

Washington University School of Medicine

Digital Commons@Becker

2020-Current year OA Pubs

Open Access Publications

9-29-2020

Gadobutrol-enhanced cardiac magnetic resonance imaging for detection of coronary artery disease

Andrew E Arai

Pamela K Woodard

et al.

Follow this and additional works at: https://digitalcommons.wustl.edu/oa_4



Part of the [Medicine and Health Sciences Commons](#)

Please let us know how this document benefits you.

Gadobutrol-Enhanced Cardiac Magnetic Resonance Imaging for Detection of Coronary Artery Disease



Andrew E. Arai, MD,^a Jeanette Schulz-Menger, MD,^b Daniel Berman, MD,^c Heiko Mahrholdt, MD,^d Yuchi Han, MD, MMSc,^e W. Patricia Bandettini, MD,^a Matthias Gutberlet, MD, PhD,^f Arun Abraham, MBBS,^g Pamela K. Woodard, MD,^h Joseph B. Selvanayagam, MBBS, DPHIL,ⁱ Gerry P. McCann, MD,^j Christian Hamilton-Craig, MBBS, PhD,^k U. Joseph Schoepf, MD,^l Ru San Tan, MBBS,^m Christopher M. Kramer, MD,ⁿ Matthias G. Friedrich, MD,^o Daniel Haverstock, MS,^p Zheyu Liu, PhD,^p Guenther Brueggenwerth, MD,^q Claudia Bacher-Stier, MD, PhD,^q Marta Santiuste, MD, PhD,^p Dudley J. Pennell, MD,^{r,s} for the GadaCAD Investigators

ABSTRACT

BACKGROUND Gadolinium-based contrast agents were not approved in the United States for detecting coronary artery disease (CAD) prior to the current studies.

OBJECTIVES The purpose of this study was to determine the sensitivity and specificity of gadobutrol for detection of CAD by assessing myocardial perfusion and late gadolinium enhancement (LGE) imaging.

METHODS Two international, single-vendor, phase 3 clinical trials of near identical design, "GadaCAD1" and "GadaCAD2," were performed. Cardiovascular magnetic resonance (CMR) included gadobutrol-enhanced first-pass vasodilator stress and rest perfusion followed by LGE imaging. CAD was defined by quantitative coronary angiography (QCA) but computed tomography coronary angiography could exclude significant CAD.

RESULTS Because the design and results for GadaCAD1 (n = 376) and GadaCAD2 (n = 388) were very similar, results were summarized as a fixed-effect meta-analysis (n = 764). The prevalence of CAD was 27.8% defined by a $\geq 70\%$ QCA stenosis. For detection of a $\geq 70\%$ QCA stenosis, the sensitivity of CMR was 78.9%, specificity was 86.8%, and area under the curve was 0.871. The sensitivity and specificity for multivessel CAD was 87.4% and 73.0%. For detection of a 50% QCA stenosis, sensitivity was 64.6% and specificity was 86.6%. The optimal threshold for detecting CAD was a $\geq 67\%$ QCA stenosis in GadaCAD1 and $\geq 63\%$ QCA stenosis in GadaCAD2.

CONCLUSIONS Vasodilator stress and rest myocardial perfusion CMR and LGE imaging had high diagnostic accuracy for CAD in 2 phase 3 clinical trials. These findings supported the U.S. Food and Drug Administration approval of gadobutrol-enhanced CMR (0.1 mmol/kg) to assess myocardial perfusion and LGE in adult patients with known or suspected CAD. (J Am Coll Cardiol 2020;76:1536-47) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).



Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the ^aNational Heart, Lung, and Blood Institute, National Institutes of Health, DHHS, Bethesda, Maryland; ^bHelios Klinikum Berlin Buch Klinik für Kardiologie und Nephrologie Abteilung Kardio-MRT, Berlin, Germany; ^cCedar-Sinai Medical Center, Los Angeles, California; ^dRobert-Bosch-Krankenhaus Zentrum für Innere Medizin (ZIM) III Abteilung für Kardiologie, Stuttgart, Germany; ^eHospital of the University of Pennsylvania, Philadelphia, Pennsylvania; ^fHerzzentrum Leipzig Abteilung für Diagnostische und Interventionelle Radiologie, Leipzig, Germany; ^gRoyal Perth Hospital, Perth, Western Australia, Australia; ^hWashington University School of Medicine, St. Louis, Missouri; ⁱFlinders University, Flinders Medical Centre, Adelaide, South Australia, Australia; ^jDepartment of Cardiovascular Sciences University of Leicester and the NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, United Kingdom; ^kThe Prince Charles Hospital Cardiology Research Centre, Brisbane, Queensland, Australia; ^lMedical University of South Carolina, Charleston, South Carolina; ^mNational Heart Centre Singapore, Singapore; ⁿUniversity of Virginia Health System, Charlottesville, Virginia; ^oDepartments of Medicine and Diagnostic Radiology, McGill University Health Centre, Montreal, Quebec, Canada; ^pBayer Pharmaceuticals LLC, Whippany, New Jersey; ^qBayer AG, Berlin, Germany; ^rCardiovascular Research Centre and CMR Unit at Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom; and the ^sNational Heart and Lung Institute, Imperial College, London, United Kingdom. Funding was provided by Bayer AG, Siemens Healthineers, and in part by the Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health. Dr. Arai has a Cooperative Research and Development Agreement (CRADA) with Bayer, Siemens, and Circle CVI Inc.; and has patents and invention reports related to perfusion quantification and cine MRI. Dr. Schulz-Menger has

CMR is a reference standard for assessing ventricular function (1) and for imaging myocardial infarction (MI) (2). In meta-analysis, stress perfusion CMR performs with high diagnostic accuracy, particularly when compared with invasive fractional flow reserve (FFR) (3). The MR INFORM (MR Perfusion Imaging to Guide Management of Patients with Stable Coronary Artery Disease) clinical trial (4) demonstrated that stress perfusion CMR can safely manage patients with stable angina with less revascularization but equivalent patient outcome to an invasive FFR-guided strategy. Large prospective single-center studies such as CE-MARC (Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease) (5) and multicenter, multivendor studies such as MR-IMPACT (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial) (6) and MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial II) (7) showed that stress perfusion CMR has good diagnostic performance and is superior or not inferior to single-photon emission computed tomography (SPECT) (5,6,8). Stress perfusion CMR and LGE imaging appear in multiple U.S. and international guidelines (9-11). Despite over 25 years of clinical trials and validations, there was no U.S. Food and Drug Administration (FDA) approval for gadolinium-based contrast agents (GBCAs) for stress perfusion CMR or LGE imaging in the United States prior to the current 2 clinical trials.

SEE PAGE 1548

GadaCAD1 and GadaCAD2 (Gadobutrol-enhanced CMR to detect Coronary Artery Disease) were phase 3 clinical trials (NCT01890421 and NCT01890434) designed to evaluate gadobutrol, a multipurpose GBCA, for the detection of CAD and to support

regulatory approval for use in CMR in the United States, performed on Siemens CMR scanners (Erlangen, Germany). Gadobutrol (Gadavist Bayer Pharma AG, Leverkusen, Germany) was previously FDA approved for central nervous system magnetic resonance imaging, for magnetic resonance angiography in adult and pediatric patients including term neonates, and for breast magnetic resonance imaging in adult patients. Based on the chemical structure of the gadolinium chelate, gadobutrol is 1 of 3 macrocyclic GBCAs currently on the market. It provides high stability and high relaxivity (12,13).

The specific aim of the GadaCAD clinical trials was to assess the diagnostic accuracy of gadobutrol-enhanced vasodilator stress perfusion CMR and LGE imaging to detect CAD in 2 nearly identical studies using an independent blinded read. The clinical trials had requirements from the FDA to meet or exceed specific diagnostic accuracy criteria for sensitivity and specificity. Gadobutrol-enhanced perfusion CMR had to have higher sensitivity than unenhanced stress cine CMR wall motion for CAD detection. The standard of reference defining CAD was invasive coronary angiography, but coronary computed tomography angiography (CTA) could be used to exclude CAD.

METHODS

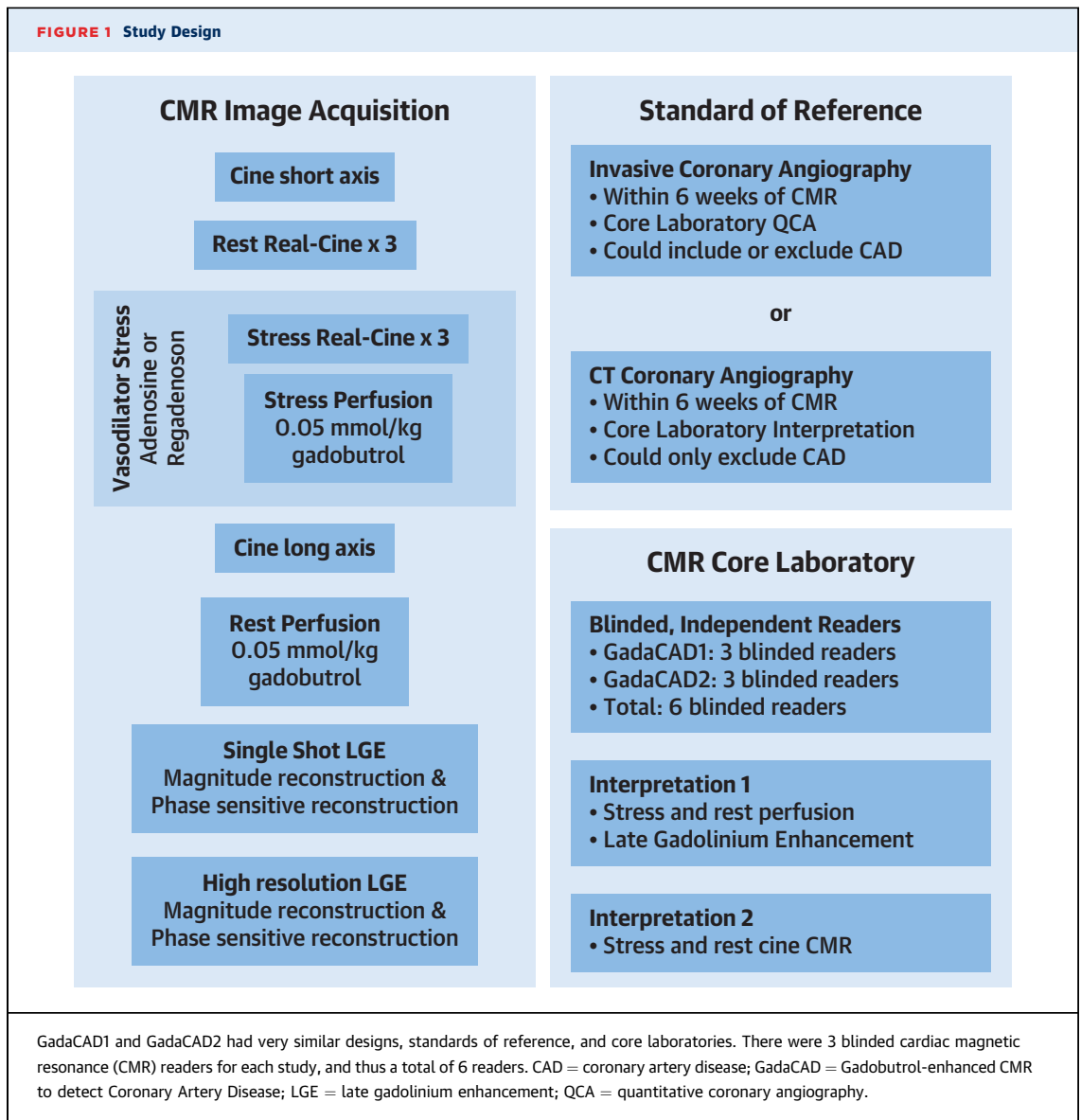
STUDY POPULATION. Inclusion criteria required that subjects were undergoing evaluation for known or suspected CAD based on typical or atypical chest discomfort, were age ≥ 18 years, and were willing to undergo the study procedures. Female subjects of child-bearing potential had to agree to use medically approved birth control during the study. The main exclusion criteria were contraindications to CMR, contraindications to vasodilators, suspected clinical

ABBREVIATIONS AND ACRONYMS

CI	= confidence interval
FFR	= invasive fractional flow reserve
GBCA	= gadolinium-based contrast agents
LGE	= late gadolinium enhancement
QCA	= quantitative coronary angiography
SPECT	= single-photon emission computed tomography

served as an advisor for Bayer. Dr. Berman has served as a consultant for Bayer. Dr. Han has received research grants from Gilead Sciences and General Electric; has served as a consultant for Acceleron, Bracco, and Complexa; and has served on the Speakers Bureau of General Electric, all unrelated to this work. Dr. Gutberlet has received speaker honorarium from Bayer, Bracco, Circle CVI, Philips, and Siemens. Dr. Woodard has received research support from Bayer, Lilly, and Roche; has a research agreement with Siemens; and has served as a consultant for Medtronic. Dr. Schoepf has received research support from and/or served as a consultant for Bayer, Bracco, Elucid BioImaging, GE, Guerbet, HeartFlow, and Siemens. Dr. Friedrich has received grants and personal fees from Circle Cardiovascular Imaging Inc., outside of the submitted work. Drs. Haverstock, Liu, Brueggewerth, Bacher-Stier, and Santiuste are employees of Bayer. Dr. Pennell has received research support from Siemens, ApoPharma Apotex, La Jolla, and Bayer; and has served as a consultant for Apotex, La Jolla, and Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Raymond Y. Kwong, MD, MPH, served as Guest Associate Editor for this paper. Deepak L. Bhatt, MD, served as Guest Editor-in-Chief for this paper.

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 [JACC author instructions page](#).



instability during the study period, revascularization between CMR and coronary angiography, prior coronary artery bypass graft, acute coronary syndrome, or decompensated heart failure <14 days prior to inclusion, certain arrhythmias, uncontrolled hypertension, baseline hypotension <90 mm Hg, and estimated glomerular filtration rate <30 ml/min/m². Full inclusion and exclusion criteria are available in [Supplemental Table 1](#).

All subjects signed written informed consent. The studies were conducted according to the Declaration of Helsinki, the principles of Good Clinical Practice, and were approved by the Health Authorities and local Ethics Committee of each participating institution.

EFFICACY ENDPOINTS. There were 3 coprimary endpoints regarding detection of CAD defined as a $\geq 50\%$ and $\geq 70\%$ QCA stenoses in 2 separate analyses: 1) the sensitivity for 2 of 3 readers had to be high enough that the lower bound of the 95% confidence interval (CI) was $>60\%$; 2) the specificity for 2 of 3 readers had to be high enough that the lower bound of the 2-sided 95% CI was $>55\%$; and 3) gadobutrol-enhanced stress/rest perfusion and LGE CMR had to have higher sensitivity than unenhanced wall motion CMR images performed at stress and rest. A CMR study was categorized as abnormal if either stress perfusion or LGE was abnormal with 1 exception. If stress and rest perfusion were abnormal but

TABLE 1 Typical CMR Image Acquisition Parameters

	Stress and Rest Perfusion	Stress and Rest Perfusion	Late Gadolinium Enhancement Overview, Single Shot	Late Gadolinium Enhancement High Resolution
Field strength	1.5-T	3-T	1.5- and 3-T	1.5- and 3-T
Sequence	Saturation recovery, SSFP	Saturation recovery, FLASH	Inversion recovery*	Inversion recovery*
Parallel imaging	ePAT 2, GRAPPA with external reference lines	ePAT 2, GRAPPA with external reference lines	iPAT 2, GRAPPA, internal reference lines	iPAT 2, GRAPPA, internal reference lines
Slice orientation	Short axis × 3 slices	Short axis × 3 slices	Short and long axis views	Short axis views (with possible additional views)
Spatial resolution	2.4 × 2.9 × 8.0 mm	1.9 × 2.5 × 8.0 mm	2.1 × 2.1 × 8.0 mm	1.3 × 1.3 × 8.0 mm
Temporal resolution, ms	~110 ms	~110 ms	~200 ms	~160 ms
Echo time, ms	~1.0 ms	~1.0 ms	~1.0 ms	~2.0 ms
Repetition time, ms	~2.7 ms	~2.9 ms	~2.8 ms	~5.9 ms
Inversion time, ms	100 ms	100 ms	~300-380 ms	~300-380 ms, optimized per patient
Trigger pulse	Every heartbeat	Every heartbeat	Every other heartbeat	Every other heartbeat

Typical acquisition parameters are listed; increases in field of view for larger patients will affect values for individual patients. Repetition time was estimated from temporal resolution and number of lines of k-space acquired. Inversion time ranges were modified during GadaCAD1 and thus have a broad range, but were generally longer at 3-T than for 1.5-T. *Magnitude and phase sensitive reconstruction (PSIR).
 ePAT = parallel image acceleration factor; FLASH = fast low angle shot; GRAPPA = Generalized Autocalibrating Partially Parallel Acquisitions; iPAT = parallel image acceleration factor; SSFP = steady state free precession.

LGE was normal, the perfusion finding was categorized as an artifact and the study as normal.

Imaging and vasodilator stress methods. The study-specific procedures are summarized in [Figure 1 and Table 1](#). The study used Siemens 1.5- and 3.0-T CMR scanners running the “Cardiac Dot software” that assists with image acquisition. Imaging included segmented cine CMR, real-time cine CMR at baseline and during stress, vasodilator stress and rest first-pass perfusion CMR, and single-shot LGE imaging about 5 min after rest perfusion, followed by segmented LGE imaging ([Table 1](#)). Magnitude (14) and phase-sensitive inversion recovery LGE images were reconstructed (15). The inversion time suggested by protocol could be adjusted by the technologist. Gadobutrol 0.05 mmol/kg was injected at 4 ml/s during vasodilator stress and again about 10 min later for rest perfusion (total dose of 0.1 mmol/kg body weight). No additional contrast was given for LGE imaging. The vasodilator could be either adenosine (140 µg/kg/min infusion for up to 6 min) or regadenoson (0.4 mg intravenous injection) based on site specific availability or preference. The rationale for some of the CMR methods are detailed in the [Supplemental Appendix](#).

Core laboratory analyses. CMR studies were read centrally, independently, and blinded to all non-imaging data by a total of 6 experts with ≥5 years of experience; 3 readers were assigned to each trial. Image analysis was through a study-specific image review program linked to the core laboratory image archive. Stress perfusion, rest perfusion, and LGE were summarized using the 17-segment American Heart Association 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 not normal. Cine wall motion was interpreted on a different day.

QCA was performed at a central core laboratory by the consensus of 2 experts who were blinded to all other data. Coronary artery stenoses were measured in the left main, left anterior descending (LAD), circumflex, and right coronary arteries if ≥2 mm in diameter and were compared with corresponding proximal reference segments (Medis, Leiden, the Netherlands). The standard of reference was set at ≥70% and at ≥50% diameter QCA stenosis. A blinded, core laboratory assessment of coronary CTA could exclude CAD in the absence of significant coronary calcium and stenosis.

STATISTICAL ANALYSIS. Generally, 2 adequate and well controlled trials are required to support FDA approval of medications. The sample size for stress perfusion CMR was determined by an assumed sensitivity of 75% with a lower bound of the 95% CI of 60% and an assumed specificity of 67% with a lower bound of the 95% CI of 55% and a 2-sided α-level of 0.05 and 90% power. These assumptions required a sample size that included 110 subjects with CAD and 180 subjects without CAD. Because the prevalence of disease could not be guaranteed, simulations were considered over a range of prevalence from 30% to 60% leading to estimates of 375 subjects per trial for approximately 80% power and assumed a disease prevalence of 40% to 55%.

Efficacy analysis used data from all subjects who underwent pharmacological stress, had complete electronic clinical report forms, had adequate

TABLE 2 Demographics, Type of Stress, and Adverse Events

	Subcategory	GadaCAD1	GadaCAD2
Sample size		376	388
Age, yrs		58.5 ± 12.0	58.9 ± 10.2
Male		260 (69.1)	239 (61.4)
Ethnicity	Hispanic	5 (1.3)	22 (5.7)
	Non-Hispanic	365 (97.1)	366 (94.1)
	Other	6 (1.6)	1 (0.3)
Race	White	277 (73.7)	261 (67.1)
	Black	2 (0.5)	67 (17.2)
	Asian	94 (25.0)	48 (12.3)
	Other	3 (0.8)	0 (0.0)
Country/region	Europe	256 (68.1)	None
	United States	28 (7.4)	291 (75.0)
	Korea	91 (24.2)	None
	Singapore	None	22 (5.7)
	Canada	None	18 (4.6)
	Australia/New Zealand	1 (0.3)	57 (14.7)
Risk factors	Body mass index, kg/m ²	27.1 ± 4.6	29.3 ± 5.3
	Hypertension	228 (62.0)	251 (65.2)
	Diabetes	89 (24.2)	108 (28.1)
	Dyslipidemia	230 (62.5)	271 (70.4)
	Family history CAD	143 (38.9)	151 (39.2)
	Smoking	90 (24.5)	53 (13.8)
	eGFR, ml/min/1.73 m ²	84.2 ± 18.4	82.0 ± 18.7
Prior CAD	MI	47 (12.8)	63 (16.4)
	PCI	10 (2.7)	24 (6.2)
	PCI with stent	59 (16.0)	74 (19.2)
	CABG	0 (0.0)	0 (0.0)
Type of stress CMR	1.5-T	183 (48.7)	275 (70.9)
	3.0-T	193 (51.3)	113 (29.1)
	Adenosine	315 (83.8)	201 (51.8)
	Regadenoson	61 (16.2)	187 (48.2)
Adverse events prior to gadobutrol	Any AE	76 (17.8)	142 (29.7)
	Stressor-related AE	64 (15.0)	136 (28.5)
Adverse events <6 h after gadobutrol	Any AE	48 (11.3)	82 (17.2)
	Stressor-related AE	20 (4.7)	49 (10.3)
	Gadobutrol-related AE	3 (0.7)	1 (0.2)

Values are n, mean ± SD, or n (%). Serious adverse events (AE) related to gadobutrol: death (0), anaphylaxis (1). CABG = coronary artery bypass graft; CAD = coronary artery disease; CMR = cardiac magnetic resonance; eGFR = estimated glomerular filtration rate; GadaCAD = Gadobutrol-enhanced CMR to detect Coronary Artery Disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

unenanced and gadobutrol-enhanced CMR as determined by the core laboratory, and had complete standard of reference images. The analysis was performed on a per-subject basis.

Subject characteristics are presented as mean ± SD if normally distributed, and median (25%, 75% CI) if not normally distributed. Diagnostic accuracy is summarized by sensitivity, specificity, area under the curve, positive predictive value, and negative predictive value. The 95% Clopper-Pearson CI were calculated. Receiver-operator characteristic (ROC) curves were determined from exact results at thresholds ranging from a 20% QCA stenosis to a 95%

QCA stenosis. ROC curves were compared with the DeLong method ([Supplemental Appendix](#)).

Results were summarized at the individual reader level, the clinical trial level, and as a meta-analysis combining both clinical trials. To provide an overall summary result, a fixed-effect meta-analysis method was used to summarize diagnostic accuracy statistics for the 6 readers. This methodology was chosen as the 2 clinical trials had similar sensitivity and specificity, nearly identical methodology, the same study drug and dose, the same standard of reference methods and core laboratories, and populations with similar prevalence of CAD. At the clinical trial level, the majority read was used to determine whether the study was abnormal or normal on a patient-by-patient basis. Majority read meant the result by either 2 or 3 readers who came to the same determination of a study being normal or abnormal.

RESULTS

DEMOGRAPHICS. The GadaCAD studies were multi-center, multinational studies enrolling patients with an overall sample size for efficacy of 376 subjects in GadaCAD1 and 388 subjects in GadaCAD2. For GadaCAD1 and GadaCAD2, safety was assessed in the 426 and 478 subjects who received gadobutrol. Inadequate CMR image quality led to exclusion of 17 (4.0%) and 26 (5.4%) subjects in GadaCAD1 and GadaCAD2, respectively, while suitability of coronary angiography or CTA led to exclusion of 28 (6.6%) and 45 (9.4%) subjects, respectively ([Supplemental Table 2](#)). The demographic characteristics of the study participants are summarized in [Table 2](#).

PREVALENCE OF CAD. In GadaCAD1, 12.8% of subjects had a history of MI compared with 16.4% in GadaCAD2 ([Table 2](#)). Fewer patients in GadaCAD1 had a history of prior percutaneous coronary intervention (PCI) (18.7%) than in GadaCAD2 (25.4%).

The post-testing prevalence of CAD was 28.7% in GadaCAD1 and 27.1% in GadaCAD2 ([Table 3](#)) as defined by the presence of at least 1 coronary artery stenosis ≥70% by core laboratory QCA. In GadaCAD1, the standard of reference was invasive angiography in 79.0% (297 of 376 subjects) and in GadaCAD2 was 68.0% (264 of 388 subjects) and coronary CTA in remaining subjects.

Of the 108 subjects in GadaCAD1 with a ≥70% QCA stenosis, 68 had single-vessel CAD and 40 had multivessel CAD defined as ≥70% QCA stenosis in 2 or more coronary arteries. Of the 105 subjects in GadaCAD2 with a ≥70% QCA stenosis, 58 had single-vessel

CAD and 47 had multivessel CAD. The proportions of subjects with significant CAD, without significant CAD, with single-vessel CAD, and with multivessel disease were similar for the 2 trials.

For participants with a $\geq 50\%$ QCA stenosis (Table 3), many patients had intermediate-severity stenoses in the range between 50% to $<70\%$ QCA stenosis. In GadaCAD1, 33 of 141 subjects (23.4%) had intermediate-severity stenoses and in GadaCAD2 the proportion was 45 of 150 subjects (30.0%).

EXAMPLE OF IMAGE QUALITY. Figure 2 depicts image quality from a participant who had no history of MI but was found to have 2 small subendocardial infarctions by LGE imaging and vasodilator-inducible perfusion defects that were more extensive than the MIs (Videos 1, 2, 3, 4, 5, and 6).

DIAGNOSTIC ACCURACY VERSUS QCA STENOSIS.

The meta-analysis (Table 4, Figure 3) of both clinical trials and all 6 readers provides a vantage point from which to compare other levels of analysis, including at the trial level and at the individual-reader level. Against a standard of reference of a $\geq 70\%$ QCA stenosis, the sensitivity was 78.9% with a lower limit of the 95% CI at 75.5% in the meta-analysis combining both clinical trials. The specificity was 86.8% with a lower limit of the 95% CI at 85.0%. The area under the curve was 0.871 and corresponded to positive predictive value and negative predictive value of 69.7% and 91.4%, respectively. The sensitivity for multivessel CAD was 87.4% (95% CI: 77.0% to 97.2%) and for single-vessel CAD was 73.05 (95% CI: 62.1% to 84.0%).

Overall, the combined results represented the sensitivity and specificity of the individual readers quite well (Figure 3). In general, the sensitivity for detecting a $\geq 70\%$ QCA stenosis was slightly higher in GadaCAD1 (81.5%) than GadaCAD2 (77.1%) as summarized by the majority read (Table 4). Individually, 5 of the 6 readers were within 2.9% of the meta-analysis sensitivity and were within 4.8% of the meta-analysis specificity. In pairwise comparisons of ROC curves, there were no significant differences between readers within either clinical trial. The Central Illustration summarizes the main study methods and main study results.

For detection of a $\geq 50\%$ QCA stenosis, the sensitivity of the meta-analysis decreased to 64.6%, while specificity was minimally different from the results using a $\geq 70\%$ QCA stenosis (Tables 4 and 5). For GadaCAD1 and GadaCAD2 analyzed as individual trials, sensitivity was within 2.1% and specificity was within 1.1% of the combined results. At the reader level, 5 of 6 readers had a sensitivity within 3.3% of

TABLE 3 Prevalence of Coronary Artery Disease in GadaCAD1 and GadaCAD2

Coronary Artery Disease	GadaCAD1	GadaCAD2
Sample size	376	388
Standard of reference $\geq 70\%$ QCA		
No significant CAD	268 (71.3)	283 (72.9)
$\geq 70\%$ stenosis by QCA	108 (28.7)	105 (27.1)
Single-vessel CAD	68 (18.1)	58 (14.9)
Multivessel CAD	40 (10.6)	47 (12.1)
Standard of reference $\geq 50\%$ QCA		
No significant CAD	235 (62.5)	238 (61.3)
$\geq 50\%$ stenosis by QCA	141 (37.5)	150 (39.9)
Single-vessel CAD	57 (15.1)	59 (15.2)
Multivessel CAD	84 (22.3)	91 (23.5)
QCA stenosis $\geq 50\%$ but $<70\%$ *	33/141 (23.4)	45/150 (30.0)

Values are n, n (%), or n/N (%). *Total number is the number of subjects with $\geq 50\%$ QCA stenosis.
 CAD = coronary artery disease; GadaCAD = Gadobutrol-enhanced CMR to detect Coronary Artery Disease; QCA = quantitative coronary angiography.

the meta-analysis and all 6 readers had a specificity within 3.5% of the meta-analysis.

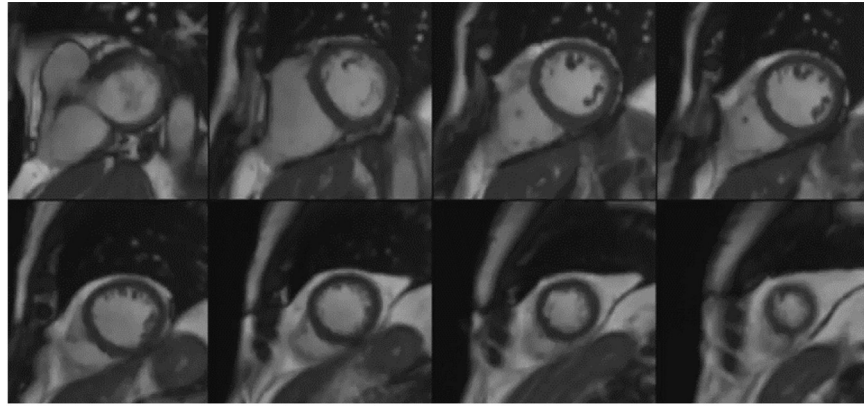
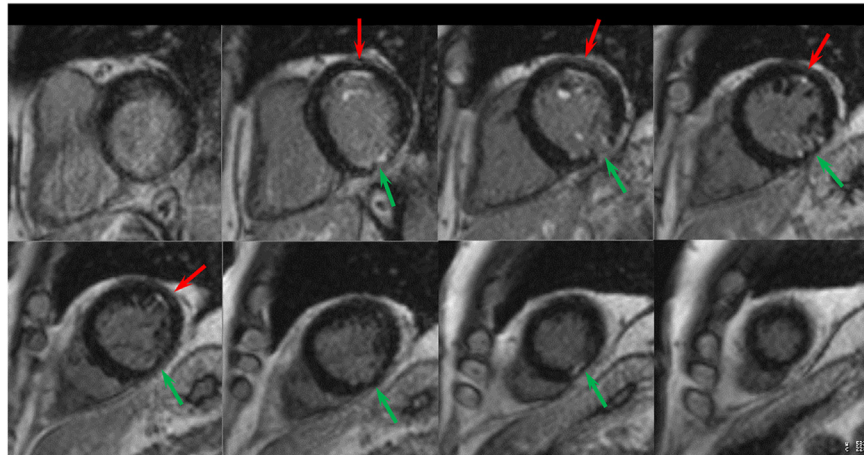
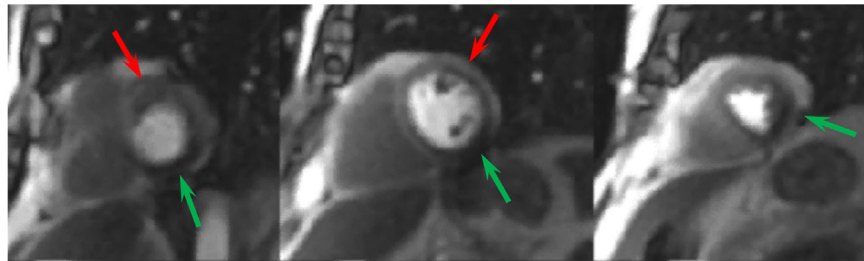
SENSITIVITY ANALYSIS FOR INTERMEDIATE STENOSIS (50% TO $<70\%$ BY QCA).

By ROC analysis, the optimal threshold for detecting CAD was a $\geq 67\%$ QCA stenosis in GadaCAD1 and a $\geq 63\%$ QCA stenosis in GadaCAD2 (Supplemental Table 3). To further analyze the decrease in sensitivity between a $\geq 70\%$ QCA stenosis and a $\geq 50\%$ QCA stenosis, 78 subjects had an intermediate-severity stenosis defined as $\geq 50\%$ to $<70\%$ QCA stenosis (Table 3). In GadaCAD1, 18% of subjects with an intermediate stenosis had an abnormal CMR, whereas in GadaCAD2, 29% of subjects with an intermediate stenosis had an abnormal CMR.

SUMMARY OF STUDY ENDPOINTS.

The meta-analysis combining results from the 6 readers met all study endpoints for both definitions of CAD: $\geq 70\%$ QCA stenosis and $\geq 50\%$ QCA stenosis (Table 4). The lower bound of the 95% CI exceeded the pre-defined thresholds for both sensitivity and specificity. In addition, the sensitivity of gadobutrol-enhanced perfusion and LGE CMR was better than vasodilator-induced wall motion abnormalities (Supplemental Table 4). With significant CAD defined by a 70% QCA stenosis, all 6 readers met every endpoint for sensitivity, specificity, and the comparison with stress cine wall motion (Supplemental Table 4). When defining CAD at a 50% QCA stenosis, 5 of 6 readers did not meet or exceed the lower limit of the sensitivity endpoint but all readers met all other study endpoints (Table 5).

ADVERSE EVENTS. The great majority of adverse events were stressor-related (Table 2). There were no deaths. Of the 4 adverse events related to gadobutrol, only 1 was considered serious: an anaphylactic reaction.

FIGURE 2 Example of Image QualityCine CMR
Short AxisLGE CMR
Short AxisStress
Perfusion
Short AxisRest
Perfusion
Short Axis

This patient had multivessel coronary stenoses and no clinically recognized prior myocardial infarction (MI), a 95% right coronary artery stenosis, 70% diagonal stenosis, and a 50% obtuse marginal stenosis. Nonmotion-corrected stress perfusion images (**bottom**) show an obvious inferior and inferolateral perfusion defect (**green arrows**) and a second less severe anterolateral perfusion defect (**red arrows**). The perfusion defects were more extensive than the small subendocardial MI detected with LGE imaging (**middle**). See [Videos 1, 2, 3, 4, 5, and 6](#), including the cine CMR (**top**), which showed a subtle inferior wall motion abnormality and perfusion images. Abbreviations as in [Figure 1](#).

TABLE 4 Diagnostic Accuracy Statistics at the Individual Reader Level, Clinical Trial Level, and Level of Combined Results for Both Studies Versus the Standard of Reference of a $\geq 70\%$ Stenosis by QCA

Study	Data Level	Sample Size	CAD(+)	CAD(-)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC	PPV, %	NPV, %	TP	TN	FP	FN
GadaCAD1 and 2	Meta-analysis 6 readers	764	213	551	78.9 (75.5-82.0)	86.8 (85.0-88.3)	0.871	69.7	91.4	168	478	73	45
GadaCAD1	Clinical trial	376	108	268	81.5 (72.9-88.3)	89.6 (85.3-92.9)	0.880	75.9	92.3	88	240	28	20
GadaCAD2	Clinical trial	388	105	283	77.1 (67.9-84.8)	86.6 (82.0-90.3)	0.861	68.1	91.0	81	245	38	24
GadaCAD1	Reader 1	376	108	268	89.8 (82.5-94.8)	82.8 (77.8-87.2)	NA	67.8	95.3	97	222	46	11
	Reader 2	376	108	268	79.6 (70.8-86.8)	91.0 (87.0-94.2)	NA	78.2	91.7	86	244	24	22
	Reader 3	376	108	268	78.7 (69.8-86.0)	90.7 (86.5-93.9)	NA	77.3	91.4	85	243	25	23
GadaCAD2	Reader 4	388	105	283	77.1 (67.9-84.8)	82.0 (77.0-86.3)	NA	61.4	90.6	81	232	51	24
	Reader 5	388	105	283	71.4 (61.8-79.8)	87.3 (82.8-90.9)	NA	67.6	89.1	75	247	36	30
	Reader 6	388	105	283	76.2 (66.9-84.0)	86.9 (82.4-90.6)	NA	68.4	90.8	80	246	37	25

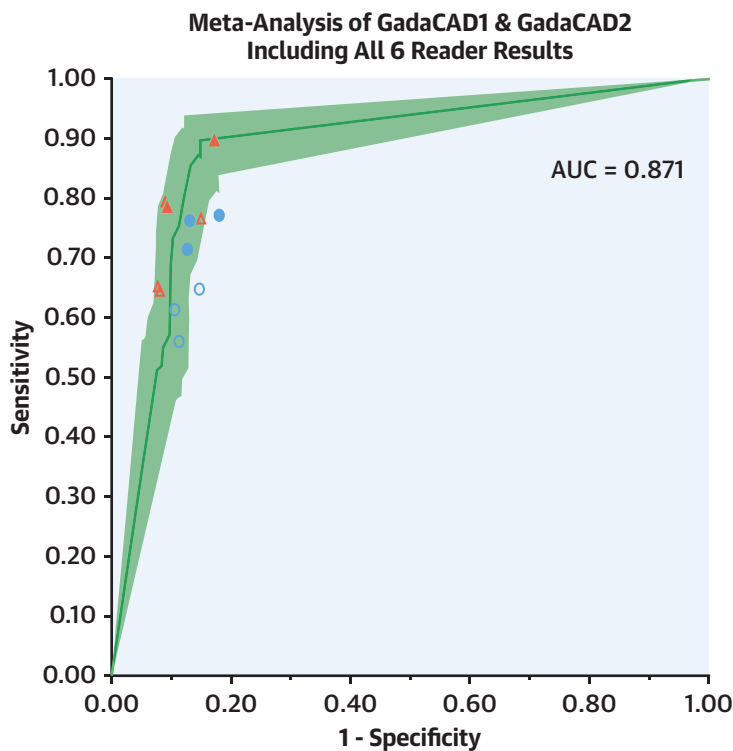
AUC = area under the curve; CI = confidence interval; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive; other abbreviations as in Table 3.

DISCUSSION

The GadaCAD1 and GadaCAD2 studies were pivotal, phase 3 clinical trials that led to FDA approval of gadobutrol-enhanced CMR to assess stress and rest

myocardial perfusion and LGE in adult patients with known or suspected CAD. The GadaCAD studies had high diagnostic accuracy for detection of CAD. The results were consistent at the individual reader level, the clinical trial level, and at the meta-analysis level

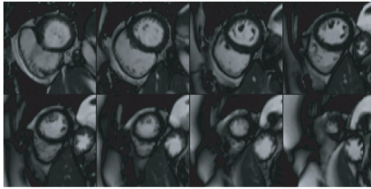
FIGURE 3 Receiver-Operator Characteristic Curve for the Meta-Analysis Combining the Results of GadaCAD1 and GadaCAD2



The green line plots the receiver-operator characteristic curve with shading surrounding the line representing the 95% confidence interval (CI). Solid red triangles plot the results for the 3 readers from GadaCAD1 versus a 70% QCA stenosis. Solid blue circles plot the results for the 3 readers from GadaCAD2 versus a 70% QCA stenosis. The open symbols plot results for the 2 clinical trials versus a 50% QCA stenosis using the same color scheme. Abbreviations as in Figure 1.

CENTRAL ILLUSTRATION Cardiac Magnetic Resonance Image Acquisition Order

Cine Short Axis (normal global & regional function)



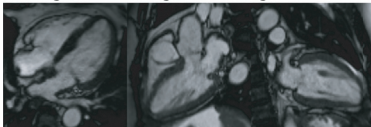
Stress Real-time Cine (no stress-induced RWMA)



Rest Real-time Cine (normal regional wall motion)



Cine Long Axis (normal global and regional function)



CMR Image Acquisition Order

Cine Short Axis (volumetric)

Rest Real-time Cine x 3 slices

Vasodilator Stress Adenosine or Regadenoson	Stress Real-time Cine x 3 slices
	Stress Perfusion 0.05 mmol/kg gadobutrol

Cine Long Axis x 3 views

Rest Perfusion

0.05 mmol/kg
gadobutrol

Single Shot LGE

Magnitude Reconstruction &
Phase Sensitive Reconstruction

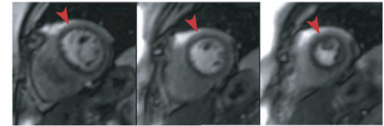
High Resolution LGE

Magnitude Reconstruction &
Phase Sensitive Reconstruction

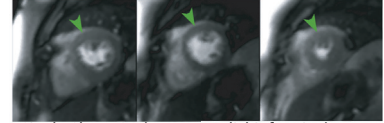
Standard of Reference

Core Lab QCA	Core Lab CMR
70% QCA stenosis	3 independent experts GadaCAD1
50% QCA stenosis	3 independent experts GadaCAD2

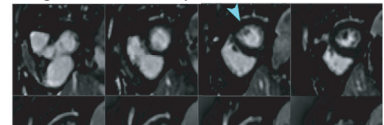
Stress Perfusion (diffuse from 3-vessel disease)



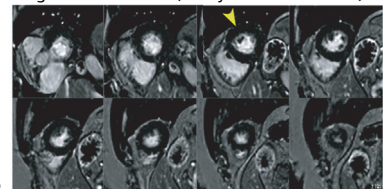
Rest Perfusion (normal)



Single Shot LGE (no myocardial infarction)



High Resolution LGE (no myocardial infarction)



Arai, A.E. et al. *J Am Coll Cardiol.* 2020;76(13):1536-47.

The main findings in this patient were diffuse and severe perfusion defects during stress that were not present during rest perfusion imaging and the absence of a myocardial infarction. The stress perfusion defect appears as a dark band about 50% to 75% in transmural extent in all segments with a thin band of brighter gray near the epicardium (red arrows). Rest perfusion appears normal as documented by uniformly gray enhancement (green arrows). Both sets of late gadolinium enhancement (LGE) images showed no myocardial infarction as the myocardium appears relatively uniformly black myocardium (cyan and yellow arrows). Cine short axis cardiac magnetic resonance (CMR) in multiple, contiguous short-axis imaging planes provided measurements of left ventricular volumes, ejection fraction, and mass. Lower-resolution real-time cine CMR were obtained before and during vasodilator stress to assess for induced regional wall motion abnormalities (RWMA), which cannot be assessed on static images but were not seen on review of the video versions. Long-axis cine CMR confirmed the global and regional left ventricular function. QCA = quantitative coronary angiography.

combining the 2 trials. First-pass perfusion and LGE CMR with gadobutrol (0.1 mmol/kg dose, divided into 2 separate and equal injections) is now indicated in the United States to assess stress and rest myocardial perfusion and myocardial infarction in adult patients with known or suspected CAD.

The results of GadaCAD1 and GadaCAD2 are in accord with meta-analyses of CMR stress perfusion (3), are comparable to the large CE-MARC study (5), and are a slightly better than the MR IMPACT clinical trials (6,7). In the European Society of Cardiovascular Radiology MRCT registry, stress perfusion represents ~25% of CMR scans performed and had few moderate or severe adverse events (16). Stress perfusion CMR risk stratifies patients with stable angina in the multicenter SPINS (Stress CMR Perfusion Imaging in the United States) study (17), a negative CMR has low

long-term cardiac events (18), and stress perfusion CMR has low spending on subsequent ischemia testing (19), a finding also applicable to European economics (20).

A prior clinical trial aimed at getting approval for a different GBCA to image MI (21) did not make it through U.S. regulatory processes. Although the MR IMPACT I and II clinical trials (6,7) brought approval in several European countries, these studies did not succeed in the FDA regulatory process, which appeared to have focused on a 50% QCA stenosis, a factor that may have contributed to low apparent sensitivity as explained in subsequent paragraphs. As a multivendor study, MR IMPACT II had a more complicated trial design compared with the single-vendor GadaCAD studies, but had superior diagnostic accuracy compared with SPECT (8).

TABLE 5 Diagnostic Accuracy Statistics at the Individual Reader Level, Clinical Trial Level, and Level of Combined Results for Both Studies Versus a Standard of Reference of a $\geq 50\%$ Stenosis by QCA

Study	Data Level	Sample Size	CAD(+)	CAD(-)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC	PPV, %	NPV, %	TP	TN	FP	FN
GadaCAD1 and 2	Meta-analysis 6 readers	764	291	473	64.6 (61.3-67.8)	88.6 (87.0-90.4)	0.871	78.0	80.3	188	420	159	103
GadaCAD1	Clinical trial	376	141	235	66.7 (58.2-74.4)	90.6 (86.2-94.0)	0.880	81.0	81.9	94	213	22	47
GadaCAD2	Clinical trial	388	150	238	62.7 (54.4-70.4)	89.5 (84.9-93.1)	0.861	79.0	79.2	94	213	25	56
GadaCAD1	Reader 1	376	141	235	76.6 (68.7-83.3)	85.1 (80.0-89.4)	NA	75.5	85.8	108	200	35	33
	Reader 2	376	141	235	65.2 (56.8-73.1)	92.3 (88.2-95.4)	NA	83.6	81.6	92	217	18	49
	Reader 3	376	141	235	64.5 (56.0-72.4)	91.9 (87.7-95.1)	NA	92.7	81.2	91	216	19	50
GadaCAD2	Reader 4	388	150	238	64.7 (56.5-72.3)	85.3 (80.1-89.5)	NA	73.5	79.3	97	203	35	53
	Reader 5	388	150	238	56.0 (47.7-64.1)	88.7 (83.9-92.4)	NA	75.7	76.2	84	211	27	66
	Reader 6	388	150	238	61.3 (53.0-69.2)	89.5 (84.9-93.1)	NA	78.6	78.6	92	213	25	58

Abbreviations as in Tables 3 and 4.

The FDA approval of gadobutrol-enhanced CMR has important clinical implications (17,22). Multiple observational registries have demonstrated an association of revascularization with and survival benefit in patients with extensive ischemia SPECT. Although the randomized, controlled ISCHEMIA trial (23) did not find a significant difference in hard outcomes in patients with moderate or severe ischemia assigned to an invasive strategy plus optimal medical therapy (OMT) versus OMT alone, improved health status outcomes in the invasive arm were observed (17,22,24). Stress tests are recognized by all major guidelines, and will continue to be used to diagnose and manage CAD.

The published data on FFR suggest that managing patients based on anatomic coronary artery stenoses severity leads to higher rates of revascularization and no benefit or worse outcomes compared with managing patients based on physiological significance of the stenosis by FFR (25-29). The MR INFORM study (4) extended this concept to managing patients based on stress perfusion CMR. MR INFORM was an unblinded, international, multicenter, prospective, randomized, clinical-effectiveness trial. CMR was noninferior to invasive FFR with respect to major adverse cardiac events. Because the CMR strategy had significantly fewer coronary revascularization procedures than invasive FFR, the CMR strategy has potential to reduce costs.

The large number of intermediate-severity stenoses between 50% and <70% may have contributed to the relatively low sensitivity for a $\geq 50\%$ QCA stenosis in the GadaCAD studies. It is widely accepted that most 50% to <70% stenoses are not functionally significant (30). In a post hoc analysis of the GadaCAD data, the proportion of intermediate coronary stenoses that led to abnormal CMR scans was comparable

to the fraction of intermediate-severity stenoses in the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and DEFER (Deferral of percutaneous coronary intervention) studies that caused abnormal invasive FFR (30,31).

Although stress perfusion CMR has generally used 50% to 100% higher GBCA doses (32) than other indications, the GadaCAD studies have proven that single-dose gadobutrol (0.1 mmol/kg) is sufficient to evaluate CAD (32). A dose ranging study concluded that 0.1 mmol/kg of gadopentetate dimeglumine was as efficacious as higher doses (33). For the GadaCAD studies, the gadobutrol dose was based on the results of a phase 2 clinical trial (Myocardial Perfusion MRI; NCT01490294) that did not reveal benefit of increasing the dose to 0.2 mmol/kg, but did show benefit compared with a dose of 0.05 mmol/kg. The published data does not support a dose-related tendency for higher sensitivity for stress-perfusion CMR at 0.2 mmol/kg (5,6,34-38) versus 0.15 mmol/kg (7,39-41) and versus 0.1 mmol/kg (42-45) total doses of GBCA. The Supplemental Materials describe methods aimed at obtaining diagnostic quality images with the dose of contrast used.

The study did not recommend or exclude aminophylline to reverse the vasodilators. Aminophylline is not generally needed for adenosine stress due to the short half-life, but could be considered to get closer to “rest” perfusion after regadenoson to improve distinction of artifacts from perfusion defects. LGE imaging is considered the most accurate way to detect MI and improves interpretation of stress perfusion CMR (46).

STUDY LIMITATIONS. A QCA reference to define CAD is imperfect but practical for large-scale recruitment. However, the 70% stenosis threshold is widely used

to infer the presence of hemodynamic significance of the obstruction. Although FFR might have been a more ideal reference standard, only about 3% of subjects in the GadaCAD studies had FFR performed clinically in a post-study survey (unpublished data, A. Arai, March 2019). In the United States, invasive FFR utilization remains relatively low despite clinical trial evidence (27-29).

The GadaCAD trials did not test a higher dose of gadobutrol or different specific GBCA so the results should not be extrapolated beyond what was studied. The GadaCAD trials were not designed to differentiate diagnostic accuracy of different image acquisition sequences or magnetic field strength. The studies allowed use of adenosine or regadenoson as a vasodilator due to divergent geographic preferences or regulatory approval status. The study did not randomize adenosine and regadenoson and, thus, was not designed to compare these agents.

Despite methods aimed to obtain identical slices for stress and rest perfusion, matching was not always perfect (Figure 2), but LGE images can also be used to help interpret stress perfusion images (46).

CONCLUSIONS

Gadobutrol-enhanced CMR has high diagnostic accuracy for detecting CAD and is now FDA approved at a

dose of 0.1 mmol/kg to assess myocardial perfusion and LGE in adults with known or suspected CAD.

ADDRESS FOR CORRESPONDENCE: Dr. Andrew E. Arai, National Institutes of Health, National Heart, Lung, and Blood Institute, Building 10, Room B1D416, MSC 1061, 10 Center Drive, Bethesda, Maryland 20892-1061. E-mail: araia@nih.gov OR andrewarai@hotmail.com. Twitter: [@dj_pennell](https://twitter.com/dj_pennell).

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: Stress perfusion CMR imaging with gadobutrol can be utilized to assess left ventricular function, stress and rest perfusion, and the transmural extent of MI in adults with known or suspected CAD. Adverse and side effects of stress perfusion CMR are dominated by those of the vasodilator agent.

TRANSLATIONAL OUTLOOK: Additional prospective studies are needed to compare the sensitivity, specificity, predictive value, advantages, and limitations of gadobutrol-enhanced CMR for assessment of CAD in specifically defined subpopulations.

REFERENCES

- Bellenger NG, Burgess MI, Ray SG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J* 2000;21:1387-96.
- 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;361:374-9.
- Takx RA, Blomberg BA, El 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.
- Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med* 2019;380:2418-28.
- 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* 2012;379:453-60.
- Schwittler J, Wacker CM, van Rossum AC, et al. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. *Eur Heart J* 2008;29:480-9.
- Schwittler 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;34:775-81.
- Schwittler 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.
- Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407-77.
- von Knobelsdorff-Brenkenhoff F, Pilz G, Schulz-Menger J. Representation of cardiovascular magnetic resonance in the AHA/ACC guidelines. *J Cardiovasc Magn Reson* 2017;19:70.
- Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014;63:380-406.
- Frenzel T, Lengsfeld P, Schirmer H, Hutter J, Weinmann HJ. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Invest Radiol* 2008;43:817-28.
- Szomolanyi P, Rohrer M, Frenzel T, et al. Comparison of the relaxivities of macrocyclic gadolinium-based contrast agents in human plasma at 1.5, 3, and 7 T, and blood at 3 T. *Invest Radiol* 2019;54:559-64.
- Simonetti OP, Kim RJ, Fieno DS, et al. An improved MR imaging technique for the visualization of myocardial infarction. *Radiology* 2001;218:215-23.

15. Kellman P, Arai AE, McVeigh ER, Aletras AH. Phase-sensitive inversion recovery for detecting myocardial infarction using gadolinium-delayed hyperenhancement. *Magn Reson Med* 2002;47:372-83.
16. Uhlig J, Lucke C, Vliegenthart R, et al. Acute adverse events in cardiac MR imaging with gadolinium-based contrast agents: results from the European Society of Cardiovascular Radiology (ESCR) MRCT Registry in 72,839 patients. *Eur Radiol* 2019;29:3686-95.
17. Kwong RY, Ge Y, Steel K, et al. Cardiac magnetic resonance stress perfusion imaging for evaluation of patients with chest pain. *J Am Coll Cardiol* 2019;74:1741-55.
18. Lipinski MJ, McVey CM, Berger JS, Kramer CM, Salerno M. Prognostic value of stress cardiac magnetic resonance imaging in patients with known or suspected coronary artery disease: a systematic review and meta-analysis. *J Am Coll Cardiol* 2013;62:826-38.
19. 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 Cardiol Img* 2020;13:1505-17.
20. Moschetti K, Petersen SE, Pilz G, et al. Cost-minimization analysis of three decision strategies for cardiac revascularization: results of the "suspected CAD" cohort of the European Cardiovascular Magnetic Resonance Registry. *J Cardiovasc Magn Reson* 2016;18:3.
21. Kim RJ, Albert TS, Wible JH, et al. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. *Circulation* 2008;117:629-37.
22. Vincenti G, Masci PG, Monney P, et al. Stress perfusion CMR in patients with known and suspected CAD: prognostic value and optimal ischemic threshold for revascularization. *J Am Coll Cardiol Img* 2017;10:526-37.
23. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;382:1395-407.
24. Spertus JA, Jones PG, Maron DJ, et al. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med* 2020;382:1408-19.
25. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-16.
26. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014;371:1208-17.
27. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
28. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
29. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 2010;56:177-84.
30. 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;55:2816-21.
31. Pijls NHJ, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. *J Am Coll Cardiol* 2007;49:2105-11.
32. Nacif MS, Arai AE, Lima JA, Bluemke DA. Gadolinium-enhanced cardiovascular magnetic resonance: administered dose in relationship to United States Food and Drug Administration (FDA) guidelines. *J Cardiovasc Magn Reson* 2012;14:18.
33. Wolff SD, Schwitter J, Coulden R, et al. Myocardial first-pass perfusion magnetic resonance imaging: a multicenter dose-ranging study. *Circulation* 2004;110:732-7.
34. Greulich S, Bruder O, Parker M, et al. Comparison of exercise electrocardiography and stress perfusion CMR for the detection of coronary artery disease in women. *J Cardiovasc Magn Reson* 2012;14:36.
35. Klein C, Nagel E, Gebker R, et al. Magnetic resonance adenosine perfusion imaging in patients after coronary artery bypass graft surgery. *J Am Coll Cardiol Img* 2009;2:437-45.
36. Merkle N, Wöhrle J, Grebe O, et al. Assessment of myocardial perfusion for detection of coronary artery stenoses by steady-state, free-precession magnetic resonance first-pass imaging. *Heart* 2007;93:1381-5.
37. Salerno M, Taylor A, Yang Y, et al. Adenosine stress cardiovascular magnetic resonance with variable-density spiral pulse sequences accurately detects coronary artery disease: initial clinical evaluation. *Circ Cardiovasc Imaging* 2014;7:639-46.
38. Watkins S, McGeoch R, Lyne J, et al. Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation* 2009;120:2207-13.
39. Klem I, Greulich S, Heitner JF, et al. Value of cardiovascular magnetic resonance stress perfusion testing for the detection of coronary artery disease in women. *J Am Coll Cardiol Img* 2008;1:436-45.
40. Sakuma H, Suzawa N, Ichikawa Y, et al. Diagnostic accuracy of stress first-pass contrast-enhanced myocardial perfusion MRI compared with stress myocardial perfusion scintigraphy. *AJR Am J Roentgenol* 2005;185:95-102.
41. Kitagawa K, Sakuma H, Nagata M, et al. Diagnostic accuracy of stress myocardial perfusion MRI and late gadolinium-enhanced MRI for detecting flow-limiting coronary artery disease: a multicenter study. *Eur Radiol* 2008;18:2808-16.
42. Cheng AS, Pegg TJ, Karamitsos TD, et al. Cardiovascular magnetic resonance perfusion imaging at 3-tesla for the detection of coronary artery disease: a comparison with 1.5-tesla. *J Am Coll Cardiol* 2007;49:2440-9.
43. Huber A, Sourbron S, Klaus V, et al. Magnetic resonance perfusion of the myocardium: semiquantitative and quantitative evaluation in comparison with coronary angiography and fractional flow reserve. *Invest Radiol* 2012;47:332-8.
44. Motwani M, Maredia N, Fairbairn TA, et al. High-resolution versus standard-resolution cardiovascular MR myocardial perfusion imaging for the detection of coronary artery disease. *Circ Cardiovasc Imaging* 2012;5:306-13.
45. Paetsch I, Jahnke C, Wahl A, et al. Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. *Circulation* 2004;110:835-42.
46. Klem I, Heitner JF, Shah DJ, et al. Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. *J Am Coll Cardiol* 2006;47:1630-8.

KEY WORDS coronary artery disease, CMR, gadobutrol, myocardial infarction, myocardial perfusion

APPENDIX For an expanded Methods section, supplemental tables, and videos, please see the online version of this paper.