NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review consultation document

Review of Clinical Guideline (CG95) – Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin

1. Background information

Guideline issue date: 2010
2 year review: 2012 (first review)
National Collaborating Centre: National Clinical Guidelines Centre

2. Consideration of the evidence

Literature search

Through an assessment of abstracts from a high-level randomized control trial (RCT) search, new evidence was identified related to the following clinical areas within the guideline:

- Use of biomarkers
- Making a diagnosis
- Multislice CT coronary angiography for emergency department triage of patients with acute chest pain

Through this stage of the process, a sufficient number of studies relevant to the clinical areas above (except clinical areas covered by the relevant technology appraisals) were identified from the high level RCT search to allow an assessment for a proposed review decision and are summarized in Table 1 below.

From initial intelligence gathering, qualitative feedback from other NICE departments, the views expressed by the Guideline Development Group, as well as the high-level RCT search, additional focused literature searches were also conducted for the following clinical areas:

- The diagnostic utility of calcium scoring, non-invasive and invasive tests imaging techniques including CT coronary angiography and MR perfusion imaging in the diagnosis of patients with acute chest pain and stable chest pain of suspected cardiac origin
- The utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with acute chest pain of suspected cardiac origin
- The incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of patients with stable chest pain of suspected cardiac origin

The results of the focused searches are summarized in Table 2 below. All references identified through the high-level RCT search, initial intelligence gathering and the focused searches can be viewed in Appendix 1.

Table 1: Summary of articles from the high level RCT search

Clinical area 1: Use of biomarkers		
	Summary of evidence	**Relevance to guideline recommendations**
Clinical Question What is the utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with acute chest pain of suspected cardiac origin? **Relevant section of guideline** 4.4.2 Use of biomarkers **Recommendations** 1.2.5.1 to 1.2.5.4	Refer to Question 2 of the focus search in Table 2	
Clinical area 2: Making a diagnosis		

	Summary of evidence	Relevance to guideline recommendations
Clinical question What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with acute chest pain of suspected cardiac origin? **Relevant section of guideline** 1.2.6 Making a diagnosis **Recommendations** 1.2.1.2 to 1.2.1.3	Through an assessment of the abstracts from the high-level RCT search, two studies relevant to the clinical question covered in this clinical area of the guideline were identified. • One study[1] conducted a systematic review to assess the prognostic accuracy of the thrombolysis in myocardial infarction (TIMI) risk score in patients in the emergency department with potential acute coronary syndromes. The results showed that TIMI risk score is an effective risk stratification tool for patients in the emergency department with potential acute coronary syndromes but the authors concluded that TIMI risk score should not be used as the sole means of determining patient disposition. • One study[2] conducted a systematic review to assess the safety and efficiency in sample validation studies of all available instruments for ruling out acute coronary syndrome in patients with chest pain. The results showed that no instrument assisting clinicians in the diagnostic investigation of patients with suspected acute coronary syndrome consistently fulfils the safety requirements of clinicians.	No new evidence was identified which would invalidate current guideline recommendation(s).

	Summary In terms of evidence on making a diagnosis for a patient with chest pain, no single risk score or instrument was effective in diagnosing the cause of the chest pain. This is in keeping with the current guideline recommendations which states: 1.2.1.2 Determine whether the chest pain may be cardiac and therefore whether this guideline is relevant, by considering: • the history of the chest pain • the presence of cardiovascular risk factors • history of ischaemic heart disease and any previous treatment • previous investigations for chest pain. 1.2.1.3 Initially assess people for any of the following symptoms, which may indicate an acute coronary syndrome: • pain in the chest and/or other areas (for example, the arms, back or jaw) lasting longer than 15 minutes • chest pain associated with nausea and vomiting, marked • sweating, breathlessness, or particularly a combination of these	

	chest pain associated with haemodynamic instability • new onset chest pain, or abrupt deterioration in previously stable angina, with recurrent chest pain occurring frequently and with little or no exertion, and with episodes often lasting longer than 15 minutes.	
Clinical area 3: Multislice CT coronary angiography for emergency department triage of patients with acute chest pain		
	Summary of evidence	**Relevance to guideline recommendations**
Q: What is the diagnostic utility MSCT coronary angiography in the diagnosis of patients with acute chest pain of suspected cardiac origin? **Relevant section of guideline** 4.4.3 Multislice CT coronary angiography	Through an assessment of the abstracts from the high-level RCT search, one study relevant to the clinical question covered in this clinical area of the guideline was identified. • One study[3] conducted a systematic review to determine the accuracy of 64-section coronary computed tomography angiography in predicting 30 day major adverse cardiac events for patients presenting with symptoms concerning for acute coronary syndrome. The results showed that coronary computed tomography angiography was best for identifying patients who can safely be discharged home rather than diagnosing patients who have positive symptoms.	No new evidence was identified which would invalidate current guideline recommendation(s).

for emergency department triage of patients with acute chest pain **Recommendations** The GDG appraised the evidence for the use of multislice CT coronary angiography in unselected patients with chest pain of suspected cardiac origin and was of the opinion that there was insufficient evidence currently on which make a recommendation for its use in the emergency department in such	**Summary** In terms of the evidence on multislice CT coronary angiography for emergency department triage of patients with acute chest pain, the current evidence showed that it was more effective to decide whether it is safe to discharge a patient rather than diagnose a patient presenting with chest pain. During development of the guideline the GDG appraised the evidence for the use of multislice CT coronary angiography in unselected patients with chest pain of suspected cardiac origin and was of the opinion that there was insufficient evidence currently on which make a recommendation for its use in the emergency department in such patients. This still remains an evolving area and before CT coronary angiography can be incorporated into an acute chest pain pathway, a de novo, NHS based, economic evaluation should be undertaken	

patients		

Table 2: Summary of articles from the focused search

Clinical area 1: The diagnostic utility of calcium scoring, non-invasive and invasive tests imaging techniques including CT coronary angiography and MR perfusion imaging in the diagnosis of patients with acute chest pain and stable chest pain of suspected cardiac origin		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the diagnostic utility of calcium scoring, non-invasive and invasive tests, imaging techniques including CT coronary angiography and MR perfusion imaging in the diagnosis of patients with acute chest pain and stable chest pain of suspected cardiac origin?	Through an assessment of the abstracts from the focus searches, 44 studies (15 studies were on patients with acute chest pain and 29 studies on patients with stable chest pain) relevant to the clinical question covered in this clinical area of the guideline were identified. **ACUTE CHEST PAIN** • One review[4] conducted a meta-analysis to assess the diagnostic accuracy of multi-detector computerized tomography angiography in the emergency room in patients with acute chest pain. The results showed that multi-detector computerized tomography angiography has an excellent diagnostic accuracy in detection of significant coronary artery stenosis in patients with acute chest pain. • One review[5] conducted a meta-analysis to assess clinical utility of computed tomography angiography versus electrocardiography and	Potential new evidence that may change current recommendation(s)

Relevant section of guideline 4.4 Investigations and Diagnosis 5.2 Investigations and diagnosis of patients with stable chest pain suspected to be stable angina **Recommendations** 1.3.4.7 to 1.3.6.4	biomarkers in the diagnosis of chest pain patients presenting to emergency departments. The results indicated that computed tomography angiography was effective in ruling out the presence of acute coronary syndromes in low to intermediate risk patients presenting to the emergency department with acute chest pain compared to electrocardiography and biomarkers. • One study[6] compared the cost of cardiac computed tomography based evaluation versus standard of care in patients with suspected acute coronary syndrome in the emergency department. The results showed that cardiac computed tomography-based evaluation resulted in overall lower cost than the standard of care for possible acute coronary syndrome patients. • One study[7] assessed the diagnostic accuracy of 64-slice computed tomographic coronary angiography in the emergency room in patients with acute chest pain syndrome. The results showed that computed tomographic coronary angiography was effective in detection of coronary disease in patients with acute chest pain syndrome. • One study[8] compared the cost of cardiac computed tomography based evaluation versus standard of care in patients with acute	

	chest pain. The results showed that there was a significant potential cost saving in patients who are sent for cardiac computed tomography compared to standard of care. • One study[9] compared the efficiency, cost, and safety of a diagnostic strategy employing early coronary computed tomographic angiography to a strategy employing rest-stress myocardial perfusion imaging in the evaluation of acute low-risk chest pain in the emergency department. The results showed that coronary computed tomographic angiography resulted in more rapid and cost-efficient and safe diagnosis than rest-stress myocardial perfusion imaging in patients with acute low-risk chest pain. • One study[10] evaluated the utility of routine provocative cardiac testing versus cardiac biomarkers in low-risk young adult (younger than 40 years) patients with acute coronary syndrome in an emergency department. The results showed that routine stress testing added little to the diagnostic evaluation of this patient group compared to cardiac biomarkers. • One study[11] determined the usefulness of coronary computed tomography angiography versus troponin and electrocardiography results in patients with acute chest pain in an emergency	

	department. The results indicated that early coronary computed tomography angiography may significantly improve patient diagnosis in the emergency department compared to troponin and electrocardiography results. • One study[12] assessed whether coronary computed tomographic angiography is diagnostically more effective than standard evaluation in the emergency department in patients with symptoms suggestive of acute chest pain. The results showed that coronary computed tomographic angiography improved the efficiency of clinical decision making, as compared with a standard evaluation in the emergency department. • One study[13] evaluated the safety and efficacy of the computed tomography coronary angiography versus standard evaluation in patients with acute chest pain in the emergency department. The results indicated that clinical decisions based on computed tomography coronary angiography is safe and effective in patients with acute chest pain compared to standard evaluation. • One study[14] assessed the use of stress echocardiography (echo) to identify cardiac pathology compared with stress electrocardiography alone in patients with acute chest pain in the chest pain unit. The	

	results showed that addition of echo to stress electrocardiography testing in emergency department chest pain unit patients was more effective than individual tests. • One study[15] evaluated diagnostic accuracy of exercise electrocardiography versus 64-slice CT coronary angiography for the detection of significant coronary artery stenosis in patients with low-to-intermediate pre-test likelihood of coronary artery disease. The results showed that CT coronary angiography provided optimal diagnostic performance in patients with acute chest pain when compared to exercise electrocardiography. • One study[16] examined the diagnostic capacity of multidetector computed tomography for acute coronary syndrome in patients presenting with acute chest pain versus electrocardiography and biomarkers presenting to emergency department. The results showed that multidetector computed tomography had a high diagnostic capacity for the early evaluation of acute coronary syndrome in patients presenting with acute chest pain versus electrocardiography and biomarkers. • One study[17] evaluated the performance of 320-row computed tomography angiography in the identification of significant coronary	

	artery disease in patients presenting with acute chest pain versus quantitative coronary angiography presenting to emergency department. The results indicated that computed tomography angiography was effective in the identification of significant coronary artery disease in patients with acute chest pain compared to quantitative coronary angiography. • One RCT was identified which aimed to determine whether coronary computed tomographic angiography can be used for safe discharge of patients with possible acute coronary syndromes.[18] The study concluded that a coronary computed tomographic angiography-based strategy for low-to-intermediate-risk patients presenting with a possible acute coronary syndrome facilitated a safe discharge from the emergency department. **Summary** Overall, nine studies showed that various forms of computerized angiographies such as multi-detector computerized tomography angiography, computed tomography angiography, coronary computed tomographic angiography, computed tomography coronary angiography and multidetector computed tomography were diagnostically effective in	

	detecting coronary artery disease in patients presenting with acute chest pain in the emergency departments. Furthermore, two studies indicated a cost saving with computed tomography. Routine provocative cardiac testing, stress echocardiography (echo) and stress electrocardiography were not clinically effective in detecting coronary artery disease in patients presenting with acute chest pain in the emergency departments. Therefore, new evidence is identified which is not in keeping with the current guideline recommendations which state: 1.2.6.5 Reassess people with chest pain without raised troponin levels (determined from appropriately timed samples) and no acute resting 12-lead ECG changes to determine whether their chest pain is likely to be cardiac. 1.2.6.7 Only consider early chest computed tomography to rule out other diagnoses such as pulmonary embolism or aortic dissection, not to diagnose acute coronary syndromes. **STABLE CHEST PAIN** • One study[19] assessed the diagnostic ability of dobutamine stress	No new evidence was

	echocardiography in comparison to the angiographic findings in patients with suspected coronary artery disease. The results indicated that dobutamine stress echo is a sensitive and specific method in non invasive diagnosis of suspected coronary artery disease when compared to angiographic studies. • One study[20] evaluated the accuracy of adenosine myocardial contrast echocardiography versus cardiac magnetic resonance imaging in diagnosing coronary artery disease in patients with suspected coronary artery disease. The results showed that myocardial contrast echocardiography was effective in detecting coronary artery disease but the authors concluded further investigation is warranted to confirm these findings. • One study[21] assessed the diagnostic accuracy cardiovascular magnetic resonance stress testing versus exercise electrocardiography for the detection of coronary artery disease in women with chest pain or symptoms suggestive of coronary artery disease. The results showed that cardiovascular magnetic resonance stress perfusion imaging had higher accuracy for the detection of coronary artery disease in women when compared to exercise electrocardiography.	identified which would invalidate current guideline recommendation(s)

	• One study[22] assessed the diagnostic accuracy of cardiac magnetic resonance imaging versus coronary angiography in patients with coronary artery disease. The results showed cardiac magnetic resonance imaging to be effective in the detection of coronary artery disease when compared to coronary angiography. • One study[23] evaluated the diagnostic performance of stress perfusion cardiac MR for detecting significant coronary artery disease (>=70% narrowing) in comparison with invasive coronary angiography as a reference standard. The results were inconclusive on the performance of stress perfusion cardiac MR in detecting coronary artery disease. • One study[24] assessed the diagnostic accuracy of dipyridamole stress cardiovascular magnetic resonance imaging versus coronary angiography in patients with suspected coronary artery disease. The results showed that dipyridamole stress cardiovascular magnetic resonance imaging yielded high diagnostic accuracy for the detection of coronary artery disease when compared to coronary angiography. • One study[25] assessed the diagnostic accuracy of myocardial perfusion from a stress echocardiography modality versus coronary	

	angiography in patients with suspected coronary artery disease. The results showed that myocardial perfusion imaging from a stress echocardiography modality had the highest sensitivity and accuracy for the detection of coronary artery disease > 50% when compared to coronary angiography in patients with suspected coronary artery disease. • One study[26] compared the diagnostic accuracy of conventional coronary angiography to the coronary 64-multislice spiral computed tomography in patients with known or suspected coronary artery disease. The results showed that 64-multislice spiral computed tomography was not clinically effective in detecting coronary artery disease when compared to conventional coronary angiography. • One study[27] evaluated the cost-effectiveness of using 64 multidetector-row computed tomography coronary angiography as a non-invasive imaging modality versus routine coronary angiography for patients at risk for coronary artery disease. The results showed computed tomography coronary angiography achieved gains of QALY comparable to that of routine coronary angiography, but at a lower cost. • One study[28] assessed the diagnostic effectiveness of computed	

	tomography angiography compared to quantitative coronary angiography to detect obstructive coronary artery disease. The results were inconclusive and the authors concluded further investigation is warranted to find out the effectiveness of computed tomography angiography. • One study[29] assessed the diagnostic accuracy of 256-row computed tomographic angiography versus invasive coronary angiography in patients with suspected coronary artery disease. The results showed computed tomographic angiography to be a highly sensitive test of coronary artery disease when compared to invasive coronary angiography in patients with coronary artery disease. • One study[30] evaluated the diagnostic performance of coronary computed tomography versus invasive coronary angiography in patients with chest discomfort and suspected angina. The initial results showed that coronary computed tomography as an initial step for angina diagnosis was more effective in patients with an intermediate probability of coronary artery disease. • One study[31] assessed the diagnostic accuracy of 320-row multidetector computed tomography coronary angiography versus	

	invasive coronary angiography in patients with known or suspected coronary artery disease. The results showed that 320-row computed tomography coronary angiography allowed accurate non-invasive assessment of significant coronary artery disease compared to invasive coronary angiography in patients with known or suspected coronary artery disease. • One study[32] determined the ability of multi-slice CT coronary angiography for the detection of significant stenoses in the coronary arteries, in comparison to conventional invasive coronary angiography in patients with suspected coronary artery disease. The results showed that multi-slice CT coronary angiography had a higher diagnostic performance in the assessment of significant coronary artery disease when compared to invasive coronary angiography. • One study[33] compared the diagnostic performance of CT angiography versus exercise electrocardiography in a symptomatic population with a low-intermediate prevalence of coronary artery disease. The results indicated that CT angiography was more effective in detecting coronary artery disease when compared to exercise electrocardiography in patients with suspected coronary	

	artery disease. • One study[34] investigated the accuracy of 64-slice CT versus invasive coronary angiography in consecutive patients with suspected or proven coronary artery disease. The results showed that 64-slice CT is highly accurate for the detection of significant coronary artery disease when compared to invasive coronary angiography. • One study[35] aimed to compare the diagnostic accuracy of three commonly used software packages (Emory Cardiac Toolbox, 4D-MSPECT and Quantitative Perfusion SPECT) for the detection of coronary artery disease. The results showed that the diagnostic performances of all three programs to detect coronary artery disease are similar. • One study[36] aimed to determine the diagnostic accuracy of the 3 most commonly used non-invasive myocardial perfusion imaging modalities, single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography perfusion imaging versus coronary angiography for the diagnosis of obstructive coronary artery disease. The results showed that all three tests were equally effective in detecting coronary artery	

	disease when compared to coronary angiography in patients with suspected coronary artery disease. • One study[37] determined the diagnostic performance of 1.5-T whole-heart coronary magnetic resonance angiography versus coronary angiography in patients with suspected coronary artery disease. The results showed that 1.5-T whole-heart coronary magnetic resonance angiography was effective in detecting significant coronary artery disease when compared to coronary angiography in patients with suspected coronary artery disease. • One study[38] evaluated adenosine magnetic resonance perfusion imaging in the diagnostic workup of patients with suspected stable angina with computed tomography coronary angiography as first-line diagnostic modality. The results showed that computed tomography coronary angiography was more effective in the detection of patients with coronary artery disease compared to magnetic resonance perfusion. • One study[39] determined the comparative diagnostic accuracy of real-time three-dimensional echocardiography for the diagnosis of coronary artery disease during dobutamine stress echocardiography against coronary angiography reference. The results were	

	inconclusive and the authors concluded that further studies should be conducted to assess the effectiveness of real-time three-dimensional echocardiography. • One review[40] conducted a meta-analysis to evaluate the accuracy of quantitative stress myocardial contrast echocardiography compared with coronary angiography or single-photon emission computed tomography in patients with suspected coronary artery disease. The results support the use of quantitative myocardial contrast echocardiography as a non-invasive test for detection of coronary artery disease when compared with coronary angiography or single-photon emission computed tomography. • One review[41] investigated the diagnostic value of Single Photon Emission Computed Tomography, positron emission tomography (PET) and PET/ computed tomography versus invasive coronary angiography in the diagnosis of coronary artery disease. The review results indicated that PET has high diagnostic value for diagnosing coronary artery disease when compared to Single Photon Emission Computed Tomography, computed tomography and coronary angiography. • One review[42] aimed to determine the diagnostic accuracy of	

	exercise stress testing for coronary artery disease versus angiography in patients with known coronary artery disease. The results showed that exercise stress testing was not clinically as effective as angiography to detect coronary artery disease. • One review[43] compared the diagnostic performance of stress myocardial perfusion imaging for the diagnosis of obstructive coronary artery disease, using conventional coronary angiography as the reference standard. The results of the review showed that myocardial perfusion imaging is superior for the diagnosis of obstructive coronary artery disease compared with ECHO and SPECT. • One review[44] evaluated the diagnostic accuracy of the first generation dual-source computed tomography versus coronary angiography in the diagnosis of coronary artery disease. The results indicated that dual-source computed tomography has a role in the evaluation of patients with chest pain as a simple non-invasive examination to diagnose or exclude significant coronary artery disease compared to coronary angiography. • One review[45] assessed the incremental value of the CT coronary calcium score versus conventional coronary angiography in the	

	detection of coronary artery disease. The results indicated good diagnostic performance for CT coronary calcium score in the detection of coronary artery disease when compared to conventional coronary angiography. • One review[46] conducted a meta-analysis to assess the diagnostic accuracy of stress perfusion cardiovascular magnetic resonance versus coronary angiography for the diagnosis of significant obstructive coronary artery disease in patients with new onset stable typical or atypical angina pectoris. The results showed that stress perfusion cardiovascular magnetic resonance is highly sensitive for detection of coronary artery disease when compared to coronary angiography in patients with suspected coronary artery disease. • One review[47] assessed the diagnostic accuracy of the dual-source computed tomography versus invasive coronary angiography in patients with suspected or known coronary artery disease. The results showed that dual-source computed tomography showed a high level of diagnostic performance in the detection of coronary artery disease when compared to invasive coronary angiography.	

	Summary The systematic reviews showed that quantitative stress myocardial contrast echocardiography, PET, stress myocardial perfusion imaging, CT coronary calcium score, dual-source computed tomography, stress perfusion cardiovascular magnetic resonance, and dual-source computed tomography were effective in diagnosing coronary artery disease when compared to coronary angiography. One review showed that exercise stress testing was not effective in the diagnosis of coronary artery disease when compared to angiography. The studies identified showed that dobutamine stress echocardiography, adenosine myocardial contrast echocardiography, cardiovascular magnetic resonance stress testing and its various methods of delivery, myocardial perfusion imaging, dipyridamole stress echocardiography, coronary computed tomography and its various forms, emory cardiac toolbox, 4D-MSPECT and quantitative perfusion SPECT, coronary magnetic resonance angiography, and adenosine magnetic resonance perfusion imaging were all effective in detecting coronary artery disease when compared to coronary angiography. One study showed that coronary artery calcium and another study showed that real-time three-dimensional	

	echocardiography was not effective in detecting coronary artery disease when compared to coronary angiography. Overall, no new evidence was identified that would invalidate the current guideline recommendations which state: 1.3.4.7 For people with chest pain in whom stable angina cannot be diagnosed or excluded by clinical assessment alone and who have an estimated likelihood of CAD of 10–29% (see recommendation 1.3.3.16) offer CT calcium scoring. If the calcium score is: • zero, consider other causes of chest pain • 1–400, offer 64-slice (or above) CT coronary angiography • greater than 400, offer invasive coronary angiography. If this is not clinically appropriate or acceptable to the person and revascularisation is not being considered, offer non-invasive functional imaging. See section 1.3.6 for further guidance on non-invasive functional testing. 1.3.4.8 For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography), offer non-invasive functional testing when there is uncertainty about whether chest pain is caused by	

	myocardial ischaemia. See section 1.3.6 for further guidance on non-invasive functional testing. An exercise ECG may be used instead of functional imaging. **1.3.5 Additional diagnostic investigations** 1.3.5.1 Offer non-invasive functional imaging (see section 1.3.6) for myocardial ischemia if invasive coronary angiography or 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance. 1.3.5.2 Offer invasive coronary angiography as a second-line investigation when the results of non-invasive functional imaging are inconclusive. **1.3.6 Use of non-invasive functional testing for myocardial Ischemia** 1.3.6.1 When offering non-invasive functional imaging for myocardial ischemia use: • 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. Take account of locally available technology and expertise, the person and their preferences, and any contraindications when deciding on the imaging method. [This recommendation updates and replaces recommendation 1.1 of Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction (NICE technology appraisal guidance 73)]. 1.3.6.2 Use adenosine, dipyridamole or dobutamine as stress agents for MPS with SPECT and adenosine or dipyridamole for first-pass contrast-enhanced MR perfusion. 1.3.6.3 Use exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities. 1.3.6.4 Do not use MR coronary angiography for diagnosing stable angina.	
Clinical area 2: The utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with acute chest pain		

of suspected cardiac origin.		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with acute chest pain of suspected cardiac origin? **Relevant section of guideline** 4.4.2 Use of biomarkers **Recommendations** 1.2.5.1 to 1.2.5.4	Through an assessment of the abstracts from the focus searches, 30 studies relevant to the clinical question covered in this clinical area of the guideline were identified. • One study[48] assessed the efficacy of high sensitivity troponin T versus troponin T in the detection of acute myocardial infarction in patients presenting with acute chest pain. The results showed that high sensitivity troponin T was superior to troponin T for the diagnosis of acute myocardial infarction. • One study[49] examined the diagnostic performance of high sensitivity cardiac troponin T versus old cardiac troponin in the detection of acute myocardial infarction in patients with acute chest pain. The results showed that the high sensitivity cardiac troponin T assay displays an excellent diagnostic performance for the workup of patients with chest pain at the time of their initial presentation compared to the old cardiac troponin. • One study[50] aimed at assessing the diagnostic performance of high sensitive cardiac troponin T vs. the standard cardiac troponin T in a	Potential new evidence that may change current recommendation(s).

	population with acute chest pain. The results showed that the high sensitivity cardiac troponin T assay is very effective in the early diagnosis of acute myocardial infarction compared to standard cardiac troponin T in patients with acute chest pain. • One study[51] assessed the efficacy of high-sensitive cardiac troponin versus cardiac troponin T in the detection of acute myocardial infarction in patients presenting with acute chest pain. The results showed that high-sensitive cardiac troponin provided an excellent early diagnostic accuracy to detect acute myocardial infarction in patients with acute chest pain. • One study[52] compared the diagnostic performance of a new high-sensitivity troponin T assay to that of conventional cardiac troponin for the diagnosis of acute myocardial infarction. The results confirmed that the high-sensitivity troponin T assay was more effective and had a higher sensitivity than conventional cardiac troponin in the diagnosis of acute myocardial infarction. • One study[53] determined the diagnostic performance of the new high-sensitivity cardiac troponin T assay versus cardiac troponin for early detection of non-ST-segment myocardial infarction in patients with acute coronary syndrome. The result showed that the high-	

	sensitivity cardiac troponin T assay was more effective and enabled earlier detection of evolving non-ST-segment myocardial infarction compared to cardiac troponin. • One study[54] evaluated a sensitive troponin I assay versus traditional myocardial necrosis markers for the early diagnosis of myocardial infarction in patients with acute chest pain. The results showed that the use of a sensitive assay for troponin I improved early diagnosis of acute myocardial infarction compared to traditional myocardial necrosis markers in patients with acute chest pain. • One study[55] compared the diagnostic accuracy of high-sensitivity troponin T with myeloperoxidase (MPO) and pregnancy-associated plasma protein A (PAPP-A) for early diagnosis of acute myocardial infarction in patients with acute chest pain in the emergency department. The results showed that the diagnostic performance of high-sensitivity troponin T was more effective and superior to that of MPO and PAPP-A for early diagnosis of acute myocardial infarction. • One study[56] determined the performance of the new high sensitivity cardiac troponin T assay versus cardiac troponin assay, myoglobin and heart-type fatty acid binding protein (h-FABP) for early diagnosis of myocardial infarction in patients with suspected acute	

	coronary syndrome. The results indicated that the high sensitivity cardiac troponin T assay allowed an earlier prediction of non-ST-segment elevation myocardial infarction than the less sensitive cardiac troponin T assay, myoglobin h-FABP and assays. • One study[57] conducted a prospective RCT to assess the impact of triple marker (cardiac troponin I, myoglobin and the MB isoenzyme of creatine kinase) testing on patient management and the diagnostic efficiencies of different biomarker strategies were examined in patients presenting with chest pain. The results showed that measurement of cardiac troponin I alone is sufficient for diagnosis and measurement of a marker panel does not facilitate diagnosis. • One study[58] conducted a RCT aimed to determine whether point-of-care cardiac biomarker panel consisting of MB isoenzyme of creatine kinase, myoglobin, and troponin assessment reduced health care costs and was likely to be cost-effective in patients presenting with chest pain. The results showed that point-of-care assessment does not reduce costs despite reducing admissions. • One study[59] conducted a RCT to find out how the new high-sensitivity cardiac troponin T assay compares with the old cardiac	

	troponins assay for risk assessment in patients with acute coronary syndrome. The results showed that the new high-sensitivity cardiac troponin T assay, compared with the old cardiac troponins assay, identified more patients with myocardial damage and who were at an increased risk for new cardiac events. • One study[60] compared the early diagnostic value for the detection of non-ST-segment elevation myocardial infarction by high-sensitive troponin T and that of conventional troponins in patients with acute chest pain. The results showed that the use of high-sensitive troponin T improves the early diagnostic accuracy compared with conventional troponins. • One study[61] evaluated the diagnostic performance of a high sensitive troponin assay as compared to a standard cardiac troponin assay in the diagnosis of acute myocardial infarction in patients presenting to the emergency department with chest pain. The results showed that high sensitive troponin assay presented superior diagnostic accuracy in the diagnosis of acute myocardial infarction compared to the standard cardiac troponin. • One study[62] examined the diagnostic accuracy of new, sensitive cardiac troponin assays versus standard assay (Troponin T) in the	

	emergency department who presented with symptoms suggestive of acute myocardial infarction. The results showed that the diagnostic performance of sensitive cardiac troponin assays is excellent, and these assays can substantially improve the early diagnosis of acute myocardial infarction compared to standard assay (Troponin T). • One study[63] examined the diagnostic accuracy of high sensitive cardiac troponin versus standard assays in elderly patients presenting with symptoms suggestive of acute myocardial infarction. The results showed that high sensitive cardiac troponin assays are effective and have a high diagnostic accuracy also in the elderly compared to standard assays. • One study[64] evaluated the analytical performance of a high-sensitivity cardiac troponin T assay versus standard assay in the diagnosis of acute myocardial infarction in patients with acute chest pain. The results showed that the high-sensitivity cardiac troponin T assay was effective in detecting acute myocardial infarction compared to standard assay. • One study[65] examined the diagnostic accuracy of high sensitive cardiac troponin versus standard assay in patients presenting with symptoms suggestive of acute myocardial infarction. The results	

	showed that high sensitive cardiac troponin assays are effective in detecting acute myocardial infarction compared to standard assay. • One study[66] aimed to analyze the diagnostic potential of a newly developed high-sensitive troponin T assay and compared these results with those of a contemporary troponin T assay with suspected acute coronary syndrome. The results showed that high-sensitive troponin T assay provided better diagnostic performance compared to contemporary troponin T assay to detect acute coronary syndrome. • One study[67] assessed whether multiple biomarkers (myeloperoxidase, soluble CD40 ligand, placental growth factor, matrix metalloproteinase 9, high-sensitivity C-reactive protein, cardiac troponin I, N-terminal pro-B-type natriuretic peptide) of numerous pathophysiological pathways would increase the diagnostic accuracy for detecting myocardial infarction in patients with acute chest pain. The results showed 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. • One study[68] assessed the role of novel biomarkers (amino terminal	

	pro-B-type natriuretic peptide [NT-proBNP], ischemia modified albumin, heart fatty acid binding protein, high-sensitivity troponin I [hsTnI], and unbound free fatty acids [FFAu]) for the diagnostic evaluation of acute coronary syndrome in patients with acute chest pain. The results indicated that NT-proBNP, , high-sensitivity troponin I or FFAu are effective and added diagnostic information in the detection of acute coronary syndrome whereas ischemia modified albumin and heart fatty acid binding protein were not effective in the detection of acute coronary syndrome. • One study[69] evaluated the efficacy of high-sensitivity C-reactive protein versus cardiac troponin in aiding in the identification of an acute coronary syndrome in patients admitted to the chest pain unit for possible acute coronary syndrome. The results showed that high-sensitivity C-reactive protein did not enhance the diagnostic accuracy for acute coronary syndrome. • One study[70] evaluated the potential role of copeptin together with high sensitive troponin-I versus myoglobin for a rapid and early rule-out of acute myocardial infarction in patients with acute chest pain. The results showed that copeptin concentrations are more sensitive than myoglobin as an early marker of myocardial damage.	

	• One study[71] evaluated clinical performance of AQT90 FLEX TnI (troponin I) assay compared with central laboratory troponin assays in diagnosing acute myocardial infarction. The results showed that AQT90 FLEX TnI was not clinically effective in diagnosing acute myocardial infarction compared to central laboratory troponin assays. • One study[72] compared diagnostic values of pentraxin 3 (PTX3) for acute coronary syndrome with troponin T and heart-type fatty acid binding protein (H-FABP) in patients with acute chest pain. The results indicated that PTX3 was effective, sensitive and specific biomarker for the diagnosis of acute coronary syndrome compared to troponin T and H-FABP. • One study[73] compared the diagnostic performance of serum ischemia modified albumin and sensitive cardiac troponin I assay for the detection of acute coronary syndrome in patients presenting to the emergency department with acute chest pain. The results indicated that ischemia modified albumin improved the early diagnosis of acute coronary syndrome and non-ST-segment-elevation acute coronary syndrome in patients with acute chest pain.	

	• One study[74] evaluated the value of adding natriuretic peptides (myocyte stress markers) to troponins (myocardial injury markers) for diagnosing acute coronary syndrome in emergency department patients with chest pain. The results indicated that adding natriuretic peptides to troponins improved detection of acute coronary syndrome. • One cohort study of 703 patients evaluated whether high sensitivity troponin can immediately exclude acute myocardial infarction.[75] The results of the study indicated that undetectable high sensitivity troponin at presentation had a high negative predictive value. • One study was identified which prospectively tested whether copeptin adds information to that provided by a high sensitivity troponin assay in the early evaluation of patients with suspected acute myocardial infarction, particularly non-ST-segment evaluation myocardial infarction.[76] The study concluded that a strategy using copeptin with a high sensitivity troponin assay at prespecified cut-offs improves the ruling out of non-ST-segment evaluation myocardial infarction. • Similarly, another study investigated whether copeptin could be used alongside cardiac troponin in early evaluation of patients with	

	suspected myocardial infarction.[77] The results of the study indicated that, in this group of patients, the combination of copeptin with troponin improves diagnostic performance especially early after onset of chest pain. • The incremental value of copeptin for rapid rule out of acute myocardial infarction was evaluated in one study.[78] The results of the study demonstrated that copeptin levels were significantly higher in acute myocardial infarction patients compared with those in patients with other diagnoses. **Summary** The identified new evidence indicated that high sensitive troponin is diagnostically more effective that the conventional cardiac troponin in detecting acute myocardial infarction and acute coronary syndromes. Furthermore, 5 studies were identified which indicated that copeptin together with high sensitive troponin-I improves diagnostic performance in early diagnosis of patients with suspected myocardial infarction. This is potentially new evidence compared to what is currently recommended in the guideline which states:	

	1.2.5.1 Take a blood sample for troponin I or T measurement on initial assessment in hospital. These are the preferred biochemical markers to diagnose acute myocardial infarction. 1.2.5.2 Take a second blood sample for troponin I or T measurement 10–12 hours after the onset of symptoms. 1.2.5.3 Do not use biochemical markers such as naturetic peptides and high sensitivity C-reactive protein to diagnose an acute coronary syndrome. 1.2.5.4 Do not use biochemical markers of myocardial ischemia (such as ischemia-modified albumin) as opposed to markers of necrosis when assessing people with acute chest pain. One study showed sensitive assay for troponin I improved early diagnosis of acute myocardial infarction compared to traditional myocardial necrosis markers in patients with acute chest pain. Another study showed that high-sensitivity troponin T was more effective and superior to that of myeloperoxidase and pregnancy-associated plasma protein A for early	

	diagnosis of acute myocardial infarction. Two studies showed that cardiac troponin is effective in the early diagnosis of acute myocardial infarction when compared to myeloperoxidase, soluble CD40 ligand, placental growth factor, matrix metalloproteinase 9, high-sensitivity C-reactive protein, myoglobin and the MB isoenzyme of creatine kinase. One study showed that point of care biomarker panel (CK-MB, myoglobin, and troponin) did not reduce costs despite reducing admissions when compared to standard care. Single studies showed that ischemia modified albumin, heart fatty acid binding protein high-sensitivity C-reactive protein and AQT90 FLEX TnI (troponin I) assay were not effective in the diagnosing acute coronary syndrome. Single studies showed that amino terminal pro-B-type natriuretic peptide, high-sensitivity troponin I, unbound free fatty acids, pentraxin 3, ischemia modified albumin, and addition of natriuretic peptides (myocyte stress markers) to troponins are quite effective in diagnosing acute coronary syndromes but these are just single studies and more evidence is required to support these findings before recommendations within the guideline can be altered.	
Clinical area 3: The incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of patients with stable chest pain of suspected cardiac origin		
Clinical question	**Summary of evidence**	**Relevance to guideline**

		recommendations
Q: What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of patients with stable chest pain of suspected cardiac origin? **Relevant section of guideline** 1.3.2 Clinical assessment **Recommendations** 1.3.2.1 to 1.3.2.2	Through an assessment of the abstracts from the focus searches, 2 studies relevant to the clinical question covered in this clinical area of the guideline were identified. • One study[79] assessed the value of individual historical and examination findings for diagnosing acute myocardial infarction in patients with acute chest pain. The results showed that history and examination findings are effective in diagnosing acute myocardial infarction in patients with acute chest pain. • One study[80] developed and assessed prediction models (Diamond-Forrester) that better estimate the pretest probability of coronary artery disease in patients with stable chest pain without evidence for previous coronary artery disease. The authors concluded that updated prediction models including age, sex, symptoms, coronary calcium scores, and cardiovascular risk factors allowed for accurate estimation of the pre-test probability of coronary artery disease in stable chest pain without evidence for previous coronary artery disease. They also concluded that the updated model predicts less high probabilities compared with the Diamond–Forrester model and using the updated model could lead to decreased referral to cardiac	Potential new evidence that may change current recommendation(s).

	coronary angiography, a higher yield of angiography, and increased use of non-invasive testing for risk stratification. **Summary** One study showed that history and examination findings are effective in diagnosing acute myocardial infarction in patients with acute chest pain. This is in keeping with the current guideline recommendation which state: **1.3.2 Clinical assessment** 1.3.2.1 Take a detailed clinical history documenting: • the age and sex of the person • the characteristics of the pain, including its location, radiation, severity, duration and frequency, and factors that provoke and relieve the pain • any associated symptoms, such as breathlessness • any history of angina, MI, coronary revascularisation, or other cardiovascular disease and • any cardiovascular risk factors. 1.3.2.2 Carry out a physical examination to:	

	• identify risk factors for cardiovascular disease • identify signs of other cardiovascular disease • identify non-coronary causes of angina (for example, severe aortic stenosis, cardiomyopathy) and • exclude other causes of chest pain. Another study showed that the updated version of the Diamond–Forrester model is more effective and allowed for accurate estimation of the pretest probability of coronary artery disease in stable chest pain without evidence for previous coronary artery disease. This could lead to decreased referral to cardiac coronary angiography, a higher yield of angiography, and increased use of non-invasive testing for risk stratification. Potential new evidence is identified which could alter the current guideline recommendations which state: **1.3.3 Making a diagnosis based on clinical assessment** 1.3.3.1 Anginal pain is: • constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms	

	• precipitated by physical exertion • relieved by rest or GTN within about 5 minutes. Use clinical assessment and the typicality of anginal pain features listed below to estimate the likelihood of CAD (see table 1-Adapted from Pryor DB, Shaw L, McCants CB et al. (1993) Value of the history and physical in identifying patients at increased risk for coronary artery disease. Annals of Internal Medicine 118(2):81–90.): • three of the features above are defined as typical angina. • two of the three features above are defined as atypical angina. • one or none of the features above are defined as non-anginal chest pain.	

Two ongoing clinical trials (publication dates unknown) were identified focusing on CT coronary angiogram versus traditional care in emergency department assessment of potential acute coronary syndrome and a study to rule out myocardial infarction by cardiac computed tomography

No evidence was identified that was relevant to research recommendations in the original guideline.

Guideline Development Group and National Collaborating Centre perspective

A questionnaire was distributed to GDG members and the National Collaborating Centre to consult them on the need for an update of the guideline. The questionnaire was designed to ask GDG members their opinion on the use of the current guideline, whether they are aware of any new literature relating to areas covered by the guideline, the potential to make better use of resources, the potential for avoiding unlawful discrimination and whether they feel an update of the guideline is required. Eight responses were received and three respondents indicated that there was no new relevant literature that potentially changes current recommendations. Five respondents mentioned new evidence on the following areas:

- Novel imaging techniques, particularly computerised tomography coronary angiography and magnetic resonance perfusion imaging for diagnosis of chest pain.
- Diagnostic assessment in patients with suspected stable angina.
- Further research on biomarkers is available including the introduction of highly sensitive troponins is impacting on timescales for testing in patients with suspected acute coronary syndrome.
- A key area of the guideline, the pre-test likelihood table has been updated recently, which is critical in the diagnostic pathway. There is additional evidence for the validity of using Diamond and Forrester to assess pre-test likelihood of coronary artery disease in contemporary practice, and the use of electronic tools rather than tables needs to be considered.

One respondent mentioned that computerised tomography and magnetic resonance imaging techniques are more widely available, hence might have become more cost effective. In terms of ongoing research relevant to the guideline, four respondents did not identify any but one respondent identified the following trials:

- SCOTHEART Trial. The primary objective of the study is to see if coronary artery calcium score and computed tomography coronary angiogram alters the proportion of patients diagnosed with angina due to coronary heart disease.

In terms of any efficacy or safety concerns about the recommended practice, five respondents said there were none while the other two mentioned the safety issues in regards to radiation exposure due to use of computerised tomography.

Overall, four respondents commented that there was insufficient evidence or variation of practice to warrant an update of current guideline at this time. However, two other respondents were unsure and two respondents disagreed and proposed the following areas to be further reviewed: novel imaging techniques to diagnose patients with acute chest pain, evidence on highly sensitive troponin and additional evidence for the validity of using Diamond and Forrester to assess pre-test likelihood of coronary artery disease.

Implementation and post publication feedback

In total 81 enquiries were received from post-publication feedback, most of which were routine. Key themes emerging from post-publication feedback related to non-compliance with recommendation on taking an initial troponin reading, and audit of the guideline. This feedback did not contribute towards the development of the clinical questions as described above.

No new evidence was identified through post publication enquiries or implementation feedback that would indicate a need to update the guideline.

Relationship to other NICE guidance

The following NICE guidance is related to CG95:

Guidance	Review date
CG130: Hyperglycaemia in acute coronary syndromes (Oct 2011)	To be confirmed
CG127: The clinical management of primary hypertension in adults (Aug 2011)	To be confirmed
CG126: The management of stable angina (Jul 2011)	To be confirmed
CG27: Referral for suspected cancer (June 2005)	To be updated
CG107: Hypertension in pregnancy (May 2011)	To be confirmed
CG108: Chronic heart failure (Aug 2010)	To be reviewed Aug 2013
CG109:Transient loss of consciousness in adults and young people (Aug 2010)	To be reviewed Aug 2013
CG94: Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction (Mar 2010)	Guideline is currently under review
CG69: Respiratory tract infections (Jul 2009)	Reviewed in 2011 (Not to be updated)
CG68: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) (Jul 2008)	Reviewed in 2011 (Not to be updated)
CG48 MI: secondary prevention (Oct 2007)	To be updated
IPG286: Thoracoscopic epicardial	To be confirmed

radiofrequency ablation for atrial fibrillation (Jan 2009)	
MTG4 BRAHMS copeptin assay to rule out myocardial infarction in patients with acute chest pain (Jun 2011)	To be confirmed
TA47: Glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes (Sept 2002)	TA47 was updated by CG94, 2010.
TA52: Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction (Oct 2002)	As per review proposal project incorporated verbatim into the forthcoming clinical guideline on the 'management of acute coronary syndromes including myocardial infarction.'
TA71: Guidance on the use of coronary artery stents (Oct 2003)	Sections 1.2-1.4 of this guidance have been replaced by TA152 Coronary artery disease - drug-eluting stents (July 2008)
TA73: Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction (Nov 2003)	This guidance has been partially updated by 'Chest pain of recent onset' (NICE clinical guideline 95) and 'Management of stable angina' (NICE clinical guideline 126). Section 1.2 of the guidance should be updated within the clinical guideline on 'The management of stable angina' currently in development. The rest is placed on the static list in 2010
TA80: Clopidogrel in the treatment of non-ST-segment elevation acute coronary syndrome (July 2004)	Recommendations 1.1 and 1.2 were updated by CG94 and recommendations 1.3 was incorporated into CG94

TA88: Bradycardia – dual chamber pacemakers (Feb 2005)	It is currently subject to a technology appraisal review proposal project at the moment
TA90: Clopidogrel and dipyridamole for the prevention of artherosclerotic events (May 2005)	It has been updated and replaced by TA210- Vascular disease - clopidogrel and dipyridamole
TA94: Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease (Jan 2006)	As per review proposal project in late 2011, this piece of guidance is to be updated within a review of the NICE guideline CG67: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease
TA95: Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias (review of TA11) (Jan 2006)	This appraisal is currently being reviewed as an MTA (along with TA120). Expected publication date is Sept 2013
TA120: Cardiac resynchronisation therapy for the treatment of heart failure (May 2007)	This appraisal is currently being reviewed as an MTA. Expected publication date is Sept 2013
TA122: Alteplase for the treatment of acute ischaemic stroke (June 2007)	This guidance has been updated and replaced by TA264 issued in September 2012
TA152: Coronary artery disease - drug-eluting stents (July 2008)	To be confirmed
TA182 Acute coronary syndrome – prasugrel (Oct 2009)	It will be updated as an MTA. Publication dates to be confirmed
TA210: Vascular disease - clopidogrel and dipyridamole (Dec 2010)	To be reviewed Jul 2013
TA230 Myocardial infarction (persistent ST-segment elevation) –	It will be incorporated verbatim into the forthcoming clinical guideline on

bivalirudin (July 2011)	the 'management of acute coronary syndromes including myocardial infarction.'
TA236: Acute coronary syndromes – ticagrelor (Oct 2011)	The guidance on TA236 for people with STEMI will be incorporated into the forthcoming NICE clinical guideline on the management of myocardial infarction with ST-segment elevation. The guidance on ticagrelor for people with NSTEMI and unstable angina will be considered for review at the same time as clinical guideline 94 (Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment elevation myocardial infarction) which is currently under review
Related NICE guidance in progress	
Quality Standard: Acute coronary syndromes (including myocardial infarction)	To be confirmed

Anti-discrimination and equalities considerations

No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope is inclusive of adults only.

Conclusion

From the evidence and intelligence gathering identified through the process, it suggests that some areas of the guideline may need updating at this stage, particularly in relation to:

- Computerised tomographic angiographies for the diagnosis of acute coronary syndromes in patients with acute chest pain.
- The use of high sensitive troponins compared to the conventional cardiac troponins to diagnose acute coronary syndromes in patients with acute chest pain.
- The use of updated Diamond-Forrester prediction model to better estimate the pre-test probability of coronary artery disease in patients with stable chest pain without evidence for previous coronary artery disease.

3. Review recommendation

This guideline is potentially related to the upcoming quality standard for acute coronary syndromes (including myocardial infarction).

The guideline should be considered for an update.

Centre for Clinical Practice
12 October 2012

Appendix I

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