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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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*Cost Effectiveness of non-invasive Cardiac Testing

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Contributorship statement:

HT, MD, MB, LDS, CHJ were involved in economic and statistical analysis. LDS was the senior project statistician, was involved in original study design and takes overall responsibility for statistical portion of the manuscript. All of these individuals contributed to drafting and revision of the manuscript.

VH was involved in study design, patient recruitment, data collection and project management form the projects inception to its conclusion. She also contributed to drafting and revision of the manuscript

NW was responsible for blinded review of clinical data and contributed to drafting and revision of the manuscript.

AC was involved in the original study design, was responsible for the day-to-day clinical aspects of running the trial and was involved in the recruitment and follow up of patients as well as analysis of the cardiac MR studies. He wrote the final manuscript and contributed to its revision. He takes overall responsibility for the integrity of the clinical data.

Article summary:

Article focus:

1. **Is non-invasive imaging a safe and appropriate gate-keeper to coronary angiography in patients with stable chest pain ?**
2. **Is there any difference in cost-effectiveness and cost-utility between the different non-invasive approaches and conventional coronary angiography**
3. **Are patients disadvantaged in any meaningful way by having a non-invasive test to decide whether they should go forward for coronary angiography ?**
4. **How does stress perfusion CMR compare to the more established tests of SPECT-MIBI and stress echocardiography as a gate-keeper to coronary angiography ?**

Key messages:

1. **Non-invasive testing may be used safely as a gate-keeper to coronary angiography in patients with stable chest pain without any material disadvantage to them in terms of survival and quality of life up to 6 years after initial randomisation.**
2. **SPECT-MIBI appears marginally superior statistically to the other non-invasive methods although clinically meaningful differences are small between all strategies.**
3. **Stress perfusion CMR appears to be an effective technique in a stable out-patient population with undiagnosed chest pain.**

Strengths and limitations:

1. **This is the only large randomised prospective trial of a strategy of non-invasive gate-keeper cardiac imaging versus upfront angiography in the literature.**
2. **The cost-utility data are derived from NHS tariffs and our results are not necessarily directly transferrable to other healthcare systems**

Data sharing statement:

There are no additional data available

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 [1]. Revascularisation using bypass surgery (CABG) or percutaneous coronary intervention (PCI) is effective for patients with severe disease [2] but a significant minority of patients do not gain symptomatic relief [3]. Data from the COURAGE trial have demonstrated the lack of prognostic benefit from revascularization in the absence of reversible ischemia [4]. The yield of coronary angiography is variable with one recent large study of nearly 400, 000 patients demonstrating a normalcy rate approaching 40% [5]. 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 [6] [7] [8] [9].

The '**C**ost-**E**ffectiveness of non-invasive **Ca**rdiac **T**esting' (**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 [10]. 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 [10] and is reviewed briefly here. All patients referred to Papworth Hospital, UK for non-urgent angiography were eligible for the

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

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

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

Coronary angiography.

Standard diagnostic angiography was performed from the right femoral artery approach [12]. A minimum of 5 views of the left and 3 views of the right coronary system were taken [13]. All examinations were reported by an experienced staff cardiologist and segmental location of disease (if any) recorded.

Stress echocardiography

Beta-blocker medications were stopped 2 days beforehand. Dobutamine was infused at rates of 10- 40 mcg/kg/min, increased at 3 minute intervals. If necessary, 300-600

micrograms of atropine were added at peak stress to achieve 90% of target heart rate. Images were acquired in standard planes in the final minute of each 3 minute stage. Intravenous microspheres were used to delineate the endocardial surface. All examinations were reported by one of two staff cardiologists experienced in stress echocardiography. Studies were positive for ischemia if stress-induced deterioration in contractility was observed.

SPECT

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

CMR

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

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 [10].

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 [18]. 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.

Patients completed the EuroQoL EQ-5D questionnaire [19] at baseline randomisation, 6 months post-treatment, 18 months post-randomization, 18 months post-treatment and 24 months post-treatment. The social tariff for the EQ-5D was applied in order to calculate utility values [20]. For exploratory purposes daily utilities were estimated using linear interpolation.

Quality adjusted survival and cost estimates were censored at the last follow up so that mean values over a range of time horizons were estimated using inverse weighting methods [21]. In the base case we used a time horizon of 3 years since it was the longest period over which results were stable, with acceptable precision. Confidence intervals for costs and QALYs were estimated using bootstrapping with 5000 samples [22].

Sensitivity analysis

Sensitivity of cost-utility results for different time horizons was assessed by re-estimating results up to 12, 18, 24, 36 and 48 months after randomization. In addition, cardiologists were divided into interventional and non-invasive according to their usual practice, and results were recalculated for each subgroup. With the exception of this *post-hoc* data interrogation, all other results presented derive from intention-to-treat analysis.

The study had IRB approval and full written informed consent was obtained from all participants. All authors had full access to the data and take responsibility for the manuscript as written.

Results

Recruitment and compliance

Between September 2001 and September 2004, 3,201 patients were assessed, 1,981 were excluded and 322 refused entry to the trial. Refusals were more likely to come from women

(46% compared with 31% enrolled into the study, p<0.001) and were significantly older (mean age 64.6, (SD 10.1) compared with study group mean age 61.8, (9.4), p<0.001).

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

One-hundred-seventy-five (78%) SPECT patients, 180 (80%) CMR patients and 169 (75%) stress echo patients were referred on for angiography (**Figure 1**). Between 20% and 25% of patients undergoing non-invasive tests did not require further investigation. Four patients died and four withdrew from the trial early on. Of the remaining patients, revascularization was required in 34% (301/890). There was no significant difference between the groups in patient management (**Figure 1**).

Survival

During the study there were 43 deaths (4.8%). Kaplan-Meier survival curves for the 4 groups are plotted in **Figure 2**. SPECT and stress echo groups were not significantly different from angiography. The CMR group had higher mortality than the angiography group, the hazard ratio was 2.6 (95%CI 1.1 to 6.2), p=0.032 (**Table 2**). The significant effect of CMR on survival remained when CABG or PCI were included in the models. However, mortality was low in all groups and the absolute mean difference in survival was less than 1 month over 3 years (**Table 2**). Mean survival estimates over 3 years with 95% confidence intervals are shown in **Table 2**.

There were 178 non-fatal adverse events in 116 patients, mostly hospital admissions for chest pain.

Cost-utility

Table 3 shows some of the highest incurred follow up costs for the 4 groups and shows that patient management varied substantially between individuals. Although angiography was the most expensive of the four initial diagnostic tests, the strategy of initial angiography had lower mean overall cost than stress echo, and was similar to CMR up to 3 years (**Table 2**). Extra costs for patients in the three non-invasive groups was largely due to patients undergoing follow-on angiography. There were no significant differences in overall costs between the groups.

During the study there were no significant differences in EQ-5D between the groups. **Figure 3** shows daily mean EQ-5D utility over time based on interpolation between measurements for survivors who completed the EQ-5D. Using inverse-weighting we calculated QALYs over different time horizons and these are presented up to 3 years in Table 2. Mean QALYs over 3 years in the angiography group was 2.24, which was not significantly different from the other groups. The mean differences between groups are so close to zero in all 3 cases that the cost per QALY estimates are unstable and a cost-minimization approach may be more appropriate. This would favour SPECT.

Sensitivity analysis

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

Discussion

CECaT is the first completed prospective randomized trial to look at the clinical and cost-effectiveness of non-invasive imaging in the diagnosis and management of angina. To the best of the authors' knowledge there has been no comparable outcomes trial published on this scale evaluating three independent non-invasive 'gatekeeper' modalities versus initial angiography in stable chest pain. The trial is also unusual in the length of prospective follow up extending to 6 years for mortality outcomes.

We have demonstrated that use of any one of stress CMR, stress echo or stress SPECT as the initial test for a stable chest pain patient leads to non-inferior outcomes in quality of life and cost utility compared to patients randomised to upfront invasive coronary angiography. Typically, non invasive tests perform well in low risk populations because of a negative predictive value which is usually better than the positive predictive value. However, the patient risk profile was relatively high in our study, and despite this there was no significant difference between an initial functional or anatomic approach.

There are several reasons why initial angiography may not have led to clear benefit in our study. Firstly, although angiography has stood at the heart of the diagnostic chest pain pathway, the traditional binary cut-off values of 50% or 70% percentage stenosis by visual estimation were shown in the FAME study to bear little relation to the true physiologic significance of luminal narrowing [23].

Secondly, data from various countries suggest that not only is coronary angiography often inappropriate when formally rated by expert observers [24] [25] but that disparate national or regional rates of angiography do not translate into clear mortality benefits between countries [26] [27] [28] [29] and on occasion may even demonstrate an inverse relationship [30]. Contemporary US data from approximately 500,000 PCI procedures collected prospectively in the National Cardiovascular Data Registry demonstrated that, of 145,000 elective PCI cases, roughly 12% were judged inappropriate. Furthermore, the rate of inappropriate

elective PCI between hospital sites ranged from 0-55% suggesting significant variability in practice [31]. The data suggest a better way of selecting patients for invasive investigation is needed.

Ischemia-driven revascularisation has been shown to be of benefit in a number of trials, most recently in the FAME study in which an invasive method of measuring the flow reserve of the microcirculation (Fractional Flow Reserve, FFR) was used to allocate patients to intervention or observation vs a clinical decision on intervention based on angiography alone [32]. At 2 years follow up there were clear survival and MACE benefits to the FFR-based approach.

The ACRE study reported that, up to 6 years after diagnosis, medical management was a more cost-effective strategy for angina compared with PCI [33]. The lack of evidence for survival from revascularisation - except for selected patients with evidence of ischemia - was also seen in the COURAGE trial [4]. Critics have suggested this may be because randomization to PCI versus OMT was made *after* coronary angiography had been performed, potentially leading to a recruitment bias of patients with less severe disease. In the CECaT trial this bias was avoided by randomization to a management strategy defined by the non-invasive test result for each of the 3 functional arms of the trial. In a relatively high risk population, we demonstrated no clinically significant survival or economic detriment from using non-invasive imaging as a gate-keeper to catheterization. Similarly, quality of life was not significantly different across all four groups and these differences extended to a warranty period of at least 3 years.

We did observe a marginal decrease in survival in the CMR arm. The reasons for the difference are unclear but do not relate to patient characteristics or management with CABG or PCI. Although statistically significant, the mean survival difference from the other groups was only 4 weeks over 3 years and is unlikely to be clinically meaningful. Since recent work

has established a strong correspondence between FFR measurements and stress CMR perfusion indices it would be surprising if CMR were genuinely inferior to other modalities for risk stratification [34]. Indeed several recent publications have highlighted the incremental prognostic data (above that obtained from clinical variables) derived from several thousand perfusion CMR studies [35] [36].

Given the recent publication of the CEMARC trial [37] in which a clear diagnostic superiority was demonstrated for stress CMR over SPECT, it is interesting that our data nonetheless show an equivalence in functional health status between those randomized to SPECT versus CMR in the CECaT trial. The implication may be that although CMR detects the presence of *any* ischemia with a greater sensitivity it is the *overall burden* of ischemia that alters a patient's prognosis. As such, it has not yet been demonstrated that the higher diagnostic accuracy of CMR translates into better long-term patient outcomes – a fact acknowledged by Greenwood et al subsequent to CEMARC's publication [38]. In this context the CECaT nuclear results are congruent with numerous past publications and reconfirm the reassuring warranty period of a normal SPECT study.

Cost effectiveness

There was no significant difference in cost-effectiveness between the angiography -as-default group and the non-invasive test groups up to 3 years, perhaps relating to the higher-than-anticipated rate of referral for angiography after negative functional tests. Protocol deviation of this kind is not infrequent in trials of non-invasive technology. In the recent PARR-2 study of patients undergoing fluorodeoxyglucose positron emission tomography for the assessment of viability, roughly 25 % of the study population did not adhere to protocol [39]. The willingness of a cardiologist to defer referral for coronary angiography in the face of a normal non-invasive study may in part reflect individual prejudices and job description (interventional versus non-invasive) as demonstrated in a recent survey of cardiology attitudes [40] and was also reflected in our own data.

In CECaT, 20-25% of patients receiving a non-invasive test did not go on to have angiography. A proportion of the additional cost in the non-invasive arms related to angiography and PCI in the patients with a *negative* test, although only very few subsequently required CABG - a robust marker of significant disease - during follow-up. This readiness to employ PCI in a group in whom the indication/benefit is debatable was also seen in the ACRE trial [33] and reflects understandable clinical response to uncertainty but also the easy access to PCI in healthcare systems without barriers to self-referral [41]. Similarly, studies from the US have demonstrated a greater willingness to use coronary angiography when available 'on site' as is increasingly seen even in small-to-medium sized hospitals [42] [43] [44].

Cost effectiveness of each non-invasive technique

Nuclear myocardial perfusion imaging

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

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

CMR

There are no other real-world data in the literature of which the authors are aware regarding the cost effectiveness of CMR .

Stress echo

Stress echocardiography may be a more cost-effective strategy than angiography for men aged 50-60 with CAD prevalence of 50%[53], [47]. There is also some evidence that stress echo is more cost-effective than SPECT as an initial test [54] [55] , especially in women with suspected CAD [56]. A similar benefit was not seen in our study probably because of the high disease prevalence in our population. The lack of superiority of either stress echocardiography or a combined strategy of exercise testing and stress echo compared to upfront catheterisation was also evident in a recent Polish study of 600 patients with a similar age, gender and disease prevalence to our own study population [57].

Taken overall, our data clearly demonstrate a limited future role for cost-effective non-invasive imaging if referring physicians are not willing to accept a negative result as ground truth. This might be interpreted as reflecting a need for greater physician education since we

showed a clear difference in onward referral rates for angiography after a negative test between interventional and non-invasive cardiologists.

Clinical effectiveness

We demonstrated that SPECT can obviate the need for coronary angiography for a significant number of patients without any clinical detriment. In the stress echo group clinical outcomes were also comparable to the angiography subgroup at 18 months. The CMR group had statistically marginally poorer survival and this follows our earlier finding that CMR patients had significantly worse exercise tolerance at 18 months after randomisation [(10)]. This is difficult to explain on the basis of Pryor risk score or other baseline clinical variables. However, the mean difference in survival between the CMR arm and the other groups was only 4 weeks and thus of marginal clinical significance. More importantly, the CMR group were not otherwise disadvantaged – compared to the angiographic control group - with respect to major adverse events, other resource use, or quality of life.

Limitations

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

We used the technology that was available to us at the onset of the trial. At that time, we were not able to use attenuation correction for SPECT imaging; however this was also not used in the much more recent CEMARC trial[(37)]. Similarly, we performed our CMR exams in a mobile facility on a 1.5T scanner with only modest coil technology and limited temporal and anatomic coverage that would compare unfavourably with the 3T whole heart high resolution perfusion studies available today.

The trial aimed to reflect the strategy of using non-invasive imaging as a gateway to angiography in *contemporary clinical practice*. The test results were considered in conjunction with other information available at the time. Thus it was not the aim to formally assess diagnostic accuracy of the non-invasive tests in this context. This trial-based study was limited to 3 year cost-effectiveness follow up - longer-term economic models would provide lifetime estimates of the cost-effectiveness of the non-invasive strategies.

Conclusions

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

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: support from the UK National Health Service R&D Health Technology Assessment Program (project no. 99/26/04) and the UK Medical Research Council [Programme number U015232027] for the submitted work ; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to 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*

Demographics	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (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%)
Mean (SD) BMI (kg/m^2)	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[a]				
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 without symtoms	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%)

* 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

Figure Legends

Figure 1 CONSORT diagram describing recruitment and randomization

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

Figure 3 Quality of life assessed by EQ5D over time

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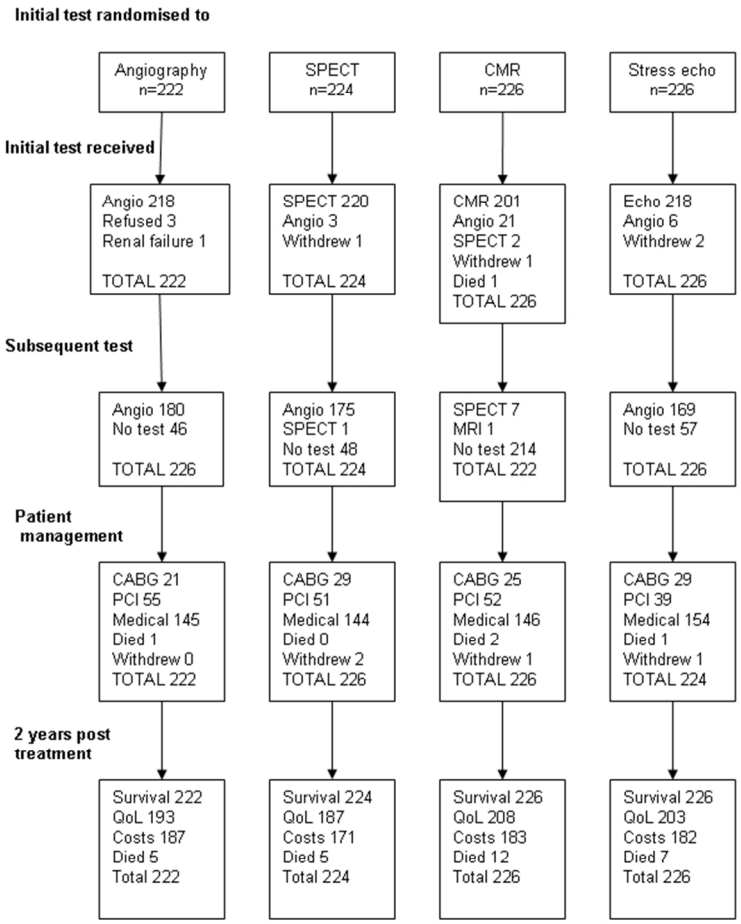

CONSORT diagram describing trial recruitment and randomisation
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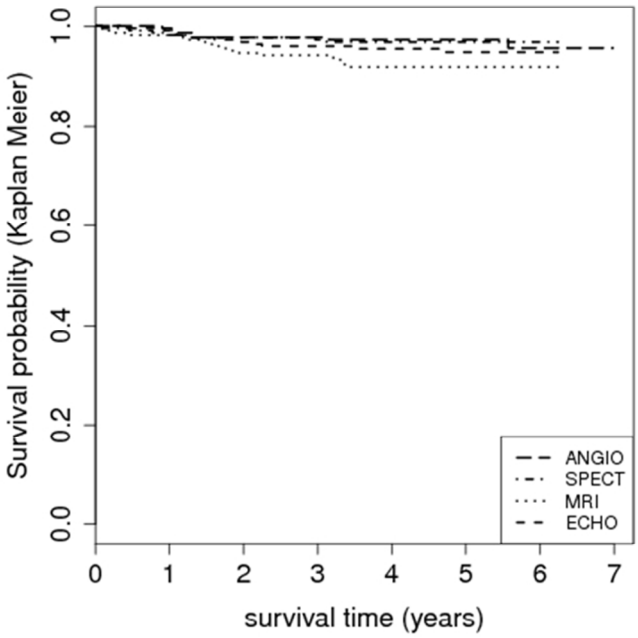

Kaplan-Meier survival estimates according to initial modality of diagnosis
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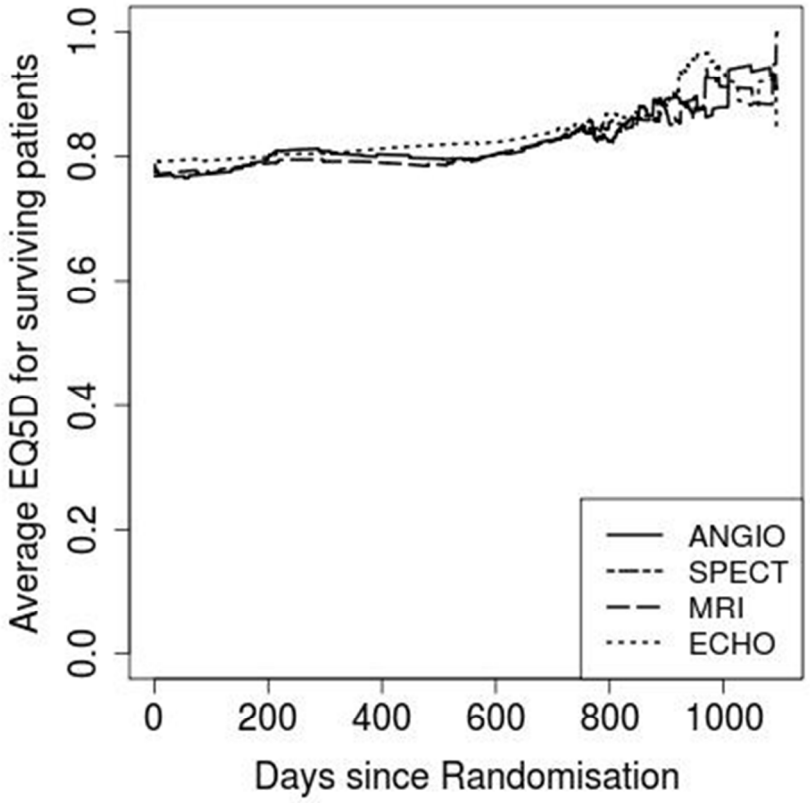

169x169mm (72 x 72 DPI)

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

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

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Abstract

Objectives: to compare outcomes and cost effectives of various initial imaging strategies on the management of stable chest pain in a long term prospective randomized trial.

Setting: regional cardiothoracic referral center in the east of England

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

Primary outcome measures: 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

Results: 898 patients were randomized. Compared to angiography, mortality was marginally higher in the groups randomized to CMR (hazard ratio 2.6, 95%CI 1.1, 6.2), but similar in the SPECT-MIBI (hazard ratio 1.0, 95%CI 0.4, 2.9) and ECHO groups (hazard ratio 1.6, 95%CI 0.6, 4.0). Although SPECT-MIBI was marginally superior to other non-invasive tests there were no other significant differences between the groups in mortality, quality adjusted survival or costs.

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

Article summary:

Article focus:

1. **Is non-invasive imaging a safe and appropriate gate-keeper to coronary angiography in patients with stable chest pain ?**
2. **Is there any difference in cost-effectiveness and cost-utility between the different non-invasive approaches and conventional coronary angiography**
3. **Are patients disadvantaged in any meaningful way by having a non-invasive test to decide whether they should go forward for coronary angiography ?**
4. **How does stress perfusion CMR compare to the more established tests of SPECT-MIBI and stress echocardiography as a gate-keeper to coronary angiography ?**

Key messages:

1. **Non-invasive testing may be used safely as a gate-keeper to coronary angiography in patients with stable chest pain without any material disadvantage to them in terms of survival and quality of life up to 6 years after initial randomisation.**
2. **SPECT-MIBI appears marginally superior statistically to the other non-invasive methods although clinically meaningful differences are small between all strategies.**
3. **Stress perfusion CMR appears to be an effective technique in a stable out-patient population with undiagnosed chest pain.**

Strengths and limitations:

1. **This is the only large randomised prospective trial of a strategy of non-invasive gate-keeper cardiac imaging versus upfront angiography in the literature.**
2. **The cost-utility data are derived from NHS tariffs and our results are not necessarily directly transferrable to other healthcare systems**

Introduction

CAD is common and its management is costly [1]. Revascularisation using bypass surgery (CABG) or percutaneous coronary intervention (PCI) is effective for patients with severe disease [2] but a significant minority of patients do not gain symptomatic relief [3]. Data from the COURAGE trial did not show prognostic benefit from revascularization in any patient subgroup[4]. The yield of coronary angiography is variable with one recent large study of nearly 400, 000 patients demonstrating a normalcy rate approaching 40% [5]. 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 [6] [7] [8] [9].

The '**C**ost-**E**ffectiveness of non-invasive **Ca**rdiac **T**esting' (**CECaT**) trial was an unblinded non-inferiority trial 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 [10]. 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 [10] and is reviewed briefly here. All patients referred to Papworth Hospital, UK for non-urgent angiography were eligible for the study. Inclusion criteria were: established or suspected chronic stable angina and a positive

exercise tolerance test result with subsequent referral for angiography. Exclusion criteria were: recent MI (<3 months), revascularisation (<6 months); urgent need for revascularisation; contra-indication to adenosine or CMR; inability to exercise.

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

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

Coronary angiography.

Standard diagnostic angiography was performed from the right femoral artery approach [12]. A minimum of 5 views of the left and 3 views of the right coronary system were taken [13]. All examinations were reported by an experienced staff cardiologist and segmental location of disease (if any) recorded.

Stress echocardiography

Beta-blocker medications were stopped 2 days beforehand. Dobutamine was infused at rates of 10- 40 mcg/kg/min, increased at 3 minute intervals. If necessary, 300-600 micrograms of atropine were added at peak stress to achieve 90% of target heart

rate. Images were acquired in standard planes in the final minute of each 3 minute stage. Intravenous microspheres were used to delineate the endocardial surface. All examinations were reported by one of two staff cardiologists experienced in stress echocardiography. Studies were positive for ischemia if stress-induced deterioration in contractility was observed.

SPECT

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

CMR

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

either: a) in a region of normal wall thickness; or b) in a region of myocardial thinning in the absence of a history of prior myocardial infarction.

Outcomes

The primary outcome in the original CECaT trial was exercise treadmill time at 18 months post-randomisation using the modified Bruce protocol, in which exercise intensity was increased every 3 minutes. There was a range of secondary outcomes including diagnostic accuracy, clinical events, health-related quality and cost-effectiveness of life up to 18 months after randomisation[10].

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 at the end of follow up was determined from the Office for National Statistics database, UK (http://www.ons.gov.uk/).

Quality of life was measured using the EuroQoL EQ-5D questionnaire [18] which was completed at baseline, 6 and 18 months post-randomisation, and at 6, 18 and 24 months post-treatment. The social tariff for the EQ-5D was applied in order to calculate utility values [19]. Because post-**treatment** measurements were at variable times post-**randomisation** (randomisation date is time zero for a randomised trial) daily utilities were estimated using linear interpolation.

Sample size calculations

The sample size of 898 patients was based on exercise performance and was calculated according to the methodology published in the initial report of the CECaT study [10].

Statistical and economic analysis

For this study, survival was summarised using Kaplan-Meier estimates and the groups were compared using Cox proportional hazards regression. This assumes that the instantaneous risk of death (hazard) for a reference value of a covariate will vary through time, but that the

hazards for other values of the covariate will be a constant multiple of this baseline hazard, and this multiple will not vary through time. This assumption was tested using Schoenfeld residuals and there was little evidence against it. The diagnostic test was entered into the Cox regression as a 4-level fixed covariate, with angiography as the reference category. In sensitivity analysis CABG and PCI were included in the regression analyses as time-varying covariates, taking a value 0 up to the time of intervention and 1 thereafter, to ensure that any differences between the groups was not due to differences in treatment. Inclusion of treatment (CABG/PCI) did not affect comparison of diagnostic 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 reference costs 2005/06 prices. 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.

Quality adjusted survival and cost estimates were censored at the last follow up at 2 years after treatment, resulting in varying duration of follow-up from the time of randomisation to the different diagnostic strategies, so that mean values over a range of time horizons were estimated using inverse weighting methods [20]. This method allows for differing follow up times between patients by splitting follow up time into intervals, and up-weighting the observed quality adjusted survival and costs in an interval in proportion to the inverse of the Kaplan-Meier estimate of the proportion observed during the interval. In the base case we used a time horizon of 3 years since it was the longest period over which results were stable, with acceptable precision. Confidence intervals for costs and QALYs were estimated using bootstrapping with 5000 samples [21].

Sensitivity analysis

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

The study had IRB approval and full written informed consent was obtained from all participants. All authors had full access to the data and take responsibility for the manuscript as written.

Results

Recruitment and compliance

Between September 2001 and September 2004, 3,201 patients were assessed, 1,981 were excluded and 322 refused entry to the trial. Refusals were more likely to come from women (46% compared with 31% enrolled into the study, p<0.001) and were significantly older (mean age 64.6, (SD 10.1) compared with study group mean age 61.8, (9.4), p<0.001).

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

One-hundred-seventy-five (78%) SPECT patients, 180 (80%) CMR patients and 169 (75%) stress echo patients were referred on for angiography (**Figure 1**). Between 20% and 25% of patients undergoing non-invasive tests did not require further investigation. Twenty-one percent of patients who had negative tests were referred for angiography and the proportion was similar in each group (SPECT n=45, CMR n=50, ECHO n=48, p=0.858). Of these 14

(31%) SPECT, 26 (52%) CMR and 23 (48%) ECHO resulted in a positive angiogram (p=0.130). Four patients died and four withdrew from the trial early on. Of the remaining patients, revascularization was required in 34% (301/890 – see **Figure 1** for numbers in each arm). There was no significant difference between the groups in initial patient management (Figure 1, p=0.527). Beyond the initial management strategy 42 subsequent revascularisation procedures were required in the angiography arm compared with 30 in the SPECT, 44 in the CMR and 41 in the ECHO arms. The median times between randomisation and initial revascularisation were 122 days in the angiography group, 192 days for SPECT, 184 days for CMR and 177.5 days for ECHO, resulting in a delay due to functional testing of approximately 2 months.

Survival

During the study there were 7 (3%), 7 (3%), 18 (8%) and 11 (5%) deaths in the angiography , SPECT, CMR and ECHO groups respectively. Kaplan-Meier survival curves for the 4 groups are plotted in **Figure 2**. Survival in the SPECT (hazard 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 significantly different from angiography but the CMR group had higher mortality, with hazard ratio 2.6 (95%CI 1.1 to 6.2), p=0.032 (**Table 2**). The significant effect of CMR on survival remained when CABG or PCI were included in the models. However, mortality was low in all groups and the absolute mean difference in survival was less than 1 month over 3 years (**Table 2**). Mean survival estimates over 3 years with 95% confidence intervals are shown in **Table 2**.

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

Cost-utility

Table 4 shows some of the highest incurred follow up costs for the 4 groups and shows that patient management varied substantially between individuals. Although angiography was the most expensive of the four initial diagnostic tests, the strategy of initial angiography had lower mean overall cost than stress echo, and was similar to CMR up to 3 years (**Table 2**). Extra costs for patients in the three non-invasive groups was largely due to patients undergoing follow-on angiography. There were no significant differences in overall costs between the groups.

During the study there were no significant differences in EQ-5D between the groups. **Figure 3** shows daily mean EQ-5D utility over time based on interpolation between measurements for survivors who completed the EQ-5D. Using inverse-weighting we calculated QALYs over different time horizons and these are presented up to 3 years in Table 2. Mean QALYs over 3 years in the angiography group was 2.24, which was not significantly different from the other groups. **Figure 4** shows the joint distribution of the difference in mean cost against the difference in mean QALY for each diagnostic strategy group and angiography alone, and shows the uncertainty in these estimates. **Figure 5** shows the Cost-Effectiveness Acceptability Curve and demonstrated that SPECT has a high chance (>70%) of being cost-effective whatever the willingness-to-pay threshold is but for CMR and ECHO there is much less certainty about this decision. The mean differences between groups were close to zero in all 3 cases so that the cost-per-QALY estimates are unstable and a cost-minimization approach may be more appropriate. This would favour SPECT, which was both cheaper and more effective on average than angiography, and had the lowest overall cost (Table 2).

Sensitivity analysis

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

respectively. Patients who were managed by interventional cardiologists incurred higher costs due to the greater number of tests and revascularization procedures performed, with minimal incremental benefit in QALY.

Discussion

CECaT is the first completed prospective randomized trial to look at the clinical and cost-effectiveness of non-invasive imaging in the diagnosis and management of angina. To the best of the authors' knowledge there has been no comparable outcomes trial published on this scale evaluating three independent non-invasive 'gatekeeper' modalities versus initial angiography in stable chest pain. The trial is also unusual in the length of prospective follow up extending to 6 years for mortality outcomes.

We have demonstrated that use of any one of stress CMR, stress echo or stress SPECT as the initial test for a stable chest pain patient leads to non-inferior outcomes in quality of life and cost utility compared to patients randomised to upfront invasive coronary angiography. Typically, non invasive tests perform well in low risk populations because of a negative predictive value which is usually better than the positive predictive value. However, the patient risk profile was relatively high in our study, and despite this there was no significant difference between an initial functional or anatomic approach.

There are several reasons why initial angiography may not have led to clear benefit in our study. Firstly, although angiography has stood at the heart of the diagnostic chest pain pathway, the traditional binary cut-off values of 50% or 70% percentage stenosis by visual estimation were shown in the FAME study to bear little relation to the true physiologic significance of luminal narrowing [22].

Secondly, data from various countries suggest that not only is coronary angiography often inappropriate when formally rated by expert observers [23] [24] but that disparate national or

regional rates of angiography do not translate into clear mortality benefits between countries [25] [26] [27] [28] and on occasion may even demonstrate an inverse relationship [29].

Contemporary US data from approximately 500,000 PCI procedures collected prospectively in the National Cardiovascular Data Registry demonstrated that, of 145,000 elective PCI cases, roughly 12% were judged inappropriate. Furthermore, the rate of inappropriate elective PCI between hospital sites ranged from 0-55% suggesting significant variability in practice [30]. The data suggest a better way of selecting patients for invasive investigation is needed.

Ischemia-driven revascularisation has been shown to be of benefit in a number of trials, most recently in the FAME study in which an invasive method of measuring the flow reserve of the microcirculation (Fractional Flow Reserve, FFR) was used to allocate patients to intervention or observation vs a clinical decision on intervention based on angiography alone [31]. At 2 years follow up there were clear survival and MACE benefits to the FFR-based approach.

The ACRE study reported that, up to 6 years after diagnosis, medical management was a more cost-effective strategy for angina compared with PCI [32]. The lack of evidence for survival from revascularisation was also seen in the COURAGE trial [4]. Critics have suggested this may be because randomization to PCI versus optimal medical therapy was made *after* coronary angiography had been performed, potentially leading to a recruitment bias of patients with less severe disease. In the CECaT trial this bias was avoided by randomization to a management strategy defined by the non-invasive test result for each of the 3 functional arms of the trial. In a relatively high risk population, we demonstrated no clinically significant survival or economic detriment from using non-invasive imaging as a gate-keeper to catheterization. Similarly, quality of life was not significantly different across all four groups and these differences extended to a warranty period of at least 3 years.

We did observe a marginal decrease in survival in the CMR arm. The reasons for the difference are unclear but do not relate to patient characteristics or management with CABG or PCI. Although statistically significant, the mean survival difference from the other groups was only 4 weeks over 3 years and is unlikely to be clinically meaningful. Since recent work has established a strong correspondence between FFR measurements and stress CMR perfusion indices it would be surprising if CMR were genuinely inferior to other modalities for risk stratification [33]. Indeed several recent publications have highlighted the incremental prognostic data (above that obtained from clinical variables) derived from several thousand perfusion CMR studies [34] [35].

Given the recent publication of the CEMARC trial [36] in which a clear diagnostic superiority was demonstrated for stress CMR over SPECT, it is interesting that our data nonetheless show an equivalence in functional health status between those randomized to SPECT versus CMR in the CECaT trial. The implication may be that although CMR detects the presence of *any* ischemia with a greater sensitivity it is the *overall burden* of ischemia that alters a patient's prognosis. As such, it has not yet been demonstrated that the higher diagnostic accuracy of CMR translates into better long-term patient outcomes – a fact acknowledged by Greenwood et al subsequent to CEMARC's publication [37]. In this context the CECaT nuclear results are congruent with numerous past publications and reconfirm the reassuring warranty period of a normal SPECT study.

Cost effectiveness

There was no significant difference in cost-effectiveness between the angiography -as-default group and the non-invasive test groups up to 3 years, perhaps relating to the higher-than-anticipated rate of referral for angiography after negative functional tests. Protocol deviation of this kind is not infrequent in trials of non-invasive technology. In the recent PARR-2 study of patients undergoing fluorodeoxyglucose positron emission tomography for the assessment of viability, roughly 25 % of the study population did not adhere to protocol

[38]. The willingness of a cardiologist to defer referral for coronary angiography in the face of a normal non-invasive study may in part reflect individual prejudices and job description (interventional versus non-invasive) as demonstrated in a recent survey of cardiology attitudes [39] and was also reflected in our own data.

In CECaT, 20-25% of patients receiving a non-invasive test did not go on to have angiography. A proportion of the additional cost in the non-invasive arms related to angiography and PCI in the patients with a *negative* test, although only very few subsequently required CABG - a robust marker of significant disease - during follow-up. This readiness to employ PCI in a group in whom the indication/benefit is debatable was also seen in the ACRE trial [32] and reflects understandable clinical response to uncertainty but also the easy access to PCI in healthcare systems without barriers to self-referral [40]. Similarly, studies from the US have demonstrated a greater willingness to use coronary angiography when available 'on site' as is increasingly seen even in small-to-medium sized hospitals [41] [42] [43].

Cost effectiveness of each non-invasive technique

Nuclear myocardial perfusion imaging

The END study used propensity matching to compare a large cohort of patients referred for either gate-keeper myocardial perfusion imaging or upfront angiography – this non randomised study demonstrated a significant cost reduction in the (44) nuclear arm. In contrast to this and other work[45] [46] [47] we were unable to show a significant difference in cost effectiveness in our own study. To some extent this reflected the participating physician bias towards angiography during the period of trial recruitment (2001-2006) with many patients referred for angiography despite normal perfusion studies. This continues in the contemporary era with Chan et al demonstrating that almost 80% of Delphi-adjudicated

inappropriate elective PCIs were performed following either low risk ischemia imaging in mildly symptomatic patients or intermediate risk imaging in entirely asymptomatic patients [30].

In the CECaT study, when PCI was performed despite a negative initial non-invasive test, this occurred because subsequent angiography indicated 'significant' stenosis. This was a clinical judgment based on 'eyeball assessment' of lesion severity as has been reported in clinical trials with angiographic end points [48]. However, the severity and functional significance of many stenoses may be over-called, even by quantitative assessment, when compared with physiological assessment of fractional flow reserve across the lesion [49] [50]. Further improvement in cost-effectiveness could likely have been achieved in the nuclear arm of the trial. Our post-trial practice is to perform the stress SPECT first - and if this is negative - cancel the rest test, likely augmenting the relative cost-effectiveness of SPECT [51].

CMR

There are relatively few data available regarding the cost effectiveness of CMR . One recent mathematical modelling study estimated that CMR likely has greater cost effectiveness/utility compared to SPECT despite greater base case cost of the former [52] . The economic superiority of CMR was also recently described by the CEMARC group, although interestingly the base case costs employed for CMR and SPECT in their analysis differed by only a few pounds. Their own sensitivity analysis in fact demonstrated that if the costs of the two tests varied by more than 100 pounds (which was the case in our study) then in fact – as we found - SPECT became the dominant strategy in a low-to-intermediate risk population. [53]

Stress echo

Stress echocardiography may be a more cost-effective strategy than angiography for men aged 50-60 with CAD prevalence of 50%[54, 47]. There is also some evidence that stress echo is more cost-effective than SPECT as an initial test [55, 56], especially in women with suspected CAD [57]. A similar benefit was not seen in our study probably because of the high disease prevalence in our population. The lack of superiority of either stress echocardiography or a combined strategy of exercise testing and stress echo compared to upfront catheterisation was also evident in a recent Polish study of 600 patients with a similar age, gender and disease prevalence to our own study population [58].

Taken overall, our data clearly demonstrate a limited future role for cost-effective non-invasive imaging if referring physicians are not willing to accept a negative result as ground truth. This might be interpreted as reflecting a need for greater physician education since we showed a clear difference in onward referral rates for angiography after a negative test between interventional and non-invasive cardiologists.

Clinical effectiveness

We demonstrated that SPECT can obviate the need for coronary angiography for a significant number of patients without any clinical detriment. In the stress echo group clinical outcomes were also comparable to the angiography subgroup at 18 months. The CMR group had statistically marginally poorer survival and this follows our earlier finding that CMR patients had significantly worse exercise tolerance at 18 months after randomisation [10]. This is difficult to explain on the basis of Pryor risk score or other baseline clinical variables. However, the mean difference in survival between the CMR arm and the other groups was only 4 weeks and thus of marginal clinical significance. More importantly, the CMR group were not otherwise disadvantaged – compared to the angiographic control group - with respect to major adverse events, other resource use, or quality of life.

Limitations

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

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

The trial completed recruitment in 2004 and we used the technology that was available to us at the onset of the trial. At that time, we were not able to use attenuation correction for SPECT imaging; however this was also not used in the much more recent CEMARC trial[36]. Similarly, we performed our CMR exams in a mobile facility on a 1.5T scanner with only modest coil technology and limited temporal and anatomic coverage that would compare unfavourably with the 3T whole heart high resolution perfusion studies available today.

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

Conclusions

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

532 **Table 1 Baseline characteristics***

Demographics	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (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 symtoms	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%)

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

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

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 (£)	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

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

	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

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

	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

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

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

Table 4 Summary of the frequency of use of the main resource use elements during follow up of up to 3 years (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 (£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

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

Figure Legends

Figure 1 CONSORT diagram describing recruitment and randomization

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

Figure 3 Quality of life assessed by EQ5D over time

Figure 4 Bootstrapped estimates of the joint distribution of mean cost difference against mean QALY difference up to 3-years post randomisation

Figure 5 Estimated probability of being cost-effective compared with angiography alone against the amount (£) a health provider is willing to pay for one additional QALY

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: support from the UK National Health Service R&D Health Technology Assessment Program (project no. 99/26/04) and the UK Medical Research Council [Programme number U015232027] for the submitted work ; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to 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.

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There are no additional data available

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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
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Interventions	Interventions intended for each group	140-144 & 163-165
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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		
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Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	582
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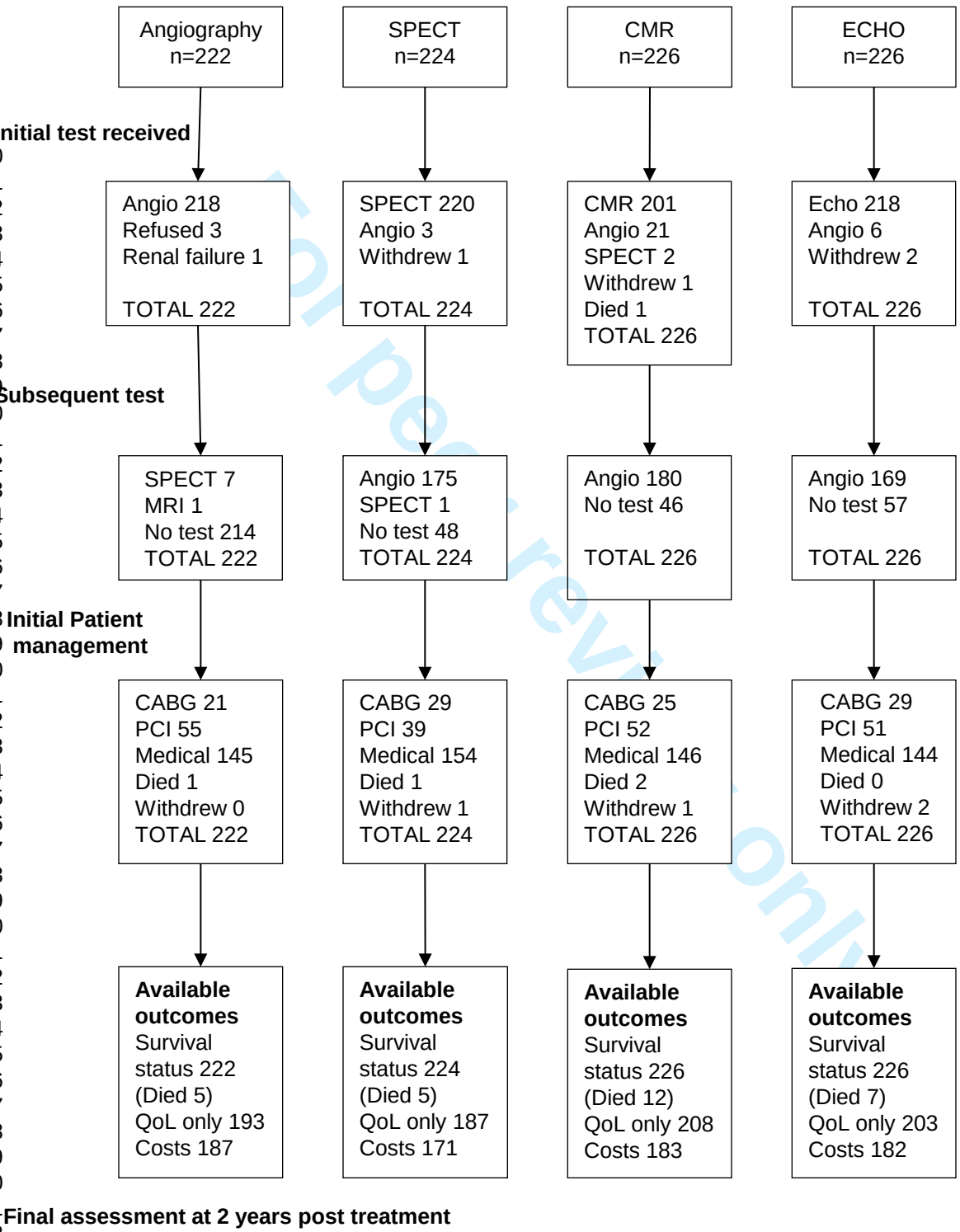
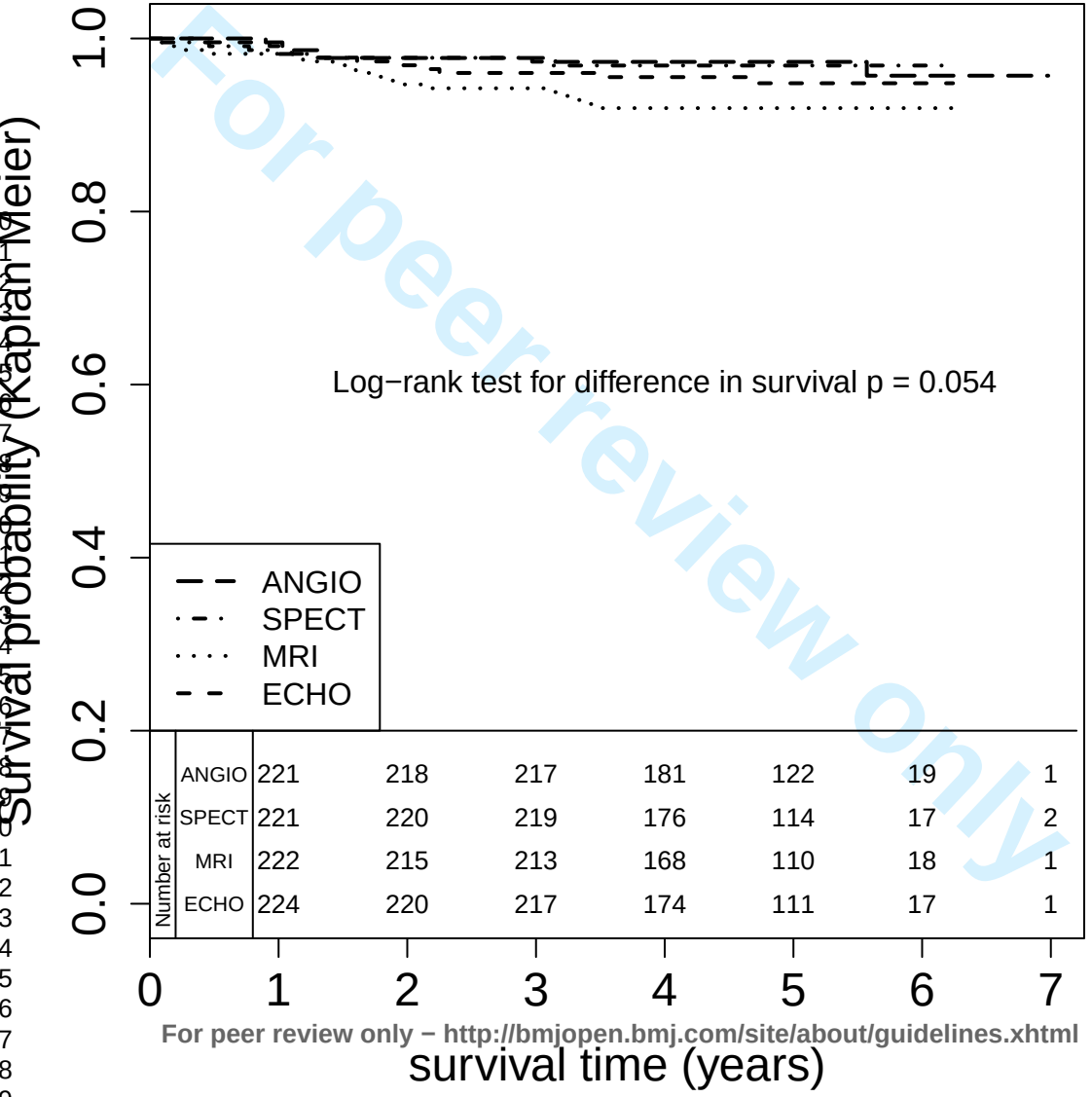
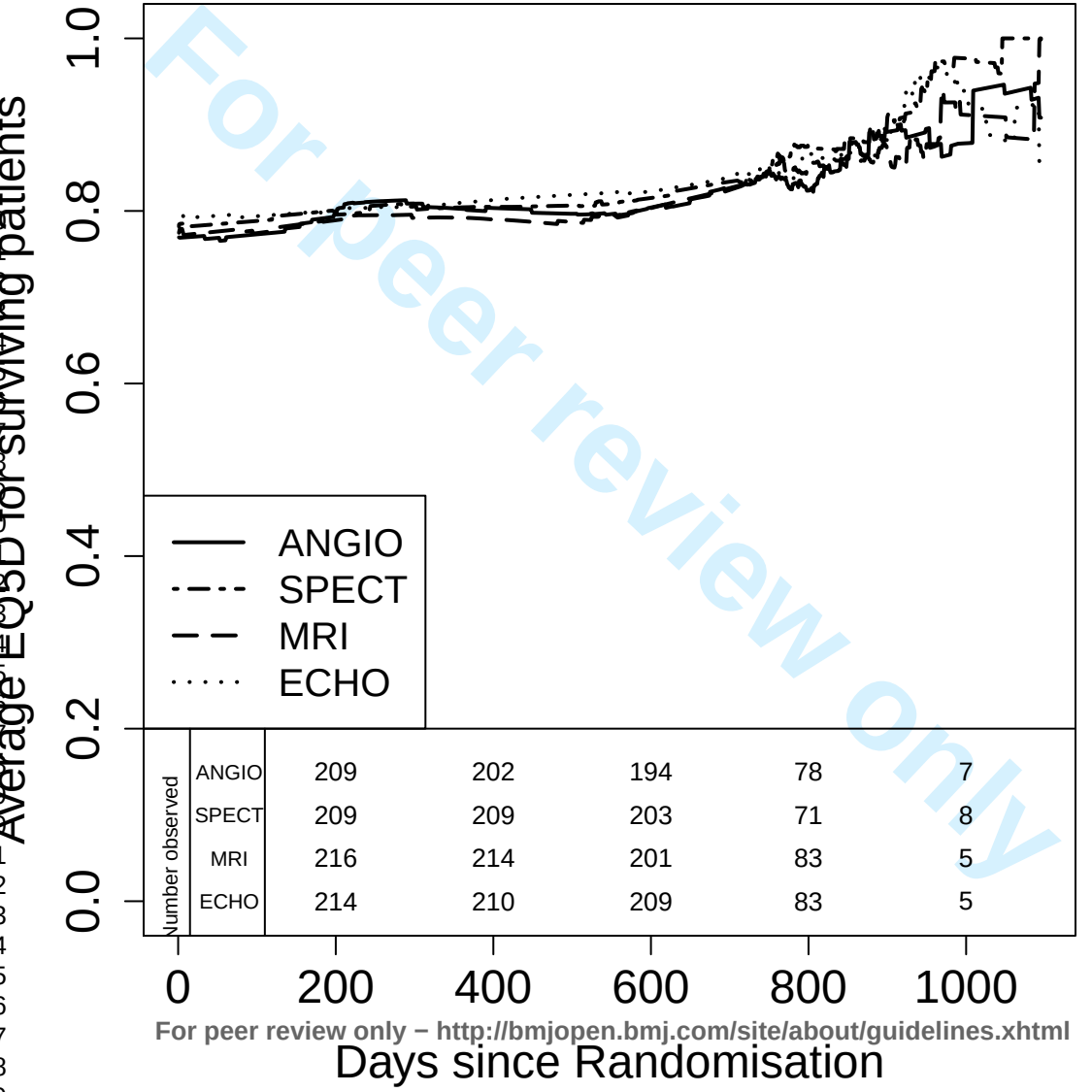
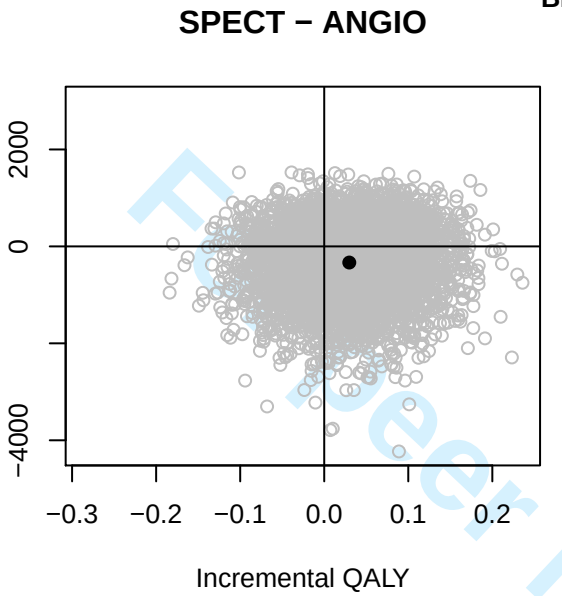
Funding	Source of funding	546-548

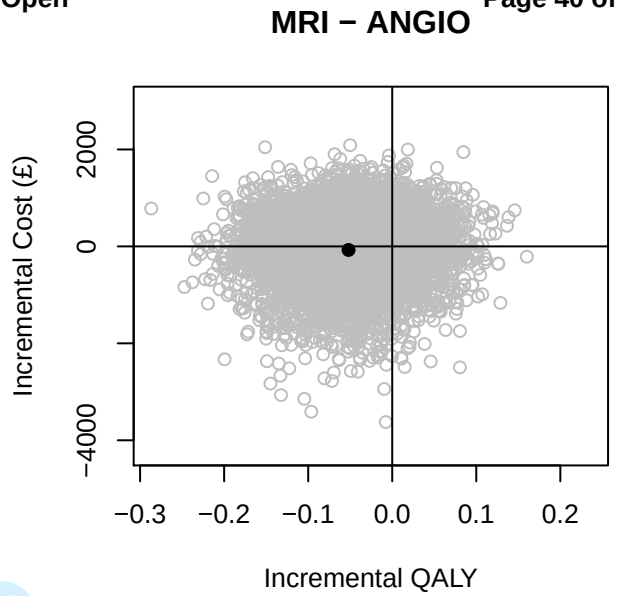
Figure 1 Trial summary

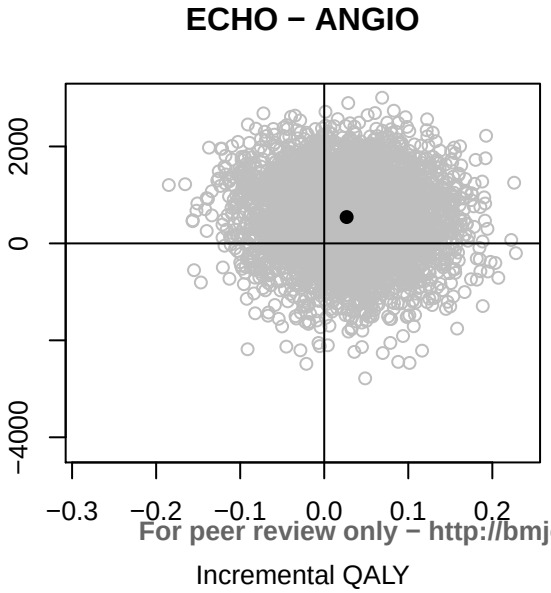




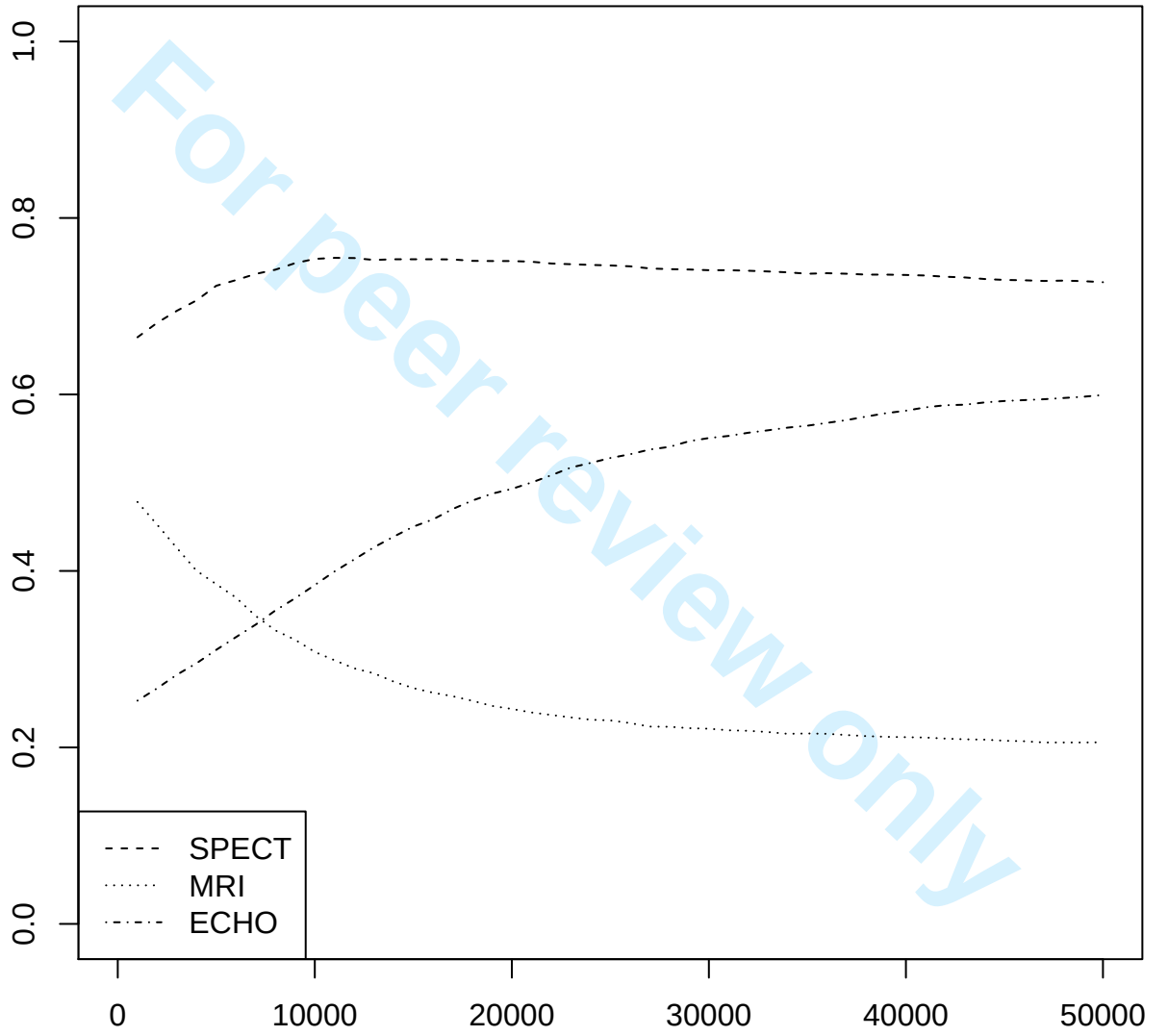








Cost effectiveness acceptability curves



BMJ open

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

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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

The CECaT study group were:

Johanna Armstrong, Martin Buxton, Noreen Caine, Richard Coulden, Andrew Crean, Matthew Dyer, Margaret Gillham, Hester Goddard, Kim Goldsmith, Vikki Hughes, Evelyn Lee, Roger Patel, Peter Schofield, Linda Sharples, Emer Sonnex, David Stone, Carmen Treacy

Abstract

Objectives: to compare outcomes and cost effectives of various initial imaging strategies on the management of stable chest pain in a long term prospective randomized trial.

Setting: regional cardiothoracic referral center in the east of England

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

Primary outcome measures: 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

Results: 898 patients were randomized. Compared to angiography, mortality was marginally higher in the groups randomized to CMR (hazard ratio 2.6, 95%CI 1.1, 6.2), but similar in the SPECT-MIBI (hazard ratio 1.0, 95%CI 0.4, 2.9) and ECHO groups (hazard ratio 1.6, 95%CI 0.6, 4.0). Although SPECT-MIBI was marginally superior to other non-invasive tests there were no other significant differences between the groups in mortality, quality adjusted survival or costs.

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

Trial registration: ISRCTN 47108462, UKCRN 3696

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

Article summary:

Article focus:

1. Is non-invasive imaging a safe and appropriate gate-keeper to coronary angiography in patients with stable chest pain ?
2. Is there any difference in cost-effectiveness and cost-utility between the different non-invasive approaches and conventional coronary angiography
3. Are patients disadvantaged in any meaningful way by having a non-invasive test to decide whether they should go forward for coronary angiography ?
4. How does stress perfusion CMR compare to the more established tests of SPECT-MIBI and stress echocardiography as a gate-keeper to coronary angiography ?

Key messages:

1. Non-invasive testing may be used safely as a gate-keeper to coronary angiography in patients with stable chest pain without any material disadvantage to them in terms of survival and quality of life up to 6 years after initial randomisation.
2. SPECT-MIBI appears marginally superior statistically to the other non-invasive methods although clinically meaningful differences are small between all strategies.
3. Stress perfusion CMR appears to be an effective technique in a stable out-patient population with undiagnosed chest pain.

Strengths and limitations:

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

Introduction

CAD is common and its management is costly [1]. Revascularisation using bypass surgery (CABG) or percutaneous coronary intervention (PCI) is effective for patients with severe disease [2] but a significant minority of patients do not gain symptomatic relief [3]. Data from the COURAGE trial did not show prognostic benefit from revascularization in any patient subgroup[4]. The yield of coronary angiography is variable with one recent large study of nearly 400, 000 patients demonstrating a normalcy rate approaching 40% [5]. 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 [6] [7] [8] [9].

The '**C**ost-**E**ffectiveness of non-invasive **Ca**rdiac **T**esting' (**CECaT**) trial was an unblinded non-inferiority trial 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 [10]. 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 [10] and is reviewed briefly here. All patients referred to Papworth Hospital, UK for non-urgent angiography were eligible for the study. Inclusion criteria were: established or suspected chronic stable angina and a positive

exercise tolerance test result with subsequent referral for angiography. Exclusion criteria were: recent MI (<3 months), revascularisation (<6 months); urgent need for revascularisation; contra-indication to adenosine or CMR; inability to exercise.

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

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

Coronary angiography.

Standard diagnostic angiography was performed from the right femoral artery approach [12]. A minimum of 5 views of the left and 3 views of the right coronary system were taken [13]. All examinations were reported by an experienced staff cardiologist and segmental location of disease (if any) recorded.

Stress echocardiography

Beta-blocker medications were stopped 2 days beforehand. Dobutamine was infused at rates of 10- 40 mcg/kg/min, increased at 3 minute intervals. If necessary, 300-600 micrograms of atropine were added at peak stress to achieve 90% of target heart

rate. Images were acquired in standard planes in the final minute of each 3 minute stage. Intravenous microspheres were used to delineate the endocardial surface. All examinations were reported by one of two staff cardiologists experienced in stress echocardiography. Studies were positive for ischemia if stress-induced deterioration in contractility was observed.

SPECT

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

CMR

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

either: a) in a region of normal wall thickness; or b) in a region of myocardial thinning in the absence of a history of prior myocardial infarction.

Outcomes

The primary outcome in the original CECaT trial was exercise treadmill time at 18 months post-randomisation using the modified Bruce protocol, in which exercise intensity was increased every 3 minutes. There was a range of secondary outcomes including diagnostic accuracy, clinical events, health-related quality and cost-effectiveness of life up to 18 months after randomisation[10].

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 at the end of follow up was determined from the Office for National Statistics database, UK (http://www.ons.gov.uk/).

Quality of life was measured using the EuroQoL EQ-5D questionnaire [18] which was completed at baseline, 6 and 18 months post-randomisation, and at 6, 18 and 24 months post-treatment. The social tariff for the EQ-5D was applied in order to calculate utility values [19]. Because post-**treatment** measurements were at variable times post-**randomisation** (randomisation date is time zero for a randomised trial) daily utilities were estimated using linear interpolation.

Sample size calculations

The sample size of 898 patients was based on exercise performance and was calculated according to the methodology published in the initial report of the CECaT study [10].

Statistical and economic analysis

For this study, survival was summarised using Kaplan-Meier estimates and the groups were compared using Cox proportional hazards regression. This assumes that the instantaneous risk of death (hazard) for a reference value of a covariate will vary through time, but that the

hazards for other values of the covariate will be a constant multiple of this baseline hazard, and this multiple will not vary through time. This assumption was tested using Schoenfeld residuals and there was little evidence against it. The diagnostic test was entered into the Cox regression as a 4-level fixed covariate, with angiography as the reference category. In sensitivity analysis CABG and PCI were included in the regression analyses as time-varying covariates, taking a value 0 up to the time of intervention and 1 thereafter, to ensure that any differences between the groups was not due to differences in treatment. Inclusion of treatment (CABG/PCI) did not affect comparison of diagnostic 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 reference costs 2005/06 prices. 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.

Quality adjusted survival and cost estimates were censored at the last follow up at 2 years after treatment, resulting in varying duration of follow-up from the time of randomisation to the different diagnostic strategies, so that mean values over a range of time horizons were estimated using inverse weighting methods [20]. This method allows for differing follow up times between patients by splitting follow up time into intervals, and up-weighting the observed quality adjusted survival and costs in an interval in proportion to the inverse of the Kaplan-Meier estimate of the proportion observed during the interval. In the base case we used a time horizon of 3 years since it was the longest period over which results were stable, with acceptable precision. Confidence intervals for costs and QALYs were estimated using bootstrapping with 5000 samples [21].

Sensitivity analysis

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

The study had IRB approval and full written informed consent was obtained from all participants. All authors had full access to the data and take responsibility for the manuscript as written.

Results

Recruitment and compliance

Between September 2001 and September 2004, 3,201 patients were assessed, 1,981 were excluded and 322 refused entry to the trial. Refusals were more likely to come from women (46% compared with 31% enrolled into the study, p<0.001) and were significantly older (mean age 64.6, (SD 10.1) compared with study group mean age 61.8, (9.4), p<0.001).

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

One-hundred-seventy-five (78%) SPECT patients, 180 (80%) CMR patients and 169 (75%) stress echo patients were referred on for angiography (**Figure 1**). Between 20% and 25% of patients undergoing non-invasive tests did not require further investigation. Twenty-one percent of patients who had negative tests were referred for angiography and the proportion was similar in each group (SPECT n=45, CMR n=50, ECHO n=48, p=0.858). Of these 14

(31%) SPECT, 26 (52%) CMR and 23 (48%) ECHO resulted in a positive angiogram (p=0.130). Four patients died and four withdrew from the trial early on. Of the remaining patients, revascularization was required in 34% (301/890 – see **Figure 1** for numbers in each arm). There was no significant difference between the groups in initial patient management (Figure 1, p=0.527). Beyond the initial management strategy 42 subsequent revascularisation procedures were required in the angiography arm compared with 30 in the SPECT, 44 in the CMR and 41 in the ECHO arms. The median times between randomisation and initial revascularisation were 122 days in the angiography group, 192 days for SPECT, 184 days for CMR and 177.5 days for ECHO, resulting in a delay due to functional testing of approximately 2 months.

Survival

During the study there were 7 (3%), 7 (3%), 18 (8%) and 11 (5%) deaths in the angiography , SPECT, CMR and ECHO groups respectively. Kaplan-Meier survival curves for the 4 groups are plotted in **Figure 2**. Survival over the whole trial period in the SPECT (hazard 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 significantly different from angiography but the CMR group had higher mortality, with hazard ratio 2.6 (95%CI 1.1 to 6.2), p=0.032. The significant effect of CMR on survival remained when CABG or PCI were included in the models. However, mortality was low in all groups and the absolute mean difference in survival was less than 1 month over 3 years (**Table 2**). Mean survival estimates over 3 years with 95% confidence intervals are shown in **Table 2**. All patients had complete adverse event data up to 18 months post-randomisation during which there were 178 non-fatal adverse events in 114 patients, mostly hospital admissions for chest pain (**Table 3)**. Beyond this time only adverse events that resulted in admissions were recorded as they were relevant for the economic analysis. No patient suffered any adverse event at the time of the initial randomised imaging test.

Cost-utility

Table 4 shows some of the highest incurred follow up costs for the 4 groups and shows that patient management varied substantially between individuals. Although angiography was the most expensive of the four initial diagnostic tests, the strategy of initial angiography had lower mean overall cost than stress echo, and was similar to CMR up to 3 years (**Table 2**). Extra costs for patients in the three non-invasive groups was largely due to patients undergoing follow-on angiography. There were no significant differences in overall costs between the groups.

During the study there were no significant differences in EQ-5D between the groups. **Figure 3** shows daily mean EQ-5D utility over time based on interpolation between measurements for survivors who completed the EQ-5D. Using inverse-weighting we calculated QALYs over different time horizons and these are presented up to 3 years in **Table 2**. Mean QALYs over 3 years in the angiography group was 2.24, which was not significantly different from the other groups. **Figure 4** shows the joint distribution of the difference in mean cost against the difference in mean QALY for each diagnostic strategy group and angiography alone, and shows the uncertainty in these estimates. **Figure 5** shows the Cost-Effectiveness Acceptability Curve and demonstrated that SPECT has a high chance (>70%) of being cost-effective whatever the willingness-to-pay threshold is but for CMR and ECHO there is much less certainty about this decision. The mean differences between groups were close to zero in all 3 cases so that the cost-per-QALY estimates are unstable and a cost-minimization approach may be more appropriate. This would favour SPECT, which was both cheaper and more effective on average than angiography, and had the lowest overall cost ( ).

Sensitivity analysis

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

respectively. Patients who were managed by interventional cardiologists incurred higher costs due to the greater number of tests and revascularization procedures performed, with minimal incremental benefit in QALY.

Discussion

CECaT is the first completed prospective randomized trial to look at the clinical and cost-effectiveness of non-invasive imaging in the diagnosis and management of angina. To the best of the authors' knowledge there has been no comparable outcomes trial published on this scale evaluating three independent non-invasive 'gatekeeper' modalities versus initial angiography in stable chest pain. The trial is also unusual in the length of prospective follow up extending to 6 years for mortality outcomes.

We have demonstrated that use of any one of stress CMR, stress echo or stress SPECT as the initial test for a stable chest pain patient leads to non-inferior outcomes in quality of life and cost utility compared to patients randomised to upfront invasive coronary angiography. Typically, non invasive tests perform well in low risk populations because of a negative predictive value which is usually better than the positive predictive value. However, the patient risk profile was relatively high in our study, and despite this there was no significant difference between an initial functional or anatomic approach.

There are several reasons why initial angiography may not have led to clear benefit in our study. Firstly, although angiography has stood at the heart of the diagnostic chest pain pathway, the traditional binary cut-off values of 50% or 70% percentage stenosis by visual estimation were shown in the FAME study to bear little relation to the true physiologic significance of luminal narrowing [(22)].

Secondly, data from various countries suggest that not only is coronary angiography often inappropriate when formally rated by expert observers [(23)] [(24)] but that disparate national or

regional rates of angiography do not translate into clear mortality benefits between countries [25] [26] [27] [28] and on occasion may even demonstrate an inverse relationship [29].

Contemporary US data from approximately 500,000 PCI procedures collected prospectively in the National Cardiovascular Data Registry demonstrated that, of 145,000 elective PCI cases, roughly 12% were judged inappropriate. Furthermore, the rate of inappropriate elective PCI between hospital sites ranged from 0-55% suggesting significant variability in practice [30]. The data suggest a better way of selecting patients for invasive investigation is needed.

Ischemia-driven revascularisation has been shown to be of benefit in a number of trials, most recently in the FAME study in which an invasive method of measuring the flow reserve of the microcirculation (Fractional Flow Reserve, FFR) was used to allocate patients to intervention or observation vs a clinical decision on intervention based on angiography alone [31]. At 2 years follow up there were clear survival and MACE benefits to the FFR-based approach.

The ACRE study reported that, up to 6 years after diagnosis, medical management was a more cost-effective strategy for angina compared with PCI [32]. The lack of evidence for survival from revascularisation was also seen in the COURAGE trial [4]. Critics have suggested this may be because randomization to PCI versus optimal medical therapy was made *after* coronary angiography had been performed, potentially leading to a recruitment bias of patients with less severe disease. In the CECaT trial this bias was avoided by randomization to a management strategy defined by the non-invasive test result for each of the 3 functional arms of the trial. In a relatively high risk population, we demonstrated no clinically significant survival or economic detriment from using non-invasive imaging as a gate-keeper to catheterization. Similarly, quality of life was not significantly different across all four groups and these differences extended to a warranty period of at least 3 years.

We did observe a marginal decrease in survival in the CMR arm. The reasons for the difference are unclear but do not relate to patient characteristics or management with CABG or PCI. Although statistically significant, the mean survival difference from the other groups was only 4 weeks over 3 years and is unlikely to be clinically meaningful. Since recent work has established a strong correspondence between FFR measurements and stress CMR perfusion indices it would be surprising if CMR were genuinely inferior to other modalities for risk stratification [33]. Indeed several recent publications have highlighted the incremental prognostic data (above that obtained from clinical variables) derived from several thousand perfusion CMR studies [34] [35].

Given the recent publication of the CEMARC trial [36] in which a clear diagnostic superiority was demonstrated for stress CMR over SPECT, it is interesting that our data nonetheless show an equivalence in functional health status between those randomized to SPECT versus CMR in the CECaT trial. The implication may be that although CMR detects the presence of *any* ischemia with a greater sensitivity it is the *overall burden* of ischemia that alters a patient's prognosis. As such, it has not yet been demonstrated that the higher diagnostic accuracy of CMR translates into better long-term patient outcomes – a fact acknowledged by Greenwood et al subsequent to CEMARC's publication [37]. In this context the CECaT nuclear results are congruent with numerous past publications and reconfirm the reassuring warranty period of a normal SPECT study.

Cost effectiveness

There was no significant difference in cost-effectiveness between the angiography -as-default group and the non-invasive test groups up to 3 years, perhaps relating to the higher-than-anticipated rate of referral for angiography after negative functional tests. Protocol deviation of this kind is not infrequent in trials of non-invasive technology. In the recent PARR-2 study of patients undergoing fluorodeoxyglucose positron emission tomography for the assessment of viability, roughly 25 % of the study population did not adhere to protocol

[38]. The willingness of a cardiologist to defer referral for coronary angiography in the face of a normal non-invasive study may in part reflect individual prejudices and job description (interventional versus non-invasive) as demonstrated in a recent survey of cardiology attitudes [39] and was also reflected in our own data.

In CECaT, 20-25% of patients receiving a non-invasive test did not go on to have angiography. A proportion of the additional cost in the non-invasive arms related to angiography and PCI in the patients with a *negative* test, although only very few subsequently required CABG - a robust marker of significant disease - during follow-up. This readiness to employ PCI in a group in whom the indication/benefit is debatable was also seen in the ACRE trial [32] and reflects understandable clinical response to uncertainty but also the easy access to PCI in healthcare systems without barriers to self-referral [40]. Similarly, studies from the US have demonstrated a greater willingness to use coronary angiography when available 'on site' as is increasingly seen even in small-to-medium sized hospitals [41] [42] [43].

Cost effectiveness of each non-invasive technique

Nuclear myocardial perfusion imaging

The END study used propensity matching to compare a large cohort of patients referred for either gate-keeper myocardial perfusion imaging or upfront angiography – this non randomised study demonstrated a significant cost reduction in the [44] nuclear arm. In contrast to this and other work[45] [46] [47] we were unable to show a significant difference in cost effectiveness in our own study. To some extent this reflected the participating physician bias towards angiography during the period of trial recruitment (2001-2006) with many patients referred for angiography despite normal perfusion studies. This continues in the contemporary era with Chan et al demonstrating that almost 80% of Delphi-adjudicated

inappropriate elective PCIs were performed following either low risk ischemia imaging in mildly symptomatic patients or intermediate risk imaging in entirely asymptomatic patients [30].

In the CECaT study, when PCI was performed despite a negative initial non-invasive test, this occurred because subsequent angiography indicated 'significant' stenosis. This was a clinical judgment based on 'eyeball assessment' of lesion severity as has been reported in clinical trials with angiographic end points [48]. However, the severity and functional significance of many stenoses may be over-called, even by quantitative assessment, when compared with physiological assessment of fractional flow reserve across the lesion [49] [50]. Further improvement in cost-effectiveness could likely have been achieved in the nuclear arm of the trial. Our post-trial practice is to perform the stress SPECT first - and if this is negative - cancel the rest test, likely augmenting the relative cost-effectiveness of SPECT [51].

CMR

There are relatively few data available regarding the cost effectiveness of CMR . One recent mathematical modelling study estimated that CMR likely has greater cost effectiveness/utility compared to SPECT despite greater base case cost of the former [52] . The economic superiority of CMR was also recently described by the CEMARC group, although interestingly the base case costs employed for CMR and SPECT in their analysis differed by only a few pounds. Their own sensitivity analysis in fact demonstrated that if the costs of the two tests varied by more than 100 pounds (which was the case in our study) then in fact – as we found - SPECT became the dominant strategy in a low-to-intermediate risk population. [53]

Stress echo

Stress echocardiography may be a more cost-effective strategy than angiography for men aged 50-60 with CAD prevalence of 50%[54, 47]. There is also some evidence that stress echo is more cost-effective than SPECT as an initial test [55, 56], especially in women with suspected CAD [57]. A similar benefit was not seen in our study probably because of the high disease prevalence in our population. The lack of superiority of either stress echocardiography or a combined strategy of exercise testing and stress echo compared to upfront catheterisation was also evident in a recent Polish study of 600 patients with a similar age, gender and disease prevalence to our own study population [58].

Taken overall, our data clearly demonstrate a limited future role for cost-effective non-invasive imaging if referring physicians are not willing to accept a negative result as ground truth. This might be interpreted as reflecting a need for greater physician education since we showed a clear difference in onward referral rates for angiography after a negative test between interventional and non-invasive cardiologists.

Clinical effectiveness

We demonstrated that SPECT can obviate the need for coronary angiography for a significant number of patients without any clinical detriment. In the stress echo group clinical outcomes were also comparable to the angiography subgroup at 18 months. The CMR group had statistically marginally poorer survival and this follows our earlier finding that CMR patients had significantly worse exercise tolerance at 18 months after randomisation [10]. This is difficult to explain on the basis of Pryor risk score or other baseline clinical variables. However, the mean difference in survival between the CMR arm and the other groups was only 4 weeks and thus of marginal clinical significance. More importantly, the CMR group were not otherwise disadvantaged – compared to the angiographic control group - with respect to major adverse events, other resource use, or quality of life.

Limitations

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

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

The trial completed recruitment in 2004 and we used the technology that was available to us at the onset of the trial. At that time, we were not able to use attenuation correction for SPECT imaging; however this was also not used in the much more recent CEMARC trial[36]. Similarly, we performed our CMR exams in a mobile facility on a 1.5T scanner with only modest coil technology and limited temporal and anatomic coverage that would compare unfavourably with the 3T whole heart high resolution perfusion studies available today.

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

Conclusions

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

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: support from the UK National Health Service R&D Health Technology Assessment Program (project no. 99/26/04) and the UK Medical Research Council [Programme number U015232027] for the submitted work ; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to 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.

Contributorship statement:

HT, MD, MB, LDS, CHJ were involved in economic and statistical analysis. LDS was the senior project statistician, was involved in original study design and takes overall responsibility for statistical portion of the manuscript. All of these individuals contributed to drafting and revision of the manuscript.

VH was involved in study design, patient recruitment, data collection and project management from the project's inception to its conclusion. She also contributed to drafting and revision of the manuscript

NW was responsible for blinded review of clinical data and contributed to drafting and revision of the manuscript.

AC was involved in the original study design, was responsible for the day-to-day clinical aspects of running the trial and was involved in the recruitment and follow up of patients as

well as analysis of the cardiac MR studies. He wrote the final manuscript and contributed to its revision. He takes overall responsibility for the integrity of the clinical data.

Data sharing statement:

There are no additional data available

591 **Table 1 Baseline characteristics***

Demographics	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (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 symtoms	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%)

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

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

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)	(2.16,2.31)	(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 at £20k per QALY	-	0.82	0.29	0.55
Probability cost effective at £30k per QALY	-	0.79	0.25	0.59

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

	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

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

	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

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

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

Table 4 Summary of the frequency of use of the main resource use elements during follow up of up to 3 years (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 (£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

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

Figure Legends

Figure 1 CONSORT diagram describing recruitment and randomization

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

Figure 3 Quality of life assessed by EQ5D over time

Figure 4 Bootstrapped estimates of the joint distribution of mean cost difference against mean QALY difference up to 3-years post randomisation

Figure 5 Estimated probability of being cost-effective compared with angiography alone against the amount (£) a health provider is willing to pay for one additional 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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Contributorship statement:

HT, MD, MB, LDS, CHJ were involved in economic and statistical analysis. LDS was the senior project statistician, was involved in original study design and takes overall responsibility for statistical portion of the manuscript. All of these individuals contributed to drafting and revision of the manuscript.

VH was involved in study design, patient recruitment, data collection and project management from the project's inception to its conclusion. She also contributed to drafting and revision of the manuscript

NW was responsible for blinded review of clinical data and contributed to drafting and revision of the manuscript.

AC was involved in the original study design, was responsible for the day-to-day clinical aspects of running the trial and was involved in the recruitment and follow up of patients as well as analysis of the cardiac MR studies. He wrote the final manuscript and contributed to its revision. He takes overall responsibility for the integrity of the clinical data.

Article summary:

Article focus:

1. **Is non-invasive imaging a safe and appropriate gate-keeper to coronary angiography in patients with stable chest pain ?**
2. **Is there any difference in cost-effectiveness and cost-utility between the different non-invasive approaches and conventional coronary angiography**
3. **Are patients disadvantaged in any meaningful way by having a non-invasive test to decide whether they should go forward for coronary angiography ?**
4. **How does stress perfusion CMR compare to the more established tests of SPECT-MIBI and stress echocardiography as a gate-keeper to coronary angiography ?**

Key messages:

1. **Non-invasive testing may be used safely as a gate-keeper to coronary angiography in patients with stable chest pain without any material disadvantage to them in terms of survival and quality of life up to 6 years after initial randomisation.**
2. **SPECT-MIBI appears marginally superior statistically to the other non-invasive methods although clinically meaningful differences are small between all strategies.**
3. **Stress perfusion CMR appears to be an effective technique in a stable out-patient population with undiagnosed chest pain.**

Strengths and limitations:

1. **This is the only large randomised prospective trial of a strategy of non-invasive gate-keeper cardiac imaging versus upfront angiography in the literature.**
2. **The cost-utility data are derived from NHS tariffs and our results are not necessarily directly transferrable to other healthcare systems**

Data sharing statement:

There are no additional data available

Abstract

Objectives: to compare outcomes and cost effectives of various initial imaging strategies on the management of stable chest pain in a long term prospective randomized trial.

Setting: regional cardiothoracic referral center in the east of England

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

Primary outcome measures: 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

Results: 898 patients were randomized. Compared to angiography, mortality was marginally higher in the groups randomized to CMR (hazard ratio 2.6, 95%CI 1.1, 6.2), but similar in the SPECT-MIBI (hazard ratio 1.0, 95%CI 0.4, 2.9) and ECHO groups (hazard ratio 1.6, 95%CI 0.6, 4.0). Although SPECT-MIBI was marginally superior to other non-invasive tests there were no other significant differences between the groups in mortality, quality adjusted survival or costs.

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

Trial registration: ISRCTN 47108462, UKCRN 3696

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

Introduction

CAD is common and its management is costly [1]. Revascularisation using bypass surgery (CABG) or percutaneous coronary intervention (PCI) is effective for patients with severe disease [2] but a significant minority of patients do not gain symptomatic relief [3]. Data from the COURAGE trial did not show prognostic benefit from revascularization in any patient subgroup[4]. The yield of coronary angiography is variable with one recent large study of nearly 400, 000 patients demonstrating a normalcy rate approaching 40% [5]. 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 [6] [7] [8] [9].

The '**C**ost-**E**ffectiveness of non-invasive **Ca**rdiac **T**esting' (**CECaT**) trial was an unblinded non-inferiority trial 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 [10]. 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 [10] and is reviewed briefly here. All patients referred to Papworth Hospital, UK for non-urgent angiography were eligible for the study. Inclusion criteria were: established or suspected chronic stable angina and a positive

exercise tolerance test result with subsequent referral for angiography. Exclusion criteria were: recent MI (<3 months), revascularisation (<6 months); urgent need for revascularisation; contra-indication to adenosine or CMR; inability to exercise.

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

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

Coronary angiography.

Standard diagnostic angiography was performed from the right femoral artery approach [12]. A minimum of 5 views of the left and 3 views of the right coronary system were taken [13]. All examinations were reported by an experienced staff cardiologist and segmental location of disease (if any) recorded.

Stress echocardiography

Beta-blocker medications were stopped 2 days beforehand. Dobutamine was infused at rates of 10- 40 mcg/kg/min, increased at 3 minute intervals. If necessary, 300-600 micrograms of atropine were added at peak stress to achieve 90% of target heart

rate. Images were acquired in standard planes in the final minute of each 3 minute stage. Intravenous microspheres were used to delineate the endocardial surface. All examinations were reported by one of two staff cardiologists experienced in stress echocardiography. Studies were positive for ischemia if stress-induced deterioration in contractility was observed.

SPECT

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

CMR

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

either: a) in a region of normal wall thickness; or b) in a region of myocardial thinning in the absence of a history of prior myocardial infarction.

Outcomes

The primary outcome in the original CECaT trial was exercise treadmill time at 18 months post-randomisation using the modified Bruce protocol, in which exercise intensity was increased every 3 minutes. There was a range of secondary outcomes including diagnostic accuracy, clinical events, health-related quality and cost-effectiveness of life up to 18 months after randomisation[10].

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 at the end of follow up was determined from the Office for National Statistics database, UK (http://www.ons.gov.uk/).

Quality of life was measured using the EuroQoL EQ-5D questionnaire [18] which was completed at baseline, 6 and 18 months post-randomisation, and at 6, 18 and 24 months post-treatment. The social tariff for the EQ-5D was applied in order to calculate utility values [19]. Because post-**treatment** measurements were at variable times post-**randomisation** (randomisation date is time zero for a randomised trial) daily utilities were estimated using linear interpolation.

Sample size calculations

The sample size of 898 patients was based on exercise performance and was calculated according to the methodology published in the initial report of the CECaT study [10].

Statistical and economic analysis

For this study, survival was summarised using Kaplan-Meier estimates and the groups were compared using Cox proportional hazards regression. This assumes that the instantaneous risk of death (hazard) for a reference value of a covariate will vary through time, but that the

hazards for other values of the covariate will be a constant multiple of this baseline hazard, and this multiple will not vary through time. This assumption was tested using Schoenfeld residuals and there was little evidence against it. The diagnostic test was entered into the Cox regression as a 4-level fixed covariate, with angiography as the reference category. In sensitivity analysis CABG and PCI were included in the regression analyses as time-varying covariates, taking a value 0 up to the time of intervention and 1 thereafter, to ensure that any differences between the groups was not due to differences in treatment. Inclusion of treatment (CABG/PCI) did not affect comparison of diagnostic 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 reference costs 2005/06 prices. 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.

Quality adjusted survival and cost estimates were censored at the last follow up at 2 years after treatment, resulting in varying duration of follow-up from the time of randomisation to the different diagnostic strategies, so that mean values over a range of time horizons were estimated using inverse weighting methods [20]. This method allows for differing follow up times between patients by splitting follow up time into intervals, and up-weighting the observed quality adjusted survival and costs in an interval in proportion to the inverse of the Kaplan-Meier estimate of the proportion observed during the interval. In the base case we used a time horizon of 3 years since it was the longest period over which results were stable, with acceptable precision. Confidence intervals for costs and QALYs were estimated using bootstrapping with 5000 samples [21].

Sensitivity analysis

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

The study had IRB approval and full written informed consent was obtained from all participants. All authors had full access to the data and take responsibility for the manuscript as written.

Results

Recruitment and compliance

Between September 2001 and September 2004, 3,201 patients were assessed, 1,981 were excluded and 322 refused entry to the trial. Refusals were more likely to come from women (46% compared with 31% enrolled into the study, p<0.001) and were significantly older (mean age 64.6, (SD 10.1) compared with study group mean age 61.8, (9.4), p<0.001).

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

One-hundred-seventy-five (78%) SPECT patients, 180 (80%) CMR patients and 169 (75%) stress echo patients were referred on for angiography (**Figure 1**). Between 20% and 25% of patients undergoing non-invasive tests did not require further investigation. Twenty-one percent of patients who had negative tests were referred for angiography and the proportion was similar in each group (SPECT n=45, CMR n=50, ECHO n=48, p=0.858). Of these 14

(31%) SPECT, 26 (52%) CMR and 23 (48%) ECHO resulted in a positive angiogram (p=0.130). Four patients died and four withdrew from the trial early on. Of the remaining patients, revascularization was required in 34% (301/890 – see **Figure 1** for numbers in each arm). There was no significant difference between the groups in initial patient management (Figure 1, p=0.527). Beyond the initial management strategy 42 subsequent revascularisation procedures were required in the angiography arm compared with 30 in the SPECT, 44 in the CMR and 41 in the ECHO arms. The median times between randomisation and initial revascularisation were 122 days in the angiography group, 192 days for SPECT, 184 days for CMR and 177.5 days for ECHO, resulting in a delay due to functional testing of approximately 2 months.

Survival

During the study there were 7 (3%), 7 (3%), 18 (8%) and 11 (5%) deaths in the angiography , SPECT, CMR and ECHO groups respectively. Kaplan-Meier survival curves for the 4 groups are plotted in **Figure 2**. Survival over the whole trial period in the SPECT (hazard 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 significantly different from angiography but the CMR group had higher mortality, with hazard ratio 2.6 (95%CI 1.1 to 6.2), p=0.032. The significant effect of CMR on survival remained when CABG or PCI were included in the models. However, mortality was low in all groups and the absolute mean difference in survival was less than 1 month over 3 years (**Table 2**). Mean survival estimates over 3 years with 95% confidence intervals are shown in **Table 2**. All patients had complete adverse event data up to 18 months post-randomisation during which there were 178 non-fatal adverse events in 114 patients, mostly hospital admissions for chest pain (**Table 3)**. Beyond this time only adverse events that resulted in admissions were recorded as they were relevant for the economic analysis. No patient suffered any adverse event at the time of the initial randomised imaging test.

Cost-utility

Table 4 shows some of the highest incurred follow up costs for the 4 groups and shows that patient management varied substantially between individuals. Although angiography was the most expensive of the four initial diagnostic tests, the strategy of initial angiography had lower mean overall cost than stress echo, and was similar to CMR up to 3 years (**Table 2**). Extra costs for patients in the three non-invasive groups was largely due to patients undergoing follow-on angiography. There were no significant differences in overall costs between the groups.

During the study there were no significant differences in EQ-5D between the groups. **Figure 3** shows daily mean EQ-5D utility over time based on interpolation between measurements for survivors who completed the EQ-5D. Using inverse-weighting we calculated QALYs over different time horizons and these are presented up to 3 years in **Table 2**. Mean QALYs over 3 years in the angiography group was 2.24, which was not significantly different from the other groups. **Figure 4** shows the joint distribution of the difference in mean cost against the difference in mean QALY for each diagnostic strategy group and angiography alone, and shows the uncertainty in these estimates. **Figure 5** shows the Cost-Effectiveness Acceptability Curve and demonstrated that SPECT has a high chance (>70%) of being cost-effective whatever the willingness-to-pay threshold is but for CMR and ECHO there is much less certainty about this decision. The mean differences between groups were close to zero in all 3 cases so that the cost-per-QALY estimates are unstable and a cost-minimization approach may be more appropriate. This would favour SPECT, which was both cheaper and more effective on average than angiography, and had the lowest overall cost ( ).

Sensitivity analysis

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

respectively. Patients who were managed by interventional cardiologists incurred higher costs due to the greater number of tests and revascularization procedures performed, with minimal incremental benefit in QALY.

Discussion

CECaT is the first completed prospective randomized trial to look at the clinical and cost-effectiveness of non-invasive imaging in the diagnosis and management of angina. To the best of the authors' knowledge there has been no comparable outcomes trial published on this scale evaluating three independent non-invasive 'gatekeeper' modalities versus initial angiography in stable chest pain. The trial is also unusual in the length of prospective follow up extending to 6 years for mortality outcomes.

We have demonstrated that use of any one of stress CMR, stress echo or stress SPECT as the initial test for a stable chest pain patient leads to non-inferior outcomes in quality of life and cost utility compared to patients randomised to upfront invasive coronary angiography. Typically, non invasive tests perform well in low risk populations because of a negative predictive value which is usually better than the positive predictive value. However, the patient risk profile was relatively high in our study, and despite this there was no significant difference between an initial functional or anatomic approach.

There are several reasons why initial angiography may not have led to clear benefit in our study. Firstly, although angiography has stood at the heart of the diagnostic chest pain pathway, the traditional binary cut-off values of 50% or 70% percentage stenosis by visual estimation were shown in the FAME study to bear little relation to the true physiologic significance of luminal narrowing [22].

Secondly, data from various countries suggest that not only is coronary angiography often inappropriate when formally rated by expert observers [23] [24] but that disparate national or

regional rates of angiography do not translate into clear mortality benefits between countries [25] [26] [27] [28] and on occasion may even demonstrate an inverse relationship [29].

Contemporary US data from approximately 500,000 PCI procedures collected prospectively in the National Cardiovascular Data Registry demonstrated that, of 145,000 elective PCI cases, roughly 12% were judged inappropriate. Furthermore, the rate of inappropriate elective PCI between hospital sites ranged from 0-55% suggesting significant variability in practice [30]. The data suggest a better way of selecting patients for invasive investigation is needed.

Ischemia-driven revascularisation has been shown to be of benefit in a number of trials, most recently in the FAME study in which an invasive method of measuring the flow reserve of the microcirculation (Fractional Flow Reserve, FFR) was used to allocate patients to intervention or observation vs a clinical decision on intervention based on angiography alone [31]. At 2 years follow up there were clear survival and MACE benefits to the FFR-based approach.

The ACRE study reported that, up to 6 years after diagnosis, medical management was a more cost-effective strategy for angina compared with PCI [32]. The lack of evidence for survival from revascularisation was also seen in the COURAGE trial [4]. Critics have suggested this may be because randomization to PCI versus optimal medical therapy was made *after* coronary angiography had been performed, potentially leading to a recruitment bias of patients with less severe disease. In the CECaT trial this bias was avoided by randomization to a management strategy defined by the non-invasive test result for each of the 3 functional arms of the trial. In a relatively high risk population, we demonstrated no clinically significant survival or economic detriment from using non-invasive imaging as a gate-keeper to catheterization. Similarly, quality of life was not significantly different across all four groups and these differences extended to a warranty period of at least 3 years.

We did observe a marginal decrease in survival in the CMR arm. The reasons for the difference are unclear but do not relate to patient characteristics or management with CABG or PCI. Although statistically significant, the mean survival difference from the other groups was only 4 weeks over 3 years and is unlikely to be clinically meaningful. Since recent work has established a strong correspondence between FFR measurements and stress CMR perfusion indices it would be surprising if CMR were genuinely inferior to other modalities for risk stratification [33]. Indeed several recent publications have highlighted the incremental prognostic data (above that obtained from clinical variables) derived from several thousand perfusion CMR studies [34] [35].

Given the recent publication of the CEMARC trial [36] in which a clear diagnostic superiority was demonstrated for stress CMR over SPECT, it is interesting that our data nonetheless show an equivalence in functional health status between those randomized to SPECT versus CMR in the CECaT trial. The implication may be that although CMR detects the presence of *any* ischemia with a greater sensitivity it is the *overall burden* of ischemia that alters a patient's prognosis. As such, it has not yet been demonstrated that the higher diagnostic accuracy of CMR translates into better long-term patient outcomes – a fact acknowledged by Greenwood et al subsequent to CEMARC's publication [37]. In this context the CECaT nuclear results are congruent with numerous past publications and reconfirm the reassuring warranty period of a normal SPECT study.

Cost effectiveness

There was no significant difference in cost-effectiveness between the angiography -as-default group and the non-invasive test groups up to 3 years, perhaps relating to the higher-than-anticipated rate of referral for angiography after negative functional tests. Protocol deviation of this kind is not infrequent in trials of non-invasive technology. In the recent PARR-2 study of patients undergoing fluorodeoxyglucose positron emission tomography for the assessment of viability, roughly 25 % of the study population did not adhere to protocol

[38]. The willingness of a cardiologist to defer referral for coronary angiography in the face of a normal non-invasive study may in part reflect individual prejudices and job description (interventional versus non-invasive) as demonstrated in a recent survey of cardiology attitudes [39] and was also reflected in our own data.

In CECaT, 20-25% of patients receiving a non-invasive test did not go on to have angiography. A proportion of the additional cost in the non-invasive arms related to angiography and PCI in the patients with a *negative* test, although only very few subsequently required CABG - a robust marker of significant disease - during follow-up. This readiness to employ PCI in a group in whom the indication/benefit is debatable was also seen in the ACRE trial [32] and reflects understandable clinical response to uncertainty but also the easy access to PCI in healthcare systems without barriers to self-referral [40]. Similarly, studies from the US have demonstrated a greater willingness to use coronary angiography when available 'on site' as is increasingly seen even in small-to-medium sized hospitals [41] [42] [43].

Cost effectiveness of each non-invasive technique

Nuclear myocardial perfusion imaging

The END study used propensity matching to compare a large cohort of patients referred for either gate-keeper myocardial perfusion imaging or upfront angiography – this non randomised study demonstrated a significant cost reduction in the (44) nuclear arm. In contrast to this and other work[45] [46] [47] we were unable to show a significant difference in cost effectiveness in our own study. To some extent this reflected the participating physician bias towards angiography during the period of trial recruitment (2001-2006) with many patients referred for angiography despite normal perfusion studies. This continues in the contemporary era with Chan et al demonstrating that almost 80% of Delphi-adjudicated

inappropriate elective PCIs were performed following either low risk ischemia imaging in mildly symptomatic patients or intermediate risk imaging in entirely asymptomatic patients [30].

In the CECaT study, when PCI was performed despite a negative initial non-invasive test, this occurred because subsequent angiography indicated 'significant' stenosis. This was a clinical judgment based on 'eyeball assessment' of lesion severity as has been reported in clinical trials with angiographic end points [48]. However, the severity and functional significance of many stenoses may be over-called, even by quantitative assessment, when compared with physiological assessment of fractional flow reserve across the lesion [49] [50]. Further improvement in cost-effectiveness could likely have been achieved in the nuclear arm of the trial. Our post-trial practice is to perform the stress SPECT first - and if this is negative - cancel the rest test, likely augmenting the relative cost-effectiveness of SPECT [51].

CMR

There are relatively few data available regarding the cost effectiveness of CMR . One recent mathematical modelling study estimated that CMR likely has greater cost effectiveness/utility compared to SPECT despite greater base case cost of the former [52] . The economic superiority of CMR was also recently described by the CEMARC group, although interestingly the base case costs employed for CMR and SPECT in their analysis differed by only a few pounds. Their own sensitivity analysis in fact demonstrated that if the costs of the two tests varied by more than 100 pounds (which was the case in our study) then in fact – as we found - SPECT became the dominant strategy in a low-to-intermediate risk population. [53]

Stress echo

Stress echocardiography may be a more cost-effective strategy than angiography for men aged 50-60 with CAD prevalence of 50%[54, 47]. There is also some evidence that stress echo is more cost-effective than SPECT as an initial test [55, 56], especially in women with suspected CAD [57]. A similar benefit was not seen in our study probably because of the high disease prevalence in our population. The lack of superiority of either stress echocardiography or a combined strategy of exercise testing and stress echo compared to upfront catheterisation was also evident in a recent Polish study of 600 patients with a similar age, gender and disease prevalence to our own study population [58].

Taken overall, our data clearly demonstrate a limited future role for cost-effective non-invasive imaging if referring physicians are not willing to accept a negative result as ground truth. This might be interpreted as reflecting a need for greater physician education since we showed a clear difference in onward referral rates for angiography after a negative test between interventional and non-invasive cardiologists.

Clinical effectiveness

We demonstrated that SPECT can obviate the need for coronary angiography for a significant number of patients without any clinical detriment. In the stress echo group clinical outcomes were also comparable to the angiography subgroup at 18 months. The CMR group had statistically marginally poorer survival and this follows our earlier finding that CMR patients had significantly worse exercise tolerance at 18 months after randomisation [10]. This is difficult to explain on the basis of Pryor risk score or other baseline clinical variables. However, the mean difference in survival between the CMR arm and the other groups was only 4 weeks and thus of marginal clinical significance. More importantly, the CMR group were not otherwise disadvantaged – compared to the angiographic control group - with respect to major adverse events, other resource use, or quality of life.

Limitations

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

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

The trial completed recruitment in 2004 and we used the technology that was available to us at the onset of the trial. At that time, we were not able to use attenuation correction for SPECT imaging; however this was also not used in the much more recent CEMARC trial[36]. Similarly, we performed our CMR exams in a mobile facility on a 1.5T scanner with only modest coil technology and limited temporal and anatomic coverage that would compare unfavourably with the 3T whole heart high resolution perfusion studies available today.

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

Conclusions

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

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: support from the UK National Health Service R&D Health Technology Assessment Program (project no. 99/26/04) and the UK Medical Research Council [Programme number U015232027] for the submitted work ; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to 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.

583 **Table 1 Baseline characteristics***

Demographics	Angiography (n=222)	SPECT (n=224)	Cardiac MRI (n=226)	Stress Echo (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 symtoms	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%)

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

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

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)	(2.16,2.31)	(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 at £20k per QALY	-	0.82	0.29	0.55
Probability cost effective at £30k per QALY	-	0.79	0.25	0.59

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

	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

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

	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

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

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

Table 4 Summary of the frequency of use of the main resource use elements during follow up of up to 3 years (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 (£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

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

Figure Legends

Figure 1 CONSORT diagram describing recruitment and randomization

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

Figure 3 Quality of life assessed by EQ5D over time

Figure 4 Bootstrapped estimates of the joint distribution of mean cost difference against mean QALY difference up to 3-years post randomisation

Figure 5 Estimated probability of being cost-effective compared with angiography alone against the amount (£) a health provider is willing to pay for one additional QALY

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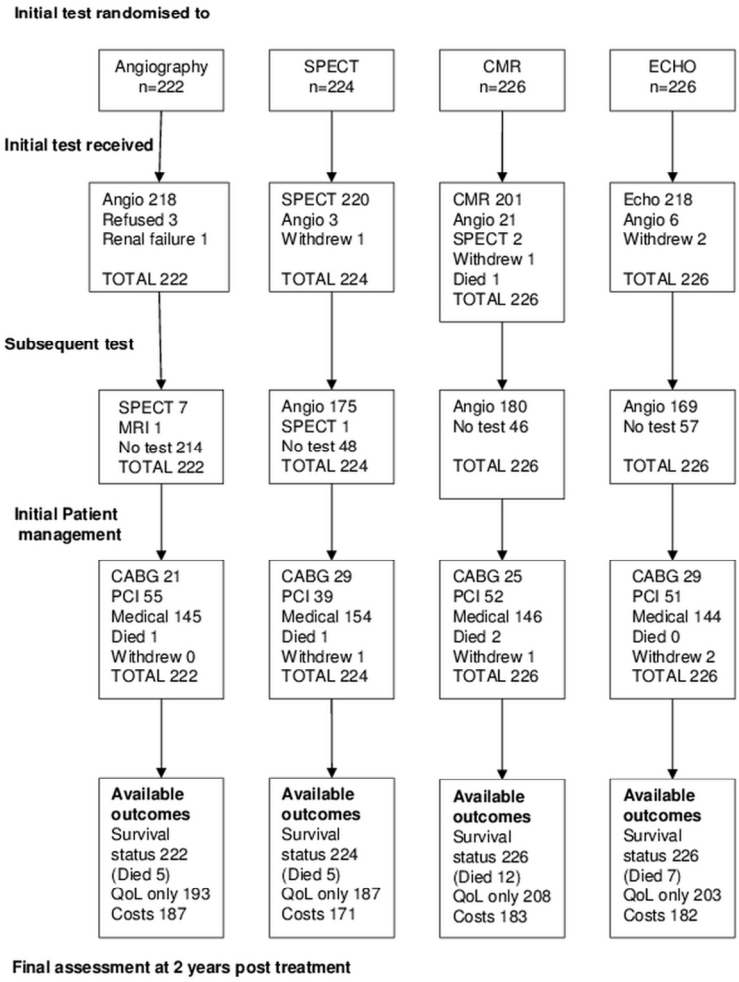
Figure 1 Trial summary



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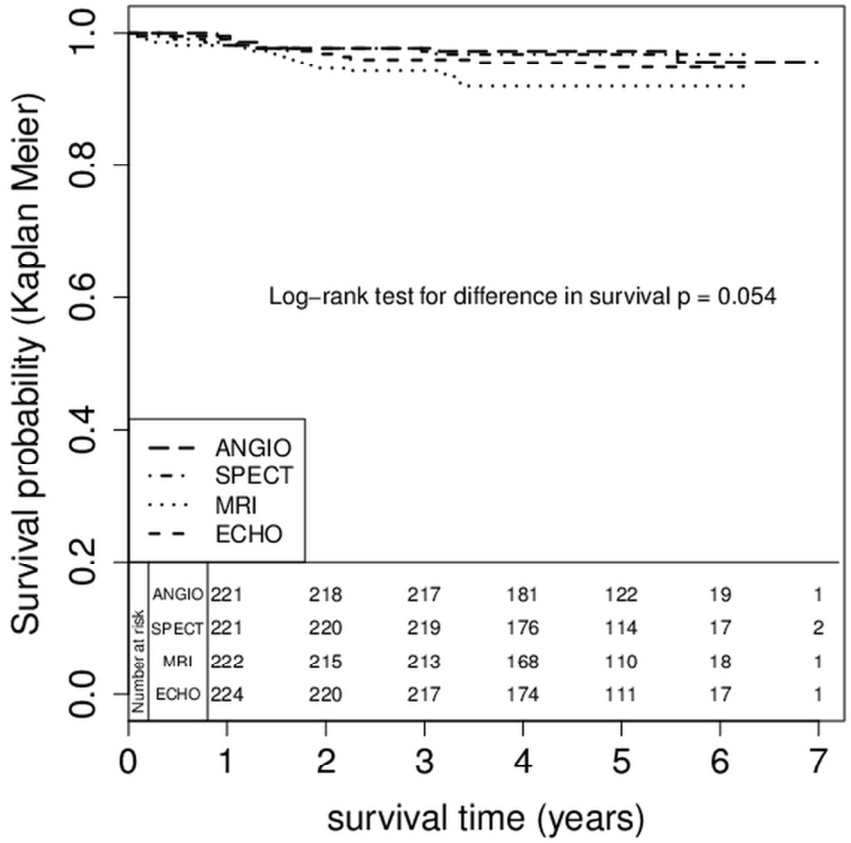

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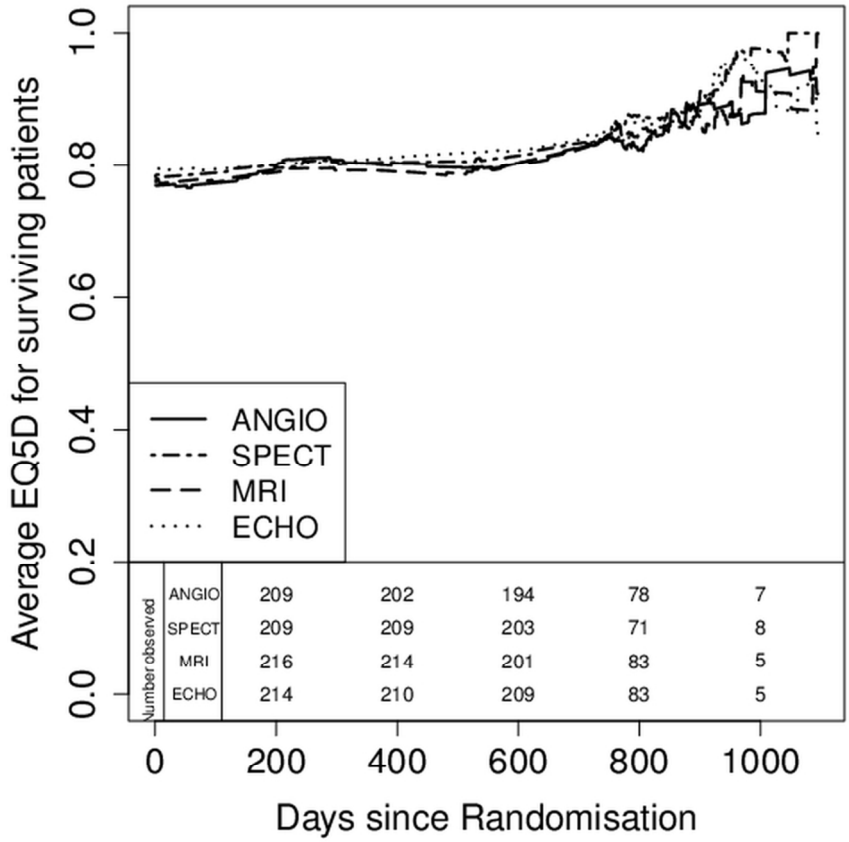

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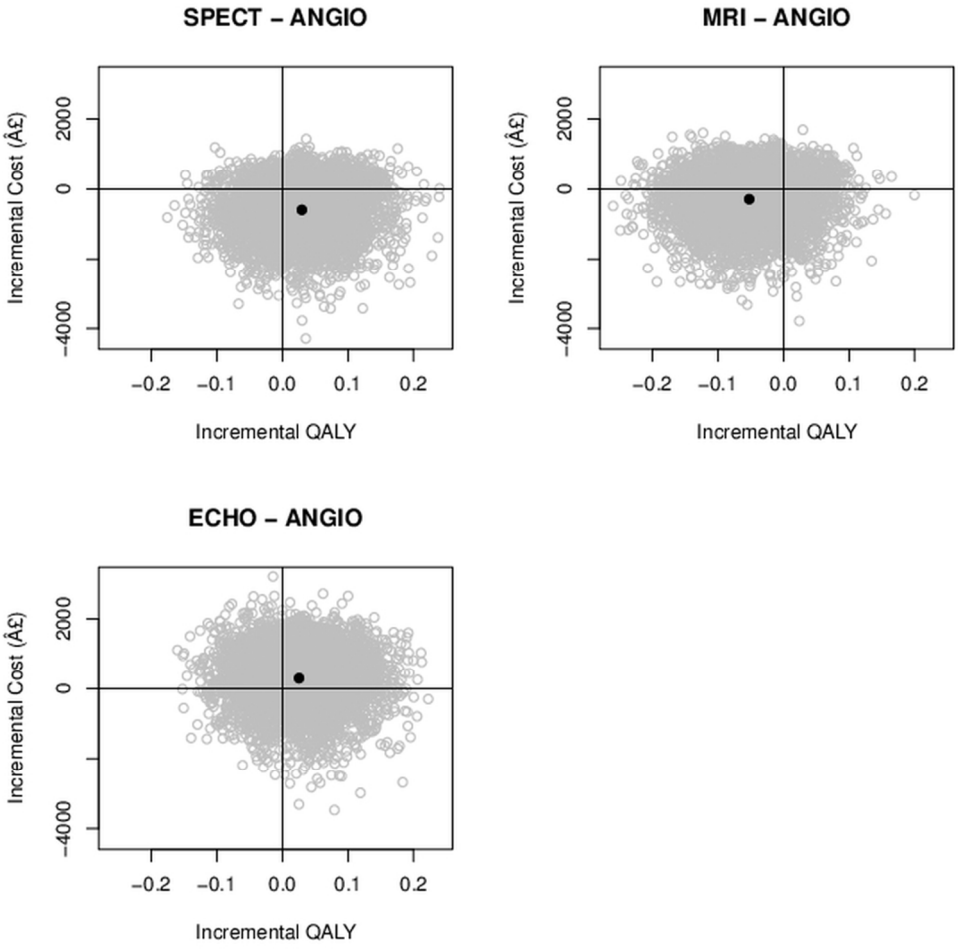

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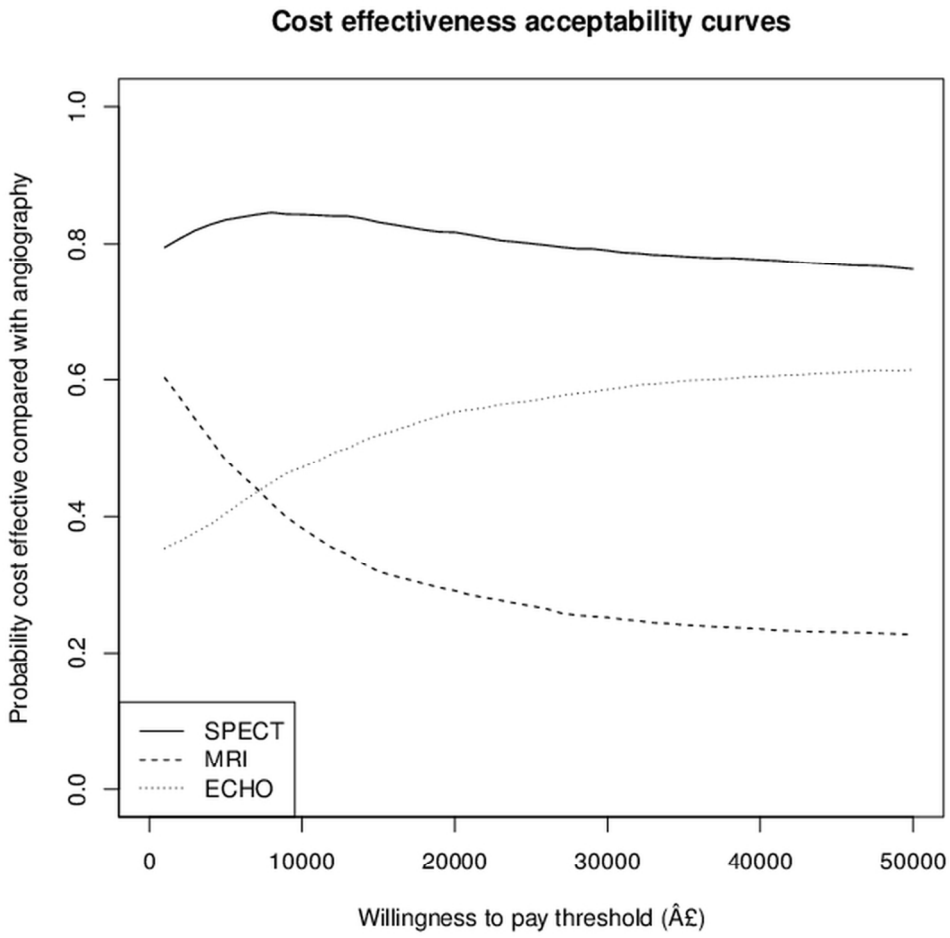

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CONSORT checklist CECaT Trial BMJ Open Re-Submission

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