Novel Prognostic Markers Derived from Cardiovascular Magnetic Resonance Imaging in Patients with Stable Chronic Coronary Artery Disease

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Abstract. Background: In patients with coronary artery disease (CAD), risk stratification remains a challenge. Recently, epicardial adipose tissue (EAT) assessed by cardiovascular magnetic resonance imaging (CMRI) has emerged as a new marker in patients with CAD. Thus, we aimed to investigate the association of CMR parameters with all-cause and cardiac mortality in patients with CAD. Patients and Methods: CMRI examination was performed in 260 patients with CAD. Results: In the 40 patients who died, left ventricular (LV) ejection fraction, right ventricular fractioning shortening, LV remodeling index and indexed EAT were significantly reduced, whereas LV mass index, LV end-diastolic volume index, LV end-systolic volume index, LV end-diastolic diameter and the extent of late gadolinium enhancement expressed as a percentage of the maximum possible score to estimate the extent of LGE relative to LV mass (LGE %), were significantly elevated. Using multivariate analysis, age, LV mass index, extent of LGE % and indexed EAT proved to be independently associated with all-cause and cardiac mortality. Conclusion: Age, LV mass index, the extent of LGE % and indexed EAT are independent predictors of mortality that might contribute to a more accurate risk stratification of patients with CAD.

According to epidemiological studies, coronary artery disease (CAD) will globally remain one of the leading causes of death in the future (1). Although CAD-related morbidity and mortality has significantly decreased over the past decades due to improved preventive, technical and therapeutic strategies, the prevalence of ischemic cardiomyopathy is still rising (2). However, the large population of patients with chronic CAD is heterogeneous, regarding both the severity of the underlying CAD and the prognosis (3). Since several patients die despite preserved left ventricular ejection fraction (LVEF) (4, 5), whereas others with low LVEF may never experience a major adverse event (6, 7), the currently used strategy of risk stratification based on LVEF alone is insufficient. Therefore, in times of constrained financial budgets, the increasing prevalence of CAD will necessitate early and effective risk stratification in order to select for the most beneficial and cost-effective approach for the individual. Cardiac magnetic resonance imaging (CMRI) has become a unique tool for investigating the morphology and function of the cardiovascular system. A plethora of CMRI parameters (extent of fibrosis, LV mass, LV dimensions) have already been evaluated but no gold-standard for risk stratification currently exists.

The aim of our study was to elucidate to what extent CMRI parameters and age were associated with all-cause and cardiac mortality also taking into account the role of epicardial adipose tissue (EAT), that has emerged as a new marker with potential prognostic importance in patients with CAD.

Patients and Methods

Study population. Between January 2004 and December 2013, 260 patients with chronic stable CAD that underwent late gadolinium-enhancement CMRI to quantify LV function and myocardial scarring as part of their routine clinical work-up were enrolled. Due to claustrophobia, CMRI examination was discontinued in six
Image acquisition. All studies were performed using 1.5 Tesla whole-body imaging systems (Magnetom Sonata, and Avanto; Siemens Healthcare Sector, Erlangen, Germany). A dedicated 4-element element phased-array cardiac matrix coil was used for the Sonata and a 6-element phased-array cardiac matrix coil in combination with two elements of the inbuilt spine matrix coil was used for the Avanto. Images were acquired during repeated end-expiratory breath-holds. Scout images (coronal, sagittal, and axial planes) were obtained for planning of the final double-oblique long-axis and short-axis views. To evaluate functional parameters, electrocardiogram-gated cine images were then acquired using a segmented steady-state free precession [fast imaging with steady-state precession (true-FISP)] sequence (time to echo/time of repetition 1.6/3.2 ms, temporal resolution 35 ms, in-plane spatial resolution 1.4×1.8 mm, slice thickness 8 mm, interslice gap 2 mm). Seven to 12 short-axis views covering the whole left and right ventricle were obtained. For the assessment of the epicardial adipose tissue, we used a dark blood prepared T1-weighted multislice turbo spin-echo pulse sequence with a water suppression prepulse to obtain a transversal 4-chamber view and short-axis images in the same orientations used for the cine short-axis images. Imaging parameters were as follows: time of repetition=800 ms, time to echo=24 ms, slice thickness=6 mm, interslice gap=2 mm, and field of view=30 to 34 cm.

Late gadolinium enhancement (LGE) imaging. Ten minutes after injection of a gadolinium-based contrast agent (Magnevist; Bayer-Schering Pharma AG, Berlin, Germany), LGE images were acquired in continuous short-axis views, the 4-chamber and the 2-chamber long-axis view using an inversion recovery Turbo FLASH 2D sequence: field of view=300-340 mm, TR 9.56 ms, TE 4.38 ms, TI 200-360 ms, flip angle 25°; matrix 166×256 and slice thickness 6 mm. LGE was only considered to be present if it was also present in the same slice after swapping phase encoding, thus excluding artifacts.

Volumetric assessment of the absolute mass of EAT. The amount of EAT was calculated by using the modified Simpson’s rule with integration over the image slices (EAT volume=Σ [EAT area×(slice thickness+interslice gap)] (10). The contours of EAT were outlined at end-diastole in the short-axis views covering the entire LV and RV. For EAT mass determination, the area subtended by the manual tracings was determined in each slice and multiplied by the slice thickness to yield the fat volume. Total EAT volume was obtained after the data summation of all slices. To obtain EAT mass, the volume of EAT was multiplied by the specific weight of fat (taken as 0.92 g/cm³). To adjust for differences in height and weight, the given EAT mass was indexed to body surface area (BSA). The observer who quantified the EAT was blinded to patient details.

Follow-up data and definition of study endpoints. The long-term follow-up was performed by patient interview at our Outpatient Clinic and by telephone contact. The date of this contact was used for calculating the follow-up time duration. The observers were unaware of the CMRI results and collected data with a standardized questionnaire. Reported clinical events were confirmed by review of the corresponding medical records in our electronic Hospital Information System, contact with the general practitioner, referring cardiologist, or the treating hospital. The definition of cardiac event required the documentation of significant arrhythmia or cardiac arrest or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factor. In cases of out-of-hospital death not followed by autopsy, sudden unexpected death was classified as cardiac death.

Statistical analysis. Descriptive statistics [mean±standard deviation (SD)] were used for continuous variables. BMI was calculated by the common formula: BMI (kg/m²)=weight (kg)/height (m)². BSA was assessed by a variation of the DuBois and DuBois formula: BSA (m²)=square root(weight (kg)×height (cm)/2.303) × 0.007184 (13). Differences in baseline demographic, clinical and CMRI
characteristics between patients who died and those who survived were analyzed using the unpaired, two-tailed Student’s t-test for continuous parameters and the Mann–Whitney U-test (Chi-square test) for categorial data.

Since we aimed to study to what extent CMRI results and age were associated with events, all CMRI data with a value of \( p < 0.05 \) (in a comparison between patients with and without the occurrence of events) were eligible to univariate analysis. Cox proportional hazard regression models were constructed for age and CMRI parameters. Those variables which appeared to be associated with events at a value of \( p < 0.2 \) level in univariate analysis, were eligible for multivariate analysis. Hazard ratios (HRs) with their corresponding confidence intervals (CIs) are reported. To check the proportional hazard assumption for different categories was plotted against time to ensure that the curves were reasonably parallel. F-Test for extra sum of square principles was applied to assess goodness of fit of the final model.

Kaplan–Meier analysis was performed for the independent predictors of all cause and cardiac mortality. For this analysis the study population was divided into two groups according to established cut-off values. If the latter were lacking, we used the median value of the entire study population. Difference in survival over time was evaluated by a log-rank test.

Analysis was performed using SPSS statistical software (version 14.0; SPSS Inc., Chicago, IL, USA).

Results

Among the CAD patients included in the study 184 (74%) were men with a mean age of 64.9±10.8 years. Thirty-one (13%) had undergone previous percutaneous intervention (PCI)/stenting and CABG was performed in another 51 (21%) patients. A history of prior non-STEMI was reported in 26 (11%) patients and STEMI was known in 123 (50%) patients. The baseline demographic and clinical characteristics in patients with all-cause and cardiac mortality are presented in Table I. The length of follow-up was from 8 days to 8.6 years (interquartile range=1.6-4.2 years).

All-cause mortality and cardiac mortality during follow-up.

During the follow-up, 40 (16%) patients died. A cardiac death was reported in 25 (62.5%) patients, and a non-cardiac death occurred in 15 (37.5%) patients (Table II).

Relation of all-cause and cardiac mortality to demographic, clinical and CMR parameters. As shown in Table I, higher age, a higher prevalence of diabetes, dyspnea (NYHA II-IV), atrial fibrillation, prior STEMI, the use of diuretics and insulin were significantly associated with all-cause mortality. The same variables were also more frequent in patients with cardiac death, except for the presence of atrial fibrillation, which did not differ in these patients. Patients with cardiac death significantly suffered more often from hyperlipidemia and the use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers was significantly lower in these patients.

The CMRI findings with respect to all-cause and cardiac mortality are listed in Table III. Mean systolic LV-EF in the whole study cohort was 36.8±15.8%. LV-EF and RV-EF, LVRI and indexed EAT were significantly lower in patients who died, whereas LV mass index, LV-EDVI, LV-ESVI, LV-EDD and the extent LGE % were significantly elevated in these patients.

Predictors of all cause mortality. By univariate analysis, significant associations were observed between age, LV mass index, extent LGE %, indexed EAT mass and the occurrence of all-cause death (Figure 1A). Using multivariate analysis, age, LV mass index, extent LGE % and indexed EAT mass proved to be independently associated with all-cause mortality (Figure 1B). Introduction of the additional variables age, extent LGE % and indexed EAT mass significantly improved the model fit (chi-square 44 vs. 12, F-test \( p < 0.0001 \); Figure 2A) with respect to considering LV mass index alone.

Survival analysis for all-cause mortality. Figure 3 illustrates the Kaplan–Meier curves for the independent predictors of all-cause mortality. An age above 65 years was associated with significantly higher all-cause mortality (\( p = 0.0001 \), Figure 3A). During the whole follow-up period, an LV mass index above the median of 85 g/m² correlated significantly with a higher rate of all-cause death (\( p = 0.001 \); Figure 3B). As far as the extent LGE % is concerned, a value above the median of 34% correlated with a significantly higher rate of all-cause death during the first 7 years but this seemed to be neutralized after 8 years (\( p = 0.003 \); Figure 3C). After two years, a reduced indexed EAT mass below 22 g/m² was associated with a markedly higher rate of all-cause death (\( p = 0.01 \); Figure 3D).

Predictors of cardiac mortality. Cardiac mortality was associated with age, LV mass index, extent LGE % and indexed EAT mass by univariate analysis (Figure 4A). In multivariate analysis, age, LV mass index, extent LGE % and indexed EAT mass proved to be independently associated with cardiac mortality (Figure 4B). The stepwise inclusion of parameters reaching the predefined threshold for the multivariate Cox model significantly improved the model predictability for extent LGE % alone (Chi-square 25) compared to the final model that additionally included age, LV mass index and indexed EAT mass (Chi-square 61, F-test \( p < 0.0001 \); Figure 2B).

Survival analysis for cardiac mortality. Kaplan–Meier curves for the independent predictors of cardiac mortality are shown in Figure 3. The rate of cardiac death was also significantly higher in patients older than 65 years (\( p = 0.0002 \); Figure 3E). An LV mass index above the median of 85 g/m² contributed to significantly higher cardiac mortality (\( p = 0.007 \); Figure 3F). An extent LGE % above the median of 34% was associated with a markedly higher rate of cardiac death.
After 1 year, an indexed EAT mass below 22 g/m² yielded a significantly higher rate of cardiac deaths (p=0.005, Figure 3H).

**Discussion**

The main finding in the present study was that age, LV mass index, extent LGE % and indexed EAT are independent predictors of all-cause mortality and cardiac death in patients with chronic stable CAD.

**Influence of age.** Increasing age is a well-known factor influencing all-cause and cardiac mortality in patients with CAD. Therefore, our result that age is a strong independent predictor is consistent with previous findings.
LV mass index (g/m²) 106.3±29.9 85.4±24.0 <0.0001 109.3±27.1 86.5±25.1 <0.0001

LVEF (%) 23.8±9.5 39.3±15.6 <0.0001 18.8±6.5 38.8±15.3 <0.0001

Levy et al. has been linked to increased mortality in CAD patients. Brown et al. showed that an echocardiographically increased LV mass (16). Similarly, that the likelihood of dying was twice as high in patients with LV mass resulted in a significantly higher rate of all-cause mortality and cardiovascular events in our study population of patients with chronic CAD.

Importance of LV mass index. LV mass is another factor that has been linked to increased mortality in CAD patients. Brown et al. followed-up 7,924 adults for 16.8 years and found out that the likelihood of dying was twice as high in patients with an echocardiographically increased LV mass (16). Similarly, Levy et al. reported an increased risk from 1.60 to 1.67 per 50 g/m (of height) increment of LV mass measured by echocardiography over a 4-year period (17). Among 4,824 patients followed up for 15 years, Sullivan et al. showed that patients with CAD with increased LV mass were characterized by a significantly higher mortality (18). In a CMRI study by Krittayaphong et al. in 2,194 patients, LV mass index proved to be an independent predictor for cardiovascular events in patients with known or suspected CAD (19). According to these results our findings also showed that LV mass index was a strong independent predictor of all-cause and cardiac mortality. Our results proved that a LV mass index above the median was significantly associated with higher all-cause as well as cardiac mortality. Therefore, our data support the concept that pathological hypertrophy is associated with higher rates of cardiovascular events (18, 20-23).

Indexed EAT mass (g/m²): Novel Prognostic CMR Markers in CAD

Table III. Cardiovascular magnetic resonance imaging characteristics on function, morphology and tissue Data are mean±standard deviation

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=40</th>
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<th>N=208</th>
<th></th>
<th>N=25</th>
<th></th>
<th>N=223</th>
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<tr>
<td>LVEF (%)</td>
<td>23.8±9.5</td>
<td>39.3±15.6</td>
<td>&lt;0.0001</td>
<td>18.8±6.5</td>
<td>38.8±15.3</td>
<td>&lt;0.0001</td>
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<tr>
<td>LV mass index (g/m²)</td>
<td>106.3±29.9</td>
<td>85.4±24.0</td>
<td>&lt;0.0001</td>
<td>109.3±27.1</td>
<td>86.5±25.1</td>
<td>&lt;0.0001</td>
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<tr>
<td>LVRI (g/ml)</td>
<td>0.7±0.2</td>
<td>0.8±0.2</td>
<td>0.001</td>
<td>0.7±0.2</td>
<td>0.8±0.2</td>
<td>0.01</td>
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<td>LV-ESVI (ml/m²)</td>
<td>117.1±47.7</td>
<td>71.3±42.3</td>
<td>&lt;0.0001</td>
<td>131.4±51.1</td>
<td>73.0±42.1</td>
<td>&lt;0.0001</td>
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<tr>
<td>LV-EDD (mm)</td>
<td>66.5±7.3</td>
<td>60.9±10.0</td>
<td>0.001</td>
<td>67.1±8.1</td>
<td>61.2±9.8</td>
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<td>SWT (mm)</td>
<td>10.6±2.8</td>
<td>10.9±4.4</td>
<td>0.6</td>
<td>10.2±2.2</td>
<td>10.9±4.4</td>
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<tr>
<td>RVEDD (mm)</td>
<td>42.0±7.3</td>
<td>41.9±8.4</td>
<td>0.9</td>
<td>41.8±7.1</td>
<td>42.0±7.6</td>
<td>0.9</td>
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<tr>
<td>RVFS (%)</td>
<td>25.0±8.9</td>
<td>28.8±7.6</td>
<td>0.01</td>
<td>22.8±9.0</td>
<td>28.7±7.6</td>
<td>0.0004</td>
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<td>LGE extent (% of myocardial mass)</td>
<td>47.2±19.5</td>
<td>31.3±22.5</td>
<td>&lt;0.0001</td>
<td>57.4±19.6</td>
<td>31.3±21.6</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>Indexed EAT mass (g/m²)</td>
<td>22.8±6.8</td>
<td>29.4±10.3</td>
<td>0.0001</td>
<td>21.8±6.4</td>
<td>29.1±10.2</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EAT: Epicardial adipose tissue, LGE: late gadolinium enhancement, LV: left ventricular, LV-EDD: left ventricular end diastolic diameter, LV-EDVI: left ventricular enddiastolic volume index, LVRI: left ventricular remodelling index, RVEDD: right ventricular end diastolic diameter, RVFS: right ventricular fractional shortening.

LGE as a predictor of cardiac mortality. In 195 patients with signs or symptoms of CAD, Kwong et al. demonstrated that LGE % was the strongest predictor of cardiac mortality (adjusted HR=10.9, p<0.0001) during a follow-up of 16 months (29). Steel et al. performed LGE CMRI in 264 symptomatic patients. At a median follow-up of 17 months, LGE % was associated with a significantly higher rate of all-cause death during the first 7 years. However, this effect was no longer apparent after 8 years.
multivariate analysis, the extent of LGE % was the strongest independent predictor of cardiac death in our study population. In contrast to our observations of the effect of LGE % on all-cause mortality, an LGE % extent above the median of 34% of LV mass maintained its incremental prognostic value to predict cardiac mortality over the whole study period (Figure 5A).

**Role of EAT with regard to all-cause and cardiac mortality.** Despite the well-known negative effects of obesity, especially the central or visceral type, as a predisposing factor for the development of cardiovascular disease and its known harmful effects on cardiac function, several previous studies showed a worse prognosis with regard to all-cause and cardiac mortality in patients with congestive heart failure who were normal or underweight as defined by BMI (31-34). However, BMI is only an index of relative body size and not of body composition and fat distribution. The use of CMRI has remarkably improved our ability to precisely and reliably quantify and visualize ectopic fat deposition e.g. around the heart (10) that can be further classified into EAT and pericardial adipose tissue. In patients with congestive heart failure, EAT gradually declines with decreasing LV function (35, 36). Since EAT derives its blood supply from the coronary arteries (37), progressive CAD may result in a slowdown of EAT perfusion and progressive EAT reduction. The decrease in EAT with impaired cardiac function and heart failure suggests a complex interaction of regulatory pathways between EAT and the dysfunctional myocardium, that may develop abnormal metabolic needs as soon as the myocardium alters in structure and function (38). Moreover, in a previous study among 50 consecutive patients with heart failure and echocardiographically severely reduced LVEF (≤35%) due to ischemic or dilated cardiomyopathy (39), our group found a

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Figure 1. A) Univariate analysis of baseline CMR parameters and age for the assessment of all cause mortality. An association (p<0.2) was observed between age, LV mass index, extent LGE and indexed EAT for all cause mortality. B) Multivariate analysis of baseline CMR parameters and age for the assessment of all cause mortality. Age, LV mass index, extent LGE and indexed EAT were independently associated with all cause mortality.
statistically significant higher risk of cardiac death among patients with congestive heart failure, and an indexed EAT below 22 g/m² \((p=0.02)\). In the present study of patients with chronic stable CAD, EAT proved to be an independent prognostic marker of all-cause and cardiac mortality in multivariate analysis. Kaplan–Meier analysis showed a markedly higher rate of all-cause death \((p=0.01)\) after 2 years and a significantly higher rate of cardiac death \((p=0.005)\) after 1 year for those with EAT mass below 22 g/m².

These results underline the hypothesis that as soon as an impairment of the LVEF appears, the lack of the protective effects of EAT on the adjacent myocardium, coronary arteries and the cardiac autonomic nerves and ganglia seems to be of consequence \((37, 40, 41)\). It is known that EAT can locally secrete anti-inflammatory and anti-atherogenic adipokines such as adiponectin and adrenomedullin \((41, 42)\). In patients with chronic CAD, significantly reduced intracoronary levels of adiponectin and adrenomedullin have been found \((43, 44)\). Moreover, lipid storage for the energy needs of the myocardium, especially in times of high energy demand, as well as buffering of the myocardium against the lipotoxic effects of abundant dietary lipids is another physiological function of EAT \((45)\). A decline of EAT may lead to increased lipid accumulation in cardiac myocytes, which has shown to be an important cause of cardiac dysfunction, inducing cardiomyocyte apoptosis, cardiac fibrosis and impairment of the contractile function of the heart in animal studies \((46-48)\). Therefore, the increased all-cause and cardiac mortality recorded in our study along with the reported decline in EAT in patients with CAD and heart failure provides further support for the important role of EAT in these patients due to a multifaceted cross-talk and functional interaction between EAT and the adjacent tissues.

**Limitations.** Our study population included a high proportion of patients at high risk \((115, 46\%)\) of patients presenting with 3-vessel disease and 123 \((50\%)\) with a history of prior STEMI, limiting the transferability of our findings to ambulatory settings with lower risk cohorts. Furthermore, the relatively small number of hard events limited the set of parameters included in uni- and multivariate analysis mainly to CMRI parameters to avoid model-overfitting, but excluded the role of other clinical factors (e.g. extent of CAD, prior STEMI or the presence of diabetes) that may also influence prognosis for these patients. Another limitation is that the data presented were only from a single center. Therefore, larger multicenter trials are required to confirm our results and to allow the study of further parameters that might be of interest regarding these patients.

**Clinical implications.** In light of the fact that LVEF alone has been shown to be of limited use for adequately risk stratifying patients \((4, 5, 7)\), our study suggests that a combined approach focusing on patient age, LV mass index, the extent of scar tissue and the amount of EAT may be advisable.

Since all these parameters are assessed during routine CMRI protocols of the heart, this image modality offers a one-stop shop in the assessment of all-cause as well as cardiac mortality risk parameters. Further larger longitudinal cohort studies are required to define optimal cut-off values for the CMRI risk factors and to establish their value as prognostic factors in CAD. Moreover, the identified risk factors may not only play a role for risk stratification but may also be used for monitoring the sustainability of therapeutic strategies.
Figure 3. Kaplan-Meier analysis. A-D for all cause mortality. Cumulative survival according to age (cut-off 65 years, A), LV mass index (cut-off median 85g/m², B), LGE extent (cut-off median 34%, C) and indexed EAT (cut-off 22 g/m², D). E-H for cardiac mortality. Cumulative survival according to age (cut-off 65 years, E), LV mass index (cut-off median 85g/m², F), LGE extent (cut-off median 34%, G) and indexed EAT (cut-off 22 g/m², H).
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