Appendix A: Summary of evidence from surveillance

2017 surveillance – Acute heart failure (2014)
NICE guideline CG187

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Summary of evidence from surveillance

Organisation of care

Q – 01 **For people with suspected or confirmed acute heart failure is a specialist management unit more clinically or cost effective than general medical hospital care?**

Recommendations derived from this review question

1.1.1 All hospitals admitting people with suspected acute heart failure should provide a specialist heart failure team that is based on a cardiology ward and provides outreach services.

1.1.2 Ensure that all people being admitted to hospital with suspected acute heart failure have early and continuing input from a dedicated specialist heart failure team.

1.1.3 Plan the following with people with acute heart failure in line with chronic heart failure (NICE clinical guideline 108):

- discharge from hospital after the acute phase **and**
- subsequent management in primary care, including ongoing monitoring and care provided by the multidisciplinary team **and**
- information and communication about their condition, its treatment and prognosis.

1.1.4 A follow-up clinical assessment should be undertaken by a member of the specialist heart failure team within 2 weeks of the person being discharged from hospital.

Surveillance decision

This review question should not be updated.

Follow-up

2017 surveillance summary

An RCT(1) (BEAT-HF, n=1437) assessed remote monitoring compared with usual care in people being discharged from hospital after admission for heart failure. Remote monitoring used telephone coaching and telemonitoring technology. No significant differences were seen between groups in 30-day or 180-day readmission, or 180 day mortality.

An RCT(2) (n=349) assessed a multidisciplinary disease management programme compared with control in people admitted to hospital with heart failure. The abstract did not provide details about the

control group. Median follow-up was about 2 years. Multidisciplinary disease management was associated with lower all-cause mortality and re-hospitalisation due to heart failure. However, the effect on all-cause mortality was associated with use of guideline-based medication in the multidisciplinary management group.

An RCT(3) (n=252) assessed a nurse-based follow-up compared with conventional medical follow-up in people discharged from hospital after acute heart failure in Brazil. The primary outcome was first visit to the emergency department, admission to hospital or death over 6 months. Nurse-based follow-up included home visits and telephone contact and reduced primary outcome events compared with standard follow-up. The authors noted that this intervention might be suitable for a 'developing middle income country'.

An RCT(4) (n=40) assessed 30 days of telephone-based loop-diuretic adherence monitoring compared with passive monitoring in people being discharged after an admission to hospital for heart failure. No significant differences in adherence rates or rates of re-admission to hospital within 30 days was seen.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Evidence identified in surveillance did not show beneficial effects of telemonitoring. However, multidisciplinary management and nurse-led follow-up may be useful after admission to hospital with acute heart failure.

The NICE guideline on chronic heart failure recommends that 'Heart failure care should be delivered by a multidisciplinary team with an integrated approach across the healthcare community.' Therefore, the findings of benefits of multidisciplinary care supports this recommendation, and the cross-reference from the acute heart failure guideline to the chronic heart failure guideline.

Although neither guideline recommends nurse-based follow-up, the authors of the relevant study noted that this intervention may be suitable in middle-income countries because of 'social, cultural and economic constraints' affecting the effectiveness of treatment for heart failure outside the hospital. Therefore, this study may not be highly relevant to the UK, where specialist heart failure teams are established.

New evidence is unlikely to change guideline recommendations.

Palliative care

2017 surveillance summary

An RCT(5) (n=232) assessed a palliative care intervention compared with standard care in people admitted to hospital with heart failure. The palliative care intervention was associated with improvements on quality of life scores and symptom burden at 1 month. Advanced care planning was also significantly improved with the palliative care intervention.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The NICE guideline on chronic heart failure recommends that: 'The palliative needs of patients and carers should be identified, assessed and managed at the earliest opportunity.' The new evidence showing benefits of palliative care therefore supports this recommendation, and the cross-reference from the acute heart failure guideline to the chronic heart failure guideline.

New evidence is unlikely to change guideline recommendations.

Diagnosis, assessment and monitoring

Q – 02 In people with suspected (or under investigation for) acute heart failure, is the addition of natriuretic peptides to the standard initial investigations using ECG, chest x-ray and blood tests) more accurate compared to standard initial investigations, clinical judgement and each other?

Recommendations derived from this review question

1.2.1 Take a history, perform a clinical examination and undertake standard investigations – for example, electrocardiography, chest X-ray and blood tests – in line with chronic heart failure (NICE clinical guideline 108).

1.2.2 In people presenting with new suspected acute heart failure, use a single measurement of serum natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NT-proBNP]) and the following thresholds to rule out the diagnosis of heart failure.

- BNP less than 100 ng/litre
- NT-proBNP less than 300 ng/litre.

1.2.3 In people presenting with new suspected acute heart failure with raised natriuretic peptide levels (see recommendation 1.2.2), perform transthoracic Doppler 2D echocardiography to establish the presence or absence of cardiac abnormalities.

Surveillance decision

This review question should not be updated.

Natriuretic peptide measurement

2017 surveillance summary

A systematic review(6) (number of studies and participants not reported in the abstract) assessed the diagnosis of acute heart failure in the emergency department. Investigations of interest were history and physical examination, electrocardiogram, chest X-ray, BNP, NT-proBNP, lung ultrasound, bedside echocardiography, and bioimpedance. Diagnosis was based on clinical data plus test results. Tests with positive likelihood ratios of more than 4 were: auscultation of S3, pulmonary oedema on both chest X-ray and lung ultrasound and reduced ejection fraction observed on bedside echocardiogram. Tests with low negative likelihood ratios were BNP < 100 ng/litre, NT-proBNP < 300 ng/litre and B-line pattern on lung ultrasound.

A systematic review(7) (37 studies, 15,263 test results) assessed the diagnostic accuracy of BNP, NT-proBNP, and mid-regional proatrial natriuretic peptide (MRproANP) in people presenting with suspected acute heart failure. At a threshold of 100 ng/litre, BNP had sensitivity of 95% and negative predictive value of 94%. At a threshold of 300 ng/litre, NT-proBNP had sensitivity of 99% and negative predictive value of 98%. At a threshold of 120 ng/litre, MRproANP had a sensitivity of 95% and a negative predictive value ranging from 90% to 97%. Specificity was noted to be variable so the authors noted that these tests should not be used as a sole source of diagnostic information.

A systematic review and meta-analysis(8) (26 studies, number of participants not reported in the abstract) assessed the association between cardiac troponin and clinical outcomes in people with acute heart failure. Detectable or raised cardiac troponin was associated with increased length of stay in hospital, in-hospital mortality, and a composite of mortality and major adverse events during admission. Short, intermediate and long-term, mortality and readmission were also significantly greater in people with raised cardiac troponin levels.

A diagnostic study(9) (n=236) assessed the accuracy of lung ultrasound, chest X-ray and

NT-proBNP in diagnosing acute heart failure in people presenting to the emergency department with non-traumatic dyspnoea. Lung ultrasound had sensitivity of 58% and specificity of 88%. Chest X-ray had sensitivity of 74% and specificity of 86%. NT-proBNP 98% had sensitivity of and specificity of 28%. Combining chest X-ray and lung ultrasound had the best overall performance with sensitivity of 85%, specificity of 78% and negative predictive value of 87%. The authors noted that they could not identify a single ideal test to diagnose acute heart failure in the emergency department.

An RCT(10) (n=197) assessed a validated diagnostic prediction model for acute heart failure compared with standard care. The model included patient's age, pre-test probability of acute heart failure, and NT-proBNP measurement. The model provided the treating doctor with guideline-based treatment thresholds. Diagnosis was confirmed by 2 independent cardiologists with 60-day follow-up information. The overall diagnostic accuracy of the model was 76%, with sensitivity of 68.2% and specificity of 83.9%. However, there was no significant difference in diagnostic accuracy between the model and standard care.

A systematic review and meta-analysis(11) assessed studies measuring NT-proBNP in heart failure that reported results separately for people with renal dysfunction. Analysis of diagnosis of heart failure included 9 studies (n=4,287) In people with renal dysfunction, NT-proBNP had an area under the curve (AUC) of 0.66 to 0.89, with a median cut-off of 1,980 ng/l, whereas in people without renal dysfunction the AUC was 0.72 to 0.95 with a cut-off of 450 ng/l. Analysis of prognosis included 30 studies (n=32,203). High levels of NT-proBNP were associated with increased risk of mortality and this increase in risk was much the same in people with renal dysfunction as it was in people without renal dysfunction. However, the abstract reported only the results for each group, rather than a comparison between these two groups.

Topic expert feedback

Topic experts highlighted the diagnostic study that compared lung ultrasound, chest X-ray and NT-proBNP(9). Topic experts noted that lung ultrasound was becoming used more widely because it is quicker than a chest X-ray. However, current evidence(6,9) indicates that lung ultrasound may add to the information obtained from chest X-rays, but would not eliminate the need for chest X-rays.

Impact statement

Evidence suggests that standard investigations clinical history taking, and echocardiography remain important in diagnosis of heart failure. Additionally, measurements of BNP or NT-proBNP are highly sensitive tests for heart failure. The reported variability of specificity indicates that additional information is needed to confirm a diagnosis of heart failure. Although MRproANP also performed well, there is no clear rationale to add this test, when both BNP and NT-proBNP are available.

Evidence also suggests that people with renal dysfunction may have higher NT-proBNP values. However, this finding has no impact on the guideline at this time because measurement of NT-proBNP is only one part of establishing a diagnosis of heart failure, and people with renal dysfunction would be included in the overall cut-off for ruling out acute heart failure. The finding of increased risk of death with higher NT-proBNP values has no impact on guidance at this time because no evidence was identified to direct treatment decisions by NT-proBNP levels.

New evidence is unlikely to change guideline recommendations.

Q – 03 **In adults with suspected acute heart failure does early echocardiography compared to later echocardiography in addition to standard investigations (using ECG, chest x-ray and blood tests) improve outcome?**

Recommendations derived from this review question

1.2.4 In people presenting with new suspected acute heart failure, consider performing transthoracic Doppler 2D echocardiography within 48 hours of admission to guide early specialist management.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Q – 04 **Is the addition of invasive monitoring more clinically/cost-effective over and above non-invasive monitoring to improve outcome?**

Recommendations derived from this review question

1.2.5 Do not routinely offer pulmonary artery catheterisation to people with acute heart failure.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Initial pharmacological treatment

Q – 05 **In patients with acute heart failure are opiates as an adjunct to other first line therapies more clinically and cost effective compared to other treatments alone?**

Recommendations derived from this review question

1.3.1 For guidance on patient consent and capacity follow recommendations 1.2.12 and 1.2.13 in patient experience in adult NHS services (NICE guideline CG138).

1.3.2 Do not routinely offer opiates to people with acute heart failure.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Q – 06 In patients with acute heart failure which diuretic administration strategy is the most clinically/cost-effective to improve outcome?

Recommendations derived from this review question

1.3.3 Offer intravenous diuretic therapy to people with acute heart failure. Start treatment using either a bolus or infusion strategy.

1.3.4 For people already taking a diuretic, consider a higher dose of diuretic than that on which the person was admitted unless there are serious concerns with patient adherence to diuretic therapy before admission.

1.3.5 Closely monitor the person's renal function, weight and urine output during diuretic therapy.

1.3.6 Discuss with the person the best strategies of coping with an increased urine output.

Surveillance decision

This review question should not be updated.

Diuretic administration strategies

2017 surveillance summary

A systematic review and meta-analysis(12) (10 studies, n=518) assessed continuous infusion of loop diuretics compared with bolus administration in people with acute heart failure. Continuous infusion was associated with significantly greater weight loss than bolus administration. No significant differences were seen for urinary output, electrolyte imbalances, change in creatinine level, ototoxicity, cardiac mortality, all-cause mortality, or length of stay in hospital.

An RCT(13) (n=161) assessed dosing strategies for furosemide and dopamine in people with acute heart failure. Participants received continuous infusion of furosemide 20 mg/hour, furosemide 5 mg/hour plus dopamine 5 microgram/kg/min, or furosemide 5 mg/hour. No significant differences between groups were seen for urinary output, dyspnoea relief, all-cause mortality at 60 days or at 1 year, readmission to hospital for heart failure at day 60 or at 1 year, or length of stay in hospital. Furosemide 20 mg/hour was associated with a greater occurrence of worsening renal function compared with the other groups.

An RCT(14) (n=109) assessed 3 strategies for dosing furosemide in people with acute heart failure. Participants were randomised within 2 hours of admission to: furosemide 10 mg/hour continuous infusion, furosemide 20 mg bolus every 6 hours or furosemide 20 mg bolus every 8 hours. The continuous infusion strategy produced significantly greater diuresis in 24 hours compared with either bolus strategy. However secondary outcomes such as dyspnoea, orthopnoea, extension of rales and peripheral oedema, blood pressure, respiratory and heart rates, and pulse oximetry did not differ significantly. Hypokalaemia was significantly more common in the continuous infusion group than in the bolus groups.

An RCT(15) (n=90) assessed furosemide infusion plus dopamine compared with furosemide alone and with furosemide bolus in 2 doses in people with acute heart failure. Furosemide bolus dosing was associated with greater 24-hour diuresis and shorter hospital stay. No differences in serum sodium or potassium levels were seen. The dosage of study drugs was not reported in the abstract.

An RCT(16) (n=82) assessed continuous infusion compared with bolus administration of loop diuretics in people with acute heart failure. The drugs used and dosage were not reported in the abstract. At discharge, continuous infusion was associated with higher serum creatinine and lower estimated glomerular filtration rate, greater reduction in BNP. However, the continuous infusion group also had more frequent use of hypertonic saline for hyponatraemia, and dopamine infusions. Additionally, continuous infusion was associated with longer stay in hospital and higher rates of readmission or death at 6 months.

An RCT(17) (n=59) assessed continuous infusion of diuretics compared with switching to oral diuretics after 48 hours. The abstract did not specify the drugs or dosages used. Significant improvements in the Barthel index at 10 days, and a higher number of daily steps were seen in the oral diuretic group compared with the continuous infusion group.

An RCT(18) (n=57) assessed continuous infusion compared with bolus administration of furosemide in people with acute heart failure. The dosage of furosemide was not reported in the abstract. Continuous infusion was associated with higher urinary output, greater reduction in BNP, increased creatinine, and lower estimated glomerular filtration rate. However, continuous infusion was also associated with significantly more adverse events.

An RCT(19) (n=44) assessed furosemide 40 mg plus 1.7% hypertonic saline compared with furosemide 40 mg plus glucose infusion in people with acute heart failure. Urinary volume and creatinine clearance were significantly greater in the furosemide plus salt solution group than in the furosemide plus glucose group.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Studies assessing continuous versus bolus infusions of diuretics find that continuous infusion increases urinary output and weight loss, but may be associated with more adverse events.

Although there are signs that continuous infusion may have drawbacks, the guideline committee noted that 'the relative advantage of an infusion strategy increases as the diuretic dose rises, due to the slow rate at which boluses of diuretic need to be administered.'

The evidence base mostly consists of small studies, but had grown somewhat since the original evidence review was conducted for the guideline. However, it is unlikely to eliminate the uncertainty that the guideline committee noted 'was large to draw clear conclusions about clear clinical benefit or harm'.

The guideline committee also commented on the need for an international multicentre trial to confirm findings on the use of hypertonic saline; however, the evidence identified in surveillance does not meet these criteria.

New evidence is unlikely to change guideline recommendations.

Vasopressin antagonists

2017 surveillance summary

Several studies on the vasopressin antagonist tolvaptan were identified.(20–29)

However, these studies were not thought to have an impact on current recommendations because tolvaptan is not licensed in the UK for treatment of acute heart failure at this time.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Tolvaptan is currently licensed 'to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease'. NICE has technology appraisal guidance on Tolvaptan for treating autosomal dominant polycystic kidney disease.' Therefore, the guideline should not be updated to include tolvaptan at this time.

New evidence is unlikely to change guideline recommendations.

Q – 07 In patients with acute heart failure are vasodilators more clinically or cost effective than placebo to improve clinical outcomes?

Recommendations derived from this review question

1.3.7 Do not routinely offer nitrates to people with acute heart failure.

1.3.8 If intravenous nitrates are used in specific circumstances, such as for people with concomitant myocardial ischaemia, severe hypertension or regurgitant aortic or mitral valve disease, monitor blood pressure closely in a setting where at least level 2 care* can be provided.

1.3.9 Do not offer sodium nitroprusside to people with acute heart failure.

* Level 2 care is for people needing more detailed observation or intervention, including support for a single failing organ system or postoperative care and for those stepping down from higher levels of care. From Intensive Care Society, Levels of Critical Care for Adult Patients (2009).

Surveillance decision

This review question should not be updated.

Vasodilatory drugs

2017 surveillance summary

Vasodilators and inotropes

A systematic review with meta-analysis and meta-regression(30) (35 studies, n=3,016) assessed the effects of vasodilators and inotropes in people with acute heart failure and reduced left-ventricular ejection fraction. All included studies used pulmonary artery catheterisation, but the abstract did not specify all the included drugs. Both vasodilators and inotropes improved mean pulmonary artery wedge pressure and right atrial pressure, and the effect sizes appeared to be similar, although no statistical comparison of the two drug classes was reported in the abstract.

Hydralazine and isosorbide dinitrate

An RCT(31) (n=147) assessed hydralazine 50 mg plus isosorbide dinitrate 20 mg three times daily or placebo for 24 weeks. The study stopped early because of poor recruitment. No significant differences in death or readmission for heart failure were seen between the intervention and placebo groups. Secondary outcomes of dyspnoea at 7 days, weight loss, and 6-minute walk test at week 24 also showed no significant differences.

Nicorandil

An RCT(32) (n=106) assessed nicorandil plus usual care compared with usual care alone in people with acute heart failure. Participants were randomised within 1 hour of admission. Nicorandil was administered as a 0.2 mg/kg bolus followed by 0.2 mg/kg/hour for 24 hours. Usual care was not specified in the abstract. Nicorandil-treated patients had significantly improved dyspnoea at 1 hour and 6 hours compared with usual care, and estimated left ventricular filling pressure was significantly improved at 1 hour and 24 hours. However, no difference was seen in all-cause mortality or readmission rates at 60 days. Nicorandil is not currently licensed in the UK for treatment of acute heart failure.

Nesiritide and ularitide

Several studies on vasodilatory recombinant natriuretic peptides were identified including:

- recombinant BNP
  - nesiritide(33–36)
  - unspecified recombinant BNP preparation(37)
- ularitide, a recombinant urodilatin preparation(38)
- recombinant atrial natriuretic peptide(39,40)

However, these studies were not thought to have an impact on current recommendations because none of these agents are licensed in the UK for any indication at this time.

Trimetazidine

One study of trimetazidine(41) was identified; however, it was not thought to have an impact on current recommendations because

trimetazidine is not licensed in the UK for any indication at this time.

Serelaxin

Several studies on serelaxin, a recombinant relaxin-2 preparation with vasodilatory effects, were identified;(42–46) however, these studies were not thought to have an impact on current recommendations because serelaxin is not licensed in the UK for any indication at this time, and development has been discontinued.

Topic expert feedback

Topic experts highlighted a study on ularitide.(38)

Impact statement

Studies on agents that are not licensed in the UK indicate research activity in this area. However, no information was identified to indicate that these agents may become available in the UK in the near future, and so these studies cannot impact on current recommendations.

Additionally, a meta-analysis suggests that vasodilators are effective, although one study of the vasodilator hydralazine in combination with isosorbide dinitrate showed no evidence of benefit over placebo. However, this study stopped early so may not have had adequate power to detect an effect.

New evidence is unlikely to change guideline recommendations.

Q – 08 In patients with acute heart failure are inotropes or vasopressors safe and clinically / cost effective compared to medical care or each other to improve outcome?

Recommendations derived from this review question

1.3.10 Do not routinely offer inotropes or vasopressors to people with acute heart failure.

1.3.11 Consider inotropes or vasopressors in people with acute heart failure with potentially reversible cardiogenic shock. Administer these treatments in a cardiac care unit or high dependency unit or an alternative setting where at least level 2 care* can be provided.

* Level 2 care is for people needing more detailed observation or intervention, including support for a single failing organ system or postoperative care and for those stepping down from higher levels of care. From Intensive Care Society, Levels of Critical Care for Adult Patients (2009).

Surveillance decision

This review question should not be updated.

Inotropes

2017 surveillance summary

A network meta-analysis(47) (20 studies, n=5,315) assessed dobutamine, levosimendan, and milrinone in people with acute heart failure. None of the drugs showed a significant effect over placebo or each other on mortality. Milrinone, followed by dobutamine had greatest probability of improving mortality. Levosimendan is not available in the UK.

Several studies on levosimendan were identified.(34,47,48) However, these studies were not thought to have an impact on current recommendations because levosimendan is not licensed in the UK at this time.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

New evidence on levosimendan indicates research activity in this area but does not affect current recommendations because levosimendan is not available in the UK. The Specialist Pharmacy Service indicates that

'there are no immediate plans to license and market the product in the UK'.

The lack of evidence of an effect of dobutamine and milrinone supports current recommendations not to routinely offer these drugs in acute heart failure.

New evidence is unlikely to change guideline recommendations.

NQ – 01 Other initial pharmacological treatments

New review questions considered

New evidence on other initial pharmacological treatments was identified and considered for possible addition to the guideline as new review questions.

Surveillance decision

New review questions should not be added.

Other initial pharmacological treatments

2017 surveillance summary

Statins

An RCT(49) (number of participants not reported in the abstract) assessed oral atorvastatin 80 mg daily for 3 days followed by 10 mg daily until discharge compared with usual care in people with acute heart failure. No significant differences between groups were seen in in-hospital mortality, mortality at 90 days, or levels of NT-proBNP, C-reactive protein, cystatin C or albumin:creatinine ratio.

Glucocorticoids

An RCT(50) (n=102) assessed glucocorticoid treatment compared with usual care in people with acute heart failure. Details about glucocorticoid preparation or administration were not reported in the abstract. The study was terminated early due to insufficient patient enrolment. Glucocorticoid treatment was associated with significantly greater reductions in serum creatinine at day 7 compared with usual care. Cardiovascular deaths at 30 days were significantly reduced in the glucocorticoid group.

Urapidil

Several studies on urapidil, an antihypertensive, were identified;(51–53) however, these studies were not thought to have an impact on current recommendations because urapidil is not licensed in the UK for any indication at this time.

Anakinra

An RCT(54) (n=30) assessed the interleukin-1 blocker, anakinra, compared with placebo in people with acute heart failure. Anakinra was administered as 100 mg twice daily for 3 days then once daily for 11 days. Anakinra was associated with a greater reduction in C-reactive protein than placebo. Anakinra is not licensed in the UK for the treatment of acute heart failure.

Omecamtiv mecarbil

An RCT(55) (ATOMIC-HF; n=606) assessed the investigational cardiac myosin activator, omecamtiv mecarbil, in people with acute heart failure and left ventricular ejection fraction of less than 40% and elevated BNP levels. Omecamtiv mecarbil was administered by infusion to 3 groups in increasing doses (but not specified in the abstract), and compared with placebo. Overall, omecamtiv mecarbil did not significantly relieve dyspnoea; however, the highest dose was associated with significantly greater relief of dyspnoea at 48 hours and at 5 days. Omecamtiv mecarbil was associated with increased left ventricular systolic ejection time and end-systolic dimension. Omecamtiv mecarbil is not licensed in the UK.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Short-term use of high-dose statins showed no evidence of effectiveness in people with acute heart failure.

Glucocorticoid treatment appeared to have benefits on creatinine and 30-day mortality. However, this small study is unlikely to be sufficient to develop recommendations on glucocorticoid use in acute heart failure.

Studies on urapidil, anakinra, and omecamtiv mecarbil indicate research activity in these areas, but cannot inform recommendations at this time because they are not licensed for use in acute heart failure and no information was identified to indicate that this status will change in the near future.

New evidence is unlikely to impact on the guideline.

Initial non-pharmacological treatment

Q – 09 In people with confirmed acute heart failure and cardiogenic pulmonary oedema is non-invasive positive pressure ventilation (CPAP and/or bilevel NIPPV) more clinical and cost effective than standard medical care alone to improve outcome?

Recommendations derived from this review question

1.4.1 Do not routinely use non-invasive ventilation (continuous positive airways pressure [CPAP] or non-invasive positive pressure ventilation [NIPPV]) in people with acute heart failure and cardiogenic pulmonary oedema.

1.4.2 If a person has cardiogenic pulmonary oedema with severe dyspnoea and acidaemia consider starting non-invasive ventilation without delay:

- at acute presentation or
- as an adjunct to medical therapy if the person's condition has failed to respond.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Q – 10 What are the predictors of outcome in invasively ventilated acute heart failure patients?

Recommendations derived from this review question

1.4.3 Consider invasive ventilation in people with acute heart failure that, despite treatment, is leading to or is complicated by:

- respiratory failure or
- reduced consciousness or physical exhaustion.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Q – 11 In patients with acute heart failure is ultrafiltration more clinically / cost effective than diuretic therapy alone or in addition to diuretic therapy to improve outcome?

Recommendations derived from this review question

1.4.4 Do not routinely offer ultrafiltration to people with acute heart failure.

1.4.5 Consider ultrafiltration for people with confirmed diuretic resistance**.

**Diuretic resistance is defined as dose escalation beyond a person's previously recognised dose ceiling or a dose approaching the maximum recommended daily dose without incremental improvement in diuresis. From Diuretics and ultrafiltration in acute decompensated heart failure.

Surveillance decision

This review question should not be updated.

Ultrafiltration versus diuretics

2017 surveillance summary

A systematic review and meta-analysis(56) (10 studies, n=857) assessed ultrafiltration compared with diuretics in people with acute heart failure. Although p-values were not reported in the abstract, 95% confidence intervals crossed the point of no effect for the following outcomes: weight loss, hospital stay, readmission for heart failure or readmission for any cause, and mortality.

A systematic review and meta-analysis(57) (7 studies, n=771) assessed ultrafiltration compared with diuretics in people with acute heart failure. Ultrafiltration was associated with greater weight loss and fluid removal than diuretics, but no differences were seen for renal function. Readmission for heart failure was significantly lower with ultrafiltration, but no difference was seen for mortality.

A systematic review and meta-analysis(58) (12 studies, n=659) assessed the effects of ultrafiltration in people with acute heart failure, however the control group was not defined in the abstract. The authors noted that only 1 study provided usable data. Ultrafiltration was associated with significantly greater fluid removal and weight loss but had no significant effects on all-cause mortality or readmission to hospital for any cause.

A systematic review and meta-analysis(59) (6 studies, n=523) assessed ultrafiltration compared with diuretics in people with acute heart failure. No significant differences were seen in all-cause mortality, readmission for heart failure, unscheduled medical consultations for heart failure, or worsening renal function.

An RCT(60) (AVOID-HF; n=224) assessed ultrafiltration compared with intravenous loop diuretics in people admitted to hospital with heart failure. The study planned to recruit 810 participants, but stopped early. No significant differences in time to first heart failure event were seen between groups. However, significantly more people in the ultrafiltration group had an adverse event 'of special interest' and serious product-related adverse events.

An RCT(61) (n=56) assessed ultrafiltration compared with usual care (details not specified in the abstract) in people with acute heart failure. Weight loss and mortality did not differ significantly between groups. People in the ultrafiltration group had a lower rate of readmission in the year after the study.

Topic expert feedback

Topic experts highlighted meta-analyses(56,57) and the AVOID-HF study(60), but concluded that new evidence does not indicate a need to update recommendations in this area.

Impact statement

Although the studies of ultrafiltration varied in the reported outcomes, on balance, there was no strong evidence of benefit of ultrafiltration on mortality or readmission for heart failure.

Although ultrafiltration may increase fluid removal compared with diuretics, it may increase adverse events.

These findings provide support for the current recommendation to not routinely offer ultrafiltration to people with acute heart failure.

New evidence is unlikely to change guideline recommendations.

NQ – 02 Other initial non-pharmacological treatments

New review questions considered

New evidence on other initial non-pharmacological treatments was identified and considered for possible addition to the guideline as new review questions.

Surveillance decision

New review questions should not be added.

Other initial non-pharmacological treatments

2017 surveillance summary

Nutrition

An RCT(62) (n=120) assessed individualised nutrition support compared with usual care in people with acute heart failure. The trial stopped early after analysis of the first 120 patients; however, the intended enrolment was not reported in the abstract. The intervention was associated with a significant reduction in the composite outcome of all-cause death or readmission for worsening heart failure. Both components also showed significant improvements with intervention when considered individually.

Neuromuscular electrical stimulation

An RCT(63) (n=70) assessed neuromuscular electrical stimulation compared with usual care in people with acute heart failure. The study recruited 195 people, but only 70 were randomised, but the reasons for the reduced sample were not reported in the abstract. The final analysis included only 49 people. People in the neuromuscular electrical stimulation group had daily 'lower extremity' training sessions. The neuromuscular stimulation group had a significantly higher 6 minute walking distance, and lower dobutamine use, compared with usual care.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The study on nutrition support in people with heart failure emphasises the importance of adequate nutrition in people with acute heart failure. NICE has guidance on nutrition support in adults, and the evidence identified in surveillance did not suggest any special considerations were necessary for people with acute heart failure.

The study on neuromuscular electrical stimulation indicated that daily lower extremity training sessions had benefits on walking capacity and reduced dobutamine use. However, the final analysis had a very small sample size, which is unlikely to be sufficient to develop recommendations in this area.

New evidence is unlikely to impact on the guideline.

Treatment after stabilisation

Q – 12 **In people with acute heart failure already on beta-blocker therapy should beta-blockers be reduced or discontinued, and if so should they be reinstated in hospital after stabilisation?**

Q – 13 **For people with confirmed acute heart failure not already on beta-blocker therapy should beta-blocker treatment commence in hospital after stabilisation or following discharge?**

Recommendations derived from these review questions

1.5.1 In a person presenting with acute heart failure who is already taking beta-blockers, continue the beta-blocker treatment unless they have a heart rate less than 50 beats per minute, second or third degree atrioventricular block, or shock.

1.5.2 Start or restart beta-blocker treatment during hospital admission in people with acute heart failure due to left ventricular systolic dysfunction, once their condition has been stabilised – for example, when intravenous diuretics are no longer needed.

1.5.3 Ensure that the person's condition is stable for typically 48 hours after starting or restarting beta-blockers and before discharging from hospital.

1.5.5 Closely monitor the person's renal function, electrolytes, heart rate, blood pressure and overall clinical status during treatment with beta-blockers, aldosterone antagonists or angiotensin-converting enzyme inhibitors.

Surveillance decision

This review question should not be updated.

Stopping beta blockers

2017 surveillance summary

A systematic review and meta-analysis(64) (6 studies, n=3,143) assessed the effects of stopping beta-blocker treatment in people with acute heart failure. The included studies were 1 RCT and 5 observational studies. Withdrawing beta blocker therapy was associated with significantly increased in-hospital mortality, short-term mortality, and short-term readmission to hospital plus death.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Evidence identified in surveillance indicates that stopping beta-blockers may have detrimental effects in people with acute heart failure. However, the new evidence did not address clinical situations for which stopping beta blockers is currently recommended, such as a heart rate less than 50 beats per minute, second or third degree atrioventricular block, or shock. Thus, current recommendations should not be updated.

New evidence is unlikely to change guideline recommendations.

Q – 14 **For people with confirmed acute heart failure not already on angiotensin converting enzyme (ACE)-inhibitor therapy, should ACE inhibitor therapy commence in hospital or following discharge?**

Q – 15 **For people with confirmed acute heart failure not already on aldosterone antagonists should aldosterone antagonist therapy commence in hospital after stabilization or following discharge?**

Recommendations derived from these review questions

1.5.4 Offer an angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker if there are intolerable side effects) and an aldosterone antagonist during hospital admission to people with acute heart failure and reduced left ventricular ejection fraction. If the angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) is not tolerated an aldosterone antagonist should still be offered.†

1.5.5 Closely monitor the person's renal function, electrolytes, heart rate, blood pressure and overall clinical status during treatment with beta-blockers, aldosterone antagonists or angiotensin-converting enzyme inhibitors.

† In February 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) published advice on the concomitant use of spironolactone and renin-angiotensin system drugs in heart failure concerning the risk of potentially fatal hyperkalaemia. See the MHRA advice for more information.

Surveillance decision

These review questions should not be updated.

2017 surveillance summary

An RCT(65) (n=21) assessed angiotensin receptor blocker add-on therapy compared with placebo in people with low cardiac output in people with acute heart failure and an ejection fraction of less than 45%. The angiotensin receptor blocker group received lostartan but the dosage was not reported in the abstract. At 7 days, BNP levels were significantly lower in the losartan group than in the placebo group. In the losartan group, BNP levels fell, whereas BNP increased in the placebo group. Haemodynamic measurements did not differ significantly between groups.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The evidence identified in surveillance indicates possible beneficial effects of angiotensin receptor blockers on BNP levels. However, this study provides no evidence to influence the currently recommended position of angiotensin receptor blockers as a second-line treatment if a person has intolerable side effects with angiotensin-converting enzyme inhibitor.

New evidence is unlikely to change guideline recommendations.

NQ – 03 Other treatments after stabilisation

New review questions considered

New evidence on other initial non-pharmacological treatments was identified and considered for possible addition to the guideline as new review questions.

Surveillance decision

New review questions should not be added.

2017 surveillance summary

Carbohydrate antigen (CA-125)-guided therapy

An RCT(66) (n=380) assessed CA-125-guided therapy compared with usual care. The intervention arm aimed to reduce CA-125 to under 35 U/ml by monitoring patients, adjusting diuretic dose, promoting statin adherence. The CA-125-guided therapy significantly reduced both first and recurrent outcome events (readmission to hospital and deaths up to a year after discharge). However, of the composite endpoint, the effect was driven by reductions in readmissions but not mortality.

Pulmonary artery pressure guided therapy

An RCT(67) (n=550) assessed therapy guided by pulmonary artery pressure compared with control in people with acute heart failure who received a permanent pulmonary artery pressure sensor. In the intervention group, pulmonary artery pressure readings were used to adjust treatment, whereas in the control group, investigators had no access to the pulmonary artery pressure readings. The report analysed data from 245 participants with high compliance (93%) with transmitting daily measurements. The group receiving pulmonary artery pressure-directed treatment had significantly lower admissions to hospital for heart failure and 30-day all-cause mortality compared with control.

Dobutamine plus ivabradine

An RCT(68) n=58) assessed ivabradine plus dobutamine compared with dobutamine control in people with acute heart failure. The NICE technology appraisal, Ivabradine for treating chronic heart failure, notes: 'Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists.' This means that ivabradine may not be relevant in treating acute heart failure in the UK, but remains relevant for treating chronic heart failure.

Calcium channel blockers

An RCT(69) (n=104) assessed clevidipine compared with usual care in people with acute heart failure who had systolic blood pressure greater than 160 mm Hg and dyspnoea of at least 50% on visual analogue scale. The primary outcome was median time to, and percent attaining, a systolic blood pressure within a pre-specified target BP range at 30 minutes. More people in the clevidipine group reached the target blood pressure and blood pressure reduction was quicker than in the usual care group. At 45 minutes, people in the clevidipine group had greater reduction in dyspnoea than the usual care group. Serious adverse events and deaths at 30 days were about the same in both groups, although statistical comparisons were not reported in the abstract.

Liraglutide

An RCT(70) (n=300) assessed liraglutide compared with placebo in people with acute heart failure. Liraglutide was titrated to a dose of 1.8 mg/day within the first 30 days and continued for 180 days. The primary end point was a rank score of time to death, time to readmission for heart failure, and time-averaged proportional change in NT-proBNP level from baseline to 180 days. No significant effects of liraglutide were seen for the primary outcome, or the individual measures of deaths or readmission for heart failure. Subgroup analysis of people with diabetes showed no differences between liraglutide and placebo. Liraglutide is not licensed in the UK for treatment of acute heart failure.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Overall, new evidence is deemed insufficient to impact on recommendations at this time for the following reasons:

- There is no clear association between CA-125 and acute heart failure. CA-125 is most commonly detected in people with cancer.
- The study of pulmonary artery pressure directed therapy reported only data for people with high compliance with transmitting their daily measurements. This was a subgroup analysis of the CHAMPION study, which was considered during development of Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure (NICE interventional procedures guidance 463). This guidance recommended that this procedure should only be used with special arrangements for clinical governance, consent and audit or research.
- Ivabradine is currently not licensed for acute heart failure and should only be used in chronic heart failure when patients have stable disease.
- Clevidipine is licensed for rapid reduction of blood pressure in the perioperative setting. The findings of benefit on reducing blood pressure and dyspnea may be unlikely to be sufficient to drive use of clevidipine over other antihypertensives in people with acute heart failure.
- Liraglutide is not licensed for use in acute heart failure in the UK, and the evidence showed no evidence of benefit in acute heart failure.

New evidence is unlikely to change guideline recommendations.

Valvular surgery and percutaneous intervention

Q – 16 For people with aortic stenosis are percutaneous or surgical valvular interventions more clinically or cost effective compared to best medical therapy or each other?

Recommendations derived from this review question

1.6.1 Offer surgical aortic valve replacement to people†† with heart failure due to severe aortic stenosis assessed as suitable for surgery.

1.6.2 Consider transcatheter aortic valve implantation (TAVI) in selected people††, with heart failure caused by severe aortic stenosis, who are assessed as unsuitable for surgical aortic valve replacement. Details of all people undergoing TAVI should be entered into the UK Central Cardiac Audit database.

1.6.3 For guidance on coronary revascularisation see Chronic heart failure (NICE clinical guideline 108)

†† For information about patient selection, see Transcatheter aortic valve implantation for aortic stenosis (NICE interventional procedure guidance 421).

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Q – 17 **For people with heart failure with mitral regurgitation, are surgical valvular or percutaneous interventions more clinically or cost effective compared to best medical therapy or each other?**

Recommendations derived from this review question

1.6.4 Consider surgical mitral valve repair or replacement for people with heart failure due to severe mitral regurgitation assessed as suitable for surgery.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Mechanical assist devices

Q – 18 **For people with acute heart failure which, of the following, is the most clinically / cost effective intervention:**

- **intra-aortic balloon counterpulsation**
- **left ventricular assist devices or**
- **medical care alone?**

Recommendations derived from this review question

1.7.1 At an early stage, the specialist should have a discussion with a centre providing mechanical circulatory support about:

- people with potentially reversible severe acute heart failure or
- people who are potential candidates for transplantation.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Editorial and factual corrections identified during surveillance

No editorial or factual corrections were identified during surveillance.

Research recommendations

Prioritised research recommendations

At pre-specified surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 In people with acute heart failure, congestion and worsening renal function, does the addition of low-dose dopamine to standard therapy lead to greater diuresis and renal protection compared with adding placebo to standard therapy?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database because this guideline was published less than 4 years ago.

RR – 02 In people with acute heart failure and persistent congestion, does the addition of a thiazide diuretic to standard therapy lead to greater diuresis compared with adding placebo to standard therapy?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database because this guideline was published less than 4 years ago.

RR – 03 In people with acute heart failure and hypoperfusion syndrome, is the use of intra‑aortic balloon counter‑pulsation pump (IABP) better than the use of intravenous inotropes?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database because this guideline was published less than 4 years ago.

RR – 04 In people with decompensated heart failure, fluid congestion and diuretic resistance, does ultrafiltration lead to more rapid and effective decongestion compared with continuing diuretic treatment?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

The research recommendation will be retained because there is evidence of research activity in this area.

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