Cardiac Magnetic Resonance Myocardial Feature Tracking for Optimized Risk Assessment After Acute Myocardial Infarction in Patients With Type 2 Diabetes

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COMPLICATIONS

Type 2 diabetes predicts outcome following acute myocardial infarction (AMI). Since underlying mechanics are incompletely understood, we investigated left ventricular (LV) and left atrial (LA) pathophysiological changes and their prognostic implications using cardiovascular magnetic resonance (CMR). Consecutive patients (N = 1,147; n = 265 with diabetes, n = 882 without diabetes) underwent CMR 3 days after AMI. Analyses included LV ejection fraction (LVEF); global longitudinal strain (GLS) and circumferential and radial strains; LA reservoir, conduit, and booster pump strains; and infarct size, edema, and microvascular obstruction. Predefined end points were major adverse cardiovascular events (MACE) within 12 months. Patients with diabetes had impaired LA reservoir (19.8% vs. 21.2%, P < 0.01) and conduit (7.6% vs. 9.0%, P < 0.01) strains but not ventricular function or myocardial damage. They were at higher risk of MACE than patients without diabetes (10.2% vs. 5.8%, P < 0.01), with most MACE occurring in patients with LVEF ≥35%. While LVEF (P = 0.045) and atrial reservoir strain (P = 0.024) were independent predictors of MACE in patients without diabetes, GLS was in patients with diabetes (P = 0.010). Considering patients with diabetes and LVEF ≥35% (n = 237), GLS and LA reservoir strain below median were significantly associated with MACE. In conclusion, in patients with diabetes, LA and LV longitudinal strain permit optimized risk assessment early after reperfused AMI with incremental prognostic value over and above that of LVEF.

Coronary artery disease and acute myocardial infarction (AMI) are major causes of global morbidity and mortality (1,2). Following AMI, precise risk stratification is a prerequisite for treatment strategy guidance and mortality reduction (3). Diabetes mellitus (DM) is considered one of the major risk factors for coronary artery disease (4). The term diabetic cardiomyopathy has been introduced based on the observation of accelerated heart failure (HF) in patients with DM beyond macrovascular ischemic heart disease (5). Pathophysiologically, the course of diabetic cardiomyopathy is characterized by first left ventricular (LV) hypertrophy resulting in decreased chamber size followed by diastolic and finally systolic dysfunction (6–8). Diastolic dysfunction is also the first alteration that can be measured during an ischemic event and precedes wall motion abnormalities or reduction in LV ejection fraction (LVEF) in the ischemic cascade (9). Consequently, although

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LVEF is the most established marker for risk stratification in ischemic heart disease (10), it may not be suitable to detect subtle changes early during the ischemic cascade or associated with diabetic cardiomyopathy. Cardiovascular magnetic resonance (CMR) imaging allows comprehensive myocardial evaluation including volume, morphology, and deformation assessments following AMI (11–15). Deformation imaging especially has proven incremental prognostic value over and beyond that of LVEF following AMI (16–18), and data from CMR tagging show discrete reduction in systolic function prior to changes in LVEF in DM (6). Consequently, the current study sought to investigate the interplay of type 2 DM and AMI using state-of-the-art CMR imaging to better understand the impact of DM and to identify optimized risk stratification strategies in this high-risk patient collective.

RESEARCH DESIGN AND METHODS

Study Population

The population of this multicenter CMR study consisted of 1,235 patients with AMI participating in two randomized trials, namely, Abciximab Intracoronary Versus Intravenous Drug Application in ST-Elevation Myocardial Infarction (AIDA STEMI) and Thrombus Aspiration in Thrombus-Containing Culprit Lesions in Non-ST-Elevation Myocardial Infarction (TATORT NSTEMI). Detailed study protocols and main results have been published previously (19–21). In brief, AIDA STEMI randomly assigned patients presenting with STEMI in the first 12 h after symptom onset to intracoronary or intravenous abciximab bolus during primary percutaneous coronary intervention (PCI) with subsequent 12-h intravenous infusion in both groups (19). Consecutive patients were enrolled in the CMR substudy (n = 795) at eight sites in Germany with proven expertise in CMR imaging (20). The results did not show a difference regarding clinical outcome or CMR parameters of myocardial damage between the treatment groups (19,20). The TATORT NSTEMI trial randomized 440 patients with NSTEMI at seven sites in Germany to investigate the effect of aspiration thrombectomy on microvascular damage in CMR imaging (21). Compared with standard PCI, additional aspiration thrombectomy did not improve reperfusion injury as assessed by microvascular obstruction (MO), infarct size (IS), or clinical outcome. Patients in both studies received reperfusion therapy with primary PCI and state-of-the-art postinfarction medical treatment according to guideline recommendations (2,22).

AIDA STEMI and TATORT NSTEMI were registered with ClinicalTrials.gov and approved by the ethics committees of the participating sites. This CMR-Feature Tracking (FT) study was supported by a grant from the German Center for Cardiovascular Research and conducted according to the Declaration of Helsinki. Patients gave written informed consent for study participation. Clinical patient characteristics including information on diagnosed DM were obtained by a structured interview at admission.

CMR Imaging Protocol

All patients underwent CMR imaging on clinical 1.5- or 3.0-T scanners within 10 days after MI. The standardized protocol has been published previously and included ECG-gated balanced steady-state free precession sequences to assess LV function and T1-weighted late gadolinium enhancement imaging to determine myocardial and microvascular damage (11,20,21). All sequences were acquired in two- and four-chamber long-axis views as well as continuous stacks of short-axis slices covering the whole LV. The same CMR protocol was used in all AMI patients.

CMR Analysis

Infarct characteristics and LVEF were analyzed at a core laboratory by blinded investigators using certified evaluation software (cvi[42]; Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada) (11,20). All parameters were determined in sequential short-axis planes. Established threshold techniques were applied to assess IS and MO, area at risk, and myocardial salvage as percentage of LV mass.

Image analysis and postprocessing were provided by an experienced core laboratory at the University Medical Center Göttingen using dedicated software (2D CPA MR,

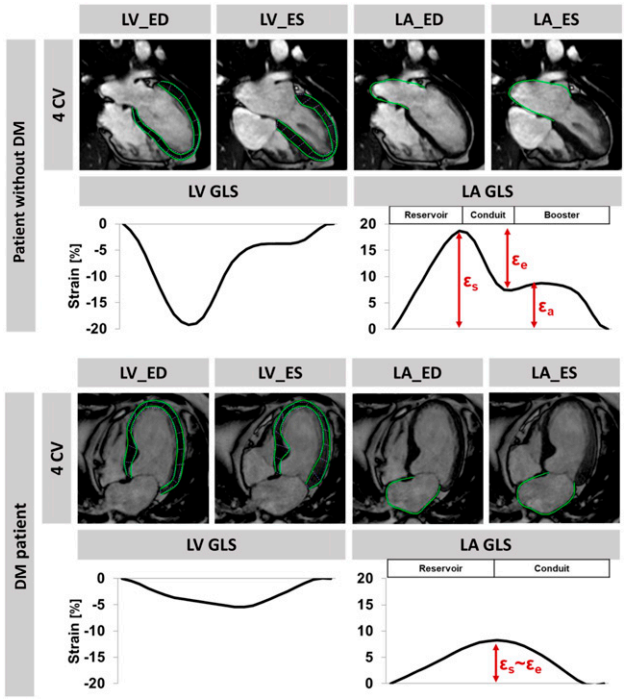

Figure 1—CMR-FT and strain analysis. The top shows a four-chamber view (CV) with endocardial- and epicardial-tracked LV as well as endocardial-tracked borders in the LA exemplary shown at end diastole (ED) and end systole (ES). Below, the corresponding strain curves of LV GLS as well as εs, εe, and εa are shown for a patient without DM with preserved GLS and εs and no MACE during follow-up. The bottom refers to a patient with DM with impaired GLS and εs paralleled by a loss of εa with a MACE during follow-up.

Table 1—Baseline characteristics

Variable	All patients (n = 1,231)	DM (n = 288)	No DM (n = 9A43)	P
Age (years)	64 (53, 73)	71 (60, 77)	62 (51, 71)	**<0.01**
Male sex	921/1,231 (74.8)	187/288 (64.9)	734/943 (77.8)	**<0.01**
Cardiovascular risk factors				
Current smoking	498/1,143 (43.6)	82/259 (31.7)	416/884 (47.1)	**<0.01**
Hypertension	885/1,228 (72.1)	258/288 (89.6)	627/940 (66.7)	**<0.01**
Hyperlipoproteinemia	469/1,223 (38.3)	150/288 (52.1)	319/935 (34.1)	**<0.01**
BMI (kg/m^2)	27.5 (25.0, 30.5)	29.1 (26.0, 32.4)	27.2 (24.8, 30.0)	**<0.01**
Previous MI	90/1,230 (7.3)	29/288 (10.1)	61/942 (6.5)	0.05
Previous PCI	108/1,231 (8.8)	39/288 (13.5)	69/943 (7.3)	**<0.01**
Previous CABG	28/1,231 (2.3)	13/288 (4.3)	15/943 (1.6)	**<0.01**
ST-segment elevation	792/1,231 (64.3)	160/288 (55.6)	632/943 (67.0)	**<0.01**
Systolic blood pressure (mmHg)	135 (120, 150)	140 (124, 155)	133 (118, 150)	**<0.01**
Diastolic blood pressure (mmHg)	80 (70, 90)	80 (70, 90)	80 (70, 90)	0.58
Heart rate (beats/min)	76 (67, 86)	80 (70, 88)	75 (66, 85)	**<0.01**
Time from symptom onset to PCI hospital admission* (min)	180 (109, 310)	190 (123, 378)	177 (105, 295)	**0.02**
Door-to-balloon time* (min)	30 (22, 42)	28 (21, 39)	30 (22, 43)	0.06
Atrial fibrillation	70/1,231 (5.7)	21/287 (7.3)	48/940 (5.1)	0.16
Killip class on admission				
1	1,085/1,231 (88.1)	235/288 (81.6)	850/943 (90.1)	**<0.01**
2	102/1,231 (8.3)	36/288 (12.5)	66/943 (7.0)	
3	26/1,231 (2.1)	9/288 (3.1)	17/943 (1.8)	
4	18/1,231 (1.5)	8/288 (2.8)	10/943 (1.1)	
Number of diseased vessels				**<0.01**
1	613/1,231 (49.8)	107/288 (37.2)	506/943 (53.7)	
2	371/1,231 (30.1)	98/288 (34.0)	273/943 (29.0)	
3	247/1,231 (20.1)	83/288 (28.8)	164/943 (17.4)	
Infarct-related artery				**0.01**
Left anterior descending	496/1,231 (40.3)	117/288 (40.6)	379/943 (40.2)	
Left circumflex	268/1,231 (21.8)	74/288 (25.7)	194/943 (20.6)	
Left main	6/1,231 (0.5)	3/288 (1.0)	3/943 (0.3)	
Right coronary artery	449/1,231 (36.5)	88/288 (30.6)	361/943 (38.3)	
Bypass graft	12/1,231 (1.0)	6/288 (2.1)	6/943 (0.6)	
Stent implanted	1,195/1,231 (97.1)	279/288 (96.9)	916/943 (97.1)	0.92
TIMI flow grade before PCI				**0.03**
0	609/1,231 (49.5)	122/288 (42.4)	487/943 (51.6)	
1	137/1,231 (11.1)	31/288 (10.8)	106/943 (11.2)	
2	257/1,231 (20.9)	73/288 (25.3)	184/943 (19.5)	
3	228/1,231 (18.5)	62/288 (21.5)	166/943 (17.6)	
TIMI flow grade post-PCI				0.08
0	25/1,231 (2.0)	4/288 (1.4)	21/943 (2.2)	
1	24/1,231 (1.9)	10/288 (3.5)	14/943 (1.5)	
2	94/1,231 (7.6)	17/288 (5.9)	77/943 (8.2)	
3	1,088/1,231 (88.4)	257/288 (89.2)	831/943 (88.1)	
MACE within 12 months	94/1,231 (7.6)	38/288 (13.2)	56/943 (5.9)	**<0.01**
Death within 12 months	46/1,231 (3.7)	23/288 (8.0)	23/943 (2.4)	**<0.01**
Concomitant medications				
Glycoprotein IIb/IIIa inhibitor	819/1,231 (66.5)	171/288 (59.4)	648/943 (68.7)	**<0.01**
Aspirin	1,228/1,231 (99.8)	287/288 (99.7)	941/943 (99.8)	0.55
Clopidogrel/prasugrel/ticagrelor	1,212/1,212 (100)	286/286 (100)	926/926 (100)	1.00
β-Blocker	1,170/1,229 (94.1)	269/286 (94.1)	901/943 (95.5)	0.34
ACE inhibitor/AT-1 antagonist	1,124/1,229 (91.5)	249/286 (87.1)	875/943 (92.8)	**<0.01**
Aldosterone antagonist	167/1,229 (13.6)	39/286 (13.6)	128/943 (13.6)	1.00
Statin	1,172/1,229 (95.4)	266/286 (93.0)	906/943 (96.1)	**0.04**

Data are n/N (%) or median (IQR). P values were calculated for the comparison between patients with and without MACE. P values in boldface type indicate a significant difference. *Only assessed in patients with STEMI (n = 792).

Table 2—CMR imaging results

Variable	All patients	DM	No DM	*P*
Myocardial damage				
Area at risk (% LV)	29.4 (20.3, 42.6)	26.4 (19.1, 39.9)	30.0 (20.8, 43.2)	0.11
IS (% LV)	13.3 (5.4. 21.8)	12.8 (5.0, 22.5)	13.5 (5.7, 21.7)	0.74
Myocardial salvage (% LV)	14.6 (8.4, 23.4)	14.2 (7.9, 20.9)	14.6 (8.4, 24.1)	0.26
Myocardial salvage index	54.8 (34.2, 75.0)	54.0 (33.5, 77.4)	54.9 (34.3, 74.3)	0.88
MO (% LV)	0.4 (0.0, 2.0)	0.5 (0.0, 2.3)	0.3 (0.0, 1.9)	0.65
LV volumes and function				
EF (%)	50.6 (43.5, 57.5)	50.1 (42.7, 57.5)	50.7 (43.8, 57.6)	0.50
EDV (mL)	143.4 (117.0, 171.0)	136.2 (112.8, 163.0)	145.5 (119.0, 172.8)	**<0.01**
ESV (mL)	69.6 (53.2, 90.8)	65.9 (51.4, 88.1)	70.3 (53.8, 91.1)	0.10
SV (mL)	68.8 (55.1, 83.2)	65.3 (51.8, 76.6)	70.0 (56.6, 85.4)	**<0.01**
Mass (g)	130.5 (109.0, 154.3)	125.6 (105.2, 149.6)	131.5 (111.0, 155.6)	**0.03**
GLS (%)	−16.4 (−20.1, −12.4)	−16.1 (−19.9, −11.8)	−16.4 (−20.2, −12.6)	0.22
GCS (%)	−23.9 (−28.7, −19.1)	−23.7 (−29.2, −18.7)	−23.9 (−28.4, −19.2)	0.91
GRS (%)	20.3 (15.4, 25.8)	20.7 (14.7, 26.7)	20.2 (15.6, 25.5)	0.81
LA volume and function				
Maximum volume (mL/m^2)	35.0 (26.5, 44.4)	35.0 (25.7, 47.3)	35.0 (26.9, 43.9)	0.23
Reservoir strain (%)	20.9 (16.2, 25.7)	19.8 (14.9, 24.8)	21.2 (16.6, 26.2)	**<0.01**
Conduit strain (%)	8.7 (5.6, 11.7)	7.6 (4.9, 10.4)	9.0 (6.1, 12.1)	**<0.01**
Booster pump strain (%)	11.5 (8.6, 15.3)	11.4 (8.4, 15.8)	11.5 (8.7, 15.2)	0.95
Reservoir SR (s^{-1})	0.9 (0.7, 1.1)	0.8 (0.7, 1.1)	0.9 (0.7, 1.1)	**0.04**
Conduit SR (s^{-1})	−0.6 (−0.8, −0.4)	−0.5 (−0.7, −0.3)	−0.6 (−0.8, −0.4)	**<0.01**
Booster pump SR (s^{-1})	−1.0 (−1.3, −0.7)	−1.0 (−1.3, −0.7)	−1.0 (−1.2, −0.7)	0.99

Data are *n*/*N* (%) or median (IQR). *P* values were calculated for the comparison between patients with and without DM. *P* values in boldface type indicate a significant difference.

Cardiac Performance Analysis, Version 1.1.2; TomTec Imaging Systems, Unterschleißheim, Germany) (Fig. 1). Global longitudinal strain (GLS) was derived from two- and four-chamber long-axis views, while global circumferential strain (GCS) and global radial strain (GRS) were derived from balanced steady-state free precession sequences at basal, midventricular, and apical locations as previously described (16,23). Furthermore, left atrial (LA) strain and strain rate (SR) were quantified in two- and four-chamber views and reported as LA reservoir, conduit, and contractile booster pump functions as previously described (24,25). In brief, LV and LA endocardial borders were manually traced followed by the application of an automatic border tracking algorithm. Accurate tracking was ensured by visual review and manual adjustments, if necessary. Final values were based on the average of three independent analyses (26). Scans that did not allow for reliable tracking were excluded. The CMR-FT core laboratory in Göttingen has repeatedly proven excellent reproducibility and low inter- and intraobserver variability for strain assessments and synchrony analyses (16,23,27).

Clinical End Points

The clinical end point of this study was the 12-month rate of major adverse cardiovascular events (MACE), consisting of all-cause death, reinfarction, and new congestive HF. Each patient contributed only once to the composite end point to avoid double counting in case of multiple events per patient (death > reinfarction > new congestive HF). A fully blinded clinical end points committee adjudicated all events on the basis of data provided by the study sites. More detailed end point definitions have been previously reported (19–21).

Statistical Analysis

Categorical variables are presented as frequencies and percentages. Continuous variables were nonnormally distributed as defined by the Shapiro-Wilk test and are provided as median with interquartile range (IQR). Comparisons were performed using the χ^2 test for categorical data and the nonparametric Mann-Whitney *U* test for continuous variables. Baseline characteristics and CMR findings are described according to the presence or absence of DM. Predictors of MACE were identified in univariable and multivariable Cox regression analyses in patients with and without DM. Hazard ratios (HRs) with corresponding 95% CIs are provided. Univariable Cox regression analyses included established risk features (age, sex, hypertension, hypercholesterolemia, BMI, previous PCI or coronary artery bypass graft [CABG], and Killip class), angiographic risk factors including pre- and post-PCI thrombolysis in MI (TIMI) flow, and LV functional (LVEF, GCS, GRS, and GLS) and LA functional metrics (reservoir strain [εs], conduit strain [εe], booster pump strain [εa], reservoir SR, conduit SR, and booster pump SR, including atrial fibrillation). Only significant predictors in univariable analyses ($P < 0.05$) were included in the multivariable model. To avoid collinearity and to account for patients and MACE, multivariable models included all univariable significant baseline parameters and only one strain parameter for LV (GLS) (16) and LA (reservoir strain [εs]) (18) function.

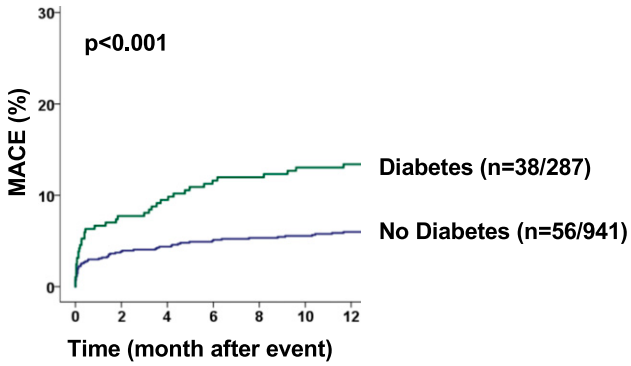

Figure 2—Kaplan-Meier curve demonstrating increased risk of MACE after AMI in patients with DM compared with patients without DM (patient number also includes patients with insufficient CMR imaging protocols, excluding the three patients lost to follow-up).

Furthermore, patients with DM were stratified according to LVEF <35% and ≥35% and according to median LV and LA longitudinal strain to assess the composite 12-month MACE end point with the Kaplan-Meier method and log-rank testing. Case-control matching was performed for patients with and without DM with deviations of matched parameters <10%, resulting in a match of 170 patients each. Receiver operating characteristic area under the curve (AUC) comparisons were performed using the method suggested by DeLong et al. (28). Analyses were performed with SPSS, version 23.0 (IBM Corporation, Armonk, NY), and MedCalc, version 18.2.1 (MedCalc, Ostend, Belgium), software. A two-tailed $P < 0.05$ was considered statistically significant.

Data and Resource Availability

Regarding data availability, we confirm that all relevant data are within the article. Because of potentially identifying information, all data underlying the findings are fully available without restriction on request by researchers who meet the criteria for access to confidential patient data. Data can be accessed from the imaging patient database based at the University Medical Center Göttingen in accordance with the local ethics committee.

RESULTS

Of the 1,235 patients with AMI participating in the AIDA STEMI CMR ($n = 795$) and the TATORT NSTEMI study ($n = 440$), 1,147 had complete CMR protocols ($n = 265$ with DM, $n = 882$ without DM) (Supplementary Fig. 1). CMR was performed in median of 3 days (IQR 2, 4) after AMI. Follow-up data 12 months after the index event were available in 1,142 (99.7%) patients. There were 78 MACE in total: 27 in patients with DM (10.2%) of whom 15 died (5.7%) and 51 in patients without DM (5.8%) of whom 20 died (2.3%).

Patient Characteristics

Baseline and angiographic characteristics and their association with DM status are illustrated in Table 1 for the entire study population. Patients were predominantly male (75%) with a median age of 64 years (IQR 53, 73). Individuals with DM were significantly older ($P < 0.01$), less often male or smokers, and had a higher prevalence of hypertension and hyperlipoproteinemia as well as a higher BMI (all $P < 0.01$). Patients with DM were more likely to have NSTEMI as well as previous PCI and CABG surgery (all $P < 0.01$). Furthermore, there were significant differences regarding Killip class on admission ($P < 0.01$), number of diseased vessels ($P < 0.01$), infarct-related arteries ($P = 0.01$), and TIMI flow grade before PCI between patients with and without DM. The time from onset to PCI was longer in patients with DM ($P = 0.02$).

Table 3—Predictors of MACE in univariable and multivariable Cox regression analysis in patients without DM

	Univariable		Multivariable	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	**1.05 (1.02–1.07)**	**<0.001**	**1.03 (1.01–1.06)**	**0.014**
Killip class	**1.78 (1.29–2.49)**	**<0.001**	1.27 (0.85–1.90)	0.249
LVEF (%)	**0.93 (0.91–0.95)**	**<0.001**	**0.97 (0.94–1.00)**	**0.045**
GLS (%)	**1.13 (1.07–1.19)**	**<0.001**	1.05 (0.98–1.12)	0.197
GCS (%)	**1.08 (1.03–1.13)**	**<0.001**	Not in model	
GRS (%)	**0.93 (0.90–0.97)**	**0.001**	Not in model	
Reservoir strain (%)	**0.89 (0.85–0.93)**	**<0.001**	**0.95 (0.90–0.99)**	**0.024**
Conduit strain (%)	**0.85 (0.79–0.92)**	**<0.001**	Not in model	
Booster pump strain (%)	**0.88 (0.83–0.94)**	**<0.001**	Not in model	
Reservoir SR (s^{-1})	**0.12 (0.04–0.36)**	**<0.001**	Not in model	
Conduit SR (s^{-1})	**4.12 (1.38–12.25)**	**0.011**	Not in model	
Booster pump SR (s^{-1})	**4.34 (1.89–10.00)**	**0.001**	Not in model	

To avoid collinearity and to account for patients and MACE numbers, multivariable models include all significant baseline parameters ($P < 0.05$) in univariable analyses but only LVEF and one LV strain (GLS) as well as one LA strain (εs) parameter. *P* values in boldface type indicate a significant difference.

Table 4—Predictors of MACE in univariable and multivariable Cox regression analysis in patients with DM

	Univariable		Multivariable	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	**1.04 (1.01–1.08)**	**0.012**	1.01 (0.97–1.06)	0.511
Killip class	**2.01 (1.49–2.71)**	**<0.001**	**1.91 (1.30–2.82)**	**0.001**
TIMI flow grade post-PCI	**0.61 (0.41–0.91)**	**0.014**	1.04 (0.55–1.97)	0.906
Atrial fibrillation	**2.52 (1.06–6.04)**	**0.038**	1.41 (0.44–4.58)	0.563
LVEF (%)	**0.96 (0.92–0.99)**	**0.008**	0.99 (0.96–1.03)	0.739
LV GLS (%)	**1.14 (1.07–1.22)**	**<0.001**	**1.11 (1.03–1.20)**	**0.010**
LV GCS (%)	**1.08 (1.03–1.14)**	**0.002**	Not in model	
LA reservoir strain (%)	**0.94 (0.89–0.99)**	**0.028**	0.99 (0.93–1.05)	0.747
LA booster pump strain (%)	**0.91 (0.85–0.99)**	**0.024**	Not in model	

To avoid collinearity and to account for patients and MACE numbers, multivariable models included all significant baseline parameters ($P < 0.05$) in univariable regression analyses but only LVEF and one LV strain (GLS) as well as one LA strain (reservoir strain [εs]) parameter. *P* values in boldface type indicate a significant difference.

CMR Functional and Infarct Characteristics

Infarct characteristics as well as LV and LA functional metrics are provided in Table 2. Tissue characterization parameters were similar between patients with and without DM, including IS (12.8% vs. 13.5%, $P = 0.74$) and MO (0.5% vs. 0.3%, $P = 0.65$). There were no differences in LV functional metrics between patients with and without DM, including LVEF (50.1% vs. 50.7%, $P = 0.50$), GLS (−16.1% vs. −16.4%, $P = 0.22$), GCS (−23.7% vs. −23.9%, $P = 0.91$), and GRS (20.7% vs. 20.2%, $P = 0.81$). In comparison with patients without DM, LA function was impaired in patients with DM, including LA reservoir (19.8% vs. 21.2%, $P < 0.01$) and conduit functions (7.6% vs. 9.0%, $P < 0.01$).

Prognostic Value of LV and LA Function

Patients with DM were more likely to experience MACE during the 12-month follow-up shown in univariable Cox regression (HR 2.31 [95% CI 1.53–3.49], $P < 0.001$) and Kaplan-Meier–associated log-rank testing ($P < 0.001$) (Fig. 2). In patients without DM, age, LVEF, and total atrial strain (εs) were independently associated with MACE in multivariable Cox regression analysis (Table 3). In contrast, LVEF was no longer independently associated with MACE in the subset of patients with DM (Table 4). In patients with DM, GLS appeared as the only functional CMR parameter with independent association to MACE. Accordingly, Kaplan-Meier plots of patients with DM showed the inability of LVEF to differentiate patients with high and low risk for MACE (Fig. 3*A*) and demonstrated that the majority of MACE occurred in patients with LVEF ≥35% ($n = 22$ [9.3%] vs. 5 [18.5%] for ≥35% LVEF vs. <35% LVEF, respectively). Considering only patients with DM and LVEF ≥35% ($n = 237$), GLS and LA reservoir strain below the median were significantly associated with higher 12-month event rates (Fig. 3*B–D*). There was a nonsignificant numerical increase in AUC for mortality prediction in patients with DM (LVEF AUC 0.63 vs. LVEF + GLS AUC 0.77 [$P = 0.098$] or LVEF + GLS + εs AUC 0.78 [$P = 0.062$]) and less pronounced in patients without DM (LVEF AUC 0.68 vs. LVEF + GLS AUC 0.69 [$P = 0.0335$] or LVEF + GLS + εs AUC 0.79 [$P = 0.067$]). Case-control matching on the basis of variables found to be different between patients with and without DM in Mann-Whitney *U* testing (LV mass, end-diastolic volume [EDV], stroke volume [SV], and atrial function) revealed a match of 170 patients with DM to 170 patients without DM. In Kaplan-Meier plots with associated log-rank testing, LVEF statistically significantly classified high- and low-risk groups in the overall population ($P = 0.001$) and the non-DM subpopulation ($P < 0.001$) but not in the patients with DM ($P = 0.144$) (Fig. 4).

DISCUSSION

The current study is the first to comprehensively compare the prognostic value of LV deformation indexes determined by CMR-FT between patients with and without DM in a large, multicenter population of patients following AMI. The results indicate a significantly higher 12-month MACE rate in patients with DM, with the majority of MACE occurring in patients with LVEF ≥35%. In patients without DM, LVEF and total atrial strain independently predicted adverse events. However, in patients with DM, LV GLS emerged as the only functional independent predictor of poor prognosis. In patients with DM with LVEF >35%, LV GLS and LA reservoir provided incremental prognostic value for MACE above LVEF. Therefore, estimates of LV and LA longitudinal function enable optimized risk assessment in patients with DM after AMI.

DM is a major cardiovascular risk factor and associated with increased mortality. Data from the Framingham Heart Study have reported a twofold increase in mortality comparing study participants with and without DM (29). Furthermore, perhaps unsurprisingly, DM is highly and significantly associated with increased mortality following AMI. The present data confirm a similar twofold increase in risk for MACE. However, this increased risk for MACE seems irrespective of morphologic infarction properties,

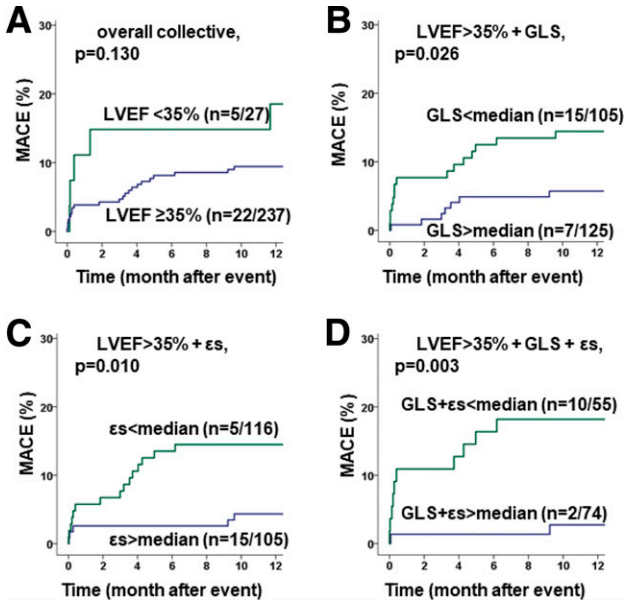

Figure 3—Kaplan-Meier curve of patients with DM showing first the inability of LVEF to differentiate those with high and low risk for MACE and demonstrating that the majority of MACE occur in patients with LVEF ≥35% (*A*), while GLS (median −16.1%) and εs (median 19.8%) allow such classification in patients with LVEF ≥35% (*B–D*).

since CMR-derived infarction characteristics (11) including IS, MO, area at risk, and myocardial salvage were statistically similar between patients with and without DM.

To date, LVEF is considered the most established parameter for risk assessment in cardiovascular disease (10). Traditionally, a threshold of 35% is clinically used to subject patients to defibrillator implantation following AMI (30). Due to constant advances in the treatment of AMI (2), most patients, however, present with an LVEF ≥35% following AMI. Consequently, although the relative risk is lower, the majority of MACE are found within the initially termed low-risk group of LVEF ≥35%, thus reducing the diagnostic value of LVEF in general. This observation also applies to the present collective and especially patients with DM where LVEF was shown to be unable to stratify patients according to high and low risk for MACE. Additionally, changes in cardiac morphology beyond macrovascular dysfunction caused by DM have to be taken into consideration, which affect and reduce the diagnostic value of LVEF in this selected patient population. Reports have indicated that DM-associated decreases in LV chamber size as appreciated by a significant reduction in EDV but not end-systolic volume (ESV) result in reduced SVs but preserved LVEF (6). Similar observations were made within the present AMI collective. EDV was significantly reduced between patients with and without DM, while ESV was not. As a result, SV was reduced in patients with AMI and DM compared with those with AMI without DM, while both groups showed similar values for LVEF (median >50%, respectively). Indeed, LVEF was a strong and independent predictor of MACE in patients with AMI and DM but not in those with AMI without DM, as appreciated from multivariable Cox regression analyses. Consequently, established CMR volumetric and tissue characterization techniques (11,14) might not meet the requirements for risk stratification in the DM population, and novel techniques are warranted for improved risk stratification. Recently, CMR imaging has demonstrated the ability to detect early changes in endothelial damage in DM (31), which might elaborate on the pathophysiological understanding and the early interplay of DM and vascular disease. Their potential impact on LV remodeling in DM may result in decreased cavity size and SVs but preserved LVEF, similar to changes observed in HF with preserved EF (HFpEF). It is important to note that preserved LVEF does not necessarily equal preserved LV

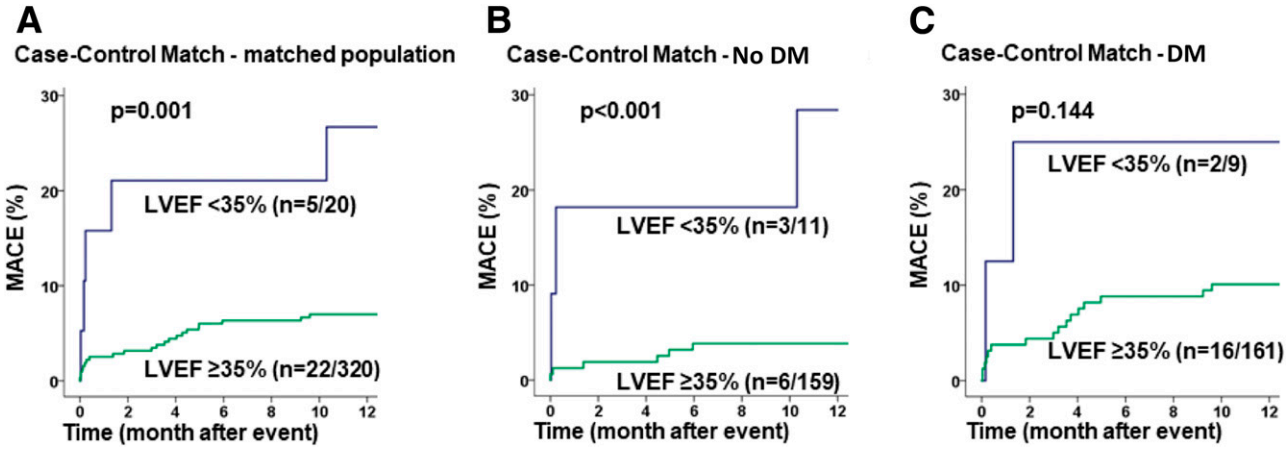

Figure 4—Kaplan-Meier curve for case-control matched patients with and without DM (n = 340). LVEF discriminates low- and high-risk patients within the case-control matched population (*A*) as well as the subgroup of patients without DM (*B*) but fails to differentiate risks in patients with DM (*C*).

function as shown by deformation imaging in HFpEF (32), which may also apply to patients with DM and AMI. Indeed, evidence indicates changes of LV myocardial deformation in DM, including GCS and GLS (33,34). On the one hand, LV functional deformation parameters were similar between patients with and without DM. On the other hand, subtle changes in LV contractility caused by DM could be masked by the stronger impact of AMI on GLS followed by GCS in both groups (9,35). Notwithstanding, the additional value coming from deformation imaging in risk stratification outperformed LVEF in patients with AMI with DM but not in those with AMI without DM. In addition, diastolic dysfunction is strongly linked to atrial dysfunction, as known from the HFpEF population (9,36,37), and has been demonstrated to strongly predict outcome following AMI (9,38). In patients with uncomplicated type 2 DM, a decrease of atrial reservoir and conduit strain paralleled by an increase in active booster pump strain was demonstrated and, as opposed to volumetric assessments, was independently linked to functional capacity (39). Indeed, in the current study population, patients with DM suffered from further impairments of atrial reservoir and conduit strain compared with those without DM, which added incremental diagnostic value in patients with DM in addition to LVEF as appreciated from Kaplan-Meier curves. However, as opposed to patients without DM, atrial strain held no independent prognostic value in multivariable analyses in patients with DM. On the one hand, GLS might sufficiently capture LV longitudinal dysfunction, which essentially is also reflected in total atrial strain (40), and on the other hand, it might additionally be attributed to limits of sample size in patients with DM as opposed to those without DM. Nevertheless, on the basis of our data, deformation imaging of both ventricular and atrial function allows superior risk stratification in patients with DM.

Limitations

Several limitations apply. Classification of DM was based on previous medical records and medical treatment. Hemoglobin A_{1c} levels (%) at admission were not systematically assessed and are therefore not available for the current analysis. Furthermore, hemoglobin A_{1c} frequently reaches normal levels under adequate medical therapy. This CMR substudy was conducted among eight centers that took part in the multicenter trials AIDA STEMI and TATORT NSTEMI. Consequently, although the CMR protocol was identical and analyses were performed in a core laboratory, imaging was performed on different scanner platforms/vendors using different field strengths. CMR was performed in median on day 3 (IQR 2, 4), but outliers exist, with imaging occurring within 10 days. This was potentially a result of a more severe course of disease, preventing earlier CMR imaging. This could also represent a selection bias, with more severely impaired patients not undergoing imaging at all. Nevertheless, there was no statistical difference between patients with and without DM; thus, statements regarding the impact of DM remain comparable. Only one-quarter of all patients had DM. On the one hand, this might have led to loss of significance in multivariable models as opposed to patients without DM with threefold the patient number. On the other hand, variables retaining significance in patients with DM can be considered robust.

Conclusion

In patients with DM, a volumetric approach using LVEF for risk stratification may be less reliable because of DM-associated LV remodeling resulting in smaller cavity sizes and SVs but preserved LVEF. LV deformation assessment overcomes this limitation with incremental prognostic value over and above that of LVEF in patients with DM but not those without DM. Cardiac dysfunction in patients with DM also comprises impaired LA function, which may additionally indicate DM-associated LV diastolic dysfunction and adds further value for precise risk stratification, especially in patients with preserved EF.

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