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Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates
The CE-MARC 2 Randomized Clinical Trial

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IMPORTANCE Among patients with suspected coronary heart disease (CHD), rates of invasive angiography are considered too high.

OBJECTIVE To test the hypothesis that among patients with suspected CHD, cardiovascular magnetic resonance (CMR)–guided care is superior to National Institute for Health and Care Excellence (NICE) guidelines–directed care and myocardial perfusion scintigraphy (MPS)–guided care in reducing unnecessary angiography.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, 3-parallel group, randomized clinical trial using a pragmatic comparative effectiveness design. From 6 UK hospitals, 1202 symptomatic patients with suspected CHD and a CHD pretest likelihood of 10% to 90% were recruited. First randomization was November 23, 2012; last 12-month follow-up was March 12, 2016.

INTERVENTIONS Patients were randomly assigned (240:481:481) to management according to UK NICE guidelines or to guided care based on the results of CMR or MPS testing.

MAIN OUTCOMES AND MEASURES The primary end point was protocol-defined unnecessary coronary angiography (normal fractional flow reserve >0.8 or quantitative coronary angiography [QCA] showing no percentage diameter stenosis ≥70% in 1 view or ≥50% in 2 orthogonal views in all coronary vessels ≥2.5 mm diameter) within 12 months. Secondary end points included positive angiography, major adverse cardiovascular events (MACEs), and procedural complications.

RESULTS Among 1202 symptomatic patients (mean age, 56.3 years [SD, 9.0]; women, 564 [46.9%] ; mean CHD pretest likelihood, 49.5% [SD, 23.8%]), number of patients with invasive coronary angiography after 12 months was 102 in the NICE guidelines group (42.5% [95% CI, 36.2%-49.0%])], 85 in the CMR group (17.7% [95% CI, 14.4%-21.4%]); and 78 in the MPS group (16.2% [95% CI, 13.0%-19.8%]). Study-defined unnecessary angiography occurred in 69 (28.8%) in the NICE guidelines group, 36 (7.5%) in the CMR group, and 34 (7.1%) in the MPS group; adjusted odds ratio of unnecessary angiography: CMR group vs NICE guidelines group, 0.21 (95% CI, 0.12-0.34, $P < .001$); CMR group vs the MPS group, 1.27 (95% CI, 0.79-2.03, $P = .32$). Positive angiography proportions were 12.1% (95% CI, 8.2%-16.9%; 29/240 patients) for the NICE guidelines group, 9.8% (95% CI, 7.3%-12.8%; 47/481 patients) for the CMR group, and 8.7% (95% CI, 6.4%-11.6%; 42/481 patients) for the MPS group. A MACE was reported at a minimum of 12 months in 1.7% of patients in the NICE guidelines group, 2.5% in the CMR group, and 2.5% in the MPS group (adjusted hazard ratios: CMR group vs NICE guidelines group, 1.37 [95% CI, 0.52-3.57]; CMR group vs MPS group, 0.95 [95% CI, 0.46-1.95]).

CONCLUSIONS AND RELEVANCE In patients with suspected angina, investigation by CMR resulted in a lower probability of unnecessary angiography within 12 months than NICE guideline–directed care, with no statistically significant difference between CMR and MPS strategies. There were no statistically significant differences in MACE rates.

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Supplemental content

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Coronary heart disease (CHD) is a leading cause of death and disability worldwide. Several methods are available to diagnose CHD, risk-stratify patients, and determine the need for revascularization. Myocardial perfusion scintigraphy (MPS) by single-photon emission computed tomography is the most commonly used test worldwide for the assessment of myocardial ischemia, with robust evidence supporting its prognostic value. However, cardiovascular magnetic resonance (CMR) is increasingly recognized as having high diagnostic accuracy and prognostic value.[1,2]

CMR *cardiovascular magnetic resonance*
CCT *cardiac computed tomography*
FFR *fractional flow reserve*
MACE *major adverse cardiovascular event*
MPS *myocardial perfusion scintigraphy*
QCA *quantitative coronary angiography*

Despite the widespread availability and recommendations for noninvasive imaging in international guidelines,[3-5] invasive coronary angiography is commonly used early in diagnostic pathways in patients with suspected CHD. Evidence from large populations presenting with chest pain has confirmed that the majority will not have significant obstructive coronary disease[6,7]; a large US study reported that approximately 60% of elective cardiac catheterizations found no obstructive CHD.[8] Thus, avoiding unnecessary angiography should reduce patient risk and provide significant financial savings.

Current guidelines for investigation of stable chest pain advocate management based on the pretest likelihood of CHD.[3-5] However, pretest likelihood models can overestimate CHD risk, therefore paradoxically increasing the probability of invasive coronary angiography.[9] To date, there are no large-scale comparative effectiveness trials of different functional imaging strategies recommended by current guidelines.

The Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2 (CE-MARC 2) trial was designed to test the hypothesis that in patients with suspected CHD, CMR-guided care is superior to national guidelines-directed care[4] and MPS-guided care[10] in reducing the occurrence of unnecessary invasive angiography within 12 months.

Key Points

Question In patients with suspected coronary heart disease, does a strategy involving cardiovascular magnetic resonance (CMR) result in less unnecessary angiography than a myocardial perfusion scintigraphy (MPS) strategy or a national guideline that included sending high-risk patients directly to angiography?

Findings In this clinical trial, both CMR and MPS strategies significantly reduced unnecessary angiography rates compared with national guidelines (7.5% for CMR, 7.1% for MPS, 28.8% for national guidelines); no statistically significant differences were seen between CMR and MPS strategies. There was no statistically significant difference in major cardiovascular event rates at 12 months between the 3 groups.

Meaning Noninvasive functional imaging strategies reduced unnecessary angiography compared with guidelines-directed care.

Methods

Trial Design

CE-MARC 2 was a multicenter, 3-parallel group, randomized clinical trial. It used a pragmatic comparative effectiveness design[11] to determine the efficacy and safety of 3 strategies (CMR-guided care, MPS-guided care [following American College of Cardiology Foundation and American Heart Association appropriate use criteria],[10] and UK National Institute for Health and Care Excellence [NICE] guidelines [CG95][4]) for investigating patients with suspected CHD. The study was conducted in accordance with the protocol (available with the statistical analysis plan in Supplement 1), which was approved by the UK National Research Ethics Service (12/YH/0404) and institutional review boards of the participating centers. Study conduct was in accordance with the Declaration of Helsinki; all patients provided written informed consent.

Trial Population

Patients with suspected angina pectoris were eligible if they were 30 years or older, had a CHD pretest likelihood of 10% to 90%,[4,12] and were suitable for revascularization. Exclusion criteria included nonanginal chest pain, a normal MPS or cardiac computed tomography (CCT) result within the previous 2 years, being clinically unstable, previous myocardial infarction, previous coronary revascularization, and contraindication to any study noninvasive imaging test (eTable 4 in Supplement 2).[11] Self-reported race/ethnicity was collected using Office for National Statistics fixed categories.[13]

Randomization

Patients were assigned using minimization, incorporating a random element and 1:2:2 allocation ratio[14] through an automated 24-hour secure-access telephone service by the Clinical Trials Unit. Allocation was to 1 of 5 equally sized groups (A:B:C:D:E, stratifying on center, age [30-64 years and ≥65 years], CHD pretest likelihood [10%-29%, 30%-60%, 61%-90%], and sex) following whether management was by NICE guidelines-directed care (NICE guidelines group; group A) CMR-guided care (CMR group; groups B or C) or MPS-guided care (MPS group; groups D or E). Patients randomized to the NICE guidelines group were scheduled for CCT for patients with a pretest likelihood of 10% to 29%, MPS for patients with a pretest likelihood of 30% to 60% or sent directly to coronary angiography for patients with CHD pretest likelihoods of 61% to 90%.

Diagnostic Testing

All investigations were performed and interpreted by certified local physicians using protocols conforming to international standards.[15-18] Quality assurance was undertaken centrally throughout the trial by blinded, independent, modality-specific imaging experts (eTable 3 in Supplement 2). Ten percent of scans for each modality at each recruiting center

were centrally reviewed for image quality and report accuracy. Detailed protocols for each imaging modality and criteria for reporting a positive result have been published[11]; a positive scan for CMR, MPS, or CCT resulted in protocol-defined invasive coronary angiography and fractional flow reserve (FFR) measurement.[11] FFR measurement (PressureWire, St Jude Medical) was performed in all coronary vessels of 2.5 mm diameter or more with a 40% to 90% stenosis.[11] When FFR measurement was not possible for clinical or safety reasons, quantitative coronary angiography (QCA) was performed. All FFR and QCA results were analyzed at the Glasgow Angiographic Core Laboratory by a single, independent, blinded observer. Positive angiography was defined as any lesion with an FFR value of 0.8 or less, or, if FFR measurement was not performed, a percentage diameter stenosis of 70% or higher in 1 view or 50% or higher in 2 orthogonal views.

End Points

The primary end point was protocol-defined unnecessary coronary angiography occurring within 12 months, defined by a normal FFR value (or QCA) in all vessels 2.5 mm or more in diameter. By design, this included any unnecessary angiography occurring after a false-positive test result, patients with high CHD pretest likelihood sent directly to coronary angiography (NICE guidelines group only), and imaging results that were either inconclusive or negative but overruled by the responsible physician.[11] Secondary end points included a composite of major adverse cardiovascular events (MACEs: cardiovascular death, myocardial infarction, unplanned coronary revascularization, and hospital admission for cardiovascular cause), and positive angiography rates (recommended by the independent data monitoring and ethics committee). Complications directly related to trial investigations resulting in prolonged hospital stay or specific treatment were prespecified as safety secondary end points. Quality-of-life outcomes and cost-effectiveness analyses will be reported subsequently.

Trial Oversight

An independent data monitoring and ethics committee and trial steering committee assessed study conduct, integrity, and safety every 6 months (eTable 2 in Supplement 2).

Statistical Analysis

Allowing for 20% noncompletion, 1200 patients would provide the study with 99% power to detect a difference in unnecessary angiography between CMR-guided care and NICE guidelines–directed care (using 2:1 allocation), and 94% power between CMR-guided and MPS-guided care based on projected unnecessary angiography proportions of 4.5% for the CMR group, 11.7% for the MPS group, and 30% for the NICE guidelines group (2-sided, 5% significance for continuity-corrected χ^2 test).[19]

Logistic regressions were used to model odds of an unnecessary angiogram for CMR-guided management vs both NICE- and MPS-guided management, including stratification factors (treating centers as fixed effects). Analyses used intention-to-treat populations and were repeated in per-protocol populations. Multiple imputation (by fully conditional specification) was used for missing baseline, test, and end point data to ensure all participants could be included in the analysis, and avoid treating unknown values as certainly known (eg, with mean imputation and no-event imputation).[20] Ten fully imputed analysis data sets were generated because the proportion of patients with any missing data was less than 10%, and primary end point analyses on each data set were combined to produce the overall intention-to-treat effect using Rubin rules.[21]

The proportion of patients in each group with a MACE at 12 months and absolute differences in MACE rates were calculated. Confidence intervals for proportions and their differences were calculated by exact methods. Time to first MACE was modeled using Cox proportional hazards regression, including stratification and other prespecified factors (hypertension, ethnicity, smoking, and diabetes) and illustrated using Kaplan-Meier estimates. CMR and MPS groups were combined into a single "functional imaging" group to compare unnecessary angiography vs NICE guidelines–directed care in the 61% to 90% and 10% to 29% CHD pretest likelihood subgroups. Subgroup analyses were undertaken by including interaction effects in regression models. Statistical tests were 2-sided and called significant at the 5% level. Analyses used SAS (SAS Institute), version 9.4, after all randomized patients had completed the 12-month follow-up; there were no interim analyses.

Results

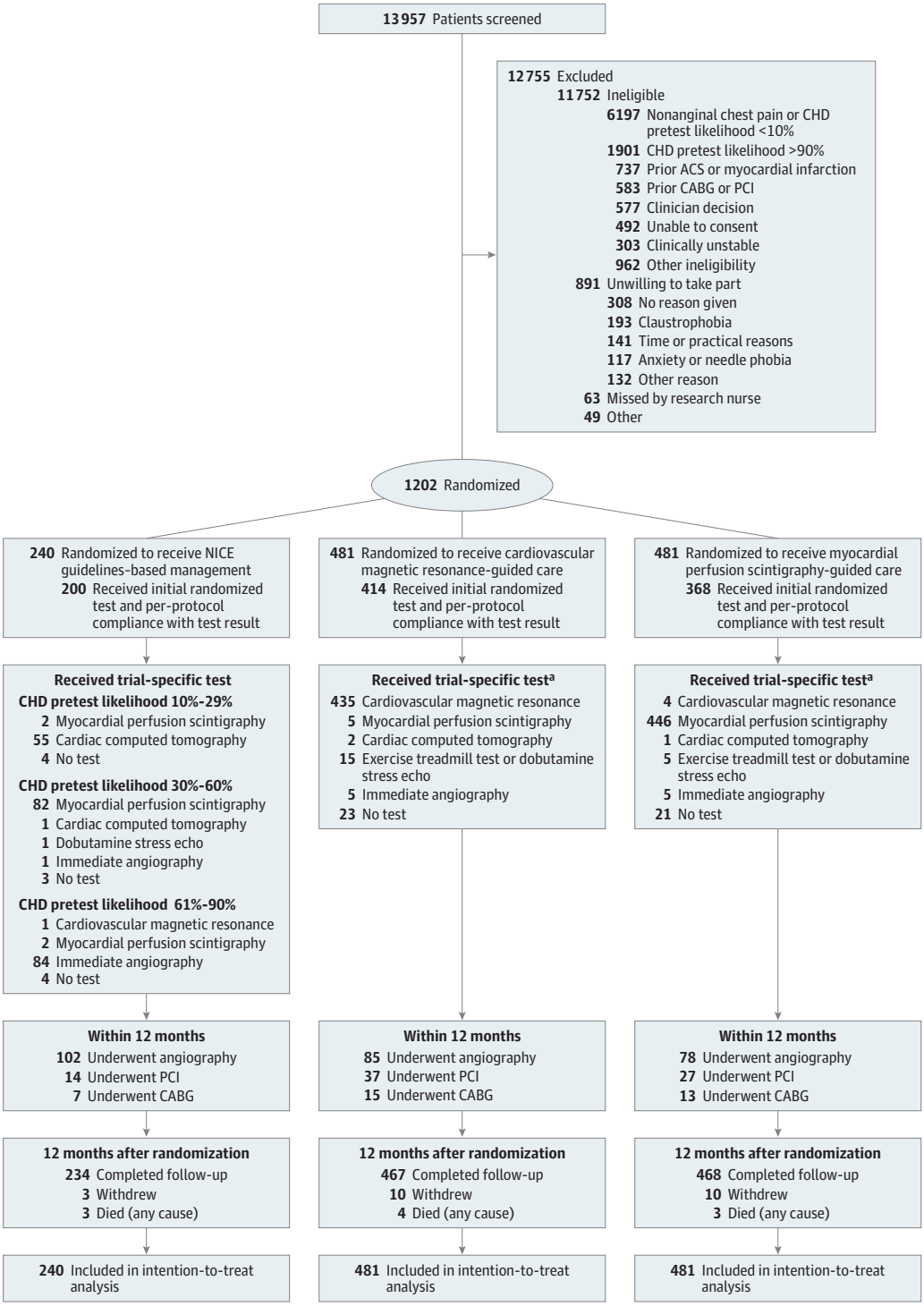
Trial Population

Between November 23, 2012, and March 13, 2015, 13 957 patients were screened, of whom 2205 were eligible (**Figure 1** lists reasons for noneligibility and nonconsent). From 6 UK centers (Leeds, Glasgow, Leicester, Bristol, Oxford, London [St Georges]), 1202 patients (55% of eligible) were recruited and allocated to NICE guidelines–directed care (n = 240) or management by CMR (n = 481) or MPS (n = 481) (Figure 1).

Baseline Characteristics

The mean age of patients was 56.3 years (SD, 9.0), 638 patients (53%) were men, the mean body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was 29.1 (SD, 5.2), and 1107 patients (92%) were classified ethnically as white (**Table 1**). The study population had a substantial burden of cardiovascular risk factors: 150 patients (12.5%) had diabetes, 458 patients (38.1%) had hypertension, 702 patients (58.4%) were past or current tobacco users, 483 patients (40.2%) had dyslipidemia, and 651 patients (54.2%) had a family history of premature CHD. Patients had a median of 2 of these 5 risk factors. All patients were symptomatic, with 401 patients (33.4%) reporting typical chest pain and 801 patients (66.6%) reporting atypical chest pain as their primary symptom. The assessment of cardiac risk, calculated according to the 2013 atherosclerotic cardiovascular disease risk score from the American College of Cardiology Foundation and American Heart Association guidelines,[22] showed that 441 of 923 patients (47.8%) had a 10-year risk of events of 7.5% or higher. The mean pretest likelihood of obstructive CHD according to the Duke score was 49.5% (SD, 23.8%).[12]

Figure 1. Flow of Patients Through the Study of Noninvasive Imaging and Angiography Rates



ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CHD, coronary heart disease; NICE, National Institute for Health and Care Excellence; PCI, percutaneous coronary intervention.

[a] Patients may have received more than 1 test, in addition to or as an alternative to their strategy.

Test Conduct

Of 481 patients assigned to the CMR group, 435 patients (90.4%) had CMR as the initial test (median time from randomization, 20 days [interquartile range, 13-34]), 5 patients (1.0%) had MPS, 5 patients (1.0%) went directly to angiography, and 23 patients (4.8%) had no test. Of 481 patients

Table 1. Baseline Characteristics of Patients With Suspected Coronary Heart Disease (CHD) by Study Group

Characteristic	Total Patients, No. (%) (N = 1202)	Guided Care, No. (%) NICE (n = 240)	CMR (n = 481)	MPS (n = 481)
Age, mean (SD), y	56.3 (9.03)	56.5 (9.21)	56.5 (9.10)	55.9 (8.87)
Women	564 (46.9)	112 (46.7)	227 (47.2)	225 (46.8)
Nonwhite race/ethnicity	95 (7.9)	19 (7.9)	38 (7.9)	38 (7.9)
Cardiac risk factors				
BMI, mean (SD)	29.1 (5.23)	29.0 (5.24)	29.2 (5.36)	29.1 (5.12)
Hypertension	458 (38.1)	99 (41.3)	177 (36.8)	182 (37.8)
Diabetes	150 (12.5)	24 (10.0)	53 (11.0)	73 (15.2)
Dyslipidemia	483 (40.2)	99 (41.3)	186 (38.7)	198 (41.2)
Former or current smoker	702 (58.4)	147 (61.3)	284 (59.0)	271 (56.3)
Family history of premature CHD[a]	651 (54.2)	140 (58.3)	252 (52.4)	259 (53.8)
Peripheral vascular disease	27 (2.2)	10 (4.2)	8 (1.7)	9 (1.9)
Cerebrovascular disease	42 (3.5)	8 (3.3)	17 (3.5)	17 (3.5)
Nature of angina				
Atypical	801 (66.6)	158 (65.8)	318 (66.1)	325 (67.6)
Typical	401 (33.4)	82 (34.2)	163 (33.9)	156 (32.4)
Medications				
Antiplatelet therapy	689 (57.3)	150 (62.5)	271 (56.3)	268 (55.7)
β-Blocker	381 (31.7)	74 (30.8)	150 (31.2)	157 (32.6)
Statin or other lipid-lowering therapy	500 (41.6)	108 (45.0)	191 (39.7)	201 (41.8)
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	303 (25.2)	66 (27.5)	115 (23.9)	122 (25.4)
Other antianginal medication	701 (58.3)	142 (59.2)	283 (58.8)	276 (57.4)
Risk Burden				
Pretest likelihood, %[b]				
Mean (SD), %	49.5 (23.78)	50.7 (23.28)	49.9 (24.25)	48.6 (23.57)
10-29[c]	314 (26.1)	61 (25.4)	128 (26.6)	125 (26.0)
30-60[c]	450 (37.4)	88 (36.7)	179 (37.2)	183 (38.0)
61-90[c]	438 (36.4)	91 (37.9)	174 (36.2)	173 (36.0)
No. of risk factors per patient, mean (SD)	2.0 (1.13)	2.1 (1.05)	2.0 (1.18)	2.0 (1.11)
10-y ASCVD risk ≥7.5%, No./total patients (%)[d]	441/923 (47.8)	93/179 (52.0)	175/377 (46.4)	173/367 (47.1)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMR, cardiovascular magnetic resonance; MPS, myocardial perfusion scintigraphy; NICE, National Institute for Health and Care Excellence.

[a] Family history of premature CHD defined as diagnosis of the disease in a male first-degree relative before aged 55 years or in a female first-degree relative aged 65 years.

[b] According to Pryor et al.[12]

[c] Categories used to decide stratification in the NICE guidelines group.

[d] According to eligibility criteria of Goff et al.[22]

assigned to the MPS group, 446 patients (92.7%) had MPS as the initial test (median time from randomization, 28 days [interquartile range, 22-39]), 4 patients (0.8%) had CMR, 5 patients (1.0%) went directly to angiography, and 21 patients (4.4%) had no test. Of 240 patients assigned to the NICE guidelines group, 56 patients (23.3%) had CCT (median time from randomization, 34 days [interquartile range, 14-44]), 86 patients (35.8%) had MPS, 85 patients (35.4%) went directly to angiography, and 11 patients (4.6%) had no test. The numbers of patients adherent to receiving both their initial randomized test and per-protocol compliance with their test result were 200 patients (83.3%) in the NICE guidelines group, 414 patients (86.1%) in the CMR group, and 368 patients (76.5%) in the MPS group.

Study sites reported their interpretation of the initial test as positive for CHD in 54 of 435 patients (12.4%) in the CMR group, in 81 of 446 patients (18.2%) in the MPS group, and in 19 of 142 patients (13.4%) in the NICE guidelines group. There was no difference in revascularization rates (Figure 1) between the 3 groups (P = .47). The rate of patients with incomplete data required for analysis of the primary end point was low: 18 of 240 patients (7.5%) in the NICE guidelines group, 50 of 481 patients (10.4%) in the CMR group, and 33 of 481 patients (6.9%) in the MPS group. Of these, 11 of 240 patients (4.6%) in the NICE guidelines group, 23 of 481 patients (4.8%) in the CMR group, and 21 of 481 patients (4.4%) in the MPS group were related to missing test results.

Primary End Point

Overall, 265 patients (22.0%) underwent at least 1 coronary angiogram (10 patients underwent 2 angiograms) within 12 months of randomization: 102 of 240 patients (42.5%) in the NICE guidelines group, 85 of 481 patients (17.7%) in the CMR group, and 78 of 481 patients (16.2%) in the MPS group. The primary end point of unnecessary angiography occurred in 69 patients (28.8%) in the NICE guidelines group, 36 patients (7.5%) in the CMR group, and 34 patients (7.1%) in the MPS group. Of these angiograms, 98 angiograms (70.5%) had no visual stenosis and were not assessed further, 40 angiograms (28.8%) reached the conclusion by FFR measurement and 1 angiogram (0.7%) involved QCA only. The adjusted odds ratio of unnecessary angiography for the CMR group vs the NICE

Table 2. Summary of Trial End Points for Patients With Suspected Coronary Heart Disease, by Each Guided Care Group

	Total Patients (N = 1202)	Guided Care			Absolute Differences, % (95% CI)	
		NICE Guidelines (n = 240)	CMR (n = 481)	MPS (n = 481)	CMR vs NICE	CMR vs MPS
Primary End Point						
Unnecessary invasive angiography, No. of patients (%)	139 (11.6)	69 (28.8)	36 (7.5)	34 (7.1)	−21.3 (−28.7 to −13.6)	0.4 (−6.0 to 6.8)
Components of the primary end point						
False-positive noninvasive test	35	5	18	12		
Direct to angiography (by strategy)	59	59				
Negative noninvasive test, not per-protocol	41	5	15	21		
Inconclusive noninvasive test or result	4		3	1		
Secondary End Points						
Positive angiography occurrence, No. of patients (%)	118 (9.8)	29 (12.1)	47 (9.8)	42 (8.7)	−2.3 (−10.0 to 5.4)	1.0 (−5.4 to 7.5)
True-positive noninvasive test	73	4	38	31		
Direct to angiography (by strategy)	23	23				
Negative noninvasive test, not per-protocol	9	1	2	6		
Inconclusive noninvasive test or result	2		2			
Acute or urgent angiography indication	9	1	4	4		
Angiography as alternative initial investigation	2		1	1		
Major adverse cardiovascular events, No. of events (No. of patients)	44 (36)	7 (6)	20 (15)	17 (15)	1.0 (−6.7 to 8.8)	0.0 (−6.4 to 6.4)
Cardiovascular death	5	1[a]	1	3		
Myocardial infarction	9	2	5	2		
Revascularization						
Unplanned PCI	12	2	6	4		
Unplanned CABG	1		1			
Arrhythmia	9	2	4	3		
Heart failure	4			4		
Stroke or TIA	4		3	1		

Abbreviations: CABG, coronary artery bypass graft; CMR, cardiovascular magnetic resonance; MACE, major adverse cardiovascular events; MPS, myocardial perfusion scintigraphy; NICE, National Institute for Health and Care Excellence; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

[a] This event occurred 2 days after the 3-year cutoff, so is excluded from summaries of absolute MACE rates at 3 years. All other events occurred within 3 years of randomization. Three-year MACE rates include all participants (median follow-up, 16 months).

guidelines group was 0.21 (95% CI, 0.12-0.34; $P < .001$) and 1.27 (95% CI, 0.79-2.03; $P = .32$) for the CMR group vs the MPS group. **Table 2** shows individual components of the primary end point. For both comparisons, the primary analysis was repeated in the per-protocol population, with no effect on the trial results. Sensitivity analyses using random center effects or adjusting for further risk factors (hypertension, ethnicity, smoking status) or using the per-protocol population did not change overall trial conclusions (eTable 5 in Supplement 2). Exploratory subgroup analyses showed consistent results across subgroups (**Figure 2**).

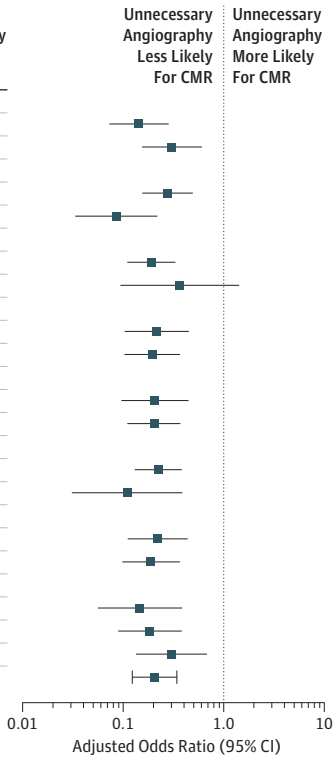
Secondary End Points

Positive angiography was observed in 29 patients (12.1% [95% CI, 8.2%-16.9%]) in the NICE guidelines group, 47 patients (9.8% [95% CI, 7.3%-12.8%]) in the CMR group, and 42 patients (8.7% [95% CI, 6.4%-11.6%) in the MPS group ($P = .36$). During the minimum 1-year follow-up (median, 15.8 months [interquartile range, 12.1-24.2]), 36 patients (3.0%) had at least 1 MACE: NICE guidelines group, 6 patients (2.5%); CMR group, 15 patients (3.1%); MPS group, 15 patients (3.1%) (Table 2). Annualized MACE rates were 1.6% for the NICE guidelines group, 2.0% for the CMR group, and 2.0% for the MPS group. Adjusted hazard ratios for MACE were 1.37 (95% CI, 0.52-3.57; $P = .52$) for the CMR group vs the NICE guidelines group and 0.95 (95% CI, 0.46-1.95; $P = .88$) for the CMR group vs the MPS group. Hard events (cardiovascular death and myocardial infarction) occurred in 3 patients (1.3%) in the NICE guidelines group, 5 patients (1.0%) in the CMR group, and 4 patients (0.8%) in

Figure 2. Effect of Specific Patient Characteristics on Results for CMR-Guided Care vs NICE Guidelines-Directed Care and MPS-Guided Care Among Patients With Suspected Coronary Heart Disease

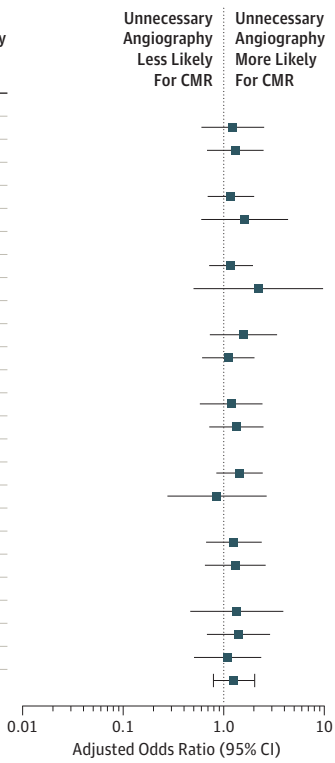
A Cardiovascular magnetic resonance vs NICE guidelines

Subgroup	Cardiovascular Magnetic Resonance		NICE Guidelines		Adjusted Odds Ratio of Unnecessary Angiography Within 12 mo (95% CI)
	Unnecessary Angiography, No.	Participants, No.	Unnecessary Angiography, No.	Participants, No.	
Sex					
Men	15	254	41	128	0.14 (0.07-0.28)
Women	21	227	28	112	0.31 (0.15-0.61)
Age group, y					
30-64	26	389	44	192	0.28 (0.15-0.49)
≥65	10	92	25	48	0.09 (0.03-0.22)
Race/ethnicity (white vs nonwhite)					
White	31	443	63	221	0.19 (0.11-0.33)
Asian, black, other, or not stated	5	38	6	19	0.37 (0.09-1.42)
Hypertension					
Yes	13	177	28	99	0.22 (0.10-0.45)
No	23	304	41	141	0.19 (0.10-0.37)
Smoking Status					
Never smoked	15	197	25	93	0.21 (0.10-0.45)
Former or current smoker	21	284	44	147	0.20 (0.11-0.37)
Diabetes					
No diabetes	32	428	58	216	0.22 (0.13-0.38)
Type I or type II	4	53	11	24	0.11 (0.03-0.39)
Known family history of CHD					
No or not known	19	229	31	100	0.22 (0.11-0.44)
Yes	17	252	38	140	0.19 (0.10-0.37)
BMI					
0-25	7	101	16	52	0.15 (0.06-0.39)
26-30	18	196	35	101	0.18 (0.09-0.38)
>30	11	184	18	87	0.30 (0.13-0.68)
Overall	36	481	69	240	0.21 (0.12-0.34)



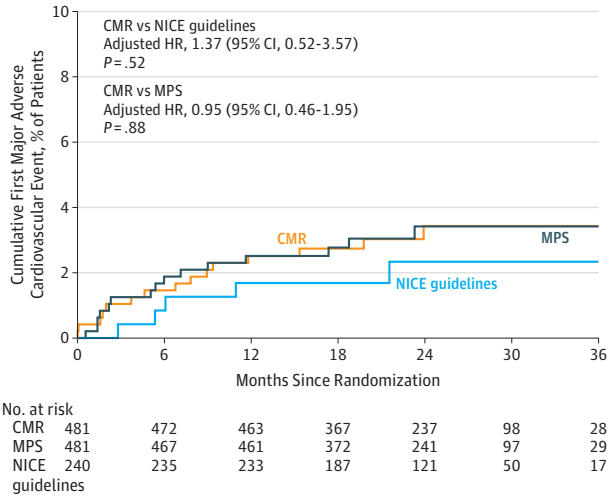
B Cardiovascular magnetic resonance vs myocardial perfusion scintigraphy

Subgroup	Cardiovascular Magnetic Resonance		Myocardial Perfusion Scintigraphy		Adjusted Odds Ratio of Unnecessary Angiography Within 12 mo (95% CI)
	Unnecessary Angiography, No.	Participants, No.	Unnecessary Angiography, No.	Participants, No.	
Sex					
Men	15	254	15	256	1.23 (0.60-2.52)
Women	21	227	19	225	1.30 (0.68-2.49)
Age group, y					
30-64	26	389	26	388	1.18 (0.69-2.01)
≥65	10	92	8	93	1.61 (0.60-4.36)
Race/ethnicity (white vs nonwhite)					
White	31	443	31	443	1.18 (0.72-1.95)
Asian, black, other, or not stated	5	38	3	38	2.21 (0.50-9.74)
Hypertension					
Yes	13	177	11	182	1.57 (0.73-3.39)
No	23	304	23	299	1.11 (0.61-2.02)
Smoking Status					
Never smoked	15	197	15	210	1.19 (0.58-2.43)
Former or current smoker	21	284	19	271	1.33 (0.72-2.48)
Diabetes					
No diabetes	32	428	25	408	1.43 (0.84-2.44)
Type I or type II	4	53	9	73	0.86 (0.28-2.67)
Known family history of CHD					
No or not known	19	229	19	222	1.26 (0.67-2.38)
Yes	17	252	15	259	1.30 (0.65-2.61)
BMI					
0-25	7	101	7	103	1.35 (0.46-3.92)
26-30	18	196	14	197	1.40 (0.68-2.89)
>30	11	184	13	181	1.09 (0.50-2.35)
Overall	36	481	34	481	1.27 (0.79-2.03)



CMR indicates cardiovascular magnetic resonance; ITT, intention to treat; NICE, National Institute for Health and Care Excellence; MPS, myocardial perfusion scintigraphy. Variables in the adjusted analysis for odds ratios included hypertension, ethnicity, and smoking status.

Figure 3. Time to First Major Adverse Cardiovascular Event After a Minimum of 12-Month Follow-up From Randomization Among Patients With Suspected Coronary Heart Disease (Median, 16 Months)



CMR indicates cardiovascular magnetic resonance; NICE, National Institute for Health and Care Excellence; MPS, myocardial perfusion scintigraphy. Hazard ratios from time to first major adverse cardiovascular event (and likelihood ratio test *P* values) were calculated by Cox proportional hazards modeling, adjusted for randomizing center, age category, sex, coronary heart disease pretest likelihood category, hypertension, race/ethnicity, diabetes, and smoking status. The median months of follow-up for the NICE guidelines group was 19.9 months (interquartile range [IQR], 12.1-24.1), 15.3 months (IQR, 12.2-24.2) for the CMR group, and 17.3 months (IQR, 12.1-24.2) for the MPS group.

the MPS group (*P* = .93). **Figure 3** shows the Kaplan-Meier cumulative incidence estimate of first MACE. In the study, 5 test-related medical complications were reported: CMR (1 case: mild urticarial reaction), MPS (0 cases), CCT (1 case: vasovagal episode), and angiography (3 cases: ventricular tachycardia, pseudo-aneurysm and popliteal deep venous thrombosis, right coronary artery spasm and transient ST elevation).

Functional Imaging Assessment

Using functional imaging as a first-line strategy (CMR or MPS) in patients with a 61% to 90% (high; n = 389) CHD pretest likelihood resulted in substantially reduced odds of unnecessary angiography compared with the NICE guidelines group; 29 of 307 patients (9.4%) for functional imaging groups vs 51 of 82 patients (62.2%) for the NICE guidelines group, odds ratio (OR) 0.048 (95% CI, 0.02-0.10), *P* < .001. Among those with less than 30% (low; n = 330) CHD pretest likelihood, the odds of unnecessary angiography were also numerically lower by a functional imaging approach compared with anatomical (CCT) assessment (13 of 269 patients (4.8%) for funtional imaging vs 7 of 61 patients (11.5%) for anatomical assessment; OR, 0.44 [95% CI, 0.17-1.17]; *P* = .099).

Discussion

CE-MARC 2 was a multicenter, randomized clinical trial in a large community-based population of symptomatic patients undergoing assessment for suspected CHD, in whom further investigation was appropriate according to international guidelines. A CMR-guided strategy significantly reduced unnecessary angiography occurrence compared with NICE guidelines-guided care, but was not significantly different from an MPS-guided strategy (following US appropriate use criteria).[10] Between the 3 strategies, there was no difference in MACE rates at 12 months or disease detection (positive angiography) rates.

There is concern that coronary angiography is overused in the diagnostic pathway of suspected CHD and that the majority of patients investigated will not have significant obstructive coronary disease.[6,7] Avoiding unnecessary invasive angiography could have significant financial benefits, avoids exposing patients to unnecessary risk, and is also a strong patient desire.[23] For this reason, this outcome was chosen as the patient-focused primary end point.

Current international guidelines for investigation and management of suspected CHD all suggest risk stratification based on pretest likelihood estimation.[12,24,25] The Duke score, used in NICE guidelines, is based upon the original Diamond Forrester model, but includes additional demographic factors to further stratify risk.[12] These models, derived more than 3 decades ago, tend to overestimate CHD risk because patient demographics, risk factors, and treatment have changed considerably over time.[26] In the CE-MARC 2 trial, the reduction in unnecessary angiography by a CMR or MPS strategy appears largely driven by the overestimation of disease probability from using the Duke score. Current NICE guidelines categorize a pretest likelihood of 60% to 90% as being at high-risk of CHD, and recommend direct referral for angiography. In the CE-MARC 2 trial, this explained the majority of patients in the NICE-guidelines group who got referred for angiography (82 of 102 patients; 80.4%), and the majority of unnecessary angiograms (59 of 69 patients; 85.5%). This was further emphasized by the preplanned, subanalysis of any functional imaging (CMR or MPS) in the 60% to 90% (high risk) pretest likelihood population, which showed substantially reduced odds of unnecessary angiography in this combined subgroup compared with the NICE guideline group.

Overall, rates of disease detection (positive angiography) were comparable for the 3 strategies, suggesting no penalty for using functional imaging as a gatekeeper for angiography, even in high-risk subgroups. Consistent with published studies, the CE-MARC 2 trial showed a low overall rate of MACE in a stable chest pain population, with no early difference between strategies.

It remains a point of debate as to whether all of protocol-defined unnecessary angiograms in this study were clinically unnecessary; some would argue that negative tests are the "price to pay" for not missing important disease in others. This assumes a population perspective, and our trial primary end point was derived after close consultation with patient and public representatives: from an individual patient perspective, an angiogram that does not change their treatment or their clinical outcome is considered by patients to have been unnecessary. Guidelines are clear that physicians do not need to un-

dertake angiography to either diagnose angina or offer primary prevention and symptom control.

To our knowledge, there have been no randomized clinical trials comparing the performance of current management guidelines and a broad functional imaging approach in terms of important clinical end points. Although cross-sectional imaging (CMR and CCT) has improved diagnostic ability, benefits in terms of health outcomes are more difficult to demonstrate, partly due to complexity of subsequent treatment effects. Functional vs anatomical assessment as a potential gatekeeper to the catheterization laboratory is a topic of ongoing debate.[27,28] The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial showed no improvement in clinical outcomes using CCT vs a variety of functional tests in patients investigated for suspected CHD; whereas the CCT strategy increased rates of cardiac catheterization (12.2% for CCT vs 8.1% for a variety of functional tests, $P = .02$) and 90 day coronary revascularization (6.2% for CCT vs 3.2% for a variety of functional tests, $P < .001$).[27] This may be important following a recent observational study of 544 US centers showing higher rates of inappropriate percutaneous coronary intervention at sites performing the highest rates of angiography, suggesting anatomical assessment could predispose patients to unnecessary therapy.[29] Although numbers are small, in the CE-MARC 2 trial an increased rate of unnecessary angiography was suggested in the low-risk subgroup of the NICE guidelines group, the majority of whom underwent CCT.

Limitations

This study has several important limitations. First, the false-positive and false-negative rates are often quantities of interest in evaluating diagnostic methods. The CE-MARC 2 trial only angiographically verified a subset of patients, contingent on strategy findings, and so cannot provide accurate estimates. The original CE-MARC trial defined the false-positive and false-negative rates for CMR and MPS, and showed CMR-guided strategy as being superior to the MPS-guided strategy.[1] In the current study, there was no statistical difference between the CMR and MPS strategies for reduction in unnecessary angiography, despite the finding from the CE-MARC trial. However, the CE-MARC trial was able to detect small differences due to its paired design (all patients underwent all tests), whereas the current study compared independent groups, which confers lower power.

Second, the study population was predominantly white northern European, therefore findings may not translate to other populations; geographic heterogeneity of CHD incidence is well known.[25]

Third, at trial initiation, contemporary guidelines used the Duke score,[3,4] with the NICE guidelines classifying high risk for CHD as 60% to 90% pretest likelihood. It is now recognized that this may overestimate CHD risk, such that recent guidelines[5] have adopted a recalibrated risk model.[25]

Fourth, the primary end point was objective (using FFR measurement), although performance was not clinically possible in all cases; blinded core laboratory analysis of QCA data avoided subjective visual angiography interpretation.

Fifth, overall full adherence to the protocol was high, with some unavoidable variation due to individual clinical practice, which could have introduced bias (eg, abnormal imaging results not proceeding to angiography). To mitigate this, analysis was by intention-to-treat principles and the primary end point was purposely all inclusive (ie, false-positives, true-negatives when not believed by clinicians, and also test failures). The slightly different rates of incomplete data (not statistically significant) between study groups was not of concern, as the data completeness rate was high overall. Per-protocol and sensitivity analyses (eTable 5 in Supplement 2) did not alter the trial conclusions.

Sixth, although clinically robust, a MACE is not a proxy for a missed diagnosis or treatment (eg, missed opportunity for revascularization by not having angiography [due to a false-negative result]). However, it remains debatable whether revascularization for stable angina has prognostic benefit over optimal medical therapy, which will be answered by the ongoing International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial.[30]

Seventh, quality of life and cost-effectiveness analyses will be important for understanding the patient-centered perspectives and payer/policy implications of these findings; these data are currently being collected and analyzed.

Conclusions

In patients with suspected angina, investigation by CMR resulted in a lower probability of unnecessary angiography within 12 months than NICE guideline–directed care, with no statistically significant difference between CMR and MPS strategies. There were no statistically significant differences in MACE rates at 12 months after randomization.

ARTICLE INFORMATION

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