National Institute for Health and Clinical Excellence

Chest Pain

Guideline Consultation Comments Table

26 May 2009 – 21 July 2009

General Comments

Status	Organisation	Order no.	Version	Page no	Line no	Comment	Response
SH	Abbott Vascular	1	Full	General		Thank you for the opportunity to review the guidance Abbott Vascular has no comments to make.	Noted with thanks
SH	British Cardiovascular Society	1	Full	General		Structural versus functional assessment • Assessment of patients with chest pain has should include diagnostic and prognostic elements • There are essentially 2 approaches to assessing patients with suspected coronary artery disease; an anatomic approach addressing whether there are significant stenoses in the coronary arteries and a functional approach, addressing whether myocardial ischaemia is present • In the NICE draft document there is a weighting of diagnostic tests towards those assessing anatomy i.e. CT calcium scoring leading to CT coronary angiography and traditional coronary angiography • Chest pain is a common symptom and is often not anginal in nature. Many patients with known coronary artery disease have chest pain which is not anginal in nature, often in addition to their	Bullet point: 1 We agree prognostic assessment is important, but this was not part of the scope of this guideline which is about diagnosis of chest pain. Prognostic assessment will be included in the angina guideline currently being developed. 2 Agreed and we have included both functional and or anatomical testing in the diagnostic pathway ((Refer to appendix of the NICE guideline) 3 The evidence for both anatomical and ischaemia testing was examined to make the recommendations and testing for ischaemia first line is clearly included for those with an intermediate pretest likelihood of CAD. There is appropriate weighting given to the different tests

						anginal pain. • Tests focused on investigating coronary anatomy assess different things from those assessing function/ischaemia. It should be expected that if an “anatomical” test, coronary angiography, is used as the gold standard, it would have a better correlation with another “anatomical” test, CT coronary angiography than with tests of function/ischaemia such as MPS using SPECT and stress echocardiography. We know from pressure wire studies in the cardiac catheter lab that many stenoses which are thought to be tight and “flow limiting”, do not cause myocardial ischaemia when objectively assessed. Therefore some of the “discrepancy” between the gold standard coronary angiography and functional/ischaemic tests is because either a “tight” stenosis is not causing myocardial ischaemia or a “moderate” stenosis is ischaemic. • There is recent evidence which favours treating coronary lesions which have been shown to be functionally ischaemic rather than treating on the basis on the coronary anatomy alone. (Tonino PA, De Bruyne B, Pijls NH et al. Fractional flow resesrve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2008;360:213-24). • There is an increasing emphasis on the assessment of myocardial ischaemia and treatment directed towards ischaemic substrate in current routine cardiological practice rather than treatment driven by coronary anatomy alone. Radiation • The NICE report cites the data on tests which utilize ionizing radiation but then do not	based on current clinical evidence and health economic evaluation. 4 We agree that tests for ischaemia are first line in patients with a prior diagnosis of CAD and this is recommended. 5 and 6 We acknowledge the distinction between functional and anatomical testing in Section 1, p27 lines 10-13, making the point that neither is necessary nor sufficient for diagnosing angina. We also acknowledge at length the problems relating to the angiographic gold standard used for non-invasive testing (Section 1, p 23/24, lines 27-30/1-11). The approach in this guideline was to focus on the clinical assessment for diagnosis, supported as necessary by functional or anatomical testing in cases where there was lingering uncertainty. The pressure wire data referred to its value for guiding stenting (a subject outside the scope of this guideline), not for diagnosing angina. Indeed there was no difference in 12 month rates of angina in the angiographic and IVUS groups 7. Agreed. Angina is a manifestation of ischaemia. For this reason, the guideline focuses on diagnosis by clinical assessment, reserving additional tests for patients in whom diagnostic doubt remains. This usually involves functional testing but cost-effectiveness analysis led to a recommendation for

							emphasise this as an important criterion in the choice of diagnostic tests. The strategy of CT coronary angiography in a middle age woman at the current time in most UK centres would result in over 15milliSieverts of radiation which has been estimated as leading to approximately a 1 in 250 lifetime risk of cancer arising from that test. (Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007;298:317-23). It is particularly a problem in women in whom the radiation is directed over the breasts, which are radiosensitive. In most middle age women with chest pain myocardial ischaemia can be effectively excluded by non-invasive functional testing without using ionizing radiation. If using a test with ionizing radiation as the protocolised first test the problem may be compounded as many patients present multiple times with chest pain over the course of a decade or two and need repeat assessment. • Cited radiation doses for tests are often derived from optimal data. In the real world doses are usually higher. For instance CT coronary angiography can be performed either prospectively which utilizes less radiation or retrospectively, which has a higher dose but generally results in better pictures. Most scans are done retrospectively. It would be worth using audit data to document real life radiation doses in compiling the guideline. • Although some patients will only need to have a CT calcium score test as they will have no calcium in their coronaries a significant proportion will need to proceed to CT coronary angiography with increased radiation levels. • There is increasing evidence that in some patients, the absence of calcium in the	anatomical testing in those few patients with a high (>60%) or low (<30%) likelihood of disease in whom diagnosis had not already been made by clinical assessment. The combination of a typical history plus high grade coronary stenosis is sufficient for a diagnosis of angina while a very atypical history and a zero calcium score is sufficient for rule-out. Radiation We acknowledge that radiation exposure is a problem to be taken seriously but make the following points. Bullet Point 1. Radiation exposure for calcium scoring that does not proceed to angiography is negligible 2. Gated imaging and dual source machines are substantially reducing radiation exposure in MDCT angiography – contemporary scanners providing complete angiographic assessment in the 7-8-millisievert range with a scan time for the entire heart of just 250 milliseconds. 3. We need to make clearer the fact that this guideline's recommendations ensure that the majority of patients are diagnosed either on clinical grounds alone or on clinical grounds supported by the result of a functional test. The guideline is conservative therefore in its recommendations for anatomical testing with radiation exposure. Thus the majority of patients with non-specific chest pain are excluded on clinical assessment, the minority in whom diagnostic doubt persists having a calcium score (negligible radiation) proceeding to angiography only if calcium is demonstrated. Similarly the majority of patients with typical angina and a high probability of disease are diagnosed on clinical criteria alone, only

						coronaries does not preclude significant coronary stenoses. (Schuijf JD, van der Wall EE, Bax JJ. Lesions without calcium: lessons from CT angiography. Heart. 2009;95:1038-40. Epub 2009). • The movement away from functional testing for low risk patients would not only expose many patients to unnecessary ionizing radiation but would also lead to a disrupted patient pathway for many patients. In many cardiology units where chest pain clinics exist, exercise treadmill testing is done at the same place and at the same time as the clinical assessment. Although the negative predictive value of calcium scoring is better than exercise testing many patients can be reassured on the basis of a clinical history and a normal exercise test. This is particularly the cases for patients at low risk of coronary disease who tend to be a relatively young age group, have normal baseline ECGs and are able to exercise. A high proportion of patients can be reassured in a single visit without the need to navigate a second department or even a second visit, with the inherent difficulties of complicating the system of care. • If the combination of clinical assessment and exercise ECG is inconclusive or the patients cannot exercise then many departments with good access to stress echo can get a reliable diagnosis without using ionizing radiation. For other units the options can be either a CT based strategy or an MPS based strategy, depending on whether an anatomical or a functional strategy is adopted. SUMMARY • In summary, I would request that we challenge the recommendation of a first line CT based	proceeding to angiography if doubt persists. 4. Rates of CAD in patients with a zero calcium score are very low accounting for the high diagnostic sensitivity of the method (specificity of course is low). This is made clear in the Marwan paper which also reports that most false negative cases are those with unstable (not stable) chest pain – the group for whom the guideline makes NO recommendation for MDCT. 5. We agree that most young people attending chest pain clinics can be reassured on clinical grounds without the need for testing. This is a central recommendation of the guideline. We also agree that the sensitivity and NPV of calcium scanning is better than ETT. Cost-effectiveness analysis is also unfavourable for ETT. The convenience argument is more finely balanced calcium scoring being a quicker (and more objective) test but in existing arrangements more difficult to organise – a point which should be given further consideration by the NICE Implementation Team 6. Concerning serial non-invasive testing (you suggest exercise testing, then stress echo) there are strong cost-effectiveness arguments against this.

						strategy for the assessment of patients presenting with stable chest pain. Most cardiologists would support a functional assessment in the first instance and we should only resort to tests with significant ionizing radiation if equivalent tests not involving radiation are either unavailable or significantly less good.	
SH	British Heart Foundation	2	Full	General		The proposals in section 2 of this draft guideline will mean major changes to the patient pathway and services run by cardiac departments. This brings two major areas of concern: Firstly, whether hospitals will have the capacity to switch from an exercise test based diagnostic service to one that relies heavily on sophisticated imaging modalities such as CT, MRI and SPECT? Currently all cardiologists are able to interpret an exercise ECG, but very few centres have experts who are experienced in cardiac CT and MRI - even if they have the necessary equipment. Secondly, the interpretation of such tests, particularly SPECT and stress echo, and to some extent CT angiography and MRI, require a high degree expertise for interpretation. While the Guideline Development Group (GDG) has evaluated evidence in favour of these tests published by expert practitioners, it is unclear what assessment the GDG has made of how the tests will perform in NHS Trusts that do not have the same level of expertise. It is likely that the sensitivities and specificities of some of these tests will be less good in non-expert centres than in the published literature.	I have referred your comments to the implementation team as the remit of the GDG is to look at the evidence. Point 1 - Most trusts do have 64 slice CT available, although it may not currently be used for cardiac patients. Point 2 – The GDG recognised and discussed this point and took it into account during their discussions. The health economic analyses found that the outputs of the models were sensitive to changes in test accuracy and in addition the analyses that the GDG asked be undertaken during the development of the guideline included a more conservative estimate of the test accuracy of 64-slice CT coronary angiography in the base case.
SH	British Nuclear Medicine Society 1	7	Full 1	General		There has been an appraisal of the use of cardiac CT in patients presenting with chest pain to the A+E department, but no key question has addressed the use of Nuclear Cardiology in the A+E department. The “ERASE” trial JAMA. 2002;288(21):2693-2700 is a	The trial referred to recruited in 1997-9 and confined itself to patients with suspected ACS but nondiagnostic ECGs in the pre-troponin era. Nuclear imaging had no effect on triage decisions in patients with AMI and UA but in

						randomised controlled trial of the effectiveness of rest myocardial perfusion imaging in patients presenting to the A+E department	patients without cardiac ischaemia it reduced by 10% rates of hospitalisation. Hard to know what relevance this has to contemporary practice where troponin measurement is such an important driver of triage decisions in patients of this type.
SH	British Nuclear Medicine Society 1	21	Full 2	General		The combination of imaging of CT coronary angiography with PET or SPECT agents to assess perfusion has been shown to increase diagnostic accuracy. This has not been considered by the GDG	The evidence based for this technique is currently small and it was the GDG's view that it was insufficient to consider for general care at this time. In addition, it gives a higher radiation dose than the investigations recommended in the guideline.
SH	British Nuclear Medicine Society 1	22	Full	General		In assessing the various imaging modalities, it is of great concern that prognosis assessment was not considered. The ability of a test to determine prognosis in a patient presenting with chest pain is arguably more important than the ability to determine presence or absence of CAD. This may extend into therapy. The "courage" study would suggest that patients adequately treated with medical therapy have as good a prognosis as those treated by angiography and angioplasty. In patients presenting with recent onset chest pain, assessment of prognosis helps determine who should have a trial of medical therapy.	We agree that prognostic assessment is important but this was outside the scope of this guideline which considers only diagnosis of chest pain. Similarly this guideline makes no recommendations concerning treatment of suspected angina which is the subject of another guideline currently in progress.
SH	British Nuclear Medicine Society 1	23	Full	General		The increased capacity required for CT angiography will have major resource implications. Low risk patients will generally be younger and CT has an important radiation effect in this age group.	I have referred your comments on implementation to the NICE implementation team. With regard to your comments on radiation, the advice is to only refer for investigation if there is a concern that they may have angina. The advice is to first carry out calcium scoring therefore only relatively few of those younger people with a raised calcium score will go on to have 64 slice (or above) CT coronary angiography. If done with 64 slices with prospective gating which can be done through updating software the radiation exposure is 7-8 milli Sieverts.

							Please refer to the introduction to the stable chest pain section of the NICE guideline where this has been clarified.
SH	British Nuclear Medicine Society 1	24	Full	General		The discussion of future developments is unbalanced without proper consideration of the likely future capabilities of SPECT and PET. Although advances in cardiac CT are considered, no consideration is given to improvements in MPS. Thus new solid state gamma cameras, new acquisition protocols both of which reduce radiation dose and improve resolution are not evaluated. New perfusion tracers e.g. Rubidium perfusion imaging is not considered. The latter technique takes less than 1 hour for the whole study	We agree that many of these technologies may prove more effective in future, the guideline is based on current evidence. The evidence will be reviewed in 3 years time and if there have been changes it will be updated. The suggestions you make might be better suited to a NICE Technology Appraisal and the British Nuclear Medicine Society may wish to make a recommendation to that effect on the NICE website.
SH	British Nuclear Medicine Society 2	12	Full 2	General		There is no mention of technical advancements in hardware and software which can reduce radiation dose and allow significantly quicker scans. There is also no mention of positron emission tomography, PET, anywhere in the document.	The GDG acknowledged the technical advancements in their deliberations, and the recommendations are based on currently available evidence in patients with chest pain. The evidence base for PET is currently very small, and the GDGs view was that it was insufficient to consider for general use at this time.
SH	British Nuclear Medicine Society 2	14	Full 2	General		There is significant emphasis and economic modelling around CT calcium scoring and coronary angiography and evidence for MPS appear to be considerably undermined.	The evidence from both the published economic analyses and the de novo models undertaken for this guideline included both anatomical and functional technologies. MPS was frequently shown not to be cost-effective compared to CT and CA (often more costly and less effective than 64CT angiography). The first line functional testing model using SPECT MPS favoured MPS compared to invasive CA for populations with an intermediate pre-test likelihood.
SH	British Nuclear Medicine Society 2	15	Full 2	General		The pathway suggested for low pre test likelihood patients would mean major restructuring of the Rapid access chest pain clinics and providing significant resources for training and equipment.	Our message was not clear in the consultation draft. Thank you for pointing this out. A vast majority of people presenting with a low pre-test likelihood would not have angina symptoms and be ruled out without any further

							investigation. Only those where there are typical or atypical angina symptoms and a pretest likelihood >10% would be investigated. This has been clarified in the document.
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	10	Full	General		We believe that these proposed guidelines are heavily biased towards calcium scoring and MDCT coronary angiography (CTA) as a first line investigation for stable angina. There are currently not the data to support this dramatic change and this is a long way from what is considered mainstream cardiology practice in the UK. In the USA the scenario is very different, but the healthcare model is very different and practice is skewed, based around issues of reimbursement. It seems a somewhat retrograde step to replace physiological/pharmacological assessment of ischaemia with another test that is based on risk prediction (i.e. CAC scoring). We already have models for cardiovascular risk assessment, and whilst not perfect, they are safe, simple to use and generally widely applicable and available. Furthermore the proposed guidelines are based almost entirely towards anatomical testing (CAC scoring, CTA) and greatly under-rate the central and important role of functional ischemia testing (e.g. by SPECT, CMR, or stress echo). The revised guidelines will have to give these functional investigations a much greater role and significantly reduce the emphasis of a purely anatomical assessment. We also believe that the potential issue of widespread <u>population exposure</u> to additional investigations involving ionising radiation has not been fully considered or debated. We know from published data that the radiation exposure from a diagnostic angiogram is in the order of 5-7mSv. This alone is estimated to carry a risk of solid tumour development of 1:2500 angiograms	We make few recommendations for calcium scoring and CTCA as first line investigations for stable angina. The guideline focuses on clinical assessment recommending no diagnostic tests if the probability of angina exceeds 90% or if probability is very low (as defined in the guideline). For patients in whom doubt remains after the initial assessment the guideline adopts a conventional approach of functional testing for those patients with stable chest pain and an intermediate (30-60%) likelihood of disease in whom diagnostic uncertainty remains after initial assessment. Cost-effectiveness analysis led to recommending anatomical testing only in those few patients with a high (>60%) or low (<30%) likelihood of disease in whom a confident diagnosis had not already been obtained by clinical assessment. As regards radiation exposure we take this seriously but point out that this is negligible for calcium scoring that does not proceed to angiography. In this low risk group the majority of patients will have zero scores for which further CTCA is not recommended. Only in patients with scores of 0-400 or >400 do we recommend proceeding to CTCA or invasive angiography. In this small population, all of whom will have coronary atherosclerosis, we consider the benefits of defining disease severity outweigh the risk attributable to radiation which, as you say, will become substantially lower with the widespread use of gated imaging and dual source machines. Indeed, contemporary scanners can now provide complete angiographic assessment in

						[Berrington de Gonzalez A. Lancet 2004; 363: 345-51]. In addition the FDA states that a 10mSv CT study may be associated with an increase in the possibility of fatal cancer of approximately 1 in 2000 cases. However, it remains unclear how this risk is affected by patient age, sex, and scan protocol. Recent data suggest that use of 64-slice CTCA is associated with a non-negligible life time risk of cancer. This risk varies markedly and is considerably greater for women, younger patients, and for combined cardiac and aortic scans [JAMA. 2007;298(3):317-323]. With improvements in MDCT, including hardware and dose reduction algorithms, radiation exposure from CTA may get down to 'acceptable' levels in the future. However, this is NOT the case at the present time. The most contemporary data published comes from the PROTECTION-1 trial [JAMA 2009] – this study looked at cardiac CTA dose reduction algorithms across 50 international centres. These were all centres of excellence invited to participate based on their prior publications in cardiac CT – i.e. NOT representative of the typical centre undertaking this examination. Even from this highly experienced group of investigators using the state of the art equipment the mean effective dose was 12mSv (~600 chest X-rays) with a range of 5mSv to 30mSv! This is not trivial and on a population level has lead to major concerns being expressed in the literature. Indeed, even the most recent consensus document from the AHA on ionising radiation in cardiac imaging (Circulation 2009; 119: 1056-65) states in its conclusion (p1061) that "*considerations should include options for answering the clinical question at hand by means that do not use ionizing radiation or choosing the type of study that exposes the patient to the lowest amount of radiation.*"	the sub-millisievert range with a scan time for the entire heart of just 250 milliseconds.

SH	British Society of Echocardiography	1	Full	General		1. The guideline represents a predominantly anatomical approach (EBCT, CT angiography) to a pathophysiological response (pain) to myocardial ischaemia. Ischaemia is due to an imbalance of myocardial oxygen supply relative to demand and only partly related to anatomical constraints. Physiological assessment through exercise testing, stress echocardiography or other functional imaging are therefore appropriate and evidence based investigations for new chest pain 2. In investigating acute chest pain suspected to be due to an ACS, EBCT and CT coronary angiography are relatively new modalities that, while tested in observational studies from selected centres, have not been practiced widely in routine unselected clinical practice or tested in RCTs against algorithms based on a physiological approach. Recent reviews have emphasised this and recommended trials prior to widespread introduction. (Shapiro, J Cardiovasc Comput Tomogr. 2009 Mar-Apr;3(2):100-3. and Scoenhagen, Int J Cardiovasc Imaging. 2007 Aug;23(4):429-32. The AHA have given cautious recommendation only to the use of CT angiography (Class IIa, Level of Evidence: B). In contrast trials have demonstrated the effectiveness of stress echo in suspected ACS. (eg Senior et al, Eur Heart J 2007;28:204–211.) 3. The initial use of EBCT is not robust. Obstructive	Point 1 The guideline adopts a conventional approach of functional testing for those patients with stable chest pain and an intermediate (30-60%) likelihood of disease in whom diagnostic uncertainty remains after initial assessment. Cost-effectiveness analysis led to a recommendation for anatomical testing only in those few patients with a high (>60%) or low (<30%) likelihood of disease in whom a confident diagnosis had not already been obtained by clinical assessment. Point 2. Agreed. The guideline makes no recommendations for EBCT or CT angiography for the investigation of suspected ACS. As regards non-invasive testing (stress echo) the guideline adopts a diagnostic pathway for ACS that seeks to address contemporary criteria based on symptoms, ECG changes and troponins Point 3 All non-invasive tests deliver false negative results in patients with a low probability of disease. We acknowledge this in Section 1, p25 line 15. Our guideline recommends MDCT for calcium scoring only in a small group of patients with a low (<30%) likelihood of disease – IF diagnostic doubt persists after clinical assessment. Rates of CAD in patients with a zero calcium score are very low accounting for the high diagnostic sensitivity of the method (specificity of course is low). This is made clear in the Marwan paper which also reports that most false negative cases are those with unstable (not stable) chest pain – the group for whom ther guideline makes NO recommendation for MDCT. Point 4. The BMJ paper was not considered

						coronary disease is present in patients without calcification as described in the paper by Marwan et al (Clinical Characteristics of Patients with Obstructive Coronary Lesions in the Absence of Coronary Calcification: An Evaluation by Coronary CT Angiography Heart. Published Online First: 22 April 2009. doi:10.1136/hrt.2008.153353) 4. In investigating stable angina much weight appears to have been put on the poor diagnostic value of exercise testing. This may have been influenced by data from Newham Hospital RACPC (the published paper was a study involving data from 6 centres but Newham Hospital RACPC provided the majority of subjects BMJ. 2008; 337: a2240). However this clinic did not appear to follow up the RACPC evaluation with confirmation of diagnosis and did not appear to use stress echo or other functional testing. The event rates in patients labelled as non-cardiac pain must be reviewed in this context (Sekhri et al Heart 2007;93:458-463) Data from a chest pain clinic in West London (Tenkorang et al, *Heart* 2006;92;1084-1090) report that the 1 year cardiovascular mortality of patients diagnosed with non-cardiac pain based on an exercise testing / functional imaging protocol, was 0% (compared to 4.3% in those diagnosed with CAD) We therefore propose that the emphasis on an anatomical CT based approach for suspected ACS and also stable chest pain is unjustified by current data. In contrast there is abundant data to confirm that functional imaging, including dobutamine stress echocardiography, is both clinically and cost effective,	because it made no diagnostic evaluation of the ETT, only a prognostic evaluation. As for the Tenkorang paper, it was not considered because it included only 594 chest pain patients and was not designed to evaluate the incremental diagnostic performance of the ETT. Finally we should emphasise that we have NOT adopted an “anatomical CT based approach for suspected ACS”. Indeed, we make NO recommendations for either anatomical or functional testing in suspected ACS.

SH	Department of Health	1	Full	General		I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Noted with thanks
SH	NETSCC HTA ref 1	2	Full	General		These techniques were not included in the economic evaluation (based on the findings of one study), and little attention was given to these techniques in the review of the literature.	Both the de novo and reviewed published economic evaluation(s) undertaken for this guideline included both invasive and non-invasive technologies.
SH	NETSCC HTA ref 1	3	Full	General		These techniques do have an important role (both in functional and anatomical imaging) and the technology continues to be developed (e.g. 3D colour Doppler echo is now the commonly used technology having recently replaced 2D).	The clinical and health economic evaluation includes both functional and anatomical imaging. We acknowledge that the technologies continue to develop, but the recommendations are made on currently available evidence. The guideline will be reviewed in 3 years, and updated as appropriate from new published evidence
SH	NETSCC HTA ref 1	4	Full	General		The use of calcium scoring is over emphasized. It appears this is a key diagnostic criterion with a 100% positive predictive value. I don't have a problem with this, however; approximately two-thirds of patients are excluded from trials using CT with calcium scoring due to factors including impaired renal function, history of CAD, positive initial biomarkers, arrhythmia etc. Thus, although calcium scoring is useful, the population it will service is very limited. The guidelines need to address this matter explicitly.	Our guideline recommends MDCT for calcium scoring only in a small group of patients with a low (<30%) likelihood of disease – and only if diagnostic doubt persists after clinical assessment. All trials of non-invasive tests report selected patient populations, and there are very few true contra-indications to calcium scoring (as opposed to CT angiography). Nevertheless we agree that we need to consider alternative testing strategies for patients in whom calcium scoring is not feasible.
SH	NETSCC HTA ref 1	5	Full	General		A recent trial and two articles discussing this matter (which do not appear in the literature review) include:	The discussion papers do not meet the methodological requirement for inclusion in the guideline. The trial was published after the searching for the topic during the guideline process. The trial's conclusions do not alter the recommendations that were based upon the evidence reviewed in the guideline.
SH	NETSCC HTA ref 1	6	Full	General		1. Hoffman et al. Coronary Computed Tomography Angiography for Early Triage of Patients With Acute Chest Pain	The trial was published after the searching for the topic during the guideline process. The trial's conclusions do not alter the

						The ROMICAT Trial. J Am Coll Cardiol 2009; 53(18): 1642-50	recommendations that were based upon the evidence reviewed in the guideline.
SH	NETSCC HTA ref 1	7	Full	General		2. Hendel. Is Computed Tomography Coronary Angiography the Most Accurate and Effective Noninvasive Imaging Tool to Evaluate Patients With Acute Chest Pain in the Emergency Department? Circ Cardiovasc Imaging. 2009;2:264-275.	The methodology for identification and inclusion of clinical effectiveness studies does not include the reviewing of literature based on personal opinion / discussion. Therefore this paper was not included.
SH	NETSCC HTA ref 1	8	Full	General		3. Hoffman & Bamberg. Is Computed Tomography Coronary Angiography the Most Accurate and Effective Noninvasive Imaging Tool to Evaluate Patients With Acute Chest Pain in the Emergency Department? Circ Cardiovasc Imaging 2009; 2: 251-263.	The methodology for identification and inclusion of clinical effectiveness studies does not include the reviewing of literature based on personal opinion / discussion. Therefore this paper was not included.
SH	NETSCC HTA ref 1	9	Full	General		This is a high quality, comprehensive and very detailed report (albeit long). There are some key assumptions or statements that require additional evidence (described below). Nevertheless, the authors and GDG should be commended for their efforts.	Noted with thanks
SH	NETSCC HTA ref 1	10	Full	General		Economic evaluation – I do have some concerns regarding the outcomes used/not used, and have described these below.	See comments below
SH	NETSCC HTA ref 1	11	Full	General		Otherwise the modeling appears to be of a high standard and rigor.	Noted with thanks
SH	NETSCC HTA ref 1	24	Full	General		The reference style is Inconsistent throughout the document – sometimes author initials included, other times not – sometimes 3 authors listed in text followed by et al, other times 6 authors then et al	Thank you for pointing this out, the reference style has been corrected to be consistent.
SH	NETSCC HTA ref 1	25	Full	General		I have made minor editorial comments in Section 5	Noted with thanks
SH	NETSCC HTA ref 1	26	Full	General		Yes – the research recommendations are clear and justified	Noted with thanks
SH	NETSCC HTA ref 1 (NCCHTA)	1	Full	General		I am concerned that non-invasive imaging techniques have been overlooked, and that the implicit message from the Guidelines is these techniques are no longer worth considering or useful.	Non invasive functional and anatomical imaging have both been included and the recommendations take into account the clinical evidence and cost effectiveness of these techniques. Rather that there is an implicit message that non invasive imaging techniques

							are no longer worth considering or useful, there are explicit recommendations that they are.
SH	NETSCC HTA rep 2	2	Full 1	General		This whole work is a terrific tour-de-force. Because there are so many specific critical comments below, I feel the need to acknowledge at the start the fantastic effort that this draft guideline represents. Seemed admirably thorough.	Noted with thanks
SH	NETSCC HTA rep 2	5	Full 1	General		Systematically presented and appraised evidence. My comments below are unlikely to alter the main conclusions.	Noted with thanks
SH	NETSCC HTA rep 2	73	Full 1	General		Please note comments in sections 2.2 and 3.1 above wrt particular aspects of evidence	Noted
SH	NETSCC HTA rep 2	103	Full 1	General		No particular issue	Noted
SH	NHS Direct	1	Full	General		Guideline welcomed by NHS Direct. No comments on content.	Noted with thanks
SH	Plymouth NHS Trust / Peninsula Heart and Stroke Network	2	Full	General		I appreciate the GDG has recommended 30% pre-test likelihood as the cut off to go from CTA to functional imaging. I would urge that this be reconsidered. This should be increased to 40%. CTA is undoubtedly more accurate and the concern over then needing functional imaging is not born out by clinical experience. In a busy (>1,000 CTA per year) institution using CTA for patients with a likelihood up to 50% results in a subsequent functional imaging requirement of <5%.	Interestingly some other stakeholders considered there was too much emphasis on anatomical imaging. The recommendations for CT coronary angiography with a cut off of < 30% followed an examination of the cost effectiveness of functional imaging and CT coronary angiography.
SH	Royal College of Nursing	1	Full	General	General	The RCN welcomes this document. It is comprehensive.	Noted with thanks
SH	Royal College of Nursing	2	Full	General	General	The document gives a high quality summary of the evidence considered but seems to have missed out the following: - There is no mention anywhere of cardiac rehabilitation, psychological support or education for those patients with a diagnosis of angina or in whom the diagnosis is excluded. There is quite a dearth literature on the anxiety even of having a diagnosis 'ruled out' in patients presenting with chest pain. - There is also no mention of emergency	Noted with thanks. Bullet point 1 -This guideline addresses the diagnosis of angina, not its management. A further guideline is under development on the management of angina. With regard to the support of people who have had angina ruled out, as there are a number of other diagnoses they may have, it is difficult to give detailed advice on support and education. Section 1 of the guideline addresses information and support generally.

						assessment e.g. in the ambulance setting - arguably where the vast majority of patients first present.	Bullet point 2 – As patients can present in a number of different settings, we have given advice on assessment and management in any setting including the ambulance. We have restructured the guideline and hope this is now clearer.
SH	Royal College of Pathologists	1	Full	General		The Royal College of Pathologists has no comment to make at this stage of the consultation process for the above named guideline	Noted with thanks
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	2	Full	General		I appreciate the GDG has recommended 30% pre-test likelihood as the cut off to go from CTA to functional imaging. I would urge that this be reconsidered. This should be increased to 60%. CTA is undoubtedly more accurate and the concern over then needing functional imaging is not born out by clinical experience. In a busy (>1,000 CTA per year) institution using CTA for patients with a likelihood up to 50% results in a subsequent functional imaging requirement of <5%.	Interestingly some other stakeholders considered there was too much emphasis on anatomical imaging . The cut off of < 30% pre test likelihood is based on the analysis of cost effectiveness.
SH	Sanofi-Aventis	1	Full	General		Please note that sanofi-aventis would like to thank NICE for the opportunity to comment on this draft guideline. Sanofi-aventis have no comments at this time.	Noted with thanks
SH	South Asian Health Foundation	1	Full	General		On behalf of the cardiovascular group at SAHF, we hold this to be a comprehensive piece of work. It is a huge effort, and we feel that you have covered chest pain in immaculate detail, and highlighted the lack of differences that actually sometimes is seen between South Asian and white people - for instance, typical symptoms being associated with coronary outcomes in both South Asian and white patients, which you cite. [CMAJ • September 23, 2008; 179 (7)] Excellent work - we have nothing to add!	Noted with thanks

Status	Organisation	Order no.	Version	Page no	Line no	Comment	Response
SH	Action Heart	1	NICE	General		Action Heart is happy to accept the NICE version as is, and looks forward to the next stage in the process.	Noted with thanks
SH	Boston Scientific	1	NICE	21		The Guideline highlights gender and ethnic differences in symptoms of stable angina. Could the guideline also include diabetic patients as an important subgroup in which symptoms of stable angina might be different? Considering that the diabetic population increases very quickly and that their coronary disease is usually more aggressive, it would be important to highlight potential diagnosis differences in this Clinical Guideline.	It was not in the scope to look for evidence of different symptoms in people with diabetes. The guideline has included the importance of diabetes as a risk factor which increases the likelihood of coronary artery disease.
SH	Joint Royal Colleges Ambulance Liaison Committee	1	NICE	General		We should welcome this helpful guideline which addresses a topic of considerable burden to ambulance services.	Noted with thanks
SH	Joint Royal Colleges Ambulance Liaison Committee	2	NICE	6		Agree with the key priorities, but wondered if the statement about a normal 12 lead ECG not excluding significant heart disease could be given more prominence 'up front' in this section.	This has been added
SH	Joint Royal Colleges Ambulance Liaison Committee	3	NICE	11	1.2.1.6	We will need to give careful consideration about how to minimise risk to patients who are left at home by ambulance staff following a 999 presentation with recent onset chest pain. There is a need for more research into the use of clinical judgement by ambulance technicians and paramedics in this area. There have been examples in recent years of ambulance staff getting this wrong with catastrophic results for patients and families, and for the paramedics.	We understand your concern, but this research is beyond the scope of this guideline.
SH	Joint Royal Colleges Ambulance Liaison Committee	4	NICE	13	1.2.4.1	There is no evidence that the pre-hospital ECG delays hospital admission. There is concern about other interventions e.g. iv access resulting in delay, but a more helpful statement would focus on the need to expedite admission in this group of patients. There is no mention of the utility of biomarkers in the	Bullet point 1: The first recommendation in the 'Immediate Management' section states that a blood sample for troponin should be in hospital. We have also made it clearer that other interventions can take place pre-hospital but that transfer to hospital should not be delayed.

						pre-hospital setting to assess chest pain patients (the literature is not yet helpful on this point, and a statement to that effect would help dissuade ambulance services from inappropriate introduction as has happened previously). There is no mention of aspirin in the pre-hospital setting (a later recommendation not to give to patients in whom the likelihood of angina is low could also reasonable be applied to the pre-hospital setting, but isn't here).	We have not been specific about setting as patients can first present in primary or secondary care, to the ambulance service or to NHS Direct. Therefore unless specifically stated, the recommendations apply to any appropriate setting. We have tried to clarify the wording
SH	Joint Royal Colleges Ambulance Liaison Committee	5	NICE	13	1.2.4.5.	These statements could helpfully have more prominence. There is nothing about pain management in the pre-hospital setting Research recommendations	We have also made it clearer that other interventions can take place pre-hospital but that transfer to hospital should not be delayed.
SH	Joint Royal Colleges Ambulance Liaison Committee	6	NICE	14	1.2.4.7		
SH	Joint Royal Colleges Ambulance Liaison Committee	7	NICE	31	4.3	There could usefully be a research recommendation on the utility of the pre-hospital ECG in the wider chest pain group – the evidence thus far has focussed on STEMI. We don't know, for example, if paramedics can identify other ECG abnormalities other than some common arrhythmias. There is a need for research into the clinical governance arrangements for ECG transmission and advice from hospital staff to ambulance crews. Currently there are no formal recommendations on this. Surprising omission of a research question about use of oxygen as there is considerable uncertainty, and even the recommendation on use of oxygen against a target saturation is merely expert opinion rather than evidence based. Two systematic reviews have recently concluded	Thank you for your suggestion. The GDG had great difficulty in limiting the research recommendations to the requisite number. While this is an important area, it was not one of the GDG's top five.

						that we need more research. (I declare my interest! - TQ) We need research on ambulance staff use of clinical judgement as mentioned above.	
SH	Plymouth NHS Trust / Peninsula Heart and Stroke Network	3	NICE	24		As above 40-60% would serve our patients better	The thresholds given are based on the analysis of the clinical and cost effective sensitivities and specificities.
SH	Plymouth NHS Trust / Peninsula Heart and Stroke Network	4	NICE	26		Patients with no calcium can and do have severe CAD. These are the patients at greatest risk of plaque rupture. Their plaque is usually positively remodelled as well as low density (both independent predictors of plaque rupture). The incidence of serious contrast induced complications from the 90mls of contrast given for coronary CTA is < 1/10,000. The radiation dose from a modern CT service is now low (1 to 5 mSv) as alluded to above. This is only going to fall further. The additional cost of CTA at the time of a calcium scoring study is small and primarily related to cheap consumables. As a clinician I cannot agree that scanning a chest pain patient with possible CAD (albeit low likelihood) and stopping at a calcium score is in that patient's best interests. Suggest drop all the calcium scoring in favour of CTA for all 10-40% likelihood patients	We accept this point with certain reservations. Calcium scoring - like all diagnostic tests (including CTCA) - is not diagnostically perfect but sensitivity is high and it performs well as a CAD rule out in low risk populations. False negative findings tend to aggregate in patients with ACS rather than patients with stable chest pain who are the subject of this guideline. While the cost of proceeding to CTCA is low the high sensitivity of calcium scoring in this low risk (and by definition young) population makes unjustified the the added radiation exposure of CTCA, small though it may be.
SH	Roche Products Ltd	1	NICE	20	20	Evidence supports that in additional to raised total and LDL cholesterol, low-HDL is also a cardiovascular risk factor. Therefore, the term dyslipidaemia would be more appropriate than hyperlipidaemia	Revised
SH	Royal College of General Practitioners	1	NICE	22	1	The 220,000 deaths refer to deaths from CVD, not CHD, which is down to 95,000	Thank you for your comment, this has been amended.
SH	Royal College of General Practitioners	2	NICE	43		in the algorithm but also later in the text, antiplatelet therapy is mentioned for Acute Coronary Syndrome but nothing about administration of an effective statin e.g. atorvastatin 80mg. Also, should we not give 300mg of	Treatment with a statin is started once a diagnosis is made as recommended in guidelines for management of ACS and STEMI.

						Clopidogrel with Aspirin 300mg or instead of Aspirin if aspirin contraindicated because of severe sensitivity or active peptic ulcer disease?	The GDG's view is that clopidogrel should not be given prior to diagnosis, and once a diagnosis is made will be administered as recommended in the ACS and STEMI guidelines. If patients have aspirin sensitivity they should not routinely be given anything as a substitute. This is not stated explicitly in NICE guidelines which do not generally advise on drug sensitivities.
SH	Royal College of General Practitioners	3	NICE	59		CT Coronary angiography – there should be a mention of the amount of radiation this method gives the patient. We do describe the possible complications from a PCI. Why not describe the possible radiation complications from CT coronary angiography? The patient will then take an informed decision.	A recommendation has been added about explaining radiation risks. However, only a few of these low-pre-test likelihood patients would move to CT angiography, most would only have Calcium scoring.
SH	Royal College of Nursing	3	NICE	11	11	Section 1.2.1.6We agree with the key points here, but wondered if the statement about a normal 12 lead ECG not excluding significant heart disease could be given more prominence 'up front' in this section.	This has been added
SH	Royal College of Nursing	4	NICE	11	11	Sectin 1.2.1.6 Careful consideration needs to be given about how to minimise risk to patients who are left at home by ambulance staff following a 999 presentation with recent onset chest pain. There is a need for more research into the use of clinical judgement by ambulance technicians and paramedics in this area. There have been examples in recent years of some ambulance staff getting this wrong with catastrophic results for patients and families and for the paramedics	We understand your concern, but this research is beyond the scope of this guideline.
SH	Royal College of Nursing	5	NICE	13	13	Section 1.2.4.1There is no evidence that the pre-hospital ECG delays hospital admission. There is concern about other interventions e.g. iv access resulting in delay, but a more helpful statement should focus on the need to expedite admission for this group of patients.	We have made it clearer that other interventions can take place pre-hospital but that transfer to hospital should not be delayed.
SH	Royal College of Nursing	6	NICE	13	13	Section 1.2.4.5. It would be helpful if this statement has more prominence.	This has been added

SH	Royal College of Nursing	7	NICE	14		Section 1.2.4.7As above It would be helpful if this statement has more prominence.	We are limited to ten key priorities and this one was not regarded by the GDG as a top priority. Organisations such as the RCN can however give it prominence to their own members.
SH	Royal College of Nursing	8	NICE	Section 1.2.1	General	• There is no mention of the utility of biomarkers in the pre-hospital setting to assess chest pain patients (the literature is not yet helpful on this point, and a statement to that effect would dissuade healthcare professionals including ambulance services from inappropriate introduction as has happened previously). • There is no mention of aspirin in the pre-hospital setting (a later recommendation advises against routinely offer of aspirin to patients in whom the likelihood of angina is low. This could also be reasonably applied to the pre-hospital setting, but is not stated here) • There does not appear to be any recommendation about pain management in the pre-hospital setting. This would be helpful.	Bullet point 1: The first recommendation in the 'Immediate Management' section states that a blood sample for troponin should be in hospital. We have also made it clear that transfer to hospital should not be delayed. Bullet Point 2 & 3 – We have not been specific about setting as patients can first present in primary or secondary care, to the ambulance service or to NHS Direct. Therefore unless specifically stated, the recommendations apply to any appropriate setting. We have tried to clarify the wording.
SH	Royal College of Nursing	9	NICE	31	31	Section 4.3 We welcome this section. There could usefully be a research recommendation on the utility of the pre-hospital ECG in the wider chest pain group - the evidence thus far has focussed on STEMI. We do not know, for example, if paramedics can identify other ECG abnormalities other than some common arrhythmias.	Thank you for your suggestion. The GDG had great difficulty in limiting the research recommendations to the requisite number. While this is an important area, it was not one of the GDG's top five.
SH	Royal College of Nursing	10	NICE	31	31	Section 4.3 There is a need for research into the clinical governance arrangements for ECG transmission and advice from hospital staff to ambulance crews. Currently there are no formal recommendations on this.	Thank you for your suggestion. Clinical governance is beyond the remit of the guideline and therefore beyond the remit of the research recommendations.

SH	Royal College of Nursing	11	NICE	31	31	Sectin 4.3 Would suggest the inclusion of research question about use of oxygen as there is considerable uncertainty. The recommendation on use of oxygen against target saturation is merely expert opinion rather than evidence based. Two systematic reviews have recently concluded that we need more research.	Thank you for your suggestion. The GDG had great difficulty in limiting the research recommendations to the requisite number. While this is an important area, it was not one of the GDG's top five.
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	3	NICE	24		As above 50-60% would serve our patients better	The thresholds given are based on the analysis of the clinical and cost effective sensitivities and specificities.
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	4	NICE	26		Patients with no calcium can and do have severe CAD. These are the patients at greatest risk of plaque rupture. Their plaque is usually positively remodelled as well as low density (both independent predictors of plaque rupture). This particularly true in the younger age group The incidence of serious contrast induced complications from the 90mls of contrast given for coronary CTA is < 1/10,000. The radiation dose from a modern CT service is now low (1 to 4 mSv) as alluded to above. This is only going to fall further. The additional cost of CTA at the time of a calcium scoring study is small and primarily related to cheap consumables. As calcium scoring is 25% of the total radiation dose of CTA one could argue omitting calcium scoring altogether. As a clinician I cannot agree that scanning a chest pain patient with possible CAD (albeit low likelihood) and stopping at a calcium score is in that patient's best interests. Suggest drop all the calcium scoring in favour of CTA for all 10-40% likelihood patients	We accept this point with certain reservations. Calcium scoring - like all diagnostic tests (including CTCA) - is not diagnostically perfect but sensitivity is high and it performs well as a CAD rule out in low risk populations. False negative findings tend to aggregate in patients with ACS rather than patients with stable chest pain who are the subject of this guideline. While the cost of proceeding to CTCA is low the high sensitivity of calcium scoring in this low risk (and by definition young) population makes unjustified the the added radiation exposure of CTCA, small though it may be.
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	5	NICE	General		Research topics in 4.1 & 4.5 are good but their remit should extend beyond that of merely cost effectiveness.	As cost effectiveness includes clinical effectiveness, these research recommendations would include clinical research.

Acute Chest Pain Comments

Status	Organisation	Order no.	Version	Page no	Line no	Comment	Response
PR	Dr A. Chahal	1	Full 1	10	10	Make clear after ETT go on to accurate diagnostic testing (although page 9 line 20 states possible to make diagnosis clinically alone)	Exercise ECG Is not recommended as a diagnostic test in patients without confirmed CAD, and is not included in the diagnostic pathway.
PR	Dr A. Chahal	2	Full 1	15	1	A 'normal' 12-lead ECG alone does not rule out ACS	Agreed, and this is stated in the recommendations
PR	Dr A. Chahal	3	Full 1	22	11	Likely underestimated	This section has been updated.
PR	Dr A. Chahal	4	Full 1	26	20	Why Diamond Forrester compared with alternatives?	Diamond and Forrester algorithm is used universally to give pre-test likelihoods of prevalence of angina
PR	Dr A. Chahal	5	Full 1	30	20	Typo/grammar 'and based in a royal'	Thank you this has been corrected.
PR	Dr A. Chahal	6	Full 1	149	17	Typo – this section 4.2	Deleted.
PR	Steve Goodacre	1	Full 1	19	6	2.3.1 Use of biochemical markers 2.3.1.2 Take a second blood sample for troponin I or T measurement 10-12 hours after the onset of symptom even if the pain has resolved This guidance has the potential to substantially increase hospital admissions, and thus health service costs, without any clear evidence of benefit. Median time from symptom onset to presentation at hospital is 2-3 hours so a second sample would be taken 7-10 hours after arrival. This exceeds the 4-hour limit for the emergency department so, unless a chest pain unit or clinical decision unit were available, most patients with possible ACS would require hospital admission. The only economic analysis to address this issue (Goodacre & Calvert 2003) suggested that hospital admission for biomarker testing is not cost-effective according to usual NICE criteria. Unfortunately this study seems to have been selectively cited in the guideline (see comments	Yes, shorter waits in A&E are to be desired. However, we were driven to recommend 10-12 hours on safety grounds, translating to 7-10 hours after hospital arrival. The 4 hour limit of course translates to 6-7 hours after onset of chest pain and the residual gap will no doubt be closed when the availability of high sensitivity troponin allows earlier testing. We agree that chest pain units could resolve the difficulty around late troponin testing.

						below) Chest pain units, and by extension clinical decision units, could provide a cost-effective alternative to hospital admission or discharge. RCT evidence and economic evaluation shows that chest pain unit care is more effective and cost-effective than routine care (*BMJ* 2004;328:254-7), although a cluster RCT showed that establishing a chest pain unit may attract more attendances with chest pain (*BMJ* 2007;335:659-662).	
PR	Steve Goodacre	2	Full 1	148	1	Table 10 cites "heartburn" as a differentiating symptom of reflux oesophagitis / oesophageal spasm. This is potentially misleading and dangerous. Pain described as burning or like indigestion is associated with an increased likelihood of MI (*Q J Med* 2003;96:893-898).	The Table permission was granted from the consensus document of the Joint European Society of Cardiology / American College of Cardiology Committee, as such it has been extracted as detailed, and permission does not allow alteration of the document. Eur Heart J, volume 23, issue 15, August 2002. We did not conduct an evidence review on non cardiac causes of chest pain because this was beyond the scope of the guideline.
PR	Steve Goodacre	3	Full 1	170		4.4.2 Use of biomarkers The statements cite cost-effectiveness evidence from Goodacre & Calvert 2003 that biomarker testing at presentation (#7) and 6 hours after onset of pain (#8) is cost-effective, but do not cite evidence from the same study that it is not cost-effective if it involves hospital admission.	The evidence statement has been revised to include this. .
PR	Steve Goodacre	4	Full 1	192	24	4.4.2.4. Health economic evidence Again, regarding the Goodacre & Calvert (2003) study, it is true that the costs of biomarkers have decreased since 2003 and this would increase the cost-effectiveness of biomarker strategies that do not require hospital admission. However, the costs of hospital admission have increased, so any strategy that involves hospital admission (such as a 10-12 hour troponin in a hospital with no chest pain unit or clinical decision unit) will be less cost-effective than previously estimated.	Point accepted. Text revised accordingly. However please also refer to response to comment on 4.4.2. The available evidence on the cost-effectiveness of chest pain units was excluded from the Guideline as issues relating to service delivery are not included in the scope of NICE Clinical Guidelines.

						The current health economic evidence does not support the recommendation that patients with possible ACS should receive troponin testing 10-12 hours after symptom onset. However, the economic evidence cited is very limited and does not address recent developments, such as point of care testing and chest pain units. There is a clear need for an updated and comprehensive economic analysis.	
SH	British Heart Foundation	1	Full 1	22	4	The consultation document states there were 220,000 deaths attributed to coronary heart disease (CHD), with reference to BHF statistics. Our statistics indicate that there were 198,000 deaths from CHD in 2006-07 so this should be amended to reflect this or to clarify whether this relates to the number of deaths from all cardiovascular disease.	Thank you for this correction. From your website (http://www.heartstats.org/temp/2008.Chaptersp1.pdf) , 94 000 deaths were attributed to CHD and this has been amended.
SH	British Nuclear Medicine Society 1	1	Full 1	10	1	This statement should be rewritten for clarity. The footnote is not obvious and may be missed. Thus one would assume that all patients with chest pain should be referred to coronary calcium scoring and CT angiography. The statement should start "For those patients with a low pretest likelihood of CAD…."	This has been revised
SH	British Nuclear Medicine Society 1	2	Full 1	10	4	A coronary calcium score of zero does not equate with zero risk for CAD as indicated in the evidence	Like all diagnostic tests, the diagnostic sensitivity of calcium scanning is not 100% However, its sensitivity is probably higher than that of other commonly used functional tests, particularly when diagnostic probability is low. Certainly, the evidence suggests that false negative (zero) scores are uncommon and tend to aggregate in patients presenting with ACS, not stable chest pain.
SH	British Nuclear Medicine Society 1	3	Full 1	10	10	This will require a hefty investment in other imaging modalities	I will refer this comment to the implementation team.
SH	British Nuclear Medicine Society 1	4	Full 1	10	12	There is also a role for functional imaging in patients with CAD and equivocal chest pain. For example a patient might have CAD, but the chest	We agree and functional imaging is recommended as an initial diagnostic test in people with confirmed CAD when the cause of the chest pain is uncertain (see

						pain is not being caused by the CAD. A normal functional scan 1) suggests excellent prognosis even in presence of CAD 2) Indicates that other sources of chest pain should be investigated	recommendation 1.3.4.9).
SH	British Nuclear Medicine Society 1	5	Full 1	27	10	We very much support this statement but believe it should be in the summary guidance as well	We are limited to 10 key priorities and it is a difficult choice.
SH	British Nuclear Medicine Society 1	6	Full 1	138	32	Ischaemia misspelt	Amended.
SH	British Pain Society	1	Full 1	11	6	Section 1.1.1.1 – I am delighted to see such an important (and usually overlooked) aspect of this condition given a position of appropriate prominence. NICE is to be applauded for acknowledging the role of misunderstanding, leading to fear and anxiety, which can have such an impact on patients suffering from ischaemic heart disease.	Noted with thanks.
SH	British Pain Society	2	Full 1	12	5	Very important to stress that many, if not all, of these issues have been appearing in other respected guidelines (eg ESC guidelines) and are frequently ignored by healthcare professionals	I will refer this comment to the implementation team so that this may be addressed in their materials
SH	British Pain Society	3	Full 1	12	21	2.1.1.2 “Determine if the chest pain is of cardiac origin” – is it worth stating that alternative diagnoses should be considered at this stage?	Patients will only enter the guideline if chest pain is initially suspected to be cardiac and recommendations to consider other causes are included later in the pathway
SH	British Pain Society	4	Full 1	16	20	Section 2.1.5.1 – while it’s important not to overlook diagnoses such as aortic dissection, other, more common possibilities must also be considered. A quick neurological assessment of skin sensation is fast and simple to perform, but neuropathic pain needs to be *considered* as a source of chest pain. It is, in my experience, frequently overlooked.	We recognise there are multiple causes of chest pain, but it is not practical to include all possibilities. The GDG felt it important to include examples of those that are life threatening and which may present with similar symptoms to an ACS.
SH	British Pain Society	5	Full 1	18	1	2.2.1.2 – a vital part of treating the pain effectively should include the word “reassurance” – most people in the grip of an ongoing ACS find it a very	The GDG discussed using the word ‘reassurance’ and agreed that it would be difficult, and sometimes dangerous, to reassure a patient when they may have

						frightening experience	a potentially life threatening condition. We do agree however that clinicians should reduce a patients anxiety as much as possible and we have reflected this in the wording.
SH	British Pain Society	6	Full 1	27	9	Would it be reasonable to state that "the demonstration of obstructive CAD is neither necessary nor sufficient for a diagnosis of myocardial ischaemia"?	This has been made clearer in the introduction.
SH	British Pain Society	7	Full 1	32	11	No Pain Physician included in GDG members despite the word 'Pain' appearing in the guideline title. Five cardiologists, though!	The GDG membership has to be kept small enough to facilitate a good discussion. Please refer to the NICE Guidelines Manual for further information. The scoping meeting for this guideline, where GDG membership was discussed, was held on the 24th September 2007, there was no mention of including a pain physician being a primary health professional managing patients with undiagnosed chest pain at that time.
SH	British Pain Society	8	Full 1	54	25	"angina is a symptom of myocardial ischaemia" – this is a view that has been accepted by mainstream cardiology on the basis of little or no evidence. Many patients are admitted as an emergency to A&E with severe angina but no objective evidence of myocardial ischaemia. The danger is that this leads to the assumption that there must be (potentially threatening) ischaemia present in angina but our methods of detection are inadequate. In turn, this leads to incorrect statements being made (see below – syndrome X), patient confusion, and in the long term, significant psychological harm. Would it be better to say that "angina is a pain syndrome that may be linked to myocardial ischaemia" which then allows the possibility that ischaemia needn't be detected in the presence of angina?	Agreed. We have made it clear in the guideline introduction that demonstration of ischaemia is neither necessary nor sufficient for a diagnosis of angina
SH	British Pain Society	9	Full 1	55	24	"small vessel disease" – patients are often told they have small vessel disease in the absence of angiographic CAD. This is a falsehood – as far as I am aware, no myocardial small vessel disease	Reference to small vessel disease has been deleted.

						has ever been demonstrated at post mortem in patients diagnosed with syndrome X who died of other causes. Furthermore, all the disease processes I know of that cause small vessel disease have reduced life expectancy (eg diabetes, autoimmune conditions, vasculitis). Cardiac syndrome X patients have normal or slightly greater than normal life expectancy due to the fact that they never die of MI. This is a dangerous fallacy that should be eradicated from the medical lexicon, and is a lazy assumptive diagnosis on the basis of no evidence whatsoever.	
SH	British Pain Society	10	Full 1	66	13	Again, no mention of the word 'reassurance'. This is not the same as giving information, which I agree is another important part of the communication between the patient with chest pain and the relevant healthcare professionals	The GDG discussed using the word 'reassurance' and agreed that it would be difficult, and sometimes dangerous, to reassure a patient when they may have a potentially life threatening condition. We do agree however that clinicians should reduce a patients anxiety as much as possible and we have reflected this in the wording.
SH	British Pain Society	11	Full 1	80	17	I think 'sneezing' should probably read 'squeezing'	Amended.
SH	British Pain Society	12	Full 1	94	12	Is there a case for abolishing the term 'atypical chest pain' altogether? On close questioning of thousands of angina sufferers, I can vouch for the fact that no two accounts are identical, and therefore it is rather difficult to decide what constitutes 'typical' chest pain. Simple descriptors of the pain would suffice – terms such as crushing, stabbing, burning are already in common parlance, and although unusual, I have certainly seen patients whose angina has a paroxysmal onset – should we be calling this 'atypical angina'? No, thought not – too confusing!	The terms typical angina, atypical angina and non anginal chest pain are specifically used as defined in the Diamond and Forrester definition and this has been made clear in the recommendations which include further details of what these definitions are.
SH	British Pain Society	13	Full 1	117	15	Is the inclusion of nitroglycerin's effectiveness as a diagnostic tool valid in the absence of knowledge regarding the mechanism of nitro-induced pain relief?	The GDG felt that a positive response to nitroglycerin pain relief might be used in current clinical practice as a positive sign that acute chest pain is of cardiac origin and the GDG examined its diagnostic utility in

							this regard. A positive response to nitroglycerin pain relief may occur in other conditions, and i the review of the literature found that response was of no diagnostic value in patients with acute chest pain.
SH	British Pain Society	14	Full 1	156	8	Once more, the word 'reassurance' does not appear once in the entire section devoted to managing an acute admission with chest pain. THIS IS A VITALLY-IMPORTANT ASPECT OF PATIENT CARE, AND HARM MAY BE CAUSED IF IT IS NOT EXPLICITLY STATED AND INCLUDED IN THE GUIDELINE	The GDG discussed using the word 'reassurance' and agreed that it would be difficult, and sometimes dangerous, to reassure a patient when they may have a potentially life threatening condition. We do agree however that clinicians should reduce a patients anxiety as much as possible and we have reflected this in the wording.
SH	British Pain Society	15	Full 1	18	2	States prompt and effective pain relief may be achieved with GTN but does not state how this should be administered (i.e. sublingual or does this include IV). Also opiate should be opioid.	This has been revised to sublingual or buccal GTN, and opiates revised to opioids.
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	1	Full 1	10	1	We have major concerns about this guidance. The recommendation of calcium scoring and MDCT coronary angiography (CTA) as a first line investigation for stable angina would represent a major paradigm shift in cardiology practice in the UK. At the present time there are scant data (if any) that show any prognostic benefit of this strategy over and above functional testing which has over 4 decades of experience. There are no large scale RCT's that have compared this strategy head-to-head with current best practice and no data directly applicable to a UK healthcare model. Indeed, currently none of the international cardiology guidelines (ACC-AHA or ESC) recommend this strategy. Furthermore, the gap between the delivery of this new technology in US based clinical trials and UK general cardiology practise currently is vast. We would also wish to be reassured that the evidence review group has considered publication and search strategy biases in their data collection in that the CT data is benefiting disproportionally as	This guideline recommends diagnosis by clinical assessment with non-invasive testing reserved for patients in whom there is diagnostic uncertainty with an intermediate probability of disease. For the majority of these patients the guideline recommends functional testing (SPECT/stress echo etc), with calcium scoring ONLY in those with a diagnostic probability of 10-30% in whom there is lingering diagnostic uncertainty - a very small group given the fact that all patients with "non-specific chest pain" (as defined) receive a non-cardiac diagnosis and no further testing. We have now rewritten much of the guideline to make this clear. Note the guideline is interested in the cost-effectiveness of DIAGNOSTIC strategies (not prognostic). As regards technological availability, this is not a consideration in the writing of NICE guidelines, although consultation by the radiologist on the GDG with colleagues indicates that the majority of UK Trusts have access to calcium scoring.

						it is recent whereas much of the ETT and SPECT data predates PubMed and is difficult to search for. Even if one believed in this suggested strategy, it is somewhat opaque to just mention in footnote 2 that this applies ONLY to low risk patients. To the unfamiliar/inexperienced this could clearly be overlooked or misinterpreted.	
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	2	Full 1	10	4	The recommendation that "*if the calcium score is zero other cause of chest pain should be investigated*" is misinformed and cannot be supported. Whilst the presence of coronary artery calcium (CAC) is synonymous with the presence of atherosclerosis, the opposite is absolutely NOT true. Quite clearly younger patients can have significant (even critical) obstructive luminal disease without calcification. Indeed, there are a number of studies that have shown that the percentage of patients with zero CAC and significant stenosis ranged from 0 - 39%. *For patients with a CAC score of 1-400, CTA is now 'recommended'*. Whilst CTA is a very sensitive for rule-out test for coronary disease, it is much less specific. Even enthusiasts admit that at present there are no validated approaches to quantitatively express plaque burden on CTA. Likewise, accurate quantification of the degree of stenosis remains difficult, resulting in frequent overestimation of the severity of disease on CTA. Thus with these guidelines, in a significant group of patients there would be the requirement to proceed to functional testing, adding in an extra step to the diagnostic pathway; currently functional testing is performed before anatomical testing (angiography) and certainly before revascularisation as is recommended by the	Like all diagnostic tests, the diagnostic sensitivity of calcium scanning is not 100% However, its sensitivity is probably higher than that of other commonly used functional tests, particularly when diagnostic probability is low. Certainly, the evidence suggests that false negative (zero) scores are uncommon and tend to aggregate in patients presenting with ACS, not stable chest pain. Cost-effectiveness analysis led to the recommendation of anatomical testing in patients with a positive calcium score. Visualisation of coronary luminal narrowing sufficient to support a diagnosis of angina is indeed feasible with the current generation of scanners so long as dense calcification (score>400) does not obscure the view. Certainly most operators would wish to proceed to angiography in this patient group. Note however, that the group to which this applies is very small, patients with non-specific chest pain having already been excluded from further testing following clinical assessment (afact that has now been stated with greater clarity)

						AHA/ACC guidelines.	
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	3	Full 1	10	10	Not to use ETT at all is dogmatic and over-simplistic and we don't believe cost effective, provided the limitations are acknowledged up front (which they are in cardiology practice). We assume that this will be commented on extensively by other cardiology groups outside of BSCMR	The GDG reviewed the evidence for both the clinical and cost effectiveness of exercise ECG and concluded that the diagnostic performance compared to other tests was such that it should not be recommended in preference to other available tests, and that other diagnostic strategies were more cost effective.
SH	NETSCC HTA ref 1	22	Full 1	19	13	The recommendation not to use markers such as naturetic peptide does not follow from the review. No evidence or discussion is provided for this recommendation. Because the Scope does not specify this as "out of scope", some discussion/evidence for this recommendation should be provided in the document (I agree with the recommendation based on what I know about this, but I am not a clinician)	The definition of MI used in the guideline is based on biochemical markers of myocardial necrosis, and the guideline recommends the use of troponin which is both sensitive and specific, and is also the preferred biomarker recommended in the Universal Definition of MI. Naturetic peptides are not accepted measures for making a diagnosis of acute MI and no evidence was found that that evaluated their use with the revised or new definition of myocardial infarction as a diagnostic comparator. The GDG recognised that there has been extensive publication on the value of naturetic peptide as a prognostic marker across the spectrum of coronary artery disease, but this is not in the scope of this guideline.
SH	NETSCC HTA ref 1	27	Full 1	6	19 25	Appendix alpha-numbering needs to be consistent throughout. There are two Appendix B and two Appendix C	This has been revised
SH	NETSCC HTA ref 1	28	Full 1	40	3	As above	
SH	NETSCC HTA ref 1	29	Full 1	22	12	Disagreement in number of parenthesis	This section has been updated.
SH	NETSCC HTA ref 1	30	Full 1	22	15	Disagreement in number of parenthesis	This section has been updated.
SH	NETSCC HTA ref 1	31	Full 1	58	Table	"Killip class" should be defined/described in the glossary	This has been added
SH	NETSCC HTA ref 1	32	Full 1	167	26	Pound sign missing for 453.96	Added

SH	NETSCC HTA ref 1	33	Full 1	169	9	Section “XXX” needs to be specified	Noted and changed
SH	NETSCC HTA ref 1	34	Full 1	180	Table 12	“MACE” not defined in table note, text or glossary	Amended.
SH	NETSCC HTA ref 1	35	Full 1	182 183	Table 13	Table format – needs boarders	Changed
SH	NETSCC HTA ref 1	36	Full 1	189	Table 15	Width of RH column is excessive	This has been changed
SH	NETSCC HTA ref 1	37	Full 1	193	5	Delete extra full stop	Done
SH	NETSCC HTA ref 1	38	Full 1	196	26	Delete extra full stop	Done
SH	NETSCC HTA ref 1	39	Full 1	203	Table 19	Define MSCTCA in table note and glossary (and text?)	This has been spelled out
SH	NETSCC HTA ref 1	40	Full 1	205	21	Define MSCT please (in glossary and text)	This has been spelled out.
SH	NETSCC HTA ref 1	41	Full 1	206	31	References incomplete	Corrected
SH	NETSCC HTA rep 2	3	Full 1	91	5 7	I’m not sure if this is the correct place to make this comment, but why should it matter if women present with different symptoms from men? The crucial question is surely whether the diagnostic or prognostic value of any given symptom differs between women and men. Similar comment re ethnicity.	This was included in the guideline as it may be perceived in current clinical practice that the symptoms with which men and women present are different to the extent that this makes a difference to how patients should be assessed and investigated. The evidence did not support this, and any impact of gender is mediated by the influence of gender on the pre-test likelihood of coronary disease rather than on symptomatic presentation. The same conclusion was reached for ethnicity.
SH	NETSCC HTA rep 2	6	Full 1	71	11	The systematic review by Swap and Nagurney apparently included prior SRs. My question is – why were these prior SRs not included in their own right for this appraisal?	The methodology adopted by this guideline was to include the most up to date systematic reviews, and ones that had been published some time before were not included. Where the most recent systematic reviews were published within 2 years of one another, they were all included.
SH	NETSCC HTA rep 2	7	Full 1	125	7 9	I was unsure about the whole basis for this question about the performance of the 12 lead	This is an evidence statement which is a summary of the conclusions of the systematic review which

						ECG. ECG changes are part of the standard definition of MI and so to evaluate an ECG against a reference which itself includes evidence from an ECG feels like a tautology. Perhaps the GDG are asking about the use of an early ECG taken in A&E (or by a paramedic) to diagnose an MI later established with a "proper" ECG. If so, this should be made clearer.	examined the value of an ECG in primary care in making a diagnosis of MI. The evidence statement and relevant narrative have been revised to make it clearer that patients presented with acute chest pain in primary care.
SH	NETSCC HTA rep 2	8	Full 1	128	12 16	The same issue crops up here. These studies would fail on item 7 of the QUADAS tool, "Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?"	This is correct. A comment has been added to the narrative.
SH	NETSCC HTA rep 2	10	Full 1	71	29 30	In fact one particular combination does very well indeed as a rule out tactic but it only applies to 8% of the population	The GDG considered from the data that no one component was diagnostically useful; the study did not look at combinations.
SH	NETSCC HTA rep 2	11	Full 1	74	1	Table 4; Pain in R arm/ shoulder, NLR is 0.9 (missed out by GDG)	Added.
SH	NETSCC HTA rep 2	12	Full 1	74	1	Table 4; Absence of chest wall tenderness. The OR of 0.17 and CI probably need to be reciprocated, though figures given by GDG are exactly as quoted by Bruyninckx et al	The table has been reproduced according to text, as permissions were granted on this basis.
SH	NETSCC HTA rep 2	13	Full 1	81	13 20	I cannot see need for quoting PPV and NPV when we already have a table of LRs (table 7). PPV and NPV are too dependent on prevalence, whereas LRs can be explicitly combined with any prior probability (or background prevalence).	The GDG considered that PPV and NPV should be included in addition to LRs when these values were provided in the studies.
SH	NETSCC HTA rep 2	14	Full 1	81	22 23	Although some reasonably impressive LRs are obtained for excluding MI, they rely on combinations of atypical symptoms which may only apply to a small proportion of the population	Thank you for your comment, it is correct that this may apply to a small proportion of the population; the results are reproduced as detailed in the study. A comment to the text has been added highlighting the point.
SH	NETSCC HTA rep 2	15	Full 1	83	2 10	Were the scores for individual signs and symptoms empirically based?	This study has been deleted as it is included in a systematic review that is discussed in the clinical evidence section.
SH	NETSCC HTA rep 2	16	Full 1	84	1	Table 8; the GDG have a policy of reproducing published Tables. The tendency of Sanchis et al to quote OR and CI ONLY for factors whose multivariate p-value falls below some arbitrary	This study has been deleted as it is included in a systematic review that is discussed in the clinical evidence section.

						level is undesirable, since we are robbed of the opportunity to compare findings for the non-significant factors with results from other studies.	
SH	NETSCC HTA rep 2	17	Full 1	85	1	Table 9; same comment	This study has been deleted as it is included in a systematic review that is discussed in the clinical evidence section.
SH	NETSCC HTA rep 2	18	Full 1	86	13 22	Is this text simply copied from page 83 – if so, is it really necessary to repeat it?	This study has been deleted as it is included in a systematic review that is discussed in the clinical evidence section.
SH	NETSCC HTA rep 2	19	Full 1	87	22 26	The p-values have no use and should be deleted. The previous lines 18-22 are very helpful and do not require the addition of p-values.	This study has been deleted as it is included in a systematic review that is discussed in the clinical evidence section.
SH	NETSCC HTA rep 2	20	Full 1	87	28 32	It is scarcely surprising that the new risk score constructed by Sanchis et al did better than the TIMI; it was being reapplied to the same data from which it was derived (whereas for TIMI, this was a new data set for testing). In fact Sanchis et al did then test both scores on an independent validation cohort which is a fairer comparison. Even then, the new cohort comprised patients from that same hospital, and as only 8 events occurred, statistically precise comparisons were difficult to make between the new risk score and the TIMI.	This study has been deleted as it is included in a systematic review that is discussed in the clinical evidence section.
SH	NETSCC HTA rep 2	21	Full 1	91	10 27	This is a population based study, not one of subjects presenting with suspected CAD. I was surprised to see Framingham data included in this review and question its relevance. I am not sure the inference asserted in lines 25-26 is justified (similar comment appears in section 2).	Thank you for your comment. Agree, and this study has been removed.
SH	NETSCC HTA rep 2	22	Full 1	93	10	Table 2 does not make best use of available data; odds ratios should be presented. I realize this is the fault of Patel et al, not of the GDG.	The systematic review did not report odds ratios, nor provide sufficient data for calculation of odds ratios. Table 2 provides the best available representation of the data in the systematic review.
SH	NETSCC HTA rep 2	23	Full 1	96	4	Did Canto et al report odds ratios or other statistics which would enable us to judge the importance of any differences between women and men	Statistical analyses were not performed because of the considerable heterogeneity of the included studies.

SH	NETSCC HTA rep 2	24	Full 1	98	22	“Women were significantly more likely…”. Are these women with a first cardiac event being compared with men with a first cardiac event? Or with control women?	Thank you for your comment. The information compares women with cardiac event versus control women. As this information not answer the fundamental question in this section of the guideline it has been removed.
SH	NETSCC HTA rep 2	25	Full 1	99	1	Table 3. None of the p-values in the Table address the fundamental question, namely does the odds ratio associated with any particular risk factor differ between men and women. A p-value for interaction is required but not quoted in the Table. Lines 1-9 give the p-values required.	Thank you for this comment; it is correct that Table 3 does not answer the fundamental question in this section of the guideline and the Table has been removed.
SH	NETSCC HTA rep 2	26	Full 1	100	4 6	This analysis is only of a survivor cohort. And will therefore be prone to bias	Thank you for your comment, this information has been added to the text.
SH	NETSCC HTA rep 2	27	Full 1	137	1 6	Is this information relevant? If not, delete.	Thank you for your comment, it is correct the information is not relevant and has been deleted.
SH	NETSCC HTA rep 2	28	Full 1	141	27	“by 88%”; this is not a very suitable statistic, akin to a relative risk. The two percentages themselves (90 and 48%) are sufficient.	Agree, and this has been deleted.
SH	NETSCC HTA rep 2	29	Full 1	163	2 4	Pain relief may have happened because of regression to the mean rather than the morphine.	Correct, this has been noted in the text.
SH	NETSCC HTA rep 2	30	Full 1	164	3 4	Another case of regression to the mean? If pain is a fluctuating phenomenon, and people contact emergency services when pain is worst, it will generally improve by the time it is measured again.	Correct, the data supports this and a further comment has been added.
SH	NETSCC HTA rep 2	31	Full 1	180	4 14	I think an unorthodox subgroup analysis has been carried out because the normal group in the standard management arm are being compared with the troponin negative group in the Troponin management arm. As these “negative” groups are differently defined in the two arms of the study, the value of randomization is lost and inferences are less secure.	Thank you for your comment, a comment has been added to the text stating the limitation of the analysis.
SH	NETSCC HTA rep 2	65	Full 1	102	2 6	To say that women who present with acute MI (or ACS) show different characteristics from male presenters is not of particular clinical importance. If women are more likely to have diabetes, they should surely be managed on the basis of their diabetes, not their gender. The only importance of	It was not in the scope to look for evidence of different symptoms in people with diabetes. The guideline has included the importance of diabetes as a risk factor which increases the likelihood of coronary artery disease.

						gender would arise if diabetes carried more serious prognostic implications for women than it carried for men in this clinical population.	
SH	NETSCC HTA rep 2	66	Full 1	117	5 7	A similar comment to the previous comment about gender also applies to the ethnicity analysis.	The GDG developed the most appropriate questions to be addressed in the guideline, and included this question on ethnicity (also for women) and presentation with acute chest pain. The GDG considered that the potential differences in risk factors according to gender should be examined in this question. Which may increases the likelihood of coronary artery disease.
SH	NETSCC HTA rep 2	67	Full 1	197	26	Perhaps the pre test probability is therefore 5% if we know little about a patient. Would it be helpful to suggest, or address the question of what threshold of post test probability would alter clinical management? This would then tell us how high PLRs would have to be to effect a change of management.	Thank you for suggestion. We agree that pre-test probability would be 5%. Ideally the guideline needs to address both clinical and cost-effectiveness and so a broader approach than the one you have suggested would be needed. We have tried to take account of the available evidence for both, in the consideration of biomarkers for patients presenting with acute chest pain.
SH	NETSCC HTA rep 2	75	Full 1	22	5	Phrase “prevalence 3.7%” seemed anomalous when sentence was talking about mortality	Correct, this has been deleted.
SH	NETSCC HTA rep 2	76	Full 1	74	1	Table 4; Pain in R arm/ shoulder, NLR is 0.9 (missed out by GDG)	Added.
SH	NETSCC HTA rep 2	77	Full 1	94	1	Table 2 has strung out unnecessarily on to top of this page	Reformatted
SH	NETSCC HTA rep 2	78	Full 1	118	31	No need to state the number and percentage with a negative response, it follows from subtraction of the positive responses from the total.	These have been removed.
SH	NETSCC HTA rep 2	79	Full 1	119	1	Similar comment	These have been removed.
SH	NETSCC HTA rep 2	80	Full 1	119	3	Similar comment	These have been removed.
SH	NETSCC HTA rep 2	81	Full 1	133	8	CI for NLR may need 2 decimal places if available!	The two decimal places are not given in the systematic review.
SH	NETSCC HTA rep 2	82	Full 1	135	27 30	This sentence is virtually repeated in lines 30(p.135) to line 2(p.136). I think copying and pasting has been done but some information still needs to be edited.	This has been amended.

SH	NETSCC HTA rep 2	83	Full 1	135	28	Depression cannot be said to be an independent factor from univariate analysis.	This was ST-segment depression rather than depression.
SH	NETSCC HTA rep 2	84	Full 1	138	29 32	Same sort of copy/paste error?	The text was incorrect and has been amended.
SH	NETSCC HTA rep 2	85	Full 1	141	23 24	Sensitivity and specificity 44 and 91% on both lines – another copy/paste error?	In fact the values are correct, the independent and physician interpretation gave the same sensitivity and specificity values.
SH	NETSCC HTA rep 2	86	Full 1	149	17	"This section 4.3.."? (typo)	Deleted.
SH	NETSCC HTA rep 2	87	Full 1	163	9	"male gender". It says "female gender" when summarizing this study on page 157.	Thank you for pointing this out, on p 157 is should read male gender, and it has been amended.
SH	NETSCC HTA rep 2	88	Full 1	185	29 32	Another copy/paste error	Thank you for your comment. Amended.
SH	NETSCC HTA rep 2	89	Full 1	189	1	Table 15, some column headers need to be better aligned	This has been changed
SH	NETSCC HTA rep 2	105	Full 1	202 203		The authors of the GDG have generally adopted a policy of simply reproducing Tables of data (and text) directly from the studies they cite. I often longed for the GDG to attempt some of their own meta-analysis, or at least tabulation, in a way which was more suited to their purpose. Often the studies cited by the GDG do not provide the most statistically valuable information. In some cases, the GDG would simply be unable to extract more relevant information without contacting authors of the original studies. But in other cases, they could convert sensitivity and specificity into PLRs and NLRs (e.g. Tables 18,19).	The Tables were reproduced in accordance with the precise form that they were published in order to seek permissions. It is recognised that some of the statistical information may not be relevant and that it would have been helpful to convert all data to be presented in a consistent format throughout the guideline. Time constraints on the production of the guideline did not afford the opportunity to perform calculations across all of the guideline. Often the necessary information to provide PLR and NLR was missing from the original studies. The review of the literature has been faithful to the results presented in the studies reviewed.
SH	Randox Laboratories Ltd	1	Full 1	19	7	We feel this could be rewritten to accommodate any new biomarkers that could become available in the future. It could be changed to "Take a blood sample to diagnose MI using the preferred biochemical markers which are currently Troponin I and T (July 09)".	It is NICE policy to present the current evidence. Should there be new evidence this will be reviewed when the guideline is revised. It is not NICE policy to date recommendations. It is very clear in the guideline and on the website when it was published.
SH	Randox Laboratories Ltd	2	Full 1	19	10	Again this could be changed to make it more accessible for new biomarkers that may be developed in the future. The sentence should read "Take a second blood sample at the	It is NICE policy to present the current evidence. Should there be new evidence this will be reviewed when the guideline is revised.

						proficiency time for the biochemical marker after the onset of symptoms even if the pain has resolved. The current proficiency time for Troponin T or I is 10-12 hours).	It is not NICE policy to date recommendations. It is very clear in the guideline and on the website when it was published.
SH	Randox Laboratories Ltd	3	Full 1	19	16	This point is excluding measurement of any ischemia biochemical markers. It is well established that troponin is a marker of necrosis and is only released after cell death has occurred. Necrosis is irreversible. It is therefore important to identify patients with ischemia before necrosis occurs. Research is focussed on ischemic markers and this sentence should not exclude the use of ischemic markers. If, however, it has been decided that ischaemia-modified albumin measurement is inappropriate then this should be stated. Other markers of ischemia in the future may prove more effective.	We agree that that other markers of ischemia may prove effective in future and we have made a research recommendation to encourage research in this area. But, the remit of this guideline is to review the current best evidence. The GDG also noted that for optimal diagnostic performance, biochemical markers in people with chest pain.should be cardiac specific.
SH	Randox Laboratories Ltd	4	Full 1	49	1	We feel that these suggestions for research are biased and have a narrow focus on a singular marker that is still unproven in a clinical setting. This may be due to the effective marketing of larger companies promoting high sensitivity troponin. See also Full, page 199 line 7 “the GDG recognised that troponin assays were evolving and the highly sensitive assays currently being developed and evaluated, are likely to lead to opportunities for earlier testing”. There are to date to our knowledge no publications proving high sensitivity troponin results in earlier detection of MI. Currently troponin is a marker of necrosis. From the information provided the aim of the guideline includes providing “guidance on determining whether or not myocardial ischaemia is the cause of chest pain” (full guideline, page 23 line 4). Furthermore emphasis is placed on “the importance of prompt and accurate diagnosis because treatments are available to ameliorate symptoms and prolong life” (full guideline page	The research recommendation includes the evaluation of the diagnostic performance of biomarkers for which additional evidence for their diagnostic value is required. This not restricted to new high sensitivity troponin methods. We acknowledge that the initial paragraph of the research recommendation may have been misleading and this has been revised.

						23, line 24). Recent scientific publications have shown that a multi-marker approach (heart fatty acid binding protein (FABP), Myoglobin and troponin measurements) can improve the sensitivity of MI detection. These publications also demonstrate that the smaller FABP is released much earlier than troponin and is proven to be an early marker of MI. Troponin is tightly bound in cardiac muscle so irreversible necrosis must occur before it is released, whereas FABP is located in the cytoplasm and therefore, it is released earlier. We are not sure that early markers of ischaemia should be described as "putative" (full, page 49, line 7). Furthermore, research should be promoted into determining earlier markers of MI as these would be expected to reduce the occurrence of MI, alert individuals they are at risk and in so doing reduce financial and logistical costs of keeping individuals in A&E waiting for a second troponin test at 10-12 hours. The FABP references are listed below. 1. McCann CJ et al, Investigation of a multimarker approach to the initial assessment of patients with acute chest pain. Adv Ther. 2009; 26(5): 531-4. 2. Liyan C et al, Prognostic value of combination of heart-type fatty acid-bnding protein and ischemia-modified albumin in patients with acute coronary syndromes and normal troponin T values. J Clin Lab Anal. 2009; 23(1): 14-8. 3. McCann CJ et al, Prognostic value of a multimarker approach for patients presenting to hospital with acute chest pain. Am J Cardiol. 2009; 103(1): 22-8.	

						4. Laio J et al, Heart-type fatty acid binding protein for on-site diagnosis of early acute myocardial infarction. Intl J Cardiol. 2009; 133 (3); 420-3. 5. Valle HA et al, Clincial assessment of heart-fatty acid binding protein in early diagnosis of acute coronary syndrome. Eur J Emerg Med. 2008; 15(3): 140-4. 6. McCann CJ et al, Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac Troponin T. Eur Heart J. 2008: 29; 2843-50. 7. Bruins Slot MH et al, Heart-type fatty acid-binding protein in acute myocardial infarction evaluation (FAME): background and design of a diagnostic study in primary care. BMC Cardiovasc Disord. 2008: 15(8); 8. 8. Figiel L et al, Heart-fatty acid binding protein-a reliable marker of myocardial necrosis in a heterogeneous group of patients with acute coronary syndrome without persistent ST elevation. Kardiol Pol. 2008; 66(3): 253-9. 9. Horacek JM et al, Use of multiple biomarkers for evaluation of anthracycline-induced cardiotoxicity in patients with acute myeloid leukaemia. Exp Oncol. 2008;30(2):157-9. 10. Pudil R et al, Use of the biochip microarray system in detection of myocardial injury caused by	

						radiofrequency catheter ablation. Clin Chem Lab Med. 2008;46(12):1726-8. 11. Mion MM et al, Analytical and clinical performance of a fully automated cardiac multi-markers strategy based on protein biochip microarray technology, Clin Biochem. 2007; 40(16-17):1245-51. 12. Kilcullen N et al, Heart-type fatty acid-binding protein predicts long-term mortality after acute coronary syndrome and identifies high-risk patients across the range of troponin values. J Am Coll Cardiol. 2007;50(21):2061-7. 13. O'Donoghue M et al, Prognostic utility of heart-type fatty acid binding protein in patients with acute coronary syndromes. Circulation. 2006;114(6):550-7. 14. Zaninotto M et al, Analytical and clinical evaluation of a new heart-type fatty acid-binding protein automated assay. Clin Chem Lab Med. 2006;44(11):1383-5. 15. McMahon G et al, Multi-marker approach with the use of biochip cardiac array technology for early diagnosis in patients with acute coronary syndromes, in preparation (submitted). 16. Wang J et al, Conjugation of biomolecules with magnetic protein microspheres for the assay of early biomarkers associated	

						with acute myocardial infarction. Annal Chem. 2009; Jun 25. 17. Wang J et al, Carboxylated magnetic microbead-assisted fluoroimmunoassay for early biomarkers of acute myocardial infarction. Colloids Surf B Biointerfaces 2009; 72(1): 112-20. 18. Wang J et al, Superparamagnetic microsphere-assisted fluoroimmunoassay for rapid assessment of acute myocardial infarction. Biosens bioelectron. 2009; 24(10): 3097-102.	
SH	Randox Laboratories Ltd	5	Full 1	169	20	The line states "Troponin I and T are first detected 3 to 4 hours after an acute MI". Is there a published paper that states this? From the information provided in the rest of "Investigations and Diagnosis" section it appears that troponin is elevated after 6 to 12 hours.	While introduction section states that troponin I and T are detected 3 to 4 hours after onset of acute MI, levels peak at 6 to 12 hours, the text has been amended to state the peak to avoid confusion.
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	6	Full 1	10	1	Despite the suggestion in the previous point that patients with stable angina should be stratified in terms of risk prior to further diagnostic investigation (this is elucidated in the main text) – this sentence implies that <u>all patients</u> with stable angina should have a Coronary Calcium score. This is misleading to the casual reader, as this is <u>not</u> the recommendation. The Key points section should be made clearer by expanding on the pre-test probability assessment – Low = CT, Intermediate = functional imaging, High= angiogram.	We agree that this was not very clear and the key priorities have been revised.

Stable Chest Pain Comments

Status	Organisation	Order no.	Version	Page no	Line no	Comment	Response
SH	British Nuclear Medicine Society 1	8	Full 2	4	1	The Venn diagram is misleading and should have much more overlap between angina and functional testing . There can be less overlap with anatomical testing.	This is illustrative and not done to scale as we would not have the evidence to make accurate.
SH	British Nuclear Medicine Society 1	9	Full 2	9	11	The prognostic significance of any lesion found on angiography is not discussed. Thus a functional image (used first) may suggest that there is no prognostically significant CAD. We strongly suggest there is still a role for functional imaging in this regard	The guideline recommends that if there is uncertainty regarding the functional significance of CAD after angiography a functional test is recommended. Additionally, a functional tests is the first line test where there is established coronary disease. The prognostic value of tests was out with the scope of the guideline.
SH	British Nuclear Medicine Society 1	10	Full 2	9	15	64 slice CT angiography is likely to be ineffective in this patient population who are highly likely to have very high coronary calcium scores	This has been revised
SH	British Nuclear Medicine Society 1	11	Full 2	11	1	Dobutamine stress MPS is a also a well recognised technique for the investigation of IHD (refs available on req)	Agreed and the recommendation has been revised to include this
SH	British Nuclear Medicine Society 1	12	Full 2	11	16	In patients with very low likelihood of CAD, no testing is required (atypical chest pain, no risk factors). This is alluded to later on, but should be emphasised here	The recommendations have been revised to make this more explicit and the order revised
SH	British Nuclear Medicine Society 1	13	Full 2	11	19	A coronary calcium score of zero does not completely exclude CAD. The NPV of a normal calcium score falls in young patients (to 85% in some studies) and is problematic in patients with suspected ACS (up to 12% may have soft plaque only).	Yes we take the point. However, the diagnostic sensitivity of all tests falls below 100% particularly in low probability groups. Thius is particularly true of the ETT, the evidence showing that bv calcium scoring performs more cost-effectively in this group. It is also noteworthy that false negative findings in calcium scoring tend to aggregate in patients with ACS rather than patients with stable chest pain for whom calcium scoring was recommended.
SH	British Nuclear Medicine Society 1	14	Full 2	11	20	CTCA in a low risk group is very good at ruling out disease but has a poor post test probability of disease in patients with an abnormal study (68%) suggesting a relatively high number of false positives (W Bob Meijboom JACC 2007;50:1469-75)	We accept this point. In our GL we recommended calcium scoring ± CTCA only in patients with a low pre-test probability 10-30% in whom there remained lingering doubt. The purpose therefore was for diagnostic rule-out an

							area in which CTCA performs well (as you state). Very few of these patients will, in the event, be shown to have CAD and we recommend CTCA only when calcium scores are low (<400) to optimise diagnostic performance. In patients with more densely calcified coronary arteries we recommend invasive angiography.
SH	British Nuclear Medicine Society 1	15	Full 2	12	26	This will require heavy investment in non-invasive imaging	We will bring this to the attention of the NICE implementation team.
SH	British Nuclear Medicine Society 1	16	Full 2	69	5	This is an outdated reference and is planar imaging and not SPECT.	The diagnostic performance of exercise thallium myocardial perfusion scintigraphy was examined in the systematic review and has been included for completeness.
SH	British Nuclear Medicine Society 1	17	Full 2	78	1	This statement is incomplete and stated cost savings unintelligible	This has been clarified.
SH	British Nuclear Medicine Society 1	18	Full 2	84	25	The new gamma cameras and image acquisition protocols (resolution recovery) will improve count statistics and allow imaging of very obese patients with an acceptable radiation dose	Thank you. The narrative as been added to.
SH	British Nuclear Medicine Society 1	19	Full 2	85	12	Ischaemia misspelt	Thank you for pointing this out. It has been corrected.
SH	British Nuclear Medicine Society 1	20	Full 2	132	19	Cardiac CT does not require the injection of a radioactive dye	Thank you for pointing this out. It has been corrected.
SH	British Nuclear Medicine Society 2	1	Full 2	10	1	This seems sensible and is known to be cost effective.	Thank you for your response.
SH	British Nuclear Medicine Society 2	2	Full 2	11	17	This is very controversial. It is difficult to understand why the exercise ECG has been completely abandoned as a first line investigation in this group of patients. It is also not clear why CT calcium scoring should be the first investigational step, given that it is not a functional test and involve radiation exposure in a group that is inherently low risk.	The GDG were aware that exercise ECG was frequently used in current clinical practice. However, their appraisal of the evidence found that exercise testing had a low sensitivity (average 60-70%), compared with the very high sensitivity of calcium scoring (> 95%), and concluded that calcium scoring was a more reliable rule out in this group, with a very

							modest radiation exposure.
SH	British Nuclear Medicine Society 2	3	Full 2	12	26	Same comment as above. Whilst exercise ECG should be excluded in the intermediate pre-test probability patients, and replaced with myocardial perfusion imaging, stress echocardiography or CT coronary angiography, not clear that this should be the case in the low risk and high risk groups.	The aim of this guideline is to make a diagnosis of angina, not to assess prognosis in those with an established diagnosis. The appraisal of the evidence found that the diagnostic performance of exercise ECG compared with other diagnostic tests was relatively poor and as such is not recommended for diagnostic testing in patients without a prior history of coronary artery disease. In the low risk group, coronary calcium scoring with or without CT coronary angiography is a more effective rule out. In the high risk group, invasive coronary angiography is more effective as a first line investigation followed by functional imaging if doubt should remain. Exercise ECG may have a role for prognostic testing, but this was outside the scope of this guideline to evaluate.
SH	British Nuclear Medicine Society 2	4	Full 2	15	8	Is it not true of most diagnostic tests that it is very difficult to achieve 100% sensitivity and specificity?	We agree. The GDG compared the sensitivity and specificity of the various investigations in the different circumstances.
SH	British Nuclear Medicine Society 2	5	Full 2	69	5	This is an outdated reference and is planar imaging and not SPECT.	The diagnostic performance of exercise thallium myocardial perfusion scintigraphy was examined in the systematic review and has been included for completeness.
SH	British Nuclear Medicine Society 2	6	Full 2	70	19	This is probably true reflection of MPS sensitivity.	Thank you for your comment.
SH	British Nuclear Medicine Society 2	7	Full 2	75	17	Radiation exposure in low risk patients.	More information has been added about this.
SH	British Nuclear Medicine Society 2	8	Full 2	77	19	This is extremely controversial and contradicts what is written in Page 10	This statement is based on outputs from the economic model presented in the 2008 HTA on 64CT angiography, and replicated for this Guideline. Page 10 considers results of alternative model for patients with a moderate pre-test likelihood of disease, for whom the

							GDG considered that Functional techniques were more appropriate to confirm diagnosis of angina.
SH	British Nuclear Medicine Society 2	9	Full 2	84	25	What evidence to suggest that patient weight of 140 or over degrades images?	A further comment has been added to the narrative.
SH	British Nuclear Medicine Society 2	10	Full 2	84	28	With resolution recovery software reconstruction the radiation dose can be potentially halved.	Thank you. The narrative as been added to.
SH	British Nuclear Medicine Society 2	11	Full 2	84	28	One day protocol is possible.	Thank you. The narrative as been added to.
SH	British Nuclear Medicine Society 2	13	Full 2	93	10	What about NICE MPS technology appraisal?	The Mowatt paper is the research paper which informed the Appraisal.
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	4	Full 2	9	15	"First line investigations in those with a high (>60%) pre-test likelihood of angina": There is no logic in offering CTA (64-slice or above) to those at high risk and not being considered for angiography as an anatomical test will take one no further down the decision pathway. This group of patients will by the current recommendations be treated with appropriate primary prevention and symptomatic relief (anti-ischaemic therapy). What is required then in this group of patients is for a functional test to assess ischaemic burden. Over the years ischaemia has clearly be shown to relate to prognosis, and it is the presence of ischaemia that will change patient management at this stage. Performing CTA in this group of high-risk patients is wholly inappropriate. By definition they are the group most likely to have calcific disease and hence will be especially prone to over-reporting (i.e. false positive results) of disease severity if CTA is undertaken. For those performing CTA, it is well accepted that this is the most difficult group to deal with/report. This recommendation as it stands risks exposing a significant proportion of patients to unnecessary ionising radiation when there are a number of safer alternative non-invasive tests that could be used	This has been revised

						to assess ischaemia. **Thus CTA should be removed entirely from section 3.2.2.2 and the focus should remain on non-invasive functional imaging.**	
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	5	Full 2	9	26	For the reasons stated above, CTA should also be removed from this section (3.2.2.4). "Exclude CAD as the cause of symptoms and investigate other causes if no significant CAD is found during invasive coronary angiography". This statement is at best ambiguous and at worst misleading. What does 'no significant disease' really mean? There are now over-whelming data that show that eye-balling a stenosis on a 2D angiographic image provides a very poor predictor of functional significance of that lesion. Thus this statement could lead to large numbers of patients being denied appropriate investigation and treatment for myocardial ischaemia if the angiogram is taken at face value in all cases. Certainly for the less experienced this is a common pitfall. Interventional cardiologists will testify to the frequent occurrence of incorrect appreciation of lesion severity (or lack thereof) when patients are referred for percutaneous coronary intervention. Once again current international cardiology guidelines recommend a functional assessment of lesion severity, either by non-invasive ischaemia assessment or further invasive tests (e.g. FFR or IVUS).	We agree that functional imaging is required if there is uncertainty whether the demonstrated anatomical disease is the cause of myocardial ischaemia and the guideline includes a recommendation for this. The care pathway includes further guidance about the interpretation of angiographic results, and this has also now been included in the recommendations, This is as an aid to clinical decision making and all investigations require appropriate interpretation.
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	6	Full 2	10	15	"Section 3.2.2.6. MPS using SPECT is recommended for the diagnosis of suspected CAD in the following circumstances": This statement is misleading. It has been taken from the NICE technology appraisal 73, which was only an appraisal of MPS – no other non-invasive functional	We agree however we cannot alter a TA recommendation. We have thus put it as a footnote so it is less confusing.

						tests for myocardial ischaemia were considered. As stated in 3.2.2.5, *the choice of imaging method (SPECT, stress echo/CMR, perfusion CMR) should take account of locally available technology and expertise, and the person and their preferences, including any contraindications*. Thus in section 3.2.2.6, the opening sentence should include, in addition to SPECT, first-pass contrast-enhanced magnetic resonance (MR), stress echo and MR imaging for stress-induced wall motion abnormalities. As it stands it is inappropriate, misleading and contradictory to focus on just one imaging modality for the non-invasive assessment of ischaemia.	
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	7	Full 2	11	16	"For people with a low pre-test likelihood that chest pain is caused by angina (less than 30%) and an uncertain diagnosis: *3.2.2.12 After clinical assessment and a resting 12-lead ECG, offer CT calcium scoring."* This group of patients by definition will include a whole mixture of diagnoses, many of them with non-cardiac related symptoms. It seems wholly inappropriate to subject such a large patient population to a test that involves ionising radiation (all be it low for CAC). Indeed many patients in this group will have incidental coronary calcium which is totally unrelated to their presenting symptoms. The mere presence of this, by these current recommendations will then initiate a second evaluation by CTA (and a further significant dose of ionising radiation). In a proportion of these patients CTA will be difficult to interpret (due to calcium) and will then require a third-line functional test (which may involve yet further ionising radiation if SPECT is the modality locally available). If this (SPECT) turns out to be negative the patient will have had a considerable radiation burden (in excess of 30mSV for combined CTA and SPECT). If the	Patients who following clinical assessment have non specific chest pain are generally not investigated further, and the recommendations have been revised to make this clearer. The recommendations have also been revised to make it clearer that when the likelihood of CAD is < 10% other causes of chest pain should be considered. In those with atypical and typical anginal symptoms and a low likelihood of disease CT coronary angiography is likely to rule out coronary disease and is cost effective. The GDG recognised the importance of avoiding unnecessary radiation exposure, and have included a coronary calcium score prior to CT coronary angiography in the pathway to minimise radiation exposure.

						SPECT is positive the patient will then go on to angiography and possible PCI. This additional level of radiation exposure will be a) considerable, b) over a short time period, and c) focused on the mediastinum with significant non-target organ exposure (e.g. breast tissue). One has to remember that patients are presenting with functional symptoms and that for those specialising in the assessment of cardiac disease, it is a functional assessment of ischaemia that is required early in the diagnostic pathway.	
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	8	Full 2	12	9	Comments on this section (3.2.3.1.) are an extension to the comments above. We agree that non-invasive functional imaging of ischaemia is entirely appropriate if invasive coronary angiography or 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance. However it is the order in which these investigations are being recommended that we disagree. In patients with previously confirmed CAD it is the functional assessment of ischaemia that provides information on which to base further management decisions. Based on guidelines, this practice is now widely adopted in the UK and leads to significant reduction in unnecessary investigations. For example, by performing a functional assessment early in the diagnostic pathway, all those that are positive will be listed for an angio?proceed (i.e. will have the diagnosis confirmed and revascularisation performed at a single visit). This leads to a significant financial saving for the NHS (reducing the need for a separate angiogram and then PCI procedure) and is safer and quicker for the patient. For those that are negative on functional ischaemia testing, if angiography is pursued then any lesions of borderline significance will have already been assessed for ischaemia and reassurance (and	The recommendation in the guideline is that if a patient has established CAD a functional test is recommended for the reasons you outline. We have made this clearer in the order of the recommendations.

						appropriate treatment) can be given to the patient immediately.	
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	9	Full 2	12	25	As it stands this statement is technically correct, in that MR coronary angiography on its own is not robust enough for the detection/exclusion of CAD. However, cardiovascular MR is a multi-parametric test that can evaluate the significance of CAD in a number of ways in a single examination (LV function, perfusion, viability and coronary imaging). There are a number of studies (albeit small and single centre) that have suggested that MR coronary angiography can be useful as an adjunct to ischaemia testing by stress perfusion MR and lead to an improvement in diagnostic sensitivity. In addition, MR coronary angiography is the reference test for the identification of aberrant coronary arteries and their course (CTA is also excellent for this indication but would probably not be the first line choice due to the issue of radiation).	We don't disagree with point but this is beyond remit of guideline. As with any guideline clinical judgement should be used in individual cases.
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	11	Full 2	170	27	We also need to ask how applicable PROTECTION-1 is to current UK practice. There are limited (but growing) number of 64-MDCT systems in UK NHS hospitals. However the vast majority of centres do not have the experience of those in the PROTECTION-1 study and so it is unlikely that those effective dose values are being replicated. In addition there is a shortage of cardiologists and radiologists with the necessary skills and experience to undertake CTA at the current time. This will obviously change, but at the present time the proposed guidelines are both unworkable and inapplicable to UK cardiology practice. Finally, we appreciate that these guidelines have been written by an evidence review group, who focus on trial quality, synthesis of results and economic appraisal. Whilst these factors are important, the summary (Full,	

						section2, p170) is clearly subject to a high level of bias. These guidelines have to be acceptable to mainstream clinicians (cardiologists) and patients alike. Ignoring issues around patient safety and long terms risks of cancer cannot be justified. Even the economic arguments do not hold up if one considers that there is a paucity of MDCT systems and trained specialists to operate them across the whole of the NHS. The UK absolutely needs quality standards and commissioning criteria for cardiac CT. Until these are in place, CAC scoring and CTA cannot be recommended for widespread adoption.	Interestingly , some other stakeholders felt the threshold for recommending CT coronary angiography was too conservative. We acknowledge that radiation exposure is a problem to be taken seriously but make the following points. a) Radiation exposure for calcium scoring that does not proceed to angiography is negligible b) Gated imaging and dual source machines are substantially reducing radiation exposure in MDCT angiography – contemporary scanners providing complete angiographic assessment in the 7-8-millisievert range with a scan time for the entire heart of just 250 milliseconds. c) We need to make clearer the fact that this guideline's recommendations ensure that the majority of patients are diagnosed either on clinical grounds alone or on clinical grounds supported by the result of a functional test. The guideline is conservative therefore in its recommendations for anatomical testing with radiation exposure. Thus the majority of patients with non-specific chest pain are excluded on clinical assessment, the minority in whom diagnostic doubt persists having a calcium score (negligible radiation) proceeding to angiography only if calcium is demonstrated. Similarly the majority of patients with typical angina and a high probability of disease are diagnosed on clinical criteria alone, only proceding to angiography if doubt persists.
SH	NETSCC HTA ref 1	12	Full 2	150	25	The rank order of strategies is not the same – at prevalence rates of 50% or greater the next most optimal approach is ECG-CA whereas below 50% it is SPECT-CA	The text has been revised to say that the rank order of strategies in terms of total cost, accurate diagnoses and QALYs remains the same across all modelled levels of CAD prevalence.

SH	NETSCC HTA ref 1	13	Full 2	175	Table 48 (and other analysis with QALYs)	This shows that the "assumed" prevalence of CAD has a far greater influence on the results than any of the diagnostic tests. This affects costs, diagnostic accuracy and survival. It appears that the "prevalence" is a proxy for prior expectation (or probability or "pre-test likelihood") that a patient has CAD. A huge range of prevalence rates are used throughout – and the prevalence rates do make a difference to the ordering of the most-to-least cost-effective strategy. This is worth a comment in the discussion at least; and ideally some evidence on the true prevalence should be sought and used. (See next comment)	Agreed, but the decision variable is which technology for a given CAD not vice versa. The pre-test probability (prevalence) will vary depending on where the patient is in the treatment pathway and what risk factors they present with.
SH	NETSCC HTA ref 1	16	Full 2	156	10 18	More information is needed here on the cost per QALY (maybe a table of results from Mowatt et al. 2004). Essentially, the results presented in this paragraph are used to justify limiting the subsequent modeling to the short-term diagnostic period only. There appears to be quite a range of £/QALY from different strategies at various prevalence levels. More "evidence" from Mowatt et al. 2004 is needed here to back up this claim (and link this to other areas in the Guideline and Appendix F – especially p19 where considerably more wording is given to justifying not modeling the longer-term.). Nevertheless, the whole justification for not modeling the longer-term rests on a single study by Mowatt et al. 2004 study. The GDG may consider whether this justification is reasonable or otherwise.	The results under discussion here are the results from a probabilistic analysis presented by Hernandez et al. The principal rationale for confining the de novo models to the short term was the diagnostic scope of the Guideline and not the results of Mowatt 04. Have reworded text in chapter 5 and the Appendix to clarify this.
SH	NETSCC HTA ref 1	17	Full 2	156	10 18	Moreover, given the changes to the Mowatt et al. 2008 model, and then the subsequent changes undertaken for the Guideline analysis, a leap of faith is required to assume that "the values coming out of the short term model are roughly equivalent to the cost per QALY outcomes emerging from the longer term model." The "roughly equivalent" statement was qualified with "at prevalence levels of 30% and above". Whether this assumption continues to hold is unknown.	"the values coming out of the short term model are roughly equivalent to the cost per QALY outcomes emerging from the longer term model" Is an observation about the ICERs of the modelling undertaken in the MPS HTA which we stand by. For the lower prevalence rates, the de novo analysis indicates that 64slice CT angiography tends to dominate stress ECG and always dominates MPS SPECT and, as such, consideration of the ICER value is not necessary. The ICERs for straight to invasive CA are substantially bigger than those using CT

							angiography.
SH	NETSCC HTA ref 1	23	Full 2	194	9	Discounting benefits at 6% requires a comment/discussion. This is unusually high for the UK (at the time the recommended rate was 1.5%), and revised in 2004 to 3%. A lower discount rate for benefits will reduce the ICER	Here we are simply reporting the results of the analysis presented in the original papers. No evidence that the ICERs are sensitive to the discount rates used and unlikely to affect the conclusions of the analysis. No revision made.
SH	NETSCC HTA ref 1	42	Full 2		42	Table size needs to be reduced	Done
SH	NETSCC HTA ref 1	43	Full 2	80	29	Remove full-stop after “a”	Thank you for pointing this out. It has been corrected.
SH	NETSCC HTA ref 1	44	Full 2	150	28	Table reference link needs fixing	Corrected but sometimes lost when given to NICE
SH	NETSCC HTA ref 1	45	Full 2	181	3	Link to Table 50 broken	Corrected by sometimes lost when given to NICE
SH	NETSCC HTA ref 1	46	Full 2	183	9	Link to Table 51 broken	Corrected by sometimes lost when given to NICE
SH	NETSCC HTA rep 2	32	Full 2	32	4	907 patients, not 970? (see Table 7 on same page)	Correct, thank you for your comment. Amended to 907.
SH	NETSCC HTA rep 2	33	Full 2	34	15	Delete Table 8 as it contains no clinically useful information. Statistically significant effects do not equate to diagnostic information. The chi-square values do not even indicate the direction of association	Deleted.
SH	NETSCC HTA rep 2	34	Full 2	35	1	Table 9: similar comment as for Table 8	Deleted.
SH	NETSCC HTA rep 2	35	Full 2	36	29	“168 patient group” – typo?	Corrected.
SH	NETSCC HTA rep 2	36	Full 2	37	19	There are far too many predictors here given the modest number of clinical events. There were only 45 cases of severe disease, and a statistical rule of thumb says	The GDG appraised this study as part of other evidence in the section on assessment. The GDG were aware of the limitations of the study,

						there should be at least 10 events per predictor. Estimates derived from this model fitting will be very unstable. Also there were 109 cases of "any disease", meaning even in that analysis there were only 49 non-diseased cases, meaning it is only safe to fit 4 predictors. I realize this analysis was only part of the study of Pryor et al, but I think the GDG should be sceptical about the findings.	and did not base any recommendations solely on this study but the results of the study were considered with other evidence in the section. The model described in the study had been tested and validated in a previous stable chest pain population also discussed in the guideline (Pryor 1983), although as pointed out the study is underpowered to determine predictors. Comments on the limitation of the study have been added to the narrative.
SH	NETSCC HTA rep 2	37	Full 2	38	7	Insert word "greater" before "estimated"?	Inserted.
SH	NETSCC HTA rep 2	38	Full 2	38	13 14	Checking findings for left main disease in Pryor et al's paper, the c-index was 0.73 (95%CI 0.59-0.87). I only checked this because the GDG reported the same c-index and CI for left main disease as for severe disease (lines 12-13). I found repeatedly through the report that similar sentences occurred where I suspect some copying and pasting had been done! Some checking needs to be done as I may well have missed some similar mistakes elsewhere.	Thank you for pointing this out; it has been amended. Further checking will be done during proofreading before the document is published.
SH	NETSCC HTA rep 2	39	Full 2	38	12 13 16	The c-index is a proportion not a percentage so delete "%" character	Deleted.
SH	NETSCC HTA rep 2	40	Full 2	49	9 13	This is a population based study, not one of subjects presenting with suspected CAD. I was surprised to see Framingham data included in this review and question its relevance. I am not sure the inference asserted in lines 11-12 is justified.	The GDG considered that this section on gender differences required an introduction; as such these studies were highlighted by the GDG as important in the introduction.
SH	NETSCC HTA rep 2	41	Full 2	51	30 31	Were cardiologist and symptom score *independently* predictive?	Cardiologist score and symptom score were independently predictive, amended.
SH	NETSCC HTA rep 2	42	Full 2	52	3 7	Rather than quoting the p-values for hazard ratios within each sex, the point would be better made by quoting the interaction p-value (both highly significant in Table 2 of Zaman et al)	Amended.
SH	NETSCC HTA rep 2	43	Full 2	53	6	The ± sign was outlawed by the BMJ; Altman and others have suggested such data is better presented as 62.8(SD 11.7). I would suggest changing to this latter	This will be amended before final publication.

						convention throughout the report. Sometimes ± means SE; this is why it is better to be explicit.	
SH	NETSCC HTA rep 2	44	Full 2	53	10	P=0.001? (typo)	Correct, amended.
SH	NETSCC HTA rep 2	45	Full 2	58	18 29	I found this text extremely difficult to understand, even after consulting the Zaman et al paper. Are these statistical tests conducted among subgroups, or are they again a series of interaction tests? I suspect it is the former but the latter might be more appropriate. However, I am not asking the authors for fresh analysis but clarification.	The results section in the publication was difficult to understand. It appears that the tests were conducted among subgroups, and a comment has been added that this appears to be the case, however, a comment has also been made that alternatively it maybe a series of interaction tests and again that this is not clear in the study. Additionally, further comment has been added that *P* values were not reported for the quoted hazard ratios.
SH	NETSCC HTA rep 2	46	Full 2	62	12	The chi-square value is unhelpful	Deleted.
SH	NETSCC HTA rep 2	47	Full 2	62	12 18	Are there any clinically useful statistics that can be gleaned from the publications cited? Sn, Sp, PLR, NLR etc? If this is a good study, it would be so helpful to lift some directly useful information.	The paper did not report these statistics.
SH	NETSCC HTA rep 2	48	Full 2	67 79		I do think PLR and NLRs would be by far the most useful data to present. I think the GDG have adopted the policy of simply reporting verbatim the results of studies they cite, but in many cases some simple recalculations would lead to more clinically useful information. I also suggest that an attempt to combine results of all these studies into a simple Table would make it far more digestible. It is very hard work to read all the text in this section (and other similar sections in the report).	The statistics were cited from the papers because sometimes not all the relevant information was provided for calculation of PLR and NLR. The GDG decided that all statistical information should be included. While potentially one table would have been helpful, due to the different populations / prevalence of CAD, and missing data, it could have been misleading. Also, due to the nature of the reporting and data, the table would have contained so much information that it would be difficult to read. We did attempt to provide one large Table, but due to the reasons cited it was decided to present the data in narrative form. Time constraints did not allow for recalculation.
SH	NETSCC HTA rep 2	49	Full 2	75	14 16	Just because no evidence was found, this does not mean that recommendations based chiefly on Caucasian subjects cannot apply to Asian subjects.	Correct, this was an evidence statement. The recommendations do not make a distinction between the two populations.

SH	NETSCC HTA rep 2	50	Full 2	77	6 10	Do these relative risks apply specifically to subjects exposed to 64 slice angiography?	The relative risks were determined from a Monte Carlo simulation model that estimated radiation dose to organs according to information from standard cardiac 64-slice CT protocol. The age- and sex-specific lifetime attributable risk (LAR) of individual cancers was estimated for those malignancies specified in the Biological Effects of Ionizing Radiation (BEIR) VII report. Whole body LAR was estimated by summing site specific LARs for these organs and adding a composite equivalent dose for the BEIR VII categories. The relative risks for different age's and sex were compared to the risk of an 80 year old man This has been clarified in the evidence statement.
SH	NETSCC HTA rep 2	51	Full 2	79	20 21	Since NLR is generally expected to be below 1 and to lower the probability of disease, I suggest rephrasing as follows "..much *less* likely is a negative (normal) test to be found in a subjects *with* the disease than in a subject *without* the condition."	Thank you for your comment, the text has been amended as you suggested.
SH	NETSCC HTA rep 2	52	Full 2	79	27 28	It is not true to say that LR changes with disease prevalence. Both PLR and NLR are functions of sensitivity and specificity alone, and as sensitivity and specificity are classically regarded as independent of disease prevalence, so are LRs.	Thank you for your correction. This is correct, and has been amended. A contingency table has been added and further mathematical clarification of the definition of sensitivity, specificity, PLR, NLR, PPV, NPV and prevalence has been given in the narrative.
SH	NETSCC HTA rep 2	53	Full 2	87	7 32	The GDG reports a meta-regression analysis from a 1989 paper – this paper makes no allowance for differing sample sizes of studies with weighted regression, and this critique might be mentioned in the GDG report, as it may well alter the effects reported. However the GDG might consider mentioning regression coefficients quoted by Gianrossi et al rather than the statistical significance – coefficients quantify the actual impact on sensitivity and specificity	This has been noted and the regression coefficients have been added to the narrative.
SH	NETSCC HTA rep 2	54	Full 2	90	10 12	If the NLR is 0.38, and the p-value is 0.09, I estimate the correct CI should be approx 0.09 to 1.56. It may be worth mentioning this (check my calculation first!)	Well spotted, we did state in the text that the CI values quoted in the systematic review appeared to be incorrect. The correct CI have been added to the narrative.

SH	NETSCC HTA rep 2	55	Full 2	98	9 10	I think the GDG has misunderstood the practical significance of the odds ratios, whose interpretation depend crucially on the units in which the exposure variable was expressed. If the odds ratio per year of publication was 0.96, the odds ratio per decade will be 0.66 (ie expected diagnostic performance of a study published in 2005 will be one third less than for a study published in 1995). The odds ratio for proportion of men probably refers to “per extra 1% of men”; again if this were changed to “per extra 10% of men”, the odds ratio would be much more impressive.	Thank you for your comment. The results have been described as detailed in the paper. A sROC was provided comparing diagnostic performance for 1995 and 2005 showing a decline in performance over the decade, although the area under the curves was not provided. The authors did not provide an interpretation of their findings with respect to publication year or proportion of men. It is not clear if the odds ratio for proportion of men refers to “per extra 1% of men”; or to “per extra 10% of men
SH	NETSCC HTA rep 2	56	Full 2	98	18	Was age dichotomized; if so how? (will help interpretation of age effect)	Age was not dichotomized (mean age used).
SH	NETSCC HTA rep 2	57	Full 2	99	26 29	I have problems with the GDG quoting diagnostic performance on a “per artery/ per segment/ per coronary territory” basis, instead of “per patient”. This issue crops up several times in the report. I would have thought a NICE appraisal should concentrate much more on the “per patient” estimates. Apart from the need to focus on patients rather than pieces of anatomy, there is also a statistical issue. As there is inevitably a statistical dependence between repeated observations on a single patient, the confidence intervals will probably be too narrow; robust standard errors rather than naïve standard errors will be required.	Thank you for your comment. The GDG were primarily interested in ‘per patient’ estimates. Where data were reported per coronary artery or per segment, the GDG decided to include the information.
SH	NETSCC HTA rep 2	58	Full 2	101	8 10	I realize the sentence is a direct quote from Sharples et al but it is poorly expressed. “A difference in mean exercise time from coronary angiography of 1 minute was defined as the minimum clinically significant difference. Therefore if the confidence limits for the difference were both between -1 and +1, the difference was considered not clinically significant.”	Thank you for your comment, the sentence has been amended as you suggest.
SH	NETSCC HTA rep 2	59	Full 2	104	16 17	A correlation coefficient is a poor way to compare methods of measurement, see Bland and Altman’s classic Lancet paper of 1986.	This has been deleted.
SH	NETSCC HTA rep 2	60	Full 2	120	1	Table 32, here again is the issue of the unit of analysis. It is of note that whenever the patient is the unit, sensitivity is higher but specificity is lower. Presumably	The study did not examine scanning increasing numbers of segments and arteries and its effect on the probability of detecting at least one

						the more vessels or segments that are looked at, the greater the probability of detecting at least one abnormality within a patient.	abnormality within a patient. A meta-analysis on 64-slice CT coronary angiography found that sensitivity increases and the specificity decreases as the size of the unit analysed increases from coronary artery segments to vessels, and to patients (Vanhoenacker et al, Radiology, 2007 224, 419-428). The study on page 120 is consistent with the finding by Vanhoenacker.
SH	NETSCC HTA rep 2	61	Full 2	122	9	When the specificity and NPV are quoted as 67%, in each case that is from a denominator of only 3!	It is correct that there were only 3 patients in the denominator, it is noted in the guideline narrative that the very small patient numbers made the results inconclusive.
SH	NETSCC HTA rep 2	62	Full 2	125	5	Table 32; age is a continuous variable and is expressed per year while all other variables are dichotomous. Comparing its effect with the dichotomous variables is difficult, but a 20 year increase is associated with an odds ratio of only 1.24.	Thank you for your comment, the table of results is presented as given in the paper.
SH	NETSCC HTA rep 2	63	Full 2	131 144		Same comment as for pages 67-79, see above	
SH	NETSCC HTA rep 2	68	Full 2	7	9 10	Absence of evidence is not evidence of absence. May be more appropriate to say “Be aware that there is no reason to expect major differences in symptoms..”	This is a recommendation and has been reworded what to do.
SH	NETSCC HTA rep 2	69	Full 2	7	28	Table 1 only allows one to base an estimate on the initial clinical assessment, not the ECG.	It refers to the footnote about ECG changes. This is now on a separate line.
SH	NETSCC HTA rep 2	70	Full 2	9	9	“more than 60%” – there ought to be an upper limit (less than 100%). Suggest “more than 60% but less than 95%*”. There would be little point in carrying out further investigations if the pre-test probability was very close to 100%. * or 99% instead of 95%?	Agreed and an upper limit of 90% has been included
SH	NETSCC HTA rep 2	71	Full 2	11	14	Similar comment. Suggest “less than 30% but more than 5%”. GDG may feel 5% too high, use 1% if preferred?	Agreed and a lower threshold of < 10% has been included
SH	NETSCC HTA rep 2	90	Full 2	4	9	There are low likelihood values in Table 1 but unlike the high likelihood values, they are not shaded (at least not visible on my copy)	All shading has been removed.
SH	NETSCC HTA rep 2	91	Full 2	55	20	On this line and many other lines throughout the report, “form” is typed where GDG mean “from”	Amended on this line and this has been check throughout the guideline.

SH	NETSCC HTA rep 2	92	Full 2	74	8	“multislice” typo	Corrected.
SH	NETSCC HTA rep 2	93	Full 2	74	25	“>100” seems a typo – do authors mean “>1000”?	This has been corrected,
SH	NETSCC HTA rep 2	94	Full 2	76	24	CI for specificity; mistyped.	This value was the value that was quoted in the paper.
SH	NETSCC HTA rep 2	95	Full 2	82	1	“pooled” typo	Thank you for pointing this out. It has been corrected.
SH	NETSCC HTA rep 2	96	Full 2	89	6	Second occurrence of “in the” to be deleted	Thank you for pointing this out. It has been corrected.
SH	NETSCC HTA rep 2	97	Full 2	126	25	“predicative” should be “predictive” ; occurs several times in report.	Thank you for pointing this out. It has been corrected.
SH	NETSCC HTA rep 2	98	Full 2	150	28	Hyperlink has failed here and a few other points in report.	Corrected by sometimes lost when given to NICE
SH	NETSCC HTA rep 2	99	Full 2	159	23	Do you really mean SF-5D or SF12? (see also p.160, line 19)	Corrected to SF-6D.
SH	NETSCC HTA rep 2	100	Full 2	161	21	Sentence needs rephrasing; extra words needed?	Thank you for pointing this out. The text has been corrected.
SH	NETSCC HTA rep 2	101	Full 2	163	4	Table 43; should EBCT rows have “>” signs instead of “=” signs? Eg >37 etc	Thank you for pointing this out. Table 43 has been corrected.
SH	Plymouth NHS Trust / Peninsula Heart and Stroke Network	1	Full 2	132 133		The radiation burden attached to coronary CTA is incorrect. Scans are now acquired using prospective gating and other dose reduction strategies. The mean doses are now < 5 mSv. For over a year our mean doses over hundreds of patients are of this order and the most recent publications provide evidence of this.	The narrative has been added to recognise that radiation exposure is lower with newer scanning techniques.
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	1	Full 2	132 133		The radiation burden attached to coronary CTA is incorrect. Scans are now acquired using prospective gating and other dose reduction strategies. The mean doses are now < 3 mSv. For over a year our mean doses over hundreds of patients are of this order and the most recent publications provide evidence of this.	The narrative has been added to recognise that radiation exposure is lower with newer scanning techniques.
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	7	Full 2	11	16	What is the evidence base for the use of Calcium scoring in patients below the age of 40-45? To my knowledge the population studies so far have looked at older patients. Is it safe to extrapolate from this data to younger age groups?	Knez et al 2004 page 106 found that the total calcium score was an acceptable clinical test according to ROC curve analyses across all ages including < 40 years.

SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	8	Full 2	101 148		–calcium scoring, non-invasive and invasive angiography. Whilst radiation burden involved with CT has been looked at carefully making accurate predictions about radiation dose remains very difficult due to the rapid changes in CT technology. Individual risks have been included for CT but an analysis of the population risk from implementing these protocols should be included. Whilst the individual risk benefit may be satisfactory it is the responsibility of the guideline developers to assess radiation burden to the population as a whole and the impact this may have. This is particularly the case when multiple other groups are advocating the increased use of CT in the diagnosis and management of other disease processes. The medical radiation exposure to the population is increasing rapidly.	We acknowledge that radiation exposure is a problem to be taken seriously but make the following points. a) Radiation exposure for calcium scoring that does not proceed to angiography is negligible b) Gated imaging and dual source machines are substantially reducing radiation exposure in MDCT angiography – contemporary scanners providing complete angiographic assessment in the 7-8-millisieverts range with a scan time for the entire heart of just 250 milliseconds. c) We need to make clearer the fact that this guideline's recommendations ensure that the majority of patients are diagnosed either on clinical grounds alone or on clinical grounds supported by the result of a functional test. The guideline is conservative therefore in its recommendations for anatomical testing with radiation exposure. Thus the majority of patients with non-specific chest pain are excluded on clinical assessment, the minority in whom diagnostic doubt persists having a calcium score (negligible radiation) proceeding to angiography only if calcium is demonstrated. Similarly the majority of patients with typical angina and a high probability of disease are diagnosed on clinical criteria alone, only proceeding to angiography if doubt persists.
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	9	Full 2	132	19	"radioactive" should be removed	Thank you for pointing this out. It has been corrected.
SH	Royal College of Radiologists & British Society of Cardiovascular	10	Full 2	11	18	**Investigating patients with low pre-test probability** with CT Calcium scoring may be appropriate as absence of calcium in this group of patients has a low probability of significant CAD and has been shown to	Yes, we take your point. Clearly a calcium score of 400 is a somewhat arbitrary cut-off and we accept that some very expert imagers might regard this as being too low.

	Imaging					have a low risk of cardiovascular events (1). Where patients have calcified plaques, further imaging with cardiac CT angiogram (CCTA) is appropriate as stated. However, using a cut off value of a score of 400 is arbitrary and number of expert cardiac CT centres would continue to perform CT angiogram as it can still provide useful information to help in further investigation and management(2). Stress functional imaging should be performed after CCTA if there is suspicion of moderate disease (50-75%) confined to either left or dominant right coronary artery(3). If there is moderate stenosis in left and also dominant right coronary arteries, a catheter angiogram with a view to fractional flow reserve may be more useful due to chance of balanced ischaemia with stress functional imaging. Those with severe stenosis on CCTA can proceed to catheter angiography or be treated as angina.	
SH	Royal College of Radiologists & British Society of Cardiovascular Imaging	11	Full 2	10	1	**Investigating patients with moderate pre-test probability** with functional imaging test as the first test can similarly miss out patients with 3 vessel disease and left main stem stenosis (4) where functional imaging is supposed to be less sensitive. These are the very same patients which imaging needs to identify as a priority due to their highest risk. Performing CCTA (along with calcium scoring for risk assessment) as the first line of imaging test in this patient group (moderate pre-test probability) will appropriately identify these patients(5-7). Where appropriate these may need further functional imaging or catheterisation as described above in patients with low pre-test probability. Studies show that up to 70-75% of patients in this group have either absent or mild CAD (<50% stenosis) and thus do not require further work up. 10-15% patients may have significant stenosis requiring cardiac catheterisation and about 10-15% patients have moderate stenosis necessitating functional imaging. Moreover CCTA identifies non-coronary and non-cardiac causes of chest pain in up to 15% of patients, some with significant	Interestingly some other stakeholders considered there was too much emphasis on anatomical testing. The aim of the guideline is to diagnose if chest pain is due to angina. The recommendation for functional imaging in this group followed a careful review of the evidence for clinical and cost effectiveness of various diagnostic strategies. This takes into account the overall sensitivity of functional imaging to detect coronary artery disease. The diagnosis of left main stem disease per se was outside the scope of this guideline and the prognostic assessment of patients with angina is part of guidelines for angina management.

						incidental findings(6, 8). Following chart can be helpful for those with moderate pre-test probability as proposed by Schuiif et al (10): **References** 1. Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and Prognostic Value of Absence of Coronary Artery Calcification. J Am Coll Cardiol Img 2009; 2:675-688. 2. Pundziute G, Schuijf JD, Jukema JW, et al. Impact of coronary calcium score on diagnostic accuracy of multislice computed tomography coronary angiography for detection of coronary artery disease. J Nucl Cardiol 2007; 14:36-43. 3. Min JK, Shaw LJ. Noninvasive Diagnostic and Prognostic Assessment of Individuals With Suspected Coronary Artery Disease: Coronary Computed Tomographic Angiography Perspective. Circ Cardiovasc Imaging 2008; 1:270-281. 4. Berman DS, Kang X, Slomka PJ, et al. Underestimation of extent of ischemia by gated SPECT myocardial perfusion imaging in patients with left main coronary artery disease. J Nucl Cardiol 2007; 14:521-528. 5. Sheth T, Amlani S, Ellins ML, et al. Computed tomographic coronary angiographic assessment of high-risk coronary anatomy in patients with suspected coronary artery disease and intermediate pretest probability. Am Heart J 2008; 155:918-923. 6. Mittal TK KA, Dalby M, Mason M, Barbir M, Dalal P, Ilsley C. Cardiac CT Angiography as the First Line Technique followed by selective Stress Nuclear Imaging in Patients with Low to Intermediate Pre-test Probability of Coronary Artery Disease In:4th Annual Scientific Meeting	

						of Society of Cardiovascular CT. Orlando, Florida: Elsevier, 2009. 7. Schuijf JD, Bax JJ. CT angiography: an alternative to nuclear perfusion imaging? Heart 2008; 94:255-257. 8. Mittal TK PA, Park B, Patel T, Kelion A. Strategy of Using Cardiac CT Angiography with Stress Nuclear Imaging in Patients with Intermediate Pre-test Probability of Coronary Artery Disease In:3rd Annual Scientific Meeting of Society of Cardiovascular CT. Orlando, Florida: Elsevier, 2008; S5.	
SH	NETSCC HTA ref 1	14	Appendix F	General		The choice of using diagnostic accuracy as the main outcome is somewhat problematic. That is, how should the additional £ per person accurately diagnosed is interpreted? What does this really mean? How do we judge if this is good value for money or not?	Agreed that choice of outcome measure not ideal, but consistent with other published economic analyses in this area consistent with the scope of this diagnostic guideline. Have expanded discussion of this in the Appendix.
SH	NETSCC HTA ref 1	15	Appendix F	General		What is meaningful is whether different strategies lead to better survival or not. I would like to see an analysis of the incremental cost per death averted – this is a compromise between modelling the longer-term in a Markov process with QALYs and the short-term diagnostic period - and it has some tangible meaning.	Agreed with the proviso that this is a diagnostic and not a prognostic Guideline. Such an analysis would still require a time point at which to measure survival. This would require additional assumptions and modelling.
SH	NETSCC HTA ref 1	18	Appendix F	Appendix F 9 10	Table 4	The sensitivity analysis reducing the specificity of CT from 80% to 67%: The text states (p9) that Strategy 10 (Ca-CT-CA) has a "much higher ICER than the base case" but Table 4 shows the ICER to be less than ½ of the base case (i.e. £1718 vs £3454 in the base case). Intuitively, the ICER should be higher as more patients will have a false positive result following CT and go on to CA incurring additional costs. Please check the figures.	The figures are correct. The reduced ICER at 20% CAD prevalence can be explained by the much larger incremental benefit produced by a move from strategy 2 to 10 in the sensitivity analysis than the base case.
SH	NETSCC HTA ref 1	19	Appendix F	General	General	There are relatively few limitations discussed – only best/conservative estimates of test accuracy, and uncertainty around the cost of CA.	The limitations discussed here relate only the first line functional model. Other limitations are presented for this model and for the stable modelling in general in the discussion section, however, have now expanded this discussion in

							the Appendix.
SH	NETSCC HTA ref 1	20	Appendix F	General	General	The failure to model stress-echo or stress-MRI is also mentioned as a limitation. The justification not to model stress-echo/stress-MRI was based on an economic evaluation by Sharples et al. 2007.	Agreed. Have expanded the discussion of limitations in the Appendix.
SH	NETSCC HTA ref 1	21	Appendix F	General		I dislike the use of the term "Robust" –this is the authors' subjective opinion only, and the degree of what constitutes "robust" differs between modellers! It portrays a degree of trust. This could be removed throughout.	Agreed – Text has been revised accordingly removing use of "Robust(ness)".