

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive

Clinical guideline

CG95: Chest pain of recent onset

Publication date

March 2010

Previous review dates

2 year review: 2012

Surveillance report for GE

December 2014

Surveillance recommendation

GE is asked to consider the proposal to update the following clinical questions in the guideline using the Standing Committee for Updates via the Clinical Guidelines Update Team:

Stable chest pain

- What is the incremental benefit and cost effectiveness of a clinical history, cardiovascular risk factors and a physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?
- What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin?

Acute chest pain

- What is the utility and cost effectiveness of non-invasive tests in the evaluation of individuals with acute chest pain of suspected cardiac origin?
- What is the diagnostic utility of Multislice Computed Tomography (MSCT) coronary angiography in the diagnosis of patients with acute chest pain of suspected cardiac origin?
- What is the effectiveness and cost effectiveness of new, high-sensitivity troponin assay methods and other new cardiac biomarkers in low, medium, and high risk people with acute chest pain? (research recommendation)

It is proposed that the acute and stable sections are updated separately but in sequence by the same standing committee.

GE is asked to note that this 'yes to update' proposal will not be consulted on.

Key findings

			Potential impact on guidance	
			Yes	No
Evidence from previous surveillance review			✓	
Evidence identified from literature search			✓	
Feedback from Guideline Development Group			✓	
Anti-discrimination and equalities considerations			✓	
Feedback from Triage Panel meeting			✓	
No update	CGUT update	Standard update	Transfer to static list	Change review cycle
	✓			

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Surveillance review of CG95: Chest pain of recent onset

Recommendation for Guidance Executive

Background information

Guideline issue date: March 2010

2 year review: 2012

4 year review: 2014

NCC: National Clinical Guidelines Centre (formerly National Collaborating Centre for Acute and Chronic Conditions)

Outcome of four year surveillance review

1. A literature search for systematic reviews and RCTs was carried out between May 2012 (the end of the search period for the previous surveillance review) and June 2014 and relevant abstracts were assessed. Clinical feedback on the guideline was obtained from 7 members of the Guideline Development Group through a questionnaire, five of which felt that the guideline requires an update relating, in particular, to new higher sensitivity troponin assays, cardiac imaging and other biomarkers.

Outcome of two year surveillance review

2. A surveillance review was carried out in 2012 when it was recommended that the guideline needed an update, particularly in relation to computerised tomographic (CT) angiographies for the diagnosis of ACS in patients with acute chest pain; the use of highly sensitive troponins compared to the conventional cardiac troponins to diagnose ACS in patients with acute chest pain; and the use of updated Diamond-Forrester prediction model to better estimate the pre-test probability of coronary artery disease (CAD) in patients with stable chest

pain without evidence for previous CAD. An update was not scheduled into the work programme following the two year surveillance review due to capacity.

3. New evidence that may impact on recommendations was identified relating to the following areas within the guideline:

Clinical area: Assessment of patients with stable chest pain - recommendation – 1.3.1.1 , 1.3.2.1 , 1.3.2.2 , 1.3.3.1 , 1.3.3.2 , 1.3.3.3 , 1.3.3.4 , 1.3.3.16		
<p>Q: What is the incremental benefit and cost effectiveness of a clinical history, in evaluation of individuals with stable chest pain of suspected cardiac origin?</p> <p>Q: What is the incremental benefit and cost-effectiveness of assessment of cardiovascular risk factors in evaluation of individuals with stable chest pain of suspected cardiac origin?</p> <p>Q: What is the incremental benefit and cost-effectiveness of a physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?</p>		
Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from 2-year surveillance review</u> One study¹ was identified which found that an updated version of the Diamond–Forrester model, including age, sex, symptoms, coronary calcium scores, and cardiovascular risk factors, allowed for a more accurate estimation of the pre-test probability of CAD in stable chest pain without evidence for previous CAD. The authors concluded that this could lead to decreased referral for cardiac coronary angiography (CCA), a higher yield of angiography, and increased use of non-invasive testing for risk stratification.</p> <p><u>Evidence identified from 4-year surveillance review</u> A systematic review² assessing the diagnostic accuracy of clinical prediction models, reported that the six models identified showed good diagnostic accuracy for determining short-term outcomes in a pre-hospital population with suspected ACS.</p>	<p>Clinical feedback at the 2-year surveillance review suggested that there is additional evidence for the validity of using Diamond and Forrester to assess pre-test likelihood of CAD in contemporary practice.</p> <p>Feedback at the 4-year surveillance review indicated that there is evidence that the Diamond-Forrester risk prediction model over-estimates disease probability in patients with suspected angina.</p> <p>Feedback was also provided at</p>	<p>At the 2-year surveillance review, it was considered that the evidence relating to the use of an updated Diamond-Forrester prediction model in patients with stable chest pain could potentially have an impact on the current guideline. Although no further evidence was found relating to an updated Diamond-Forrester prediction model at the 4-year review, feedback from the GDG indicated that the Diamond-Forrester model may over estimate disease probability in suspected angina.</p> <p>Evidence from the 4-year surveillance review showed that 6 unspecified clinical prediction models demonstrated good diagnostic accuracy for determining short-term outcomes in a pre-hospital population</p>

<p>A meta-analysis³ aimed to determine the diagnostic value of single symptoms and signs for coronary heart disease (CHD) in patients with chest pain. In total, 172 studies were included covering 42 signs and symptoms. The findings indicated that the most accurate predictors for a diagnosis of stable CHD were history of CHD, known acute MI, typical angina, history of diabetes mellitus, exertional pain, history of angina pectoris, and male sex. These are consistent with the factors listed in the guideline.</p>	<p>both review points indicating that parameters to assess the pre-test likelihood of coronary disease in patients with stable chest pain have changed. Further information was sought from the GDG regarding these changes and the following reference was provided: Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J2011;32:1316-30. An assessment of the abstract indicated that the Diamond-Forrester model overestimates the probability of CAD, particularly in women. A subsequent update and extension of the model in relation to the predictive value of age, sex, and type of chest pain improved its performance.</p>	<p>with suspected ACS. Furthermore, clinical feedback indicated that the parameters to assess the pre-test likelihood of coronary disease in patients with stable chest pain have changed. Further evidence was provided which supported the view that the Diamond-Forrester model overestimates the probability of CAD, particularly in women. The evidence also suggested that an updated and extended version of the model improved its performance, supporting the evidence found at the 2-year surveillance review.</p> <p>The diagnostic pathway presented in the guideline for people who present with stable chest pain, states that the application of the Diamond Forrester algorithm, as modified by consideration of additional risk factors, may permit a diagnosis of angina if the probability estimate is sufficiently high. The new evidence relating to an updated version of this model may therefore impact on this statement.</p>
<p>Clinical area: Investigations and diagnosis of patients with stable chest pain suspected to be stable angina - recommendations – 1.3.3.16, 1.3.4.4, 1.3.4.5, 1.3.4.6, 1.3.4.7, 1.3.4.8, 1.3.6.1</p>		
<p>Q: What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin?</p>		
<p>Evidence summary</p>	<p>GDG/clinical perspective</p>	<p>Impact</p>

<p><u>Evidence identified from 2-year surveillance review</u></p> <p>Through a focused search, 29 studies⁴⁻³² were identified related to non-invasive and invasive tests for patients with stable chest pain. The evidence showed that various non-invasive techniques including stress echocardiography, PET, myocardial perfusion imaging, CT coronary calcium score, coronary computed tomography, single-photon emission computed tomography (SPECT) and cardiovascular magnetic resonance, were effective in diagnosing CAD when compared to coronary angiography. Other studies found that exercise stress testing, real-time three-dimensional echocardiography and coronary artery calcium were not effective in the diagnosis of CAD when compared to angiography.</p>	<p>Clinical feedback indicated that there is new evidence about diagnostic assessment in patients with suspected stable angina, including the comparative effectiveness of different imaging modalities.</p>	<p>At the 2-year review it was considered that there was no new evidence which would invalidate the current guideline recommendations regarding assessment of patients with stable chest pain.</p>
<p><u>Evidence identified from 4-year surveillance review</u></p> <p>Computed coronary tomographic angiography</p> <p>A systematic review and meta-analysis³³ was identified which compared CCTA versus invasive coronary angiography in the diagnosis of CHD. For the diagnosis of obstructive stenosis, compared to invasive coronary angiography as the reference standard, CCTA had high sensitivity and specificity, and at a pre-test probability of CHD of 50% or less, resulted in a lower cost per patient. However, at a pre-test probability of CHD of 70% or higher, invasive coronary angiography provided a lower cost per patient. For the diagnosis of functionally relevant stenosis, using intracoronary pressure measurement as the reference standard, CCTA had a higher sensitivity but lower specificity than invasive coronary angiography and both types of coronary angiography resulted in substantially higher cost per patient. As such, the review recommended that neither type of angiography should be used in the diagnosis of</p>	<p>It was suggested that novel imaging techniques are now more widely available, particularly CT coronary angiography and MR perfusion imaging for diagnosis of chest pain. CT coronary angiography is also able to pick up other issues with lungs and mediastinum which might be missed in the old paradigm.</p>	<p>Computed coronary tomographic angiography</p> <p>There was new evidence identified at the 4-year review which suggested that CCTA is an effective first line imaging test for the diagnosis of CAD, although it was not clear from all the abstracts what the level of CAD risk was in the study populations. There was also evidence relating to the diagnostic effectiveness of lower radiation CCTA.</p>
	<p>Radiation exposure from CT imaging is now lower with the newer scanners, so exposure will be less.</p>	<p>The new evidence for CCTA together with clinical feedback may potentially impact on the current guideline recommendations relating to the use of CCTA for the diagnosis of CAD in patients with stable chest pain, particularly the level of CAD risk at which to undertake CCTA. Currently the guideline only recommends 64-slice (or above) CT coronary angiography in people who have an estimated likelihood of CAD of 10–29% and have a calcium score of 1-400. For people with an estimated likelihood of CAD of 10–29% and a calcium score over 400, invasive coronary angiography is recommended. Non-invasive functional</p>

<p>functionally relevant stenosis.</p> <p>The results of a meta-analysis³⁴ (n=2567) indicated that patients undergoing CCTA as the first imaging test for the detection of CAD were more likely to undergo percutaneous or surgical revascularisation, and there was a reduction in the time to diagnosis and costs of care compared to non-CCTA patients.</p> <p>A meta-analysis³⁵ (n=3300) was identified which compared image quality, diagnostic accuracy, and radiation dose of prospectively triggered CCTA with retrospectively gated CTA in patients with suspected or known CAD. The results indicated that the image quality and diagnostic accuracy of both types of CTA were similarly high, but with lower radiation doses provided by prospectively triggered coronary CTA.</p> <p>The findings of a systematic review and meta-analysis³⁶ indicated that prospective ECG gating CCTA had high positive and negative predictive values (94% and 99% respectively) for the diagnosis of significant coronary stenosis. The authors concluded that the use of CCTA with prospective ECG gating allows for a reduced radiation exposure without a sacrifice in diagnostic efficacy in a population with high disease prevalence.</p> <p>A pilot RCT³⁷ (n=180) found that CCTA was associated with increased revascularisation, lower costs and lower effective radiation dose compared with myocardial perfusion single-photon emission (MPS) CT in patients presenting with stable chest pain and suspected CAD. CTA and MPS resulted in comparable improvements in angina-specific health status.</p>	<p>low radiation CT angiography is now available.</p> <p>One GDG member identified that the US guideline recommends exercise ECG as first diagnostic test for many patients, and neither the European nor the US guidelines recommend invasive coronary angiography for patients with high probability of disease.</p> <p>One GDG member suggested that the right test to use in lower risk groups is individualised and does not fit into a risk profile. As such, most health care professionals will determine the right diagnostic approach on a patient by patient basis.</p> <p>There is also a concern that the time needed to organise tests, such as nuclear scans and CT angiography is longer and may leave some high risk patients waiting for too long.</p>	<p>imaging is recommended for people who have an estimated likelihood of CAD of 30–60%, or for people who have an estimated likelihood of 61–90% and for whom coronary revascularisation is not being considered or invasive coronary angiography is not clinically appropriate. Invasive coronary angiography is recommended for people who have an estimated likelihood of 61–90% and for whom coronary revascularisation is being considered and invasive coronary angiography is clinically appropriate.</p> <p>Functional stress testing</p> <p>The GDG found that the diagnostic performance for diagnosing CAD did not support the use of one functional imaging test in preference to another and they concluded that the tests were generally comparable and any could be used. The new evidence from the 4 year surveillance review relating to functional imaging generally supports this conclusion and is therefore consistent with the guideline recommendation which states: When offering non-invasive functional imaging for myocardial ischaemia use:</p> <ul style="list-style-type: none"> • myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or • stress echocardiography or
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<p>A systematic review³⁸ was identified which compared 64-slice CCTA and coronary angiography (CA). Ten studies, including 1188 patients with angina with suspected or known CAD, were included in the review. At a patient level, 64-slice CCTA had positive predictive values ranging from 86-97% and negative predictive values of 76.9-100%. The authors concluded that the findings supported the use of 64-slice CCTA as a non-invasive alternative to CA for standalone diagnosis of significant stenosis in patients with angina.</p> <p>The results of a systematic review and meta-analysis³⁹ (n=3,539) indicated that "triple rule-out" computed tomography (TRO CT) had high sensitivity and specificity for diagnosing CAD, although with greater radiation exposure and contrast exposure compared to non-TRO CT.</p> <p>A systematic review⁴⁰ was identified which assessed the clinical effectiveness and cost-effectiveness of new-generation computed tomography (NGCCT) for diagnosing CAD in patients who are difficult to image using 64-slice computed tomography (e.g. obese patients, patients with high or irregular heartbeats and patients who have high levels of coronary calcium or a previous stent or bypass graft). The results indicated that NGCCT had good diagnostic accuracy for diagnosing CAD in difficult-to-image patients. An NGCCT only strategy was most cost-effective in patients with suspected CAD, whereas invasive coronary angiography after a positive NGCCT was the most cost-effective strategy in patients with known CAD.</p> <p><i>Functional stress testing</i></p>		<ul style="list-style-type: none"> • first-pass contrast-enhanced magnetic resonance (MR) perfusion or • MR imaging for stress-induced wall motion abnormalities.
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<p>A meta-analysis⁴¹ (n=761) reported that stress perfusion cardiac MRI had a high sensitivity and specificity (89.1% and 84.9% respectively) for diagnosing flow-limiting obstructive CAD.</p> <p>The results of two RCTs^{42,43} suggested that stress real-time myocardial contrast echocardiography (RTMCE) increased the detection of CAD compared to conventional stress echocardiography.</p> <p>The results of a meta-analysis⁴⁴ (n=13304) suggested that compared to exercise tolerance testing, stress imaging with MPI and stress echocardiography were the most accurate at stratifying cardiac risk in patients over 65 years of age with known or suspected CAD.</p> <p>A systematic review⁴⁵ was identified which found that referral bias reduced the sensitivity and increased the specificity of exercise echocardiography and MPI for CAD. The authors concluded that further research was needed to assess the ability of these and other tests to rule-in rather than rule-out CAD.</p> <p>The results of a meta-analysis⁴⁶ (n=11,862) found that Positron emission tomography (PET) had higher mean sensitivity than SPECT (92.6% v 88.3%) for diagnosing >50% stenosis in patients with known or suspected CAD. A second systematic review and meta-analysis⁴⁷ indicated that rubidium (Rb)-82 PET provided more accurate diagnosis of obstructive CAD in comparison to SPECT. However, the review was limited by heterogeneity among study populations and referral bias in some studies. Finally, the results of a meta-analysis⁴⁸ indicated</p>		
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that SPECT demonstrated moderate accuracy in diagnosing functional stenotic CAD, with a sensitivity and specificity of 77% and 77% respectively.

The results of a meta-analysis⁴⁹ suggested that cardiac magnetic resonance (CMR) had higher sensitivity for the detection of obstructive CAD than SPECT.

A systematic review and meta-analysis⁵⁰ was identified which aimed to assess the diagnostic accuracy of CMR imaging assessing myocardial viability in patients with chronic left ventricular (LV) dysfunction due to CAD. The review included 24 studies including 698 patients, evaluating myocardial viability using three techniques. Of the techniques assessed, Contrast delayed enhancement CMR had the highest sensitivity (95%) for predicting improved segmental LV contractile function after revascularisation, and low-dose dobutamine had the highest specificity (91%). The authors concluded that integrating the two methods would increase accuracy in evaluating patients with chronic LV dysfunction.

An RCT⁵¹ was identified which assessed the effect of provider-directed imaging stress testing in lower-risk chest pain patients presenting to the emergency department. Patients were randomised to receive a CMR stress test (n=60) or a provider-selected stress test (n=60) (e.g. stress echo, CMR, cardiac catheterisation, nuclear, and coronary CT). The results of the study indicated that the median cost was higher for those receiving the CMR mandated test, with no differences in other outcomes between the two groups.

A systematic review and meta-analysis⁵² examining the

<p>diagnostic accuracy of magnetocardiography (MCG) reported that MCG had a sensitivity of 83% and a specificity of 77% for the diagnosis of CAD. However, the authors reported that there was significant heterogeneity present in all meta-analyses.</p> <p>A systematic review and meta-analysis⁵³ was identified which assessed the efficacy of Tissue Doppler imaging (TDI) in the diagnosis of CAD. The results showed that among CAD patients, TDI was associated with a decrease in the maximum systolic velocity at rest, and a decrease in maximum early diastolic velocity and maximum late diastolic velocity post stress. The authors concluded that TDI may have a role in the evaluation of CAD.</p>		
<p>Clinical area: Investigations and diagnosis of patients with acute chest pain - recommendations 1.2.6.6, 1.2.6.7</p>		
<p>Q: What is the utility and cost effectiveness of non-invasive tests in the evaluation of individuals with acute chest pain of suspected cardiac origin?</p>		
<p>Evidence summary</p>	<p>GDG/clinical perspective</p>	<p>Impact</p>
<p><u>Evidence identified from 2-year surveillance review</u> Through a focused search two studies were identified relating to stress testing in patients with acute chest pain. One study⁵⁴ found that the addition of stress echocardiography to electrocardiography (ECG) was more effective than the individual tests alone in assessing patients with acute chest pain. The results of another study⁵⁵ suggested that routine cardiac provocative cardiac testing added little to the diagnostic evaluation of low-risk young adult patients with acute coronary syndromes (ACS) compared to cardiac biomarkers.</p> <p><u>Evidence identified from 4-year surveillance review</u> An RCT⁵⁶ (n=1508) found that stress myocardial perfusion</p>	<p>Clinical feedback indicated that the guideline needs to be updated. One of the reasons supporting this was that cardiac imaging has moved on over the last 4 years although no further details were provided.</p>	<p>The evidence identified at the 2-year surveillance review found limited evidence for stress testing in the assessment of patients presenting with acute chest pain in the emergency department. The evidence was considered to be in keeping with the current recommendations relating to the evaluation of individuals with acute chest pain, which include resting 12-lead ECG and troponin testing, as well as carrying out a physical examination and taking a detailed clinical history.</p>

<p>imaging (SMPI) added to a standard triage strategy (including clinical evaluation, serial ECGs, and cardiac markers) more effectively identified patients with ACS, with reduced hospital admission rates for participants who underwent SMPI compared to those who received just clinical assessment.</p> <p>The findings of an RCT⁵⁷, including 105 intermediate-risk participants without a definite diagnosis of ACS following ECG and troponin testing, indicated that stress cardiac magnetic resonance (CMR) imaging in an observation unit reduced coronary artery revascularisation, hospital readmissions, and recurrent cardiac testing compared to usual care provided by cardiologists and internists.</p> <p>The results of a systematic review and meta-analysis⁵⁸ (n=634) indicated that CMR had a higher sensitivity but lower specificity than low-dose dobutamine CMR for the assessment of myocardial stunning after acute myocardial infarction.</p>		<p>The new evidence identified at the 4-year review suggests that non-invasive cardiac imaging, including stress myocardial perfusion imaging and stress cardiac magnetic resonance imaging, may be an alternative method for excluding other diagnoses in people with symptoms of ACS but with an uncertain diagnosis following ECG and troponin testing. Currently the guideline recommends a chest X-ray to help exclude complications of ACS, and early chest computed tomography (CT) should only be considered to rule out other diagnoses. The new evidence relating to non-invasive cardiac imaging may potentially impact on these recommendations.</p>
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Clinical area: Investigations and diagnosis of patients with acute chest pain - recommendation [1.2.6.7](#)

Q: What is the diagnostic utility of Multislice Computed Tomography (MSCT) coronary angiography in the diagnosis of patients with acute chest pain of suspected cardiac origin?

Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from 2-year surveillance review</u> Through a high-level search, one systematic review⁵⁹ was identified which determined that 64-section coronary computed tomography angiography (CCTA) was best for identifying patients with symptoms of ACS who can safely be discharged home rather than diagnosing patients who have positive symptoms. An additional focused literature search identified 13 studies⁶⁰⁻⁷² relating to computerised angiographies in patients with acute chest pain. Overall, the studies showed that various</p>	<p>Clinical feedback indicated that there is evolving evidence for the use of CT coronary angiography in patients with acute chest pain and that the newer scanners that are now available have reduced radiation exposure.</p>	<p>During development of the guideline the GDG appraised the evidence for the use of MSCT for emergency department triage of patients with acute chest pain and was of the opinion that there was insufficient evidence on which to make a recommendation for its use in such patients. They acknowledged that this was an evolving area, which was the subject of</p>

<p>forms of computerised angiography were diagnostically effective in detecting coronary artery disease (CAD) in patients presenting with acute chest pain in emergency departments. Two of the studies also showed that computed tomography was cost effective.</p> <p><u>Evidence identified from 4-year surveillance review</u></p> <p>An RCT⁷³ comparing early CCTA and standard emergency department evaluation in patients with acute chest pain found that CCTA reduced hospital length of stay and admission rates, and lessened the increased cumulative radiation dose in women with suspected ACS compared to men. The results also indicated that there were no differences in major adverse cardiac events between CCTA and standard care, or between men and women.</p> <p>The results of a systematic review and meta-analysis⁷⁴ indicated that CCTA led to an increase in referral rates for invasive coronary angiography and coronary revascularisation compared to usual care triage of acute chest pain in the emergency department. An RCT⁷⁵ also found that CCTA increased the frequency of revascularisations as well as improving the detection of significant coronary stenosis in patients with acute chest pain.</p> <p>An RCT⁷⁶ (n=60) was identified which aimed to examine the dose reduction potential of low kV triple-rule-out dual-source CT angiography (TRO-CTA) in non-obese patients with acute chest pain. The subjective image quality of the low-dose TRO-CTA was rated similar to the standard protocol TRO-CTA. There were also no differences in the signal-to-noise and contrast-to-noise ratios in different vascular segments between</p>		<p>on-going research, but the published evidence found to date was in small cohorts of patients and further research is required.</p> <p>There is new evidence identified at the 2 and 4 year surveillance reviews, as well as clinical feedback, which suggests that computed tomography is effective in the assessment of people with acute chest pain, including in the triage of patients in an emergency department. There may now be sufficient new evidence on which to make a recommendation for the use of computed tomography in such patients, thus impacting on the current guideline recommendation which states: Only consider early chest computed tomography (CT) to rule out other diagnoses such as pulmonary embolism or aortic dissection, not to diagnose ACS.</p>
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<p>the two groups. However, vessel attenuation was higher in the low dose TRO-CTA group than in the standard protocol group.</p>		
<p>Clinical area: Investigations and diagnosis of patients with acute chest pain (research recommendation) - recommendations – 1.2.1.10, 1.2.5</p>		
<p>Q: What is the effectiveness and cost effectiveness of new, high-sensitivity troponin assay methods and other new cardiac biomarkers in low, medium, and high risk people with acute chest pain?</p>		
<p>Evidence summary</p>	<p>GDG/clinical perspective</p>	<p>Impact</p>
<p><u>Evidence identified from 2-year surveillance review</u> Through a focused literature search, 27 studies⁷⁷⁻⁹⁴ were identified. The new evidence indicated that high sensitive troponins are more effective than conventional cardiac troponins in the early diagnosis of acute myocardial infarction and ACS.</p> <p>A further four studies⁹⁵⁻⁹⁸ were identified which indicated that copeptin, together with high sensitive troponin, improves diagnostic performance in early diagnosis of patients with suspected MI.</p> <p>It was considered that the new evidence relating to high-sensitive troponin and copeptin could potentially impact on the current recommendations in the guideline.</p> <p>Six more studies⁹⁹⁻¹⁰⁴ were identified which looked at other biomarkers for ACS, including amino terminal pro-B-type natriuretic peptide, unbound free fatty acids, high-sensitivity C-reactive protein, pentraxin 3 and serum ischemia modified</p>	<p>At both the 2-year and 4-year review points, clinical feedback was provided which identified that there is new evidence relating to highly sensitive troponin assays for testing patients with suspected ACS. Feedback suggested that the new troponin assays are now increasingly used and have reduced the timescales from symptom onset to results from 10-12 hours to 3-6 hours.</p> <p>NICE currently has no plans to update MTG4. Feedback from the Newcastle and York External Assessment Centre has indicated that that the claimed benefits of the</p>	<p>The clinical evidence for the following biomarkers was assessed as part of a review question in the guideline: troponin I, troponin T, creatine kinase (CK), creatine kinase-MB (CKMB), creatine kinase-MB isoforms (CKMB isoforms) and myoglobin. An additional research recommendation was made with the aim of investigating newer more sensitive troponin assays which may offer advantages over previous assays in terms of diagnostic accuracy, and allow exclusion of MI earlier than the 12 hour time frame currently required. The research recommendation also sought to assess other proposed biomarkers compared to the best available troponin assays.</p> <p>At the 2-year surveillance review, it was considered that the evidence relating to</p>

<p>albumin. These were just single studies and it was therefore considered that more evidence would be required to support these findings before consideration for inclusion in the guideline.</p> <p><u>Evidence identified from 4-year surveillance review</u></p> <p>The results of an RCT¹⁰⁵ (n=542) suggested that a rapid diagnostic pathway (including Thrombolysis in Myocardial Infarction score, electrocardiography and 0- and 2-hour troponin tests) increased the proportion of patients with chest pain discharged within 6 hours compared to a standard-care diagnostic pathway (including troponin test on arrival at hospital, prolonged observation, and a second troponin test 6-12 hours after onset of pain) for the assessment of patients with acute chest pain consistent with ACS.</p> <p>An RCT¹⁰⁶ was identified which assessed changes in contemporary sensitive troponin I (TnI) levels in 7,863 patients after MI or unstable angina. The findings indicated that both baseline TnI levels and increases in TnI levels after 1 year were linked with an increased risk of CHD death and myocardial infarction. A second study, a systematic review and meta-analysis¹⁰⁷ including 4 studies (n=2033), also found that elevated high-sensitivity troponin (hs-Tn) were associated with an increased risk of mortality. It is unlikely that this new evidence will impact on current recommendations.</p> <p>New Diagnostics guidance, published in October 2014, reviewed the clinical and cost-effectiveness of three types of high-sensitive troponin assay (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays) compared to standard troponin testing over</p>	<p>copeptin assay have been superseded by high-sensitivity troponin assays in terms of faster diagnosis of MI.</p>	<p>high sensitive troponins compared to the conventional cardiac troponins to diagnose ACS in patients with acute chest pain could potentially impact on the current guideline recommendations. The new Diagnostics guidance reviewed the clinical and cost-effectiveness of high-sensitive troponins compared to standard troponin testing over 10–12 hours, and recommended the Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay as options for the early rule out of non-ST-segment-elevation myocardial infarction (NSTEMI) in people presenting to an emergency department with chest pain and suspected ACS. The assays are recommended for use with ‘early rule-out protocols’, which typically include a blood sample for cardiac troponin I or T taken at initial assessment in an emergency department and a second blood sample taken after 3 hours. Currently CG95 only recommends: Take a blood sample for troponin I or T measurement on initial assessment in hospital. These are the preferred biochemical markers to diagnose acute MI; and take a second blood sample for troponin I or T measurement 10–12 hours after the onset of symptoms. The evidence identified at the 2 and 4 year surveillance reviews, together with the Diagnostics Guidance and clinical</p>
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<p>10–12 hours. The guidance recommends the Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay as options for the early rule out of non-ST-segment-elevation myocardial infarction (NSTEMI) in people presenting to an emergency department with chest pain and suspected ACS. The assays are recommended for use with ‘early rule-out protocols’, which typically include a blood sample for cardiac troponin I or T taken at initial assessment in an emergency department and a second blood sample taken after 3 hours.</p> <p>The results of a meta-analysis¹⁰⁸ indicated that circulating miRNAs, particularly miR-499 and miR-133a, had good diagnostic accuracy for myocardial infarction.</p> <p>A systematic review and meta-analysis¹⁰⁹ (n=941) was identified which assessed the early diagnostic performance of glycogen phosphorylase isoenzyme BB (GPBB) in patients with suspected AMI. The results of the meta-analysis found that GPBB had a sensitivity of 0.854 and specificity of 0.767, although there was high heterogeneity across the included studies. The authors concluded that GPBB does not currently provide efficient diagnosis of AMI when used as a stand-alone test.</p> <p>Two systematic reviews and meta-analyses^{110,111} were identified which found that the addition of heart-type fatty acid binding protein (H-FABP) to troponin increased sensitivity but decreased specificity compared to troponin alone for the diagnosis of MI.</p> <p>MTG4 (NICE medical technologies guidance), published in</p>		<p>feedback, indicate that high sensitive troponins are effective in the diagnosis of acute MI and ACS, and therefore may impact on the current recommendations in the guideline.</p> <p>Evidence was identified at the 2-year surveillance review regarding the improved diagnostic performance of copeptin together with high sensitive troponin in patients with MI. It was considered that this evidence could potentially impact on the current guideline recommendations. However, MTG4, which was published in June 2011, reviewed the evidence for copeptin assay including two studies considered at the 2 year surveillance review. It found that whilst the assay showed potential to reduce the time taken to rule out MI when used in combination with cardiac troponin testing, there was insufficient evidence on its use in clinical practice to support the case for routine adoption in the NHS and recommended that further research be undertaken in the UK clinical setting to compare the BRAHMS copeptin assay in combination with cardiac troponin testing against sequential cardiac troponin testing for ruling out MI. Further evidence relating to copeptin was identified at the 4 year surveillance review which also showed that copeptin and troponin combined had</p>
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<p>June 2011, was identified through the intelligence gathering search for the guideline. MTG4 stated that the BRAHMS copeptin assay shows potential to reduce the time taken to rule out myocardial infarction in patients presenting with acute chest pain, when used in combination with cardiac troponin testing. However, it stated that there is currently insufficient evidence on its use in clinical practice to support the case for routine adoption of the BRAHMS copeptin assay in the NHS and recommended that further research be undertaken in the UK clinical setting to compare the BRAHMS copeptin assay in combination with cardiac troponin testing against sequential cardiac troponin testing for ruling out MI. As part of the evidence base for this guidance, two studies considered at the previous surveillance review (Keller et al., 2010; Reichlin et al., 2009) were considered. Through the literature search for the 4-year surveillance review, two systematic reviews^{112,113} were identified which published after MTG4. The studies found that copeptin and troponin combined improved sensitivity for the diagnosis of acute MI compared with troponin alone.</p>		<p>increased sensitivity for diagnosing MI. NICE currently has no plans to update MTG4 and feedback has indicated that that the claimed benefits of the copeptin assay have been superseded by high-sensitivity troponin assays in terms of faster diagnosis of MI.</p> <p>Evidence was also identified in relation to other biomarkers, including heart-type fatty acid binding protein which increased the sensitivity of troponin compared to troponin alone, and miRNAs which had good diagnostic accuracy for MI.</p> <p>In summary, the evidence and clinical feedback relating to high sensitive troponins and other biomarkers for MI, suggest that there is potentially new evidence in this area which should be considered for inclusion in the guideline.</p>
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Ongoing research

4. The following ongoing trials relevant to this guideline were identified through clinical feedback and the literature search for the surveillance review:
 - The impact of the HEART risk score in the early assessment of patients with acute chest pain: design of a stepped wedge, cluster randomised trial. Estimated study completion date – November 2014.
 - HTA - 13/04/108: The RAPID-CTCA trial (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA) The role of early CT Coronary Angiography in the evaluation, intervention and outcome of patients presenting to the Emergency Department with suspected or confirmed Acute Coronary Syndrome

- The role of cardiovascular magnetic resonance imaging and computed tomography angiography in suspected non-ST-elevation myocardial infarction patients: design and rationale of the CARdiovascular Magnetic rEsoNance imaging and computed Tomography Angiography (CARMENTA) trial.
- Role of multidetector computed tomography in the diagnosis and management of patients attending the rapid access chest pain clinic, The Scottish computed tomography of the heart (SCOT-HEART) trial. The study is expected to report in 2014.
- Design and rationale of the MR-INFORM study: stress perfusion cardiovascular magnetic resonance imaging to guide the management of patients with stable coronary artery disease.
- DETermination of the role of OXYgen in suspected Acute Myocardial Infarction trial. Estimated Study Completion Date: December 2015.
- A randomized controlled trial of oxygen therapy in acute myocardial infarction Air Verses Oxygen In myocarDial infarction study (AVOID Study).

Anti-discrimination and equalities considerations

5. Clinical feedback from the GDG indicated that there is geographical variation in access to diagnostic testing for patients with stable chest pain.

Implications for other NICE programmes

6. This guideline relates to the Quality Standard for Acute coronary syndromes (including myocardial infarction) ([QS68](#) published September 2014) and to the Quality Standard for Stable angina ([QS21](#) published August 2012).
7. None of the quality statements in QS68 are likely to be affected by the proposed areas for update.
8. The proposed area for update 'Assessment of patients with stable chest pain' is likely to affect [Quality statement 1: Diagnostic investigation](#) in QS21. In particular, recommendation 1.3.3.16 from CG95 was used as the guideline source for Statement 1 and recommendations 1.3.3.1, 1.3.3.16 and 1.3.4.4-7 are the sources for the definitions attached to this statement.

Triage Panel recommendation

9. The new evidence identified through the surveillance review of CG95 which may potentially impact on guideline recommendations was considered by the Triage Panel to determine the most appropriate route to commission an update.
 - i. Assessment of patients with stable chest pain:

- a. *What is the incremental benefit and cost effectiveness of a clinical history, cardiovascular risk factors and a physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?*
- The Triage Panel agreed that this question needs to be updated to reflect new evidence relating to a revised version of the Diamond and Forrester model. The evidence suggested that the current Diamond and Forrester model overestimates the probability of coronary artery disease (CAD). The revised model would therefore impact on the recommended appropriate first-line diagnostic investigation required based on a person's estimated likelihood of CAD. It was felt that the review question could be amended to ensure focus around diagnosing CAD.
 - **Decision:** NICE to update this clinical question using the Standing Committee for Updates via the Clinical Guidelines Update Team.
- ii. Investigations and diagnosis of patients with stable chest pain suspected to be stable angina:
- a. *What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin?*
- The Triage Panel agreed that this question would need to be updated and suggested that the body of evidence on all imaging modalities, including functional imaging should be evaluated whilst the current economic model could be adapted to include more comparators.
 - **Decision:** NICE to update this clinical question using the Standing Committee for Updates via the Clinical Guidelines Update Team.
- iii. Investigations and diagnosis of patients with acute chest pain:
- a. *What is the utility and cost effectiveness of non-invasive tests in the evaluation of individuals with acute chest pain of suspected cardiac origin?*
- The Triage Panel indicated that the new evidence relating to this question was less convincing. However, the group felt that if an update of Computed Tomography (CT) angiography for acute chest pain was being considered, evidence relating to functional imaging should also be evaluated. In terms of priorities, the group suggested that functional testing for acute coronary syndromes (ACS) should be a lower priority.
 - **Decision:** NICE to update this clinical question using the Standing Committee for Updates via the Clinical Guidelines Update Team.

- b. *What is the diagnostic utility of Multislice Computed Tomography (MSCT) coronary angiography in the diagnosis of patients with acute chest pain of suspected cardiac origin?*
- The Triage Panel agreed that the evidence relating to this question has moved on significantly since the guideline was developed and that the guideline recommendation relating to CT scanning would need updating. It was acknowledged that there is an ongoing HTA trial (RAPID-CTCA) in this area but that this is unlikely to report for at least two years. However, in order to avoid hindering recruitment to the trial and repeating any review of evidence already undertaken, the group agreed that an update should consider the role of CT angiography in patient groups who would not be eligible for the trial.
 - **Decision:** NICE to update this clinical question using the Standing Committee for Updates via the Clinical Guidelines Update Team.
- c. *What is the effectiveness and cost effectiveness of new, high-sensitivity troponin assay methods and other new cardiac biomarkers in low, medium, and high risk people with acute chest pain?*
- The Triage Panel agreed that this question needs to be updated as the guideline recommendation relating to the use of standard troponin assays has been superseded by current clinical practice and the recently published [Diagnostics guidance \(DG15\)](#) which recommends high-sensitivity troponin testing for the early rule out or diagnosis of acute myocardial infarction in people with acute chest pain. The Triage Panel indicated that there was potential for CG95 to cross reference to the Diagnostics guidance but that an additional check was needed to determine if any supplementary recommendations might be required.
 - **Decision:** NICE to update this clinical question using the Standing Committee for Updates via the Clinical Guidelines Update Team.

Conclusion

10. Through the surveillance review of CG95 new evidence which may potentially impact guideline recommendations was identified in the following areas:

- Assessment of patients with stable chest pain
- Investigations and diagnosis of patients with stable chest pain suspected to be stable angina
- Investigations and diagnosis of patients with acute chest pain

11. All these areas were considered by the Triage Panel and were assessed as requiring an update at this time. It was determined that all the areas identified should be updated using the Standing Committee for Updates via the Clinical Guidelines Update Team.

12. For all other areas of the guideline no evidence was identified which would impact on recommendations.

Mark Baker – Centre Director
Sarah Willett – Associate Director
Diana O'Rourke – Technical Analyst

Centre for Clinical Practice
December 2014

Appendix 1 Decision Matrix

Surveillance and identification of triggers for updating CG95. The table below provides summaries of the evidence for key questions for which studies were identified.

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
95-01: What are the education and information needs in adults presenting with chest pain to optimise their understanding of the diagnostic process and their participation in decisions about their investigations?			
No evidence identified.	An RCT ¹¹⁴ (n=204) was identified which aimed to assess the impact on patient preferences of a decision aid showing the pre-test probability of acute coronary syndrome (ACS) and available management options. The results suggested that compared to usual care, the decision aid increased patient knowledge and reduced the proportion of patients who decided to undergo observation unit admission and cardiac stress testing, with no major adverse cardiac events.	None identified through GDG questionnaire.	The new evidence is consistent with the current guideline recommendations which state: clearly explain the options to people at every stage of investigation; make joint decisions with them and take account of their preferences; provide information about any proposed investigations using everyday, jargon-free language; and offer information about the risks of diagnostic testing.
A. People presenting with acute chest pain			
95-02: What is the incremental benefit and cost effectiveness of a clinical history in evaluation of individuals with acute chest pain of suspected cardiac origin?			

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
95-03: What is the incremental benefit and cost effectiveness of assessment of cardiovascular risk factors in evaluation of individuals with acute chest pain of suspected cardiac origin?			
95-04: What is the incremental benefit and cost effectiveness of a physical examination in evaluation of individuals with acute chest pain of suspected cardiac origin?			
<p>Through a high level search two systematic reviews were identified. The results of one of the studies¹¹⁵ showed that the Thrombolysis in Myocardial Infarction (TIMI) risk score is an effective risk stratification tool for patients in the emergency department with potential ACS but the authors concluded that it should not be used as the sole means of determining patient disposition. Another study¹¹⁶ found that no instrument assisting in the diagnostic investigation of patients with suspected ACS consistently fulfils the safety requirements of clinicians.</p> <p>Through a focused search one study¹¹⁷ was identified which found that individual historical and examination findings are effective in diagnosing AMI in patients with acute chest pain. This was considered to be in keeping</p>	<p>The results of a systematic review and meta-analysis¹¹⁸ indicated that telemedicine systems, including early telemetry of electrocardiograms (ECG), can reduce the risk of in-hospital mortality from AMI.</p> <p>An RCT¹¹⁹ (n=7083) was identified which evaluated the impact on quality and safety of electronic risk alerts to primary care physicians for patients with chest pain. The study found that the electronic alerts made no difference in terms of risk-appropriate management of both high and low risk patients.</p> <p>An RCT¹²⁰ (n=550) was identified which assessed the impact of providing pre-test probability estimates for both ACS and</p>	<p>None identified through GDG questionnaire.</p>	<p>The new evidence relating to telemedicine systems suggests that they may reduce the risk of mortality from ACS. The use of telemedicine is not specifically covered in the guideline, although the GDG's preferred option was for a pre-hospital ECG, ideally with advanced notification to hospital, providing this did not delay transfer of the patient to hospital. It is unlikely that this evidence will impact on current recommendations which state: Refer people to hospital as an emergency if an ACS is suspected and they currently have chest pain or they are currently pain free, but had chest pain in the last 12 hours, and a resting 12-lead ECG is abnormal or not available; and take a resting 12-lead ECG as soon as possible. When people are referred, send the results to hospital before they arrive if possible.</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>with the current guideline recommendation.</p>	<p>pulmonary embolism and prescriptive clinical advice on radiation exposure and health care costs. Patients with chest pain and dyspnoea, non-diagnostic ECGs, and no obvious diagnosis were included. The findings indicated that pre-test probability estimates and clinical advice reduced exposure to chest radiation and health care costs, with no increase in adverse events.</p> <p>The findings of a secondary analysis from an RCT¹²¹ indicated that in patients with CAD, symptoms of chest pain and arm pain are more common in patients with ACS, and symptoms of shortness of breath and dizziness are more common in patients without ACS. The findings of a meta-analysis³ also indicated that the most accurate tests for diagnosing ACS were pain radiation to right arm/shoulder and palpitation, and visceral pain.</p>		<p>In terms of electronic risk alerts in primary care, the evidence suggests that these demonstrated no impact on the management of patients, therefore it is unlikely to impact on current guideline recommendations.</p> <p>With regards to risk scores for ACS, the evidence identified at the 2-year review suggested that no single risk score or instrument was effective in diagnosing the cause of chest pain. This was considered to be in keeping with the current guideline recommendations. However, a study identified at the 4-year review suggested that the use of pre-test probability estimates reduced unnecessary diagnostic assessments for patients with symptoms suggestive of ACS but with non-diagnostic ECGs. For the assessment in hospital for people with a suspected ACS, the guideline recommends resting 12-lead ECG and troponin testing, as well as carrying out a physical examination and taking a detailed clinical history. The guideline further states: Only consider early chest computed tomography (CT) to</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			<p>rule out other diagnoses such as pulmonary embolism or aortic dissection, not to diagnose ACS. It is probable that pre-test likelihood estimates would take into account the information gathered by clinicians through physical examinations and in taking a clinical history. It is therefore unlikely that this evidence would impact on the current guideline recommendations.</p> <p>Evidence relating to symptoms associated with ACS is consistent with the current guideline recommendations which state: Initially assess people for any of the following symptoms, which may indicate an ACS, including pain in the chest and/or other areas (for example, the arms, back or jaw) lasting longer than 15 minutes, and chest pain associated with nausea and vomiting, marked sweating or breathlessness.</p>
95-05: Are the symptoms and description of the symptoms different in women presenting with acute chest pain of suspected cardiac origin compared with men?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-06: Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with acute chest pain of suspected			

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
cardiac origin compared with Caucasians?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-07: What is the diagnostic utility of pain relief with nitrates in the identification of patients with acute chest pain of cardiac origin?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-08: What is the utility and cost effectiveness of the resting ECG in evaluation of individuals with chest pain of suspected cardiac origin?			
No evidence identified.	<p>A systematic review and meta-analysis¹²² was identified which found insufficient evidence to support the use of ECG-based signal analysis technologies for detecting ischemia or infarct in patients with ACS compared with the standard 12-lead ECG.</p> <p>The findings of an RCT¹²³ (n=354) indicated that use of an ECG technician (ECG-T) reduced in-hospital first medical contact-to-ECG times compared to a control intervention.</p>	None identified through GDG questionnaire.	The new evidence suggests that using ECG technicians can speed up the process for undertaking in-hospital ECGs for patients with chest pain. The current recommendation relating to ECGs states: Take a resting 12-lead ECG as soon as possible. There are no recommendations relating to who should take the ECG other than that a review of resting 12-lead ECGs should be obtained by a healthcare professional qualified to interpret them as well as taking into account automated interpretation. It is therefore unlikely that the new evidence will impact on the current recommendations.
95-09: What is the utility and cost effectiveness of non-invasive tests in the evaluation of individuals with acute chest pain of suspected cardiac origin? (new question)			
Through a focused search two studies were identified relating to stress testing in patients with acute chest pain. One	An RCT ⁵⁶ (n=1508) found that stress myocardial perfusion imaging (SMPI) added to a	Clinical feedback indicated that the guideline needs to be updated. One of the reasons	The evidence identified at the 2-year surveillance review found limited evidence for stress testing in the assessment of

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>study⁵⁴ found that the addition of stress echocardiography to electrocardiography (ECG) was more effective than the individual tests alone in assessing patients with acute chest pain. The results of another study⁵⁵ suggested that routine cardiac provocative cardiac testing added little to the diagnostic evaluation of low-risk young adult patients with ACS compared to cardiac biomarkers.</p>	<p>standard triage strategy (including clinical evaluation, serial ECGs, and cardiac markers) more effectively identified patients with ACS, with reduced hospital admission rates for participants who underwent SMPPI compared to those who received just clinical assessment.</p> <p>The findings of an RCT⁵⁷, including 105 intermediate-risk participants without a definite diagnosis of ACS following ECG and troponin testing, indicated that stress cardiac magnetic resonance (CMR) imaging in an observation unit reduced coronary artery revascularisation, hospital readmissions, and recurrent cardiac testing compared to usual care provided by cardiologists and internists.</p> <p>The results of a systematic review and meta-analysis⁵⁸ (n=634) indicated that CMR had a higher</p>	<p>supporting this was that cardiac imaging has moved on over the last 4 years although no further details were provided.</p>	<p>patients presenting with acute chest pain in the emergency department. The evidence was considered to be in keeping with the current recommendations relating to the evaluation of individuals with acute chest pain, which include resting 12-lead ECG and troponin testing, as well as carrying out a physical examination and taking a detailed clinical history.</p> <p>The new evidence identified at the 4-year review suggests that non-invasive cardiac imaging, including stress myocardial perfusion imaging and stress cardiac magnetic resonance imaging, may be an alternative method for excluding other diagnoses in people with symptoms of ACS but with an uncertain diagnosis following ECG and troponin testing. Currently the guideline recommends a chest X-ray to help exclude complications of ACS, and early chest computed tomography (CT) should only be considered to rule out other diagnoses. The new evidence relating to non-invasive cardiac imaging may potentially impact on these recommendations.</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	sensitivity but lower specificity than low-dose dobutamine CMR for the assessment of myocardial stunning after acute myocardial infarction.		
95-10: What is the utility and cost effectiveness of the chest X ray in evaluation of individuals with chest pain of suspected cardiac origin?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-11: In adults presenting with acute chest pain of suspected cardiac origin, what is the clinical and cost effectiveness of giving oxygen compared with a placebo?			
No evidence identified.	<p>An update of a systematic review¹²⁴ of RCTs was identified which investigated whether routine use of inhaled oxygen in AMI improves patient-centred outcomes, including pain and death. One new trial was identified through the search for the systematic review, resulting in a total of four trials involving 430 participants. The results showed that use of oxygen increased the risk of death compared to air, although the authors concluded that this could be the results of chance due to the small number of deaths recorded.</p> <p>The results of an RCT¹²⁵ (n=136)</p>	None identified through GDG questionnaire.	The evidence reviewed in the guideline suggested that supplementary oxygen may be harmful in patients with an acute MI. It was therefore recommended that: Do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to: people with oxygen saturation (SpO ₂) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO ₂ of 94–98%; or people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO ₂ of 88–92% until blood gas analysis is available.

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>combined through meta-analysis with the results of two previous studies indicated that there were no differences in mortality and infarct size in patients with STEMI administered with high-concentration or titrated oxygen for 6 hours after presentation. However, there was clinical uncertainty over the results and the authors concluded that further studies would be needed.</p>		<p>The new evidence was inconclusive regarding the harmful effects of oxygen in people with MI, although one study suggested that it may lead to an increased risk of mortality. The new evidence is therefore consistent with the current guideline recommendations.</p>
<p>95-12: In adults presenting with acute chest pain, what is the clinical and cost effectiveness of pain (e.g. sublingual and buccal nitrates, diamorphine, morphine with anti-emetic) management?</p>			
<p>No evidence identified.</p>	<p>An RCT¹²⁶ (n=1763) was identified which evaluated the impact of a combination of anxiolytics and analgesics (midazolam and morphine) compared to analgesics (morphine) alone in the pre-hospital treatment of patients with suspected ACS. The findings of the study indicated that combined anxiolytics and analgesics were more effective at reducing anxiety compared to analgesics alone. However, there was no difference</p>	<p>None identified through GDG questionnaire.</p>	<p>The new evidence regarding pain relief is consistent with current guideline recommendations which state: Offer pain relief as soon as possible. This may be achieved with GTN (sublingual or buccal), but offer intravenous opioids such as morphine, particularly if an acute myocardial infarction (MI) is suspected.</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	in patients' estimation of pain between the two groups.		
95-13: In adults presenting with chest pain of suspected cardiac origin, what is the clinical and cost effectiveness of anti-platelet therapy (aspirin, clopidogrel alone or in combination) compared with a placebo?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-14: In patients presenting with suspected acute coronary syndromes, what is the clinical and cost effectiveness of early treatment with glucose-insulin-potassium compared with a placebo? (new question)			
No evidence identified.	The results of an RCT ¹²⁷ (n=911) suggested that there were no differences in progression to myocardial infarction or 30-day survival following out-of hospital emergency administration of glucose-insulin-potassium (GIK) in patients with suspected ACS. However, there was a reduction in the composite outcome of cardiac arrest or in-hospital mortality in patients who received GIK compared to placebo.	None identified through GDG questionnaire.	Administration of glucose-insulin-potassium was not covered in the guideline. There was limited evidence from the study that it might improve outcomes of cardiac arrest or in-hospital mortality. However, further consistent evidence would be needed before this can be considered for inclusion in the guideline.
95-15: What is the utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with chest pain of suspected cardiac origin?			
Three studies were identified relating to cardiac biomarkers which were all considered to support the current guideline recommendations.	Two studies were identified which examined point of care (POC) tests in patients with suspected of acute myocardial infarction (AMI). One RCT ¹³¹ (n=2243) and economic	None identified through GDG questionnaire.	The evidence from the 2-year surveillance review on troponin supports the current recommendation in the guideline which states: Take a blood sample for troponin I or T measurement on initial assessment in

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>One study¹²⁸ showed that measurement of cardiac troponin I is sufficient for diagnosis of patients with chest pain when compared to myoglobin and the MB isoenzyme of creatine kinase (CK-MB).</p> <p>Another study¹²⁹ found that that the most clinically accurate biomarker for the early diagnosis of myocardial infarction is the use of cardiac troponin T assay alone, rather than a multiple-biomarker approach.</p> <p>The results of another study¹³⁰ showed that point-of-care cardiac biomarker panel consisting of CK-MB, myoglobin, and troponin did not reduce health care costs.</p>	<p>analysis evaluated a POC panel of CK-MB(mass), myoglobin and troponin compared with standard care across 6 hospitals. There was heterogeneity in the results in terms of the difference in the proportion of patients successfully discharged and the mean cost per patient for POC assessment. Another systematic review¹³² examining the diagnostic accuracy of POC tests found that the negative predictive values for single biomarker testing ranged from 31 to 97%, and for a multi-marker approach from 59 to 100%, for test results within 6 hours after symptom onset or in a median time from symptoms onset to testing of 3 hours.</p> <p>The new evidence does not support the use of point-of-care tests in patients due to the heterogeneity in the results in both studies.</p>		<p>hospital. These are the preferred biochemical markers to diagnose acute MI.</p> <p>In relation to point-of-care tests, there was no consistent evidence from both the 2 and 4 year surveillance reviews of their effectiveness.</p>
<p>95-16: What is the diagnostic utility of Multislice Computed Tomography (MSCT) coronary angiography in the diagnosis of patients with acute</p>			

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
chest pain of suspected cardiac origin?			
<p>Through a high-level search, one systematic review⁵⁹ was identified which determined that 64-section coronary computed tomography angiography (CCTA) was best for identifying patients with symptoms of ACS who can safely be discharged home rather than diagnosing patients who have positive symptoms. This evidence was considered to be in line with the current recommendations.</p> <p>An additional focused literature search identified 13 studies⁶⁰⁻⁷² relating to computerised angiographies in patients with acute chest pain. Overall, the studies showed that various forms of computerised angiography were diagnostically effective in detecting coronary artery disease (CAD) in patients presenting with acute chest pain in emergency departments. Two of the studies also showed that computed tomography was cost effective. It was considered that this evidence that may potentially</p>	<p>An RCT⁷³ comparing early CCTA and standard emergency department evaluation in patients with acute chest pain found that CCTA reduced hospital length of stay and admission rates, and lessened the increased cumulative radiation dose in women with suspected ACS compared to men. The results also indicated that there were no differences in major adverse cardiac events between CCTA and standard care, or between men and women.</p> <p>The results of a systematic review and meta-analysis⁷⁴ indicated that CCTA led to an increase in referral rates for invasive coronary angiography and coronary revascularisation compared to usual care triage of acute chest pain in the emergency department. An RCT⁷⁵ also found that CCTA increased the frequency of revascularisations as well as</p>	<p>Clinical feedback indicated that there is evolving evidence for the use of CT coronary angiography in patients with acute chest pain and that the newer scanners that are now available have reduced radiation exposure.</p>	<p>During development of the guideline the GDG appraised the evidence for the use of MSCT for emergency department triage of patients with acute chest pain and was of the opinion that there was insufficient evidence on which to make a recommendation for its use in such patients. They acknowledged that this was an evolving area, which was the subject of on-going research, but the published evidence found to date was in small cohorts of patients and further research is required.</p> <p>There is new evidence identified at the 2 and 4 year surveillance reviews, as well as clinical feedback, which suggests that computed tomography is effective in the assessment of people with acute chest pain, including in the triage of patients in an emergency department. There may now be sufficient new evidence on which to make a recommendation for the use of computed tomography in such patients, thus impacting on the current guideline recommendation which states: Only</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
change the current guideline recommendation relating to computed tomography for assessment of acute chest pain.	<p>improving the detection of significant coronary stenosis in patients with acute chest pain.</p> <p>An RCT⁷⁶ (n=60) was identified which aimed to examine the dose reduction potential of low kV triple-rule-out dual-source CT angiography (TRO-CTA) in non-obese patients with acute chest pain. The subjective image quality of the low-dose TRO-CTA was rated similar to the standard protocol TRO-CTA. There were also no differences in the signal-to-noise and contrast-to-noise ratios in different vascular segments between the two groups. However, vessel attenuation was higher in the low dose TRO-CTA group than in the standard protocol group.</p>		consider early chest computed tomography (CT) to rule out other diagnoses such as pulmonary embolism or aortic dissection, not to diagnose ACS.
B. People presenting with stable chest pain			
95-17: What is the incremental benefit and cost effectiveness of a clinical history, in evaluation of individuals with stable chest pain of suspected cardiac origin?			
95-18: What is the incremental benefit and cost-effectiveness of assessment of cardiovascular risk factors in evaluation of individuals with stable chest pain of suspected cardiac origin?			

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
95-19: What is the incremental benefit and cost-effectiveness of a physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?			
<p>One study¹ was identified which found that an updated version of the Diamond–Forrester model, including age, sex, symptoms, coronary calcium scores, and cardiovascular risk factors, allowed for a more accurate estimation of the pre-test probability of CAD in stable chest pain without evidence for previous CAD. The authors concluded that this could lead to decreased referral for cardiac coronary angiography (CCA), a higher yield of angiography, and increased use of non-invasive testing for risk stratification.</p> <p>It was considered that this new evidence could potentially change the current guideline recommendations.</p>	<p>The results of meta-analysis¹³³ (n=927) suggested that there was an increased risk of CAD in patients with breast arterial calcifications seen on a mammography.</p> <p>A systematic review² assessing the diagnostic accuracy of clinical prediction models, reported that the six models identified showed good diagnostic accuracy for determining short-term outcomes in a pre-hospital population with suspected ACS.</p> <p>A meta-analysis³ aimed to determine the diagnostic value of single symptoms and signs for coronary heart disease (CHD) in patients with chest pain. In total, 172 studies were included covering 42 signs and symptoms. The findings indicated that the most</p>	<p>Clinical feedback at the 2-year surveillance review suggested that there is additional evidence for the validity of using Diamond and Forrester to assess pre-test likelihood of CAD in contemporary practice.</p> <p>Feedback at the 4-year surveillance review indicated that there is evidence that the Diamond-Forrester risk prediction model over-estimates disease probability in patients with suspected angina.</p> <p>Feedback was also provided at both review points indicating that parameters to assess the pre-test likelihood of coronary disease in patients with stable chest pain have changed. Further information was sought from the GDG regarding these</p>	<p>The new evidence identified relating to increased risk of CAD in patients with breast arterial calcifications is not currently covered in the guideline. However, it is unlikely that it will impact on the current recommendations for diagnosing stable angina caused by CAD which state diagnose stable angina based on clinical assessment alone or plus diagnostic testing. In terms of clinical assessment, this would include taking a detailed clinical history, including any cardiovascular risk factors, for which breast arterial calcifications seen on a mammography could be one risk factor.</p> <p>At the 2-year surveillance review, it was considered that the evidence relating to the use of an updated Diamond-Forrester prediction model in patients with stable chest pain could potentially have an impact on the current guideline. Although no further evidence was found relating to an updated Diamond-Forrester prediction</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>accurate predictors for a diagnosis of stable CHD were history of CHD, known acute MI, typical angina, history of diabetes mellitus, exertional pain, history of angina pectoris, and male sex. These are consistent with the factors listed in the guideline.</p>	<p>changes and the following reference was provided: Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 2011;32:1316-30. An assessment of the abstract indicated that the Diamond-Forrester model overestimates the probability of CAD, particularly in women. A subsequent update and extension of the model in relation to the predictive value of age, sex, and type of chest pain improved its performance.</p>	<p>model at the 4-year review, feedback from the GDG indicated that the Diamond-Forrester model may over estimate disease probability in suspected angina.</p> <p>Evidence from the 4-year surveillance review showed that 6 unspecified clinical prediction models demonstrated good diagnostic accuracy for determining short-term outcomes in a pre-hospital population with suspected ACS. Furthermore, clinical feedback indicated that the parameters to assess the pre-test likelihood of coronary disease in patients with stable chest pain have changed. Further evidence was provided which supported the view that the Diamond-Forrester model overestimates the probability of CAD, particularly in women. The evidence also suggested than an updated and extended version of the model improved its performance, supporting the evidence found at the 2-year surveillance review.</p> <p>The diagnostic pathway presented in the guideline for people who present with stable chest pain, states that the</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			application of the Diamond Forrester algorithm, as modified by consideration of additional risk factors, may permit a diagnosis of angina if the probability estimate is sufficiently high. The new evidence relating to an updated version of this model may therefore impact on this statement.
95-20: Are the symptoms and description of the symptoms different in women presenting with stable chest pain of suspected cardiac origin compared with men?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-21: Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with stable chest pain of suspected cardiac origin compared with Caucasians?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-22: What is the utility (incremental value) and cost effectiveness of a resting ECG in evaluation of individuals with stable chest pain of suspected cardiac origin?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-23: What is the utility (incremental value) and cost effectiveness of a chest X ray in evaluation of individuals with stable chest pain of suspected cardiac origin?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-24: What is the utility and cost effectiveness of coronary artery calcium scoring in evaluation of patients with stable chest pain?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
95-25: What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin?			
<p>Through a focused search, 29 studies⁴⁻³² were identified related to non-invasive and invasive tests for patients with stable chest pain. The evidence showed that various non-invasive techniques including stress echocardiography, PET, myocardial perfusion imaging, CT coronary calcium score, coronary computed tomography, single-photon emission computed tomography (SPECT) and cardiovascular magnetic resonance, were effective in diagnosing CAD when compared to coronary angiography. Other studies found that exercise stress testing, real-time three-dimensional echocardiography and coronary artery calcium were not effective in the diagnosis of CAD when compared to angiography. Overall, it was considered that there was no new evidence which would invalidate the current guideline recommendations regarding assessment of patients with stable chest pain.</p>	<p>Computed coronary tomographic angiography (CCTA) A systematic review and meta-analysis³³ was identified which compared CCTA versus invasive coronary angiography in the diagnosis of CHD. For the diagnosis of obstructive stenosis, compared to invasive coronary angiography as the reference standard, CCTA had high sensitivity and specificity, and at a pre-test probability of CHD of 50% or less, resulted in a lower cost per patient. However, at a pre-test probability of CHD of 70% or higher, invasive coronary angiography provided a lower cost per patient. For the diagnosis of functionally relevant stenosis, using intracoronary pressure measurement as the reference standard, CCTA had a higher sensitivity but lower specificity than</p>	<p>Clinical feedback indicated that there is new evidence about diagnostic assessment in patients with suspected stable angina, including the comparative effectiveness of different imaging modalities.</p> <p>It was suggested that novel imaging techniques are now more widely available, particularly CT coronary angiography and MR perfusion imaging for diagnosis of chest pain. CT coronary angiography is also able to pick up other issues with lungs and mediastinum which might be missed in the old paradigm.</p> <p>Radiation exposure from CT imaging is now lower with the newer scanners, so exposure will be less.</p>	<p>At the 2-year review it was considered that there was no new evidence which would invalidate the current guideline recommendations regarding assessment of patients with stable chest pain.</p> <p>Computed coronary tomographic angiography There was new evidence identified at the 4-year review which suggested that CCTA is an effective first line imaging test for the diagnosis of CAD, although it was not clear from all the abstracts what the level of CAD risk was in the study populations. There was also evidence relating to the diagnostic effectiveness of lower radiation CCTA.</p> <p>The new evidence for CCTA together with clinical feedback may potentially impact on the current guideline recommendations relating to the use of CCTA for the diagnosis of CAD in patients with stable chest pain, particularly the level of CAD risk at which to undertake CCTA.</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>invasive coronary angiography and both types of coronary angiography resulted in substantially higher cost per patient. As such, the review recommended that neither type of angiography should be used in the diagnosis of functionally relevant stenosis.</p> <p>The results of a meta-analysis³⁴ (n=2567) indicated that patients undergoing CCTA as the first imaging test for the detection of CAD were more likely to undergo percutaneous or surgical revascularisation, and there was a reduction in the time to diagnosis and costs of care compared to non-CCTA patients.</p> <p>A meta-analysis³⁵ (n=3300) was identified which compared image quality, diagnostic accuracy, and radiation dose of prospectively triggered CCTA with retrospectively gated CTA in patients with suspected or known CAD. The</p>	<p>It was reported that the value of zero calcium score for excluding CAD has been questioned. Furthermore, the advice to do a calcium score prior to CT angiography is now increasingly ignored because low radiation CT angiography is now available.</p> <p>One GDG member identified that the US guideline recommends exercise ECG as first diagnostic test for many patients, and neither the European nor the US guidelines recommend invasive coronary angiography for patients with high probability of disease.</p> <p>One GDG member suggested that the right test to use in lower risk groups is individualised and does not fit into a risk profile. As such, most health care professionals will determine the right diagnostic approach on a</p>	<p>Currently the guideline only recommends 64-slice (or above) CT coronary angiography in people who have an estimated likelihood of CAD of 10–29% and have a calcium score of 1-400. For people with an estimated likelihood of CAD of 10–29% and a calcium score over 400, invasive coronary angiography is recommended. Non-invasive functional imaging is recommended for people who have an estimated likelihood of CAD of 30–60%, or for people who have an estimated likelihood of 61–90% and for whom coronary revascularisation is not being considered or invasive coronary angiography is not clinically appropriate. Invasive coronary angiography is recommended for people who have an estimated likelihood of 61–90% and for whom coronary revascularisation is being considered and invasive coronary angiography is clinically appropriate.</p> <p>Functional stress testing The GDG found that the diagnostic performance for diagnosing CAD did not support the use of one functional imaging</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>results indicated that the image quality and diagnostic accuracy of both types of CTA were similarly high, but with lower radiation doses provided by prospectively triggered coronary CTA.</p> <p>The findings of a systematic review and meta-analysis³⁶ indicated that prospective ECG gating CCTA had high positive and negative predictive values (94% and 99% respectively) for the diagnosis of significant coronary stenosis. The authors concluded that the use of CCTA with prospective ECG gating allows for a reduced radiation exposure without a sacrifice in diagnostic efficacy in a population with high disease prevalence.</p> <p>A pilot RCT³⁷ (n=180) found that CCTA was associated with increased revascularisation, lower costs and lower effective radiation dose compared with myocardial perfusion single-photon emission</p>	<p>patient by patient basis.</p> <p>There is also a concern that the time needed to organise tests, such as nuclear scans and CT angiography is longer and may leave some high risk patients waiting for too long.</p>	<p>test in preference to another and they concluded that the tests were generally comparable and any could be used. The new evidence from the 4 year surveillance review relating to functional imaging generally supports this conclusion and is therefore consistent with the guideline recommendation which states: When offering non-invasive functional imaging for myocardial ischaemia use:</p> <ul style="list-style-type: none"> • myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or • stress echocardiography or • first-pass contrast-enhanced magnetic resonance (MR) perfusion or • MR imaging for stress-induced wall motion abnormalities.

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>(MPS) CT in patients presenting with stable chest pain and suspected CAD. CTA and MPS resulted in comparable improvements in angina-specific health status.</p> <p>A systematic review³⁸ was identified which compared 64-slice CCTA and coronary angiography (CA). Ten studies, including 1188 patients with angina with suspected or known CAD, were included in the review. At a patient level, 64-slice CCTA had positive predictive values ranging from 86-97% and negative predictive values of 76.9-100%. The authors concluded that the findings supported the use of 64-slice CCTA as a non-invasive alternative to CA for standalone diagnosis of significant stenosis in patients with angina.</p> <p>The results of a systematic review and meta-analysis³⁹ (n=3,539) indicated that "triple rule-out"</p>		

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>computed tomography (TRO CT) had high sensitivity and specificity for diagnosing CAD, although with greater radiation exposure and contrast exposure compared to non-TRO CT.</p> <p>A systematic review⁴⁰ was identified which assessed the clinical effectiveness and cost-effectiveness of new-generation computed tomography (NGCCT) for diagnosing CAD in patients who are difficult to image using 64-slice computed tomography (e.g. obese patients, patients with high or irregular heartbeats and patients who have high levels of coronary calcium or a previous stent or bypass graft). The results indicated that NGCCT had good diagnostic accuracy for diagnosing CAD in difficult-to-image patients. An NGCCT only strategy was most cost-effective in patients with suspected CAD, whereas invasive coronary angiography after a</p>		

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>positive NGCCT was the most cost-effective strategy in patients with known CAD.</p> <p>Functional stress testing A meta-analysis⁴¹ (n=761) reported that stress perfusion cardiac MRI had a high sensitivity and specificity (89.1% and 84.9% respectively) for diagnosing flow-limiting obstructive CAD.</p> <p>The results of two RCTs^{42,43} suggested that stress real-time myocardial contrast echocardiography (RTMCE) increased the detection of CAD compared to conventional stress echocardiography.</p> <p>The results of a meta-analysis⁴⁴ (n=13304) suggested that compared to exercise tolerance testing, stress imaging with MPI and stress echocardiography were the most accurate at stratifying cardiac risk in patients over 65</p>		

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>years of age with known or suspected CAD.</p> <p>A systematic review⁴⁵ was identified which found that referral bias reduced the sensitivity and increased the specificity of exercise echocardiography and MPI for CAD. The authors concluded that further research was needed to assess the ability of these and other tests to rule-in rather than rule-out CAD.</p> <p>The results of a meta-analysis⁴⁶ (n=11,862) found that Positron emission tomography (PET) had higher mean sensitivity than SPECT (92.6% v 88.3%) for diagnosing >50% stenosis in patients with known or suspected CAD. A second systematic review and meta-analysis⁴⁷ indicated that rubidium (Rb)-82 PET provided more accurate diagnosis of obstructive CAD in comparison to SPECT. However, the review was</p>		

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>limited by heterogeneity among study populations and referral bias in some studies. Finally, the results of a meta-analysis⁴⁸ indicated that SPECT demonstrated moderate accuracy in diagnosing functional stenotic CAD, with a sensitivity and specificity of 77% and 77% respectively.</p> <p>The results of a meta-analysis⁴⁹ suggested that cardiac magnetic resonance (CMR) had higher sensitivity for the detection of obstructive CAD than SPECT.</p> <p>A systematic review and meta-analysis⁵⁰ was identified which aimed to assess the diagnostic accuracy of CMR imaging assessing myocardial viability in patients with chronic left ventricular (LV) dysfunction due to CAD. The review included 24 studies including 698 patients, evaluating myocardial viability using three</p>		

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>techniques. Of the techniques assessed, Contrast delayed enhancement CMR had the highest sensitivity (95%) for predicting improved segmental LV contractile function after revascularisation, and low-dose dobutamine had the highest specificity (91%). The authors concluded that integrating the two methods would increase accuracy in evaluating patients with chronic LV dysfunction.</p> <p>An RCT⁵¹ was identified which assessed the effect of provider-directed imaging stress testing in lower-risk chest pain patients presenting to the emergency department. Patients were randomised to receive a CMR stress test (n=60) or a provider-selected stress test (n=60) (e.g. stress echo, CMR, cardiac catheterisation, nuclear, and coronary CT). The results of the study indicated that the median cost was higher for those receiving</p>		

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>the CMR mandated test, with no differences in other outcomes between the two groups.</p> <p>A systematic review and meta-analysis⁵² examining the diagnostic accuracy of magnetocardiography (MCG) reported that MCG had a sensitivity of 83% and a specificity of 77% for the diagnosis of CAD. However, the authors reported that there was significant heterogeneity present in all meta-analyses.</p> <p>A systematic review and meta-analysis⁵³ was identified which assessed the efficacy of Tissue Doppler imaging (TDI) in the diagnosis of CAD. The results showed that among CAD patients, TDI was associated with a decrease in the maximum systolic velocity at rest, and a decrease in maximum early diastolic velocity and maximum late diastolic velocity post stress. The authors concluded that TDI may have a</p>		

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>role in the evaluation of CAD.</p> <p><u>Coronary angiography</u> An RCT¹³⁴ (n=223) was identified which assessed the impact on early complications of a simultaneous injection of trinitroglycerin (TNG) with contrast agent during angiography. The study found that frequency of nausea, coronary artery spasm and chest pain were lower in the group which received TNG with contrast agent than in the control group.</p>		
Research recommendations			
95-RR1: Is multislice CT coronary angiography a cost-effective first-line test for ruling out obstructive CAD in people with suspected troponin-negative acute coronary syndromes?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
95-RR2: What is the effectiveness and cost effectiveness of new, high-sensitivity troponin assay methods and other new cardiac biomarkers in low, medium, and high risk people with acute chest pain?			
Through a focused literature search, 27 studies ⁷⁷⁻⁹⁴ were identified. The new evidence indicated that high sensitive troponins are more effective than conventional cardiac troponins in the early diagnosis of acute myocardial	The results of an RCT ¹⁰⁵ (n=542) suggested that a rapid diagnostic pathway (including Thrombolysis in Myocardial Infarction score, electrocardiography and 0- and 2-hour troponin tests) increased the	At both the 2-year and 4-year review points, clinical feedback was provided which identified that there is new evidence relating to highly sensitive troponin assays for testing	The clinical evidence for the following biomarkers was assessed as part of a review question in the guideline: troponin I, troponin T, creatine kinase (CK), creatine kinase-MB (CKMB), creatine kinase-MB isoforms (CKMB isoforms) and

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>infarction and ACS.</p> <p>A further four studies⁹⁵⁻⁹⁸ were identified which indicated that copeptin, together with high sensitive troponin, improves diagnostic performance in early diagnosis of patients with suspected MI.</p> <p>It was considered that the new evidence relating to high-sensitive troponin and copeptin could potentially impact on the current recommendations in the guideline.</p> <p>Six more studies⁹⁹⁻¹⁰⁴ were identified which looked at other biomarkers for ACS, including amino terminal pro-B-type natriuretic peptide, unbound free fatty acids, high-sensitivity C-reactive protein, pentraxin 3 and serum ischemia modified albumin. These were just single studies and it was therefore considered that more evidence would be required to support these findings before consideration for inclusion in the guideline.</p>	<p>proportion of patients with chest pain discharged within 6 hours compared to a standard-care diagnostic pathway (including troponin test on arrival at hospital, prolonged observation, and a second troponin test 6-12 hours after onset of pain) for the assessment of patients with acute chest pain consistent with ACS.</p> <p>An RCT¹⁰⁶ was identified which assessed changes in contemporary sensitive troponin I (TnI) levels in 7,863 patients after MI or unstable angina. The findings indicated that both baseline TnI levels and increases in TnI levels after 1 year were linked with an increased risk of CHD death and myocardial infarction. A second study, a systematic review and meta-analysis¹⁰⁷ including 4 studies (n=2033), also found that elevated high-sensitivity troponin (hs-Tn) were associated with an increased risk of mortality. It is unlikely that</p>	<p>patients with suspected ACS. Feedback suggested that the new troponin assays are now increasingly used and have reduced the timescales from symptom onset to results from 10-12 hours to 3-6 hours.</p> <p>NICE currently has no plans to update MTG4. Feedback from the Newcastle and York External Assessment Centre has indicated that the claimed benefits of the copeptin assay have been superseded by high-sensitivity troponin assays in terms of faster diagnosis of MI.</p>	<p>myoglobin. An additional research recommendation was made with the aim of investigating newer more sensitive troponin assays which may offer advantages over previous assays in terms of diagnostic accuracy, and allow exclusion of MI earlier than the 12 hour time frame currently required. The research recommendation also sought to assess other proposed biomarkers compared to the best available troponin assays.</p> <p>At the 2-year surveillance review, it was considered that the evidence relating to high sensitive troponins compared to the conventional cardiac troponins to diagnose ACS in patients with acute chest pain could potentially impact on the current guideline recommendations. The new Diagnostics guidance reviewed the clinical and cost-effectiveness of high-sensitive troponins compared to standard troponin testing over 10–12 hours, and recommended the Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay as</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>this new evidence will impact on current recommendations.</p> <p>New Diagnostics guidance, published in October 2014, reviewed the clinical and cost-effectiveness of three types of high-sensitive troponin assay (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnl+3 assays) compared to standard troponin testing over 10–12 hours. The guidance recommends the Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay as options for the early rule out of non-ST-segment-elevation myocardial infarction (NSTEMI) in people presenting to an emergency department with chest pain and suspected ACS. The assays are recommended for use with ‘early rule-out protocols’, which typically include a blood sample for cardiac troponin I or T taken at initial</p>		<p>options for the early rule out of non-ST-segment-elevation myocardial infarction (NSTEMI) in people presenting to an emergency department with chest pain and suspected ACS. The assays are recommended for use with ‘early rule-out protocols’, which typically include a blood sample for cardiac troponin I or T taken at initial assessment in an emergency department and a second blood sample taken after 3 hours. Currently CG95 only recommends: Take a blood sample for troponin I or T measurement on initial assessment in hospital. These are the preferred biochemical markers to diagnose acute MI; and take a second blood sample for troponin I or T measurement 10–12 hours after the onset of symptoms. The evidence identified at the 2 and 4 year surveillance reviews, together with the Diagnostics Guidance and clinical feedback, indicate that high sensitive troponins are effective in the diagnosis of acute MI and ACS, and therefore may impact on the current recommendations in the guideline.</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>assessment in an emergency department and a second blood sample taken after 3 hours.</p> <p>The results of a meta-analysis¹⁰⁸ indicated that circulating miRNAs, particularly miR-499 and miR-133a, had good diagnostic accuracy for myocardial infarction.</p> <p>A systematic review and meta-analysis¹⁰⁹ (n=941) was identified which assessed the early diagnostic performance of glycogen phosphorylase isoenzyme BB (GPBB) in patients with suspected AMI. The results of the meta-analysis found that GPBB had a sensitivity of 0.854 and specificity of 0.767, although there was high heterogeneity across the included studies. The authors concluded that GPBB does not currently provide efficient diagnosis of AMI when used as a stand-alone test.</p>		<p>Evidence was identified at the 2-year surveillance review regarding the improved diagnostic performance of copeptin together with high sensitive troponin in patients with MI. It was considered that this evidence could potentially impact on the current guideline recommendations. However, MTG4, which was published in June 2011, reviewed the evidence for copeptin assay including two studies considered at the 2 year surveillance review. It found that whilst the assay showed potential to reduce the time taken to rule out MI when used in combination with cardiac troponin testing, there was insufficient evidence on its use in clinical practice to support the case for routine adoption in the NHS and recommended that further research be undertaken in the UK clinical setting to compare the BRAHMS copeptin assay in combination with cardiac troponin testing against sequential cardiac troponin testing for ruling out MI. Further evidence relating to copeptin was identified at the 4 year surveillance review which also showed that copeptin and troponin combined had</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>Two systematic reviews and meta-analyses^{110,111} were identified which found that the addition of heart-type fatty acid binding protein (H-FABP) to troponin increased sensitivity but decreased specificity compared to troponin alone for the diagnosis of MI.</p> <p>MTG4 (NICE medical technologies guidance), published in June 2011, was identified through the intelligence gathering search for the guideline. MTG4 stated that the BRAHMS copeptin assay shows potential to reduce the time taken to rule out myocardial infarction in patients presenting with acute chest pain, when used in combination with cardiac troponin testing. However, it stated that there is currently insufficient evidence on its use in clinical practice to support the case for routine adoption of the BRAHMS copeptin assay in the NHS and recommended that further research</p>		<p>increased sensitivity for diagnosing MI. NICE currently has no plans to update MTG4 and feedback has indicated that the claimed benefits of the copeptin assay have been superseded by high-sensitivity troponin assays in terms of faster diagnosis of MI.</p> <p>Evidence was also identified in relation to other biomarkers, including heart-type fatty acid binding protein which increased the sensitivity of troponin compared to troponin alone, and miRNAs which had good diagnostic accuracy for MI.</p> <p>In summary, the evidence and clinical feedback relating to high sensitive troponins and other biomarkers for MI, suggest that there is potentially new evidence in this area which should be considered for inclusion in the guideline.</p>

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>be undertaken in the UK clinical setting to compare the BRAHMS copeptin assay in combination with cardiac troponin testing against sequential cardiac troponin testing for ruling out MI. As part of the evidence base for this guidance, two studies considered at the previous surveillance review (Keller et al., 2010; Reichlin et al., 2009) were considered.</p> <p>Through the literature search for the 4-year surveillance review, two systematic reviews^{112,113} were identified which published after MTG4. The studies found that copeptin and troponin combined improved sensitivity for the diagnosis of acute MI compared with troponin alone.</p>		
95-RR3: In what circumstances should telephone advice be given to people calling with chest pain? Is the appropriateness influenced by age, sex or symptoms?			
No evidence identified.	An RCT ¹³⁵ (n=1944) was identified which tested an educational intervention to reduce pre-hospital delay in patients with ACS. All	None identified through GDG questionnaire.	The purpose of the research recommendation was to develop a robust system for giving appropriate telephone advice to people with chest pain. The

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>patients received usual in-hospital care. Those in the intervention group also received an individualised education session using motivational techniques which was reinforced a month later by telephone. The findings of the study indicated that the intervention reduced the pre-hospital median delay time compared to the control group, and that those who received the intervention reported their symptoms more promptly.</p>		<p>guideline stated that research should be conducted to clarify if an emergency response in all circumstances is appropriate, or if there are identifiable factors such as age, sex, or associated symptoms that would allow a modified response and a more appropriate use of resources.</p> <p>The new evidence suggests that an educational intervention, including follow up by telephone, may reduce the time taken for an individual to seek help for potential ACS. However, the evidence does not clarify the appropriate circumstances in which telephone advice should be given. Therefore it is unlikely that the new evidence will impact on the current guideline recommendations.</p>
<p>95-RR4: Can a national registry of people presenting with suspected angina be established to allow cohort analysis of treatments, investigations and outcomes in this group?</p>			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
<p>95-RR5: What is the clinical and cost effectiveness of multislice CT coronary angiography compared with functional testing in the diagnosis of angina in a population of people with stable chest pain who have a moderate (30–60%) pre-test likelihood of CAD?</p>			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.

Conclusions from the 2-year surveillance review (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
95-RR6: How should information about the diagnostic pathway and the likely outcomes, risks and benefits, with and without treatment, be most effectively presented to particular groups of people, defined by age, ethnicity and sex?			
No evidence identified.	No new evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.

Appendix 2 References

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