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Prognostic Value of Routine Cardiac Magnetic Resonance Assessment of Left Ventricular Ejection Fraction and Myocardial Damage

An International, Multicenter Study

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Background—Cardiac magnetic resonance (CMR) is considered the reference standard for assessment of left ventricular ejection fraction (LVEF) and myocardial damage. However, few studies have evaluated the relationship between CMR findings and patient outcome, and of these, most are small and none multicenter. We performed an international, multicenter study to assess the prognostic importance of routine CMR in patients with known or suspected heart disease.

Methods and Results—From 10 centers in 6 countries, consecutive patients undergoing routine CMR assessment of LVEF and myocardial damage by cine and delayed-enhancement imaging (DE-CMR), respectively, were screened for enrollment. Clinical data, CMR protocol information, and findings were collected at all sites and submitted to the data coordinating center for verification of completeness and analysis. The primary end point was all-cause mortality. A total of 1560 patients (age, 59±14 years; 70% men) were enrolled. Mean LVEF was 45±18%, and 1049 (67%) patients had hyperenhanced tissue (HE) on DE-CMR indicative of damage. During a median follow-up time of 2.4 years (interquartile range, 1.2, 2.9 years), 176 (11.3%) patients died. Patients who died were more likely to be older ($P<0.0001$), have coronary disease ($P=0.004$), have lower LVEF ($P<0.0001$), and have more segments with HE ($P<0.0001$). In multivariable analysis, age, LVEF, and number of segments with HE were independent predictors of mortality. Among patients with near-normal LVEF (≥50%), those with above-median HE (>4 segments) had reduced survival compared to patients with below- or at-median HE ($P=0.02$).

Conclusions—Both LVEF and amount of myocardial damage as assessed by routine CMR are independent predictors of all-cause mortality. Even in patients with near-normal LVEF, significant damage identifies a cohort with a high risk for early mortality. **(*Circ Cardiovasc Imaging*. 2011;4:610-619.)**

Key Words: magnetic resonance imaging ■ ventricular ejection fraction ■ myocardial infarction ■ prognosis

Cardiac magnetic resonance (CMR) has become an important diagnostic tool in clinical practice,[1,2] which may be largely attributed to the robust implementation of cine- and delayed contrast-enhancement CMR (DE-CMR) techniques. Cine-CMR with quantitative analysis is considered the reference standard for assessment of morphology and left ventricular ejection fraction (LVEF).[3,4] LVEF is one of the most important predictors of survival in patients with coronary artery disease (CAD),[5] heart failure,[6] and cardiomyopathy.[7,8] Previous studies establishing the prognostic importance of LVEF used traditional modalities such as echocardiography,[5,7,9] radionuclide ventriculography,[6,10] and ECG-gated single-photon emission CT.[11] To date, few CMR investigations have evaluated the relation between CMR-based LVEF measurement and prognosis, and of these, none were multicenter.[12–18] The assessment of the prognostic significance of CMR-based LVEF is important because the agreement of LVEF measurements in the same patient assessed with different modalities is moderate at best.[19]

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Similarly, DE-CMR is considered the reference standard for the assessment of myocardial damage (necrosis, scar).[20,21]

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This technique offers high-spatial resolution imaging of pathophysiological processes related to myocardial infarction (MI)[22–25] or nonischemic heart disease[12,26–29] that was previously achievable only by postmortem histopathological evaluation. Given its advantages, DE-CMR increasingly is being used as a surrogate end point in clinical trials that test new therapies for acute MI.[30] However, similar to cine-CMR, of the few studies that have assessed the prognostic importance of DE-CMR, most were small, and none were multicenter. The purpose of the present study was to examine the prognostic value of a routine CMR assessment of LVEF and myocardial damage in a broad, real-life population enrolled consecutively from several centers.

Methods

Study Design

This observational, multicenter study was funded in part by Siemens Medical Solutions (Erlangen, Germany), which did not have access to the data. Data collection and analysis were independently performed at Duke University Medical Center, which served as the data coordinating center (DCC). The lead investigators had full access to the data and wrote the article without need for approval by the sponsor. The participating centers were located in the United States (3), Europe (England, 1; Germany, 3; France, 1; The Netherlands, 1), and South America (Brazil, 1). Among the 10 sites, 7 were university hospitals, and 3 were tertiary cardiovascular care centers. Institutional Review Board approval was received at each center according to local regulations. In most centers (n=8), data were collected retrospectively, and deidentified data were submitted to the DCC. Therefore, informed consent was waived by the Institutional Review Board. In 2 centers, patients were enrolled prospectively (n=646), and written informed consent was obtained from all patients.

Patients and Data Collection

An outline of patient screening, enrollment, and data collection is shown in Figure 1. At each cardiovascular MRI center, consecutive patients of either gender undergoing an MRI (either cardiac, vascular, or both) were screened. All patients who completed a routine cardiac study for assessment of both function and myocardial damage (with a complete stack of cine and DE imaging) and with at least 1 year of follow-up (unless death occurred within the follow-up period) were enrolled.

The participating centers decided a priori on the study design and a limited number of data items to be collected by each site. A standard data collection form, including demographic information, a targeted medical history, CMR protocol information and findings, and follow-up information, was completed for each patient. The medical history was obtained by review of medical records by the local study investigators and was limited to determining the presence or absence of the following: known or suspected heart disease, known or suspected CAD, and MI ≤7 days before the index CMR scan. Follow-up status was ascertained by review of medical records, interrogation of the Social Security Death Index for US sites, and physician and patient/family telephone contact. The prespecified primary end point was all-cause mortality. Hard copies of the data collection forms were stored at each study site. All data except for the patient identifiers were submitted electronically to the DCC, where their completeness was verified. All submitted patients with complete data were included in the final analysis.

Cardiac Magnetic Resonance

Imaging Protocol

Images were acquired on clinical 1.5-T Siemens scanners using phased-array receiver coils according to the routine scan protocol at each site. A typical protocol was as follows: First, localizers were acquired to identify the cardiac position and the standard long- and short-axis of the heart, and then cine images were acquired in multiple short-axis (to cover the LV from base to apex) and 3 long-axis views (2, 3, and 4 chamber) using a steady-state free-precession (SSFP) sequence.[31] For DE-CMR, an inversion-recovery

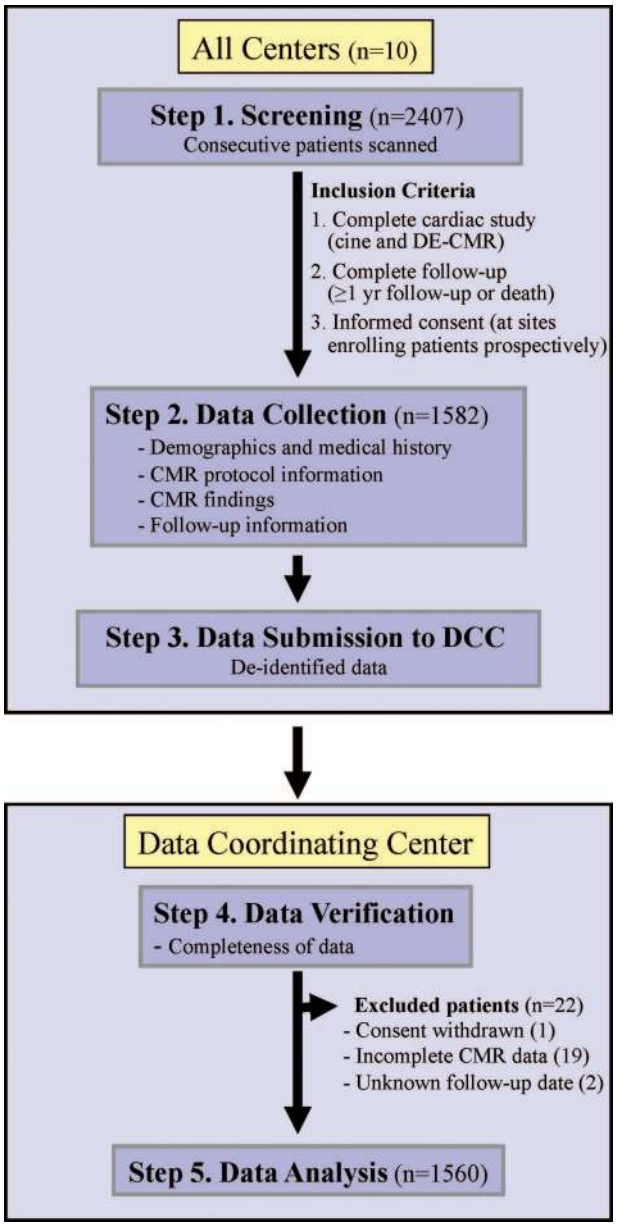

Figure 1. Outline of patient enrollment and data collection. The first 3 steps occurred at the individual participating centers and involved patient screening, data collection from enrolled patients, and data submission after deidentification. Steps 4 and 5 included data verification and analysis at the DCC. At each cardiovascular MRI center, consecutive patients of either gender undergoing an MRI (either cardiac, vascular, or both) were screened. All patients screened were subsequently enrolled unless they had only a vascular study (no cardiac imaging), had an incomplete cardiac study (eg, cine imaging without DE-CMR), did not have a full year of follow-up, or did not give informed consent (at sites enrolling patients prospectively). After submission of enrolled patient data to the DCC, 22 patients were excluded because of withdrawal of consent (n=1), incomplete CMR protocol information or CMR findings (n=19), or incomplete follow-up data (n=2). CMR indicates cardiac magnetic resonance; DCC, data coordinating center; DE, delayed enhancement.

pulse-sequence for T1 weighting was required,[32] with either an SSFP or gradient-recalled echo (GRE) data readout, and images were obtained 10 to 20 minutes after gadolinium contrast injection (0.1–0.2 mmol/kg) in the identical views as cine-CMR.

Image Analysis

The study site investigators analyzed images on locally available workstations and were blinded to follow-up data. The LVEF was determined on cine images either by planimetry of endocardial and epicardial contours in both diastole and systole or by a visual assessment providing a numeric estimate of LVEF following each site's institutional protocol (ie, following the same process used for their routine clinical interpretations). For the assessment of regional wall motion, the standard American Heart Association 17-segment model was used[33] with a 5-point scoring system (0=normal; 1=mild, moderate hypokinesis; 2=severe hypokinesis; 3=akinesis; 4=dyskinesis). To provide an estimate of the extent of regional wall motion abnormalities, a mean wall motion score was computed by summation of all scores divided by the number of segments. Similarly, the presence and location of hyperenhanced tissue (HE) on DE-CMR, which was assumed to represent irreversibly damaged myocardial tissue,[12,25] was assessed by visual inspection using the standard 17-segment model.[33] At the DCC, regional enhancement was classified according to the presence or absence of HE within each segment. Study investigators had been instructed to score HE on a 5-point scale (0=no hyperenhancement; 1=1%–25%; 2=26%–50%; 3=51%–75%; 4=76%–100%)[22]; however, after data collection, it became clear that the 5-point scale was used to index the spatial area of HE by some centers and the maximum transmurality of HE at any given point by other centers. Thus, for the purpose of data analysis performed at the DCC, the total LV amount of HE was expressed simply as the number of segments with any HE (ie, for each patient, HE score could range from 0–17).

Statistical Analysis

Continuous data are presented as mean±SD or in cases where the distribution was not normal, as median and interquartile range. Two-sample *t* tests were used to compare mean values of continuous data between 2 groups. Chi-square tests were used to compare discrete data between groups. Based on the observed median value of number of segments with HE, the study population was divided into 2 groups, and the survival of both cohorts was further analyzed according to the Kaplan–Meier method. The significance of differences in event rates between groups was assessed with the Cox regression analysis. Multivariable Cox regression analysis was performed using stepwise regression techniques, including all clinical variables (that were not collinear) and the best CMR covariates (see Table 1 for covariates) to identify the best overall model. Because the unadjusted relationship between the number of segments with HE and outcomes was nonlinear, a transformation (segments with HE^2) was implemented. The incremental prognostic value of CMR variables was examined by the change in likelihood ratio χ^2 of the model after addition of each candidate variable. To account for possible differences according to study site, it was included as a covariate in all multivariable analyses. Results were expressed as hazard ratios with associated 95% CIs. The relationships between mortality and the categories of LVEF and segments with HE were assessed using Cox regression analysis adjusted for site and age. Based on these models, predicted event rates were calculated at a fixed time point of 2 years. All statistical tests were 2 tailed, and $P<0.05$ was regarded as significant.

Results

Study Population

Patients undergoing an MRI study between September 1999 and January 2004 were screened for study enrollment at 10 centers (Figure 1). All patients screened were subsequently enrolled unless they only had a vascular study (no cardiac imaging), had an incomplete cardiac study (eg, cine imaging without DE-CMR), did not have a full year of follow-up, or did not give informed consent (at sites enrolling patients prospectively). Data on 1582 patients who met inclusion criteria were submitted to the DCC (the last data collection form was submitted in June 2006). After data submission, 22 patients were excluded because of incomplete CMR data (n=19), unknown follow-up date (n=2), or withdrawal of patient consent (n=1). Each site contributed on average 156±109 patients (range, 50–346); 925 patients were from US sites, 561 were from Europe, and 74 were from Brazil. The most frequently used pulse sequence for DE-CMR was the 2D segmented inversion-recovery GRE sequence, which was used in 1431 (92%) studies. Rarely, other pulse sequences were used, including the 2D real-time, subsecond SSFP sequence[34] in 93 (6%) studies followed by the 3D segmented GRE sequence in 22 (1.4%), 2D segmented SSFP sequence in 7 (0.4%), and the 2D subsecond GRE sequence in 6 (0.4%).

The general characteristics of the final study population comprising 1560 patients are shown in Table 1. Overall, the mean age of the group was 59.0±14.1 years. The majority (64%) had known or suspected CAD, and a few patients (n=77) had an MI within 7 days before the CMR study. The mean LVEF was relatively preserved (45±18%). The majority (71%) had at least 1 regional wall motion abnormality. HE was found in 1049 (67%) patients, and for the entire population, patients had a median of 4.0 segments with HE (interquartile range, 0, 9.0). Compared to patients without HE, patients with HE were older, more often men, and more likely to have known or suspected heart disease and CAD. They also were more likely to have a lower LVEF and a higher wall motion score. Table 1 also shows the baseline characteristics in the subgroups with and without CAD. Patients with CAD were older, had lower LVEF, and had more segments with HE than those without CAD.

Survival Analysis

The median follow-up time was 2.4 years (interquartile range, 1.2, 2.9 years), and the longest follow-up was 5.8 years. A total of 176 (11.3%) patients died during the follow-up period. The hazard ratios for all-cause mortality are shown in Table 2. Patients who died were more likely to be older ($P<0.0001$), have CAD ($P=0.004$), have lower LVEF ($P<0.0001$) and higher wall motion score ($P<0.0001$), and have more segments with HE ($P<0.0001$). In multivariable Cox regression analysis in which all candidate variables from univariable analysis were considered, age, LVEF, and the number of segments with HE were significant independent predictors of all-cause mortality. We assessed the incremental predictive value of LVEF and HE by creating 3 different models: (1) clinical parameters alone, (2) clinical+LVEF, and (3) clinical+LVEF+number of HE segments (Table 3). The addition of LVEF to clinical parameters led to a significant improvement in the predictive value of the model as reflected by the increase in global χ^2 (83.02 versus 126.01, $P<0.0001$). The addition of segments with HE resulted in further significant improvement in the model for predicting all-cause mortality as the χ^2 increased to 137.87 ($P<0.001$).

Figure 2 illustrates Kaplan–Meier survival curves (adjusted for age and study site) stratified according to the amount of HE.

Table 1. Baseline Characteristics and CMR Findings

Characteristic	Overall	HE+	HE−	*P*
All patients, n	1560	1049	511	
Age, y	59.0±14.1	61.4±12.3	53.9±16.2	<0.0001
Male sex	1086 (70)	808 (77)	278 (54)	<0.0001
Clinical history				
Known/suspected heart disease	1465 (94)	1042 (99)	423 (83)	<0.0001
Known/suspected CAD	1006 (64)	906 (86)	100 (20)	<0.0001
MI within 7 d	77 (5)	76 (7)	1 (0.2)	<0.0001
CMR				
LVEF, %	45.4±18.4	38.9±16.5	58.8±14.3	<0.0001
Any WMA	1111 (71)	982 (94)	129 (25)	<0.0001
Wall motion score	0.9 (0, 1.8)	1.4 (0.6, 2.1)	0 (0, 0.1)	<0.0001
No. of segments with HE	4.0 (0, 9.0)	7.0 (4.0, 11.0)	N/A	N/A
Patients with CAD, n	1006	906	100	
Age, y	62.7±11.5	62.3±11.5	67.0±10.4	<0.0001
Male sex	772 (77)	712 (79)	60 (60)	<0.0001
Clinical history				
MI within 7 d	77 (8)	76 (9)	1 (1)	0.01
CMR				
LVEF, %	39.3±16.6	37.7±15.7	54.0±17.2	<0.0001
Any WMA	930 (92)	879 (97)	51 (51)	<0.0001
Wall motion score	1.4 (0.6, 2.1)	1.5 (0.8, 2.1)	0.06 (0, 1.0)	<0.0001
No. of segments with HE	7.0 (4.0, 11.0)	8.0 (5.0, 11.0)	N/A	N/A
Patients without CAD, n	554	143	411	
Age, y	52.2±15.8	56.3±15.5	50.8±15.7	0.0003
Male sex	314 (57)	96 (67)	218 (53)	0.003
Clinical history				
Known/suspected heart disease	459 (83)	136 (95)	323 (79)	<0.0001
CMR				
LVEF, %	56.4±16.3	46.1±19.4	59.9±13.3	<0.0001
Any WMA	181 (33)	103 (72)	78 (19)	<0.0001
Wall motion score	0.0 (0, 0.2)	0.4 (0, 1.5)	0 (0, 0.0)	<0.0001
No. of segments with HE	0.0 (0, 1.0)	4.0 (2.0, 8.0)	N/A	N/A

Data are presented as mean±SD, n (%), or median (interquartile range), unless otherwise indicated. CAD indicates coronary artery disease; CMR, cardiovascular magnetic resonance; HE+, patients with hyperenhanced tissue on delayed-enhancement CMR; HE−, patients without hyperenhanced tissue on delayed-enhancement CMR; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; WMA, wall motion abnormality.

Patients with above-median (>4 segments) HE had significantly reduced survival compared to patients with below- or at-median (≤4 segments) HE ($P<0.002$) (Figure 2A). When only patients with near-normal LVEF (≥50%) were considered, again, patients with above-median HE had reduced survival compared to patients with less HE ($P=0.02$) (Figure 2B).

Given that LVEF was determined by planimetry (n=1022; mean, 44.1±18.7%) or estimated visually (n=538; mean, 47.9±17.2%) following each site's institutional protocol, these subgroups were further evaluated separately. Cox regression analysis showed that the hazard ratio for mortality by planimetered LVEF (0.965) was nearly identical to that by visual estimation (0.964) and to the population as a whole (0.964). Multivariable analysis demonstrated that in the subgroup with LVEF determined by planimetry, the same variables were associated with mortality as in the entire population (Table 2).

Figure 3A details the relationship between categories of LVEF and all-cause mortality. To account for possible differences in follow-up time among categories, mortality rates were calculated for a fixed time point of 2 years for this analysis. For each decrement in LVEF, there was a steadily increasing event rate ($P<0.0001$). Likewise, Figure 3B demonstrates that increasing number of segments with HE was associated with higher mortality rates ($P<0.0001$). However, the relationship was slightly different from LVEF in that mortality rates appeared to be similar in groups with ≤4 segments with HE.

In the cohort of patients with known or suspected CAD (n=1006), again, age, LVEF, and number of segments with

Table 2. HRs for All-Cause Mortality in All Patients and Patients With LVEF as Determined by Planimetry

	All-Cause Mortality			
	Univariable		Multivariable*†	
Characteristic	HR (95% CI)	*P*	HR (95% CI)	*P*
All patients (n=1560)				
Clinical				
Male sex	1.08 (0.78–1.51)	0.64	0.88 (0.62–1.24)	0.45
Age, y	1.03 (1.02–1.05)	<0.0001	1.03 (1.02–1.04)	<0.0001
Known/suspected heart disease	2.84 (0.90–8.89)	0.07	1.21 (0.37–3.96)	0.75
Known/suspected CAD	1.71 (1.18–2.47)	0.004	…	…
MI within 7 d	0.63 (0.29–1.35)	0.23	…	…
CMR				
LVEF, %	0.96 (0.95–0.97)	<0.0001	0.98 (0.96–0.99)	<0.0001
Any WMA	2.54 (1.60–4.02)	0.0001	…	…
Wall motion score	1.89 (1.60–2.24)	<0.0001	…	…
Any HE on DE-CMR	1.69 (1.16–2.46)	0.007	…	…
No. of segments with HE	1.007 (1.005–1.009)	<0.0001	1.004 (1.002–1.006)	0.0005
Patients with LVEF by planimetry (n=1022)				
Clinical				
Male sex	1.21 (0.79–1.85)	0.39	0.97 (0.63–1.49)	0.89
Age, y	1.04 (1.02–1.05)	<0.0001	1.03 (1.01–1.05)	0.0003
Known/suspected heart disease	3.53 (0.49–25,33)	0.21	1.26 (0.17–9.44)	0.82
Known/suspected CAD	1.48 (0.89–2.45)	0.13	…	…
MI within 7 d	0.34 (0.08–1.38)	0.13	…	…
CMR				
LVEF, %	0.97 (0.95–0.98)	<0.0001	0.98 (0.96–0.99)	0.002
Any WMA	2.70 (1.39–5.35)	0.004	…	…
Wall motion score	1.88 (1.50–2.35)	<0.0001	…	…
Any HE on DE-CMR	1.54 (0.93–2.56)	0.09	…	…
No. of segments with HE	1.007 (1.005–1.009)	<0.0001	1.004 (1.002–1.007)	0.001

DE indicates delayed enhancement; HR, hazard ratio. Other abbreviations as in Table 1.
*Multivariable analysis adjusted for study site.
†Collinear variables were not included in the multivariable analyses.

HE were significant independent predictors of all-cause mortality (Table 4). In patients without CAD, age and LVEF were independent predictors of mortality. Although the number of segments with HE did not reach statistical significance, the cohort without CAD comprised a smaller population (n=554), and the hazard ratios for all 3 variables (LVEF, age, and number of segments with HE) were nearly identical to the cohort with CAD, suggesting a similar risk for death related to these parameters in both groups.

Table 3. Incremental Prognostic Value of LVEF and Number of Segments With HE (All Patients)*

	All-Cause Mortality		
Model	Model χ^2	Change in χ^2	*P*
Clinical	83.02	…	…
Clinical with LVEF	126.01	42.99	<0.0001
Clinical with LVEF and No. of segments with HE	137.87	11.86	<0.001

Abbreviations as in Table 1.
*All models were adjusted for study site.

Discussion

Recent advances in CMR technology allow a robust, highly accurate, and reproducible assessment of cardiac function and myocardial damage within the same examination. Thus, CMR has become an important noninvasive test for assessment of cardiac patients in clinical routine.[35] Published studies indicate that CMR for detection of MI is accurate[36] and provides results equal or superior to radionuclide imaging.[23,37] Additionally, CMR is increasingly used for the evaluation of nonischemic cardiomyopathies and offers unique diagnostic information on the underlying etiology.[38] However, despite the diagnostic utility, few studies have assessed the prognostic importance of findings on a routine CMR examination. To our knowledge, the current study is the largest as well as the first multicenter investigation to evaluate the prognostic significance of LVEF and myocardial damage as determined by CMR.

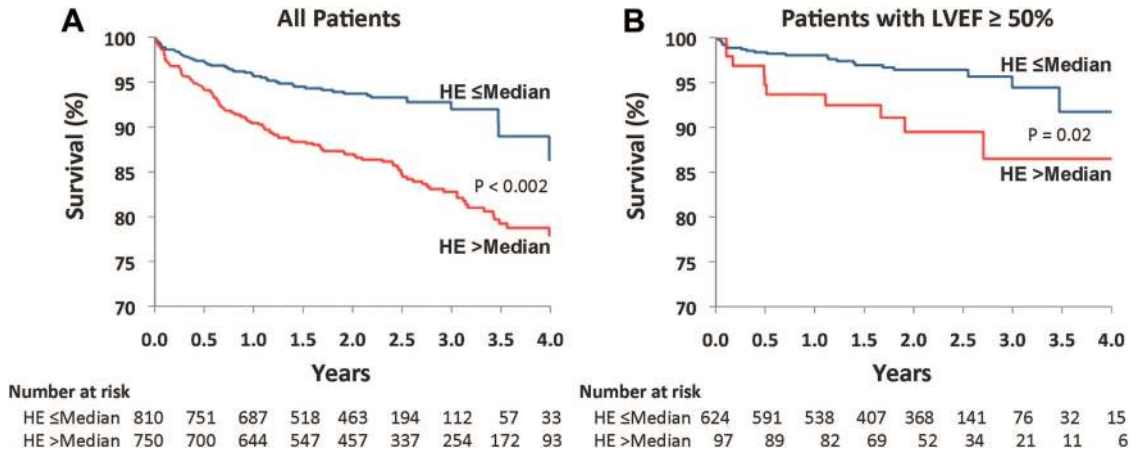

Figure 2. Kaplan–Meier estimates of survival. Survival curves in all patients (**A**) and in patients with LVEF ≥50% (**B**) stratified according to the amount of HE (adjusted for age and study site). In both the entire group and the patients with near-normal LVEF, those with above-median HE (>4 segments) had reduced survival compared with patients with below- or at-median HE (≤4 segments). HE indicates hyperenhanced tissue; LVEF, left ventricular ejection fraction.

Several studies have established that LVEF is a strong predictor of adverse outcome in various patient cohorts.[5,6,8] Previous investigations ascertaining the prognostic importance of LVEF used established imaging modalities, such as echocardiography,[5,7,9,39] radionuclide ventriculography,[6,10] and ECG-gated single-photon emission CT,[11] and generally included large numbers of patients. Among the largest studies investigating the prognostic value of LVEF determined by ECG-gated single-photon emission CT was that by Travin et al[11] of 3207 patients. Using echocardiography, Gottdiener et al[39] investigated the relationship of LVEF and mortality in 5532 patients, whereas Zaret et al[10] included 3197 patients in whom LVEF was measured with radionuclide ventriculography. Curtis et al[6] investigated the relationship between LVEF measurements by echocardiography and radionuclide or contrast ventriculography and mortality in 7788 patients. Although CMR allows the determination of LVEF with superior precision and reproducibility, agreement of LVEF measurements among different modalities used in the same patient is moderate at best.[19] Therefore, the relationship between CMR-determined LVEF and mortality requires separate evaluation. To date, the largest published CMR studies evaluating prognosis were single-center investigations involving 513 patients[40] and 857 patients.[16] The present multicenter study in 1560 patients corroborates those previous reports in that CMR-determined LVEF was found to be an important predictor of adverse outcome.

Additionally, the current results suggest that the association between LVEF and mortality holds across the full spectrum of LVEF. This is in contrast to some studies where higher LVEF values were associated with a linear decrease in mortality up to an LVEF of 45%, but further increases in LVEF above this point were not associated with further reductions in mortality.[6] The possible difference in findings may be due to dissimilarities in the patient population. In the current study, a broad spectrum of patients with known or suspected heart disease presenting for routine CMR imaging were included, and there was a nearly 5-fold difference in mortality between patients in the lowest and highest LVEF groups. In the investigation by Curtis et al,[6] enrollment was restricted to stable outpatients given a clinical diagnosis of heart failure, and there was only a 2.2-fold relative difference

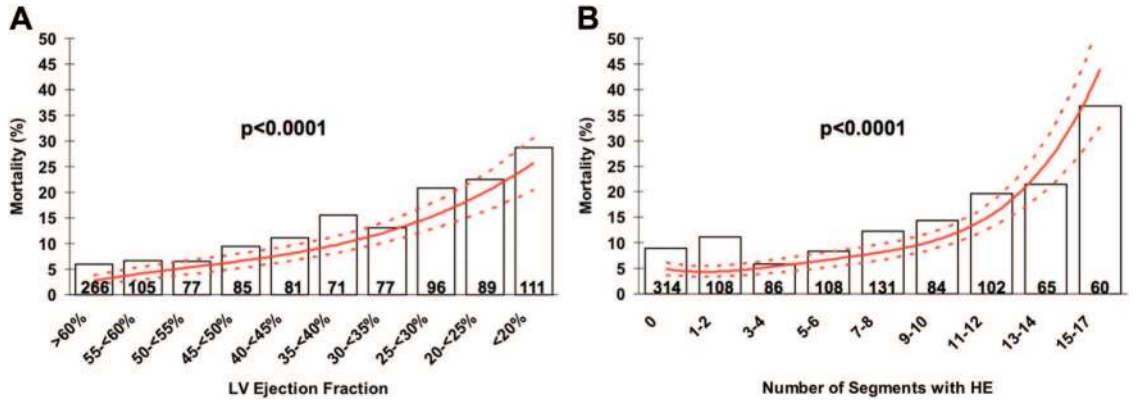

Figure 3. Mortality rate as a function of LVEF and amount of myocardial damage. The height of the bar and the number within represent the observed mortality rate at 2 years and total number of subjects for each category of LVEF (**A**) and HE (**B**). Solid lines represent Cox regression estimates (smoothed) of 2-year mortality adjusted for age and study site. Dashed lines represent 95% CIs. With each decrement in LVEF, there was a steadily increasing mortality rate. Likewise, increasing number of segments with HE was associated with higher mortality rates, although rates appeared to be similar in groups with ≤4 segments of HE. Abbreviations as in Figure 2.

Table 4. HRs for All-Cause Mortality in Subgroups

	All-Cause Mortality			
	Univariable		Multivariable*†	
Characteristic	HR (95% CI)	*P*	HR (95% CI)	*P*
Patients with CAD (n=1006)				
Clinical				
Male sex	0.91 (0.62–1.33)	0.62	0.83 (0.56–1.23)	0.35
Age, y	1.04 (1.02–1.05)	<0.0001	1.03 (1.02–1.05)	<0.0001
MI within 7 d	0.55 (0.26–1.18)	0.13	…	…
CMR				
LVEF, %	0.96 (0.95–0.97)	<0.0001	0.97 (0.96–0.99)	0.0003
Any WMA	1.90 (0.78–4.66)	0.16	…	…
Wall motion score	1.98 (1.57–2.48)	<0.0001	…	…
Any HE on DE-CMR	1.03 (0.57–1.86)	0.93	…	…
No. segments with HE	1.007 (1.005–1.009)	<0.0001	1.005 (1.002–1.007)	<0.0001
Patients without CAD (n=554)				
Clinical				
Male sex	1.19 (0.61–2.32)	0.62	0.97 (0.48–1.97)	0.93
Age, y	1.02 (1.00–1.05)	0.03	1.02 (1.00–1.05)	0.047
CMR				
LVEF, %	0.97 (0.96–0.99)	0.001	0.97 (0.96–0.99)	0.01
Any WMA	2.55 (1.32–4.95)	0.006	…	…
Wall motion score	1.78 (1.27–2.49)	0.0009	…	…
Any HE on DE-CMR	1.93 (0.99–3.75)	0.052	…	…
No. segments with HE	1.007 (1.003–1.012)	0.002	1.003 (0.997–1.009)	0.29

Abbreviations as in Tables 1 and 2.
*Multivariable analysis adjusted for study site.
†Collinear variables were not included in the multivariable analysis.

in mortality rates. Moreover, in the study by Curtis et al, neither the technique (echocardiography, equilibrium radionuclide angiography, or contrast ventriculography was used) nor interpretation of LVEF measurement was standardized.

In addition to the accurate assessment of LVEF, CMR provides high-resolution images of irreversible myocardial damage.[12,27,41] Of the studies that have assessed the prognostic importance of CMR-identified myocardial damage,[12,13,15,42–44] none were multicenter, and in most, the primary end point was a composite, including "softer" events such as hospitalizations, occurrence of arrhythmias, and MI.[12,18,42] Only a few studies used all-cause mortality as a primary end point. Yan et al[15] demonstrated in 144 patients with prior MI that certain infarct characteristics (ie, extent of periinfarct zone) on DE-CMR predicted all-cause mortality independent of age and LVEF. Kim et al[17] studied patients with suspected CAD and without a history of clinical MI. The presence of unrecognized non-Q-wave MI on DE-CMR was associated with an 11-fold higher mortality rate. In the largest study to date assessing the prognostic significance of DE-CMR, Cheong et al[16] evaluated 857 patients from a tertiary-care center and demonstrated that a myocardial scar index independently predicted all-cause mortality or cardiac transplantation. The results of the present multicenter study are consistent with these prior investigations. Moreover, similar to the study by Cheong et al, we found that even in patients with near-normal LVEF (≥50%) the presence of substantial myocardial damage identifies a cohort with increased risk for all-cause mortality. Thus, CMR may be a useful risk stratification tool in patients generally considered to be at low risk based on LVEF criteria.

Several possible mechanisms have been proposed in linking myocardial damage and increased mortality. Experimental studies have shown that abnormal conduction properties within or surrounding myocardial scar are critical for reentry circuits to form, which are believed to be an important electrophysiological substrate for ventricular tachyarrhythmias[45–47] and sudden cardiac death.[48] Initial studies have shown that DE-CMR may be helpful in identifying patients at risk for ventricular tachycardia among those with prior infarcts[43,44] as well as nonischemic cardiomyopathy.[12,13] These investigations suggest a potential role of DE-CMR in risk stratification for cardiac arrhythmias and sudden death as well as for selection of patients for implantable cardioverter-defibrillator therapy.

Limitations

Enrollment was prospective in 2 centers and retrospective in 8. Clinical variables such as the presence of CAD were obtained by review of medical records by local site investigators but did not require specific test results to be submitted to the DCC. The findings on routine CMR were not compared

to a comprehensive list of traditional clinical risk factors known to be associated with adverse outcome because data collection was limited to a few prespecified variables. Likewise, we do not have quantitative measures of cardiac morphology, such as LV end-diastolic and end-systolic volumes. However, we demonstrated in a relatively large study population that myocardial hyperenhancement (indicating damage) has prognostic importance independent of LVEF, which is believed to be one of the strongest and most robust predictors of mortality. We did not ascertain the cause of death, and the primary end point was chosen to be all-cause rather than cardiac mortality. However, many believe that the most appropriate end point is total mortality (recommended by a policy statement written by the North American Society for Pacing and Electrophysiology[49]) because it is objective, clinically relevant, and unbiased, which often is not the case for cardiac mortality.[50] We did not collect data regarding the clinical indications for CMR, which limits our ability to generalize the findings to other cohorts. However, patients were consecutively enrolled from 10 busy CMR centers across Europe, the United States, and Brazil; the inclusion criteria (Figure 1) were broad; and the sample size was relatively large. Hence, we believe that the patient cohort is likely to be reflective of the current real-life clinical practice of CMR. On this issue, it is informative that a recent multicenter study (using many of the same CMR centers as the present study) reported the most common indications for CMR were evaluation of cardiomyopathy/myocarditis (32%), risk stratification in suspected coronary disease (31%), and assessment of viability (15%).[35] In one third of patients, LVEF was assessed visually. However, because the same process used for routine clinical interpretations was followed at each site, this again reflects the real-life clinical practice of CMR. Moreover, the results (Figure 3A) clearly demonstrate a steadily increasing event rate with each decrement in LVEF, suggesting that the main conclusions would not be substantially changed if all studies had been assessed quantitatively. The presence and extent of HE was interpreted qualitatively by different readers at each site. Although all sites used a standard 17-segment and 5-point scoring model,[36] we found that some centers scored hyperenhancement based on the maximum transmural extent at any given point in the segment rather than the area of hyperenhancement within the segment. This precluded calculating the amount of HE as a percentage of LV mass as described previously,[17] and the absolute inflection point at which an increase in mortality risk occurs could not be accurately determined in this study. However, the principal relationship between HE and mortality could be established. We did not differentiate CAD-type hyperenhancement from other non-CAD-type patterns. Although both have been shown to be associated with adverse events, there may be differences in the prognostic importance between damaged tissue from MI or nonischemic heart diseases. Similarly, although our results demonstrate that lower LVEF (compared with higher LVEF) and more HE (compared with less HE) portend worse prognosis, one should not assume that LVEF or hyperenhancement has a uniform effect on mortality across the cardiac disorders included in the current broad population. Finally, there could be a potential bias in the estimated mortality rates because patients were not censored during year 1 except for those who died.

Conclusions

In patients undergoing a routine CMR study, including cine and delayed-enhancement imaging, both LVEF and the amount of myocardial tissue damage are independent predictors of all-cause mortality. Furthermore, even in patients with near-normal LVEF who generally are considered to be at low risk, significant myocardial damage identified a cohort with significantly worse prognosis. These findings warrant future studies to investigate the role of CMR in clinical management decisions based on risk stratification.

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Disclosures

Dr Pennell is a consultant to Siemens. Drs Judd and Kim are inventors with a US patent on delayed-enhancement MRI, which is owned by Northwestern University.

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CLINICAL PERSPECTIVE

Cardiac magnetic resonance (CMR) is considered the reference standard for assessment of left ventricular ejection fraction (LVEF) and myocardial damage. However, few studies have evaluated the relationship between CMR findings and patient outcome, and of these, most are small and none multicenter. We performed an international, multicenter study to assess the prognostic importance of routine CMR in patients with known or suspected heart disease. Consecutive patients from 10 centers in 6 countries who underwent routine CMR assessment of LVEF and myocardial damage by cine- and delayed-enhancement CMR, respectively, were screened. A total of 1560 patients were enrolled (age, 59±14 years; 70% men). Mean LVEF was 45±18%, and 1049 (67%) patients had hyperenhanced tissue on delayed-enhancement CMR indicative of damage. During a median follow-up time of 2.4 years, 176 (11.3%) patients died. Patients who died were more likely to be older, have coronary artery disease, have lower LVEF, and have more segments with hyperenhanced tissue. In multivariable analysis, age, LVEF, and number of segments with hyperenhanced tissue were independent predictors of mortality. The number of segments with hyperenhanced tissue provided incremental prognostic value beyond clinical data and LVEF. Even in patients with near-normal LVEF, significant damage identifies a cohort at high risk for early mortality. In this study, we demonstrated that in a large population from several CMR centers, unique CMR information on myocardial damage from ischemic and nonischemic etiologies provides independent and incremental prognostic value.