Prognostic Value of CMR and SPECT in Suspected Coronary Heart Disease: Long Term Follow-Up of the CE-MARC Study

John P. Greenwood, MB ChB, PhD[1]; Bernhard A. Herzog, MD[1]; Julia M. Brown, MSc[2]; Colin C. Everett, MSc[2]; Jane Nixon, PhD[2]; Petra Bijsterveld, MA[1]; Neil Maredia, MB ChB, MD[1]; Manish Motwani, MB ChB, PhD[1]; Catherine J. Dickinson, BM BCh, MA, PhD[3]; Stephen G. Ball, MB BChir, PhD[1]; Sven Plein, MD, PhD[1]

[1] Multidisciplinary Cardiovascular Research Centre & the Division of Biomedical Imaging, Leeds Institute of Cardiovascular & Metabolic Medicine, University of Leeds, United Kingdom

[2] Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, United Kingdom.

[3] Department of Nuclear Cardiology, Leeds General Infirmary, United Kingdom

Address for correspondence:
Prof. J.P Greenwood,
Multidisciplinary Cardiovascular Research Centre & Leeds Institute of Cardiovascular & Metabolic Medicine,
University of Leeds,
Leeds,
LS2 9JT,
United Kingdom
Tel: +44 113 3922650; Fax: +44 113 3922311; E-mail: j.greenwood@leeds.ac.uk

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Abstract

Background: There are no prospective, prognostic data comparing cardiovascular magnetic resonance (CMR) and single photon emission computed tomography (SPECT) in the same population of patients with suspected coronary heart disease (CHD).

Objective: To establish the ability of CMR and SPECT to predict major adverse cardiovascular events (MACE).

Design: Annual follow-up of the CEMARC study for a minimum 5 years for MACE (cardiovascular death, acute coronary syndrome, unscheduled revascularization or hospital admission for cardiovascular cause). Current Controlled Trials ISRCTN77246133.

Setting: Secondary and tertiary care cardiology services.

Participants: 752 patients from CE-MARC who were under investigation for suspected CHD

Measurements: Prediction of time to MACE was assessed by univariable (log-rank test) and multivariable (Cox proportional hazards regression) analysis.

Results: 744(99%) of 752 patients recruited had complete follow-up. Of 628 who underwent CMR, SPECT and the reference standard test of X-ray angiography, 104(16.6%) had at least one MACE. Abnormal CMR (hazard ratio (HR) 2.77; 95%CI, 1.85-4.16; p<0.0001) and abnormal SPECT (HR 1.62; 95%CI, 1.11-2.38; p=0.014) were both strong and independent predictors of MACE. Only CMR remained a significant predictor after adjustment for other cardiovascular risk factors, angiography result or after stratification for initial patient treatment.

Limitations: Single-centre observational study design, albeit conducted in a high-volume institution for both CMR and SPECT.

Conclusions: Five-year follow-up of CE-MARC indicates that compared to SPECT, CMR is a stronger predictor of risk of MACE, independent of cardiovascular risk factors, angiography result or initial patient treatment. This further supports the role of CMR as an alternative to

SPECT for the diagnosis and management of patients with suspected coronary heart disease.

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Introduction

Cardiovascular magnetic resonance (CMR) is an accepted non-invasive investigation for the detection of coronary heart disease (CHD), being attractive because of its lack of ionising radiation, high spatial resolution, and versatility in providing morphological and functional cardiac assessment in a single study (1-3).

CE-MARC (Clinical Evaluation of MAgnetic Resonance imaging in Coronary heart disease) was the largest prospective evaluation of CMR versus nuclear myocardial perfusion imaging using single photon emission computed tomography (SPECT) to date (4). It was designed to establish the diagnostic performance of a multi-parametric CMR examination in unselected patients with suspected CHD and to compare the diagnostic performance of CMR and SPECT for the detection of significant CHD, using X-ray angiography as the reference standard (5). In line with previous smaller studies (6,7), CE-MARC demonstrated a high diagnostic accuracy of CMR, with higher sensitivity and negative predictive value compared to SPECT (4).

Data on the prognostic value of CMR remain limited, and there are no directly comparative prognostic data in relation to other non-invasive imaging modalities in the same patient population. A predefined objective of CE-MARC was to assess the ability of CMR and SPECT to predict major adverse cardiovascular events (MACE) at 5-year follow-up.

Methods

Study Design and Study Population

The design and primary outcome analysis of CE-MARC have been published (4,5). Briefly, patients with suspected stable angina were prospectively enrolled if they had at least one major cardiovascular risk factor and a cardiologist considered them to require further investigation. By protocol, all patients were scheduled to undergo CMR and SPECT (in random

order), followed by X-ray coronary angiography (the reference standard) within 4 weeks regardless of the treating physician's chosen clinical pathway (4,5). After x-ray angiography, the SPECT result could be made available on request to enable a decision about revascularisation (to mask the treating clinician to this result was deemed unethical); however, CMR results were kept masked. The study was conducted in accordance with the Declaration of Helsinki (2000) and approved by the UK National Research Ethics Service (05/Q1205/126); all patients provided informed written consent. Extended 5 year follow up was conducted with Ethics approval (14/YH/0137) and under Section 251 approval (14/CAG/1018).

Image Acquisition and Analysis

In CE-MARC, CMR and SPECT were analysed blind, by paired readers with >10 years' experience in their respective modalities. The multi-parametric CMR (1.5Tesla Philips Intera; Best, The Netherlands) protocol comprised stress perfusion (adenosine 140μg/kg/min for 4 minutes), cine imaging, rest perfusion, coronary MR angiography and late gadolinium enhancement (LGE). The CMR result was positive if any of the following was found: evidence of regional wall motion abnormality, regional hypoperfusion (ischemia) on stress compared with rest CMR perfusion scans, coronary artery stenosis on MR angiography (≥50% left main stem, ≥70% in any other vessel ≥2.5mm in diameter) or myocardial infarction on LGE images (4,5). If all components were negative, the CMR study was judged to be negative.

SPECT used a dedicated cardiac gamma camera for image acquisition (MEDISO Cardio-C, Budapest, Hungary). Patients underwent a two-day protocol using ^{99m}Tc-tetrofosmin with a standard dose of 400MBq adjusted by weight to a maximum 600MBq per examination. Stress and rest Electrocardiographic-gated images were acquired using an identical intravenous adenosine protocol to that in CMR. Diagnosis was made on the basis of all available SPECT data and an overall clinical judgment. Rest and stress perfusion and regional wall motion were

reviewed and ancillary findings (RV uptake and transient ischaemic dilatation) were recorded. The study was considered abnormal if any of the components was abnormal (6-8). Specific imaging and reporting parameters for CMR and SPECT have been previously described (4,9).

Follow-Up and Clinical Endpoints

Annual follow-up for 5 years was planned for all recruited patients. A detailed medical history since randomisation was obtained from all hospital and general practitioners' records and cross-referenced to information obtained by direct telephone contact with each patient. Mortality and cause of death were obtained from the Office for National Statistics via the Health and Social Care Information Centre. MACE was defined as the composite endpoint of: cardiovascular death, myocardial infarction/acute coronary syndrome, unscheduled coronary revascularization or hospital admission for any cardiovascular cause (stroke/TIA, heart failure, arrhythmia)(7). In addition, 'hard' clinical events were defined as a composite of cardiovascular death and non-fatal myocardial infarction/acute coronary syndrome in order to allow direct comparison with prior published outcome data for CMR and SPECT. Unscheduled coronary revascularization was defined as any revascularization that occurred due to clinical deterioration and excluded procedures which were planned on the basis of the index coronary angiography results. All clinical events were adjudicated by a clinical events committee blinded to any of the CMR or SPECT results.

Statistical Analysis

Statistical analyses were performed independently by the Clinical Trials Research Unit, University of Leeds, UK. The study was prospectively powered to demonstrate the prognostic value of CMR and SPECT with follow-up for at least 3 years, based on a predicted clinical event rate of ~3% per year (5). Due to the lower overall event rate per year seen within the study, follow-up was extended by the Trial Steering Committee to 5 years. Both the total

number of events and the first adjudicated event per patient were summarised; the main analysis was based on the first adjudicated event. Only patients with a CMR, SPECT and angiography result, with follow up data, were included in this analysis. The prediction of first MACE was assessed using univariable (log-rank test) and multivariable analysis (Cox proportional hazards regression modelling). The major cardiovascular risk factors of age, gender, total cholesterol, hypertension, smoking, diabetes and family history were included in the multivariable model, as they are known to have a strong association with MACE. Additional analysis was undertaken with adjustment for the Genders Risk Score (10) instead of the individual cardiovascular risk factors. Further analyses were undertaken using the above methods to adjust for the effect of X-ray angiography results. Stratified Cox Proportional Hazards Modelling was undertaken to account for initial patient treatment. Difference in Akike Information criteria was used to determine which model better explained the variation in time to MACE between the multivariable models, with a value >10 taken to indicate a better model (11). Kaplan-Meier curves were produced for time to MACE. Patients who did not experience MACE were recorded as the last time they were known to be alive and MACE-free. Statistical analysis was undertaken using SAS software (version 9.4) with hypothesis testing using a two-sided 5% significance level (5).

Role of the Funding source

This study was funded by the British Heart Foundation (RG/05/004). B.A. Herzog was funded by the Swiss Foundation for Medical-Biological Scholarships (SNSF No. PASMP3_136985). None of the funding sources were involved in i) the design and conduct of the study; ii) collection, management, analysis, and interpretation of the data; iii) preparation, review, or approval of the manuscript; and iv) decision to submit the manuscript for publication.

Results

Baseline Characteristics

Between March 2006 and August 2009, 752 patients with suspected angina were prospectively randomised. Follow-up was obtained in 99% of patients; 5(1%) patients were lost to follow-up (all emigrated) and 3(0.4%) withdrew their consent. Median follow-up was 80.7(inter-quartile range: 68.3-91.6) months. 628 patients had CMR, SPECT and angiography results and formed the main outcome population (Figure 1). Baseline characteristics of all study patients and of the final analysis population are given in Table 1.

Events at 5 Years

In the full study population of 752 patients there were a total of 204 MACE events. In the analysis population of 628 patients there were 171 MACE events, occurring in 104(16.6%) patients. Table 2A and 2B give a detailed breakdown of all MACE events and the first adjudicated event for each patient for both the full study population and the analysis population. In addition there were 43 and 32 non-cardiac deaths for the full study population and the analysis population respectively; these are not included in the MACE endpoint.

In the full study population there were 33(4.4%) 'hard' clinical events and 25(4.0%) in the analysis population. Abnormal CMR and SPECT findings were associated with similar event rates for MACE (25.2% and 21.2%) and also hard clinical events (7.9% and 7.4%). Normal CMR and SPECT findings were associated with very low similar event rates for MACE (10% and 14.1%) and hard clinical events (1.4% and 2.5%). In comparison, significant stenosis or normal findings at angiography were associated with MACE rates of 25.4% and 11.1% respectively. Event rates were similar between patients who were revascularised or not (19% versus 15.6%), with higher event rates for patients who were abnormal rather than normal on CMR or angiography, whether they were revascularised or not. In contrast, for SPECT event

rates were higher for patients with a normal result who were revascularised than for those who were not revascularised (Table 3).

Prediction of MACE

In the univariable analysis both abnormal CMR and abnormal SPECT significantly predicted time to MACE at a minimum of 5 years follow-up (hazard ratio (HR)=2.77, 95%CI 1.85-4.16, p<0.0001; HR 1.62, 95%CI 1.10-2.38, p=0.014 respectively). As expected significant stenosis on the reference standard angiogram also significantly predicted time to MACE (HR 2.64, 95%CI 1.79-3.91, p<0.0001). Figure 2 shows the difference in the Kaplan Meier curves by baseline CMR, SPECT or angiography result.

In multivariable analysis only CMR remained significantly associated with time to MACE after adjustment for the pre-defined major cardiovascular risk factors (HR 2.34, 95%CI 1.51-3.63, p=0.0001) with the CMR model better explaining variation in the time to MACE than the SPECT model (difference in Akike Information Criteria=13.52 and 0.68 for SPECT) (Table 4). CMR also remained a significant predictor of MACE after adding the angiography result to the multivariable models (HR 1.81, 95%CI 1.05-3.14, p=0.03) (Appendices A and B) and when the multivariable analysis was stratified by initial treament (HR 2.8, 95%CI 1.74-4.5, p<0.0001), whereas SPECT did not (Appendices C and D). CMR better explained the variation in the models in all cases. Adjustment for the Genders Risk Score made little diference to the models (Appendices E and F).

When we compared the additional value of adding CMR to a model containing SPECT and the predefined cardiovascular risk factors, and the additional value of adding SPECT to a model containing CMR, then only CMR added additional value (CMR likelihood ratio chi-squared=12.232, p=0.0003, SPECT likelihod ratio chi-squared=0.007, p=0.93). The multivariate model with CMR explained more of the variation than SPECT (difference in Akike

Information Criteria=10.85 for CMR and 1.99 for SPECT).

Discussion

The primary analysis of CE-MARC has shown that in a large unselected patient population with suspected angina, both CMR and SPECT have a high diagnostic accuracy for detection of significant CHD (5). The current pre-planned long-term outcome analysis from CE-MARC represents the first comparison of prospective prognostic data for CMR and SPECT in the same patient population, and has shown that, a) at a minimum of 5 year follow-up both abnormal CMR and SPECT are strong independent predictors of MACE, with CMR better explaining the variation in time to MACE than SPECT; b) only CMR significantly adds to prediction of time to MACE over and above major cardiovascular risk factors, the angiographic findings or the effect of initial treatment, with CMR better explaining the variation in time to MACE than SPECT. These findings demonstrate that CMR is a robust alternative to SPECT in predicting patient outcome and adds further weight to the growing evidence base for CMR in the diagnosis and management of patients with suspected CHD.

The prognostic SPECT results from CE-MARC are in line with numerous previous SPECT studies (12-20). SPECT myocardial perfusion imaging has independent and incremental prognostic value after considering both clinical and physiological stress (exercise) variables. In particular, a normal SPECT scan is associated with a very low risk for future cardiac events (12-16,21), whereas an abnormal scan result is associated with an intermediate to high risk for future cardiac events, depending on the degree of the abnormality (13,14,17-20). Furthermore, SPECT can be used to guide clinical management by identifying patients with the greatest potential survival benefit from coronary revascularization (22). Although the evidence base is much smaller, CMR has also been shown to have prognostic value in

patients with stable CHD. For example, myocardial ischemia detected by CMR stress perfusion or dobutamine stress CMR can identify patients at high risk for subsequent cardiac death and nonfatal myocardial infarction (23-25). In addition, myocardial scar detected by LGE CMR provides strong and complementary prognostic information and the presence of LGE in patients without an inducible perfusion abnormality is associated with a >11-fold hazards ratio increase in hard cardiovascular events (25). Recently, the first systematic review and meta-analysis of CMR prognosis studies has shown that CMR can provide excellent prognostic stratification of patients with known or suspected coronary artery disease, comparable to published SPECT data (26).

It is important to note however that the previously published large SPECT studies were retrospectively designed and were heterogeneous for population, perfusion tracer and scanning protocol. Similarly, all previous CMR outcome studies have had a retrospective design and have evaluated ischemia and scar separately. CE-MARC is the first large-scale prospective study to provide prognostic data for both multi-parametric CMR and SPECT from the same unselected patient population. All patients with suspected angina enrolled in CE-MARC were prospectively scheduled for CMR, SPECT, and X-ray angiography (irrespective of the non-invasive imaging results) at the time of recruitment, in order to minimize selection bias. It is also important to note that almost 100% of patients were successfully followed-up for at least 5 years. These design characteristics make CE-MARC a powerful resource to determine the relative prognostic value of CMR and SPECT in the setting of suspected stable CHD.

In CE-MARC, normal findings by either CMR or SPECT were associated with a very low annual rate of hard cardiovascular events, which is in line with previous SPECT studies (17,27) and comparable to that of the general population in industrialized countries. The difference in

the prediction of risk seen within this study is likely a reflection of the higher diagnostic accuracy of CMR compared with SPECT in detecting both ischemia and scar. For ischemia detection, a recent meta-analysis directly comparing both modalities showed a significantly higher diagnostic performance of CMR versus SPECT (28), in line with results from the larger studies MR-IMPACT II (29) and CE-MARC (4). For the detection of scar, CMR and SPECT have shown similar rates of detection of transmural myocardial infarction, but due to superior spatial resolution, CMR detects sub-endocardial infarction that is commonly missed by SPECT (30). Importantly, sub-endocardial infarction is known to have incremental prognostic value beyond common clinical, angiographic and functional predictors (31). CE-MARC has thus shown that the higher diagnostic accuracy of a combined CMR assessment of ventricular function, perfusion and scar compared with a similar SPECT assessment translates into a superior prognostic performance of CMR in patients with suspected CHD.

Limitations

The limitations CE-MARC have been reported previously and include the single-centre design, albeit conducted in a high-volume institution for both CMR and SPECT (4). Any extrapolation to low volume centres should be made with caution. However, a single site and unified pharmacological stress protocol ensured consistency in CMR and SPECT and improved direct comparison between the modalities. We did not use computed tomography (CT) correction for SPECT attenuation artefacts, which is an important issue in nuclear myocardial perfusion imaging, as these artefacts are known to lead to false-positive perfusion defects (8). However, CT attenuation correction was not standard in most nuclear institutions worldwide at time of recruitment and its use remains controversial (32,33). We integrated the findings from gated-SPECT to differentiate real perfusion defects from artefacts (34) which has been shown to improve the prognostic value of SPECT (13), as per the European and American guidelines

for nuclear cardiology (35,36). A larger study or longer follow-up may have demonstrated that SPECT was also an independent predictor in the multivariable model. Finally, this was an observational study of both modalities in the same patient population, rather than a randomised trial of each modality showing their direct impact on outcomes. This means that direct statistical comparison of SPECT and CMR cannot be undertaken. In addition since CMR, SPECT and angiography results are highly correlated cautious interpretation of the multivariable models that include angiography is required.

Conclusions: Five-year follow-up of CE-MARC demonstrates that compared to SPECT, CMR was a stronger predictor of risk of MACE, independent of clinical cardiovascular risk factors, angiography result or initial patient treatment. This further supports the role of CMR as an alternative to SPECT for the diagnosis and management of patients with suspected CHD.

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Author Contributions: JPG: planned study, collected data, analysed data, interpreted the results and wrote the first draft of the manuscript. BAH: analysed data and interpreted the results. JMB: planned the study, provided statistical oversight, analysed the data interpreted the results and drafted the manuscript. CCE: provided statistical analysis and interpreted the results. JN: planned the study, analysed the data and interpreted the results. PB: collected and analysed the data. NM: collected and analysed the data. MM: analysed data and interpreted the results. CJD: planned the study, collected data, analysed data and interpreted the results. SGB: planned the study, analysed data and interpreted the results. SP: planned the study, collected data, analysed data and interpreted the results. JMB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in manuscript revision and agree to its submission.

Declaration of interest: All authors have no conflicts of interest.

Reproducible Research Statement:

Protocol: available on request from Professor Greenwood (j.greenwood@leeds.ac.uk)

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Data: not available

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449 **Figure 1. Study profile**
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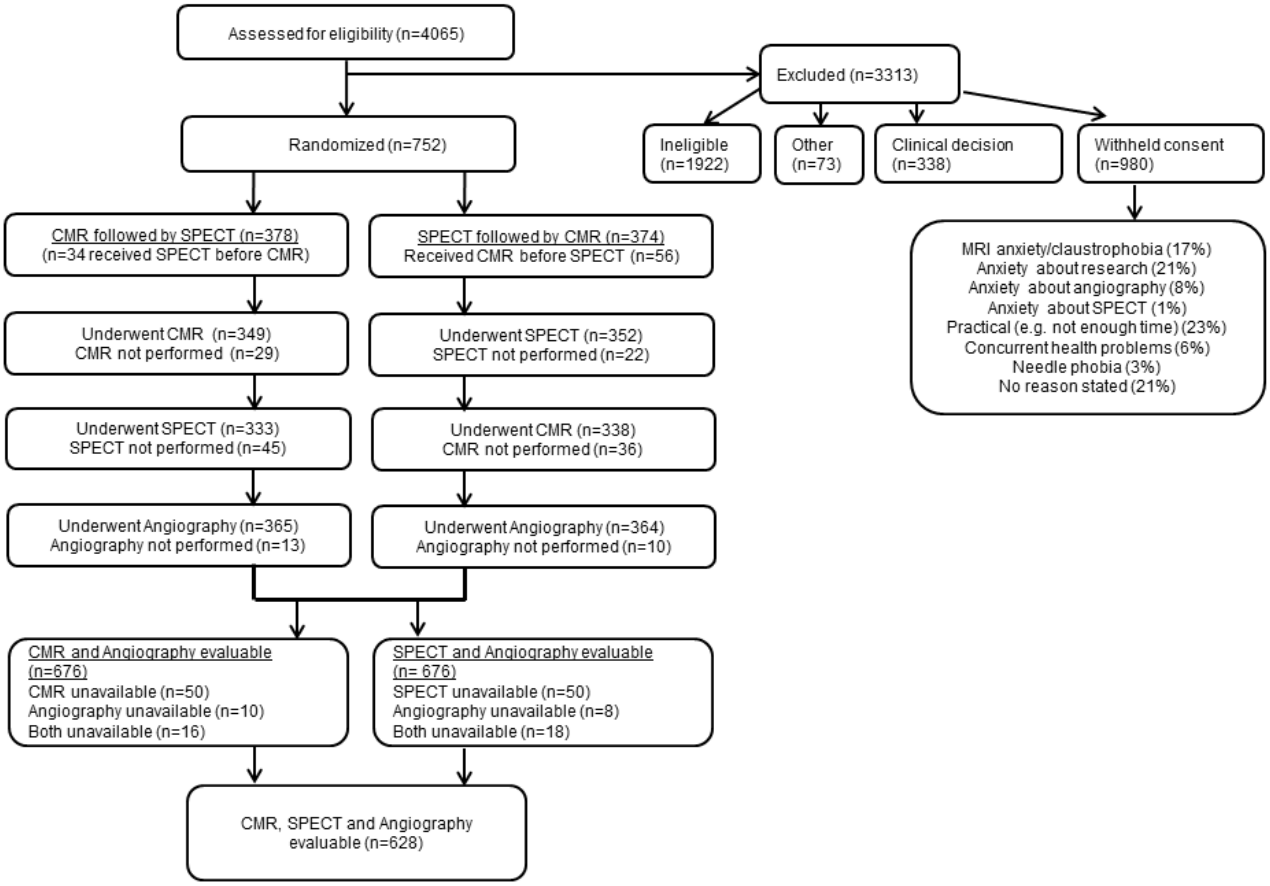

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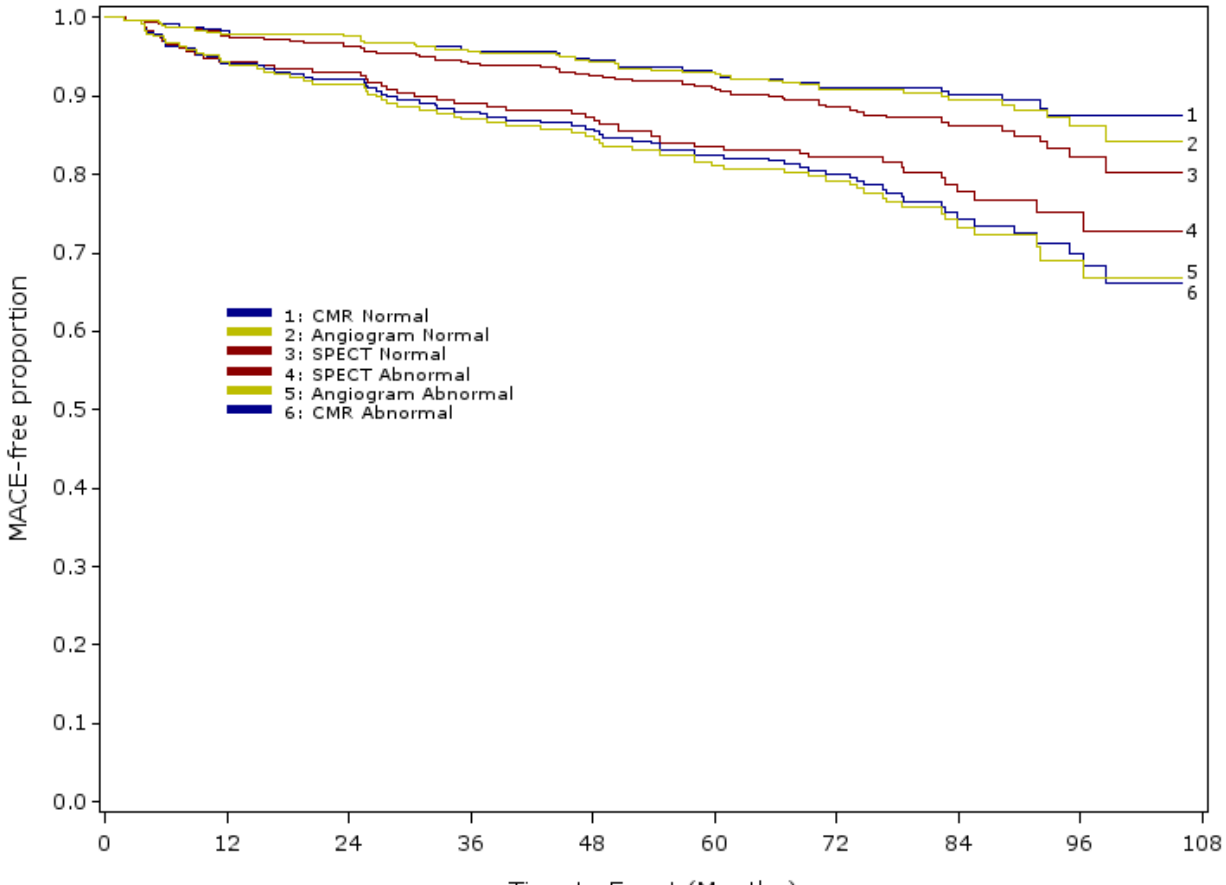
Figure 2. Kaplan-Meier event curves for MACE by modality (CMR and SPECT)



Numbers at Risk									
CMR Normal	350	342	338	327	322	316	255	169	50
CMR Abnormal	278	262	253	238	230	220	182	94	45
SPECT Normal	397	387	380	366	359	351	281	177	63
SPECT Abnormal	231	217	211	199	193	185	156	86	32
Angiogram Normal	380	370	367	356	351	344	281	184	64
Angiogram Abnormal	248	234	224	209	201	192	156	79	31

Table 1. Baseline characteristics

	All randomized patients (n=752)	CMR,SPECT and Angiography assessable (n=628)
Age	**60.2 (9.7)**	**60.4 (9.5)**
Male	**471 (63%)**	**393 (63%)**
Body Mass Index (kg/m^2)	**29.2 (4.4)**	**29.0 (4.3)**
Ethnic Origin		
Caucasian	**711 (95%)**	**597 (95%)**
Black	**6 (1%)**	**4 (1%)**
Asian	**30 (4%)**	**23 (4%)**
Other	**5 (1%)**	**4 (1%)**
Smoking Status		
Never smoked	**257 (34%)**	**224 (36%)**
Ex-smoker	**350 (47%)**	**294 (47%)**
Current smoker	**145 (19%)**	**110 (18%)**
Systolic Blood Pressure (mmHg)	**137.9 (20.7)**	**137.7 (21.0)**
Diastolic Blood Pressure (mmHg)	**79.0 (11.3)**	**78.8 (11.3)**
Previous admission for AMI or ACS	**60 (8%)**	**52 (8%)**
Previous PCI	**38 (5%)**	**35 (6%)**
Hypertension	**394 (52%)**	**314 (50%)**
Diabetes mellitus	**96 (13%)**	**83 (13%)**
Type 1	**4 (4%)**	**4 (5%)**
Type 2	**92 (96%)**	**79 (95%)**
Family history of premature heart disease		
Yes	**430 (57%)**	**365 (58%)**
No	**268 (36%)**	**217 (35%)**
Unknown	**54 (7%)**	**46 (7%)**
Total Cholesterol (mmol/L)	**5.2 (1.2)**	**5.2 (1.2)**
Simplified Framingham Risk Score*	**13.7 (3.6; n=692)**	**13.6 (3.6; n=576)**
Medication		
Aspirin or Clopidogrel	**454 (60%)**	**373 (59%)**
Statin	**336 (49%)**	**280 (45%)**
ACEi or A2 receptor blockers	**258 (38%)**	**208 (33%)**
β-blocker	**235 (34%)**	**186 (30%)**
Patients undergoing x-ray angiography†	**n=726**	**n=628**
Any significant stenosis	**282 (39%)**	**248 (39%)**
Triple vessel disease	**45 (6%)**	**37 (6%)**
Double vessel disease	**88 (12%)**	**80 (13%)**

Single vessel disease	**149 (21%)**	**131 (21%)**
LMS disease	**23 (3%)**	**21 (3%)**
LAD disease	**183 (25%)**	**158 (25%)**
LCx disease	**133 (18%)**	**120 (19%)**
RCA disease	**110 (15%)**	**93 (15%)**

Data are mean (SD) or n (%) unless otherwise stated. *Percentage risk of an event in the absence of chest pain over 10 years; patients with previous coronary heart disease had no risk score calculated; those older than age 75 years were assumed to be 75 years (37). †Numbers of patients undergoing x-ray angiography includes those with completed or partly completed non-invasive test results. AMI=acute myocardial infarction. ACS=acute coronary syndrome. PCI=percutaneous coronary intervention. ACEi=angiotensin converting enzyme inhibitor. LMS=left main stem. LAD=left anterior descending. LCx=left circumflex. RCA=right coronary artery.

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Table 2.

A) Total events at minimum 5 years

	All randomized patients (n=752)	CMR and SPECT assessable (n=628)
MACE (total)	**216**	**171**
Cardiovascular death	**12**	**7**
ST elevation myocardial infarction	**7**	**5**
ACS - troponin positive	**24**	**21**
ACS - troponin negative	**15**	**11**
Unscheduled revascularization	**54**	**43**
Hospitalization for any other CV cause	**104**	**84**
Stroke / TIA	**46**	**31**
Heart failure	**10**	**7**
Arrhythmia	**48**	**46**

B) First adjudicated event per-patient only at 5 years

MACE (total)	**132 (17.8%)**	**104 (16.6%)**
Cardiovascular death	**8 (1.1%)**	**5 (0.8%)**
ST elevation myocardial infarction	**5 (0.7%)**	**3 (0.5%)**
ACS - troponin positive	**20 (2.7%)**	**17 (2.7%)**
ACS - troponin negative	**12 (1.6%)**	**9 (1.4%)**
Unscheduled revascularization	**32 (4.3%)**	**27 (4.3%)**
Hospitalization for any other CV cause	**55 (7.3%)**	**43 (6.8%)**
Stroke / TIA	**32 (4.3%)**	**25 (4.0%)**
Heart failure	**7 (0.9%)**	**3 (0.5%)**
Arrhythmia	**16 (2.2%)**	**15 (2.4%)**

Data are n (%). MACE=major adverse cardiovascular event; ACS=acute coronary syndrome; CV=cardiovascular; TIA=transient ischaemic attack.

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Table 3. Summary of Number of Patients with each Combination of Test Results, Initial Treatment and Numbers Experiencing MACE

MRI Result	SPECT Result	Any significant angiographic stenosis	Planned Revascularisation	Numbers (%)	No (%) Experiencing 1 or more MACE
Positive	Positive	Yes	Yes	119 / 151 (78.8%)	21 / 119 (17.6%)
Positive	Positive	Yes	No	32 / 151 (21.2%)	14 / 32 (43.8%)
Positive	Positive	No	Yes	1 / 20 (5.0%)	0 / 1 (0.0%)
Positive	Positive	No	No	19 / 20 (95.0%)	6 / 19 (31.6%)
Positive	Negative	Yes	Yes	44 / 63 (69.8%)	12 / 44 (27.3%)
Positive	Negative	Yes	No	19 / 63 (30.2%)	10 / 19 (52.6%)
Positive	Negative	No	Yes	3 / 44 (6.8%)	1 / 3 (33.3%)
Positive	Negative	No	No	41 / 44 (93.2%)	6 / 41 (14.6%)
Negative	Positive	Yes	Yes	9 / 14 (64.3%)	1 / 9 (11.1%)
Negative	Positive	Yes	No	5 / 14 (35.7%)	1 / 5 (20.0%)
Negative	Positive	No	Yes	1 / 46 (2.2%)	0 / 1 (0.0%)
Negative	Positive	No	No	45 / 46 (97.8%)	6 / 45 (13.3%)
Negative	Negative	Yes	Yes	15 / 20 (75.0%)	2 / 15 (13.3%)
Negative	Negative	Yes	No	5 / 20 (25.0%)	2 / 5 (40.0%)
Negative	Negative	No	Yes	6 / 270 (2.2%)	1 / 6 (16.7%)
Negative	Negative	No	No	264 / 270 (97.8%)	22 / 264 (8.3%)

Table 4.

A) CMR - predictors of MACE by multivariable analysis

Predictors	Hazard Ratio	95% confidence interval	P value
Abnormal CMR	2.3	[1.5, 3.6]	**0.0001**
Age	1.0	[1.0, 1.1]	**0.0005**
Male gender	1.1	[0.71, 1.7]	0.65
Diabetes mellitus	1.1	[0.65, 2.0]	0.68
Current smoker	1.2	[0.67, 2.0]	0.59
Total cholesterol	0.99	[0.83, 1.2]	0.88
Hypertension	1.0	[0.70, 1.5]	0.85
Family history	0.86	[0.57, 1.3]	0.45

B) SPECT - predictors of MACE by multivariable analyses

Predictors	Hazard Ratio	95% confidence interval	P value
Abnormal SPECT	1.41	[0.94, 2.1]	0.10
Age	1.1	[1.0, 1.1]	**<0.0001**
Male gender	1.2	[0.79, 1.9]	0.37
Diabetes mellitus	1.2	[0.71, 2.1]	0.48
Current smoker	1.2	[0.7, 2.1]	0.48
Total cholesterol	1.0	[0.84, 1.2]	0.97
Hypertension	1.1	[0.72, 1.6]	0.73
Family history	0.95	[0.63, 1.4]	0.81

CMR=cardiovascular magnetic resonance; SPECT=single photon emission computed tomography

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Appendices

A) CMR - predictors of MACE by multivariable analysis including angiography result

Predictors	Hazard Ratio	95% confidence interval	P value
Abnormal CMR	1,8	[1.0, 3.1]	**0.033**
Significant stenosis	1.5	[0.9, 2.6]	0.12
Age	1,0	[1.0,1.1]	**0.0007**
Male gender	1.0	[0.64, 1.6]	0.96
Diabetes mellitus	0.095	[0.63, 1.9]	0.74
Current smoker	1.2	[0.66, 2.0]	0.62
Total cholesterol	0.97	[0.82, 1.2]	0.75
Hypertension	1.1	[0.71, 1.6]	0.79
Family history	0.86	[0.57, 1.3]	0.48

CMR=cardiovascular magnetic resonance

B) SPECT - predictors of MACE by multivariable analyses including angiography result

Predictors	Hazard Ratio	95% confidence interval	P value
Abnormal SPECT	0.96	[0.6, 1.52]	0.85
Significant stenosis	2.2	[1.4, 3.6]	**0.0011**
Age	1.1	[1.0,1.1]	**0.0002**
Male gender	1.0	[0.65, 1.6]	0.92
Diabetes mellitus	1.1	[0.66, 2.0]	0.63
Current smoker	1.2	[0.7, 2.1]	0.56
Total cholesterol	0.97	[0.81, 1.2]	0.71
Hypertension	1.1	[0.72, 1.6]	0.75
Family history	0.90	[0.60, 1.4]	0.62

SPECT=single photon emission computed tomography

C) CMR - predictors of MACE by multivariable analysis stratified by initial treatment

Predictors	Hazard Ratio	95% confidence interval	P value
Abnormal CMR	2.8	[1.7, 4.5]	**<0.0001**
Age	1.0	[1.0, 1.1]	**0.0005**
Male gender	1.2	[0.75, 1.8]	0.49
Diabetes mellitus	1.2	[0.67, 2.0]	0.61
Current smoker	1.1	[0.65, 2.0]	0.63
Total cholesterol	1.0	[0.84, 1.2]	0.99
Hypertension	1.0	[0.68, 1.5]	0.94
Family history	0.87	[0.58, 1.3]	0.49

CMR=cardiovascular magnetic resonance

D) SPECT - predictors of MACE by multivariable analyses stratified by initial treatment

Predictors	Hazard Ratio	95% confidence interval	P value
Abnormal SPECT	1.44	[0.93, 2.2]	0.1
Age	1.1	[1.0, 1.1]	**<0.0001**
Male gender	1.2	[0.79, 1.9]	0.36
Diabetes mellitus	1.2	[0.71, 2.1]	0.51
Current smoker	1.2	[0.7, 2.1]	0.47
Total cholesterol	1.0	[0.84, 1.2]	0.98
Hypertension	1.1	[0.72, 1.6]	0.73
Family history	0.96	[0.64, 1.4]	0.83

SPECT=single photon emission computed tomography

E) CMR - predictors of MACE by multivariable analysis

Predictors	Hazard Ratio	95% confidence interval	P value
Abnormal CMR	2.3	[1.5, 3.5]	**0.0002**
Genders Score*	1.0	[1.0,1.0]	**0.016**

CMR=cardiovascular magnetic resonance. *Genders score: Hazard ratio given for each percentage point increase in predicted Pre-test likelihood.

F) SPECT - predictors of MACE by multivariable analyses

Predictors	Hazard Ratio	95% confidence interval	P value
Abnormal SPECT	1.3	[0.8, 1.9]	0.1
Genders score*	1.0	[1.0,1.0]	**0.0007**

SPECT=single photon emission computed tomography. *Genders score: Hazard ratio given for each percentage point increase in predicted Pre-test likelihood.

Full mailing addresses of all authors:

John P. Greenwood, Manish Motwani, Stephen G. Ball, Sven Plein,
Multidisciplinary Cardiovascular Research Centre & the Division of Biomedical Imaging,
Leeds Institute of Cardiovascular & Metabolic Medicine,
University of Leeds,
LIGHT Building,
Clarendon Way,
Leeds, LS2 9JT, United Kingdom

Bernhard A. Herzog,
Heart Clinic Lucerne
St. Anna-Strasse 32
6006 Lucerne
Switzerland

Julia M. Brown, Colin C. Everett, Jane Nixon,
Clinical Trials Research Unit,
Leeds Institute of Clinical Trials Research,
University of Leeds,
Clarendon Road,
Leeds, LS2 9JT, United Kingdom

Petra Bijsterveld, Catherine J. Dickinson,
Department of Cardiology,
Old X39, Main Site,
Leeds General Infirmary,
Great George Street,
Leeds, LS1 3EX, United Kingdom

Neil Maredia,
Consultant Cardiologist,
James Cook University Hospital,
Marton Road,
Middlesbrough,
TS4 3BW, UK