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Long-Term Prognostic Value of Dobutamine Stress CMR

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OBJECTIVES The aim of this study was to assess the long-term value of high-dose dobutamine cardiac magnetic resonance (DCMR) for the prediction of cardiac events in a large cohort of patients with known or suspected coronary artery disease.

BACKGROUND High-dose DCMR has been shown to be a useful technique for diagnosis and intermediate-term prognostic stratification.

METHODS Clinical data and DCMR results were analyzed in 1,463 consecutive patients undergoing DCMR between 2000 and 2004. Ninety-four patients were lost to follow-up. The remaining 1,369 patients were followed up for a mean of 44 ± 24 months. Cardiac events, defined as cardiac death and nonfatal myocardial infarction, were related to clinical and DCMR results.

RESULTS Three-hundred fifty-two patients underwent early revascularization (≤3 months of DCMR) and were excluded from analysis. Of the remaining 1,017 patients, 301 patients (29.6%) experienced inducible wall motion abnormalities (WMA). Forty-six cardiac events were reported. In those with and without inducible WMA, the proportion of patients with cardiac events was 8.0% versus 3.1%, respectively, $p = 0.001$ (hazard ratio: 3.3; 95% confidence interval: 1.8 to 5.9 for the presence of inducible WMA; $p < 0.001$). A DCMR without inducible WMA carried an excellent prognosis, with a 6-year cardiac event-free survival of 96.8%. In all 1,369 patients in the patient group with stress-inducible WMA, those patients with medical therapy demonstrated a trend to a higher cardiac event rate (8.0%) than those with early revascularization (5.4%) ($p = 0.234$). Patients with normal DCMR and medical therapy or early revascularization demonstrated similar cumulative cardiac event rates (3.1% vs. 3.2%, $p = 0.964$).

CONCLUSIONS In a large cohort of patients, DCMR has an added value for predicting cardiac events during long-term follow-up, improving the differentiation between high-risk and low-risk patients. Patients with inducible WMA and following early revascularization, demonstrate lower cardiac event rates than patients with medical therapy alone. (J Am Coll Cardiol Img 2011;4:161–72) © 2011 by the American College of Cardiology Foundation

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High-dose dobutamine cardiac magnetic resonance (DCMR) is a useful technique for diagnosis (1–3) and prognostic stratification of patients with known or suspected coronary artery disease (CAD) (4–8). Patients without stress-induced wall motion abnormalities (WMAs) in DCMR have been reported to have a low event rate at short- and intermediate-term follow-up (mean follow-up: 40 ± 24 months; median follow-up: 27 months) (4–8).

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However, it is not known whether the low-risk guarantee of a DCMR without inducible WMA can be maintained for longer-term follow-up and whether patients with a normal study might require repeat testing. Assessment of the long-term prognosis of DCMR is important, because the test might not only identify high-risk patients in whom further interventions are necessary but also distinguish low-risk patients in whom additional procedures and intensive medical follow-up are not required.

In addition, current available reports about the prognostic value of DCMR are limited by the small numbers of patients and cardiac events (4–8).

Accordingly, we performed this study to determine the long-term prognostic utility of DCMR results for forecasting future cardiac events in a large cohort of patients with known or suspected CAD.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting
CAD = coronary artery disease
CI = confidence interval
DCMR = dobutamine cardiac magnetic resonance
DSE = dobutamine stress echocardiography
HR = hazard ratio
LGE = late-gadolinium enhancement
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MRI = magnetic resonance imaging
PCI = percutaneous coronary intervention
RWMA = resting wall motion abnormality
WMA = wall motion abnormality
WMSI = wall motion score index

METHODS

Study population and design. Consecutive patients (n = 1,463) with known or suspected CAD, who were clinically referred for magnetic resonance imaging (MRI) to assess cardiac function and to test for ischemia with high-dose dobutamine were enrolled between 2000 and 2004. A few of the patients in the current study were also included in previous studies evaluating the prognostic value of a combined protocol for ischemia testing (with high-dose dobutamine and adenosine) (n = 123 patients [8.4% of the whole study population]) (5), comparing infarct size relative to left ventricular (LV) function/volumes (9) and infarct size relative to contractile reserve with low-dose dobutamine (n = 111 patients [7.6% of the whole study population]) (10). The current study evaluates the relative merits of high-dose DCMR for the prediction of long-term prognosis in a large cohort of patients.

Patients with contraindications for MRI (noncompatible biometallic implants or claustrophobia) or contraindications for administration of dobutamine (severe arterial hypertension [≥220/120 mm Hg], unstable angina pectoris, significant aortic stenosis [aortic valve mean gradient >50 mm Hg or aortic valve area <1 cm^2], complex cardiac arrhythmias, significant hypertrophic obstructive cardiomyopathy, myocarditis, endocarditis, and pericarditis) were excluded from enrollment (11). Informed consent was obtained from all patients. The study was conducted in accordance with the standards of the Charité institutional ethics committee.

MRI. As previously described, DCMR stress images were collected on a 1.5-T Gyroscan ACS-NT/Intera MRI scanner (Philips Healthcare, Best, the Netherlands) equipped with Powertrack 6000 gradients and a 5-element cardiac synergy coil (5). Patients were positioned in the supine position. Three short-axis views (apical, mid-ventricular, basal) and 3 long-axis views (4-, 2-, and 3-chamber) were acquired during breath-holds of approximately 8 s with vectorcardiographic gating.

The heart was imaged according to the recommendations of the Society for Cardiovascular Magnetic Resonance (12) with a balanced, fast-field echo sequence with parallel imaging (SENSE, acceleration factor 2). Typical parameters were a field of view of 400 × 400 mm^2, matrix of 256 × 256 pixels, slice thickness of 10.00 or 8.00 mm, flip angle of 50°, time to echo of 1.82 ms, and time to repeat of 3.65 ms. Temporal resolution was 25 to 50 ms.

DCMR. Patients were generally instructed to discontinue beta-blockers 24 h before DCMR, unless the referring physician did not approve this. The imaging methodology of high-dose DCMR has been described in detail previously (2). Briefly, high-dose DCMR was performed with the standard high-dose regimen (dobutamine up to 40 $\mu g/kg^{-1}/min^{-1}$) plus atropine (up to 2 mg) if needed to reach the target heart rate, defined as 85% maximum exercise, adjusted for age. Magnetic resonance parameters were identical at rest and during high-dose DCMR. Termination criteria were as previously published (11). Myocardial ischemia (positive DCMR) was defined as a new (induced) or worsening WMA or a biphasic response in ≥1 segment of the LV during infusion of dobutamine. As a safety precaution, dobutamine infusion and imaging were terminated at the earliest detection of WMAs in 2 adjacent segments. Images were analyzed

during and immediately after the examination by 2 experienced investigators with a quad screen format. Differences in classification were decided in a consensus review. Cine images were analyzed without post-processing. Determination of interobserver variability was already reported in a previous study (5).

MRI analysis. To determine global function, endocardial borders were outlined manually on long-axis cine images with previously validated software (ViewForum, Philips). Papillary muscles were regarded as part of the ventricular cavity. Left ventricular end-systolic volume, LV end-diastolic volume, and left ventricular ejection fraction (LVEF) were calculated. End-diastolic basal septal wall thickness was measured quantitatively.

For segmental analysis of LV function, the standard 17-segment model was used (13). LV wall motion was assessed with a visual scoring system in which 0 = normal wall motion, 1 = mild hypokinesia, 2 = severe hypokinesia, 3 = akinesia, and 4 = dyskinesia. Wall motion score index (WMSI), assessed at rest and during maximum stress, was defined as the cumulative sum of individual segment scores divided by the number of interpreted segments. The change (delta) in WMSI and LV function from rest to high-dose DCMR was recorded.

Follow-up. The long-term follow-up was performed by hospital chart review and telephone contact. Cardiac events were assessed by physicians who were unaware of the former stress test results of patients. The date of the last interview or review was used to calculate follow-up time. Follow-up was completed in 2009 and was successful in 1,369 of 1,463 (94%) patients (Fig. 1). The patient population with complete follow-up was split initially, depending on DCMR results. This resulted in a study population of 811 of 1,369 (59.2%) patients with DCMR without inducible WMA and 558 of 1,369 (40.8%) patients with inducible WMA. Cardiac risk factors for the whole study population and a comparison of risk factors between patients with positive and negative DCMR are demonstrated in Table 1.

To avoid the possibility of a cardiac event resulting from early revascularization procedure (within 3 months after DCMR), 352 of 1,369 (25.7%) patients with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) within the first 3 months after DCMR were excluded (Fig. 1). This resulted in 1,017 patients for general analysis.

In a subgroup analysis, cumulative cardiac event rates were compared between patients with early revascularization (352 patients) and the remaining 1,017 patients with regard to DCMR result and after therapy (>3 months of DCMR).

The primary end point was the occurrence of cardiac events defined as cardiac death (caused by end-stage heart failure, acute myocardial infarction (MI), or sudden cardiac death) and nonfatal MI (9). Nonfatal MI was defined by clinical presentation,

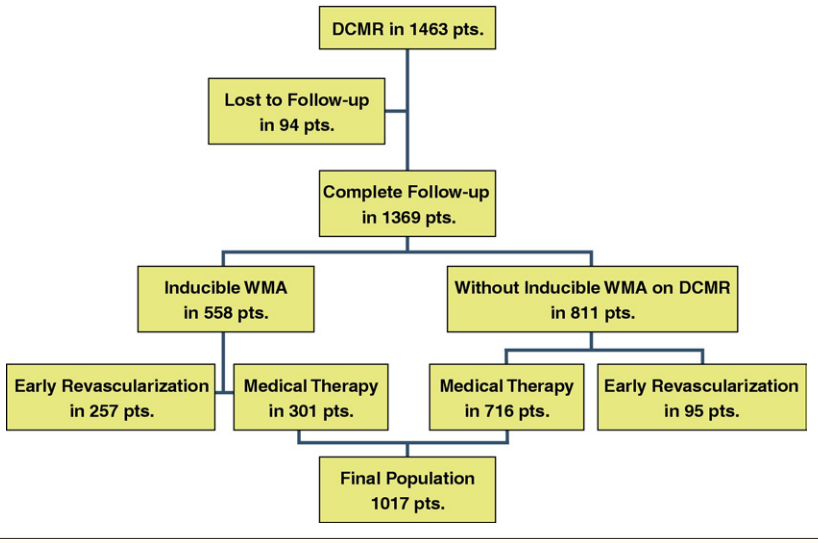

Figure 1. Composition of the Study Population

Early revascularization was defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) ≤3 months of dobutamine cardiac magnetic resonance (DCMR). WMA = wall motion abnormality.

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Table 1. Composition of the Study Population

Variable	Total Population (n = 1,369)	Without WMA on DCMR (n = 811)	Inducible WMA (n = 558)	p Value
Age (yrs)	61.6 ± 10.1	61.1 ± 10.5	61.9 ± 9.4	0.135
Sex (men)	961 (70.2)	542 (66.9)	419 (75.2)	<0.001
BMI (kg/m^2)	27.4 ± 3.9	27.3 ± 4.0	27.6 ± 3.9	0.109
Diabetes mellitus	249 (18.2)	123 (15.2)	126 (22.6)	<0.001
Hypertension	1,047 (76.6)	589 (72.7)	458 (82.2)	<0.001
HLP	1,024 (74.9)	572 (70.6)	452 (81.1)	<0.001
Smoker	627 (45.9)	357 (44.1)	270 (48.5)	0.086
Family history CAD	488 (35.7)	284 (35.0)	204 (36.6)	0.695
Previous CAD	800 (58.5)	429 (52.9)	371 (66.6)	<0.001
Previous PCI/CABG	654 (47.8)	347 (42.8)	307 (55.1)	<0.001
No. of risk factors	3.1 ± 1.3	2.9 ± 1.3	3.3 ± 1.3	<0.001
RWMA	594 (43.4)	290 (35.8)	304 (54.6)	<0.001

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DCMR = dobutamine cardiac magnetic resonance; HLP = hyperlipoproteinemia; MI = myocardial infarction; PCI = percutaneous coronary intervention; RWMA = resting wall motion abnormality.

elevated cardiac enzyme levels, and/or typical changes in the electrocardiogram. Patients were censored at the time of the cardiac event.

Other events (termed any events) included cardiac events, noncardiac death, revascularization by PCI or CABG, and hospital stay due to ventricular arrhythmia, unstable angina, or congestive heart failure. In the case of 2 simultaneous cardiac events, the worst event was selected for use in follow-up (cardiac death > nonfatal MI > revascularization > hospital admission).

In accordance with dobutamine stress echocardiography (DSE) studies, in patients with DCMR without inducible WMA who were treated medically (716 of 1,017 patients), the annual cardiac event rate was reported (14). In addition, the cardiac event rate in the first 3 years and from the fourth to the sixth year of follow-up was recorded (15).

Statistical analysis. Statistical analysis was performed with SPSS for Windows (release 18.0; SPSS, Chicago, Illinois). All continuous parameters are given as mean ± 1 SD. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between patients who reached the primary end point and those who did not were analyzed with the Wilcoxon Mann-Whitney *U* test for continuous variables and the chi-square test for dichotomous variables.

We aimed to study to what extent MRI results were associated with cardiac events. For this purpose, all clinical and MRI data with a p value < 0.1 (in a comparison between patients with and without the occurrence of cardiac events) were eligible. Cox proportional hazard regression models were constructed for clinical and MRI variables. The variables seemed to be associated with cardiac events at the $p < 0.1$ level in univariable analysis. Unadjusted and adjusted hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) are reported. We selected a multivariable Cox proportional hazards regression model by a forward/backward inclusion strategy of potential cardiac risk factors and MRI data in a model limited to 4 parameters. Selection and deselection were based on Wald statistics. Potential parameters tested were all parameters with $p < 0.1$ in univariate analysis.

The C-statistic in binary outcome is equivalent to the area under the curve (16). We evaluated the Cox regression predictor for all 4 models over 5 years and constructed area under the curve statistics. Significance was evaluated by the DeLong test (17).

After adjustment for multiple confounders, stress-induced WMA as determined by MRI seemed significantly related with cardiac events. Therefore, in a Kaplan-Meier analysis, the medically treated study population was divided into 2 groups, on the basis of DCMR result. Difference in survival over time was evaluated by a log-rank test.

We tested early revascularization as a time-dependent covariate in a Cox regression model and did not find any significant impact of time regarding DCMR results and outcome. Early revascularization was a significant independent risk, however ($p = 0.001$).

For all tests, $p < 0.05$ was considered statistically significant. All tests were 2-sided.

Table 2. Clinical Data

Variable	Total Population (n = 1,017)	Events: No (n = 971)	Events: Yes (n = 46)	p Value
Age (yrs)	61.2 ± 10.5	61.0 ± 10.5	64.6 ± 8.9	0.024
Sex (men)	689 (67.7)	652 (67.3)	38 (82.6)	0.032
BMI (kg/m^2)	27.4 ± 4.0	27.4 ± 4.0	27.6 ± 3.9	0.714
Diabetes mellitus	171 (16.8)	154 (15.9)	17 (37.0)	<0.001
Hypertension	743 (73.1)	708 (73.0)	35 (76.1)	0.670
HLP	715 (70.4)	676 (69.7)	39 (84.8)	0.029
Smoker	443 (43.6)	419 (43.2)	24 (52.2)	0.079
Family history CAD	357 (35.1)	340 (35.0)	17 (37.0)	0.843
Previous CAD	529 (52)	489 (50.4)	40 (87.0)	<0.001
Previous Q-wave MI	251 (24.7)	230 (23.7)	21 (45.7)	0.001
Previous PCI/CABG	435 (42.8)	401 (41.3)	34 (73.9)	<0.001
No. of risk factors	3.0 ± 1.3	2.9 ± 1.3	3.4 ± 1.5	0.014
β-blocker	566 (55.7)	530 (54.6)	36 (78.3)	0.002
Calcium channel blocker	194 (19.1)	178 (18.3)	16 (34.8)	0.005
ACE inhibitor	621 (61.1)	588 (60.5)	33 (71.7)	0.249
Warfarin/aspirin	722 (71)	677 (69.7)	45 (97.8)	<0.001
Statin	548 (53.9)	509 (52.4)	39 (84.8)	<0.001
Nitrate	198 (19.5)	177 (18.2)	21 (45.7)	<0.001
Diuretic	285 (28.0)	262 (27.0)	23 (50)	0.001

Continuous data are expressed as mean ± 1 SD; categorical data are summarized as frequencies and percentages.
ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

RESULTS

Study population. Of all patients included, 94 of 1,463 (6.5%) experienced arrhythmias at the time of DCMR. There was no hard event during DCMR testing. Patients with arrhythmias during testing did not differ significantly with regard to the number of cardiac events at long-term follow-up from patients without arrhythmias during DCMR, p = 0.126.

The study population consisted of 301 of 1,017 (29.6%) patients with inducible WMA and 716 of 1,017 (70.4%) patients with DCMR without inducible WMA. Clinical data are presented in Table 2, and hemodynamic data from the participants are shown in Table 3. As demonstrated in Table 2, age, diabetes mellitus, hypercholesterolemia, previous CAD or revascularization, and absolute number of risk factors were significantly lower in patients without than in patients with cardiac events.

Of those patients with early revascularization, 257 of 352 (73.0%) had inducible WMA; 95 of 352 (27.0%) had a negative DCMR. Patients who received early revascularization demonstrated a greater extent of ischemia (number of segments

Table 3. Hemodynamic Data

Variable	Total Population (n = 1,017)	Events: No (n = 971)	Events: Yes (n = 46)	p Value
Resting HR (beats/min)	71 ± 13	71 ± 13	70 ± 12	0.496
Peak HR (beats/min)	136 ± 18	136 ± 18	131 ± 20	0.057
MPHR reached	785 (77.2)	754 (77.7)	31 (67.4)	0.100
Resting SBP (mm Hg)	134 ± 48	134 ± 49	131 ± 26	0.674
Peak SBP (mm Hg)	151 ± 79	152 ± 80	142 ± 34	0.417
Resting DBP (mm Hg)	72 ± 11	72 ± 11	70 ± 12	0.193
Peak DBP (mm Hg)	72 ± 29	72 ± 30	70 ± 14	0.564
Rest rate/pressure product	9,530 ± 3,524	9,552 ± 3,575	9,090 ± 2,165	0.385
Peak rate/pressure product	20,598 ± 11,362	20,694 ± 11,567	18,582 ± 5,184	0.218

Hemodynamic data from the participants are demonstrated. Continuous data are expressed as mean ± 1 SD; categorical data are summarized as frequencies and percentages.
DBP = diastolic blood pressure; HR = heart rate; MPHR = maximum age-related predicted heart rate; SBP = systolic blood pressure.

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with new WMA at DCMR 3.3 ± 2.7 vs. 1.8 ± 2.6 in medically treated patients, $p < 0.001$). Patients who received early revascularization included a significantly higher proportion of subjects with diabetes (22% vs. 17%, $p = 0.024$), hypertension (87% vs. 73%, $p < 0.001$), hyperlipoproteinemia (88% vs. 70%, $p < 0.001$), previous CAD (77% vs. 52%, $p < 0.001$), previous revascularization (62% vs. 43%, $p < 0.001$), a higher number of cardiovascular risk factors (3.4 ± 1.1 vs. 3.0 ± 1.3, $p < 0.001$), and resting wall motion abnormality (RWMA) (58% vs. 39%, $p < 0.001$) compared with patients with medical therapy.

In patients with DCMR without inducible WMA, 95 of 811 patients (11.7%) underwent early revascularization. In comparison with patients with DCMR without inducible WMA and medical therapy (716 of 811 patients), those with DCMR without inducible WMA and early revascularization demonstrated significantly more previous CAD (86% vs. 49%, $p < 0.001$), previous revascularization (72% vs. 39%, $p < 0.001$), a higher number of cardiovascular risk factors (3.4 ± 1.1 vs. 2.9 ± 1.3, $p < 0.001$), and RWMA (57% vs. 33%, $p < 0.001$).

In a comparison of the risk profile in patients with inducible WMA, patients with early revascularization demonstrated significantly more hypertension (88% vs. 78%; $p = 0.003$), hyperlipoproteinemia (86% vs. 77%; $p = 0.008$), previous CAD (74% vs. 61%; $p = 0.001$), and an increased number of cardiovascular risk factors (3.4 ± 1.1 vs. 3.2 ± 1.3, $p = 0.013$) compared with patients treated medically.

In the 94 patients lost to follow-up, the overall study composition was not significantly different from that of the remaining study population with complete follow-up. In addition, in comparing the risk profile, there was a significantly lower age (57 ± 12 years vs. 61 ± 10 years, $p < 0.001$) and a lower number of patients with previous CAD (39% vs. 59%, $p < 0.001$). Patients lost to follow-up also demonstrated a significantly lower rate of inducible WMA (40.7% vs. 17%; $p < 0.001$).

Clinical outcome of patients during follow-up. The average duration of follow-up was 44 ± 24 months, with a median of 38 months (24; 59); 46 patients (4.5%) suffered from a cardiac event during follow-up. Mean time between DCMR and cardiac event was 36 ± 18 months. Thirty-three patients (3.2%) had cardiac death, and 13 patients (1.3%) developed nonfatal MI during follow-up. Noncardiac death was reported in 23 patients (2.3%). Furthermore, 109 patients (10.7%) were hospitalized during follow-up, because of ventricular arrhythmias (5 patients, 0.5%) or unstable angina (104 patients, 10.2%). One hundred and fifteen patients (11.3%) underwent PCI, and 33 patients (3.2%) underwent CABG >3 months after MRI.

In those patients who underwent revascularization ≤3 months after DCMR due to inducible WMA, 14 (5.4%) cardiac events were reported. Seven of 257 patients (2.7%) had cardiac death and 7 of 257 (2.7%) developed nonfatal MI during follow-up. In the remaining 95 patients with DCMR without inducible WMA who underwent early revascularization, 3 (3.2%) cardiac events were reported. Two patients (2.1%) had cardiac death, and 1 patient (1.1%) developed nonfatal MI during follow-up.

The outcome of all patients with complete follow-up dependent on DCMR result and the following therapy (medical treatment or early revascularization) is shown in Figure 3.

MRI variables. The MRI findings are listed in Table 4. LVEF was significantly higher in patients without than in patients with cardiac events. As demonstrated, left ventricular end-systolic volume, left ventricular end-diastolic volume, the number of dysfunctional segments at rest and stress, WMSI at rest and stress, and inducible WMA were significantly associated with cardiac events. Approximately 30% of the patients experienced an inducible WMA during testing.

Predictive value of clinical data and DCMR results. A univariable Cox model was used to identify the predictive value for cardiac events for all clinical data and MRI data (Table 5). Inducible WMA was an independent predictor of cardiac events in this patient population (HR: 3.3, CI: 1.8 to 5.9, $p < 0.001$).

Multivariate predictors of cardiac events are presented in Table 6. Inducible WMA during testing remained an adverse predictor of cardiac events (HR: 3.0, 95% CI: 1.6 to 5.4, $p < 0.001$).

The chi-square value was different between patients with previous CAD alone (chi-square: 23.0) and those with additional diabetes mellitus (chi-square: 34.5). The overall chi-square value was increased further by adding WMSI at rest (chi-square: 73.9) and inducible WMA (chi-square: 86.5).

The receiver-operator characteristic curve (Fig. 2) demonstrates that there was a significant difference between the models including WMSI at rest and those based on clinical parameters only ($p = 0.003$). Adding a positive DCMR shows no significant difference in the other parameters ($p = 0.693$); however, it showed a trend for higher sensitivity

Table 4. Magnetic Resonance Imaging Data

Variable	Total Population (n = 1,017)	Events: No (n = 971)	Events: Yes (n = 46)	p Value
LVEF (%)	57.2 ± 10.3	57.4 ± 9.8	52.3 ± 18.0	0.001
LVEF (%) <40%	64 (6.3)	55 (5.7)	9 (20.5)	<0.001
LVESV (ml)	65.8 ± 37.3	64.4 ± 34.0	95.4 ± 75.9	<0.001
LVEDV (ml)	149.0 ± 59.6	148.0 ± 58.2	176.0 ± 80.4	0.002
End-diastolic wall thickness (mm) septum	10.4 ± 2.6	10.4 ± 2.6	11.1 ± 2.4	0.049
RWMA	392 (38.5)	360 (37.1)	32 (69.6)	<0.001
No. of dysfunctional segments at rest	1.6 ± 2.8	1.5 ± 2.6	4.4 ± 4.3	<0.001
No. of dysfunctional segments at stress	1.8 ± 2.6	1.7 ± 2.5	4.0 ± 3.5	<0.001
WMSI at rest	0.1 ± 0.2	0.1 ± 0.2	0.4 ± 0.4	<0.001
WMSI at maximum stress	0.2 ± 0.3	0.2 ± 0.2	0.4 ± 0.4	<0.001
Δ WMSI	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.2	0.333
Inducible WMA on DCMR	301 (29.6)	277 (28.5)	24 (52.2)	0.001

Continuous data are expressed as mean ± 1 SD; categorical data are summarized as frequencies and percentages.
LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; RWMA = resting wall motion abnormality; WMSI = wall motion score index.

and specificity, demonstrated by a higher cutoff value (red colored ring in Figure 2).

In medically treated patients with and without inducible WMA, the proportion of patients with cardiac events was 8.0% versus 3.1%, respectively, (p = 0.001). In the patient group with inducible WMA those patients with medical therapy demonstrated a trend to a higher cardiac event rate (8.0%) than those with early revascularization (5.4%) (p = 0.234). Patients with DCMR without inducible WMA and medical therapy or early revascularization demonstrated similar cumulative cardiac event rates (3.1% vs. 3.2%, p = 0.964) (Fig. 3).

Patients were separated according to DCMR result (patients with inducible WMA = patients at high risk; n = 301 [29.6%]) and were compared with patients without inducible WMA = patients at low-risk (n = 716 [70.4%]) for cardiac events. A Kaplan-Meier analysis of the cardiac event rate and rate of any events, in those with and without inducible WMA, is shown in Figure 4. A DCMR without inducible WMA carried an excellent prognosis, with an annual cardiac event rate of 1.1% over 6 years (0.8% in the first 3 years, and 1.4% between the fourth and sixth year).

Of 1,017 patients, 392 demonstrated RWMA; in 156 (39.8%) a positive DCMR was reported, and in 625 patients without RWMA, 145 (23.2%) showed a positive DCMR. In patients without RWMA, we found only a difference within the first 3 years; after that there is no significant difference in outcome regarding a DCMR without inducible WMA. In patients with RWMA, a positive DCMR adds a significant value for the prediction of outcome (p = 0.001).

DISCUSSION

The main finding of this study is that in a large cohort of patients DCMR provides additional independent information on risk stratification during

Table 5. Univariate Analysis for Prediction of Cardiac Events

	Hazard Ratio	95% Confidence Interval	p Value
Age	1.036	1.006–1.067	0.019
Sex (male)	0.466	0.229–0.949	0.035
Previous CAD	6.245	2.648–14.731	<0.001
Previous MI	2.513	1.433–4.408	0.001
Previous revascularization	3.972	2.056–7.671	<0.001
Aspirin/warfarin	19.158	2.641–138.990	0.003
Statins	5.352	2.393–11.974	<0.001
Ca-channel blocker	2.270	1.237–4.167	0.008
β-blocker	3.110	1.543–6.267	0.002
Diuretics	2.693	1.508–4.810	0.001
Nitrates	3.560	1.992–6.362	<0.001
Hyperlipoproteinemia	2.472	1.106–5.528	0.027
Diabetes	3.175	1.742–5.785	<0.001
No. of risk factors	1.310	1.046–1.641	0.018
LVEF (rest)	0.958	0.935–0.981	<0.001
LVEF (rest) <40%	4.012	1.928–8.347	<0.001
LVEDV	1.004	1.002–1.006	<0.001
LVESV	1.013	1.009–1.017	<0.001
WMSI (rest)	10.730	5.482–21.001	<0.001
No. of dysfunctional segments at rest	1.230	1.160–1.304	<0.001
RWMA	3.732	1.991–6.994	<0.001
WMSI (stress)	9.834	4.902–19.728	<0.001
No. of dysfunctional segm. at stress	1.244	1.163–1.331	<0.001
Inducible WMA on DCMR	3.278	1.832–5.866	<0.001

Only clinical or magnetic resonance imaging data with significant p values in univariable analysis are presented.
Abbreviations as in Table 4.

Table 6. Multivariable Cox Proportional Hazard Model for Prediction of Cardiac Events

	Hazard Ratio	95% Confidence Interval	p Value
Diabetes mellitus	2.244	1.225–4.111	0.009
Previous CAD	3.234	1.311–7.975	0.011
WMSI (rest)	7.203	3.301–15.717	<0.001
Inducible WMA on DCMR	2.992	1.639–5.396	<0.001

WMSI = wall motion score index; other abbreviations as in Table 1.

long-term follow-up. A positive result forecasts a higher rate of cardiac events. We found a high negative predictive value of DCMR: it improves the differentiation between high- and low-risk patients after accounting for known clinical predictors of cardiac events. Patients with inducible WMA and after early revascularization demonstrate lower cardiac event rates than patients with medical therapy alone.

Several studies have demonstrated a high sensitivity and specificity of DCMR in the detection of WMA (3). It has been reported to be a safe method for the diagnosis of CAD (18). Previous studies have highlighted the utility of DCMR stress to forecast cardiac prognosis and reported a low cardiac event rate at short- and intermediate-term follow-up after a DCMR without inducible WMA (4–8). In this study, we reported on a relatively large number of patients with a longer mean follow-up duration after DCMR (44 ± 24 months). However, currently available reports about the prognostic value of DCMR are also limited by the small number of patients and cardiac events.

Well-established existing risk factors for cardiac events, such as previous MI, diabetes mellitus, and WMA at rest (represented by WMSI at rest) were prevalent in the patients participating in this study and were notably disproportionally distributed between patients with and without cardiac events. To address whether the presence of risk factors in the 2 study groups influenced our results, we performed multivariable regression analysis to determine the prognostic utility of DCMR stress results after accounting for the presence of these risk factors. We demonstrated that inducible WMA (Table 6) identified during DCMR independently predicted future cardiac events (HR: 3.0, 95% CI: 1.6 to 5.4, $p < 0.001$). The receiver-operator characteristic curve demonstrates that the addition of DCMR to known clinical risk factors showed a trend for higher sensitivity and specificity, demonstrated by a higher cutoff value (Fig. 2). This demonstrates the

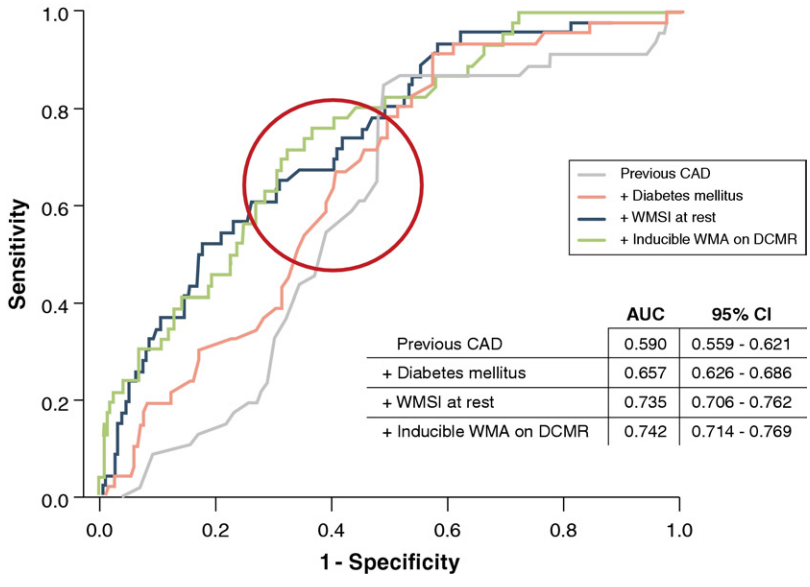

Figure 2. ROC Curve Illustrating Prognostic Value of DCMR

Receiver-operator characteristic (ROC) curve illustrating prognostic value of dobutamine cardiac magnetic resonance (DCMR) in patients. The addition of DCMR provides incremental prognostic information to baseline clinical variable (previous coronary artery disease [CAD] and diabetes mellitus). Furthermore, the addition of wall motion score index (WMSI) at rest to DCMR results adds further incremental prognostic information over baseline clinical variables and showed a trend for higher sensitivity and specificity, demonstrated by a higher cutoff value (**red colored ring**). AUC = area under the receiver-operator characteristic curve; CI = confidence interval; WMA = wall motion abnormality.

incremental value of DCMR over clinical predictors.

In patients with DCMR without inducible WMA, the annual cardiac event rate was 1.1% (0.8% in the first 3 years, and 1.4% from the fourth to the sixth year). Our results demonstrated that the low-risk warranty of a DCMR without inducible WMA was sustained during 3 years after DCMR. However, similar to DSE, the cardiac event rate was still relatively low after 3 years, and a follow-up study at that interval was recommended because the cardiac event rate almost doubled at later follow-up (15).

Furthermore, the addition of WMSI at rest to DCMR results adds further incremental prognostic information over baseline clinical variables. As shown in previous studies, parameters representing impaired LV function and parameters representing the presence or extent of CAD (known CAD; inducible WMA) or a high likelihood of CAD (diabetes mellitus) were related to the occurrence of cardiac events at long-term follow-up (14). This is to our knowledge the first study using DCMR to confirm these results in a large study population. In patients with inducible WMA treated medically the rate of cardiac death or nonfatal MI was increased 2.6-fold. In medically treated patients with and without inducible WMA, the proportion of patients with cardiac events was 8.0% versus 3.1%, respectively, ($p < 0.001$). In the patient group with inducible WMA, those patients with medical therapy only demonstrated a trend to a higher cardiac event-rate (8.0%) than those with early revascularization (5.4%) ($p = 0.234$). This analysis demonstrates a possible association between early revascularization and improved survival among patients who have evidence of ischemia on DCMR. In future studies, including a larger patient cohort and cardiac event rate, a significant difference between these patient groups can be expected. Furthermore, in patients with DCMR without inducible WMA, we found a similar cardiac event rate in those with medical therapy only or early revascularization (3.1% vs. 3.2%; $p = 0.964$), demonstrating that there does not seem to be a benefit of early revascularization in patients with DCMR without inducible WMA (Fig. 3).

Hundley et al. (4) studied the outcome of 279 patients over a mean follow-up of 20 months. They demonstrated that inducible WMA at DCMR were associated with future cardiac events in patients with normal and depressed LVEF (HR: 3.3; CI: 1.1 to 9.7; HR: 4.2; CI: 1.3 to 13.9), an effect independent of the presence of risk factors for

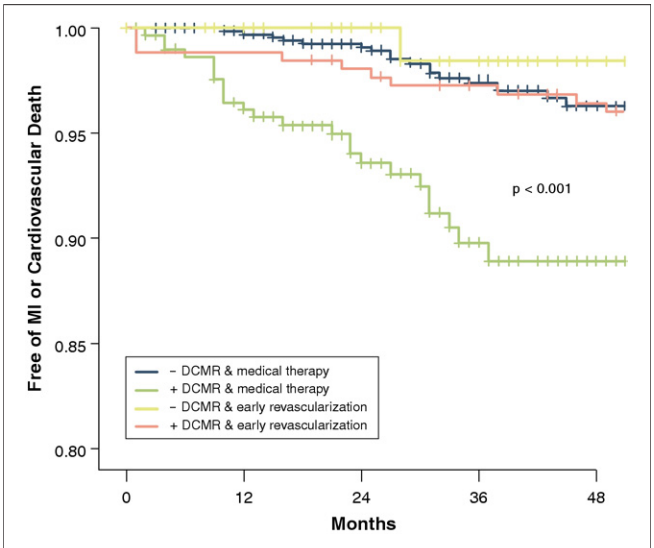

Figure 3. Kaplan-Meier Curves According to DCMR Result and After Therapy

Kaplan-Meier curve analysis showing the difference in cumulative cardiac event rate when patients are stratified according to the occurrence of cardiac events by dobutamine cardiac magnetic resonance (DCMR) result and after therapy. Cardiac events were defined as cardiac death (caused by end-stage heart failure, acute myocardial infarction [MI], or sudden cardiac death) and nonfatal MI.

CAD. In a previous study in 461 patients, followed for a median of 2.3 years by our working group, a DCMR without inducible WMA result was associated with a low cumulative event rate of 3.3% over 3 years (5). Inducible WMA detected by DCMR predicted subsequent cardiac death or nonfatal MI in univariate analysis (HR: 5.42; CI: 2.2 to 13.50; $p < 0.001$, respectively). Our results, observed in a large patient cohort, are in congruence with these previous reports, demonstrating the association of a positive DCMR with future cardiac events (HR: 3.3; CI: 1.8 to 5.9; $p < 0.001$). Dall'Armellina et al. (6) demonstrated, in 200 patients followed-up for a median of 60 months that inducible WMA were associated with a greater risk of future events beyond that associated with the resting EF and/or cardiac risk factors ($p < 0.001$). In addition, they were the only independent predictor in multivariate analysis (HR: 1.7; p 0.008). However, in this study, in severe LV impairment (LVEF <40%), inducible WMA were not additionally predictive of outcome over LVEF at rest (6,19).

In previous studies of cardiac prognosis after DCMR a trend toward an association between the number of LV myocardial segments with inducible WMA and more frequent adverse events (4,20,21) has been demonstrated (7). In our large study

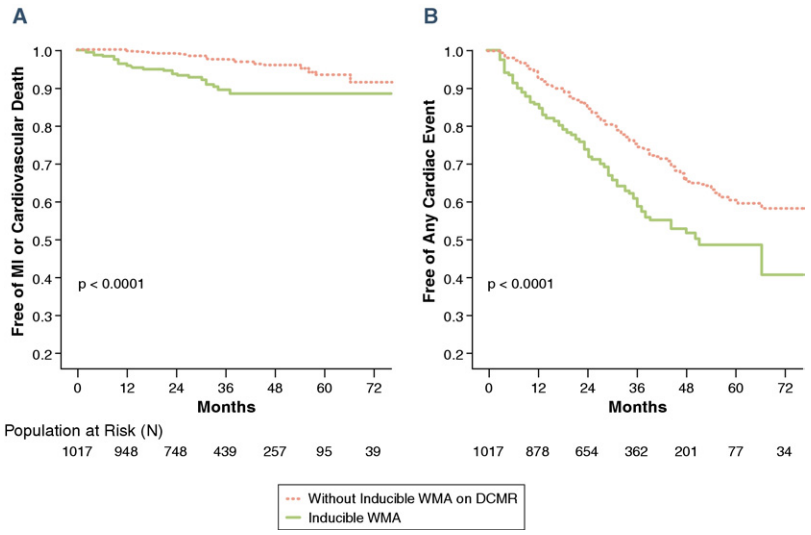

Figure 4. Kaplan-Meier Curves According to Cardiac Events or any Cardiac Events by DCMR

Kaplan-Meier curve analysis showing the difference in cumulative cardiac event rate when patients are stratified according to the occurrence of cardiac events **(A)** or of any cardiac events **(B)** by DCMR. Cardiac events were defined as cardiac death (caused by end-stage heart failure, acute MI, or sudden cardiac death) and nonfatal MI. Any cardiac events included cardiac events; noncardiac death; revascularization by percutaneous coronary intervention; coronary artery bypass graft; ventricular arrhythmia; unstable angina, or congestive heart failure warranting hospital admission. Abbreviations as in Figures 2 and 3.

population in univariate analysis, there was no relationship between the number of LV myocardial segments with inducible WMA and incremental cardiac events. This is in congruence with DSE, in which HR for prediction of cardiac events increased if 2 segments demonstrated ischemia compared with the situation in patients with "limited" ischemia (1 segment). However, there was no further increase in HR if > 2 segments showed ischemia (14).

Most of our patients had an intermediate to high pretest probability of CAD; therefore, these results can be applicable to a wide spectrum of patients in whom stress testing is clinically indicated. Identification of patients at low risk of cardiac events (negative DCMR) has an important impact on management of patients with suspected CAD, by avoiding the risk and the cost related to further diagnostic and therapeutic approaches that are unlikely to improve outcome in low-risk patients (22).

In addition, our results—obtained in a single center with a high volume of DCMR—might be applied to other centers, due to a known high inter-institutional observer agreement in the interpretation of DCMR (23), which is a clear advantage of DSE (24). In addition, no ionizing radiation needs to be applied during cardiac magnetic resonance; therefore it can be repeated as necessary for follow-up purposes (25).

Study limitations. The data presented were observed only at a single center. Multicenter trials are needed to confirm our results.

Due to the retrospective, observational approach, follow-up could not be assessed in 100% of our patients. Ninety-four patients (6%) were lost to follow-up, due to incomplete patient datasets. We cannot rule out that cardiac events occurred in the patients with missing follow-up; however, patients without complete follow-up included a significantly lower proportion of subjects with previous CAD and lower rate of inducible WMA compared with patients with complete follow-up. Therefore, we do not consider that this would have changed the results of our study significantly.

In addition, patients with DCMR without inducible WMA and inducible WMA were not matched for demographic factors (e.g., risk factors, age or other demographic factors). For that reason, participants demonstrating inducible WMA at DCMR showed significantly more diabetes, hypertension, hyperlipoproteinemia, previous CAD, previous revascularization, a higher number of cardiovascular risk factors, and RWMA.

The decision for revascularization or medical treatment was mainly made by the referring physician. Not all of our patients with a positive DCMR were referred for invasive cardiac procedures. At the

time of DCMR, only 1 study had been published about the short-term prognostic value of DCMR (4). In addition, only 2 studies about the diagnostic accuracy had been published (1,2). Therefore, DCMR results were not always used for decision-making (e.g., in favor of catheterization by the referring physician). In patients with DCMR without inducible WMA, 11.7% underwent early revascularization. In comparison with patients with DCMR without inducible WMA and medical therapy, those with DCMR without inducible WMA and early revascularization demonstrated a significant higher risk profile. This might have influenced the decision for early revascularization versus medical treatment. In addition, a few of the patients might have also refused further revascularization even if ischemia was proven by inducible WMA on DCMR.

Furthermore, segmental wall motion was visually analyzed. Newer imaging protocols that involve simultaneous assessment of WMA, myocardial perfusion, and late-gadolinium enhancement (LGE) yield improved results in certain patient populations (26). In addition, studies evaluating myocardial strain with quantitative assessment of wall motion by MRI tagging combined with rapid post-processing algorithms might overcome this limitation (27,28). Moreover, myocardial strain might have prognostic value, because strain assessment enables evaluation of border zone function, which has been related to inducibility of monomorphic ventricular tachycardia (29).

Currently, most cardiac magnetic resonance procedures involve the use of contrast media (25). LGE was performed in only a few of our patients. Recently it has been described that the amount of myocardial scarring detected by cardiac magnetic resonance is related to the long-term clinical outcome (9,10) and might thus be a much better predictor of lethal events than individual clinical markers (30), which are limited by low positive predictive values (31). As demonstrated by Kwong et al. (32), the presence of LGE in patients with chest pain referred for dobutamine stress might serve as a marker of adverse cardiac prognosis. Further studies combining DCMR and LGE might offer additional prognostic information in subjects with suspected ischemia (33).

CONCLUSIONS

In a large cohort of patients, DCMR has an added value for predicting cardiac events during long-term follow-up, improving the differentiation between high-risk and low-risk patients. Patients with inducible WMA and after early revascularization demonstrate lower cardiac event rates than patients with medical therapy alone. Further multicenter trials are needed to assess the prognostic value of DCMR.

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