Differences in the prognostic relevance of myocardial ischaemia and scar by cardiac magnetic resonance in patients with and without diabetes mellitus

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Aims
To evaluate the prognostic significance of myocardial ischaemia and scar in patients with and without diabetes mellitus (DM) who undergo dobutamine stress cardiac magnetic resonance (DCMR) and late gadolinium enhancement (LGE) imaging for known and suspected coronary artery diseases (CADs).

Methods and results
A total of 1969 consecutive patients [age 63 ± 12 years, 29% female, left ventricular ejection fraction = 59 ± 12%] referred for a cardiac magnetic resonance (CMR) examination including DCMR and LGE with the suspicion of CAD or progression of CAD in three tertiary cardiac centres were analysed. Cardiac death and nonfatal myocardial infarction (MI) were registered as hard cardiac events. Patients with a revascularization procedure within the first 3 months after CMR were censored at the time of ‘early’ revascularization. Patients were followed for 3.2 ± 1.5 years (median 2.9, interquartile range 2–4.3 years). In total, 90 (4.6%) cardiac deaths and MI were registered. Among them, 328 patients (16.6%) had diabetes. The proportion of dobutamine-induced wall motion abnormalities (DWMA) and LGE was higher in patients with DM when compared with those without DM (27 vs. 19% and 53.6 vs. 41.2%, respectively, P < 0.001 for both for proportions). Both DWMA and LGE were independent predictors of cardiac death and MI in patients without DM (HR for DWMA 8, CI 4.5–14.3, HR for LGE 2.1, CI 1.1–4.1) and with DM (HR for DWMA 8.6, CI 3.5–21, HR for LGE 4.5, CI 1.5–13.1). Tests for interaction showed that LGE more strongly influences prognosis in patients with than in those without DM (P = 0.03 for interaction), whereas the presence of DWMA is related to similarly poor outcomes in patients with and without DM (P = NS).

Conclusion
Myocardial scar by LGE is a hallmark of markedly poorer outcome in patients with DM, while the presence of inducible myocardial ischaemia seems to be predictive both in patients with and without DM. Both markers surpass the predictive value of conventional atherogenic risk factors both in patients with and without DM.

Keywords
late gadolinium enhancement • myocardial scar • diabetes mellitus • coronary artery disease • cardiovascular magnetic resonance imaging • prognosis • outcome

Introduction
The presence of diabetes mellitus (DM) is associated with an early onset and high prevalence of coronary artery disease (CAD). In this regard, the lack of anginal symptoms and the presence of silent myocardial ischaemia or even infarction in patients with DM represent a major challenge for clinicians. Moreover, the risk of future cardiac events is almost two-fold higher in patients with DM. Thus, patients with DM but without prior myocardial infarction (MI) have similar risk for future MI, as patients with previous MI. In light of these data, risk stratification of such patients gains major importance in the clinical routine.
Of all cardiac imaging modalities, the versatility of cardiac magnetic resonance (CMR) allows the best assessment of myocardial function, ischaemia, and viability within a single examination and without the use of radiation. Using late gadolinium enhancement (LGE), myocardial scars were found in patients without anginal symptoms or electrocardiographic signs of previous MI. An additional stress examination to detect myocardial ischaemia allows for the detection of either stress-induced perfusion defects (i.e. adenosine stress) or onset of new myocardial wall motion abnormalities (WMA) (dobutamine stress). Although the vasodilator tests appear to be more often used in the clinical practice, robust data are available on the role of dobutamine CMR (DCMR) in the diagnosis and risk stratification of patients with suspected and known CAD. Even though CMR is a well-established modality for the detection of myocardial ischaemia and scar, limited data are available to date on the prognostic impact of these two variables in patients with DM.

We, therefore, sought (i) to compare the incidence of myocardial ischaemia and scar by DCMR and LGE, respectively, (ii) and to evaluate their prognostic impact compared with conventional atherogenic risk factors, in patients with and without DM, who underwent CMR for known or suspected CAD.

Methods

Study population

The study was performed in concordance to the standards of our local ethics committees. A written informed consent was obtained in all patients. A total of 1969 consecutive patients (63 ± 12 years, 29% female) were prospectively enrolled and underwent DCMR and LGE in three high-volume tertiary cardiovascular centres (University Hospital Heidelberg, German Heart Centre Berlin, and King’s College London) from January 2000 to January 2008. The decision to perform a DCMR was left at the discretion of the referring physician and was usually based on the cardiovascular profile of each patient, clinical presentation as well as the results of previous stress test (i.e. exercise electrocardiogram (ECG)). Only patients who were primarily referred for suspected CAD or CAD progression were included in our analysis. The centres performing the examination were not directly involved in the referral process for DCMR. In addition, LGE acquisitions are part of our DCMR protocol when no contraindications exist. All patients included in our study received DCMR with LGE. At the time of DCMR, clinical data, including conventional cardiovascular risk factors and history of CAD defined as either prior MI, prior revascularization, or angiographically confirmed CAD (>50% stenosis), were collected. The following conventional cardiovascular risk factors were taken into account: (i) DM, defined as a previous diagnosis of DM (HbA1c > 6.5 mg/dL, 48 mmol/mol IFCC) or anti-diabetic medication at the time of the examination; (ii) obesity defined as body mass index (BMI) > 30 kg/m²; (iii) arterial hypertension defined as a previous diagnosis of arterial hypertension (blood pressure values > 140/90 mmHg) or the presence of anti-hypertensive medication; (iv) hyperlipidaemia defined as a previous diagnosis of hyperlipidaemia (LDL values > 130 mg/dL) or the presence of lipid-lowering medication; (v) previous or current smoking; and (vi) family history of CAD. Patients with clinical instability due to an acute coronary syndrome (unstable angina, MI) within the last 4 weeks, uncontrolled blood pressure values (systolic blood pressure ≥ 180 mmHg at baseline) as well as patients with an implantable device unsuited for a CMR examination were excluded from the analysis. Furthermore, owing to the association of nephrogenic systemic sclerosis with the administration of gadolinium, patients with a reduced glomerular filtration rate (< 30 mL/min/1.73 m²) were also excluded from the study.

Image acquisition

The examinations were performed on 1.5-Tesla (Achieva System, Philips Medical Systems, Best, the Netherlands located in Heidelberg and Philips Intera CV, Best, the Netherlands located in Berlin) and 3.0-Tesla (London, Philips Achieva) clinical whole-body CMR scanners.

Dobutamine stress protocol

The image acquisition and dobutamine stress protocols were previously described.

Late gadolinium enhancement

Standard protocols for each scanner were used for LGE image acquisitions. In short, LGE images were generally acquired 10–15 min after bolus injection of 0.2 mmol/kg gadolinium DTPA (Magnevist, Bayer-Schering, Germany) with an inversion-recovery 3D spoiled gradient echo sequence. Inversion time was determined using a real-time plan scan. Typical parameters were a field of view of 400 × 400 mm², a matrix of 256 × 256 pixels, a slice thickness of 5.00 mm, overlapping slices (50%), a flip angle of 15 degrees, a time to echo of 1.36 ms, and a time to repeat of 4.53 ms.

Image analysis

View Forum software (Philips Medical Systems, Best, the Netherlands) was used to analyse the acquired images. Short-axis as well as long-axis views were evaluated, and segmental WMA at rest and during peak stress were graded according to the current 17-segment model recommended by the AHA guidelines (0 = normal wall motion, 1 = hypokinesia, 2 = akinesia, and 3 = dyskinesia). The presence of resting wall motion abnormalities (RWMA) was noted, and a ≥ 1 grade worsening during dobutamine stress in at least one segment was considered as a positive result for inducible ischaemia and defined as dobutamine-induced wall motion abnormalities (DWMA). The same 17-segment model was used to score the presence of LGE. The presence, type (ischaemic and/or non-ischaemic) as well as extension of LGE was noted. Both DWMA and LGE were read during the routine examination of the patient by examiners with Level III CMR accreditation. The assessment of LGE was preformed visually. Only segments that showed LGE in at least two corresponding acquisitions (i.e. short axis and long axis) were considered.

Follow-up and definition of the end points

The study end points were considered non-fatal MIs and cardiac deaths, defined as sudden death caused by arrhythmia or MI or end-stage heart failure. Non-fatal MI was defined as an angina of >30 min duration and/or a ST segment elevation of ≥ 2 mm in two consecutive ECG leads and a specific kinetic in cardiac biomarkers (i.e. troponin T of ≥0.03 μg/L). Data on follow-up were obtained either from the patients’ electronic charts (outpatient visits, admission charts) or, when needed, through study nurses unaware of the CMR result who contacted each individual or an immediate family member, general practitioner, or the referring physician by phone in the case of death and noted the occurrence of any of the study end point. The follow-up time was calculated from the day of the CMR examination to the day the end point was reached or the day of the last telephone interview or review of the electronic charts. Patients were followed up regularly at 6 months intervals. Patients who underwent early revascularization (in the first 3 months) were censored at the time of the revascularization procedures.
Statistical analysis
Continuous variables are expressed as mean ± standard deviation, while categorical variables are expressed as proportions. Unpaired Student’s t-tests were used to compare continuous variables between patients who reached the end point and those who did not reach it, as well as for patients with and without DM. Group differences between ordinal variables were tested using the exact Mann–Whitney test, and differences between nominal variables were assessed using Fisher’s exact tests. All tests were two-tailed. The association of the studied parameters with the end point in patients with and without DM was evaluated using a series of Cox proportional hazard models. At first, a univariate model was constructed for each cohort by entering the studies demographic (age, gender), clinical (more than three cardiovascular risk factors, previous CAD, and previous revascularization procedures), and CMR-derived parameters (RWMA, LGE, and DWMA). The multivariate models were constructed by a backward approach with deletion of the least significant variables until all variables had a P-value of < 0.2. A test for interaction was performed to evaluate the effect on prognosis of each of the studied CMR-derived parameters in patients with vs. without DM. Furthermore, to evaluate for possible confounders between the DM and non-DM population, further interaction tests were performed including gender, hypertension, hyperlipidaemia, obesity, previous CAD, and previous revascularization. Kaplan–Meier curves were used to estimate survival and to calculate the annual rates for cardiac events. To test for inter-observer variability, a random subset of cases (n = 150) cine and LGE images were re-read by observers blinded to patient identity, clinical, and other CMR data (S.K. and G.K.). Both the observers have been certified according to Level III criteria regarding SCMR and ESC regulations. Agreement between blinded observers and clinical reads for the interpretation of wall motion and LGE was calculated using k-statistics. MedCalc Statistical Software version 12.7.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) was used for the analysis. A P-value of < 0.05 was considered statistically significant.

Results

Demographic and clinical data
Patients were followed for 3.2 ± 1.5 years (median 2.9, interquartile range 2–4.3 years). In total, 90 (4.6%) hard events were registered, 81 (4.1%) patients had an early revascularization procedure, and 73 patients had a late revascularization procedure.

RWMA were noted in 744 (38%) patients, 852 (43%) showed LGE, and DWMA was detected in 393 (20%) patients. Of these, 616 (31%) patients showed LGE without DWMA, 157 (8%) DWMA without LGE, and 236 (12%) had both LGE and DWMA. 328 (17%) patients were diagnosed with DM at the time of the CMR examination. As seen in Table 1, patients with DM exhibited significantly higher burden of cardiovascular risk factors and higher rates of previous CAD, previous revascularization, RWMA, LGE, and DWMA compared with patients without DM.

Type of LGE
From 852 patients with positive LGE, the majority exhibited CAD-related patterns, including 635 (75%) patients with subendocardial and 155 (18%) with transmural patterns. The remaining 62 (7%) patients had non-CAD-related patterns, including 16 patients with cardiac amyloidosis, 2 patients cardiac sarcoidosis, 18 patients hypertrophic cardiomyopathy, and 26 patients with idiopathic dilated cardiomyopathy.

Univariate and multivariate analyses
Univariate predictors of cardiac deaths and MI in patients without and with DM are shown in Table 2A and B. After inclusion of age, gender, cardiovascular risk factors, previous CAD, previous revascularization, RWMA, DWMA, and LGE by backward multivariable analysis, LGE and inducible WMA were independent predictors of atherogenic risk factors of cardiac death and MI in both patients with and without DM ($\chi^2 = 35$ and $\chi^2 = 61$, respectively, $P < 0.001$ for both). Testing for interaction LGE but not DWMA exhibited different influence in patients with and without DM ($P = 0.03$ for LGE and $P = 0.8$ for DWMA in terms of interaction with DM, respectively). Moreover, the additional interaction tests did not show any direct influence of gender ($P = 0.3$), hypertension ($P = 0.2$), obesity ($P = 0.2$), hyperlipidaemia ($P = 0.1$), previous CAD ($P = 0.8$), and previous revascularization procedures ($P = 0.4$) in patients with and without DM.

Kaplan–Meier survival curves
Figure 1 presents the survival probability in patients without and with DM based on the two CMR parameters that showed to be independently related to prognosis. The presence of DWMA alone was related to a similar yearly likelihood of cardiac deaths and MI of up to 3% in patients without ($\chi^2 = 76$, $P < 0.001$, HR = 7.1, CI = 3.2–5.4) and with DM ($\chi^2 = 31$, $P < 0.001$, HR = 7.5, CI = 3–19.4). Conversely, as seen in Table 3, the yearly rate of cardiac deaths and MI of up to 4% in patients with DM and LGE ($\chi^2 = 9$, $P = 0.002$, HR = 4.3, CI = 3–9.5) was two-fold higher compared with that of up to 2% in patients without DM but with LGE ($\chi^2 = 8.5$, $P = 0.003$, HR = 2.1, CI = 1.3–3.6). Thus, patients with LGE and DM exhibited markedly poorer outcomes compared with all other subgroups.

Testing the effect of conventional risk factors on survival, the presence of these factors was not predictive for the poor outcome in patients with DM. Merely the presence of CAD was predictive of the combined end point in patients without DM (Figure 2).

Inter-observer variability
Agreement between observers interpreting CMR data during clinical reads vs. blinded reads on a patient level was 94% (weighted k = 0.86; 95% CI = 0.77–0.95) and 97% (weighted k = 0.93; 95% CI = 0.87–0.99), respectively, for the presence or absence of inducible WMA and LGE, respectively.

Discussion
In a cohort of 1969 patients with known or suspected CAD who underwent DCMR and LGE, we found the following:

(i) A higher prevalence of resting WMA, myocardial scar, and ischaemic myocardium in patients with DM when compared with those without DM.

(ii) LGE and inducible WMA are predictors for death/MI, which surpass the value of conventional atherogenic risk factors both in patients with and without DM.
In this respect, we found a higher prevalence of arterial disease, notably arterial hypertension, hyperlipidaemia, and obesity in our diabetic cohort. Moreover, patients with DM had a higher prevalence of previous CAD and revascularization procedures. In our study, patients with DM exhibited approximately a two-fold risk for future cardiovascular events, which is in agreement with previous clinical trials.

Appropriate diagnostic recommendations integrating prognostic indicators for a careful follow-up of patients with DM with known or suspected CAD are lacking. Several imaging modalities were shown to aid in the risk stratification of patients with DM. CMR is a unique technique for the detection of (i) myocardial scar with high blood-to-tissue contrast due to ‘nulling’ of the remote myocardium.
Table 2  Univariate und multivariate predictors of cardiac events for the studied cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate analysis</th>
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<th>Multivariate analysis</th>
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<tr>
<td></td>
<td></td>
<td>HR (CI)</td>
<td>P</td>
<td>HR (CI)</td>
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<tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Gender</td>
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<tr>
<td>&gt;3 Risk factors (excluding DM)</td>
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<tr>
<td>Previous revascularization</td>
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<td>0.4</td>
<td></td>
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</tr>
<tr>
<td>Prev. CAD</td>
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<td>0.2</td>
<td>1.8 (1.1–3.1)</td>
<td>0.02</td>
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<tr>
<td>RWMA</td>
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<td>DWMA</td>
<td>8.1 (4.5–14.5)</td>
<td>&lt;0.001</td>
<td>8 (4.5–14.3)</td>
<td>&lt;0.001</td>
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<td>LGE</td>
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<td>0.04</td>
<td>2.1 (1.1–4.1)</td>
<td>0.04</td>
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<tr>
<td>With DM (n = 328)</td>
<td></td>
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</tr>
<tr>
<td>Age</td>
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<td>0.2</td>
<td></td>
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</tr>
<tr>
<td>Gender</td>
<td>1.5 (0.5–4.5)</td>
<td>0.5</td>
<td></td>
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<tr>
<td>&gt;3 Risk factors (including DM)</td>
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<td>0.6</td>
<td></td>
<td></td>
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<tr>
<td>Previous revascularization</td>
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<tr>
<td>Prev. CAD</td>
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<td>0.8</td>
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<tr>
<td>RWMA</td>
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<td>8.6 (3.5–21)</td>
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<td>0.3</td>
<td>4.5 (1.5–13.1)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

For both tables: >3 risk factors: more than three cardiovascular risk factors as specified; prev. CAD, previous coronary artery disease; RWMA, resting wall motion abnormalities; DWMA, dobutamine-induced wall motion abnormalities; LGE, late gadolinium enhancement.

Figure 1  Survival analysis in patients with known or suspected CAD with or without DM undergoing DCMR and CMR with LGE. In the non-diabetic population, the presence of scar in addition to inducible ischaemia does not further increases the likelihood of cardiac events. Conversely, in the diabetic population, the presence of scar and inducible ischaemia together significantly increases the likelihood of cardiac events compared with either scar or ischaemia alone.
and of (ii) inducible WMA during stress testing. Both myocardial scar and inducible WMA are established markers of the adverse outcome in patients with ischaemic heart disease.\textsuperscript{6}

**Myocardial ischaemia and prognosis in diabetes mellitus**

Consistent with previous studies, as well as our previous reports, the presence of DWMA was a robust predictor of the poor outcome in our cohort, irrespective of the presence or absence of DM.\textsuperscript{7,8,11} In addition, inducible WMA showed the highest HR for death/MI compared with all other variables, which is in agreement with data originating from a recent meta-analysis in this field.\textsuperscript{5} Although patients with DM had a higher prevalence of CAD, RWMA, DWMA, and LGE, only LGE and inducible WMA were independent predictors of the outcome in our multivariate model. However, in the case of inducible WMA, LGE did not add to the likelihood of developing cardiac events above DWMA (Figure 3). The prognostic power of induced myocardial ischaemia is mainly attributed to the detection of jeopardized myocardium. Because patients with DM are more likely to develop earlier and more extensive CAD,\textsuperscript{17,18} DWMA carries a strong prognostic value in this population cohort. This hypothesis could be confirmed in our patient cohort. However, the predictive value of DWMA was similar in patients with and without DM.

**Myocardial scar and prognosis in diabetes mellitus**

The prognostic value of LGE was already confirmed in several clinical conditions such as myocarditis,\textsuperscript{19} aortic stenosis,\textsuperscript{20} hypertrophic cardiomyopathy,\textsuperscript{21} atrial fibrillation,\textsuperscript{22} and chronic heart failure.\textsuperscript{23} In our study, similarly to DWMA, the presence of LGE was an independent predictor of cardiac deaths and MI both in patients with and without DM. How LGE translates to an adverse prognosis is not completely understood. It can be anticipated that the distortion in electrical current generation and conduction in areas of scarred myocardium may result to increased rates of ventricular arrhythmias in such patients.\textsuperscript{24} Moreover, the presence of myocardial scar is usually accompanied by decreased systolic performance, which may translate in an increased risk of sudden death due to arrhythmias or heart failure. At a molecular level, increased levels of LDL-cholesterol, decreased levels of HDL-cholesterol as well as endothelial dysfunction might explain the increased rate of cardiovascular events seen in patients with DM. Apart from that and independent from the progression of CAD, altered fatty acid metabolism, deregulated mitochondrial phosphorylation, and decreased glucose oxidation play an additional deleterious role in the prognosis of patients with DM.\textsuperscript{25,26}

When analysing the association of DM and other risk predictors, we found that the detection of LGE in DM is an indicator for death and MI. Thus, in diabetic patients, the presence of scar may worsen their outcome. Furthermore, the poor hallmark of LGE in patients with DM is already clinically evident within the first year of follow-up, whereas in patients without DM, the presence of LGE does not substantially increase the cumulative event rate within the first 3 years (Table 3). Interestingly, although RWMA were more prevalent in the diabetic cohort, the multivariate model did not identify this parameter to be associated with prognosis. This may be attributed to the fact that RWMA does not necessarily reflect myocardial scar but may translate to hibernating or stunned myocardium with favourable functional and clinical outcomes compared with scarred tissue.\textsuperscript{4}

Our findings are in agreement with previous studies, where increased mortality was reported for patients who exhibited LGE. Kwong et al. showed in 195 patients without a clinical history of MI a higher likelihood of future cardiac events in those who had LGE during CMR,\textsuperscript{4} a finding that was recently confirmed in a prospective study performed in a cohort of elderly presumably healthy individuals.\textsuperscript{27} Similarly to our study, LGE was an independent predictor of future cardiac events. In another recent study in patients with DM without clinical signs of MI, the authors found a strong correlation of LGE with an unfavourable prognosis in the diabetic population, which surpassed the prognostic value of conventional clinical, demographic, and imaging-derived cardiovascular risk factors.\textsuperscript{28} Another report that included patients with impaired fasting glucose but without overt DM also demonstrated the independent prognostic value of LGE in patients with pre-diabetes.\textsuperscript{29}

### Clinical implications

To the best of our knowledge, this is the first study to compare the prognostic value of two very important CMR-derived parameters, i.e. inducible ischaemia and scar in patients with DM. In light of our findings, it seems reasonable to recommend an invasive strategy for patients with suspicion of CAD and the presence of LGE alone. DCMR, on the other hand, is still expected to play a central role in the management of these patients.
especially in patients with diabetic nephropathy and contraindications to gadolinium administration due to severely impaired renal function.

**Limitations**

First, the analysis involving the diabetic cohort was performed retrospectively, and no 1:1 matching in respect to age and gender and cardiovascular disease burden was performed. However, the high number of individuals included in the analysis and the long-term follow-up period support pertinent conclusions derived from our data set. Moreover, the survival analysis did not point to any relevant independent change in the likelihood of cardiac events depending on the cardiovascular disease burden of patients, as measured by the number of cardiovascular risk factors, previous CAD or previous revascularization procedures, and findings confirmed by interaction tests (Figure 2). Furthermore, our study cohort consists of preselected patients who were referred for further evaluation in tertiary cardiovascular centres. The indication to perform a complete

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**Figure 2** Survival analysis in patients with and without DM based on the cardiovascular burden of each group. (A and B) Note the absence of an effect on the survival in patients without and with DM when the number of cardiovascular risk factors is considered. (C and D) A history of CAD had an influence on survival in patients without but not in those presenting with DM. (E and F) Furthermore, previous revascularization procedures did not influence the outcome of patients with and without DM.
CMR examination was left at the discretion of the referring clinician. Thus, there may be a selective bias towards patients with a substantial cardiovascular disease burden (either through previous CAD or the presence of cardiovascular risk factors). In this context, it is unclear if our data can be translated to an ambulatory setting with patients at lower cardiovascular risk. In addition, the diabetic cohort was not separated in Type 1 and Type 2 diabetes, and no information related to the type of anti-diabetic medication as well as glycaemic control (i.e. HbA1c) was available in the majority of patients. Furthermore, 3T machines may lead to minimal differences in image quality and consequently visual image interpretation. Lastly, a coronary angiography was not systematically performed in patients with inducible ischaemia, as the decision to perform an invasive diagnosis was left to the discretion of the referring physician.

Conclusions
Both myocardial scar and inducible ischaemia by CMR exhibit a strong prognostic value in patients with DM, surpassing that provided by conventional cardiovascular risk factors. Inducible myocardial ischaemia exhibits similar value for the estimation of future cardiac events irrespective of the presence or absence of DM. The presence of myocardial scar in patients with DM, on the other hand, seems to be a hallmark of particularly the poor outcome so that such patients may be candidates for more aggressive pharmacologic, interventional, or surgical treatment options.

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