



**Stress cardiovascular MR, stress SPECT and stress echocardiography are non- inferior to upfront invasive coronary angiography as gate-keepers in the investigation and management of patients with stable chest pain: mid term outcomes from the CECaT\* Trial (a randomised controlled trial)**

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Manuscripts

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4 **Title: Stress cardiovascular MR, stress SPECT and stress echocardiography are**  
5 **non- inferior to upfront invasive coronary angiography as gate-keepers in the**  
6 **investigation and management of patients with stable chest pain: mid term**  
7 **outcomes from the CECaT\* Trial (a randomised controlled trial)**  
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13 \*Cost Effectiveness of non-invasive Cardiac Testing  
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3 **Contributorship statement:**  
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6  
7 **HT, MD, MB, LDS, CHJ were involved in economic and statistical analysis. LDS was**  
8 **the senior project statistician, was involved in original study design and takes overall**  
9 **responsibility for statistical portion of the manuscript. All of these individuals**  
10 **contributed to drafting and revision of the manuscript.**  
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14  
15  
16  
17 **VH was involved in study design, patient recruitment, data collection and project**  
18 **management from the projects inception to its conclusion. She also contributed to**  
19 **drafting and revision of the manuscript**  
20  
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24  
25 **NW was responsible for blinded review of clinical data and contributed to drafting and**  
26 **revision of the manuscript.**  
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30  
31 **AC was involved in the original study design, was responsible for the day-to-day**  
32 **clinical aspects of running the trial and was involved in the recruitment and follow up**  
33 **of patients as well as analysis of the cardiac MR studies. He wrote the final**  
34 **manuscript and contributed to its revision. He takes overall responsibility for the**  
35 **integrity of the clinical data.**  
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3 **Article summary:**  
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5 **Article focus:**  
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- 7 1. Is non-invasive imaging a safe and appropriate gate-keeper to coronary  
8 angiography in patients with stable chest pain ?  
9  
10 2. Is there any difference in cost-effectiveness and cost-utility between the  
11 different non-invasive approaches and conventional coronary angiography  
12  
13 3. Are patients disadvantaged in any meaningful way by having a non-invasive  
14 test to decide whether they should go forward for coronary angiography ?  
15  
16 4. How does stress perfusion CMR compare to the more established tests of  
17 SPECT-MIBI and stress echocardiography as a gate-keeper to coronary  
18 angiography ?  
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27 **Key messages:**  
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- 29 1. Non-invasive testing may be used safely as a gate-keeper to coronary  
30 angiography in patients with stable chest pain without any material  
31 disadvantage to them in terms of survival and quality of life up to 6 years after  
32 initial randomisation.  
33  
34 2. SPECT-MIBI appears marginally superior statistically to the other non-invasive  
35 methods although clinically meaningful differences are small between all  
36 strategies.  
37  
38 3. Stress perfusion CMR appears to be an effective technique in a stable out-  
39 patient population with undiagnosed chest pain.  
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49 **Strengths and limitations:**  
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- 51 1. This is the only large randomised prospective trial of a strategy of non-invasive  
52 gate-keeper cardiac imaging versus upfront angiography in the literature.  
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54 2. The cost-utility data are derived from NHS tariffs and our results are not  
55 necessarily directly transferrable to other healthcare systems  
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***Data sharing statement:***

**There are no additional data available**

For peer review only

## Abstract

### Background

A significant minority of patients with chest pain due to coronary artery disease (CAD) do not experience resolution of symptoms with revascularization. Coronary angiography is the standard for diagnosis, but early results from the CECaT trial showed that functional imaging tests can be used as a gateway for angiography. Cost-effectiveness is assessed in this paper up to 6 years after randomization.

### Methods

Patients were randomized to an initial test: angiography (control); Single Photon Emission Computed Tomography; stress cardiac magnetic resonance imaging (CMR); or stress echocardiography. It was recommended that follow-up angiography be performed only after a positive functional test. Clinical outcomes, quality of life and resource use up to 2 years post-treatment were used to estimate cost-effectiveness of each strategy compared to angiography. Incremental cost-effectiveness was assessed from an NHS perspective.

### Results

898 patients were randomized. Compared to angiography, mortality was marginally higher in the group randomized to CMR (hazard ratio 2.6, 95%CI 1.1, 6.2). There were no other significant differences between the groups in mortality, quality adjusted survival or costs.

### Conclusions

Non-invasive cardiac imaging can be used as the initial diagnostic test to diagnose CAD without adverse effects on patient outcomes or increased costs, relative to angiography.

**Key words:** MRI, cardiovascular magnetic resonance, comparative effectiveness, SPECT, stress echo, coronary angiography

## Introduction

CAD is common and its management is costly <sup>(1)</sup>. Revascularisation using bypass surgery (CABG) or percutaneous coronary intervention (PCI) is effective for patients with severe disease <sup>(2)</sup> but a significant minority of patients do not gain symptomatic relief <sup>(3)</sup>. Data from the COURAGE trial have demonstrated the lack of prognostic benefit from revascularization in the absence of reversible ischemia <sup>(4)</sup>. The yield of coronary angiography is variable with one recent large study of nearly 400, 000 patients demonstrating a normalcy rate approaching 40% <sup>(5)</sup>. Therefore non-invasive testing to identify those with a low likelihood of obstructive CAD may be safer, cheaper and more appropriate than upfront angiography. This approach is codified in multiple AHA/ACC guidelines on the investigation of stable or suspected angina pectoris in which initial non-invasive imaging is rated as highly appropriate <sup>(6) (7) (8) (9)</sup>.

The 'Cost-Effectiveness of non-invasive Cardiac Testing' (CECaT) trial was designed to assess three functional tests - stress echocardiography, single photon emission computed tomography (SPECT) and stress cardiac magnetic resonance imaging (CMR) - as a gatekeeper to coronary angiography (CA) in patients referred for CA with suspected coronary artery disease (CAD). Early clinical and cost-effectiveness estimates have been published and showed that the CMR group had slightly lower mean exercise treadmill time according to the Bruce protocol but otherwise the tests could be considered equally effective <sup>(10)</sup>. This report provides the main cost-effectiveness and mortality outcomes up to 6 years after randomisation.

## Methods

### Study design

The design of the study has been described elsewhere <sup>(10)</sup> and is reviewed briefly here. All patients referred to Papworth Hospital, UK for non-urgent angiography were eligible for the



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3 study. Inclusion criteria were: established or suspected chronic stable angina and a positive  
4  
5 ETT result with subsequent referral for angiography. Exclusion criteria were: recent MI (<3  
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7 months), revascularisation (<6 months); urgent need for revascularisation; contra-indication  
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9 to adenosine or CMR; inability to exercise.

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13 Trial design was of four parallel arms with a 1:1:1:1 randomisation ratio. Randomisation was  
14  
15 computer generated and stratified according to Pryor risk assessment<sup>(11)</sup>. Within each Pryor  
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17 risk group, randomisation was in blocks of length 6 or 8. Sequentially numbered group  
18  
19 designation was held in the Research & Development (R&D) Office and was not available to  
20  
21 trial personnel. Patients were randomised to their initial diagnostic test - stress SPECT,  
22  
23 stress CMR, stress echocardiography, or angiography - by R&D within 4 weeks of  
24  
25 recruitment and only after they had given consent and been registered.

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29 Non invasive imaging results were returned with a recommendation to proceed with  
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31 angiography only when reported as 'positive' for inducible ischemia. Protocol adherence to  
32  
33 this recommendation was not mandated by trial design and patients proceeded to  
34  
35 angiography if considered clinically indicated. Treatment with PCI or CABG (performed  
36  
37 within six months of angiography) or to medical therapy was according to standard practice.

### 41 42 **Coronary angiography.**

43  
44 Standard diagnostic angiography was performed from the right femoral artery approach<sup>(12)</sup>.  
45  
46 A minimum of 5 views of the left and 3 views of the right coronary system were taken<sup>(13)</sup>. All  
47  
48 examinations were reported by an experienced staff cardiologist and segmental location of  
49  
50 disease (if any) recorded.

### 51 52 53 54 **Stress echocardiography**

55  
56 Beta-blocker medications were stopped 2 days beforehand. Dobutamine was infused at  
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58 rates of 10- 40 mcg/kg/min, increased at 3 minute intervals. If necessary, 300-600  
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3 micrograms of atropine were added at peak stress to achieve 90% of target heart  
4 rate. Images were acquired in standard planes in the final minute of each 3 minute stage.  
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6 Intravenous microspheres were used to delineate the endocardial surface. All examinations  
7  
8 were reported by one of two staff cardiologists experienced in stress echocardiography.  
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10 Studies were positive for ischemia if stress-induced deterioration in contractility was  
11  
12 observed.  
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### 14 15 16 17 **SPECT**

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19 Rest/stress 99mTc sestamibi (99mTc MIBI) SPECT was performed (2 day protocol). A 6  
20  
21 minute adenosine infusion (140 µg/kg/min) was employed. 400 MBq 99m-Tc MIBI was  
22  
23 administered at 3 minutes after infusion of adenosine was started. Gated SPECT imaging  
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25 occurred 60 minutes after injection. Tomographic images were assessed for fixed and  
26  
27 reversible defects by a single observer (as per established criteria)<sup>(14)</sup>.  
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### 30 31 **CMR**

32  
33 Stress CMR imaging was performed as currently recommended by the Society of  
34  
35 Cardiovascular Magnetic Resonance <sup>(15)</sup>. A 1.5T mobile CMR system and 4-channel phased  
36  
37 array surface coil were used (Signa CV/i, GE Medical Systems). Stress/rest dynamic first-  
38  
39 pass perfusion imaging was performed. A hybrid fast gradient echo/echoplanar sequence  
40  
41 was employed <sup>(16)</sup>. Adenosine was infused at 140 mcg/kg/min for 4 minutes. After 3 minutes,  
42  
43 a bolus of Gadolinium-DTPA (0.1mmol/kg) was delivered at 5mls/sec, followed by a 25ml  
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45 saline flush. First-pass imaging of the heart occurred over 80 heart beats. A volumetric  
46  
47 notched-saturation pre-pulse preserved a constant saturation-recovery time during slice  
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49 acquisition <sup>(17)</sup>. 6-8 short axis slices were obtained every 2 heart beats. Rest imaging was  
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51 repeated after a minimum interval of 15 minutes. Studies were reported as positive if there  
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53 was an inducible perfusion defect visible for at least 5 frames either: a) in a region of normal  
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55 wall thickness; or b) in a region of myocardial thinning in the absence of a history of prior  
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57 myocardial infarction.  
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## Outcomes

The primary outcomes of this follow up study were survival up to a minimum of 2 years post-treatment, quality-adjusted survival and cost-utility of each strategy. Survival status was determined from the Office for National Statistics database, UK (<http://www.ons.gov.uk/>).

## Sample size calculations

The sample size was based on exercise performance and was calculated according to the methodology published in the initial report of the CECaT study <sup>(10)</sup>.

## Statistical and economic analysis

For this study, survival was summarised using Kaplan-Meier estimates and the groups were compared using Cox proportional hazards regression. In sensitivity analysis CABG and PCI were included in the regression analyses as time-dependent covariates to ensure that any differences between the groups was not due to differences in treatment. Inclusion of treatment did not affect comparison of treatment strategies and results of these analyses are not included here.

Patient-specific hospital resource use was collected for 2 years post-treatment with revascularisation or medical management. Costs were based on National Health Service 2008/09 prices. Costs available from previous years were inflated using the Hospital and Community Health Services Pay and Prices Index <sup>(18)</sup>. An annual discount rate of 3.5% was applied to all costs and quality-adjusted life-years (QALYs) after 12 months post-randomisation. Resources costed were: imaging tests; revascularisation; inpatient/outpatient episodes; adverse events; cardiac-related medications. Patient-reported admissions for MI were verified with the admitting hospital and adjudicated.

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3 Patients completed the EuroQoL EQ-5D questionnaire <sup>(19)</sup> at baseline randomisation, 6  
4 months post-treatment, 18 months post-randomization, 18 months post-treatment and 24  
5 months post-treatment. The social tariff for the EQ-5D was applied in order to calculate  
6 utility values <sup>(20)</sup>. For exploratory purposes daily utilities were estimated using linear  
7 interpolation.  
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15 Quality adjusted survival and cost estimates were censored at the last follow up so that  
16 mean values over a range of time horizons were estimated using inverse weighting methods  
17 <sup>(21)</sup>. In the base case we used a time horizon of 3 years since it was the longest period over  
18 which results were stable, with acceptable precision. Confidence intervals for costs and  
19 QALYs were estimated using bootstrapping with 5000 samples <sup>(22)</sup>.  
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### 27 **Sensitivity analysis**

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29 Sensitivity of cost-utility results for different time horizons was assessed by re-estimating  
30 results up to 12, 18, 24, 36 and 48 months after randomization. In addition, cardiologists  
31 were divided into interventional and non-invasive according to their usual practice, and  
32 results were recalculated for each subgroup. With the exception of this *post-hoc* data  
33 interrogation, all other results presented derive from intention-to-treat analysis.  
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41 The study had IRB approval and full written informed consent was obtained from all  
42 participants. All authors had full access to the data and take responsibility for the manuscript  
43 as written.  
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## 49 **Results**

### 50 **Recruitment and compliance**

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53 Between September 2001 and September 2004, 3,201 patients were assessed, 1,981 were  
54 excluded and 322 refused entry to the trial. Refusals were more likely to come from women  
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3 (46% compared with 31% enrolled into the study,  $p<0.001$ ) and were significantly older  
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5 (mean age 64.6, (SD 10.1) compared with study group mean age 61.8, (9.4),  $p<0.001$ ).  
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9 898 patients were randomised. Groups were well matched at baseline (table 1). In each  
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11 group 69% of patients were high risk for CAD (Pryor score  $> 0.8$ ). The trial was closed to  
12  
13 recruitment in September 2004 after enrolling the pre-specified number of subjects.  
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16  
17 One-hundred-seventy-five (78%) SPECT patients, 180 (80%) CMR patients and 169 (75%)  
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19 stress echo patients were referred on for angiography (**Figure 1**). Between 20% and 25% of  
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21 patients undergoing non-invasive tests did not require further investigation. Four patients  
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23 died and four withdrew from the trial early on. Of the remaining patients, revascularization  
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25 was required in 34% (301/890). There was no significant difference between the groups in  
26  
27 patient management (**Figure 1**).  
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### 31 **Survival**

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33 During the study there were 43 deaths (4.8%). Kaplan-Meier survival curves for the 4 groups  
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35 are plotted in **Figure 2**. SPECT and stress echo groups were not significantly different from  
36  
37 angiography. The CMR group had higher mortality than the angiography group, the hazard  
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39 ratio was 2.6 (95%CI 1.1 to 6.2),  $p=0.032$  (**Table 2**). The significant effect of CMR on  
40  
41 survival remained when CABG or PCI were included in the models. However, mortality was  
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43 low in all groups and the absolute mean difference in survival was less than 1 month over 3  
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45 years (**Table 2**). Mean survival estimates over 3 years with 95% confidence intervals are  
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47 shown in **Table 2**.  
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51 There were 178 non-fatal adverse events in 116 patients, mostly hospital admissions for  
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53 chest pain.  
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### 58 **Cost-utility**

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3 **Table 3** shows some of the highest incurred follow up costs for the 4 groups and shows that  
4 patient management varied substantially between individuals. Although angiography was the  
5 most expensive of the four initial diagnostic tests, the strategy of initial angiography had  
6 lower mean overall cost than stress echo, and was similar to CMR up to 3 years (**Table 2**).  
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8 Extra costs for patients in the three non-invasive groups was largely due to patients  
9 undergoing follow-on angiography. There were no significant differences in overall costs  
10 between the groups.  
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19 During the study there were no significant differences in EQ-5D between the groups. **Figure**  
20 **3** shows daily mean EQ-5D utility over time based on interpolation between measurements  
21 for survivors who completed the EQ-5D. Using inverse-weighting we calculated QALYs over  
22 different time horizons and these are presented up to 3 years in Table 2. Mean QALYs over  
23 3 years in the angiography group was 2.24, which was not significantly different from the  
24 other groups. The mean differences between groups are so close to zero in all 3 cases that  
25 the cost per QALY estimates are unstable and a cost-minimization approach may be more  
26 appropriate. This would favour SPECT.  
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### 38 **Sensitivity analysis**

39 The comparisons between the diagnostic strategy groups did not change substantially when  
40 we varied the time horizon; the main effect of this was that the variation surrounding  
41 estimates increased as the time horizon lengthened due to the heavy censoring (results not  
42 shown). **Tables 2a and 2b** show results for interventional and non-invasive cardiologists  
43 respectively. Patients who were managed by interventional cardiologists incurred higher  
44 costs due to the greater number of tests and revascularization procedures performed, with  
45 minimal incremental benefit in QALY.  
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### 55 **Discussion**

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3 CECaT is the first completed prospective randomized trial to look at the clinical and cost-  
4 effectiveness of non-invasive imaging in the diagnosis and management of angina. To the  
5 best of the authors' knowledge there has been no comparable outcomes trial published on  
6 this scale evaluating three independent non-invasive 'gatekeeper' modalities versus initial  
7 angiography in stable chest pain. The trial is also unusual in the length of prospective follow  
8 up extending to 6 years for mortality outcomes.  
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17 We have demonstrated that use of any one of stress CMR, stress echo or stress SPECT as  
18 the initial test for a stable chest pain patient leads to non-inferior outcomes in quality of life  
19 and cost utility compared to patients randomised to upfront invasive coronary angiography.  
20 Typically, non invasive tests perform well in low risk populations because of a negative  
21 predictive value which is usually better than the positive predictive value. However, the  
22 patient risk profile was relatively high in our study, and despite this there was no significant  
23 difference between an initial functional or anatomic approach.  
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33 There are several reasons why initial angiography may not have led to clear benefit in our  
34 study. Firstly, although angiography has stood at the heart of the diagnostic chest pain  
35 pathway, the traditional binary cut-off values of 50% or 70% percentage stenosis by visual  
36 estimation were shown in the FAME study to bear little relation to the true physiologic  
37 significance of luminal narrowing <sup>(23)</sup>.  
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45 Secondly, data from various countries suggest that not only is coronary angiography often  
46 inappropriate when formally rated by expert observers <sup>(24) (25)</sup> but that disparate national or  
47 regional rates of angiography do not translate into clear mortality benefits between countries  
48 <sup>(26) (27) (28) (29)</sup> and on occasion may even demonstrate an inverse relationship <sup>(30)</sup>.  
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54 Contemporary US data from approximately 500,000 PCI procedures collected prospectively  
55 in the National Cardiovascular Data Registry demonstrated that, of 145,000 elective PCI  
56 cases, roughly 12% were judged inappropriate. Furthermore, the rate of inappropriate  
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3 elective PCI between hospital sites ranged from 0-55% suggesting significant variability in  
4 practice <sup>(31)</sup>. The data suggest a better way of selecting patients for invasive investigation is  
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7 needed.

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11 Ischemia-driven revascularisation has been shown to be of benefit in a number of trials,  
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13 most recently in the FAME study in which an invasive method of measuring the flow reserve  
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15 of the microcirculation (Fractional Flow Reserve, FFR) was used to allocate patients to  
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17 intervention or observation vs a clinical decision on intervention based on angiography alone  
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19 <sup>(32)</sup>. At 2 years follow up there were clear survival and MACE benefits to the FFR-based  
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21 approach.  
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25 The ACRE study reported that, up to 6 years after diagnosis, medical management was a  
26  
27 more cost-effective strategy for angina compared with PCI <sup>(33)</sup>. The lack of evidence for  
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29 survival from revascularisation - except for selected patients with evidence of ischemia - was  
30  
31 also seen in the COURAGE trial <sup>(4)</sup>. Critics have suggested this may be because  
32  
33 randomization to PCI versus OMT was made *after* coronary angiography had been  
34  
35 performed, potentially leading to a recruitment bias of patients with less severe disease. In  
36  
37 the CECaT trial this bias was avoided by randomization to a management strategy defined  
38  
39 by the non-invasive test result for each of the 3 functional arms of the trial. In a relatively  
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41 high risk population, we demonstrated no clinically significant survival or economic detriment  
42  
43 from using non-invasive imaging as a gate-keeper to catheterization. Similarly, quality of life  
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45 was not significantly different across all four groups and these differences extended to a  
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47 warranty period of at least 3 years.  
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51 We did observe a marginal decrease in survival in the CMR arm. The reasons for the  
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53 difference are unclear but do not relate to patient characteristics or management with CABG  
54  
55 or PCI. Although statistically significant, the mean survival difference from the other groups  
56  
57 was only 4 weeks over 3 years and is unlikely to be clinically meaningful. Since recent work  
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3 has established a strong correspondence between FFR measurements and stress CMR  
4 perfusion indices it would be surprising if CMR were genuinely inferior to other modalities for  
5 risk stratification <sup>(34)</sup>. Indeed several recent publications have highlighted the incremental  
6 prognostic data (above that obtained from clinical variables) derived from several thousand  
7 perfusion CMR studies <sup>(35) (36)</sup>.  
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15 Given the recent publication of the CEMARC trial <sup>(37)</sup> in which a clear diagnostic superiority  
16 was demonstrated for stress CMR over SPECT, it is interesting that our data nonetheless  
17 show an equivalence in functional health status between those randomized to SPECT  
18 versus CMR in the CECaT trial. The implication may be that although CMR detects the  
19 presence of *any* ischemia with a greater sensitivity it is the *overall burden* of ischemia that  
20 alters a patient's prognosis. As such, it has not yet been demonstrated that the higher  
21 diagnostic accuracy of CMR translates into better long-term patient outcomes – a fact  
22 acknowledged by Greenwood et al subsequent to CEMARC's publication <sup>(38)</sup>. In this context  
23 the CECaT nuclear results are congruent with numerous past publications and reconfirm the  
24 reassuring warranty period of a normal SPECT study.  
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### 37 **Cost effectiveness**

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39 There was no significant difference in cost-effectiveness between the angiography -as-  
40 default group and the non-invasive test groups up to 3 years, perhaps relating to the higher-  
41 than-anticipated rate of referral for angiography after negative functional tests. Protocol  
42 deviation of this kind is not infrequent in trials of non-invasive technology. In the recent  
43 PARR-2 study of patients undergoing fluorodeoxyglucose positron emission tomography for  
44 the assessment of viability, roughly 25 % of the study population did not adhere to protocol  
45 <sup>(39)</sup>. The willingness of a cardiologist to defer referral for coronary angiography in the face of  
46 a normal non-invasive study may in part reflect individual prejudices and job description  
47 (interventional versus non-invasive) as demonstrated in a recent survey of cardiology  
48 attitudes <sup>(40)</sup> and was also reflected in our own data.  
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5 In CECaT, 20-25% of patients receiving a non-invasive test did not go on to have  
6 angiography. A proportion of the additional cost in the non-invasive arms related to  
7 angiography and PCI in the patients with a *negative* test, although only very few  
8 subsequently required CABG - a robust marker of significant disease - during follow-up. This  
9 readiness to employ PCI in a group in whom the indication/benefit is debatable was also  
10 seen in the ACRE trial <sup>(33)</sup> and reflects understandable clinical response to uncertainty but  
11 also the easy access to PCI in healthcare systems without barriers to self-referral <sup>(41)</sup>.  
12  
13 Similarly, studies from the US have demonstrated a greater willingness to use coronary  
14 angiography when available 'on site' as is increasingly seen even in small-to-medium sized  
15 hospitals <sup>(42) (43) (44)</sup>.

### 26 27 **Cost effectiveness of each non-invasive technique**

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31 Nuclear myocardial perfusion imaging

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35 The END study used propensity matching to compare a large cohort of patients referred for  
36 either gate-keeper myocardial perfusion imaging or upfront angiography – this non  
37 randomised study demonstrated a significant cost reduction in the <sup>(45)</sup> nuclear arm. In  
38 contrast to this and other work <sup>(46) (47) (48)</sup> we were unable to show a significant difference in  
39 cost effectiveness in our own study. To some extent this reflected the participating physician  
40 bias towards angiography during the period of trial recruitment (2001-2006) with many  
41 patients referred for angiography despite normal perfusion studies. This continues in the  
42 contemporary era with Chan et al demonstrating that almost 80% of Delphi-adjudicated  
43 inappropriate elective PCIs were performed following either low risk ischemia imaging in  
44 mildly symptomatic patients or intermediate risk imaging in entirely asymptomatic patients  
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56 <sup>(31)</sup>.

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3 In the CECaT study, when PCI was performed despite a negative initial non-invasive test,  
4 this occurred because subsequent angiography indicated 'significant' stenosis. This was a  
5 clinical judgment based on 'eyeball assessment' of lesion severity as has been reported in  
6 clinical trials with angiographic end points <sup>(49)</sup>. However, the severity and functional  
7 significance of many stenoses may be over-called, even by quantitative assessment, when  
8 compared with physiological assessment of fractional flow reserve across the lesion <sup>(50)</sup> <sup>(51)</sup>.  
9 Further improvement in cost-effectiveness could likely have been achieved in the nuclear  
10 arm of the trial. Our post-trial practice is to perform the stress SPECT first - and if this is  
11 negative - cancel the rest test, likely augmenting the relative cost-effectiveness of SPECT  
12 <sup>(52)</sup>.

#### 23 24 25 CMR

26  
27 There are no other real-world data in the literature of which the authors are aware regarding  
28 the cost effectiveness of CMR .  
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#### 32 33 Stress echo

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35 Stress echocardiography may be a more cost-effective strategy than angiography for men  
36 aged 50-60 with CAD prevalence of 50%<sup>(53)</sup>,<sup>47</sup>. There is also some evidence that stress echo  
37 is more cost-effective than SPECT as an initial test <sup>(54)</sup> <sup>(55)</sup>, especially in women with  
38 suspected CAD <sup>(56)</sup>. A similar benefit was not seen in our study probably because of the high  
39 disease prevalence in our population. The lack of superiority of either stress  
40 echocardiography or a combined strategy of exercise testing and stress echo compared to  
41 upfront catheterisation was also evident in a recent Polish study of 600 patients with a  
42 similar age, gender and disease prevalence to our own study population <sup>(57)</sup>.  
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54 Taken overall, our data clearly demonstrate a limited future role for cost-effective non-  
55 invasive imaging if referring physicians are not willing to accept a negative result as ground  
56 truth. This might be interpreted as reflecting a need for greater physician education since we  
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3 showed a clear difference in onward referral rates for angiography after a negative test  
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5 between interventional and non-invasive cardiologists.  
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### 8 9 ***Clinical effectiveness***

10 We demonstrated that SPECT can obviate the need for coronary angiography for a  
11  
12 significant number of patients without any clinical detriment. In the stress echo group clinical  
13  
14 outcomes were also comparable to the angiography subgroup at 18 months. The CMR  
15  
16 group had statistically marginally poorer survival and this follows our earlier finding that CMR  
17  
18 patients had significantly worse exercise tolerance at 18 months after randomisation<sup>(10)</sup>. This  
19  
20 is difficult to explain on the basis of Pryor risk score or other baseline clinical variables.  
21  
22 However, the mean difference in survival between the CMR arm and the other groups was  
23  
24 only 4 weeks and thus of marginal clinical significance. More importantly, the CMR group  
25  
26 were not otherwise disadvantaged – compared to the angiographic control group - with  
27  
28 respect to major adverse events, other resource use, or quality of life.  
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### 32 33 ***Limitations***

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35 This study was carried out in a single specialist cardiothoracic centre with a significant  
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37 proportion of high risk, predominantly white European, male patients. Those eligible who  
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39 refused the trial were older and were more likely to be women.  
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43 We used the technology that was available to us at the onset of the trial. At that time, we  
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45 were not able to use attenuation correction for SPECT imaging; however this was also not  
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47 used in the much more recent CEMARC trial<sup>(37)</sup>. Similarly, we performed our CMR exams in  
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49 a mobile facility on a 1.5T scanner with only modest coil technology and limited temporal and  
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51 anatomic coverage that would compare unfavourably with the 3T whole heart high resolution  
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53 perfusion studies available today.  
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3 The trial aimed to reflect the strategy of using non-invasive imaging as a gateway to  
4 angiography in *contemporary clinical practice*. The test results were considered in  
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6 conjunction with other information available at the time. Thus it was not the aim to formally  
7  
8 assess diagnostic accuracy of the non-invasive tests in this context. This trial-based study  
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10 was limited to 3 year cost-effectiveness follow up - longer-term economic models would  
11  
12 provide lifetime estimates of the cost-effectiveness of the non-invasive strategies.  
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### 15 16 17 **Conclusions**

18  
19 We have demonstrated in the CECaT trial that stress echo, stress CMR and stress SPECT  
20  
21 may each be used to defer invasive coronary angiography without clinical detriment or  
22  
23 significant excess costs in an outpatient population with stable chest pain.  
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### 39 40 **Competing interests**

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42  
43 All authors have completed the ICMJE uniform disclosure form at  
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49 Medical Research Council [Programme number U015232027] for the submitted work ; no  
50  
51 financial relationships with any organisations that might have an interest in the submitted  
52  
53 work in the previous three years; no other relationships or activities that could appear to  
54  
55 have influenced the submitted work  
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**Contributorship statement**

HT performed literature review, data analysis and interpretation; NW was involved in image analysis, drafting the manuscript and critical revision; VH was involved in recruiting the patients, data management, administering health questionnaires, data analysis and drafting the manuscript; MD and MB were responsible for data analysis, health economic assessment, drafting the manuscript and critical revision; LDS was responsible for study design, trial management, statistical analysis, drafting the manuscript and critical revision; CJ performed statistical and health economic analysis, drafting the manuscript and critical revision; AMC was involved in study design, patient recruitment, image interpretation, trial management, drafting the manuscript and critical revision and is the overall guarantor of manuscript integrity.

All authors have read the manuscript in its submitted form and have provided final approval for publication.

**Table 1 Baseline characteristics\***

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
Demographics				
Mean (SD) age (years)	60.7 (9.1)	62.1 (9.5)	62.2 (9.0)	61.9 (9.9)
Males (%)	149 (67%)	157 (70%)	153 (68%)	160 (71%)
Mean (SD) BMI (kg/m <sup>2</sup> )	27.6 (4.2)	27.3 (4.3)	28.0 (4.4)	27.9 (4.2)
History/risk factors				
Previous MI (%)	63 (28%)	52 (23%)	69 (31%)	59 (26%)
Previous CVA (%)	10 (5%)	13 (6%)	8 (4%)	12 (5%)
Peripheral VD (%)	20 (9%)	21 (9%)	17 (8%)	18 (8%)
Diabetes(%)				
IDDM	12 (5%)	8 (4%)	11 (5%)	5 (2%)
NIDDM	16 (7%)	18 (8%)	21 (9%)	22 (10%)
Family history CAD	60 (27%)	55 (25%)	63 (28%)	59 (26%)
Smoking history (%)				
<25 pack years	149 (67%)	162 (72%)	148 (65%)	155 (69%)
>=25 pack years	73 (33%)	62 (28%)	78 (35%)	71 (31%)
Treated hyperlipidaemia	164 (74%)	171 (76%)	179 (79%)	179 (79%)
(%)				
Treated hypertension (%)	117 (53%)	132 (59%)	115 (51%)	129 (57%)
Exercise tolerance <sup>a</sup>				
Mean (SD) total exercise time (mins)	11.29 (4.56)	10.46 (4.41)	10.43 (4.43)	10.89 (4.36)
Angina during EET	108 (49%)	96 (43%)	111 (49%)	117 (52%)
ECG changes on exercise test				
1-2 mm ST depression with symptoms	53 (24%)	43 (19%)	54 (24%)	57 (25%)

>= 2mm ST depression	16 (7%)	24 (11%)	20 (9%)	24 (11%)
without symptoms				
ST elevation/ no change	153 (69%)	157 (70%)	152 (67%)	145 (64%)
<hr/>				
CCS class				
0-I	60 (27%)	54 (24%)	78 (35%)	58 (26%)
II	138 (62%)	144 (64%)	122 (54%)	132 (58%)
III-IV	24 (11%)	26 (12%)	26 (11%)	36 (16%)

\* There were no significant differences between the groups in any variable



**Table 2 Cost-effectiveness summaries to 3 years post randomization**

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
Hazard ratio for death	Baseline	0.99	2.60	1.42
(95%CI)		(0.35,2.85)	(1.09,6.22)	(0.54,3.74)
Mean survival (years)	2.96	2.95	2.90	2.94
(95%CI)	(2.92, 2.99)	(2.90, 2.99)	(2.83, 2.95)	(2.89, 2.97)
Mean difference vs. CA	-	-0.01	-0.06	-0.02
(95%CI)	-	(-0.07,0.05)	(-0.14, 0.01)	(-0.08, 0.04)
Mean QALYs	2.24	2.27	2.18	2.27
(95%CI)	(2.16,2.30)	(2.20,2.33)	(2.11,2.25)	(2.20,2.33)
Mean difference vs. CA	-	0.03	-0.05	0.03
(95%CI)	-	(-5.30,1.20)	(-4.50,2.01)	(-3.08,3.95)
Mean discounted costs (£)	5189	4549	4839	5421
(95%CI)	(4235, 6410)	(4095, 5030)	(4363, 5329)	(4753, 6148)
Mean difference vs. CA	-	-640	-349	232
(95%CI)		(-1933, 436)	(-1642, 735)	(-1123, 1441)

**Table 2a Cost-effectiveness summaries for patients managed by interventional cardiologists to 3 years post randomization**

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
Mean survival (years)	2.96	2.97	2.89	2.96
(95%CI)	(2.91, 2.98)	(2.93, 3.00)	(2.80, 2.97)	(2.90, 2.98)
Mean difference vs. CA	-	0.01	-0.07	0
(95%CI)	-	(-0.05,0.07)	(-0.17, 0.02)	(-0.07,0.05)
Mean QALYs	2.25	2.29	2.21	2.2
(95%CI)	(2.14,2.36)	(2.19,2.38)	(2.10,2.32)	(2.09,2.29)
Mean difference vs. CA	-	0.03	-0.04	-0.06
(95%CI)	-	(-5.48,2.06)	(-5.22,2.21)	(-3.11,6.17)
Mean discounted costs (£)	5664	5095	5176	6198
(95%CI)	(4591, 6862)	(4361, 5882)	(4476, 5887)	(5028, 7521)
Mean difference vs. CA	-	-569	-487	534
(95%CI)	-	(-2001, 751)	(-1906, 806)	(-1136, 2251)

**Table 2b Cost-effectiveness summaries for patients managed by non-interventional cardiologists to 3 years post randomization**

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
Mean survival (years)	2.95	2.93	2.9	2.92
(95%CI)	(2.89, 2.99)	(2.85, 2.98)	(2.81, 2.97)	(2.85, 2.98)
Mean difference vs. CA	-	-0.02	-0.05	-0.03
(95%CI)	-	(-0.11,0.06)	(-0.15, 0.04)	(-0.11, 0.05)
Mean QALYs	2.23	2.25	2.17	2.32
(95%CI)	(2.14,2.31)	(2.16,2.33)	(2.07,2.26)	(2.23,2.41)
Mean difference vs. CA	-	0.02	-0.06	0.09
(95%CI)	-	(-7.32,1.90)	(-5.98,3.37)	(-5.84,3.39)
Mean discounted costs (£)	4924	4151	4637	4693
(95%CI)	(3639, 6731)	(3583, 4748)	(3994, 5307)	(4054, 5365)
Mean difference vs. CA	-	-774	-287	-231
(95%CI)	-	(-2672, 692)	(-2183,1229)	(-2133, 1238)

**Table 3 Summary of the frequency of use of the main resource use elements during follow up (excluding initial diagnostic test)**

Resource use (unit cost)	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
CABG (£7195)	28	33	28	34
PCI (£3660)	57	46	60	62
Other hospital admission (£467 per day)	36	29	28	53
Angiography (£951)	12	183	175	181
SPECT (£902)	16	3	3	6
Cardiac MRI (£307)	5	5	12	5
Echocardiography (£59)	30	17	24	18
PET scan (£842)	0	3	0	1
Preadmission clinic (£85)	22	21	27	24
Follow up clinic (£85)	19	22	31	21
Outpatient visits (£143)	247	270	300	284
Myocardial Infarctions	3	4	5	10

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3 **Figure Legends**  
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7 **Figure 1 CONSORT diagram describing recruitment and randomization**  
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11 **Figure 2 Kaplan-Meier survival estimates according to initial modality of diagnosis**  
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15 **Figure 3 Quality of life assessed by EQ5D over time**  
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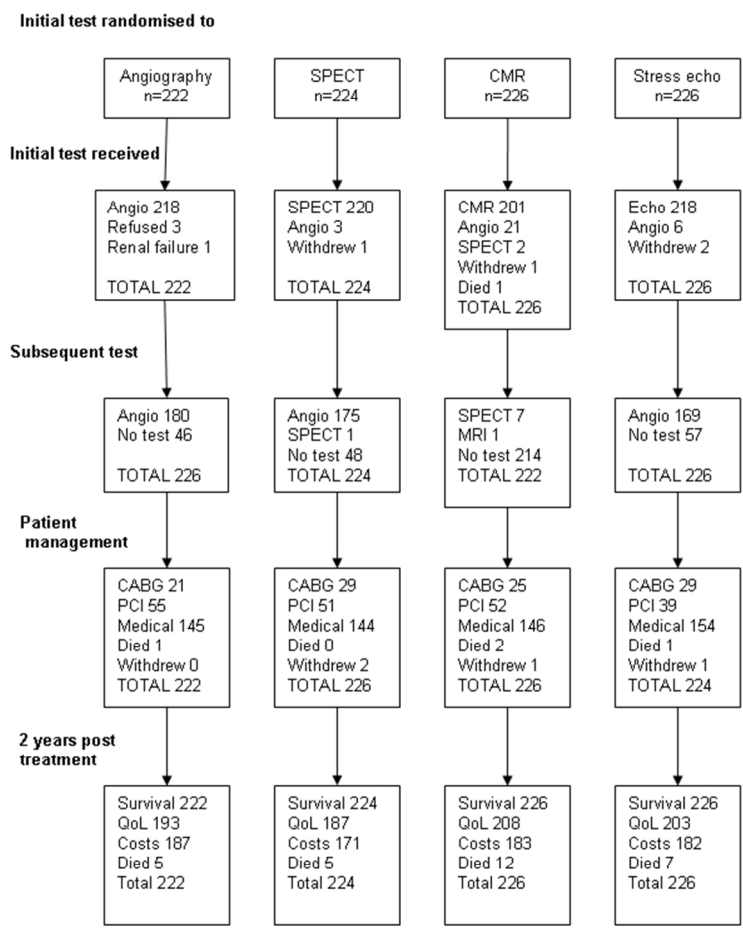
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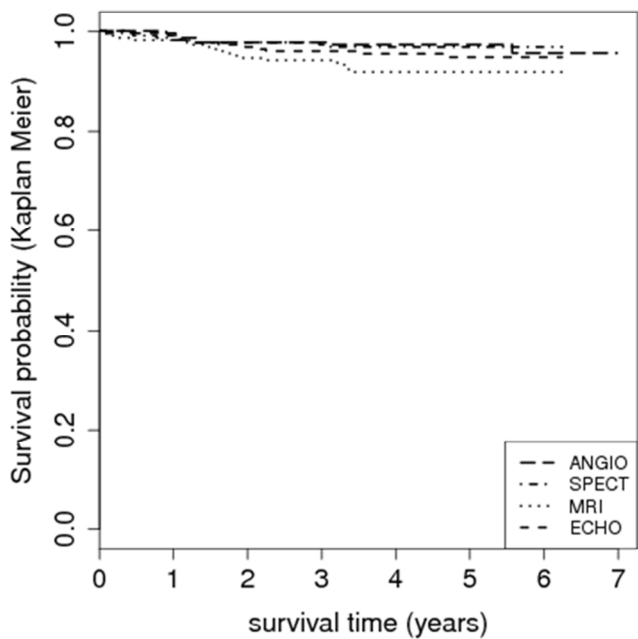
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CONSORT diagram describing trial recruitment and randomisation  
190x254mm (96 x 96 DPI)

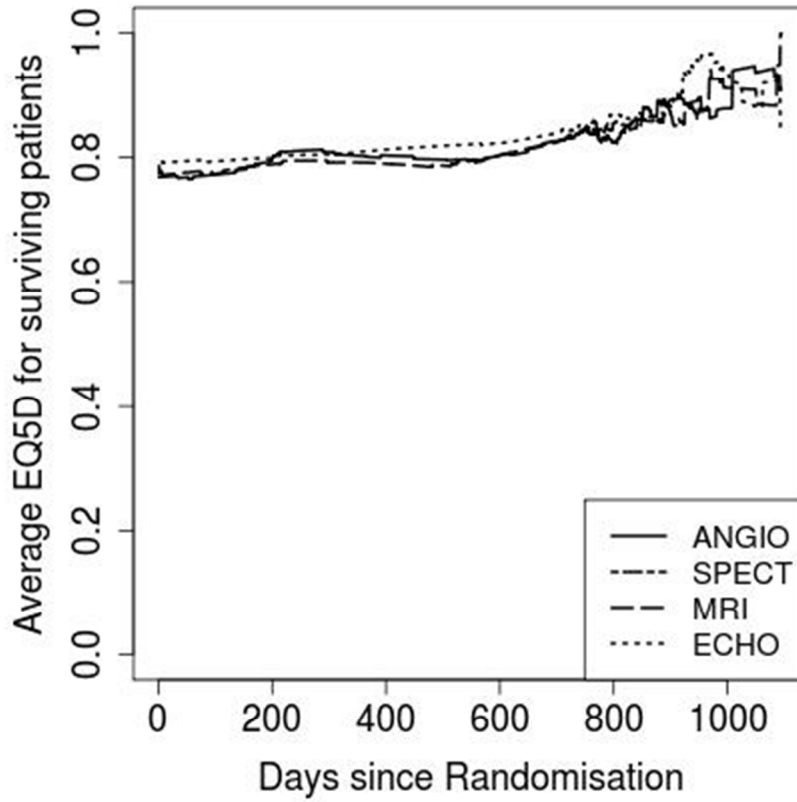
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Kaplan-Meier survival estimates according to initial modality of diagnosis  
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Review only

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169x169mm (72 x 72 DPI)

only





**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**

Journal:	<i>BMJ Open</i>
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Article Type:	Research
Date Submitted by the Author:	20-Oct-2013
Complete List of Authors:	Thom, Howard; Institute of Public Health, Biostatistics West, Nicholas; Papworth Hospital, Cardiology Hughes, Vikki; Papworth Hospital, Research & Development Dyer, Matthew; Brunel University, Health Economics Research Group Buxton, Martin; Brunel University, Health Economics Research Group Sharples, Linda; Institute of Public Health, Biostatistics Jackson, Christopher; Institute of Public Health, Biostatistics Crean, Andrew; Toronto General Hospital, Cardiology
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Health economics, Health policy, Health services research, Medical management, Radiology and imaging
Keywords:	Adult cardiology < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Cardiology < INTERNAL MEDICINE, Cardiovascular imaging < RADIOLOGY & IMAGING

SCHOLARONE™  
Manuscripts

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4 1 **Title: Cost effectiveness of initial stress cardiovascular MR, stress SPECT or stress**  
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6 2 **echocardiography as a gatekeeper test, compared to upfront invasive coronary**  
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8 3 **angiography in the investigation and management of patients with stable chest**  
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10 4 **pain: mid term outcomes from the CECaT\* randomised controlled trial**  
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14 6 \*Cost Effectiveness of non-invasive Cardiac Testing  
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56 29 **Clinical Trial registration:** ISRCTN 47108462, UKCRN 3696  
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3 30 **The CECaT study group were:**  
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5 31 Johanna Armstrong, Martin Buxton, Noreen Caine, Richard Coulden, Andrew Crean,  
6

7 32 Matthew Dyer, Margaret Gillham, Hester Goddard, Kim Goldsmith, Vikki Hughes, Evelyn  
8

9 33 Lee, Roger Patel, Peter Schofield, Linda Sharples, Emer Sonnex, David Stone, Carmen  
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11 34 Treacy  
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13 35 **Key words:** MRI, cardiovascular magnetic resonance, comparative effectiveness, SPECT,  
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15 36 stress echo, coronary angiography  
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17 37 **Trial registration:** ISRCTN 47108462, UKCRN 3696  
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3 58 **Abstract**

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5 59 **Objectives:** to compare outcomes and cost effectiveness of various initial imaging strategies on  
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7 60 the management of stable chest pain in a long term prospective randomized trial.

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9 61 **Setting:** regional cardiothoracic referral center in the east of England

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11 62 **Participants:** 898 patients (69% male) entered the study with 869 alive at 2yr follow up.  
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13 63 Patients were included if they presented for assessment of stable chest pain with a positive  
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15 64 exercise test and no prior history of ischemic heart disease. Exclusion criteria were recent  
16  
17 65 infarction, unstable symptoms or any contra-indication to stress MRI.

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19 66 **Primary outcome measures:** The primary outcomes of this follow up study were survival up  
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21 67 to a minimum of 2 years post-treatment, quality-adjusted survival and cost-utility of each  
22  
23 68 strategy

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25 69 **Results:** 898 patients were randomized. Compared to angiography, mortality was  
26  
27 70 marginally higher in the groups randomized to CMR (hazard ratio 2.6, 95%CI 1.1, 6.2), but  
28  
29 71 similar in the SPECT-MIBI (hazard ratio 1.0, 95%CI 0.4, 2.9) and ECHO groups (hazard ratio  
30  
31 72 1.6, 95%CI 0.6, 4.0). Although SPECT-MIBI was marginally superior to other non-invasive  
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33 73 tests there were no other significant differences between the groups in mortality, quality  
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35 74 adjusted survival or costs.

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37 75 **Conclusions:** Non-invasive cardiac imaging can be used safely as the initial diagnostic test  
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39 76 to diagnose CAD without adverse effects on patient outcomes or increased costs, relative to  
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41 77 angiography. These results should be interpreted in the context of recent advances in  
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43 78 imaging technology.

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3 86 **Article summary:**

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5 87 **Article focus:**

- 6  
7 88 1. Is non-invasive imaging a safe and appropriate gate-keeper to coronary  
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9 89 angiography in patients with stable chest pain ?
- 10  
11 90 2. Is there any difference in cost-effectiveness and cost-utility between the  
12  
13 91 different non-invasive approaches and conventional coronary angiography
- 14  
15 92 3. Are patients disadvantaged in any meaningful way by having a non-invasive  
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17 93 test to decide whether they should go forward for coronary angiography ?
- 18  
19 94 4. How does stress perfusion CMR compare to the more established tests of  
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21 95 SPECT-MIBI and stress echocardiography as a gate-keeper to coronary  
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23 96 angiography ?

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25 97  
26  
27 98 **Key messages:**

- 28  
29 99 1. Non-invasive testing may be used safely as a gate-keeper to coronary  
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31 100 angiography in patients with stable chest pain without any material  
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33 101 disadvantage to them in terms of survival and quality of life up to 6 years after  
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35 102 initial randomisation.
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37 103 2. SPECT-MIBI appears marginally superior statistically to the other non-invasive  
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39 104 methods although clinically meaningful differences are small between all  
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41 105 strategies.
- 42  
43 106 3. Stress perfusion CMR appears to be an effective technique in a stable out-  
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45 107 patient population with undiagnosed chest pain.

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49 109 **Strengths and limitations:**

- 50  
51 110 1. This is the only large randomised prospective trial of a strategy of non-invasive  
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53 111 gate-keeper cardiac imaging versus upfront angiography in the literature.
- 54  
55 112 2. The cost-utility data are derived from NHS tariffs and our results are not  
56  
57 113 necessarily directly transferrable to other healthcare systems

## 114 Introduction

115

116 CAD is common and its management is costly<sup>(1)</sup>. Revascularisation using bypass surgery  
117 (CABG) or percutaneous coronary intervention (PCI) is effective for patients with severe  
118 disease<sup>(2)</sup> but a significant minority of patients do not gain symptomatic relief<sup>(3)</sup>. Data from  
119 the COURAGE trial did not show prognostic benefit from revascularization in any patient  
120 subgroup<sup>(4)</sup>. The yield of coronary angiography is variable with one recent large study of  
121 nearly 400, 000 patients demonstrating a normalcy rate approaching 40%<sup>(5)</sup>. Therefore  
122 non-invasive testing to identify those with a low likelihood of obstructive CAD may be safer,  
123 cheaper and more appropriate than upfront angiography. This approach is codified in  
124 multiple AHA/ACC guidelines on the investigation of stable or suspected angina pectoris in  
125 which initial non-invasive imaging is rated as highly appropriate<sup>(6) (7) (8) (9)</sup>.

126

127 The 'Cost-Effectiveness of non-invasive Cardiac Testing' (CECaT) trial was an unblinded  
128 non-inferiority trial designed to assess three functional tests - stress echocardiography,  
129 single photon emission computed tomography (SPECT) and stress cardiac magnetic  
130 resonance imaging (CMR) - as a gatekeeper to coronary angiography (CA) in patients  
131 referred for CA with suspected coronary artery disease (CAD). Early clinical and cost-  
132 effectiveness estimates have been published and showed that the CMR group had slightly  
133 lower mean exercise treadmill time according to the Bruce protocol but otherwise the tests  
134 could be considered equally effective<sup>(10)</sup>. This report provides the main cost-effectiveness  
135 and mortality outcomes up to 6 years after randomisation.

136

## 137 Methods

### 138 Study design

139 The design of the study has been described elsewhere<sup>(10)</sup> and is reviewed briefly here. All  
140 patients referred to Papworth Hospital, UK for non-urgent angiography were eligible for the  
141 study. Inclusion criteria were: established or suspected chronic stable angina and a positive

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3 142 exercise tolerance test result with subsequent referral for angiography. Exclusion criteria  
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5 143 were: recent MI (<3 months), revascularisation (<6 months); urgent need for  
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7 144 revascularisation; contra-indication to adenosine or CMR; inability to exercise.  
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11 146 Trial design was of four parallel arms with a 1:1:1:1 randomisation ratio. Randomisation was  
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13 147 computer generated and stratified according to Pryor risk assessment<sup>(11)</sup>. Within each Pryor  
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15 148 risk group, randomisation was in blocks of length 6 or 8. Sequentially numbered group  
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17 149 designation was held in the Research & Development (R&D) Office and was not available to  
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19 150 trial personnel. Patients were randomised to their initial diagnostic test - stress SPECT,  
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21 151 stress CMR, stress echocardiography, or angiography - by R&D within 4 weeks of  
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23 152 recruitment and only after they had given consent and been registered.  
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27 154 Non invasive imaging results were returned with a recommendation to proceed with  
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29 155 angiography only when reported as 'positive' for inducible ischemia. Protocol adherence to  
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31 156 this recommendation was not mandated by trial design and patients proceeded to  
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33 157 angiography if considered clinically indicated. Treatment with PCI or CABG (performed  
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35 158 within six months of angiography) or to medical therapy was according to standard practice.  
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### 38 160 **Coronary angiography.**

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41 161 Standard diagnostic angiography was performed from the right femoral artery approach<sup>(12)</sup>.  
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43 162 A minimum of 5 views of the left and 3 views of the right coronary system were taken<sup>(13)</sup>. All  
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45 163 examinations were reported by an experienced staff cardiologist and segmental location of  
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47 164 disease (if any) recorded.  
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### 50 166 **Stress echocardiography**

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53 167 Beta-blocker medications were stopped 2 days beforehand. Dobutamine was infused at  
54  
55 168 rates of 10- 40 mcg/kg/min, increased at 3 minute intervals. If necessary, 300-600  
56  
57 169 micrograms of atropine were added at peak stress to achieve 90% of target heart  
58  
59  
60

1  
2  
3 170 rate. Images were acquired in standard planes in the final minute of each 3 minute stage.  
4  
5 171 Intravenous microspheres were used to delineate the endocardial surface. All examinations  
6  
7 172 were reported by one of two staff cardiologists experienced in stress echocardiography.  
8  
9 173 Studies were positive for ischemia if stress-induced deterioration in contractility was  
10  
11 174 observed.

175

**176 SPECT**

177 Rest/stress 99mTc sestamibi (99mTc MIBI) SPECT was performed (2 day protocol). A 6  
178 minute adenosine infusion (140 µg/kg/min) was employed. 400 MBq 99m-Tc MIBI was  
179 administered at 3 minutes after infusion of adenosine was started. Gated SPECT imaging  
180 occurred 60 minutes after injection. Tomographic images were assessed for fixed and  
181 reversible defects by a single observer (as per established criteria)<sup>(14)</sup>.

182

**183 CMR**

184 Stress CMR imaging was performed at a standard similar to that which was subsequently  
185 recommended by the Society of Cardiovascular Magnetic Resonance <sup>(15)</sup>. A 1.5T mobile  
186 CMR system and 4-channel phased array surface coil were used (Signa CV/i, GE Medical  
187 Systems). Stress/rest dynamic first-pass perfusion imaging was performed. A hybrid fast  
188 gradient echo/echoplanar sequence was employed <sup>(16)</sup>. Adenosine was infused at 140  
189 mcg/kg/min for 4 minutes. After 3 minutes, a bolus of Gadolinium-DTPA (0.1mmol/kg) was  
190 delivered at 5mls/sec, followed by a 25ml saline flush. First-pass imaging of the heart  
191 occurred over 80 heart beats. A volumetric notched-saturation pre-pulse preserved a  
192 constant saturation-recovery time during slice acquisition <sup>(17)</sup>. 6-8 short axis slices were  
193 obtained every 2 heart beats. Rest imaging was repeated after a minimum interval of 15  
194 minutes. Cine steady state free precession images and late gadolinium enhancement  
195 images were also acquired as described in the original CECaT protocol <sup>(10)</sup> Studies were  
196 reported as positive if there was an inducible perfusion defect visible for at least 5 frames



1  
2  
3 197 either: a) in a region of normal wall thickness; or b) in a region of myocardial thinning in the  
4  
5 198 absence of a history of prior myocardial infarction.  
6

7 199

## 8 9 200 **Outcomes**

10  
11 201 The primary outcome in the original CECaT trial was exercise treadmill time at 18 months  
12  
13 202 post-randomisation using the modified Bruce protocol, in which exercise intensity was  
14  
15 203 increased every 3 minutes. There was a range of secondary outcomes including diagnostic  
16  
17 204 accuracy, clinical events, health-related quality and cost-effectiveness of life up to 18 months  
18  
19 205 after randomisation<sup>(10)</sup>.

20  
21 206 The primary outcomes of this follow up study were survival up to a minimum of 2 years post-  
22  
23 207 treatment, quality-adjusted survival and cost-utility of each strategy. Survival status at the  
24  
25 208 end of follow up was determined from the Office for National Statistics database, UK  
26  
27 209 (<http://www.ons.gov.uk/>).

28  
29 210 Quality of life was measured using the EuroQoL EQ-5D questionnaire<sup>(18)</sup> which was  
30  
31 211 completed at baseline, 6 and 18 months post-randomisation, and at 6, 18 and 24 months  
32  
33 212 post-treatment. The social tariff for the EQ-5D was applied in order to calculate utility values  
34  
35 213<sup>(19)</sup>. Because post-treatment measurements were at variable times post-randomisation  
36  
37 214 (randomisation date is time zero for a randomised trial) daily utilities were estimated using  
38  
39 215 linear interpolation.  
40

41 216

## 42 43 217 **Sample size calculations**

44  
45 218 The sample size of 898 patients was based on exercise performance and was calculated  
46  
47 219 according to the methodology published in the initial report of the CECaT study<sup>(10)</sup>.

48  
49 220

## 50 51 221 **Statistical and economic analysis**

52  
53 222 For this study, survival was summarised using Kaplan-Meier estimates and the groups were  
54  
55 223 compared using Cox proportional hazards regression. This assumes that the instantaneous  
56  
57 224 risk of death (hazard) for a reference value of a covariate will vary through time, but that the  
58  
59  
60

1  
2  
3 225 hazards for other values of the covariate will be a constant multiple of this baseline hazard,  
4  
5 226 and this multiple will not vary through time. This assumption was tested using Schoenfeld  
6  
7 227 residuals and there was little evidence against it. The diagnostic test was entered into the  
8  
9 228 Cox regression as a 4-level fixed covariate, with angiography as the reference category. In  
10  
11 229 sensitivity analysis CABG and PCI were included in the regression analyses as time-varying  
12  
13 230 covariates, taking a value 0 up to the time of intervention and 1 thereafter, to ensure that any  
14  
15 231 differences between the groups was not due to differences in treatment. Inclusion of  
16  
17 232 treatment (CABG/PCI) did not affect comparison of diagnostic strategies and results of these  
18  
19 233 analyses are not included here.  
20  
21 234  
22  
23 235 Patient-specific hospital resource use was collected for 2 years post-treatment with  
24  
25 236 revascularisation or medical management. Costs were based on National Health Service  
26  
27 237 reference costs 2005/06 prices. An annual discount rate of 3.5% was applied to all costs and  
28  
29 238 quality-adjusted life-years (QALYs) after 12 months post-randomisation. Resources costed  
30  
31 239 were: imaging tests; revascularisation; inpatient/outpatient episodes; adverse events;  
32  
33 240 cardiac-related medications. Patient-reported admissions for MI were verified with the  
34  
35 241 admitting hospital and adjudicated.  
36  
37 242  
38  
39 243 Quality adjusted survival and cost estimates were censored at the last follow up at 2 years  
40  
41 244 after treatment, resulting in varying duration of follow-up from the time of randomisation to  
42  
43 245 the different diagnostic strategies, so that mean values over a range of time horizons were  
44  
45 246 estimated using inverse weighting methods<sup>(20)</sup>. This method allows for differing follow up  
46  
47 247 times between patients by splitting follow up time into intervals, and up-weighting the  
48  
49 248 observed quality adjusted survival and costs in an interval in proportion to the inverse of the  
50  
51 249 Kaplan-Meier estimate of the proportion observed during the interval. In the base case we  
52  
53 250 used a time horizon of 3 years since it was the longest period over which results were stable,  
54  
55 251 with acceptable precision. Confidence intervals for costs and QALYs were estimated using  
56  
57 252 bootstrapping with 5000 samples<sup>(21)</sup>.  
58  
59  
60

1  
2  
3 253 **Sensitivity analysis**

4  
5 254 Sensitivity of cost-utility results for different time horizons was assessed by re-estimating  
6  
7 255 results up to 12, 18, 24, 36 and 48 months after randomization. In addition, cardiologists  
8  
9 256 were divided into those who did and did not perform percutaneous coronary intervention as  
10  
11 257 part of their routine clinical practice, and results were recalculated for each subgroup. With  
12  
13 258 the exception of this *post-hoc* data interrogation, all other results presented derive from  
14  
15 259 intention-to-treat analysis.  
16

17 260

18  
19 261 The study had IRB approval and full written informed consent was obtained from all  
20  
21 262 participants. All authors had full access to the data and take responsibility for the manuscript  
22  
23 263 as written.  
24

25 264

26  
27 265 **Results**

28  
29 266 **Recruitment and compliance**

30  
31 267 Between September 2001 and September 2004, 3,201 patients were assessed, 1,981 were  
32  
33 268 excluded and 322 refused entry to the trial. Refusals were more likely to come from women  
34  
35 269 (46% compared with 31% enrolled into the study,  $p<0.001$ ) and were significantly older  
36  
37 270 (mean age 64.6, (SD 10.1) compared with study group mean age 61.8, (9.4),  $p<0.001$ ).  
38

39 271

40  
41 272 898 patients were randomised. Groups were well matched at baseline (table 1). In each  
42  
43 273 group 69% of patients were high risk for CAD (Pryor score  $> 0.8$ ). The trial was closed to  
44  
45 274 recruitment in September 2004 after enrolling the pre-specified number of subjects.  
46

47 275

48  
49 276 One-hundred-seventy-five (78%) SPECT patients, 180 (80%) CMR patients and 169 (75%)  
50  
51 277 stress echo patients were referred on for angiography (**Figure 1**). Between 20% and 25% of  
52  
53 278 patients undergoing non-invasive tests did not require further investigation. Twenty-one  
54  
55 279 percent of patients who had negative tests were referred for angiography and the proportion  
56  
57 280 was similar in each group (SPECT  $n=45$ , CMR  $n=50$ , ECHO  $n=48$ ,  $p=0.858$ ). Of these 14  
58  
59  
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2  
3 281 (31%) SPECT, 26 (52%) CMR and 23 (48%) ECHO resulted in a positive angiogram  
4  
5 282 (p=0.130). Four patients died and four withdrew from the trial early on. Of the remaining  
6  
7 283 patients, revascularization was required in 34% (301/890 – see **Figure 1** for numbers in  
8  
9 284 each arm). There was no significant difference between the groups in initial patient  
10  
11 285 management (Figure 1, p=0.527). Beyond the initial management strategy 42 subsequent  
12  
13 286 revascularisation procedures were required in the angiography arm compared with 30 in the  
14  
15 287 SPECT, 44 in the CMR and 41 in the ECHO arms. The median times between  
16  
17 288 randomisation and initial revascularisation were 122 days in the angiography group, 192  
18  
19 289 days for SPECT, 184 days for CMR and 177.5 days for ECHO, resulting in a delay due to  
20  
21 290 functional testing of approximately 2 months.  
22

291

### 292 **Survival**

293 During the study there were 7 (3%), 7 (3%), 18 (8%) and 11 (5%) deaths in the angiography  
294 , SPECT, CMR and ECHO groups respectively. Kaplan-Meier survival curves for the 4  
295 groups are plotted in **Figure 2**. Survival in the SPECT (hazard ratio 1.0, 95%CI 0.4, 2.9) and  
296 stress echo (hazard ratio 1.6, 95%CI 0.6, 4.0) groups were not significantly different from  
297 angiography but the CMR group had higher mortality, with hazard ratio 2.6 (95%CI 1.1 to  
298 6.2), p=0.032 (**Table 2**). The significant effect of CMR on survival remained when CABG or  
299 PCI were included in the models. However, mortality was low in all groups and the absolute  
300 mean difference in survival was less than 1 month over 3 years (**Table 2**). Mean survival  
301 estimates over 3 years with 95% confidence intervals are shown in **Table 2**.

302 All patients had complete adverse event data up to 18 months post-randomisation during  
303 which there were 178 non-fatal adverse events in 114 patients, mostly hospital admissions  
304 for chest pain (**Table 3**). Beyond this time only adverse events that resulted in admissions  
305 were recorded as they were relevant for the economic analysis. No patient suffered any  
306 adverse event at the time of the initial randomised imaging test.

307

### 308 **Cost-utility**

1  
2  
3 309 **Table 4** shows some of the highest incurred follow up costs for the 4 groups and shows that  
4  
5 310 patient management varied substantially between individuals. Although angiography was the  
6  
7 311 most expensive of the four initial diagnostic tests, the strategy of initial angiography had  
8  
9 312 lower mean overall cost than stress echo, and was similar to CMR up to 3 years (**Table 2**).  
10  
11 313 Extra costs for patients in the three non-invasive groups was largely due to patients  
12  
13 314 undergoing follow-on angiography. There were no significant differences in overall costs  
14  
15 315 between the groups.  
16

17 316  
18  
19 317 During the study there were no significant differences in EQ-5D between the groups. **Figure**  
20  
21 318 **3** shows daily mean EQ-5D utility over time based on interpolation between measurements  
22  
23 319 for survivors who completed the EQ-5D. Using inverse-weighting we calculated QALYs over  
24  
25 320 different time horizons and these are presented up to 3 years in Table 2. Mean QALYs over  
26  
27 321 3 years in the angiography group was 2.24, which was not significantly different from the  
28  
29 322 other groups. **Figure 4** shows the joint distribution of the difference in mean cost against the  
30  
31 323 difference in mean QALY for each diagnostic strategy group and angiography alone, and  
32  
33 324 shows the uncertainty in these estimates. **Figure 5** shows the Cost-Effectiveness  
34  
35 325 Acceptability Curve and demonstrated that SPECT has a high chance (>70%) of being cost-  
36  
37 326 effective whatever the willingness-to-pay threshold is but for CMR and ECHO there is much  
38  
39 327 less certainty about this decision. The mean differences between groups were close to zero  
40  
41 328 in all 3 cases so that the cost-per-QALY estimates are unstable and a cost-minimization  
42  
43 329 approach may be more appropriate. This would favour SPECT, which was both cheaper and  
44  
45 330 more effective on average than angiography, and had the lowest overall cost (Table 2).  
46

47 331

### 48 332 **Sensitivity analysis**

49  
50 333 The comparisons between the diagnostic strategy groups did not change substantially when  
51  
52 334 we varied the time horizon; the main effect of this was that the variation surrounding  
53  
54 335 estimates increased as the time horizon lengthened due to the heavy censoring (results not  
55  
56 336 shown). **Tables 2a and 2b** show results for interventional and non-invasive cardiologists  
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59  
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1  
2  
3 337 respectively. Patients who were managed by interventional cardiologists incurred higher  
4  
5 338 costs due to the greater number of tests and revascularization procedures performed, with  
6  
7 339 minimal incremental benefit in QALY.  
8

9 340

## 10 341 **Discussion**

11  
12  
13 342 CECaT is the first completed prospective randomized trial to look at the clinical and cost-  
14  
15 343 effectiveness of non-invasive imaging in the diagnosis and management of angina. To the  
16  
17 344 best of the authors' knowledge there has been no comparable outcomes trial published on  
18  
19 345 this scale evaluating three independent non-invasive 'gatekeeper' modalities versus initial  
20  
21 346 angiography in stable chest pain. The trial is also unusual in the length of prospective follow  
22  
23 347 up extending to 6 years for mortality outcomes.  
24

25 348

26  
27 349 We have demonstrated that use of any one of stress CMR, stress echo or stress SPECT as  
28  
29 350 the initial test for a stable chest pain patient leads to non-inferior outcomes in quality of life  
30  
31 351 and cost utility compared to patients randomised to upfront invasive coronary angiography.  
32  
33 352 Typically, non invasive tests perform well in low risk populations because of a negative  
34  
35 353 predictive value which is usually better than the positive predictive value. However, the  
36  
37 354 patient risk profile was relatively high in our study, and despite this there was no significant  
38  
39 355 difference between an initial functional or anatomic approach.  
40

41 356

42  
43 357 There are several reasons why initial angiography may not have led to clear benefit in our  
44  
45 358 study. Firstly, although angiography has stood at the heart of the diagnostic chest pain  
46  
47 359 pathway, the traditional binary cut-off values of 50% or 70% percentage stenosis by visual  
48  
49 360 estimation were shown in the FAME study to bear little relation to the true physiologic  
50  
51 361 significance of luminal narrowing <sup>(22)</sup>.  
52

53 362

54  
55  
56 363 Secondly, data from various countries suggest that not only is coronary angiography often  
57  
58 364 inappropriate when formally rated by expert observers <sup>(23) (24)</sup> but that disparate national or  
59  
60

1  
2  
3 365 regional rates of angiography do not translate into clear mortality benefits between countries  
4  
5 366 <sup>(25) (26) (27) (28)</sup> and on occasion may even demonstrate an inverse relationship <sup>(29)</sup>.

6  
7 367 Contemporary US data from approximately 500,000 PCI procedures collected prospectively  
8  
9 368 in the National Cardiovascular Data Registry demonstrated that, of 145,000 elective PCI  
10  
11 369 cases, roughly 12% were judged inappropriate. Furthermore, the rate of inappropriate  
12  
13 370 elective PCI between hospital sites ranged from 0-55% suggesting significant variability in  
14  
15 371 practice <sup>(30)</sup>. The data suggest a better way of selecting patients for invasive investigation is  
16  
17 372 needed.  
18  
19 373

20  
21 374 Ischemia-driven revascularisation has been shown to be of benefit in a number of trials,  
22  
23 375 most recently in the FAME study in which an invasive method of measuring the flow reserve  
24  
25 376 of the microcirculation (Fractional Flow Reserve, FFR) was used to allocate patients to  
26  
27 377 intervention or observation vs a clinical decision on intervention based on angiography alone  
28  
29 378 <sup>(31)</sup>. At 2 years follow up there were clear survival and MACE benefits to the FFR-based  
30  
31 379 approach.  
32  
33

34 380  
35 381 The ACRE study reported that, up to 6 years after diagnosis, medical management was a  
36  
37 382 more cost-effective strategy for angina compared with PCI <sup>(32)</sup>. The lack of evidence for  
38  
39 383 survival from revascularisation was also seen in the COURAGE trial <sup>(4)</sup>. Critics have  
40  
41 384 suggested this may be because randomization to PCI versus optimal medical therapy was  
42  
43 385 made *after* coronary angiography had been performed, potentially leading to a recruitment  
44  
45 386 bias of patients with less severe disease. In the CECaT trial this bias was avoided by  
46  
47 387 randomization to a management strategy defined by the non-invasive test result for each of  
48  
49 388 the 3 functional arms of the trial. In a relatively high risk population, we demonstrated no  
50  
51 389 clinically significant survival or economic detriment from using non-invasive imaging as a  
52  
53 390 gate-keeper to catheterization. Similarly, quality of life was not significantly different across  
54  
55 391 all four groups and these differences extended to a warranty period of at least 3 years.  
56  
57 392



1  
2  
3 393 We did observe a marginal decrease in survival in the CMR arm. The reasons for the  
4  
5 394 difference are unclear but do not relate to patient characteristics or management with CABG  
6  
7 395 or PCI. Although statistically significant, the mean survival difference from the other groups  
8  
9 396 was only 4 weeks over 3 years and is unlikely to be clinically meaningful. Since recent work  
10  
11 397 has established a strong correspondence between FFR measurements and stress CMR  
12  
13 398 perfusion indices it would be surprising if CMR were genuinely inferior to other modalities for  
14  
15 399 risk stratification<sup>(33)</sup>. Indeed several recent publications have highlighted the incremental  
16  
17 400 prognostic data (above that obtained from clinical variables) derived from several thousand  
18  
19 401 perfusion CMR studies<sup>(34)(35)</sup>.

20  
21 402  
22  
23 403 Given the recent publication of the CEMARC trial<sup>(36)</sup> in which a clear diagnostic superiority  
24  
25 404 was demonstrated for stress CMR over SPECT, it is interesting that our data nonetheless  
26  
27 405 show an equivalence in functional health status between those randomized to SPECT  
28  
29 406 versus CMR in the CECaT trial. The implication may be that although CMR detects the  
30  
31 407 presence of *any* ischemia with a greater sensitivity it is the *overall burden* of ischemia that  
32  
33 408 alters a patient's prognosis. As such, it has not yet been demonstrated that the higher  
34  
35 409 diagnostic accuracy of CMR translates into better long-term patient outcomes – a fact  
36  
37 410 acknowledged by Greenwood et al subsequent to CEMARC's publication<sup>(37)</sup>. In this context  
38  
39 411 the CECaT nuclear results are congruent with numerous past publications and reconfirm the  
40  
41 412 reassuring warranty period of a normal SPECT study.

42  
43  
44 413

#### 45 414 **Cost effectiveness**

46  
47 415 There was no significant difference in cost-effectiveness between the angiography -as-  
48  
49 416 default group and the non-invasive test groups up to 3 years, perhaps relating to the higher-  
50  
51 417 than-anticipated rate of referral for angiography after negative functional tests. Protocol  
52  
53 418 deviation of this kind is not infrequent in trials of non-invasive technology. In the recent  
54  
55 419 PARR-2 study of patients undergoing fluorodeoxyglucose positron emission tomography for  
56  
57 420 the assessment of viability, roughly 25 % of the study population did not adhere to protocol  
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59  
60



1  
2  
3 421 <sup>(38)</sup>. The willingness of a cardiologist to defer referral for coronary angiography in the face of  
4  
5 422 a normal non-invasive study may in part reflect individual prejudices and job description  
6  
7 423 (interventional versus non-invasive) as demonstrated in a recent survey of cardiology  
8  
9 424 attitudes <sup>(39)</sup> and was also reflected in our own data.  
10

11 425

12  
13 426 In CECaT, 20-25% of patients receiving a non-invasive test did not go on to have  
14  
15 427 angiography. A proportion of the additional cost in the non-invasive arms related to  
16  
17 428 angiography and PCI in the patients with a *negative* test, although only very few  
18  
19 429 subsequently required CABG - a robust marker of significant disease - during follow-up. This  
20  
21 430 readiness to employ PCI in a group in whom the indication/benefit is debatable was also  
22  
23 431 seen in the ACRE trial <sup>(32)</sup> and reflects understandable clinical response to uncertainty but  
24  
25 432 also the easy access to PCI in healthcare systems without barriers to self-referral <sup>(40)</sup>.  
26

27 433 Similarly, studies from the US have demonstrated a greater willingness to use coronary  
28  
29 434 angiography when available 'on site' as is increasingly seen even in small-to-medium sized  
30  
31 435 hospitals <sup>(41) (42) (43)</sup>.  
32

33 436

### 35 437 ***Cost effectiveness of each non-invasive technique***

36 438

37  
38  
39 439 Nuclear myocardial perfusion imaging  
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42  
43 441 The END study used propensity matching to compare a large cohort of patients referred for  
44  
45 442 either gate-keeper myocardial perfusion imaging or upfront angiography – this non  
46  
47 443 randomised study demonstrated a significant cost reduction in the (44) nuclear arm. In  
48  
49 444 contrast to this and other work <sup>(45) (46) (47)</sup> we were unable to show a significant difference in  
50  
51 445 cost effectiveness in our own study. To some extent this reflected the participating physician  
52  
53 446 bias towards angiography during the period of trial recruitment (2001-2006) with many  
54  
55 447 patients referred for angiography despite normal perfusion studies. This continues in the  
56  
57 448 contemporary era with Chan et al demonstrating that almost 80% of Delphi-adjudicated  
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3 449 inappropriate elective PCIs were performed following either low risk ischemia imaging in  
4  
5 450 mildly symptomatic patients or intermediate risk imaging in entirely asymptomatic patients  
6  
7 451 <sup>(30)</sup>.

8  
9 452

10  
11 453 In the CECaT study, when PCI was performed despite a negative initial non-invasive test,  
12  
13 454 this occurred because subsequent angiography indicated 'significant' stenosis. This was a  
14  
15 455 clinical judgment based on 'eyeball assessment' of lesion severity as has been reported in  
16  
17 456 clinical trials with angiographic end points <sup>(48)</sup>. However, the severity and functional  
18  
19 457 significance of many stenoses may be over-called, even by quantitative assessment, when  
20  
21 458 compared with physiological assessment of fractional flow reserve across the lesion <sup>(49) (50)</sup>.

22  
23 459 Further improvement in cost-effectiveness could likely have been achieved in the nuclear  
24  
25 460 arm of the trial. Our post-trial practice is to perform the stress SPECT first - and if this is  
26  
27 461 negative - cancel the rest test, likely augmenting the relative cost-effectiveness of SPECT  
28  
29 462 <sup>(51)</sup>.

30  
31 463

32  
33 464 CMR

34  
35 465 There are relatively few data available regarding the cost effectiveness of CMR . One recent  
36  
37 466 mathematical modelling study estimated that CMR likely has greater cost effectiveness/utility  
38  
39 467 compared to SPECT despite greater base case cost of the former <sup>(52)</sup> . The economic  
40  
41 468 superiority of CMR was also recently described by the CEMARC group, although  
42  
43 469 interestingly the base case costs employed for CMR and SPECT in their analysis differed by  
44  
45 470 only a few pounds. Their own sensitivity analysis in fact demonstrated that if the costs of the  
46  
47 471 two tests varied by more than 100 pounds (which was the case in our study) then in fact – as  
48  
49 472 we found - SPECT became the dominant strategy in a low-to-intermediate risk population.

50  
51 473 <sup>(53)</sup>

52  
53 474

54  
55 475 Stress echo

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3 476 Stress echocardiography may be a more cost-effective strategy than angiography for men  
4  
5 477 aged 50-60 with CAD prevalence of 50%<sup>(54), (47)</sup>. There is also some evidence that stress  
6  
7 478 echo is more cost-effective than SPECT as an initial test<sup>(55) (56)</sup>, especially in women with  
8  
9 479 suspected CAD<sup>(57)</sup>. A similar benefit was not seen in our study probably because of the high  
10  
11 480 disease prevalence in our population. The lack of superiority of either stress  
12  
13 481 echocardiography or a combined strategy of exercise testing and stress echo compared to  
14  
15 482 upfront catheterisation was also evident in a recent Polish study of 600 patients with a  
16  
17 483 similar age, gender and disease prevalence to our own study population<sup>(58)</sup>.  
18  
19 484

20  
21 485 Taken overall, our data clearly demonstrate a limited future role for cost-effective non-  
22  
23 486 invasive imaging if referring physicians are not willing to accept a negative result as ground  
24  
25 487 truth. This might be interpreted as reflecting a need for greater physician education since we  
26  
27 488 showed a clear difference in onward referral rates for angiography after a negative test  
28  
29 489 between interventional and non-invasive cardiologists.  
30  
31 490

### 32 33 491 ***Clinical effectiveness***

34  
35 492 We demonstrated that SPECT can obviate the need for coronary angiography for a  
36  
37 493 significant number of patients without any clinical detriment. In the stress echo group clinical  
38  
39 494 outcomes were also comparable to the angiography subgroup at 18 months. The CMR  
40  
41 495 group had statistically marginally poorer survival and this follows our earlier finding that CMR  
42  
43 496 patients had significantly worse exercise tolerance at 18 months after randomisation<sup>(10)</sup>. This  
44  
45 497 is difficult to explain on the basis of Pryor risk score or other baseline clinical variables.  
46  
47 498 However, the mean difference in survival between the CMR arm and the other groups was  
48  
49 499 only 4 weeks and thus of marginal clinical significance. More importantly, the CMR group  
50  
51 500 were not otherwise disadvantaged – compared to the angiographic control group - with  
52  
53 501 respect to major adverse events, other resource use, or quality of life.  
54  
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2  
3 504 **Limitations**

4  
5 505 This study was carried out in a single specialist cardiothoracic centre with a significant  
6  
7 506 proportion of high risk, predominantly white European, male patients. Those eligible who  
8  
9 507 refused the trial were older and were more likely to be women.

10  
11 508

12  
13 509 Survival data from the national registry did not include cause of death so that deaths due to  
14  
15 510 cardiovascular causes could not be reported separately.

16  
17 511

18  
19 512 The trial completed recruitment in 2004 and we used the technology that was available to us  
20  
21 513 at the onset of the trial. At that time, we were not able to use attenuation correction for  
22  
23 514 SPECT imaging; however this was also not used in the much more recent CEMARC trial<sup>(36)</sup>.  
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25 515 Similarly, we performed our CMR exams in a mobile facility on a 1.5T scanner with only  
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27 516 modest coil technology and limited temporal and anatomic coverage that would compare  
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29 517 unfavourably with the 3T whole heart high resolution perfusion studies available today.

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33 519 The trial aimed to reflect the strategy of using non-invasive imaging as a gateway to  
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35 520 angiography in *contemporary clinical practice*. The test results were considered in  
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37 521 conjunction with other information available at the time. Thus it was not the aim to formally  
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39 522 assess diagnostic accuracy of the non-invasive tests in this context. This trial-based study  
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41 523 was limited to 3 year cost-effectiveness follow up - longer-term economic models would  
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43 524 provide lifetime estimates of the cost-effectiveness of the non-invasive strategies and could  
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45 525 include advances in imaging technology.

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49 527 **Conclusions**

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51 528 We have demonstrated in the CECaT trial that stress echo, stress CMR and stress SPECT  
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53 529 may each be used to defer invasive coronary angiography without clinical detriment or  
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55 530 significant excess costs in an outpatient population with stable chest pain.

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532 **Table 1 Baseline characteristics\***

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
<b>Demographics</b>				
Mean (SD) age (years)	60.7 (9.1)	62.1 (9.5)	62.2 (9.0)	61.9 (9.9)
Males (%)	149 (67%)	157 (70%)	153 (68%)	160 (71%)
<b>History/risk factors</b>				
Previous MI (%)	63 (28%)	52 (23%)	69 (31%)	59 (26%)
Previous CVA (%)	10 (5%)	13 (6%)	8 (4%)	12 (5%)
<b>Diabetes(%)</b>				
IDDM	12 (5%)	8 (4%)	11 (5%)	5 (2%)
NIDDM	16 (7%)	18 (8%)	21 (9%)	22 (10%)
Family history CAD	60 (27%)	55 (25%)	63 (28%)	59 (26%)
<b>Smoking history (%)</b>				
<25 pack years	149 (67%)	162 (72%)	148 (65%)	155 (69%)
≥25 pack years	73 (33%)	62 (28%)	78 (35%)	71 (31%)
Treated hyperlipidaemia	164 (74%)	171 (76%)	179 (79%)	179 (79%)
(%)				
Treated hypertension (%)	117 (53%)	132 (59%)	115 (51%)	129 (57%)
<b>Exercise tolerance using the modified Bruce protocol</b>				
Mean (SD) total exercise time (mins)	11.29 (4.56)	10.46 (4.41)	10.43 (4.43)	10.89 (4.36)
<b>ECG changes on exercise test</b>				
1-2 mm ST depression with symptoms	53 (24%)	43 (19%)	54 (24%)	57 (25%)
≥ 2mm ST depression without symptoms	16 (7%)	24 (11%)	20 (9%)	24 (11%)

ST elevation**/ no change	153 (69%)	157 (70%)	152 (67%)	145 (64%)
CCS class				
0-I	60 (27%)	54 (24%)	78 (35%)	58 (26%)
II	138 (62%)	144 (64%)	122 (54%)	132 (58%)
III-IV	24 (11%)	26 (12%)	26 (11%)	36 (16%)

533 \* There were no significant differences between the groups in any variable

534 \*\* ST elevation was observed in 3 angiography, 2 CMR and 1 ECHO patients.

535 **Table 2 Cost-effectiveness summaries to 3 years post randomization**

536

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
Hazard ratio for death	Baseline	0.99	2.60	1.42
(95%CI)		(0.35,2.85)	(1.09,6.22)	(0.54,3.74)
Mean survival (years)	2.96	2.95	2.90	2.94
(95%CI)	(2.92, 2.99)	(2.90, 2.99)	(2.83, 2.95)	(2.89, 2.97)
Mean difference vs. CA	-	-0.01	-0.06	-0.02
(95%CI)	-	(-0.07,0.05)	(-0.14, 0.01)	(-0.08, 0.04)
Mean QALYs	2.24	2.27	2.18	2.27
(95%CI)	(2.16,2.30)	(2.20,2.33)	(2.11,2.25)	(2.20,2.33)
Mean difference vs. CA	-	0.03	-0.05	0.03
(95%CI)	-	(-5.30,1.20)	(-4.50,2.01)	(-3.08,3.95)
Mean discounted costs (£)	5322	4989	5249	5865
(95%CI)	(4343,6526)	(4514,5466)	(4737,5756)	(5181, 6634)
Mean difference vs. CA	-	-333	-73	544
(95%CI)	-	(-1613,760)	(-1379, 1040)	(-809, 1791)
Probability cost effective at £20k per QALY	-	0.75	0.24	0.49
Probability cost effective at £30k per QALY	-	0.74	0.22	0.55

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538 **Table 2a Cost-effectiveness summaries for patients managed by interventional**  
 539 **cardiologists to 3 years post randomization**  
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	Angiography (n=73)	SPECT (n=96)	Cardiac MRI (n=93)	Stress Echo (n=98)
Mean survival (years)	2.96	2.97	2.89	2.96
(95%CI)	(2.91, 2.98)	(2.93, 3.00)	(2.80, 2.97)	(2.90, 2.98)
Mean difference vs. CA	-	0.01	-0.07	0
(95%CI)	-	(-0.05,0.07)	(-0.17, 0.02)	(-0.07,0.05)
Mean QALYs	2.25	2.29	2.21	2.2
(95%CI)	(2.14,2.36)	(2.19,2.38)	(2.10,2.32)	(2.09,2.29)
Mean difference vs. CA	-	0.03	-0.04	-0.06
(95%CI)	-	(-5.48,2.06)	(-5.22,2.21)	(-3.11,6.17)
Mean discounted costs (£)	5810	5610	5656	6733
(95%CI)	(4733, 7033)	(4872, 6381)	(4947, 6389)	(5530, 8140)
Mean difference vs. CA	-	-200	-154	923
(95%CI)	-	(-1620, 1160)	(-1568, 1165)	(-770, 2712)
Probability cost effective at £20k per QALY		0.67	0.37	0.19
Probability cost effective at £30k per QALY		0.66	0.35	0.21



541 **Table 2b Cost-effectiveness summaries for patients managed by non-interventional**  
 542 **cardiologists to 3 years post randomization**

543

	Angiography (n=149)	SPECT (n=128)	Cardiac MRI (n=133)	Stress Echo (n=128)
Mean survival (years)	2.95	2.93	2.9	2.92
(95%CI)	(2.89, 2.99)	(2.85, 2.98)	(2.81, 2.97)	(2.85, 2.98)
Mean difference vs. CA	-	-0.02	-0.05	-0.03
(95%CI)	-	(-0.11,0.06)	(-0.15, 0.04)	(-0.11, 0.05)
Mean QALYs	2.23	2.25	2.17	2.32
(95%CI)	(2.14,2.31)	(2.16,2.33)	(2.07,2.26)	(2.23,2.41)
Mean difference vs. CA	-	0.02	-0.06	0.09
(95%CI)	-	(-7.32,1.90)	(-5.98,3.37)	(-5.84,3.39)
Mean discounted costs (£)	5015	4521	5009	5077
(95%CI)	(3749, 6728)	(3931, 5132)	(4358, 5702)	(4398, 5767)
Mean difference vs. CA	-	-494	-6	-62
(95%CI)		(-2317, 956)	(-1831, 1492)	(-1774, 1568)
Probability cost effective at £20k per QALY		0.70	0.25	0.82
Probability cost effective at £30k per QALY		0.69	0.24	0.85

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546 **Table 3 Summary adverse events during initial 18 months follow up\***

Adverse event	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
Total adverse events	38	34	44	62
Chest pain (not myocardial infarction)	21	20	28	35
Angina	7	5	4	3
Myocardial infarction	2	0	3	6

547 \* Note that beyond this time only events that required hospital admission were recorded.

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550 **Table 4** Summary of the frequency of use of the main resource use elements during follow up  
 551 of up to 3 years (excluding initial diagnostic test)

552

Resource use (unit cost)	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
CABG (£7195)	28	33	28	34
PCI (£3660)	57	46	60	62
Other hospital admission (£467 per day)	36	29	28	53
Angiography (£1032)	12	183	175	181
SPECT (£983)	16	3	3	6
Cardiac MRI (£388)	5	5	12	5
Echocardiography (£435)	30	17	24	18
PET scan (£842)	0	3	0	1
Preadmission clinic (£85)	22	21	27	24
Follow up clinic (£85)	19	22	31	21
Outpatient visits (£143)	247	270	300	284

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554 \* Cardiac drugs were also included but are not shown here due to many different  
 555 combinations of drugs and doses prescribed.

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558 **Figure Legends**

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560 **Figure 1 CONSORT diagram describing recruitment and randomization**

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562 **Figure 2 Kaplan-Meier survival estimates according to initial modality of diagnosis**

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564 **Figure 3 Quality of life assessed by EQ5D over time**

565

566 **Figure 4 Bootstrapped estimates of the joint distribution of mean cost difference**

567 **against mean QALY difference up to 3-years post randomisation**

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569 **Figure 5 Estimated probability of being cost-effective compared with angiography**

570 **alone against the amount (£) a health provider is willing to pay for one additional**

571 **QALY**

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35 602 **Exclusive licence statement**  
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3 614 **Contributorship statement**  
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7 616 HT performed literature review, data analysis and interpretation; NW was involved in image  
8  
9 617 analysis, drafting the manuscript and critical revision; VH was involved in recruiting the  
10  
11 618 patients, data management, administering health questionnaires, data analysis and drafting  
12  
13 619 the manuscript; MD and MB were responsible for data analysis, health economic  
14  
15 620 assessment, drafting the manuscript and critical revision; LDS was responsible for study  
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17 621 design, trial management, statistical analysis, drafting the manuscript and critical revision;  
18  
19 622 CJ performed statistical and health economic analysis, drafting the manuscript and critical  
20  
21 623 revision; AMC was involved in study design, patient recruitment, image interpretation, trial  
22  
23 624 management, drafting the manuscript and critical revision and is the overall guarantor of  
24  
25 625 manuscript integrity.  
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29 627 All authors have read the manuscript in its submitted form and have provided final approval  
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31 628 for publication.  
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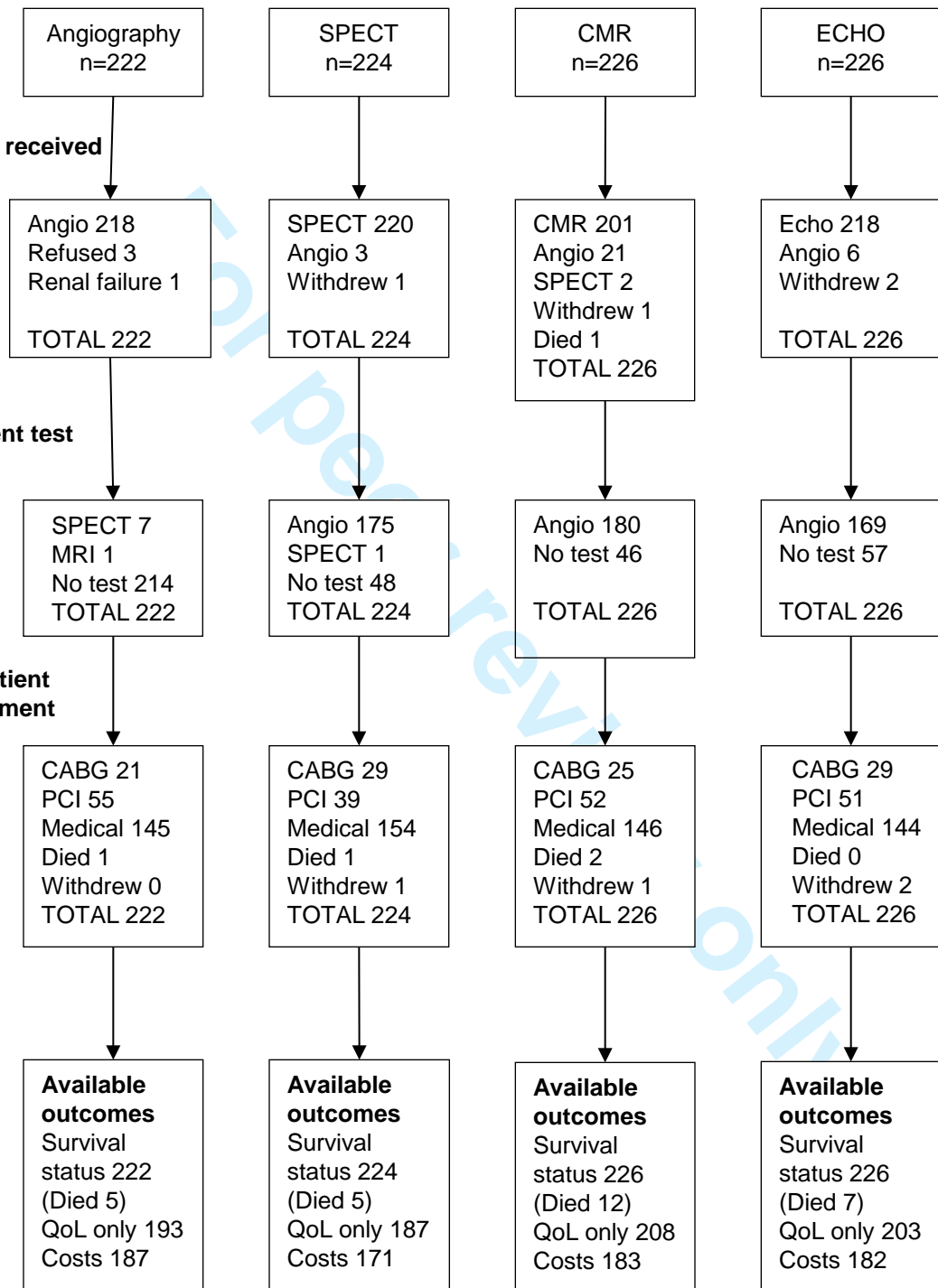
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## CONSORT checklist CECaT Trial BMJ Open Re-Submission

Item	Description	Reported on line number
Title	Identification of the study as randomized	4
Authors *	Contact details for the corresponding author	26
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	140
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	153-157
Interventions	Interventions intended for each group	140-144 & 163-165
Objective	Specific objective or hypothesis	147
Outcome	Clearly defined primary outcome for this report	219
Randomization	How participants were allocated to interventions	159
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	140
Results		
Numbers randomized	Number of participants randomized to each group	285 & 582
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	582
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	585
Harms	Important adverse events or side effects	318-9
Conclusions	General interpretation of the results	540
Trial registration	Registration number and name of trial register	124
Funding	Source of funding	546-548

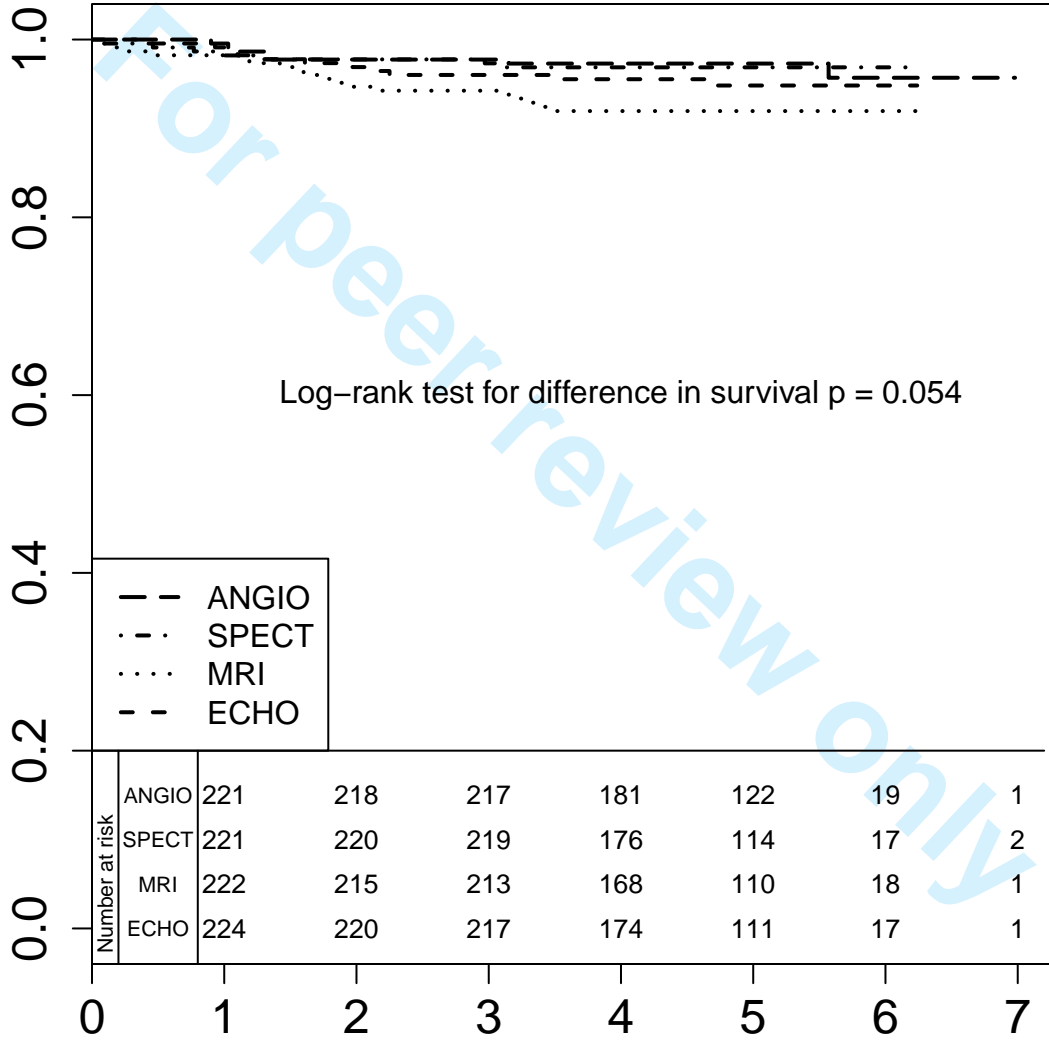
Figure 1 Trial summary

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Final assessment at 2 years post treatment

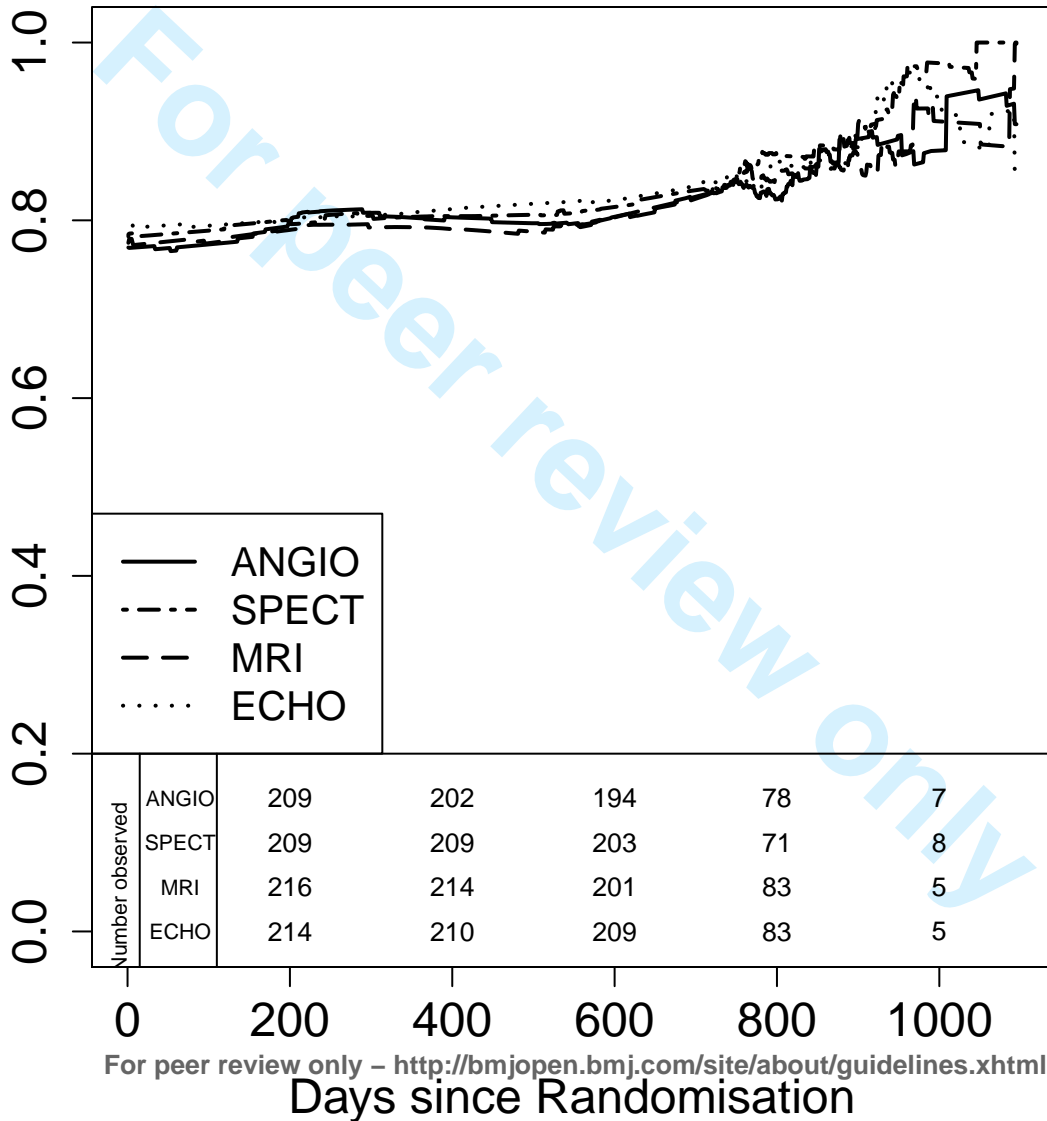
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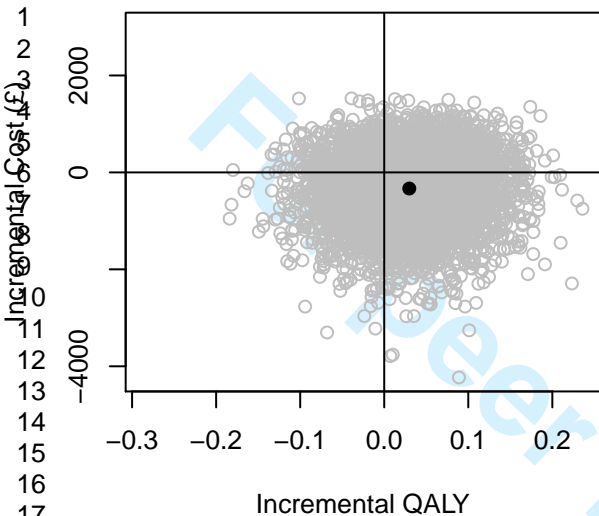
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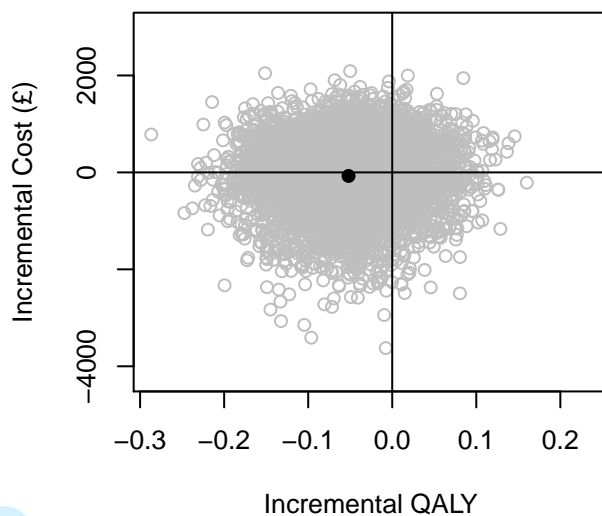




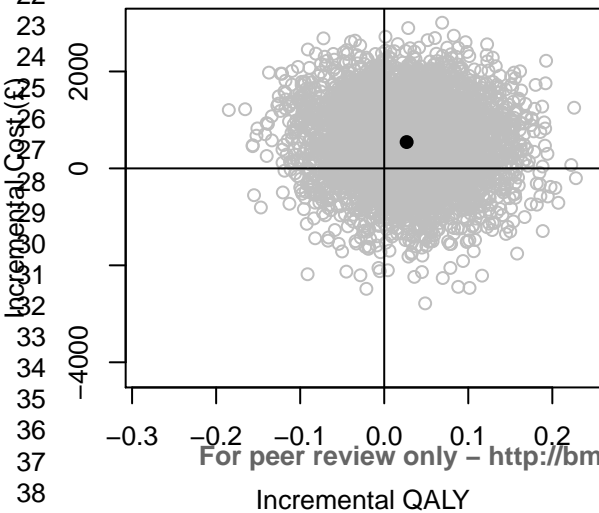
**SPECT – ANGIO**



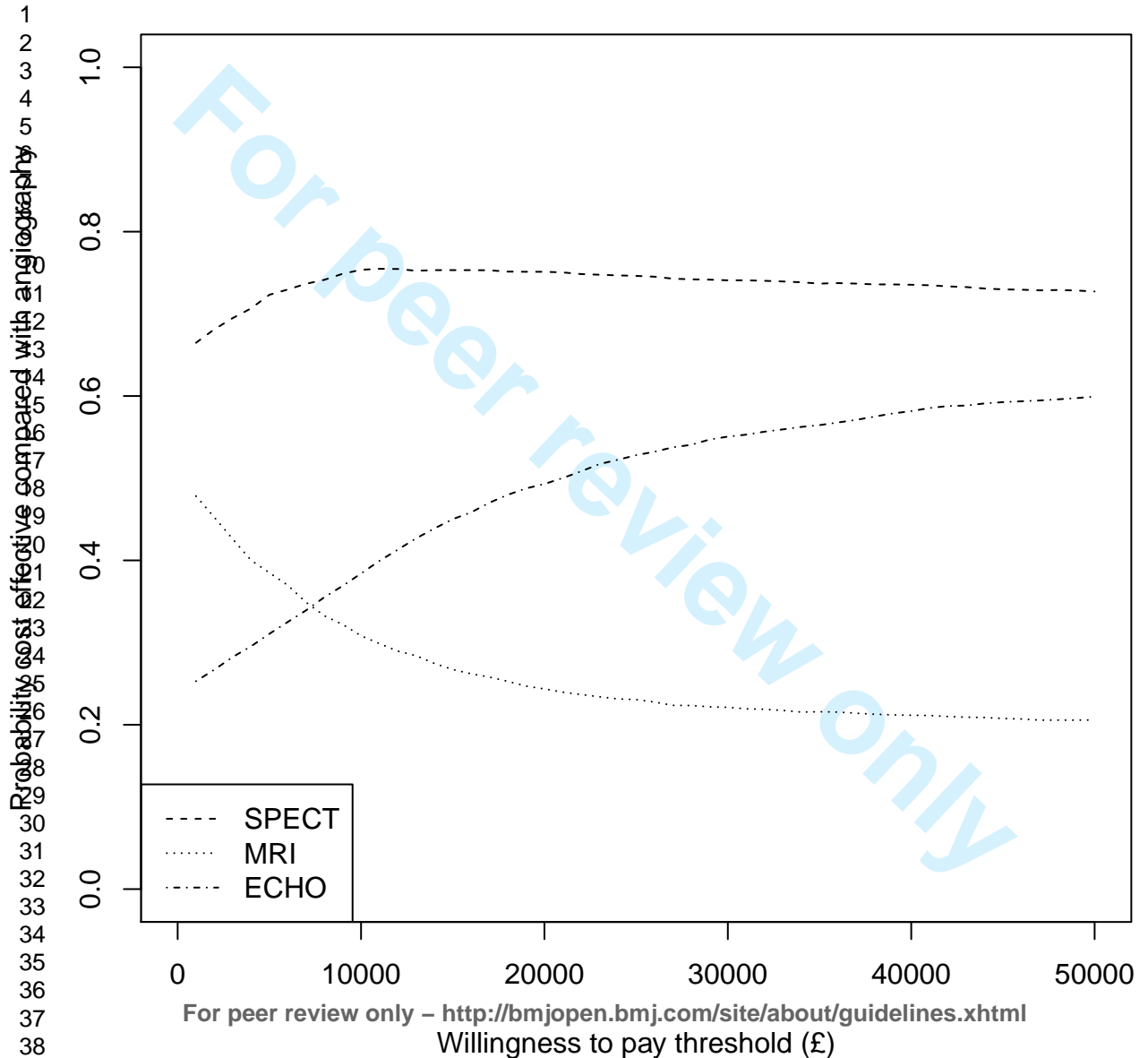
**MRI – ANGIO**



**ECHO – ANGIO**



# Cost effectiveness acceptability curves





**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**

Journal:	<i>BMJ Open</i>
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Article Type:	Research
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<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Health economics, Health policy, Health services research, Medical management, Radiology and imaging
Keywords:	Adult cardiology < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Cardiology < INTERNAL MEDICINE, Cardiovascular imaging < RADIOLOGY & IMAGING

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**Title: 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**

\*Cost Effectiveness of non-invasive Cardiac Testing

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**Clinical Trial registration:** ISRCTN 47108462, UKCRN 3696

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7 32 Matthew Dyer, Margaret Gillham, Hester Goddard, Kim Goldsmith, Vikki Hughes, Evelyn

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9 33 Lee, Roger Patel, Peter Schofield, Linda Sharples, Emer Sonnex, David Stone, Carmen

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3 58 **Abstract**

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5 59 **Objectives:** to compare outcomes and cost effectiveness of various initial imaging strategies on  
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7 60 the management of stable chest pain in a long term prospective randomized trial.

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9 61 **Setting:** regional cardiothoracic referral center in the east of England

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11 62 **Participants:** 898 patients (69% male) entered the study with 869 alive at 2yr follow up.  
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13 63 Patients were included if they presented for assessment of stable chest pain with a positive  
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15 64 exercise test and no prior history of ischemic heart disease. Exclusion criteria were recent  
16  
17 65 infarction, unstable symptoms or any contra-indication to stress MRI.

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19 66 **Primary outcome measures:** The primary outcomes of this follow up study were survival up  
20  
21 67 to a minimum of 2 years post-treatment, quality-adjusted survival and cost-utility of each  
22  
23 68 strategy

24  
25 69 **Results:** 898 patients were randomized. Compared to angiography, mortality was  
26  
27 70 marginally higher in the groups randomized to CMR (hazard ratio 2.6, 95%CI 1.1, 6.2), but  
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29 71 similar in the SPECT-MIBI (hazard ratio 1.0, 95%CI 0.4, 2.9) and ECHO groups (hazard ratio  
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31 72 1.6, 95%CI 0.6, 4.0). Although SPECT-MIBI was marginally superior to other non-invasive  
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33 73 tests there were no other significant differences between the groups in mortality, quality  
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35 74 adjusted survival or costs.

36  
37 75 **Conclusions:** Non-invasive cardiac imaging can be used safely as the initial diagnostic test  
38  
39 76 to diagnose CAD without adverse effects on patient outcomes or increased costs, relative to  
40  
41 77 angiography. These results should be interpreted in the context of recent advances in  
42  
43 78 imaging technology.

44  
45 79 **Trial registration:** ISRCTN 47108462, UKCRN 3696

46  
47 80 **Key words:** MRI, cardiovascular magnetic resonance, comparative effectiveness, SPECT,  
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49 81 stress echo, coronary angiography.

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3 86 **Article summary:**  
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5 87 *Article focus:*  
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- 7 88 1. Is non-invasive imaging a safe and appropriate gate-keeper to coronary angiography  
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9 89 in patients with stable chest pain ?  
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11 90 2. Is there any difference in cost-effectiveness and cost-utility between the different  
12  
13 91 non-invasive approaches and conventional coronary angiography  
14  
15 92 3. Are patients disadvantaged in any meaningful way by having a non-invasive test to  
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17 93 decide whether they should go forward for coronary angiography ?  
18  
19 94 4. How does stress perfusion CMR compare to the more established tests of SPECT-  
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21 95 MIBI and stress echocardiography as a gate-keeper to coronary angiography ?  
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24  
25 97 *Key messages:*  
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- 27 98 1. Non-invasive testing may be used safely as a gate-keeper to coronary angiography  
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29 99 in patients with stable chest pain without any material disadvantage to them in terms  
30  
31 100 of survival and quality of life up to 6 years after initial randomisation.  
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33 101 2. SPECT-MIBI appears marginally superior statistically to the other non-invasive  
34  
35 102 methods although clinically meaningful differences are small between all strategies.  
36  
37 103 3. Stress perfusion CMR appears to be an effective technique in a stable out-patient  
38  
39 104 population with undiagnosed chest pain.  
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43 106 *Strengths and limitations:*  
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- 45 107 1. This is the only large randomised prospective trial of a strategy of non-invasive gate-  
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47 108 keeper cardiac imaging versus upfront angiography in the literature.  
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49 109 2. The cost-utility data are derived from NHS tariffs and our results are not necessarily  
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51 110 directly transferrable to other healthcare systems  
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## 112 Introduction

113

114 CAD is common and its management is costly<sup>(1)</sup>. Revascularisation using bypass surgery  
115 (CABG) or percutaneous coronary intervention (PCI) is effective for patients with severe  
116 disease<sup>(2)</sup> but a significant minority of patients do not gain symptomatic relief<sup>(3)</sup>. Data from  
117 the COURAGE trial did not show prognostic benefit from revascularization in any patient  
118 subgroup<sup>(4)</sup>. The yield of coronary angiography is variable with one recent large study of  
119 nearly 400, 000 patients demonstrating a normalcy rate approaching 40%<sup>(5)</sup>. Therefore  
120 non-invasive testing to identify those with a low likelihood of obstructive CAD may be safer,  
121 cheaper and more appropriate than upfront angiography. This approach is codified in  
122 multiple AHA/ACC guidelines on the investigation of stable or suspected angina pectoris in  
123 which initial non-invasive imaging is rated as highly appropriate<sup>(6) (7) (8) (9)</sup>.

124

125 The 'Cost-Effectiveness of non-invasive Cardiac Testing' (CECaT) trial was an unblinded  
126 non-inferiority trial designed to assess three functional tests - stress echocardiography,  
127 single photon emission computed tomography (SPECT) and stress cardiac magnetic  
128 resonance imaging (CMR) - as a gatekeeper to coronary angiography (CA) in patients  
129 referred for CA with suspected coronary artery disease (CAD). Early clinical and cost-  
130 effectiveness estimates have been published and showed that the CMR group had slightly  
131 lower mean exercise treadmill time according to the Bruce protocol but otherwise the tests  
132 could be considered equally effective<sup>(10)</sup>. This report provides the main cost-effectiveness  
133 and mortality outcomes up to 6 years after randomisation.

134

## 135 Methods

### 136 Study design

137 The design of the study has been described elsewhere<sup>(10)</sup> and is reviewed briefly here. All  
138 patients referred to Papworth Hospital, UK for non-urgent angiography were eligible for the  
139 study. Inclusion criteria were: established or suspected chronic stable angina and a positive



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3 140 exercise tolerance test result with subsequent referral for angiography. Exclusion criteria  
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5 141 were: recent MI (<3 months), revascularisation (<6 months); urgent need for  
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7 142 revascularisation; contra-indication to adenosine or CMR; inability to exercise.  
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11 144 Trial design was of four parallel arms with a 1:1:1:1 randomisation ratio. Randomisation was  
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13 145 computer generated and stratified according to Pryor risk assessment<sup>(11)</sup>. Within each Pryor  
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15 146 risk group, randomisation was in blocks of length 6 or 8. Sequentially numbered group  
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17 147 designation was held in the Research & Development (R&D) Office and was not available to  
18  
19 148 trial personnel. Patients were randomised to their initial diagnostic test - stress SPECT,  
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21 149 stress CMR, stress echocardiography, or angiography - by R&D within 4 weeks of  
22  
23 150 recruitment and only after they had given consent and been registered.  
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27 152 Non invasive imaging results were returned with a recommendation to proceed with  
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29 153 angiography only when reported as 'positive' for inducible ischemia. Protocol adherence to  
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31 154 this recommendation was not mandated by trial design and patients proceeded to  
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33 155 angiography if considered clinically indicated. Treatment with PCI or CABG (performed  
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35 156 within six months of angiography) or to medical therapy was according to standard practice.  
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37 157

### 38 158 **Coronary angiography.**

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41 159 Standard diagnostic angiography was performed from the right femoral artery approach<sup>(12)</sup>.  
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43 160 A minimum of 5 views of the left and 3 views of the right coronary system were taken<sup>(13)</sup>. All  
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45 161 examinations were reported by an experienced staff cardiologist and segmental location of  
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47 162 disease (if any) recorded.  
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### 50 164 **Stress echocardiography**

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53 165 Beta-blocker medications were stopped 2 days beforehand. Dobutamine was infused at  
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55 166 rates of 10- 40 mcg/kg/min, increased at 3 minute intervals. If necessary, 300-600  
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57 167 micrograms of atropine were added at peak stress to achieve 90% of target heart  
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3 168 rate. Images were acquired in standard planes in the final minute of each 3 minute stage.  
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5 169 Intravenous microspheres were used to delineate the endocardial surface. All examinations  
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7 170 were reported by one of two staff cardiologists experienced in stress echocardiography.  
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9 171 Studies were positive for ischemia if stress-induced deterioration in contractility was  
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11 172 observed.

173

**174 SPECT**

175 Rest/stress 99mTc sestamibi (99mTc MIBI) SPECT was performed (2 day protocol). A 6  
176 minute adenosine infusion (140 µg/kg/min) was employed. 400 MBq 99m-Tc MIBI was  
177 administered at 3 minutes after infusion of adenosine was started. Gated SPECT imaging  
178 occurred 60 minutes after injection. Tomographic images were assessed for fixed and  
179 reversible defects by a single observer (as per established criteria)<sup>(14)</sup>.

180

**181 CMR**

182 Stress CMR imaging was performed at a standard similar to that which was subsequently  
183 recommended by the Society of Cardiovascular Magnetic Resonance <sup>(15)</sup>. A 1.5T mobile  
184 CMR system and 4-channel phased array surface coil were used (Signa CV/i, GE Medical  
185 Systems). Stress/rest dynamic first-pass perfusion imaging was performed. A hybrid fast  
186 gradient echo/echoplanar sequence was employed <sup>(16)</sup>. Adenosine was infused at 140  
187 mcg/kg/min for 4 minutes. After 3 minutes, a bolus of Gadolinium-DTPA (0.1mmol/kg) was  
188 delivered at 5mls/sec, followed by a 25ml saline flush. First-pass imaging of the heart  
189 occurred over 80 heart beats. A volumetric notched-saturation pre-pulse preserved a  
190 constant saturation-recovery time during slice acquisition <sup>(17)</sup>. 6-8 short axis slices were  
191 obtained every 2 heart beats. Rest imaging was repeated after a minimum interval of 15  
192 minutes. Cine steady state free precession images and late gadolinium enhancement  
193 images were also acquired as described in the original CECaT protocol <sup>(10)</sup> Studies were  
194 reported as positive if there was an inducible perfusion defect visible for at least 5 frames

1  
2  
3 195 either: a) in a region of normal wall thickness; or b) in a region of myocardial thinning in the  
4  
5 196 absence of a history of prior myocardial infarction.  
6

7 197

### 8 9 198 **Outcomes**

10  
11 199 The primary outcome in the original CECaT trial was exercise treadmill time at 18 months  
12  
13 200 post-randomisation using the modified Bruce protocol, in which exercise intensity was  
14  
15 201 increased every 3 minutes. There was a range of secondary outcomes including diagnostic  
16  
17 202 accuracy, clinical events, health-related quality and cost-effectiveness of life up to 18 months  
18  
19 203 after randomisation<sup>(10)</sup>.

20  
21 204 The primary outcomes of this follow up study were survival up to a minimum of 2 years post-  
22  
23 205 treatment, quality-adjusted survival and cost-utility of each strategy. Survival status at the  
24  
25 206 end of follow up was determined from the Office for National Statistics database, UK  
26  
27 207 (<http://www.ons.gov.uk/>).

28  
29 208 Quality of life was measured using the EuroQoL EQ-5D questionnaire<sup>(18)</sup> which was  
30  
31 209 completed at baseline, 6 and 18 months post-randomisation, and at 6, 18 and 24 months  
32  
33 210 post-treatment. The social tariff for the EQ-5D was applied in order to calculate utility values  
34  
35 211<sup>(19)</sup>. Because post-treatment measurements were at variable times post-randomisation  
36  
37 212 (randomisation date is time zero for a randomised trial) daily utilities were estimated using  
38  
39 213 linear interpolation.  
40

41 214

### 42 43 215 **Sample size calculations**

44  
45 216 The sample size of 898 patients was based on exercise performance and was calculated  
46  
47 217 according to the methodology published in the initial report of the CECaT study<sup>(10)</sup>.  
48

49 218

### 50 51 219 **Statistical and economic analysis**

52  
53 220 For this study, survival was summarised using Kaplan-Meier estimates and the groups were  
54  
55 221 compared using Cox proportional hazards regression. This assumes that the instantaneous  
56  
57 222 risk of death (hazard) for a reference value of a covariate will vary through time, but that the  
58  
59  
60

1  
2  
3 223 hazards for other values of the covariate will be a constant multiple of this baseline hazard,  
4  
5 224 and this multiple will not vary through time. This assumption was tested using Schoenfeld  
6  
7 225 residuals and there was little evidence against it. The diagnostic test was entered into the  
8  
9 226 Cox regression as a 4-level fixed covariate, with angiography as the reference category. In  
10  
11 227 sensitivity analysis CABG and PCI were included in the regression analyses as time-varying  
12  
13 228 covariates, taking a value 0 up to the time of intervention and 1 thereafter, to ensure that any  
14  
15 229 differences between the groups was not due to differences in treatment. Inclusion of  
16  
17 230 treatment (CABG/PCI) did not affect comparison of diagnostic strategies and results of these  
18  
19 231 analyses are not included here.  
20  
21 232  
22  
23 233 Patient-specific hospital resource use was collected for 2 years post-*treatment* with  
24  
25 234 revascularisation or medical management. Costs were based on National Health Service  
26  
27 235 reference costs 2005/06 prices. An annual discount rate of 3.5% was applied to all costs and  
28  
29 236 quality-adjusted life-years (QALYs) after 12 months post-randomisation. Resources costed  
30  
31 237 were: imaging tests; revascularisation; inpatient/outpatient episodes; adverse events;  
32  
33 238 cardiac-related medications. Patient-reported admissions for MI were verified with the  
34  
35 239 admitting hospital and adjudicated.  
36  
37 240  
38  
39 241 Quality adjusted survival and cost estimates were censored at the last follow up at 2 years  
40  
41 242 after treatment, resulting in varying duration of follow-up from the time of randomisation to  
42  
43 243 the different diagnostic strategies, so that mean values over a range of time horizons were  
44  
45 244 estimated using inverse weighting methods<sup>(20)</sup>. This method allows for differing follow up  
46  
47 245 times between patients by splitting follow up time into intervals, and up-weighting the  
48  
49 246 observed quality adjusted survival and costs in an interval in proportion to the inverse of the  
50  
51 247 Kaplan-Meier estimate of the proportion observed during the interval. In the base case we  
52  
53 248 used a time horizon of 3 years since it was the longest period over which results were stable,  
54  
55 249 with acceptable precision. Confidence intervals for costs and QALYs were estimated using  
56  
57 250 bootstrapping with 5000 samples<sup>(21)</sup>.  
58  
59  
60

1  
2  
3 251 **Sensitivity analysis**

4  
5 252 Sensitivity of cost-utility results for different time horizons was assessed by re-estimating  
6  
7 253 results up to 12, 18, 24, 36 and 48 months after randomization. In addition, cardiologists  
8  
9 254 were divided into those who did and did not perform percutaneous coronary intervention as  
10  
11 255 part of their routine clinical practice, and results were recalculated for each subgroup. With  
12  
13 256 the exception of this *post-hoc* data interrogation, all other results presented derive from  
14  
15 257 intention-to-treat analysis.  
16

17 258

18  
19 259 The study had IRB approval and full written informed consent was obtained from all  
20  
21 260 participants. All authors had full access to the data and take responsibility for the manuscript  
22  
23 261 as written.  
24

25 262

26  
27 263 **Results**

28  
29 264 **Recruitment and compliance**

30  
31 265 Between September 2001 and September 2004, 3,201 patients were assessed, 1,981 were  
32  
33 266 excluded and 322 refused entry to the trial. Refusals were more likely to come from women  
34  
35 267 (46% compared with 31% enrolled into the study,  $p<0.001$ ) and were significantly older  
36  
37 268 (mean age 64.6, (SD 10.1) compared with study group mean age 61.8, (9.4),  $p<0.001$ ).  
38

39 269

40  
41 270 898 patients were randomised. Groups were well matched at baseline (table 1). In each  
42  
43 271 group 69% of patients were high risk for CAD (Pryor score  $> 0.8$ ). The trial was closed to  
44  
45 272 recruitment in September 2004 after enrolling the pre-specified number of subjects.  
46

47 273

48  
49 274 One-hundred-seventy-five (78%) SPECT patients, 180 (80%) CMR patients and 169 (75%)  
50  
51 275 stress echo patients were referred on for angiography (**Figure 1**). Between 20% and 25% of  
52  
53 276 patients undergoing non-invasive tests did not require further investigation. Twenty-one  
54  
55 277 percent of patients who had negative tests were referred for angiography and the proportion  
56  
57 278 was similar in each group (SPECT  $n=45$ , CMR  $n=50$ , ECHO  $n=48$ ,  $p=0.858$ ). Of these 14  
58  
59  
60

1  
2  
3 279 (31%) SPECT, 26 (52%) CMR and 23 (48%) ECHO resulted in a positive angiogram  
4  
5 280 ( $p=0.130$ ). Four patients died and four withdrew from the trial early on. Of the remaining  
6  
7 281 patients, revascularization was required in 34% (301/890 – see **Figure 1** for numbers in  
8  
9 282 each arm). There was no significant difference between the groups in initial patient  
10  
11 283 management (Figure 1,  $p=0.527$ ). Beyond the initial management strategy 42 subsequent  
12  
13 284 revascularisation procedures were required in the angiography arm compared with 30 in the  
14  
15 285 SPECT, 44 in the CMR and 41 in the ECHO arms. The median times between  
16  
17 286 randomisation and initial revascularisation were 122 days in the angiography group, 192  
18  
19 287 days for SPECT, 184 days for CMR and 177.5 days for ECHO, resulting in a delay due to  
20  
21 288 functional testing of approximately 2 months.  
22  
23  
24

289

### 290 **Survival**

291 During the study there were 7 (3%), 7 (3%), 18 (8%) and 11 (5%) deaths in the angiography  
292 , SPECT, CMR and ECHO groups respectively. Kaplan-Meier survival curves for the 4  
293 groups are plotted in **Figure 2**. Survival over the whole trial period in the SPECT (hazard  
294 ratio 1.0, 95%CI 0.4, 2.9) and stress echo (hazard ratio 1.6, 95%CI 0.6, 4.0) groups were not  
295 significantly different from angiography but the CMR group had higher mortality, with hazard  
296 ratio 2.6 (95%CI 1.1 to 6.2),  $p=0.032$ . The significant effect of CMR on survival remained  
297 when CABG or PCI were included in the models. However, mortality was low in all groups  
298 and the absolute mean difference in survival was less than 1 month over 3 years (**Table 2**).  
299 Mean survival estimates over 3 years with 95% confidence intervals are shown in **Table 2**.  
300 All patients had complete adverse event data up to 18 months post-randomisation during  
301 which there were 178 non-fatal adverse events in 114 patients, mostly hospital admissions  
302 for chest pain (**Table 3**). Beyond this time only adverse events that resulted in admissions  
303 were recorded as they were relevant for the economic analysis. No patient suffered any  
304 adverse event at the time of the initial randomised imaging test.  
305

306

### 306 **Cost-utility**

1  
2  
3 307 **Table 4** shows some of the highest incurred follow up costs for the 4 groups and shows that  
4  
5 308 patient management varied substantially between individuals. Although angiography was the  
6  
7 309 most expensive of the four initial diagnostic tests, the strategy of initial angiography had  
8  
9 310 lower mean overall cost than stress echo, and was similar to CMR up to 3 years (**Table 2**).  
10  
11 311 Extra costs for patients in the three non-invasive groups was largely due to patients  
12  
13 312 undergoing follow-on angiography. There were no significant differences in overall costs  
14  
15 313 between the groups.  
16

17 314  
18  
19 315 During the study there were no significant differences in EQ-5D between the groups. **Figure**  
20  
21 316 **3** shows daily mean EQ-5D utility over time based on interpolation between measurements  
22  
23 317 for survivors who completed the EQ-5D. Using inverse-weighting we calculated QALYs over  
24  
25 318 different time horizons and these are presented up to 3 years in **Table 2**. Mean QALYs over  
26  
27 319 3 years in the angiography group was 2.24, which was not significantly different from the  
28  
29 320 other groups. **Figure 4** shows the joint distribution of the difference in mean cost against the  
30  
31 321 difference in mean QALY for each diagnostic strategy group and angiography alone, and  
32  
33 322 shows the uncertainty in these estimates. **Figure 5** shows the Cost-Effectiveness  
34  
35 323 Acceptability Curve and demonstrated that SPECT has a high chance (>70%) of being cost-  
36  
37 324 effective whatever the willingness-to-pay threshold is but for CMR and ECHO there is much  
38  
39 325 less certainty about this decision. The mean differences between groups were close to zero  
40  
41 326 in all 3 cases so that the cost-per-QALY estimates are unstable and a cost-minimization  
42  
43 327 approach may be more appropriate. This would favour SPECT, which was both cheaper and  
44  
45 328 more effective on average than angiography, and had the lowest overall cost ( ).  
46  
47 329

### 330 **Sensitivity analysis**

331 The comparisons between the diagnostic strategy groups did not change substantially when  
332 we varied the time horizon; the main effect of this was that the variation surrounding  
333 estimates increased as the time horizon lengthened due to the heavy censoring (results not  
334 shown). **Tables 2a and 2b** show results for interventional and non-invasive cardiologists



1  
2  
3 335 respectively. Patients who were managed by interventional cardiologists incurred higher  
4  
5 336 costs due to the greater number of tests and revascularization procedures performed, with  
6  
7 337 minimal incremental benefit in QALY.  
8

9 338

## 10 339 **Discussion**

11  
12  
13 340 CECaT is the first completed prospective randomized trial to look at the clinical and cost-  
14  
15 341 effectiveness of non-invasive imaging in the diagnosis and management of angina. To the  
16  
17 342 best of the authors' knowledge there has been no comparable outcomes trial published on  
18  
19 343 this scale evaluating three independent non-invasive 'gatekeeper' modalities versus initial  
20  
21 344 angiography in stable chest pain. The trial is also unusual in the length of prospective follow  
22  
23 345 up extending to 6 years for mortality outcomes.  
24

25 346

26  
27 347 We have demonstrated that use of any one of stress CMR, stress echo or stress SPECT as  
28  
29 348 the initial test for a stable chest pain patient leads to non-inferior outcomes in quality of life  
30  
31 349 and cost utility compared to patients randomised to upfront invasive coronary angiography.  
32  
33 350 Typically, non invasive tests perform well in low risk populations because of a negative  
34  
35 351 predictive value which is usually better than the positive predictive value. However, the  
36  
37 352 patient risk profile was relatively high in our study, and despite this there was no significant  
38  
39 353 difference between an initial functional or anatomic approach.  
40

41 354

42  
43 355 There are several reasons why initial angiography may not have led to clear benefit in our  
44  
45 356 study. Firstly, although angiography has stood at the heart of the diagnostic chest pain  
46  
47 357 pathway, the traditional binary cut-off values of 50% or 70% percentage stenosis by visual  
48  
49 358 estimation were shown in the FAME study to bear little relation to the true physiologic  
50  
51 359 significance of luminal narrowing <sup>(22)</sup>.  
52

53 360

54  
55  
56 361 Secondly, data from various countries suggest that not only is coronary angiography often  
57  
58 362 inappropriate when formally rated by expert observers <sup>(23) (24)</sup> but that disparate national or  
59  
60



1  
2  
3 363 regional rates of angiography do not translate into clear mortality benefits between countries  
4  
5 364 <sup>(25) (26) (27) (28)</sup> and on occasion may even demonstrate an inverse relationship <sup>(29)</sup>.

6  
7 365 Contemporary US data from approximately 500,000 PCI procedures collected prospectively  
8  
9 366 in the National Cardiovascular Data Registry demonstrated that, of 145,000 elective PCI  
10  
11 367 cases, roughly 12% were judged inappropriate. Furthermore, the rate of inappropriate  
12  
13 368 elective PCI between hospital sites ranged from 0-55% suggesting significant variability in  
14  
15 369 practice <sup>(30)</sup>. The data suggest a better way of selecting patients for invasive investigation is  
16  
17 370 needed.  
18

19 371  
20  
21 372 Ischemia-driven revascularisation has been shown to be of benefit in a number of trials,  
22  
23 373 most recently in the FAME study in which an invasive method of measuring the flow reserve  
24  
25 374 of the microcirculation (Fractional Flow Reserve, FFR) was used to allocate patients to  
26  
27 375 intervention or observation vs a clinical decision on intervention based on angiography alone  
28  
29 376 <sup>(31)</sup>. At 2 years follow up there were clear survival and MACE benefits to the FFR-based  
30  
31 377 approach.  
32

33  
34 378  
35 379 The ACRE study reported that, up to 6 years after diagnosis, medical management was a  
36  
37 380 more cost-effective strategy for angina compared with PCI <sup>(32)</sup>. The lack of evidence for  
38  
39 381 survival from revascularisation was also seen in the COURAGE trial <sup>(4)</sup>. Critics have  
40  
41 382 suggested this may be because randomization to PCI versus optimal medical therapy was  
42  
43 383 made *after* coronary angiography had been performed, potentially leading to a recruitment  
44  
45 384 bias of patients with less severe disease. In the CECaT trial this bias was avoided by  
46  
47 385 randomization to a management strategy defined by the non-invasive test result for each of  
48  
49 386 the 3 functional arms of the trial. In a relatively high risk population, we demonstrated no  
50  
51 387 clinically significant survival or economic detriment from using non-invasive imaging as a  
52  
53 388 gate-keeper to catheterization. Similarly, quality of life was not significantly different across  
54  
55 389 all four groups and these differences extended to a warranty period of at least 3 years.  
56

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1  
2  
3 391 We did observe a marginal decrease in survival in the CMR arm. The reasons for the  
4  
5 392 difference are unclear but do not relate to patient characteristics or management with CABG  
6  
7 393 or PCI. Although statistically significant, the mean survival difference from the other groups  
8  
9 394 was only 4 weeks over 3 years and is unlikely to be clinically meaningful. Since recent work  
10  
11 395 has established a strong correspondence between FFR measurements and stress CMR  
12  
13 396 perfusion indices it would be surprising if CMR were genuinely inferior to other modalities for  
14  
15 397 risk stratification<sup>(33)</sup>. Indeed several recent publications have highlighted the incremental  
16  
17 398 prognostic data (above that obtained from clinical variables) derived from several thousand  
18  
19 399 perfusion CMR studies<sup>(34) (35)</sup>.

20  
21 400

22  
23 401 Given the recent publication of the CEMARC trial<sup>(36)</sup> in which a clear diagnostic superiority  
24  
25 402 was demonstrated for stress CMR over SPECT, it is interesting that our data nonetheless  
26  
27 403 show an equivalence in functional health status between those randomized to SPECT  
28  
29 404 versus CMR in the CECaT trial. The implication may be that although CMR detects the  
30  
31 405 presence of *any* ischemia with a greater sensitivity it is the *overall burden* of ischemia that  
32  
33 406 alters a patient's prognosis. As such, it has not yet been demonstrated that the higher  
34  
35 407 diagnostic accuracy of CMR translates into better long-term patient outcomes – a fact  
36  
37 408 acknowledged by Greenwood et al subsequent to CEMARC's publication<sup>(37)</sup>. In this context  
38  
39 409 the CECaT nuclear results are congruent with numerous past publications and reconfirm the  
40  
41 410 reassuring warranty period of a normal SPECT study.

42  
43 411

#### 44 45 412 **Cost effectiveness**

46  
47 413 There was no significant difference in cost-effectiveness between the angiography -as-  
48  
49 414 default group and the non-invasive test groups up to 3 years, perhaps relating to the higher-  
50  
51 415 than-anticipated rate of referral for angiography after negative functional tests. Protocol  
52  
53 416 deviation of this kind is not infrequent in trials of non-invasive technology. In the recent  
54  
55 417 PARR-2 study of patients undergoing fluorodeoxyglucose positron emission tomography for  
56  
57 418 the assessment of viability, roughly 25 % of the study population did not adhere to protocol  
58  
59  
60

1  
2  
3 419 <sup>(38)</sup>. The willingness of a cardiologist to defer referral for coronary angiography in the face of  
4  
5 420 a normal non-invasive study may in part reflect individual prejudices and job description  
6  
7 421 (interventional versus non-invasive) as demonstrated in a recent survey of cardiology  
8  
9 422 attitudes <sup>(39)</sup> and was also reflected in our own data.

10  
11 423

12  
13 424 In CECaT, 20-25% of patients receiving a non-invasive test did not go on to have  
14  
15 425 angiography. A proportion of the additional cost in the non-invasive arms related to  
16  
17 426 angiography and PCI in the patients with a *negative* test, although only very few  
18  
19 427 subsequently required CABG - a robust marker of significant disease - during follow-up. This  
20  
21 428 readiness to employ PCI in a group in whom the indication/benefit is debatable was also  
22  
23 429 seen in the ACRE trial <sup>(32)</sup> and reflects understandable clinical response to uncertainty but  
24  
25 430 also the easy access to PCI in healthcare systems without barriers to self-referral <sup>(40)</sup>.

26  
27 431 Similarly, studies from the US have demonstrated a greater willingness to use coronary  
28  
29 432 angiography when available 'on site' as is increasingly seen even in small-to-medium sized  
30  
31 433 hospitals <sup>(41) (42) (43)</sup>.

32  
33 434

### 34 35 435 ***Cost effectiveness of each non-invasive technique***

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37 436

38  
39 437 Nuclear myocardial perfusion imaging

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41 438

42  
43 439 The END study used propensity matching to compare a large cohort of patients referred for  
44  
45 440 either gate-keeper myocardial perfusion imaging or upfront angiography – this non  
46  
47 441 randomised study demonstrated a significant cost reduction in the <sup>(44)</sup> nuclear arm. In  
48  
49 442 contrast to this and other work <sup>(45) (46) (47)</sup> we were unable to show a significant difference in  
50  
51 443 cost effectiveness in our own study. To some extent this reflected the participating physician  
52  
53 444 bias towards angiography during the period of trial recruitment (2001-2006) with many  
54  
55 445 patients referred for angiography despite normal perfusion studies. This continues in the  
56  
57 446 contemporary era with Chan et al demonstrating that almost 80% of Delphi-adjudicated  
58  
59  
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1  
2  
3 447 inappropriate elective PCIs were performed following either low risk ischemia imaging in  
4  
5 448 mildly symptomatic patients or intermediate risk imaging in entirely asymptomatic patients  
6  
7 449 <sup>(30)</sup>.

8  
9 450

10  
11 451 In the CECaT study, when PCI was performed despite a negative initial non-invasive test,  
12  
13 452 this occurred because subsequent angiography indicated 'significant' stenosis. This was a  
14  
15 453 clinical judgment based on 'eyeball assessment' of lesion severity as has been reported in  
16  
17 454 clinical trials with angiographic end points <sup>(48)</sup>. However, the severity and functional  
18  
19 455 significance of many stenoses may be over-called, even by quantitative assessment, when  
20  
21 456 compared with physiological assessment of fractional flow reserve across the lesion <sup>(49) (50)</sup>.

22  
23 457 Further improvement in cost-effectiveness could likely have been achieved in the nuclear  
24  
25 458 arm of the trial. Our post-trial practice is to perform the stress SPECT first - and if this is  
26  
27 459 negative - cancel the rest test, likely augmenting the relative cost-effectiveness of SPECT  
28  
29 460 <sup>(51)</sup>.

30  
31 461

32  
33 462 CMR

34  
35 463 There are relatively few data available regarding the cost effectiveness of CMR . One recent  
36  
37 464 mathematical modelling study estimated that CMR likely has greater cost effectiveness/utility  
38  
39 465 compared to SPECT despite greater base case cost of the former <sup>(52)</sup>. The economic  
40  
41 466 superiority of CMR was also recently described by the CEMARC group, although  
42  
43 467 interestingly the base case costs employed for CMR and SPECT in their analysis differed by  
44  
45 468 only a few pounds. Their own sensitivity analysis in fact demonstrated that if the costs of the  
46  
47 469 two tests varied by more than 100 pounds (which was the case in our study) then in fact – as  
48  
49 470 we found - SPECT became the dominant strategy in a low-to-intermediate risk population.

50  
51 471 <sup>(53)</sup>

52  
53 472

54  
55 473 Stress echo

1  
2  
3 474 Stress echocardiography may be a more cost-effective strategy than angiography for men  
4  
5 475 aged 50-60 with CAD prevalence of 50%<sup>(54), (47)</sup>. There is also some evidence that stress  
6  
7 476 echo is more cost-effective than SPECT as an initial test <sup>(55) (56)</sup>, especially in women with  
8  
9 477 suspected CAD <sup>(57)</sup>. A similar benefit was not seen in our study probably because of the high  
10  
11 478 disease prevalence in our population. The lack of superiority of either stress  
12  
13 479 echocardiography or a combined strategy of exercise testing and stress echo compared to  
14  
15 480 upfront catheterisation was also evident in a recent Polish study of 600 patients with a  
16  
17 481 similar age, gender and disease prevalence to our own study population <sup>(58)</sup>.  
18  
19 482

20  
21 483 Taken overall, our data clearly demonstrate a limited future role for cost-effective non-  
22  
23 484 invasive imaging if referring physicians are not willing to accept a negative result as ground  
24  
25 485 truth. This might be interpreted as reflecting a need for greater physician education since we  
26  
27 486 showed a clear difference in onward referral rates for angiography after a negative test  
28  
29 487 between interventional and non-invasive cardiologists.  
30  
31 488

### 32 33 489 ***Clinical effectiveness***

34  
35 490 We demonstrated that SPECT can obviate the need for coronary angiography for a  
36  
37 491 significant number of patients without any clinical detriment. In the stress echo group clinical  
38  
39 492 outcomes were also comparable to the angiography subgroup at 18 months. The CMR  
40  
41 493 group had statistically marginally poorer survival and this follows our earlier finding that CMR  
42  
43 494 patients had significantly worse exercise tolerance at 18 months after randomisation <sup>(10)</sup>. This  
44  
45 495 is difficult to explain on the basis of Pryor risk score or other baseline clinical variables.  
46  
47 496 However, the mean difference in survival between the CMR arm and the other groups was  
48  
49 497 only 4 weeks and thus of marginal clinical significance. More importantly, the CMR group  
50  
51 498 were not otherwise disadvantaged – compared to the angiographic control group - with  
52  
53 499 respect to major adverse events, other resource use, or quality of life.  
54  
55 500

### 56 57 58 501 ***Limitations***

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60

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2  
3 502 This study was carried out in a single specialist cardiothoracic centre with a significant  
4  
5 503 proportion of high risk, predominantly white European, male patients. Those eligible who  
6  
7 504 refused the trial were older and were more likely to be women.  
8

9 505

10  
11 506 Survival data from the national registry did not include cause of death so that deaths due to  
12  
13 507 cardiovascular causes could not be reported separately.  
14

15 508

16  
17 509 The trial completed recruitment in 2004 and we used the technology that was available to us  
18

19 510 at the onset of the trial. At that time, we were not able to use attenuation correction for  
20

21 511 SPECT imaging; however this was also not used in the much more recent CEMARC trial<sup>(36)</sup>.  
22

23 512 Similarly, we performed our CMR exams in a mobile facility on a 1.5T scanner with only  
24

25 513 modest coil technology and limited temporal and anatomic coverage that would compare  
26

27 514 unfavourably with the 3T whole heart high resolution perfusion studies available today.  
28

29 515

30  
31 516 The trial aimed to reflect the strategy of using non-invasive imaging as a gateway to  
32

33 517 angiography in *contemporary clinical practice*. The test results were considered in  
34

35 518 conjunction with other information available at the time. Thus it was not the aim to formally  
36

37 519 assess diagnostic accuracy of the non-invasive tests in this context. This trial-based study  
38

39 520 was limited to 3 year cost-effectiveness follow up - longer-term economic models would  
40

41 521 provide lifetime estimates of the cost-effectiveness of the non-invasive strategies and could  
42

43 522 include advances in imaging technology.  
44

45 523

## 46 47 524 **Conclusions**

48  
49 525 We have demonstrated in the CECaT trial that stress echo, stress CMR and stress SPECT  
50

51 526 may each be used to defer invasive coronary angiography without clinical detriment or  
52

53 527 significant excess costs in an outpatient population with stable chest pain.  
54

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1  
2  
3 530 **Acknowledgements**  
4

5 531

6  
7 532 The original CECaT study was funded by a grant from the UK National Health Service R&D  
8  
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10  
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30  
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33 545 **Exclusive licence statement**  
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52 554 **Contributorship statement**  
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54 555

55  
56 556 HT performed literature review, data analysis and interpretation; NW was involved in image  
57  
58 557 analysis, drafting the manuscript and critical revision; VH was involved in recruiting the  
59  
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3 558 patients, data management, administering health questionnaires, data analysis and drafting  
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5 559 the manuscript; MD and MB were responsible for data analysis, health economic  
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7 560 assessment, drafting the manuscript and critical revision; LDS was responsible for study  
8  
9 561 design, trial management, statistical analysis, drafting the manuscript and critical revision;  
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11 562 CJ performed statistical and health economic analysis, drafting the manuscript and critical  
12  
13 563 revision; AMC was involved in study design, patient recruitment, image interpretation, trial  
14  
15 564 management, drafting the manuscript and critical revision and is the overall guarantor of  
16  
17 565 manuscript integrity.

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21 567 All authors have read the manuscript in its submitted form and have provided final approval  
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23 568 for publication.

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27 570 **Contributorship statement:**

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31 572 HT, MD, MB, LDS, CHJ were involved in economic and statistical analysis. LDS was the  
32  
33 573 senior project statistician, was involved in original study design and takes overall  
34  
35 574 responsibility for statistical portion of the manuscript. All of these individuals contributed to  
36  
37 575 drafting and revision of the manuscript.

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39 576

40  
41 577 VH was involved in study design, patient recruitment, data collection and project  
42  
43 578 management from the project's inception to its conclusion. She also contributed to drafting  
44  
45 579 and revision of the manuscript

46  
47 580

48  
49 581 NW was responsible for blinded review of clinical data and contributed to drafting and  
50  
51 582 revision of the manuscript.

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53 583

54  
55 584 AC was involved in the original study design, was responsible for the day-to-day clinical  
56  
57 585 aspects of running the trial and was involved in the recruitment and follow up of patients as  
58  
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2  
3 586 well as analysis of the cardiac MR studies. He wrote the final manuscript and contributed to  
4  
5 587 its revision. He takes overall responsibility for the integrity of the clinical data.

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9 589 ***Data sharing statement:***

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11 590 There are no additional data available  
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591 **Table 1 Baseline characteristics\***

	Angiography	SPECT	Cardiac MRI	Stress Echo
Demographics	(n=222)	(n=224)	(n=226)	(n=226)
Mean (SD) age (years)	60.7 (9.1)	62.1 (9.5)	62.2 (9.0)	61.9 (9.9)
Males (%)	149 (67%)	157 (70%)	153 (68%)	160 (71%)
History/risk factors				
Previous MI (%)	63 (28%)	52 (23%)	69 (31%)	59 (26%)
Previous CVA (%)	10 (5%)	13 (6%)	8 (4%)	12 (5%)
Diabetes(%)				
IDDM	12 (5%)	8 (4%)	11 (5%)	5 (2%)
NIDDM	16 (7%)	18 (8%)	21 (9%)	22 (10%)
Family history CAD	60 (27%)	55 (25%)	63 (28%)	59 (26%)
Smoking history (%)				
<25 pack years	149 (67%)	162 (72%)	148 (65%)	155 (69%)
>=25 pack years	73 (33%)	62 (28%)	78 (35%)	71 (31%)
Treated hyperlipidaemia	164 (74%)	171 (76%)	179 (79%)	179 (79%)
(%)				
Treated hypertension (%)	117 (53%)	132 (59%)	115 (51%)	129 (57%)
Exercise tolerance using the modified Bruce protocol				
Mean (SD) total exercise time (mins)	11.29 (4.56)	10.46 (4.41)	10.43 (4.43)	10.89 (4.36)
ECG changes on exercise test				
1-2 mm ST depression with symptoms	53 (24%)	43 (19%)	54 (24%)	57 (25%)
>= 2mm ST depression without symptoms	16 (7%)	24 (11%)	20 (9%)	24 (11%)

ST elevation**/ no change	153 (69%)	157 (70%)	152 (67%)	145 (64%)
CCS class				
0-I	60 (27%)	54 (24%)	78 (35%)	58 (26%)
II	138 (62%)	144 (64%)	122 (54%)	132 (58%)
III-IV	24 (11%)	26 (12%)	26 (11%)	36 (16%)

592 \* There were no significant differences between the groups in any variable

593 \*\* ST elevation was observed in 3 angiography, 2 CMR and 1 ECHO patients.

594 **Table 2 Cost-effectiveness summaries to 3 years post randomization**

595

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
Hazard ratio for death	Baseline	0.99	2.60	1.42
(95%CI)		(0.35,2.85)	(1.09,6.22)	(0.54,3.74)
Mean survival (years)	2.96	2.95	2.90	2.94
(95%CI)	(2.92, 2.99)	(2.90, 2.99)	(2.83, 2.95)	(2.89, 2.97)
Mean difference vs. CA	-	-0.01	-0.06	-0.02
(95%CI)	-	(-0.07,0.05)	(-0.14, 0.01)	(-0.08, 0.04)
Mean QALYs	2.24	2.27	2.18	2.27
(95%CI)	(2.16,2.31)	(2.20,2.33)	(2.11,2.25)	(2.19,2.33)
Mean difference vs. CA	-	0.03	-0.05	0.03
(95%CI)	-	(-5.21,1.38)	(-5.21,1.38)	(-3.04,4.21)
Mean discounted costs	5243	4644	4947	5530
(£)				
(95%CI)	(4282,6461)	(4194,5126)	(4480,5431)	(4857, 6262)
Mean difference vs. CA	-	-599	-296	287
(95%CI)	-	(-1901,503)	(-1603, 824)	(-1109, 1537)
Probability cost effective	-	0.82	0.29	0.55
at £20k per QALY				
Probability cost effective	-	0.79	0.25	0.59
at £30k per QALY				

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597 **Table 2a Cost-effectiveness summaries for patients managed by interventional**  
 598 **cardiologists to 3 years post randomization**

599

	Angiography (n=73)	SPECT (n=96)	Cardiac MRI (n=93)	Stress Echo (n=98)
Mean survival (years)	2.96	2.97	2.89	2.96
(95%CI)	(2.91, 2.98)	(2.93, 3.00)	(2.80, 2.97)	(2.90, 2.98)
Mean difference vs. CA	-	0.01	-0.07	0
(95%CI)	-	(-0.05,0.07)	(-0.17, 0.02)	(-0.07,0.05)
Mean QALYs	2.25	2.29	2.21	2.2
(95%CI)	(2.14,2.36)	(2.19,2.38)	(2.10,2.32)	(2.10,2.29)
Mean difference vs. CA	-	0.03	-0.04	-0.06
(95%CI)	-	(-5.31,2.30)	(-4.96,2.41)	(-3.06,6.42)
Mean discounted costs (£)	5754	5205	5307	6329
(95%CI)	(4651, 6941)	(4475, 5979)	(4610, 6032)	(5120, 7713)
Mean difference vs. CA	-	-549	-447	574
(95%CI)		(-1973, 799)	(-1841, 897)	(-1097, 2262)
Probability cost effective at £20k per QALY		0.72	0.42	0.20
Probability cost effective at £30k per QALY		0.70	0.39	0.21

600 **Table 2b Cost-effectiveness summaries for patients managed by non-interventional**  
 601 **cardiologists to 3 years post randomization**

602

	Angiography (n=149)	SPECT (n=128)	Cardiac MRI (n=133)	Stress Echo (n=128)
Mean survival (years)	2.95	2.93	2.9	2.92
(95%CI)	(2.89, 2.99)	(2.85, 2.98)	(2.81, 2.97)	(2.85, 2.98)
Mean difference vs. CA	-	-0.02	-0.05	-0.03
(95%CI)	-	(-0.11,0.06)	(-0.15, 0.04)	(-0.11, 0.05)
Mean QALYs	2.23	2.25	2.17	2.31
(95%CI)	(2.14,2.31)	(2.16,2.33)	(2.07,2.26)	(2.22,2.40)
Mean difference vs. CA	-	0.02	-0.06	0.09
(95%CI)	-	(-6.92,1.90)	(-5.50,3.45)	(-5.45,3.71)
Mean discounted costs (£)	4936	4216	4723	4780
(95%CI)	(3681, 6665)	(3635, 4799)	(4068, 5381)	(4136, 5467)
Mean difference vs. CA	-	-719	-212	-156
(95%CI)		(-2527, 695)	(-2007, 1258)	(-1990, 1353)
Probability cost effective at £20k per QALY		0.75	0.29	0.85
Probability cost effective at £30k per QALY		0.72	0.27	0.86

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605 **Table 3 Summary adverse events during initial 18 months follow up\***

	Angiography	SPECT	Cardiac MRI	Stress Echo
Adverse event	(n=222)	(n=224)	(n=226)	(n=226)
Total adverse events	38	34	44	62
Chest pain (not myocardial infarction)	21	20	28	35
Angina	7	5	4	3
Myocardial infarction	2	0	3	6

606 \* Note that beyond this time only events that required hospital admission were recorded.

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609 **Table 4** Summary of the frequency of use of the main resource use elements during follow up  
 610 of up to 3 years (excluding initial diagnostic test)

611

Resource use (unit cost)	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
CABG (£7195)	28	33	28	34
PCI (£3660)	57	46	60	62
Other hospital admission (£467 per day)	36	29	28	53
Angiography (£625)	12	183	175	181
SPECT (£405)	16	3	3	6
Cardiac MRI (£565)	5	5	12	5
Echocardiography (£435)	30	17	24	18
PET scan (£842)	0	3	0	1
Preadmission clinic (£85)	22	21	27	24
Follow up clinic (£85)	19	22	31	21
Outpatient visits (£143)	247	270	300	284

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613 \* Cardiac drugs were also included but are not shown here due to many different  
 614 combinations of drugs and doses prescribed.

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3 617 **Figure Legends**

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7 619 **Figure 1 CONSORT diagram describing recruitment and randomization**

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11 621 **Figure 2 Kaplan-Meier survival estimates according to initial modality of diagnosis**

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15 623 **Figure 3 Quality of life assessed by EQ5D over time**

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19 625 **Figure 4 Bootstrapped estimates of the joint distribution of mean cost difference**

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21 626 **against mean QALY difference up to 3-years post randomisation**

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25 628 **Figure 5 Estimated probability of being cost-effective compared with angiography**

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27 629 **alone against the amount (£) a health provider is willing to pay for one additional**

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29 630 **QALY**

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**Title: 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**

\*Cost Effectiveness of non-invasive Cardiac Testing

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**Clinical Trial registration:** ISRCTN 47108462, UKCRN 3696



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3 45 **Contributorship statement:**  
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5 46  
6

7 47 **HT, MD, MB, LDS, CHJ were involved in economic and statistical analysis. LDS was**  
8  
9 48 **the senior project statistician, was involved in original study design and takes overall**  
10  
11 49 **responsibility for statistical portion of the manuscript. All of these individuals**  
12  
13 50 **contributed to drafting and revision of the manuscript.**  
14

15 51  
16  
17 52 **VH was involved in study design, patient recruitment, data collection and project**  
18  
19 53 **management from the project's inception to its conclusion. She also contributed to**  
20  
21 54 **drafting and revision of the manuscript**  
22

23 55  
24  
25 56 **NW was responsible for blinded review of clinical data and contributed to drafting and**  
26  
27 57 **revision of the manuscript.**  
28

29 58  
30  
31 59 **AC was involved in the original study design, was responsible for the day-to-day**  
32  
33 60 **clinical aspects of running the trial and was involved in the recruitment and follow up**  
34  
35 61 **of patients as well as analysis of the cardiac MR studies. He wrote the final**  
36  
37 62 **manuscript and contributed to its revision. He takes overall responsibility for the**  
38  
39 63 **integrity of the clinical data.**  
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3 73 **Article summary:**

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5 74 **Article focus:**

- 6  
7 75 1. Is non-invasive imaging a safe and appropriate gate-keeper to coronary  
8  
9 76 angiography in patients with stable chest pain ?
- 10  
11 77 2. Is there any difference in cost-effectiveness and cost-utility between the  
12  
13 78 different non-invasive approaches and conventional coronary angiography
- 14  
15 79 3. Are patients disadvantaged in any meaningful way by having a non-invasive  
16  
17 80 test to decide whether they should go forward for coronary angiography ?
- 18  
19 81 4. How does stress perfusion CMR compare to the more established tests of  
20  
21 82 SPECT-MIBI and stress echocardiography as a gate-keeper to coronary  
22  
23 83 angiography ?
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26 84

27 85 **Key messages:**

- 28  
29 86 1. Non-invasive testing may be used safely as a gate-keeper to coronary  
30  
31 87 angiography in patients with stable chest pain without any material  
32  
33 88 disadvantage to them in terms of survival and quality of life up to 6 years after  
34  
35 89 initial randomisation.
- 36  
37 90 2. SPECT-MIBI appears marginally superior statistically to the other non-invasive  
38  
39 91 methods although clinically meaningful differences are small between all  
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41 92 strategies.
- 42  
43 93 3. Stress perfusion CMR appears to be an effective technique in a stable out-  
44  
45 94 patient population with undiagnosed chest pain.
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49 96 **Strengths and limitations:**

- 50  
51 97 1. This is the only large randomised prospective trial of a strategy of non-invasive  
52  
53 98 gate-keeper cardiac imaging versus upfront angiography in the literature.
- 54  
55 99 2. The cost-utility data are derived from NHS tariffs and our results are not  
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57 100 necessarily directly transferrable to other healthcare systems
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101 ***Data sharing statement:***  
102 **There are no additional data available**

For peer review only

1  
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3 103 **Abstract**

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5 104 **Objectives:** to compare outcomes and cost effectiveness of various initial imaging strategies on  
6  
7 105 the management of stable chest pain in a long term prospective randomized trial.

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9 106 **Setting:** regional cardiothoracic referral center in the east of England

10  
11 107 **Participants:** 898 patients (69% male) entered the study with 869 alive at 2yr follow up.  
12  
13 108 Patients were included if they presented for assessment of stable chest pain with a positive  
14  
15 109 exercise test and no prior history of ischemic heart disease. Exclusion criteria were recent  
16  
17 110 infarction, unstable symptoms or any contra-indication to stress MRI.

18  
19 111 **Primary outcome measures:** The primary outcomes of this follow up study were survival up  
20  
21 112 to a minimum of 2 years post-treatment, quality-adjusted survival and cost-utility of each  
22  
23 113 strategy

24  
25 114 **Results:** 898 patients were randomized. Compared to angiography, mortality was  
26  
27 115 marginally higher in the groups randomized to CMR (hazard ratio 2.6, 95%CI 1.1, 6.2), but  
28  
29 116 similar in the SPECT-MIBI (hazard ratio 1.0, 95%CI 0.4, 2.9) and ECHO groups (hazard ratio  
30  
31 117 1.6, 95%CI 0.6, 4.0). Although SPECT-MIBI was marginally superior to other non-invasive  
32  
33 118 tests there were no other significant differences between the groups in mortality, quality  
34  
35 119 adjusted survival or costs.

36  
37 120 **Conclusions:** Non-invasive cardiac imaging can be used safely as the initial diagnostic test  
38  
39 121 to diagnose CAD without adverse effects on patient outcomes or increased costs, relative to  
40  
41 122 angiography. These results should be interpreted in the context of recent advances in  
42  
43 123 imaging technology.

44  
45 124 **Trial registration:** ISRCTN 47108462, UKCRN 3696

46  
47 125 **Key words:** MRI, cardiovascular magnetic resonance, comparative effectiveness, SPECT,  
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49 126 stress echo, coronary angiography  
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## 127 **Introduction**

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129 CAD is common and its management is costly<sup>(1)</sup>. Revascularisation using bypass surgery  
130 (CABG) or percutaneous coronary intervention (PCI) is effective for patients with severe  
131 disease<sup>(2)</sup> but a significant minority of patients do not gain symptomatic relief<sup>(3)</sup>. Data from  
132 the COURAGE trial did not show prognostic benefit from revascularization in any patient  
133 subgroup<sup>(4)</sup>. The yield of coronary angiography is variable with one recent large study of  
134 nearly 400, 000 patients demonstrating a normalcy rate approaching 40%<sup>(5)</sup>. Therefore  
135 non-invasive testing to identify those with a low likelihood of obstructive CAD may be safer,  
136 cheaper and more appropriate than upfront angiography. This approach is codified in  
137 multiple AHA/ACC guidelines on the investigation of stable or suspected angina pectoris in  
138 which initial non-invasive imaging is rated as highly appropriate<sup>(6) (7) (8) (9)</sup>.

139

140 The 'Cost-Effectiveness of non-invasive **Cardiac Testing**' (**CECaT**) trial was an unblinded  
141 non-inferiority trial designed to assess three functional tests - stress echocardiography,  
142 single photon emission computed tomography (SPECT) and stress cardiac magnetic  
143 resonance imaging (CMR) - as a gatekeeper to coronary angiography (CA) in patients  
144 referred for CA with suspected coronary artery disease (CAD). Early clinical and cost-  
145 effectiveness estimates have been published and showed that the CMR group had slightly  
146 lower mean exercise treadmill time according to the Bruce protocol but otherwise the tests  
147 could be considered equally effective<sup>(10)</sup>. This report provides the main cost-effectiveness  
148 and mortality outcomes up to 6 years after randomisation.

149

## 150 **Methods**

### 151 **Study design**

152 The design of the study has been described elsewhere<sup>(10)</sup> and is reviewed briefly here. All  
153 patients referred to Papworth Hospital, UK for non-urgent angiography were eligible for the  
154 study. Inclusion criteria were: established or suspected chronic stable angina and a positive

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3 155 exercise tolerance test result with subsequent referral for angiography. Exclusion criteria  
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5 156 were: recent MI (<3 months), revascularisation (<6 months); urgent need for  
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7 157 revascularisation; contra-indication to adenosine or CMR; inability to exercise.  
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11 159 Trial design was of four parallel arms with a 1:1:1:1 randomisation ratio. Randomisation was  
12  
13 160 computer generated and stratified according to Pryor risk assessment<sup>(11)</sup>. Within each Pryor  
14  
15 161 risk group, randomisation was in blocks of length 6 or 8. Sequentially numbered group  
16  
17 162 designation was held in the Research & Development (R&D) Office and was not available to  
18  
19 163 trial personnel. Patients were randomised to their initial diagnostic test - stress SPECT,  
20  
21 164 stress CMR, stress echocardiography, or angiography - by R&D within 4 weeks of  
22  
23 165 recruitment and only after they had given consent and been registered.  
24

25 166

26  
27 167 Non invasive imaging results were returned with a recommendation to proceed with  
28  
29 168 angiography only when reported as 'positive' for inducible ischemia. Protocol adherence to  
30  
31 169 this recommendation was not mandated by trial design and patients proceeded to  
32  
33 170 angiography if considered clinically indicated. Treatment with PCI or CABG (performed  
34  
35 171 within six months of angiography) or to medical therapy was according to standard practice.  
36

37 172

### 38 39 173 **Coronary angiography.**

40  
41 174 Standard diagnostic angiography was performed from the right femoral artery approach<sup>(12)</sup>.  
42  
43 175 A minimum of 5 views of the left and 3 views of the right coronary system were taken<sup>(13)</sup>. All  
44  
45 176 examinations were reported by an experienced staff cardiologist and segmental location of  
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47 177 disease (if any) recorded.  
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### 50 51 179 **Stress echocardiography**

52  
53 180 Beta-blocker medications were stopped 2 days beforehand. Dobutamine was infused at  
54  
55 181 rates of 10- 40 mcg/kg/min, increased at 3 minute intervals. If necessary, 300-600  
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57 182 micrograms of atropine were added at peak stress to achieve 90% of target heart  
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3 183 rate. Images were acquired in standard planes in the final minute of each 3 minute stage.  
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5 184 Intravenous microspheres were used to delineate the endocardial surface. All examinations  
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7 185 were reported by one of two staff cardiologists experienced in stress echocardiography.  
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9 186 Studies were positive for ischemia if stress-induced deterioration in contractility was  
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11 187 observed.

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15 **SPECT**

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17 190 Rest/stress 99mTc sestamibi (99mTc MIBI) SPECT was performed (2 day protocol). A 6  
18  
19 191 minute adenosine infusion (140 µg/kg/min) was employed. 400 MBq 99m-Tc MIBI was  
20  
21 192 administered at 3 minutes after infusion of adenosine was started. Gated SPECT imaging  
22  
23 193 occurred 60 minutes after injection. Tomographic images were assessed for fixed and  
24  
25 194 reversible defects by a single observer (as per established criteria)<sup>(14)</sup>.

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27 19528  
29 **CMR**

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31 197 Stress CMR imaging was performed at a standard similar to that which was subsequently  
32  
33 198 recommended by the Society of Cardiovascular Magnetic Resonance <sup>(15)</sup>. A 1.5T mobile  
34  
35 199 CMR system and 4-channel phased array surface coil were used (Signa CV/i, GE Medical  
36  
37 200 Systems). Stress/rest dynamic first-pass perfusion imaging was performed. A hybrid fast  
38  
39 201 gradient echo/echoplanar sequence was employed <sup>(16)</sup>. Adenosine was infused at 140  
40  
41 202 mcg/kg/min for 4 minutes. After 3 minutes, a bolus of Gadolinium-DTPA (0.1mmol/kg) was  
42  
43 203 delivered at 5mls/sec, followed by a 25ml saline flush. First-pass imaging of the heart  
44  
45 204 occurred over 80 heart beats. A volumetric notched-saturation pre-pulse preserved a  
46  
47 205 constant saturation-recovery time during slice acquisition <sup>(17)</sup>. 6-8 short axis slices were  
48  
49 206 obtained every 2 heart beats. Rest imaging was repeated after a minimum interval of 15  
50  
51 207 minutes. Cine steady state free precession images and late gadolinium enhancement  
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53 208 images were also acquired as described in the original CECaT protocol <sup>(10)</sup> Studies were  
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55 209 reported as positive if there was an inducible perfusion defect visible for at least 5 frames  
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3 210 either: a) in a region of normal wall thickness; or b) in a region of myocardial thinning in the  
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5 211 absence of a history of prior myocardial infarction.  
6

7 212

### 8 213 **Outcomes**

9  
10 214 The primary outcome in the original CECaT trial was exercise treadmill time at 18 months  
11  
12 215 post-randomisation using the modified Bruce protocol, in which exercise intensity was  
13  
14 216 increased every 3 minutes. There was a range of secondary outcomes including diagnostic  
15  
16 217 accuracy, clinical events, health-related quality and cost-effectiveness of life up to 18 months  
17  
18 218 after randomisation<sup>(10)</sup>.

19  
20 219 The primary outcomes of this follow up study were survival up to a minimum of 2 years post-  
21  
22 220 treatment, quality-adjusted survival and cost-utility of each strategy. Survival status at the  
23  
24 221 end of follow up was determined from the Office for National Statistics database, UK  
25  
26 222 (<http://www.ons.gov.uk/>).  
27

28  
29 223 Quality of life was measured using the EuroQoL EQ-5D questionnaire<sup>(18)</sup> which was  
30  
31 224 completed at baseline, 6 and 18 months post-randomisation, and at 6, 18 and 24 months  
32  
33 225 post-treatment. The social tariff for the EQ-5D was applied in order to calculate utility values  
34  
35 226<sup>(19)</sup>. Because post-treatment measurements were at variable times post-randomisation  
36  
37 227 (randomisation date is time zero for a randomised trial) daily utilities were estimated using  
38  
39 228 linear interpolation.  
40

41 229

### 42 230 **Sample size calculations**

43  
44 231 The sample size of 898 patients was based on exercise performance and was calculated  
45  
46 232 according to the methodology published in the initial report of the CECaT study<sup>(10)</sup>.  
47

48 233

### 49 234 **Statistical and economic analysis**

50  
51 235 For this study, survival was summarised using Kaplan-Meier estimates and the groups were  
52  
53 236 compared using Cox proportional hazards regression. This assumes that the instantaneous  
54  
55 237 risk of death (hazard) for a reference value of a covariate will vary through time, but that the  
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3 238 hazards for other values of the covariate will be a constant multiple of this baseline hazard,  
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5 239 and this multiple will not vary through time. This assumption was tested using Schoenfeld  
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7 240 residuals and there was little evidence against it. The diagnostic test was entered into the  
8  
9 241 Cox regression as a 4-level fixed covariate, with angiography as the reference category. In  
10  
11 242 sensitivity analysis CABG and PCI were included in the regression analyses as time-varying  
12  
13 243 covariates, taking a value 0 up to the time of intervention and 1 thereafter, to ensure that any  
14  
15 244 differences between the groups was not due to differences in treatment. Inclusion of  
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17 245 treatment (CABG/PCI) did not affect comparison of diagnostic strategies and results of these  
18  
19 246 analyses are not included here.  
20  
21 247  
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23 248 Patient-specific hospital resource use was collected for 2 years post-*treatment* with  
24  
25 249 revascularisation or medical management. Costs were based on National Health Service  
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27 250 reference costs 2005/06 prices. An annual discount rate of 3.5% was applied to all costs and  
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29 251 quality-adjusted life-years (QALYs) after 12 months post-randomisation. Resources costed  
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31 252 were: imaging tests; revascularisation; inpatient/outpatient episodes; adverse events;  
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33 253 cardiac-related medications. Patient-reported admissions for MI were verified with the  
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35 254 admitting hospital and adjudicated.  
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37 255  
38  
39 256 Quality adjusted survival and cost estimates were censored at the last follow up at 2 years  
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41 257 after treatment, resulting in varying duration of follow-up from the time of randomisation to  
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43 258 the different diagnostic strategies, so that mean values over a range of time horizons were  
44  
45 259 estimated using inverse weighting methods<sup>(20)</sup>. This method allows for differing follow up  
46  
47 260 times between patients by splitting follow up time into intervals, and up-weighting the  
48  
49 261 observed quality adjusted survival and costs in an interval in proportion to the inverse of the  
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51 262 Kaplan-Meier estimate of the proportion observed during the interval. In the base case we  
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53 263 used a time horizon of 3 years since it was the longest period over which results were stable,  
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55 264 with acceptable precision. Confidence intervals for costs and QALYs were estimated using  
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57 265 bootstrapping with 5000 samples<sup>(21)</sup>.  
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3 266 **Sensitivity analysis**

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5 267 Sensitivity of cost-utility results for different time horizons was assessed by re-estimating  
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7 268 results up to 12, 18, 24, 36 and 48 months after randomization. In addition, cardiologists  
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9 269 were divided into those who did and did not perform percutaneous coronary intervention as  
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11 270 part of their routine clinical practice, and results were recalculated for each subgroup. With  
12  
13 271 the exception of this *post-hoc* data interrogation, all other results presented derive from  
14  
15 272 intention-to-treat analysis.  
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17 273

18  
19 274 The study had IRB approval and full written informed consent was obtained from all  
20  
21 275 participants. All authors had full access to the data and take responsibility for the manuscript  
22  
23 276 as written.  
24

25 277

26  
27 278 **Results**

28  
29 279 **Recruitment and compliance**

30  
31 280 Between September 2001 and September 2004, 3,201 patients were assessed, 1,981 were  
32  
33 281 excluded and 322 refused entry to the trial. Refusals were more likely to come from women  
34  
35 282 (46% compared with 31% enrolled into the study,  $p<0.001$ ) and were significantly older  
36  
37 283 (mean age 64.6, (SD 10.1) compared with study group mean age 61.8, (9.4),  $p<0.001$ ).  
38

39 284

40  
41 285 898 patients were randomised. Groups were well matched at baseline (table 1). In each  
42  
43 286 group 69% of patients were high risk for CAD (Pryor score  $> 0.8$ ). The trial was closed to  
44  
45 287 recruitment in September 2004 after enrolling the pre-specified number of subjects.  
46

47 288

48  
49 289 One-hundred-seventy-five (78%) SPECT patients, 180 (80%) CMR patients and 169 (75%)  
50  
51 290 stress echo patients were referred on for angiography (**Figure 1**). Between 20% and 25% of  
52  
53 291 patients undergoing non-invasive tests did not require further investigation. Twenty-one  
54  
55 292 percent of patients who had negative tests were referred for angiography and the proportion  
56  
57 293 was similar in each group (SPECT  $n=45$ , CMR  $n=50$ , ECHO  $n=48$ ,  $p=0.858$ ). Of these 14  
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59  
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2  
3 294 (31%) SPECT, 26 (52%) CMR and 23 (48%) ECHO resulted in a positive angiogram  
4  
5 295 (p=0.130). Four patients died and four withdrew from the trial early on. Of the remaining  
6  
7 296 patients, revascularization was required in 34% (301/890 – see **Figure 1** for numbers in  
8  
9 297 each arm). There was no significant difference between the groups in initial patient  
10  
11 298 management (Figure 1, p=0.527). Beyond the initial management strategy 42 subsequent  
12  
13 299 revascularisation procedures were required in the angiography arm compared with 30 in the  
14  
15 300 SPECT, 44 in the CMR and 41 in the ECHO arms. The median times between  
16  
17 301 randomisation and initial revascularisation were 122 days in the angiography group, 192  
18  
19 302 days for SPECT, 184 days for CMR and 177.5 days for ECHO, resulting in a delay due to  
20  
21 303 functional testing of approximately 2 months.  
22  
23 304

### 305 **Survival**

26  
27 306 During the study there were 7 (3%), 7 (3%), 18 (8%) and 11 (5%) deaths in the angiography  
28  
29 307 , SPECT, CMR and ECHO groups respectively. Kaplan-Meier survival curves for the 4  
30  
31 308 groups are plotted in **Figure 2**. Survival over the whole trial period in the SPECT (hazard  
32  
33 309 ratio 1.0, 95%CI 0.4, 2.9) and stress echo (hazard ratio 1.6, 95%CI 0.6, 4.0) groups were not  
34  
35 310 significantly different from angiography but the CMR group had higher mortality, with hazard  
36  
37 311 ratio 2.6 (95%CI 1.1 to 6.2), p=0.032. The significant effect of CMR on survival remained  
38  
39 312 when CABG or PCI were included in the models. However, mortality was low in all groups  
40  
41 313 and the absolute mean difference in survival was less than 1 month over 3 years (**Table 2**).  
42  
43 314 Mean survival estimates over 3 years with 95% confidence intervals are shown in **Table 2**.  
44  
45 315 All patients had complete adverse event data up to 18 months post-randomisation during  
46  
47 316 which there were 178 non-fatal adverse events in 114 patients, mostly hospital admissions  
48  
49 317 for chest pain (**Table 3**). Beyond this time only adverse events that resulted in admissions  
50  
51 318 were recorded as they were relevant for the economic analysis. No patient suffered any  
52  
53 319 adverse event at the time of the initial randomised imaging test.  
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55 320

### 58 321 **Cost-utility**

1  
2  
3 322 **Table 4** shows some of the highest incurred follow up costs for the 4 groups and shows that  
4  
5 323 patient management varied substantially between individuals. Although angiography was the  
6  
7 324 most expensive of the four initial diagnostic tests, the strategy of initial angiography had  
8  
9 325 lower mean overall cost than stress echo, and was similar to CMR up to 3 years (**Table 2**).  
10  
11 326 Extra costs for patients in the three non-invasive groups was largely due to patients  
12  
13 327 undergoing follow-on angiography. There were no significant differences in overall costs  
14  
15 328 between the groups.

16  
17 329  
18  
19 330 During the study there were no significant differences in EQ-5D between the groups. **Figure**  
20  
21 331 **3** shows daily mean EQ-5D utility over time based on interpolation between measurements  
22  
23 332 for survivors who completed the EQ-5D. Using inverse-weighting we calculated QALYs over  
24  
25 333 different time horizons and these are presented up to 3 years in **Table 2**. Mean QALYs over  
26  
27 334 3 years in the angiography group was 2.24, which was not significantly different from the  
28  
29 335 other groups. **Figure 4** shows the joint distribution of the difference in mean cost against the  
30  
31 336 difference in mean QALY for each diagnostic strategy group and angiography alone, and  
32  
33 337 shows the uncertainty in these estimates. **Figure 5** shows the Cost-Effectiveness  
34  
35 338 Acceptability Curve and demonstrated that SPECT has a high chance (>70%) of being cost-  
36  
37 339 effective whatever the willingness-to-pay threshold is but for CMR and ECHO there is much  
38  
39 340 less certainty about this decision. The mean differences between groups were close to zero  
40  
41 341 in all 3 cases so that the cost-per-QALY estimates are unstable and a cost-minimization  
42  
43 342 approach may be more appropriate. This would favour SPECT, which was both cheaper and  
44  
45 343 more effective on average than angiography, and had the lowest overall cost ( ).

46  
47 344

#### 48 49 345 **Sensitivity analysis**

50  
51 346 The comparisons between the diagnostic strategy groups did not change substantially when  
52  
53 347 we varied the time horizon; the main effect of this was that the variation surrounding  
54  
55 348 estimates increased as the time horizon lengthened due to the heavy censoring (results not  
56  
57 349 shown). **Tables 2a and 2b** show results for interventional and non-invasive cardiologists  
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60

1  
2  
3 350 respectively. Patients who were managed by interventional cardiologists incurred higher  
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5 351 costs due to the greater number of tests and revascularization procedures performed, with  
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7 352 minimal incremental benefit in QALY.  
8

9 353

## 10 354 **Discussion**

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13 355 CECaT is the first completed prospective randomized trial to look at the clinical and cost-  
14  
15 356 effectiveness of non-invasive imaging in the diagnosis and management of angina. To the  
16  
17 357 best of the authors' knowledge there has been no comparable outcomes trial published on  
18  
19 358 this scale evaluating three independent non-invasive 'gatekeeper' modalities versus initial  
20  
21 359 angiography in stable chest pain. The trial is also unusual in the length of prospective follow  
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23 360 up extending to 6 years for mortality outcomes.  
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25 361

26  
27 362 We have demonstrated that use of any one of stress CMR, stress echo or stress SPECT as  
28  
29 363 the initial test for a stable chest pain patient leads to non-inferior outcomes in quality of life  
30  
31 364 and cost utility compared to patients randomised to upfront invasive coronary angiography.  
32  
33 365 Typically, non invasive tests perform well in low risk populations because of a negative  
34  
35 366 predictive value which is usually better than the positive predictive value. However, the  
36  
37 367 patient risk profile was relatively high in our study, and despite this there was no significant  
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39 368 difference between an initial functional or anatomic approach.  
40

41 369

42  
43  
44 370 There are several reasons why initial angiography may not have led to clear benefit in our  
45  
46 371 study. Firstly, although angiography has stood at the heart of the diagnostic chest pain  
47  
48 372 pathway, the traditional binary cut-off values of 50% or 70% percentage stenosis by visual  
49  
50 373 estimation were shown in the FAME study to bear little relation to the true physiologic  
51  
52 374 significance of luminal narrowing <sup>(22)</sup>.  
53

54 375

55  
56 376 Secondly, data from various countries suggest that not only is coronary angiography often  
57  
58 377 inappropriate when formally rated by expert observers <sup>(23)</sup> <sup>(24)</sup> but that disparate national or  
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1  
2  
3 378 regional rates of angiography do not translate into clear mortality benefits between countries  
4  
5 379 <sup>(25) (26) (27) (28)</sup> and on occasion may even demonstrate an inverse relationship <sup>(29)</sup>.

6  
7 380 Contemporary US data from approximately 500,000 PCI procedures collected prospectively  
8  
9 381 in the National Cardiovascular Data Registry demonstrated that, of 145,000 elective PCI  
10  
11 382 cases, roughly 12% were judged inappropriate. Furthermore, the rate of inappropriate  
12  
13 383 elective PCI between hospital sites ranged from 0-55% suggesting significant variability in  
14  
15 384 practice <sup>(30)</sup>. The data suggest a better way of selecting patients for invasive investigation is  
16  
17 385 needed.  
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19 386

20  
21 387 Ischemia-driven revascularisation has been shown to be of benefit in a number of trials,  
22  
23 388 most recently in the FAME study in which an invasive method of measuring the flow reserve  
24  
25 389 of the microcirculation (Fractional Flow Reserve, FFR) was used to allocate patients to  
26  
27 390 intervention or observation vs a clinical decision on intervention based on angiography alone  
28  
29 391 <sup>(31)</sup>. At 2 years follow up there were clear survival and MACE benefits to the FFR-based  
30  
31 392 approach.  
32  
33

34 393  
35 394 The ACRE study reported that, up to 6 years after diagnosis, medical management was a  
36  
37 395 more cost-effective strategy for angina compared with PCI <sup>(32)</sup>. The lack of evidence for  
38  
39 396 survival from revascularisation was also seen in the COURAGE trial <sup>(4)</sup>. Critics have  
40  
41 397 suggested this may be because randomization to PCI versus optimal medical therapy was  
42  
43 398 made *after* coronary angiography had been performed, potentially leading to a recruitment  
44  
45 399 bias of patients with less severe disease. In the CECaT trial this bias was avoided by  
46  
47 400 randomization to a management strategy defined by the non-invasive test result for each of  
48  
49 401 the 3 functional arms of the trial. In a relatively high risk population, we demonstrated no  
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51 402 clinically significant survival or economic detriment from using non-invasive imaging as a  
52  
53 403 gate-keeper to catheterization. Similarly, quality of life was not significantly different across  
54  
55 404 all four groups and these differences extended to a warranty period of at least 3 years.  
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57  
58 405



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3 406 We did observe a marginal decrease in survival in the CMR arm. The reasons for the  
4  
5 407 difference are unclear but do not relate to patient characteristics or management with CABG  
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7 408 or PCI. Although statistically significant, the mean survival difference from the other groups  
8  
9 409 was only 4 weeks over 3 years and is unlikely to be clinically meaningful. Since recent work  
10  
11 410 has established a strong correspondence between FFR measurements and stress CMR  
12  
13 411 perfusion indices it would be surprising if CMR were genuinely inferior to other modalities for  
14  
15 412 risk stratification<sup>(33)</sup>. Indeed several recent publications have highlighted the incremental  
16  
17 413 prognostic data (above that obtained from clinical variables) derived from several thousand  
18  
19 414 perfusion CMR studies<sup>(34)(35)</sup>.

20  
21 415

22  
23 416 Given the recent publication of the CEMARC trial<sup>(36)</sup> in which a clear diagnostic superiority  
24  
25 417 was demonstrated for stress CMR over SPECT, it is interesting that our data nonetheless  
26  
27 418 show an equivalence in functional health status between those randomized to SPECT  
28  
29 419 versus CMR in the CECaT trial. The implication may be that although CMR detects the  
30  
31 420 presence of *any* ischemia with a greater sensitivity it is the *overall burden* of ischemia that  
32  
33 421 alters a patient's prognosis. As such, it has not yet been demonstrated that the higher  
34  
35 422 diagnostic accuracy of CMR translates into better long-term patient outcomes – a fact  
36  
37 423 acknowledged by Greenwood et al subsequent to CEMARC's publication<sup>(37)</sup>. In this context  
38  
39 424 the CECaT nuclear results are congruent with numerous past publications and reconfirm the  
40  
41 425 reassuring warranty period of a normal SPECT study.

42  
43 426

#### 44 45 427 **Cost effectiveness**

46  
47 428 There was no significant difference in cost-effectiveness between the angiography -as-  
48  
49 429 default group and the non-invasive test groups up to 3 years, perhaps relating to the higher-  
50  
51 430 than-anticipated rate of referral for angiography after negative functional tests. Protocol  
52  
53 431 deviation of this kind is not infrequent in trials of non-invasive technology. In the recent  
54  
55 432 PARR-2 study of patients undergoing fluorodeoxyglucose positron emission tomography for  
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57 433 the assessment of viability, roughly 25 % of the study population did not adhere to protocol  
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59  
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2  
3 434 <sup>(38)</sup>. The willingness of a cardiologist to defer referral for coronary angiography in the face of  
4  
5 435 a normal non-invasive study may in part reflect individual prejudices and job description  
6  
7 436 (interventional versus non-invasive) as demonstrated in a recent survey of cardiology  
8  
9 437 attitudes <sup>(39)</sup> and was also reflected in our own data.  
10

11 438

12  
13 439 In CECaT, 20-25% of patients receiving a non-invasive test did not go on to have  
14  
15 440 angiography. A proportion of the additional cost in the non-invasive arms related to  
16  
17 441 angiography and PCI in the patients with a *negative* test, although only very few  
18  
19 442 subsequently required CABG - a robust marker of significant disease - during follow-up. This  
20  
21 443 readiness to employ PCI in a group in whom the indication/benefit is debatable was also  
22  
23 444 seen in the ACRE trial <sup>(32)</sup> and reflects understandable clinical response to uncertainty but  
24  
25 445 also the easy access to PCI in healthcare systems without barriers to self-referral <sup>(40)</sup>.  
26

27 446 Similarly, studies from the US have demonstrated a greater willingness to use coronary  
28  
29 447 angiography when available 'on site' as is increasingly seen even in small-to-medium sized  
30  
31 448 hospitals <sup>(41) (42) (43)</sup>.  
32

33 449

#### 35 450 **Cost effectiveness of each non-invasive technique**

37 451

38  
39 452 Nuclear myocardial perfusion imaging  
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41 453

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43 454 The END study used propensity matching to compare a large cohort of patients referred for  
44  
45 455 either gate-keeper myocardial perfusion imaging or upfront angiography – this non  
46  
47 456 randomised study demonstrated a significant cost reduction in the (44) nuclear arm. In  
48  
49 457 contrast to this and other work <sup>(45) (46) (47)</sup> we were unable to show a significant difference in  
50  
51 458 cost effectiveness in our own study. To some extent this reflected the participating physician  
52  
53 459 bias towards angiography during the period of trial recruitment (2001-2006) with many  
54  
55 460 patients referred for angiography despite normal perfusion studies. This continues in the  
56  
57 461 contemporary era with Chan et al demonstrating that almost 80% of Delphi-adjudicated  
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59  
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1  
2  
3 462 inappropriate elective PCIs were performed following either low risk ischemia imaging in  
4  
5 463 mildly symptomatic patients or intermediate risk imaging in entirely asymptomatic patients  
6  
7 464 <sup>(30)</sup>.

8  
9 465  
10  
11 466 In the CECaT study, when PCI was performed despite a negative initial non-invasive test,  
12  
13 467 this occurred because subsequent angiography indicated 'significant' stenosis. This was a  
14  
15 468 clinical judgment based on 'eyeball assessment' of lesion severity as has been reported in  
16  
17 469 clinical trials with angiographic end points <sup>(48)</sup>. However, the severity and functional  
18  
19 470 significance of many stenoses may be over-called, even by quantitative assessment, when  
20  
21 471 compared with physiological assessment of fractional flow reserve across the lesion <sup>(49) (50)</sup>.

22  
23 472 Further improvement in cost-effectiveness could likely have been achieved in the nuclear  
24  
25 473 arm of the trial. Our post-trial practice is to perform the stress SPECT first - and if this is  
26  
27 474 negative - cancel the rest test, likely augmenting the relative cost-effectiveness of SPECT  
28  
29 475 <sup>(51)</sup>.

30  
31 476

32  
33 477 CMR

34  
35 478 There are relatively few data available regarding the cost effectiveness of CMR . One recent  
36  
37 479 mathematical modelling study estimated that CMR likely has greater cost effectiveness/utility  
38  
39 480 compared to SPECT despite greater base case cost of the former <sup>(52)</sup> . The economic  
40  
41 481 superiority of CMR was also recently described by the CEMARC group, although  
42  
43 482 interestingly the base case costs employed for CMR and SPECT in their analysis differed by  
44  
45 483 only a few pounds. Their own sensitivity analysis in fact demonstrated that if the costs of the  
46  
47 484 two tests varied by more than 100 pounds (which was the case in our study) then in fact – as  
48  
49 485 we found - SPECT became the dominant strategy in a low-to-intermediate risk population.

50  
51 486 <sup>(53)</sup>

52  
53 487

54  
55 488 Stress echo

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2  
3 489 Stress echocardiography may be a more cost-effective strategy than angiography for men  
4  
5 490 aged 50-60 with CAD prevalence of 50%<sup>(54), (47)</sup>. There is also some evidence that stress  
6  
7 491 echo is more cost-effective than SPECT as an initial test <sup>(55) (56)</sup>, especially in women with  
8  
9 492 suspected CAD <sup>(57)</sup>. A similar benefit was not seen in our study probably because of the high  
10  
11 493 disease prevalence in our population. The lack of superiority of either stress  
12  
13 494 echocardiography or a combined strategy of exercise testing and stress echo compared to  
14  
15 495 upfront catheterisation was also evident in a recent Polish study of 600 patients with a  
16  
17 496 similar age, gender and disease prevalence to our own study population <sup>(58)</sup>.  
18  
19 497

20  
21 498 Taken overall, our data clearly demonstrate a limited future role for cost-effective non-  
22  
23 499 invasive imaging if referring physicians are not willing to accept a negative result as ground  
24  
25 500 truth. This might be interpreted as reflecting a need for greater physician education since we  
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27 501 showed a clear difference in onward referral rates for angiography after a negative test  
28  
29 502 between interventional and non-invasive cardiologists.  
30  
31 503

### 32 33 504 ***Clinical effectiveness***

34  
35 505 We demonstrated that SPECT can obviate the need for coronary angiography for a  
36  
37 506 significant number of patients without any clinical detriment. In the stress echo group clinical  
38  
39 507 outcomes were also comparable to the angiography subgroup at 18 months. The CMR  
40  
41 508 group had statistically marginally poorer survival and this follows our earlier finding that CMR  
42  
43 509 patients had significantly worse exercise tolerance at 18 months after randomisation <sup>(10)</sup>. This  
44  
45 510 is difficult to explain on the basis of Pryor risk score or other baseline clinical variables.  
46  
47 511 However, the mean difference in survival between the CMR arm and the other groups was  
48  
49 512 only 4 weeks and thus of marginal clinical significance. More importantly, the CMR group  
50  
51 513 were not otherwise disadvantaged – compared to the angiographic control group - with  
52  
53 514 respect to major adverse events, other resource use, or quality of life.  
54  
55 515

### 56 57 58 516 ***Limitations***

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2  
3 517 This study was carried out in a single specialist cardiothoracic centre with a significant  
4  
5 518 proportion of high risk, predominantly white European, male patients. Those eligible who  
6  
7 519 refused the trial were older and were more likely to be women.  
8

9 520

10  
11 521 Survival data from the national registry did not include cause of death so that deaths due to  
12  
13 522 cardiovascular causes could not be reported separately.  
14

15 523

16  
17 524 The trial completed recruitment in 2004 and we used the technology that was available to us  
18  
19 525 at the onset of the trial. At that time, we were not able to use attenuation correction for  
20  
21 526 SPECT imaging; however this was also not used in the much more recent CEMARC trial<sup>(36)</sup>.  
22  
23 527 Similarly, we performed our CMR exams in a mobile facility on a 1.5T scanner with only  
24  
25 528 modest coil technology and limited temporal and anatomic coverage that would compare  
26  
27 529 unfavourably with the 3T whole heart high resolution perfusion studies available today.  
28

29 530

30  
31 531 The trial aimed to reflect the strategy of using non-invasive imaging as a gateway to  
32  
33 532 angiography in *contemporary clinical practice*. The test results were considered in  
34  
35 533 conjunction with other information available at the time. Thus it was not the aim to formally  
36  
37 534 assess diagnostic accuracy of the non-invasive tests in this context. This trial-based study  
38  
39 535 was limited to 3 year cost-effectiveness follow up - longer-term economic models would  
40  
41 536 provide lifetime estimates of the cost-effectiveness of the non-invasive strategies and could  
42  
43 537 include advances in imaging technology.  
44

45 538

#### 46 539 **Conclusions**

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48  
49 540 We have demonstrated in the CECaT trial that stress echo, stress CMR and stress SPECT  
50  
51 541 may each be used to defer invasive coronary angiography without clinical detriment or  
52  
53 542 significant excess costs in an outpatient population with stable chest pain.  
54

55 543

#### 56 544 **Acknowledgements**

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4  
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6  
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8  
9 548 supported by the Medical Research Council [Programme number U015232027].  
10

11 549

12  
13 550 **Competing interests**

14  
15 551

16  
17 552 All authors have completed the ICMJE uniform disclosure form at  
18  
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24  
25 556 financial relationships with any organisations that might have an interest in the submitted  
26  
27 557 work in the previous three years; no other relationships or activities that could appear to  
28  
29 558 have influenced the submitted work

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31 559 **Exclusive licence statement**

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33 560

34  
35 561 The Corresponding Author has the right to grant on behalf of all authors and does grant on  
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48 567

49 568 **Contributorship statement**

50  
51 569

52  
53  
54 570 HT performed literature review, data analysis and interpretation; NW was involved in image  
55  
56 571 analysis, drafting the manuscript and critical revision; VH was involved in recruiting the  
57  
58 572 patients, data management, administering health questionnaires, data analysis and drafting  
59  
60

1  
2  
3 573 the manuscript; MD and MB were responsible for data analysis, health economic  
4  
5 574 assessment, drafting the manuscript and critical revision; LDS was responsible for study  
6  
7 575 design, trial management, statistical analysis, drafting the manuscript and critical revision;  
8  
9 576 CJ performed statistical and health economic analysis, drafting the manuscript and critical  
10  
11 577 revision; AMC was involved in study design, patient recruitment, image interpretation, trial  
12  
13 578 management, drafting the manuscript and critical revision and is the overall guarantor of  
14  
15 579 manuscript integrity.  
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17 580  
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19 581 All authors have read the manuscript in its submitted form and have provided final approval  
20  
21 582 for publication.  
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583 **Table 1 Baseline characteristics\***

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
<b>Demographics</b>				
Mean (SD) age (years)	60.7 (9.1)	62.1 (9.5)	62.2 (9.0)	61.9 (9.9)
Males (%)	149 (67%)	157 (70%)	153 (68%)	160 (71%)
<b>History/risk factors</b>				
Previous MI (%)	63 (28%)	52 (23%)	69 (31%)	59 (26%)
Previous CVA (%)	10 (5%)	13 (6%)	8 (4%)	12 (5%)
<b>Diabetes(%)</b>				
IDDM	12 (5%)	8 (4%)	11 (5%)	5 (2%)
NIDDM	16 (7%)	18 (8%)	21 (9%)	22 (10%)
Family history CAD	60 (27%)	55 (25%)	63 (28%)	59 (26%)
<b>Smoking history (%)</b>				
<25 pack years	149 (67%)	162 (72%)	148 (65%)	155 (69%)
≥25 pack years	73 (33%)	62 (28%)	78 (35%)	71 (31%)
Treated hyperlipidaemia	164 (74%)	171 (76%)	179 (79%)	179 (79%)
(%)				
Treated hypertension (%)	117 (53%)	132 (59%)	115 (51%)	129 (57%)
<b>Exercise tolerance using the modified Bruce protocol</b>				
Mean (SD) total exercise time (mins)	11.29 (4.56)	10.46 (4.41)	10.43 (4.43)	10.89 (4.36)
<b>ECG changes on exercise test</b>				
1-2 mm ST depression with symptoms	53 (24%)	43 (19%)	54 (24%)	57 (25%)
≥ 2mm ST depression without symptoms	16 (7%)	24 (11%)	20 (9%)	24 (11%)

ST elevation**/ no change	153 (69%)	157 (70%)	152 (67%)	145 (64%)
CCS class				
0-I	60 (27%)	54 (24%)	78 (35%)	58 (26%)
II	138 (62%)	144 (64%)	122 (54%)	132 (58%)
III-IV	24 (11%)	26 (12%)	26 (11%)	36 (16%)

584 \* There were no significant differences between the groups in any variable

585 \*\* ST elevation was observed in 3 angiography, 2 CMR and 1 ECHO patients.



586 **Table 2 Cost-effectiveness summaries to 3 years post randomization**

587

	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
Hazard ratio for death	Baseline	0.99	2.60	1.42
(95%CI)		(0.35,2.85)	(1.09,6.22)	(0.54,3.74)
Mean survival (years)	2.96	2.95	2.90	2.94
(95%CI)	(2.92, 2.99)	(2.90, 2.99)	(2.83, 2.95)	(2.89, 2.97)
Mean difference vs. CA	-	-0.01	-0.06	-0.02
(95%CI)	-	(-0.07,0.05)	(-0.14, 0.01)	(-0.08, 0.04)
Mean QALYs	2.24	2.27	2.18	2.27
(95%CI)	(2.16,2.31)	(2.20,2.33)	(2.11,2.25)	(2.19,2.33)
Mean difference vs. CA	-	0.03	-0.05	0.03
(95%CI)	-	<b>(-5.21,1.38)</b>	<b>(-5.21,1.38)</b>	<b>(-3.04,4.21)</b>
Mean discounted costs	<b>5243</b>	<b>4644</b>	<b>4947</b>	<b>5530</b>
(£)				
(95%CI)	<b>(4282,6461)</b>	<b>(4194,5126)</b>	<b>(4480,5431)</b>	<b>(4857, 6262)</b>
Mean difference vs. CA	<b>-</b>	<b>-599</b>	<b>-296</b>	<b>287</b>
(95%CI)		<b>(-1901,503)</b>	<b>(-1603, 824)</b>	<b>(-1109, 1537)</b>
Probability cost effective	<b>-</b>	<b>0.82</b>	<b>0.29</b>	<b>0.55</b>
at £20k per QALY				
Probability cost effective	<b>-</b>	<b>0.79</b>	<b>0.25</b>	<b>0.59</b>
at £30k per QALY				

588

589 **Table 2a Cost-effectiveness summaries for patients managed by interventional**  
 590 **cardiologists to 3 years post randomization**  
 591

	Angiography (n=73)	SPECT (n=96)	Cardiac MRI (n=93)	Stress Echo (n=98)
Mean survival (years)	2.96	2.97	2.89	2.96
(95%CI)	(2.91, 2.98)	(2.93, 3.00)	(2.80, 2.97)	(2.90, 2.98)
Mean difference vs. CA	-	0.01	-0.07	0
(95%CI)	-	(-0.05,0.07)	(-0.17, 0.02)	(-0.07,0.05)
Mean QALYs	2.25	2.29	2.21	2.2
(95%CI)	(2.14,2.36)	(2.19,2.38)	(2.10,2.32)	(2.10,2.29)
Mean difference vs. CA	-	0.03	-0.04	-0.06
(95%CI)	-	<b>(-5.31,2.30)</b>	<b>(-4.96,2.41)</b>	<b>(-3.06,6.42)</b>
Mean discounted costs (£)	<b>5754</b>	<b>5205</b>	<b>5307</b>	<b>6329</b>
(95%CI)	<b>(4651, 6941)</b>	<b>(4475, 5979)</b>	<b>(4610, 6032)</b>	<b>(5120, 7713)</b>
Mean difference vs. CA	<b>-</b>	<b>-549</b>	<b>-447</b>	<b>574</b>
(95%CI)		<b>(-1973, 799)</b>	<b>(-1841, 897)</b>	<b>(-1097, 2262)</b>
Probability cost effective at £20k per QALY		<b>0.72</b>	<b>0.42</b>	<b>0.20</b>
Probability cost effective at £30k per QALY		<b>0.70</b>	<b>0.39</b>	<b>0.21</b>

592 **Table 2b Cost-effectiveness summaries for patients managed by non-interventional**  
 593 **cardiologists to 3 years post randomization**

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	Angiography (n=149)	SPECT (n=128)	Cardiac MRI (n=133)	Stress Echo (n=128)
Mean survival (years)	2.95	2.93	2.9	2.92
(95%CI)	(2.89, 2.99)	(2.85, 2.98)	(2.81, 2.97)	(2.85, 2.98)
Mean difference vs. CA	-	-0.02	-0.05	-0.03
(95%CI)	-	(-0.11,0.06)	(-0.15, 0.04)	(-0.11, 0.05)
Mean QALYs	2.23	2.25	2.17	2.31
(95%CI)	(2.14,2.31)	(2.16,2.33)	(2.07,2.26)	(2.22,2.40)
Mean difference vs. CA	-	0.02	-0.06	0.09
(95%CI)	-	<b>(-6.92,1.90)</b>	<b>(-5.50,3.45)</b>	<b>(-5.45,3.71)</b>
Mean discounted costs (£)	<b>4936</b>	<b>4216</b>	<b>4723</b>	<b>4780</b>
(95%CI)	<b>(3681, 6665)</b>	<b>(3635, 4799)</b>	<b>(4068, 5381)</b>	<b>(4136, 5467)</b>
Mean difference vs. CA	<b>-</b>	<b>-719</b>	<b>-212</b>	<b>-156</b>
(95%CI)		<b>(-2527, 695)</b>	<b>(-2007, 1258)</b>	<b>(-1990, 1353)</b>
Probability cost effective at £20k per QALY		<b>0.75</b>	<b>0.29</b>	<b>0.85</b>
Probability cost effective at £30k per QALY		<b>0.72</b>	<b>0.27</b>	<b>0.86</b>

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597 **Table 3 Summary adverse events during initial 18 months follow up\***

	Angiography	SPECT	Cardiac MRI	Stress Echo
Adverse event	(n=222)	(n=224)	(n=226)	(n=226)
Total adverse events	38	34	44	62
Chest pain (not	21	20	28	35
myocardial infarction)				
Angina	7	5	4	3
Myocardial infarction	2	0	3	6

598 \* Note that beyond this time only events that required hospital admission were recorded.

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601 **Table 4** Summary of the frequency of use of the main resource use elements during follow up  
 602 of up to 3 years (excluding initial diagnostic test)

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Resource use (unit cost)	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (n=226)
CABG (£7195)	28	33	28	34
PCI (£3660)	57	46	60	62
Other hospital admission (£467 per day)	36	29	28	53
Angiography (£625)	12	183	175	181
SPECT (£405)	16	3	3	6
Cardiac MRI (£565)	5	5	12	5
Echocardiography (£435)	30	17	24	18
PET scan (£842)	0	3	0	1
Preadmission clinic (£85)	22	21	27	24
Follow up clinic (£85)	19	22	31	21
Outpatient visits (£143)	247	270	300	284

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605 \* Cardiac drugs were also included but are not shown here due to many different  
 606 combinations of drugs and doses prescribed.

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3 609 **Figure Legends**

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7 611 **Figure 1 CONSORT diagram describing recruitment and randomization**

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11 613 **Figure 2 Kaplan-Meier survival estimates according to initial modality of diagnosis**

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15 615 **Figure 3 Quality of life assessed by EQ5D over time**

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19 617 **Figure 4 Bootstrapped estimates of the joint distribution of mean cost difference**

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21 618 **against mean QALY difference up to 3-years post randomisation**

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25 620 **Figure 5 Estimated probability of being cost-effective compared with angiography**

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27 621 **alone against the amount (£) a health provider is willing to pay for one additional**

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29 622 **QALY**

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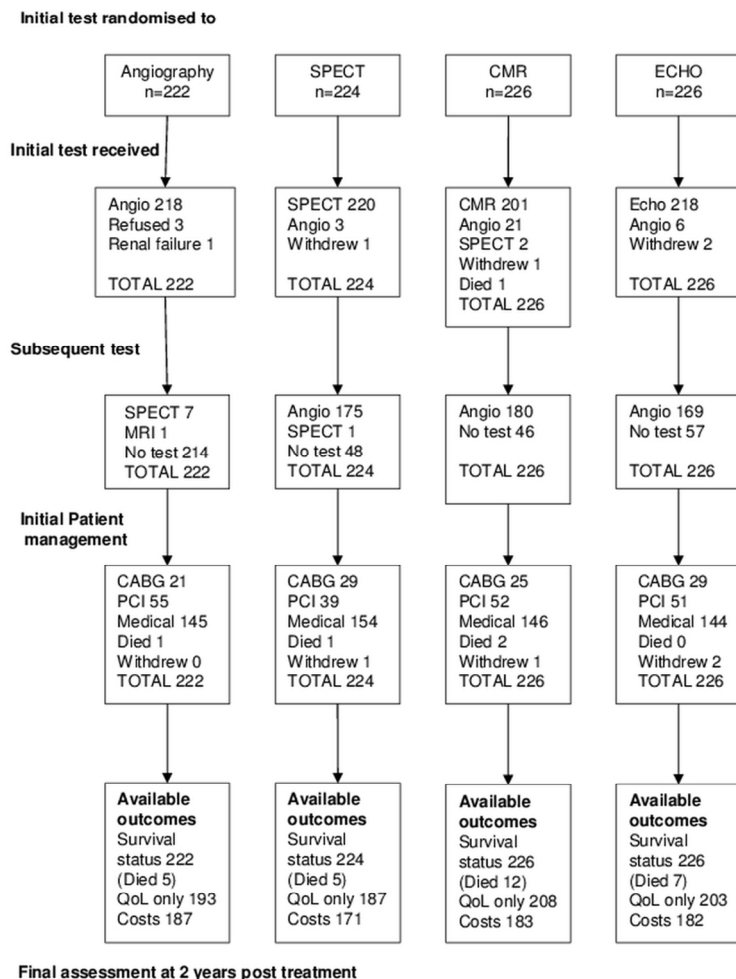
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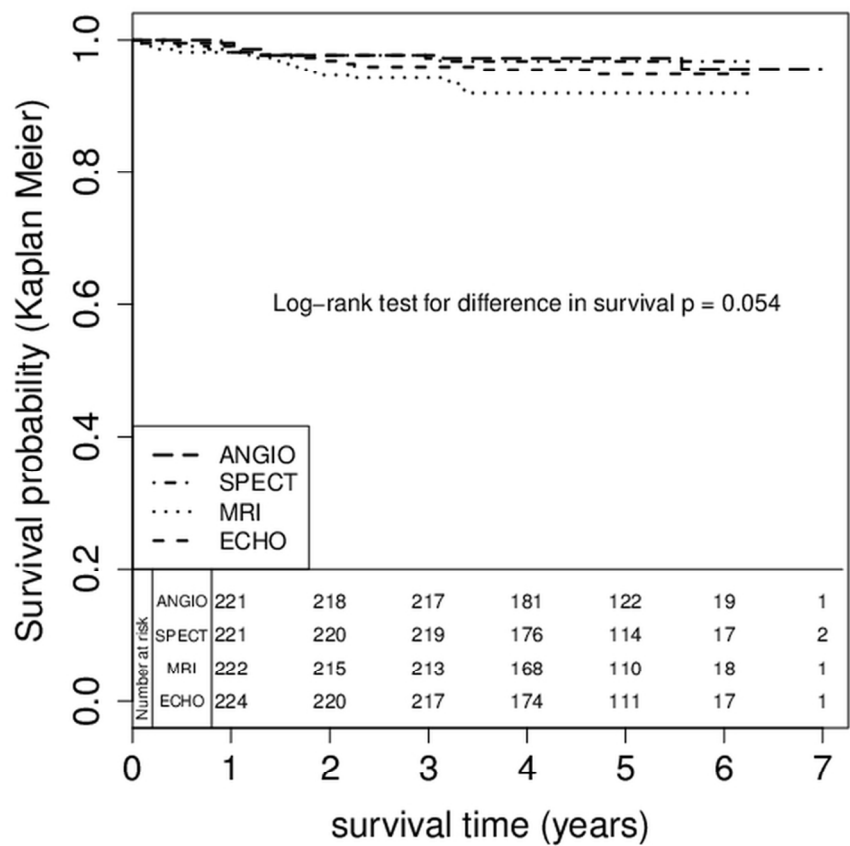
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Figure 1 Trial summary



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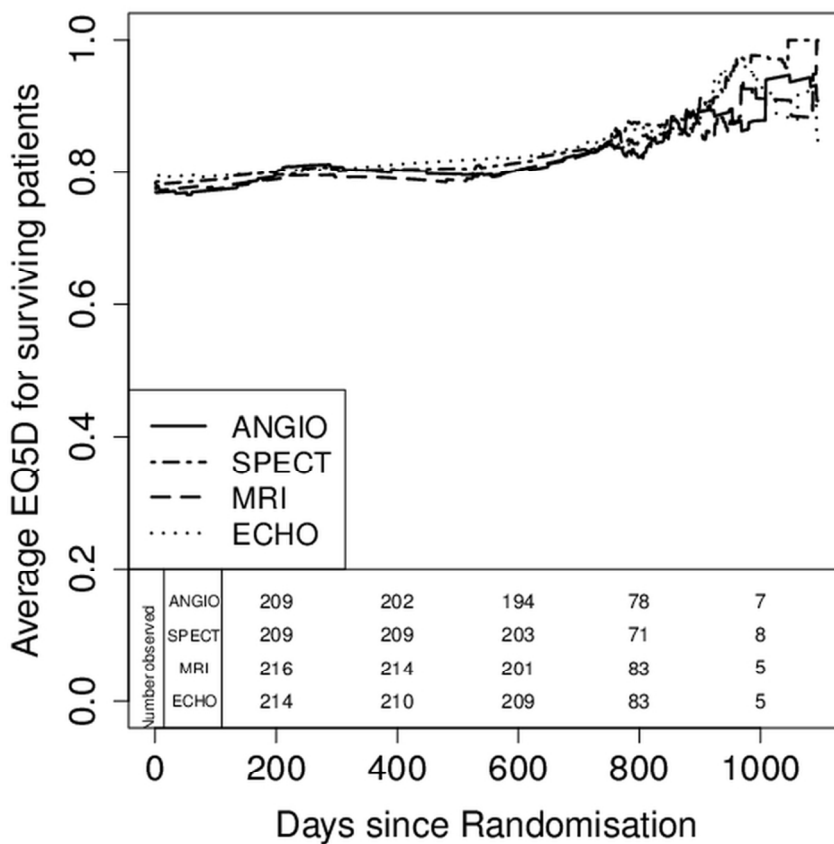
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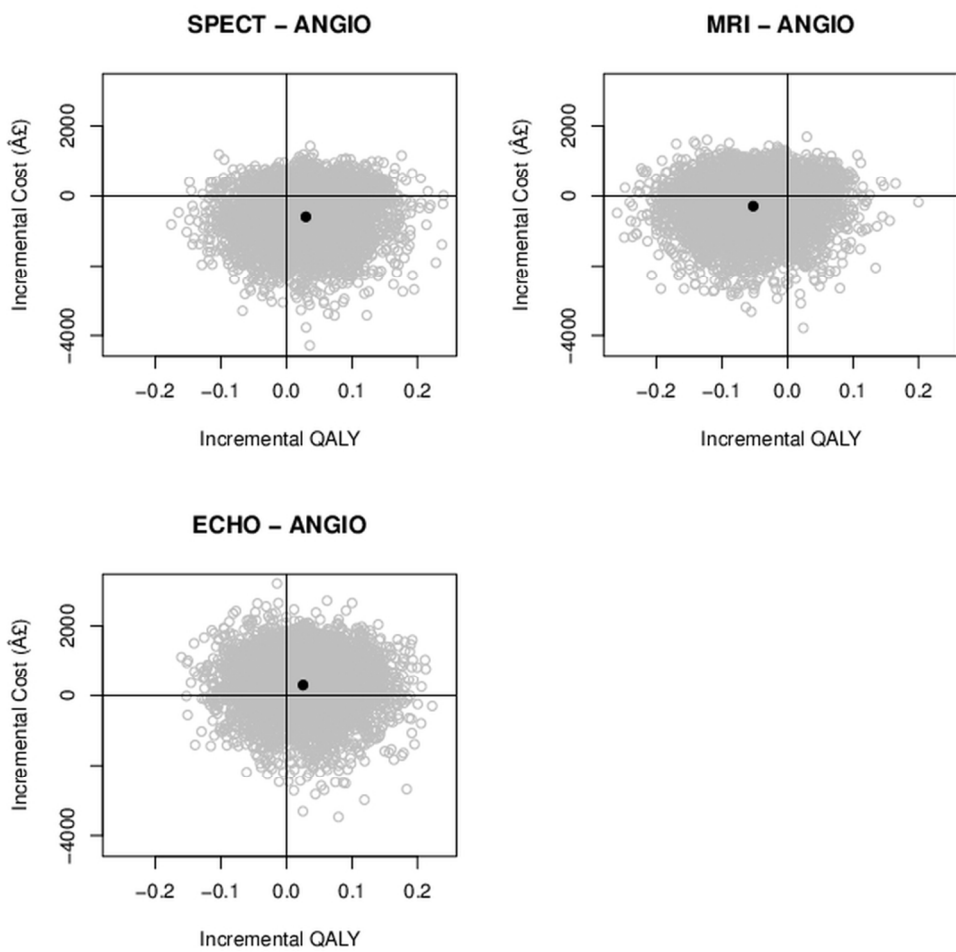
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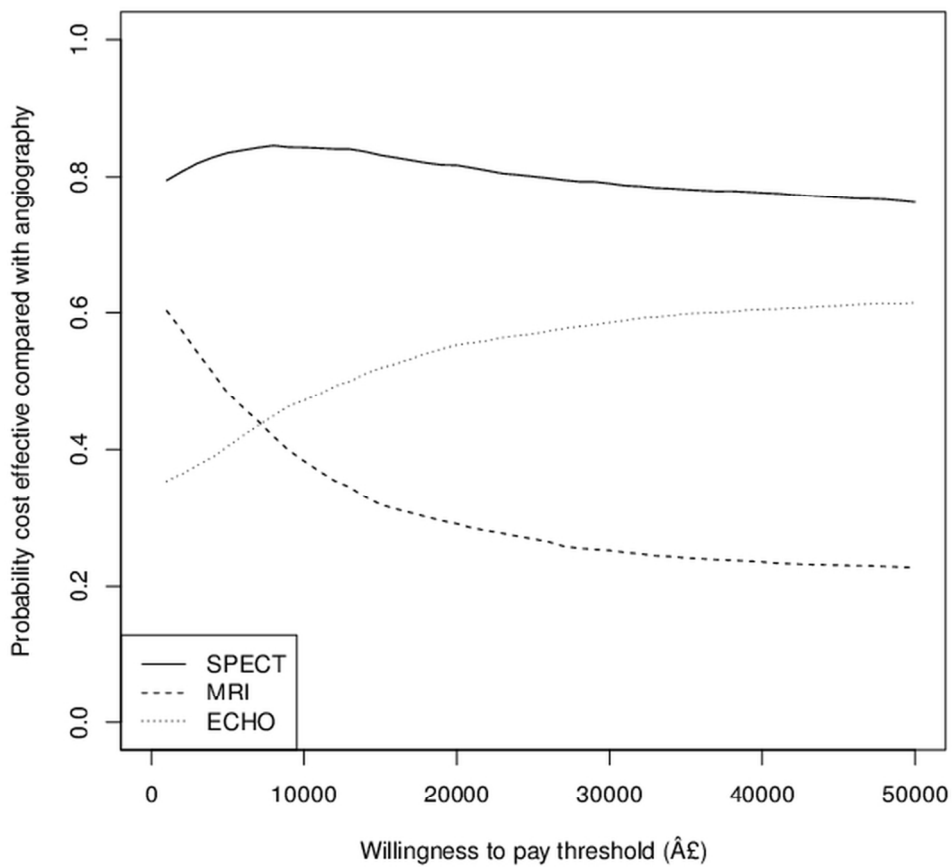
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### Cost effectiveness acceptability curves



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## CONSORT checklist CECaT Trial BMJ Open Re-Submission

Item	Description	Reported on line number
Title	Identification of the study as randomized	4
Authors *	Contact details for the corresponding author	26
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	140
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	153-157
Interventions	Interventions intended for each group	140-144 & 163-165
Objective	Specific objective or hypothesis	147
Outcome	Clearly defined primary outcome for this report	219
Randomization	How participants were allocated to interventions	159
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	140
Results		
Numbers randomized	Number of participants randomized to each group	285 & 582
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	582
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	585
Harms	Important adverse events or side effects	318-9
Conclusions	General interpretation of the results	540
Trial registration	Registration number and name of trial register	124
Funding	Source of funding	546-548