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Scar extent, left ventricular end-diastolic volume, and wall motion abnormalities identify high-risk patients with previous myocardial infarction: a multiparametric approach for prognostic stratification

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Aims We sought to investigate whether combining left ventricular (LV) volumes, regional wall motion abnormalities, and scar tissue extent obtained by cardiac magnetic resonance (CMR) improves risk stratification of patients with previous myocardial infarction (MI).

Methods and results In 231 consecutive patients (age 64 ± 11 years, males 89%) with previous MI, we quantified LV volumes and regional wall motion abnormalities by cine CMR, and measured the extent of the infarction scar by late gadolinium enhancement (LGE). During follow-up (median, 3.2 years) cardiac events (cardiac death or appropriate intra-cardiac defibrillator shocks) occurred in 19 patients. After adjustment for age, an extent of LGE >12.7%, an LV end-diastolic volume >105 mL/m^2, and a wall motion score index >1.7 were independent associated with adverse cardiac events at multivariate analysis ($P < 0.05$, $P < 0.001$, and $P < 0.01$, respectively). The patients with none of these factors, and those with one or two factors, showed a lower risk of cardiac events [hazard ratio (HR) = 0.112, $P < 0.01$ and HR = 0.261, $P < 0.05$] than those with three factors. The cumulative event-rate estimated at 4 years was 29.6% in patients with all three factors, 7.7% in those with one or two factors, and 3.5% in patients with none of these factors.

Conclusion A multiparametric CMR approach, which includes the measure of scar tissue extent, LV end-diastolic volume and regional wall motion abnormalities, improves risk stratification of patients with previous MI.

Keywords Scar tissue • Left ventricular volumes • Wall motion abnormalities • Cardiac magnetic resonance • Previous myocardial infarction

Introduction

The prognostic stratification of patients with previous myocardial infarction (MI) is based on the evaluation of a variety of factors, derived from clinical examination, biohumoral tests, and cardiac imaging.[1,2] Using different imaging modalities, left ventricular (LV) systolic dysfunction, LV dilatation and remodelling, the severity and extent of regional wall motion abnormalities, and the extent of necrotic tissue have all been shown to be of prognostic relevance in patients with previous MI.[3–7] Specifically, the dilatation

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of both LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV), which represent the result of adverse cardiac remodelling, has been related to high incidence of cardiac death.[4,8] After adjustment for conventional clinical covariates, the LVEDV was the only echocardiographic predictor of death in the BEST study.[8] The unfavourable impact of extensive wall motion abnormalities [defined by a wall motion score index (WMSI) >1.5] has been shown to be independent and incremental to the LV ejection fraction (EF).[9] The extent of the scar tissue has been associated with increased incidence of death.[6,7] In the study by Kwon *et al.*,[7] a greater extent of cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) was associated with increased mortality or the need for cardiac transplantation.

Cardiac magnetic resonance is a non-invasive, non-ionizing, and three-dimensional imaging technique that allows accurate quantification of LV volumes, LV global and regional function, and scar tissue extent in a one-stop-shop modality.[10] We hypothesized that the integration of the parameters derived from CMR, together with conventional risk factors, could improve the prognostic stratification of patients with previous MI. Specifically, we aimed to assess the prognostic stratification power of the combined assessment of scar tissue extent, LV volume, and regional systolic function detected by CMR, together with conventional risk factors, in patients with previous MI.

Methods

Patients

We studied 280 consecutive patients [64.3 ± 10.9 years old, 26 (9%) female] with clinical evidence of a previous MI referred to routine CMR from July 2001 to March 2007. The infarction was documented by clinical records or by the presence of diagnostic Q-waves in a 12-lead ECG recording, and was older than 3 months in every patient. The inclusion criteria also included angiographically documented coronary stenosis reducing luminal diameter by at least 50% in one major coronary artery and stable clinical conditions.

We excluded patients with unstable angina or recent evidence of myocardial ischaemia ($n = 23$), patients with at least moderate valve disease ($n = 13$), patients with hypertrophic cardiomyopathy ($n = 4$), or with history of malignancy and/or chemotherapy ($n = 9$). We also excluded patients with absolute CMR contraindications (severe claustrophobia, defibrillators, or aneurysm clips), and those with irregular heart rhythm (permanent atrial fibrillation). In every patient, CMR examination was done 6 months before or after a revascularization procedure. Patients were studied either as out-patient ($n = 48$) or during the hospitalization ($n = 183$). The clinical variables, including medications taken and cardiovascular risk factors, were collected before CMR examination. The study was approved by the local Ethics Committee; the investigation conformed to the principles outlined in the Declaration of Helsinki. All patients gave their informed consent before the study.

Cardiac magnetic resonance data acquisition

Cardiac magnetic resonance was performed using a 1.5T whole body scanner (GE Medical Systems, Milwaukee, WI, USA). A 8-channel cardiac phased-array receiver surface coil was used for signal reception. A breath-hold steady-state free-precession ECG-triggered sequence was used to evaluate global LV function. In each patient, a set of contiguous short-axis views were acquired from the mitral plane to the apex and two long-axis views (one vertical and one horizontal) were acquired, with a minimum of 30 cine frames for each slice with the following parameters: slice thickness 8 mm, no gap, eight views per segment, NEX 1, field of view 40 cm, phase field of view 1, matrix 224 × 224, reconstruction matrix 256 × 256, flip angle 45°,TR/TE 3.5/1.5, and bandwidth 125 KHz. Late gadolinium enhancement images were obtained 8–10 min after bolus injection of gadolinium derivates (Omniscan®, Amersham, GE Medical System or Magnevist®, Shering). Images were acquired in the same short-axis and long-axis slices as used for cine CMR. The fast Gradient Echo Inversion Recovery sequence was utilized with the following parameters: repetition time 4.2 ms, echo time minimum, flip angle 20°, matrix 224 × 224, number of excitations 1.00, field of view 36 mm, slice thickness 8 mm, no inter-slice gap. The inversion time was optimized to null signal from the normal myocardium.

Cardiac magnetic resonance data analysis

To determine LV function, endocardial borders were manually drawn on all LV short-axis images by means of previously validated software (Mass®, MEDIS, The Netherlands). The LV mass, LVESV, and LVEDV, normalized for the body mass index (mL/m^2), were then calculated and the LVEF was derived. LV was divided into 17 segments including six basal, six middle, four distal segments, and the apex.[11] Wall motion of each segment was graded semi-quantitatively according to a four-point scale where 1 is normal, 2 is hypokinetic, 3 is akinetic, and 4 is dyskinetic. The score of the segments belonging to an LV wall was averaged to derive the WMSI. The ratio mass/EDV was considered as an LV remodelling index.[12,13]

The global LGE extent was measured using a semiautomatic, software.[14] In each image, boundaries of contrast-enhanced areas were automatically traced (using a signal intensity cut-off of >5 SD over the average of normal remote myocardium) and manually corrected when needed. The reproducibility of this method has been previously validated.[14]

The transmural LGE extent was measured by standard techniques.[15] For each segment, the LGE transmural extent was expressed as percentage of total segment area and clustered as follows: (1–25; 26–50; 51–75; or >75%). Furthermore, LVEDV, WMSI, and LGE extent were then dichotomized according to their median values.

Follow-up

A questionnaire compiled by a clinical physician during periodic ambulatory work up in our institute (182 patients, 79%) or telephone contact (49 patients, 21%) was used to follow-up.

The length of follow-up was from 3 months to ~8 years. The events considered were cardiac death, and appropriate implantable cardiac defibrillator (ICD) shock. The cause of death was derived from medical records or death certificates. The definition of cardiac death required the documentation of significant arrhythmia or cardiac arrest or death attributable to congestive heart failure or MI in the absence of any other precipitating factor. In case of out-of-hospital death not followed by autopsy, sudden unexpected death was classified as cardiac death. Implantable cardiac defibrillator shocks were designated appropriate if triggered by lethal arrhythmias: ventricular tachycardia above the programmed cut-off of the ICD (12 intervals at >180 b.p.m.), or ventricular fibrillation. A complete interrogation of the ICD was performed by the referring physician in order to confirm the appropriateness of the shock.[16] According to major events, patients were subsequently divided into two groups: with and without cardiac events.

Table 1 Clinical characteristics of the entire population and patients with and without cardiac events (cardiac deaths and appropriate implantable cardiac defibrillator shocks)

	Entire population (n = 231)	Cardiac events (n = 19)	No. cardiac events (n = 212)	P-value
Age (years)	64.3 ± 10.9	69.0 ± 9.6	63.9 ± 10.9	0.04
Female (%)	11.2	10.5	11.2	1.00
BMI	26.4 (24.3; 28.4)	26.7 (24.5; 28.2)	26.4 (24.3; 28.6)	0.79
Family history of CAD (%)	50.7	42.1	51.4	0.44
Hypertension (%)	55.0	68.4	53.8	0.22
Diabetes (%)	32.8	15.8	34.3	0.10
Hypercholesterolaemia (%)	52.0	57.9	51.4	0.59
Smoker (%)	49.1	58.8	48.3	0.40
Anterior MI (%)	48.3	55.6	47.7	0.52
No. of stenosed vessels	2 (1; 3)	3 (2; 3)	2 (1; 3)	0.08
MI more than 1 (%)	12.7	31.3	10.8	0.02
MI to CMR interval (years)	6.6 ± 7.5	10.6 ± 8.6	6.2 ± 7.5	0.03
Prior PCI (%)	60.5	40.0	62.1	0.17
Prior CABG (%)	38.8	62.5	36.7	0.15
Beta-blocker (%)	79.9	92.9	78.4	0.30
ACE-I/ARB (%)	77.5	85.7	76.6	0.74

BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2 Cardiac magnetic resonance variables of the entire population and patients with and without cardiac events

	Entire population (231)	Cardiac events (death and appropriate ICD shocks)		
		Yes (n = 19)	No (n = 212)	P-value
LVEDV (mL/m^2)	113.7 ± 43	139.5 ± 51	111.4 ± 42	<0.01
LVESV(mL/m^2)	73.5 ± 44	100.1 ± 51	71.1 ± 43	<0.01
LVEDV >105 mL/m^2 (%)	41.1	84.2	37.3	<0.001
LVEF (%)	39.7 ± 16	31.6 ± 14	40.5 ± 16	0.02
LVEF ≤30% (%)	68.7	52.6	70.1	0.11
LV mass (g/m^2)	84 ± 21	88 ± 26	84 ± 21	0.38
LV mass/EDV (g/mL)	0.80 ± 0.26	0.66 ± 0.15	0.82 ± 0.26	0.01
WMSI	1.8 ± 0.5	2 ± 0.3	1.8 ± 0.5	0.10
WMSI >1.7 (%)	54.0	84.2	51.2	<0.01
LGE extent (%)	15 ± 9	19 ± 10	14 ± 9	0.01
LGE extent >12.7% (%)	50.9	79.0	48.3	0.01
Segments with LGE (%)	7.1 ± 3.6	8.7 ± 4.0	7.0 ± 3.6	0.04
LGE transmural extent 1–25% (number of segments)	1.7 ± 1.9	2.2 ± 1.9	1.7 ± 1.9	0.30
LGE transmural extent 26–50% (number of segments)	1.9 ± 1.7	2.4 ± 1.5	1.8 ± 1.7	0.14
LGE transmural extent 51–75% (number of segments)	1.8 ± 1.9	2.3 ± 1.8	1.8 ± 1.9	0.25
LGE transmural extent 76–100% (number of segments)	1.8 ± 2.5	1.8 ± 2.2	1.8 ± 2.5	0.94

LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LGE, late gadolinium enhancement; WMSI, wall motion score index.

Statistical analysis

Continuous variables were expressed as mean ± SD or median (25th; 75th percentiles); categorical variables were expressed as percentage. The comparison between continuous variables in patients with and without cardiac events was performed by Student's independent t-test or the Wilcoxon test as appropriate. The comparison between categorical variables was performed by the Chi-square test or by Fisher's exact test if an expected cell count was 5. The correlation between continuous variables was tested with Pearson's correlation coefficient. In a *post hoc* analysis, LVEDV, WMSI and global LGE

extent were considered as dichotomous variables according to their median value. Univariate Cox regression analysis was used to determine which variables were associated with cardiac-related death or appropriate ICD shocks. The following variables were tested as continuous: age, LVEDV, LVESV, LVEF, mass/EDV, global LGE extent, transmural LGE extent, MI to CMR interval, and number of stenosed coronary arteries. The following variables were tested as categorical: gender, hypertension, obesity, diabetes, dyslipidaemia, smoking, medical treatment, LGE transmural extent 1–25, 26–50; 51–75; or >75%, anterior MI, and MI >1. After clustered in according to the median values, EDV, WMSI and LGE were tested also in categorical form. For variables found to be significant in univariate analysis, each model was then adjusted for age. The hazard ratios (HRs) related to the different patient characteristics were assessed after adjusting by age. The adequacy of the models was compared using the Akaike information criterion (AIC) performed for each model. The Kaplan–Meier life-table method was used to summarize the follow-up experience in the patient population. Nelson–Aalen cumulative hazard of mortality at 2-year, 3-year, and 4-year follow-up was also estimated. Statistical significance was set at $P < 0.05$ (two-sided). Finally, the entire study cohort was risk stratified according to the positivity or negativity above LVEDV (≤ or> of the median value), LGE extent (≤ or> of the median value),[16] and WMSI (≤ or> of the median value). All analyses were performed using Stata, version 10.

Results

Each of the 231 enrolled patients completed the CMR protocol without major complications. Thirty-one patients (13%) had an ICD placed after the CMR study. During follow-up (median, 3.2 years), 19 major cardiac events occurred: 10 cardiac-related deaths and 9 appropriate ICD shocks. The clinical characteristics of the whole group of patients and of the patients with or without cardiac events are reported in *Table 1*. According to the median values, EDV, WMSI, and LGE extent were clustered as follows: EDV >/≤105 mL/m^2, WMSI >/≤1.7, and LGE extent >/≤12.7%. Patients with cardiac events had larger LV volumes (LVEDV, LVESV, LVEDV >105 mL/m^2), lower mass/EDV, greater extent of the scar tissue (LGE extent, LGE >12.7%, segments with LGE), lower LVEF, and more extensive wall motion abnormalities (WMSI >1.7) than those without events (*Table 2*).

Variables associated with mortality

In addition to age, several CMR variables were associated with cardiac events at univariate Cox regression analysis; as shown in *Table 3* these variables were LVEDV, LVESV, LVEDV >105 mL/m^2, LVEF, mass/EDV, WMSI, WMSI >1.7, LGE extent >12.7%. Among these variables, an LVEDV >105 mL/m^2, a WMSI >1.7, and an extent of LGE >12.7% showed the highest association with risk of cardiac events during follow-up. These factors were inter-related; specifically, both LGE, and WMSI had a positive correlation ($r = 0.575$; $P < 0.001$) and a positive pairwise correlation with the LVEDV ($r = 0.458$; $P < 0.001$ and $r = 0.594$; $P < 0.001$) and with the LVESV ($r = 0.521$; $P < 0.001$ and $r = 0.673$; $P < 0.001$). The same variables had a negative correlation with the LVEF ($r = -0.570$; $r = -0.770$; $P < 0.001$) and mass/EDV ($r = -0.367$; $r = -0.439$; $P < 0.001$). There were no correlations between age and other parameters.

After adjusting for age, an LVEDV >105 mL/m^2, a WMSI >1.7, and an LGE extent >12.7% remained the CMR parameters associated with the higher risk of cardiac events, as shown by low value of AIC (*Table 3*).

Furthermore, patients were divided into three subgroups on the basis of the presence of the above variables associated with cardiac events: three markers (65 patients; 13 cardiac events, 20%); one to two markers (one marker in 32 patients, 0 event and two markers in 54 patients, 4 events, 7.4%); and none of the three markers (80 patients, 2 events, 2.5%). As shown in *Table 4*, patients with all the

Table 3 Hazard ratios for cardiac events (cardiac death and appropriate implantable cardiac defibrillator shocks) by cardiac magnetic resonance variables both before and after adjustment for age

	Not adjusted	Adjusted for age	
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	AIC
Age (years)	1.062 (1.007–1.119)*		
LVEDV (mL/m^2)	1.011 (1.003–1.019)**	1.010 (1.002–1.019)*	167.311
LVESV(mL/m^2)	1.01 (1.002–1.018)**	1.009 (1.001–1.017)*	167.955
LVEDV >105 mL/m^2	8.332 (2.407–28.842)***	7.909 (2.285–27.378)***	157.093
LVEF (%)	0.967 (0.938–0.997)*	0.971 (0.942–1.001)	168.541
LVEF <30%	2.122 (0.837–5.384)	1.918 (0.751–4.899)	170.525
LV mass/EDV (g/mL)	0.073 (0.008–0.662)*	0.080 (0.009–0.712)*	166.217
WMSI	3.070 (1.170–8.050)*	2.796 (1.059–7.379)*	167.649
WMSI >1.7	6.495 (1.880–22.443)**	5.973 (1.728–20.639)**	160.984
LGE extent (%)	1.033 (0.991–1.078)	1.037 (0.990–1.086)	169.978
LGE >12.7	3.711 (1.221–11.283)*	3.347 (1.096–10.217)*	166.935

LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LGE, late gadolinium enhancement; WMSI, wall motion score index.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

Table 4 Clinical characteristics of patients according to markers (no marker, one to two markers and three markers) associated with cardiac events

	No marker ($n = 80$)	One to two markers ($n = 86$)	Three markers ($n = 65$)	*P*-value
Age (years)	65.2 ± 9.8	62.6 ± 12.0	65.4 ± 10.5	0.20
Female (%)	18.8	9.3	3.1	0.01
BMI	27.3 (24.2; 30.0)	26.2 (25.2; 28.2)	26.1 (23.7; 28.1)	0.19
Family history of CAD (%)	50.6	52.9	48.4	0.86
Hypertension (%)	54.4	51.8	59.4	0.65
Diabetes (%)	27.9	38.8	29.7	0.28
Hypercholesterolaemia (%)	51.9	54.1	50.0	0.88
Smoker (%)	44.3	51.9	50.8	0.59
Anterior MI (%)	35.0	51.2	62.5	0.004
No. of stenosed vessels	2 (1; 2)	2 (1; 3)	2 (2; 3)	0.008
MI >1 (%)	3.3	9.5	28.6	<0.001
MI to CMR interval (years)	4.2 ± 5.7	6.8 ± 7.6	9.2 ± 8.5	0.005
Prior PCI (%)	71.7	56.8	50.0	0.12
Prior CABG (%)	26.2	41.7	60.0	0.04
Beta-blocker (%)	81.6	73.5	85.4	0.35
ACE-I/ARB (%)	69.4	79.2	85.4	0.18

Three markers: LGE extent >12.7%, WMSI >1.7, and LVEDV >105 mL/m^2. One or two markers: LGE extent >12.7% and/or WMSI >1.7 and/or LVEDV >105 mL/m^2. No marker: LGE extent ≤12.7%, WMSI ≤1.7, LVEDV <105 mL/m^2.

Table 5 Hazard ratios for cardiac events (cardiac death and appropriate implantable cardiac defibrillator shocks) according to LVEDV > or ≤105 mL/m^2, WMSI > or≤1.7, LGE extent > or ≤12.7%

	Patients	Cardiac events Yes ($n = 19$) (%)	HR (95% CI)
Three markers	65	20.0	Ref.
One to two markers	86	4.7	0.261 (0.085–0.801)*
No marker	80	2.5	0.112 (0.025–0.498)**

Three markers: LGE extent >12.7%, WMSI >1.7, and LVEDV >105 mL/m^2. One or two markers: LGE extent >12.7% and/or WMSI >1.7 and/or LVEDV >105 mL/m^2. No marker: LGE extent ≤12.7%, WMSI ≤1.7, LVEDV <105 mL/m^2.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

three markers had higher frequency of anterior MI, multiple MI, longer interval time from MI to CMR interval, prior CABG, and a significant higher number of stenosed vessels, in respect to those with one to two markers and no marker.

Patients having none or only one or two of these markers had a lower risk (HR = 0.261; $P < 0.05$ and HR = 0.112; $P < 0.01$, respectively) of a worse outcome than patients having all three markers (*Table 5*).

The estimated Kaplan–Meier survival curves of the three groups of patients are shown in *Figure 1*. The cumulative risk of mortality estimated at 2, 3, and 4 years was lower in patients with none of the three markers with respect to those with one or two factors and to the patients with all three factors (*Table 6*). LVEF was not an independent variable when adjusted for age.

Discussion

This study shows that scar tissue extent, LV dilatation, and wall motion abnormalities, together with age, are independently associated with cardiac death; furthermore, a combined evaluation of these parameters fine-tunes the prognostic stratification of patients with previous MI. Specifically, when the WMSI is >1.7, the extent of scar tissue exceeds 12.7% of the LV mass, and LV volume is >105 mL/m^2, the survival free of cardiac death is lower than when two, one, or none of these factors are present. Thus, although scar tissue extent, LV dilatation, and wall motion abnormalities are correlated, they provide an integrated prognostic information that likely reflects a different pathophysiological significance in patients with previous MI. The integrative prognostic information provided by these three cardiac indexes arises from the different pathophysiological significances of these parameters in patients with previous MI. The substitution of viable myocardium with the scar tissue is a regional phenomenon that represents the evolution of an acute myocardial damage; this phenomenon begins in the acute phase of the infarction and is fully completed within 6 months.[17] Post-ischaemic LV remodelling is the consequence of myocardial necrosis, and involves the infarction area (which can become thinner and expands), the remote zones (where the

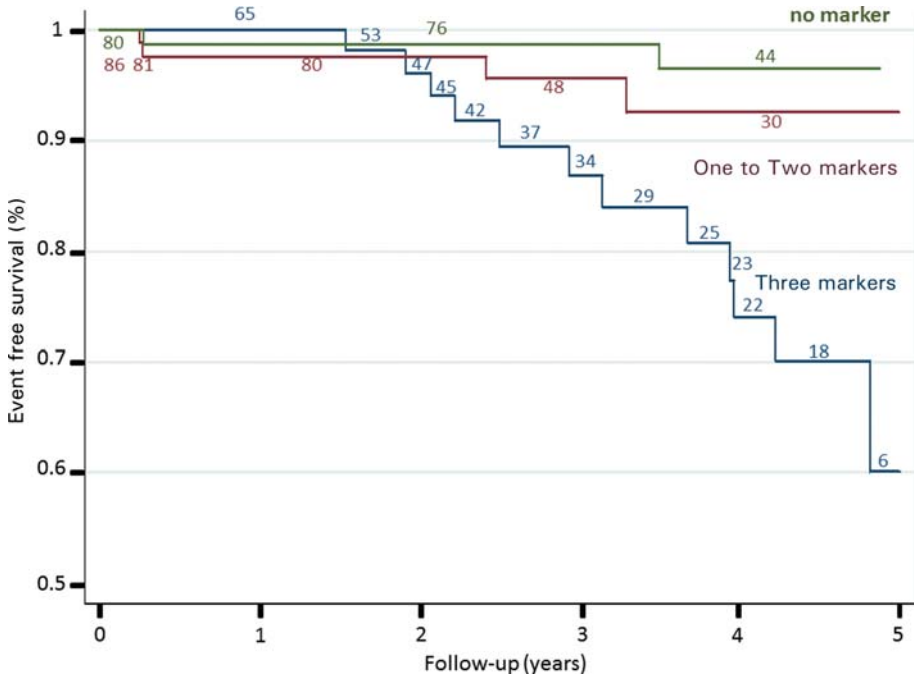

Figure 1 Kaplan–Meier survival curves with three, one or two markers, and no marker at cardiac magnetic resonance. Number of patients at risk is shown for each curve. Note the significantly better event-free survival of the patients with no marker with respect to those with one or two markers, and to those with three cardiac magnetic resonance markers.

Table 6 Cumulative hazard of cardiac mortality during the follow-up

Years	Three markers	One or two markers	No marker
2	3.9 (1.0, −15.8)	2.4 (0.6, −9.6)	1.3 (0.2, 9.2)
3	13.9 (6.2, 31.3)	2.4 (1.4, 14.3)	1.3 (0.2, 9.2)
4	29.6 (15.5, 56.5)	7.7 (2.6, 22.3)	3.5 (0.8, 14.8)

Nelson–Aalen cumulative hazard % (95% CI). Three markers: LGE extent >12.7%, WMSI >1.7, and LVEDV >105 mL/m^2. One or two markers: LGE extent >12.7% and/or WMSI >1.7 and/or LVEDV >105 mL/m^2. No marker: LGE extent ≤12.7%, WMSI ≤1.7, LVEDV <105 mL/m^2.

myocardium can become hypertrophied), and LV cavity (which can enlarge and distort).[18] The LV wall motion abnormalities can be considered the final result of the infarcted and remote zones although they also reflect residual myocardial viability and ischaemia, and loading conditions.[19]

The results of our study partially contrast with recent CMR studies showing the prognostic power of one of the above-mentioned variables with respect to the others. The apparent divergence between these results and ours likely reflects the different population cohort. As a matter of fact, in previous studies both revascularized and non-revascularized patients were enrolled,[20] as well as patients with both acute and previous MI,[21] or patients with severe LV dysfunction,[7] with signs and symptoms of coronary artery disease but without known previous MI,[22] or diabetic patients.[23] At variance, we selected patients with clinical evidence of previous MI and a large spectrum of LV function, with an LVEF ranging from 9% to normal values, with a mean value of 44%. We also excluded patients with recent evidence of myocardial ischaemia and patients with recent revascularization procedure. In addition, the type of censored events can potentially affect the results; while we only considered cardiac death as a censored event, in other studies all causes of mortality and/or heart transplantation were considered.[21]

Our results are similar to those of Roes *et al.*,[24] showing that infarct size, detected by LGE CMR, was the stronger associated with all-cause mortality in patients with previous MI. Differently from Rose's study, we used WMSI as a variable of regional LV dysfunction,[9,25,26] showing the incremental prognostic value when severe scar extent, LVEDV enlargement and severe WM abnormalities were whole present in the same patient with a probability of cardiac death in 4 years ranging from 7.7% in the presence of one or two of these signs to 29.6 in the presence of all three.

The results of this study strengthen the usefulness of the multiparametric approach, consisting of clinical, functional, and morphological data in order to more accurately stratify risk stratification of patients with previous MI. This is based on the evidence that the causes of cardiac death are multifactorial,[1,27] and thus it is likely that relying on any one of these prognostic indices or their absence may lead to suboptimal prognostic results. The efficacy of the multiparametric approach in prognostic risk stratification has been previously documented by Kwong *et al.*,[23] who studied

107 diabetic patients with unrecognized MI during a median follow-up of 17 months; the authors have shown that the presence of the scar tissue assessed with the LGE technique has a strong association with major acute cardiac events and mortality hazards, and in particular is incremental to clinical, ECG, and LV function in diabetic patients. More recently Bingham and Hachamovitch,[28] studying 908 patients during a follow-up of 2.6 years, showed that the analysis of ventricular volume, aortic flow, myocardial viability, and stress perfusion, assessed with CMR, added incremental value for prediction of adverse events over pre-CMR data in patients with and without previous MI and normal or depressed LV function. The relevance of a multiparametric approach rises also from the evidence that the adoption of the LVEF as unique marker of cardiac death due to life-threatening ventricular arrhythmias is suboptimal because of its low positive predictive value.[1] Accordingly, we documented that markers of non-sustained ventricular tachycardia are different depending on the presence or absence of LV dilatation.[29] In fact necrotic and viable myocardium coexistence within the same wall segments was associated with occurrence of NSVT in patients without LV dilatation, whereas LV mass and LVESV were associated with occurrence of NSVT in those with LV dilatation.[29]

In a view of the multiparametric approach in the prognostic risk stratification domain, CMR plays a fundamental role because it is currently the gold standard method for assessing LV function, geometry, and morphology.[10,16] Furthermore, this technique is non-invasive and non-ionizing, highly reproducible,[16] and thus accurate in the follow-up of patients with ischaemic LV dysfunction.[30]

Limitation of the study

This study is affected by several limitations. The small number of events occurring during follow-up did not allow performing a multivariate analysis that includes all variables identified at univariate analysis; for this reason, we performed a model with the three CMR variables identified both at univariate analysis and after adjustment for patient age, they also showed a lower value of AIC.

Similarly, the number of patients and the events did not allow to assess the HR of cardiac events for all the possible combination among the variables LGE, EDV, and WMSI.

Further dichotomizing variables according to their median value is a *post hoc* analysis and thus the cut-points obtained cannot be applicable to other cohorts. Therefore, a larger study validating these findings is needed.

We did not explore several biohumoral parameters that are known to carry prognostic information, such as natriuretic peptides. We also did not explore the prognostic impact of a functional parameter as contractile reserve, elicited by the low-dose dobutamine stress test. However, although previous studies documented that the prognostic information provided by contractile reserve in patients with severe LV dysfunction,[26] this prognostic impact was not confirmed in a recent large clinical trial.[31] Furthermore, we did not evaluate the middle hyperenhanced zone that identifies the peri-infarcted zone, and which is associated with a higher incidence of cardiovascular events.[20] We did not include this parameter in order to be closer to the everyday situation of patients undergoing CMR for diagnostic and prognostic purposes and because the distinction between peri-infarct border zone and partial volume can be challenging at the image resolution commonly used in the clinical field.[32]

Conclusion

In patients with previous MI, the extent of scar tissue and regional wall motion abnormalities as well as the increase in LVEDV provide incremental prognostic information, which allows identifying patients at higher risk of cardiac death. The combination of clinical, biohumoral, and imaging variables in larger studies could allow generation of a multiparametric score for risk stratification of patients with previous MI.

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