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Randomised trial of stable chest pain investigation: 3-year clinical and quality of life results from CE-MARC 2

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ABSTRACT

Aims Guidelines for suspected cardiac chest pain have used historical risk stratification tools, advocating invasive coronary angiography (ICA) first-line in those at highest risk. We aimed to determine whether different strategies to manage suspected stable angina affected medium-term cardiovascular event rates and patient-reported quality of life (QoL) measures.

Methods CE-MARC 2, a three-arm parallel group trial, randomised patients with suspected stable cardiac chest pain and a Duke Clinical pretest likelihood of coronary artery disease between 10% and 90%. Patients were randomised to either first-line cardiovascular magnetic resonance (CMR), single-photon emission computed tomography (SPECT) or the UK National Institute for Health and Care Excellence (NICE) CG95 (2010) guidelines-directed care. For the three arms, 1-year and 3-year first major adverse cardiovascular event (MACE) rates and QoL assessed by the Seattle Angina Questionnaire, Short Form 12 (V.12) Questionnaire and EuroQol-5 Dimension Questionnaire were recorded.

Results 1202 patients were randomised to CMR (n=481), SPECT (n=481) and NICE (n=240). Forty-two patients (18 CMR, 18 SPECT, 6 NICE) experienced one or more MACEs. The percentage rates (95% CIs) of MACE in the CMR, SPECT and NICE groups at 3 years were 3.7% (2.4%, 5.8%), 3.7% (2.4%, 5.8%) and 2.1% (0.9%, 4.8%), respectively. QoL scores did not significantly differ across domains.

Conclusion Despite a fourfold increase in referrals for ICA, the NICE CG95 (2010) guidelines risk-stratified care strategy did not significantly reduce 3-year MACE or improve QoL, as compared with functional imaging with CMR or SPECT.

Trial registration number ClinicalTrials.gov Registry (NCT01664858).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ UK national guidelines on managing patients with stable chest pain (2010, CG95) recommended a risk-stratified management approach. However, if the risk model does not fit the local contemporary population, too many needless interventions (or too few necessary ones) may be produced, without any consequent downstream benefits in terms of quality of life or events avoided.

WHAT THIS STUDY ADDS

⇒ Management by stress cardiovascular magnetic resonance (CMR) or single photon emission computed tomography (SPECT) as a first-line investigation resulted in fewer invasive angiograms within 12 months of randomisation than management following National Institute for Health and Care Excellence (NICE) guidelines CG95 (2010). Despite fewer angiograms, there was no significant difference in subsequent cardiovascular events at 3 years' follow-up, and while some differences in quality of life domains were observed, the effects were small.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Compared with NICE CG95 (2010), functional imaging first-line by CMR or SPECT resulted in significantly less-invasive procedures, but with no penalty in terms of 3-year major adverse cardiovascular event or quality of life outcome measures. The lack of difference in outcomes between CMR and SPECT suggests that a choice may be made between the two based on availability, cost, patient preference and shared decision-making.

BACKGROUND

Coronary artery disease (CAD) is a leading cause of death and disability worldwide. In secondary care, several non-invasive imaging tests are available to determine whether stable angina is due to obstructive CAD, which include CT coronary angiography (CTCA), myocardial perfusion scintigraphy by single-photon emission computed tomography (SPECT) and cardiovascular magnetic resonance (CMR).

In 2010, UK national guidelines on managing patients with stable chest pain

recommended risk-stratified management.[1] Using the Duke clinical risk score,[2] participants with a pretest likelihood (PTL) of CAD of 10%–29% or 30%–60% were, respectively, recommended CTCA or functional imaging to decide the need for invasive coronary angiography (ICA). Those with PTL 61%–90% were recommended first-line ICA. This final aspect raised concerns, that already high rates of ICA would be increased further, since in contemporary practice, the Duke clinical risk score has been shown to overestimate CAD prevalence.[3]

The CE-MARC 2 trial[4] showed that patient management by a uniform strategy of first-line CMR or SPECT resulted in fourfold fewer ICA procedures where no obstructive disease was evident, compared with the standard care strategy of National Institute for Health and Care Excellence (NICE) CG95 (2010)-based management, with no significant differences in major adverse cardiovascular event (MACE) rates after 1 year of follow-up.[5] Prespecified secondary analyses of the trial were patient-reported quality of life (QoL) measures and medium-term cardiovascular outcomes at 3 years, which are reported here.

METHODS

Trial design

CE-MARC 2 was a three-arm, parallel-group, multicentre, randomised, superiority trial of three distinct patient management strategies, the design of which has been previously published.[4 5]

Patient and public involvement

Patient and public advisors were involved prior to the funding application in setting the trial research question, study design and outcome measures. They were also members of the trial management group and oversaw all aspects of trial delivery, and specifically reviewed all patient-facing trial documents.

Participants

Patients were recruited from six UK secondary care rapid access chest pain clinics. After completing the baseline assessments, PTL of CAD based on the Duke clinical risk score was calculated to confirm eligibility, and to allow stratification.[3] In brief, patients were eligible if they were aged ≥30 years, had stable suspected angina requiring further assessment, a defined Duke clinical PTL of CAD between 10% and 90%, were suitable for revascularisation if required and provided written informed consent. Exclusion criteria included non-anginal chest pain, a normal SPECT or CTCA result within the previous 2 years, being clinically unstable, previous myocardial infarction (MI), previous coronary revascularisation and contraindication to any study non-invasive imaging test.

Interventions

Patients were randomised by minimisation (with age, sex, PTL category and recruiting site as balancing factors and a random element based on computer-generated random numbers) in a 2:2:1 ratio between CMR:SPECT:CG95 (2010)-directed care.[6]

a. Patients randomised to CMR-guided care were scheduled for a CMR scan comprising left ventricle function, adenosine stress and rest perfusion imaging and late-gadolinium enhancement. Referral for ICA was indicated by an inconclusive or abnormal finding (two or more adjacent segments with 50% or more transmural extent of ischaemia, scar or ischaemia–scar combination) or where a normal finding was over-ruled by the treating clinician.[5]
b. Patients randomised to SPECT-guided care were scheduled for SPECT imaging, comprising stress and rest studies carried out ideally within 5 days, using radioisotope traces 99mTc tetrofosmin/sestamibi, with stress imaging either by adenosine or using exercise. Referral for ICA was indicated by an inconclusive or abnormal finding (summed stress score ≥4), or where a normal finding was over-ruled by the treating clinician.[5]
c. Standard care—following contemporary UK guidelines for chest pain of recent onset (CG95, 2010),[1] participants were directed to one of three investigations, depending on the PTL of CAD calculated by site at baseline. Those with a calculated PTL of 61%–90% were directed to ICA. A PTL of 30%–60% led to a scheduled SPECT, in line with recommendations for functional cardiac imaging as a first-line test. A PTL of 10%–29% resulted in referral for CTCA, as per guidelines, where coronary artery calcium (CAC) scoring indicated one of either no further action (CAC score of 0), CTCA (CAC scores of 1–400) or referral for ICA (CAC scores over 400). Where CTCA was performed, a positive finding was any lesion of ≥50% in an epicardial coronary artery ≥2.5 mm in diameter. Referral for ICA was indicated by abnormal or inconclusive CTCA/SPECT findings, or normal findings over-ruled by the treating clinician.

Outcome measures

The primary outcome measure was rates of ICA with no evidence of obstructive disease and has been published, along with the secondary outcome measure of rates of positive angiography and MACE within 12 months.[5] MACE was defined as any cardiovascular death, non-fatal MI, unplanned revascularisation and hospitalisation for cardiovascular cause (acute coronary syndrome troponin negative, MI (types 1, 2, 4b), arrhythmia, stroke, heart failure; MI defined according to the third universal definition).[7] An additional post-hoc clinical outcome measure of 'hard event' rate was defined as the time until first of cardiovascular death or MI.

Patient-reported QoL was measured using the Seattle Angina Questionnaire (SAQ) UK English, the Short Form 12 (V.12) Questionnaire (SF12v2), and the EuroQol 5-Dimension Questionnaire, 3 and 5 Levels (EQ-5D-3L and 5L), at randomisation, 6 months, 1 year, 2 years and 3 years; the validity and reliability of the 19-item SAQ,

Table 1 Patient characteristics and QoL scale scores at randomisation

	CMR-guided care (n=481)	SPECT-guided care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Patient age (years), mean (SD)	56.5 (9.10)	55.9 (8.87)	56.5 (9.21)	56.3 (9.03)
Male	254 (52.8%)	256 (53.2%)	128 (53.3%)	638 (53.1%)
White	443 (92.1%)	443 (92.1%)	221 (92.1%)	1107 (92.1%)
Current smoker	123 (25.6%)	106 (22.0%)	65 (27.1%)	294 (24.5%)
Diabetic: type II	48 (10.0%)	64 (13.3%)	21 (8.8%)	133 (11.1%)
Hypertension	177 (36.8%)	182 (37.8%)	99 (41.3%)	458 (38.1%)
Family history of premature CHD	252 (52.4%)	259 (53.8%)	140 (58.3%)	651 (54.2%)
Body mass index, mean (SD)	29.2 (5.36)	29.1 (5.12)	29.0 (5.24)	29.1 (5.23)
Duke clinical PTL category (as randomised)				
10%–29%	128 (26.6%)	125 (26.0%)	61 (25.4%)	314 (26.1%)
30%–60%	179 (37.2%)	183 (38.0%)	88 (36.7%)	450 (37.4%)
61%–90%	174 (36.2%)	173 (36.0%)	91 (37.9%)	438 (36.4%)
Duke clinical PTL % (as analysed), mean (SD)	49.9 (24.25)	48.6 (23.57)	50.7 (23.28)	49.5 (23.78)
Baseline medication use				
Beta-blockers	150 (31.2%)	157 (32.6%)	74 (30.8%)	381 (31.7%)
Statins or other lipid-lowering medications	191 (39.7%)	201 (41.8%)	108 (45.0%)	500 (41.6%)
ACE inhibitor or angiotensin II receptor blocker	115 (23.9%)	122 (25.4%)	66 (27.5%)	303 (25.2%)
Antiplatelet agents	271 (56.3%)	268 (55.7%)	150 (62.5%)	689 (57.3%)
Other antianginal agents	283 (58.8%)	276 (57.4%)	142 (59.2%)	701 (58.3%)
SAQ-UK Angina Frequency score*	70.0 (50.0–80.0)	70.0 (60.0–80.0)	70.0 (50.0–80.0)	70.0 (50.0–80.0)
SAQ-UK Angina Stability score*	50.0 (25.0–50.0)	50.0 (25.0–50.0)	50.0 (25.0–50.0)	50.0 (25.0–50.0)
SAQ-UK Physical Limitation score*	77.8 (58.3–91.7)	75.0 (58.3–88.9)	77.8 (55.6–88.9)	77.8 (58.3–91.7)
SAQ-UK Quality of Life score*	50.0 (41.7–66.7)	50.0 (41.7–66.7)	50.0 (33.3–66.7)	50.0 (37.5–66.7)
SAQ-UK Treatment Satisfaction score*	100.0 (81.3–100.0)	100.0 (81.3–100.0)	93.8 (81.3–100.0)	100.0 (81.3–100.0)
SF12v2 Bodily Pain score†	75.0 (50.0–75.0)	75.0 (50.0–75.0)	75.0 (50.0–75.0)	75.0 (50.0–75.0)
SF12v2 General Health score†	60.0 (25.0–60.0)	60.0 (25.0–60.0)	60.0 (25.0–60.0)	60.0 (25.0–60.0)
SF12v2 Mental Health score†	62.5 (50.0–75.0)	62.5 (50.0–75.0)	62.5 (50.0–75.0)	62.5 (50.0–75.0)
SF12v2 Physical Function score†	50.0 (50.0–91.1)	50.0 (45.0–75.0)	50.0 (50.0–75.0)	50.0 (50.0–75.0)
SF12v2 Role Emotional score†	87.5 (62.5–100.0)	87.5 (50.0–100.0)	75.0 (50.0–100.0)	87.5 (62.5–100.0)
SF12v2 Role Performance score†	62.5 (50.0–87.5)	62.5 (50.0–75.0)	62.5 (50.0–87.5)	62.5 (50.0–78.9)
SF12v2 Social Functioning score†	75.0 (50.0–100.0)	75.0 (50.0–100.0)	75.0 (50.0–100.0)	75.0 (50.0–100.0)
SF12v2 Vitality score†	50.0 (25.0–75.0)	50.0 (25.0–75.0)	50.0 (25.0–75.0)	50.0 (25.0–75.0)
SF12v2 Physical Component score†	45.2 (37.4–51.7)	44.6 (37.8–50.9)	43.9 (38.5–51.4)	44.6 (37.8– 51.4)
SF12v2 Mental Component score†	50.7 (43.3–57.3)	50.5 (41.6–56.8)	49.6 (40.8–56.7)	50.5 (41.9–56.9)
EQ-5D-3L Utility‡	0.796 (0.691–0.883)	0.760 (0.689–0.848)	0.743 (0.656–0.883)	0.760 (0.689–0.850)
EQ-5D-5L Utility‡	0.879 (0.778–0.937)	0.859 (0.777–0.937)	0.859 (0.733–0.937)	0.861 (0.777–0.937)

Values are n (%), except where mean (SD) are stated and for the SAQ-UK, SF12v2 and EQ-5D values, for which median (lower quartile–upper quartile) are given. Further baseline characteristics are given in Greenwood *et al*.[5]
*Baseline SAQ reported by 1187 (99%) of 1202 patients.
†Baseline SF12 reported by 1192 (99%) of 1202 patients.
‡ED-5D baseline reported by 1168 (97%) of 1202 patients.
CHD, coronary heart disease; CMR, cardiovascular magnetic resonance; EQ-5D, EuroQol-5 Dimension Questionnaire; NICE, National Institute for Health and Care Excellence; PTL, pretest likelihood; QoL, quality of life; SAQ, Seattle Angina Questionnaire; SF12v2, Short Form 12 (V.12) Questionnaire; SPECT, single-photon emission computed tomography.

Table 2 Summary of clinical outcomes

	CMR-guided care (n=481)	SPECT-guided care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Number of events (number of patients)	26 (18)	22 (18)	8 (6)	56 (42)
Total follow-up (patient-years to first MACE or last contact)	1396.8	1397.6	704.3	3498.7
Annualised first MACE rate (%/year, 95% CI)	1.29 (0.78 to 1.98)	1.29 (0.78 to 1.98)	0.85 (0.34 to 1.73)	1.20 (0.87 to 1.60)
MACE within 1 year, % (95% CI)	2.5 (1.4 to 4.4)	2.5 (1.4 to 4.4)	1.7 (0.6 to 4.4)	
Absolute difference (comparator—CMR, 95% CI)	–	0.0 (–2.0 to 2.0)	–0.8 (–3.0 to 1.3)	
MACE within 3 years, % (95% CI)	3.8 (2.4 to 5.9)	3.8 (2.4 to 5.9)	2.1 (0.9 to 5.0)	
Absolute difference (comparator—CMR, 95% CI)	–	0.0 (–2.4 to 2.4)	–1.7 (–4.2 to 0.8)	
'Hard event' within 1 year, % (95% CI)	0.6 (0.2 to 1.9)	0.4 (0.1 to 1.7)	0.8 (0.2 to 3.3)	
Absolute difference (comparator—CMR, 95% CI)	–	–0.2 (–1.1 to 0.7)	0.2 (–1.1 to 1.6)	
'Hard event' within 3 years, % (95% CI)	1.5 (0.7 to 3.1)	1.1 (0.4 to 2.5)	0.8 (0.2 to 3.3)	
Absolute difference (comparator—CMR, 95% CI)	–	–0.4 (–1.8 to 1.0)	–0.6 (–2.2 to 1.0)	
Frequency of individual MACE events				
Type 3 MI and CV death: MI*	–	1	–	1
CV death: MI*	–	1	1	2
CV death: pulmonary embolism*	–	1	–	1
CV death: stroke*	1	–	–	1
CV death: unknown*	–	1	–	1
Unplanned PCI	7	5	2	14
Unplanned CABG	1	–	–	1
Type 1 MI*	7	1	2	10
Type 2 MI*	–	2	–	2
Arrhythmia	6	3	2	11
Stroke/TIA	4	3	–	7
Heart failure	–	4	1	5
Non-MACE event				
Non-CV deaths	7	1	2	10
Previously published findings[5]				
Primary outcome: unnecessary angiography within 12 months, n (%)	36 (7.5)	34 (7.1)	69 (28.8)	139 (11.6)
Secondary outcome: positive angiography within 12 months, n (%)	47 (9.8)	42 (8.7)	29 (12.1)	118 (9.8)

*Denotes an event count as part of the post-hoc 'hard event' outcome measure, comprising CV death and non-fatal MI (excluding periprocedural MI due to PCI or CABG).
CABG, coronary artery bypass graft; CMR, cardiovascular magnetic resonance; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; PCI, percutaneous coronary intervention; SPECT, single-photon emission CT; TIA, transient ischaemic attack.

the SF12v2 and the EQ-5D have been previously demonstrated in cardiovascular studies (see online supplemental file 1 for details). Questionnaire scores were calculated according to scoring guidelines. For the SF12v2, we report the eight domain scales and two summary scores and the five domains of the SAQ.

Statistical methods

A sample size of 1200 patients provided at least 80% power for comparisons of the primary outcome measure.[4 5] Allowing for 20% loss to follow-up, 1200 patients allowed us to estimate differences in 3-year MACE rates with the following precisions:

(1) CMR versus NICE would provide an estimate within ±3.9%–5.7%, assuming CMR to be 4% points greater than for NICE and 3-year NICE rates between 3% and 9%. (2) CMR versus SPECT would provide an estimate within ±3.3%–4.7%, assuming 4%-point difference and baseline 3-year rate of 3%–9%. Recruiting at least 50% of trial participants to the QoL substudy provides over 90% power (two-sided

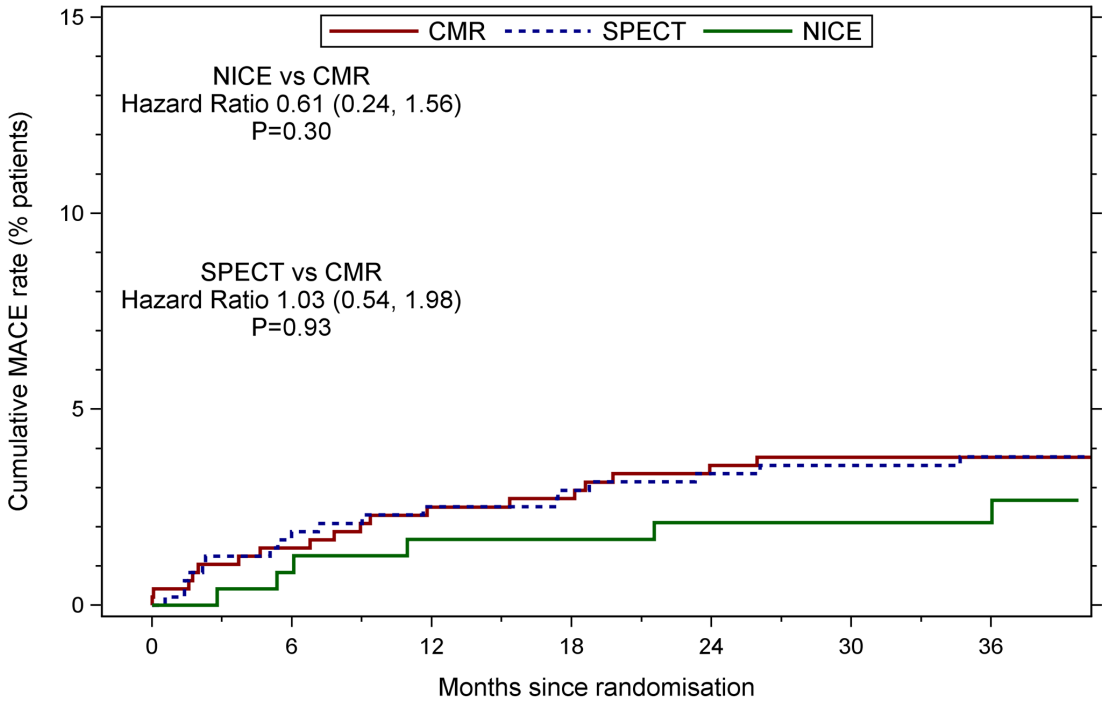

Figure 1 Kaplan-Meier estimates (with 95% CI) of time to first major adverse cardiovascular event (MACE) by arm. HRs are adjusted for randomising centre, sex, age category, pretest likelihood category, hypertension, smoking status and ethnicity (online supplemental appendix A). CMR, cardiovascular magnetic resonance; NICE, National Institute for Health and Care Excellence; SPECT, single-photon emission CT.

5% significance level) to detect a clinically relevant difference of 10 points in the SAQ with an SD of 30. There were no formal interim analyses and no criteria for early trial termination.

Analysis was by intention-to-treat principles and comparisons of interest were NICE CG95 (2010) versus CMR and SPECT versus CMR. Time to first MACE was estimated by the Kaplan-Meier method, reporting proportion of patients with MACE at 1 and 3 years and univariate HR. The adjusted HR of risk of first MACE was estimated using Cox proportional hazard regression, adjusting for the four minimisation factors and also hypertension, smoking status and ethnicity.

The primary analysis of each QoL domain of the SAQ, SF12v2 and EQ-5D utilities was on a complete case basis including only questionnaires received and scored. Analyses were mixed-effects linear regression models of each scale score over time including the four minimisation factors, with fixed effects for baseline scale value, randomised arm, time and arm–time interaction, and random effects for patient and patient-time. A number of sensitivity analyses were included: (1) a fixed effect for baseline–time interaction, to allow for patients with higher scores at baseline having different trajectories to those with worse (lower) baseline scores; (2) ordinal proportional odds regression model to model the odds of having higher scores at follow-up in single-item scales; (3) a repeated measures covariance pattern model, replacing the assumption of linear changes over time, with that of a common unstructured correlation structure within each patient. Complete case analysis assumes the distribution of any missing data is the same as the observed data. Sensitivity analysis based on linear regression of imputed data was performed using multiple imputation by chained equations,[8] 100 burn-in iterations with 60 fully imputed datasets (based on Fraction of Missing Information) created for each scale. Imputation was informed by minimisation factors and the following baseline variables: coronary artery bypass graft, percutaneous coronary intervention, angiogram, body mass index, vascular disease, cardiovascular disease, rheumatoid arthritis, beta-blocker use, statin, ACE inhibitor. No subgroup analyses were performed.

RESULTS

Between 23 November 2012 and 13 March 2015, 1202 participants were randomised to receive CMR-guided care (N=481), SPECT-guided care (N=481) or NICE CG95 (2010)-guided care (N=240). Over 97% of patients returned baseline QoL data. The flow of participants and their baseline clinical characteristics have been previously published.[5] Table 1 presents a summary of demographic characteristics and baseline QoL data. There were no differences in baseline

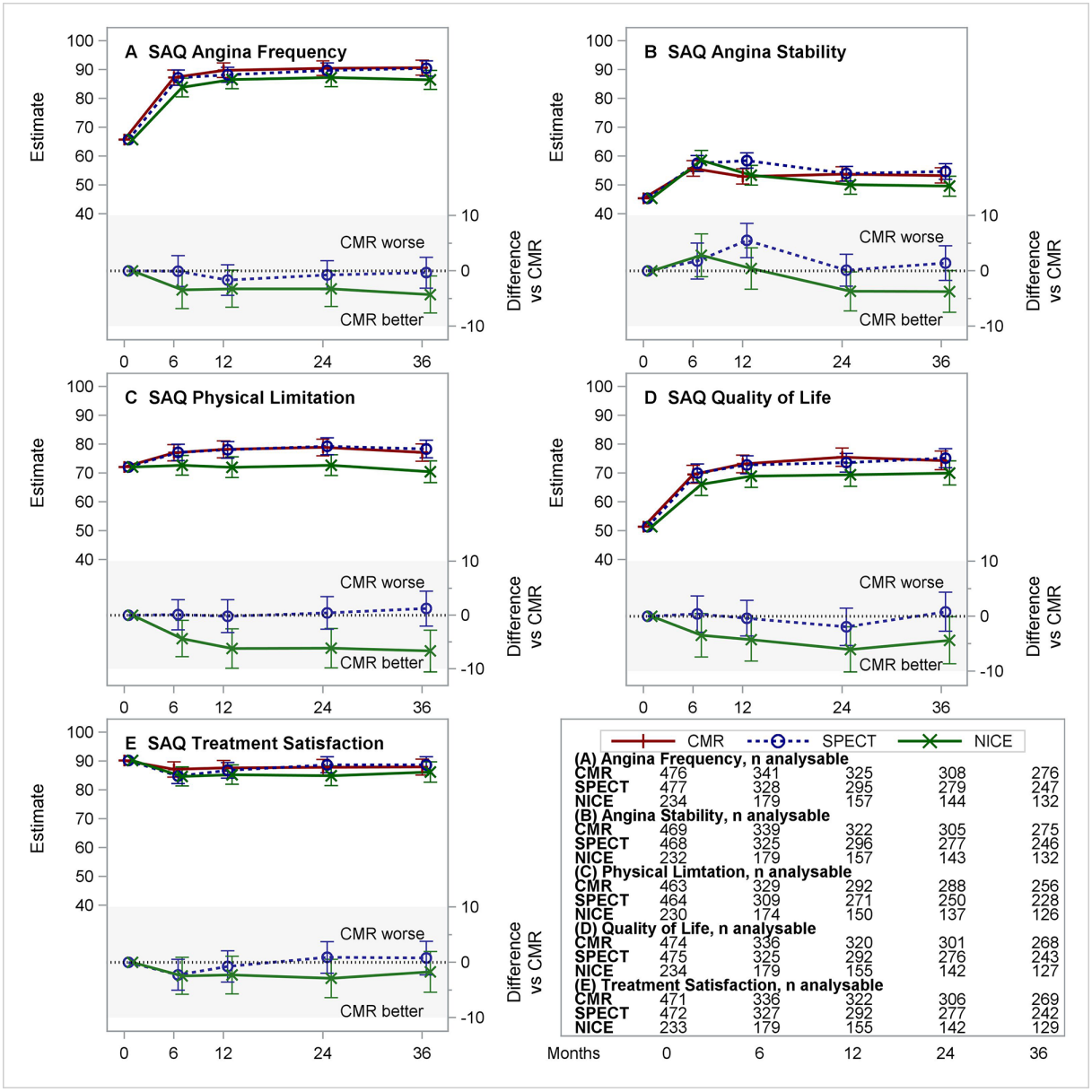

Figure 2 Estimated means for CMR, SPECT and NICE CG95 (2010) (and differences vs CMR) for the five domains of the SAQ. (A–E) Each panel presents the estimated least-squares means (with 95% CI) over time from repeated measures model for CMR, SPECT and NICE CG95 (2010)-based care (top section) and differences (with 95% CI) NICE–CMR and SPECT–CMR (lower section, shaded). Negative differences represent benefits for CMR versus comparator. Tables show the number of patients included from the complete case analysis. CMR, cardiovascular magnetic resonance; NICE, National Institute for Health and Care Excellence; SAQ, Seattle Angina Questionnaire; SPECT, single-photon emission CT.

medication usage across the three trial arms (table 1). At 12 months, only statin therapy showed a statistically significant difference/change, with greater usage in the NICE arm compared with the CMR and SPECT arms (proportional net change +12.5%, +5.4%, +4.4%, respectively; Breslow-Day X^2 7.053, p=0.029).

Clinical events

The annualised first MACE rate was low at 1.2% per year (table 2). Forty-two patients (18 CMR, 18 SPECT, 6 NICE) experienced 56 MACEs (26 CMR, 22 SPECT, 8 NICE). There was only a small absolute difference between the CMR and NICE arms in terms of 1-year and 3-year MACE, and no difference between the CMR and SPECT arms. The unadjusted HR of time to first MACE for NICE versus CMR was 0.66 (95% CI 0.26 to 1.67, p=0.38), and 1.00 (95% CI 0.52 to 1.92, p=1.00) for SPECT versus CMR. The adjusted HRs were similar to the unadjusted HRs (figure 1 and online supplemental appendix A). The 3-year 'hard event' rates were 1.5% (0.7% to 3.1%), 1.1% (0.4% to 2.5%) and 0.8% (0.2% to 3.3%) for CMR, SPECT and NICE, respectively.

Quality of life

Overall, 1168 (97%) of participants returned baseline questionnaire booklets at the point of randomisation.

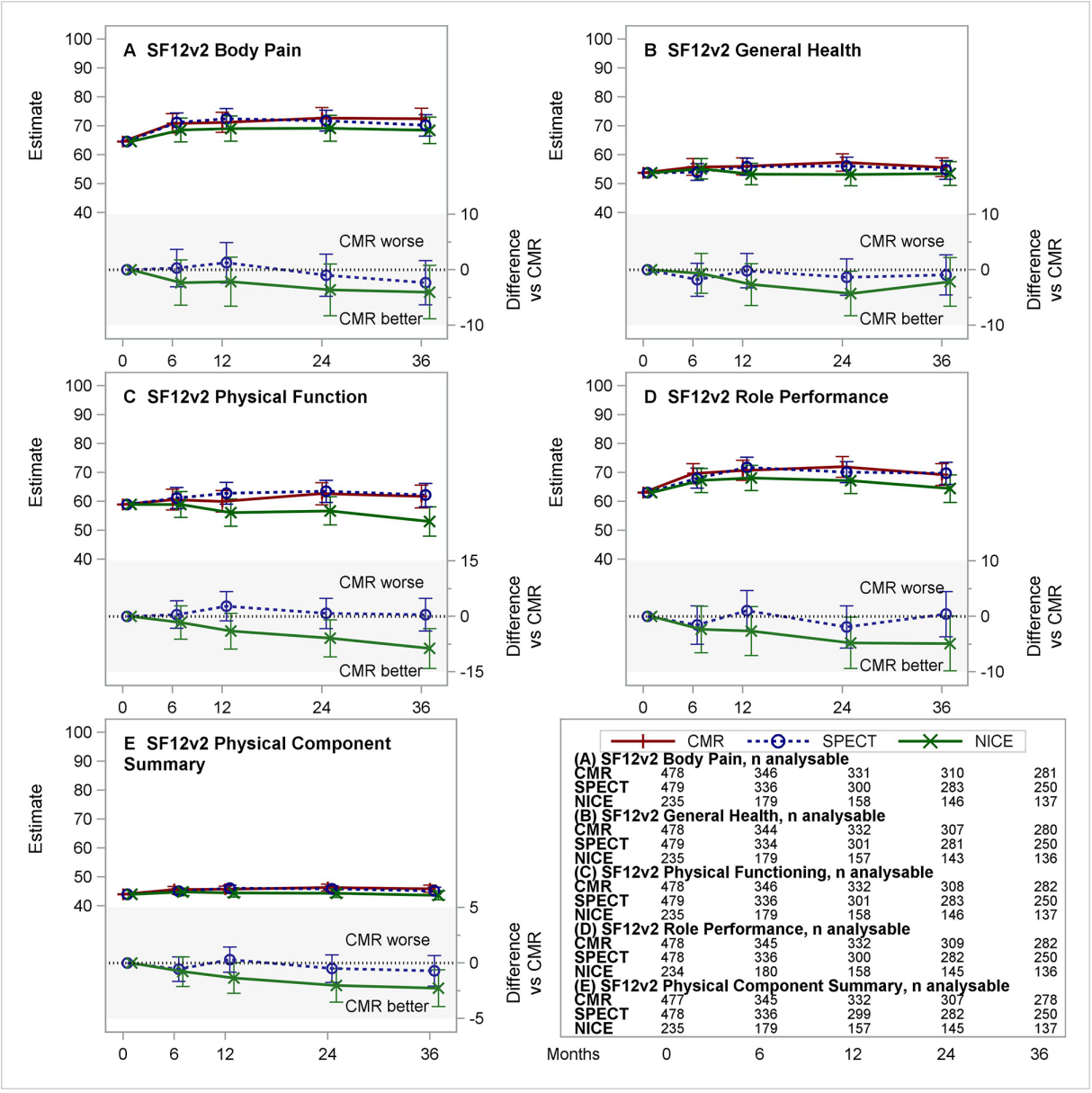

Figure 3 Estimated means for CMR, SPECT and NICE CG95 (2010) (and differences vs CMR) for the five physical domain and summary scores of the SF12v2. (A–E) Each panel presents the estimated least-squares means (with 95% CI) over time from repeated measures model for CMR, SPECT and NICE CG95 (2010)-based care (top section) and differences (with 95% CI) NICE–CMR and SPECT–CMR (lower section, shaded). Negative differences represent benefits for CMR versus comparator. Tables show the number of patients included from the complete case analysis. CMR, cardiovascular magnetic resonance; NICE, National Institute for Health and Care Excellence; SF12v2, Short Form 12 (V.2) Questionnaire; SPECT, single-photon emission CT.

However, 670 (55%) of participants returned questionnaire booklets at the 3-year time point (annual returns listed for each questionnaire in figures 2–5), with 554 (46%) returning a complete set of questionnaire data at all five predefined time points (online supplemental appendix B). Online supplemental appendices report the frequency of floor and ceiling values and observed summary statistics for the SAQ (online supplemental appendix C), SF12v2 (online supplemental appendix D) and EQ-5D (online supplemental appendix E) by trial arm at each time point.

Table 3 summarises the intervention effect on the SAQ-UK scores over time based on complete case analysis. Figure 2 provides the estimated group means (and differences vs CMR) over time for the five domains of the SAQ-UK. Considering the multiplicity of comparisons, there was no apparent difference in scores over time between randomised treatment groups. Observed differences in the rates of change in QoL domains were small in relation to the range of the scale. The largest difference was estimated in the Angina Stability domain (estimate −0.224 points per month (95% CI −0.376 to

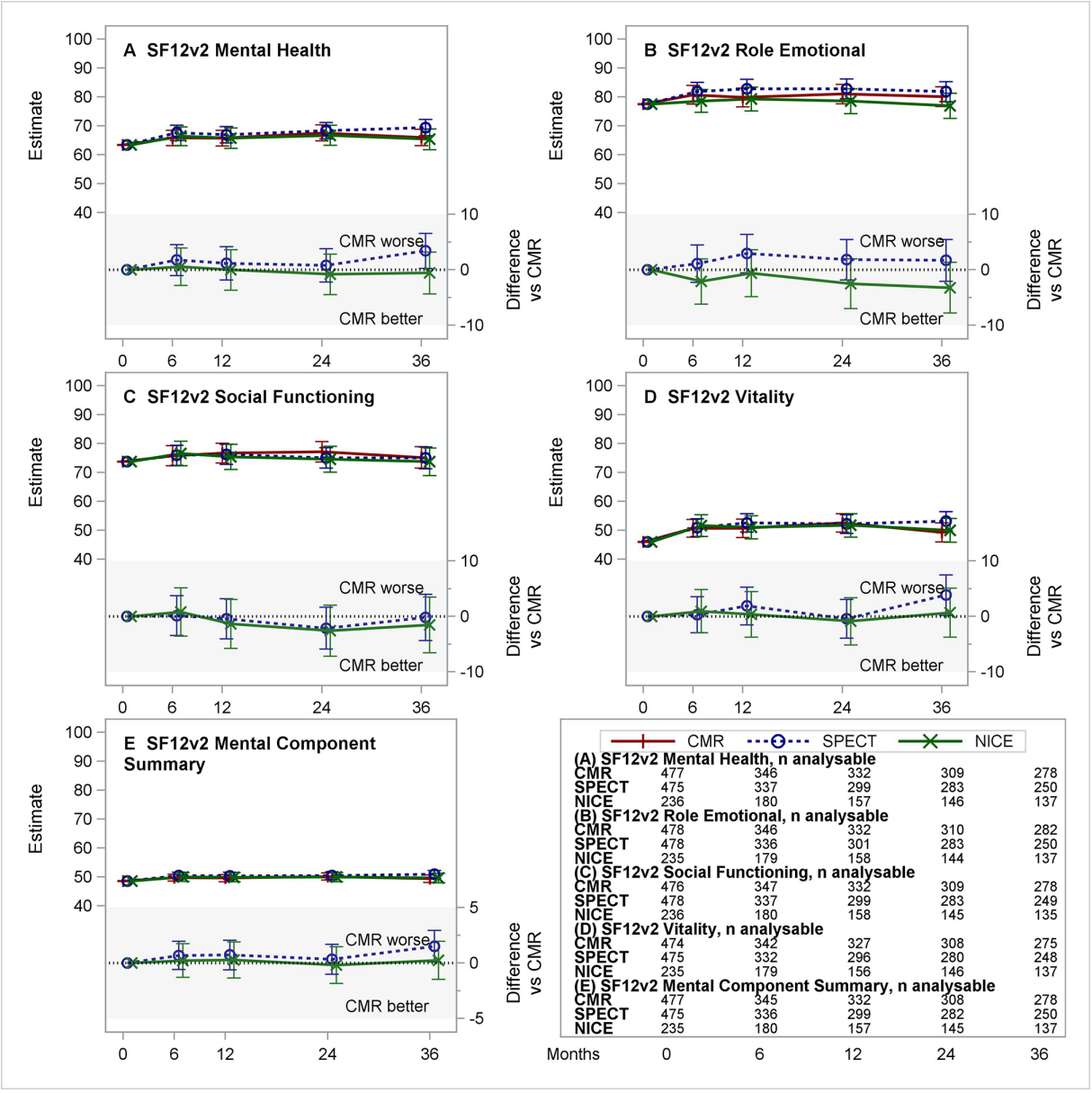

Figure 4 Estimated means for CMR, SPECT and NICE CG95 (2010) managed care (and differences vs CMR) for the five mental domain and summary scores of the SF12v2. (A–E) Each panel presents the estimated least-squares means (with 95% CI) over time from repeated measures model for CMR, SPECT and NICE CG95 (2010)-based care (top section) and differences (with 95% CI) NICE–CMR and SPECT–CMR (lower section, shaded). Negative differences represent benefits for CMR versus comparator. Table in lower right provides number of patients included from the complete case analysis. CMR, cardiovascular magnetic resonance; NICE, National Institute for Health and Care Excellence; SF12v2, Short Form 12 (V.2) Questionnaire; SPECT, single-photon emission CT.

–0.073)) and corresponds to a difference of 8 points (on a scale of 0–100) over a 3-year follow-up. The sensitivity analyses did not alter any of the findings or conclusions (online supplemental appendix C).

The intervention effect on SF12v2 domain and summary scores over time, based on complete case analysis, are summarised in table 3. Figures 3 and 4 provide the estimated group means (and differences vs CMR) over time for the five SF12v2 Physical domains, the five SF12v2 Mental domains and summaries. Considering the multiplicity of comparisons, there were no apparent differences in scores over time between randomised treatment groups (table 3). Observed differences in the rates of change in QoL domains were small in relation to the range of the scale. The largest difference was estimated in the Physical Functioning domain (estimate –0.224 points per month (95% CI –0.386 to –0.062)) and corresponds to a difference of 8 points (on a scale of 0–100) over a 3-year follow-up. The sensitivity analyses did not alter any of the findings or conclusions (online supplemental appendix D).

Table 3 summarises the effect of intervention on the EQ-5D-3L and the EQ-5D-5L Utility scores, based on complete case analysis. Figure 5 provides the estimated

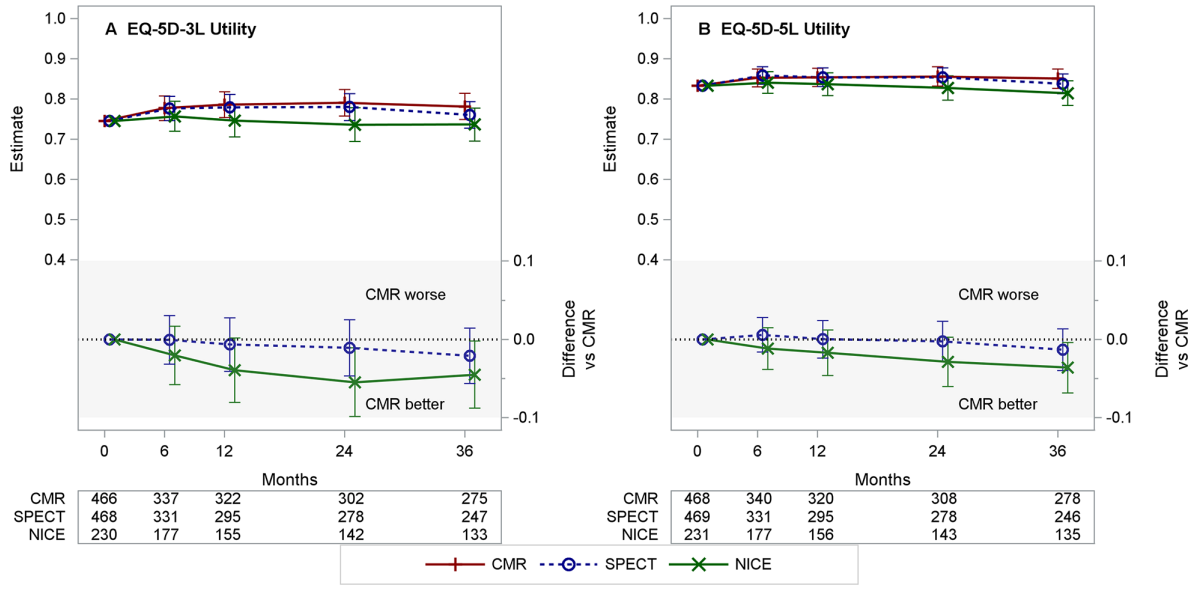

Figure 5 Estimated means for CMR, SPECT and NICE CG95 (2010) managed care (and differences vs CMR) for the EQ-5D-3L and EQ-5D-5L Utilities. (A, B) Each panel presents the estimated least-squares means (with 95% CI) over time from repeated measures model for CMR, SPECT and NICE CG95 (2010)-based care (top section) and differences (with 95% CI) NICE–CMR and SPECT–CMR (lower section, shaded). Negative differences represent benefits for CMR versus comparator. Table ishow the number of patients included from the complete case analysis. CMR, Cardiac Magnetic Resonance based care; EQ-5D-3L[–5 L], Euroqol 5-dimension questionnaire, 3 [5] levels; NICE, NICE CG95 (2010) based management; SPECT, Single Photon Emission CT based care.CMR, cardiovascular magnetic resonance; EQ-5D-3L/5L, EuroQol 5-Dimension Questionnaire, 3/5 Levels; NICE, National Institute for Health and Care Excellence; SPECT, single-photon emission CT.

group mean utility values (and differences vs CMR) over time. Although the estimated interaction effects for CMR versus NICE and for CMR versus SPECT both favoured the CMR arm, 95% CIs all enclosed the null value of zero indicating no significant difference. The sensitivity analyses did not alter any of the findings or conclusions (online supplemental appendix E).

Exploring patterns of missing data, the most consistent predictors of missing 36-month data were randomising centre, patient age, baseline scale values, current and prior use of beta-blockers, ACE inhibitors/angiotensin II receptor blockers and other antianginal medications; randomised allocation and PTL at randomisation were not.

DISCUSSION

The CE-MARC 2 trial compared three management strategies for secondary care patients with suspected stable angina. After the planned fixed 3 years' follow-up of 1202 patients, there was no statistically significant difference in time to first MACE rates between the three arms of the trial. There were small numerical differences between trial arms, which differed in their pattern of clinical events, but which were too few to draw any inferences. In terms of 'hard' clinical events (death or MI), the rates were also comparable between the three trial arms; while again there were small numerical differences between trial arms, the study was not powered for this endpoint. Observed differences in QoL domains were small. MACE events and QoL were secondary outcome measures and these results supplement the main clinical trial findings,[5] which showed a significantly higher rate of non-obstructive ('unnecessary') ICA findings for the NICE guidelines-based management strategy compared with the two functional imaging strategies, and only a small increase in positive detection of CAD.

We previously reported in high-risk patients with estimated PTL of 61%–90% of CAD, that the actual observed rate of disease was considerably lower than would be predicted, such that the odds of a non-obstructive ICA (or 'unnecessary angiography') for those randomised to NICE (CG95) guidelines-based management were 20 times greater than for those randomised to either CMR or SPECT-guided care.[5] Since publication of NICE CG95 (2010), improved cardiovascular clinical prediction models have been proposed by the CAD Consortium and the PROMISE trial investigators.[3 9] Both of these groups have developed models in much larger, more contemporary datasets. Despite this, implementation of these models into clinical practice without prior contemporary local[10] recalibration for the population at risk may lead to the same outcome as in CE-MARC 2.

The near identical outcomes for CMR and SPECT patients were not expected. The similar specificities and superior sensitivities for CMR versus SPECT observed in the CE-MARC trial suggested we might see better disease detection in participants undergoing CMR, and so reduced MACE and better QoL.[11 12] The numbers of patients undergoing ICA within 12 months in these two arms were similar and the numbers of patients with an

Table 3 Complete case analysis of QoL domains

	CG95 (2010) vs CMR				SPECT vs CMR			
			95% CI				95% CI	
Domain/analysis	Estimate	SE	Lower	Upper	Estimate	SE	Lower	Upper
Seattle Angina Questionnaire (UK version) (0=worst, 100=best)								
Angina Frequency	−0.023	0.056	−0.133	0.087	0.002	0.044	−0.084	0.088
Angina Stability*	−0.224	0.077	−0.376	−0.073	−0.080	0.064	−0.206	0.046
Physical Limitation	−0.072	0.055	−0.180	0.036	0.035	0.045	−0.054	0.124
Quality of Life	−0.053	0.068	−0.187	0.081	−0.004	0.054	−0.110	0.102
Treatment Satisfaction	0.010	0.060	−0.108	0.128	0.106	0.048	0.012	0.200
SF12v2 (0=worst, 100=best)								
Body Pain*	−0.078	0.070	−0.216	0.060	−0.106	0.059	−0.222	0.011
General Health*	−0.065	0.069	−0.200	0.071	0.005	0.056	−0.104	0.114
Physical Functioning	−0.224	0.083	−0.386	−0.062	−0.036	0.065	−0.164	0.093
Role Performance	−0.100	0.070	−0.238	0.039	0.019	0.059	−0.098	0.136
Physical Component Summary	−0.052	0.025	−0.101	−0.003	−0.016	0.021	−0.057	0.024
Mental Health	−0.043	0.063	−0.167	0.081	0.044	0.052	−0.058	0.146
Role Emotional	−0.061	0.071	−0.201	0.079	0.002	0.060	−0.116	0.121
Social Functioning*	−0.083	0.076	−0.232	0.067	−0.030	0.064	−0.156	0.097
Vitality*	−0.026	0.074	−0.171	0.120	0.074	0.060	−0.045	0.192
Mental Component Summary	−0.006	0.028	−0.061	0.050	0.020	0.023	−0.026	0.065
EQ-5D-3L (−0.594=worst, 1=perfect health)								
Utility[26]	−0.0009	0.0007	−0.0022	0.0004	−0.0007	0.0006	−0.0018	0.0004
EQ-5D-5L (−0.281=worst, 1=perfect health)								
Utility[27]	−0.0009	0.0005	−0.0019	0.0001	−0.0006	0.0004	−0.0014	0.0001

Estimates given are the arm–time interaction effects, estimating by how much the NICE CG95 and SPECT arm scores change per month, relative to those in the CMR arm. Negative values represent CMR getting better scores (vs comparator) over time, positive values represent CMR patients getting worse scores over time.
*This domain scale derives from a single question comprising five possible responses.
CMR, cardiovascular magnetic resonance; EQ-5D-3L/5L, EuroQol 5-Dimension Questionnaire, 3/5 Levels; NICE, National Institute for Health and Care Excellence; QoL, quality of life; SF12v2, Short Form 12 (V.2) Questionnaire; SPECT, single-photon emission CT.

ICA free from any obstructive disease were almost identical. Despite this, a greater proportion of SPECT patients had ICA due to a clinician referring for ICA despite a negative SPECT result, and a lower proportion of patients with a positive SPECT were subsequently referred for ICA, suggesting that overall clinician confidence in the SPECT result was lower than that for CMR.

Several randomised trials have evaluated non-invasive cardiac imaging for the management of patients with stable suspected cardiac chest pain, with predefined secondary endpoints of patient-reported QoL measures. These have predominantly involved CTCA versus standard care or versus functional testing (comprising a mixture of exercise ECG and functional imaging). The conclusions from the CE-MARC 2 QoL analysis are in line with other trials. The PROMISE trial randomised 10 003 patients to either functional testing or CTCA and found no difference in the composite outcome measure, EQ-5D-3L and SAQ after median 2.5 years' follow-up.[13 14] CRESCENT randomised 350 patients to CTCA or functional testing and found significant improvements in the SAQ Angina Frequency domain for CTCA versus functional testing at 12 months, but not in any other domain, or in EQ-5D or SF36.[15] The follow-up CRESCENT-II trial of 268 patients found no differences in SAQ domain, EQ-5D or SF36 at 12 months.[16] The SCOT-HEART trial of standard care (exercise stress ECG only and no additional testing) versus standard care+CTCA in 4146 patients reported, after median clinical follow-up of 4.8 years, an HR of 0.59 (95% CI 0.41 to 0.84) for the primary composite endpoint of CAD death or non-fatal MI in favour of standard care+CTCA.[17–19] Despite a clinical strategy of coronary artery imaging for all patients, surprisingly, the CTCA strategy did not reduce the likelihood of undergoing ICA. Since CTCA involves ionising radiation, the strategy effectively doubles the number of tests involving ionising radiation in the referral population (most relevant in younger patients, especially females). The patient population for SCOT-HEART appears to have similar baseline SAQ scores and clinical characteristics

to CE-MARC 2. However, in SCOT-HEART, CTCA was associated with less improvements in physical limitation, angina frequency and QoL at 6 months compared with standard care alone,[18] though these absolute differences were small (<5-point difference) and no adjustment for multiple comparisons was performed. The reasons for this finding are complex, but likely include the possibility that an increase in the diagnosis of mild and moderate non-obstructive CAD detected by CTCA labels the patient with a life-long medical condition, creating anxiety and stress. Furthermore, in SCOT-HEART, medication for symptoms was discontinued in patients with no obstructive CAD, and this may have led to a deterioration in symptoms and QoL in patients with microvascular angina and/or vasospastic angina. This is one reason that the term 'unnecessary angiography' is no longer favoured, as the cardiology community embrace the more inclusive description of ischaemia with non-obstructive coronary arteries.

In terms of other CMR trials, the recently published MAGNET trial randomised 200 patients to either first-line ICA or first-line CMR, finding no significant difference at 3 years in the composite outcome of cardiac death and MI, despite a large reduction in revascularisation among those undergoing CMR.[20] At 3-year follow-up, no between-arm differences were observed in any SAQ domain, though the CMR-guided group were reported to have higher domain scores at 1 year. Finally, MR-INFORM randomised 918 patients to a revascularisation strategy guided either by CMR or by ICA±fractional flow reserve measurement. Randomisation to CMR-guided care resulted in a lower rate of ICA, without an increase in the 1-year rate of composite cardiovascular outcome measure of all-cause death, non-fatal MI or revascularisation.[21] Although EQ-5D was collected as part of this trial, no QoL data have been published yet.

Limitations

The CE-MARC 2 trial population was predominantly white northern European, potentially limiting generalisability to other populations.[5] Guidelines-based management relied on the Duke clinical risk score,[22] a validated score used in the American Heart Association/American College of Cardiology guidelines[23] at the time of trial recruitment, but which has since been reported to overestimate the PTL of CAD in contemporary trial populations.[3] While the NICE CG95 guidelines were updated in 2016 to recommend CTCA as the initial investigation for all patients with de-novo atypical or typical angina, the European Society of Cardiology 2019 guidelines for the diagnosis and management of chronic coronary syndromes[24] still recommend a range of initial investigations dependent on estimated PTL. This can include anatomical or functional imaging tests for patients at lower to intermediate risk, but also direct to ICA for those with high PTL, much like the original NICE CG95 (2010) guidelines evaluated in this trial.

While the observed annualised event rate of 1.2% per year was lower than anticipated, it was in line with published stable CAD trials such as SCOT-HEART,[17] and provided an important safety outcome measure for the trial. Although the rate of MACE was lower for NICE CG95 (2010) versus CMR patients, the low event rate meant that even a large reduction in risk (adjusted HR of 0.66) did not conclude superiority for NICE versus CMR. Despite this limitation, CE-MARC 2 is a high-quality dataset which contributes importantly to the clinical evidence base and future meta-analysis.[25]

The validity of our QoL analyses relies on two key assumptions. The first relates to the unobserved data due to non-response. In CE-MARC 2, 55% of patients had analysable 3-year follow-up scale values (46% returned all five questionnaire booklets) and provided a powered complete case analysis. The primary complete case analysis included all observed data in a mixed-effects model under the assumption that data were missing at random. This model included the effects of the randomising site, baseline scale value and patient age, which were found to be consistently predictive of missing data, suggesting that the assumption was reasonable. A planned sensitivity analysis based on multiply imputed datasets[8] produced similar results, and did not alter our conclusions.

The second assumption was that the sample size was sufficiently large that the distribution of the sample means would be normally distributed. Due to the lower-than-expected patient risk profile, observed scale values suffered from ceiling effects. At a number of time points, some domain scores had distributions comprising 25%–50% ceiling values. The distribution of the QoL domain scale scores in CE-MARC 2 raises questions as to the utility of these scales in this population. Comparable trials reported similarly skewed distributions in their QoL outcomes.[14 18] Additionally, a large validation study of the original SAQ indicated pronounced ceiling effects in stable CAD for four of the five SAQ domain scores. Questionnaires may need to be refined to be more sensitive to change in this patient group.

CONCLUSION

Despite a fourfold increase in referrals for ICA, the NICE CG95 (2010) guidelines risk-stratified care strategy did not reduce 3-year MACE or improve QoL, as compared with functional imaging with CMR or SPECT.

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Competing interests CB is employed by the University of Glasgow which holds research and/or consultancy agreements with AstraZeneca, Abbott Vascular, Boehringer Ingelheim, GSK, HeartFlow, Neovasc and Novartis.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the UK National Research Ethics Service (12/YH/0404) and institutional review boards of the participating centres. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary Appendix

Randomised trial of stable chest pain investigation (CE-MARC 2): 3-year clinical and quality of life results

Content

Questionnaire choice, validation and reliability

Patient-reported QoL was measured using the Seattle Angina Questionnaire (SAQ) UK English,(1) the SF12v2 (2) and the Euroqol EQ-5D-3L (3) and -5L (4) at randomisation, 6 months, 1 year, 2 years and 3 years. The validity and reliability of the 19-item SAQ (1,5), the SF12 (6) and the EQ-5D (7,8) has been previously demonstrated in cardiovascular studies

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Supplemental Appendix A:

Tables provide the unadjusted and adjusted hazard ratios for time to first Major Adverse Cardiovascular Event (MACE) for the NICE vs CMR comparison, and for the SPECT vs CMR comparison. For the multivariable models, the full model fits with adjusted hazard ratios are given, except where estimation is not feasible due to small numbers. Categorical prognostic factors with 3 or more levels do not include P-Values for each level, rather the overall effect.

In all tables, a hazard ratio greater than 1 indicates increased risk of having a MACE (or experiencing MACE sooner) compared to the reference category level.

Table A.1: Unadjusted univariable hazard ratios for MACE for covariates in all 1,202 participants

Effect	Hazard Ratio (95% CI)	P-Value
Randomising Centre	Likelihood Ratio Chi-Sq: X^2 (5 df) = 1.612	0.900
Sex (MALE vs Female)	0.90 (0.49 to 1.64)	0.721
Age Group (65Y OR OLDER vs Under 65)	1.48 (0.75 to 2.95)	0.278
Pre-Test Likelihood category (Overall Effect)	Likelihood Ratio Chi-Sq: X^2 (4 df) = 6.427	0.169
Hypertension (YES vs No)	2.21 (1.20 to 4.07)	0.011
Smoking Status (Overall effect)	Likelihood Ratio Chi-Sq: X^2 (2 df) = 4.745	0.093
Ethnicity (NON-WHITE vs White)	1.25 (0.45 to 3.50)	0.682
Type II Diabetes (YES vs No+T1)	1.64 (0.73 to 3.70)	0.257
Body Mass Index (per kg/m2)	1.01 (0.96 to 1.07)	0.682

Note: all covariates except Type II diabetes and Body Mass Index were pre-specified as being included in the analysis Type II diabetes and Body Mass Index are post hoc analyses presented in response to manuscript review and are not included in subsequent tables. Note the adjustment for PTL category includes adjustment for the effect of diabetes on outcome.

Table A.2: Univariable and Full Model Fit results for comparison of NICE CG95 (2010) vs CMR (NICE and CMR participants only)

Effect	Hazard Ratio (95% CI)	P-Value
Univariable: Unadjusted		
NICE CG95 (2010) vs 3T-CMR	0.66 (0.26, 1.67)	P=0.38
Multivariable: Adjusted		
NICE CG95 (2010) vs 3T-CMR	0.61 (0.24, 1.56)	P = 0.303
Randomising Centre (Overall effect)	Likelihood Ratio Chi-Sq: X^2 (5df) = 6.93	P = 0.226
Sex: MALE vs Female	0.51 (0.20, 1.28)	P = 0.151
Age Group: 65Y OR OLDER vs Under 65	1.38 (0.47, 4.09)	P = 0.557
Pre-test Likelihood category (Overall effect)	Likelihood Ratio Chi-Sq: X^2 (4df) = 6.25	P = 0.181
PTL: 0-9% vs 10-29%	-	
PTL: 30-60% vs 10-29%	4.32 (0.92, 20.30)	
PTL: 61-90% vs 10-29%	4.01 (0.77, 20.94)	
PTL: 91-100% vs 10-29%	-	
Hypertension: YES vs No	2.38 (1.00, 5.68)	P = 0.051
Smoking Status (Overall effect)	Likelihood Ratio Chi-Sq: X^2 (2df) = 4.19	P = 0.123
Smoking status: EX vs Never	1.48 (0.50, 4.35)	
Smoking status: CURRENT vs Never	2.95 (1.01, 8.58)	
Ethnicity: NON-WHITE vs White	2.49 (0.60, 10.27)	P = 0.208

Table A.3: Univariable and Full Model Fit results for comparison of CMR vs SPECT (CMR and SPECT participants only)

Effect	Hazard Ratio (95% CI)	P-Value
Univariable: Unadjusted		
SPECT vs 3T-CMR	1.00 (0.52, 1.92)	P=1.00
Multivariable: Unadjusted		
3T-CMR vs SPECT	1.03 (0.54, 1.98)	P = 0.928
Randomising Centre (Overall effect)	Likelihood Ratio Chi-Sq: X^2 (5df) = 0.47	P = 0.993
Sex: MALE vs Female	0.80 (0.36, 1.78)	P = 0.593
Age Group: 65Y OR OLDER vs Under 65	1.32 (0.54, 3.22)	P = 0.547
Pre-test Likelihood category (Overall effect)	Likelihood Ratio Chi-Sq: X^2 (4df) = 3.38	P = 0.496
PTL: 0-9% vs 10-29%	-	
PTL: 30-60% vs 10-29%	1.24 (0.44, 3.55)	
PTL: 61-90% vs 10-29%	2.32 (0.79, 6.80)	
PTL: 91-100% vs 10-29%	1.43 (0.16, 13.11)	
Hypertension: YES vs No	2.20 (1.11, 4.38)	P = 0.025
Smoking Status (Overall effect)	Likelihood Ratio Chi-Sq: X^2 (2df) = 4.95	P = 0.084
Smoking status: EX vs Never	1.98 (0.87, 4.53)	
Smoking status: CURRENT vs Never	2.62 (1.04, 6.59)	
Ethnicity: NON-WHITE vs White	1.69 (0.55, 5.15)	P = 0.356

Appendix B: Completion of questionnaires

Table B.1 Returned questionnaire booklets

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Baseline				
Not completed	3 (0.6%)	2 (0.4%)	4 (1.7%)	9 (0.7%)
In clinic	472 (98.1%)	474 (98.5%)	233 (97.1%)	1179 (98.1%)
Home (Postal)	2 (0.4%)	4 (0.8%)	2 (0.8%)	8 (0.7%)
Home (Telephone)	4 (0.8%)	1 (0.2%)	1 (0.4%)	6 (0.5%)
6 months				
Not completed	133 (27.7%)	144 (29.9%)	60 (25.0%)	337 (28.0%)
In clinic	1 (0.2%)	2 (0.4%)	-	3 (0.2%)
Home (Postal)	343 (71.3%)	326 (67.8%)	177 (73.8%)	846 (70.4%)
Home (Telephone)	4 (0.8%)	9 (1.9%)	3 (1.3%)	16 (1.3%)
12 months				
Not completed	149 (31.0%)	180 (37.4%)	82 (34.2%)	411 (34.2%)
In clinic	1 (0.2%)	1 (0.2%)	-	2 (0.2%)
Home (Postal)	323 (67.2%)	292 (60.7%)	155 (64.6%)	770 (64.1%)
Home (Telephone)	8 (1.7%)	8 (1.7%)	3 (1.3%)	19 (1.6%)
24 months				
Not completed	171 (35.6%)	197 (41.0%)	94 (39.2%)	462 (38.4%)
In clinic	2 (0.4%)	1 (0.2%)	-	3 (0.2%)
Home (Postal)	305 (63.4%)	279 (58.0%)	144 (60.0%)	728 (60.6%)
Home (Telephone)	3 (0.6%)	4 (0.8%)	2 (0.8%)	9 (0.7%)
36 months				
Not completed	199 (41.4%)	231 (48.0%)	102 (42.5%)	532 (44.3%)
In clinic	2 (0.4%)	-	-	2 (0.2%)
Home (Postal)	280 (58.2%)	250 (52.0%)	138 (57.5%)	668 (55.6%)

NB: “Completed” refers to a questionnaire booklet returned to the trial team, regardless of how complete each item, scale or questionnaire.

Appendix C: Supplementary analyses of the Seattle Angina Questionnaire (SAQ-UK)

Table C.1: Overall distribution of observed SAQ-UK scale values, and frequency of floor/ceiling values at baseline, 12 and 36months follow-up. (Ranges 0=worst health, 100=best health)

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Angina Frequency (AF)				
Baseline				
n	476	477	234	1187
Mean (SD)	65.2 (23.88)	66.2 (22.71)	66.2 (22.17)	65.8 (23.07)
Median (Interquartile Range)	70 (50 to 80)	70 (60 to 80)	70 (50 to 80)	70 (50 to 80)
n (%) Min, Max value	9 (1.9%), 33 (6.9%)	3 (0.6%), 34 (7.1%)	2 (0.9%), 16 (6.8%)	14 (1.2%), 83 (7.0%)
12 months				
n	325	295	157	777
Mean (SD)	88.4 (19.62)	88.6 (16.33)	85.4 (21.05)	87.9 (18.77)
Median (Interquartile Range)	100 (80 to 100)	100 (80 to 100)	100 (80 to 100)	100 (80 to 100)
n (%) Min, Max value	1 (0.3%), 197 (60.6%)	1 (0.3%), 149 (50.5%)	1 (0.6%), 79 (50.3%)	3 (0.4%), 425 (54.7%)
36 months				
n	276	247	132	655
Mean (SD)	90.4 (16.77)	91.0 (14.43)	86.1 (22.67)	89.8 (17.41)
Median (Interquartile Range)	100 (90 to 100)	100 (80 to 100)	100 (80 to 100)	100 (80 to 100)
n (%) Min, Max value	0 (0.0%), 179 (64.9%)	0 (0.0%), 149 (60.3%)	1 (0.8%), 79 (59.8%)	1 (0.2%), 407 (62.1%)
Angina Stability (AS)				
Baseline				
n	469	468	232	1169
Mean (SD)	45.9 (27.87)	45.5 (26.01)	43.5 (28.13)	45.3 (27.19)
Median (Interquartile Range)	50 (25 to 50)	50 (25 to 50)	50 (25 to 50)	50 (25 to 50)
n (%) Min, Max value	61 (13.0%), 53 (11.3%)	48 (10.3%), 44 (9.4%)	33 (14.2%), 26 (11.2%)	142 (12.1%), 123 (10.5%)
12 months				
n	322	296	157	775
Mean (SD)	53.1 (18.57)	59.3 (20.74)	53.3 (20.04)	55.5 (19.92)
Median (Interquartile Range)	50 (50 to 50)	50 (50 to 75)	50 (50 to 50)	50 (50 to 50)
n (%) Min, Max value	8 (2.5%), 29 (9.0%)	4 (1.4%), 49 (16.6%)	5 (3.2%), 17 (10.8%)	17 (2.2%), 95 (12.3%)

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
36 months				
n	275	246	132	653
Mean (SD)	53.9 (17.63)	55.1 (19.94)	50.0 (16.35)	53.6 (18.36)
Median (Interquartile Range)	50 (50 to 50)	50 (50 to 50)	50 (50 to 50)	50 (50 to 50)
n (%) Min, Max value	3 (1.1%), 27 (9.8%)	4 (1.6%), 30 (12.2%)	2 (1.5%), 7 (5.3%)	9 (1.4%), 64 (9.8%)
Physical Limitation (PL)				
Baseline				
n	463	464	230	1157
Mean (SD)	72.9 (22.33)	72.0 (21.83)	71.2 (24.00)	72.2 (22.46)
Median (Interquartile Range)	77.8 (58.3 to 91.7)	75 (58.3 to 88.9)	77.8 (55.6 to 88.9)	77.8 (58.3 to 91.7)
n (%) Min, Max value	0 (0.0%), 57 (12.3%)	0 (0.0%), 44 (9.5%)	1 (0.4%), 24 (10.4%)	1 (0.1%), 125 (10.8%)
12 months				
n	292	271	150	713
Mean (SD)	79.8 (23.28)	79.7 (22.91)	74.0 (26.00)	78.5 (23.82)
Median (Interquartile Range)	88.9 (66.7 to 100)	87.5 (66.7 to 100)	83.3 (55.6 to 97.2)	86.1 (66.7 to 100)
n (%) Min, Max value	1 (0.3%), 94 (32.2%)	2 (0.7%), 84 (31.0%)	0 (0.0%), 33 (22.0%)	3 (0.4%), 211 (29.6%)
36 months				
n	256	228	126	610
Mean (SD)	79.9 (24.00)	80.0 (23.63)	72.0 (28.81)	78.3 (25.10)
Median (Interquartile Range)	89.6 (63.9 to 100)	88.9 (66.7 to 100)	83.3 (47.2 to 100)	88.9 (61.1 to 100)
n (%) Min, Max value	0 (0.0%), 92 (35.9%)	0 (0.0%), 71 (31.1%)	1 (0.8%), 36 (28.6%)	1 (0.2%), 199 (32.6%)
Quality of Life (QoL)				
Baseline				
n	474	475	234	1183
Mean (SD)	52.7 (20.76)	51.4 (20.01)	49.0 (21.33)	51.4 (20.60)
Median (Interquartile Range)	50 (41.7 to 66.7)	50 (41.7 to 66.7)	50 (33.3 to 66.7)	50 (37.5 to 66.7)
n (%) Min, Max value	4 (0.8%), 11 (2.3%)	2 (0.4%), 5 (1.1%)	3 (1.3%), 5 (2.1%)	9 (0.8%), 21 (1.8%)
12 months				
n	320	292	155	767
Mean (SD)	73.6 (23.77)	72.9 (20.98)	69.2 (27.07)	72.5 (23.51)
Median (Interquartile Range)	83.3 (58.3 to 91.7)	75 (58.3 to 91.7)	75 (50 to 91.7)	75 (58.3 to 91.7)
n (%) Min, Max value	3 (0.9%), 57 (17.8%)	0 (0.0%), 40 (13.7%)	2 (1.3%), 30 (19.4%)	5 (0.7%), 127 (16.6%)

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
36 months				
n	268	243	127	638
Mean (SD)	76.0 (22.69)	76.3 (21.03)	71.7 (25.33)	75.3 (22.67)
Median (Interquartile Range)	83.3 (58.3 to 91.7)	83.3 (66.7 to 91.7)	83.3 (58.3 to 91.7)	83.3 (58.3 to 91.7)
n (%) Min, Max value	0 (0.0%), 61 (22.8%)	1 (0.4%), 41 (16.9%)	1 (0.8%), 23 (18.1%)	2 (0.3%), 125 (19.6%)
Treatment Satisfaction (TS)				
Baseline				
n	471	472	233	1176
Mean (SD)	90.6 (12.99)	90.0 (14.61)	89.9 (13.40)	90.2 (13.74)
Median (Interquartile Range)	100 (81.3 to 100)	100 (81.3 to 100)	93.8 (81.3 to 100)	100 (81.3 to 100)
n (%) Min, Max value	0 (0.0%), 244 (51.8%)	0 (0.0%), 250 (53.0%)	0 (0.0%), 113 (48.5%)	0 (0.0%), 607 (51.6%)
12 months				
n	322	292	155	769
Mean (SD)	87.2 (19.91)	86.1 (18.29)	85.6 (19.65)	86.5 (19.24)
Median (Interquartile Range)	100 (81.3 to 100)	93.8 (81.3 to 100)	93.8 (81.3 to 100)	100 (81.3 to 100)
n (%) Min, Max value	1 (0.3%), 179 (55.6%)	0 (0.0%), 134 (45.9%)	0 (0.0%), 73 (47.1%)	1 (0.1%), 386 (50.2%)
36 months				
n	269	242	129	640
Mean (SD)	88.6 (20.30)	89.4 (16.92)	86.7 (19.97)	88.5 (19.01)
Median (Interquartile Range)	100 (81.3 to 100)	100 (81.3 to 100)	100 (81.3 to 100)	100 (81.3 to 100)
n (%) Min, Max value	2 (0.7%), 169 (62.8%)	0 (0.0%), 137 (56.6%)	0 (0.0%), 71 (55.0%)	2 (0.3%), 377 (58.9%)

Table C2: Comparison of primary and sensitivity mixed effects (random coefficients) modelling of SAQ domains

	CG95 (2010) vs CMR				SPECT vs CMR			
			95% CI				95% CI	
Domain / Analysis	Estimate	Standard Error	Lower	Upper	Estimate	Standard Error	Lower	Upper
Angina Frequency								
Primary	-0.023	0.056	-0.133	0.087	0.002	0.044	-0.084	0.088
Baseline*Time	-0.024	0.056	-0.134	0.086	0.002	0.044	-0.084	0.088
Multiple Imputation	-0.048	0.060	-0.167	0.071	0.022	0.049	-0.075	0.119
Angina Stability								
Primary	-0.224	0.077	-0.376	-0.073	-0.080	0.064	-0.206	0.046
Baseline*Time	-0.224	0.077	-0.376	-0.073	-0.080	0.064	-0.206	0.046
Multiple Imputation	-0.191	0.072	-0.332	-0.049	-0.067	0.060	-0.184	0.051
Proportional Odds	-0.030	0.010	-0.050	-0.010	-0.010	0.009	-0.027	0.007
Physical Limitation								
Primary	-0.072	0.055	-0.180	0.036	0.035	0.045	-0.054	0.124
Baseline*Time	-0.072	0.055	-0.180	0.036	0.034	0.045	-0.055	0.123
Multiple Imputation	-0.048	0.061	-0.169	0.072	0.037	0.049	-0.060	0.134
Quality of Life								
Primary	-0.053	0.068	-0.187	0.081	-0.004	0.054	-0.110	0.102
Baseline*Time	-0.065	0.068	-0.198	0.068	-0.014	0.054	-0.120	0.091
Multiple Imputation	-0.043	0.071	-0.183	0.097	0.004	0.056	-0.107	0.114
Treatment Satisfaction								
Primary	0.010	0.060	-0.108	0.128	0.106	0.048	0.012	0.200
Baseline*Time	0.008	0.060	-0.109	0.125	0.100	0.048	0.006	0.193
Multiple Imputation	0.027	0.063	-0.097	0.150	0.100	0.049	0.003	0.196

Estimate=Estimated interaction effect between NICE (or SPECT) and time in months. Negative values indicate CMR improving vs comparator, positive values indicate comparator improving vs CMR.

Lower/Upper = Limits of 95% Confidence Interval for the difference

Baseline*Time=Fitting the primary analysis model, with an additional fixed interaction effect for baseline-by-time, allowing patients with different health statuses to have different trajectories during the follow-up.

Proportional Odds=Replacing linear mixed model with an ordinal proportional odds model, modelling the odds of moving up to greater values. Only done for the Angina Stability scale, derived from a single 5-item question. Values <0 represent reduced log-odds per month of moving to higher scores for CG95/SPECT vs CMR, values >0 represent increased log-odds per month of moving up to higher scores vs CMR. Thus the estimate of -0.0301 for Angina Stability in the NICE comparison indicates that the odds of a NICE patient having a higher Angina Stability score change by exp(-0.0301) – 1 = -2.97% per month compared to the CMR arm.

Table C3: Comparison of primary and sensitivity analyses of SAQ domains at 12 and 36 months post-randomisation

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err.**	**Lower**	**Upper**	**Est.**	**Std Err.**	**Lower**	**Upper**
Angina Frequency										
CMR (n=325)	12 months	Primary	89.823	1.310	87.253	92.394				
		BL*Time	89.239	1.307	86.674	91.805				
		Mult. Imput.	90.249	1.811	86.698	93.800				
SPECT (n=295)	12 months	Primary	88.202	1.320	85.612	90.793	-1.621	1.404	-4.377	1.134
		BL*Time	87.689	1.317	85.105	90.274	-1.550	1.405	-4.308	1.208
		Mult. Imput.	88.721	1.756	85.278	92.164	-1.528	1.371	-4.219	1.163
CG95 (2010) (n=157)	12 months	Primary	86.612	1.652	83.370	89.855	-3.211	1.701	-6.550	0.128
		BL*Time	86.045	1.646	82.814	89.276	-3.195	1.703	-6.536	0.147
		Mult. Imput.	86.700	2.097	82.587	90.813	-3.549	1.698	-6.882	-0.215
CMR (n=276)	36 months	Primary	90.742	1.314	88.164	93.321				
		BL*Time	90.179	1.312	87.604	92.754				
		Mult. Imput.	91.016	1.798	87.491	94.542				
SPECT (n=247)	36 months	Primary	90.437	1.330	87.827	93.047	-0.305	1.416	-3.083	2.473
		BL*Time	89.977	1.328	87.372	92.582	-0.202	1.412	-2.973	2.569
		Mult. Imput.	91.266	1.808	87.721	94.811	0.250	1.434	-2.568	3.068
CG95 (2010) (n=132)	36 months	Primary	86.488	1.661	83.229	89.747	-4.254	1.715	-7.619	-0.889
		BL*Time	85.960	1.653	82.715	89.204	-4.219	1.710	-7.575	-0.863
		Mult. Imput.	85.999	2.248	81.583	90.415	-5.017	1.802	-8.560	-1.474
Angina Stability										
CMR (n=322)	12 months	Primary	53.023	1.338	50.396	55.649				
		BL*Time	53.293	1.339	50.665	55.922				
		Mult. Imput.	55.108	1.714	51.744	58.473				
SPECT (n=296)	12 months	Primary	58.556	1.357	55.894	61.219	5.534	1.582	2.428	8.639
		BL*Time	58.787	1.357	56.123	61.451	5.494	1.583	2.388	8.600
		Mult. Imput.	60.101	1.828	56.509	63.692	4.992	1.563	1.923	8.062
CG95 (2010) (n=157)	12 months	Primary	53.456	1.747	50.029	56.884	0.434	1.914	-3.322	4.190
		BL*Time	53.702	1.746	50.276	57.128	0.409	1.914	-3.349	4.166

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err.**	**Lower**	**Upper**	**Est.**	**Std Err.**	**Lower**	**Upper**
		Mult. Imput.	55.479	2.083	51.388	59.571	0.371	1.992	-3.544	4.286
CMR (n=275)	36 months	Primary	53.344	1.345	50.704	55.984				
		BL*Time	53.647	1.351	50.997	56.298				
		Mult. Imput.	54.941	1.671	51.662	58.221				
SPECT (n=246)	36 months	Primary	54.789	1.380	52.081	57.497	1.446	1.602	-1.699	4.590
		BL*Time	55.033	1.386	52.313	57.754	1.386	1.602	-1.759	4.530
		Mult. Imput.	56.069	1.759	52.613	59.525	1.128	1.490	-1.802	4.058
CG95 (2010) (n=132)	36 months	Primary	49.641	1.763	46.181	53.100	-3.703	1.933	-7.497	0.091
		BL*Time	49.892	1.765	46.429	53.356	-3.755	1.934	-7.550	0.040
		Mult. Imput.	51.677	1.991	47.767	55.588	-3.264	1.806	-6.814	0.286
Physical Limitation										
CMR (n=292)	12 months	Primary	78.276	1.483	75.365	81.186				
		BL*Time	79.672	1.475	76.778	82.566				
		Mult. Imput.	79.392	2.091	75.289	83.494				
SPECT (n=271)	12 months	Primary	78.093	1.488	75.173	81.014	-0.182	1.558	-3.239	2.875
		BL*Time	79.244	1.476	76.348	82.140	-0.428	1.553	-3.476	2.620
		Mult. Imput.	78.726	2.052	74.701	82.751	-0.665	1.501	-3.611	2.280
CG95 (2010) (n=150)	12 months	Primary	72.073	1.837	68.467	75.679	-6.202	1.872	-9.876	-2.529
		BL*Time	73.377	1.823	69.799	76.955	-6.296	1.865	-9.955	-2.636
		Mult. Imput.	72.797	2.365	68.157	77.437	-6.595	1.812	-10.151	-3.038
CMR (n=256)	36 months	Primary	77.136	1.528	74.137	80.135				
		BL*Time	78.389	1.525	75.397	81.381				
		Mult. Imput.	77.396	2.156	73.164	81.628				
SPECT (n=228)	36 months	Primary	78.353	1.547	75.317	81.388	1.217	1.655	-2.032	4.466
		BL*Time	79.469	1.539	76.449	82.488	1.079	1.654	-2.166	4.325
		Mult. Imput.	78.337	2.179	74.059	82.614	0.941	1.591	-2.185	4.068
CG95 (2010) (n=126)	36 months	Primary	70.453	1.923	66.679	74.227	-6.683	1.991	-10.590	-2.776
		BL*Time	71.706	1.913	67.951	75.461	-6.683	1.988	-10.585	-2.782
		Mult. Imput.	70.940	2.401	66.228	75.653	-6.455	1.941	-10.269	-2.641
Quality of Life										

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err.**	**Lower**	**Upper**	**Est.**	**Std Err.**	**Lower**	**Upper**
CMR (n=320)	12 months	Primary	73.206	1.583	70.099	76.312				
		BL*Time	72.203	1.574	69.114	75.292				
		Mult. Imput.	71.029	2.356	66.405	75.653				
SPECT (n=292)	12 months	Primary	72.860	1.591	69.738	75.982	-0.346	1.646	-3.576	2.884
		BL*Time	72.078	1.583	68.971	75.184	-0.126	1.645	-3.355	3.103
		Mult. Imput.	71.068	2.274	66.608	75.528	0.039	1.699	-3.298	3.376
CG95 (2010) (n=155)	12 months	Primary	68.943	1.973	65.071	72.815	-4.263	1.992	-8.172	-0.353
		BL*Time	68.101	1.961	64.252	71.951	-4.102	1.991	-8.009	-0.195
		Mult. Imput.	66.689	2.575	61.637	71.742	-4.339	1.959	-8.183	-0.495
CMR (n=268)	36 months	Primary	74.419	1.665	71.152	77.687				
		BL*Time	73.636	1.656	70.385	76.886				
		Mult. Imput.	71.822	2.429	67.056	76.589				
SPECT (n=243)	36 months	Primary	75.247	1.680	71.950	78.545	0.828	1.805	-2.713	4.370
		BL*Time	74.415	1.671	71.136	77.695	0.780	1.796	-2.745	4.305
		Mult. Imput.	72.646	2.466	67.804	77.488	0.824	1.817	-2.747	4.394
CG95 (2010) (n=127)	36 months	Primary	70.054	2.115	65.904	74.205	-4.365	2.192	-8.667	-0.063
		BL*Time	69.139	2.099	65.020	73.258	-4.497	2.182	-8.778	-0.215
		Mult. Imput.	67.175	2.785	61.706	72.645	-4.647	2.176	-8.922	-0.373
Treatment Satisfaction										
CMR (n=322)	12 months	Primary	87.597	1.363	84.923	90.272				
		BL*Time	86.351	1.358	83.686	89.016				
		Mult. Imput.	87.333	1.987	83.435	91.231				
SPECT (n=292)	12 months	Primary	86.882	1.375	84.184	89.580	-0.715	1.434	-3.531	2.100
		BL*Time	85.799	1.370	83.111	88.487	-0.552	1.434	-3.366	2.263
		Mult. Imput.	87.446	1.911	83.700	91.192	0.113	1.421	-2.677	2.903
CG95 (2010) (n=155)	12 months	Primary	85.342	1.709	81.987	88.696	-2.256	1.737	-5.665	1.154
		BL*Time	84.184	1.700	80.848	87.520	-2.167	1.737	-5.575	1.241
		Mult. Imput.	85.416	2.205	81.091	89.742	-1.917	1.880	-5.613	1.779
CMR (n=269)	36 months	Primary	87.962	1.426	85.163	90.762				

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err.**	**Lower**	**Upper**	**Est.**	**Std Err.**	**Lower**	**Upper**
		BL*Time	86.774	1.424	83.980	89.569				
		Mult. Imput.	87.263	2.012	83.315	91.210				
SPECT (n=242)	36 months	Primary	88.749	1.445	85.914	91.584	0.787	1.556	-2.268	3.841
		BL*Time	87.657	1.442	84.828	90.486	0.883	1.556	-2.170	3.936
		Mult. Imput.	88.533	2.026	84.558	92.507	1.270	1.558	-1.789	4.328
CG95 (2010) (n=129)	36 months	Primary	86.260	1.813	82.702	89.818	-1.702	1.886	-5.403	1.998
		BL*Time	85.154	1.806	81.610	88.698	-1.621	1.884	-5.319	2.078
		Mult. Imput.	85.928	2.401	81.214	90.642	-1.335	2.078	-5.421	2.751

Primary: fixed effects baseline value, time (categorical), randomised arm, arm-by-time interaction, age, sex, randomising centre, pre-test likelihood category. Correlation handled by repeated measures within patients, unstructured covariance pattern.

BL*Time: As for primary, but also including fixed effect for baseline*time interaction.

Appendix D: Supplementary analyses of SF12v2

Table D.1: Overall distribution of observed SF12v2 scale values, and frequency of floor/ceiling values at baseline, 12 and 36months follow-up. (Ranges 0=worst health, 100=best health)

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Body Pain (BP)				
Baseline				
n	478	479	235	1192
Mean (SD)	65.6 (25.75)	64.6 (27.22)	62.9 (26.29)	64.7 (26.45)
Median (Interquartile Range)	75 (50 to 75)	75 (50 to 75)	75 (50 to 75)	75 (50 to 75)
n (%) Min, Max value	14 (2.9%), 94 (19.7%)	22 (4.6%), 96 (20.0%)	8 (3.4%), 39 (16.6%)	44 (3.7%), 229 (19.2%)
12 months				
n	331	300	158	789
Mean (SD)	73.0 (28.93)	74.2 (28.10)	70.9 (29.44)	73.0 (28.71)
Median (Interquartile Range)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)
n (%) Min, Max value	13 (3.9%), 133 (40.2%)	10 (3.3%), 125 (41.7%)	8 (5.1%), 57 (36.1%)	31 (3.9%), 315 (39.9%)
36 months				
n	281	250	137	668
Mean (SD)	75.4 (28.58)	72.1 (29.96)	71.0 (29.59)	73.2 (29.32)
Median (Interquartile Range)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)
n (%) Min, Max value	11 (3.9%), 125 (44.5%)	15 (6.0%), 97 (38.8%)	5 (3.6%), 55 (40.1%)	31 (4.6%), 277 (41.5%)
General Health (GH)				
Baseline				
n	478	479	235	1192
Mean (SD)	53.8 (26.13)	54.0 (25.48)	53.5 (26.80)	53.8 (25.98)
Median (Interquartile Range)	60 (25 to 60)	60 (25 to 60)	60 (25 to 60)	60 (25 to 60)
n (%) Min, Max value	26 (5.4%), 15 (3.1%)	25 (5.2%), 17 (3.5%)	18 (7.7%), 8 (3.4%)	69 (5.8%), 40 (3.4%)
12 months				
n	332	301	157	790
Mean (SD)	56.6 (28.07)	57.4 (26.54)	55.4 (26.98)	56.7 (27.25)
Median (Interquartile Range)	60 (25 to 85)	60 (25 to 85)	60 (25 to 85)	60 (25 to 85)
n (%) Min, Max value	24 (7.2%), 15 (4.5%)	15 (5.0%), 12 (4.0%)	13 (8.3%), 6 (3.8%)	52 (6.6%), 33 (4.2%)
36 months				
n	280	250	136	666

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Mean (SD)	57.5 (28.40)	56.8 (27.21)	56.8 (27.51)	57.1 (27.74)
Median (Interquartile Range)	60 (25 to 85)	60 (25 to 85)	60 (25 to 85)	60 (25 to 85)
n (%) Min, Max value	21 (7.5%), 15 (5.4%)	16 (6.4%), 9 (3.6%)	8 (5.9%), 7 (5.1%)	45 (6.8%), 31 (4.7%)
Physical Functioning (PF)				
Baseline				
n	478	479	235	1192
Mean (SD)	60.2 (31.05)	58.1 (30.89)	58.2 (31.44)	59.0 (31.05)
Median (Interquartile Range)	50 (50 to 91.1)	50 (45 to 75)	50 (50 to 75)	50 (50 to 75)
n (%) Min, Max value	39 (8.2%), 119 (24.9%)	41 (8.6%), 108 (22.5%)	24 (10.2%), 57 (24.3%)	104 (8.7%), 284 (23.8%)
12 months				
n	332	301	158	791
Mean (SD)	62.6 (33.50)	64.0 (33.29)	58.5 (33.06)	62.3 (33.35)
Median (Interquartile Range)	75 (50 to 100)	75 (50 to 100)	50 (25 to 75)	75 (50 to 100)
n (%) Min, Max value	39 (11.7%), 105 (31.6%)	31 (10.3%), 101 (33.6%)	19 (12.0%), 38 (24.1%)	89 (11.3%), 244 (30.8%)
36 months				
n	282	250	137	669
Mean (SD)	65.7 (33.26)	63.2 (35.70)	57.1 (36.50)	63.0 (34.95)
Median (Interquartile Range)	75 (50 to 100)	75 (45 to 100)	50 (25 to 100)	75 (45 to 100)
n (%) Min, Max value	26 (9.2%), 99 (35.1%)	33 (13.2%), 91 (36.4%)	25 (18.2%), 39 (28.5%)	84 (12.6%), 229 (34.2%)
Role Performance (RP)				
Baseline				
n	478	478	234	1190
Mean (SD)	64.3 (26.07)	62.0 (26.11)	63.0 (27.61)	63.1 (26.39)
Median (Interquartile Range)	62.5 (50 to 87.5)	62.5 (50 to 75)	62.5 (50 to 87.5)	62.5 (50 to 78.9)
n (%) Min, Max value	11 (2.3%), 91 (19.0%)	17 (3.6%), 75 (15.7%)	11 (4.7%), 42 (17.9%)	39 (3.3%), 208 (17.5%)
12 months				
n	332	300	158	790
Mean (SD)	70.6 (30.18)	70.9 (28.48)	69.0 (29.63)	70.4 (29.41)
Median (Interquartile Range)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)
n (%) Min, Max value	19 (5.7%), 113 (34.0%)	12 (4.0%), 98 (32.7%)	7 (4.4%), 49 (31.0%)	38 (4.8%), 260 (32.9%)
36 months				
n	282	250	136	668

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Mean (SD)	70.2 (29.63)	69.1 (31.03)	67.1 (29.64)	69.2 (30.14)
Median (Interquartile Range)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)
n (%) Min, Max value	15 (5.3%), 91 (32.3%)	14 (5.6%), 91 (36.4%)	5 (3.7%), 41 (30.1%)	34 (5.1%), 223 (33.4%)
Physical Component Summary (PCS)				
Baseline				
n	477	478	235	1190
Mean (SD)	44.2 (9.71)	43.9 (9.25)	44.0 (9.45)	44.1 (9.47)
Median (Interquartile Range)	45.2 (37.4 to 51.7)	44.6 (37.8 to 50.9)	43.9 (38.5 to 51.4)	44.6 (37.8 to 51.4)
n (%) Min, Max value	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)
12 months				
n	332	299	157	788
Mean (SD)	46.3 (10.34)	46.6 (10.19)	45.3 (10.22)	46.2 (10.26)
Median (Interquartile Range)	47.7 (40.8 to 55.6)	48.2 (40.6 to 55.4)	46.3 (38.4 to 53.8)	47.6 (39.9 to 55)
n (%) Min, Max value	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)
36 months				
n	278	250	137	665
Mean (SD)	46.9 (11.16)	45.8 (11.19)	45.2 (10.99)	46.1 (11.14)
Median (Interquartile Range)	49.5 (40.6 to 55.9)	48.1 (38.3 to 55.6)	46.7 (37.1 to 55.6)	48.5 (38.6 to 55.9)
n (%) Min, Max value	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)
Mental Health (MH)				
Baseline				
n	477	475	236	1188
Mean (SD)	64.1 (21.17)	63.7 (21.08)	61.5 (23.30)	63.4 (21.58)
Median (Interquartile Range)	62.5 (50 to 75)	62.5 (50 to 75)	62.5 (50 to 75)	62.5 (50 to 75)
n (%) Min, Max value	3 (0.6%), 21 (4.4%)	1 (0.2%), 21 (4.4%)	5 (2.1%), 10 (4.2%)	9 (0.8%), 52 (4.4%)
12 months				
n	332	299	157	788
Mean (SD)	65.8 (23.92)	66.8 (21.50)	66.6 (23.03)	66.4 (22.83)
Median (Interquartile Range)	75 (50 to 87.5)	75 (50 to 87.5)	75 (50 to 87.5)	75 (50 to 87.5)
n (%) Min, Max value	5 (1.5%), 33 (9.9%)	2 (0.7%), 23 (7.7%)	2 (1.3%), 10 (6.4%)	9 (1.1%), 66 (8.4%)
36 months				
n	278	250	137	665

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Mean (SD)	66.8 (23.21)	69.6 (20.45)	66.3 (22.42)	67.7 (22.06)
Median (Interquartile Range)	75 (50 to 87.5)	75 (50 to 87.5)	75 (50 to 87.5)	75 (50 to 87.5)
n (%) Min, Max value	4 (1.4%), 20 (7.2%)	2 (0.8%), 22 (8.8%)	2 (1.5%), 9 (6.6%)	8 (1.2%), 51 (7.7%)
Role Emotional (RE)				
Baseline				
n	478	478	235	1191
Mean (SD)	79.5 (24.82)	76.2 (26.71)	76.1 (26.70)	77.5 (26.00)
Median (Interquartile Range)	87.5 (62.5 to 100)	87.5 (50 to 100)	75 (50 to 100)	87.5 (62.5 to 100)
n (%) Min, Max value	6 (1.3%), 222 (46.4%)	9 (1.9%), 201 (42.1%)	4 (1.7%), 99 (42.1%)	19 (1.6%), 522 (43.8%)
12 months				
n	332	301	158	791
Mean (SD)	79.3 (26.89)	80.8 (25.62)	77.7 (28.47)	79.5 (26.73)
Median (Interquartile Range)	100 (60.7 to 100)	100 (75 to 100)	87.5 (62.5 to 100)	100 (62.5 to 100)
n (%) Min, Max value	10 (3.0%), 169 (50.9%)	4 (1.3%), 151 (50.2%)	5 (3.2%), 77 (48.7%)	19 (2.4%), 397 (50.2%)
36 months				
n	282	250	137	669
Mean (SD)	80.2 (25.01)	79.9 (26.17)	76.0 (27.09)	79.2 (25.89)
Median (Interquartile Range)	100 (62.5 to 100)	98 (75 to 100)	75 (50 to 100)	87.5 (62.5 to 100)
n (%) Min, Max value	2 (0.7%), 144 (51.1%)	6 (2.4%), 123 (49.2%)	3 (2.2%), 59 (43.1%)	11 (1.6%), 326 (48.7%)
Social Functioning (SF)				
Baseline				
n	476	478	236	1190
Mean (SD)	74.0 (28.24)	74.7 (27.40)	71.2 (28.92)	73.7 (28.05)
Median (Interquartile Range)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)
n (%) Min, Max value	17 (3.6%), 207 (43.5%)	15 (3.1%), 207 (43.3%)	8 (3.4%), 94 (39.8%)	40 (3.4%), 508 (42.7%)
12 months				
n	332	299	158	789
Mean (SD)	77.0 (28.12)	77.1 (27.51)	75.6 (30.12)	76.8 (28.28)
Median (Interquartile Range)	87.5 (50 to 100)	75 (50 to 100)	100 (50 to 100)	100 (50 to 100)
n (%) Min, Max value	13 (3.9%), 166 (50.0%)	9 (3.0%), 149 (49.8%)	6 (3.8%), 81 (51.3%)	28 (3.5%), 396 (50.2%)
36 months				
n	278	249	135	662

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Mean (SD)	77.1 (27.82)	76.6 (28.97)	73.9 (29.75)	76.2 (28.64)
Median (Interquartile Range)	100 (50 to 100)	100 (50 to 100)	75 (50 to 100)	100 (50 to 100)
n (%) Min, Max value	8 (2.9%), 140 (50.4%)	9 (3.6%), 128 (51.4%)	4 (3.0%), 64 (47.4%)	21 (3.2%), 332 (50.2%)
Vitality (VT)				
Baseline				
n	474	475	235	1184
Mean (SD)	47.4 (25.62)	44.8 (25.69)	45.7 (26.00)	46.0 (25.73)
Median (Interquartile Range)	50 (25 to 75)	50 (25 to 75)	50 (25 to 75)	50 (25 to 75)
n (%) Min, Max value	47 (9.9%), 13 (2.7%)	59 (12.4%), 14 (2.9%)	27 (11.5%), 6 (2.6%)	133 (11.2%), 33 (2.8%)
12 months				
n	327	296	156	779
Mean (SD)	50.5 (26.92)	50.7 (24.86)	51.4 (25.60)	50.7 (25.86)
Median (Interquartile Range)	50 (25 to 75)	50 (25 to 75)	50 (25 to 75)	50 (25 to 75)
n (%) Min, Max value	39 (11.9%), 11 (3.4%)	26 (8.8%), 8 (2.7%)	14 (9.0%), 4 (2.6%)	79 (10.1%), 23 (3.0%)
36 months				
n	275	248	137	660
Mean (SD)	50.2 (26.85)	51.1 (25.08)	51.6 (27.15)	50.8 (26.23)
Median (Interquartile Range)	50 (25 to 75)	50 (25 to 75)	50 (25 to 75)	50 (25 to 75)
n (%) Min, Max value	30 (10.9%), 10 (3.6%)	23 (9.3%), 6 (2.4%)	14 (10.2%), 8 (5.8%)	67 (10.2%), 24 (3.6%)
Mental Component Summary (MCS)				
Baseline				
n	477	475	235	1187
Mean (SD)	49.2 (9.86)	48.6 (10.46)	47.9 (11.10)	48.7 (10.36)
Median (Interquartile Range)	50.7 (43.3 to 57.3)	50.5 (41.6 to 56.8)	49.6 (40.8 to 56.7)	50.5 (41.9 to 56.9)
n (%) Min, Max value	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)
12 months				
n	332	299	157	788
Mean (SD)	49.3 (10.83)	49.7 (9.76)	49.7 (10.72)	49.6 (10.40)
Median (Interquartile Range)	52.2 (42.2 to 57.4)	52.3 (43.9 to 57.4)	53 (43.1 to 57.5)	52.3 (43 to 57.4)
n (%) Min, Max value	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)
36 months				
n	278	250	137	665

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
Mean (SD)	49.4 (10.43)	50.4 (9.23)	49.4 (10.20)	49.8 (9.95)
Median (Interquartile Range)	52.3 (41.8 to 57.4)	52.7 (44.7 to 57.4)	51.9 (42.9 to 57.4)	52.4 (43 to 57.4)
n (%) Min, Max value	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)	0 (0.0%), 0 (0.0%)

Table D2: Comparison of primary and sensitivity mixed effects (random coefficients) modelling of SF12v2

	CG95 (2010) vs CMR				SPECT vs CMR			
			95% CI				95% CI	
Domain / Analysis	Estimate	Standard Error	Lower	Upper	Estimate	Standard Error	Lower	Upper
Body Pain								
Primary	-0.0777	0.070	-0.2156	0.0602	-0.1058	0.059	-0.2221	0.0106
Baseline*Time	-0.0780	0.070	-0.2161	0.0601	-0.1081	0.059	-0.2246	0.0084
Multiple Imputation	-0.0841	0.078	-0.2368	0.0687	-0.0878	0.063	-0.2116	0.0360
Proportional Odds	-0.0091	0.010	-0.0281	0.0100	-0.0172	0.008	-0.0333	-0.0011
General Health								
Primary	-0.0647	0.069	-0.2000	0.0706	0.0048	0.056	-0.1042	0.1138
Baseline*Time	-0.0627	0.069	-0.1978	0.0724	0.0051	0.056	-0.1039	0.1142
Multiple Imputation	-0.0391	0.069	-0.1756	0.0974	0.0119	0.057	-0.1010	0.1248
Proportional Odds	-0.0063	0.010	-0.0256	0.0130	-0.0019	0.008	-0.0181	0.0143
Mental Component Summary								
Primary	-0.0057	0.028	-0.0612	0.0498	0.0196	0.023	-0.0260	0.0652
Baseline*Time	-0.0088	0.028	-0.0643	0.0466	0.0152	0.023	-0.0304	0.0607
Multiple Imputation	0.0002	0.028	-0.0554	0.0557	0.0206	0.025	-0.0296	0.0708
Mental Health								
Primary	-0.0431	0.063	-0.1674	0.0812	0.0440	0.052	-0.0578	0.1458
Baseline*Time	-0.0438	0.063	-0.1681	0.0805	0.0402	0.052	-0.0614	0.1418
Multiple Imputation	-0.0470	0.065	-0.1758	0.0817	0.0571	0.051	-0.0429	0.1570
Physical Component Summary								
Primary	-0.0516	0.025	-0.1006	-0.0025	-0.0162	0.021	-0.0567	0.0243
Baseline*Time	-0.0512	0.025	-0.1002	-0.0022	-0.0170	0.021	-0.0575	0.0236
Multiple Imputation	-0.0513	0.027	-0.1043	0.0016	-0.0149	0.023	-0.0597	0.0299
Physical Functioning								
Primary	-0.2242	0.083	-0.3862	-0.0623	-0.0355	0.065	-0.1637	0.0926
Baseline*Time	-0.2254	0.083	-0.3874	-0.0633	-0.0414	0.065	-0.1698	0.0871
Multiple Imputation	-0.2296	0.079	-0.3851	-0.0741	-0.0335	0.067	-0.1645	0.0975
Role Emotional								
Primary	-0.0610	0.071	-0.2007	0.0787	0.0024	0.060	-0.1161	0.1209
Baseline*Time	-0.0680	0.071	-0.2083	0.0722	-0.0055	0.061	-0.1246	0.1136
Multiple Imputation	-0.0160	0.078	-0.1690	0.1370	0.0168	0.061	-0.1041	0.1377
Role Performance								
Primary	-0.0996	0.070	-0.2379	0.0387	0.0191	0.059	-0.0976	0.1358

	CG95 (2010) vs CMR				SPECT vs CMR			
			95% CI				95% CI	
Domain / Analysis	**Estimate**	**Standard Error**	**Lower**	**Upper**	**Estimate**	**Standard Error**	**Lower**	**Upper**
Baseline*Time	-0.0979	0.070	-0.2360	0.0402	0.0154	0.060	-0.1015	0.1323
Multiple Imputation	-0.0810	0.069	-0.2165	0.0546	0.0138	0.062	-0.1079	0.1354
Social Functioning								
Primary	-0.0829	0.076	-0.2324	0.0666	-0.0297	0.064	-0.1561	0.0967
Baseline*Time	-0.0857	0.076	-0.2354	0.0641	-0.0319	0.064	-0.1584	0.0946
Multiple Imputation	-0.0663	0.087	-0.2386	0.1060	-0.0384	0.072	-0.1805	0.1036
Proportional Odds	-0.0094	0.010	-0.0281	0.0094	-0.0054	0.008	-0.0212	0.0104
Vitality								
Primary	-0.0255	0.074	-0.1707	0.1197	0.0737	0.060	-0.0447	0.1922
Baseline*Time	-0.0246	0.074	-0.1699	0.1207	0.0740	0.061	-0.0451	0.1932
Multiple Imputation	-0.0222	0.079	-0.1775	0.1332	0.0791	0.061	-0.0402	0.1985
Proportional Odds	0.0006	0.009	-0.0170	0.0183	0.0078	0.008	-0.0071	0.0227

Estimate=Estimated interaction effect between NICE (or SPECT) and time in months. Negative values indicate CMR improving vs comparator, positive values indicate comparator improving vs CMR.

Lower/Upper = Limits of 95% Confidence Interval for the difference

Baseline*Time=Fitting the primary analysis model, with an additional fixed interaction effect for baseline-by-time, allowing patients with different health statuses to have different trajectories during the follow-up.

Proportional Odds=Replacing linear mixed model with an ordinal proportional odds model, modelling the odds of moving up to greater values. Only done for the Body Pain, General Health, Social Functioning and Vitality scales, derived from a single 5-item question. Values <0 represent reduced log-odds per month of moving to higher scores for CG95/SPECT vs CMR, values >0 represent increased log-odds per month of moving up to higher scores vs CMR. Thus the estimate of = -0.0172 for Body Pain in the SPECT comparison indicates that the odds of a SPECT patient having a higher Body Pain score change by exp(-0.0172) - 1 = -1.71% per month compared to the CMR arm.

Table D3: Comparison of primary and sensitivity Repeated Measures (covariance pattern) models of SF12v2 domains at 12 and 36 months post-randomisation

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err**	**Lower**	**Upper**	**Est.**	**Std Err**	**Lower**	**Upper**
Body Pain										
CMR (n=331)	12 months	Primary	71.244	1.763	67.785	74.703				
		BL*Time	71.268	1.762	67.809	74.727				
		Mult. Imput.	70.088	2.510	65.166	75.010				
SPECT (n=300)	12 months	Primary	72.525	1.771	69.049	76.001	1.281	1.862	-2.373	4.935
		BL*Time	72.514	1.771	69.039	75.990	1.246	1.862	-2.408	4.901
		Mult. Imput.	71.038	2.483	66.169	75.907	0.950	1.927	-2.835	4.735
CG95 (2010) (n=158)	12 months	Primary	69.102	2.217	64.751	73.452	-2.142	2.263	-6.583	2.299
		BL*Time	69.111	2.217	64.761	73.461	-2.157	2.263	-6.598	2.284
		Mult. Imput.	68.125	2.839	62.557	73.693	-1.963	2.196	-6.270	2.344
CMR (n=281)	36 months	Primary	72.534	1.849	68.906	76.162				
		BL*Time	72.555	1.849	68.926	76.184				
		Mult. Imput.	70.607	2.528	65.649	75.565				
SPECT (n=250)	36 months	Primary	70.213	1.872	66.539	73.887	-2.321	2.033	-6.311	1.669
		BL*Time	70.200	1.872	66.526	73.874	-2.355	2.034	-6.347	1.638
		Mult. Imput.	68.404	2.648	63.210	73.598	-2.203	2.178	-6.487	2.081
CG95 (2010) (n=137)	36 months	Primary	68.521	2.347	63.915	73.126	-4.013	2.455	-8.831	0.805
		BL*Time	68.542	2.347	63.936	73.149	-4.013	2.456	-8.832	0.807
		Mult. Imput.	66.198	2.995	60.321	72.075	-4.409	2.605	-9.529	0.711
General Health										
CMR (n=332)	12 months	Primary	56.038	1.494	53.106	58.971				
		BL*Time	56.040	1.494	53.107	58.972				
		Mult. Imput.	56.907	2.089	52.811	61.002				
SPECT (n=301)	12 months	Primary	55.894	1.503	52.944	58.844	-0.144	1.577	-3.239	2.951
		BL*Time	55.885	1.503	52.935	58.835	-0.155	1.577	-3.250	2.940
		Mult. Imput.	56.919	2.115	52.772	61.066	0.012	1.589	-3.108	3.133
CG95 (2010) (n=157)	12 months	Primary	53.386	1.885	49.685	57.086	-2.653	1.920	-6.421	1.116
		BL*Time	53.368	1.886	49.667	57.069	-2.672	1.920	-6.440	1.097

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err**	**Lower**	**Upper**	**Est.**	**Std Err**	**Lower**	**Upper**
		Mult. Imput.	54.756	2.404	50.040	59.472	-2.150	1.958	-5.994	1.693
CMR (n=280)	36 months	Primary	55.716	1.634	52.508	58.923				
		BL*Time	55.767	1.634	52.560	58.974				
		Mult. Imput.	56.521	2.252	52.102	60.940				
SPECT (n=250)	36 months	Primary	54.805	1.661	51.546	58.065	-0.910	1.847	-4.535	2.714
		BL*Time	54.835	1.661	51.576	58.095	-0.932	1.846	-4.555	2.691
		Mult. Imput.	55.906	2.225	51.541	60.272	-0.615	1.809	-4.168	2.939
CG95 (2010) (n=136)	36 months	Primary	53.555	2.098	49.438	57.673	-2.160	2.231	-6.538	2.218
		BL*Time	53.634	2.099	49.515	57.753	-2.133	2.231	-6.511	2.245
		Mult. Imput.	55.036	2.580	49.974	60.097	-1.485	2.220	-5.846	2.875
Mental Component Summary										
CMR (n=332)	12 months	Primary	49.673	0.630	48.436	50.909				
		BL*Time	49.683	0.630	48.446	50.919				
		Mult. Imput.	49.168	0.901	47.400	50.935				
SPECT (n=299)	12 months	Primary	50.411	0.636	49.163	51.658	0.738	0.683	-0.603	2.079
		BL*Time	50.419	0.636	49.171	51.667	0.736	0.684	-0.606	2.079
		Mult. Imput.	49.937	0.908	48.155	51.719	0.770	0.697	-0.598	2.138
CG95 (2010) (n=157)	12 months	Primary	49.965	0.802	48.392	51.539	0.293	0.831	-1.337	1.923
		BL*Time	49.970	0.802	48.396	51.543	0.287	0.831	-1.344	1.917
		Mult. Imput.	49.344	1.037	47.309	51.378	0.176	0.858	-1.510	1.862
CMR (n=278)	36 months	Primary	49.412	0.653	48.130	50.693				
		BL*Time	49.508	0.652	48.229	50.788				
		Mult. Imput.	49.126	0.925	47.310	50.941				
SPECT (n=250)	36 months	Primary	50.931	0.662	49.632	52.231	1.519	0.727	0.093	2.946
		BL*Time	50.926	0.660	49.630	52.221	1.417	0.725	-0.005	2.839
		Mult. Imput.	50.665	0.936	48.828	52.502	1.539	0.793	-0.021	3.100
CG95 (2010) (n=137)	36 months	Primary	49.667	0.830	48.037	51.296	0.255	0.876	-1.464	1.974
		BL*Time	49.684	0.828	48.060	51.309	0.176	0.872	-1.536	1.888
		Mult. Imput.	49.345	1.092	47.201	51.489	0.219	0.928	-1.606	2.045

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err**	**Lower**	**Upper**	**Est.**	**Std Err**	**Lower**	**Upper**
Mental Health										
CMR (n=332)	12 months	Primary	65.783	1.399	63.038	68.528				
		BL*Time	65.794	1.399	63.048	68.539				
		Mult. Imput.	64.988	1.997	61.072	68.905				
SPECT (n=299)	12 months	Primary	66.961	1.413	64.187	69.734	1.178	1.530	-1.825	4.180
		BL*Time	66.958	1.414	64.184	69.732	1.164	1.531	-1.840	4.168
		Mult. Imput.	66.151	1.970	62.288	70.014	1.162	1.546	-1.873	4.198
CG95 (2010) (n=157)	12 months	Primary	65.782	1.786	62.277	69.288	-0.001	1.860	-3.652	3.650
		BL*Time	65.784	1.787	62.278	69.291	-0.009	1.861	-3.662	3.643
		Mult. Imput.	64.646	2.313	60.107	69.184	-0.342	1.879	-4.032	3.347
CMR (n=278)	36 months	Primary	65.995	1.436	63.176	68.813				
		BL*Time	66.056	1.436	63.237	68.875				
		Mult. Imput.	65.708	1.997	61.791	69.626				
SPECT (n=250)	36 months	Primary	69.426	1.457	66.567	72.284	3.431	1.600	0.290	6.572
		BL*Time	69.433	1.456	66.576	72.291	3.377	1.600	0.237	6.517
		Mult. Imput.	69.303	1.973	65.433	73.174	3.595	1.527	0.597	6.592
CG95 (2010) (n=137)	36 months	Primary	65.434	1.827	61.849	69.019	-0.561	1.928	-4.344	3.222
		BL*Time	65.492	1.827	61.907	69.077	-0.564	1.927	-4.345	3.217
		Mult. Imput.	64.700	2.239	60.308	69.092	-1.008	1.898	-4.736	2.719
Physical Component Summary										
CMR (n=332)	12 months	Primary	45.836	0.555	44.747	46.925				
		BL*Time	45.836	0.555	44.747	46.925				
		Mult. Imput.	46.623	0.797	45.059	48.187				
SPECT (n=299)	12 months	Primary	46.161	0.559	45.065	47.258	0.325	0.581	-0.814	1.465
		BL*Time	46.156	0.559	45.060	47.252	0.320	0.581	-0.820	1.459
		Mult. Imput.	46.972	0.804	45.395	48.549	0.349	0.557	-0.744	1.441
CG95 (2010) (n=157)	12 months	Primary	44.502	0.698	43.133	45.871	-1.334	0.706	-2.720	0.053
		BL*Time	44.516	0.697	43.147	45.884	-1.321	0.706	-2.707	0.065
		Mult. Imput.	45.501	0.916	43.705	47.298	-1.122	0.698	-2.493	0.249

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err**	**Lower**	**Upper**	**Est.**	**Std Err**	**Lower**	**Upper**
CMR (n=278)	36 months	Primary	45.967	0.620	44.750	47.184				
		BL*Time	45.968	0.620	44.751	47.186				
		Mult. Imput.	46.590	0.847	44.928	48.251				
SPECT (n=250)	36 months	Primary	45.264	0.630	44.028	46.501	-0.702	0.705	-2.085	0.681
		BL*Time	45.260	0.630	44.023	46.497	-0.708	0.705	-2.092	0.676
		Mult. Imput.	45.902	0.911	44.113	47.691	-0.688	0.740	-2.143	0.766
CG95 (2010) (n=137)	36 months	Primary	43.705	0.797	42.142	45.268	-2.261	0.850	-3.930	-0.592
		BL*Time	43.724	0.797	42.160	45.288	-2.244	0.851	-3.914	-0.575
		Mult. Imput.	44.463	1.017	42.467	46.459	-2.127	0.863	-3.823	-0.432
Physical Functioning										
CMR (n=332)	12 months	Primary	60.088	1.901	56.356	63.819				
		BL*Time	60.119	1.901	56.388	63.851				
		Mult. Imput.	61.328	2.676	56.082	66.574				
SPECT (n=301)	12 months	Primary	62.905	1.916	59.144	66.665	2.817	2.018	-1.144	6.778
		BL*Time	62.847	1.916	59.087	66.607	2.728	2.018	-1.233	6.688
		Mult. Imput.	63.583	2.689	58.310	68.855	2.254	1.980	-1.632	6.141
CG95 (2010) (n=158)	12 months	Primary	56.132	2.400	51.422	60.841	-3.956	2.453	-8.770	0.859
		BL*Time	56.154	2.399	51.446	60.862	-3.966	2.452	-8.778	0.846
		Mult. Imput.	57.595	3.069	51.574	63.615	-3.734	2.534	-8.711	1.244
CMR (n=282)	36 months	Primary	61.741	2.027	57.764	65.719				
		BL*Time	61.758	2.029	57.776	65.740				
		Mult. Imput.	63.310	2.708	58.000	68.621				
SPECT (n=250)	36 months	Primary	62.245	2.062	58.198	66.293	0.504	2.266	-3.943	4.951
		BL*Time	62.224	2.064	58.174	66.274	0.466	2.270	-3.989	4.921
		Mult. Imput.	63.294	2.860	57.683	68.906	-0.016	2.230	-4.396	4.364
CG95 (2010) (n=137)	36 months	Primary	53.080	2.590	47.997	58.162	-8.662	2.732	-14.023	-3.300
		BL*Time	53.127	2.592	48.040	58.214	-8.631	2.734	-13.995	-3.266
		Mult. Imput.	54.447	3.182	48.206	60.689	-8.863	2.632	-14.029	-3.696
Role Emotional										

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err**	**Lower**	**Upper**	**Est.**	**Std Err**	**Lower**	**Upper**
CMR (n=332)	12 months	Primary	79.859	1.656	76.609	83.110				
		BL*Time	79.787	1.656	76.537	83.037				
		Mult. Imput.	78.958	2.394	74.262	83.653				
SPECT (n=301)	12 months	Primary	82.806	1.669	79.531	86.082	2.947	1.773	-0.532	6.427
		BL*Time	82.877	1.669	79.602	86.151	3.090	1.775	-0.393	6.573
		Mult. Imput.	81.650	2.326	77.089	86.212	2.692	1.773	-0.789	6.173
CG95 (2010) (n=158)	12 months	Primary	79.258	2.095	75.147	83.370	-0.601	2.154	-4.828	3.627
		BL*Time	79.267	2.095	75.157	83.378	-0.519	2.154	-4.748	3.709
		Mult. Imput.	77.543	2.695	72.256	82.831	-1.414	2.269	-5.872	3.044
CMR (n=282)	36 months	Primary	80.165	1.737	76.757	83.574				
		BL*Time	80.402	1.736	76.994	83.809				
		Mult. Imput.	79.056	2.529	74.092	84.021				
SPECT (n=250)	36 months	Primary	81.873	1.767	78.406	85.339	1.707	1.933	-2.087	5.502
		BL*Time	81.803	1.763	78.342	85.263	1.401	1.933	-2.393	5.194
		Mult. Imput.	81.050	2.453	76.236	85.864	1.993	1.972	-1.883	5.870
CG95 (2010) (n=137)	36 months	Primary	76.949	2.213	72.606	81.292	-3.216	2.329	-7.787	1.354
		BL*Time	76.943	2.208	72.610	81.276	-3.459	2.325	-8.021	1.104
		Mult. Imput.	76.124	2.817	70.594	81.654	-2.932	2.429	-7.708	1.844
Role Performance										
CMR (n=332)	12 months	Primary	70.748	1.775	67.265	74.231				
		BL*Time	70.736	1.775	67.253	74.219				
		Mult. Imput.	74.126	2.517	69.191	79.061				
SPECT (n=300)	12 months	Primary	71.806	1.787	68.299	75.312	1.057	1.849	-2.571	4.686
		BL*Time	71.780	1.787	68.273	75.287	1.044	1.850	-2.587	4.674
		Mult. Imput.	75.285	2.494	70.395	80.175	1.159	1.857	-2.487	4.805
CG95 (2010) (n=158)	12 months	Primary	68.123	2.223	63.760	72.486	-2.625	2.246	-7.033	1.783
		BL*Time	68.139	2.223	63.776	72.502	-2.597	2.247	-7.006	1.812
		Mult. Imput.	72.025	2.827	66.481	77.568	-2.101	2.334	-6.686	2.483
CMR (n=282)	36 months	Primary	69.313	1.891	65.602	73.024				

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err**	**Lower**	**Upper**	**Est.**	**Std Err**	**Lower**	**Upper**
		BL*Time	69.325	1.891	65.613	73.037				
		Mult. Imput.	72.551	2.605	67.443	77.659				
SPECT (n=250)	36 months	Primary	69.738	1.921	65.967	73.509	0.425	2.082	-3.660	4.511
		BL*Time	69.697	1.921	65.926	73.468	0.372	2.083	-3.716	4.460
		Mult. Imput.	72.844	2.721	67.505	78.183	0.294	2.094	-3.821	4.409
CG95 (2010) (n=136)	36 months	Primary	64.447	2.405	59.727	69.168	-4.866	2.514	-9.799	0.068
		BL*Time	64.501	2.406	59.778	69.223	-4.824	2.514	-9.758	0.109
		Mult. Imput.	68.379	3.021	62.451	74.306	-4.172	2.557	-9.197	0.854
Social Functioning										
CMR (n=332)	12 months	Primary	76.718	1.755	73.274	80.162				
		BL*Time	76.717	1.755	73.272	80.161				
		Mult. Imput.	76.006	2.566	70.974	81.038				
SPECT (n=299)	12 months	Primary	76.300	1.767	72.833	79.768	-0.418	1.853	-4.055	3.219
		BL*Time	76.306	1.767	72.837	79.774	-0.411	1.854	-4.050	3.227
		Mult. Imput.	75.816	2.553	70.808	80.823	-0.190	1.956	-4.032	3.651
CG95 (2010) (n=158)	12 months	Primary	75.409	2.208	71.075	79.742	-1.309	2.251	-5.726	3.108
		BL*Time	75.409	2.209	71.074	79.744	-1.308	2.252	-5.727	3.111
		Mult. Imput.	74.463	3.028	68.519	80.407	-1.543	2.439	-6.335	3.249
CMR (n=278)	36 months	Primary	75.234	1.896	71.514	78.954				
		BL*Time	75.393	1.895	71.674	79.111				
		Mult. Imput.	75.217	2.683	69.954	80.481				
SPECT (n=249)	36 months	Primary	75.049	1.925	71.271	78.827	-0.185	2.124	-4.353	3.984
		BL*Time	75.067	1.922	71.295	78.840	-0.325	2.121	-4.487	3.837
		Mult. Imput.	74.616	2.665	69.388	79.844	-0.602	2.161	-4.849	3.646
CG95 (2010) (n=135)	36 months	Primary	73.742	2.426	68.981	78.502	-1.492	2.567	-6.530	3.546
		BL*Time	73.752	2.422	68.999	78.505	-1.641	2.563	-6.669	3.388
		Mult. Imput.	73.650	3.156	67.454	79.847	-1.567	2.661	-6.799	3.664
Vitality										
CMR (n=327)	12 months	Primary	50.747	1.592	47.623	53.871				
		BL*Time	50.819	1.593	47.693	53.944				

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err**	**Lower**	**Upper**	**Est.**	**Std Err**	**Lower**	**Upper**
		Mult. Imput.	52.280	2.176	48.012	56.547				
SPECT (n=296)	12 months	Primary	52.654	1.611	49.493	55.815	1.907	1.741	-1.510	5.324
		BL*Time	52.580	1.612	49.418	55.743	1.762	1.744	-1.661	5.184
		Mult. Imput.	54.107	2.237	49.718	58.496	1.827	1.748	-1.605	5.259
CG95 (2010) (n=156)	12 months	Primary	51.135	2.028	47.154	55.115	0.387	2.111	-3.755	4.530
		BL*Time	51.183	2.028	47.202	55.164	0.364	2.111	-3.778	4.506
		Mult. Imput.	52.951	2.625	47.797	58.104	0.671	2.250	-3.752	5.093
CMR (n=275)	36 months	Primary	49.353	1.664	46.087	52.619				
		BL*Time	49.347	1.667	46.076	52.619				
		Mult. Imput.	50.866	2.265	46.423	55.309				
SPECT (n=248)	36 months	Primary	53.211	1.693	49.888	56.534	3.858	1.877	0.175	7.540
		BL*Time	53.220	1.694	49.895	56.545	3.873	1.883	0.178	7.567
		Mult. Imput.	54.926	2.295	50.423	59.429	4.060	1.880	0.365	7.755
CG95 (2010) (n=137)	36 months	Primary	50.046	2.118	45.889	54.203	0.693	2.250	-3.722	5.108
		BL*Time	50.061	2.119	45.902	54.220	0.714	2.251	-3.703	5.131
		Mult. Imput.	51.661	2.612	46.534	56.787	0.795	2.280	-3.688	5.277

Primary: fixed effects baseline value, time (categorical), randomised arm, arm-by-time interaction, age, sex, randomising centre, pre-test likelihood category. Correlation handled by repeated measures within patients, unstructured covariance pattern.

BL*Time: As for primary, but also including fixed effect for baseline*time interaction.

Appendix E: Supplementary analyses of Euroqol EQ-5D

Table E1: Overall distribution of observed EQ-5D-3L and EQ-5D-5L scale values, and frequency of floor/ceiling values at baseline, 12 and 36months follow-up. (Ranges: for -3L, -0.594= worst health. For -5L -0.281 = worst health. For both, 0=unconscious, 1=best health)

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
EQ-5D-3L Utility				
Baseline				
n	466	468	230	1164
Mean (SD)	0.757 (0.222)	0.743 (0.227)	0.728 (0.250)	0.746 (0.230)
Median (Interquartile Range)	0.796 (0.691 to 0.883)	0.760 (0.689 to 0.848)	0.743 (0.656 to 0.883)	0.760 (0.689 to 0.850)
n (%) Min, Max value	0 (0.0%), 113 (24.2%)	0 (0.0%), 103 (22.0%)	0 (0.0%), 57 (24.8%)	0 (0.0%), 273 (23.5%)
12 months				
n	322	295	155	772
Mean (SD)	0.785 (0.260)	0.776 (0.247)	0.746 (0.304)	0.774 (0.265)
Median (Interquartile Range)	0.812 (0.691 to 1.000)	0.796 (0.691 to 1.000)	0.796 (0.689 to 1.000)	0.796 (0.691 to 1.000)
n (%) Min, Max value	0 (0.0%), 130 (40.4%)	0 (0.0%), 106 (35.9%)	0 (0.0%), 59 (38.1%)	0 (0.0%), 295 (38.2%)
36 months				
n	275	247	133	655
Mean (SD)	0.791 (0.250)	0.756 (0.283)	0.741 (0.274)	0.767 (0.268)
Median (Interquartile Range)	0.848 (0.691 to 1.000)	0.796 (0.689 to 1.000)	0.796 (0.656 to 1.000)	0.796 (0.689 to 1.000)
n (%) Min, Max value	0 (0.0%), 113 (41.1%)	0 (0.0%), 86 (34.8%)	0 (0.0%), 42 (31.6%)	0 (0.0%), 241 (36.8%)
EQ-5D-5L Utility				
Baseline				
n	468	469	231	1168
Mean (SD)	0.843 (0.161)	0.831 (0.175)	0.817 (0.191)	0.833 (0.173)
Median (Interquartile Range)	0.879 (0.778 to 0.937)	0.859 (0.777 to 0.937)	0.859 (0.733 to 0.937)	0.861 (0.777 to 0.937)
n (%) Min, Max value	0 (0.0%), 98 (20.9%)	0 (0.0%), 96 (20.5%)	0 (0.0%), 50 (21.6%)	0 (0.0%), 244 (20.9%)
12 months				
n	320	295	156	771
Mean (SD)	0.845 (0.205)	0.843 (0.191)	0.829 (0.212)	0.841 (0.201)
Median (Interquartile Range)	0.922 (0.782 to 1.000)	0.892 (0.777 to 1.000)	0.887 (0.777 to 1.000)	0.896 (0.777 to 1.000)
n (%) Min, Max value	0 (0.0%), 111 (34.7%)	0 (0.0%), 96 (32.5%)	0 (0.0%), 50 (32.1%)	0 (0.0%), 257 (33.3%)

	3T CMR-Guided Care (n=481)	SPECT-Guided Care (n=481)	NICE CG95 (2010) (n=240)	Total (n=1202)
36 months				
n	278	246	135	659
Mean (SD)	0.850 (0.199)	0.826 (0.219)	0.808 (0.221)	0.833 (0.212)
Median (Interquartile Range)	0.916 (0.779 to 1.000)	0.887 (0.777 to 1.000)	0.859 (0.745 to 1.000)	0.892 (0.777 to 1.000)
n (%) Min, Max value	0 (0.0%), 110 (39.6%)	0 (0.0%), 70 (28.5%)	0 (0.0%), 38 (28.1%)	0 (0.0%), 218 (33.1%)

Table E2: Comparison of primary and sensitivity analyses of EQ5D-3L and EQ-5D-5L utilities analysed using mixed effects (random coefficients) models

	CG95 (2010) vs CMR				SPECT vs CMR			
			95% CI				95% CI	
Domain / Analysis	**Estimate**	**Standard Error**	**Lower**	**Upper**	**Estimate**	**Standard Error**	**Lower**	**Upper**
3L Utility								
Primary	-0.0009	0.0007	-0.0022	0.0004	-0.0007	0.0006	-0.0018	0.0004
Baseline*Time	-0.0009	0.0007	-0.0022	0.0004	-0.0007	0.0006	-0.0018	0.0004
Multiple Imputation	-0.0007	0.0007	-0.0021	0.0007	-0.0006	0.0006	-0.0017	0.0006
Proportional Odds	-0.0108	0.0107	-0.0317	0.0101	-0.0097	0.0118	-0.0328	0.0134
5L Utility								
Primary	-0.0009	0.0005	-0.0019	0.0001	-0.0006	0.0004	-0.0014	0.0001
Baseline*Time	-0.0009	0.0005	-0.0019	0.0001	-0.0006	0.0004	-0.0014	0.0001
Multiple Imputation	-0.0009	0.0005	-0.0019	0.0002	-0.0006	0.0004	-0.0015	0.0003
Proportional Odds	-0.0157	0.0066	-0.0286	-0.0029	-0.0111	0.0049	-0.0208	-0.0015

Estimate=Estimated interaction effect between NICE (or SPECT) and time in months. Negative values indicate CMR improving vs comparator, positive values indicate comparator improving vs CMR.

Lower/Upper = Limits of 95% Confidence Interval for the difference

Baseline*Time=Fitting the primary analysis model, with an additional fixed interaction effect for baseline-by-time, allowing patients with different health statuses to have different trajectories during the follow-up.

Proportional Odds=Replacing linear mixed model with an ordinal proportional odds model, modelling the odds of moving up to greater values. Performed as an additional analysis, in light of the skewed distribution. Values <0 represent reduced log-odds per month of moving to higher scores for CG95/SPECT vs CMR, values >0 represent increased log-odds per month of moving up to higher scores vs CMR. Thus the estimate of -0.01571 for -5L Utility in the NICE comparison indicates that the odds of a NICE patient having a higher -5L Utility change by exp(-0.0157) -1 = -1.56% per month compared to the CMR arm.

Table E3: Comparison of primary and sensitivity Repeated Measures (covariance pattern) modelling of EQ-5D-3L and EQ-5D-5L at 12 and 36months post-randomisation

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err.**	**Lower**	**Upper**	**Est.**	**Std Err.**	**Lower**	**Upper**
3L Utility										
CMR (n=322)	12 months	Primary	0.786	0.016	0.754	0.818				
		BL*Time	0.791	0.016	0.759	0.823				
		Mult. Imput.	0.795	0.023	0.749	0.841				
SPECT (n=295)	12 months	Primary	0.779	0.016	0.747	0.811	-0.007	0.017	-0.041	0.028
		BL*Time	0.782	0.016	0.750	0.814	-0.008	0.017	-0.043	0.026
		Mult. Imput.	0.784	0.023	0.739	0.830	-0.011	0.018	-0.046	0.024
CG95 (2010) (n=155)	12 months	Primary	0.746	0.021	0.706	0.787	-0.039	0.021	-0.081	0.002
		BL*Time	0.751	0.020	0.711	0.791	-0.040	0.021	-0.081	0.002
		Mult. Imput.	0.763	0.027	0.710	0.816	-0.032	0.021	-0.074	0.010
CMR (n=275)	36 months	Primary	0.782	0.017	0.749	0.814				
		BL*Time	0.786	0.017	0.754	0.818				
		Mult. Imput.	0.794	0.024	0.747	0.841				
SPECT (n=247)	36 months	Primary	0.761	0.017	0.728	0.794	-0.021	0.018	-0.056	0.015
		BL*Time	0.765	0.017	0.732	0.797	-0.021	0.018	-0.057	0.014
		Mult. Imput.	0.772	0.024	0.725	0.818	-0.022	0.018	-0.057	0.013
CG95 (2010) (n=133)	36 months	Primary	0.737	0.021	0.695	0.778	-0.045	0.022	-0.088	-0.002
		BL*Time	0.741	0.021	0.700	0.782	-0.045	0.022	-0.088	-0.002
		Mult. Imput.	0.755	0.028	0.700	0.811	-0.039	0.022	-0.082	0.005
5L (Crosswalk) Utility										
CMR (n=320)	12 months	Primary	0.801	0.014	0.773	0.829				
		BL*Time	0.804	0.014	0.776	0.831				
		Mult. Imput.	0.791	0.020	0.752	0.831				
SPECT (n=295)	12 months	Primary	0.796	0.014	0.768	0.824	-0.005	0.015	-0.034	0.025
		BL*Time	0.798	0.014	0.770	0.826	-0.006	0.015	-0.035	0.024
		Mult. Imput.	0.786	0.020	0.746	0.825	-0.006	0.015	-0.036	0.024
CG95 (2010) (n=156)	12 months	Primary	0.769	0.018	0.734	0.804	-0.032	0.018	-0.068	0.003

			Least-Squares Means				Least Squares Mean differences vs CMR			
					95% CI				95% CI	
Domain / randomised arm	**Time**	**Analysis**	**Est.**	**Std Err.**	**Lower**	**Upper**	**Est.**	**Std Err.**	**Lower**	**Upper**
		BL*Time	0.771	0.018	0.736	0.806	-0.033	0.018	-0.068	0.003
		Mult. Imput.	0.763	0.024	0.716	0.811	-0.028	0.019	-0.066	0.010
CMR (n=278)	36 months	Primary	0.801	0.015	0.772	0.830				
		BL*Time	0.803	0.015	0.775	0.832				
		Mult. Imput.	0.787	0.020	0.747	0.827				
SPECT (n=246)	36 months	Primary	0.775	0.015	0.746	0.804	-0.026	0.016	-0.057	0.005
		BL*Time	0.777	0.015	0.748	0.806	-0.026	0.016	-0.058	0.005
		Mult. Imput.	0.765	0.020	0.725	0.805	-0.022	0.015	-0.052	0.007
CG95 (2010) (n=135)	36 months	Primary	0.756	0.018	0.720	0.792	-0.045	0.019	-0.083	-0.007
		BL*Time	0.758	0.018	0.722	0.795	-0.045	0.019	-0.083	-0.007
		Mult. Imput.	0.752	0.026	0.702	0.803	-0.035	0.021	-0.076	0.006
5L Utility										
CMR (n=320)	12 months	Primary	0.854	0.012	0.831	0.877				
		BL*Time	0.856	0.012	0.834	0.879				
		Mult. Imput.	0.836	0.017	0.803	0.870				
SPECT (n=295)	12 months	Primary	0.854	0.012	0.831	0.877	0.000	0.012	-0.024	0.024
		BL*Time	0.856	0.012	0.833	0.879	-0.000	0.012	-0.024	0.024
		Mult. Imput.	0.837	0.018	0.802	0.872	0.001	0.013	-0.025	0.027
CG95 (2010) (n=156)	12 months	Primary	0.837	0.015	0.808	0.866	-0.017	0.015	-0.046	0.012
		BL*Time	0.839	0.015	0.811	0.868	-0.017	0.015	-0.046	0.012
		Mult. Imput.	0.829	0.019	0.792	0.867	-0.007	0.014	-0.035	0.022
CMR (n=278)	36 months	Primary	0.851	0.012	0.826	0.875				
		BL*Time	0.852	0.012	0.828	0.876				
		Mult. Imput.	0.832	0.017	0.798	0.866				
SPECT (n=246)	36 months	Primary	0.837	0.013	0.813	0.862	-0.013	0.014	-0.040	0.013
		BL*Time	0.840	0.012	0.815	0.864	-0.013	0.014	-0.039	0.014
		Mult. Imput.	0.818	0.018	0.783	0.854	-0.014	0.014	-0.041	0.014
CG95 (2010) (n=135)	36 months	Primary	0.815	0.016	0.784	0.845	-0.036	0.016	-0.068	-0.004
		BL*Time	0.817	0.016	0.786	0.847	-0.036	0.016	-0.068	-0.003
		Mult. Imput.	0.802	0.021	0.761	0.842	-0.030	0.016	-0.062	0.002

Primary: fixed effects baseline value, time (categorical), randomised arm, arm-by-time interaction, age, sex, randomising centre, pre-test likelihood category. Correlation handled by repeated measures within patients, unstructured covariance pattern.

BL*Time: As for primary, but also including fixed effect for baseline*time interaction.