Value of Early Cardiovascular Magnetic Resonance for the Prediction of Adverse Arrhythmic Cardiac Events After a First Noncomplicated ST-Segment–Elevation Myocardial Infarction

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Background—Infarct size (IS) determined by cardiac magnetic resonance (CMR) has proven an additional value, on top of left ventricular ejection fraction (LVEF), in prediction of adverse arrhythmic cardiac events (AACEs) in chronic ischemic heart disease. Its value soon after an acute ST-segment–elevation myocardial infarction remains unknown. Our aim was to determine whether early CMR can improve AACE risk prediction after acute ST-segment–elevation myocardial infarction.

Methods and Results—Patients admitted for a first noncomplicated ST-segment–elevation myocardial infarction were prospectively followed up. A total of 440 patients were included. All of them underwent CMR 1 week after admission. CMR-derived LVEF and IS (grams per meter squared) were quantified. AACEs included postdischarge sudden death, sustained ventricular tachycardia, and ventricular fibrillation either documented on ECG or recorded via an implantable cardioverter-defibrillator. Within a median follow-up of 2 years, 11 AACEs (2.5%) were detected: 5 sudden deaths (1.1%) and 6 spontaneous ventricular tachycardia/ventricular fibrillation. In the whole group, AACEs associated with more depressed LVEF (adjusted hazard ratio [95% confidence interval], 0.90 [0.83–0.97]; \( P \leq 0.01 \)) and larger IS (adjusted hazard ratio [95% confidence interval], 1.06 [1.01–1.12]; \( P \leq 0.01 \)). According to the corresponding area under the receiver operating characteristic curve, LVEF \( \leq 36\% \) and IS \( \geq 23.5 \text{ g/m}^2 \) best predicted AACEs. The vast majority of AACEs (10/11) occurred in patients with simultaneous depressed LVEF \( \leq 36\% \) and IS \( \geq 23.5 \text{ g/m}^2 \) (n=39).

Conclusions—In the era of reperfusion therapies, occurrence of AACEs in patients with an in-hospital noncomplicated first ST-segment–elevation myocardial infarction is low. In this setting, assessment of an early CMR-derived IS could be useful for further optimization of AACE risk prediction.

Key Words: cardiac arrhythmias • magnetic resonance imaging • myocardial infarction

Sudden cardiac death caused by ventricular arrhythmias is a catastrophic complication after myocardial infarction, and it occurs more frequently in the first year after the ischemic event.\(^1,2\) In both, prethrombolytic and post-thrombolytic era, reduced left ventricular ejection fraction (LVEF) is a major risk factor for sudden and nonsudden death. Several randomized trials have shown that an implantable cardioverter-defibrillator (ICD) can reduce mortality among patients with chronic ischemic heart disease and depressed LVEF.\(^3,4\) Surprisingly, 2 studies have failed to demonstrate benefit of ICDs when they are implanted early (<1 month) after the ischemic event, despite the fact that the risk of sudden death seems to be highest soon after the infarction.\(^5,6\) Therefore, a suitable method for selecting patients who may benefit from an ICD, especially early after an acute myocardial infarction, would add value to the risk stratification process.

Clinical Perspective on p 761

Many studies have proved that the infarct size (IS) assessed by cardiac magnetic resonance (CMR), performed in patients in a chronic stage of their ischemic disease, is an independent predictor of appropriate ICD discharge and inducibility of ventricular tachycardia (VT) in an electrophysiological study.\(^7,11\)

Our aims were both to evaluate the outcome in terms of adverse arrhythmic cardiac events (AACEs) of patients with
a first noncomplicated ST-segment–elevation myocardial infarction (STEMI) in the revascularization era and determine whether the assessment of IS in an early CMR would improve the risk stratification soon after the first, acute episode of a noncomplicated STEMI.

Methods

Study Group
We prospectively studied 529 consecutive patients admitted to our institution with a reperfused STEMI from November 2001 to September 2012. Patients admitted for a first noncomplicated STEMI, without contraindication to CMR imaging were included. We excluded patients with a previous STEMI (n=7), those with chronic ischemic cardiac disease with known impaired LVEF (n=8), in order to avoid Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)-like patients, and those in whom a CMR could not be performed (n=74) for different reasons detailed in the flowchart (Figure 1). Therefore, the final study group comprised 440 patients. Baseline characteristics and clinical data were prospectively recorded in all cases. All patients gave written informed consent, and the research protocol was approved by the appropriate review boards.

Follow-up was centrally updated every 6 months by 2 cardiologists and 2 trained nurses from at least 1 of 3 sources: (1) the outpatient clinic; (2) a telephone interview with the patient or his/her family, or (3) review of the patient’s hospital record.

Cardiac Catheterization

The reperfusion strategy was left to the discretion of the attending cardiologists: 180 (40.9%) underwent primary percutaneous revascularization and 208 (47.3%) patients were treated with thrombolysis. In the thrombolysis group, cardiac catheterization was performed in all cases: 58 (13.2%) at rescue angioplasty and 150 (34%) patients at a routine angiography (2±1 days after STEMI). Time from pain onset to reperfusion was recorded. In 52 (11.8%) patients, an early revascularization therapy was not performed because they were assisted with a delay of >12 hours from the beginning of symptoms; in those cases, a routine angiography (2±1 days after STEMI) was performed. Thrombolysis in myocardial infarction flow grade, myocardial blush grade, and angiographic data were evaluated in a core laboratory in all cases.

CMR Protocol

We performed CMR (1.5-T scanner, Sonata Magnetom, Siemens, Erlangen, Germany) at 7±2 days after STEMI. CMR was performed on the basis of an ongoing registry focused on the analysis of the structural consequences of STEMI. Images were acquired by a phased-array body surface coil during breath hold and were ECG triggered.

Cine images (true fast imaging with steady-state precession; repetitions time/echo time: 3.2/1.6 ms; flip angle: 61°; matrix: 256x256; slice thickness: 6 mm; temporal resolution: 26 ms; retrospective acquisition) were acquired at rest in 2-, 3-, and 4-chamber views and every 1 cm in short-axis views.

Late enhancement imaging was performed in the same projections used for cine images to cover the entire left ventricle ≥10 minutes after contrast administration. A segmented inversion recovery imaging with gradient echo sequence was used (repetition time/echo time: 2.5/1.1 ms; slice thickness: 6 mm; flip angle: 50°; matrix: 256x192) nullifying myocardial signal.

CMR studies were analyzed by an experienced observer blinded to all study data, using customized software (QMass MR 6.1.5, Medis, Leiden, the Netherlands). LV mass, LVEF (%), and volumes (milliliters per meter squared) were quantified by manual definition of endocardial and epicardial borders of all short-axis slices in cine images. The endocardial and epicardial borders were traced manually in late enhancement imaging, on each slice.

Microvascular obstruction (MO), defined as a hypointensity within an hyperintense region, was manually planimetered. To avoid artifacts, the presence of MO had to be confirmed both in short- and long-axis views.

Infarcted tissue was quantified in a semiautomatic manner that included manual revision and correction in all cases applying the following sequence: (1) In a first step, the presence of infarcted tissue was considered in the case of a signal intensity >2 SD with respect to a remote noninfarcted area in late gadolinium enhancement imaging; (2) Second, MO was manually included in the total IS; (3) Third, any obvious blood pool or pericardial partial voluming and artifacts were removed from the IS; (4) Finally, these regions, the total infarct area, and MO were quantified using a semiautomated algorithm. IS (absolute value in grams per meter squared) was determined and also calculated as a percentage of LV mass (IS%). MO was calculated as a percentage of the LV mass.

ICD Implantation and Programming

ICDs were implanted for secondary prevention or following MADIT criteria for primary prevention, according to treating physician’s criteria and never using the results of this early CMR. During follow-up, 17 patients received an ICD: 4 patients for secondary prevention and 13 patients for primary prevention. The median time to ICD implantation for primary prevention was 36 (interquartile range, 18–55) weeks. An empirical uniform programming was performed: 3 detection rate zones were set up, with cutoffs at 160, 200, and 250 bpm. The detection time in the slowest zone was programmed to 30 s, for the fast VT zone it was 5 s, and for the ventricular fibrillation (VF) zone, 2.5 s. Patients with ICDs were reviewed at 6-month intervals by an electrophysiologist blinded to clinical data and CMR. Stored electrograms of sustained, treated VT episodes (either with antitachycardia pacing or shocks) were reviewed and classified as either inappropriate or appropriate. The type of ventricular arrhythmia: VT or VF, heart rate, and symptoms during the episode were also collected.

End Points

The primary end point of the study was the occurrence of an AACE after 48 hours of the STEMI that might not be attributed to recurrent ischemia. AACEs included sudden death, sustained VT, and VF either registered in an ECG or recorded in the ICD.

Documentation of the cause of death was based on information obtained from witnesses, family members, death certificates, and hospital records when available. A death out of the hospital was assumed to be a sudden cardiac death if it occurred within minutes after the onset of acute symptoms or was not witnessed and occurred unexpectedly and without recognizable causes (eg, during sleep).

The secondary end point was mortality of any cause.
Statistical Analysis
Continuous, normally distributed data (Kolmogorov–Smirnov test) were expressed as the mean±SD. Data not having a normal distribution were expressed as the median and the interquartile range. Comparison of categorical variables was performed using the χ² or Fisher exact tests, and continuous variables were compared using the Mann–Whitney U test.

To assess the dependence between IS and AACE, 2 Cox regression analyses were performed, one including LVEF and IS as continuous variables and another using them as dichotomized categorical variables. IS was included alternatively as the absolute value in grams per meter squared and as a percent of the ventricular mass (IS%). Candidate covariates were chosen according to their P value <0.15 in univariate analysis and based on previous medical knowledge, independent of their P value. Then, a model was derived by using backward step-down selection. The discriminative ability of the models was assessed by Harrell C-statistic.

To create a risk score, continuous variables LVEF and IS were dichotomized according to cutoff values established on the basis of their area under characteristic curves (AUCs) for predicting AACEs. Survival functions were estimated by Kaplan–Meier analysis, and differences between strata were assessed by log-rank test. Statistical significance was considered for 2-tailed P value <0.05. SPSS version 13.0 (SPSS Inc, Chicago, IL) and STATA 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) were used.

Results
During follow-up (median, 123 weeks; interquartile range, 25–190), 11 AACEs (2.5%) were documented, including 5 (1.1%) SD, 1 case of cardiac arrest in relation to VF with subsequent resuscitation, 3 cases of sustained VT before ICD implantation, and 2 cases of ICD appropriate therapy (1 VT, 160 bpm, treated with 5 antitachycardia pacing sequences and 1 fast, syncopal VT, 250 bpm, directly treated with electric shock).

Univariate Analysis
Baseline characteristics, angiographic parameters, and CMR imaging characteristics results in the study population and their association with AACEs are displayed in Table 1. With regard to CMR parameters, AACEs were associated in the univariate analysis with a lower LVEF, a larger MO area, larger LV volumes, and a larger infarct mass (Table 1).

Multivariate Analysis
In a separate multivariate modeling approach, LVEF (hazard ratio [95% confidence interval], 0.9 [0.83–0.97] per each unit increase, \( P < 0.01 \)) and IS (grams per meter squared) (hazard ratio [95% confidence interval], 1.06 [1.02–1.11] per each unit increase, \( P = 0.01 \)) remained as independent predictors of AACEs. Harrell C index and calibration of the final multivariate model were 0.93 and 0.38, respectively (Table 2).

On the basis of AUCs, LVEF ≤36% (AUC: 0.91 [0.83–0.99]; \( P < 0.01 \)) and IS ≥23.5 g/m² (AUC: 0.88 [0.76–1.00]; \( P < 0.01 \)) or IS% ≥31% (AUC: 0.87 [0.75–0.99]; \( P < 0.01 \)) best predicted AACEs. Groups according to LVEF and IS showed different AACEs incidence. The vast majority of AACEs (10/11 events) occurred in patients with simultaneous LVEF ≤36% and IS ≥23.5 g/m² or IS% ≥31% (Figure 2).

Total Mortality
During follow-up, 17 (3.9%) patients died; of those, 5 (1.1%) were classified as sudden death and 6 (1.4%) as nonsudden cardiac death. Total mortality in patients with LVEF ≤36% and IS ≥23.5 g/m² was 20.5% (8/39 patients). In the subgroup of patients with LVEF ≤36% and IS <23.5 g/m², only 1 patient died because of a nonsudden cardiac death. Among those with LVEF >36% and IS ≥23.5 g/m², no deaths were registered; and finally, in the subgroup with LVEF >36% and IS <23.5 g/m², 8 (2.4%) patients died, 3 (0.9%) because of a nonsudden cardiac death and 1 (0.3%) because of a sudden unexpected death occurred during sleep. Survival curves are shown in Figure 3.

Discussion
Our main findings are that mortality and AACE after a first uncomplicated STEMI in the era of reperfusion therapies are extremely low, and IS assessed by an early CMR could add information to LVEF for AACE risk prediction.

Risk Prediction After Myocardial Infarction
Most recent studies have shown that nowadays mortality and sudden death after myocardial infarction are lower than in the prethrombolytic era. Reperfusion therapies, along with the extended use of drugs such as β-blockers and angiotensin converting enzyme inhibitors, have contributed to this better prognosis. In our series, prognosis after a first uncomplicated STEMI (mortality 2% per year and AACE rate of 0.5% per year) is even better than that observed in some registries. It probably reflects not only a population of low-risk patients, as is suggested by a mean LVEF of 51.5%, but also a definite improvement in prognosis as a result of an active reperfusion strategy.

LVEF is the most consistently reported risk predictor of sudden and nonsudden death after myocardial infarction. Randomized trials have shown that an ICD implantation can reduce mortality among patients with chronic ischemic heart disease and depressed LVEF. Therefore, low LVEF is widely used to recommend ICD implantation as primary prevention of sudden death in patients with chronic ischemic heart disease. Results of MADIT II trials suggest that =18 patients with ventricular dysfunction need to have an ICD implanted to prevent 1 death. Considering the cost and the potential complications of ICDs, many efforts have been made to improve risk stratification for sudden death with noninvasive tests, but the optimal way to combine and use these techniques in clinical practice remains unclear.

Predictive Value of CMR-Derived Myocardial Scar
In recent years, the use of CMR in assessing myocardial scar among myocardial infarction survivors to predict arrhythmic events has been explored. These studies included mainly patients with chronic ischemic disease who were referred for an ICD implantation or underwent CMR performance for different reasons but not in the context of acute STEMI. To the best of our knowledge, this study is the first to demonstrate the usefulness of IS, in terms of AACEs prediction, in patients with a very recent first STEMI.

In our series, implementing the scar size in an early post-STEMI patient evaluation might add a prognostic extra value to LVEF assessment. It could be explained by different
reasons: first, LVEF has a dynamic behavior after STEMI, and the extent of the scar has been demonstrated to help for predicting the absence of late systolic function recovery\textsuperscript{12,13}; second, a big scar predicts inducibility of VT in an electrophysiological study,\textsuperscript{11} and it has been related to the appearance of electric instability\textsuperscript{19} and, more importantly, to adverse

Table 2. Independent Predictors of AACEs in the Study Group

<table>
<thead>
<tr>
<th>Cox Models</th>
<th>Unadjusted Hazard Ratio</th>
<th>Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.89 (0.84–0.93)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Scar size, % of LV mass</td>
<td>1.09 (1.05–1.14)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Scar mass, g/m\textsuperscript{2}</td>
<td>1.11 (1.07–1.15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.44 (0.91–13.00)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

AACEs indicates adverse arrhythmic cardiovascular events; CI, confidence interval; HR, hazard ratio; LV, left ventricle; and LVEF, Left ventricular ejection fraction.
ventricular remodeling\textsuperscript{14} that seems to be necessary for the development of slow conduction and VT substrate.\textsuperscript{20} Some studies\textsuperscript{7,8} performed in patients with chronic ischemic disease found that scar's heterogeneity or the so-called gray zone best predicted arrhythmic events. We preferred using total scar mass for many reasons: First, in the context of an acute STEMI, edema and MO are frequent findings in an early CMR that make it difficult to assess tissue heterogeneity. Second, calculation of the IS is a more standard procedure than calculation of the gray zone, whose definition and way to determine has not been fully standardized. Finally, as stated before, the potential explanation of why a big early scar would predict AACEs seems more complex than that given for a chronic scar, where assessment of the heterogeneity may play an important role.

**Figure 2.** Number of adverse arrhythmic cardiovascular events (AACEs) according to left ventricular ejection fraction (LVEF) and infarct size (IS).

**Figure 3.** Survival according to left ventricular ejection fraction (LVEF) and infarct size (IS).

**Early Prediction of AACEs**

As already mentioned, MADIT II and Multicenter Unsustained Tachycardia Trial (MUSTT) studies included patients with chronic ischemic disease: the average times from the infarction to LVEF assessment and enrollment were 81 months in MADIT II and 39 months in MUSTT. Despite the fact that the period of highest risk of SD is considered to be the first year after myocardial infarction,\textsuperscript{1} \geq 2 randomized studies have failed to provide support for the use of ICD therapy in patients with depressed LVEF early after myocardial infarction.\textsuperscript{5,6} Although the reason of this failure remains unresolved, some theories have been proposed. One of the potential reasons might be that those studies were statistically underpowered to demonstrate a clinically important difference between groups. In fact, in those studies the rate of 1-year mortality ranges between 5.0\% and 7.6\%.\textsuperscript{5,6} This contrasts with the total mortality of 11\% in the control group of MADIT II.\textsuperscript{4} In our study, the selection of high-risk patient based on not only LVEF, but also IS showed 1-year mortality rate of 12\%, similar to that of MADIT II. It also seems reasonable to conclude that the markers used to stratify patients in these studies do not have enough prognostic value to guide therapy. Thus, although it remains unclear whether therapies targeted at a high-risk
population soon after infarction would reduce the risk of sudden unexpected death, our data provide a basis for considering early intervention in selected patients at very high risk. As it is emphasized by Solomon et al., the fact that patients who were resuscitated during the first 30 days were alive at least some months later supports this conception.

Limitations
This is a nonrandomized, observational and unincentric study performed in a long time frame (2001–2012). It reflects the results of the myocardial infarction management strategy followed in our center and cannot be extrapolated to other situations. Multicentric studies with a higher number of patients, specially with depressed LVEF, are required to determine the significance of our findings in other settings.

Patients with ICDs could be more likely to have sustained VT/VF detected; however, only 2 of the 11 events were registered and treated by the ICD; in addition, both were significant in terms of symptoms or duration: one of them was a syncopal fast VT (250 bpm) and the other, a long VT that needed a high number of antitachycardia pacing sequences to be terminated.

The low rate of AACEs found in our sample could limit the applicability of the conclusions, especially in the analysis of groups, but in fact it is based on the good prognosis of patients with a first STEMI treated according to current guidelines.

Use of a late gadolinium enhancement segmentation approach, such as full-width half maximum, was not done, noting that the 2 SD threshold may include edematous, noninfarcted myocardium.

Conclusions
In the era of reperfusion therapies, occurrence of AACEs after a first noncomplicated STEMI is extremely low. Depressed LVEF remains the most powerful predictor of adverse events. In this setting, early assessment of CMR-derived IS could allow for further optimization of AACE risk prediction and maybe for determination of ICD indication if our results become validated in further studies.

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Disclosures
None.

References
Left ventricular ejection fraction (LVEF) is the most consistently reported risk predictor of sudden and nonsudden death after myocardial infarction. Randomized trials have shown that an implantable cardioverter-defibrillator implantation can reduce mortality among patients with chronic ischemic heart disease and depressed LVEF. However, clinical trials have failed to support the use of implantable cardioverter-defibrillator therapy in patients with depressed LVEF very early after acute myocardial infarction. This may be due to the dynamic nature of LVEF, particularly after acute ST-segment–elevation myocardial infarction. In previous studies, the extent of infarct scar (infarct size [IS]) has predicted absence of subsequent LVEF recovery. IS may also predict ventricular arrhythmias and adverse ventricular remodeling. In this article, the authors hypothesized that cardiac magnetic resonance–derived IS evaluated 1 week after ST-segment–elevation myocardial infarction provided incremental predictive value for adverse arrhythmic events. In a cohort of 440 patients, the vast majority of adverse arrhythmic events (10/11 events) occurred in those with large IS and severe LV dysfunction. Conversely, those with severe LV dysfunction and small IS did not have any adverse arrhythmic events, including sudden death, ventricular tachycardia, or ventricular fibrillation. Further prospective studies are warranted to test the effectiveness of IS in conjunction with traditional risk predictors such as LVEF to guide implantable cardioverter-defibrillator placement in patients with LV dysfunction after ST-segment–elevation myocardial infarction.
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Supplemental Figure 1. Methodology applied for quantifying LGE-derived IS

1. Image Acquisition
2. Scar Automatic quantification (intensity ≥ 2SD)
3. Manual correction including MO (yellow line)
Supplemental Figure 2. Cumulative risk of AACEs according to LVEF and IS.