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Stress Perfusion Cardiac Magnetic Resonance vs SPECT Imaging for Detection of Coronary Artery Disease

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ABSTRACT

BACKGROUND GadaCAD2 was 1 of 2 international, multicenter, prospective, Phase 3 clinical trials that led to U.S. Food and Drug Administration approval of gadobutrol to assess myocardial perfusion and late gadolinium enhancement (LGE) in adults with known or suspected coronary artery disease (CAD).

OBJECTIVES A prespecified secondary objective was to determine if stress perfusion cardiovascular magnetic resonance (CMR) was noninferior to single-photon emission computed tomography (SPECT) for detecting significant CAD and for excluding significant CAD.

METHODS Participants with known or suspected CAD underwent a research rest and stress perfusion CMR that was compared with a gated SPECT performed using standard clinical protocols. For CMR, adenosine or regadenoson served as vasodilators. The total dose of gadobutrol was 0.1 mmol/kg body weight. The standard of reference was a 70% stenosis defined by quantitative coronary angiography (QCA). A negative coronary computed tomography angiography could exclude CAD. Analysis was per patient. CMR, SPECT, and QCA were evaluated by independent central core lab readers blinded to clinical information.

RESULTS Participants were predominantly male (61.4% male; mean age 58.9 ± 10.2 years) and were recruited from the United States (75.0%), Australia (14.7%), Singapore (5.7%), and Canada (4.6%). The prevalence of significant CAD was 24.5% (n = 72 of 294). Stress perfusion CMR was statistically superior to gated SPECT for specificity ($P = 0.002$), area under the receiver operating characteristic curve ($P < 0.001$), accuracy ($P = 0.003$), positive predictive value ($P < 0.001$), and negative predictive value ($P = 0.041$). The sensitivity of CMR for a 70% QCA stenosis was noninferior and nonsuperior to gated SPECT.

CONCLUSIONS Vasodilator stress perfusion CMR, as performed with gadobutrol 0.1 mmol/kg body weight, had superior diagnostic accuracy for diagnosis and exclusion of significant CAD vs gated SPECT.
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The most recent chest pain guidelines from the American Heart Association (AHA) and the American College of Cardiology recognize multiple indications for stress myocardial perfusion imaging (MPI) using cardiovascular magnetic resonance (CMR).[1] Stress perfusion CMR is appropriate for assessing stable chest pain in patients with intermediate risk and no known coronary artery disease (CAD) or known CAD, patients with stable chest pain despite guideline directed medical therapy, and to assess for ischemia with no obstructive coronary artery disease. The CMR portions of the AHA/American College of Cardiology guidelines are now comparable to European guidelines[2,3] and represent a major evolution from the prior guidelines.[4]

SEE PAGE 1839

There is a tendency in the American and European guidelines to group tests for evaluation of CAD into "stress tests" and "anatomic imaging tests" for evaluation of CAD,[1-3] such that the indications converge for most of the stress test modalities with some exceptions such as myocardial blood flow quantification by stress perfusion CMR or positron emission tomography (PET). Meta-analyses have documented significantly better performance of stress perfusion CMR and PET when compared with coronary computed tomography angiography (CCTA), stress echocardiography, or stress single-photon emission computed tomography (SPECT) MPI.[5,6] The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial also grouped "stress tests" into a single arm and compared them against an invasive strategy[7] but demonstrated no improvement of survival or reduction of the risk for myocardial infarction vs an initial invasive strategy. Similarly, an initially invasive strategy did not improve clinical outcomes or health status in patients with chronic kidney disease in the ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches-Chronic Kidney Disease) study.[8] Patients, referring physicians, and payers may not realize the variation in diagnostic performance between individual stress test modalities or recognize other modality-specific advantages that could be important in their clinical decision making.

GadaCAD1 (Gadobutrol/Gadavist-enhanced Cardiac Magnetic Resonance Imaging [CMRI] to Detect Coronary Artery Disease [CAD] [GadaCAD 1]; NCT01890421) and GadaCAD2 (Gadobutrol/Gadavist-enhanced Cardiac Magnetic Resonance Imaging [CMRI] to Detect Coronary Artery Disease [CAD] [GadaCAD 2]; NCT01890434) were international, multicenter, phase 3 clinical trials with a primary aim of assessing the diagnostic accuracy of gadobutrol enhanced vasodilator stress perfusion CMR and late gadolinium enhancement (LGE) imaging to detect CAD.[9] The current report presents results of GadaCAD2 secondary aims that have not been published and were not studied in GadaCAD1: 1) to determine if CMR had noninferior sensitivity compared with SPECT MPI in detection of significant CAD; and 2) to determine if CMR had noninferior specificity compared with SPECT in exclusion of significant CAD.

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

AUC = area under the receiver operating characteristic curve

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

CMR = cardiovascular magnetic resonance

FFR = fractional flow reserve

LGE = late gadolinium enhancement

MPI = myocardial perfusion imaging

MRI = magnetic resonance imaging

PET = positron emission tomography

QCA = quantitative coronary angiography

ROC = receiver operator characteristic

SPECT = single-photon emission computed tomography

METHODS

PATIENT POPULATION. All participants signed informed consent to participate in this clinical trial. The study was conducted according to the Declaration of Helsinki, the principles of Good Clinical Practice, and was approved by the Health Authorities and local ethics committee of each participating institution.

The main inclusion criteria were that subjects were undergoing evaluation for known or suspected CAD based on typical or atypical chest discomfort and had a clinical indication for coronary angiography, were ≥18 years old, and were willing to undergo the

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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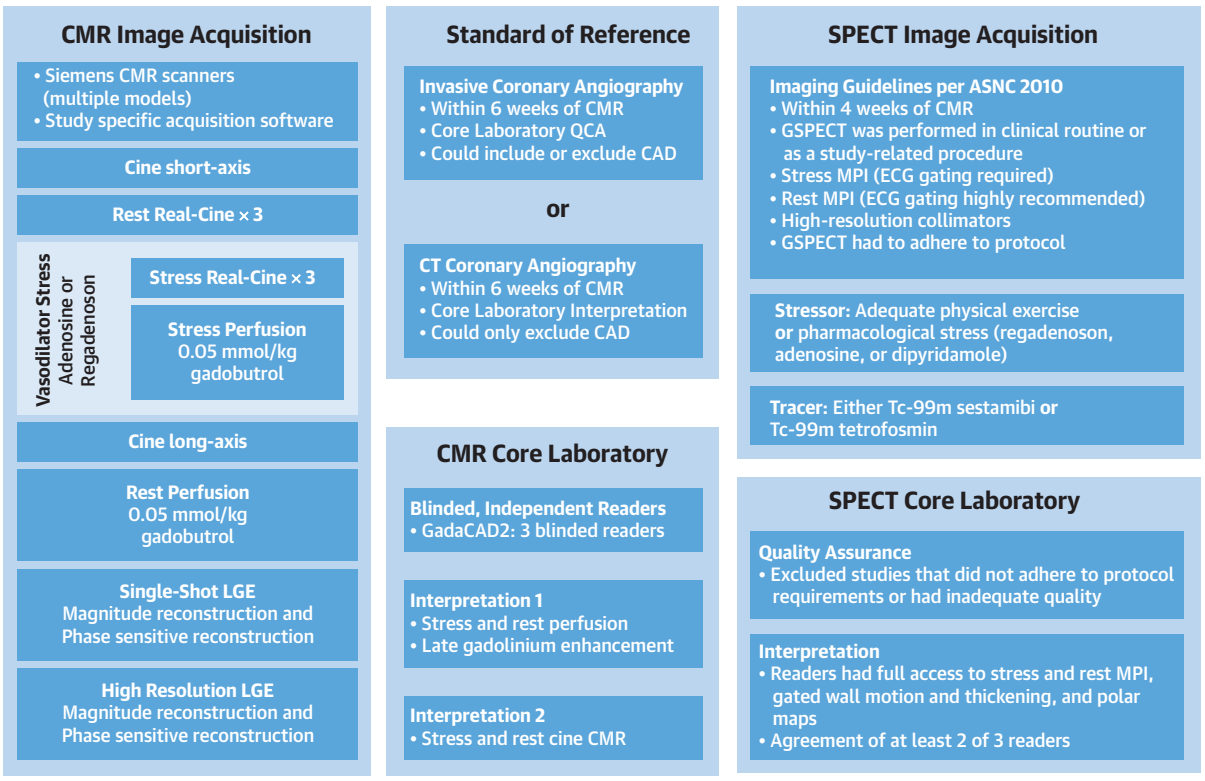
FIGURE 1 CMR and SPECT Methods, Standard of Reference, and Core Laboratories



The main cardiovascular magnetic resonance (CMR) and single-photon emission computed tomography (SPECT) acquisition methods are outlined in this figure. CMR and SPECT images were interpreted by experts, blinded to clinical information, in core laboratories. Significant coronary artery disease (CAD) was defined as a ≥70% coronary stenosis. Significant CAD could be excluded by quantitative coronary angiography (QCA) <70% maximal stenosis or by a coronary computed tomography angiography with no more than minimal coronary stenosis (<25% visually) and no coronary calcium obscuring the coronary artery lumen. ECG = electrocardiogram; GSPECT = gated myocardial perfusion single-photon emission computed tomography; LGE = late gadolinium enhancement; MPI = myocardial perfusion imaging.

study procedures. Thus, coronary angiography was not a research study. Subjects in GadaCAD2 also had to have SPECT MPI within 4 weeks before or after the study-specific CMR scan. The SPECT scan could have been done either as a clinically indicated scan or a research scan. Female subjects of child-bearing potential had to agree to use medically approved birth control during the study. Only patients with both SPECT and CMR evaluable by the core laboratories were included in this study.

The main exclusion criteria were contraindications to magnetic resonance imaging (MRI), contraindications to vasodilators, suspected clinical instability during the study period, revascularization between CMR and coronary angiography, prior coronary artery bypass graft, acute coronary syndrome <14 days before inclusion, decompensated heart failure <14 days before inclusion, certain arrhythmias, uncontrolled hypertension, baseline systolic blood pressure <90 mm Hg, and estimated glomerular filtration rate <30 mL/min/1.73 m^2. Participants were excluded if any significant clinical events or revascularization occurred between the CMR or SPECT scan and the standard of reference. Complete inclusion and exclusion criteria are listed in Supplemental Table 1.

The overall study protocols and CMR methods were previously published (Figure 1).[9] The methods and responsibilities of the independent core laboratories for evaluating and reporting CMR, CCTA, and invasive quantitative coronary angiography (QCA) were also previously published (Figure 1).[9] The SPECT-specific methods are summarized in Figure 1.

CORE LABORATORY STANDARD OF REFERENCE DEFINING SIGNIFICANT CAD. Significant CAD was defined as a ≥70% stenosis using QCA measured by core laboratory experts (Figure 1). Conversely, significant CAD was excluded based on core laboratory

QCA <70% stenosis. However, core laboratory reading of CCTA could also exclude significant CAD in participants if the CCTA was normal or nearly normal as defined by no coronary calcifications obscuring the coronary artery lumen and minimal coronary narrowing (<25% visually).

The standard of reference applied equivalently to both the CMR and SPECT results. There were separate core laboratories for invasive angiography and CCTA with different expert readers for each modality. All analyses were performed in a blinded fashion.

CMR METHODS AND CORE LABORATORY. In brief, CMR was done as a research procedure (**Figure 1**), and detailed methods were previously published.[9] The CMR had to be performed within 4 weeks of the invasive coronary angiography or 6 weeks of a negative CCTA. CMR included localizer images, cine MRI of cardiac function and regional wall motion, stress perfusion imaging, rest perfusion imaging, and LGE imaging. Gadobutrol (0.05 mmoL/kg body weight) was administered during stress perfusion and a second dose of gadobutrol (0.05 mmoL/kg body weight) was given during rest perfusion imaging approximately 10 minutes later. Thus, the total dose of gadobutrol was 0.1 mmoL/kg body weight. Stress CMR was induced by regadenoson or adenosine, as determined by local standards. CMR images were reviewed in the core laboratory by 3 independent readers as previously published. Stress perfusion, rest perfusion, and LGE were summarized using the 17-segment AHA model, but omitted the apical segment. Segments were read as normal, reversible perfusion defect (stress only), fixed perfusion (stress and rest), or mixed perfusion (reversible and fixed components). For each reader, a study was abnormal if ≥1 segment was abnormal.[9] An equivocal category was not allowed.

GATED SPECT MPI METHODS. SPECT MPI was performed either as a routine clinical study or as a research procedure (**Figure 1**). However, SPECT acquisition methods had to meet or exceed the guidelines of the 2010 American Society of Nuclear Cardiology, the standards at the time the study was designed.[10]

The tracer had to be Tc-99m sestamibi or Tc-99m tetrofosmin. Electrocardiogram gated SPECT was required for stress MPI; electrocardiogram gating was highly recommended but not mandatory for rest SPECT MPI. High-resolution collimators were required. The stressor could be adequate physical exercise or pharmacological stress. Regadenoson, adenosine, or dipyridamole were all acceptable vasodilators. It was recommended to use the same vasodilator for SPECT and CMR but this was not mandated.

SPECT CORE LABORATORY METHODS. The core laboratory determined if SPECT images were of adequate diagnostic quality, interpretability, and completeness of mandatory images. Evaluable image sets at stress and rest were interpreted independently by 3 blinded, highly experienced experts in nuclear cardiology. All available images were displayed and reviewed, and the stress and rest images were displayed simultaneously. The detection or exclusion of perfusion defects was derived using the information available from the full image data set at stress and rest, including static display of reconstructed tomographic perfusion slices at stress and rest, gated cine slices, or end-systolic and end-diastolic images for assessment of regional wall motion. If available, additional images from raw rotating projection for assessing subject motion and attenuation artifacts, and polar maps and quantitative data regarding regional perfusion in relation to normal databases using commercially available software were also considered by the interpreters for final scoring. When available, 2-view and/or attenuation images were also considered.

SPECT studies were summarized using the 17-segment AHA model but excluded the apical segment. Segments were read as normal, reversible perfusion defect (stress only), fixed perfusion (stress and rest), or mixed perfusion (reversible and fixed components). For comparison with the standard of reference, a study was abnormal if ≥1 segment was not normal.

STATISTICAL ANALYSIS. The study design called for a 2-sided, noninferiority comparison of the CMR vs SPECT for sensitivity to detect significant CAD and for specificity to exclude significant CAD. For both CMR and gated SPECT, the majority read of individual interpretations was used. Each reader recorded independent interpretations for all studies. The CMR or SPECT read for a given exam was considered positive if at least 2 of the 3 readers interpreted the study as abnormal and negative if at least 2 of 3 readers interpreted the study as negative.

Statistical significance was set at a 5% type I error. Plotted error bars represent 95% confidence limits, which were exact binomial confidence intervals calculated by the methods of Collett.[11] Sensitivity and specificity were compared with McNemar's test.[12] Diagnostic accuracy was summarized with receiver operator characteristic (ROC) curves. The area under

the curve (AUC) statistics were compared with DeLong's test.[13] Accuracy was defined as the proportion of cases correctly classified and was compared with a 2-sample proportion test. Positive and negative predictive values were compared with the generalized score statistics.[14] True positive, true negative, false positive, and false negative were compared with the Fisher exact test.[15] Two-sided, noninferiority of CMR vs SPECT for sensitivity and specificity was tested with a 95% CI for the difference and comparing the lower limit of this interval to a noninferiority margin of −15%.

RESULTS

DEMOGRAPHICS. Patient demographics are summarized in Table 1. The diagnostic accuracy of CMR and SPECT was compared in the subjects enrolled in GadaCAD2 who had complete and analyzable data for CMR, SPECT, and the invasive QCA or CCTA standard of reference. Reasons for exclusion are summarized in Figure 2.

DIAGNOSTIC ACCURACY. The prevalence of significant CAD was 72 of 294 (24.5%) as defined by a ≥70% QCA stenosis. At the patient level, results for CMR, CCTA, and invasive QCA are the same as previously published but these results are restricted to participants whose SPECT scan met study requirements and were assessed by the SPECT core laboratory to be of adequate quality. The study had 81% power to detect noninferiority of sensitivity and >95% power to detect noninferiority of specificity.

Sample CMR, SPECT, CCTA, and invasive angiography images from a patient with CAD and concordant CMR and SPECT findings are displayed in Figure 3. Despite a high-quality CCTA in this example, invasive QCA had to be the standard of reference, as CCTA was only able to exclude significant CAD by study design.

The ROC curve for CMR is shifted up and to the left of the SPECT ROC curve consistent with higher diagnostic accuracy of CMR (Figure 4). The area under the ROC curve was significantly higher for CMR than SPECT (0.88 vs 0.74; $P < 0.001$).

Other diagnostic accuracy statistics are summarized in Table 2 as well as the Central Illustration. The 2-sided, noninferiority design had 3 possible outcomes regarding comparisons of diagnostic accuracy statistics: 1) CMR could have been inferior to SPECT; 2) CMR could have been superior to SPECT; or 3) CMR could also have been noninferior and nonsuperior to SPECT. When compared with SPECT and as summarized in the Central Illustration, CMR had superior AUC ($P < 0.001$), superior accuracy ($P = 0.003$), superior specificity ($P = 0.002$), superior positive predictive value ($P < 0.001$), and superior negative predictive value ($P = 0.041$). With regard to sensitivity, CMR was noninferior and nonsuperior to SPECT.

In the contingency analysis, SPECT had more false positive results than CMR (47 vs 25). SPECT had more false negative results than CMR (26 vs 19). SPECT also had fewer true positive results than CMR (46 vs 53) and fewer true negative results than CMR (175 vs 197). The differences in the contingency table were significant ($P = 0.022$). Overall, all of these diagnostic accuracy statistics point in the direction of higher diagnostic performance of CMR compared with SPECT.

TABLE 1 GadaCAD2 Patient Characteristics

Age, y	58.9 ± 10.2
Male	239 (61.4)
Ethnicity	
Hispanic	22 (5.7)
Non-Hispanic	366 (94.1)
Other	1 (0.3)
Race	
White	261 (67.1)
Black	67 (17.2)
Asian	48 (12.3)
Other	0 (0.0)
Country/region	
United States	291 (75.0)
Singapore	22 (5.7)
Canada	18 (4.6)
Australia	57 (14.7)
Risk factors	
Body mass index, kg/m^2	29.3 ± 5.3
Hypertension	251 (65.2)
Diabetes	108 (28.1)
Dyslipidemia	271 (70.4)
Family history CAD	151 (39.2)
Smoking	53 (13.8)
eGFR, mL/min/1.73 m^2	82.0 ± 18.7
Prior CAD	
MI	63 (16.4)
PCI	24 (6.2)
PCI with stent	74 (19.2)
CABG	0 (0.0)
Type of stress CMR	
1.5-T	275 (70.9)
3.0-T	113 (29.1)
Adenosine	201 (51.8)
Regadenoson	187 (48.2)

Values are mean ± SD or n (%).

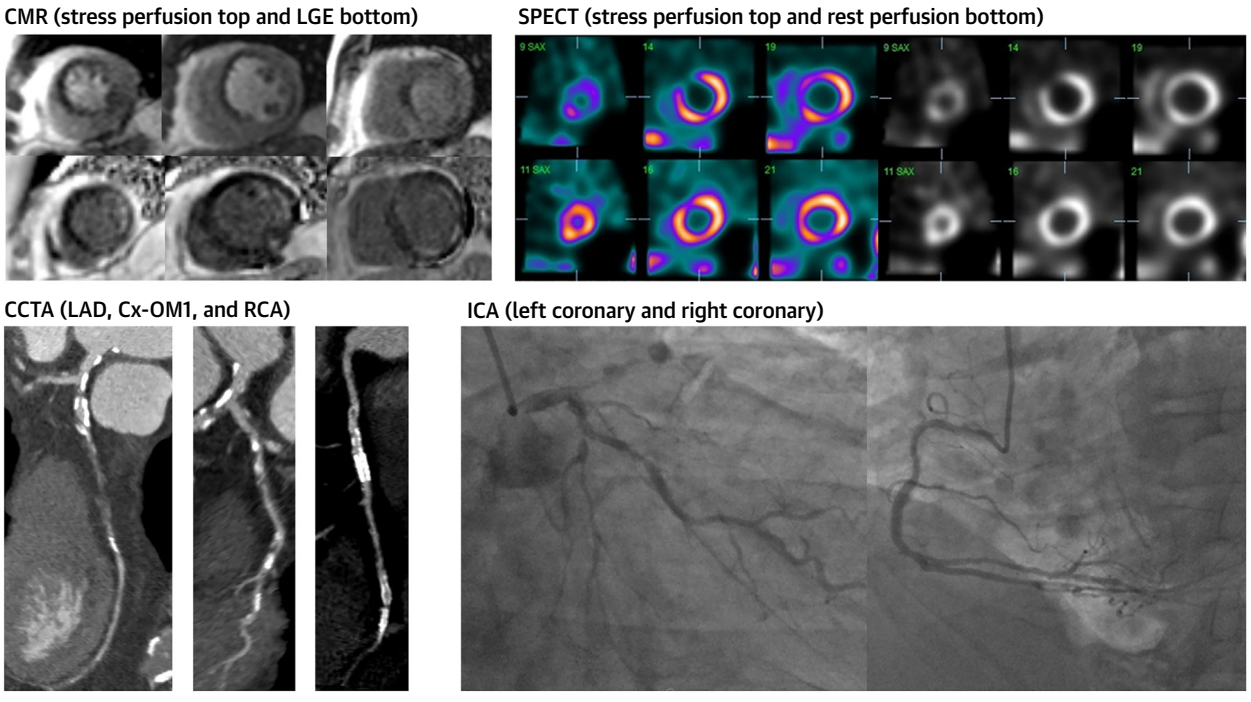
CABG = coronary artery bypass surgery; CAD = coronary artery disease; CMR = cardiac magnetic resonance; eGFR = estimated glomerular filtration rate; GadaCAD2 = Gadobutrol/Gadavist-enhanced Cardiac Magnetic Resonance Imaging (CMRI) to Detect Coronary Artery Disease (CAD) (GadaCAD 2); MI = myocardial infarction; PCI = percutaneous intervention.

FIGURE 2 Flow Chart of Inclusion for the Comparison Data Set

GadaCAD2 Subsets	Sample Size	Number of Subjects (% Relative to 478)	Reasons Subjects Were Excluded
Safety Analysis Set	n = 478		
		45 (9.4%)	Invasive coronary angiography or CCTA not suited for standard of reference evaluation
		34 (7.1%)	CMR images missing or unacceptable quality
		10 (2.1%)	CMR selected for training set
		1 (0.2%)	CMR interpretation missing from 1 reader
CMR Efficacy Analysis Set	n = 388		
		94 (19.7%)	SPECT images missing or unacceptable quality
SPECT vs CMR Comparison Set	n = 294		

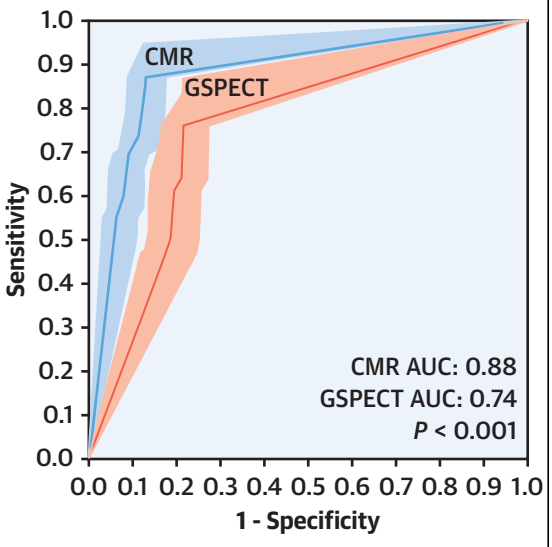
The exclusion of some patients due to missing SPECT images or image quality should not be overinterpreted. SPECT was not required for the primary aim of the GadaCAD2 trial. To maximize recruitment in the primary study, some patients did not have SPECT imaging done. The specific reason for exclusion of SPECT was not recorded in the database. CCTA = coronary computed tomography angiography; other abbreviations as in Figure 1.

FIGURE 3 Sample Images From a Study Participant With CAD



CMR and SPECT are both true positive in this patient. Despite a high-quality CCTA depicting CAD, the quantitative analysis of the invasive angiogram was the standard of reference in this patient by study design. CCTA could only serve as the standard of reference in GadaCAD2 to exclude CAD. To exclude significant CAD, a CCTA had to be normal or nearly normal as defined by no coronary calcifications obscuring the coronary artery lumen and minimal coronary narrowing (<25% visually). ICA = internal carotid artery; LAD = left anterior descending artery; RCA = right coronary artery; other abbreviations as in Figures 1 and 2.

FIGURE 4 ROC Curves for Detection of Significant CAD



Significant CAD was defined as a ≥70% coronary artery stenosis by quantitative coronary angiography. The CMR receiver operating characteristic (ROC) curve is shifted up and to the left of the SPECT ROC curve consistent with higher area under the curve ($P < 0.001$). The shaded areas represent the area extending to the 95% confidence limits. Abbreviations as in Figure 1.

CORE LABORATORY EXPERTISE. CMR quality was reviewed by 2 board-certified radiologists with 2 and 4 years of experience. The CMR blinded readers were 3 board-certified cardiologists with 14, 11, and 18 years of experience. SPECT quality was assessed by 2 board-certified radiologists/nuclear physicians with both having 9 years of experience. The 3 SPECT blinded readers included a board-certified cardiologist, radiologist, and a nuclear medicine physician with 36, 9, and 11 years of experience.

DISCUSSION

Our results confirm that stress perfusion CMR had superior diagnostic accuracy compared with gated SPECT for the detection of significant CAD defined as a ≥70% coronary stenosis by QCA. The prospective, 2-tailed, noninferiority design was able to assess inferiority, noninferiority/nonsuperiority, and superiority of CMR compared with SPECT. CMR was superior to SPECT in all diagnostic statistics except sensitivity where it was noninferior and nonsuperior to SPECT. The results agree well with prior large clinical trials and meta-analyses comparing CMR and SPECT.

Including the current study, 3 of 4 major clinical trials found that CMR has higher diagnostic accuracy than SPECT for the detection of significant CAD. The oldest study, MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease-2),[16,17] showed that CMR had superior AUC and sensitivity for detection of CAD but had inferior specificity. CE-MARC (Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease) found that CMR had superior AUC, sensitivity, and negative predictive value compared with SPECT.[18] The results from the current study complement these prior studies. On the other hand, the single-center PACIFIC 2 (Prospective Comparison of Cardiac PET, SPECT, and MRI Perfusion Imaging with Invasive Coronary Angiography in Patients with Prior CAD) study focused on patients with prior myocardial infarction or prior percutaneous coronary intervention.[19] In brief, SPECT and CMR had low sensitivities (67% and 66%, respectively) and low specificities (61% and 62%, respectively). However, the fractional flow reserve (FFR) standard was only measured in 109 of 183 (59%) subjects as FFR was not performed in the 74 (41%) with subtotal and total occlusions. Furthermore, the definition of an abnormal CMR scan subtracted the LGE from the perfusion score and required

TABLE 2 Diagnostic Accuracy Statistics vs the Standard of Reference of a ≥70% Stenosis in GadaCAD2 Study

Study	Data Level	CAD (+)	CAD (−)	Sensitivity	Specificity	AUC	Accuracy	PPV	NPV	TP	TN	FP	FN
Stress perfusion CMR	Clinical Trial	72	222	0.74	0.89	0.88	0.85	0.68	0.91	53	197	25	19
	95% CI[a]			(0.62-0.83)	(0.84-0.93)	(0.83-0.93)	(0.80-0.89)	(0.56-0.78)	(0.87-0.95)				
Gated SPECT MPI	Clinical Trial	72	222	0.64	0.79	0.74	0.75	0.49	0.87	46	175	47	26
	95% CI[a]			(0.52-0.75)	(0.73-0.84)	(0.68-0.80)	(0.70-0.80)	(0.39-0.60)	(0.82-0.91)				
Statistical test CMR vs SPECT	2-sided *P* value	-	-	0.127	0.002[b]	<0.001[b]	0.003[b]	<0.001[b]	0.041[b]		0.022[b]		

Values are n unless otherwise indicated. [a]Exact binomial confidence intervals were calculated.[11] [b]Statistically significant at 5% type I error.

AUC = area under the curve; FN = false negative; FP = false positive; MPI = myocardial perfusion imaging; NPV = negative predictive value; PPV = positive predictive value; SPECT = single-photon emission computed tomography; TN = true negative; TP = true positive; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Cardiac Magnetic Resonance Has Superior Diagnostic Performance Statistics vs Gated Single-Photon Emission Computed Tomography**

GadaCAD2

Predefined secondary aims
1. Noninferior sensitivity: CMR vs SPECT 2. Noninferior specificity: CMR vs SPECT

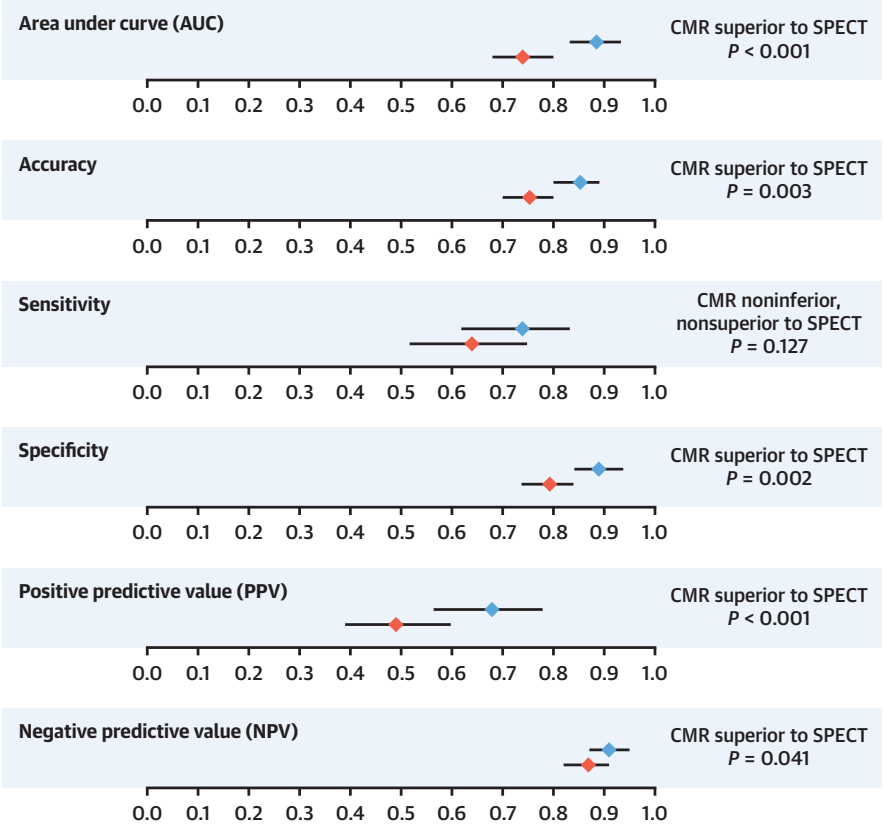
Population: Adults undergoing evaluation for known or suspected CAD based on typical or atypical chest discomfort

CMR			SPECT	
Gadobutrol (study drug) Vasodilator Stress perfusion	Cine Rest perfusion LGE	**and**	Tc99m sestamibi or Tc99m tetrofosmin Exercise or vasodilator Stress	Gated stress MPI Rest MPI

Invasive coronary angiography (QCA) **OR** **CCTA***

Independent core laboratories ≥70% QCA stenosis

Comparisons of Diagnostic Accuracy



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Cardiovascular magnetic resonance (CMR) had statistically superior diagnostic accuracy statistics compared with single-photon emission computed tomography (SPECT) for the detection of a 70% coronary artery stenosis by quantitative coronary angiography except sensitivity, where CMR was not superior and not inferior to SPECT. *CCTA could only exclude significant CAD.

greater than at least 2 segments to be abnormal. The combination of these factors would make it very difficult for CMR, which has the most sensitive method for detecting myocardial infarction, to correctly classify the 74 of 83 (41%) subjects with total/subtotal coronary occlusions as ischemic. Similarly, angiography could not differentiate ischemia from infarction in those patients.

Compared with initial validation studies of SPECT alone,[10] SPECT has also not performed as well in more recent meta-analyses, particularly with significant CAD defined by an invasive FFR ≤0.80.[5,20-22] Danad et al[21] concluded that CMR had the highest performance for diagnosis of ischemia-causing CAD compared with SPECT, stress echocardiography, CCTA, and invasive angiography using invasive FFR as the gold standard. There are some factors that may lead to differences in diagnostic accuracy between modalities. SPECT has lower spatial resolution than CMR, and SPECT tracers have nonlinear extraction in the vasodilated range of perfusion. LGE on CMR is very sensitive to subendocardial myocardial infarction that can be missed by SPECT.[23]

Although the guidelines tend to consider stress tests as a single entity, stress tests are not all created equal. The role of stress electrocardiography is markedly diminished in the most recent chest pain guideline[1] compared with prior guidelines.[4] Stress echocardiography cannot rule out angiographically significant CAD in some important subgroups.[6] In general, stress CMR and PET perform at the highest level and are uniquely quantifiable. Nevertheless, for various reasons, SPECT currently remains the most widely available stress imaging technology in North America.

STUDY LIMITATIONS. The use of an anatomic definition of CAD could contribute to lower sensitivity of both CMR and SPECT, as many stenoses are not physiologically significant.[24] Comparison with invasive FFR may have been a better standard of reference but was deemed impractical. In an unpublished retrospective review of the participants in the study, only approximately 3% with significant CAD underwent invasive FFR.

The use of CCTA as part of the standard of reference may have had both positive and negative influences on the current results. It was hoped that CCTA could help avoid bias introduced by including only subjects destined for invasive angiography but may have led to a lower prevalence of CAD than expected. The option of CCTA may have lowered the threshold to refer patients to the study compared with only allowing invasive angiography. This could have increased the number of borderline or equivocal SPECT studies and increased likelihood of false positive CMR and SPECT.

The need for several imaging procedures may also have reduced prevalence of CAD. This may also have led to a bias toward exclusion of patients with more severe SPECT abnormalities and lowered observed sensitivity.

The lack of outcomes data in this study is a limitation. In general, stress perfusion CMR has strong prognostic power in the evaluation of patients with chest pain.[25] CE-MARC2 (Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease-2) showed CMR helps avoid unnecessary angiograms.[26] More recently, CMR was shown to be cost-effective over a wide range of clinical scenarios.[27] A recent comparative effectiveness study of stress perfusion CMR vs invasive angiography found that CMR had lower incidence of coronary revascularization than FFR-based strategies and was noninferior to FFR with respect to incidence of major adverse cardiac events.[28]

Because SPECT was not required for the primary GadaCAD2 endpoints, subjects were not excluded from the main study if SPECT was not performed. The lower number of SPECT scans included in this study should not be overinterpreted as an indication of lower quality of this modality. Although SPECT studies had to meet published guidelines, the SPECT studies were performed on a variety of scanners in credentialed laboratories. The SPECT studies were not uniform in terms of protocol or tracer. However, training was provided to ensure SPECT studies met protocol requirements and clinical trial monitoring of SPECT studies was performed. Some methods that can improve the accuracy of SPECT for detection of CAD, such as 2-view imaging or attenuation correction, were not mandated. Thus, these SPECT results reflect a more “real-world” acquisition experience, which may have lower than expected diagnostic accuracy as compared with clinical trials that mandated more uniform methodology.

Classification of a CMR study or a SPECT study as normal or abnormal based on one or more abnormal segments does not recognize all subtleties of interpretation or allow classification of a study as equivocal. This methodology tends to increase sensitivity at the expense of specificity for both CMR and SPECT. Omission of the apical segment could have reduced the sensitivity of SPECT but could have had variable effect on specificity. The CMR protocol did not include myocardial perfusion quantification, which might have improved diagnostic accuracy.

CONCLUSIONS

The results of this multicenter trial indicate that CMR has a higher diagnostic accuracy than SPECT for the detection of CAD, adding significantly to the comparative diagnostic accuracy data for the 2 modalities and confirming the important role of CMR first-pass perfusion in international guidelines.[1,2]

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although stress perfusion CMR and SPECT MPI can detect ischemia due to CAD with similar sensitivity, CMR yields greater specificity, more true positives, and fewer false positives, which translates to less unnecessary testing and possibly lower costs.

TRANSLATIONAL OUTLOOK: Further prospective studies and cost-effectiveness analyses are needed to inform guidelines for appropriate use of stress perfusion imaging in clinical practice.

REFERENCES

1. Gulati M, Levy PD, Mukherjee D, et al. AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2021;78:2218–2261. https://doi.org/10.1016/j.jacc.2021.07.053

2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41:407–477. https://doi.org/10.1093/eurheartj/ehz425

3. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2021;42:1289–1367. https://doi.org/10.1093/eurheartj/ehaa575

4. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary. *J Am Coll Cardiol*. 2012;60:2564–2603.

5. Takx RA, Blomberg BA, Aidi H, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. *Circ Cardiovasc Imaging*. 2015;8:e002666.

6. Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J*. 2018;39:3322–3330.

7. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.

8. Bangalore S, Maron DJ, O'Brien SM, et al. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med*. 2020;382:1608–1618. https://doi.org/10.1056/NEJMoa1915925

9. Arai AE, Schulz-Menger J, Berman D, et al. Gadobutrol-enhanced cardiac magnetic resonance imaging for detection of coronary artery disease. *J Am Coll Cardiol*. 2020;76:1536–1547. https://doi.org/10.1016/j.jacc.2020.07.060

10. Holly TA, Abbott BG, Al-Mallah M, et al. ASNC imaging guidelines for nuclear cardiology procedures. *J Nucl Cardiol*. 2010;17:1071–3581. https://doi.org/10.1007/s12350-010-9246-y

11. Collett D. *Modelling Binary Data*. Chapman & Hall/CRC Texts in Statistical Science; 1999.

12. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika*. 1947;12:153–157. https://doi.org/10.1007/BF02295996

13. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845. https://doi.org/10.2307/2531595

14. Leisenring W, Alono T, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. *Biometrics*. 2000;56:345–351. https://doi.org/10.1111/j.0006-341X.2000.00345.x

15. Agresti A. *Categorical Data Analysis*. John Wiley and Sons; 1990.

16. Schwitter J, Wacker CM, Wilke N, et al. Superior diagnostic performance of perfusion-cardiovascular magnetic resonance versus SPECT to detect coronary artery disease: the secondary endpoints of the multicenter multivendor MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial). *J Cardiovasc Magn Reson*. 2012;14:61.

17. Schwitter J, Wacker CM, Wilke N, et al. MR-IMPACT II: Magnetic Resonance Imaging for

Myocardial Perfusion Assessment in Coronary Artery Disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J*. 2013;34:775–781. https://doi.org/10.1093/eurheartj/ehs022

18. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet*. 2011;379:453–460. https://doi.org/10.1016/S0140-6736(11)61335-4

19. Driessen RS, van Diemen PA, Raijmakers PG, et al. Functional stress imaging to predict abnormal coronary fractional flow reserve: the PACIFIC 2 study. *Eur Heart J*. 2022;43:3118–3128. https://doi.org/10.1093/eurheartj/ehac286

20. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2:1100–1107. https://doi.org/10.1001/jamacardio.2017.2471

21. Danad I, Szymonifka J, Twisk JWR, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J*. 2017;38:991–998. https://doi.org/10.1093/eurheartj/ehw095

22. Xu J, Cai F, Geng C, Wang Z, Tang X. Diagnostic performance of CMR, SPECT, and PET imaging for the identification of coronary artery disease: a meta-analysis. *Front Cardiovasc Med*. 2021;8:621389. https://doi.org/10.3389/fcvm.2021.621389

23. Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet*. 2003;361:374–379. https://doi.org/10.1016/S0140-6736(03)12389-6

24. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010;55:2816–2821.

25. Kwong RY, Steel K, Bingham S, et al. Cardiac magnetic resonance stress perfusion imaging for evaluation of patients with chest pain. *J Am Coll Cardiol*. 2019;74:1741–1755. https://doi.org/10.1016/j.jacc.2019.07.074

26. Greenwood JP, Ripley DP, Berry C, et al. 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. *JAMA*. 2016;316:1051–1060. https://doi.org/10.1001/jama.2016.12680

27. Ge Y, Pandya A, Steel K, et al. Cost-effectiveness analysis of stress cardiovascular magnetic resonance imaging for stable chest pain syndromes. *J Am Coll Cardio Img*. 2020;13:1505–1517. https://doi.org/10.1016/j.jcmg.2020.02.029

28. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med*. 2019;380:2418–2428. https://doi.org/10.1056/NEJMoa1716734

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APPENDIX For additional details about the principal investigators and consultants as well as a supplemental table, please see the online version of this paper.