface), and structured telephone support (human-to-human interface) was extendedly dominated

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compared usual care and home telemonitoring. This analysis was assessed as directly applicable with potentially serious limitations.

8.4.6 Recommendations and link to evidence

Recommendations	No recommendation
Research recommendation	**No research recommendation**
Relative values of different outcomes	The committee agreed that the critical outcomes for decision-making were all-cause mortality and all-cause hospitalisation and important outcomes were adherence to the intervention and quality of life.
Quality of the clinical evidence	Forty-six studies were included in the structured telephone support (STS) and telemonitoring (TM) review. The quality of the evidence ranged from very low to high. Studies were predominantly downgraded because of a risk of bias or imprecision due to wide confidence intervals. The committee noted that adherence to the intervention was not commonly reported by the studies. The authors of the Cochrane review constructed funnel plots to assess for reporting bias within the studies included in the review. This was taken into consideration when assessing the quality of the evidence for outcomes in strata which contained more than 5 studies. The funnel plots demonstrated a strong publication bias. Several outcomes also displayed statistical heterogeneity within the results reported by the studies. This was not explained by subgrouping the results by age, year of publication or the intensity of the intervention.
Trade-off between clinical benefits and harms	<u>Overview of evidence</u> The committee noted the likely publication bias in the evidence identified. The committee had requested inclusion of all studies in the review as it had thought it was likely that publication bias would be an issue in the evidence and that a more comprehensive search strategy not limited to larger studies would enable this to be more clearly identified. The committee was reassured that evidence was available from multiple larger studies for some interventions and endpoints but concerned that for other endpoints only data from one study was available with the most obvious deficiency being for quality of life data. The committee had reservations about the trial designs. The evidence as presented compared active interventions with usual care. One potential confounder was the effect of contact alone but without direct advice on changing management. This could result in a 'placebo' effect that would be subsumed within the likely effects of intervention. Secondly, it was possible that trial results would also be dependent on the extent and adequacy of baseline management. An ideally managed population recruited to a trial might not show any benefit from additional intervention; conversely a population with lower quality management might show a large degree of benefit reflecting reversion to local guideline standards. The committee agreed that the lack of information regarding the usual care arm of the included studies reduced their ability to be confident that the effects observed in the intervention arm were not being overestimated by less than

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Recommendations	No recommendation
Research recommendation	**No research recommendation**
	standard care within the usual care group. Furthermore, the committee did not feel that they could be confident that the usual care prescribed in the studies was representative of current UK practice. Structured telephone support The clinical evidence for STS in people with chronic heart failure suggested that there was a clinically important reduction in mortality for those who have had a recent hospital admission and those who were recruited within the community. There was no clinical effect of STS on hospitalisations in people who had recently been admitted. While in people recruited within the community, STS showed a clinically important reduction in hospitalisations. The differences between the interventions used in each study also made it difficult to interpret the effectiveness of STS overall. For example there was a significant degree of variability in the intensity (i.e. daily calls compared to monthly calls), and the focus of the STS (i.e. clinical monitoring of heart failure signs and symptoms with clinical support provided compared to self-management education). The effect of STS on QoL was variable depending on the measurement scale used e.g. the SF-36 or MLWHF. A number of the QoL outcomes were also associated with a large degree of uncertainty due to wide confidence intervals surrounding the effect estimate again making it difficult for the committee to interpret the true clinical effect. The committee agreed that the impact of STS on QoL would be variable depending on the persons willingness to engage with the intervention and the specific focus of the STS. For example STS that mainly focused on highlighting worrying symptoms might not have the same effect as an intervention aimed at providing education and support. Only one study reported patient adherence to STS which showed no clinically important effect. The committee agreed that in practice adherence to STS would be variable depending on the intensity and focus of the intervention and the motivation of the individual. The committee discussed the potential harms associated with STS. The committee agreed that a proportion of elderly patients found it alarming when their phone rang, had difficulty using or did not like using their phone and this caused them a significant degree of anxiety. Monitoring the signs and symptoms of heart failure on a regular basis may also provoke anxiety in some people due to the distress associated with having attention drawn to their diagnosis. The committee acknowledged that using ad hoc telephone appointments and calls to the appropriate clinicians was a relevant form of providing

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Recommendations	No recommendation
Research recommendation	**No research recommendation**
	support and managing a number of symptoms for people with heart failure. However, the committee did not feel as though the evidence supported a recommendation to offer or not offer structured telephone support and decided not to make a recommendation. Telemonitoring The clinical evidence for TM in people with chronic heart failure suggested that there was a clinically important reduction in mortality and hospitalisations for those who have had a recent hospital admission. Only a single study was included within the community strata for TM. The majority of the evidence that was not from a recently admitted population did not specify the exact nature of the population included within the study. These papers were therefore included within a 'mixed' strata and represented a potential combination of both recently admitted and community dwelling people. This evidence showed a clinically important reduction in mortality. However, TM did not have a clinically important effect on hospitalisation. The committee would have expected either group (e.g. recently admitted or recruited within the community) to have a different baseline risk of mortality or hospitalisations in the usual care arm. Therefore, due to the nature of the evidence included within this 'mixed' strata, the committee found it challenging to accurately interpret the clinical outcomes. The general issues raised by the committee regarding the body of evidence for TM were similar to those discussed for STS. The committee did not feel they could be confident that the evidence reflected a true clinical benefit of TM based on the lack of information regarding the standard of care in the usual care arm and the heterogeneity between the TM interventions included in the review. For example there was a significant degree of variability in the intensity (e.g .monitoring during office hours compared with 24 hours per day/seven days per week), and the nature of the technology (e.g. interactive voice response involving the manual input of data using a telephone keypad in response to questions from an interactive voice response system compared to the automatic transmission of physiological data from a measuring device to a central server). The committee also noted that telemonitoring (in a proportion of the included studies) was associated with increased opportunity for people to be contacted by the specialist heart failure team or for people to contact them for advice and support. This made it difficult to ascertain whether the decrease in mortality and hospitalisations were due to the application of telemonitoring or due to the additional access to specialist opinion and care.

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Recommendations	No recommendation
Research recommendation	**No research recommendation**
	The committee discussed the potential harms associated with TM. These included the fact that some of the devices used to remotely monitor parameters such as heart rate were unreliable and therefore clinicians were unwilling to base treatment and management decisions on this data. The committee agreed that a lack of user knowledge relating to the technology being employed could result in improper use or overconfidence in the capabilities of the technology. This could lead to people under reporting potentially important symptoms based on the assumption that the system will relay this measurement data directly to the clinician. The potential also exists for people to become dependent on the technology which may impair their ability to self-manage their condition. Similar to STS, the committee noted that monitoring the signs and symptoms of heart failure on a regular basis provoked anxiety in some people and made them hyperaware of their symptoms. The committee also agreed that a lack of user support regarding the specific TM technologies could compromise motivation and willingness to engage with the technology resulting in compliance and adherence issues which could negatively impact patient safety. The committee also agreed that telemonitoring could result in a reduction in face-to-face care. This has the potential to hinder thorough clinical assessment and good treatment decisions. The use of telemonitoring may also have a negative impact on the ability of both the care giver and receiver to establish a good clinical relationship which the committee noted was fundamental to the quality and safety of the care provided. The committee acknowledged that for a subset of specific and vulnerable people this form of monitoring would be appropriate and may be of benefit when provided for a specific length of time and for a specific purpose. In addition, the committee recognised that there was a potential inequality issue for people living in rural areas with a substantial travel time to specialist care centres. For these people telemonitoring may be appropriate and this decision should be made at an individual level. The committee did not feel as though the evidence supported a recommendation to offer or not offer TM and decided not to make a recommendation.
Trade-off between net clinical effects and costs	Six published economic evaluations were identified for this review. Four of the studies were excluded as they were considered to have very serious limitations, and one study was selectively excluded due to the availability of more applicable evidence. Reasons for exclusion are provided in Appendix J. Therefore, only one study was included in this review. This is a UK cost-utility analysis comparing STS with human to human contact, STS with human-to-machine contact, TM and usual care. The study found TM to be the most cost effective intervention (ICER: £6,616 per QALY gained compared to usual care). This study was assessed as directly applicable with potentially serious limitations. The economic evaluation was based on a network meta-analysis (NMA) comparing the interventions stated above. The committee acknowledged the difference in treatment effects determined in the guideline review and the

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Recommendations	**No recommendation**
Research recommendation	**No research recommendation**
	NMA. However, as mentioned in the 'Trade-off between clinical benefits and harms' section, overall the committee were concerned that the effects of both STS and TM in both systematic reviews were being overestimated due to the likely sub-gold standard care within the usual care arms. In addition, the committee were concerned about the large disutility applied for a heart failure hospitalisation in the model. They considered the disutility was applied for too long and as a result would skew the results towards the interventions being cost effective compared to usual care. Taking both of these limitations into account it was considered that the results from this economic evaluation suggesting that usual care had a 0% probability of being cost effective were unlikely to be true for current UK practice. Overall, the committee considered that there was too much uncertainty to determine whether STS and TM would be cost effective in current clinical practice.
Other considerations	The previous guideline (CG108) included studies where the intervention arm involved visits to the participant's home by a healthcare professional. The committee felt as though this input was likely to confound results from these studies and wasn't truly representative of remote monitoring, therefore they were excluded in the update of this evidence review. The committee discussed the research recommendation made in CG85 and concluded that a significant body of evidence had accumulated since the publication of the guideline. The committee agreed that due to the rapidly advancing nature of technology within the field, and the lack of any plateau in terms of the technology available to clinicians, made it difficult to future proof any further research recommendations. The committee agreed that until a level of consensus was reached between manufacturers regarding what physiological parameters are to be measured and with what interface, it was very difficult to suggest any further research in the area. . The committee therefore decided not to make a further research recommendation. The committee discussed current practice regarding TM and STS and agreed that this was subject to variation across the country. It was acknowledged that although many general practices may have access to the equipment it was not widely implemented due to a lack of infrastructure to support its use. The quantity of data that needs to be analysed as a result of TM has a significant effect on staff workload and associated changes to staff roles and responsibilities. This may impact their ability to perform important daily tasks and responsibilities potentially negatively impacting patient safety. The presence of publication bias within this area was acknowledged by the committee. They were aware of instances where small studies showing no effect had not been published and agreed that this also made it difficult to ascertain the potential clinical benefit of such an intervention. In addition to this the committee agreed that the intensification of more conventional methods of delivering care, such as more home visits or clinic visits could

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Recommendations	**No recommendation**
Research recommendation	**No research recommendation**
	deliver results similar to those of home telemonitoring. The committee discussed groups of people who may not be able to access STS which included those from socioeconomically disadvantaged groups who do not have access to touch tone telephone. In addition, people whose first language is not English may also have difficulty accessing this form of support.

8.5 Recommendations for monitoring heart failure

8.5.1 Clinical review

66. All people with chronic heart failure need monitoring. This monitoring should include:

- **a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status**
- **a review of medication, including need for changes and possible side effects**
- **an assessment of renal function[d]. [2010, amended 2018]**

67. More detailed monitoring will be needed if the person has significant comorbidity or if their condition has deteriorated since the previous review. [2003]

68. The frequency of monitoring should depend on the clinical status and stability of the person. The monitoring interval should be short (days to 2 weeks) if the clinical condition or medication has changed, but is needed at least 6-monthly for stable people with proven heart failure. [2003]

69. People with heart failure who wish to be involved in monitoring of their condition should be provided with sufficient education and support from their healthcare professional to do this, with clear guidelines as to what to do in the event of deterioration. [2003]

8.5.2 Measuring NT-proBNP

70. Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimisation protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m^2. [2018]

[d] This is a minimum. People with comorbidities or co-prescribed medications will need further monitoring. Monitoring serum potassium is particularly important if a person is taking digoxin or an aldosterone antagonist.

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9 Referral and approach to care

9.1 Introduction

The update to the heart failure guideline includes topics where new evidence has emerged since the publication in 2010. A review of new evidence published after 2010 was carried out in order to determine whether any changes to current recommendations where likely to be required. The decision on which topics to include in the update of the guideline was made following consultation of the scope.

This section includes multidisciplinary team working,transition and continuity between different heart failure care settings and information and support needs. The following topics were not within the scope of the update. For more information refer to Appendix R, the 2003 guideline:

- Discharge planning
- Support groups
- Anxiety and depression

See See NICE's guideline on depression in adults with a chronic physical health problem

9.2 Team working in the management of heart failure

9.2.1 Introduction

Heart failure is a complex disorder whose management involves a number of professional groups. Members of different professional groups contribute their experience and expertise to meet the complex needs of the patients. For the care to be optimised, the efforts of these professionals are best delivered through multi-disciplinary team (MDT) working. Multidisciplinary teams are well established to support people with heart failure in the UK.

A variety of models of care exist in heart failure and studies have documented the outcomes achieved by these different approaches. The role of the MDT in the care of patients with heart failure care was recognised in the NICE guidelines published in 2003. Since then has accumulated that has investigated the composition, competencies, needs for support, and the timing of different contributions of members of MDTs over a patient's journey. This question sought to establish the competencies that ought to be present in a MDT to deliver optimal care for patients with heart failure as care of these patients increasingly moves into a community setting.

9.2.2 Review question: What competencies should be present in the multidisciplinary teams involved in the outpatient or community-based care of people with heart failure?

For full details see review protocol in Appendix A.

Table 97: PICO characteristics of review question

Population	People with heart failure in a community or outpatient setting that is applicable to UK practice **Stratification**: Risk status at time of randomisation (high versus lower risk patients) High risk includes: • new diagnosis • recent decompensation (defined as hospital admission due to HF) • severe and/or unresponsive disease (defined as NYHA III/IV) and

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	• requiring medicine titration, device implantation or other surgical intervention
Intervention / Comparators:	Studies comparing MDTs with 'usual care' (regardless of how defined). For a study to be included, there must be a clear description of collaborative working between more than one healthcare profession or discipline. A study involving an intervention delivered by one specified health profession may be included where there is a clear description of multidisciplinary collaboration. The intervention must have included the delivery (on average) of at least two face-to-face meetings. **Stratification**: Length of intervention delivered in the study • ≤ three months (short) • > three months, ≤ six months (mid) • > six months (long) Where study length varied due to recruitment dates, average length was used. Where study length varied due to the needs of the patient, the shortest duration of protocol was used.
Outcomes	CRITICAL - All-cause mortality (Time to event) - Quality of life (Continuous) - Unplanned hospitalisation (Count rate) IMPORTANT - Medicine optimization and adherence - Dying in preferred place of death (for palliative care patients) - Adverse events – hypotension, hyperkalaemia, and renal function - Patient and carer experience
Study design	Systematic Review of RCTs RCTs (including cluster randomised)
Comments	Studies that were concerned with the care and discharge management of patients hospitalised for decompensation of heart failure come under the remit of the acute heart failure guidelines. Therefore, when patients were recruited in hospital, at least one face-to-face meeting was required after the patient had been discharged for the study to be included. There is no minimum duration of intervention, but the last outcome measure must be at least **three months** after the intervention begins. Studies that were concerned with interventions covered elsewhere in the guideline were excluded, as these will have separate guidance. Usual care was considered likely to differ significantly from the UK / NHS standard if the study was carried out in a country outside the OECD or in the United States.

9.2.3 Clinical evidence

A search was conducted for randomised trials comparing management involving multidisciplinary team care (MDT) with "usual care" without an MDT. Twenty two studies were included in the review [6#2495, 22, 34, 50, 56, 87, 91, 105, 106, 111, 137, 157, 193, 214, 220, 244, 257, 277, 300, 341, 352]. Interventions were heterogeneous, and were categorised into 4 main 'strands' based on the definitions in a recent Cochrane report [326]

- Home-based MDT: multidisciplinary teams from secondary care that included an aspect of caring for people in their home.
- MDT clinic: multidisciplinary teams forming an outpatient clinic
- Nurse-led or pharmacist-led clinic: enhanced outpatient service with MDT working
- Case-management: active management of high-risk people with case managers taking responsibility for caseloads working in an integrated care system.[326]

Given the heterogeneous nature of the interventions and populations in the included studies, a number of additional tables have been included in this evidence report to summarise the key features of the included studies. Table 98 shows the included studies listed alphabetically with their population risk and length of intervention stratification, as well as their intervention strand. Table 99 lists the included studies by strata and provides details of the methods for each study. Table 100 expands on the population risk stratification for each study. Table 101 gives more information on the composition of the MDT involved in the intervention arm of each study. Table 102 gives more information on the intervention delivered, and on the "usual care" arm.

Evidence from the studies is summarised in the clinical evidence summaries below (Table 103-123). No meta-analysis was conducted due to the heterogeneity in study and intervention designs; a separate evidence summary is provided for each study. Studies are grouped by the strata identified in Table 99.

Table 98: List of studies included in the review

Study	Population risk strand	Length strand	Intervention strand
Agvall 2013 [6]	Low	Long	Nurse-led clinic
Aukland-HF trial Doughty 2002[103] Walsh 2000[365]	High	Long	MDT clinic
Berger 2010[34] Adlbrecht 2011[4]	High	Long	Case management
Capomolla 2002 [56]	High	Long	MDT clinic
COACH trial Jaarsma 2008[157] (Jaarsma 2008[156], Postmus 2011[272], Jaarsma 2004[155], Jaarsma 2002[158])	High	Long	Basic: Nurse-led clinic Intensive: Home-based MDT
DEAL-HF trial De la Porte 2007 [87]	High	Long	MDT clinic
Del sindaco 2007[91] Pulignano 2010[274] Del sindaco 2012[90])	High	Long	MDT clinic
Driscoll 2014 [105]	High	Mid	Nurse-led clinic
Ducharme 2005 [106]	High	Mid	MDT clinic
Ekman 1998 [111] Ekman 2003 [112]	High	Mid	Nurse-led clinic
Gonzalez-Guerrero 2014 [137]	High	Mid	MDT clinic
HICMan trial Peters-klimm 2010 [257] Peters-klimm 2007 [258]	Low	Long	Case-management

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Study	**Population risk strand**	**Length strand**	**Intervention strand**
J-HOMECARE trial Tsuchihashi-makaya 2013[341] (Tsuchihashi-makaya 2011[342])	High	Mid	Case management
Ledwidge 2003[193] Mcdonald 2001[217] Mcdonald 2002[218])	High	Short	MDT clinic
Martensson 2005 [214]	Low	Long	Case-management
NorthStar trial Schou 2013 [300] Schou 2014 [298]	Low	Long	MDT clinic
Nucifora 2006 [244]	High	Mid	MDT clinic
OPTIMAL trial Mejhert 2004 [220]	High	Long	Nurse-led clinic
PREFER trial Brannstrom 2014 [50] Brannstrom 2013 [49] Sahlen 2016 [290]	High	Mid	Home-based MDT
PRICE trial Atienza 2004[22] Ojeda 2005[246]	High	Long	MDT clinic
Rao 2007 [277]	High	Short	MDT clinic
Varma 1999 [352]	Low	Long	MDT clinic: pharmacist-led

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Table 99: Study details (arranged by strata)

First Author / Trial name	n.	Country	Recruitment	HFREF or both	Starts inpatient	QoL	Outcomes: Mort/ Hosp	Meds	Length (months)	Last measure (months)	Face-to-face meetings
High Risk - Short interventions											
Ledwidge 2003[193]	98	Ireland	Inpatients admitted with primary diagnosis HF	both	Yes		Deaths, Admissions		1.0	3	3 inpt, 2 outpt
Rao 2007 [277]	112	UK	Patients that had been referred by GP for open access echo due to suspected HF, who had confirmed LVSD	both	No		Death, Admissions	Px	flex 3-12	3	2
High Risk - Mid-length interventions											
PREFER trial Brannstrom 2014 [50]	72	Sweden	Outpatients at geriatrics dept or PC with NYHA III-IV plus one of five markers of need for palliation	both	No	EQ-5D (appears to be EQ-5D VAS)	Deaths, Admissions		6	6	mean 20
Driscoll 2014 [105]	28	Australia	Patients with HFREF from clinic for complex heart failure patients on sub-maximal medication doses	HFREF	No	MLWHF	Death, Admissions	Px	flex 3-6	6	3
Ducharme 2005 [106]	230	Canada	Seen in ED or admitted with primary diagnosis HF	Most HFREF	On dc		Deaths, admissions		6	6	6
Ekman 1998 [111]	158 (145)	Sweden	Inpatients aged >65y screened for HF, NYHA III-IV	both	On dc	Change in NYHA	Death, Admission	Px	6	6	median 6 attend
Gonzalez-Guerrero 2014 [137]	117	Spain	Admitted under geriatric department with acute HF	both	Yes		Death or admission		6	12	4
J-HOMECARE trial Tsuchihashi-makaya	168	Japan	From cardiology hospital	both	Yes	SF-8	Deaths, Admissions		6	12	4

First Author / Trial name	n.	Country	Recruitment	HFREF or both	Starts inpatient	QoL	Outcomes: Mort/ Hosp	Meds	Length (months)	Last measure (months)	Face-to-face meetings
2013[341]											
Nucifora 2006 [244]	200	Italy	Inpatients <86y screened for congestive HF	both	Yes	MLWHF	Deaths, Admissions	Px	6	6	1 inpt, 3 outpt
High Risk - Long interventions											
Auckland-HF Doughty 2002[103]	197	New Zealand	Admitted with HF	both	On dc	MLWHFQ	Deaths. Admissions	Px	12	12	7 (inc mandated GP visits)
Berger 2010[34]	186	Austria	Hospitalised and signs/symptoms of HFREF	HFREF	On dc		Death, Admissions		12	12	6
Capomolla 2002 [56]	234	Italy	Patients in inpatient Heart Failure Unit, CHF and LVEF<40%	HFREF	On dc	Time trade-off / Utility	Cardiac death, Admissions	Px	12 (ave.)	12	mean 5.5 attend
COACH trial Jaarsma 2008[157] - basic	683	Netherlands	Patients admitted to hospital (experienced HF centres) with signs and symptoms of HF for which hospitalisation was considered necessary NYHA II-IV, stabilised before entry to study	both	Yes	NR	Deaths, Admissions		18	18	20h
COACH Jaarsma 2008[157] - enhanced	679	Netherlands	Patients admitted to hospital (experienced HF centres) with signs and symptoms of HF for which hospitalisation was considered necessary NYHA II-IV, stabilised before entry to study	both	Yes	NR	Deaths, Admissions		18	18	40h (inc phone)
DEAL-HF trial De la Porte 2007 [87]	240	Netherlands	Inpatients and cardiology outpatients recruited, NYHA	both	No	SF-36* MLWHF*	Death, Days in hospital	Px* Creat-	12	12	9

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First Author / Trial name	n.	Country	Recruitment	HFREF or both	Starts inpatient	QoL	Outcomes: Mort/ Hosp	Meds	Length (months)	Last measure (months)	Face-to-face meetings
			III-IV					inine			
Del sindaco 2007[91]	173	Italy	Hospitalised, aged 70 or more, and discharged home. NYHA III-IV and required IV diuretics	both	On dc		Deaths, Admissions		24	24	8
OPTIMAL trial Mejhert 2004 [220]	208	Sweden	Patients hospitalised with heart failure with NYHA II-IV and LV systolic dysfunction	both	On dc	Nottingham Health Profile	Death, Admissions	Px	flex 6-18m	Ave 37	mean 2.2 attend
PRICE trial Atienza 2004[22]	153	Spain	Cardiology ward with diagnosis of primary HF	both	Yes	MLWHFQ	Deaths, Admissions	Px	16 (ave.)	28	3 outpt
Low risk (stable HF)– Long interventions											
Agvall 2013 [6]	160	Sweden	Patients recruited from PC with CHF and LVEF<50%	HFREF	No	SF-36*	Death, Admissions	Px	12	12	2
HICMan trial Peters-klimm 2010 [257]	197	Germany	Patients recruited from PC with hospital admission with HF in last two years, objective CHF and LVEF<45%	HFREF	No	SF-36, KCCQ	Death, Admissions	Px	12	12	3
Martensson 2005 [214]	153	Sweden	Recruited from PC, NYHA II-IV	both	No	SF-36*	Death	Px	12	12	mean 8.6
Northstar trial Schou 2013 [300]	921	Denmark	Stable CHF on optimal meds, LVEF<45%	HFREF	No	MLWHF	Death, Admissions	Px, Adv. effects	24 (ave)	30	est 24
Varma 1999 [352]	83	UK	Elderly patients recruited from inpatient or outpatient with diagnosis CHF	both	No	SF-36* MLWHF	Death, Admissions	Adher-ence	12	12	4

**reported incompletely, therefore not included in analysis*
NR: measured but not reported
Px: prescription of ACEi+/beta-blocker+/MRA
dc: on discahrge

Table 100: Papers according to population risk: risk strata and background rate of admission (IQR 0.6-1.6, values outside IQR are highlighted)

	Risk strata (proportions are estimates)						
First Author / Trial name	**New dxa**	**ADHFb**	**Severec**	**Req. titrationd**	**Other**	**Overall risk category**	**Admissions/pt/year in control**
High Risk - Short interventions							
Ledwidge 2003[193]	46%	All	NS	None		ADHF	1.0
Rao 2007 [277]	All	None	45%	Most		New	1.0
High Risk - Mid-length interventions							
PREFER trial Brannstrom 2014 [50]	None	NS	All	None	suitable for palliative care	Severe	2.9 (high)
Driscoll 2014 [105]	None	None	20%	All	from clinic for "complex HF"	Titration	0.5 (low)
Ducharme 2005 [106]	NS	All	90%	50%		ADHF	2.0 (high)
Ekman 1998 [111]	NS	90%	mean NYHA 3.2	60%	Older patients (>65y)	ADHF	2.4 (high)
Gonzalez-Guerrero 2014 [137]	40%	All	NS	60%	from geriatric ward (ave 85y)	ADHF	0.8
J-HOMECARE trial Tsuchihashi-makaya 2013[341]	NS	All	5%	50%		ADHF	NS
Nucifora 2006 [244]	None	80%	65%	80%		ADHF	1.6
High Risk - Long interventions							
Auckland-HF Doughty 2002[103]	NS	All	All	10%		ADHF	1.6
Berger 2010[34]	NS	All	All	25%		ADHF	NS
Capomolla 2002 [56]	NS	All	35%	None		ADHF	0.6
COACH trial Jaarsma 2008[157] - basic	NS	All	50%	35%		ADHF	0.7

	Risk strata (proportions are estimates)						
COACH Jaarsma 2008[157] - enhanced	NS	All	50%	35%		ADHF	0.7
DEAL-HF trial De la Porte 2007 [87]	NS	30%	All	30%		Severe	NS
Del sindaco 2007[91]	NS	All	60%	50%	Older patients (>70y)	ADHF	NS
OPTIMAL trial Mejhert 2004 [220]	40%	All	40%	40%		ADHF	1.6
PRICE trial Atienza 2004[22]	NS	All	90%	NS		ADHF	0.5 (low)
Low Risk (stable HF) - Long interventions							
Agvall 2013 [6]	NS	NS	35%	25%		Nil – low risk	0.6
HICMan trial Peters-klimm 2010 [257]	None	25%	30%	25%		Nil – low risk	0.4 (low)
Martensson 2005 [214]	None	NS	50%	40%		Nil – low risk	NS
Northstar trial Schou 2013 [300]	None	None	11%	None		Nil – low risk	0.8
Varma 1999 [352]	NS	25%	mean NYHA class 2.2	NS	Older patients (ave 75)	Nil – low risk	0.7

(a) New dx = identified as new diagnosis of heart failure at recruitment.
(b) ADHF = "Acute decompensated heart failure" risk strata signifying recent decompensation, defined by selection to study due to visit to emergency dept or inpatient admission due to heart failure, with or without congestion.
(c) Severe = proportion NYHA III-IV at baseline (note that if recruited while decompensated, this may be higher than their chronic severity).
(d) Req. titration = Requiring medication titration, device implantation or surgical intervention – if not stated, this was estimated by looking at baseline medication
NS = not stated in study paper

Table 101: Professions / Competencies delivering interventions (studies arranged by strata)

First Author / Trial name	Doctor (secondary care)	Nurse (secondary care)	Pharma-cist	Diet-ician	Occupation-al therapist	Social worker	Physio-therapist	Primary care	Details
High Risk - Short interventions									
Ledwidge 2003[193]		HF nurse		Y					Education from nurse and dietician in hospital, followed by telephone contact weekly for 12 weeks by HF nurse specialist. Appts at clinic after 2 and 6

First Author / Trial name	Doctor (secondary care)	Nurse (secondary care)	Pharma-cist	Diet-ician	Occupation-al therapist	Social worker	Physio-therapist	Primary care	Details
									weeks (unclear composition of clinic)
Rao 2007 [277]	Cardiologist	Cardiac nurse							MDT
High Risk - Mid-length interventions									
PREFER trial Brannstrom 2014 [50]	Cardiologist + Palliative care physician	HF nurse + Palliative care nurse			Y		Y		HF team plus palliative nurse + palliative physician
Driscoll 2014 [105]	Cardiologist	Cardiac nurse							Nurse-led clinic in consultation with cardiologist, could make onward referrals to other professionals
Ducharme 2005 [106]	Cardiologist	HF nurse	Y	Y		Y			Specialist HF clinic for 6 months, contact within 72h discharge and monthly visits for 6/12
Ekman 1998 [111]	Cardiologist	HF nurse				Y		Physician	Nurse-run clinic in cooperation with doctors, communication with PC and social care
Gonzalez-Guerrero 2014 [137]	Geriatrician	Cardiac nurse							Assessment prior to d/c, at 10d, 1m and 6m post d/c by the 'team', plus t/c contact 48h post-d/c (nurse) and 3/12 (geriatrician)
J-HOMECARE trial Tsuchihashi-makaya 2013[341]	Cardiologist	Cardiac nurse	Y	Y		Y			Nurse CM in liaison with MDT for 6 months
Nucifora 2006 [244]	Cardiologist	Cardiac nurse							Pre-discharge education by experienced cardiovascular nurse, thereafter, contact with nurse to reinforce message. Face-to-face meetings with a doctor and nurse three times in next six months
High Risk - Long interventions									

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First Author / Trial name	Doctor (secondary care)	Nurse (secondary care)	Pharma-cist	Diet-ician	Occupation-al therapist	Social worker	Physio-therapist	Primary care	Details
Auckland-HF Doughty 2002[103]	Cardiologist	Cardiac nurse						Physician	Explicit partnership with primary and secondary care, involving individualised and group education, scheduled visits to clinic (unclear composition) and GP and drug titration
Berger 2010[34]	Cardiologist	HF nurse							CHF specialist nurse carried out home visits according to a schedule, or more if deterioration. Also scheduled medical reviews, with extra at request of nurse
Capomolla 2002 [56]	Cardiologist	HF nurse		Y		Y	Y	Y	MDT
COACH trial Jaarsma 2008[157] - basic	Cardiologist	HF nurse							Basic: additional visits with HF nurse at outpatient clinic, education protocol given.
COACH Jaarsma 2008[157] - enhanced	Cardiologist	HF nurse		Y		Y	Y		Intensive: weekly telephone calls after d/c, home visit by HF nurse, home visit from MDT and monthly contact.
DEAL-HF trial De la Porte 2007 [87]	Cardiologist	HF nurse		Y					MDT
Del sindaco 2007[91]	Cardiologist	HF nurse							Cardiologist case-managed, with support from nurse who made regular telephone calls
OPTIMAL trial Mejhert 2004 [220]	Cardiologist	Cardiac nurse							Nurse-led clinic (under supervision of cardiologist)
PRICE trial Atienza 2004[22]	Cardiologist	HF nurse							Formal education package delivered prior to d/c, detailing self-care, with 3/12 opt appts to optimise medical therapy and reinforce self-care messages. Unclear MDT composition
Low Risk (stable HF) - Long interventions									

First Author / Trial name	Doctor (secondary care)	Nurse (secondary care)	Pharma-cist	Diet-ician	Occupation-al therapist	Social worker	Physio-therapist	Primary care	Details
Agvall 2013 [6]		HF nurse						Physician	Specialist HF nurse working in liaison with GP
HICMan trial Peters-klimm 2010 [257]	For training primary care	For training primary care						Practice nurse and Physician	Case management by practice nurse with 1.5 day specific extra training in case management of patients with heart failure according to a clinical practice guideline. Nurse worked with primary care physician
Martensson 2005 [214]	For training primary care	For training primary care						Practice nurse and Physician	Training provided to all practice nurses and half of physicians – 3x3h sessions on pathophysiology of HF, evaluation and treatment of HF, and self-management. Upskilled practice nurse delivers self-care intervention
Northstar trial Schou 2013 [300]	Cardiologist	HF nurse							MDT, composition unclear
Varma 1999 [352]	Cardiologist		Y						Pharmacist care to encourage self-care and self-monitoring

Table 102: Key activities of MDT, studies arranged by strata

First Author / Trial name	Meds optimisation	Deliver DMPa	Deterioration management	Other	Intensity (ave no. patient-professional encounters)	Usual care
High Risk - Short interventions						
Ledwidge 2003[193]		Y	To contact clinic, where given protocol-driven advice on increasing diuretic	Carer participation in education	Fixed face-to-face 3x in hospital + 2x outpatient, plus telephone	Primary care, with referral to cardiology at discretion
Rao 2007 [277]	Y		Contact number given		min. 2 face-to-face	Primary care

First Author / Trial name	Meds optimisation	Deliver DMPa	Deterioration management	Other	Intensity (ave no. patient-professional encounters)	Usual care
High Risk - Mid-length interventions						
PREFER trial Brannstrom 2014 [50]			IV and SC medication, plus some investigations, could be done at home	regular multi-disciplinary meetings, "person-centred care at home" model	min. 1 face-to-face, actual mean 20	Primary care +/- additional measures as usual
Driscoll 2014 [105]	Y			specifically titration of beta-blocker	min. 3 face-to-face	Primary care +/- other services as usual
Ducharme 2005 [106]	Y		Given telephone number to contact during business hours. Could receive assessment and IV diuretics if needed at the clinic		Actual ave 6 face-to-face	Follow-up according to decision of treating cardiologist (not MDT)
Ekman 1998 [111]	Y	Y	Contact number given, could be reviewed and admitted directly from clinic		min. 3 face-to-face, actual median 6 contacts	Primary care
Gonzalez-Guerrero 2014 [137]	Y	Y	Could contact geriatrician every morning	Global therapeutic regimen evaluated according to the capacities of the patient	fixed 4 face-to-face, 2 telephone	Primary care, with referral to geriatrics at discretion
J-HOMECARE trial Tsuchihashi-makaya 2013[341]			Both intervention and control groups given emergency contact methods		fixed 4 face-to-face (first 2 months), 4 telephone (next 4 months)	MDT discharge education (as per intervention). Routine management by cardiologist
Nucifora 2006 [244]	Y		Contact number to leave message		Fixed 4 face-to-face, plus telephone	Routine discharge information. Primary care
High Risk - Long interventions						
Auckland-HF Doughty 2002[103]	x	Y	Could contact GP or clinic, recommend GP assessment in first instance		min. 7 face-to-face (including GP)	Primary care with other measures as usual

First Author / Trial name	Meds optimisation	Deliver DMPa	Deterioration management	Other	Intensity (ave no. patient-professional encounters)	Usual care
Berger 2010[34]	Y		Unclear		Min. 6 face-to-face, plus telephone	Primary care with other measures as usual
Capomolla 2002 [56]	Y	Y	Open access to day hospital for review and medication for decompensation without admission	Tailored interventions carried out in a day hospital	mean 5.5 (sd. 3.9)	Cardiology clinic
COACH trial Jaarsma 2008[157] - basic		Y	Basic: Encouraged to contact nurse if change		20h	Cardiology opt within two months of d/c, and six-monthly thereafter
COACH Jaarsma 2008[157] - enhanced		Y	Intensive: Encouraged to self-monitor and contact nurse if symptoms increased or gained weight		40h	Cardiology opt within two months of d/c, and six-monthly thereafter
DEAL-HF trial De la Porte 2007 [87]	Y	Y	Contact number given		fixed 9 face-to-face	Cardiology clinic
Del sindaco 2007[91]	Y	Y	Given contact number		Fixed 4 face-to-face, plus telephone	Primary care with other measures as usual
OPTIMAL trial Mejhert 2004 [220]	Y		Could vary own diuretic dose		min. 1 face-to-face, actual range 0-10, median 1, mean 2.2 (sd. 2.3)	Primary care plus personalised written HF plan, as established care in the region
PRICE trial Atienza 2004[22]	Y	Y	Contact HF clinic by phone if any changes			Cardiology and primary care
Low Risk (stable HF) - Long interventions						
Agvall 2013 [6]	Y		Contact number given		min. 2 face-to-face, 2 telephone	Primary care
HICMan trial Peters-klimm 2010 [257]	Y			Intensity of monitoring based on current symptoms. Patient reminders for	min. 3 face-to-face, 3 telephone	Primary care

First Author / Trial name	Meds optimisation	Deliver DMPa	Deterioration management	Other	Intensity (ave no. patient-professional encounters)	Usual care
				prescriptions and appointments.		
Martensson 2005 [214]			Could vary own diuretic dose	Education of primary care physician in both arms	min. 1 face-to-face, actual mean 9.6 contacts	Primary care
Northstar trial Schou 2013 [300]	Y		Contact number given	Extended follow-up	est. 24	Primary care
Varma 1999 [352]			Could vary own diuretic dose	Pharmacist discusses with pt's physician about optimising meds	fixed 4 face-to-face	Primary care

(a) DMP = Disease management programme, usually consists of structured but individualised education about HF and self-help, often including topics such as daily weights and planning for deterioration

9.2.3.1 Clinical evidence summary tables

9.2.3.1.1 High risk, Short, Home-based MDT

No studies were identified in this category.

9.2.3.1.2 High risk, Short, MDT clinic

Table 103: Clinical evidence summary: Ledwidge 2003: Short MDT clinic (MDTc) versus Primary +/- secondary care for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary +/- secondary care	Risk difference with MDTc (95% CI)
Hospitalisations	98 (1 study)	⨁⨁⊖⊖ LOW[a, b] due to risk of bias,	rate ratio 0.15 (0.03 to	255 per 1000	217 fewer per 1000 (from 79 fewer to 248 fewer)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary +/- secondary care	Risk difference with MDTc (95% CI)
	3 months	indirectness	0.69)		
Death	98 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[a, c] due to risk of bias, imprecision	RR 0.92 (0.2 to 4.34)	64 per 1000	5 fewer per 1000 (from 51 fewer to 213 more)

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by one increment for indirectness as not protocol outcome of all-cause hospitalisations
[c] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both

Table 104: Clinical evidence summary: Rao 2007: Short MDT clinic (MDTc) versus Primary care for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTc (95% CI)
Hospitalisations	112 (1 study) 9 months	⊕⊕⊕⊖ MODERATE[a] due to imprecision	Rate Ratio 1.59 (0.81 to 3.14)	245 per 1000	145 more per 1000 (from 47 fewer to 525 more)
Death	112 (1 study) 9 months	⊕⊕⊖⊖ LOW[a] due to imprecision	RR 0.45 (0.04 to 4.81)	38 per 1000	21 fewer per 1000 (from 36 fewer to 144 more)
Prescribed ACE-I	112 (1 study) 3 months	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 1.32 (1.05 to 1.66)	642 per 1000	205 more per 1000 (from 32 more to 423 more)
Prescribed beta-blocker	112 (1 study)	⊕⊕⊕⊕ HIGH	peto OR 11.29	19 per 1000	194 more per 1000 (from 75 more to 467 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTc (95% CI)
	3 months		(4.95 to 25.77)		

(a) Downgraded by one increment as confidence interval cross 1 MID or 2 increments as the confidence interval crosses both MID.

9.2.3.1.3 High risk, Short, Nurse-led or pharmacist-led clinic

No studies were identified in this category.

9.2.3.1.4 High risk, Short, Case-management

No studies were identified in this category.

9.2.3.1.5 High risk, Mid-length, Home-based MDT

Table 105: Clinical evidence summary: PREFER (Brannstrom 2014): Mid-length Home-based MDT (MDThome) vs Primary +/- secondary care for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary +/- secondary care	Risk difference with MDThome (95% CI)
Hospitalisations	72 (1 study)	⨁⨁⨁⨁ HIGH	rate ratio 0.28 (0.16 to	1472 per 1000	1060 fewer per 1000 (from 736 fewer to 1237 fewer)[a]

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary +/- secondary care	Risk difference with MDThome (95% CI)
			0.5)		
Death	72 (1 study) 6 months	⨁⨁⊖⊖ LOW[b] due to imprecision	RR 2.00 (0.66 to 6.06)	111 per 1000	111 more per 1000 (from 38 fewer to 562 more)
Quality of life EQ-5D final score (appears to be EQ-5D visual analogue scale), higher=better. Scale from: 0 to 100.	72 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[b, c] due to risk of bias, imprecision		The mean quality of life in the control groups was 52.3	The mean quality of life in the intervention groups was 8.1 higher (better) (2.03 lower to 18.23 higher)

(a) Manually calculated as Risk Difference above 1000.
(b) Downgraded by one increment as confidence interval crossed 1 MID or 2 increments as confidence interval crossed both MIDs.
(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

9.2.3.1.6 High risk, Mid-length, MDT clinic

Table 106: Clinical evidence summary: Ducharme 2005: Mid-length MDT clinic (MDTc) vs Primary / secondary care for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary/secondary	Risk difference with MDTc (95% CI)
Hospitalisations	230 (1 study) 6 months	⨁⨁⊖⊖ LOW [a, b] due to risk of bias, imprecision	rate ratio 0.68 (0.51 to 0.91)	983 per 1000	314 fewer admissions per 1000 (from 88 fewer to 481 fewer)
Death	230 (1 study)	⨁⨁⊖⊖ LOW[a, b]	RR 0.63 (0.32 to	165 per 1000	61 fewer per 1000 (from 112 fewer to 40 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary/secondary	Risk difference with MDTc (95% CI)
	6 months	due to risk of bias, imprecision	1.24)		

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 107: Clinical evidence summary: Gonzalez-Guerrero 2014: Mid-length MDT clinic (MDTc) vs Primary care +/- Geriatric clinic for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Gonzalez-guerrero 2014 (95% CI)
Hospitalisations	117 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	rate ratio 0.92 (0.6 to 1.4)	776 per 1000	62 fewer per 1000 (from 310 fewer to 310 more)
Death	117 (1 study) 12 months	⨁⨁⊖⊖ LOW[a,b] due to risk of bias, imprecision	RR 0.58 (0.32 to 1.04)	379 per 1000	159 fewer per 1000 (from 258 fewer to 15 more)
Quality of life - not reported	-	-	Not estimable	-	-

(a) Downgraded by one increment as rated to be at high risk of bias
(b) Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MIDs

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Table 108: Clinical evidence summary: Nucifora 2006: Mid-length MDT clinic (MDTc) vs Primary care for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTc (95% CI)
Hospitalisations	200 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	rate ratio 1.00 (0.73 to 1.36)	802 per 1000	0 fewer per 1000 (from 217 fewer to 289 more)
Deaths	200 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 1.79 (0.78 to 4.07)	79 per 1000	63 more per 1000 (from 17 fewer to 243 more)
Quality of life Minnesota LWHFQ (change score) lower=better. Scale from: 0 to 105.	150 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision		The mean change MLWFQ in the control groups was 10 (worse)	The mean in the intervention groups was 4 higher (worse) (1.82 lower to 9.82 higher)
Prescribed ACE-I	178 (1 study) 12 months	⨁⨁⨁⊖ MODERATE[a] due to risk of bias	RR 0.99 (0.86 to 1.15)	806 per 1000	8 fewer per 1000 (from 113 fewer to 121 more)
Prescribed beta-blocker	178 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 0.73 (0.37 to 1.42)	194 per 1000	52 fewer per 1000 (from 122 fewer to 81 more)
Taking prescribed medication	178 (1 study) 12 months	⨁⨁⊖⊖ LOW[a] due to risk of bias	RR 1.04 (0.92 to 1.17)	839 per 1000	34 more per 1000 (from 67 fewer to 143 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment as confidence interval crosses 1 MID or 2 increments as confidence interval crosses both MIDs.

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9.2.3.1.7 *High risk, Mid-length, Nurse-led or pharmacist-led clinic*

Table 109: Clinical evidence summary: Driscoll 2014: Nurse-led clinic (MDTn) vs Primary / secondary care for high risk HFREF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary/secondary	Risk difference with MDTn (95% CI)
Hospitalisations and Emergency department attendances	25 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	rate ratio 0.67 (0.07 to 6.41)	231 events per 1000 person years	76 fewer events admissions per 1000 person years (from 215 fewer to 1000 more)
Death	25 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	peto OR 8.03 (0.16 to 406)	[c]	80 more per 1000 (from 120 fewer to 280 more)[d]
Quality of life MLWHFQ (change score) lower=better. Scale from: 0 to 105.	25 (1 study) 12 months	⨁⨁⊖⊖ LOW[a] due to risk of bias		The mean change MLWHFQ in the control groups was 9.5 (deterioration)	The mean quality of life in the intervention groups was 2.80 lower (better) (13.68 lower to 8.08 higher)
Prescribed "optimal" dose beta-blocker	24 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 2.13 (1.01 to 4.47)	385 per 1000	435 more per 1000 (from 4 more to 1000 more)

(a) [a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded 1 increment as confidence interval crossed 1 MID or 2 increments as confidence interval crossed both MIDs.
(c) Cannot be estimated as no events in control arm.
(d) Absolute difference calculated by RevMan.

Table 110: Clinical evidence summary: Ekman 1998: Mid-length Nurse-led clinic (MDTn) vs Primary care (1 control) 3-6 months for high risk HF

Outcomes	No of Participants	Quality of the evidence	Relative effect	Anticipated absolute effects

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	(studies) Follow up	(GRADE)	(95% CI)	Risk with primary care	Risk difference with MDTn (95% CI)
Hospitalisations	158 (1 study) 6 months	⨁⨁⊖⊖ LOW[a, b] due to risk of bias, imprecision	rate ratio 0.92 (0.68 to 1.22)	1203 per 1000	96 fewer per 1000 (from 385 fewer to 265 more)
Death	158 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias, imprecision	RR 1.24 (0.71 to 2.16)	215 per 1000	52 more per 1000 (from 62 fewer to 250 more)
NYHA class change (a proxy for QoL) mean level (I-IV), lower=better. Scale from: 1 to 4.	158 (1 study) 6 months	⨁⨁⊖⊖ LOW[a, c] due to risk of bias, indirectness		The mean NYHA class change in the control groups was -0.3 (better)	The mean NYHA class change (a proxy for qol) in the intervention groups was 0.10 higher (less improvement) (0.15 lower to 0.35 higher)
Prescribed ACE-I	145 (1 study) 6 months	⨁⨁⊖⊖ LOW[a, b] due to risk of bias, imprecision	RR 1.12 (0.89 to 1.41)	627 per 1000	75 more per 1000 (from 69 fewer to 257 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by one increment as confidence interval cross one MID or downgraded by two increments as confidence interval crosses both MID.
(c) Downgraded due to indirectness as a proxy measure of quality of life was reported by the study.

9.2.3.1.8 High risk, Mid-length, Case-management

Table 111: Clinical Evidence Summary: J-HOMECARE (Tsuchihashi-Makaya 2013): Mid-length Case management (MDTcm) vs Cardiology clinic for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTcm (95% CI)
Hospitalisations	98 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b,c]	HR 0.52 (0.28 to	estimated risk: 213 per 1000[d]	96 fewer per 1000 (from 4 fewer to 148 fewer)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTcm (95% CI)
	12 months	due to risk of bias, indirectness, imprecision	0.98)		
Death	161 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[a, c] due to risk of bias, imprecision	RR 1.04 (0.41 to 2.63)	98 per 1000	4 more per 1000 (from 58 fewer to 159 more)
Quality of life (physical) SF-8 physical component, final score. higher=better. Scale from: 0 to 100.	138 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision		The mean SF-8 physical in the control groups was 42	The mean in the intervention groups was 2.00 higher (better) (1.18 lower to 5.18 higher)
Quality of life (mental) SF-8 mental health component, final score. higher=better. Scale from: 0 to 100.	138 (1 study) 12 months	⊕⊕⊖⊖ LOW[a] due to risk of bias		The mean SF-8 mental in the control groups was 47	The mean quality of life (mental) in the intervention groups was 2.00 higher (better) (0.67 lower to 4.67 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded for indirectness as not protocol outcome of count rates for hospitalisations.
(c) Downgraded one increment as confidence interval crosses one MID or two increments as confidence interval crosses two MID.
(d) Used estimated control rate.

9.2.3.1.9 *High risk, Long, Home-based MDT*

Table 112: Clinical Evidence Summary: COACH intensive (Jaarsma 2008): Long Home based MDT (MDThome) vs Cardiology clinic in high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDThome (95% CI)
Hospitalisations	683 (1 study)	⊕⊕⊖⊖ LOW[a, b]	rate ratio 1.10 (0.96 to 1.27)	1109 per 1000	111 more admissions per 1000 (from 44 fewer to 299 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDThome (95% CI)
	18 months	due to risk of bias, imprecision			
Death	683 (1 study) 18 months	⨁⨁⨀⨀ LOW[a, b] due to risk of bias, imprecision	HR 0.81 (0.6 to 1.08)	292 per 1000	48 fewer per 1000 (from 105 fewer to 19 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both.

9.2.3.2 High risk, Long, MDT clinic

Table 113: Clinical Evidence Summary: Auckland-HF (Doughty 2002): Long MDT clinic (MDTc) vs Primary +/- Secondary care in high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary +/- secondary care	Risk difference with MDTc (95% CI)
Hospitalisations	197 (1 study) 12 months	⨁⨁⨀⨀ LOW[a, b] due to risk of bias, imprecision	rate ratio 0.76 (0.6 to 0.96)	1588 per 1000	381 fewer admissions per 1000 (from 64 fewer to 635 fewer)
Death	197 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW[a, b] due to risk of bias, imprecision	RR 0.77 (0.45 to 1.31)	247 per 1000	57 fewer per 1000 (from 136 fewer to 77 fewer)
Quality of life Minnesota LWHFQ (change score) lower=better. Scale from: 0 to 105.	197 (1 study) 12 months	⨁⨁⨀⨀ LOW[a] due to risk of bias		The mean change in MLWHFQ in the control groups was -12.5 (improvement)	The mean change in the intervention groups was 7 lower (greater improvement) (7.82 to 6.18 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary +/- secondary care	Risk difference with MDTc (95% CI)
Prescribed ACE-I	154 (1 study) 12 months	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	RR 1.14 (0.96 to 1.35)	726 per 1000	102 more per 1000 (from 29 fewer to 254 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by one increment as confidence interval cross 1 MID or 2 increments as confidence interval crosses both MID.

Table 114: Clinical Evidence Summary: Capomolla 2002: Long MDT clinic (MDTc) vs Cardiology clinic in high risk HFREF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTc (95% CI)
Hospitalisations	234 (1 study) 12 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	rate ratio 0.18 (0.1 to 0.33)	639 per 1000	524 fewer admissions per 1000 (from 428 fewer to 575 fewer)
Cardiac Death	234 (1 study) 12 months	⨁⨁⨀⨀ LOW[a, b] due to risk of bias, indirectness	RR 0.16 (0.05 to 0.51)	172 per 1000	145 fewer per 1000 (from 84 fewer to 164 fewer)
Utility (proxy for Quality of life) higher=better. Scale from: 0 to 1.	210 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW[a, c, d] due to risk of bias, indirectness, imprecision		The mean utility in the control groups was 0.63	The mean utility in the intervention groups was 0.09 higher (better) (0.04 to 0.14 higher)
ACE-I dose prescribed (long acting only)	210 (1 study) 12 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias		The mean ace-i dose prescribed (long acting only) in the control groups was	The mean ace-i dose prescribed (long acting only) in the intervention groups was 8 mg higher (5.5 to 10.5 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTc (95% CI)
				12 mg	
Beta-blocker dose prescribed	210 (1 study) 12 months	⨁⨁⨁⊖ MODERATE[a] due to risk of bias		The mean beta-blocker dose prescribed in the control groups was 13 mg	The mean beta-blocker dose prescribed in the intervention groups was 21 mg higher (13.9 to 28.1 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded for indirectness as the outcome was not the protocol all-cause mortality.
(c) Downgraded as not a protocol outcome for quality of life.

Table 115: Clinical Evidence Summary: DEAL-HF (De la Porte 2007): Long MDT clinic (MDTc) vs Cardiology clinic for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTc (95% CI)
Hospitalisation Days in hospital	240 (1 study) 12 months	⨁⨁⨁⊖ MODERATE[a] due to indirectness	Rate Ratio 0.56 (0.49 to 0.64)	5279 per 1000	2310 fewer days in hospital per 1000 (from 1890 fewer to 2680 fewer)[b]
Death	240 (1 study) 12 months	⨁⨁⨁⊖ MODERATE[c] due to imprecision	RR 0.54 (0.28 to 1.03)	189 per 1000	87 fewer per 1000 (from 136 fewer to 6 more)

(a) Downgraded due to indirectness as not protocol outcome for hospitalisation of count rates.
(b) Manually calculated as GRADE cannot process RD above 1000.
(c) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 116: Clinical Evidence Summary: Del Sindaco 2007:Long MDT clinic (MDTc) vs Primary / secondary care for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary/secondary care	Risk difference with MDTc (95% CI)
Hospitalisations - dichotomous	173 (1 study) 24 months	⨁⊖⊖⊖ VERY LOW[a, b, c] due to risk of bias, indirectness, imprecision	RR 0.75 (0.6 to 0.93)	747 per 1000	187 fewer people admitted per 1000 (from 52 fewer to 299 fewer)
Death	172 (1 study) 24 months	⨁⊖⊖⊖ VERY LOW[a, c] due to risk of bias, imprecision	RR 0.85 (0.56 to 1.29)	314 per 1000	47 fewer per 1000 (from 138 fewer to 91 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded for indirectness as not the protocol outcomes for hospitalisations, count rate.
(c) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 117: Clinical Evidence Summary: PRICE (Atienza 2004): Long MDT clinic (MDTc) vs Cardiology for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTc (95% CI)
Hospitalisations	338 (1 study) 16 months	⨁⨁⨁⊖ MODERATE[a] due to imprecision	rate ratio 0.67 (0.54 to 0.84)	1144 per 1000	377 fewer per 1000 (from 183 fewer to 526 fewer)
Death	338 (1 study) 16 months	⨁⨁⨁⨁ HIGH	RR 1.80 (1.21 to 2.68)	172 per 1000	138 more per 1000 (from 36 more to 290 more)
Quality of life	220	⨁⨁⊖⊖		The mean quality of life in	The mean quality of life in the

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTc (95% CI)
Minnesota LWHFQ, final score. lower=better. Scale from: 0 to 105.	(1 study) 16 months	LOW[a, b] due to risk of bias, imprecision		the control groups was 35.5	intervention groups was 6.60 lower (better) (8.47 to 4.73 lower)
Prescribed ACE-I	153 (1 study) 16 months	⨁⨁⨀⨀ LOW[a, b] due to risk of bias, imprecision	RR 0.97 (0.78 to 1.21)	688 per 1000	21 fewer per 1000 (from 151 fewer to 145 more)
Prescribed beta-blocker	153 (1 study) 16 months	⨁⨁⨀⨀ LOW[a, b] due to risk of bias, imprecision	RR 1.62 (1.17 to 2.25)	390 per 1000	242 more per 1000 (from 66 more to 487 more)

(a) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

9.2.3.2.1 High risk. Long, Nurse-led or pharmacist-led clinic

Table 118: Clinical Evidence Summary: COACH basic (Jaarsma 2008): Long Nurse-led clinic (MDTn) vs Cardiology clinic in high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTn (95% CI)
Hospitalisations	679 (1 study) 18 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	rate ratio 1.01 (0.88 to 1.17)	1109 per 1000	11 more per admissions 1000 (from 133 fewer to 189 more)
Death	679 (1 study) 18 months	⨁⨁⨀⨀ LOW[a, b] due to risk of bias,	HR 0.88 (0.66 to 1.18)	292 per 1000	30 fewer per 1000 (from 88 fewer to 43 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cardiology clinic	Risk difference with MDTn (95% CI)
		imprecision			

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 119: Clinical Evidence Summary: OPTIMAL (Mejhert 2004): Long Nurse-led clinic (MDTn) vs Primary care for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTn (95% CI)
Hospitalisations	208 (1 study) 37 months	⨁⨁⊖⊖ LOW[a, b] due to risk of bias, imprecision	rate ratio 0.90 (0.79 to 1.02)	4895 per 1000	490 fewer per 1000 (from 1000 fewer to 98 more)
Death	208 (1 study) 37 months	⨁⨁⊖⊖ LOW[a, b] due to risk of bias, imprecision	RR 1.20 (0.83 to 1.73)	324 per 1000	65 more per 1000 (from 55 fewer to 236 more)
Quality of life Nottingham Health Profile Part 1, lower=better. Scale from: 0 to 600.	208 (1 study) 12 months	⨁⨁⊖⊖ LOW[a] due to risk of bias		The mean quality of life in the control groups was 127	The mean quality of life in the intervention groups was 9 higher (21 lower to 39 higher)
Prescribed ACE-I	208 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 0.9 (0.75 to 1.08)	733 per 1000	73 fewer per 1000 (from 183 fewer to 59 more)
Prescribed beta-blockers	208	⨁⨁⊖⊖	RR 0.89	619 per 1000	68 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTn (95% CI)
	(1 study) 12 months	LOW[a, b] due to risk of bias, imprecision	(0.71 to 1.12)		(from 180 fewer to 74 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both.

9.2.3.2.2 High risk, Long, Case Management

Table 120: Clinical Evidence Summary: Berger 2010: Long Case-management (MDTcm) vs Primary +/- secondary care (1/2 control), for >6 months high risk HFREF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary +/- secondary care	Risk difference MDTcm (95% CI)
Hospitalisations - dichotomous	132 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b, c] due to risk of bias, indirectness, imprecision	RR 0.91 (0.76 to 1.08)	830 per 1000	75 fewer people admitted per 1000 (from 199 fewer to 66 more)
Death	186 (1 study) 18 months	⨁⨁⊖⊖ LOW[a, c] due to risk of bias, imprecision	RR 0.56 (0.36 to 0.89)	389 per 1000	171 fewer per 1000 (from 43 fewer to 249 fewer)
Prescribed ACE-I or ARB	180 (1 study) 12 months	⨁⨁⨁⊖ MODERATE[a] due to risk of bias	RR 1.01 (0.96 to 1.06)	967 per 1000	10 more per 1000 (from 39 fewer to 58 more)
Prescribed beta-blocker	186 (1 study) 12 months	⨁⨁⊖⊖ LOW[a, c] due to risk of bias, imprecision	RR 1.13 (1.03 to 1.25)	844 per 1000	110 more per 1000 (from 25 more to 211 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded for indirectness as "count rate" was the protocol outcome for hospitalisation, and this is proportion who were hospitalised at least once.

(c) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

9.2.3.2.3 Low risk, Short

No studies were identified in these categories.

9.2.3.2.4 Low risk, Mid-length

No studies were identified in these categories.

9.2.3.2.5 Low risk, Long, Home-based MDT

No studies were identified in this category.

9.2.3.2.6 Low risk, Long, MDT clinic

Table 121: Clinical Evidence Summary: Northstar (Schou 2013): Extended follow-up in MDT clinic (MDTc) vs Primary care (1 control) >6 months for low risk HF (stable HFREF)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTc (95% CI)
Hospitalisations	920 (1 study) 2 years	⨁⨁⨁⨁ HIGH	rate ratio 0.94 (0.85 to 1.05)	1509 per 1000	91 fewer admissions per 1000 (from 226 fewer to 75 more)
Death	920 (1 study) 2 years	⨁⨁⨀⨀ LOW[a] due to imprecision	HR 1.05 (0.74 to 1.5)	139 per 1000	6 more per 1000 (from 34 fewer to 62 more)
Quality of life Minnesota LWHFQ (change score) lower=better. Scale	723 (1 study)	⨁⨁⨁⨀ MODERATE[b, c]		The mean change in MLWHFQ in the control groups was	The mean change in the intervention groups was 1 lower/better than change in the

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTc (95% CI)
from: 0 to 105.	2 years	due to risk of bias		0 (IQR -1 to 0)	control group (IQR 1 lower to 1 higher)2
Prescribed ACE-I	920 (1 study) 2 years	⨁⨁⨁⊖ MODERATE[c] due to risk of bias	RR 1.00 (0.95 to 1.04)	885 per 1000	0 fewer per 1000 (from 44 fewer to 35 more)
Prescribed beta-blocker	920 (1 study) 2 years	⨁⨁⨁⊖ MODERATE[c] due to risk of bias	RR 1.00 (0.95 to 1.05)	876 per 1000	0 fewer per 1000 (from 44 fewer to 44 more)
Adverse - serum creatinine increase >50% during follow-up	744 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a, c] due to risk of bias, imprecision	RR 0.94 (0.44 to 2.01)	35 cases renal failure per 1000	2 fewer renal failure per 1000 (from 20 fewer to 35 more)
Adverse - hyperkalaemia (potassium > 5.0mmol/l) at follow-up	723 (1 study) 2 years	⨁⨁⊖⊖ LOW[a, c] due to risk of bias, imprecision	RR 0.56 (0.29 to 1.09)	63 hyperK per 1000	28 fewer hyperK per 1000 (from 45 fewer to 6 more)
Adverse - hypotension	723 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, c] due to risk of bias, imprecision	RR 1.42 (0.24 to 8.42)	6 per 1000	2 more per 1000 (from 4 fewer to 42 more)

(a) Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MID.
(b) Precision cannot be formally assessed, but interquartile range suggests small confidence interval.
(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

9.2.3.2.7 Low risk, Long, Nurse-led or pharmacist-led clinic

Table 122: Clinical Evidence Summary: Agvall 2013: Long Nurse-led clinic (MDTcm) vs Primary care (1 control), >6 months for low-risk HFREF

Outcomes	No of Participants	Quality of the evidence	Relative effect	Anticipated absolute effects

	(studies) Follow up	(GRADE)	(95% CI)	Risk with primary care	Risk difference with MDTcm(95% CI)
Hospitalisations	160 (1 study) 12 months	⊕⊕⊖⊖ LOW[a, b] due to risk of bias, imprecision	rate ratio 0.72 (0.47 to 1.11)	630 per 1000	176 fewer admissions per 1000 (from 334 fewer to 69 more) Point estimate suggests clinical benefit from MDTcm
Death	160 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 0.82 (0.23 to 2.94)	62 per 1000	11 fewer per 1000 (from 48 fewer to 120 more)
Prescribed ACE-I or ARB	160 (1 study) 12 months	⊕⊕⊖⊖ LOW[a, b] due to risk of bias, imprecision	RR 1.19 (1.08 to 1.31)	840 per 1000	160 more per 1000 (from 67 more to 260 more)
Prescribed beta-blocker	160 (1 study) 12 months	⊕⊕⊖⊖ LOW[a, b] due to risk of bias, imprecision	RR 0.94 (0.79 to 1.13)	778 per 1000	47 fewer per 1000 (from 163 fewer to 101 more)
Renal function Serum creatinine at follow-up. Lower=better	158 (1 study) 12 months	⊕⊕⊕⊖ MODERATE[a, b] due to risk of bias		The mean serum creatinine in the control groups was 111.4 umol/l	The mean renal function in the intervention groups was 1.90 umol/l lower (11.88 lower to 8.08 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 123: Clinical Evidence Summary: Varma 1999: Long Pharmacist-led clinic (MDT pharm) vs Primary care (1 control) >6 months for low risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDT pharm (95% CI)
Hospitalisations	83	⊕⊖⊖⊖	rate	659 per 1000	323 fewer per 1000

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDT pharm (95% CI)
	(1 study) 12 months	VERY LOW[a, b] due to risk of bias, imprecision	ratio 0.51 (0.27 to 0.97)		(from 20 fewer to 481 fewer)
Death	83 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 0.98 (0.38 to 2.54)	171 per 1000	3 fewer per 1000 (from 106 fewer to 263 more)
Quality of life Minnesota LWHFQ, lower=better. Scale from: 0 to 105.	49 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision		The mean MLWHFQ final score in the control groups was 19.1	The mean quality of life in the intervention groups was 6.40 lower (better) (0.76 to 12.04 lower)
Taking prescribed medication Self-report	49 (1 study) 12 months	⨁⨁⊖⊖ LOW[a] due to risk of bias	RR 1.05 (0.93 to 1.18)	957 per 1000	48 more per 1000 (from 67 fewer to 172 more)
Taking prescribed medication Automated measure	23 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 2.56 (0.95 to 6.92)	300 per 1000	468 more per 1000 (from 15 fewer to 1000 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MID.

9.2.3.3 Low risk, Long, Case-management

Table 124: Clinical Evidence Summary: HICMann (Peters-Klimm 2010): Non-specialist case management (MDTcm) vs Primary care (1 control) >6 months for HFREF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTcm (95% CI)
Hospitalisations	178 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	rate ratio 1.23 (0.78 to 1.94)	374 per 1000	86 more admissions per 1000 (from 82 fewer to 351 more)
Death	190 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 1.07 (0.32 to 3.56)	51 per 1000	4 more per 1000 (from 35 fewer to 131 more)
Quality of life Kansas City Cardiomyopathy Questionnaire, final score. higher=better. Scale from: 0 to 100.	180 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision		The KCCQ final score in the control groups was 66.3	The mean KCCQ in the intervention groups was 1.70 higher (better) (3.28 lower to 6.68 higher)
Quality of life (physical) SF-36 physical health composite, final score. higher=better. Scale from: 0 to 100.	131 (1 study) 12 months	⨁⨁⊖⊖ LOW[a] due to risk of bias		The mean SF-physical in the control groups was 38.3	The mean SF-physical in the intervention groups was 0.3 lower (worse) (3.25 lower to 2.65 higher)
Quality of life (mental) SF-36 mental health composite, final score. higher=better. Scale from: 0 to 100.	131 (1 study) 12 months	⨁⨁⊖⊖ LOW[a] due to risk of bias		The mean SF-mental in the control groups was 46.6	The mean SF-mental in the intervention groups was 0.1 lower (worse) (3.5 lower to 3.5 higher)
Prescribed double therapy of ACE-I/ARB and B-blocker	180 (1 study) 12 months	⨁⨁⊖⊖ LOW[a] due to risk of bias	RR 1.01 (0.84 to 1.2)	720 ACE+BB per 1000	7 more ACE+BB per 1000 (from 115 fewer to 144 more)

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(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 125: Clinical Evidence Summary: Martensson 2005: Non-specialist case management (MDTcm) vs Primary care (1 control) > 6 months for high risk HF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with primary care	Risk difference with MDTcm (95% CI)
Deaths	149 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 3.20 (0.92 to 11.17)	41 per 1000	90 more per 1000 (from 3 fewer to 418 more)
Prescribed ACE-I at target dose	130 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 0.84 (0.61 to 1.17)	574 ACE-I per 1000	92 fewer ACE-I per 1000 (from 224 fewer to 97 more)
Prescribed beta-blocker at target dose	130 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 0.96 (0.51 to 1.8)	235 B-blocker per 1000	9 fewer B-blocker per 1000 (from 115 fewer to 188 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MID.

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9.2.4 Economic evidence

Published literature

Five health economic studies were identified with the relevant comparison and have been included in this review. [22],[223],[274],[272], [290] To maintain consistency with the clinical review these have also been reported according to the clinical categories specified above. One health economic study was identified for the high risk, mid-length intervention, MDT clinic category; 2 health economic studies were identified for the high risk, long intervention, MDT clinic category; 1 health economic study was identified for the high risk, long intervention, nurse led MDT; and 1 health economic study was identified for the high risk, long intervention, case management MDT. No economic evaluations were identified for the remaining categories. These are summarised in the health economic evidence profiles below (Table 126, Table 127, Table 128 and Table 129) and the health economic evidence tables in Appendix G.

One economic evaluation was selectively excluded due to the availability of more applicable evidence. This is listed in appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix D.

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Table 126: Health economic evidence profile: Home-based MDT clinic (mid-length intervention) vs usual care in high risk patients

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Sahlen 2016[290] [Sweden]	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Cost-utility analysis (health outcome: QALYs) • Within-trial analysis of a RCT study[50] • Population: adults with chronic heart failure with NYHA class III-IV symptoms and a marker of severity • Interventions: 1. Usual care 2. MDT - consisting of a heart failure nurse, palliative care nurse, cardiologist, palliative care physician, physiotherapist and occupational therapist • 6 month follow-up	2-1: Cost saving of £1,517	2-1: 0.03 QALYs	2 dominates 1 (more effective and less costly)	• Uncertainty not reported for cost effectiveness • Conclusions robust to sensitivity analyses.

Abbreviations: QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Single centre study from a county council hospital in Västerbotten County, Sweden and therefore resource use and 2012 costs may not reflect current UK NHS context.

(b) Short time horizon may not capture full costs and effects of the intervention. EQ-5D reported differently to the clinical trial evidence. Only minimal sensitivity analyses were carried out to quantify uncertainty.

Table 127: Health economic evidence profile: MDT clinic (long intervention) vs usual care in high risk patients

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Atienza 2004[22] [Spain]	Partially applicable [(a)]	Potentially serious limitations	• Cost-consequence analysis (health outcomes: 1 year mortality rate, all-cause	2-1: cost saving of £1,719	See clinical review of same paper	n/a	None undertaken.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
		(b)	readmissions, quality of life as measured by the MLWHFQ) • Within-trial analysis of same paper in clinical review • Population: people discharged from cardiology wards with a primary diagnosis of heart failure. • Interventions: 1. Usual care 2. MDT - consisting of a specialist cardiac nurse, primary care physician and cardiologist. • 16 month follow up		(mortality, all-cause hospitalisation, quality of life).		
Pulignano 2010[274] [Italy]	Partially applicable (c)	Potentially serious limitations (d)	• Cost-effectiveness analysis (health outcomes: death or readmission for heart failure and all-cause admission rate) • Within-trial analysis of a RCT study [91] • Population: people over the age of 70 with heart failure with reduced and normal ejection fraction, discharged home after a hospitalisation. • Interventions: 1. Usual care (primary/ secondary care) 2. Multidisciplinary team	2-1: cost saving of £721	See clinical review of Del Sindaco 2007[91]	Int 2 saves £4,042 per death and/or heart failure-related admission avoided. Int 2 saves £2,155 per all-cause admission avoided.	None undertaken.

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Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
			consisting of a cardiologist, experienced in geriatrics (case managers), two to four specialised nurses, and the patient's primary care physician. • 2 year follow up				

Abbreviations: QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Spanish resource use data and unit costs (year not reported, assumed to be 2004) may not reflect current NHS context. QALYs were not used as the health outcome measure

(b) Within-trial analysis and so does not reflect the full body of available evidence available for this intervention. Atienza is 1 of 5 studies included comparing MDT clinic to usual care in high risk patients. No exploration of uncertainty.

(c) Italian national health service resource use and unit costs may not reflect current UK NHS context. QALY data was not reported clearly enough to report and therefore were not used as the health outcome measure. Discounting was not applied.

(d) Within-trial analysis and therefore does not reflect the full body of evidence available for this comparison. Pulignano is 1 of 5 studies included comparing MDT clinic to usual care in high risk patients. No exploration of uncertainty.

Table 128: Health economic evidence profile: Home-based MDT (long intervention) vs nurse led MDT clinic (long intervention) vs usual care in high risk patients

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Postmus [272] [Netherlands]	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Cost-utility analysis (health outcome: QALYs) • Within-trial analysis of a RCT study[157] • Population: Patients >18 years old with evidence of structural cardiac dysfunction • Interventions: 1. Usual care (cardiology clinic)	2-1: cost saving of £58 3-1: £828 3-2: £886	2-1: 0.023 3-1: 0.019 3-2: -0.004	2 dominates 1 and 3 (more effective and less costly) (c)	• Probability intervention 2 cost-effective (€20K threshold): 62% • Conclusions robust to sensitivity analysis.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
			2. Basic MDT 3. Intensive MDT • 18 month follow-up				

Abbreviations: QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) This analysis has been undertaken from a Dutch perspective using 2009 unit costs and therefore may not reflect current NHS context. Does not include important cost aspects such as procedures during hospital admission. EQ-5D was not used.

(b) Probabilistic sensitivity analysis was not presented at £20k/QALY. No discounting was undertaken; however the time-horizon was only 18 months and so is unlikely to have a significant effect. Excluded drug costs, cost of procedures conducted during hospitalisation or short term hospital admission as not rigorously reported in associated trial.

(c) This study also reports results for sub-groups according to NYHA class. In patients with less severe heart failure (NYHA class I-II) intervention 2 dominates interventions 1 and 3. However, in patients with severe heart failure (NYHA class III-IV) intervention 1 is the most cost effective option.

Table 129: Health economic evidence profile: MDT (long intervention - case-management) vs usual care (primary +/- secondary) in high risk patients

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Moertl 2012[223] [Austrian]	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Cost-utility analysis, Markov model • Population: Patients with heart failure discharged after a heart failure hospitalisation • Comparators: 1. Usual care in community 2. Nurse-led MDT • 20 year time horizon modelled	2-1: £2,089	2-1: 0.68 QALYs	ICER: £3,072 per QALY gained (c)	• Uncertainty not reported for cost effectiveness • Conclusions robust to sensitivity analyses (including discount rate to 3% and 0%).

Abbreviations: ICER: Incremental cost effectiveness ratio; MDT: multidisciplinary team; QALY: quality-adjusted life years.

(a) Austrian payer perspective. EQ-5D not used to capture quality of life - utility scores converted from MLWHF questionnaire using previously published algorithm. Costs and effects discounted at 5%.

(b) Cost of GP visits and drug costs were not collected and not included in the analysis of the clinical trial phase.

(c) An additional comparator was also included in the study that involved intensive NT-proBNP guided patient management in addition to multidisciplinary care. This comparator dominates (more effective, less costly) both usual care and the nurse-led MDT alone.

9.2.5 Evidence statements

Clinical

Overall 22 studies were included in the review. No meta-analysis was conducted due to the heterogeneous nature of the interventions and populations in the included studies. The studies were grouped into strata based on the population risk level (high, low) and the length of the intervention (long, mid, short), and were also categorised into one of four intervention types (home-based MDT, MDT clinic, nurse-led or pharmacist-led clinic, or case management).

High risk Short

Home-based MDT

No studies were identified in this category.

MDT clinic

This category included two studies with high risk populations exposed to a short MDT clinic intervention. For the outcome of all-cause hospitalisations, the evidence was inconsistent, with one study (n=98) suggesting a clinically important reduction and the other (n=112) suggesting a clinically important increase (moderate to low quality evidence). The evidence from both studies did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.One of the studies (n=112) showed a clinically important increase in prescribing of ACE inhibitors and beta-blockers (high to moderate quality evidence).

Nurse-led or pharmacist-led clinic

No studies were identified in this category.

Case-management

No studies were identified in this category.

High risk, Mid-length

Home-based MDT

This category included one study (n=72) with a high risk population exposed to a mid-length home-based MDT intervention. The evidence showed a clinically important reduction in hospitalisations (high quality evidence) and a clinically important improvement in quality of life (very low quality evidence). Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

MDT clinic

This category included three studies with high risk populations exposed to mid-length MDT clinic interventions. The evidence on hospitalisations was low to very low quality and inconsistent, with two studies (n=7117 and n=230) suggesting a clinically important reduction, and the third study (n=200) suggesting no clinical difference. Evidence on mortality was also low to very low quality and did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase

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in all-cause mortality.. The third study also provided evidence on quality of life and heart failure medication prescribing and adherence. Very low quality evidence suggested no clinically important difference in quality of life. The evidence on medications was moderate to very low quality and inconsistent, with evidence of a clinically important decrease in prescription of beta-blockers, but no clinical difference in prescribing of ACE inhibitors or taking prescribed medication. Most of the evidence had very wide confidence intervals around the effect estimates.

Nurse-led or pharmacist-led clinic

This category included 2 studies (n=25 and n=158) with high risk populations exposed to a mid-length nurse-led clinic intervention. For the outcome of hospitalisations, low to very low quality evidence suggested a clinically important reduction. Very low quality evidence suggested mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.. The smaller study provided low quality evidence for quality of life which suggested no clinically important difference. Very low quality evidence from the same study also suggested a clinically important increase in prescribing of optimal beta-blocker doses. Evidence on all of the outcomes except for beta-blocker prescribing had very wide confidence intervals around the effect estimates. The larger study provided low quality evidence for NYHA class change and prescribing of ACE-inhibitors which showed no clinical difference in the former and a clinical benefit for the latter.

Case management

This category included one study (n=161) with a high risk population exposed to a mid-length case management intervention. Very low quality evidence showed a clinically important decrease in hospitalisations. Very low quality evidence on mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.. Low to very low quality evidence on quality of life suggested no clinically important difference.

High risk, Long

Home-based MDT

This category included one study (n=683) with a high risk population exposed to a long home-based MDT intervention. Low quality evidence suggested a clinically important increase in hospitalisations . Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality.

MDT clinic

This category included five studies (n=338, n=173, n=240, n=234, n=197) with high risk populations exposed to a long MDT clinic intervention. Moderate to very low quality evidence from the five studies consistently showed a clinically important reduction in hospitalisations or days in hospital. High to very low quality evidence from four of the studies also suggested a clinically important reduction in mortality or cardiac mortality in two studies,no clear effect in two studies and the fifth study suggested a clinically important increase.

Low to very low quality evidence on quality of life reported in three of the studies (n=220, n=210, n=197) suggested a clinically important benefit. Moderate to low quality evidence on prescribing of beta-blockers from two studies (n=153, n=210) suggested a clinically important benefit. Evidence on ACE inhibitor prescribing was inconsistent, with two studies (n=210, n=154, moderate to low quality) suggesting a clinically important benefit and a third (n=153, low quality) suggesting no clinical difference.

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Nurse-led or pharmacist-led clinic

This category included two studies (n=679 and n=208) with high risk populations exposed to a long nurse-led clinic intervention. Evidence for hospitalisations was of moderate to low quality and showed no clinical difference in the former study but a clinical benefit for the latter. The evidence for mortality was of low quality and did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality. One study (n=208) also reported quality of life and medication prescription. The evidence for quality of life was of low quality and showed no clinical difference. Evidence for prescribed ACE-inhibitors and beta-blockers were of low to very low quality and showed a clinically important reduction for both outcomes.

Case management

One study (n=186) with a high risk population undergoing a long case-management programme was included in this category. Low to very low quality evidence suggested a clinically important reduction in hospitalisations, deaths and prescription of beta-blockers. Moderate quality evidence suggested no difference in the prescription of ACE-inhibitors or ARB. Quality of life was not reported.

Low risk, Short

No studies were identified in these categories.

Low risk, Mid-length

No studies were identified in these categories.

Low risk, Long

Home-based MDT

No studies were identified in this category.

MDT clinic

One study (n=920) offering an extended follow-up in an MDT clinic for low risk stable HFREF patients was included in this category. High quality evidence showed a clinically important reduction in admissions. Low quality evidence for mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality. The evidence for the remaining outcomes quality of life, prescribed ACE-inhibitors, prescribed beta-blockers, and three adverse events (serum creatinine increase, hyperkalaemia and hypotension) all showed no clinical difference and were of moderate to very low quality.

Nurse-led clinic

This category included one study (n=160) with a long nurse-led clinic for low risk HFREF patients. Low to very low quality evidence showed a clinically important reduction in the number of admissions. Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality .Low quality evidence also showed a clinically important increase in prescribed ACE-inhibitors or ARB. No difference was found for the outcomes of prescribed beta-blockers and renal function serum creatinine, which were of moderate to low quality. Quality of life was not reported.

Pharmacist-led clinic

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One study (n=83) with a long, pharmacist-led clinic for a low risk HF population was included in this category. The evidence for admissions was of very low quality and showed a clinical reduction for both. Mortality did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality .Very low quality evidence for quality of life also showed a clinical benefit for the intervention. Self-reported taking of prescribed medication showed no clinical difference and was of low quality. An automated measure of taking prescribed medication, however, showed a clinically important increase; the evidence of which was of very low quality.

Case management

Two studies with a long, non-specialist case management approach for a low risk HF population were included in this category (n=149 and n=190). The evidence for mortality was of very low quality and did not demonstrate a clear effect with the confidence interval ranging from a decrease and increase in all-cause mortality. One study (n=149) reported two medication outcomes: prescribed ACE-inhibitors at target dose and prescribed beta-blocker at target dose, both of which were of very low quality. The former outcome showed clinical harm for case management while the latter showed no difference. The second study (n=190) also reported a few other outcomes such as hospitalisations, which was of very low quality showing clinical harm for case management. This study also reported quality of life using the Kansas City Cardiomyopathy Questionnaire (very low quality showing clinical benefit for case management) and the SF-36 mental and physical components (low quality evidence demonstrating no difference for both). This study also reported prescribed double therapy of ACE-I/ARB and B-blocker which was of low quality evidence showing no difference between the interventions.

Economic

- One cost-utility analysis found that mid-length intervention MDT clinic dominates (more effective and less costly) usual care in people with heart failure who are high risk. This was assessed as partially applicable with potentially serious limitations.
- One cost-consequence analysis found that a long intervention MDT clinic was less costly with mixed effects on health outcomes (hospitalisations: RR 0.67, mortality: RR 1.80, quality of life (MLWHFQ) MD 6.60 lower, prescribed ACEi: RR 0.97, prescribed BB: RR 1.62) compared to usual care in people with heart failure that are high risk. This was assessed as partially applicable with potentially serious limitations.
- One cost-effectiveness analysis found that a long intervention MDT clinic was less costly and more effective (saves £4,042 per death and/or heart failure-related admission avoided; saves £2,155 per all-cause admission avoided) compared to usual care in people with heart failure that are high risk. This was assessed as partially applicable with potentially serious limitations.
- One economic evaluation found that a long intervention, basic MDT dominates (more effective and less costly) both usual care and a long intervention, intensive MDT in people with heart failure who are high risk. This was assessed as partially applicable with potentially serious limitations.
- One economic evaluation found that a long intervention, case-management MDT is cost effective (ICER: £3,072 per QALY gained) compared to usual care. This was assessed as partially applicable with potentially serious limitations.

9.2.6 Recommendations and link to evidence

Recommendations	**The core specialist heart failure multidisciplinary team (MDT) should work in collaboration with the primary care team, and should include:** • **a lead physician with a subspecialty interest in heart failure (usually**

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	a consultant cardiologist) who is responsible for making the clinical diagnosis • **a specialist heart failure nurse** • **a healthcare professional with expertise in specialist prescribing for heart failure. [2018]** **The specialist heart failure MDT should directly involve, or refer people to, other services, including rehabilitation services, and tertiary and palliative care, as needed. [2018]** **The specialist heart failure MDT should:** • **diagnose heart failure** • **give information to people newly diagnosed with heart failure (see section 9.4.6)** • **manage newly diagnosed, recently decompensated or advanced heart failure (NYHA [New York Heart Association] class III to IV)** • **optimise treatment** • **start new medicines that need specialist supervision** • **continue to manage heart failure after an interventional procedure such as implantation of a cardioverter defibrillator or cardiac resynchronisation device** • **manage heart failure that is not responding to treatment. [2018]**
Relative values of different outcomes	The critical outcomes were identified as all-cause hospitalisations, mortality and quality of life. Important outcomes included medicine optimisation (including the proportion of people prescribed medication and the proportion taking the medication as prescribed). Also important were outcomes felt by the committee to indicate potential adverse events from over-treatment: renal failure, hyperkalaemia and hypotension. Patient and carer preferences, and dying in preferred place of death for palliative care patients, were also considered important, but these outcomes were not reported by any study.
Quality of the clinical evidence	Twenty two studies (23 comparisons) were identified. The studies were stratified into 2 categories of heart failure risk (high risk and low risk) and 3 lengths of intervention duration (3 months or less, between 3 and 6 months and over 6 months). The population risk (high versus low) was based on the existing recommendations for people who may benefit more from an MDT. The included those with a new diagnosis; requiring medication titration and/or surgical procedure; recent deterioration and severe and/or unresponsive disease. In the current review 14 of the 17 studies in the high risk category selected patients on the basis of recent deterioration, with only 1 selecting new patients, 1 specifically targeting patients requiring medication titration, and 1 selecting on the basis of severe HF with a need for palliation. Population risk in the studies was also described by the average number of all-cause hospital admissions per person per year in the control arms, where this could be calculated. There were only 3 studies that were 3 months or less; and all studies included in the low risk category were over 6 months long. The studies had a heterogeneous mix of populations, interventions and standards of usual care. The studies also ranged in scale from 25 participants followed for 6 months to 920 participants followed for an average of 4 years.

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	Due to the heterogeneity, meta-analysis of the studies was not considered appropriate. The quality was variable, with the main reasons for downgrading due to risk of bias being a lack of detail about randomisation/allocation concealment and imprecision due to small study size. Many of the studies had small numbers of patients or events, with large confidence intervals around the effect estimates ranging from a clinically important harm to a clinically important benefit. Quality of life was downgraded for performance bias in all studies, as it was not possible to blind participants. There was also concern that some larger studies stated intent to measure quality of life in the study protocol, but with limited or no results presented, suggesting selective reporting. The committee considered that overall, the evidence was of low quality, often imprecise, and noted that even the direction of effect was inconsistent between outcomes and between studies. The numbers of hospitalisation and deaths in many of the studies was less than might be expected, and that this may represent selection bias towards healthier patients in these trials. Therefore, there may be problems generalising the evidence to the current heart failure population in the UK. In addition, many of the studies were over twenty years old, and most not in the context of current NHS practice, further restricting their applicability. The committee considered whether further research in this area would improve recommendations in this area. While the current evaluation is hampered by heterogeneous small trials, there were some larger trials such as COACH and NorthStar, which have given some moderate and high quality findings. It was not felt to be worthwhile to prioritise research that aimed to add to or improve on these at the current time.
Trade-off between clinical benefits and harms	There was substantial heterogeneity in the study designs, patient populations, types of intervention and lengths of follow-up, and the evidence was of poor quality for many of the outcomes. Because of this, the committee generally found it challenging to identify which MDT interventions and team compositions were likely to be of the greatest benefit, and for whom. In patients in the high risk categories identified in the last guideline, there was some evidence that the involvement of the MDT may lead to the prescription of more appropriate medication, decrease number of hospitalisations and improve quality of life. It was discussed that in high risk patients, while most interventions did decrease hospitalisations, there were increased deaths in some of these studies. The possibility was raised that the avoidance of hospitalisation could have increased the risk of mortality, but as the evidence on mortality was very imprecise and based on small numbers, it was felt this was likely to be a chance finding. There seemed to be evidence of a general effect of extra hours of contact being associated with improved outcomes in high risk patients, with some

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	caveats. First, there seems to be a ceiling effect: although some shorter interventions delivered improvement, extended follow-up (over years) in a clinic offered little benefit; and delivering 40 hours of contact gave only the same benefit of 20 hours of contact. Secondly, expertise appeared to count, as contact with a primary care nurse delivering a heart-failure intervention without specialist expertise in heart failure had no benefit. The committee agreed that the overall evidence supported the general approach that the MDT be used to stabilise and optimise patients. There was no convincing evidence for substantial changes to the previous recommendation regarding *which* patients should be cared for by the specialist multidisciplinary heart failure team, though the committee agreed by consensus on some clarifications to the previous recommendation text. These included a referral to the MDT should be considered when there was a need to optimise medication or consider specialist options in medication, and implantation of device therapy. The committee discussed specifying the competencies that should be present in the specialist multidisciplinary heart failure team. Clearly, a lead physician with specialist expertise in heart failure was critical, and this will usually be a consultant cardiologist, but there may be areas where other consultants would also be suitable, such as a consultant in elderly care, . The committee noted that the main professionals involved in delivering or co-ordinating interventions in the included studies were cardiovascular or heart failure specialist nurses. Based on this evidence, the committee agreed that a nursing element was needed, and emphasised that a specialist heart failure nursing competency was necessary; as the evidence suggested that it was not possible to get the same clinical improvements from generalist nurses. There was also evidence that the presence of prescribing expertise (whether by a nurse prescriber or pharmacist) can improve the prescription of some medications, and the committee agreed that the MDT should also include specific prescribing expertise. The committee also noted that there was evidence that involvement of the patient's primary care team was shown to be beneficial, and this was in accordance with the negative experiences of some of the committee members when primary care was not involved in the management plans. It was felt that the multidisciplinary specialist HF team members provide input to the management of patients with heart failure defined above *in collaboration with their primary care team.* In this way, the primary care team can help facilitate communication and collaboration between healthcare professionals wherever the patient's care is being delivered across different settings. This may include a GP who has completed a course for special interest registration
Trade-off between net clinical effects and costs	Five relevant economic evaluations were included in this review which compared an MDT to usual care. All of these studies were assessed as partially applicable with potentially serious or very serious limitations. One economic evaluation assessed high risk patients receiving a mid-length (3-6 month) home-based MDT clinic including a cardiologist, heart failure nurse, palliative care physician, palliative care nurse, physiotherapist and

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occupational therapist. This was based on the PREFER trial by Brannstrom et al. 2014 included in the clinical review. This within-trial cost-utility analysis found that this multidisciplinary approach is more effective and less costly, and therefore dominated (more effective, less costly) usual care. This study suggests that an MDT is likely to be cost saving compared to usual care.

The remaining 4 economic evaluations assessed high risk patients receiving long term (greater than 6 months) MDT interventions. All of these economic evaluations were within-trial analyses based on RCTs included in the clinical review.

One economic evaluation compared a basic MDT, an intensive MDT and usual care. Both MDT approaches involved a cardiologist and a specialist heart failure nurse. The basic MDT consisted of 20 hours of contact time, whereas the intensive MDT consisted of 40 hours contact time. This within-trial cost-utility analysis was based on the COACH trial by Jaarsma et al. 2008 included in the clinical review. The analysis found that the basic MDT intervention dominated (more effective, less costly) both the intensive MDT intervention and usual care. This paper also undertook sub-group analyses for patients with severe (NYHA class III/IV) and less severe (NYHA class I/II) heart failure. For patients with less severe HF again the basic MDT dominated both the intensive MDT and usual care. However, for patients with severe heart failure neither the basic or intensive MDT interventions were cost effective at £20,000 per QALY threshold compared to usual care (Intensive MDT ICER: £44,625). The committee discussed that those with severe heart failure are likely to be having much more input from specialists, similar to an MDT, when receiving usual care and therefore were not surprised that a formal MDT was not cost effective in this group of patients.

One economic evaluation compared MDT involving a cardiologist and a specialist heart failure nurse compared to usual care. This was based on a RCT by Berger 2010[34] included in the clinical review. This cost-utility analysis found that the MDT was cost effective compared to usual care (ICER: £3,072 per QALY gained). This study also reported a third intervention consisting of NT-proBNP guided management in addition to multidisciplinary care. When this comparator is included in the analysis it dominates both MDT alone and usual care.

One economic evaluation compared MDT involving a cardiologist experienced in geriatrics, specialist heart failure nurses, and a primary care physician to usual care. This was based on a RCT by Del Sindaco et al. 2007 included in the clinical review. This within-trial cost-effectiveness analysis found that the MDT approach saves £4,042 per death and/or heart failure-related admission avoided, and saves £2,155 per all-cause admission avoided.

One economic evaluation compared MDT involving a cardiologist, specialist cardiac nurse and primary care physician to usual care. This was based on the PRICE RCT by Atienza 2004 included in the clinical review which also reported intervention costs. This study found that the MDT approach was less costly than usual care; however, the overall effects of the MDT were uncertain. The outcomes extracted in the clinical review show moderate quality evidence of a clinical harm of the MDT for mortality, but moderate quality evidence of a clinical benefit from reduced hospitalisations, and low quality evidence of an improvement in quality of life. As mentioned above, the evidence on mortality was very imprecise and based on small numbers.

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	Overall the committee considered that overall the MDT may be cost saving and provide a clinical benefit; however, this is uncertain. No studies were identified that assessed the cost effectiveness of short term MDT intervention in high risk heart failure patients or any length MDT intervention in low risk heart failure patients. The committee agreed that the economic evidence suggests that an MDT reduces costs overall compared to usual care due to reduced hospitalisations, and noted that although each of the studies consisted of different competencies, the committee noted that a cardiologist and specialist nurse were included in all of the economic studies reviewed and therefore agreed that a physician with a subspecialty interest in heart failure, and a specialist heart failure nurse should be included in the core MDT. The committee discussed that the current composition of MDTs in clinical practice varies. The core professionals in most teams currently consist of a cardiologist and a specialist nurse as a minimum and in some cases can include many other professionals from other specialties. The committee therefore considered that the recommendation to have an MDT with a core team consisting of a physician with subspecialty interest in heart failure, a specialist heart failure nurse, competencies to manage prescribing, that could refer to other specialties if necessary, would not have an overall cost impact.
Other considerations	Current NHS practise in this area is variable. It was said that in some areas there is a lack of access to specialist heart failure teams, despite the previous recommendations. The committee was aware of the BHF Heart Failure Audit: this was carried out in a large proportion of NHS hospitals in England and Wales, and shows that following a decompensation 70% of patients receive an appointment for a cardiologist, and 60% of patients have a referral to a specialist cardiac nurse. The committee heard from the cardiologists in the group, who considered the HF nurses to be invaluable in managing their caseloads and clinics. The specialist nurses could often take on the management of the heart failure patients who were in need of more comprehensive support. They reported that the psychological support and care that specialist nurses provide could not be replicated by a cardiologist stand-alone clinic. They also noted that it has been the practice in the UK in many areas for specialist nurses or prescribers to optimise evidence-based medication (that is, ACE-inhibitors and beta-blockers, with MRA where appropriate), but that this is currently determined locally. From another perspective, the committee heard that patients very much valued someone to speak to about their illness, and that this is currently often delivered by HF nurses. They also spoke about how the MDT can encourage self-management, and this was more than just giving information or education, but included giving a patient confidence. They felt this was often not provided to the same level in primary care, and it may not be picked up by the studies.

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	The committee heard from the general practitioners that they recognised that there were high risk HF patients who need more intensive support, particularly patients who had just been discharged from hospital after an acute decompensation. However, they felt that specialist input may not be required for people who are stable. They emphasised the importance of holistic care, which is best delivered by primary care professionals, particularly as most patients with heart failure have several other conditions. They would value a system that would offer timely extra support to patients and GPs when necessary, but kept primary care at the centre. The concept of medicines optimisation in HF was discussed. Often the studies reported adding medication and up-titration, but optimisation is about more: starting, stopping, adjusting, and monitoring, all tailored to the individual patient. It is especially important in this population that the prescriber is adjusting their approach depending on comorbidities, and whether this occurred is not well reported in the studies. The NICE guidelines on multi-morbidity (https://www.nice.org.uk/guidance/ng56) were referred to as helpful in this area. Given the large and increasing population of patients with heart failure, with limited NHS resources, the committee agreed that the recommendations needed to prioritise specialist MDT access for those in greatest need who will gain the greatest benefit. If stable patients are managed in general practice, they will need regular review, informed by their needs. The committee emphasised the importance of a personalised approach, such as that described in the NICE multi-morbidity guideline (https://www.nice.org.uk/guidance/ng56).

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9.3 Transition between heart failure care settings

9.3.1 Introduction

Given the chronic nature of heart failure and its occurrence in populations in whom multiple morbidities are common, management of heart failure involves interaction between primary and secondary care services. People with heart failure are often admitted to secondary care settings with acute deterioration in heart failure (see NICE acute heart failure; CG187) and then transferred to the care of the heart failure multidisciplinary team (MDT) for management in the community. Once their clinical care has been optimised, people with heart failure are discharged back to the care of the routine primary care service but may need to re-access care thorugh the MDT. Evidence has accumulated that that the complicated nature of these transfer processes and the complexity of liaison between different teams can affect the quality of care delivered to people with heart failure. This question reviewed patient and staff experiences of these transfer processes and sought to find evidence on how these could be improved.

9.3.2 Review question: What are the experiences/preferences of staff and patients during transition between different heart failure care settings (including primary, secondary and community care)?

For full details see review protocol in Appendix A.

Table 130: Characteristics of review question

Objective	Explore patient and staff experiences and preferences regarding transition and continuity of care at the interface of different care settings in heart failure. This may enable the identification of barriers (where the problems are) and facilitators (examples of good practice) to continuity of care when transitioning between heart failure care settings.
Population and setting	Patients with heart failure in a primary care, outpatient or community setting. Carers for such patients, both family/informal carers, and health-care professionals (HCP)
Context	Any description of patient or staff member experiences or preferences regarding transition and continuity of care at the interface of different care settings.
Review strategy	Synthesis of qualitative research. Quality of the evidence will be assessed by a GRADE CerQual approach for each review finding.

9.3.3 Qualitative evidence

9.3.3.1 Methods

A search was conducted for qualitative studies exploring experiences or preferences of people with heart failure (CHF) or health care professionals (HCP) regarding transition and continuity of care at the interface of different heart failure care settings. Fifteen qualitative studies were included in the review; [8, 14, 29, 47, 124, 126, 127, 133, 144, 202, 207, 209, 225, 294, 325] these are summarised in Table 131 below. Key findings from these studies are described in the qualitative evidence synthesis (section 9.3.3.4) and summarised in the qualitative evidence summary (section 9.3.3.5). See also the study selection flow chart in Appendix C, study evidence tables in Appendix F, and excluded studies lists in Appendix I.

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9.3.3.2 Qualitative synthesis

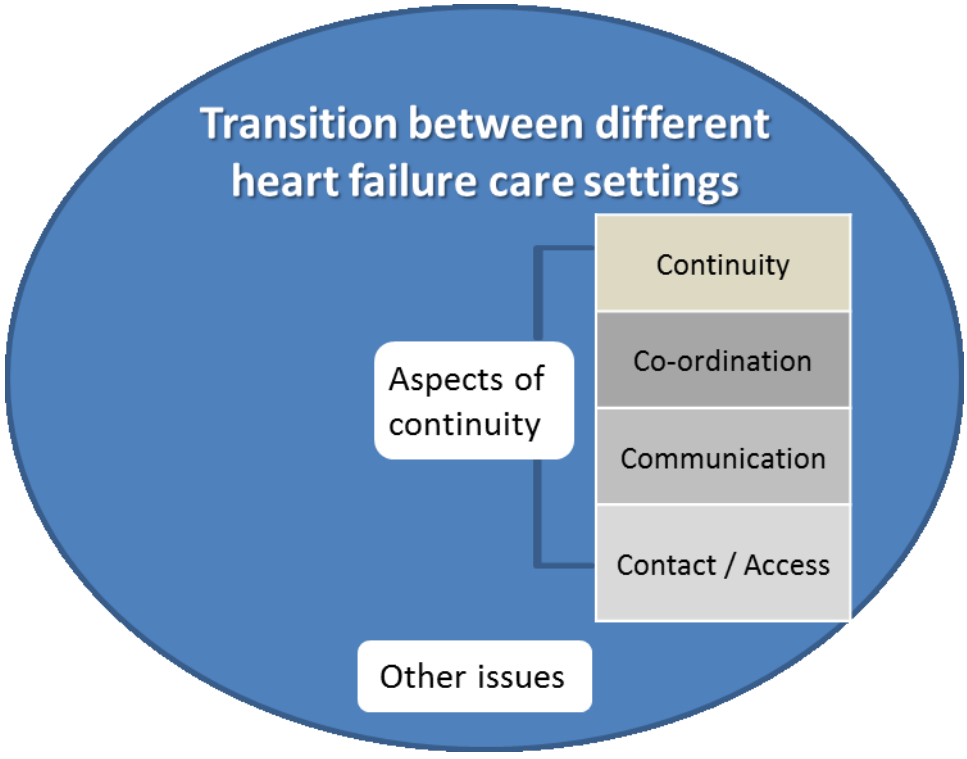
The guideline committee was aware that the issue of continuity is covered in the "Patient experience in adult NHS services" NICE Clinical Guidance February 2012 (CG138)[233], and wished to build on that guidance. Therefore, this review used the framework of the recommendations from that guidance to synthesise the heart failure specific findings from this review, while also collecting heart failure specific themes not covered in that guidance.

The most relevant recommendations from CG138 are as follows:

- Assess each patient's requirement for continuity of care and how that requirement will be met. This may involve the patient seeing the same healthcare professional throughout a single episode of care, or ensuring continuity within a healthcare team. (Continuity)
- For patients who use a number of different services (for example, services in both primary and secondary care, or attending different clinics in a hospital), ensure effective coordination and prioritisation of care to minimise the impact on the patient. (Co-ordination)
- Ensure clear and timely exchange of patient information: (Communication)
    - between healthcare professionals (particularly at the point of any transitions in care)
    - between healthcare and social care professionals (with the patient's consent).
- Give the patient (and their family members and/or carers if appropriate) information about what to do and who to contact in different situations, such as 'out of hours' or in an emergency. (Contact and Access)

This review uses these recommendations to define four findings in which to group the subfindings of our review. We fitted evidence to this framework, and separately collected evidence that did not fit into this framework, as shown in the figure below.

Figure 6: Framework for synthesising review results



9.3.3.3 Summary of included studies

Table 131: Summary of studies included in the review. Abbreviations: Pt = patients with CHF, HCP = health care professionals, NYHA = New York Heart Association Functional Classification

Study	Design	Population	Research aim	Comments
Aldred 2004 [8]	Semi-structured interviews with pt + carers, taped and transcribed verbatim. Data coded and analysed by two researchers. Four themes most relevant to aims presented.	N=10 CHF pt recently discharged from hospital and one person each that they lived with and nominated a carer. Age: mean 72 (SD 5) Severity NYHA II-IV (6/10 NYHA III)	Explore the impact of heart failure on the lives of older pt and their informal carers.	Part of larger study on palliative needs. Setting: UK, Barnsley.
Andersson 2013 [14]	Semi-structured interviews with pt about daily life with CHF, and their experience of information-giving and follow-up. Informed by grounded theory.	N= 4 pt who had been treated in a HF clinic, and were now discharged to primary care. Ages 60, 62, 63, & 84 Severity: Not stated	Investigating whether pt' need for information, education and knowledge are met to the same extent in the HF clinic and primary care.	Setting: Small town in Sweden.
Baudendistal 2015 [29]	Pt interviews with open section and a second more focused part. Content analysis by two researchers independently, then discussed within the research team.	N= 17 pt identified by GPs with CHF with LVEF<35%. Age: mean 72 (SD 12) Severity: Not stated	Explore perspectives of pt with CHF on their treatment across multiple care settings and to what extent these perspectives are represented in current quality indicators.	Part of QUALIPAT heart project, which aims to find patient-centric quality indicators for care. Setting: Academic GP practices, Heidelberg, Germany.
Boyd 2004 [47]	Semi-structured interviews with pt with advanced CHF, carers, health and care professionals. Pt interviewed every three months for up to a year. Interviews were followed by focus groups. Concurrent analysis using narrative analysis framework.	N= 20 pt with advanced CHF and their carers (family/informal 27 interviews, professional 30 interviews). Five died during follow-up and family gave bereavement interview. Age: mean 70 (range 57-92) Severity: NYHA IV	Provide a patient-centric account of the changing and evolving needs of people with advanced heart failure, and how services address these.	Part of larger palliative care project. Setting: UK, region unclear

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Study	Design	Population	Research aim	Comments
Fuat 2005 [124]	Semi-structured interview with CHF-HCP. Analysis follows "pragmatic variant" grounded theory with a degree of constant comparison.	N= 12 HCP involved in specialist HF services (cardiologists, geriatricians, general physicians and specialist GPs).	Explore reasons for the variations in the diagnosis and management of heart failure and identify barriers to the provision of uniformly high standards of care.	Setting: UK, Durham and Tees SHA
Gallacher 2011 [126]	Qualitative secondary analysis. Use archived interviews with pt collected for related research (unpublished). Analysis used "Normalisation Process". Two authors designed a coding framework, while a third adjudicated.	N= 47 pt with a CHF diagnosis based on echo, taking ACE-inhibitors and a diuretic, sampled from primary care to mirror demographics of CHF. Age: mean 73 (range 45-88) Severity: Not stated	Identify and understand the components of treatment burden to inform the development of tools to measure this, HF being a condition likely to have high treatment burden and comorbidity.	Setting: UK, not clear where or when.
Gastelurrutia 2012 [127]	Semi-structured interviews with HCP about health problems commonly comorbid with CHF (hyperuricemia, anti-platelet agents, anaemia and diabetes). Analysed using a total sample, open coding, constant comparative approach.	N= 5 internal medicine specialists and cardiologists from a tertiary hospital HF clinic.	Explore experiences in the pharmacological management of common comorbid health problems in heart failure in order to help clinical pharmacists provide real and practical help.	Setting: HF clinic in Spanish hospital.
Glogowska 2015 [133]	In-depth interviews with HCPs using a topic guide. Also allowed participants to raise their own issues, which could be carried forward to subsequent interviews. Analysed using the constant comparative method and systematic open coding.	N= 24 clinicians (doctors, nurses and rehab workers) sampled from three healthcare settings: primary, community, and hospital in each of three geographical locations (i.e. nine settings total).	Gain an understanding of the issues facing clinicians as they care for people with heart failure in the light of recent developments including the introduction of specialist heart failure nurses.	Setting: UK. Locations were healthcare networks in South West, South Central and the Midlands with different models for providing HF care.
Heckman 2014 [144]	Qualitative descriptive study about HF management in care homes, nested in a mixed-methods protocol. Three semi-structured focus groups of HCP. Data was analysed using thematic	N= 18 HCP: 16 primary care physicians and 2 nurse practitioners who provided care to one of three long-term care facilities chosen to offer	Explore perceptions of HCP regarding HF care in care homes, particularly why these HF pt were less likely to be receiving medication, despite the high burden of	Part of programme aiming to develop care processes to manage HF in care homes. Setting: Northern

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Study	Design	Population	Research aim	Comments
	content analysis by two researchers. Findings were presented back to the participants.	variety.	disease and acute care episodes.	Ontario, Canada
Lord 2015 [202]	Qualitative, service evaluation study. Semi-structured interviews with HCP. Data collated and analysed using Framework Method. Initial findings were fed back to the participants.	N= 21 HCP involved in the delivery of HF from three trusts with different models of providing HF care: 8 nurses, 6 consultants, 2 senior managers, 3 commissioners & 4 GPs.	Understand how HF services are delivered in three different trusts, and especially how 1° and 2° care interact to provide continuity of care for HF pt in a context of increasing demand and financial pressure.	Setting: UK, three settings in Birmingham and the Black Country.
Macdonald 2016 [207]	Secondary analysis of qualitative data of transcripts of interviews with pt. Use form of amplified analysis to fit themes to the Candidacy framework.	N=20 CHF pt (a selection of transcripts from two previous HF studies) Age: range 56-86 Severity: 10 advanced and 10 "stable"	Contrast the help-seeking and access to care in cancer and heart disease in order to extend concepts about illness identity, and its relationship to the concept of "Candidacy"	Compares CHF with cancer. Data was taken from the Colorectal Cancer, End-Stage HF and Stable HF studies. Setting: UK, region not stated
MacKenzie 2010 [209]	Mixed methods service evaluation of a new HF nurse service. Used a questionnaire sent to HCP for gathering quantitative and qualitative data. Free text boxes allowed for responses to four sections. No detail on analysis.	N= 86; 83 GPs (32% of those mailed) and all 3 HF specialist nurses returned questionnaires, although not stated how many added free text.	To assess acceptability and effectiveness of a new community based nurse-led HF service in an area with a dispersed population; assess the knowledge and needs of the GPs and assess the perceptions of national guidance.	Setting: UK, the Highlands Although in context of the NHS, the new HF nurse posts were funded by a charity.
Nordgren 2007 [225]	Qualitative study from lifeworld perspective. Unstructured interviews with "middle-aged" pt with CHF(65 and under), with focus on eliciting lived experience of care. Used phenomenological analysis.	N= 7 pt currently attending HF clinic aged 65 and under, chosen for richness and variety of experience. Age: range 39-65 Severity: moderate to severe with at least one hospitalisation.	Explore how "middle-aged" people with moderate-severe HF experience and understand formal care.	Setting: HF clinic in Sweden
Sanders 2008 [294]	Qualitative study nested in a larger project. Semi-structured interviews with	N= 33 HCP, including GPs (7), HF nurses (10), cardiologists (8) and geriatricians (8),	Explore views of HCP on managing heart failure pt.	Part of bigger project around communication in

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Study	Design	Population	Research aim	Comments
	HCP. Coded according to themes, subsequently explored in relation to the literature, using a variation of the constant comparison method.	from ten sites, chosen for variety.		HF (unpublished). Setting: UK, in multiple sites in North of England
Tait 2015 [187, 325]	Qualitative, using Complex Adaptive System (CAS) theory. Interviews with pt to identify all other people involved in their care, followed by attempts to interview all in these networks. A constant comparison method to improve interview. Used constructivist grounded theory to build an explanatory theory.	N= 50 pt networks, including specialist HF services and at least two of the pts' carers. Carers included family/informal care, caring professionals and healthcare professionals from both specialist and general services. Some HCP appeared in more than one pt network). Sampled to enrich applicability to palliative care. Age (pt): Not stated Severity: NYHA III-IV	Better understand the behaviour of the teams providing heart failure care to those with advanced HF in order to plan how best palliative care services can integrate into these teams.	Setting: Five Canadian cities in three provinces.

Abbreviations: Pt = people with chronic heart failure, HCP = healthcare professional

9.3.3.4 Qualitative evidence synthesis

9.3.3.4.1 Narrative review findings

The review findings were grouped within five overarching findings, as follows:

1. Continuity
2. Co-ordination
3. Communication
4. Contact and Access
5. Role of specialist heart failure services

Within most findings there were sub-findings relating to (a) challenges/problems, (b) ideas for improvement, and (c) complex transition issues. The sub-findings are presented, along with an evaluation of the quality, including an explanation for the CerQual grading that appears with each sub-finding in the summary tables in 9.3.3.5. Relevancy was judged with respect to making recommendations on this particular issue for current NHS specialist and general services, taking into account that some evidence came from studies were conducted in other countries (studies from US and outside the OECD were excluded) and before major NHS configuration changes.

1. Continuity:

Review sub-finding 1a: Lack of continuity in HF care

Both people with heart failure and health professionals felt that heart failure care was fragmented, leading to a lack of continuity. This was contrasted in one study with the more seamless care offered to people with cancer. Patients who experienced lack of continuity found it made it more difficult to form therapeutic relationships, which undermined their confidence in their management plans. Patients aged 65 and under mentioned that lack of continuity sometimes led to encounters with professionals appearing anonymous and meaningless.

This sub-finding was based on four studies [126, 144, 207, 225].

Methodological limitations were rated moderate concerns overall. Two papers were rated serious limitations as they were secondary analyses with insufficient information about the original interviews. One paper was rated as moderate limitations due to lack of context and data richness. One paper was rated as minor limitations.

Coherence was rated no or very minor concerns overall. Agreement between papers was good and appeared to fit well with related findings in other studies. The only findings that tend the other way are regarding the positive influence of GPs in continuity, and this is not inconsistent.

Relevance was rated minor concerns overall. The relevance of the sub-finding to the focus of the review was high. Concerns stemmed from two papers being from outside the UK and in a sub-set of CHF, and the data collection in a UK paper dating back to 2010. However, the finding was found in various settings, and likely to generalise well.

Adequacy was rated as no or very minor concerns. The sub-finding was general, and although explicitly supported by a limited number of studies, other studies found similar findings. The sub-finding was descriptive and the richness of data was sufficient for this.

The overall assessment of confidence was moderate, having been downgraded by one increment due to the combination of concerns in methodology and relevance.

Review sub-finding 1b: Primary care

People with heart failure and professionals working in heart failure care both recognised that primary care, and general practitioners in particular, could provide individualised care with continuity. It was acknowledged that such continuity is important to patients, and there was concern that where HF services take over a patient, this could cause patients to lose touch with primary care, with a consequent loss of continuity. In one study GPs spoke of how they wished for a “consultant” model where specialists answered questions and made recommendations, but did not take over care of the patient. In an assessment of a new heart failure service, it was emphasised by GPs that new services should integrate into the existing primary care/community multidisciplinary team, partly for this reason.

This sub-finding was based on 4 studies[202, 209, 225, 325].

Methodological limitations were rated minor overall. One paper was rated serious limitations due to the lack of explanation of methods and lack of depth of data collection. One paper was rated as moderate limitations due to the participants not being well described. Two papers were rated as minor limitations.

Coherence was rated minor concerns overall. Agreement between papers was good, showing that both patients and other health professionals value the continuity provided by GPs, and believe there is danger of that being disrupted. However, there is other data that challenges the primacy of continuity over other important factors in HF care, for instance the in-depth knowledge of the cardiologist, or the easy access to the HF nurse.

Relevance was rated minor concerns overall. The relevance of the subfinding to the focus of the review was high. Both studies that included patients were from outside the UK. A third study (of HCP)

was from the Highlands of Scotland, which has rather specific challenges of geography that may affect the importance of primary care. The remaining study however, was conducted with HCP in three different trusts, offering results that seem to generalise well over settings.

Adequacy was rated as no or very minor concerns. The subfinding was fairly general, was expected, and is supported by numbers of studies. The finding was descriptive and supported adequately by the richness of data.

The overall assessment of confidence was moderate, having been downgraded by one increment due to the combined minor concerns about methodology, coherence and relevance.

Review sub-finding 1c: Discharge from HF clinic

One study that interviewed people discharged from HF clinics to primary care found that they reported having gone from a situation where they received appointments for follow-up, to one where they were no longer called for review. For some, this felt like they were no longer ill enough to qualify for help. When asked, they expressed a wish to be called to see the GP or nurse once in a while. One patient said: "I feel a bit left out, I'm not part of the health-care system anymore…" p291 [14]

A different study speaking to HF nurses echoed this, saying that they were aware that people liked being patients in the HF clinic, and that this led to some unhappiness when it came to discharging patients. Regarding HF clinics, one says: "I see quite a lot of patients who get discharged, and they hate that. They feel safe… someone's interested and they're keeping an eye on me… They don't like to lose that. They hate to lose that." P301 [294]

It is notable that the focussed qualitative review on continuity in CG138 found the finding of "Feelings of abandonment (when treatment ends or support not available)", which seems to echo in this specific finding on discharge from HF clinic to primary care.

This sub-finding was based on 2 studies [14, 294].

Methodological limitations were rated serious overall. Two papers were rated serious limitations – the study of patient interviews because of the small number of participants (4), lack of clarity over methods, the researcher's voice is potentially prominent and lack of richness of data; the study of HCP interviews because of limited discussion and reflection on the role of the researcher and their methods.

Coherence was rated no or very minor concerns overall. Agreement between papers was good, and while it does not directly align with the sub-finding concerning the primacy of primary care in providing continuity, it fits with the overall theme of this section regarding lack of continuity within the system as a whole.

Relevance was rated minor concerns overall. The relevance of the sub-finding to the focus of the review was very high. Concern was due to one study being from outside the UK and the interviews being in Swedish. However the UK study of HCP shows that the issue is likely to extend to NHS services.

Adequacy was rated as moderate concerns. The sub-finding was specific, and so sufficiently supported by lower numbers of studies. The issues are well described and explained, but overall the richness of the data falls short.

The overall assessment of confidence was low, having been downgraded by 2 increments due to methodological limitations, and concerns over adequacy and relevance, while taking into account the support of the external literature.

2. Co-ordination

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Review sub-finding 2a: Poor co-ordination between services

People with heart failure experience the healthcare system as being poorly co-ordinated. One consequence of poor co-ordination was increased treatment burdens, as they needed to attend hospital/clinics on multiple occasions. They also experienced being given conflicting advice, for example by the cardiologist and nephrologist, leading to uncertainty and loss of confidence. People with heart failure also found the organisation of the healthcare system unclear and confusing. Individuals recalled the difficulties they had experienced trying to get referrals to rehabilitation services and nursing services that they needed. They suggested a clearer organisational process where they could identify who had responsibility, and where things like rehabilitation were offered automatically.

This sub-finding was based on six studies[29, 47, 126,#2771, 225, 325].

Methodological limitations were rated moderate overall. Two papers were rated serious limitations: a secondary analysis which did not give enough detail about data collection or context, and an interview study due to a combination of lack of researcher reflection and inadequate richness. Two papers were rated as moderate limitations due to a lack of researcher reflection, inadequate richness and lack of discussion. Two papers were rated as minor limitations.

Coherence was rated no or very minor concerns overall. The sub-finding of poor co-ordination is present throughout these six studies, and is implicit in other studies. All positive experiences encountered in this review were of individual teams, and most negative experiences in the studies are between settings – although many of these were between inpatient hospital and community, which is outside the scope of this review.

Relevance was rated minor concerns overall. The relevance of three studies was reduced as they were from outside the UK, two of the remaining studies are from before 2010, and the date of data collection from the final study is not reported. There could be concerns as to whether this is occurring in today's NHS context; however the breadth of the data, being from multiple countries, multiple settings, and multiple time points, increases its generalisability.

Adequacy was rated as no or very minor concerns. The sub-finding was general and supported by numbers of studies. The sub-finding was descriptive and supported by the richness of data.

The overall assessment of confidence was moderate, having been downgraded by 1 increment due to concerns over methodology and relevance.

Review sub-finding 2b: Models to co-ordinate care

Clinicians acknowledged that closer co-operation would improve patient care, and potentially reduce workloads. Different (non-mutually exclusive) suggestions came from within and across papers:

- Nominating a single professional to co-ordinate care.
- Heart failure nurses working in a 'cross-boundary' role to encourage close working relationships.
- Co-working between primary and secondary care, possibly through means of a 'shared-care agreement'. Such protocols were already in place for people who have other long-term conditions such as diabetes and hypertension, and enable general practitioners to manage patients in certain categories, with specialists managing patients presenting with more complexity.

Protocols such as for 'shared-care' were seen as having both pros and cons: they can improve transparency and facilitate co-working, but people with heart failure often also have other chronic problems and could end up being on multiple protocols, leading instead to confusion and increased burden of treatment.

This sub-finding was based on five studies[124, 133, 202, 294, 325].

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Methodological limitations were rated serious overall. Two papers were rated serious limitations: one due to lack of context and richness in our area of interest, the other due to lack of detail and reflection on the methods. Two papers were rated as moderate limitations: one because the aims, methodology and findings were poorly discussed, the other because there was little description of the participants. One paper was rated as minor limitations.

Coherence was rated minor concerns overall, based on the finding that clinicians see a problem and think it can be improved. Although there were a number of different improvements suggested, they were compatible with each other. It would be impossible however, to conclude in favour of any particular intervention from these data, and it is clear that there is a tension between disease-specific protocols and holistic management.

Relevance was rated minor concerns overall. The relevance of the sub-finding to the focus of the review was high, as these models may have the potential to improve patient experience at transitions. All but one study was from the UK, and they were in a number of different settings, although some are from before 2010.

Adequacy was rated as moderate concerns. The sub-finding was general, and found in a number of studies, but there was inadequate depth (for example, there were no case studies or examples of pathways in action).

The overall assessment of confidence was low, having been downgraded by two increments due to concerns regarding methodology, and adequacy along with other minor concerns.

3. Communication

Review sub-finding 3a: There is poor communication between services

People with heart failure, their informal carers and professionals within and outside HF services all felt that there was poor communication across boundaries, especially between hospital-based services and primary / community care. Inadequate and delayed transfer of information led to burden on patients and waste of resources. In some areas it contributed to lack of / under-treatment, where management plans were not shared with the prescriber.

One patient explained how this happened: "…there were times when there was a bit of a lack of communication, you know. I would go speak to my doctor [GP] and tell him I'm on such and such, and he would say 'I've not had any word about that'. And that's part of the problem; you get a printed prescription that has, for instance, if I was on 4.5mg of Bisoprolol and they [hospital] were putting it up to 7.5, often the liaison between the hospital and the doctors wasn't all that good". p107 [207]

This sub-finding was based on six studies[29, 47, 126, 133, 144, 207].

Methodological limitations were rated serious overall. Three papers were rated serious limitations, including two secondary analyses and one with limited detail and reflection. Three papers were rated moderate limitations, two due to lack of richness and context, and a third due to poorly defined aims and method.

Coherence was rated no or very minor concerns overall. Agreement between papers was good, and is supported by many of the other studies in an implicit way.

Relevance was rated no or very minor concerns overall. The relevance of the sub-finding to the focus of the review was very high, as communication was flagged as an issue during transitions between care settings. Concern was due to two studies being from outside the UK, and some being more than ten years old – but more recent studies report similar findings, suggesting that this issue has not significantly changed over time and probably generalises well.

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Adequacy was rated as no or very minor concerns. The sub-finding is fairly general and descriptive, and was sufficiently supported by the number of studies and the richness of data.

The overall assessment of confidence was moderate, having been downgraded by one increment due to methodological limitations.

Review sub-finding 3b: Barriers to communication

Healthcare professionals identified the following barriers to cross-boundary communication: fragmented and incompatible information systems, and a lack of time. HF nurses describe in one study, for example, how they struggle to speak to GPs when they have concerns about their patients (GPs are in surgery or on house-calls during most of office hours).

This sub-finding was based on 2 studies[202, 209].

Methodological limitations were rated moderate overall. One paper was rated serious limitations due to lack of depth and explanations. One paper was rated as moderate limitations due to little description of participants. More data came from the latter, therefore rated as moderate overall.

Coherence was rated no or very minor concerns overall. Agreement between papers was good. Agreement with related findings in other studies was also good.

Relevance was rated no or very minor concerns overall. The relevance of the sub-finding to the subject of the review was high. Both studies were from different areas of the UK.

Adequacy was rated as serious concerns. There is some concern about both the lack of quantity of data for a finding of generality, and a lack of depth for an explanatory finding.

The overall assessment of confidence was low, having been downgraded by two increments due to concerns over methodology and adequacy.

Review sub-finding 3c: Information after discharge from HF services

Patients reported being well informed while they were in the HF clinic, but received no information after discharge to primary care. Patients interpreted this change in an ambivalent way, as if not confident in the continuing significance of their CHF and whether they needed ongoing care for their CHF.

This sub-finding was based on 1 study[14].

Methodological limitations were rated serious overall. The included paper was rated serious due to small number of participants (4), poor explanation of methods and low richness of data, in which the researchers' voice was quite prominent.

Coherence was rated no or very minor concerns overall. This specific finding could not be properly assessed, as there was no related data for comparison.

Relevance was rated minor concerns overall. The relevance of the sub-finding to the focus of the review was very high. Concern was due to the study being from outside the UK, and the interviews being in Swedish. It is not clear to what extent the same problems occur in the NHS, but given the similarly pattern of HF clinic discharge, there is potential for the same issue to arise.

Adequacy was rated as serious concerns; it was limited by the number of participants and lack of depth.

The overall assessment of confidence was very low. The overlap between the rating of methodology and adequacy rating was taken into account when downgrading, but it was still felt necessary to downgrade by three increments due to the serious concerns raised.

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4. Contact / Access

Review sub-finding 4a: Access to Routine Care

People with heart failure who were not receiving specialist treatment reported that it was challenging to access specialist advice or secondary care, and that they have to spend time trying to access these through their general practitioner. Once receiving specialist care, or after discharge, patients reported that continued access to the support they felt they needed was also not straight-forward. Some patients felt that the illness itself made asking for help harder. One patient reports "If you have a heart issue you have to shout and speak for yourself and keep at somebody… And if you're not feeling well that's not what you want to be doing".[207] p 108 This is contrasted with patients who have cancer, who found their condition was a 'door-opener', so they did not have to assert their needs in the same way.

The inconsistent way care is offered is to people with CHF was also demonstrated by the impression from HF nurses that GPs have differing thresholds to refer back for specialist help, such that some GPs can leave people struggling in the community.

This sub-finding was based on 3 studies[126#2749, 207].

Methodological limitations were rated serious overall. Two papers were rated serious limitations as they were secondary analysis with a lack of information about how the data had originally been collected. One paper was rated as moderate limitations due to lack of description of participants.

Coherence was rated no or very minor concerns overall. Agreement between papers was good. Agreement with general, related findings in other studies was also good.

Relevance was rated minor concerns overall. The relevance of the sub-finding to the focus of the review was high, as movements in and out of HF specialist care are essentially about accessing routine care. Concern was due to two studies being from prior to 2010.

Adequacy was rated as minor concerns. This sub-finding was fairly general, and so the number of studies was a little lower than would be preferable to support it, but there were no concerns about the richness of data.

The overall assessment of confidence was low, having been downgraded by two increments due mainly to methodological concerns plus the minor concerns regarding relevance and adequacy.

Review sub-finding 4b: A Primary Contact Person

People with heart failure felt they would like one professional nominated as their primary contact person. The preferred characteristics of the relationship with their primary contact person were "a long-term relationship, characterized by openness, trust, and appreciation" p1400 [29]. Most would choose their GP as primary contact person, but some felt their cardiologist was more suitable. A key role of the primary contact would be to enable easy access for patients to care, for example timely appointments. This finding is related to finding 2b, where professionals suggested a single person co-ordinating care might improve co-operation.

This sub-finding was based on 1 study [29].

Methodological limitations were rated moderate overall as the included paper was limited in detail and reflection.

Coherence was rated no or very minor concerns overall as it compliments some of the other related review findings.

Relevance was rated serious concerns overall as the study was not from the UK, was originally in German, and had a restrictive definition of heart failure (EF<40%).

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Adequacy was rated as moderate concerns; although the sub-finding was only reported in one paper, it is well explored in that paper.

The overall assessment of confidence was low, having been downgraded by 2 increments due to relevance concerns, and also for methodology and adequacy.

Review sub-finding 4c: Access to Urgent Care

Patients found that the HF clinic provided them easy access to physicians and nurses, and healthcare professionals noted that HF nurses were able to react more quickly to sudden changes in health status than cardiologists or GPs. This leads to a discrepancy in access between those who were active on the HF clinic caseload, and those discharged to primary care. It was clear that although access to specialists was valued, consistency of care was also needed, and the two were sometimes in tension. For example in one study, a specialist nurse explained: "...patients can ring us up at any time and we can see them on that day if we need to. There is no waiting around and ringing your GP", but GPs in that study felt patients needed a more holistic approach than the HF clinic offered because "… all they care about is the heart failure." pp300, 303 [294]

People with advanced heart failure and their carers reported uncertainty about where to seek help. One patient reported: "I rang my GP who said to ring the hospital, rang hospital and was told they couldn't do anything, you have to ring GP!" p120 [8]

This sub-finding was based on 3 studies[225, 294#2771].

Methodological limitations were rated moderate overall. One paper was rated serious limitations due to lack of discussion and reflection. One paper was rated as moderate limitations due to lack of discussion and reflection on methods. One paper was rated as minor limitations.

Coherence was rated no or very minor concerns overall. Agreement between papers was good, although they revealed another instance of tension between the objectives of ease of access to specialists and continuity of care.

Relevance was rated moderate concerns overall. The relevance of the sub-finding to the focus of the review was high. One patient interview study was not in the UK, and was originally in Swedish. The UK studies are both from before 2010, and the finding is likely to be sensitive to changes in service design.

Adequacy was rated as moderate concerns. This sub-finding was adequately supported by a number of studies, but was lacking in depth.

The overall assessment of confidence was low, having been downgraded by two increments due to combined concerns regarding methodology, relevance and adequacy.

5. The role of specialist HF services

Review sub-finding 5a: Expectations

The expectations of specialist HF services from people with CHF and primary care providers were seen to differ from what the service is delivering. What people providing HF specialist services think patients and primary care want is different again. For example:

- People with heart failure value the time the HF nurse has to spend with them, and the psychosocial support they provide; GPs however said they wanted HF nurses to be a resource for primary care, for advice and a point of contact with cardiology; but HF nurses felt a pressure from GPs to fill a gap in service provision. As one HF nurse states: "GPs will try to *pass the buck* because heart failure patients are a problem because they're not stabilised… So they get a patient they even suspect has got heart failure, they'll move heaven and earth to get them

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through your clinic because they know you'll sort them out, give them everything they need, sort all their 'echoes', all their blood tests, all go back as a lovely little package." p301[294]

- Healthcare professionals involved in HF services perceived GPs as wanting patients to be taken on (or not discharged) by the HF clinic. In one of the studies, those same GPs were also heard, and on the contrary expressed willingness to manage the CHF for most of their CHF patients, suggesting that the HF clinic could concentrate on the most complex cases. One GP stated: "Now that we have open access echo available [to primary care), I am much more comfortable about being the person who makes the decision, the diagnosis, and who initiates and monitors success." p298[294]

This sub-finding was based on 3 studies[47, 202, 294].

Methodological limitations were rated serious overall. Two papers were rated serious limitations due to having limited discussion and reflection, and in one case a lack of richness of data in our area of interest. One paper was rated as moderate limitations as there is little description of the participants.

Coherence was rated minor concerns overall. This was one of the least well-defined sub-findings in the review – what was clear is that different groups had certain expectations on services, but the exact nature of the expectations differed between the studies, and few studies were able to look at the difference in expectations between different groups. The finding of conflict between interested groups due to differing expectations was clear in the two service evaluations included here (which, of the study types in the review, were the studies best able to look at this issue).

Relevance was rated moderate concerns overall. The relevance of this sub-finding to the focus of the review was somewhat indirect. The issues identified may seem quite specific to the exact model of delivering HF care, but all studies were in the UK, at different time periods, so there may be a generalisable point.

Adequacy was rated as serious concerns. The sub-finding was a complex issue, not explored in depth.

The overall assessment of confidence was very low, having been downgraded by three increments for methodology, relevance and adequacy concerns.

Review sub-finding 5b: Focus

Healthcare professionals felt that HF services should be focussed on managing CHF rather than its comorbidities. HCP from HF services felt that they did not have the ability to assess and treat some comorbidities (an example condition was iron-deficiency anaemia). They also felt that addressing people's "primary care issues" could:

- take patients out of contact with primary care, potentially causing a loss of continuity; and
- leave HF services without capacity to manage HF care across their caseload.

This sub-finding was based on 2 studies[127, 325].

Methodological limitations were rated moderate overall. One paper was rated serious limitations due to lack of information on methods and data analysis, and not all findings being supported by data. One paper was rated as minor limitations.

Coherence was rated no or very minor concerns overall. Agreement between papers was good. The sub-finding was compatible with other sub-findings in the review.

Relevance was rated moderate concerns overall. The relevance of this sub-finding to the focus of the review was somewhat indirect. There was also some concern due to both studies being from outside the UK.

Adequacy was rated as moderate concerns. The sub-finding was specific and supported by a number of studies, but is more than just descriptive, so would benefit from a greater richness of data.

The overall assessment of confidence was low, having been downgraded by two increments due to adequacy foremost, and also methodology and relevance.

Review sub-finding 5c: Decision to keep patients on the caseload

One study looked at care networks of patients with advanced heart failure. It found that specialists describe their decision to take over someone's care in the HF clinic as being based on patient need (primarily from the CHF perspective) and the perceived ability of the general practitioner to fulfil these needs. The paper shows though, that actual practice varied widely, and the research team reflect that: "complexity [of the patient] interacted with the health care providers' perspective, comfort level and available resources… to influence referral and consultation practice"p372 [325] Another study also reflected this, where some HF professionals acknowledged the GPs' importance in ensuring continuity of care, but took over care despite of this because they doubted the ability of the GPs to manage heart failure.

This sub-finding was based on 2 studies[202, 325].

Methodological limitations were rated minor overall. One paper was rated as moderate limitations, and one as minor limitations – with the latter contributing more to this sub-finding.

Coherence was rated no or very minor concerns overall. It fits with other sub-findings, in that the decision about where CHF patients are best managed has a number of objectives, which can conflict.

Relevance was rated moderate concerns overall. The relevance of this sub-finding to the focus of the review was high from a staff experience point of view. Concern was due to one study being from outside the UK, however, the second (UK-based) study was conducted in a number of locations, which supports this being a relevant and generalisable theme.

Adequacy was rated as moderate concerns. The finding was specific, but there were still an inadequate numbers of studies. This sub-finding was both descriptive and explanatory, and there was plenty of detail in the papers. One specific concern was that part of the aim of the main study in this analysis was a partly theoretical piece, designed to look at the complexity that exists in healthcare; so the finding of complexity was partially by design.

The overall assessment of confidence was low, having been downgraded by two increments due primarily to concerns over relevance and secondly methodology and adequacy.

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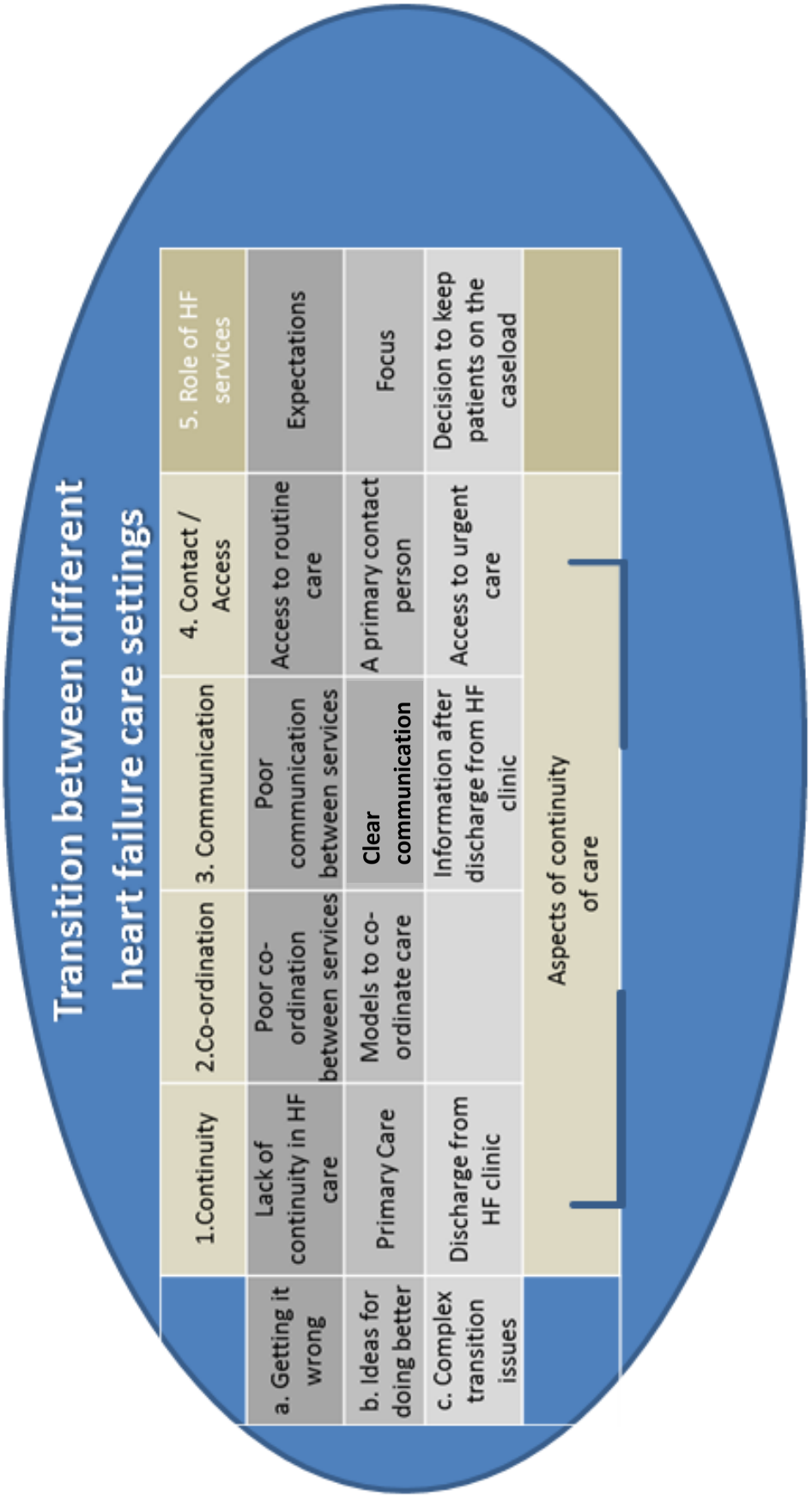

Figure 7: **Main review findings and connections between them**

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9.3.3.5 Qualitative evidence summary

Table 132: Summary of Evidence for Continuity

Study design and sample size		Findings	Quality assessment		
No of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1a Lack of Continuity in HF Care					
4 [126, 144, 207, 225]	Focus groups of HCP in care homes Interview of pt aged 65 and under Secondary analysis of pt interviews	Both people with heart failure and health professionals felt that heart failure care was fragmented leading to a lack of continuity, with negative consequences for patient experience.	Methodology Coherence Relevance Adequacy	moderate limitations no or very minor concerns minor concerns no or very minor concerns	MODERATE
1b Primary Care					
4 [202, 209, 225, 325]	Interview of pt aged 65 and under Interviews of HCP Interviews of patient and care network Questionnaire to HCP	People with heart failure and professionals working in heart failure care both identified that primary care, and general practitioners in particular, could provide individualised care with continuity. HF services can cause pt to lose touch with primary care and lose this continuity.	Methodology Coherence Relevance Adequacy	minor limitations minor concerns minor concerns no or very minor concerns	MODERATE
1c Discharge from HF Clinic					
2 [14, 294]	Interviews with pt Interviews with HCP	People with heart failure and HF nurses both spoke of discharge from HF clinic as being a loss to the patient in terms of no longer being proactively followed up.	Methodology Coherence Relevance Adequacy	serious limitations no or very minor concerns minor concerns moderate concerns	LOW

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Table 133: Summary of Co-ordination

Study design and sample size		Findings	Quality assessment		
No of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
2a Poor Co-ordination Between Services					
6 [29, 47, 126,#2771, 225, 325]	2 x interviews of pt with advanced CHF and their care network 3xInterviews with pt (inc. 1 ≤65y and 1 ≥60y with their carer) Secondary analysis of interviews of pt	People with heart failure experience the healthcare system as being poorly co-ordinated, leading to increased burdens on them and to them being given conflicting advice. This in turn resulted in uncertainty and loss of confidence.	Methodology Coherence Relevance Adequacy	moderate limitations no or very minor concerns minor concerns no or very minor concerns	MODERATE
2b Models to co-ordinate care					
5 [124, 133, 202, 294, 325]	2 x interviews of mix of HCP 2 x interviews of HCP in HF services Interviews of pt and their care networks	Health professionals were aware of several models that could be used to better co-ordinate care. Suggestions included: having a single professional to co-ordinate care; using heart failure nurses to facilitate cross-boundary working; and having conjoint working between primary and secondary care via means of a 'shared-care agreement'.	Methodology Coherence Relevance Adequacy	serious limitations minor concerns minor concerns moderate concerns	LOW

Table 134: Summary of Evidence for Communication

Study design and sample size	Findings	Quality assessment

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No of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
3a Poor communication between services					
6 [29, 47, 126, 133, 144, 207]	Focus group with HCP in care homes Interviews with pt with advanced CHF and their care network Interviews with pt 2 x secondary analysis of interviews with pt Interviews with HCP	People with heart failure, their informal carers and professionals within and outside HF services all felt that there was poor communication across boundaries, and this affected patient experience and patient care.	Methodology Coherence Relevance Adequacy	serious limitations no or very minor concerns no or very minor concerns no or very minor concerns	MODERATE
3b Barriers to clear communication					
2 [202, 209]	Interviews of HCP in HF care Questionnaire to HCP	Healthcare professionals felt that some barriers to cross-boundary communication were fragmented and incompatible information systems, and difficulties trying to speak to other health professionals.	Methodology Coherence Relevance Adequacy	moderate limitations no or very minor concerns no or very minor concerns serious concerns	LOW
3c Information after discharge from HF services					
1 [14]	Interviews with pt	People with heart failure experience being well-informed in HF clinic, but receiving no information after being discharged to primary care, which some took to mean they no longer needed care for their heart failure.	Methodology Coherence Relevance Adequacy	serious limitations no or very minor concerns minor concerns serious concerns	VERY LOW

Table 135: Summary of Evidence for Contact / Access

Study design and sample size		Findings	Quality assessment		
No of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
4a Access to Routine Care					
3 [126#2749, 207]	2 x secondary analysis of pt interviews Interview of HCP	Whether wanting continued access, a new referral or a re-referral, people with heart failure found that it took them time and effort, and that the illness itself could make it harder to stand up for themselves.	Methodology Coherence Relevance Adequacy	serious limitations no or very minor concerns minor concerns minor concerns	LOW
4b A Primary Contact Person					
1 [29]	Interviews with pt	People with heart failure expressed a preference for a primary contact person who offered a long-term relationship, openness, trust and appreciation – most would choose their GP – a key role of whom would be to provide easy access to care, e.g. timely appointments.	Methodology Coherence Relevance Adequacy	moderate limitations no or very minor concerns serious concerns moderate concerns	VERY LOW
4c Access to Urgent Care					
3 [225, 294#2771]	Interviews with pt 65 and under Interviews with pt 60 and over and carer Interviews with HCP	For people with heart failure that were under the care of HF clinics and nurses, it was noted that they had easy access to specialist doctors and nurses, who were able to react more quickly than in conventional service models, but could not provide continuity.	Methodology Coherence Relevance Adequacy	moderate limitations no or very minor concerns moderate concerns moderate concerns	LOW

Table 136: Summary of Evidence for Role of Specialist HF Services

Study design and sample size		Findings	Quality assessment		
No of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
5a Expectations					

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Study design and sample size		Findings	Quality assessment		
No of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
3 [47, 202, 294]	Interviews with HCP Interviews with HCP in HF services Interviews with pt with severe CHF and their care network	Expectations of HF services from primary care and pt can differ both from what HF services think primary care and pt want, and from what the service is capable of delivering.	Methodology Coherence Relevance Adequacy	serious limitations minor concerns moderate concerns serious concerns	VERY LOW
5b Focus					
2 [127, 325]	Interviews with HCP from HF services Interviews with severe CHF and their carer network	Healthcare professionals felt that HF services should be focussed on heart failure rather than its comorbidities, as addressing people's "primary care issues" has other consequences.	Methodology Coherence Relevance Adequacy	moderate limitations no or very minor concerns moderate concerns moderate concerns	LOW
5c Decision to keep patients on the caseload					
2 [202, 325]	Interviews with pt and care network	Healthcare professionals involved in HF specialist services vary widely on whether they take over patients, basing their decisions on the balance of a person's needs for HF care and resources, e.g. the perceived ability of their general practitioner.	Methodology Coherence Relevance Adequacy	minor limitations no or very minor concerns moderate concerns moderate concerns	LOW

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9.3.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix D.

9.3.5 Evidence statements

Qualitative

See the narrative summaries of review findings in section 1.3.3.1.

Economic

- No relevant economic evaluations were identified.

9.3.6 Recommendations and link to evidence

Recommendations	**The primary care team should carry out the following for people with heart failure at all times, including periods when the person is also receiving specailist heart failure care from the MDT:** • **ensure effective communication links between different care settings and clinical services involved in the person's care** • **lead a full review of the person's heart failure care, which may form part of a long-term conditions review** • **recall the person at least every 6 months and update the clinical record** • **ensure that changes to the clinical record are understood and agreed by the person with heart failure and shared with the specialist heart failure MDT** • **arrange access to specialist heart failure services if needed. [2018]** **Care after an acute event** **For recommendations on the diagnosis and management of acute heart failure see NICE's guideline on acute heart failure.** **The primary care team should take over routine management of heart failure as soon as it has been stabilised and its management optimised. [2018]** **Writing a care plan** **The specialist heart failure MDT should write a summary for each person with heart failure that includes:** • **diagnosis and aetiology** • **medicines prescribed, monitoring of medicines, when medicines should be reviewed and any support the person needs to take the medicines** • **functional abilities and any social care needs** • **social circumstances, including carers' needs. [2018]**

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	The summary should form the basis of a care plan for each person, which should include: • **plans for managing the person's heart failure, including follow-up care, rehabilitation and access to social care** • **symptoms to look out for in case of deterioration** • **a process for any subsequent access to the specialist heart failure MDT if needed** • **contact details for** o a named healthcare coordinator (usually a specialist heart failure nurse) o local heart failure specialist care providers, for urgent care or review. • **additional sources of information for people with heart failure. [2018]** **Give a copy of the care plan to the person with heart failure, ther family or carer if appropriate, and all health and social care professionals involved in their care. [2018]**
Findings identified in the evidence synthesis	The review findings were grouped into findings and subfindings following the structure of the recommendations on continuity of care from the NICE Guideline CG138 "Patient experience in adult NHS services" in which four aspects of continuity of care were identified: continuity, co-ordination, communication and contact/access to health professionals and services. In addition the role of specialist services was identified as an important aspect of continuity of care for people with heart failure. For each of the five subfindings of continuity, the review identified challenges, as well as suggestions for improvement, and examples of how transition in heart failure care in particular could affect patients and patient care. The guidelines "Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes" [NG5] 2015 and "Multimorbidity: clinical assessment and management" [NG56] 2016 were also identified as covering similar findings on the management of transition and continuity of patient care. Continuity: It was found that heart failure care that is spread across different healthcare settings is fragmented, and this can have a negative effect on peoples confidence in their management plans. The evidence showed that primary healthcare services, and especially general practitioners, were good at providing continuity of care and individualised, holistic care. It suggested that specialist services should, attempt to integrate into existing primary care structures. Evidence showed that discharge from HF specialist services to general practice can be seen as a 'loss' by patients. The reasons for this were thought to be multifactorial and concerned the difference between specialist and GP care. These included a real or perceived reduction in the focus on the condition, a reduced awareness of the intricacies of the condition, and unfamiliarity with the history of the condition and its exacerbations. In addition to this there may be an increase in the person with HF's sense of vulnerability at being away from specialist care or his/her access to specialist care.

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	Co-ordination: The evidence suggested that patients find the healthcare system poorly co-ordinated and confusing to navigate. This leads to increased treatment burden, and sometimes even conflicting advice. Models to improve co-ordination suggested by health care professionals (HCPs) in the studies included a single care-coordinator, a shared-care protocol between primary and secondary care, and using HF nurses as a bridge between primary and secondary care. Communication: There was a finding of poor communication across service boundaries, especially between hospital-based and primary / community services, which can lead to extra burden on patients, and under-treatment. Some of the factors HCPs felt contributed to this were a fragmented IT system and lack of time available within appointments. Patients reported that there was a paucity of information about their condition after they had been discharged from HF services. Contact/Access: The evidence suggested that people with HF can struggle to access the services they require, and referral / re-referral to HF specific-services can be inconsistent. People with heart failure felt that things may be improved if they had a primary contact, with whom they had a relationship, and most would choose their GP. It was reported that HF clinics and HF nurses can provide easy access to urgent assessment and treatment where people are able to access them. Role of specialist HF services: Expectations of HF services, such as whether they will take over "total care" of the patient (that is, including all comorbidities), and at what point they will discharge patients to primary care, differed between professionals working within, compared with those working outside of HF-services. Some professionals found that managing issues beyond HF in the HF clinic may cause an unwanted loss of continuity in primary care and take time away from HF management. Professionals in HF services felt the decision about whether to keep a patient under follow-up in the HF clinic is complex and taken on an individual basis.
Quality of the evidence	The committee acknowledged the varied confidence ratings for the different subfindings in the review, some of which were fairly low. The members weighed the confidence in the individual findings with their own experience as patients and health professionals in the NHS, and agreed that the subfindings were broadly consistent with their own experiences. Continuity: The subfinding of lack of continuity was rated as moderate confidence, due mainly to methodology concerns. The subfinding of primary care as a key player in continuity was rated as moderate confidence due to minor concerns in coherence and relevance. The committee agreed with these subfindings, but also noted that general practitioners were less able to offer continuity than historically, due to different ways of working. The subfinding about discharge from HF clinic was rated as low confidence due to methodological concerns and being limited to two papers, but the committee felt that this subfinding agreed with their experiences. The lay

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members explained how they built up a relationship with the HF clinic whilst they experienced significant health issues, and they felt vulnerable transitioning away from this to primary care. They were less sure about the major distinction being whether appointments were given or requested, and suggested the issue was more around the certainty of the hospital setting compared with uncertainty in, and continuity through, the GP setting.

Co-ordination: The finding of poor co-ordination between services was of moderate confidence, mainly due to methodological concerns, and the finding of models to co-ordinate care was rated low confidence. Lay members explained that there were resources out there, but people with heart failure were not told about them, and they were therefore under-utilised. The committee agreed that HF nurses were usefully able to provide a bridge between primary care and hospital-based services. The committee felt that HF specialist nurses would ideally co-ordinate care of HF for people who are being actively managed by specialist services, but that this could be passed to general practitioners once the patient was stabilised and on optimal treatment.

Communication: The subfinding of poor communication between services was rated as moderate confidence due to methodological limitations. The subfindings of barriers to clear communication was rated as low confidence due to methodological and adequacy concerns. The professionals on the committee felt that problems with communication occurred in their workplace. It was their experience that they commonly needed to have a three-way conversation or more, and that services can require a full-time administrator in order to facilitate good communication. The committee noted that the system relied upon letters going between care settings, in the absence of a universal NHS information system. The subfinding of information after discharge from HF services being insufficient was rated as very low due to methodology and it having come from only one paper. However, the committee recognised that this was a significant issue.

Contact/Access: The subfinding of difficulty accessing routine care was rated low confidence due mainly to methodological limitations. The subfinding of a primary contact person was rated as very low confidence, but was seen to overlap with other findings to a large extent. The subfinding regarding access to urgent care was rated low confidence due to concerns over methodology, relevance and adequacy.

Role of specialist HF services: The committee felt that some of these subfindings were inevitable in an organisation like the NHS for a condition that crosses boundaries between services. The subfinding on the expectations on HF services was rated very low confidence due to methodological concerns and lack of depth. However the committee recognised the experience of a member who had been involved in creating a local HF pathway and experienced the same issue: that people involved in different aspects of HF care had different expectations of the service. They also recognised that GPs differ in their desire to have specialist input and facility to manage heart failure and its comorbidities.

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	The subfinding of focus for HF services was rated as low confidence due to concerns in methodology, relevance and adequacy. The committee debated these findings. Some felt that that it was impossible for cardiologists to have the expertise and capacity to provide care for all the healthcare needs of patients with heart failure whose co-morbid conditions are complex, and therefore supported a focussed approach. Others felt that compartmentalisation of the clinical features into different distinct disorders does not help patients, and their own experience is that patients really value the attempt to provide an overview of all of their diagnoses and treatment. The subfinding on the decision to keep patients on the caseload was rated as low confidence due to concerns on relevance and adequacy of the data from only two papers. The committee felt that while it was important that decisions were made on an individual basis, the NICE guidelines should promote greater consistency and transparency in these decisions.
Trade-off between benefits and harms	The guideline committee appreciated the richness of the data in this qualitative review. They recognised that the nature of qualitative evidence offered an opportunity to identify recurring issues and examples of good practice. Continuity: The committee acknowledged that it is sometimes necessary for patients to move between different teams / services. For example, if a patient has been unwell, it is essential for the specialist HF service to follow-up and review their management and adjust any medication as necessary; but that once the patient is stable it is often appropriate to transfer routine care back to the GP. However, GPs and lay members had experience of patients receiving care by the specialist HF service without the involvement of their GP, to whom the patient was subsequently discharged. The committee agreed that an initial care plan should be developed by the HF MDT, and that this plan and subsequent contacts with the MDT should be communicated to primary care. The patient and primary care physicians should also be informed that intense management by the HF MDT is often only needed for a limited period, and will be replaced by monitoring in primary care once their condition is stabilised. The committee considered efficient and easy access back into specialist HF MDT when needed, was very important to ensure continuity of care for the patient. This could be achieved by having an “open appointment” arrangement with the specialist MDT should difficulties arise. Having primary care embedded within the MDT may facilitate this transfer. The committee felt that the role of the general practitioner in offering a longitudinal and individualised approach should be emphasised. They felt that the patient’s clinical record should be reviewed by the general practitioner at least every six months, whether or not the person is being routinely managed by HF specialist services. This should enable active management of comorbidities and early identification of other service needs, and prevent loss of contact, and thereby encourage continuity of management between primary care and heart failure services. The idea of a GP-led review is not to duplicate the work of the MDT, but to address the wider concerns of the person with CHF. This guideline already recommends at least 6 monthly clinical reviews of patients with heart failure, and GP-

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review of the clinical record could easily be incorporated into this existing review where patients are being managed in primary care. Even where patients are being routinely seen in the MDT, those with other long-term conditions may already be attending primary care for reviews, and the HF review could be usefully added in to existing appointments.

Co-ordination: The committee agreed that coordination between services should be a priority. The committee recognised that a single care coordinator was already advocated in the multimorbidity guideline, and this would be helpful in HF. It was felt that the named healthcare coordinator would usually be the HF specialist nurse where a person was being actively managed by the multidisciplinary specialist HF team, but at the point of transfer to routine management in primary care, this would usually change to the patient's GP.

Members also advocated collaborative working between primary and secondary care through the MDT. Lay members emphasised that there needed to be better accountability, so that decisions were not only made, but also followed through and followed up effectively. Therefore future plans, who will do what, and when, as well as where/when the next routine review will take place, should form an essential part of the care plan.

Communication: The committee felt that it was important that patients have access to their health information, for their own reference, and also to inform others. There was a suggestion that patients could hold their heart failure notes, but it was felt that this was not yet practical. However, it should be the case that they receive a copy of everything that is sent about them, as is already advised in CG138, including their current care plan after every formal review.

The committee attempted to define what would be included in the summary of the patients status and how the care plan would be formulated, but appreciated that this would vary depending on where the patient was in the HF pathway, and other individual factors. The committee agreed that it is essential that the patient is given a named contact and knows who is going to follow them up and when, along with current medication. After contact details and follow-up arrangements, the most important things to include were thought to be the diagnosis, current treatment, red flag signs that HF is deteriorating, and signposting to further information / sources of support. Where appropriate, it would also include aetiology of HF, social circumstances, carer needs, how they can access rehabilitation and other resources. The committee acknowledged that the full summary of status and care plan may not be ready to provide to the patient during their appointment in order that they can take a copy home with them, and agreed that it may comprise a letter to the patient and GP following the appointment. Letters should use appropriate language to communicate to the GP, with a glossary or similar to make them accessible to patients. It is not intended that two sets of letters should be produced.

Contact/Access: It was seen as particularly important that patients and their carers know where to get support in both routine and urgent circumstances, as per the current patient experience guideline. Pathways could be devised

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	locally, but the committee felt that it was important that patients with heart failure could contact the heart failure clinic or service if requiring advice or urgent care. It was acknowledged that two way communication between heart failure specialists and GPs is essential to ensure patients are well managed. Specialists need to provide a clear plan to allow medication lists to be updated and GPs also have a responsibility to inform the specialist team when the condition of the patient changes. The ideal system would be to allow all members of the MDT to access hospital, community and GP notes. However this is not yet possible in most areas. Role of specialist HF services: The committee acknowledged that local dialogue about what HF services should provide for people with CHF might be useful, but may not be practical. The reports of the complexity of treating the comorbidities of patients with CHF, the nature of sub-speciality medical training, and the lack of a universal information system, highlighted the fact that the general practitioner, or another generalist such as a geriatrician, should be actively involved throughout the heart failure pathway. It was felt that HF specialists should primarily be involved in HF optimisation, while collaborating with other healthcare providers, who would be providing for the wider needs of patients.
Trade-off between net effects and costs	No published economic evaluations were identified. The committee agreed that ensuring a care plan was in place and shared with the patient and necessary healthcare professionals was important to improve current barriers in co-ordination and communication for people with heart failure. The committee noted that there may be some small costs associated with the time spent on the administrative tasks such as the writing and dissemination of the care plan. However, the committee felt that providing a care plan was already standard practice in many cases, and could be achieved by changes to current paperwork rather than additional time and resource. The committee agreed that ensuring care plans are regularly updated and shared would likely improve patient treatment by reducing cases of under or over treatment and any resultant adverse events. The committee believed that the reduced treatment burden would improve patient quality of life and reduce patients' anxiety about their condition and treatment. Therefore, overall the committee considered that any additional administrative tasks and care plans are likely to be a cost-effective use of resources.
Other considerations	The current experience of HF care across the country was felt to be variable due to a number of factors.. These included the degree to which GPs were engaged with national programmes such as QOF and NICE Quality Standards programme; the degree to which GPs are involved in regionally agreed long-term conditions frameworks or other benchmarking; locally agreed protocols; and the involvement of the third sector, such as patient advocate groups, in facilitating access to care. The committee felt that clarifying the roles of primary care and the rest of the multidisciplinary specialist HF team would enable commissioners and others to reduce variation by defining the structures for high quality HF care, including effective co-ordination and communication.

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	The GP members of the committee spoke about their current involvement in the care of people with HF. They felt that it was essentially the same as for any other patient with a long term condition, and approached it in the same way. However, HF was among the most challenging conditions to manage, as people with HF tend to have multiple, complex comorbidities. This led the committee to think about including aspects of the multi-morbidity guidance when thinking about reviewing and co-ordinating care for people with HF. The committee highlighted an important sub-population of HF patients, being those that are housebound. It was recognised that they are often not reviewed by HF clinics, and not seen in the GP surgery, and therefore perhaps not routinely seen by the primary healthcare team either. It was felt that some people in these circumstances only received care once they were acutely unwell. The committee intended that these patients should be included in the recommendations regarding six-monthly review. It was reported that, in one example, reviews for housebound patients with HF were sometimes delegated to district nurses. The committee felt that HF monitoring and review should be done by someone with competencies in clinical examination and medicines optimisation.

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9.4 Information and support needs regarding diagnosis and prognosis

9.4.1 Introduction

Communication is the one of the key determinants of successful management of chronic diseases. The diagnosis of heart failure is often a shock to patients. Heart failure is a complex disorder which requires active participation of patients in its management. A large literature has developed about the perceptions and misperceptions that the diagnosis entails and about the prognosis of heart failure. Different features of the disease process are highlighted by patients and the various professional groups involved in the management of heart failure. This review aimed to identify the key factors that need to be communicated about the diagnosis of heart failure to patients and their carers, the information needed about the disease and the support required to allow care to be optimised.

9.4.2 Review question: What are the information and support needs to be considered when communicating a diagnosis and consequent prognosis, to people with heart failure, their families and carers?

For full details see review protocol in appendix A.

Table 137: Characteristics of review question

Objective	The aim of this review is to identify the information and support needs of people with heart failure, their families and carers, when healthcare professionals are communicating a diagnosis and prognosis.
Population and setting	Patients with heart failure in a UK primary care, outpatient or community setting. Studies that relate to patient/staff experiences of communication regarding diagnosis or prognosis that occur during a patient's hospitalisation for heart failure will be included, where the issues identified are also relevant to communication in the community/outpatient setting. Patient, family and carer information and support needs will be considered.
Context	Any description of support and information needs of patients, families or carers relating to communication of a diagnosis or the prognosis of heart failure. Views can be provided by patients, families, carers or healthcare staff
Review strategy	Synthesis of qualitative research: thematic analysis- information synthesised into main review findings. Results presented in detailed narrative format. Quality of the evidence was assessed by a GRADE CerQual approach for each review finding.

9.4.3 Qualitative evidence

9.4.3.1 Methods

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[236] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

9.4.3.2 Summary of included studies

A search was conducted for qualitative studies exploring the communication and support needs of people with heart failure at the time when diagnosis and prognosis are relayed to them by health care professionals. Twelve qualitative studies (15 papers) were included in the review;[8, 26, 53, 102, 117, 123,

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[133, 141, 148, 207, 231, 302, 313, 328, 370] these are summarised in Table 138 below. Key findings from these studies are summarised in Section 9.4.3 below. See also the study selection flow chart in Appendix C, study evidence tables in appendix F, and excluded studies lists in appendix I.

Table 138: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Aldred 2004[8]	Semi-structured interviews with patients + carers. Thematic analysis.	N=10 CHF patients recently discharged from hospital and one person each that they lived with and nominated a carer. Age: mean 72 (SD 5) Severity NYHA class II-IV (6/10 NYHA class III)	Explore the impact of heart failure on the lives of older patients and their informal carers.	Part of larger study on palliative needs. Setting: UK, Barnsley.
Barnes 2006[26]	Individual interviews with patients + carer (if they wished to do so) and focus groups with HCPs. Thematic analysis.	N=44 CHF patients (NYHA class III or IV) recruited from GP practices. Age: median 77 (IQR 71-83) N=79 HCPs in 9 focus groups Age range: 27-58	Explore the attitudes of older people and primary care professionals towards communication of diagnosis, prognosis and symptoms in heart failure.	Setting: four geographical locations in the UK: East Devon, West Hampshire, Bradford and Barnsley.
Browne 2014[53]	Individual interviews with patients + carer (if they wished to do so) and interviews or focus groups with HCPs. Thematic analysis using the Framework method. Coding framework linking data categories to an exploratory model provided by a theory known as Normalisation Process Theory.	N=30 CHF pts with advanced heart failure (NYHA class III or IV) and a history of hospital admissions. Age: mean 72 (range 60-86) N=20 Carers N=65 HCPs (14 interviews, 6 focus groups)	Examine patient, carer, and professional perspectives on current management of advanced heart failure and barriers and facilitators to improved care.	Setting: one health board in Scotland, UK.
Doos 2015[102]	Individual interviews with patients + carer (if they wished to do so), taped and transcribed verbatim. Thematic analysis	N=6 pts with CHF and comorbid COPD recruited at the time of hospital discharge. Age: mean 79 (range 62-91)	Explore experiences of multi-morbid COPD and HF patients during, and shortly after a hospital stay. Also, to focus	Mixed methods study: Survey followed by interviews. Setting: a large regional hospital in England, UK.

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Study	Design	Population	Research aim	Comments
	using the principles of Grounded Theory (constant comparison).	N=5 Carers	on patient and carer information needs on transitions and any perceived gaps in relation to their multi-morbidity.	
Field 2006[117]	Open-ended narrative interviews with patients, taped and transcribed verbatim. Thematic analysis using a modified grounded theory approach, incorporating constant comparison.	N=37 CHF pts at all stages of heart failure. Age range: 33-84	Examine whether heart failure patients' awareness of the purpose and side effects of their medicines equips them to participate in informed discussions about treatments, how they cope with the condition and manage their medication.	Setting: 'throughout the UK' .
Horne 2004[148]	Open semi-structured interviews with patients, taped and transcribed verbatim. Thematic analysis using a Grounded Theory approach.	N=20 CHF patients recruited by consultants and specialist nurses from two teaching hospitals. Age: mean 73 (range 60-83) Severity NYHA class II-IV (11 class IV; 7 class III)	Explore the experiences of patients with severe heart failure and identify their needs for palliative care.	Setting: Doncaster, UK. Urban and rural communities situated in former coal mining area.
Macdonald 2016[207]	Secondary analysis of qualitative data of transcripts of interviews with patient. Use form of amplified analysis to fit themes to the Candidacy framework.	N=20 CHF pts (a selection of transcripts from two previous HF studies) Age: range 56-86 Severity: 10 advanced and 10 "stable"	Contrast the help-seeking and access to care in cancer and heart disease in order to extend concepts about illness identity, and its relationship to a concept known as "Candidacy"	Compares CHF with cancer. Data was taken from the Colorectal Cancer, End-Stage HF and Stable HF studies. Setting: Scotland, UK.
Murray 2002[231]	In-depth interviews at 3-monthly intervals for up to a year with patient. Following bereavement their informal caregivers were interviewed. Focus group of key professional carers identified by patients.	N=20 pts with end stage heart failure (NYHA class IV) identified by consultants as outpatients. Age: mean 74	Compare the illness trajectories, needs, and service use of patients with cancer and those with advanced non-malignant disease (heart failure).	Setting: Edinburgh and Livingston, Scotland, UK.

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Study	Design	Population	Research aim	Comments
	Thematic analysis using the techniques of narrative analysis.			
Selman 2007[302]; Harding 2008[141]	Semi-structured interviews with patints, their carers and HCPs. Thematic analysis using a constant comparison approach.	N=20 CHF pts recruited from outpatient clinics and hospital wards. Age: mean 69 (range 43-83) Severity NYHA class III-IV (14 class III) N=11 Carers N=12 HCP from cardiology and palliative care	Selman 2007: Formulate guidance and recommendations for improving end-of-life care in chronic heart failure. To generate data on patients' and carers' preferences regarding future treatment modalities, and to investigate communication between staff, patients and carers on end-of-life issues. Harding 2008: Generate recommendations for the appropriate provision of feasible and acceptable information to chronic heart failure patients and their family carers, in line with UK and international policy guidelines.	Setting: London, UK.
Simmonds 2015[313]; Glogowska 2015[133]; Fry 2016[123]	Qualitative study using ethnographic methods (in-depth interviews, observation, impromptu interviews, field notes, patient and carer diaries, patient medical records). Pts were followed individually throughout their interactions with healthcare for up to 11 months. In-depth	N=31 pts with severe or difficult to manage heart failure and who had an unplanned hospital admission for CHF in the preceding 6 months. Age: mean 72 N=9 Carers N=55 HCPs overall	Simmonds 2015: Identify critical points on heart failure patient pathways where risk of unplanned admission is increased and identify barriers to the implementation of evidence-based interventions. Glogowska 2015: Explore perceptions and experiences of	Fry 2016[123] is linked to the dataset but did not report findings relevant to this review. Setting: three study sites, UK.

Study	Design	Population	Research aim	Comments
	interviews with a subsample of patients and/or carers. HCPs were observed delivering care for these pts. In-depth interviews with HCPs who cared for different pt. Thematic analysis involving constant comparison.	(in-depth interviews with N=23)	health care professionals working in multi-disciplinary teams that include specialist heart failure nurses when caring for the management of heart failure patients.	
Taylor 2017[328]	Semi-structured interviews with patients and their carers (if they wished to do so). Thematic analysis using the Framework method.	N=16 patients with a recent (<1 year) diagnosis of heart failure recruited from heart failure clinic. Age: median 78 (range 52-87)	Explore the experiences of patients with a recent diagnosis of heart failure with a focus on symptom onset and diagnosis parts of the pathway to explore how and when patients realised something was wrong and what the term 'heart failure' means to them.	Setting: central England, UK.
Wingham 2015[370]	Semi-structured interviews (n=22) and one focus group with carers of CHF patients and the person they cared for (on request of the carer). Thematic analysis using the Framework method.	N=26 Carers of CHF patients who had been caregivers for at least 6 months. Age: mean 66 (range 39-84)	Identify the needs of caregivers supporting a person with heart failure and inform the development of a caregiver resource to be used as part of a home-based self-management programme.	Setting: Cornwall, Birmingham and Leicester, UK.

Abbreviations: Pt = people with chronic heart failure, HCP = healthcare professional, NYHA = New York Heart Association Functional Classification, COPD = chronic obstructive pulmonary disease

9.4.3.3 Qualitative evidence synthesis

Table 139: Review findings

Main findings	Statement of finding
Diagnosis of heart failure	
1a. Communication is challenging	Clinicians find the diagnosis itself and the ensuing communication around diagnosis challenging.
1b. Timing and setting	Choosing the timing and setting of communicating the diagnosis is important.

Main findings	Statement of finding
1c. Gradual process	The persons comprehension of their diagnosis is seen as a gradual process which results in information and guidance around diagnosis being relayed to patients in a gradual manner.
1d. Terminology	As the term 'heart failure' is seen by healthcare professionals as anxiety-invoking, many make use of euphemisms or even more complex terminology instead which is often confusing for patients.
Understanding heart failure	
2a. Understanding of diagnosis	Although there is variability in patients' understanding of their diagnosis it is generally poor.
2b. Knowledge and management	Patients' desire for more knowledge about their condition and its management is highly individual.
Discussion of prognosis	
3a. Difficult conversations	Staff reported difficulties in discussing prognosis and future care options due to the unpredictable disease trajectory, uncertainty whether patients wanted to know and difficulties handling emotional involvement of patients and their families.
3b. Understanding of prognosis	Patients described that prognosis was rarely discussed and showed that their understanding of their prognosis was generally poor.
3c. Patients' concerns	Whilst patients' desire for more knowledge about their prognosis was highly individual many were worried by the uncertainty of what the future held.
Improving communication/ information flow	
4a. Education and joint working	Staff identified that communication with patients and family members would be improved through training in diagnosing and prognosticating heart failure, and through mutual education for staff from different specialities.
4b. Ongoing relationship	Staff suggested for information and education to be delivered to the patient within an ongoing relationship and in an appropriate setting.
4c. Tailoring of information	The variability in patients' ability and willingness to receive information regarding their condition requires staff to tailor the information to the needs of the individual.
4d. Improving access to information	Patients desire more detail, written information and greater access to support.

9.4.3.3.1 Narrative summary of review findings

The review findings are grouped within four overarching findings, as follows:

1. Diagnosis of heart failure
2. Understanding heart failure
3. Discussion of prognosis
4. Improving communication/information flow

Each of these four findings contain several key subfindings that are described below along with an evaluation of the quality including an explanation for the CerQual grading that appears with the subfindings in the summary tables in section 1.3.4.

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1. Diagnosis of heart failure

Review subfinding 1a: Communication is challenging

Clinicians find the first conversation disclosing the diagnosis of heart failure to the patient to be difficult. Some clinicians described the diagnosis of heart failure itself as challenging, making it even more difficult to relay information to patients.

This subfinding was based on two studies.[26, 133, 313]

Methodological limitations were rated moderate concerns overall. Both studies were rated as moderate limitations due to lack of context and the role of the researcher, plus data analysis in one study and data richness in the other.

Coherence was rated no or very minor concerns overall. Agreement between papers was good and appeared to fit well with related findings in other studies.

Relevance was rated no or very minor concerns overall. The relevance of the subfinding to the focus of the review was high. The data stemmed from two papers from the UK in a relevant population.

Adequacy was rated as minor concerns. The subfinding was general, and although explicitly supported by only a limited number of studies, other studies found similar themes. The subfinding was descriptive but the richness of data was somewhat lacking.

The overall assessment of confidence was moderate, having been downgraded by one increment due to methodological and adequacy limitations.

Review subfinding 1b: Timing and setting

The reluctance by some GPs to diagnose patients meant that some patients received a shock diagnosis when admitted to secondary care. Receiving the diagnosis during an unplanned hospital admission was deemed “unhelpful and inadequate by clinicians, patients and their carers” (Simmonds 2015) as diagnosis could not be relayed in a sensitive manner to the patient and family who had no time to assimilate the information in this busy environment. Patients with good access to hospital- and community-based heart failure specialist nursing teams reported more positive experiences of communication regarding diagnosis.

This subfinding was based on three studies.[26, 117, 313]

Methodological limitations were rated moderate concerns overall. Two studies were rated as moderate limitations due to lack of context and role of the researcher, plus data analysis in one study and data richness in the other. One study had serious limitations due to lack of context, role of the researcher, data collection and richness of data.

Coherence was rated as minor concerns overall. Agreement between papers was good and appeared to fit well with related findings in other studies. The only findings that tended to be the other way are regarding the positive experience of patients with good access to specialist nursing teams.

Relevance was rated no or very minor concerns overall. The relevance of the subfinding to the focus of the review was high. The data stemmed from three studies from the UK in a relevant population.

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Adequacy was rated as no or very minor concerns. The subfinding was general, and although explicitly supported by a limited number of studies, other studies found similar themes. The finding was descriptive and the richness of data was sufficient for this.

The overall assessment of confidence was moderate, having been downgraded by one increment due to the combination of concerns in methodology and coherence.

Review subfinding 1c: Gradual process

Diagnosis was seen by healthcare professionals as a gradual process which in turn makes the communication of the diagnosis a gradual process. They emphasised the need to provide information and guidance as part of an ongoing conversation with the patient and family. Heart failure specialist nurses and GPs were seen as key to the success of this process.

This subfinding was based on three studies.[26, 133, 207, 313]

Methodological limitations were rated moderate concerns overall. Two studies were rated as moderate limitations due to a lack of context and role of the researcher, plus data analysis in one study and data richness in the other. One study had serious limitations due to the secondary use of data and the subsequent inability to assess their methodology in detail, along with vague description of the analysis.

Coherence was rated no or very minor concerns overall. Agreement between papers was good.

Relevance was rated no or very minor concerns overall. The relevance of the subfinding to the focus of the review was very high. The data stemmed from three studies from the UK in a relevant population.

Adequacy was rated as no or very minor concerns. The subfinding was general, and although explicitly supported by a limited number of studies, other studies found similar themes. The finding was descriptive and the richness of data was sufficient for this.

The overall assessment of confidence was moderate, having been downgraded by one increment due to the concerns in methodology.

Review subfinding 1d: Terminology

Clinicians stated that they felt that the terminology affected communication. They wanted patients to understand their condition but also wished to avoid upsetting them and extinguishing their hope. Only very few healthcare professionals described using the term ‘heart failure’; it was regarded by most of them as an anxiety-invoking term (similar to a cancer diagnosis). So instead many resorted to using euphemisms (e.g. ‘ageing heart’, ‘stiff heart’, ‘heart not pumping efficiently’) or paradoxically even more complex terminology (e.g. ‘left ventricular failure’).

These alternative explanations often led to poorer communication, confusion for people with heart failure and lack of interest in their diagnosis as a consequence.

People with heart failure were often unaware of the term ‘heart failure’. Many described that the term was not mentioned initially but introduced later on by specialists, often leading to shock and confusion for the patients.

This subfinding was based on six studies.[8, 26, 133, 207, 231, 313, 328]

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Methodological limitations were rated moderate overall. Five studies were rated moderate limitations: two studies due to lack of context and role of the researcher, plus data analysis in one study and data richness in the other. Another two studies due to lack in data richness, plus missing information on the topic guide in one, and lack of reflection on the role of the researcher and loose link between findings and conclusions in the other. The fifth study due to no reflections on role of researcher and lack of detail on methodology. One study had serious limitations due to the secondary use of data and the subsequent inability to assess their methodology in detail, along with vague description of the analysis.

Coherence was rated minor concerns overall. Agreement between papers was very good except one where healthcare professionals actually used the terminology 'heart failure' with all their patients.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from three studies from the UK in a relevant population.

Adequacy was rated as no concerns. The subfinding was explicitly supported by quite a few studies in much detail.

The overall assessment of confidence was moderate, having been downgraded by one increment due to the concerns in methodology and coherence.

2. Understanding heart failure

Review subfinding 2a: Understanding of diagnosis

There is variability in the complexity and depth of patients' understanding of their diagnosis.

Most patients showed poor knowledge and misunderstanding of their condition and its implications, including treatments, their importance, side effects and limitations. Many did not connect symptoms they had to their heart failure; some even deduced their diagnosis from the medications they were taking. The lack of understanding was often compounded by confusion and short-term memory loss that is associated with heart failure.

However, other patients showed a high level of interest in their illness, were proactive in seeking information (e.g. online), knew how to manage their condition, and were well informed and equipped for informed exchanges with healthcare professionals about heart failure. In one study the authors noted, however, that this was an unusual group of younger patients and/or those with a background in health.

Healthcare professionals were sympathetic to patients' uncertainty about the meaning of their diagnosis and about treatments, as they were aware that a lack of time for communication contributed to poor understanding.

This subfinding was based on nine studies.[8, 26, 53, 117, 133, 141, 207, 231, 328]

Methodological limitations were rated serious overall. Five studies were rated moderate limitations due to a mix of reasons including a lack of the role of researcher, data richness and details of methodology. Three studies were rated serious limitations; one study due to the secondary use of data and the subsequent inability to assess their methodology in detail, along with vague description of the analysis. Two studies due to the lack of richness of data, context and the role of the researcher, as well as a lack of information on data collection in one study and the reasoning for the choice of methods in the other. One study had very serious limitations due to limited information on the background and reflection of the researcher, data collection, data richness, relevance of findings and link to conclusions.

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Coherence was rated minor concerns overall. Agreement between papers was very good with the majority demonstrating patients' lack of understanding of their diagnosis. Only very few papers also described that some patients had a very good understanding of their condition. As a certain degree of variability in people's understanding is expected and all papers were in agreement that the majority lacked the understanding, the concerns were rated as minor overall.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from nine studies from the UK in a relevant population.

Adequacy was rated as no or very minor concerns. The subfinding was general and supported by numbers of studies; it was descriptive and supported by the richness of data.

The overall assessment of confidence was low, having been downgraded by two increments due to concerns over methodology and coherence.

Review subfinding 2b: Knowledge and management

Some patients did not want to know more about their diagnosis as it would cause them to worry, and they chose to put all their trust into healthcare professionals to make decisions for them. Yet, others described having received too little information about their diagnosis and some received contradicting information that caused them confusion. These patients felt that the lack of knowledge caused them panic attacks and anxiety about the practicalities of what to do in a crisis, for example.

This subfinding was based on five studies.[26, 102, 117, 148, 328]

Methodological limitations were rated serious overall. Two studies were rated moderate limitations: one due to limitations in context, the role of researcher and data analysis, and another study due to missing information on the topic guide and the lack of data richness in sections relevant to this review. Three studies were rated serious limitations due to a lack of information on the role of the researcher, data richness as well as lack of rigour in research methods.

Coherence was rated minor concerns overall. Agreement between papers was good in that they all reported a range of people's attitudes. Variability in people's attitudes is expected, hence the concerns were rated as minor overall.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from five studies from the UK in a relevant population.

Adequacy was rated as no or very minor concerns. The subfinding was general and supported by numbers of studies; it was descriptive and supported by the richness of data.

The overall assessment of confidence was low, having been downgraded by two increments due to concerns over methodology and coherence.

3. Discussion of prognosis

Review subfinding 3a: Difficult conversations

Staff noted that discussions of prognosis are difficult, given the difficulty of diagnosis in the first place and due to the unpredictable disease trajectory of heart failure, and they were reluctant to have them. Some healthcare professionals also found it challenging to balance the need to be honest with the patient about their condition (which could raise anxiety) with building trust and maintaining hope and a positive outlook when faced with a life-threatening illness. Some healthcare professionals

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considered that patients may not want to know everything about their prognosis, perhaps hinting at a degree of paternalism or recognition of denial as a way of coping.

Some felt it was more appropriate to address prognosis over time, given these uncertainties and in response to changing circumstances, particularly when a patient might be approaching the end of their life.

A common professional perception was that these types of exchange between clinician and patient did not happen often enough. In one study cardiac staff confirmed that issues such as future care in the event of an exacerbation or end-of-life preferences are rarely raised with patients. It was suggested that lessons could be learnt from communication in cancer where clear information about prognosis is provided to patients. However, the staff reported having difficulties handling patient denial, discussing poor prognosis and dealing with the emotional involvement of patients and their families. It was said in this study that cardiac staff often lack the communication skills required to handle these sensitive issues.

This subfinding was based on six studies.[26, 53, 133, 141, 207, 231, 302]

Methodological limitations were rated serious overall. Three studies were rated moderate limitations due to the lack of the role of the researcher, plus another two out of the following limitations: lack of context, data richness, data analysis or loose linkage between findings and conclusions. Two studies were rated serious limitations, one due to the secondary use of data and the subsequent inability to assess methodology in detail, along with vague descriptions of this analysis; whilst the second study due to a lack of reflection on the researcher role in the study, limited context, reasoning for the choice of methods and richness of data. One study was rated as having very serious limitations due to the limited information on the background and reflection of the researcher, data collection, data richness, relevance of findings and a link to conclusions.

Coherence was rated no or very minor concerns overall. Agreement between papers was very good.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from six studies from the UK in a relevant population.

Adequacy was rated as no concerns. The subfinding was explicitly supported by quite a few studies in much detail.

The overall assessment of confidence was moderate, having been downgraded by one increment due to methodological limitations.

Review subfinding 3b: Understanding of prognosis

Patients often reported that prognosis was rarely discussed. Some patients were aware of the seriousness of their condition but reported a lack of understanding of the prognosis. Some patients were unaware that heart failure is a terminal condition and reported feeling very frightened when informed at the end-stage.

This subfinding was based on five studies.[8, 26, 53, 207, 231]

Methodological limitations were rated moderate overall. Three studies were rated moderate limitations due to limitations on the role of the researcher and methodology, as well as limitations in context for one study and data richness and lack of link between findings and conclusions for another study. Two studies had serious limitations: one study due to the secondary use of data and the subsequent inability to assess methodology in detail, along with vague descriptions of this analysis; and the second study due to the lack of reflection on the researcher role in the study, limited context, reasoning for choice of methods and richness of data.

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Coherence was rated minor concerns overall. Agreement between papers was very good with the majority demonstrating patients' lack of understanding of their prognosis. It was only slightly downgraded to minor concerns overall due to some variability in patients' understanding.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from five studies from the UK in a relevant population.

Adequacy was rated as no concerns. The subfinding was explicitly supported by quite a few studies.

The overall assessment of confidence was moderate, having been downgraded by one increment due to moderate methodological and minor coherence limitations.

Review subfinding 3c: Patients' concerns

Some patients preferred not to know more about their prognosis, perhaps using denial as a way of coping. Yet most others, including carers, felt they were inadequately informed by healthcare professionals, and felt uncertainty about what would happen as the disease progressed. "Thinking about the future was a common preoccupation, with patients expressing very realistic concerns that their life expectancy was limited." (Aldred 2004)

This subfinding was based on seven studies.[8, 26, 53, 117, 133, 148, 370]

Methodological limitations were rated moderate overall. Four studies were rated moderate limitations: each due to a number of limitations that included some of the following; limitations in context, role of researcher, data analysis, research methods rigour, and/or data richness in some sections relevant to our review. Three studies were rated serious limitations due to a lack of reflection on the role of the researcher and data richness; plus limited context and reasoning for the choice of methods for one study, lack of information on context and data collection for another, and lack of rigour of research methods, study aims, and relevance of findings for the third study.

Coherence was rated minor concerns overall. Agreement between papers was good in that they all reported a range of people's attitudes and concerns. Variability in people's attitudes is expected, hence the concerns were rated as minor overall.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from seven studies from the UK in a relevant population.

Adequacy was rated as no or very minor concerns. The subfinding was general and supported by a number of studies. The finding was descriptive and supported by the richness of data.

The overall assessment of confidence was moderate, having been downgraded by one increment due to moderate methodological and minor coherence limitations.

4. Improving communication/information flow

Review subfinding 4a: Education and joint working

GPs expressed a need for education around the identification and diagnosis of heart failure patients; and that with such an improvement in their own understanding their ability to communicate this information to the patient would improve. They felt that "changes needed to be made within the health profession first" before information on the identification and diagnosis of heart failure can be more clearly communicated to patients (Barnes 2006).

Further, in one study cardiology and palliative care staff reported a lack of clarity regarding what had previously been discussed with and disclosed to patients. They recommended "mutual education and

joint working" between the specialties to improve communication to the patient and family (Harding 2008).

This subfinding was based on two studies.[26, 141]

Methodological limitations were rated serious overall. One study had moderate limitations due to limitations in context, role of researcher and data analysis. Another study had very serious limitations due to the limited information on the background and reflection of the researcher, data collection, data richness, relevance of findings and link to conclusions.

Coherence was rated no or very minor concerns overall. Agreement between papers was good.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from two studies from the UK in a relevant population.

Adequacy was rated as no or very minor concerns. Although the subfinding was explicitly supported by only two studies, it was provided in much detail.

The overall assessment of confidence was moderate, having been downgraded by one increment due to serious methodological limitations.

Review subfinding 4b: Ongoing relationship

Healthcare professionals reported that because appointments with consultants are too short to relay all the information a patient would need regarding diagnosis and prognosis, patient education was often delegated to specialist nurses in the outpatient or community setting. Healthcare professionals suggested that education was best delivered within the ongoing relationship between the specialist nurse and patient, in particular during home visits where patients are more relaxed and able to assimilate information.

In support of this some patients reported that they find it easier to communicate with nurses than to cardiologists and it was suggested that the specialist nurse environment was a good place to discuss patients' condition and give information.

This subfinding was based on two studies.[26, 133, 313]

Methodological limitations were rated moderate overall. One study had moderate limitations due to limitations in context, the role of researcher and data analysis. Another study was rated as having moderate limitations due to a lack of context, reflections on the role of the researcher, and data richness in some sections relevant to this review.

Coherence was rated no or very minor concerns. Agreement between papers was very good.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from two studies from the UK in a relevant population.

Adequacy was rated as no or very minor concerns. Although the subfinding was explicitly supported by only two studies, it was illustrated in much detail.

The overall assessment of confidence was high, as the moderate limitations in methodology were offset by the richness of data provided by these two studies.

Review subfinding 4c: Tailoring of information

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Healthcare professionals suggested that information needed to be tailored to the need of the individual as some people are more able and/or willing to hear information than others. Also, people with heart failure tend to be older, more likely to accept what a doctor says and not proactive in asking questions (e.g. some patients may be unwilling to raise questions about prognosis). They may also be more likely to have short-term memory loss, are too ill to benefit from education or are in denial about their condition etc. Consequently, specialist nurses spoke of the necessity to find a balance between the education they offered patients and their capacity to receive it. As a consequence they tried to identify key issues and personalise the information accordingly. This would involve repeating these messages over time.

This subfinding was based on seven studies.[26, 53, 117, 133, 141, 231, 328]

Methodological limitations were rated moderate overall. Four studies were rated moderate limitations: each due to a number of limitations that included some of the following; limitations in context, role of researcher, data analysis, research method rigour, and/or data richness in some sections relevant to this review. Two studies were rated serious limitations due to lack of reflection on researcher role in the study, limited context and data richness, plus lack of reasoning for choice of methods in one study and limitations in data collection for the other. One study was rated very serious limitations due to the limited information on the background and reflection of the researcher, data collection, data richness, relevance of findings and link to conclusions.

Coherence was rated no or very minor concerns. Agreement between papers was very good.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from seven studies from the UK in a relevant population.

Adequacy was rated as no or very minor concerns. The subfinding was explicitly supported by seven studies, and it was illustrated in much detail.

The overall assessment of confidence was high, as the moderate limitations in methodology were offset by the richness of data provided by these seven studies.

Review subfinding 4d: Improving access to information

Patients who wished for more information sought a “better understanding of the disease process, the practical limitations, how to get help and how to cope with living with heart failure” Horne 2004). Some people with heart failure wished to be told openly and sensitively about their (poor) prognosis by clinicians, with some wanting to know more accurately when they would die. As some patients reported not having received written information of their heart failure diagnosis, ensuring that information pamphlets are passed on during consultations is vital so that patients can go through them at home in their own time.

Patients expressed the desire for information regarding both diagnosis and prognosis to be communicated using lay terms.

Family and informal carers wished to be involved in all communications in order to support the patient in their role of family information providers. Carers also asked for more information about what to do in an emergency, how to recognise when signs and symptoms needed urgent attention and how to perform cardiopulmonary resuscitation.

The provision of information on access to a telephone advice line or support group was also suggested.

This subfinding was based on six studies.[8, 26, 141, 148, 231, 370]

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Methodological limitations were rated moderate overall. Four studies were rated as moderate limitations: each due to a number of limitations that included some of the following; limitations in context, role of researcher, data analysis, research methods rigour, and/or data richness in some sections relevant to this review. One study was rated as serious limitations due to study aims, role of the researcher, rigour of research methods, data richness and relevance of findings. One study was rated very serious limitations due to the limited information on the background and reflection of the researcher, data collection, data richness, relevance of findings and link to conclusions.

Coherence was rated minor concerns overall. Although the suggestions for how to improve access to information varied, overall the agreement between papers was good.

Relevance was rated no or very minor concerns. The relevance of the subfinding to the focus of the review was very high. The data stemmed from six studies from the UK in a relevant population.

Adequacy was rated as no or very minor concerns. The findings were supported by a few studies in much detail.

The overall assessment of confidence was moderate, having been downgraded by one increment due to moderate methodological and minor coherence limitations.

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9.4.3.4 Qualitative evidence summary

Table 140: Summary of evidence

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Diagnosis of heart failure 1a. Communication is challenging					
2[26, 133, 313]	Individual interviews with pt + carers and focus groups with HCPs Ethnographic study (in-depth interviews, observation, impromptu interviews, field notes, patient and carer diaries, patient medical records) involving pt and HCPs	Clinicians find the diagnosis itself and the ensuing communication around diagnosis challenging.	Limitations	Moderate concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy	
Diagnosis of heart failure 1b. Timing and setting					
3[26, 117, 313]	Individual interviews with pt + carers and focus groups with HCPs Ethnographic study involving pt and HCPs Open-ended narrative interviews with pt	Choosing the timing and setting of communicating the diagnosis is important.	Limitations	Moderate concerns about methodological limitations	MODERATE
			Coherence	Minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Adequacy	No concerns about adequacy	
Diagnosis of heart failure 1c. Gradual process					
3[26, 133, 207, 313]	Individual interviews with pt + carers and focus groups with HCPs Secondary analysis of interview transcripts of pt. Ethnographic study involving pt and HCPs	The diagnosis itself is seen as a gradual process which results in information and guidance around diagnosis being relayed to patients in a gradual manner.	Limitations	Moderate concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No concerns about adequacy	
Diagnosis of heart failure 1d. Terminology					
6[8, 26, 133, 207, 231, 313, 328]	Semi-structured interviews with pt + carers Individual interviews with pt + carers and focus groups with HCPs Secondary analysis of interview transcripts of pt. In-depth interviews with pt and following bereavement interviews with informal carers	As the term 'heart failure' is seen by healthcare professionals as anxiety-invoking, many make use of euphemisms or even more complex terminology instead which is often confusing for patients.	Limitations	Moderate concerns about methodological limitations	MODERATE
			Coherence	Minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	and FG with professional carers Ethnographic study involving pt and HCPs Semi-structured interviews with pt and their carers			adequacy	
Understanding heart failure 2a. Understanding of diagnosis					
9[8, 26, 53, 117, 133, 141, 207, 231, 328]	Semi-structured interviews with pt + carers Individual interviews with pt + carers and focus groups with HCPs Individual interviews with pt + carer and interviews or FG with HCPs Open-ended narrative interviews with pt Secondary analysis of interview transcripts of pt In-depth interviews with pt and following bereavement interviews with informal carers and FG with professional carers Semi-structured interviews with pt, their carers and HCPs Ethnographic study involving pt and HCPs Semi-structured interviews with	Although there is variability in patients' understanding of their diagnosis it is generally poor.	Limitations	Serious concerns about methodological limitations	LOW
			Coherence	Minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about adequacy	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	pt and their carers				
Understanding heart failure 2b. Knowledge and management					
5[26, 102, 117, 148, 328]	Individual interviews with pt + carers and focus groups with HCPs Individual interviews with pt + carer Open-ended narrative interviews with pt Open semi-structured interviews with pt Semi-structured interviews with pt and their carers	Patients' desire for more knowledge about their condition and its management is highly individual.	Limitations	Serious concerns about methodological limitations	LOW
			Coherence	Minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about adequacy	
Discussion of prognosis 3a. Difficult conversations					
6[26, 53, 133, 141, 207, 231, 302]	Individual interviews with pt + carers and focus groups with HCPs Individual interviews with pt + carer and interviews or FG with HCPs Secondary analysis of interview transcripts of pt In-depth interviews with pt and following bereavement interviews with informal carers	Staff reported difficulties to discuss prognosis and future care options due to the unpredictable disease trajectory, uncertainty whether patients wanted to know and difficulties handling emotional involvement of patients and their families.	Limitations	Serious concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	and FG with professional carers Semi-structured interviews with pt, their carers and HCPs Ethnographic study involving pt and HCPs			adequacy	
Discussion of prognosis 3b. Understanding of prognosis					
5[8, 26, 53, 207, 231]	Semi-structured interviews with pt + carers Individual interviews with pt + carers and focus groups with HCPs Individual interviews with pt + carer and interviews or FG with HCPs Secondary analysis of interview transcripts of pt In-depth interviews with pt and following bereavement interviews with informal carers and FG with professional carers	Patients described that prognosis was rarely discussed and showed that their understanding of their prognosis was generally poor.	Limitations	Moderate concerns about methodological limitations	MODERATE
			Coherence	Minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about adequacy	
Discussion of prognosis 3c. Patients' concerns					
7[8, 26, 53, 117, 133, 148, 370]	Semi-structured interviews with pt + carers Individual interviews with pt + carers and focus groups with	Whilst patients' desire for more knowledge about their prognosis was highly individual many were worried by the uncertainty of what the future holds.	Limitations	Moderate concerns about methodological limitations	MODERATE
			Coherence	Minor concerns about	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	HCPs Individual interviews with pt + carer and interviews or FG with HCPs Open-ended narrative interviews with pt Open semi-structured interviews with pt Ethnographic study involving pt and HCPs Semi-structured interviews and one FG with carers of pt and the person they cared for			coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about adequacy	
Improving communication/ information flow 4a. Education and joint working					
2[26, 141]	Individual interviews with pt + carers and focus groups with HCPs Semi-structured interviews with pt, their carers and HCPs	Staff identified training needs regarding diagnosing and prognosticating heart failure and mutual education for staff of different specialities that would improve the communication with the patient and family.	Limitations	Serious concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about adequacy	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Improving communication/ information flow 4b. Ongoing relationship					
2[26, 133, 313]	Individual interviews with pt + carers and focus groups with HCPs Ethnographic study involving pt and HCPs	Staff suggested for information and education to be delivered within an ongoing relationship with the patient in an appropriate setting.	Limitations	Moderate concerns about methodological limitations	HIGH
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about adequacy	
Improving communication/ information flow 4c. Tailoring of information					
7[26, 53, 117, 133, 141, 231, 328]	Individual interviews with pt + carers and focus groups with HCPs Individual interviews with pt + carer and interviews or FG with HCPs Open-ended narrative interviews with pt In-depth interviews with pt and following bereavement interviews with informal carers	The variability in patients' ability and willingness to receive information regarding their condition requires staff to tailor the information to the needs of the individual.	Limitations	Moderate concerns about methodological limitations	HIGH
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	and FG with professional carers Semi-structured interviews with pt, their carers and HCPs Ethnographic study involving pt and HCPs Semi-structured interviews with pt and their carers			adequacy	
Improving communication/ information flow 4d. Improving access to information					
6[8, 26, 141, 148, 231, 370]	Semi-structured interviews with pt + carers Individual interviews with pt + carers and focus groups with HCPs Open semi-structured interviews with pt In-depth interviews with pt and following bereavement interviews with informal carers and FG with professional carers Semi-structured interviews with pt, their carers and HCPs Semi-structured interviews and one FG with carers of pt and the person they cared for	Patients desire more detail, written information and greater access to support.	Limitations	Moderate concerns about methodological limitations	MODERATE
			Coherence	Minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No or very minor concerns about adequacy	

Abbreviations: pt = people with chronic heart failure, HCP = healthcare professional, FG = focus group

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9.4.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix D.

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9.4.5 Evidence statements

Qualitative

See the narrative summaries of review findings in section 9.4.3.3.1.

Economic

- No relevant economic evaluations were identified.

9.4.6 Recommendations and link to evidence

Recommendations	**When giving information to people with heart failure, follow the recommendations in the NICE guideline on patient experience in adult NHS services. [2018]** **Discuss the person's prognosis in a sensitive, open and honest manner. Be frank about the uncertainty in predicting the course of their heart failure. Revisit this discussion as the person's condition evolves. [2018]** **Provide information whenever needed throughout the person's care. [2018]** **Consider training in advanced communication skills for all healthcare professionals working with people who have heart failure. [2018]** **<u>First consultations for people newly diagnosed with heart failure</u>** **The specialist heart failure MDT should offer people newly diagnosed with heart failure an extended first consultation, followed by a second consultation, to take place within 2 weeks if possible. At each consultation:** • **discuss the person's diagnosis and prognosis** • **explain heart failure terminology** • **discuss treatments** • **address the risk of sudden death, including any misconceptions about that risk** • **encourage the person and their family or carers to ask any questions they have. [2018]**
Findings identified in the evidence synthesis	The evidence from the review was grouped into four findings, each of which contained multiple sub-findings. These key findings are summarised below. Diagnosis of heart failure: the evidence suggested that clinicians find the diagnosis itself and the ensuing communication around diagnosis challenging. The timing of and setting in which the diagnosis is communicated is important, taking care to avoid busy environments that do not foster the sensitive relay of information. The diagnosis itself was seen as a gradual process allowing the information and guidance around diagnosis to be passed on to patients in a manageable way. The evidence suggested that the term 'heart failure' was regarded by healthcare professionals as anxiety-invoking, with many health care providers making use of euphemisms or even more complex terminology instead. These alternative explanations

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	often led to a poorer understanding, confusion for people with heart failure and a lack of interest in their diagnosis as a consequence. Understanding heart failure: it was found that although there is variability in patients' understanding of their diagnosis; it is generally poor and often misunderstood by people. Many did not connect symptoms they had to their heart failure; and showed poor knowledge of treatments, their importance, side effects and limitations. The lack of understanding was often compounded by confusion and short-term memory loss that is associated with heart failure. Patients' desire for more knowledge about their condition and its management is highly individual. Some patients did not want to know more about their diagnosis as it would cause them to worry. Yet, others described that having received too little or conflicting information about their diagnosis caused them anxiety. Some people were proactive in seeking information themselves and knew how to manage their condition. Discussion of prognosis: staff reported difficulties in discussing prognosis and future care options due to the unpredictable disease trajectory, uncertainty about whether patients wanted to know their prognosis, and the challenge of handling the emotional response of patients and their families. Some healthcare professionals also found it challenging to balance the need to be honest with the patient about their condition (which could raise anxiety) with building trust and the desire to maintain hope and a positive outlook for patients faced with a life-limiting illness. Patients identified that prognosis was rarely discussed and the evidence showed that their understanding of their prognosis was generally poor. Patients' desire for more knowledge about their prognosis was highly individual, whilst some preferred not to know more, many were worried by the uncertainty of what the future held. Improving communication/information flow: staff identified training and education needs regarding diagnosing and prognosticating heart failure to improve communication with the patient and family. Staff commented that single consultant appointments are too short to relay all the information a patient would need regarding diagnosis and prognosis. It was suggested that information and education be delivered within the context of a relationship of trust and continuity between the patient and the health care professional, and in an appropriate setting. Healthcare professionals identified the variability in patients' ability and willingness to receive information about their condition requires staff to tailor the information to the needs of the individual. Many patients desire more detail, preferably in lay terms, written information and greater access to support. Family and informal carers wished to be involved in all communications.
Quality of the evidence	The confidence ratings for the different sub-findings in the review were varied, ranging from high to low. The members weighed the confidence in the individual findings with their own experiences, and agreed that they were broadly consistent. Diagnosis of heart failure: All 4 sub-findings within this finding, namely communication is challenging, timing and setting, gradual process and terminology, were rated as moderate confidence. This was mainly due to methodology concerns, as well as minor coherence limitations in a 2 findings

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	and minor adequacy limitations in 1 sub-finding. Understanding heart failure: Both sub-findings within this finding, understanding of diagnosis and knowledge and management, were rated as low confidence having, in both instances, been downgraded by 2 increments due to concerns over methodology and coherence. Discussion of prognosis: All 3 sub-findings within this finding, namely difficult conversations, understanding of prognosis, and patients' concerns, were rated as moderate confidence. This was mainly due to limitations in methodology, as well as minor coherence limitations for the last 2 sub-findings. Improving communication/information flow: Two sub-findings (education and joint working and improving access to information) were rated as moderate confidence having been downgraded mainly due to serious methodological limitations. The other 2 sub-findings within this finding, ongoing relationship and tailoring of information, were rated as high confidence as the moderate methodological concerns were offset by the data richness provided by the studies.
Trade-off between benefits and harms	The committee agreed that the findings and sub-findings identified in the review resonated with their own experiences as healthcare professionals or patients within heart failure services in the NHS. The committee acknowledged that some of the sub-findings identified in the review reflect general issues around communication and information needs in health care and are addressed by recommendations in the patient experience guideline CG138. The committee identified several key recommendations in that guideline which, if implemented in heart failure services, would go some way towards addressing the issues identified in the review. Highly pertinent recommendations from CG138 include 'allow adequate time so that discussions do not feel rushed' (1.3.4.), 'clarify with the patient at the first point of contact whether and how they would like their partner, family members and/or carers to be involved in key decisions' (1.3.10), 'avoid the use of jargon and define unfamiliar words' (1.5.6), provide 'both oral and written information' (1.5.12), and to 'give the patient the opportunity to discuss their diagnosis, prognosis and treatment options' (1.5.21). The committee agreed that there was no need to replicate these recommendations in this guideline and instead decided to cross refer to the patient experience guideline. The committee decided to focus on the issues raised that are specific to the communication of the diagnosis and prognosis of heart failure. In line with the review findings, the committee was unanimous that a single consultation was too short to explain the diagnosis to the patient and the amount of information that would have to be relayed could be overwhelming. This echoed the general recommendation in the patient experience guideline to allow adequate time so that discussions do not feel rushed (section 1.3). Building on this, the committee recommended an extended first consultation followed by a prompt (usually within 2 weeks) follow-up appointment with any member of the specialist multidisciplinary team. The committee considered a 2 week gap between the first and second appointment as reasonable and reflected usual practice whilst acknowledging this may not always be possible or appropriate in all situations. To foster continuity of care and building of the future ongoing

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relationship, the committee recommended that the patient would be told who they would see at their next consultation (a member of the specialist heart failure multidisciplinary team) and explained what they can expect to happen.

The committee also discussed the importance of having family members/carers involved in communication from an early stage as receiving bad news in the form of the diagnosis of heart failure can be overwhelming for the patient. Carers may also be better able to take on board information provided regarding ongoing care and management than the patient who has just been given a diagnosis. Additionally, family members and carers often struggle with how best to help when the patient has conveyed information poorly or partially to them. For this reason, the inclusion of a family member or carer in one or more consultations will improve the understanding of the condition and the potential support provided to the patient. The committee acknowledged that this was covered by the patient experience guideline (particularly section 1.3) and agreed to include a cross reference to that guidance in their recommendations.

It was agreed that the following points should be communicated to the patient in the first 2 appointments with the heart failure MDT:

- Diagnosis.
- Explanation of the terminology.
- Symptoms of heart failure and the meaning of proscriptions (for example, dietary, physical activities).
- Available treatments, their effects and side effects.
- Prognosis.
- Mention exacerbations and risk of sudden death.

The cardiologists on the committee described that they often have to dispel misconceived ideas at the first consultation with a newly diagnosed patient. This may be the result of misunderstandings occurring when patients are referred for specialist investigation of heart failure symptoms. The committee was also aware of a lack of public awareness of heart failure as a medical condition that contributed to this.

The committee did not support the use of euphemisms and suggested that health care professionals use the term ‘heart failure’ in an open and honest manner with the patient, explaining its meaning in detail, dispelling any myths or other fears induced by the language, and providing a balanced picture of the condition. The committee discussed that imagery used to describe heart failure by some healthcare professionals can be received poorly by patients. To avoid confusion for patients it was suggested that healthcare professionals could practice some phrases to explain the condition before seeing the patient.

The committee acknowledged that discussion of prognosis should be a gradual process and may not necessarily be discussed in the first consultation as it is highly difficult to predict, particularly in the early stages of the condition. The prognosis needs to be discussed in a sensitive, open and honest manner, ensuring that the unpredictability of the prognosis and any uncertainty regarding life expectancy is conveyed. The positive effects of treatments available should also be discussed. The group acknowledged the difficulty patients may have coming to terms with information around their

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	own prognosis which highlights the importance of an immediate follow-up consultation and the engagement of family/carers (where the patient consents to their presence). This consultation provides reinforcement of the key implications of the diagnosis and prognosis and, especially where a family member or carer is present, clarification of any misperceptions. To facilitate a quick rapport with the patient and to tailor information to the patient's needs (in line with the recommendations of the patient experience guideline), the consultant committee members suggested including any preferences the patient had, regarding the level and type of information they want to be given, into the referral form from primary care. Another suggestion was for patients to complete a simple questionnaire before the first appointment identifying key areas they would like to discuss during the consultation. The committee acknowledged that the communication of these challenging issues requires specific skills that not all healthcare professionals have, and supported the provision of training in advanced communication skills to all heart failure staff. Specific information on heart failure issues could be incorporated into broader communication training for chronic or life-limiting conditions. The importance of consistency was discussed. It was agreed that the patient should receive consistent information from all MDT members. The committee recognised that this was closely linked to the separate evidence review on 'Transition between heart failure care settings' and the recommendations developed out of that review. The need for printed leaflets on heart failure to be available within the NHS was unanimously agreed by the committee as patients value the provision of information that they can take away with them to read and absorb in their own time. The committee also acknowledged that patients need to be directed to reliable sources of information outside the NHS – for example, British Heart Foundation, Pumping Marvellous, Cardiomyopathy UK.
Trade-off between net effects and costs	No previously published economic evaluations were identified for this question. The committee considered that overall the recommendations made above in conjunction with the patient experience guideline would improve patient satisfaction and help reduce anxiety about their condition and as a result lead to an improvement in quality of life. The majority of the recommendations made above will not incur any cost as they simply specify what information should be given to patients and the manner in which it should be delivered. However, the committee acknowledged that a couple of the recommendations could have cost implications. Firstly, an extended first consultation will incur an additional cost due to the required extra time from the clinician to fully explain the person's diagnosis and prognosis. However, the committee considered that a standard consultation appointment is unlikely to be long enough to allow sufficient time to explain the diagnosis and prognosis as recommended in the patient experience guideline and thought this was necessary for good clinical practice. Furthermore, this type of recommendation is endorsed by the patient experience guideline which specifies that when discussing patient views and preferences that adequate time should be allowed so that

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	discussion does not seemed rushed. In many centres, extended consultations are likely to already be occurring. The committee also acknowledged that further communication training would incur a cost. The committee were aware of training for other chronic conditions that could also be extended to heart failure specialists. Furthermore, such training is likely be undertaken in a group setting to minimise cost, or alternatively could be provided through e-learning, or at medical school in future. The committee acknowledged that the benefits of improved communication training would be advantageous across the entire treatment pathway for chronic heart failure patients as well as other conditions outside of heart failure, and therefore overall, the long-term cost effectiveness of training in effective communication is likely to be negligible.
Other considerations	The committee acknowledged 'The Second Conversation Project' which was currently piloting an educational intervention, to enable junior doctors to build their skills and confidence in navigating end of life discussions which they agreed would provide insight into the benefit of this type of training and may be extrapolated to the heart failure population.

9.5 Recommendations

9.5.1 Multi-disciplinary teams

71. The core specialist heart failure multidisciplinary team (MDT) should work in collaboration with the primary care team, and should include:

- **a lead physician with a subspecialty interest in heart failure (usually a consultant cardiologist) who is responsible for making the clinical diagnosis**
- **a specialist heart failure nurse**
- **a healthcare professional with expertise in specialist prescribing for heart failure.**

[2018]

72. The specialist heart failure MDT should directly involve, or refer people to, other services, including rehabilitation services, and tertiary and palliative care, as needed. [2018]

73. The specialist heart failure MDT should:

- **diagnose heart failure**
- **give information to people newly diagnosed with heart failure (see section 9.4.6)**
- **manage newly diagnosed, recently decompensated or advanced heart failure (NYHA [New York Heart Association] class III to IV) heart failure**
- **optimise treatment**
- **start new medicines that need specialist supervision**
- **continue to manage care after an interventional procedure such as implantation of a cardioverter defibrillator or cardiac resynchronisation device**
- **manage heart failure that is not responding to treatment. [2018]**

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9.5.2 Transition between heart failure care settings

74. The primary care team should carry out the following for people with heart failure at all times, including periods when the person is also receiving specialist heart failure from the MDT:

- **ensure effective communication links between different care settings and clinical services involved in the person's care**
- **lead a full review of the person's heart failure care, which may form part of a long-term conditions review**
- **recall the person at least every 6 months and update the summary and clinical record**
- **ensure that changes to the clinical record are understood and agreed by the person with heart failure and shared with the specialist heart failure MDT**
- **arrange access to specialist heart failure services if needed. [2018]**

9.5.2.1 Care after an acute event

For recommendations on the diagnosis and management of acute heart failure see NICE's guideline on acute heart failure.

75. People with heart failure should generally be discharged from hospital only when their clinical condition is stable and the management plan is optimised. Timing of discharge should take into account the wishes of the person and their family or carer, and the level of care and support that can be provided in the community. [2003]

76. The primary care team working within the specialist heart failure MDT should take over routine management of heart failure as soon as it has been stabilised and its management optimised. [2018]

9.5.2.2 Writing a care plan

77. The specialist heart failure MDT should write a summary for each person with heart failure that includes:

- **diagnosis and aetiology**
- **medicines prescribed, monitoring of medicines, when medicines should be reviewed and any support the person needs to take the medicines**
- **functional abilities and any social care needs**
- **social circumstances, including carers' needs. [2018]**

78. The summary should form the basis of a care plan for each person, which should include.

- **plans for managing the person's heart failure, including follow-up care, rehabilitation and access to social care**
- **symptoms to look out for in case of deterioration**
- **a process for any subsequent access to the specialist heart failure MDT if needed**
- **contact details for:**
  - **a named healthcare coordinator (usually a specialist heart failure nurse)**
  - **local heart failure specialist care providers, for urgent care or review**
- **additional sources of information for people with heart failure. [2018]**

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79. Give a copy of the care plan to the person with heart failure, ther family or carer if appropriate, and all health and social care professionals involved in their care. [2018]

9.5.3 Information and support needs regarding diagnosis and prognosis

80. When giving information to people with heart failure, follow the recommendations in the NICE guideline on patient experience in adult NHS services. [2018]

81. Discuss the person's prognosis in a sensitive, open and honest manner. Be frank about the uncertainty in predicting the course of their heart failure. Revisit this discussion as the person's condition evolves. [2018]

82. Provide information whenever needed throughout the person's care. [2018]

83. Consider training in advanced communication skills for all healthcare professionals working with people who have heart failure. [2018]

9.5.3.1 First consultations for people newly diagnosed with heart failure

84. The specialist heart failure MDT should offer people newly diagnosed with heart failure an extended first consultation, followed by a second consultation, to take place within 2 weeks if possible. At each consultation:

- **discuss the person's diagnosis and prognosis**
- **explain heart failure terminology**
- **discuss treatments**
- **address the risk of sudden death, including any misconceptions about that risk**
- **encourage the person and their family or carers to ask any questions they have. [2018]**

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10 Advanced heart failure and palliative care

The update to the heart failure guideline includes topics where new evidence has emerged since the publication in 2010. A review of new evidence published after 2010 was carried out in order to determine whether any changes to current recommendations where likely to be required. The decision on which topics to include in the update of the guideline was made following consultation of the scope.

In this section new evidence was reviewed on the use of diuretics, domiciliary oxygen therapy and criteria for discussing ICD deactivation in patients with advanced heart failure, and the use of validated risk tools to identlfy patients with an increased risk of mortality.

10.1 Diuretics in advanced heart failure

10.1.1 Introduction

The use of diuretics is undoubtedly helpful in cases of systemic fluid overload or pulmonary congestion, and remain the only group of medication where there is consensus about its benefit in relieving the breathlessness in patients who have heart failure with preserved left ventricular ejection fraction (HFPEF).

An important question arises in patients with advanced heart failure receiving palliative care in the community, is which route of administration of diuretics is most clinically and cost effective?

10.1.2 Review question: Which route of administration of diuretics (intravenous (IV), subcutaneous or oral) is most clinically and cost effective in people with advanced heart failure who are in the community, including patients receiving palliative care?

For full details see review protocol in appendix A.

Table 141: PICO characteristics of review question

Population	Advanced heart failure in the community
Interventions / comparators	• IV diuretics (furosemide or torsemide) (continuous or bolus) + oral metolazone/thiazides • IV diuretics (furosemide or torsemide) (continuous or bolus) alone • Subcutaneous diuretics (furosemide or torsemide) +/- oral metolazone/thiazides • Oral diuretics (bumetanide or furosomide and/or metolazone/thiazides). All compared to each other Thiazides are limited to: • Bendroflumethiazide (Bendrofluazide) • Cyclopenthiazide • Chlorthalidone / Chlortalidone • Indapamide • Xipamide • Metolazone
Outcomes	CRITICAL • Quality of life • Unplanned hospitalization

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	IMPORTANT • Change in dyspnoea • Weight change / change in oedema • Change in NYHA class • Patient and carer satisfaction • Time to death (survival) • Successful administration of intervention
Study design	Systematic Review RCT

10.1.3 Clinical evidence

A search was conducted for randomised trials and systematic reviews of randomised trials comparing the effectiveness of different modes of administration of diuretics in people with advanced heart failure in the community. No relevant studies were identified. See appendix I for the excluded studies table.

10.1.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix D.

10.1.5 Evidence statements

Clinical

No relevant published evidence was identified.

Economic

- No relevant economic evaluations were identified.

10.1.6 Recommendations and link to evidence

Recommendations	**No recommendation**
Research recommendation	• **In people with advanced heart failure and significant peripheral fluid overload, what is the clinical and cost effectiveness of oral, subcutaneous and intravenous diuretic therapy in the community?**
Relative values of different outcomes	The committee agreed that the outcomes critical for decision making were quality of life, unplanned hospitalisations (count rate) and unplanned hospitalisations (number of bed days), while the outcomes change in dyspnoea, weight change/change in oedema, change in NYHA class, patient and carer satisfaction, time to death or survival and successful administration of the intervention were important for decision making.
Quality of the clinical evidence	No clinical evidence was identified for inclusion within the review.

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Recommendations	No recommendation
Research recommendation	• **In people with advanced heart failure and significant peripheral fluid overload, what is the clinical and cost effectiveness of oral, subcutaneous and intravenous diuretic therapy in the community?**
Trade-off between clinical benefits and harms	As no randomised controlled studies were found that addressed the review question, the committee was not able to make a recommendation on the clinical effectiveness of IV and oral diuretics delivered in the community. The committee decided to make a research recommendation to establish the added value of IV or subcutaneous diuretics (in terms of its clinical and cost effectiveness) in the management of advanced heart failure, for the reasons discussed below.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified. Unit costs were not presented for this review due to the lack of clinical evidence available for the committee to make a judgement of cost effectiveness of the routes of administration of diuretics. However, the committee noted that delivering diuretics subcutaneously and intravenously would incur a higher cost to the NHS compared to administering oral diuretics due to the additional equipment and staff costs of delivery.. The committee agreed that due to the greater cost of subcutaneous and IV diuretics therapy compared to oral diuretics, it was important that an assessment of the cost effectiveness of these different administration routes was included in the research recommendation.
Other considerations	The committee considered the use of IV and subcutaneous diuretics in people with advanced chronic heart failure to be an area of high priority for future research. The committee highlighted that the delivery of these treatments in the community was variable across the country and was dependant on whether or not commissioning for the service was in place. The committee noted that for many advanced heart failure patients, some of whom may be approaching the end of their life, the focus of treatment may shift to symptom relief, admission avoidance, maintaining quality of life and minimising discomfort. These patients may become less responsive to conventional oral doses of loop diuretics and resistance can occur. The committee discussed whether subcutaneous diuretics may be more effective than oral diuretics but this route requires delivery by healthcare professionals. Likewise, IV diuretics could prove to be more effective than oral and subcutaneous diuretics in managing symptoms, but they are invasive, may not be feasible or appropriate in people in the later stages of heart failure. For those reasons, the committee decided to make a research recommendation to establish the added value of IV or subcutaneous diuretics (in terms of its clinical and cost effectiveness) in people with advanced heart failure, with significant peripheral fluid overload, in the community. The committee acknowledged the BHF funded pilot study (http://www.shfnf.co.uk/wp-content/uploads/2014/10/Final-Evaluation-Report-IV-Diuretics-August-2014.pdf) which consisted of a 2 year project in 10 NHS organisations across the UK in both urban and rural areas to assess

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Recommendations	**No recommendation**
Research recommendation	• **In people with advanced heart failure and significant peripheral fluid overload, what is the clinical and cost effectiveness of oral, subcutaneous and intravenous diuretic therapy in the community?**
	whether funding a home or community based IV diuretics service was safe, clinically effective, cost effective and well received by patients and carers. The committee noted that this study was not randomised and therefore did not meet the methodological threshold for inclusion within this review.

10.2 Domiciliary oxygen therapy in people with advanced heart failure

10.2.1 Introduction

Breathlessness is a common symptom in advanced heart failure even with optimal pharmacological and non –pharmacological treatments and the absence of clinical pulmonary oedema. Current British Thoracic Society guidelines (2015)[142] for home oxygen state that only hypoxaemic patients with PO2 below 7.3kpa or 8 (with peripheral oedema, polycythaemia or pulmonary hypertension) should receive any form of home oxygen therapy except for a specific group with sleep disordered breathing. They specifically state that palliative oxygen therapy should not be provided to non hypoxaemic or mildly hypoxaemic patients. However, the evidence base for these recommendations was limited.. Therefore an up-to date review of the literature in this area is warranted.

10.2.2 Review question: What is the effectiveness of domiciliary oxygen therapy in people with advanced heart failure

For full details see review protocol in appendix A.

Table 142: PICO characteristics of review question

Review population	Adults (aged 18 years and over) with advanced heart failure (whether living in a care home (community residential facility), at home or in a hospice). These patients may be approaching the end of their life and may be receiving other palliative care services. Trials of patients with heart failure and other co-morbidities such as sleep apnoea and COPD will be included (however, see exclusions).

Interventions/comparators	• Domiciliary oxygen therapy (repeated long term use (daily availability))
	• No oxygen therapy
	  ○ Medical air
	  ○ Handheld fan
	  ○ No treatment
	
	Different doses of oxygen will be pooled in the analysis.

Outcomes	CRITICIAL • Quality of life at 2 weeks (Continuous) • Change in breathlessness at 2 weeks (Continuous) • Unplanned hospitalization at 4 weeks (Count rate) • Unplanned hospitalization at 4 weeks (number of bed days) • Patient and carer satisfaction 2 weeks (Continuous)

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	IMPORTANT • Change in exercise capacity at 2 weeks (Continuous) • Change in NYHA class at 2 weeks (Continuous) Shorter term time points will also be extracted if reported in the studies but may be downgraded for indirectness in consultation with the GC.
Study design	Systematic Review RCT

10.2.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of domiciliary oxygen therapy versus no oxygen therapy or usual care as treatment for the symptoms (particularly breathlessness) of advanced heart failure.

One study was included in the review[63] which is summarised in Table 143 below. The study was a HTA report which was stopped early due to poor adherence to the prescribed oxygen therapy in the intervention arm of the trial. Evidence from this study is summarised in the clinical evidence summary below (Table 144). See also the study selection flow chart in appendix C, forest plots in appendix E, study evidence tables in appendix F, GRADE tables in appendix H and excluded studies list in appendix I.

The study originally included a third arm which comprised nocturnal oxygen therapy (assumed to be 8 hours per night). This arm of the trial was dropped before trial completion due to problems with both centre and patient recruitment. The study authors reported data for this arm of the trial for several outcomes including quality of life. The study authors conducted an exploratory analysis, including all 3 treatment arms and found no significant difference between the nocturnal therapy (NOT) and long term oxygen therapy (LTOT) arms, therefore the authors combined these arms and compared them against the best medical therapy (BMT) arm for participants recruited up until 30 April 2013. To avoid double counting and maximise the number of participants analysed in either arm we have not included this comparison and included only the data reported for LTOT versus BMT at 3 months for this outcome.

Table 143: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Clark 2015[63]	Intervention 1: Long term oxygen therapy (LTOT) prescribed for 15 hours per day including overnight hours. Intervention 2: Nocturnal oxygen therapy (NOT) (assumed to be 8 hours per night) Comparator: Best medical therapy (BMT) which consisted of	n=114 Participants with severe heart failure with NYHA class III or IV left ventricular systolic dysfunction receiving optimal medical therapy who were stable but severely symptomatic Age (mean (SD)):	• Quality of life (MLWHF) at 3 months • Quality of life (EQ-5D-3L) at 6 months • Hospitalisation at 24 months • NRS for breathlessness at 3 months • 6 minute walk test at 6 months	• Outcomes were downgraded for indirectness due to the long follow up period

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Study	Intervention and comparison	Population	Outcomes	Comments
	maximally tolerated medical management and target doses of a renin-angiotensin system inhibitor, a beta-adrenoceptor antagonist and an aldosterone antagonist	72.3 (11.3) Gender (M/F): 80/34 Ethnicity not reported UK		

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Table 144: Clinical evidence summary: long term oxygen therapy versus best medical therapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Best medical therapy	Risk difference with Long term oxygen therapy (95% CI)
Quality of life (MLWHF)	106 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision		The mean quality of life (MLWHF) in the control groups was 52	The mean quality of life (MLWHF) in the intervention groups was 5.5 lower (10.49 to 0.51 lower)
Quality of life (EQ-5D-3L)	88 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness		The mean quality of life (EQ-5D-3L) in the control groups was 0.54	The mean quality of life (EQ-5D-3L) in the intervention groups was 0.01 higher (0.1 lower to 0.12 higher)
Hospitalisation	114 (1 study) 24 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Rate ratio 0.85 (0.54 to 1.33)	360 events per 1000 person-years	54 fewer events per 1000 person-years (from 165 fewer to 119 more)
NRS for breathlessness (Scale from: 0 to 10)	88 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision		[d]	The mean NRS for breathlessness in the intervention group was 0.63 lower (1.57 lower to 0.31 higher)
6 minute walk test	74 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness		[d]	The mean 6 minute walk test in the intervention group was 0.64 metres higher (34.54 lower to 35.82 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) The majority of the evidence was from studies with follow up periods longer than stated by the review protocol.
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(d) Unable to calculate as the study reported the result as a mean difference.

10.2.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix D.

10.2.5 Evidence statements

Clinical

One study including 114 people with severe heart failure was identified for inclusion within the review. The evidence compared long term oxygen therapy (prescribed for 15 hours per day) with best medical therapy (consisting of maximally tolerated medical management and target doses of a renin-angiotensin system inhibitor, a beta-adrenoceptor antagonist and an aldosterone antagonist). The evidence from this study was very low quality due to a risk of bias, imprecision due to wide confidence intervals and indirectness of the outcomes due to the long follow up period. The study was terminated early. No clinical effect was observed for the outcomes quality of life, breathlessness and the 6 minute walk test. A clinically important reduction in hospitalisations was observed. No evidence was found for the outcomes patient and carer satisfaction, change in NYHA class and unplanned hospitalisation (number of bed days).

Economic

- No relevant economic evaluations were identified.

10.2.6 Recommendations and link to evidence

Recommendations	**Do not offer long-term home oxygen therapy for advanced heart failure. Be aware that long-term home oxygen therapy may be offered for comorbidities, such as for some people with chronic obstructive pulmonary disease (see section 1.2.5 on oxygen in the NICE guidline on chronic obstructive pulmonary disease in over 16s. [2018]**
Relative values of different outcomes	The committee agreed that the outcomes critical for decision making were quality of life, change in breathlessness, unplanned hospitalisation (both number of bed days and number of events) and patient and/or carer satisfaction. The important outcomes for decision making were change in exercise capacity and change in NYHA class.
Quality of the clinical evidence	One study was included in the review. The quality of the evidence was very low. This was due to a high risk of bias resulting from a lack of blinding and incomplete outcome data for a number of the reported outcomes. All of the outcomes were also downgraded due to the indirectness of the follow-up period. The committee originally specified short follow-up points for the outcomes of interest as they felt these would be the most appropriate for a population consisting of people with advanced heart failure who may be receiving palliative care. The included evidence reported follow-up periods of 3 months as a minimum. The committee discussed that this indicated the study population may not have been representative of people with advanced disease. The study also reported some results for a third arm nocturnal oxygen therapy (NOT) which was discontinued early due to issues with trial funding. The committee agreed that due to this early discontinuation and the

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	selective nature of the outcome reporting on this arm of the trial, the data reported for this arm would not be analysed.
Trade-off between clinical benefits and harms	In people with severe heart failure, domiciliary oxygen prescribed for up to 15 hours per day was associated with no clinically important effect on quality of life, breathlessness or the 6 minute walk test. A clinically important benefit (also consistent with clinical harm due to wide confidence intervals) was observed with regard to the number of hospitalisations. The committee discussed the risks and harms associated with oxygen therapy, which included the potential of significant anxiety for the patient caused by the noisy and imposing equipment involved. The potential risk of combustion for people in unsatisfactory living conditions was also acknowledged, that is, people who smoke or live with others who smoke The committee also discussed the possibility of high oxygen levels to further damage heart tissue as a potential harm of oxygen therapy.The committee agreed that the provision of oxygen should be based on a holistic needs assessment and would be very specific to each individual. Oxygen therapy would not be withheld from a person where a potential benefit was identified or where significant relief of breathlessness had been observed, however, the routine prescription of oxygen was not necessary for people with advanced heart failure.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified for this review. The committee agreed that domiciliary oxygen therapy is likely to be expensive as it requires regular visits to deliver new tanks of oxygen and associated equipment, as well as safe installation, risk assessment and maintenance of the oxygen. In addition, people on oxygen therapy should be regularly reviewed to assess their oxygen levels. The clinical evidence suggested there was no clinically important effect on quality of life, although this was highly uncertain. Due to the poor quality of the clinical evidence the committee could not assess the cost effectiveness of domiciliary oxygen therapy in people with advanced heart failure. However, due to the potentially high cost, and the known risks of oxygen therapy (described in the 'trade-off between clinical benefits and harms' above) the committee decided that long term oxygen therapy should not be routinely offered to people with advanced heart failure. Current practice is thought to be widely variable, but is not commonly used as part of routine care in people with heart failure. The committee considered that this recommendation would not substantially change current practice, but could lead to some small cost savings.
Other considerations	The committee felt that it was important to be aware that people with advanced heart failure with other comorbid conditions may benefit from oxygen therapy. Examples where this may be the case include chronic lung disease such as COPD (https://www.nice.org.uk/guidance/cg101), or patients with pneumonia or pulmonary embolism. In addition to this, people who are in the last weeks of life may find oxygen therapy of symptomatic benefit and comfort and should be referred to the care of the dying adult guideline (https://www.nice.org.uk/guidance/ng31). The committee also discussed the recently published British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings (https://www.brit-thoracic.org.uk/document-library/clinical-information/oxygen/2017-emergency-oxygen-guideline/bts-guideline-for-oxygen-use-in-adults-in-healthcare-and-emergency-settings/) which states that people should only be prescribed oxygen in palliative care when arterial oxygen saturation is

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	less than 90% or where people report significant relief of breathlessness from oxygen. The committee acknowledged that this guideline was not specifically formulated for people with advanced heart failure but agreed with the approach nonetheless. The committee also acknowledged the British Thoracic Society Guidelines for Home Oxygen use in adults which state that people with advanced heart failure should be offered long term oxygen therapy if they have a resting $Pa0_2$ ≤7.3 kPa or ≤8 kPa in the presence of peripheral oedema, polycythaemia (haematocrit ≥55%) or evidence of pulmonary hypertension on ECG or echocardiography. Where symptomatic hypoxaemia was identified with unknown cause, this would need to be investigated by the appropriate specialist in order that a root cause can be identified and treatment tailored appropriately. With regard to the evidence included within review, the committee acknowledged that the discontinuation of the trial due to poor adherence was suggestive that the trial population were not receiving any significant benefit from oxygen therapy to justify them adhering to the intervention.

10.3 Discussing Implantable Cardioverter Defibrillatior (ICD) deactivation

10.3.1 Introduction

An increasing number of people are undergoing an implantable Cardioverter Defibrillator (ICD) implantation, with or without Cardiac Resynchronisation Therapy (RCT). With the advent of ICDs the risk of sudden cardiac death has been reduced. However, maintaining these activities becomes undesirable towards the end stage of chronic heart failure when the patient's survival ceases to be the prime aim of treatment, and the target of therapy increasingly becomes the palliation of the symptoms. The point maybe reached when the potential benefits of an ICD are likely to be outweighed by their disadvantages.

To deactivate the ICD is a major decision that ought to be taken after consideration of all major factors involved and in an open, informed, and inclusive manner. The timing of such a decision is a complex matter related to difficulties faced by health-care professionals in trying to determine where the patient is on the trajectory of chronic heart failure. Although a number of charities and professional bodies have written policies around the optimal timing of these discussions there is no consensus in clinical practice. Diverse views have also been expressed by people with heart failure and their families or carers about the implications of deactivation of ICDs. This diversity of views is further compounded by the different healthcare professionals involved and the different potential settings in which discussions can occur.

This question looked to find evidence from the published literature as to what were the issues in this field and how these findings could be used to guide discussions about the timing of deactivation of defibrillators.

10.3.2 Review question: What criteria should determine when to discuss defibrillator deactivation?

For full details see review protocol in appendix A.

Table 145: Characteristics of review question

Objective	To understand the views of patients, family, carers and healthcare staff regarding the timing of discussions about the deactivation of ICDs.

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Population and setting	Patients with heart failure in a primary care, outpatient or community setting.
Context	Any description of patient, family, carer or healthcare staff experiences or preferences relating to the timing of discussions regarding the deactivation of an ICD.
Review strategy	Synthesis of qualitative research. Results presented in narrative format. Quality of the evidence will be assessed by a GRADE CerQual approach for each review finding.

10.3.3 Qualitative evidence

10.3.3.1 Methods

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual[236]. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

10.3.3.2 Summary of included studies

Thirteen qualitative studies were included in the review;[51, #3281, #3285, #3309, #3305, #3306, #3303, #3319, #3286, #3318, #3301, #3299, #3289] these are summarised in Table 146 below. Key findings from these studies are summarised in Section 10.3.3.3 below. See also the study selection flow chart in appendix C, study evidence tables in appendix F, and excluded studies lists in appendix I.

Five of these studies explored patient experiences, 6 explored healthcare professional experiences and 2 explored family member experiences.

Table 146: Summary of studies included in the review

Study	Design	Population	Research aim	Setting
Brannstrom 2011[51]	Interviews and thematic content analysis	15 healthcare professionals (3 cardiologists, 12 internists)	To describe healthcare professionals' experiences in end of life care for heart failure patients.	Sweden
Cheang 2015[62]	Survey and framework analysis approach	Consultants, clinical nurse specialists, other palliative nurses and non-consultant doctors that were mainly based in hospices.	To investigate why palliative care in heart failure may be underutilised, in order to identify problems in current practice that may impact the provision of care	UK
Fluur 2013[121]	Semi-structured interviews and thematic analysis	Spouses of ICD-recipients at least 6 months post implant, who were in a stable phase of their illness trajectory (mean age 61 years)	To explore future reflections of spouses living with ICD recipients, with a focus on end of life care issues.	Sweden
Fluur 2013[120]	Semi-structured interviews and thematic analysis	37 ICD-recipients with a median time since first implantation of 4.5 years and a mean age of 64 years, and who were not in the palliative	To explore patients' experiences of complex issues of battery replacement and deactivation of the	Sweden

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Study	Design	Population	Research aim	Setting
		phase of a terminal illness.	ICD	
Goldstein 2008[136]	Interviews and constant comparative methods	12 healthcare professionals (electrophysiologists, cardiologists and generalists)	To understand barriers to physician initiated discussions about ICD deactivation	USA
Goldstein 2008[135]	Interviews and constant comparative methods	15 ICD-recipients (median age 69 years), 10 patients had their device for over a year and 8 patients had received a shock	To understand patient barriers to discussions about ICDs in patients with advanced illness	USA
Kramer 2011[182]	Focus groups and grounded theory	14 nurses who were registered from the Division of Cardiovascular Diseases at the Mayo clinic	To identify nurses' concerns relating to deactivating cardiac devices	USA
Lee 2017[196]	Interviews and thematic analysis	6 family members of ICD-recipients (3 children and 3 spouses)	To explore family members' experiences of ICD decision making, in order to inform decision making and improve the quality of end of life care.	USA
Maclver 2016[208]	Interviews and grounded theory analysis	25 heart failure patients with ICDs (mean age 62 years)	To determine patient awareness and understanding of ICD deactivation	Canada
Morrison 2010[227]	Survey and coding	112 palliative care professionals (51% physicians, 48% nurses and 1% other)	To explore palliative care providers experiences and attitudes of managing ICDs	USA
Mueller 2011[229]	Focus groups and content analysis	17 industry employed allied professionals working in a clinical setting to monitor cardiac implantable electronic devices, who had performed at least one device deactivation	To identify issues related to role conflicts and moral distress experienced with the cardiovascular implantable electronic device industry	USA
Strachan 2011[322]	Interviews and grounded theory	24 ICD recipients and 6 participants who declined an ICD (age 26 to 87 years)	To examine patient experiences of end of life care issues	Canada
Svanholm 2015[323]	Phenomenological and interpretive approach	11 ICD-recipients (mean age 82.8 years) who were expecting a device replacement within 2 years	To identify areas for improvement in discussions between healthcare professionals and patients related to ICDs.	Denmark

10.3.3.3 Qualitative evidence synthesis

Three findings were identified, with multiple sub-findings. These are described below.

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Table 147: Finding 1: Attitudes and understanding

Sub-finding	Statement of sub-finding
Awareness	ICD recipients and family members were unaware that ICDs could be deactivated.
Misconception	People perceived deactivation to be equivalent to euthanasia or suicide, resulting in immediate death
Not wanting to deactivate	People did not want to deactivate regardless of the circumstances
Wanting to deactivate	People wanted to deactivate when they were bedridden with an extremely low quality of life

Table 148: Finding 2: Discussions

Sub-finding	Statement of sub-finding
Initiating the conversation	Some patients felt that healthcare professionals should start the conversation, whereas others felt that this would be emotionally distressing
Starting the conversation early	Some felt that discussions should be started early while they were able to make decisions
Having the conversation later	Some felt discussions should occur later on or when there was a change in their condition
Avoiding discussions	ICD recipients and healthcare professionals avoided discussions about deactivation

Table 149: Finding 3: Decision making

Sub-finding	Statement of sub-finding
Healthcare professionals decide	People with ICDs felt that healthcare professionals should decide whether or not a device should be deactivated
Patients decide	Healthcare professionals felt that patients should decide when to deactivate their device.

10.3.3.3.1 Narrative summary of review findings

Finding 1: Attitudes and understanding

Review sub-finding 1: Awareness

Many ICD recipients and family members were not aware that ICDs could be deactivated. Their doctors had not discussed this with them, and they had not thought about the issues related to end of life care. Finding this out came as a surprise for many, and they reported that thoughts about dying were not discussed between them, their spouses and their healthcare professionals. Others reported that they only thought a device would be deactivated in cases where it needed to be changed; the battery had run out, if they had an infection or an MRI was required. Some reported that their clinician may have told them in passing about end of life care and deactivation issues, although they didn't feel that this was fully discussed.

Explanation of quality assessment: moderate methodological limitations in the studies contributing to this sub-finding; minor concerns about the coherence of the finding; partial relevance due to the contributing studies being conducted outside of the UK; minor concerns about inadequacy as the evidence provided reasonable depth. There was an overall judgement of low confidence in this sub-finding due to the concerns regarding the methodological limitations and relevance.

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Review sub-finding 2: Misconception

Some people perceived ICD deactivation to be equivalent to euthanasia or assisted suicide, with some believing that it would lead to immediate death. In these cases they reported only wanting to consider deactivation when they were 'brain dead'. They felt that a cardiac arrest was a threat to their lives, and healthcare professionals were obligated to treat them. Some patients also said that they would never want their ICD to be deactivated because this was the equivalent to suicide and therefore against their faith.

Explanation of quality assessment: moderate methodological limitations in the studies contributing to this sub-finding; minor concerns about the coherence of the finding; partial relevance due to the contributing studies being conducted outside of the UK; moderate concerns about inadequacy as there was a relatively small amount of evidence which lacked depth. There was an overall judgement of very low confidence in this sub-finding due to the concerns regarding the methodological limitations, relevance and adequacy.

Review sub-finding 3: Not wanting to deactivate

Some people would not consider living without their ICD because they believed it was keeping them alive. Some felt that the ICD should always be replaced when the batteries ran out, regardless of other circumstances. They also described that they would chose life at all costs and would not want to deactivate their ICD when it could extend life. Others were also scared to deactivate their device. Some ICD recipients could not identify any situations in which they would chose to deactivate their device, describing this as a 'no win situation'.

Explanation of quality assessment: moderate methodological limitations in the studies contributing to this sub-finding; moderate concerns about the coherence of the findings due to conflicting reports regarding patients and family members wanting to deactivate their device; partial relevance due to the contributing studies being conducted outside of the UK; moderate concerns about inadequacy as there was a relatively small amount of evidence which lacked depth. There was an overall judgement of very low confidence in this sub-finding due to the concerns regarding the methodological limitations, relevance and adequacy.

Review sub-finding 4: Wanting to deactivate

Some ICD recipients felt that they would only deactivate their device when their quality of life was so low that they were bedridden or unable to engage in daily activities. They felt that if they had no hope of a meaningful recovery and were at a terminal point of their illness, then they would want to deactivate their device. They also felt that if they were in a lot of pain and had had numerous shocks than they might want to deactivate their device. Other elderly patients had been seeking information about whether they could refuse an ICD replacement, feeling that they might be ready to die soon; although they had not discussed these thoughts with loved ones or healthcare professionals. Family members felt that they would only agree to deactivate the ICD if all hope was gone and their partner no longer had a 'worthy' life. Many expressed that they would not want their partner to suffer and be in pain in their last days of life, which an active ICD could cause. In these cases, they felt there was no reason to prolong the inevitable and cause extra suffering by keeping an ICD going.

Similarly, some doctors agreed and in these situations did not feel like they were 'killing' the patient. Nurses also supported deactivation when the patient had been well informed. They reported that this often would happen when patients were undergoing withdrawal of other life-sustaining treatments, and was done to improve patient comfort and avoid ongoing shocks.

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Explanation of quality assessment: moderate methodological limitations in the studies contributing to this sub-finding; moderate concerns about coherence due to a conflicting sub-finding on patients and family members not wanting to deactivate their device; partial relevance due to the contributing studies being conducted outside of the UK and one of the studies discussing implantation devices other than just ICDs; moderate concerns about inadequacy as there was a relatively small amount of evidence which lacked depth. There was an overall judgement of very low confidence in this sub-finding due to the concerns regarding the methodological limitations, relevance and adequacy.

Finding 2: Discussions

Review sub-finding 5: Initiating the conversation

Some ICD recipients felt that discussions should be initiated by a healthcare professional such as a cardiologist, nurse or social worker. Others felt that healthcare professionals initiating conversations about ICD deactivation would be too emotionally distressing. Nurses felt that they were often the ones to bring up the conversation with the family during the dying process when the family started to ask 'why is it taking so long'. Doctors felt that ICD discussions were important but guidelines on how to initiate the conversation were unclear.

Explanation of quality assessment: minor methodological limitations in the studies contributing to this sub-finding; minor concerns about the coherence of the sub-finding; partial relevance due to the contributing studies being conducted outside of the UK; moderate concerns about inadequacy as there was a relatively small amount of evidence which lacked depth. There was an overall judgement of low confidence in this sub-finding due to the concerns regarding relevance and adequacy.

Review sub-finding 6: Starting the conversation early

Some ICD recipients felt that discussions should be initiated early. They felt it should be pre-implant and while they were still ‘cognitively intact’; many felt that at this time they wanted the issue to be described to them fully, so that they were aware of the issues around deactivation but did not have to make any decisions at that point. Patients did not feel it was appropriate to have discussions about ICD deactivation at the end of life when death was imminent. They also highlighted the role of healthcare professionals in allowing them to make a fully informed decision about ICD implantation. They suggested they could be given written information. Those that had already had this discussion said it was good to do this early while they were already engaged in ICD discussions with their healthcare professionals, and some that hadn't had the conversation felt that they wanted to do so soon.

Healthcare professionals felt that deactivating ICDs was unlike any other decisions they had to make, and so it was difficult for them to know when discussions should take place. They felt that ICD deactivation was not discussed early enough, which meant devices were not deactivated in time. They also felt there was a lack of forward planning in the community. Others felt that discussions did take place upon insertion but these are usually forgotten by the time they come into focus when the person’s condition has deteriorated.

Explanation of quality assessment: minor methodological limitations in the studies contributing to this sub-finding; moderate concerns about the coherence of the sub-finding due to a conflicting review on ‘having the conversation later’; partial relevance due to most of the studies being conducted outside of the UK; moderate concerns about inadequacy as there was a relatively small amount of evidence which lacked depth. There was an overall judgement of low confidence in this sub-finding due to the concerns regarding relevance, adequacy and coherence.

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Review sub-finding 7: Having the conversation later

Some ICD recipients felt that ICD deactivation should be discussed if there was a change in their condition, and if their condition had deteriorated. They felt that patients should be of sound mind but had definitely progressed to 'end of life'. Patients felt that physicians could predict when this change could result in death, and that ICD deactivation should be discussed as a reminder of the options and to determine preferences. Similarly, other patients felt that discussions of deactivation should not happen at the time of insertion. This is because of the emotional distress it would cause, and how overwhelming the information would be. Others felt that it did not make sense to begin discussions of removing a device before even implanting it

Explanation of quality assessment: minor methodological limitations in the studies contributing to this sub-finding; moderate concerns about the coherence of the sub-finding due to a conflicting review on 'starting the conversation early'; partial relevance due to the contributing study being conducted outside of the UK; moderate concerns about inadequacy as there was a relatively small amount of evidence which lacked depth. There was an overall judgement of very low confidence in this sub-finding due to the concerns regarding relevance, adequacy and coherence.

Review sub-finding 8: Avoiding discussions

Healthcare professionals, ICD recipients and family members all avoided discussions about ICD deactivation, due to the difficult nature of the conversations. Some patients said that they had brief conversations with their healthcare professionals but did not discuss this further with their family members. Others were putting off talking about it because they felt that end of life issues were not relevant to the current phase of their life and were not yet a reality; they wanted to think about this nearer the time. In 1 study, ICD recipients were not willing to discuss deactivation in the focus group.

Doctors reported that they rarely had discussions about ICD deactivation, even though they acknowledged the importance of doing so. They found that at a technical level it crossed their mind that it should be switched off, but that for some it wouldn't cross their mind to initiate a conversation with the patient. Doctors reported that it was hard to bring up discussions about deactivation because this contrasted so much with their discussions about the primary lifesaving role of the devices, and therefore initiating discussions of deactivation felt as though they were shutting off hope for patients. Others also didn't feel like they could bring up such a difficult topic if they didn't have a good relationship or rapport with the patient. Similarly nurses felt that doctors were uncomfortable having discussions about end of life issues because they are not trained to manage these situations. Healthcare professionals felt that in particular cardiology teams were reluctant to take the lead on decision-making. Some healthcare professionals also felt that electrophysiology services were unwilling to have conversations and make decisions regarding deactivation.

Explanation of quality assessment: moderate methodological limitations in the studies contributing to this sub-finding; minor concerns about the coherence; partial relevance due to most of the contributing studies being conducted outside of the UK; minor concerns about inadequacy as the evidence provided reasonable depth. There was an overall judgement of moderate confidence in this sub-finding due to the concerns regarding the methodological limitations and relevance.

Finding 3: Decision making

Review sub-finding 9: Healthcare professionals decide

People with ICDs wanted to put the decision to deactivate their ICD in the hands of healthcare professionals rather than making an active choice themselves about deactivation. They felt that it was difficult for them to make a decision themselves because they weren't qualified and that clinicians should come up with the suggestion themselves; they trusted the decisions that their

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healthcare professionals made. Spouses also felt that they would rather healthcare professionals make decisions about deactivation so they did not have to make the decisions themselves.

Healthcare professionals reported reasons they were unable to deactivate ICDs, even if they had decided to deactivate. For example, deactivation was often not possible out of hours, when staff or magnets were unavailable in community hospitals. Some healthcare professionals found that consultants were unavailable to visit dying patients in the community in order to deactivate ICDs. Others spoke of excessive time delays due to a lack of defined process in the community, unavailability of magnets or insufficient education on how to use magnets and confusion of the size of the magnet needed. Others spoke of organisational difficulties, having to make lots of phone calls in order to access technician support for deactivation. Many felt that there was no local or national policy or procedures related to ICD deactivation, which made the process long and difficult.

Explanation of quality assessment: moderate methodological limitations in the contributing studies; minor concerns about the coherence with nothing to lower confidence; partial relevance due to the contributing studies being conducted outside of the UK; minor concerns about inadequacy as the evidence provided reasonable depth. There was an overall judgement of moderate confidence in this sub-finding due to the concerns regarding methodological limitations and relevance.

Review sub-finding 10: Patients decide

Healthcare professionals felt that 'competent' ICD recipients should decide whether to deactivate their device. They highlighted the importance of discussions with the person and family, and felt that all cardiologists considering implanting a device should have an end of life discussion. Patients reported that the frequency and pain of shocks, overall quality of life and recommendations of the physician could impact their decision. Nurses felt that families sometimes put pressure on patients to get a device or to keep a device active.

Explanation of quality assessment: moderate methodological limitations in the studies contributing to this sub-finding; minor concerns about the coherence; partial relevance due to the contributing studies being conducted outside of the UK; moderate concerns about inadequacy as there was a relatively small amount of evidence which lacked depth There was an overall judgement of very low confidence in this sub-finding due to the concerns regarding methodological limitations, relevance and adequacy.

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10.3.3.4 Qualitative evidence summary

Finding 1: Attitudes and understanding

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Awareness					
7	6 interviews, 1 focus groups 2 Sweden, 3 USA, 2 Canada	ICD recipients and family members were unaware that ICDs could be deactivated.	Limitations	Moderate concerns about methodological limitations	LOW
			Coherence	Minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Minor concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Misconception					
5	5 interviews 2 Sweden,1 Denmark, 1 USA, 1 Canada	People perceived deactivation to be equivalent to euthanasia or suicide, resulting in immediate death	Limitations	Moderate concerns about methodological limitations	VERY LOW
			Coherence	Minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Moderate concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Not wanting to deactivate					
2	2 interviews 1 Sweden,1 USA	People did not want to deactivate regardless of the circumstances	Limitations	Moderate concerns about methodological limitations	VERY LOW
			Coherence	Moderate concerns about coherence	
			Relevance	Moderate concerns	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
				about relevance	
			Adequacy	Moderate concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Wanting to deactivate					
7	5 interviews, 2 focus groups 2 Sweden,3 USA, 1 Canada, 1 Denmark	People wanted to deactivate when they were bedridden with an extremely low quality of life	Limitations	Moderate concerns about methodological limitations	VERY LOW
			Coherence	Moderate concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Moderate concerns about adequacy	

Finding 2: Discussions

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Initiating the conversation					
2	1 Canada, 1 USA 1 Interviews, 1 Focus groups	Some patients felt that healthcare professionals should start the conversation, whereas others felt that this would be emotionally distressing	Limitations	Minor concerns about methodological limitations	LOW
			Coherence	Minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Moderate concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Starting the conversation early					
3	1 UK, 2 Canada 1 Survey, 2 Interviews	Some felt that discussions should be started early while they were able to make decisions	Limitations	Minor concerns about methodological limitations	LOW
			Coherence	Moderate concerns about coherence	
			Relevance	Moderate concerns	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
				about relevance	
			Adequacy	Moderate concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Having the conversation later					
1	Canada Interviews	Some felt discussions should occur later on or when there was a change in their condition	Limitations	Minor concerns about methodological limitations	VERY LOW
			Coherence	Moderate concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Moderate concerns about adequacy	

Study design and sample size	Finding	Quality assessment

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Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Avoiding discussions					
6	4 interviews, 1 survey, 1 focus groups 2 Sweden, 3 USA, 1 UK	ICD recipients and healthcare professionals avoided discussions about deactivation	Limitations	Moderate concerns about methodological limitations	LOW
			Coherence	Minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Minor concerns about adequacy	

Finding 3: Decision making

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Healthcare professionals decide					
4	4 interviews, 2 Sweden, 1 USA, 1 Canada	People with ICDs felt that healthcare professionals should decide whether or not a device should be deactivated	Limitations	Moderate concerns about methodological limitations	LOW
			Coherence	Minor concerns about coherence	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Relevance	Moderate concerns about relevance	
			Adequacy	Minor concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Patients decide					
3	1 survey, 1 interviews, 1 focus groups 2 USA, 1 Canada	Healthcare professionals felt that patients should make the decision.	Limitations	Moderate concerns about methodological limitations	VERY LOW
			Coherence	Minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Moderate concerns about adequacy	

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10.3.4 Economic evidence

The committee agreed that health economic studies would not be relevant to this review question, and so health economic evidence relating to this question was not sought.

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10.3.5 Evidence statements

Qualitative

See the narrative summaries of the review findings in section 1.3.3.1.

Economic

Health economic studies were not sought for this review question.

10.3.6 Recommendations and link to evidence

Recommendations	**If it is thought that a person may be entering the last 2 to 3 days of life, follow the NICE guideline on care of dying adults in the last days of life. [2018]** **See NICE's technology appraisal guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure.** **When discussing implantation of a cardioverter defibrillator:** • **explain the risks, benefits and consequences of cardioverter defibrillator implantation, following the principles on shared decision making in the NICE guideline on patient experience in adult NHS services** • **ensure the person knows that the defibrillator can be deactivated without affecting any cardiac resynchronisation or pacing, and reactivated later** • **explain the circumstances in which deactivation might be offered** • **discuss and dispel common misconceptions about the function of the device and the consequences of deactivation** • **provide the person and, if they wish, their family or carers with written information covering the information discussed. [2018]** **Review the benefits and potential harms of a cardioverter defibrillator remaining active in a person with heart failure:** • **at each 6-monthly review of their heart failure care** • **whenever their care goals change** • **as part of advance care planning if it is thought they are nearing the end of life. [2018]**
Findings identified in the evidence synthesis	The evidence from the review was grouped into 3 findings, each of which contained multiple sub-findings. These key findings are summarised below. Attitudes and understanding: many ICD recipients were not aware that their ICDs could be deactivated, with their doctors not discussing this with them. Other recipients had misconceptions about the effect of deactivation, perceiving it to be equivalent to euthanasia or assisted suicide, leading to immediate death. Whether ICD recipients would consider deactivation or not was highly varied. Some recipients reported that they would not consider living without their ICD as they believed it was keeping them alive. Similarly, some recipients felt that their ICD should never be deactivated when it could

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	extend their life, regardless of the circumstances. Some people were scared to deactivate. Other ICD recipients felt that they would deactivate their device when their quality of life was so low that they were bedridden or unable to engage in daily activities, if they were in a lot of pain and had received numerous shocks, or if they were elderly and felt they may be ready to die soon. Some family members and healthcare professionals reported similar sentiments about deactivation being appropriate in these circumstances. Discussions: preferences and experiences on initiating the conversation about deactivation were varied. Some ICD recipients felt that healthcare professionals should initiate the discussion, whereas others felt this would be too emotionally distressing. Nurses felt they were often the ones to raise the conversation during the dying process. Doctors reported that guidelines on how to initiate the conversation were unclear. Preferences about the timing of the discussion were also varied. Some ICD recipients felt that discussions should be initiated early, pre-implant, as part of the informed consent process, rather than having the discussions at the end of life when death was imminent. Other ICD recipients felt that ICD deactivation should be discussed if their condition had deteriorated significantly and they were nearing the end of their life, with some specifically expressing views that deactivation not be raised at the time of implantation due to the resulting emotional distress and overwhelming nature of the information. Healthcare professionals reported that it was difficult for them to know when these discussions should take place. Some felt that it was often not discussed early enough which delayed deactivation occurring; others reported that discussions taking place at the time of implantation are usually forgotten by the time they become relevant; when a person's condition deteriorates. ICD recipients, family members and healthcare professionals all reported avoiding discussions about ICD deactivation, due to the difficult nature of the conversations. Decision making: there was a dichotomy in the evidence on who should decide whether an ICD should be deactivated. People with ICDs and their family members often felt that healthcare professionals should decide whether it was appropriate for their ICD to be deactivated, as they did not feel qualified or comfortable making the decision themselves. Healthcare professionals felt that ICD recipients should be the ones to decide whether to deactivate their device in the context of end of life discussions. Some healthcare professionals felt that families sometimes put pressure on patients to keep their device active. Healthcare professionals reported practical challenges in the deactivation of ICDs after a decision had been made. Issues were experienced out of hours and in the community or community hospitals where staff or magnets were not available. Lack of a clear process and understanding about how deactivation worked in the community, and organisational issues, were also reported as making the process long and difficult.
Quality of the evidence	The decsions around discussing deactivation was considered to be similiar in all populations and the committee agreed to include studies outsideof the UK. The confidence ratings for the different sub-findings in the review were

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	varied, ranging from moderate to very low. The committee weighed the confidence in the individual findings with their own experiences, and agreed that they were broadly consistent, despite much of the evidence being downgraded in confidence due to being conducted outside of the UK in settings that differed to varying degrees from the English NHS. Attitudes and understanding: 3 of the 4 sub-findings within this finding were rated very low confidence, with the fourth rated low confidence. All of the sub-findings were downgraded due to concerns about methodological limitations and relevance, with some also being downgraded for concerns about coherence and/or adequacy. Discussions: 2 of the 3 sub-findings within this finding were rated low confidence, with the third rated very low confidence. All were downgraded for relevance and adequacy, with one also downgraded for coherence. Decision making: the sub-finding that patients felt that healthcare professionals should decide about deactivation was rated moderate confidence, with the only downgrade being for relevance. The second sub-finding – that healthcare professionals felt that patients should decide about deactivation – was rated very low confidence due to concerns about methodological limitations, relevance and adequacy.
Trade-off between benefits and harms	The committee agreed that the findings and sub-findings identified in the review resonated with their own experiences as healthcare professionals or lay members connected to heart failure services in the NHS. The committee acknowledged that some of the sub-findings identified in the review reflect general issues around communication and information needs in health care and are addressed by recommendations in the patient experience guideline CG138. The committee decided to focus on the issues raised that are specific to the deactivation of ICDs in heart failure. The committee discussed the review finding about discussing ICD deactivation. The committee agreed that deactivation should be explained and discussed pre-implantation. Although some patients may not want this information at the time of implantation, it is a necessary part of shared decision making and informed consent process. The committee agreed to make a recommendation to emphasise the importance of deactivation being discussed at this stage, and outlined some of the key issues that should be covered in that discussion, including: • the risks, benefits and consequences of implantation, • the process of deactivation and the circumstances in which deactivation may be appropriate, including the potential harms of not deactivating, • the possibility of partial deactivation of the ICD without deactivating the Cardiac Resynchronisation Therapy component (in the patients with CRT-D devices) • the possibility of reactivation if the person's condition changes or improves • common misconceptions about the function of an ICD and the consequences of deactivation. In line with the review findings, the committee agreed that the discussion should be followed up with written information so the person and their

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	family had time to digest the information and make an informed decision. The committee noted in the review findings that discussions about deactivation occurring at the time of implantation were often forgotten by the time they became relevant, that discussions were avoided by all parties, and that they were often held too late, causing delays in deactivation and potential unnecessary harm. The committee agreed that the possibility of deactivation should be revisited regularly by healthcare professionals caring for that person. The committee decided that the appropriateness of continuing the ICD should be considered by the person's health care team at each 6 monthly review of their heart failure. This did not mean that a conversation had to take place with the patient about deactivation at each 6 monthly review, but it was important that the healthcare professional considered it. Healthcare professionals should consider discussing with the person their goals of ongoing treatment and whether the ICD remains in line with those goals, as part of general advanced care planning. This may be appropriate where the symptoms of a person with heart failure have deteriorated over a period of time despite optimal treatment, people whose care goals are changing, in very elderly people, and with people thought to be nearing the end of their life. The committee acknowledged that these reviews and conversations may be led by primary care services, for example, in circumstances where the person's heart failure is stable but they are of advanced age and general advanced care planning is applicable. Alternatively, they may take place in the specialist heart failure MDT if the person's heart failure is severe or the person is otherwise high risk and being managed by the specialist team. All health care professionals caring for patients with heart failure should be prepared and equipped to raise these issues with ICD recipients. The committee noted that specific issues were relevant where a person was thought to be entering their last days of life. The committee wished to emphasise the importance of health care professionals following the guidance in the Care of the dying adult guideline in these circumstances. The committee discussed the issues raised by the review around the logistical challenges of deactivation, many of which came from a UK based study. While the committee felt that these challenges strongly resonated with their experiences of deactivation in the NHS context; commissioning, service delivery and service design issues are outside the scope of this guideline and so the committee was unable to make recommendations in this area. The committee emphasised the importance of any service that provides ICDs having services available to support the whole process from implantation to deactivation.
Trade-off between net clinical effects and costs	Economic studies were not sought for this review question. The committee considered that the recommendations made above represent best clinical practice and provide essential information to individuals to allow for shared decision making. If patients are well informed this could result in improved quality of life, due to a reduction in anxiety about the implantation, and potential future deactivation, not only for the patient but also their families and/or carers. Furthermore, informed decision making could reduce the number of painful unwanted shocks for individuals, again potentially providing some improvement in quality of life. The committee

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	acknowledged that there is likely to be a cost associated with providing written information for the patient and their family and/or carers. Some information on ICDs is already available from charitable organisations and some clinics already provide such information to their patients. Readily available information could be edited, or further supplementary information could be provided if not all aspects are covered from available materials. This is likely to require an initial upfront cost to produce a document, after which printing costs per patient are likely to be small. The committee also acknowledged that discussions around whether ICDs remain an appropriate treatment option can require longer appointment times and often require re-visiting. However, the committee agreed that this is necessary to ensure the patient is well informed and to allow time for discussion. Around 5-10% of heart failure patients have ICDs, in which discussion about deactivation is only likely to be considered in a small proportion each year. Therefore, the committee did not consider that these recommendations would have a significant resource impact.
Other considerations	The committee noted that conversations around ICD deactivation, like other conversations around end of life, can be challenging for people and their families. Health care professionals should be aware that some people may require specialist psychological support or review. The committee acknowledged the Resuscitation Council (UK), the British Cardiovascular Society and the National Council for Palliative Care's guide for healthcare professionals regarding the deactivation of implantable cardioverter-defibrillators towards the end of life http://www.bhrs.com/files/files/Guidelines/CIEDs_Deactivation.pdf. The committee were reassured that the advice outlined in this document was in agreement with the recommendations they had made.

10.4 Identifying patients with an increased risk of mortality

10.4.1 Introduction

The disease trajectory for people with heart failure is difficult to predict, with episodes of stability punctuated by episodes of severe deterioration in symptoms within an overall decline over years. The uncertainty associated with length of life from diagnosis and often repeated episodes of severe deterioration can create anxiety for both patients and clinicians. This may prevent optimal advance care planning and targeting of therapies and resources to those who will benefit most. Consequently, there is increasing interest in prognostic tools to identify people who are entering the last year of life. Despite some prediction tools being widely available there are no national guidelines on their use.

10.4.2 Review question: In adults with heart failure, which validated risk tools best identify patients with heart failure who are at increased risk of mortality in the short term (up to 1 year)?

For full details, see the review protocol in Appendix A.

Table 150: PICO characteristics of review question

Question	**In adults with heart failure, which validated risk tools best identify patients with heart failure who are at increased risk of mortality in the short term (up to 1 year)?**

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Question	In adults with heart failure, which validated risk tools best identify patients with heart failure who are at increased risk of mortality in the short term (up to 1 year)?
Objective	To determine which prognostic risk tools are the most accurate at predicting patient mortality, to support decisions about involvement of palliative care services and the use of palliative care processes.
Population	People with heart failure in a community or outpatient setting. Tools that are derived or validated in patients who are in an acute setting will also be included. The results will be stratified based on the setting in which the tools were validated in the study (admitted versus recently discharged versus community).
Risk tool	Validated risk tools identified in the literature
Target condition	• Mortality (all-cause at up to 1 year)
Statistical outcomes	• Area under the ROC curve (AUC or c-statistic) • Sensitivity, specificity, negative predictive value, positive predictive value • Predicted risk versus observed risk (calibration) • Other outcomes e.g., D statistic, R^2 statistic and Brier score • Reclassification
Study types	Prospective cohort studies Retrospective cohort studies will be included only if insufficient prospective cohort studies are identified Studies with less than 500 participants will be excluded.

10.4.3 Clinical evidence

A search was conducted for prospective and retrospective cohorts assessing the prognostic accuracy of tools for assessing the risk of mortality at 1 year in people with heart failure. Fourteen studies evaluating seven risk tools were included in the review.[10, 122, 165, 167, 174, 186, 195, 198, 216, 278, 280, 295, 304, 318] The studies are summarised in Table 151, and the risk tools are summarised in Table 152 below. See also the study selection flow chart in Appendix C, coupled sensitivity and specificity forest plots in Appendix E, study evidence tables in Appendix F, and excluded studies list in Appendix I.

Table 151: Summary of studies included in the review

Study	Risk tool	Population	Outcomes	No of events (%)	Study design

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Allen 2017[10]	• Seattle Heart Failure Model • MAGGIC project heart failure risk score	n= 10,930 Ambulatory people with heart failure, 21 years of age or older. Age (mean SD) (years): 75.1 (11.8) Male %: 52% Ejection fraction: Preserved (≥50%): 4155 (38%) Borderline (41%-49%): 1330 (12.2%) Reduced (≤40%): 3019 (27.6%) Missing: 2426 (22.2%) Family origin not reported Setting: Multicentre Country: USA Follow-up: Not reported Participants recruited between 2005 and 2008	Mortality at 1 year AUCSensitivity Specificity PPV NPV Hosmer-Lemeshow test	Mortality at 1 year 15.9% (1661 deaths)	Retrospective cohort
Frankenstein 2011[12][2]	Untitled risk tool (6MWT +NT-proBNP)	n= 676 People with heart failure due to left ventricular systolic dysfunction Age (years): 73.8 (9.9) Male %: 76 Family origin not reported Setting: Castle Hill Hospital, Hull Country: UK Follow-up: median 32 months (21-40 months) Participants recruited between November 2001 and October 2005	Mortality at 1 year AUC	Mortality at 1 year 24% (160 deaths)	Retrospective cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Kanwar 2017[165]	HeartMate II Risk Score	n=11,523 People with HF who received a continuous flow LVAD as the primary implant between 2010 and 2015 (INTERMACS registry). Age, years (mean (SD)): 57(13) Female %: 21 Family origin not reported Setting: Multicentre (over 150 hospitals) Country: United States Follow up: median 3.8 years Participants recruited between 2010 and 2015	Mortality at 1 year AROC	Mortality at 1 year 27.3% (3,145 deaths)	Retrospective cohort
Kao 2012[167]	Seattle Heart Failure Model	n=1121 People with heart failure due to left ventricular systolic dysfunction Age (years): 73.8 (9.9) Male %: 76 Family origin not reported Setting: Castle Hill Hospital, Hull Country: UK Mean follow up not reported Participants were recruited previous to 2001	Mortality at 1 year AUC Predicted versus observed 1 year mortality	Mortality at 1 year 9.6% (107 deaths)	Retrospective analysis of RCT data

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Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Ketchum 2012[17] [4]	Seattle Heart Failure Model-D	n= 961 People with NHYA class II-III heart failure and impaired systolic function (ejection fraction ≤35%) who were on guideline recommended medical therapy. Age (years): 62±12 Male %: 80 Family origin not reported Setting: Multicentre Country: USA Mean follow-up of 21 months Participants were recruited between July 2005 and February 2008	Mortality at 1 year AUC Predicted versus observed mortality at 1 year	101 deaths in a mean follow-up of 21 months	Retrospective cohort
Ky 2012[18] [6]	Seattle Heart Failure Model-D	n= 1513 People with a clinical diagnosis of heart failure as determined by a heart failure specialist Age (years): 56 (15) Male %: 66 Aetiology: Systolic heart failure: 86% Ischemic heart failure: 30% Family origin %: White: 74 African American: 22 Other: 4 Setting: Multicentre Country: USA Follow up: Maximum of 5 years Recruitment period not reported	Mortality at 1 year AUC Predicted versus observed mortality at 1 year	187 deaths over a maximum follow-up period of 5 years	Retrospective cohort

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Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Lee 2003[195]	Untitled risk score	N=1407 Newly admitted patients with a primary diagnosis of heart failure Age (years): 75.3 (11.8) Female %: 50.5 LVEF<0.40: 47.7% Family origin: Not reported Setting: 14 hospitals Country: Canada Participants were recruited previous to 2001	Mortality at 1 year AUC	Mortality at 1 year 30.5% (429 deaths)	Retrospective cohort
Levy 2006[198]	Seattle Heart Failure Model	<u>ELITE2</u> n=2,987 People with EF≤40%, age≥60 years and NYHA class II to IV heart failure Age (years): 71.7±7 Male %: 69 Family origin not reported Setting: Multicentre Country: 46 countries Follow-up not reported Participants were recruited previous to 2001 <u>RENAISSANCE</u> n=925 People with EF≤30% and NYHA class II to IV heart failure	1 year survival free from LVAD or transplantation ROC R^2	Survival (free from LVAD or transplantation) at 1 year: ELITE2: 88.5%±0.6 RENAISSANCE: 83.3±1.4 Val-HeFT: 91.0±0.4 IN-CHF: 86.7±1.2	Retrospective analysis of cohort and RCT data

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Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Age (years): 62±12 Male %: 78 Family origin not reported Setting: Multicentre Country: USA and Canada Follow-up not reported Participants were recruited previous to 2001			
		<u>Val-HeFT</u> n=5010 People with EF≤40% and NYHA class II to IV heart failure Age (years): 63±11 Male %: 80 Family origin not reported Setting: Multicentre Country: 16 countries Follow-up not reported Participants were recruited previous to 2001			
		<u>IN-CHF</u> n=872 People with heart failure of any etiology, age, EF or comorbidity Age (years): 64±12 Male %: 76 Family origin not reported Setting: Multicentre Country: Italy			

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Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Follow-up not reported Participant recruitment period not reported			
May 2007[21][6]	Seattle Heart Failure Model	n=4,077 People with HF (defined as a decrease in left ventricular function characterized by an EF≤40% or a physician-reported clinical HF diagnosis (i.e., American College of Cardiology/American Heart Association stage B/C) undergoing coronary angiography. Age (years): 67.0 (range 19-96) Male %: 61.4 Family origin not reported Setting: LDS Hospital (Salt Lake City, Utah) Country: USA Average follow-up (years): 4.4 (range 0.4-12.2) Participants were recruited between 1993 and 2005	Mortality at 1 year AUC R^2	20.2% event rate at 1 year (917 events) The study reported the composite end point of death, transplantation, and left ventricular assist device implantation. Over 90% of the overall events were mortality.	Retrospective cohort

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Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Rector 2006[278]	Untitled risk score (derived in Lee 2003)	n=769 People admitted to the Minneapolis VA medical centre with a primary diagnosis of heart failure Age (years): 73±10 Male %: 98 Ischemic heart disease: 68% Family origin not reported Setting: Minneapolis VA Medical centre Country: Canada Follow-up period: 4.5 years Participants were recruited between January 1999 and May 2003	Mortality at 1 year AUC Observed versus predicted mortality at 1 year	25% mortality at 1 year (194 events)	Retrospective cohort
Regoli 2013[280]	Seattle Heart Failure Model	n=1139 People who underwent CRT device implantation between January 2002 and January 2011 Age (years): 67.2±10.7 Male %: 77.4% Family origin not reported Setting: 5 centres Country: Europe (Italy, Switzerland and UK) Median follow-up of 40.1 months (IQR 25.2-60.0 months) Participants were recruited between January 2002 and January 2011	Mortality at 1 year AUC-ROC	300 deaths during a median follow-up of 40.1 months (IQR 25.2-60.0 months)	Retrospective cohort

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Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Sartipy 2014[29] [5]	MAGGIC project heart failure risk score	n=51,043 People with clinician judged heart failure. Age (mean) (years): 75 Female %: 40 Heart failure with preserved EF (EF≥40%): 56% NYHA class I or II: 57% NYHA class III: 38% NYHA class IV: 5% Family origin not reported Setting: Multicentre Country: Sweden Follow-up: mean 2.6 years Recruitment period is unclear	Mortality at 1 year AROC Predicted versus observed 1 year mortality	20.2% mortality at 1 year (10,208 deaths)	Retrospective cohort
Senni 2013[30] [4]	3C-HF score	n=4258 People with a diagnosis of heart failure based on symptoms and signs of congestion and objective evidence of cardiac dysfunction at rest. Age (median IQR) (years): 70 (60-77) NYHA class III-IV: 33.6% LVEF<20%: 4.4% LVEF≥50%:26.1% Female %: 38.7 Family origin not reported Setting: Multicentre Country: Countries in Europe Follow-up not reported Participants were recruited	Mortality at 1 year AUC Brier score	12.5% mortality at 1 year (534 events) The study reported the composite end point of death and transplantation. Over 90% of the overall events were mortality.	Prospective and retrospective

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Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		between 2002 and 2006			
Spinar 2016[318]	AHEAD tool	n=6315 People with acute heart failure Age (mean) (years): 77 (52-91) Female %: 44.5 Family origin not reported Setting: Multicentre Country: Spain, France, Argentina, Finland, Switzerland, USA, Tunisia, Austria Follow-up not reported Participant recruitment period is unclear	Mortality at 1 year AUC	31.6% mortality at 1 year (1995 deaths)	Retrospective cohort

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Table 152: Summary of risk tools included in the review

<table>
<tr><th>Risk tool</th><th>Description of tool</th><th>Comments</th></tr>
<tr><td>• Seattle Heart Failure Model
• Seattle Heart Failure Model-D</td><td>Multivariate risk prediction model. The Seattle HF score is calculated by multiplying the β coefficient by the variable and summing the values.
Variables included within the model are age (decade), gender (male), NYHA class,100/ejection fraction, ischemic etiology, systolic blood pressure, diuretic dose (mg/kg), allopurinol use, statin use, if sodium<138, 100/cholesterol (dL/mg), if haemoglobin more or less than 16, % lymphocytes and uric acid (mg/dL).

The SHFM-D included the original SHFM variables, and the new variables of digoxin use, carvedilol use, and creatinine, with each individual's SHFM score derived as previously described.

The SHFM has been updated on an iterative basis to incorporate new and relevant variables based on the publishing of various trials and guidelines. Specific information regarding these updates is available at https://depts.washington.edu/shfm/update.php

Online calculator available at http://depts.washington.edu/shfm/</td><td></td></tr>
<tr><td>MAGGIC project heart failure risk score</td><td>
<table>
<tr><th>Risk factor</th><th colspan="7">Addition to risk score</th></tr>
<tr><td rowspan="2">Ejection fraction (%)</td><td><20</td><td>20-24</td><td>25-29</td><td>30-34</td><td>35-39</td><td>40+</td><td></td></tr>
<tr><td>+7</td><td>+6</td><td>+5</td><td>+3</td><td>+2</td><td>0</td><td></td></tr>
<tr><td>Extra for age (years)</td><td><55</td><td>56-59</td><td>60-64</td><td>65-69</td><td>70-74</td><td>75-79</td><td>80+</td></tr>
<tr><td>EF < 30</td><td>0</td><td>+1</td><td>+2</td><td>+4</td><td>+6</td><td>+8</td><td>+10</td></tr>
<tr><td>EF 30 -39</td><td>0</td><td>+2</td><td>+4</td><td>+6</td><td>+8</td><td>+10</td><td>+13</td></tr>
<tr><td>EF 40+</td><td>0</td><td>+3</td><td>+5</td><td>+7</td><td>+9</td><td>+12</td><td>+15</td></tr>
<tr><td>Extra for systolic blood pressure (mmHg)</td><td><110</td><td>110-119</td><td>120-129</td><td>130-139</td><td>140-149</td><td>150+</td><td></td></tr>
<tr><td>EF < 30</td><td>+5</td><td>+4</td><td>+3</td><td>+2</td><td>+1</td><td></td><td></td></tr>
</table>
</td><td></td></tr>
</table>

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Risk tool	Description of tool								Comments
	EF 30 -39	+3	+2	+1	+1	0			
	EF 40+	+2	+1	+1	0	0			
	BMI (kg/m²)	<15	15-19	20-24	25-29	30+			
		+6	+5	+3	+2	0			
	Creatinine µmol/l	<90	90-109	110-129	130-149	150-169	170-209	210-249	250+
		0	+1	+2	+3	+4	+5	+6	+8
	NYHA Class	1		2		3		4	
		0		+2		+6		+8	
	Male	+1							
	Current smoker	+1							
	Diabetic	+3							
	Diagnosis of COPD	+2							
	First diagnosis of heart failure in the past 18 months	+2							
	Not on beta-blocker	+3							
	Not on ACEI/ARB	+1							
	Online calculator available at http://www.heartfailurerisk.org/								
Untitled risk tool (6MWT + NT-proBNP)		**Cut-off NT-proBNP (cut-off positive)**			**Cut-off 6MWT (cut-off positive)**				
	cut-off: male, no BBL	650 pg/ml			396m				

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<table>
<tr><th>Risk tool</th><th>Description of tool</th><th>Comments</th></tr>
<tr><td></td><td>
<table>
<tr><td>cut-off: male, BBL</td><td>743 pg/ml</td><td>368m</td></tr>
<tr><td>cut-off: female, no BBL</td><td>714 pg/ml</td><td>270m</td></tr>
<tr><td>cut-off: female, BBL</td><td>830 pg/ml</td><td>188m</td></tr>
</table>
Patients were assigned 1-point if their 6MWT distance was below the prognostic threshold and one point if their NT-proBNP value was above the prognostic threshold. Thus 3 risk-groups were identified

One year mortality rates of patients:

Group 1 (0 points): 2% risk of 1 year mortality

Group 2 (1 point): 7% risk of 1 year mortality

Group 3 (2 points): 14% risk of 1 year mortality
</td><td></td></tr>
<tr><td>AHEAD tool</td><td>1 point assigned for each age >70 years, diagnosis of atrial fibrillation, diagnosis of diabetes mellitus, creatinine > 130µmol/l, anaemia (M: 130, F: 120). Maximum score of 5.

Each parameter was calculated as 1 point (maximum of 5 points)

One year mortality rates of patients:
0: 10-15%
1: 20-25%
2: 30%
3: 40%
4: 50%
5: 60%</td><td>The paper states that these % thresholds were calculated with ‘an acceptable dose of simplification’</td></tr>
</table>

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<table>
<tr><th>Risk tool</th><th>Description of tool</th><th>Comments</th></tr>
<tr><td>HeartMate II Risk Score (HMRS)</td><td>Calculation of HMRS: (0.0274 • [age in years]) • (0.723 • [albumin g/dl]) • (0.74 • [creatinine mg/dl]) • (1.136 • [international normalized ratio (INR)]) • (0.807 • [centre LVAD volume • 15*]). *Enter value of 1 if total centre LVAD volume is • 15 and 0 if • 15.

One year survival rates of patients:
Low risk (< 1.58): 83 ± 2%
Medium risk (1.58-2.48): 72 ± 2%
High risk (> 2.48): 58 ± 3%

Online calculator available at: http://www.pmidcalc.org/23265328</td><td></td></tr>
<tr><td>3C-HF score</td><td>Dichotomized logistic regression model and corresponding points for the additive version of the 3C-HF score were calculated as follows:

<table>
<tr><th>Variable</th><th>Odds ratio</th><th>Points (additive score)</th></tr>
<tr><td>Age (per 10 years ≥ 40)</td><td>1.03</td><td>1</td></tr>
<tr><td>NYHA class III-IV vs I-II</td><td>4.09</td><td>13</td></tr>
<tr><td>LVEF <20% vs ≥20%</td><td>2.77</td><td>11</td></tr>
<tr><td>No RAS inhibitors</td><td>2.01</td><td>8</td></tr>
<tr><td>Severe valve heart disease</td><td>2.02</td><td>7</td></tr>
<tr><td>Atrial fibrillation</td><td>1.58</td><td>7</td></tr>
<tr><td>No beta blocker</td><td>1.45</td><td>4</td></tr>
<tr><td>Chronic kidney dysfunction</td><td>1.79</td><td>6</td></tr>
<tr><td>Diabetes with target organ damage</td><td>1.62</td><td>6</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Risk tool</th><th>Description of tool</th><th>Comments</th></tr>
<tr><td></td><td>
<table>
<tr><td>Anemia</td><td>1.47</td><td>4</td></tr>
<tr><td>Hypertension</td><td>0.78</td><td>-4</td></tr>
</table>
The study does not report % risk of mortality at one year for all of the 3C-HF risk score deciles. It reports a <1% risk of mortality for scores <5 and a 50% risk of mortality for scores ≥32.
An online scoring system is available at http://www.3chf.org/site/index.php
</td><td></td></tr>
<tr><td>Untitled risk score</td><td>
<table>
<tr><th>Variable</th><th>Points (additive score)</th></tr>
<tr><td>Age</td><td>+age (in years)</td></tr>
<tr><td>Respiratory rate, min (minimal 20; maximum 45)</td><td>+ rate (in breaths/min)</td></tr>
<tr><td rowspan="6">Systolic BP, mmHg</td><td>≥180: -50</td></tr>
<tr><td>160-179: -45</td></tr>
<tr><td>140-159: -40</td></tr>
<tr><td>120-139: -35</td></tr>
<tr><td>100-119: -30</td></tr>
<tr><td>90-99: -25</td></tr>
<tr><td></td><td><90: -20</td></tr>
<tr><td>Urea nitrogen (maximum, 60mg/dL)</td><td>+ level (in mg/dL)</td></tr>
<tr><td>Sodium concentration <136 mEq/L</td><td>+10</td></tr>
</table>
</td><td></td></tr>
</table>

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Risk tool	Description of tool		Comments
	Cerebrovascular disease	+10	
	Dementia	+15	
	COPD	+10	
	Hepatic cirrhosis	+35	
	Cancer	+15	
	Hemoglobin <10.0g/dL (<100g/L)	+10	
	An electronic version of the risk scoring system is available at: http://www.ccort.ca/CHFriskmodel.asp		

10.4.4 Discrimination and calibration

Table 153: Clinical evidence profile: risk tools for predicting mortality (all-cause at up to 1 year)

Risk tool	No of studies	n	Strata	Risk of bias [a]	Inconsistency [b]	Indirectness [c]	Imprecision [d]	Sensitivity (%)	Specificity (%)	AUC(or C-statistic)/NPV/ PPV	Calibration	Quality
Seattle Heart Failure Model	7 (1 study includes 4 separa	**At threshold 50% predicted mortality**										
		10,930	Outpatient mixed	LOW	No inconsistency	No indirectness	Not estimable	0.5	99.9	PPV: 61.5 NPV: 82.2		HIGH
		At threshold 20% predicted mortality										

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Risk tool	No of studies	n	Strata	Risk of bias [a]	Inconsistency [b]	Indirectness [c]	Imprecision [d]	Sensitivity (%)	Specificity (%)	AUC(or C-statistic)/NPV/PPV	Calibration	Quality
	te cohorts)	10,930	Outpatient mixed	LOW	No inconsistency	No indirectness	Not estimable	20.7	93.1	PPV: 39.6 NPV: 84.4		HIGH
		At any threshold										
		10,930	Outpatient mixed	LOW	Serious	No indirectness	Not estimable			AUC: 0.66	Hosmer-Lemeshow: 8.7, P=0.36	MODERATE
		872	Outpatient mixed	LOW	Serious	Unclear	No imprecision			AUC: 0.75 (0.70-0.80	R^2: 0.99	LOW
		1513	Outpatient mixed	LOW	Serious	Unclear	No imprecision			AUC: 0.76 (0.71-0.81)	93.7% vs 94.0%	LOW
		1121	Outpatient HFREF	LOW	Serious	Serious	Not estimable			AUC: 0.71	11.0% vs 9.6%	LOW
		961	Outpatient HFREF	LOW	Serious	No indirectness	Not estimable			AUC: 0.69	95.1±0.1% vs 94.6±0.7%	MODERATE
		2987	Outpatient HFREF	LOW	Serious	Serious	No imprecision			AUC: 0.68 (0.65-0.71)	R^2: 0.97	LOW
		925	Outpatient HFREF	LOW	Serious	Serious	No imprecision			AUC: 0.68 (0.63-0.73)	R^2: 0.97	LOW
		5010	Outpatient HFREF	LOW	Serious	Serious	No imprecision			AUC: 0.69 (0.68-0.72)	R^2: 0.98	LOW

Risk tool	No of studies	n	Strata	Risk of bias [a]	Inconsistency [b]	Indirectness [c]	Imprecision [d]	Sensitivity (%)	Specificity (%)	AUC(or C-statistic)/NPV/PPV	Calibration	Quality
		4077	Angiography	LOW	Serious	Serious	No imprecision			AUC: 0.70 (0.68-0.72)	R^2: 0.99	LOW
		1139	CRT	LOW	Serious	No indirectness	Not estimable			AUC: 0.66		MODERATE
MAGGIC project heart failure risk score	2	**At threshold 50% predicted mortality**										
		10,930	Outpatient mixed	HIGH	No inconsistency	No indirectness	Not estimable	3.1	99.2	PPV: 45.2 NPV: 82.4		MODERATE
		At threshold 20% predicted mortality										
		10,930	Outpatient mixed	HIGH	No inconsistency	No indirectness	Not estimable	69.7	61.2	PPV: 28.1 NPV: 90.3		MODERATE
		At any threshold										
		10,930	Outpatient mixed	HIGH	Serious	No indirectness	Not estimable			AUC: 0.69	Hosmer-Lemeshow: 38.6, P<0.001	LOW
		51,043	Outpatient mixed	HIGH	Serious	Unclear	Not estimable			AUC: 0.78	16.8% vs 20.2%	VERY LOW
Untitled risk tool (6MWT + NT-proBNP)	1	676	Outpatient HFREF	HIGH	No inconsistency	No indirectness	Not estimable			AUC: 0.68		MODERATE

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Risk tool	No of studies	n	Strata	Risk of bias [a]	Inconsistency [b]	Indirectness [c]	Imprecision [d]	Sensitivity (%)	Specificity (%)	AUC(or C-statistic)/NPV/PPV	Calibration	Quality
AHEAD tool	1	6315	Acute	VERY HIGH	No inconsistency	Unclear	Not estimable			AUC: 0.63		VERY LOW
HeartMate II Risk Score	1	11,523	LVAD	HIGH	No inconsistency	No indirectness	Not estimable			AUC: 0.59		MODERATE
3C-HF score	1	4258	Outpatient mixed	LOW	No inconsistency	No indirectness	No imprecision			AUC: 0.82 (0.81-0.83)	Brier score: 0.082	HIGH
Untitled risk tool (Lee 2003)	2	769	Acute	HIGH	No inconsistency	Serious	No imprecision			AUC: 0.71 (0.67-0.76)	Observed vs predicted mortality for the 5 risk scores categories: <60: 6.8% vs 7.1% 61 to 90: 14.6% vs 14.2% 91 to 120: 25.7% vs 27.0% 121 to 150: 50.9% vs 47.7% >150: 50.0% vs 67.2%	LOW
		1407	Acute	LOW	No inconsistency	Serious	Not estimable			AUC: 0.76		MODERATE

(a) *Risk of bias was assessed using the PROBAST checklist items relating to risk of bias.*

(b) *Inconsistency was assessed by inspecting the point estimate and confidence intervals of the sensitivity and specificity forest plots where this data was available, or the AUC where it was not. Particular attention was placed on the degree to which the confidence intervals overlapped. Whether the point estimate values were above or below 50% (diagnosis based on chance alone) and 70% (the threshold the committee set above which is acceptable to recommend a test) was also considered. Where there was little or no overlap between at least some of the confidence intervals and the values reported by the individual studies varied across 2 areas (for example, 50–70% and 70–100%) the*

evidence was downgraded by 1 increment, if the individual studies varied across 3 areas (for example, 0–50%, 50–70% and 70–100%) the evidence was downgraded by 2 increments. Where there was a significant degree of overlap in the confidence intervals little weight was placed on the variability of the point estimates above and below the 50% and 70% thresholds.

(c) *Indirectness was assessed using the PROBAST checklist items relating to applicability.*

(d) *Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was more than 20% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of more than 40%. Imprecision was not estimable where studies did not report confidence intervals.*

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10.4.5 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix D.

10.4.6 Evidence statements

Clinical

Evidence for 7 prognostic risk tools predicting mortality at 1 year were identified from 14 publications. The quality of the included evidence ranged from high to very low. Evidence was downgraded for a number of reasons including indirectness of the population (as they were recruited previous to 2001 when the guidelines for CHF management were changed), risk of bias for reasons including a lack of calibration data, or inconsistency due to variability in discrimination statistics reported by the studies with a concomitant lack of overlap in the confidence intervals. A single high quality study (n=10,930) reported both the sensitivity and specificity of the SHFM at 50% and 20% mortality thresholds. At a mortality threshold of 50% the SHFM showed a very poor sensitivity of 0.05 and a good specificity of 0.99 and at the 20% threshold it showed a very poor sensitivity of 0.21 and a good specificity of 0.93. The same study reported the prognostic accuracy of the MAGGIC project heart failure risk score at these thresholds. It reported a very poor sensitivity of 0.3 and a good specificity of 0.99 at the 50% mortality threshold and a moderate sensitivity of 0.7 and moderate specificity of 0.61 at the 20% mortality threshold. Seven further studies ranging from moderate to low quality, reported AUC or c-statistics for the SHFM. The largest of the studies (n=10,930) reported a moderate c-statistic of 0.66. The remaining studies were considerably smaller (ranging in sample size from 872 to 5010) and were mostly rated as low quality. The discrimination statistics reported by these studies ranged from 0.66 to 0.76 with only a proportion of them reporting confidence intervals. Moderate quality evidence was found for a single study (n=676) reporting on an untitled risk tool which combined data from the 6MWT and NT-proBNP. This tool reported a moderate c-statistic of 0.68. Moderate quality evidence was also found for a further 2 studies which reported on the Heartmate II risk score (n=11,523) and the 3C-HF score (n=4258). The Heartmate II risk score showed a moderate sensitivity of 0.59, while the 3C-HF tool reported a good c-statistic of 0.82 (0.81-0.83). Further moderate quality evidence was found for an untitled risk tool reported in 2 studies (n=2176). Both studies reported moderate discrimination statistics of 0.71 (0.67-0.76) and 0.76. A single very low quality study reported the prognostic accuracy of the AHEAD tool which reported a moderate c-statistic of 0.63. Although several of the studies met the minimum AUC threshold, only a single study reported the sensitivity and specificity of two tools at the relevant mortality thresholds of interest. These statistics provide more accurate insight into the ability of the tool to adequately stratify peoples risk of mortality at 1 year.

Economic

- No relevant economic evaluations were identified.

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10.4.7 Recommendations and link to evidence

Recommendations	**Do not use prognostic risk tools to determine whether to refer a person with heart failure to palliative care services. [2018]** **If the symptoms of a person with heart failure are worsening despite optimal specialist treatment, discuss their palliative care needs with the specialist heart failure MDT and consider a needs assessment for palliative care. [2018]**
Research recommendation	• **What is the most accurate prognostic risk toos in predicting 1 year mortality from heart failure at specific clinically relevant thresholds (for example, sensitivity, specificity, negative predictive value and positive predictive value at a threshold of 50% risk of mortality at 1 year)?**
Relative values of different outcomes	The committee were interested in which validated risk tools best identified patients with heart failure who are at increased risk of all-cause mortality in the short term (up to 1 year). The aim was to identify tools that may be used to support decisions about involvement of palliative care services and the use of palliative care processes. It was recognised that the risk of death was only one factor to consider in determining the need for palliative care services and processes, but that accurate prognostic tools would be of value in the identification and decision-making process. The committee did not intend that risk tools would be used to specifically estimate the number of years that a person may live, or as a criterion for palliative care referral. The committee agreed that all-cause mortality was the appropriate outcome, rather than heart failure or cardiovascular mortality, in the context of the broad objectives of this review question. The committee also agreed that the most relevant risk tools would be those that identified patients at increased risk of mortality at 1 year, as this was an appropriate time for putting in place supportive and palliative care processes if necessary. Risk tools that identified patients at high risk of death in the very short term (for example, in hospital, or within 30 or 60 days of discharge), or in the long term (for example 2, 5 or 10 years) were not considered appropriate for this review question as they would not necessarily capture the patients who might benefit from palliative care services and processes in a timely manner.
Quality of the clinical evidence	The review included 7 risk tools that were validated in a range of heart failure cohorts. Overall, the quality of the evidence ranged from very low to high, and varied significantly between the tools. Many of the studies included in the review reported the area under the curve (AUC) or c-statistic as the only accuracy data. The committee noted that this metric enabled comparison of the overall accuracy of the tools, and agreed a priori that a minimum AUC of 0.70 would be necessary to consider recommending a tool, but that AUC itself was unlikely to provide enough information to make a recommendation. For those tools where multiple studies reported the AUC in different cohorts, the results were inconsistent, with some studies suggesting an AUC of greater than 0.70, and others estimating a lower accuracy. Many studies also did not report calibration data and these were downgraded for risk of bias. Some studies were also downgraded for indirectness as the patients in the cohorts were recruited prior to 2001, when best practice medical treatment for heart failure changed to include beta-blockers. This means that these data may not reflect accuracy of the tools in a population treated in

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	accordance with current usual care. The committee agreed that the most important accuracy data for establishing the utility of a risk tool was the sensitivity and specificity of the tool at clinically relevant thresholds (for example, at a threshold of 50% risk of mortality at 1 year). As the main aim of the tools was to identify patients who may benefit from a palliative care approach, sensitivity was agreed to be of great importance. However, depending on how the tool was used, high specificity was also crucial as wrongly categorising a person at high risk of death could have negative consequences for that person and their family. Only 1 study reported sensitivity and specificity data at specific thresholds (50% and 20% predicted mortality) for 2 tools (Seattle Heart Failure Model (SHFM) and the MAGGIC project heart failure risk score). The sensitivity and specificity data was graded high quality for the SHFM and moderate quality for the MAGGIC risk score (the latter was downgraded due to poor calibration and failure to recalibrate).
Trade-off between clinical benefits and harms	Overall, the committee were not persuaded that any of the risks tools included in the review identified patients with a high risk of mortality with sufficient accuracy to support their use. The SHFM was the most commonly reported tool included in the review. The estimated AUC for the SHFM ranged from 0.66 to 0.76 across the 10 cohort datasets. Because of this inconsistency, the committee could not be confident that the tool would meet its minimum threshold for AUC of 0.70. The data from 1 large cohort suggested an AUC of 0.66, but at the clinically relevant thresholds, the sensitivity of the tool was very low. Sensitivity was estimated at 0.5% for a threshold of 50% predicted mortality, and 20.7% at 20% predicted mortality. This meant that the vast majority of patients who died within a year had relatively low predicted mortality risks – in other words, the tool failed to identify the patients who would die within the year. The committee agreed that a tool with such low sensitivity was therefore not helpful for identifying patients who may benefit from a more detailed palliative care assessment. In contrast, the specificity of the tool was high, 99.9% at the 50% predicted mortality threshold and 93.1% at the 20% predicted morality threshold. This suggested that at these thresholds, the tool was accurate at identifying patients who were less likely to die within the year. Based on this evidence, the committee discussed whether the tool could be used as a 'rule out' tool, to identify those patients who were unlikely to need a palliative care needs assessment. However, the committee agreed that the main focus of the review was to positively identify patients who may benefit from palliative care services and processes, not to 'rule out' patients, and decided that a recommendation to use the tool in this way would not be appropriate. The MAGGIC risk score was also reported in multiple studies, with an AUC ranging from 0.69 to 0.78. Again, the committee could not be sure that the tool would meet the minimum threshold for AUC of 0.70, especially when the confidence intervals around the AUC estimates were considered. Sensitivity and specificity data on this tool was available from the same large cohort mentioned above. Similarly to the SHFM, the sensitivity of the tool was very low (3.1%) and the specificity high (99.2%) at the clinically relevant threshold of 50% predicted mortality. Sensitivity at the threshold of 20% predicted mortality was somewhat higher (69.7%), indicating that at this threshold, the tool identified most of the patients who were at higher risk of death. However, at this threshold the MAGGIC score also labelled a

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significant proportion of patients as at high risk of death who did not die within the year ("false positives") (the specificity of the tool was only 61%). The MAGGIC data was also at high risk of bias due to poor calibration, suggesting that the absolute predicted risks from the tool did not align well with the observed risks in the population. Based on this data, the committee agreed that the MAGGIC tool would also not be an appropriate tool for positively identifying patients who may benefit from palliative care assessment.

The remaining tools considered in the review were all only considered in single study cohorts, and none of them provided sensitivity or specificity data. The AUC for these tools ranged from 0.59 to 0.82. The committee discussed the 3C-HF tool, which was the only tool in the review with an AUC of above 0.80. The committee agreed that while the overall AUC was high, without data on the tool's performance at clinically relevant thresholds for identifying high risk patients (for example, the sensitivity and specificity of the tool at a threshold of 50% predicted mortality within 1 year), combined with the fact that the tool was only validated in a single study cohort, they would not be comfortable recommending the tool for assessing individual mortality risk.

Overall, the committee agreed that the evidence did not support the use of any of the identified prognostic risk tools to identify heart failure patients at high risk of mortality. The committee also discussed the potential for serious harm from inappropriate use of risk tools in the palliative care context. Incorrectly categorising a person at high risk of death could have negative consequences for that person and their family. Further, if the tools were misused as a 'criterion' for access to palliative care services that would also cause substantial harm, given they fail to identify many of the patients who may benefit from such interventions. The committee acknowledged that tools with a reasonably high AUC may be useful to establish risk at a population or cohort level, but they fail to demonstrate sufficient accuracy at the individual level. For those reasons, the committee agreed to make an explicit recommendation that the tools should not be used to determine whether to offer referral to palliative care services.

The committee discussed that the trajectory of heart failure can be very unpredictable, especially in newly diagnosed patients and with the risk of sudden death, making prognostication is challenging in heart failure. This probably explained the poor performance of many of the identified risk tools. This uncertain trajectory makes identifying heart failure patients in need of palliative care services very difficult in clinical practice.

The committee agreed that there are also inequalities issues across the country and potentially between different conditions in terms of access to palliative care services. This may partly stem from the particular challenges of prognostication in heart failure. In addition, the palliative care expert co-optee noted that people with heart failure sometimes see themselves as 'living' with the condition rather than 'dying' with it, and may be reluctant to access palliative care services because of the perception that they are for cancer patients.

The committee discussed ways in which identification of heart failure patients in need of a specialist palliative care assessment could be improved, without the use of a formal risk tool. The committee discussed whether it would be possible to come up with an evidence-based list of markers that might trigger referral for specialist assessment. However, the evidence

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	reviewed demonstrated that clinical markers, even when combined in a sophisticated, weighted risk tool algorithm, failed to accurately identify high risk patients at an individual level. Including a list of factors in the guideline would not only be challenging (how to select key factors from the many included in the various risk tools) but also risked misapplication in practice, particularly if the factors were not considered in the context of the individual patient and their overall health status. Rather than using risk tools or a list of factors, the committee agreed that the best approach was for healthcare professionals to discuss with the specialist MDT any person with heart failure whose condition is deteriorating over a period of time, and to consider a palliative care needs assessment in those people. The committee agreed that all HF services should have a process in place to identify patients who should be referred for a formal assessment of palliative care needs, and adjust their service configuration as appropriate to ensure this can occur. The committee also agreed that if palliative care processes or services were thought to be necessary, they should be implemented or engaged early, given the uncertainty of the prognosis for many patients with heart failure. The committee emphasised that involvement of palliative care services and use of palliative care processes includes a broad spectrum of interventions, and that different levels of care and support can be provided at various stages of the person's disease pathway. People should be reassured that use of palliative care processes does not necessarily mean referral to a hospice or the withdrawal of prognostic heart failure medication, and that people can dip in and out of palliative care over the course of their disease. The committee acknowledged that palliative care processes do not necessarily require delivery by specialist palliative care doctors and nurses. For example, GPs, geriatricians and heart failure specialist nurses may be specially trained to implement palliative care processes for heart failure patients. The committee agreed that people with heart failure and their family and carers should have access to professionals with palliative care skills within the specialist HF MDT, and all specialist HF MDTs should have access to specialist palliative care services and should involve those services where necessary. **Future research** The committee discussed the need for studies of prognostic risk tools in heart failure to report accuracy data (such as sensitivity, specificity and negative and positive predictive values) at specific clinically relevant thresholds, in order for the data to inform decisions about the value of the tools at an individual level in clinical practice. The committee decided that this was a priority for future research in this area and made a research recommendation to that effect.
Trade-off between net clinical effects and costs	No previously published economic evaluations were identified comparing different risk tools. The committee considered that the cost of using a risk tool would be minimal in the majority of cases and would only require a few minutes of a consultation. Some risk tools required the additional cost of blood tests, but these also incur a very small cost (£1-£3). The committee considered that in most patients the last year of life is when a patient is most likely to benefit from palliative care services, and is when these services are likely to be most cost effective. However, as the accuracy

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	of the risk tools identified in the clinical review was too uncertain to predict the last year of life for heart failure patients, the committee were concerned about the potential large cost implications of flooding the palliative care services. Therefore, the committee agreed that it was important that if a clinician is concerned that a patient may require palliative services, that they discuss this with the specialist heart failure team for a second opinion and to check if there are any other treatments available that could be tried first which would not require palliative care services. The committee considered that this would only likely require a telephone call, email or letter and would therefore not incur significant resource. If it was still considered that the patient could possibly benefit from palliative care services, they should then be referred for a needs assessment by the palliative care team as they are best placed to determine whether palliative services are required. The committee considered the resources required for this pathway of referral with regards to staff time, but agreed that this was most likely to be current practice and would therefore not have a significant resource impact.
Other considerations	The committee noted that health care professionals should also follow the related principles and recommendations in the NICE guidelines on *Multimorbidity: clinical assessment and management* (NG56), *Care of dying adults in the last days of life* (NG31) and *End of life care for adults in the last year of life: service delivery* when published (expected publication 2018).

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10.5 Recommendations

85. Do not offer long-term home oxygen therapy for advanced heart failure. Be aware that long-term home oxygen therapy may be offered for comorbidities, such as for some people with chronic obstructive pulmonary disease (see section 1.2.5 on oxygen in the NICE guidline on chronic obstructive pulmonary disease in over 16s. [2018]

86. If it is thought that a person may be entering the last 2 to 3 days of life, follow the NICE guideline on care of dying adults in the last days of life. [2018]

See NICE's technology appraisal guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure.

87. When discussing implantation of a cardioverter defibrillator:

- **explain the risks, benefits and consequences of cardioverter defibrillator implantation, following the principles on shared decision making in the NICE guideline on patient experience in adult NHS services**
- **ensure the person knows that the defibrillator can be deactivated without affecting any cardiac resynchronisation or pacing, and reactivated later**
- **explain the circumstances in which deactivation might be offered**
- **discuss and dispel common misconceptions about the function of the device and the consequences of deactivation**
- **provide the person and, if they wish, their family or carers with written information covering the information discussed. [2018]**

88. Review the benefits and potential harms of a cardioverter defibrillator remaining active in a person with heart failure:

- **at each 6-monthly review of their heart failure care**
- **whenever their care goals change**
- **as part of advance care planning if it is thought they are nearing the end of life. [2018]**

89. Do not use prognostic risk tools to determine whether to refer a person with heart failure to palliative care services. [2018]

90. If the symptoms of a person with heart failure are worsening despite optimal specialist treatment, discuss their palliative care needs with the specialist heart failure MDT and consider a needs assessment for palliative care. [2018]

91. People with heart failure and their families or carers should have access to professionals with palliative care skills within the heart failure team. [2003]

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11 Reference list

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12 Acronyms and abbreviations

Acronym or abbreviation	Description
6MWT	6 Minute Walk Test
ACA	
ACC/AHA	American College of Cardiology/American Heart Assocation
AE	Adverse events
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin converting enzyme inhibitors
ACS	Acute Coronary Syndrome
ADHF/AHF	Acute decompensated heart failure/Acute heart failure
ADMIRE-HF	AdreView Myocardial Imaging for Risk Evaluation in Heart Failure
AF	Atrial fibrillation
AKI	Acute kidney injury
AMCKD	Anaemia management in people with chronic kidney disease
AUC	Area under the curve
ARA	Action research arm
ARB	Angiotensin II receptor blockers
ARD	Assessment Reference Date
AROC	Australasian Rehabilitation Outcomes Centre
BB	Beta-blocker
BBL	
BEST	Beta-Blocker Evaluation of Survival Trial
BHF	British Heart Foundation
BMI	Body Mass Index
BMT	Best medical therapy
BNF	British National Formulary
BNP	B-type natriuretic peptide
BP	Blood pressure
CAD	Coronary artery disease
CAS	Complex Adaptive System
CABG	Coronary artery bypass grafting
CC	Comparative cost
CCA	Cost-consequence analysis
CCS	
CDR	Clinical Decision Rule
CE	Cost effective
CEA	Cost effectiveness analysis
CERQual	Confidence in the Evidence from Reviews of Qualitative Research'
CG	Control group
CHF	Chronic heart failure
CI	Confidence intervals
CINAHL	Cumulative Index of Nursing and Allied Health Literature

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Acronym or abbreviation	Description
CKD	Chronic kidney disease
CM	Cardiomyopathy
cMRI	Cardiac Magnetic Resonance Imaging
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CR	Cardiac rehabilitation
CRT	Cardiac resynchronisation therapy
CUA	Cost-utility analysis
CV mortality	Cardiovascular mortality
CXR	Chest X-ray
DM	Diabetes mellitus
DRG	Diagnosis-related group
EBM	Evidence based medicine
ECHO	Extension for Community Healthcare Outcomes
EDTA	Ethylene diamine tetraacetic acid
EF	Ejection fraction
EGFR	Estimated glomerular filtration rate
EHO	
EIMA	
EME	Efficacy and Mechanism Evaluation
ELISA	Enzyme-linked immunosorbent assay
ESC	European Society of Cardiology
EQ-5D	Euroqual (measurement of health outcomes)
GC	Guideline Committee
GFS	
FCM	Ferric carboxymaltose
FDA	Food and Drug Administration
FG	Focus group
FN	False negative
FP	False positive
FVC	Forced vital capacity
GFR	Glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBT	Home-Based Tele-management
HCAHPS	Hospital Consumer Assessment of Healthcare Providers and Systems
HCP	Healthcare professional
HDS	Heart disease and stroke
HMRS	HeartMate II Risk Score
HEED	Health Economic Evaluations Database
HF	Heart failure
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
HLR	Heart-to-lung ratio

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Acronym or abbreviation	Description
HETG	Home-based exercise training group
HFMS	Heart Failure Monitoring System
HH	Human to human interface
HTA	Health Technology Appraisal
HTN	Hypertension
HR	Hazard ratio
HRQoL	Heath-related quality of life
ICD	Implantable Cardioverter Defibrillators
ICU	Intensive care unit
ICER	Incremental cost-effectiveness ratio
IG	Interventions group
IHD	Ischemic heart disease
IIM	Intrathoracic impedance measurement
IN-CHF	Italian Heart Failure Registry
INR	International normalized ratio
IPD	Individual patient data
IQR	Interquartile range
ISWT	Incremental shuttle walk test
ITT	Intention-to-treat analysis
IV	Intravenous
JVP	Jugular venous pressure
LTC	Long term care
LTOT	Long term oxygen therapy
LV	Left ventricle
LVAD	Left Ventricular Assist Device
LVER	Left Ventricular Ejection Fraction
LVSD	Left ventricular systolic dysfunction
LY	Life year
LYG	Life years gained
MAGGIC	Meta-analysis Global Group in Chronic Heart Failure
MD	Medical devices
MDRD	Modification of Diet in Renal Disease Study
MDT	Multidisciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MIBG	Meta-iodobenzylguanidine
MICE	Male, Infarction, Crepitations, Edema
MID	Minimal important differences
Minnesota LWHFQ	Minnesota Living With Heart Failure Questionnaire
MLWHF	Minnesota Living with Heart Failure
MCS	Mental component summary
MRA	Mineralocorticoid receptor antagonists
MRC	London Institute of Medical Sciences

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Acronym or abbreviation	Description
NSAIDS	Non-steroidal anti-inflammatory drugs
NGC	National Guideline Centre
NHLBI	National Heart, Lung and Blood Institute
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHSS	National Institutes of Health Stroke Scale
NMA	Network meta-analysis
NOT	Nocturnal therapy
NPT	Normalisation Process Theory
NP	Natriuretic peptides including BNP and NT-proBNP
NPV	Negative predictive value
NR	Not reported
NRS	Numerical rating scale
NS	Not stated [in study paper]
NT-proBNP	N-terminus pro B type natriuretic peptide
NYHA	New York Heart Association Classification
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics
PCI	Percutaneous coronary intervention
PCP	Primary care physicians
PCS	Physical component summary
PDA	Personal digital assistant
PICO	Population, intervention, comparison and outcome
PND	Paroxysmal nocturnal dyspnoea
PPV	Positive predictive value
PROBAST	Prediction study Risk of Bias Assessment Tool
PSSRU	Personal Social Services Research Unit
pt	People with chronic heart failure
QALY	Quality-adjusted life years
QOL	Quality of life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies version 2
RAS	Renin-angiotensin-system
RCT	Random control trial
RENAISSANCE	Randomized Enbrel North American Strategy to Study Antagonism of Cytokines
ROC	Receiver operating characteristics
RPE	*Rating of Perceived Exertion*
RR	Relative risk/Risk ratio
SA	Sensitivity analysis
SBP	Systolic Blood Pressure
SD	Standard deviation
SE	Standard error

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Acronym or abbreviation	Description
SETG	Supervised exercise training group
SHFM	Seattle Heart Failure Model
SHFM-D	Seattle Heart Failure Model-D
SMD	Standard Mean Difference
SPECT	Single photon emission computed tomography
STS	Structured telephone support
STS HH	Structured telephone support via human to human interface
SGA	Subgroup analysis
TIA	Transient ischaemic attack
TM	Telemonitoring
TN	True negative
TP	True positive
TSAT	Transferrin saturations
TTO	Time trade off
UHFO-IA	Utrecht Heart Failure Organisation–Initial Assessment
VAS	Visual analogue scale
Acronym or abbreviation	**Description**
ABC	In full
ABC	In full
ABC	In full

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13 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

13.1 Guideline-specific terms

Term	Definition
Acute Coronary Syndrome	Any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non—ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).
Acute decompensated heart failure/Acute heart failure	Is a sudden worsening of the signs and symptoms of heart failure. See heart failure for symptoms. Symptoms include: breathlessness after activity or at rest, feeling tired most of the time and finding exercise exhausting, swollen ankles and legs. Some people also experience other symptoms, such as a persistent cough, a fast heart rate, and dizziness.
Acute kidney injury	Is sudden damage to the kidneys that causes them to not work properly. It can range from minor loss of kidney function to complete kidney failure. AKI normally happens as a complication of another serious illness.
Angiotensin II receptor blockers	Medications that block the action of angiotensin II by preventing angiotensin II from binding to angiotensin II receptors on the muscles surrounding blood vessels. As a result, blood vessels enlarge (dilate) and blood pressure is reduced.
Atrial fibrillation	A heart condition that causes an irregular and often abnormally fast heart rate.
Beta-blockers	Any of a class of drugs which prevent the stimulation of the adrenergic receptors responsible for increased cardiac action, used to control heart rhythm, treat angina, and reduce high blood pressure
B-type natriuretic peptide	A hormone produced by your heart. Both BNP and NT-proBNP are released in response to changes in pressure inside the heart.
Cardiac resynchronisation therapy	An implanted cardiac resynchronization device is a medical device used in cardiac resynchronization therapy (CRT). It resynchronizes the contractions of the heart's ventricles by sending tiny electrical impulses to the heart muscle, which can help the heart pump blood throughout the body more efficiently.
Cardiopulmonary exercise testing	Provides assessment of the integrative exercise responses involving the pulmonary, cardiovascular, haematopoietic, neuropsychological, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function.
Cardiomyopathy	Refers to diseases of the heart muscle.
Chronic heart failure	Heart failure progressively worsens over time.
Chronic kidney disease	A condition characterized by a gradual loss of kidney function over time
Chronic obstructive pulmonary disease	Is a type of obstructive lung disease characterized by long-term breathing problems and poor airflow.
Coronary artery disease	When a waxy substance called plaque builds up inside the coronary arteries. These arteries supply oxygen-rich blood to your heart muscle
Diabetes mellitus	Type 1 diabetes mellitus occurs when the body cannot produce sufficient insulin to absorb blood sugar.
Ejection fraction	A measurement of the percentage of blood leaving your heart each time it contracts.
Glomerular filtration rate	A measure for level of kidney function to determine the stage of kidney

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Term	Definition
	disease.
Heart failure	The heart is unable to pump blood around the body properly. It usually occurs because the heart has become too weak or stiff.
Heart failure with preserved ejection fraction	A form of congestive heart failure where in the amount of blood pumped from the heart's left ventricle with each beat (ejection fraction) is greater than 50%.
HFREF	The heart muscle is not able to contract adequately and, therefore, expels less oxygen-rich blood into the body
Hypertension	Also known as high blood pressure (HBP), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated.
Implantable Cardioverter Defibrillators	Small devices to treat abnormal heart rhythms
Ischemic heart disease	When arteries are narrowed, less blood and oxygen reaches the heart muscle. This is also called coronary artery disease and coronary heart disease.
Jugular venous pressure	Indirectly observed pressure over the venous system via visualization of the internal jugular vein.
Myocardial infarction	Commonly known as a heart attack, occurs when blood flow decreases or stops to a part of the heart, causing damage to the heart muscle.
Natriuretic peptides	The excretion of sodium by the kidneys.
N-terminus pro B type natriuretic peptide	A non-active prohormone that is released from the same molecule that produces BNP. See B-type natriuretic peptide
Paroxysmal nocturnal dyspnoea	Attacks of severe shortness of breath and coughing that generally occur at night.
Percutaneous coronary intervention	is a non-surgical procedure used to treat narrowing (stenosis) of the coronary arteries of the heart found in coronary artery disease.
Systolic Blood Pressure	The top number refers to the amount of pressure in your arteries during contraction of your heart muscle.
Transferrin saturations	The value of serum iron divided by the total iron-binding capacity.
Transient ischaemic attack	A temporary disruption in the blood supply to part of the brain.

13.2 General terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.

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Term	Definition
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.

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Term	Definition
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any

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Term	Definition
	effects due to the treatment.
Cost–benefit analysis (CBA)	Cost–benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis (CCA)	Cost–consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be ‘dominated’ by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support

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Term	Definition
	the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.

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Term	Definition
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 × QALYs gained) − Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).

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Term	Definition
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: TN/(TN+FN)
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as: (£20,000 × mean QALYs) − mean cost. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
Non-randomised intervention study	A quantitative study investigating the effectiveness of an intervention that does not use randomisation to allocate patients (or units) to treatment groups. Non-randomised studies include observational studies, where allocation to groups occurs through usual treatment decisions or people's preferences. Non-randomised studies can also be experimental, where the investigator has some degree of control over the allocation of treatments. Non-randomised intervention studies can use a number of different study designs, and include cohort studies, case–control studies, controlled before-and-after studies, interrupted-time-series studies and quasi-randomised controlled trials.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.

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Term	Definition
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results or more more extreme by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new

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Term	Definition
	evidence (the likelihood).
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: TP/(TP+FP)
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without

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Term	Definition
	taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months

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Term	Definition
	pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	See Markov model
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a

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Term	Definition
	decision analysis or economic evaluation.
Transition probability	In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

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