

Prognostic Implications of Dipyridamole Cardiac MR Imaging: A Prospective Multicenter Registry¹

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Purpose:

To evaluate dipyridamole cardiac magnetic resonance (MR) imaging in the prediction of major events (MEs) in patients with ischemic chest pain in a large multicenter registry.

Materials and Methods:

Institutional ethics committee approval and written informed consent were obtained. A total of 1722 patients who were undergoing cardiac MR imaging for chest pain were included. Wall motion abnormalities (WMAs) at rest, hyperemia perfusion defect (PD), late gadolinium enhancement (LGE), and inducible WMA were analyzed (abnormal if more than one abnormal segment was seen) with the 17-segment model. A cardiac MR categorization was created: category 1, no PD, LGE, or inducible WMA; category 2, PD without LGE and inducible WMA; category 3, LGE without inducible WMA; and category 4, inducible WMA. The association with ME was analyzed by using Cox proportional hazard regression multivariate models.

Results:

During a median follow-up period of 308 days, 61 MEs (4%) occurred (36 cardiac deaths, 25 nonfatal myocardial infarctions). MEs were associated with a greater extent of WMA, PD, LGE, and inducible WMA ($P \leq .001$ for all analyses). In multivariable analyses, PD ($P = .002$) and inducible WMA ($P = .0001$) were the only cardiac MR predictors. ME rate in categories 1, 2, 3, and 4 was 2% (14 of 901 patients), 3% (six of 219 patients), 4% (15 of 409 patients), and 14% (26 of 193 patients), respectively (category 4 vs category 1, adjusted $P < .001$). Cardiac MR-directed revascularization was performed in 242 patients (14%) and reduced the risk of ME in only category 4 (7% [six of 92 patients] vs 26% [26 of 101 patients], $P = .0004$).

Conclusion:

Dipyridamole cardiac MR imaging can be used to predict MEs in patients with ischemic chest pain. Patients with inducible WMA are at the highest risk for MEs and benefit the most from revascularization.

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The assessment of prognostic and therapeutic implications of cardiac magnetic resonance (MR) imaging is gaining increasing attention. Multicenter studies are required to demonstrate the value of cardiac MR imaging in the prediction of major events (MEs) and in guiding therapy, but such studies are still scarce (1,2).

Vasodilator perfusion cardiac MR imaging can depict perfusion defects (PDs) and inducible wall motion abnormalities (WMAs) (2–7). The former reliably depicts severe coronary lesions (2,3), while the latter is associated with a more severe ischemic burden (8–11). Moreover, this technique enables the detection of areas of necrosis with late gadolinium enhancement (LGE) imaging (4,5).

The available prognostic data of this modality in patients with ischemic chest pain stems from relatively small single-center registries with a low rate of MEs (4–6). Moreover, to our knowledge, the therapeutic implications have been hardly analyzed thus far (7).

The purpose of this study was to evaluate dipyridamole cardiac MR imaging in the prediction of MEs in patients with ischemic chest pain in a multicenter registry.

Materials and Methods

Study Group

This prospective multicenter registry included consecutive patients with chest pain of possible coronary origin who underwent dipyridamole cardiac MR imaging at one of two university hospitals (Hospital Clínico Universitario de Valencia and Hospital General Castellón) or one community hospital

Advance in Knowledge

- This prospective multicenter registry of patients with stable ischemic chest pain demonstrates the prognostic value of dipyridamole cardiac MR imaging in the prediction of the risk of presumed cardiac death and nonfatal myocardial infarction.

(Hospital La Plana) between January 2007 and September 2009. Patients with acute coronary syndromes or any contraindications to dipyridamole cardiac MR imaging were not considered for participation. Of 1797 patients included in the registry database, 75 were excluded because of insufficient image quality ($n = 39$) or because the study was incomplete ($n = 36$). Thus, the final study group comprised 1722 patients.

Reasons for cardiac MR imaging were as follows: inconclusive exercise test results ($n = 397$, 23%), altered baseline electrocardiography ($n = 378$, 22%), inability to exercise ($n = 483$, 28%), evaluation of intermediate coronary lesions (50%–70% stenosis at quantitative coronary angiography, $n = 173$ [10%]) or as the first choice in patient work-up ($n = 291$, 17%).

All baseline characteristics were recorded prospectively. The cardiac MR results were available to the cardiologists in charge of the patients. Disease management and medical treatment were left at the discretion of the cardiologists (V.B., J.N., J.S., M.J.B., C.G., J.L.D.). The study protocol was approved by the ethics committee at each participating site, and all subjects gave written informed consent.

Cardiac MR Study

All patients were examined with a 1.5-T system (Sonata Magnetom; Siemens, Erlangen, Germany) according to an established study protocol (7). Images were acquired with a phased-array body surface coil during breath holds, and image acquisition was triggered by electrocardiography.

Implications for Patient Care

- Dipyridamole cardiac MR imaging enables prognostication of major events in patients with ischemic chest pain.
- Patients without evidence of ischemia have an excellent prognosis.
- Patients with severe ischemia are at the highest risk of major events and benefit the most from revascularization.

Baseline cine images were acquired by using a steady-state free precession sequence (repetition time msec/echo time msec, 2.8/1.2; flip angle, 58°; matrix, 256 × 100; section thickness, 7 mm). First, high-spatial-resolution baseline cine images were acquired at a rate of one section per breath hold in long-axis views, as well as in all short-axis sections from base to apex of the left ventricle. These images were used to determine left ventricular volumes and ejection fraction.

Vasodilatation was induced with intravenous dipyridamole (initially administered at a concentration of 0.56 mg per kilogram of body weight over 4 minutes; if well tolerated, concentration was increased to 0.84 mg/kg over 6 minutes). After dipyridamole infusion, 0.1 mmol/kg gadopentate dimeglumine (Magnograf; Schering, Berlin, Germany) was injected intravenously at a rate of 5 mL/sec.

At least four sections in the short-axis view and two sections in the two- and four-chamber long-axis views were acquired for hyperemia first-pass perfusion imaging (steady state free-precession sequence with a notched saturation pulse; repetition time msec/echo time msec/inversion time msec, 202/1/125;

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Abbreviations:

LGE = late gadolinium enhancement
ME = major event
PD = perfusion defect
WMA = wall motion abnormality

Author contributions:

Guarantors of integrity of entire study, V.B., O.H., J.N., C. García, F.C., D.M., C. Gómez, J.A., A.L.; study concepts/ study design or data acquisition or data analysis/ interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, V.B., O.H., J.N., M.J.B., E.R., C. García, J.L.D., F.C., D.M., F.J.C., A.L.; clinical studies, V.B., J.S., J.N., J.V.M., M.P.L.L., M.J.B., G.M., J.L.D., C. Gómez, F.J.C., A.L.; statistical analysis, V.B., O.H., J.N., J.L.D., D.M., J.A.; and manuscript editing, V.B., O.H., J.S., J.N., J.L.D., D.M., F.J.C., A.L.

Potential conflicts of interest are listed at the end of this article.

flip angle, 50°; matrix, 192 × 96; field of view, 350 × 220 mm; section thickness, 8 mm).

To assess segmental systolic function within the peak dipyridamole-induced vasodilatation, we performed additional multisection sequences at a lower spatial resolution in two long-axis views (two- and four-chamber view) and in three short-axis projections (basal, medial, and apical) in two breath holds with a fast acquisition multisection steady state free-precession cine image sequence (2.8/1.2; flip angle, 65°; matrix, 192 × 75; section thickness, 7 mm). These images were acquired immediately before and after administration of dipyridamole. This way, two identical sections obtained at rest and at peak stress were available and were used to evaluate inducible WMA.

LGE imaging was performed 10 minutes after contrast material injection in the same locations used for baseline cine images (segmented inversion-recovery steady state free-precession sequence; 700/1.26; flip angle, 45°; matrix, 256 × 184; field of view, 340 × 235 mm; section thickness, 8 mm). The inversion time was adjusted to null normal myocardium, as described previously (4,7).

Acquisition of rest first-pass perfusion images was performed in 392 (23%) patients. Images were acquired in 274 patients with PD in the core of a necrotic area, in 50 patients with extensive perfusion defects not associated with inducible WMA, and in 68 patients to enable us to rule out artifacts. Rest first-pass perfusion imaging was performed at the end of the study by using the same method used for hyperemia first-pass perfusion imaging.

Cardiac MR Data Analysis

Cardiac MR studies were centrally analyzed by three experienced observers who were blinded to all patient data (M.P.L., J.V.M., F.C.; 10, 7, and 5 years of experience, respectively) using customized software (Syngo; Siemens). When any doubt existed regarding the interpretation of cine, perfusion, or LGE images (332 cases, 19%), the studies were evaluated by all three operators, and the final result was adjudicated by consensus.

Figure 1

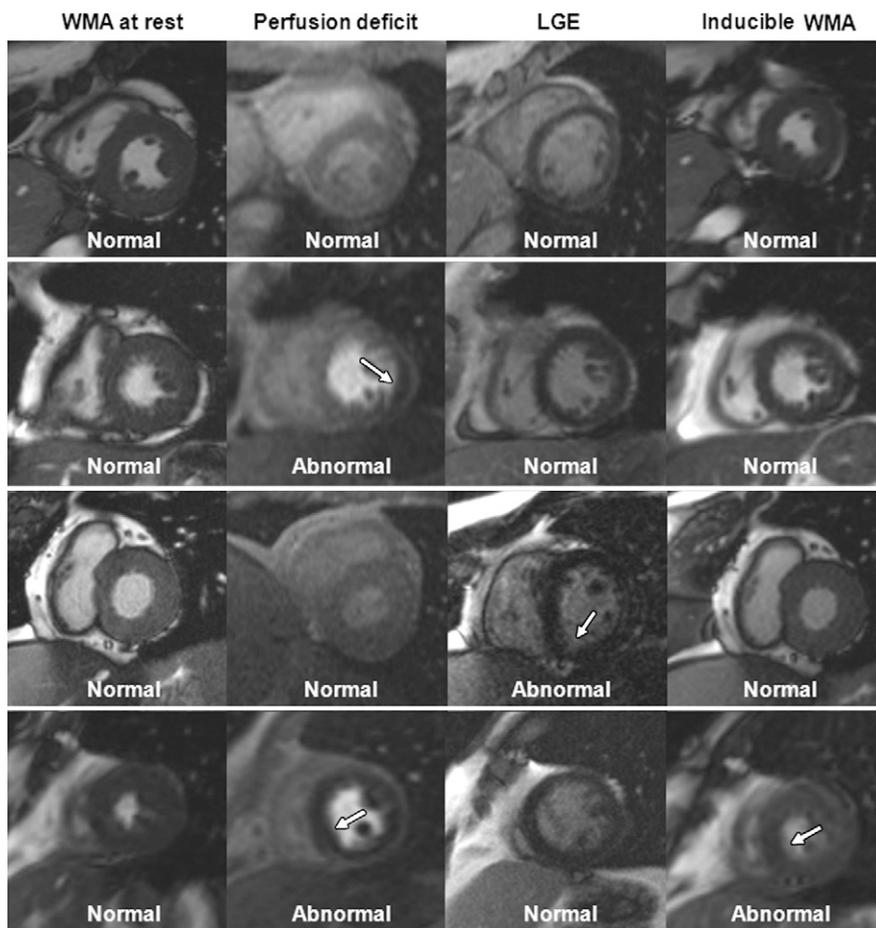


Figure 1: Dipyridamole cardiac MR images used to categorize patients. First row: Images in a patient with normal dipyridamole cardiac MR findings. Second row: Images in a patient with PD (arrow) without LGE and without inducible WMAs. Third row: Images in a patient with LGE (arrow) without PD and without inducible WMAs. Fourth row: Images in a patient with inducible WMAs and PD (arrows) and without LGE. Please see text for a detailed description.

Left ventricular ejection fraction (measured as a percentage) and end-diastolic and end-systolic volume indexes (measured in milliliters per square meter) were calculated with manual planimetry of endocardial and epicardial borders in all short-axis view cine images.

With the 17-segment model (12), four segmental cardiac MR indexes were visually defined. The first index was WMA at rest, which was defined as the number of segments that showed any degree of abnormal contractility (hypokinesis, akinesis, or dyskinesis) at rest. The second index was PD, which was defined as the number of segments that showed

persistent delay (in at least three consecutive temporal images in comparison with other segments in the same section) during the first pass of contrast material through the myocardium after dipyridamole infusion (13,14). If acquisition of rest first-pass perfusion images was considered necessary (PD in the core of a necrotic area, extensive perfusion defects not associated with inducible WMA or artifacts), PD was regarded as a persistent delay of contrast material arrival at hyperemia (after dipyridamole-induced vasodilatation) in segments that showed normal rest perfusion. The third index was LGE, which was defined as the

number of segments that showed LGE in more than 50% of the myocardial wall. In segments, LGE was considered present if signal intensity was more than 2 standard deviations above the signal intensity in a remote noninfarcted area at LGE imaging (15). In previous reports, the extent of transmural necrosis in segments usually has been divided into four degrees (0%–25%, 26%–50%, 51%–75% and 76%–100%); a cutoff value of 50% has been proved to be the most useful in the prediction of late systolic recovery (16), and the definition used in this study has been previously validated for use in the prediction of (a) late systolic recovery in patients after infarction (15) and (b) clinical events in patients with chest pain (4,7) and patients after infarction (15,17). The fourth index was inducible WMA, which was defined as the number of segments in which wall motion worsened from normokinesis to hypokinesis or from hypokinesis to akinesis after dipyridamole administration.

To avoid misinterpretation of artifacts (which, if present, generally occur in isolated segments and views), WMA at rest, PD, LGE, and inducible WMA were considered present only if they were seen on both short- and long-axis images and in more than one segment. Accordingly, these four indexes were categorized as normal (0–1 abnormal segment) or abnormal (>1 abnormal segment).

Intraobserver variability for determination of the extent (number of segments) of WMA at rest, PD, LGE, and inducible WMA in the group was less than 5%. The method used to evaluate reproducibility or cardiac MR data can be consulted elsewhere (7,15,17).

To illustrate the information provided by stress perfusion cardiac MR imaging in the prediction of MEs, a four-step cardiac MR categorization was created (Fig 1). This cardiac MR categorization was adapted from a pilot single-center study in a reduced study sample (7) where it was shown that patients with inducible WMA displayed the highest rate of a combined endpoint that included major and minor cardiac events. As previously stated, in each step of this cardiac MR categorization, an index was

considered abnormal if altered results were detected in more than one segment: (a) normal (absence of PD, LGE, and inducible WMA), (b) PD only (PD without LGE or inducible WMA), (c) LGE without inducible WMA (with or without PD), and (d) inducible WMA (regardless of PD and LGE).

Endpoints and Follow-up

The primary endpoint of this study was an ME, defined as cardiac death or nonfatal myocardial infarction (whichever occurred first). The secondary endpoints were cardiac death and nonfatal myocardial infarction separately. Cardiac death was defined as death due to acute myocardial infarction, congestive heart failure, arrhythmia, or cardiac arrest. Myocardial infarction was defined in accordance with published definitions (18).

Follow-up data were centrally updated every 3 months by two cardiologists (V.B., J.N.; 18 and 10 years of experience, respectively) and two trained nurses from at least one of the following three sources: (a) the outpatient clinic, (b) a telephone interview with the patient or his or her family conducted by a cardiologist, and (c) review of the patient's hospital record. An independent adjudication process, including review of clinical histories from local institutions, was applied, and consensus between the two cardiologists was required to finally adjudicate an event.

Cardiac MR-related Revascularization

To avoid the confounding effect of revascularization on the spontaneous evolution of patients, data of patients who underwent cardiac MR-related revascularization were censored at the time of revascularization. Cardiac MR-related revascularization was regarded as those procedures that were directly prompted by the cardiac MR results or performed within 3 months (and were free of any associated events) after the cardiac MR examination, as published previously (1,7). As an exploratory analysis, follow-up of patients who underwent revascularization was extended, and the effect of cardiac MR-directed revascularization

on MEs in each step of the cardiac MR categorization was analyzed.

Statistical Analysis

All data were tested for normal distribution by using the one-sample Kolmogorov-Smirnov test. Continuous normally distributed data were expressed as the mean \pm standard deviation and compared with the Student *t* test. Nonparametric data were expressed as the median with the interquartile range and were compared by using the Mann-Whitney *U* test. Hypothesis tests were conducted by using one-way analysis of variance, with a Bonferroni correction applied to adjust for multiple comparisons. Proportions were compared with the χ^2 test or the Fisher exact test, when appropriate. The χ^2 test for trend was applied for trends in more than two groups.

On the basis of data derived from a pilot study (601 patients) (7), we planned a study of independent cases and controls, with 15 control subjects (patients without inducible WMA) per case (patients with inducible WMA). Prior data indicate that the rate of death or nonfatal myocardial infarction among patients without inducible WMA is 0.0485. If the true ME rate for experimental subjects is 0.136, we determined that we needed to study 106 experimental subjects and 1590 control subjects to be able to reject the null hypothesis that the event rates for experimental and control subjects are equal with a probability (power) of 0.9. The type I error probability associated with this test of this null hypothesis was 0.05. We used an uncorrected χ^2 statistic to evaluate the null hypothesis.

The association of cardiac MR variables with the time to event was assessed by using a Cox proportional hazard regression model with stepwise forward multivariate procedures adjusted for baseline and cardiac MR characteristics yielding a *P* value of less than .2 in univariate analyses. Hazard ratios with the corresponding 95% confidence intervals were computed. Survival distributions for the time to the event were estimated by using the Kaplan-Meier method.

Table 1

Baseline and Cardiac MR Characteristics of the Whole Study Group and of Patients with MEs and Those without MEs

Characteristic	All Patients (n = 1722)	MEs		P Value
		Present (n = 61)	Absent (n = 1661)	
Age (y)*	64 ± 11	69 ± 10	64 ± 11	.0003 [†]
Male sex	1071 (62)	44 (72)	1027 (62)	.1 [†]
Diabetes	478 (28)	34 (56)	444 (27)	<.0001 [†]
Hypertension	1067 (62)	45 (74)	1022 (62)	.05 [†]
Hypercholesterolemia	945 (55)	39 (64)	906 (55)	.2 [†]
Current smoker	386 (22)	9 (15)	377 (23)	.1 [†]
Previous angioplasty	244 (14)	13 (21)	231 (14)	.1 [†]
Previous coronary surgery	119 (7)	10 (16)	109 (7)	.003 [†]
Previous infarction	389 (23)	28 (46)	361 (22)	<.0001 [†]
ST segment depression	137 (8)	8 (13)	129 (8)	.1 [†]
T-wave inversion	190 (11)	9 (15)	181 (11)	.4
Left bundle branch block	48 (3)	3 (5)	45 (3)	.3
Cardiac MR indexes*				
Ejection fraction	62 ± 13	53 ± 18	62 ± 13	<.0001 [†]
End-diastolic volume (mL/m ²)	72 ± 24	85 ± 38	71 ± 24	.006 [†]
End-systolic volume (mL/m ²)	29 ± 21	45 ± 37	29 ± 20	.001 [†]
WMA at rest ‡	0 (0–3)	4 (0–6.5)	0 (0–2)	<.0001 [†]
PD [†]	0 (0–5)	5 (0–8.5)	0 (0–4)	<.0001 [†]
Inducible WMA [†]	0 (0–0)	0 (0–2)	0 (0–0)	<.0001 [†]
LGE [†]	0 (0–2)	1 (0–5.5)	0 (0–2)	<.0001 [†]

Note.—Unless otherwise indicated, data in parentheses are percentages. P values are for comparison of patients with MEs and those without MEs during follow-up with the unpaired Student t test for numeric data and the χ^2 test for percentages.

* Data are mean ± standard deviation.

[†] Variables with $P \leq .2$ that were used as cofactors in the multivariate Cox regression analysis to predict time to events.

[‡] Data are number of segments, and data in parentheses are the range.

The effect of cardiac MR-related revascularization on MEs in each group of the cardiac MR categorization was assessed by using multivariable Cox proportional hazards models. To correct for the inherent referral bias, these models were adjusted for a propensity score for undergoing cardiac MR-related revascularization obtained from a stepwise logistic regression model, including baseline and cardiac MR variables. The accuracy of this propensity score was tested with the C statistic of the final model. Statistical significance was considered for a two-tailed P value of less than .05. SPSS software (version 13.0; SPSS, Chicago, Ill) was used.

Results

Baseline and cardiac MR characteristics of the study group are shown in Table 1. During a mean follow-up period of 55 weeks ± 45 (median, 44 weeks;

range, 24–78 weeks), 61 (4%) of 1722 MEs occurred, including 36 cardiac deaths and 25 nonfatal myocardial infarctions.

Angiography was performed in 450 patients (Appendix E1 [online]).

Cardiac MR Indexes and the Primary Endpoint

The baseline and cardiac MR characteristics of patients with and those without MEs are displayed in Table 1. Patients with MEs had a more depressed ejection fraction, more dilated left ventricular volume indexes, and more altered cardiac MR indexes than did those without MEs. The presence of abnormal cardiac MR indexes related to a higher rate of MEs (Fig 2).

Cardiac MR Indexes and Secondary Endpoints

The baseline and cardiac MR characteristics of patients with and those without

a secondary endpoint are displayed in Tables E1 and E2 (online). Patients with cardiac death and nonfatal myocardial infarction had a more-depressed ejection fraction and had more-dilated left ventricular volume indexes and more-altered cardiac MR indexes. The presence of all abnormal cardiac MR indexes related to a higher rate of cardiac death, while only abnormal WMA at rest and inducible WMA related to nonfatal myocardial infarction (Fig 2).

Stress Perfusion Cardiac MR Categorization and Cardiac Events

Distribution, baseline, and cardiac MR characteristics of each group of the cardiac MR categorization (normal, PD without LGE and inducible WMA, LGE without inducible WMA regardless of PD and inducible WMA) are displayed in Table E3 (online). In 193 (11%) patients with inducible WMA, WMA at rest was observed in

80 (41%) patients, PD was observed in 193 (100%), and LGE was observed in 76 (39%).

In comparison with patients in the normal cardiac MR category, the rate of MEs, cardiac death, and nonfatal myocardial infarction increased only slightly in patients with only PD and in those with LGE without inducible WMA regardless of PD; however, it rose dramatically in patients with inducible WMA (*P* values are given in Fig 3). In the adjusted survival curves, the occurrence of inducible WMA was associated with a higher rate of MEs, cardiac death, and nonfatal myocardial infarction (*P* values are given in Fig 4).

LGE Data

LGE was considered present if it was detected in more than one segment. According to the degree of transmural, LGE occurred as follows: more than 0% in 642 patients (37%), more than 25% in 575 patients (33%), more than 50% in 487 patients (28%), more than 75% in 293 patients (17%), and 100% in 112 patients (6%).

Thus, on the basis of the preestablished cutoff value (more than one segment with LGE in more than 50% of wall thickness), LGE was observed in 487 (28%) patients. WMA at rest was detected in 557 (32%) patients. Patients with LGE had WMA at rest more frequently than did those without LGE (88% vs 10%, *P* < .001).

PD was a frequent finding in patients with LGE (374 of 487 patients, 77%). Nevertheless, inducible WMA was detected in only 76 (16%) patients with LGE.

In univariate analyses, patients with LGE exhibited a higher rate of MEs than did those without LGE (Fig 2). Similar to patients in the first two cardiac MR categories (normal and only PD), we observed that patients with LGE without inducible WMA had an ME rate lower than those with inducible WMA (4% [15 of 409 patients] vs 13% [26 of 193 patients], *P* < .001) (Figs 3, 4). In the multivariate analysis (discussed in the next section), the extent of LGE was not an independent predictor of events (Table 2), and

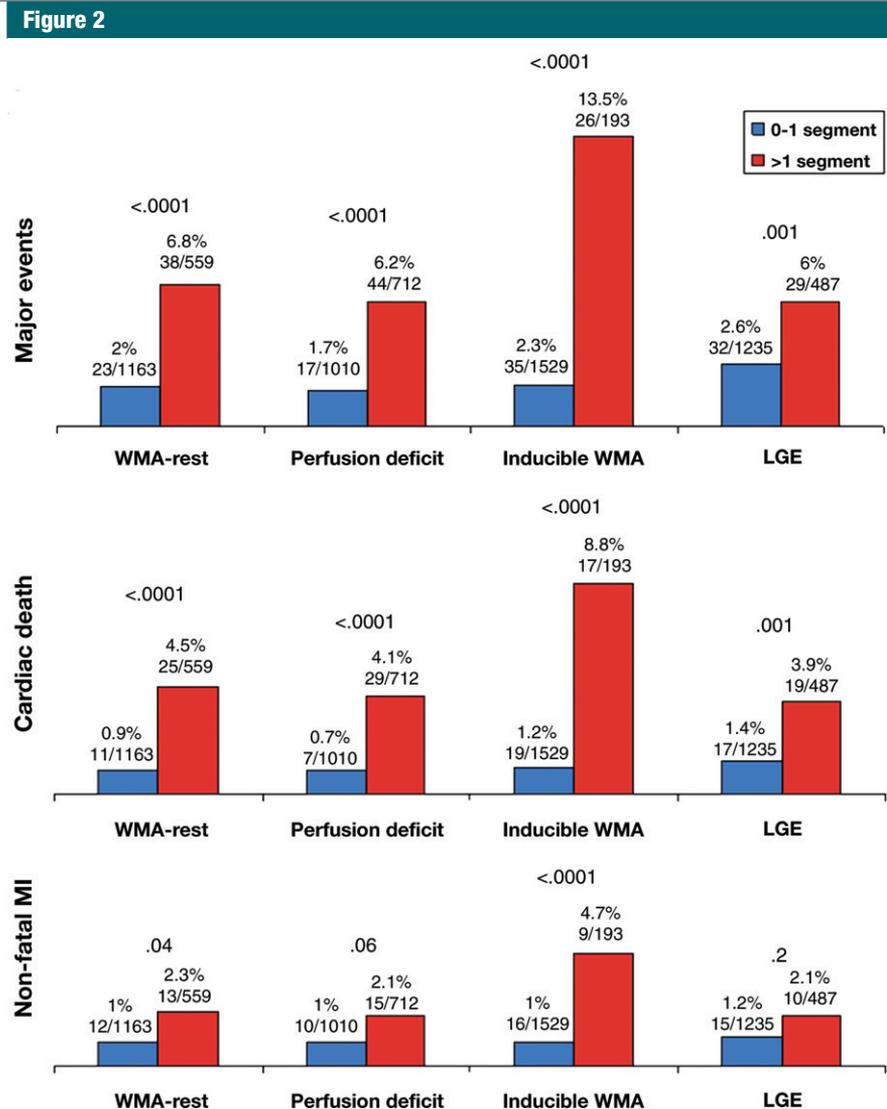


Figure 2: Graphs show rate of MEs, cardiac death, and nonfatal myocardial infarction according to the state of abnormal (more than one segment) dipyridamole cardiovascular MR indexes.

the presence of inducible WMA but not LGE independently increased the event rate (Table 3).

Multivariate Analysis

Multivariable analysis was used to identify predictors of the primary and secondary endpoints, including baseline characteristics and all segmental cardiac MR indexes as continuous variables. Of cardiac MR variables, both PD and inducible WMA independently related to MEs and cardiac death. Inducible WMA was the only segmental cardiac MR index as

sociated with nonfatal myocardial infarction (Table 2).

When the cardiac MR categorization was tested in the multivariate analysis, including baseline characteristics and all segmental cardiac MR indexes, inducible WMA but not LGE or PD independently increased the risk of MEs. The same was observed with the secondary endpoints (Table 3). The addition of inducible WMA to the multivariate model containing cardiac MR indexes as continuous variables significantly increased the χ^2 value of the model in the prediction of MEs from 88 to 185 (*P* < .0001).

Figure 4

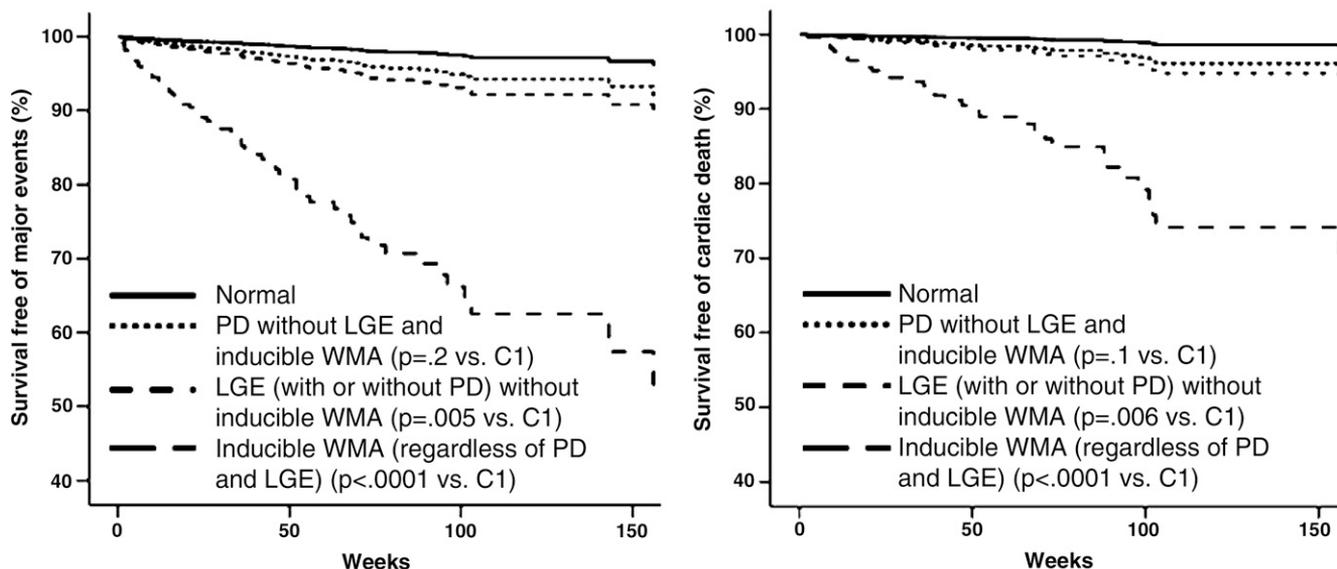


Figure 4: Graphs show adjusted survival free of MEs, cardiac death, or nonfatal myocardial infarction according to cardiac MR categorization. All *P* values are adjusted. *C1* = normal.

Figure 3

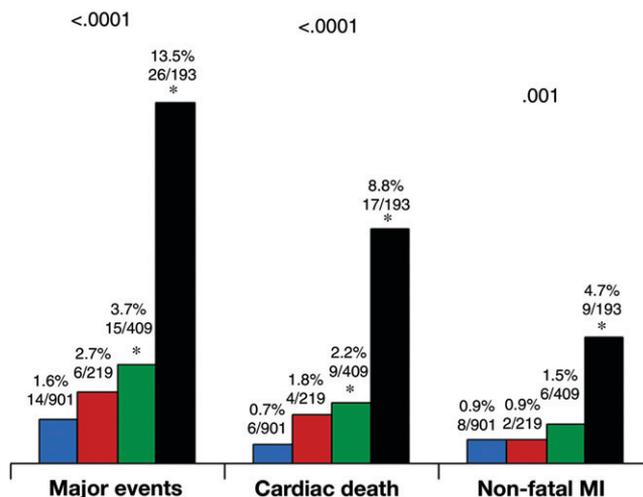


Figure 3: Graphs show rate of MEs, cardiac death, and nonfatal myocardial infarction according to the cardiac MR categorization. Blue = normal, red = PD without LGE and inducible WMA, green = LGE (with or without PD) without inducible WMA, black = inducible WMA (regardless of PD and LGE). * *P* < .05 versus normal.

Effect of Cardiac MR-related Revascularization

Cardiac MR-related revascularization was performed in 242 (14%) patients. The rates of cardiac MR-related procedures are displayed in Table E4 (online). The ME rate was 7% (16 of 242 patients) in patients who had undergone revascularization and 4% (60 of 1480 patients) in those who had not (*P* = .1). In patients with normal study results, PD only, and LGE without inducible WMA, cardiac MR-related revascularization (as

defined in Materials and Methods) did not diminish the rate of MEs in comparison with those patients who did not undergo cardiac MR-related revascularization. Conversely, cardiac MR-related revascularization significantly reduced

the risk of MEs in patients with inducible WMA (Table 4).

A propensity score for undergoing cardiac MR-related revascularization was created by using male sex, extent of PD, and inducible WMA. The accuracy

Table 2

Independent Predictors of MEs, Cardiac Death, and Nonfatal Myocardial Infarction

Outcome and Characteristic	Hazard Ratio	P Value
ME		
Age (per year)	1.03 (1.01, 1.06)	.02
Diabetes	2.05 (1.20, 3.49)	.008
Previous infarction	2.25 (1.33, 3.80)	.002
End-systolic volume (per 1 mL/m ² increase)	1.014 (1.008, 1.020)	<.0001
PD (per segment)	1.10 (1.04, 1.17)	.002
Inducible WMA (per segment)	1.17 (1.08, 1.27)	.0001
Cardiac death		
Diabetes	3.58 (1.71, 7.50)	.001
End-systolic volume (per 1 mL/m ² increase)	1.018 (1.011, 1.026)	.0002
PD (per segment)	1.15 (1.07, 1.24)	.0002
Inducible WMA (per segment)	1.15 (1.03, 1.28)	.01
Nonfatal myocardial infarction		
Previous infarction	5.01 (2.22, 11.34)	<.0001
End-diastolic volume (per 1 mL/m ² increase)	1.01 (1, 1.03)	.008
Inducible WMA (per segment)	1.24 (1.11, 1.39)	<.0001

Note.—Data in parentheses are 95% confidence intervals. Variables with $P \leq .2$ in Table 1 (age, male sex, diabetes, hypertension, current smoker, previous angioplasty, previous coronary surgery, previous infarction, ST-segment depression, T-wave inversion) and all cardiac MR indexes were included as cofactors in the multivariate analysis.

Table 3

Independent Predictors of MEs, Cardiac Death, and Nonfatal Myocardial Infarction, including Cardiac MR Categorization

Outcome and Characteristic	Hazard Ratio	P Value
MEs		
Age (per year)	1.037 (1.009, 1.066)	.009
Diabetes	1.92 (1.13, 3.26)	.02
Previous infarction	2.35 (1.36, 4.08)	.002
End-systolic volume (per 1 mL/m ² increase)	1.02 (1.01, 1.02)	<.0001
Normal cardiac MR findings	1	
PD only without LGE and inducible WMA	1.41 (0.54, 3.72)	.7
LGE without inducible WMA with or without PD	1.04 (0.46, 2.33)	.9
Inducible WMA regardless of PD and LGE	10.71 (5.22, 21.98)	<.0001
Cardiac death		
Diabetes	2.90 (1.45, 5.78)	.003
End-systolic volume (per 1 mL/m ² increase)	1.014 (1.001, 1.027)	.04
Ejection fraction (per percentage increase)	0.965 (0.935, 0.995)	.03
Normal cardiac MR study	1	
PD only without LGE and inducible WMA	2.58 (0.71, 9.3)	.2
LGE without inducible WMA with or without PD	1.77 (0.60, 5.23)	.3
Inducible WMA regardless of PD and LGE	16.23 (5.91, 44.59)	<.0001
Nonfatal myocardial infarction		
Previous infarction	3.75 (1.44, 9.81)	.007
End-diastolic volume (per 1 mL/m ² increase)	1.019 (1.008, 1.029)	.0004
Normal cardiac MR study	1	
PD only without LGE and inducible WMA	1.0 (0.21, 4.82)	.998
LGE without inducible WMA with or without PD	0.56 (0.17, 1.79)	.3
Inducible WMA regardless of PD and LGE	6.35 (2.25, 17.91)	.0005

Note.—Data in parentheses are 95% confidence intervals. Variables with a P value of .2 or less in Table 1 (age, male sex, diabetes, hypertension, current smoker, previous angioplasty, previous coronary surgery, previous infarction, ST-segment depression, T-wave inversion) and all cardiac MR indexes were included as cofactors in the multivariate analysis.

of this propensity score was tested with the C-statistic of the final model (0.830). Adjusted for baseline characteristics, cardiac MR variables, and propensity score, cardiac MR-related revascularization independently reduced the risk of MEs in patients with inducible WMA but not in patients with normal cardiac MR study results, PD only, and LGE without inducible WMA (Table 4, Fig 5).

Discussion

The main finding of the present study is that dipyridamole cardiac MR imaging, including analysis of inducible WMA, is useful in the prediction of MEs and might be helpful in therapy guidance in patients with stable ischemic chest pain; however, randomized trials are required for further confirmation.

Cardiac MR imaging enables comprehensive noninvasive assessment of patients with ischemic heart disease (2,4,5) and is commonly used for diagnostic purposes (10,11,13). However, apart from diagnosis, prognostic validation is a mandatory step for further acceptance into clinical practice (1).

So far, only single-center studies with a limited number of patients and a low rate of MEs have been performed to address the prognostic implications of stress perfusion cardiac MR imaging (4–7,19). In the present study, we evaluated the prognostic value of dipyridamole cardiac MR imaging in a large prospective multicenter registry by using a combined primary endpoint of hard events.

An important finding is that all cardiac MR indexes were strongly related to outcome; this enabled us to confirm in a large series of patients the prognostic usefulness of dipyridamole cardiac MR imaging. Of all cardiac MR indexes, inducible WMA was by far the most powerful parameter in the prediction of MEs.

The presence of PD, regardless of inducible WMA, was associated with a higher rate of MEs in both univariate and multivariate analyses. Interestingly, in patients with isolated PD but without inducible WMA, the ME rate was low and did not significantly differ from that in patients without ischemia; this enabled us to confirm previous findings

Table 4

Effect of Cardiac MR-related Revascularization on Occurrence of MEs according to Cardiac MR Categorization

Category	No. of Patients Who Underwent Revascularization	No. of Patients Who Did Not Undergo Revascularization	Hazard Ratio*	P Value
Normal (<i>n</i> = 901)	1/19 (5)	12/882 (1)	1.43 (0.10, 20.24)	.8
PD only without LE or inducible WMA (<i>n</i> = 219)	3/49 (6)	6/170 (4)	14.87 (0.64, 345.00)	.09
LGE without inducible WMA regardless of PD (<i>n</i> = 409)	6/82 (7)	16/327 (5)	1.71 (0.60, 4.87)	.3
Inducible WMA regardless of PD and LGE (<i>n</i> = 193)	6/92 (7)	26/101 (26)	0.16 (0.06, 0.44)	.0004

Note.—Unless otherwise indicated, data in parentheses are percentages. Variables with $P \leq .2$ in Table 1 (age, male sex, diabetes, hypertension, current smoker, previous angioplasty, previous coronary surgery, previous infarction, ST-segment depression), all cardiac MR indexes, and the propensity score for undergoing cardiac MR-related revascularization were included as cofactors in multivariate analysis.

* Data in parentheses are 95% confidence intervals.

(4–6) and reinforced recommendations (20) pointing to the excellent prognosis of patients without evidence of severe ischemia at stress perfusion imaging.

In agreement with previous studies (4,5), the presence of LGE related to a worse prognosis. However, the event rate was low in patients with LGE but without simultaneous inducible WMA. This suggests that in patients who were evaluated because of ischemic chest pain and who had preserved systolic function, the presence of severe residual ischemia is what really determined the clinical outcome.

Although dipyridamole is less potent than dobutamine in inducing WMA, such lesser potency can be advantageous for prognostic purposes because a small group of patients with extensive ischemic heart disease (Appendix E1 [online]) and severe clinically important ischemia (those with inducible WMA) can be identified (10,11). Our data indicate that only with the appearance of WMA during dipyridamole infusion can a PD be considered clinically relevant; this translates to a higher rate of MEs. Thus, the simple cardiac MR categorization developed in the present study enabled us to detect a group of patients with inducible WMA who were at the highest risk for MEs.

Beyond its diagnostic and prognostic value, the usefulness of dipyridamole cardiac MR imaging in therapeutic decision-making has been barely investigated. We have addressed this issue in this large multicenter registry; however, since this was not a randomized

Figure 5

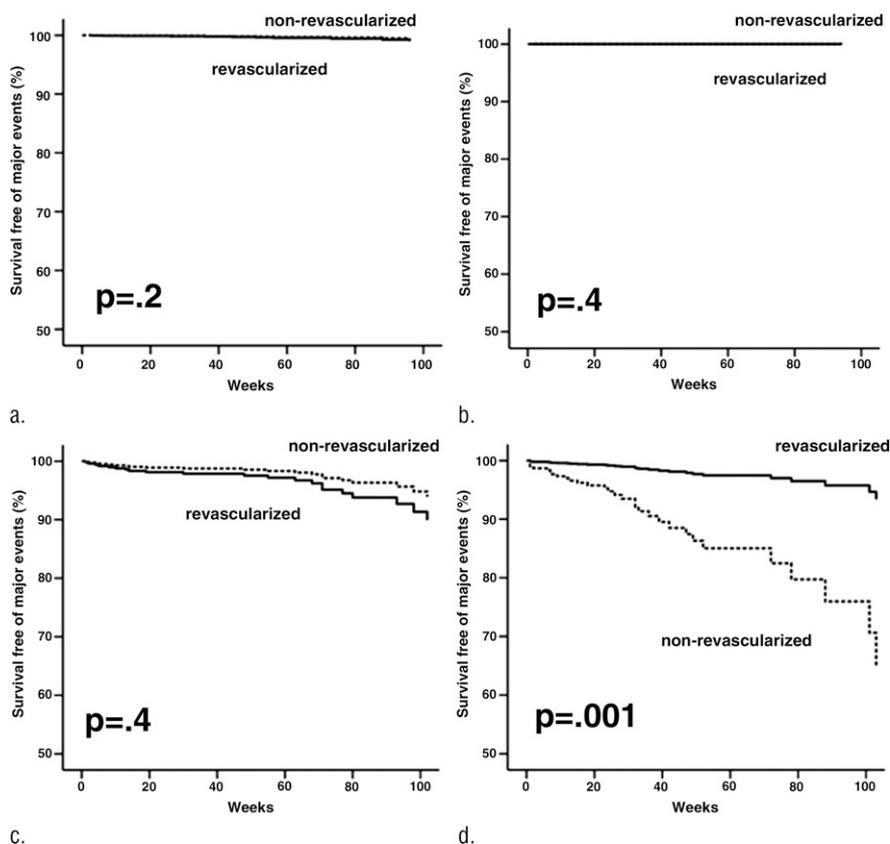


Figure 5: Graphs show effect of revascularization according to cardiac MR categorization. Adjusted survival free of MEs in patients who underwent revascularization and those who did not. (a) Normal; (b) PD only; (c) LGE without inducible WMA regardless of PD; (d) inducible WMA.

study, the results have to be considered exploratory.

The vast majority of our study group did not display ischemia (normal cardiac

MR category). Almost all of these patients received medical treatment and had a very low rate of ME, indicating that stress perfusion cardiac MR imaging

might enable us to identify a large group of patients with an excellent prognosis and no need for angiography or revascularization.

In patients with PD and/or LGE but without simultaneous inducible WMA, cardiac MR-related revascularization did not improve outcome. However, in the small subset of patients (11%) with severe ischemia (inducible WMA), cardiac MR-related revascularization significantly reduced the event rate. These results are in line with current recommendations (20,21) that stress the importance of the physiologic importance of coronary lesions and indicate that in patients with stable ischemic heart disease, reduction of MEs can be expected only in patients with severe ischemia. In this complex scenario, stress perfusion cardiac MR imaging might add valuable information for use in therapeutic decision making.

Although propensity score adjustment is an accepted statistical approach (22), we cannot exclude an inherent referral bias influencing the effects of cardiac MR-related revascularization. Randomized trials on the utility of dipyridamole cardiac MR imaging in the prediction of the effects of coronary revascularization are required to clarify this issue.

In conclusion, in patients with a history of chest pain, vasodilator cardiac MR imaging with dipyridamole and analysis of inducible WMA yields strong prognostic information and is used to predict benefits from revascularization. Moreover, this modality enables simple and effective risk stratification.

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