NICE National Institute for Health and Care Excellence

Appendix B: Stakeholder consultation comments table

2019 surveillance of Chest pain of recent onset: assessment and diagnosis (2010)

Consultation dates: 4 to 17 July 2019

1. Do you agree with the proposal not to update the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Royal College of Nursing	Agree	Agree and the evidence provided on the document is comprehensive and satisfactory. They have consulted appropriately.	Thank you very much for your comments. We note that you agree with the proposal not to update the guideline. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Aortic Dissection Awareness UK&I	Disagree	We disagree with the proposal not to update the guideline. The three main conditions presenting with "Chest Pain of Recent Onset" are MI/ACS, Pulmonary Embolism, and Aortic Dissection/Acute Aortic Syndrome. MI/ACS is covered by CG95, and CG144 is being updated to include PE. However there are no guidelines covering AD/AAS. All patients suffering these conditions, including AD, should have the benefit of appropriate NICE guidance.	Thank you very much for your detailed response. We note that you do not agree with the proposal not to update this guideline. We note your view that the diagnostic pathway for aortic dissection and myocardial infarction should be integrated until one or other condition is ruled out. As detailed in the summary of evidence (Appendix A) several recommendations in this guideline flag various points at which health care professionals should consider the possibility that a person presenting with recent onset chest pain of suspected cardiac origin may have aortic dissection. We have

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		We submit that Aortic Dissection must be included in CG95 because: • There is evidence of a serious problem of misdiagnosis and delay in recognising AD, which is costing patients' lives. 38% of AD cases are missed on initial presentation to ED. As a comparison, AD kills more people annually in the UK than Road Traffic Accidents. • Clinical understanding of diagnosing and treating AD has moved on in recent years, however, a significant amount of old thinking and myths still exist which need correcting and updating • The Emergency and Radiology Departments of University Hospitals Bristol NHS Trust have done a lot of work on this subject, developing and implementing Best Clinical Practice addressing all of these challenges. This work could form the basis of some new NICE guidance. • From this work and other, we know that AD can, with the right guidance, be suspected at the history-taking stage and included in the differential diagnosis along with MI, PE and others. Without considering AD in parallel with ACS and PE from the start, this will not happen. • Many symptoms of AD/AAS and MI/ACS are shared, and the two can be difficult to tell apart. It is therefore vital that the diagnostic pathway for AD and MI is integrated until one or other is ruled out. Integration is also important since AD is time-critical, with a 1% mortality rate per hour (50% will die within 2 days), hence delays in	considered this point in detail, but we do not think that further guidance on diagnosis of aortic dissection would be appropriate within the NICE guideline on chest pain, based on the majority view from experts we engaged with in this surveillance review. Therefore, this guideline will not be updated in that area. However, we have carefully reviewed your response, including the content of your cited awareness conference video and Think Aorta campaign information and agree this is an important clinical issue. We will explore this issue further through our topic selection process with a view to considering whether NICE should develop a new guideline on diagnosis of aortic dissection. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.

		considering AD whilst other diagnoses are ruled our will mean more deaths. • Once AD is suspected as a cause of the Chest Pain of Recent Onset, a CT-Aorta scan is the gold standard for definitively diagnosing AD. However, there are currently barriers to obtaining an urgent CT-Aorta, based on its relative rarity, a lack of a clear recognition pathway, competition for CT resource and myths about long-term radiation and contrast risks being relevant to what is an immediately life-threatening condition. By contrast, no such barriers exist for ordering a CT-PA, yet CT Aorta has the same detection rate as CTPA (~5%). • Mistaking AD for ACS and anti-coagulating a patient can prove very challenging for subsequent surgery and can be dangerous for the AD patient. A small number of AD patients will also present with concomitant MI. • Much of the above is further discussed in a clinical video from the 2018 AD Awareness Conference, see https://youtu.be/wdU4Dfu5-98 , which we would commend to you. Relevant evidence and data about AD can be found at https://thinkaorta.org/wp-content/uploads/2018/04/SCTS-2018-AD-Poster.pdf NICE is in the key position of being able to exert its influence to improve the treatment of AD in the UK at the point of diagnosis of chest pain of recent onset. Having evaluated our patient feedback and the evidence we have provided, we trust you will see fit to include AD in CG95.	

Resuscitation Council (UK)	Yes	No comments provided	Thank you very much for your response. We note that you agree with the proposal not to update the guideline. We have considered all stakeholder feedback in detail and retain our proposal to not update the guideline at this time.
The Royal College of Radiologists	Yes	Yes, we agree it is reasonable to not update this guideline yet. It seems unlikely that there would be significant changes at present.	Thank you very much for your comments. We note that you agree with the proposal not to update the guideline. We have considered all stakeholder feedback in detail and retain our proposal to not update the guideline at this time.
Abbott Diagnostics Division, Abbott Laboratories	Disagree	Disagree - the Guidance is in need of revision. Comments from Abbott Diagnostics Division, Abbott Laboratories on whether NICE should update CG95. In summary Abbott Diagnostics Division, Abbott Laboratories, believe that NICE should review and update CG95 as since the last review there has been new evidence published and the way that hsTroponin is used in routine practice in the UK/England has changed. Also new Guidelines from SIGN, ESC and IFCC have made recommendation that should also be in a revised CG95. Changes which may have a real impact on patient care included strengthening the recommendation on using sex specific hsTroponin 99th percentile cut-offs and emphasising the utility of early rule out to potential reduce the length of time a patient remains in the ED. (A) Regarding the title and scope of the Document. Could using the term "Chest pain" alone (rather than symptoms suspicious for ACS/symptoms of suspected cardiac origin of recent onset or similar) be viewed as	Thank you very much for your detailed comments. We note that you disagree with the proposal not to update the guideline. We have carefully considered your comments based on your headings used. You refer to new guidelines from SIGN, ESC and IFCC, which are considered in the responses to individual studies below. You comment that the recommendation on using sex-specific high sensitivity troponin 99th percentile cut-offs should be strengthened. You state that the utility of early rule out to potentially reduce length of stay in ED should be emphasised. These points are addressed below. A) Title and scope You note that the term 'chest pain' alone is used in the guideline title (rather than symptoms suspicious for ACS/symptoms of suspected cardiac origin of recent onset or similar) and that this could potentially discriminate against people more likely to have atypical presentations for ACS.

		discriminating against those who are more likely to have atypical presentations for ACS, e.g. women, the elderly? See Section 1.2.1.3: "Initially assess people for any of the following symptoms, which may indicate an ACS: • Pain in the chest and/or other areas (for example, the arms, back or jaw) lasting longer than 15 minutes • Chest pain associated with nausea and vomiting, marked sweating, breathlessness, or particularly a combination of these • Chest pain associated with haemodynamic instability new onset chest pain, or abrupt deterioration in previously stable angina, with • Recurrent chest pain occurring frequently and with little or no exertion, and with episodes often lasting longer than 15minutes. [2010]" (B) Early rule out of ACS/MI in the ED. CG95, page 11, states …."1.2.5.3 consider performing a single high-sensitivity troponin test only at presentation to rule out NSTEMI if the first troponin test is below the lower limit of detection (negative). [new 2016]". The wording of this statement should be reviewed – for example, rather than "consider" use the term "recommend", based on the fact that substantial evidence now exists to support this recommendation, and it would only be applied	We understand your comment to refer to patients with atypical presentations for ACS (e.g. without chest pain). While we accept that some patients with ACS may have such atypical presentations, the remit and scope of this guideline covers adults with recent onset chest pain/discomfort of suspected cardiac origin. Nonetheless, we recognise that we have a gap in our guideline portfolio for this population. We will therefore pass this information to our Topic Selection Steering Group to consider the best approach for developing guidance for this population. On a separate point also related to the title, a topic expert in this surveillance review commented that the current title of the guideline is not specific enough in terms of the population covered. We plan to amend the title of the guideline so that the content is more clearly reflected. A potential revision of the guideline title is 'Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis.' B) Early rule out of ACS/MI in the ED You comment that the wording for the strength of recommendation 1.2.5.3 should be changed from 'consider' to 'recommend' reflecting the evidence now available to support this. The guideline update (page 137) describes the discussions of the committee in the generation of this recommendation. The committee commented that they expected the consequence from wrongful discharge of a low risk patient who has an ACS is lower than in other risk groups and that the high proportion of people presenting to emergency departments who represent this low prevalence group who could be discharged home after a single blood test would result in a considerably decreased demand on services and reduced costs. Patients would also be advised to return

		to "people at low risk of MI (as indicated by a validated tool)". (1) Roffi European Heart Journal 2015 - ESC Guidance2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, see Figure 3 … recommends considering an admission / 1 hour protocol (including some patients with hsTroponin < LOD ruled out at admission) as an alternative to a 3 hour protocol. (2) Keller et al JAMA , 2011; 306 (24): 2684-2693 …high NPV of admission rule out with ARCHITECT hsTroponin <LOD. (3) Gimenez et al Int J Cardiol 2013; 168: 3896-3901… ARCHITECT hsTroponin I <1.9 ng/L a safe rule out strategy. "Undetectable levels of hs-cTn at presentation have a very high NPV and seem to allow the simple and rapid rule out of AMI." (4) Gimenez et al The American Journal of Medicine (2015) 128, 861-870 … "Using a simple algorithm incorporating baseline hs-cTnI values and the absolute change within the first hour allows safe rule-out as well as accurate rule-in of acute myocardial infarction in 70% of patients presenting with suspected acute myocardial infarction." (5) Shah et al Lancet 2015 … "Low plasma troponin concentrations identify two-thirds of patients at very low risk of cardiac events who could be discharged from hospital. Implementation of this approach could substantially reduce hospital admissions and have major benefits for both patients and health-care providers." The	to the emergency department if their chest pain recurred. Therefore, the committee decided to include this recommendation. You cite several studies in your comment to support your view, which we have carefully considered. 1) Roffi *et al*., 2015: • This work was published prior to the start date for the acute chest pain searches in this surveillance review (10th May 2016) and therefore is not eligible for consideration in this surveillance review. • This work would have not been eligible for inclusion in the surveillance summary of evidence based on study design. • This guideline was published prior to the 2016 update of CG95 and would have been available for consideration in guideline development. 2) Keller *et al*., 2011 and 3) Giminez *et al*., 2013: • These studies were published prior to the start date for the acute chest pain searches in this surveillance review (10th May 2016) and therefore are not eligible for consideration in this surveillance review. • These studies were published prior to the 2016 update of CG95 and would have been available for consideration in development. • These studies would also have been available for consideration in the development of the diagnostics guidance (DG15) on early rule out of acute myocardial infarction using high-sensitivity troponin tests. 4) Giminez *et al*., 2015 and 5) Shah *et al*., 2015:

		approach described was focused on use of a 5ng/L cutoff to rule out, however the data presented remains supportive of the LoD approach. (6) Carlton et al JAMA Cardiol. 2016;1(4):405-412. States…. "High-sensitivity troponin I [Abbott ARCHITECT] concentrations determined at presentation to the ED that were below the limit of detection identified 18.8% of patients potentially suitable for discharge, with a high sensitivity for acute myocardial infarction. (7) Body and Reynauld Clinical Chemistry 63:1 21–23 (2017) states… " In summary, there is now a large and convincing body of evidence to support the assertion that low hs-cTn cutoffs can be used to rule out AMI with a single blood test." The approach described was focused on use of a low cutoff to rule out, however the data presented remains supportive of the LoD approach in general. (8) Chapman et al Circulation. 2017;135:1586–1596. states… "Use of the High-STEACS pathway incorporating low high sensitivity cardiac troponin concentrations rules out myocardial infarction in more patients at presentation and misses 5-fold fewer index myocardial infarctions than guideline-approved pathways based exclusively on the 99th centile." The approach described was focused on use of a low cutoff to rule out, however the data presented remains supportive of the LoD approach in general. (9) The ESC Guideline the "Fourth universal definition of myocardial infarction (2018) Thygesen et al European Heart Journal (2019) 40, 237–269" states "Strategies employing either very low levels of hs-cTn on presentation or the lack of any change and persistently	• These studies were published in 2015, prior to the start date for the acute chest pain searches in this surveillance review (10th May 2016), and therefore are not eligible for consideration in this surveillance review. • These studies were published prior to the 2016 update of CG95 and would have been available for consideration in guideline development. • These studies were published after the publication in October 2014 of the diagnostics guidance (DG15) on early rule out of acute myocardial infarction using high-sensitivity troponin tests. As the recommendations in the diagnostics guidance on the use of high-sensitivity troponins (DG15) cover the use of early rule out protocols and the values that laboratories should report, these studies will be forwarded for consideration in the development of the update of the diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15). Any potential impact of the DG15 update on CG95 recommendation 1.2.5.3 will be considered at the next surveillance of this guideline. 6) Carlton *et al.*, 2016: • This study was identified in the focused searches for cross-sectional and cohort studies on diagnostic accuracy of high-sensitivity troponins performed in this surveillance review. However, as this study was a pooled analysis, this was not included in the summary of evidence. • This study was published after the publication in October 2014 of the diagnostics guidance (DG15) on early rule out of

		normal hs-cTn values over a 1 – 2 h period after presentation have been advocated to exclude acute myocardial injury, and MI as well. A single sample rule out strategy using a very low value (in many cases the LoD of the assay) has high sensitivity for myocardial injury and therefore high negative predictive value to exclude MI." (10) Note that the NICE AAC and NHS England are considering hsTroponin (Abbott and Roche) as a Rapid Uptake Product to move laboratories that are not using early rule out (they may still be using a 6 hour or longer pathway) to an early rule out strategy (2 or 3 hour pathway or ven admission rule out) with consequent benefits to the ED. A revision of CG95 would help drive this process. (C) Regarding wording of Section 1.2.5.3 "if the first troponin test is below the lower limit of detection (negative)" – the wording here may be interpreted as inferring that only values below the limit of detection are "negative" and thus every value above the limit of detection could be regarded as "positive". If this was not the intent we would strongly suggest rewording this statement. In addition, the terms "negative" and "positive" infer use of a single cut-off, which may not be appropriate for a biomarker that reflects a continuum of disease, with evidence as described that sex-specific cut-offs may have utility. (D) Ensuring equality in Health NICE CG95 currently states in section 1.2.5.7 …. "that 99th percentile thresholds for troponin I and T may differ between sexes. [2010, amended 2016]". Without sex	acute myocardial infarction using high-sensitivity troponin tests. As the recommendations in the diagnostics guidance on the use of high-sensitivity troponins (DG15) cover the use of early rule out protocols and the values that laboratories should report, this study will be forwarded for consideration in the development of the update of the diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15). Any potential impact of the DG15 update on CG95 recommendation 1.2.5.3 will be considered at the next surveillance of this guideline. 7) Body *et al.*, 2017: • This publication was not identified in this surveillance review. However, as this is an editorial it would not have been eligible based on study design (cross-sectional studies, cohort studies and randomised controlled trials were eligible). 8) Chapman *et al.*, 2017: • This study was identified in this surveillance review. Studies were excluded if they included mixed AMI populations/patients with STEMI and the results were not reported separately for the STEMI and NSTEMI/unstable angina populations (in line with details in the CG95 guideline protocol). This abstract was excluded from this surveillance review on this basis. As the recommendations in the diagnostics guidance on the use of high-sensitivity troponins (DG15) cover the use of early rule out protocols and the values that laboratories should report, this study will be forwarded for consideration in the development of the

		specific cut-offs, published studies indicate that many MIs may be "missed" in women. The available literature suggests that women receive less guideline-specified care (invasive management, pharmacotherapy) than men and have a disproportionate mortality. Thus a change to recommendation of the use of sex specific cut-offs for the 99th percentile should be strongly considered. Sex specific male and female 99th percentile cut-offs are recommended by many other guidelines and by most assay manufacturers. (1) Shah BMJ 2015 …. "Although having little effect in men, a high sensitivity troponin assay with sex specific diagnostic thresholds may double the diagnosis of myocardial infarction in women and identify those at high risk of reinfarction and death." (2) The ESC Guideline the "Fourth universal definition of myocardial infarction (2018) Thygesen et al European Heart Journal (2019) 40, 237–269" states "Significantly lower values are observed among women compared with men, and therefore sex specific 99th percentile URLs are recommended for hs-cTn assays." (3) SIGN ACS Guideline 2016 states… "Sex-specific thresholds of cardiac troponin should be used for the diagnosis of myocardial infarction in men and women." (4) Apple et al Clinical Chemistry 63:1; 73–81 (2017) The IFCC Task Force Clinical Applications of Cardiac Bio-Markers states…. "changing from a single to sex-specific 99th percentile, recognizing that this value for women will be less than for men" (5) Wu et al Clin Chem 2018 Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin	update of the diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15). Any potential impact of the DG15 update on CG95 recommendation 1.2.5.3 will be considered at the next surveillance of this guideline. 9) Thygesen *et al*., 2019: • This work was not identified in this surveillance review but would not have been eligible based on study design (as this is an expert consensus document). 10) Thank you for forwarding this feedback. As the recommendations in the diagnostics guidance on the use of high-sensitivity troponins (DG15) cover the use of early rule out protocols and the values that laboratories should report, this comment will be forwarded to developers to inform the update of the diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15). C) Regarding wording of Section 1.2.5.3 You comment on the use of the wording relating to the lower limit of detection in recommendation 1.2.5.3. As the recommendations in the diagnostics guidance on the use of high-sensitivity troponins (DG15) cover the use of early rule out protocols and the values that laboratories should report, this comment will be forwarded to developers to inform the update of the diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15). Any potential impact of the DG15 update on CG95 recommendation 1.2.5.3 will be considered at the next surveillance of this guideline. D) Ensuring equality in health

		in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine states…" 99th percentile sex-specific upper reference limits to define the reference interval" (6) Wu et al al EHJ-ACC 2016 DOI: 10.1177/2048872616661693 …." Nearly one in three patients with acute myocardial infarction had other diagnoses at first medical contact, who less frequently received guideline indicated care and had significantly higher mortality rates. There is substantial potential, greater for NSTEMI than STEMI, to improve outcomes through earlier and more accurate diagnosis of acute myocardial infarction." In this paper women were 50% more likely than men to have an initial diagnosis different from their final diagnosis. See also this discussion: https://www.nhs.uk/news/heart-and-lungs/one-in-three-heart-attack-cases-misdiagnosed/ (7) Alabas et al et al J Am Heart Assoc. 2017;6:e007123. DOI: 10.1161/JAHA.117.007123 states… "We found a survival disadvantage for women with ST segment–elevation myocardial infarction and non–ST segment– elevation myocardial infarction who were followed for 10 years after acute myocardial infarction." "Our novel findings suggest that if treatments for acute myocardial infarction were provided equally between sexes, then differences in deaths between men and women	You comment that CG95 recommendation 1.2.5.7 states that, when interpreting high-sensitivity troponin measures, a range of factors be considered, including that the 99th percentile thresholds may differ between sexes. Your comment also describes the need for the use of sex-specific cut-offs for high-sensitivity troponins. We note that recommendation 1.2 of the diagnostics guidance on the use of high-sensitivity troponins in myocardial infarction (DG15) also states that the 99th percentile thresholds for troponin I and T may differ between sexes. We have carefully considered the publications cited in your comment. 1) Shah *et al.*, 2015: • This study was published prior to the start date for the acute chest pain searches in this surveillance review (10th May 2016) and therefore is not eligible for consideration in this surveillance review. • This study was published after the publication in October 2014 of the diagnostics guidance (DG15). As recommendation 1.2 in DG15 describes the consideration of differences in sex-specific thresholds, this study will be forwarded for consideration in the development of the update of the diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15). Any potential impact of the DG15 update on CG95 recommendation 1.2.5.7 will be considered at the next surveillance of this guideline. 2) Thygesen *et al.*, 2019:

		would be smaller and premature cardiovascular deaths among women would be reduced." (E) Regarding "Section 1.2.6: Making a diagnosis" Please refer to the updated Fourth Universal Definition of Myocardial Infarction (UDMI) rather than the Third UDMI and update this document accordingly "Fourth universal definition of myocardial infarction (2018) Thygesen et al European Heart Journal (2019) 40, 237–269".	• This work was not identified in this surveillance review but would not have been eligible based on study design (as this was an expert consensus document). • This study was published after the publication in October 2014 of the diagnostics guidance (DG15). As recommendation 1.2 in DG15 describes the consideration of differences in sex-specific thresholds, this publication will be forwarded for consideration in the development of the update of the diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15). Any potential impact of the DG15 update on CG95 recommendation 1.2.5.7 will be considered at the next surveillance of this guideline. 3) SIGN ACS guideline 2016. This guideline document was not identified in this surveillance review but would not have been eligible based on study design. 4) Apple *et al.*, 2017. This publication was identified in this surveillance review but (as a mini-review) was excluded based on study design. 5) Wu *et al.*, 2018. This publication was identified in this surveillance review but (as an expert consensus document) was excluded based on study design. 6) Wu *et al.* 2016 and 7) Alabas *et al.*, 2017. These studies were not identified in this surveillance review. However, as these studies do not directly address the clinical review questions in CG95, these studies would not have been eligible for inclusion. E) Regarding "Section 1.2.6: Making a diagnosis"

			We note that the universal definition for myocardial infarction has been updated from the 3rd to a 4th version (Thygesen *et al.* European Heart Journal (2019) 40, 237–269). We queried the potential impact of this change with the topic experts engaged with this surveillance review. Based on their response, we do not consider that this change in definition will have any impact on recommendations in the guideline. We propose to make the following editorial amendment to recommendation 1.2.6.1 to reflect this change: revision of footnote from Thygesen K, Alpert JS, Jaffe AS *et al.* (2012) Third universal definition of myocardial infarction. Circulation 126: 2020–5 to: Thygesen K, Alpert JS, Jaffe AS *et al.* (2019) Fourth universal definition of myocardial infarction. European Heart Journal 40 (3): 237-269 We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Roche Diagnostics	No	We believe that this guideline should be updated to reflect the wider evidence base that is available to support the use of high sensitive Troponin assays as part of rapid algorithms and should include the 7 diagnostic accuracy studies given the benefits they have demonstrated and the impact they would have for patients and the wider NHS system. For example, a reduction in length of stay and associated costs whilst demonstrating high NPVs. Additionally they are two more studies from Mills et all (2011) (2012) that have demonstrated a clinical benefit to the patients with suspected ACS concluding that: In patients with suspected ACS, implementation of a sensitive troponin assay increased the diagnosis of MI and identified	Thank you very much for your detailed comments. We have carefully considered these below. We note that you do not agree with the proposal not to update this guideline. You state that you consider that the guideline should be updated based on the evidence base available on the use of high sensitivity troponins. In this surveillance review we performed focused searches for evidence on diagnostic accuracy and clinical outcomes associated with the use of high-sensitivity troponins. Having summarised this evidence (Appendix A), we concluded that the new evidence

		patients at high risk of recurrent MI and death. Lowering the diagnostic threshold of plasma troponin was associated with major reductions in morbidity and mortality. Full citations of the papers can be found below: Mills NL, Churchhouse AMD, Lee KK, et al. Implementation of a Sensitive Troponin I Assay and Risk of Recurrent Myocardial Infarction and Death in Patients With Suspected Acute Coronary Syndrome. JAMA. 2011;305(12):1210–1216. doi:10.1001/jama.2011.338 Mills NL, Lee KK, McAllister DA, et al. Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. BMJ. 2012;344:e1533. Published 2012 Mar 15. doi:10.1136/bmj.e1533 Also there is a recent study (2019) from Sweden demonstrated that clinical implementation of a 1-hour high-sensitivity cardiac troponin algorithm combined with the HEART score was associated with a reduction in admission rate and health care burden, with very low rates of adverse clinical events supporting our above point of other parameters than mortality should be evaluated. Full citation of the paper can be found below: Lina Ljung et al, A Rule-Out Strategy Based on High-Sensitivity Troponin and HEART Score Reduces Hospital Admissions,Annals of Emergency Medicine, Volume 73, Issue 5,2019,Pages 491-499,ISSN 0196-0644,https://doi.org/10.1016/j.annemergmed.2018.11.039.	identified in our searches was unlikely to change guideline recommendations on high-sensitivity troponins. We have carefully considered the publications cited in your comment. Mills *et al*., 2011 and Mills *et al*., 2012. These studies were published prior to the start date for the acute chest pain searches in this surveillance review (10th May 2016) and therefore are not eligible for consideration in this surveillance review. These studies would have been available for consideration in the development of the 2016 update of this guideline. Ljung *et al*., 2019. This study was identified in the focused search for evidence of the effect of high-sensitivity troponins on clinical outcomes but was excluded based on study design (as only RCTs were eligible for inclusion in the surveillance summary of clinical studies). We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.

British Society for Cardiovascular Magnetic Resonance (BSCMR)	No (disagree).	The current version of CG95 is essentially a cost containment guideline, which raises the following concerns for clinicians and patients: 1) It is rarely correct that one size fits all in medicine. In an era of precision medicine, UK practice should focus on the right test, for the right patient at the right time. There is no evidence that CTCA is the best first line investigation in stable chest pain in those patients at high risk (high pre-test probability) of CAD. Indeed there is plenty of evidence to the contrary (e.g. Meijboom, J Am Coll Cardiol 2007;50:1469–75; data from COME-CCT consortium, BMJ 15th June 2019). CTCA has excellent sensitivity for CAD, however, when disease is present its low specificity can lead to repeat downstream tests. This is most likely in the higher risk populations. 2) In the 2016 CG95 update, only the initial index tests costs were included. This fails to consider all of the additional downstream non-invasive and invasive tests and treatment costs. PROMISE showed increased rates of invasive angiography and revascularization with CTCA as a first-line test, with no improvement in clinical outcomes, ie more testing, more procedures, and no benefit in terms of patient outcomes. 3) The 2016 update used inappropriate metrics (i.e. cost per correct diagnosis) to evaluate the cost-effectiveness of non-invasive diagnostic strategies, failing to follow recommended methods for cost-effectiveness evaluation (NICE. Guide to the methods of technology appraisal [Internet]. London; 2013. Available	Thank you for your comments. We note that you disagree with the decision to not update the guideline. We have carefully considered your comments and our responses are numbered according to your headings used. 1) You comment that there is no evidence that CCTA is the best first line test for stable chest pain in patients at high risk of CAD and provide two study citations to support your view. We have considered these two studies for eligibility. The study by Meijboom *et al.* was published in 2007, prior to the surveillance search start date of May 2015, and therefore is not eligible for this surveillance review. COME-CCT (Haase *et al.*, 2019, BMJ 365: l1945) is a meta-analysis of individual patient data from prospective diagnostic accuracy studies. This study was not within the topic of our focused searches and therefore was not identified in this surveillance review. This study would have been considered eligible for consideration in the guideline and so has been added to the surveillance summary of evidence (Appendix A) with no impact expected on existing recommendations. It is noted that some of the diagnostic accuracy studies included in this work may also have been included in the guideline update. This study showed good diagnostic performance for CCTA and concluded that CCTA had greatest accuracy for CAD when the clinical pre-test probability was between 7% and 67%. However, this work does not allow any comparison between CCTA and alternative first line imaging options and so would not provide direct evidence of whether an alternative imaging test would be superior to CCTA. You state that low specificity of CCTA may result in repeat downstream tests, particularly in higher risk populations. We note that the clinical review for the 2016 update did not identify large differences in specificity between CCTA and other non-invasive

		from:http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf). 4) The 2016 update used a mixture of NHS costs and NHS tariff, introducing bias into the analysis. 5) In the scenario analysis of the cost effectiveness of CTCA (CG95 2016), it was suggested that CTCA would need to be approximately three times more expensive for it to be no longer cost effective compared to functional imaging. In fact this scenario has now happened in the NHS; CTCA tariffs increased from £100 to £290 and functional imaging tariffs have reduced. Thus the difference in price between modalities is now small, and when this is considered with the additional downstream costs from CTCA, it is likely that CTCA no may longer be cost effective based on QALYs and willingness to pay. 6) The 2010 version of CG95 used an outdated pre-test probability model. More contemporary models are more accurate and so much more useful in clinical practice. 7) There are a range of recent comparative effectiveness trials that should be considered as part of the new clinical evidence guidelines. These include PROMISE (NEJM 2015), SCOTHEART (2018), CE-MARC 2 (JAMA 2016) and MR-INFORM (NEJM 2019). The pathway should be considered in the new clinical guidelines and the focus should not just be on the cheapest index cost. To our knowledge, the evidence from the CE-MARC 2 trial has not been taken into account. This large, multicentre trial was exclusively undertaken in the UK, and would seem to be highly relevant.	tests. Specificity was accounted for in the cost-effectiveness analysis and played a role in the CG95 committee's decision-making. The economic model for the 2016 update included a number of strategies, many of which involved sequential testing. The costs of downstream tests for people who were falsely classified positive on their first diagnostic test were included. In several of these strategies the downstream test was ICA, which is costly, but differences in specificity between the non-invasive tests were relatively small. The 2016 economic model conducted subgroup analysis on patients with various levels of pre-test likelihood, which did not materially alter the conclusions. 2) You refer to the PROMISE study in your comment. The PROMISE study (Douglas *et al*., 2015) was included in the 2016 guideline update and so has been considered. A publication linked to the PROMISE study had also been included in the surveillance summary of evidence. The costs of subsequent tests were included in the economic model for the CG95 update. The cost per case identified for each testing strategy/pathway is inclusive of these costs. 3) There were insufficient data to construct a robust cost utility analysis during guideline development. Several options for modelling the downstream consequences of false positive and negative diagnoses were discussed with the committee but, because of the number of differential diagnoses and the need to make a large number of assumptions, the committee did not think any of the approaches would improve certainty over the simple decision tree. 4) The choice of using the enhanced tariff rather than the reference cost for CMR was a deliberate one made by the committee because they thought it more representative of clinical practice.

		8) Has NICE taken account of the quality of life and symptoms analysis from SCOT-HEART (Heart. 2017 Jul;103(13):995-1001)? Angina and quality of life were worse in the CTCA group, vs. standard care. The NICE-CG 95 in favour of anatomical imaging with CTCVA advocates a strategy that is associated with relative impairment in angina and quality of life, which in this regard, is counterintuitive to the needs of patients and carers.	5) The latest version of the tariff lists the unit cost for CTCA as £285, which is a fairly big increase compared with the £122 used in CG95. The CMR cost has also risen by a small amount and is now listed as £564 compared with £515. Although the cost of ECHO has reduced from £271 to £195 and the cost of SPECT from £367 to £277 respectively, we think the poorer performance of these tests (their comparable specificity and much lower sensitivity) compared with CTCA means that updating the model with new prices would not qualitatively alter its conclusions. 6) While it may be that more contemporary models are now available, it is not altogether clear how this would change the results, given that they were not sensitive to the various levels of pre-test probability and stenosis that were used in subgroup analysis. 7) We have considered the studies cited in your comment. The PROMISE study (Douglas *et al.*, 2015, NEJM 372 (14): 1291-1300) was included in the 2016 guideline update. The 2015 SCOT-HEART Lancet publication was included in the guideline update. The subsequent SCOT-HEART 2018 publication has already been identified and considered in this surveillance review. The large (n=1202), UK-based CE-MARC 2 study (Greenwood *et al.*, 2016 JAMA 13; 316 (10): 1051-1060) was not included in the 2016 guideline update. This study was not within the topic of our focused searches and so was not identified in this surveillance review. This RCT compared cardiac magnetic resonance (CMR)-guided care with NICE guideline-directed care and is relevant to the clinical review question on non-invasive imaging for stable chest pain. This study

			has been added to the surveillance summary of evidence (Appendix A). The MR-INFORM study (Nagel *et al.*, 2019 NEJM 380: 2418-2428) (n=918) was published in June 2019 so would not have been identified in the surveillance review searches performed in May 2019. This RCT compared MR perfusion imaging-guided management with management guided by invasive coronary angiography with measurement of fractional flow reserve in patients with suspected CAD. This study is relevant to the clinical review question on non-invasive imaging for stable chest pain and has been added to the surveillance summary of evidence (Appendix A). Since these RCTs vary in terms of interventions and comparators and neither evaluate the imaging method of interest directly against the first line test of CCTA, it is considered that further evidence would be required to have potential impact on the recommendation to use CCTA as a first line diagnostic imaging test in people with stable chest pain (recommendation 1.3.4.3). You comment that the focus should not just be on cheapest index cost. We note that the focus in the guideline was on cost per correct diagnosis. Strategies involving CCTA performed well in the analysis not only because it is inexpensive but because it is the most sensitive non-invasive test. 8) You query whether the SCOT-HEART study has been included. This study (Williams *et al.*, 2017) has already been included and summarised in this surveillance review, where we note that, in patients randomised to standard care alone or standard care plus CCTA, CCTA resulted in less marked improvements in symptoms

			and quality of life, which were attributed to the detection of moderate non-obstructive coronary artery disease. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
HeartFlow	No	HeartFlow appreciates the time and effort that NICE invested in developing the surveillance proposal consultation document. We believe the Surveillance Team has done an exceptional job evaluating the literature, clinical environment and obtaining expert feedback. Our comments focus on two sections: • 1.3.4 Diagnostic testing for people in whom stable angina cannot be excluded by clinical assessment alone. • 1.3.5 Additional diagnostic investigations Section 1.3.4 (Diagnostic testing for people in whom stable angina cannot be excluded by clinical assessment alone) recommends offering CT coronary angiography in patients with stable chest pain where there are concerns the pain could be ischaemic. The 2019 surveillance summary concluded that new evidence is unlikely to change guideline recommendations citing four reports from the SCOT-HEART study. HeartFlow agrees that the new evidence supports the current guideline and is unlikely to change the guideline recommendations. The SCOT-HEART study provides the most robust evidence on diagnosing and managing patients with stable chest pain. We would like to bring to your attention several other studies that were	Thank you for your feedback and detailed comments, which we have carefully considered based on your headings used. We note that you do not agree with the decision to not update the guideline. We acknowledge that HeartFlow is covered by NICE guidance on HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography (MTG32, published February 2017). It is proposed that MTG32 be reviewed in February 2020 to check whether the MTG32 guidance is up to date. The NICE guidance on HeartFlow (MTG32) is included in the NICE Pathway on chest pain. 1.3.4 Diagnostic testing for people in whom stable angina cannot be excluded by clinical assessment alone We note that you agree the that new evidence on CCTA from the SCOT-HEART study identified in this surveillance supports the current guideline and is not likely to change guideline recommendations. Thank you for providing details of additional publications published since the 2016 guideline update that you state further support the recommended use of CCTA. We have considered this below. Hoffman *et al.*, 2017. This study was not identified in this surveillance review (as it was not within the topic of our focused

		published since the 2016 guideline update that further support this recommendation. • Hoffmann, U., et al. (2017) Prognostic value of Noninvasive Cardiovascular Testing in Patients with Stable Chest Pain: Insights from the PROMISE Trial. Circulation 2017. • Chang, H.J., et al. (2018) Selective Referral Using CCTA Versus Direct Referral for Individuals Referred to Invasive Coronary Angiography for Suspected CAD. J Am Coll Cardiol Cardiovascular Imaging 2018. • Stocker, T.J., et al. (2018) Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the Prospective Multicenter Registry on RadiaTion Dose Estimates of Cardiac CT AngIOgraphy IN Daily Practice in 2-17 (PROTECTION VI). European Heart Journal 2018. • Sharma, A., et al. (2019) Stress Testing Versus CT Angiography in Patients with Diabetes and Suspected Coronary Artery Disease. J Am Coll Cardiol 2019. Section 1.3.5 (Additional diagnostic investigations) recommend offering non-invasive functional imaging if the CT coronary angiography has shown CAD of uncertain functional significance. A topic expert suggested FFRCT as a priority area for consideration. The focused search centered on diagnostic accuracy and identified 4 eligible studies. Additionally, a topic expert suggested the PLATFORM study to demonstrate clinical utility. The FORECAST study was also flagged as a UK based ongoing	searches). This study is relevant to the clinical review question on accuracy, clinical utility and cost-effectiveness of non-invasive diagnostic tests in stable chest pain of suspected cardiac origin. This study has been added to the surveillance summary of evidence (Appendix A). Findings are supportive of the use of CCTA in recommendation 1.3.4.3 and therefore have no expected impact on recommendations in the guideline. Chang *et al.*, 2018. This study was not identified in this surveillance review (as it was not within the topic of our focused searches). This study has been added to the surveillance summary of evidence (Appendix A). Findings are supportive of the use of CCTA in recommendation 1.3.4.3 and therefore have no expected impact on recommendations in the guideline. Stocker *et al.*, 2018. This study was not identified in this surveillance review (as it was not within the topic of our focused searches). While this study provided evidence on reductions in radiation exposure from CCTA, it did not report eligible outcome data and so has not been added to the surveillance summary of evidence. Sharma *et al.*, 2019. This study was not included in this surveillance review (as it was not within the topic of our focused searches). This study is relevant to the clinical review question on accuracy, clinical utility and cost-effectiveness of non-invasive diagnostic tests in stable chest pain of suspected cardiac origin. This study has been added to the summary of evidence (Appendix A). Findings are supportive of the use of CCTA in recommendation 1.3.4.3 and therefore have no expected impact on recommendations in the guideline. 1.3.5 Additional diagnostic testing Your comment states that there is significant evidence available on the use of CT-FFR as a non-invasive functional test for patients

		study. The review of this evidence resulted in the conclusion that while the evidence for FFRCT identified in this surveillance is promising, this is based on a relatively small number of studies. Furthermore, section 1.3.5 indicated the new evidence is unlikely to change guideline recommendations. HeartFlow believes that significant evidence exists demonstrating the value of FFRCT to address the unmet need by providing a non-invasive functional test for patients whose CT coronary angiography has shown CAD of uncertain functional significance. Additionally, the Medical Technologies Guidance (MTG32) states the following in recommendations: • "The case for adopting HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography (CCTA) is supported by the evidence." • "FFRCT should be considered as an option for patients with stable, recent onset chest pain who are offered CCTA as part of the NICE pathway on chest pain." In addition to 4 diagnostic accuracy studies outlined in Table 2, we would like to bring to your attention three additional studies demonstrating the accuracy of FFRCT: • Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) study – prospective accuracy study of 254 patients in 10 centers around the world. CCTA was performed prior to non-emergent ICA in stable patients with suspected CAD. FFRCT had a per-	where CCTA has shown CAD of uncertain functional significance, citing statements from the NICE guidance on HeartFlow (MTG32). As CT-FFR is covered by another NICE product, we propose to include a cross-referral from this guideline (CG95) to link to the NICE guidance on HeartFlow (MTG32). Thank you for providing details of the 3 additional studies on the accuracy of CT-FFR. We have considered these below. Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) study: Norgaard *et al.*, 2014. This study was published prior to the start date for the stable chest pain searches in this surveillance review (21st May 2016) and therefore is not eligible for consideration in this surveillance review. This study would also have been available for consideration in the development of the NICE guidance on HeartFlow (MTG32). PACIFIC FFRCT substudy: Driessen *et al.*, 2019. This study was not identified in our surveillance review. This study provides evidence of the diagnostic accuracy of CT-FFR. Diagnostic accuracy evidence was incorporated into the NICE guidance on HeartFlow (MTG32). This study will be forwarded to the developers of the NICE guidance on HeartFlow (MTG32) for consideration in their next review of this guidance in 2020. FFRCT vs CT stress myocardial perfusion imaging (CTP): Ko *et al.*, 2019. This study was not identified in our surveillance review, as it was published after our searches had been conducted. This study provides evidence of the diagnostic accuracy of CT-FFR. This study will be forwarded to the developers of the NICE guidance on HeartFlow (MTG32) for consideration in their next review of this guidance in 2020.

		patient accuracy of 81% compared with 53% for CCTA, and 77% for ICA and a per-vessel accuracy of 86% compared with 65% for CCTA, and 82% for ICA. Norgaard, B.L., et al. (2014) Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol, 2014. • PACIFIC FFRCT substudy - Using invasive FFR as the reference standard, FFRCT demonstrated the highest diagnostic performance with an AUC value of 0.94 compared with CCTA (0.83), SPECT (0.70), and PET (0.87) (all p-values < 0.001). The investigators concluded that FFRCT "showed the highest diagnostic performance for vessel-specific ischemia" and that these findings "support the use of FFRCT in clinical practice for diagnosing ischemia and revascularization decision making." Driessen, R.S. et al. (2018) Comparison of coronary computed tomography angiography, fractional flow reserve and perfusion imaging for ischemia diagnosis. J Am Coll Cardiol 2019. • FFRCT vs CT stress myocardial perfusion imaging (CTP) – Using invasive FFR as the reference standard in 51 patients, FFRCT is superior to visually and semi-	You suggest that the ADVANCE registry study should also be considered (Patel *et al*., 2019). This study was not identified in our surveillance review. This study provides evidence of the impact of CT-FFR on care and clinical outcomes. Clinical effectiveness evidence was incorporated into the NICE guidance on HeartFlow (MTG32). This study will be forwarded to the developers of the NICE guidance on HeartFlow (MTG32) for consideration in their next review of this guidance in 2020. Your comment also describes long-term evidence for the use of CT-FFR, citing additional publications, which we have considered carefully. PLATFORM. This study is already included in the surveillance summary of evidence. ADVANCE. This study has been considered as described above and will be forwarded to the developers of the NICE guidance on HeartFlow (MTG32) for consideration in their next review of this guidance. Norgaard *et al*., 2018. This study was identified in our surveillance review but was not included in the summary of evidence as it did not report eligible diagnostic outcome data. This study will be forwarded to the developers of the NICE guidance on HeartFlow (MTG32) for consideration in their next review of this guidance. McNabney *et al*., 2019 and Ihdayhid *et al*., 2019. These studies were not identified in our surveillance review. These studies provide evidence of the impact of CT-FFR on care and clinical outcomes. Clinical effectiveness evidence was incorporated into the NICE guidance on HeartFlow (MTG32). These studies will be forwarded to

		quantitatively assessed static res/stress CTP in detecting haemodynamically-significant coronary stenosis. Ko, B.S., et al. (2019) Non-invasive CT-derived fractional flow reserve and static rest and stress CT myocardial perfusion imaging for detection of haemodynamically significant coronary stenosis. The International Journal of Cardiovascular Imaging, 2019. We agree that the PLATFORM study should be included in the evidence supporting the clinical utility of FFRCT. We also suggest that the ADVANCE study, a large multicenter real-world study, be included in this review. • ADVANCE study –5083 patients from 38 sites around the world. Patients with a positive FFRCT (FFRCT ≤ 0.80) have a significantly higher risk to experience MI or cardiovascular-related death than patients with a negative FFRCT (FFRCT > 0.80, p = 0.01) regardless of age. Most patients for whom medical therapy was the recommended treatment strategy at enrollment (n = 2679) continued only on medical therapy at 1-year (n = 2490, 92.9%) demonstrating that deferral of ICA is unlikely to result in a later return for revascularization. Patel, M.R., et al. (2019) 1-Year Impact on Medical Practice and Clinical Outcomes of FFRCT: The ADVANCE Registry. J Am Coll Cardiol Cardiovasc Imaging, 2019	the developers of the NICE guidance on HeartFlow (MTG32) for consideration in their next review of this guidance. We note your comment that evidence is available to support the use of FFRCT and your view that it should be included in this guideline for patients whose CT coronary angiography has shown CAD of uncertain functional significance. We have carefully considered this evidence and confirm that (while the guideline will not be updated in this area) that the evidence will be forwarded to the developers of the NICE guidance on HeartFlow for consideration in their next review of this guidance. We note that the NICE guidance on HeartFlow (MTG32) is included in the NICE Pathway on chest pain. We also propose to amend this guideline to include a cross-referral to link to the NICE guidance on HeartFlow (MTG32). We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.

		Lastly, long term (1 – 5 years) outcomes have been studied and reported in over 6,500 patients indicating the safety of patient management strategies that incorporate the FFRCT Analysis. Patients in these publications had low event rates, similar to those of other contemporaneous trials with similar patient populations. The data demonstrates that clinicians can safely and confidently choose medical therapy, deferring ICA, for patients with a negative FFRCT Analysis (FFRCT > 0.80). These patients have a favorable long-term prognosis with low rates of MACE. In addition, the decision to defer ICA is durable with few patients returning for later revascularization. Conversely, patients with a positive FFRCT Analysis (FFRCT ≤ 0.80) have a significantly higher risk of experiencing MI or cardiovascular-related death, and the lower the FFRCT, the higher this risk. Clinicians are more likely to refer these patients for ICA and potential revascularization. Most patients with a positive FFRCT who are sent to the cath lab undergo revascularization, indicating that physicians are able to effectively triage patients who need invasive assessment. The following publications demonstrate the long-term outcomes of FFRCT: • PLATFORM 1-year (referenced in the Surveillance proposal consultation document) • ADVANCE 1-year (referenced above)	

		• Norgaard, B.L., et al. (2018) Clinical Outcomes Using Coronary CT Angiography and FFRCT-Guided Management of Stable Chest Pain Patients. J Am Coll Cardiol, 2018. • McNabney, C.G., et al. (2019) Prognosis of CT-derived Fractional Flow Reserve in the Prediction of Clinical Outcomes. Radiology: Cardiothoracic Imaging, 2019. • Ihdayhid, A.R., et al. (2019) Prognostic Value and Risk Continuum of Noninvasive Fractional Flow Reserve Derived from Coronary CT Angiography. Radiology, 2019. Based on the additional studies above and NICE's MTG32, HeartFlow believes that there is significant evidence supporting the accuracy and value of FFRCT and that it should be included in the guidelines for patients whose CT coronary angiography has shown CAD of uncertain functional significance. We also wish to request that MTG32 is cross-referenced in the guidelines.	
Royal College of Physicians (RCP)	Yes	We have no objection to the plan not to update.	Thank you very much for your comments. We note that you agree with the proposal not to update the guideline. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Sanofi Genzyme	No	Relevant HCPs in the ACS clinical area have indicated to Sanofi there is a place for lipid diagnosis and management in the local hospital chest pain protocols in terms of modifiable risk factors.	Thank you very much for your comments. We note that you disagree with the proposal not to update the guideline. While CG95 recommendations refer in places to the consideration of cardiovascular risk factors in the diagnostic pathway, no

		In addition, cardiologists have also suggested there is a place for modification of risk factors within the cardiovascular disease prevention guidelines. Therefore, Sanofi would be disappointed that if the CG95 is not updated and that an opportunity will be lost to identify modifiable lipid related risk factors, such has high LDL-c. Or Non-HDL-c. Admission for chest pain is a critical touch point at which this specific risk could be identified and addressed. With cardiovascular disease prevention and management central to the NHS long term plan, Sanofi recommend that CG95 should be updated.	recommendations specifically refer to lipid diagnosis or management. Management and symptom control once the cause of chest pain/discomfort is known is outside the scope of this guideline. The NICE guideline on cardiovascular disease (CG181) (which CG95 cross-refers to) includes a set of recommendations on lipid modification therapy for the primary prevention of CVD. We also note that recommendations 1.2.6.9 and 1.3.3.9 recommend that health care professionals follow related guidance for people with risk factors for cardiovascular disease: • '1.2.6.9 If an ACS has been excluded at any point in the care pathway, but people have risk factors for cardiovascular disease, follow the appropriate guidance, for example, the NICE guidelines on cardiovascular disease and hypertension in adults. [2010] • 1.3.3.9 If a diagnosis of stable angina has been excluded at any point in the care pathway, but people have risk factors for cardiovascular disease, follow the appropriate guidance, for example, the NICE guideline on cardiovascular disease and the NICE guideline on hypertension in adults. [2010]' We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
The British Cardiovascular Society	Yes	The British Cardiovascular Society notes NICE view on this and has no objection	Thank you very much for your comments. We note that you agree with the proposal not to update the guideline. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.

2. Do you have any comments on areas excluded from the scope of the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Royal College of Nursing	No	Agree with the reasons provided to exclude some elements from the guidelines as stated.	Thank you very much for your response. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Aortic Dissection Awareness UK&I		The Scope of the Guideline has to date excluded the most lethal cause of Chest Pain of Recent Onset - Aortic Dissection. We do not understand how professional clinical guidance on Chest Pain of Recent Onset can make such a serious omission. We disagree with the exclusion of AD from the Scope.	Thank you very much for your detailed response. We note that you do not agree with the proposal not to update this guideline. We note your view that the diagnostic pathway for aortic dissection and myocardial infarction should be integrated until one or other condition is ruled out. As detailed in the summary of evidence (Appendix A) several recommendations in this guideline flag various points at which health care professionals should consider the possibility that a person presenting with recent onset chest pain of suspected cardiac origin may have aortic dissection. We have considered this point in detail, but we do not think that further guidance on diagnosis of aortic dissection would be appropriate within the NICE guideline on chest pain, based on the majority view from experts we engaged with in this surveillance review. Therefore, this guideline will not be updated in that area. However, we have carefully reviewed your response, including the content of your cited awareness conference video and Think Aorta campaign information and agree this is an important clinical issue. We will explore this issue further through our topic selection process with a view to considering whether NICE should develop a new guideline on diagnosis of aortic dissection.

			We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Resuscitation Council (UK)	No	No comments provided	Thank you very much for your response. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
The Royal College of Radiologists	Not answered	No comments provided	Not applicable
Abbott Diagnostics Division, Abbott Laboratories		Some modifications to the title of this guidance and importantly the document should referenced to the 4th UDMI not the 3rd UDMI. (E) Regarding "Section 1.2.6: Making a diagnosis" Please refer to the updated Fourth Universal Definition of Myocardial Infarction (UDMI) rather than the Third UDMI and update this document accordingly "Fourth universal definition of myocardial infarction (2018) Thygesen et al European Heart Journal (2019) 40, 237–269". (A) Regarding the title and scope of the Document. Could using the term "Chest pain" alone (rather than symptoms suspicious for ACS/symptoms of suspected cardiac origin of recent onset or similar) be viewed as discriminating against those who are more likely to have atypical presentations for ACS, e.g. women, the elderly? See Section 1.2.1.3: "Initially assess people for any of the following symptoms, which may indicate an ACS: • Pain in the chest and/or other areas (for example, the arms, back or jaw) lasting longer	Comments relating to the title of the guidance and the current 4th version of the universal definition for myocardial infarction are addressed below (based on your headings used). E) We note that the universal definition for myocardial infarction has been updated from the 3rd to a 4th version (Thygesen *et al.* European Heart Journal (2019) 40, 237–269). We queried the potential impact of this change with the topic experts engaged with this surveillance review. Based on their response, we do not consider that this change in definition will have any impact on recommendations in the guideline. We propose to make the following editorial amendment to recommendation 1.2.6.1 to reflect this change: revision of footnote from Thygesen K, Alpert JS, Jaffe AS *et al.* (2012) Third universal definition of myocardial infarction. Circulation 126: 2020–5 to: Thygesen K, Alpert JS, Jaffe AS *et al.* (2019) Fourth universal definition of myocardial infarction. European Heart Journal 40 (3): 237-269. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.

		than 15 minutes • Chest pain associated with nausea and vomiting, marked sweating, breathlessness, or particularly a combination of these • Chest pain associated with haemodynamic instability new onset chest pain, or abrupt deterioration in previously stable angina, with • Recurrent chest pain occurring frequently and with little or no exertion, and with episodes often lasting longer than 15minutes. [2010]"	A) Regarding the title and scope of the document You note that the term 'chest pain' alone is used in the guideline title (rather than symptoms suspicious for ACS/symptoms of suspected cardiac origin of recent onset or similar) and that this could potentially discriminate against people more likely to have atypical presentations for ACS. We understand your comment to refer to patients with atypical presentations for ACS (e.g. without chest pain). While we accept that some patients with ACS may have such atypical presentations, the remit and scope of this guideline covers adults with recent onset chest pain/discomfort of suspected cardiac origin. Nonetheless, we recognise that we have a gap in our guideline portfolio for this population. We will therefore pass this information to our Topic Selection Steering Group to consider the best approach for developing guidance for this population. On a separate point also related to the title, a topic expert in this surveillance review commented that the current title of the guideline is not specific enough in terms of the population covered. We plan to amend the title of the guideline so that the content is more clearly reflected. A potential revision of the guideline title is 'Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis.'
Roche Diagnostics		The decision to not update should be based on a wider response than what was received. There was a limited response by the Clinicians consulted and would appear to have been influenced by primarily only 1 topic expert. It is	Thank you very much for your response. Topic experts were consulted in line with our guideline surveillance processes. We sent questionnaires to 12 topic experts and received 6 responses. Responding topic experts included consultant nurses, a

		not clear whether the others that did respond were experts in the use of high sensitive Troponin assay. The consultation focused on the outcomes of the HighSTEACS trial primarily that there was no difference in the primary and secondary outcomes at 1 year in patients reclassified with the hs-cTnI assay being observed. The limitations of this study need to be considered and the impact they may have had on the outcome of the trial. For example, the hospitals involved in the trials were not given guidance on accelerated algorithms and instead used 6 and 12 hours to diagnose. This study does not reflect the recommendations in NICE DG15 for the assay used in this trial with NICE DG15 stating that samples should typically be taken on admission and at 3 hours. Furthermore, the use of sex specific cut-offs lead to an increase in women being reclassified with no final diagnosis of MI and therefore showed no benefit in clinical practice. The trial did demonstrate a benefit in reduction in length of stay but as an outcome this is excluded. CG95 refers to the 3rd Universal definition of MI whereas there is now a 4th version available. Further consideration should be given to the guideline update to reflect any impact of this change The review is incorrect and the ESC (Figure 3, Page 276, ESC 2015 Guidelines) do recommend specific test to diagnose chest pain in both the rule out and rule in arms of the 1 hour algorithm recommended. There are x2 commercially available Troponin-hs test recommended the Roche Elecsys Troponin T-hs and the Abbott ARCHITECT Troponin I high sensitive. Full citation of the ESC 2015	general practitioner, and consultants in cardiology and cardiothoracic radiology. Topic expert feedback (which included a citation to a single study) was followed up by focused searches by the surveillance team for diagnostic and clinical evidence on the use of high-sensitivity troponins in people with acute chest pain. Therefore, the proposal not to update the guideline in this area has been informed by consideration of topic expert feedback, identified research evidence and consultation comments received from stakeholders. You correctly note that the HighSTEACS trial was included in the summary of evidence as part of our consultation. However, this study was one of several that were identified in our surveillance focused searches and included in the summary of evidence relating to high-sensitivity troponins. As noted in the consultation document, studies identified in searches are summarised from the information presented in their abstracts and, therefore available details on study limitations and other aspects of study design, methods and results may be limited. We note that the universal definition for myocardial infarction has been updated from the 3rd to a 4th version (Thygesen *et al.* European Heart Journal (2019) 40, 237–269). We queried the potential impact of this change with the topic experts engaged with this surveillance review. Based on their response, we do not consider that this change in definition will have any impact on recommendations in the guideline. We propose to make the following editorial amendment to recommendation 1.2.6.1 to reflect this change: revision of footnote from Thygesen K, Alpert JS, Jaffe AS *et al.* (2012) Third universal definition of myocardial infarction. Circulation 126: 2020–5 to: Thygesen K, Alpert JS, Jaffe AS *et al.* (2019) Fourth universal

		guideline can be found below: Marco Roffi et al, ESC Scientific Document Group, 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC), European Heart Journal, Volume 37, Issue 3, 14 January 2016, Pages 267–315, https://doi.org/10.1093/eurheartj/ehv320	definition of myocardial infarction. European Heart Journal 40 (3): 237-269 Thank you very much for providing clarification that the ESC 2015 guideline (Roffi *et al.*, 2015) does recommend specific tests for chest pain (as in Figure 3). This guideline publication would not have been eligible for inclusion in the surveillance summary of evidence based on study design. The use of specific high-sensitivity troponin tests is covered in detail by the NICE guidance on myocardial infarction (acute): early rule out using high-sensitivity troponin tests (DG15). We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
British Society for Cardiovascular Magnetic Resonance (BSCMR)	Disagree	Microvascular angina and vasospastic angina – these important conditions cannot be diagnosed by CTCA and may be relevant causes of chest pain in the majority (3 in 4) of patients who attend a Chest Pain Clinic who do not have obstructive coronary disease. Functional tests can diagnose these conditions. The BHF CorMicA trial (J Am Coll Cardiol. 2018 Dec 11;72(23 Pt A):2841-2855) provides relevant evidence.	The CorMicA trial (Ford *et al.*, 2018) was not within the topic of the focused searches and so was not identified in this surveillance review. This study may be considered relevant to the clinical review question on non-invasive imaging for stable chest pain and has been added to the surveillance summary of evidence (Appendix A). This RCT randomised patients (n=151) with symptoms of angina and/or signs of ischaemia but no CAD to either stratified medical therapy or standard care (invasive coronary angiography). However, since this RCT does not evaluate the imaging method of interest directly against the first line test of CCTA, it is considered that further evidence would be required to have potential impact on the recommendation to use CCTA as a first line diagnostic imaging test in people with stable chest pain (recommendation 1.3.4.3). We note that recommendation 1.3.5.1 states that non-invasive functional imaging should be offered if CCTA has shown CAD of uncertain functional significance or is non-diagnostic. Therefore, we would consider that the specific types of angina referred to in your

			comment should be identified by non-invasive functional imaging (as in recommendation 1.3.5.1). We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
HeartFlow	No	No comments provided	Thank you very much for your response. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Royal College of Physicians (RCP)		We note that NICE recognise that the implementation of this is patchy but have not taken this into consideration in what is recommended. We realise that implementation is not the remit of this exercise but is a concern.	Thank you very much for your comments. We will ensure that the information on implementation issues that we have identified in this surveillance review are disseminated via appropriate channels within NICE. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Sanofi Genzyme	No	No comments provided	Thank you very much for your response. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
The British Cardiovascular Society	Not answered	No comments provided	Not applicable

3. Do you have any comments on equalities issues?			
Stakeholder	**Overall response**	**Comments**	**NICE response**

Royal College of Nursing	Yes	From an equalities point of view, it should be noted that where local rural hospitals may not have the facilities of CCTA scanners close at hand the logistics of these tests to be performed in a timely manner may differ	Thank you very much for your comments. The information on implementation issues that we have identified in this surveillance review will be disseminated via appropriate channels within NICE. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Aortic Dissection Awareness UK&I		Excluding AD from the scope of CG95 creates a healthcare inequality for patients affected by Aortic Dissection, who will not be correctly diagnosed when they present with Chest Pain of Recent Onset if the NICE guideline in its current form is followed. The guideline in its present form therefore discriminates against people with AD, compared to those with other causes of Chest Pain of Recent Onset. In particular, there is discrimination against the sub-group of young, female patients in whom 14% of maternal deaths are caused by Aortic Dissection.	Thank you very much for your detailed response. We note that you do not agree with the proposal not to update this guideline. We note your view that the diagnostic pathway for aortic dissection and myocardial infarction should be integrated until one or other condition is ruled out. As detailed in the summary of evidence (Appendix A) several recommendations in this guideline flag various points at which health care professionals should consider the possibility that a person presenting with recent onset chest pain of suspected cardiac origin may have aortic dissection. We have considered this point in detail, but we do not think that further guidance on diagnosis of aortic dissection would be appropriate within the NICE guideline on chest pain, based on the majority view from experts we engaged with in this surveillance review. Therefore, this guideline will not be updated in that area. However, we have carefully reviewed your response, including the content of your cited awareness conference video and Think Aorta campaign information and agree this is an important clinical issue. We will explore this issue further through our topic selection process with a view to considering whether NICE should develop a new guideline on diagnosis of aortic dissection. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.

Resuscitation Council (UK)	No	No comments provided	Thank you very much for your response. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
The Royal College of Radiologists	Not answered	No comments provided	Not applicable
Abbott Diagnostics Division, Abbott Laboratories		There are unaddressed equality issues which are not dealt with in the current version of the guidance which should prompt a revision. Ensuring equality in Health NICE CG95 currently states in section 1.2.5.7 …. "that 99th percentile thresholds for troponin I and T may differ between sexes. [2010, amended 2016]". Without sex specific cut-offs, published studies indicate that many MIs may be "missed" in women. The available literature suggests that women receive less guideline-specified care (invasive management, pharmacotherapy) than men and have a disproportionate mortality. Thus a change to recommendation of the use of sex specific cut-offs for the 99th percentile should be strongly considered. Sex specific male and female 99th percentile cut-offs are recommended by many other guidelines and by most assay manufacturers. (1) Shah BMJ 2015 …. "Although having little effect in men, a high sensitivity troponin assay with sex specific diagnostic thresholds may double the diagnosis of myocardial infarction in women and identify those at high risk of reinfarction and death."	You comment that CG95 recommendation 1.2.5.7 states that, when interpreting high-sensitivity troponin measures, a range of factors be considered, including that the 99th percentile thresholds may differ between sexes. Your comment also describes the need for the use of sex-specific cut-offs for high-sensitivity troponins. We note that recommendation 1.2 of the diagnostics guidance on the use of high-sensitivity troponins in myocardial infarction (DG15) also states that the 99th percentile thresholds for troponin I and T may differ between sexes and believe this addresses your point. We have carefully considered the publications cited in your comment. 1) Shah *et al.*, 2015: • This study was published prior to the start date for the acute chest pain searches in this surveillance review (10th May 2016) and therefore is not eligible for consideration in this surveillance review. • This study was published after the publication in October 2014 of the diagnostics guidance (DG15). As recommendation 1.2 in DG15 describes the consideration of differences in sex-specific thresholds, this study will be forwarded for consideration in the development of the update of the diagnostics guidance on early rule out of acute

		(2) The ESC Guideline the "Fourth universal definition of myocardial infarction (2018) Thygesen et al European Heart Journal (2019) 40, 237–269" states "Significantly lower values are observed among women compared with men, and therefore sex specific 99th percentile URLs are recommended for hs-cTn assays." (3) SIGN ACS Guideline 2016 states… "Sex-specific thresholds of cardiac troponin should be used for the diagnosis of myocardial infarction in men and women." (4) Apple et al Clinical Chemistry 63:1; 73–81 (2017) The IFCC Task Force Clinical Applications of Cardiac Bio-Markers states…. "changing from a single to sex-specific 99th percentile, recognizing that this value for women will be less than for men" (5) Wu et al Clin Chem 2018 Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine states…" 99th percentile sex-specific upper reference limits to define the reference interval" (6) Wu et al al EHJ-ACC 2016 DOI: 10.1177/2048872616661693 …." Nearly one in three patients with acute myocardial infarction had other diagnoses at first medical contact, who less frequently received guideline indicated care and had significantly higher mortality rates. There is substantial potential, greater for NSTEMI than STEMI, to improve outcomes	myocardial infarction using high-sensitivity troponin tests (DG15). Any potential impact of the DG15 update on CG95 recommendation 1.2.5.7 will be considered at the next surveillance of this guideline. 2) Thygesen *et al.*, 2019. This consensus document was not identified in this surveillance review but would not have been eligible based on study design. 3) SIGN ACS guideline 2016. This guideline publication was not identified in this surveillance review but would not have been eligible based on study design. 4) Apple *et al.*, 2017. This publication was identified in this surveillance review but (as a mini-review) was excluded based on study design. 5) Wu *et al.*, 2018. This publication was identified in this surveillance review but (as an expert consensus document) was excluded based on study design. 6) Wu *et al.* 2016 and 7) Alabas *et al.*, 2017. These studies were not identified in this surveillance review. However, as these studies do not directly address the clinical review questions in CG95, these studies would not have been eligible for inclusion. 8) Tan *et al.*, 2017. This publication was identified in this surveillance review but (as a consensus document) was excluded based on study design. You note that the term 'chest pain' alone is used in the guideline title (rather than symptoms suspicious for ACS/symptoms of suspected cardiac origin of recent onset or similar) and that this

		through earlier and more accurate diagnosis of acute myocardial infarction." In this paper women were 50% more likely than men to have an initial diagnosis different from their final diagnosis. See also this discussion: https://www.nhs.uk/news/heart-and-lungs/one-in-three-heart-attack-cases-misdiagnosed/ (7) Alabas et al et al J Am Heart Assoc. 2017;6:e007123. DOI: 10.1161/JAHA.117.007123 states… "We found a survival disadvantage for women with ST segment–elevation myocardial infarction and non–ST segment– elevation myocardial infarction who were followed for 10 years after acute myocardial infarction." "Our novel findings suggest that if treatments for acute myocardial infarction were provided equally between sexes, then differences in deaths between men and women would be smaller and premature cardiovascular deaths among women would be reduced." (8) Tan et al. Heart Asia 2017;9:81–87 Asia-Pacific consensus statement on the optimal use of high-sensitivity troponin assays in acute coronary syndromes diagnosis: focus on hs-TnI "Gender differences may be particularly important clinically. Studies comparing cardiac troponin I levels measured by Abbott's high-sensitivity ARCHITECT STAT assay showed that the 99th percentile is consistently lower in women than men (table 2). Thus, if the 99th percentile for the overall population is used, a number of women with ACS may not be identified. In contrast, using gender-specific thresholds may double the number of women who are correctly diagnosed with MI, without affecting the number of diagnosed men."	could potentially discriminate against people more likely to have atypical presentations for ACS. We understand your comment to refer to patients with atypical presentations for ACS (e.g. without chest pain). While we accept that some patients with ACS may have such atypical presentations, the remit and scope of this guideline covers adults with recent onset chest pain/discomfort of suspected cardiac origin. Nonetheless, we recognise that we have a gap in our guideline portfolio for this population. We will therefore pass this information to our Topic Selection Steering Group to consider the best approach for developing guidance for this population. On a separate point also related to the title, a topic expert in this surveillance review commented that the current title of the guideline is not specific enough in terms of the population covered. We plan to amend the title of the guideline so that the content is more clearly reflected. A potential revision of the guideline title is 'Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis.'

		Also the title of the guidance might be discriminator: Could using the term "Chest pain" alone (rather than symptoms suspicious for ACS/symptoms of suspected cardiac origin of recent onset or similar) be viewed as discriminating against those who are more likely to have atypical presentations for ACS, e.g. women, the elderly? See Section 1.2.1.3: "Initially assess people for any of the following symptoms, which may indicate an ACS: • Pain in the chest and/or other areas (for example, the arms, back or jaw) lasting longer than 15 minutes • Chest pain associated with nausea and vomiting, marked sweating, breathlessness, or particularly a combination of these • Chest pain associated with haemodynamic instability new onset chest pain, or abrupt deterioration in previously stable angina, with • Recurrent chest pain occurring frequently and with little or no exertion, and with episodes often lasting longer than 15minutes. [2010]"	
Roche Diagnostics	No	No comments	Thank you very much for your response. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
British Society for Cardiovascular	Yes	Microvascular angina and vasospastic angina strongly associate with female sex (BHF CorMicA trial, JACC 2018)	The 2015 SCOT-HEART publication was included in the 2016 guideline update.

Magnetic Resonance (BSCMR)		whereas obstructive coronary disease strongly associates with male sex (SCOT-HEART Lancet 2015). Therefore, a default strategy of anatomical imaging with CTCA at a population level favours a positive diagnosis of obstructive coronary disease in men and a false negative diagnosis with respect to microvascular angina in women. This discrepancy introduces a sex-bias in the guideline recommendations, based on the natural differences in ischaemic heart disease in women and men, and helps explain why angina and symptoms improve less in an anatomical imaging strategy. NICE-CG95 designates functional tests as a second line, which becomes an indeterminate pathway in a cost-constrained healthcare system. This promulgates the under-recognition and under-treatment of microvascular and vasospastic angina, which preponderantly affect women.	The CorMicA trial (Ford *et al.*, 2018) was not within the topic of the focused searches and so was not identified in this surveillance review. This study may be considered relevant to the clinical review question on non-invasive imaging for stable chest pain and has been added to the summary of evidence (Appendix A). This RCT randomised patients (n=151) with symptoms of angina and/or signs of ischaemia but no CAD to either stratified medical therapy or standard care (invasive coronary angiography). However, since this RCT does not evaluate the imaging method of interest directly against the first line test of CCTA, it is considered that further evidence would be required to have potential impact on the recommendation to use CCTA as a first line diagnostic imaging test in people with stable chest pain (recommendation 1.3.4.3). We note that recommendation 1.3.5.1 states that non-invasive functional imaging should be offered if CCTA has shown CAD of uncertain functional significance or is non-diagnostic. Therefore, we would consider that the specific types of angina referred to in your comment (microvascular and vasospastic angina) should be identified by non-invasive functional imaging (as in recommendation 1.3.5.1). We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
HeartFlow	No	No comments provided	Thank you very much for your response. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Royal College of Physicians (RCP)	No	No equality issues identified	Thank you very much for your response.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

			We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
Sanofi Genzyme	No	No comments provided	Thank you very much for your response. We have considered all stakeholder feedback in detail but retain our proposal to not update the guideline at this time.
The British Cardiovascular Society	Not answered	No comments provided	Not applicable