PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost effectiveness of initial stress cardiovascular MR, stress SPECT or stress echocardiography as a gatekeeper test, compared to upfront invasive coronary angiography in the investigation and management of patients with stable chest pain: mid term outcomes from the CECaT* randomised controlled trial
AUTHORS	Thom, Howard; West, Nicholas; Hughes, Vikki; Dyer, Matthew; Buxton, Martin; Sharples, Linda; Jackson, Christopher; Crean, Andrew

VERSION 1 - REVIEW

REVIEWER	Marc Dorenkamp, MD, MBA Dept. of Cardiology Charité - Universitätsmedizin Berlin Campus Virchow-Klinikum There are no conflicts of interests.
REVIEW RETURNED	26-Jun-2013

GENERAL COMMENTS	The original CECaT trial investigated the best diagnostic approach for patients with suspected, or known, coronary artery disease (CAD), using invasive coronary angiography, single photon computed emission tomography (SPECT), cardiac magnetic resonance (CMR) or stress echocardiography. The time horizon was 18 months. The authors found that all three non-invasive diagnostic approaches were slightly more expensive than invasive angiography and produced similar quality-adjusted life-years (QALYs). Among the noninvasive strategies, SPECT was the most favorable one. The present study assessed the cost-effectiveness up to 6 years after randomization. The authors conclude that, relative to invasive angiography, non-invasive cardiac imaging can be used as the initial diagnostic test to diagnose CAD without adverse effects on patient outcomes or increased costs. The manuscript is relevant and should be publishable after the following issues are addressed: 1. p. 9, lines 33-35: “Stress CMR imaging was performed as currently recommended by the Society of Cardiovascular Magnetic Resonance”: patients were recruited between September 2001 and September 2004. The recommendations regarding CMR were

	published in 2004. Where the recommendations applied in retrospect? 2. p. 10, paragraph “Outcomes” (lines 5-11): this paragraph states that the primary outcomes were survival, QALYs, and cost-utility. Those outcomes are different from the primary outcomes defined in the original CECaT trial (which were exercise treadmill time and cost-effectiveness). Where the outcomes of the present study defined in retrospect? The manuscript defines primary outcome variables; were there any secondary outcome variables? Do the data from the Office for National Statistics differ between patients who died of cardiovascular disease versus non-cardiovascular disease? If not, this should be mentioned as a limitation. 3. p. 10, lines 42-44 “Costs were based on National Health Service 2008/09 prices”: The unit costs for “CABG”, “PCI” and “Other hospital admission” given in Table 3 are exactly the same as presented in the original 2007 CECaT trial. Those costs were based on 2005/06 prices. Do the costs for “CABG”, “PCI”, and “Other hospital admission” refer to 2008/09 (as stated in the text) or to 2005/06 prices? Moreover, some of the costs given in Table 3 differ significantly from the costs given in the original CECaT trial (e.g., echocardiography £59 versus £435). In doubt, the results should be recalculated. 4. p. 11, lines 31-35 “In addition, cardiologists were divided into interventional and noninvasive according to their usual practice, and results were recalculated for each subgroup”: While this is an interesting and relevant scenario, more information on the difference between those two groups of cardiologists should be given. What is the quantifiable difference between an invasive and a conservative cardiologist with respect to “their usual practice”? More details and/or a reference should be given. 5. p. 12, lines 17-23 & Figure 1: The numbers given in the text and in Figure 1 should be carefully checked. For example in Figure 1, 222 patients were in the angiography group. Of those, 180 patients underwent “Angio” as a subsequent test. Of the 226 patients in the CMR group, 214 patients underwent no further test. Are those numbers correct, because from a clinical point of view they are not very plausible? Furthermore, the SPECT group consisted of 224 patients (top row in Figure 1), but in the fourth row of boxes, this group suddenly included 226 patients, and in the bottom row again 224 patients (in the stress echo group there are similar inconsistencies).

	Finally, the numbers in the bottom of boxes do not seem to add up. For instance, if 5 of 222 angiography patients died, why is the number of survivors still 222 (the same effect can be observed in the SPECT, CMR and stress echo group)? 6. p. 16, lines 15: the CMR protocol and diagnostic criteria of the CE-MARC differ significantly from the protocol and diagnostic criteria (and technology) employed in the CECaT trial (CE-MARC uses stress and rest perfusion, left ventricular cine, late gadolinium enhancement, and whole heart coronary angiography). This should be discussed in the text. 7. p. 18, lines 25-29: two recent studies have evaluated the cost-effectiveness of CMR in patients with suspected CAD: Boldt J et al. Journal of Cardiovascular Magnetic Resonance 2013;15:30 and Walker S et al. Heart 2013;99:873-81. Both studies should be added as references and their results should be discussed briefly in the text. Minor issues: 8. p. 8, line 5: “ETT”: The abbreviation should be introduced where the term is mentioned first. 9. p. 12, line 9 & Table 1 “Baseline characteristics”: Table 1 should be shortened as the data were already published in the original CECaT trial. 10. p. 15, line 33: “OMT”: The abbreviation should be introduced where the term is mentioned first. 11. p. 19, line 52: myocardial perfusion studies performed at 3T are not necessarily superior to those performed at 1.5T.

REVIEWER	Leslee J. Shaw, PhD, FACC, FASNC, FAHA Emory University School of Medicine Atlanta, Georgia, USA
REVIEW RETURNED	27-Jun-2013

THE STUDY	There are no questions about the descriptions of this trial.
GENERAL COMMENTS	The current manuscript details additional analyses from the CeCAT trial. Previous results compared changes in functional capacity by randomized testing arm. In fact, the primary aim of this trial was exercise performance and not the 2 year survival as reported in this manuscript. Thus, it is unlikely that the current sample size is insufficiently powered. However, this would be the first randomized comparison of survival across noninvasive, stress imaging modalities. As the authors and editors are aware, there is a paucity of comparative outcomes evidence to guide clinical decision making as to the optimal choice of a given stress imaging modality. To that end, the current results from the CeCAT trial are novel. In general, the follow-up methods for data collection of survival status and for the collection of cost data is acceptable and within common standards. However, a separate statistical methods section

	should be included. In particular, the inverse weighting analytical methods should be defined in more detail. The Cox modeling methods should also be provided. The authors note a sizeable number of hospitalizations for acute coronary syndromes or chest pain. Excluding the lower risk, chest pain admissions, an analysis of the acute myocardial infarction (MI) or acute coronary syndrome (ACS) admissions by randomization would be of interest to readers. The combination of death or MI is a common endpoint used in prognostic analyses of noninvasive imaging reports. What were the a priori secondary aims with regards to MI or ACS as important endpoints in the outcome analyses? Given the small number of deaths, it would seem that a model of combined endpoints may be informative. The authors report that SPECT imaging had a reduced survival with a hazard ratio and confidence intervals <1.0. It would be important for all aspects of this Cox model to be delineated including the model statistics and Harrell's C statistic. As well, the number of deaths identified in each randomized arm should be delineated, as well by their test findings (i.e., positive / negative). As part of this, more details should be provided with regards to the Cox model including revascularization as a time dependent covariate. Although trials have failed to reveal a survival benefit with revascularization in patients with stable ischemic heart disease, the timing of angiography and subsequent revascularization should be defined. There may be interesting patterns between the diagnostic modalities between anatomic, perfusion, or wall motion abnormalities in terms of prompting direct revascularization. One may envision that invasive angiography would result in early revascularization as compared to the other modalities. As well, given that aggregate costs include revascularization and downstream angiography, the timing of this procedure as early (directly the result of test findings) as compared to late (the result of clinical worsening) angiography or revascularization would be important to delineate. It may be that all of the interventional procedures following CMR occurred as a result of worsening, downstream chest pain or post-MI which would explain the elevated hazard for death. Additional details of the intercurrent management of these patients would be informative and provide insight into the survival and cost findings. The CONSORT figure reports a reduced frequency of PCI in the stress echocardiography arm. Are there statistical differences in the rate of revascularization (by imaging results) for the randomized arms? Did the costs include drug costs? Although costs were detailed, why didn't the authors perform a formal cost effectiveness analysis, as planned, including cost effectiveness planes? The data is presented as a cost savings or minimization analysis. One can envision that provided the low mortality rate that the authors decided that these findings supported equivalent survival. However, throughout the manuscript, the authors discuss the use of a cost effectiveness analysis. The authors should provide more details as to why a formal incremental cost effectiveness analysis was not included. Specific comments: Many of the key messages highlighted on page 4 of this manuscript should be detailed in the abstract and throughout the manuscript. The abstract does not appear to reflect much of the important findings from this report. On page 7, the authors wrote: "Data from the COURAGE trial have demonstrated the lack of prognostic benefit from revascularization in

	the absence of reversible ischemia." This sentence is incorrect as the COURAGE trial was a negative trial and no patient subset demonstrated a benefit with revascularization. Please re-write this sentence. The reasons for excluding patients from the trial should be enumerated perhaps with a CONSORT figure of the excluded patients. Table 1 reports exercise tolerance. What protocol was used? Given that these results note a fairly good exercise capacity, the framing of this patient population as lower risk clearly frames the current findings of similar survival and a low rate of follow-up deaths. Did the authors combine no change with ST elevation in this table? These should be separated. The number at risk should be added to the survival curves. Please include the p value for this analysis. Given that the EQ 5D data was collected at specified time intervals that were approximately every 6 months. It would be preferable not to plot this as a line but perhaps median and interquartile range values at the time point of data collection. Please include the number of patients completing this information below the x axis at each of the prespecified time intervals. Details of patient loss to follow-up and response rates for the EQ 5D should be provided.

REVIEWER	Simon Walker, Research Fellow, University of York
REVIEW RETURNED	09-Jul-2013

RESULTS & CONCLUSIONS	I'm unsure whether such strong conclusions can be drawn on the non inferiority of non invasive strategies given the results presented. I would also find it very beneficial to see estimates of probabilities of cost-effective at 20 and 30k thresholds.
GENERAL COMMENTS	This is a well presented study which clearly addresses the questions it set out to answer. However, I feel the conclusions drawn may be a little strong given the data. I'd be interested to see the CEACs presented for the strategies. In terms of methods, I am slightly concerned by the exclusion of medication costs and costs beyond 2 years. Can the authors explain how this might impact upon their results? I would suspect more in the non invasive arms may be forced to rely on medical management to control their angina symptoms. Specific comments: On pg 14, you state that non invasive tests tend to do better in low risk populations because of negative predictive power, can you provide a reference for this.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Marc Dorenkamp, MD, MBA
Dept. of Cardiology
Charité - Universitätsmedizin Berlin
Campus Virchow-Klinikum

There are no conflicts of interests.

The original CECaT trial investigated the best diagnostic approach for patients with suspected, or known, coronary artery disease (CAD), using invasive coronary angiography, single photon computed emission tomography (SPECT),
cardiac magnetic resonance (CMR) or stress echocardiography. The time horizon was 18 months. The authors found that all three non-invasive diagnostic approaches were slightly more expensive than invasive angiography and produced similar quality-adjusted life-years (QALYs). Among the noninvasive strategies, SPECT was the most favorable one.

The present study assessed the cost-effectiveness up to 6 years after randomization. The authors conclude that, relative to invasive angiography, non-invasive cardiac imaging can be used as the initial diagnostic test to diagnose CAD without adverse effects on patient outcomes or increased costs. The manuscript is relevant and should be publishable after the following issues are addressed:

1. p. 9, lines 33-35: “Stress CMR imaging was performed as currently recommended by the Society of Cardiovascular Magnetic Resonance”: patients were recruited between September 2001 and September 2004. The recommendations regarding CMR were published in 2004. Where the recommendations applied in retrospect?

It is correct that the trial began prior to publication of these guidelines. However the imaging protocol for perfusion that we used met the later published guidelines – the text has been amended to make this clearer.

2. p. 10, paragraph “Outcomes” (lines 5-11): this paragraph states that the primary outcomes were survival, QALYs, and cost-utility. Those outcomes are different from the primary outcomes defined in the original CECaT trial (which were exercise treadmill time and cost-effectiveness). Were the outcomes of the present study defined in retrospect? The manuscript defines primary outcome variables; were there any secondary outcome variables? Do the data from the Office for National Statistics differ between patients who died of cardiovascular disease versus non-cardiovascular disease? If not, this should be mentioned as a limitation.

The paragraph on outcomes has been amended to make clearer that this is a medium-term follow up from a trial that has reported on its primary endpoints.

Unfortunately our data from the national registry do not include cause of death so that we have included this as a limitation in the discussion.

3. p. 10, lines 42-44 “Costs were based on National Health Service 2008/09 prices”: The unit costs for “CABG”, “PCI” and “Other hospital admission” given in Table 3 are exactly the same as presented in the original 2007 CECaT trial. Those costs were based on 2005/06 prices. Do the costs for “CABG”, “PCI”, and “Other hospital admission” refer to 2008/09 (as stated in the text) or to 2005/06 prices? Moreover, some of the costs given in Table 3 differ significantly from the costs given in the original CECaT trial (e.g., echocardiography £59 versus £435). In doubt, the results should be recalculated.

This was an error for which we apologise. The correct national reference costs 2005/06 for

CABG/PTCA and tests have now been used, along with local Papworth costs for tests such as stress ECHO for which a reference cost did not exist. Results have been recalculated.

4. p. 11, lines 31-35 “In addition, cardiologists were divided into interventional and noninvasive according to their usual practice, and results were recalculated for each subgroup”: While this is an interesting and relevant scenario, more
information on the difference between those two groups of cardiologists should be given. What is the quantifiable difference between an invasive and a conservative cardiologist with respect to “their usual practice”? More details and/or a reference should be given.

Referring cardiologists were all employed by a single health region and therefore their exact job plans were precisely known. In this context, a non-invasive cardiologist is defined as one who does not undertake percutaneous coronary intervention. Conversely, an interventional cardiologist is one who regularly undertakes coronary intervention as part of their job description. We have made this clearer in the text.

5. p. 12, lines 17-23 & Figure 1: The numbers given in the text and in Figure 1 should be carefully checked. For example in Figure 1, 222 patients were in the angiography group. Of those, 180 patients underwent “Angio” as a subsequent test. Of the 226 patients in the CMR group, 214 patients underwent no further test. Are those
numbers correct, because from a clinical point of view they are not very plausible? Furthermore, the SPECT group consisted of 224 patients (top row in Figure 1), but in the fourth row of boxes, this group suddenly included 226 patients, and in the bottom row again 224 patients (in the stress echo group there are similar inconsistencies). Finally, the numbers in the bottom of boxes do not seem to add up. For instance, if 5 of 222 angiography patients died, why is the number of survivors still 222 (the same effect can be observed in the SPECT, CMR and stress echo group)?

I think the CONSORT diagram that was uploaded with the manuscript was corrupted so that we have recreated it, checked it carefully and clarified the final row, which reports the number of cases who had each outcome recorded.

6. p. 16, lines 15: the CMR protocol and diagnostic criteria of the CE-MARC differ significantly from the protocol and diagnostic criteria (and technology) employed in the CECaT trial (CE-MARC uses stress and rest perfusion, left
ventricular cine, late gadolinium enhancement, and whole heart coronary angiography). This should be discussed in the text.

This is an important point and requires clarification. In fact the protocols in the CEMARC study and our CECaT trial are perhaps not as different as the reviewer believes, although for reasons of space limitation we perhaps did not make this as clear in the text as necessary. Our trial also included stress/rest perfusion (as stated) as well as cine SSFP imaging for ventricular function and late gadolinium enhancement imaging for myocardial scar. These were not included in the Methods section for reasons of severe space limitation. We have amended the text to reference the full CMR protocol provided in our earlier CECaT publication. We did not think this was of great importance since the only CMR information employed in the CECaT study was the presence or absence of an inducible perfusion defect. Since we recruited patients without known coronary disease or myocardial infarction, we chose to group all inducible perfusion defects as a positive result - regardless of whether the defect was present because of reversible ischemia or because of the presence of underlying scar – both were regarded by trial design as a reason to proceed with invasive coronary angiography in patients without a prior history of confirmed atherosclerotic disease.

The reviewer is correct that we did not perform whole heart coronary magnetic resonance

angiography as was done as part of the CEMARC trial. At the time of the trial that pulse sequence technology was not available to us on our platform (1.5T GE magnet housed within an articulated truck !). The CEMARC trial was performed 4-5 years later at a time when coronary MRA was becoming more popular due to the introduction of more robust 'whole heart' 3D techniques. However even at that centre where there is considerable expertise in CMR, 12% of patients had uninterpretable coronary MR angiograms. Even after exclusion of these cases there were overlapping confidence intervals for the overall diagnostic accuracy of CMR perfusion plus coronary MRA versus perfusion alone. We therefore do not believe that lack of coronary MRA was a significant or relevant limitation to our own study.

7. p. 18, lines 25-29: two recent studies have evaluated the cost-effectiveness of CMR in patients with suspected CAD: Boldt J et al. Journal of Cardiovascular Magnetic Resonance 2013;15:30 and Walker S et al. Heart 2013;99:873-81. Both studies should be added as references and their results should be discussed briefly in the text.

Thank you for drawing our attention to these 2 publications. We have included some appropriate comments in the discussion section of the manuscript and referenced both articles as suggested.

Minor issues:
8. p. 8, line 5: "ETT": The abbreviation should be introduced where the term is mentioned first.

This has been spelled out.

9. p. 12, line 9 & Table 1 "Baseline characteristics": Table 1 should be shortened as the data were already published in the original CECaT trial.

We have shortened this slightly but after careful consideration prefer to leave in much of this important basic information.

10. p. 15, line 33: "OMT": The abbreviation should be introduced where the term is mentioned first.

This has been spelled out.

11. p. 19, line 52: myocardial perfusion studies performed at 3T are not necessarily superior to those performed at 1.5T.

This is a fair point. There is evidence that both contrast to noise and signal to noise are increased at 3T compared to 1.5T and at least one clinical study suggesting higher diagnostic superiority of 3T over 1.5T in relation to stress perfusion CMR. However, it is fair to say that there are insufficient studies with adequate head-to-head comparison to state that 3T is superior unequivocally, even though that seems to us to be the (unproven) consensus from clinicians – including us - who regularly interpret studies performed at both field strengths.

Reviewer: Leslee J. Shaw, PhD, FACC, FASNC, FAHA
Emory University School of Medicine
Atlanta, Georgia, USA

The current manuscript details additional analyses from the CeCAT trial. Previous results compared changes in functional capacity by randomized testing arm. In fact, the primary aim of this trial was exercise performance and not the 2 year survival as reported in this manuscript. Thus, it is unlikely that the current sample size is insufficiently

powered. However, this would be the first randomized comparison of survival across noninvasive, stress imaging modalities. As the authors and editors are aware, there is a paucity of comparative outcomes evidence to guide
clinical decision making as to the optimal choice of a given stress imaging modality. To that end, the current results from the CeCAT trial are novel.

In general, the follow-up methods for data collection of survival status and for the collection of cost data is acceptable and within common standards. However, a separate statistical methods section should be included. In particular, the inverse weighting analytical methods should be defined in more detail.

We have given brief details of this methodology and a reference. We are reluctant to provide further details in the text as most of the readers would probably prefer to take this on trust. However we are happy to provide the relevant reference and our software to the journal/reviewers if that would help.

The Cox modeling methods should also be provided. The authors note a sizeable number of hospitalizations for acute
coronary syndromes or chest pain. Excluding the lower risk, chest pain admissions, an analysis of the acute myocardial infarction (MI) or acute coronary syndrome (ACS) admissions by randomization would be of interest to
readers. The combination of death or MI is a common endpoint used in prognostic analyses of noninvasive imaging reports. What were the a priori secondary aims with regards to MI or ACS as mportant endpoints in the outcome analyses? Given the small number of deaths, it would seem that a model of combined endpoints may be informative.

We have included a table of patient-reported adverse events but there were few recorded and confirmed episodes of non-fatal MI and Acute Coronary Syndrome so that the plot of time to MACE is not sufficiently different to the survival plot to provide important additional information.

The authors report that SPECT imaging had a reduced survival with a hazard ratio and confidence intervals <1.0. It would be important for all aspects of this Cox model to be delineated including the model statistics and Harrell's C statistic. As well, the number of deaths identified in each randomized arm should be delineated, as well by their test findings (i.e., positive / negative). As part of this, more details should be provided with regards to the Cox model including revascularization as a time dependent covariate. Although trials have failed to reveal a survival benefit with
revascularization in patients with stable ischemic heart disease, the timing of angiography and subsequent revascularization should be defined.There may be interesting patterns between the diagnostic modalities between
anatomic, perfusion, or wall motion abnormalities in terms of prompting direct revascularization. One may envision that invasive angiography would result in early revascularization as compared to the other modalities. As well, given that aggregate costs include revascularization and downstream angiography, the timing of this procedure as early (directly the result of test findings) as compared to late (the result of clinical worsening) angiography or revascularization would be important to delineate. It may be that all of the interventional procedures following CMR occurred as a result of worsening, downstream chest pain or post-MI which would explain the elevated hazard for death. Additional details of the intercurrent management of these patients would be informative and provide insight into the survival and cost findings. The CONSORT figure reports a reduced frequency of PCI in the stress echocardiography arm. Are there statistical differences in the rate of revascularization (by imaging results) for the randomized arms? Did the costs include drug costs? Although costs were detailed, why didn't the authors perform a formal cost effectiveness analysis, as planned, including cost effectiveness planes? The data is presented as a costsavings or minimization analysis. One can envision that provided the low mortality rate that the authors decided that these findings

supportedequivalent survival. However, throughout the manuscript, the authors discuss the use of a cost effectiveness analysis. The authors should provide more details as to why a formal incremental cost effectiveness
analysis was not included.

In our analysis we are not estimating risk or predicting survival with our models so the C-statistic is not relevant. The more relevant assessment of the model assumptions would be examination of Schoenfeld residuals which we completed as part of the analysis and which we have added to the Statistical Methods section.

We have spelt out the survival methods in more detail.
We have added the hazard ratios for all 3 groups in both the abstract and results, and the number of deaths in each group is given in the results.

Medians, 95% intervals and ranges are provided below for the time to initial CABG or PCI when the procedures are not conducted at the same time.

0% 2.5% 50% 97.5% 100%
ANGIO (n=85) 23.0 64.0 122.0 410.3 456.0
SPECT (n=67) 18.0 91.2 192.0 420.4 469.0
MRI (n=87) 72.0 90.2 184.0 658.1 831.0
ECHO (n=82) 81.0 103.0 178.5 336.7 432.0

We are reluctant to provide too much detail as regards the timing and order of subsequent tests and interventions since there is a danger that the messages of the paper get lost in details of individuals or many small subgroup of cases. We have provided the numbers of cases in each group who have each intervention and the timings of the interventions after randomisation which we hope will provide sufficient information on patient management.

There were no statistically significant differences in initial management between the groups and this has been added. Further details of subsequent revascularisation procedures are also included.

Drug costs are included in the cost-effectiveness analysis but not summarized in Table 3 because almost all patients were on a complex mixture of medications.

In the original submitted draft we had reduced the cost-effectiveness results to a minimum in order to meet the word limit. Much of this has now been reinstated in the results.

Specific comments:
Many of the key messages highlighted on page 4 of this manuscript should be detailed in the abstract and throughout the manuscript. The abstract does not appear to reflect much of the important findings from this report.

We have tried to incorporate these messages in the abstract whilst keeping the length within acceptable limits.

On page 7, the authors wrote: “Data from the COURAGE trial have demonstrated the lack of prognostic benefit from revascularization in the absence of reversible ischemia.” This sentence is incorrect as the COURAGE trial was a negative trial and no patient subset demonstrated a benefit with revascularization. Please re-write this sentence.

This has been revised.

The reasons for excluding patients from the trial should be enumerated perhaps with a CONSORT figure of the excluded patients.

This appears in the original published HTA report and we are reluctant to repeat it here in the interests of brevity.

Table 1 reports exercise tolerance. What protocol was used? Given thatthese results note a fairly good exercise capacity, the framing of this patient population as lower risk clearly frames the current findings of similar survival and a low rate of follow-up deaths. Did the authors combine no change with ST elevation in this table? These should be
separated.

We have clarified that the modified Bruce protocol was used to assess exercise tolerance. Only 6 patients had an ST elevation, 3 in the angiography group, 1 in the CMR group and 2 in the ECHO group. We think this does not warrant an extra row in the table but have included a footnote to this effect.

The number at risk should be added to the survival curves. Please include the p value for this analysis.

The numbers at risk and global p-value from the likelihood ratio test have been added to figure 1.

Given that the EQ 5D data was collected at specified time intervals that were approximately every 6 months. It would be preferable not to plot this as a line but perhaps median and interquartile range values at the time point of data collection. Please include the number of patients completing this information below the x axis at each of the prespecified time intervals.

Based on clinical referees' advice at the trial planning stage secondary outcomes were collected at 2 sets of time intervals, at 6 and 12 months after randomisation and at 6, 18 and 24 months after treatment, the latter considered important for longer term cost-effectiveness analysis as presented here. It does mean that the follow up measurements were taken at varying times after randomisation so that the interpolated line plots give a more accurate reflection of the changes in EQ5D through time. We have tried to clarify this in the text but accept that, although the design makes sense in terms of the changes that occur during clinical management, it is not straightforward to explain briefly.

Details of patient loss to follow-up and response rates for the EQ 5D should be provided.

Figure 3 shows the numbers of records included in the analysis through time.

Reviewer: Simon Walker, Research Fellow, University of York

I'm unsure whether such strong conclusions can be drawn on the non inferiority of non invasive strategies given the results presented. I would also find it very beneficial to see estimates of probabilities of cost-effective at 20 and 30k thresholds.

Further cost-effectiveness results are included along with the probabilities requested. We have stopped short of calculating ICERs due to the small (close to zero) denominators.

This is a well presented study which clearly addresses the questions it set out to answer. However, I feel the conclusions drawn may be a little strong given the data. I'd be interested to see the CEACs

presented for the
strategies.

This is now included as figure 5 and in the results section.

In terms of methods, I am slightly concerned by the exclusion of medication costs and costs beyond 2 years. Can the authors explain how this might impact upon their results? I would suspect more in the non invasive arms may be forced to rely on medical management to control their angina symptoms.

The medication costs were included but do not appear in Table 4 due to the many different combinations of drugs prescribed – a footnote has been added to the table to clarify. These, and other costs, were included beyond 2 years but these were extensively censored. We used Inverse-Weighting to overcome this censoring, as explained in the statistical and economic methods section.

Specific comments:

On pg 14, you state that non invasive tests tend to do better in low risk populations because of negative predictive power, can you provide a reference for this.

The point we were trying to make is that the dominant strength of many of the non-invasive modalities is their ability to accurately rule out disease. Clearly there will be fewer false negatives in populations with a low prevalence of disease than those with a high disease prevalence. We are not able to support this statement with any single reference but believe it is nonetheless a reasonable proposition.

VERSION 2 – REVIEW

REVIEWER	Marc Dorenkamp, MD, MBA Charité - Universitätsmedizin Berlin Dept. of Cardiology Campus Virchow-Klinikum
REVIEW RETURNED	30-Oct-2013

GENERAL COMMENTS	Since the first round of review, the manuscript has improved substantially. However, I still have a problem with the costs given in table 4. The authors state that costs were based on NHS reference costs 2005/06 prices (p. 9, lines 236-7). When compared to the costs given in the original CeCaT trial (also based on 2005/06 costs), there are still some discrepancies: 1. In the current manuscript, the costs for "Angiography" are 1032 BP, in the CeCaT trial they were 625 BP (day case) or 935 BP (overnight). 2. Why is "SPECT" (983 BP) associated with significantly higher costs than "CMR" (388 BP)? This is not very plausible and it is in sharp contrast to the costs given in the original CeCaT trial (SPECT 405 BP, CMR 565 BP) and also in contrast to the costs given in a recent publication from the UK (SPECT 293 BP, CMR 313 BP; Walker S et al. Heart 2013;99:873-81). These discrepancies need to be explained as they may affect the overall results.

VERSION 2 – AUTHOR RESPONSE

1. In the current manuscript, the costs for "Angiography" are 1032 BP, in the CECaT trial they were 625 BP (day case) or 935 BP (overnight).

2. Why is "SPECT" (983 BP) associated with significantly higher costs than "CMR" (388 BP)? This is not very plausible and it is in sharp contrast to the costs given in the original CeCaT trial (SPECT 405 BP, CMR 565 BP) and also in contrast to the costs given in a recent publication from the UK (SPECT 293 BP, CMR 313 BP; Walker S et al.Heart 2013;99:873-81).

These discrepancies need to be explained as they may affect the overall results.

We completely agree that these discrepancies need to be resolved and are grateful that they were highlighted. The discrepancy has arisen because in the original CECaT HTA publication we used Papworth Hospital reference costs for the economic analysis. For this paper we displayed our results according to NHS national tariff prices. However we agree that this creates the potential for confusion and have therefore reverted to using Papworth tariffs as in the original paper, in order to facilitate comparison between that work and this.

We hope this clears up any remaining confusion.