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Incidence and Prognostic Implication of Unrecognized Myocardial Scar Characterized by Cardiac Magnetic Resonance in Diabetic Patients without Clinical Evidence of Myocardial Infarction

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Abstract

Background—Silent myocardial infarctions (MI) are prevalent among diabetic patients and inflict significant morbidity and mortality. While late gadolinium enhancement (LGE) imaging by cardiac MRI (CMR) can provide sensitive characterization of myocardial scar, its prognostic significance in diabetic patients without any clinical evidence of MI is unknown.

Method and Results—We performed clinically-indicated CMR in 187 diabetic patients who were grouped by an absence (STUDY group, n=109) or presence (CONTROL group, n=78) of clinical evidence of MI (clinical history of MI or Q waves on ECG). CMR imaging and follow-up were successful in 107 (98%) STUDY and 74 (95%) CONTROL patients. Cox regression analyses were performed to associate LGE with major adverse cardiovascular events (MACE) including death, acute MI, new congestive heart failure or unstable angina, stroke, and significant ventricular arrhythmias. LGE by CMR was present in 30/107 (28%) STUDY patients. At a median follow-up of 17 months, 38/107 patients (36%) experienced MACE including 18 deaths. Presence of LGE was associated with a >3-fold hazards increase for MACE and for death (HR: 3.71 and 3.61, P<0.001 and P=0.007, respectively). Adjusted to a model that combines patient age, gender, ST or T changes on ECG, and LV end-systolic volume index, LGE maintained a >4-fold hazards increase to MACE (adjusted HR: 4.13, 95% CI 1.74-9.79, P=0.001). In addition, LGE provided significant prognostic value with MACE and with death, adjusted to a diabetic-specific risk model for 5-year events. A

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Clinical Perspective: With a high prevalence of atypical cardiac symptoms and ECG findings non-specific for acute coronary syndrome, a noninvasive technique that improves the detection of occult myocardial infarction (MI) in diabetic patients may serve to advance the management of the cardiovascular complications of this current global epidemic. In this study, we reported the clinical utility and prognostic implication of late gadolinium enhancement (LGE) by cardiac MRI in detecting myocardial scar from MI in a diabetic cohort without any history or ECG evidence of MI. With excellent tissue contrast and spatial resolution, LGE imaging offers a novel method of myocardial characterization not otherwise captured by regional contractile function and nuclear scintigraphy. There was a high prevalence of LGE at 28% amongst diabetics without a history of MI. This finding was associated with a >3-fold increase in cardiac events and in death. Amongst patients who were detected by LGE imaging to have an unrecognized MI, the reduced median event-free survival was not different from that of a diabetic control cohort who presented with a clinical MI. Furthermore, this study demonstrated that LGE findings provides incremental prognostic value when compared to patient age, gender, ST-T changes on ECG, left ventricular systolic function, and the validated UKPDS 5-year risk engine. In summary, LGE by cardiac MRI can detect subclinical MI and characterize a group of diabetic patients at high risk of cardiac events and death.

Conflict of Interest Disclosures: None

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presence of LGE was the strongest multivariable predictor of MACE and death by stepwise selection in the STUDY patients.

Conclusions—CMR can characterize occult myocardial scar consistent with MI in diabetics without clinical evidence of MI. This imaging finding demonstrates strong association with MACE and mortality hazards, incremental to clinical, ECG, and left ventricular function combined.

Keywords

Diabetes Mellitus; Magnetic Resonance Imaging; Myocardial Infarction; Morbidity; Mortality

The prevalence of diabetes has been projected to increase steeply over next decades[1], affecting more than 300 million patients worldwide.[2] As a consequence, the burden of cardiovascular disease and premature mortality will be expected to rise correspondingly, accounting for an estimated 50-80% of all deaths in diabetics.[3] Despite atypical or absence of cardiovascular symptoms, diabetic patients are at substantially higher risk of serious cardiac events than non-diabetic patients.[4] Late gadolinium enhancement (LGE) imaging using contrast-enhanced cardiac magnetic resonance imaging (CMR) can detect and characterize myocardial scar that is missed by ECG[5], conventional wall motion[6] or nuclear scintigraphic techniques[7], but is associated with important cardiac events including death and recurrent myocardial infarction (MI).[5] In this observational study, we tested the hypothesis that characterization of myocardial scar by LGE imaging can provide strong prognostic value for major adverse cardiac events (MACE) including death in a clinical cohort of diabetic patients without known prior MI. We also aimed to compare the event-free survival of diabetic patients without any clinical evidence of MI but who were found to have LGE by CMR to a control group of diabetic patients with a known history of MI.

Methods

Patient Population

We studied a consecutive series of patients with diabetes mellitus who were referred for a clinical CMR. The diagnosis of diabetes mellitus was based on a history of persistent fasting hyperglycemia[1] and anti-diabetic drug therapy at the time of the CMR referral. Patients were referred to CMR for recent symptoms suspected to be related to coronary artery disease (Table 1). All patients were referred for assessment of left ventricular (LV) regional and global function. Stress CMR imaging was also requested and performed in 88 (47%) patients. LGE imaging was a part of the CMR protocol and performed in all patients. Patients were excluded with: a) suspected or confirmed (by biopsy) myocarditis or infiltrative cardiomyopathy (including cardiac hemochromatosis, amyloidosis, or sarcoidosis), b) concurrent unstable angina, c) NYHA class IV heart failure, d) hemodynamic instability, e) claustrophobia precluding CMR, and f) metallic hazards. As illustrated on Figure 1, patients were categorized into 2 groups by clinical evidence of MI: A) A study group (STUDY) consisted of 109 diabetic patients *without* clinical evidence of MI (no MI by clinical history or medical record *and* no evidence of significant Q waves on ECG in ≥ 2 contiguous leads) and B) a control group (CONTROL) consisted of 78 diabetic patients *with* clinical evidence of MI (historical evidence or significant Q waves in ≥ 2 contiguous leads). Patients with prior coronary intervention and ECG T-wave abnormality were excluded from the STUDY group. All patients provided informed consent before CMR and the institutional ethics committee of Partners Healthcare system approved the study.

Clinical History and ECG Evaluation

All patients underwent a detailed history at the time of CMR. Clinical evidence of MI was based on either documentation of MI by history or medical record or significant Q waves (≥ 2

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contiguous leads) on ECG. History of hypercholesterolemia was defined by any indication for cholesterol-lowering drug treatment according to the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP) guidelines.[8-11] Hypertension history was defined by systolic blood pressure (BP) > 140 or diastolic BP > 90 mmHg, consistent from ≥2 readings obtained from ≥2 visits, or a need for antihypertensive treatment according to the JNC 7 criteria.[12] Significant smoking was defined by >10 pack-years of tobacco use. Resting 12-lead ECGs were obtained on average 3.7±9.0 days from CMR. We excluded any ECG in which a cardiac event or revascularization occurred between the ECG and the CMR. We applied the Minnesota Code criteria for significant Q-waves (codes 1-1 through 1-2, except 1-2-8) as ECG evidence of MI.[13] This was interpreted by computer analysis followed by visual over-reading by a single reader blinded to the CMR results and the clinical outcome. We used the Sokolow-Lyon index to indicate LV hypertrophy on ECG.[14]

CMR Imaging

All patients were studied supine in a 1.5T CMR system (Signa® CV/*i*, GE Healthcare, USA) with a 4-element or 8-element phased-array surface coil. CMR study consisted of cine steady-state free precession imaging (TR/TE 3.4/1.2ms, in-plane spatial resolution 1.6×2mm) of LV function and LGE imaging (TR/TE 4.8/1.3ms, TI 200-300ms) for myocardial scar. All images were acquired using ECG gating and breath-holding. Cine and LGE imaging were obtained in 8-14 matching short-axis (8 mm thick with 0 mm spacing) and 3 radial long-axis planes. A previously described segmented inversion-recovery pulse sequence for LGE was used[15] starting at 15 minutes after cumulative 0.15 mmol/kg dose of gadolinium-DTPA. Parallel imaging techniques (ASSET with an accelerating factor of 1.5 to 2) were used to shorten the patients' breath-hold duration throughout some studies. A single reader categorized LGE as either typical MI (involving the subendocardium) or atypical (subepicardial, patchy midwall or diffuse circumferential subendocardial pattern).

Quantitative Analysis of LGE and LV Function Parameters

All images were analyzed with specialized software (CineTool 5.4.1, GE Healthcare) and were analyzed blinded to the clinical outcome, study group assignment, and patient history. We interpreted LGE as present or absent by the consensus of 2 cardiologists. LGE was considered present only if myocardial enhancement was confirmed on both short-axis and matching long-axis locations. The myocardial mass of LGE (gram) was then quantified by a semi-automatic detection method, using a signal intensity threshold of > 2 standard deviation above a remote reference region as previously reported.[16,17] Following the AHA/ACC 17-segment nomenclature[18], we graded the maximal segmental transmural extent of LGE as 0%, 1-25%, 26-50%, 51-75%, 76-99%, and 100%. We also followed the coronary distribution of the 17-segment model and analyzed the maximal transmural extent in each of left anterior descending, right coronary, and left circumflex coronary artery distribution. We manually traced epicardial and endocardial borders of matching short-axis cine locations at end-systole and end-diastole to determine the LV ejection fraction (LVEF), end-diastolic volume index (LVEDVI), end-systolic volume index (LVESVI), and the LV myocardial mass (end-diastole only).[19,20] LVEF was measured by standard Simpson's Rule using summation of short-axis locations without inter-slice spacing. Segmental wall motion abnormality was graded as present or absent concordant on both the short-axis and the radial long axis views.

Follow-Up

At least 6 months following the CMR, clinical information was obtained from patient telephone interviews using a standard questionnaire, medical records, or by contacting patients' physicians. The median follow-up duration was 17 (range 6 – 57) months. Patients' survival was obtained from the National Social Security Death Index if patients could not be contacted.

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[21] MACE included any of the following: 1) all-cause mortality, 2) new acute MI, 3) unstable angina requiring hospitalization, 4) development or progression of heart failure requiring hospitalization, 5) ventricular arrhythmias requiring appropriate discharge from implantable cardioverter-defibrillator (ICD), and 6) acute cerebral vascular accidents confirmed by neurological MRI or CT imaging. We reviewed all available data including death certificates from regional registry to determine whether a cardiac etiology was the immediate cause of death. New acute MI was defined by elevation of serum troponin. Unstable angina was defined by new chest pain hospitalization without non-cardiac origin of chest pain, and either angiographic coronary stenosis of ≥70% or ischemia on noninvasive imaging. Heart failure was defined by a need for hospitalization for new or worsening symptoms of heart failure. We reviewed any available ICD records in patients who underwent ICD implantation after CMR, for ventricular arrhythmias that required ICD discharge. When a patient experienced >1 MACE, the first event was chosen. When ≥2 MACE occurred simultaneously, the worse event was chosen (death>MI>unstable angina>congestive heart failure>ventricular arrhythmias requiring ICD discharge). CMR results, including LGE and LV function parameters, were made available to the attending physicians on the day of the CMR.

Coronary angiography

Any referral to coronary angiography after CMR was performed per discretion of the attending physician. Coronary angiography performed after CMR was interpreted by the consensus of two cardiologists who reported any significant (>=70%) epicardial coronary stenosis from 2 orthogonal views.

Statistical Analysis

Demographic characteristics by LGE presence were compared by Student's t-test or Fisher's exact test. The survival functions of the cohort patients with and without LGE were compared using Kaplan-Meier statistics and tested for difference by the log-rank tests. In order to determine the *rate* of hazard change over time in this patient cohort, we plotted the cumulative hazard function for MACE and all-cause mortality using the log-event-free-survival plot and log-survival plot, respectively. We fitted Cox proportional-hazards models to estimate the unadjusted hazard ratios (HR) of all the variables. A P-value of < 0.05 was used to determine significance in all testing. The interobserver agreement in qualitative interpretation of LGE has previously been demonstrated by Bland Altman analysis.[5]

We performed 2 separate multivariable Cox regression analyses. In the first analysis, we determined the set of predictors that formed the best overall models for the prediction of MACE and for all-cause mortality, respectively. All clinical, ECG, and CMR variables were considered using a stepwise forward selection strategy with $P < 0.05$ as the inclusion and exclusion levels. We also determined the strongest multivariable predictor for MACE and mortality, respectively, when all variables were considered. In the second analysis, we determined whether there was any incremental prognostic information by LGE imaging beyond patient age, gender, and LV systolic function. In each of the final models, the validity of the proportional-hazards assumption was tested by adding a time-dependent interaction variable for each of the predictors in the models. This assumption was tested valid for all the variables in the final models. All analyses were performed with SAS 9.1 (SAS Institute, Cary, N.C.) for Windows.

Prognostic Implication of LGE by CMR Compared to Standard Validated Risk Model for Diabetic Patients

We used the validated diabetes-specific United Kingdom Prospective Diabetes Study (UKPDS) risk engine by Stevens et al. to assess the 5-year probability of a cardiac event in the STUDY group patients. The UKPDS risk model for $R_T(t=5)$, the 5-year probability of MACE

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in a patient who had diabetes diagnosed for T years, with the assumption of an absence of non-cardiac death, was calculated by the following equation:

$$R_T(t=5)=1-\mathrm{EXP}[-q*d^T*(1-d^t)/(1-d)],$$

where d is the risk ratio of 1.087 per year of diabetes diagnosis; $q=q_0\beta_1^{\text{Age-55}}\beta_2^{\text{Sex}}\beta_3^{\text{Race}}\beta_4^{\text{Smoking}}\beta_5^{\text{H-6.72}}\beta_6^{(\text{SBP-135.7})/10}\beta_7^{\ln(\text{LR})-1.59}$; *Age* is the patient age at diagnosis of diabetes; Sex = 1 for female, otherwise = 0; Race = 1 for Black race, otherwise = 0; Smoking = 1 for current cigarette smoking, otherwise = 0; HgA_{1c} = Hemoglobin A_{1c} in percent obtained within 2 years; SBP = systolic blood pressure in mmHg obtained at the time of CMR; ln(LR) = Natural log of total cholesterol/high density lipoprotein ratio (LR) obtained within 2 years. As defined by Stevens et al., the parameter estimates by maximum likelihood were as follows: q0=0.0112; β_1=1.059; β_2=0.525; β_3=0.39; β_4=1.35; β_5=1.183; β_6=1.088; β_7=3.845. We determined the univariable prognostic association of $R_T(t=5)$ with MACE and death. We then sought to determine the prognostic value of LGE by CMR after adjustment to $R_T(t=5)$.

Statement of Responsibility

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics of the STUDY group

Demographic characteristics of the STUDY group, stratified by presence of LGE, are shown on Table 1. From a consecutive series of 109 patients, 2 (2%) had incomplete CMR study and were excluded from further analysis. Both of these patients were uneventful at the end of the study period. The remaining 107 (67 male, mean age 59±13 years) formed the STUDY cohort. There was a high prevalence of concurrent coronary risk factors such as hypertension and hypercholesterolemia and a minority of patients had prior coronary intervention. On average, STUDY patients had diabetes diagnosed for 10.7±8.5 years. LGE by CMR was present in 30/107 (28%) patients in the STUDY group. Presence of LGE on CMR was associated with a history of cardiac bypass surgery, significant T wave abnormality, elevated 5-year UKPDS event probability, prolonged QRS duration, presence of wall motion abnormality, and reduced global LV function (LVEF, LVEDV, and LVESV indices).

Cardiovascular Outcome of the STUDY Group

At the end of study follow-up (median 17, range 6 – 57 months), 38 patients (36%) in the STUDY group experienced MACE including 18 deaths, 2 acute MI, 10 unstable angina, 5 exacerbations of heart failure, 1 cerebral vascular accident, and 2 ventricular tachycardia necessitating ICD discharge. We could confirm that 14 of the 18 deaths (78%) were cardiac, 2 (11%) were unknown, and 2 (11%) were non-cardiac (both with metastatic cancers). Amongst the cardiac deaths, all had LV dysfunction, 12 of the 14 died as a result of worsening heart failure and 2 had sudden arrhythmic events which failed resuscitation. The 2 patients who developed an acute MI had ST elevation with elevated troponins and severe angiographic coronary stenoses. During followup, 28 of the 107 (26%) STUDY patients were referred to coronary angiography at an average of 160±278 (range 3 to 1282) days after CMR. Nineteen of these 28(68%) patients had angiographically significant coronary stenosis, 10 (53%) undergoing coronary interventions. Coronary intervention during follow-up was not associated with MACE in the STUDY patients (HR 0.75, 95% CI 0.31-1.85, P=0.39). Univariable

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association of clinical, ECG, and CMR variables with MACE and with all-cause mortality is illustrated in Table 2. In the STUDY cohort, while percutaneous coronary intervention, resting wall motion abnormality, LVESVi, LVEDVi, and LVEF were significant predictors of MACE, the presence of LGE demonstrates the strongest association with MACE (χ^2 LR 15.54, HR 3.71, P<0.001) and with all-cause mortality (χ^2 LR 7.27, HR 3.61, P=0.007). The myocardial extent of LGE (as a percent of total LV mass) was associated with hazards to MACE during the study follow-up period, with an estimated 63% increase in hazards for every 10% increase in the myocardial extent of LGE. Average segmental transmural extent of LGE and the number of myocardial segments with LGE were significantly associated with all-cause mortality. Maximal transmural extent of LGE demonstrated a trend association with increased hazards to MACE and with increased hazards to death. LGE involvement in the RCA territory (by maximal transmural extent or number of segments with scar) had a stronger association with MACE or with all-cause mortality than the other 2 coronary territories. Among STUDY patients with resting wall motion abnormality, hypokinesis/akinesis was observed in the anterior, inferior, and lateral LV in 16(15%), 17(16%), and 9(8%) patients, respectively. Location of wall motion abnormality did not demonstrate independent association with MACE or death.

Temporal Pattern of Hazards of Patients in the STUDY Group

Kaplan-Meier curves, stratified by the presence of LGE, for MACE (left) and for all-cause mortality (right) of patients in the STUDY group are illustrated in the top graphs of Figure 2. Both MACE and all-cause mortality were significantly increased in diabetic patients with LGE compared to those without LGE. The bottom graphs of Figure 2 illustrate the corresponding *cumulative hazard function* for MACE (left) and for all-cause mortality (right), respectively, over time during the follow-up period. The *rate* of hazard increase is demonstrated by the slope of the cumulative hazard function curves. The left plot demonstrates that STUDY patients who had LGE experienced MACE at a substantially higher rate than patients who did not have LGE in the first 1 year after study entry. However, patients who were found to have no LGE at study entry developed an increasing rate of experiencing hazards in MACE after the first 2 years of study follow-up. The right plot demonstrates the cumulative hazard function for patient mortality in the study cohort. A similar pattern of increasing hazards for patient mortality was observed as for MACE. Hazards of all-cause mortality increased at an increasing rate beyond the first 2 years of study follow-up.

Multivariable Analyses of Patients in the STUDY Group

When all variables in Table 1 were considered in the multivariable forward selection strategy, presence of LGE was the strongest multivariable predictor selected for association with MACE and with all-cause mortality. At the predefined selection level of entry (P=0.05), no other variable qualified to enter the selection models after LGE was selected, for MACE and for all-cause mortality, respectively. Furthermore, adjusted to patients' age, gender, any abnormal ST or T changes on ECG, and LVESVi, the presence of LGE showed significant incremental prognostic value to MACE, increasing model χ^2 by 9.38 (p=0.002) with a more than 4-fold adjusted hazards increase to MACE (adjusted HR 4.13, 95%CI 1.75-9.74, P=0.001) (Figure 3). In addition, when adjusted to patients' age, gender, and LVESVi, the presence of LGE had significant incremental predictive value for all-cause mortality, increasing model χ^2 LR by 7.32 (p=0.007) with a more than 5-fold adjusted hazards increase to all-cause mortality (adjusted HR 5.03, 95%CI 1.62-15.58, P=0.005) (Figure 3). Adjusted to the effects of resting wall motion abnormality, LGE provided incremental association with MACE and death (adjusted HR 4.59, P<0.001; and 4.73, P=0.01, respectively).

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Prognostic Association of LGE Adjusted to the UKPDS 5-year Probability Risk Model and Metabolic Parameters in the STUDY Group

Metabolic panel (HgA_{1c} and fasting LR) performed within 12 months of CMR was available in 98 of 107 STUDY patients (92%). Mean $R_T(t=5)$ in the STUDY group was 0.082±0.078 (range 0.003-0.395). While a significant higher mean $R_T(t=5)$ was found among STUDY patients with LGE (0.111±0.088 vs. 0.070±0.062, P=0.01), $R_T(t=5)$ did not demonstrate significant prognostic association with MACE or death. Adjusted to the $R_T(t=5)$, LGE maintained strong association with MACE (HR 3.89, 95%CI 1.92-7.87, P<0.001) and death (HR 3.38, 95%CI 1.24-9.25, P=0.02). Adjusted to each of HgA_{1c}, duration of diabetes in years, LR, SBP, LGE maintained strong association with MACE (HR 3.37, P<0.001; HR 3.46, P<0.001; HR 3.37, P<0.001; and HR 3.74, P<0.001, respectively) and with death (HR 3.49, P=0.01; HR 3.46, P=0.01; HR 3.05, P=0.03; and HR 3.62, P=0.007, respectively). In addition, LGE percent (per 10% of LV mass involved) maintained significant association with MACE adjusted to $R_T(t=5)$, HgA_{1c}, duration of diabetes in years, LR, and SBP (HR 1.61, P=0.02; HR 1.60, P=0.02; HR 1.58, P=0.03; HR 1.61, P=0.02; and HR 1.64, P=0.01, respectively).

Comparing the Demographic Features and Outcomes of the STUDY and the CONTROL Groups

Demographic characteristics of the STUDY and the CONTROL groups were compared and are illustrated on Table 1. Compared to the STUDY group, patients in the CONTROL group were older, had more frequent coronary intervention, had lower LVEF and larger LVEDVi, and were more likely to have wall motion abnormality. In the first 12 months after CMR, 25 of the 74 (34%) patients had coronary angiography at an average of 48±78 days (range 26-303 days) after the CMR study. There was a high burden of CAD with 22 of these 25 patients (88%) having coronary stenosis (>70%) involving at least 1 vessel.

At the end of the study follow-up period, patients in the CONTROL group experienced 33 MACE including 13 deaths, 4 acute MI, 8 unstable angina hospitalizations, and 8 heart failure hospitalizations. Amongst the 13 patient deaths, 10 (77%) were confirmed to died from worsening heart failure, 2 (15%) were unknown, and 1 (8%) was non-cardiac in etiology (history of mesothelioma on chemotherapy). The left plot of Figure 4 demonstrates the event-free survival function by Kaplan-Meier curves comparing the STUDY group (stratified by presence or absence of LGE) and the CONTROL group. Consistent with existing literature, patients in the CONTROL group (diabetics with clinical evidence of MI) had significant worse event-free survival compared to patients in the STUDY group with absence of LGE (P=0.001). However, those patients in the STUDY group with LGE by CMR followed a worsened event-free survival distribution that was similar to patients in the CONTROL group (P=0.18). The range of the median event-free survival times from the STUDY group with LGE (0.43 years, range 0.005-3.62, interquartile range 0.21-1.46) fell within the range of the CONTROL group (0.90 years, range 0.002-4.58, interquartile range 0.23-1.95). The right plot of Figure 4 demonstrates that patients in the STUDY group with LGE by CMR experienced a high *rate* of hazards increase, similar to patients in the CONTROL group, throughout the course of the follow-up period.

Discussion

The current study found a high prevalence (28%) of myocardial scar detected by LGE on CMR in diabetic patients without clinical evidence of MI. Importantly, LGE was associated with substantial hazards to MACE and all-cause mortality (greater than 3-fold hazards increase to MACE and to mortality, respectively). Furthermore, diabetic patients without clinical evidence of MI but with LGE evidence of myocardial scar had a cardiac event rate that was very similar to diabetic patients with clinical evidence of prior MI. Among diabetic patients without clinical

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evidence of MI, LGE was the strongest (and the only significant) multivariable predictor of MACE and mortality. It added incremental prognostic value to common clinical risk markers such as patient age, gender, ST-T changes on ECG, LV global systolic function, and the UKPDS 5-year risk model.

Clinical Implications

There is a clear need to identify diabetic patients at high risk of cardiovascular events. We found that LGE imaging can detect a high prevalence of myocardial scar that represented "footprints" of prior subclinical coronary events. These occult myocardial scars were associated with a high risk of future cardiac events, and therefore identify a subpopulation of diabetic patients who may benefit from more intensive medical or revascularization treatment strategies. While other imaging techniques have reported value for risk stratification of diabetic patients without prior MI[22,23], LGE imaging by CMR may offer a unique noninvasive method in detecting unrecognized myocardial scar at high spatial resolution and tissue contrast. Furthermore, CMR may detect subclinical MI missed by nuclear methods[7,24] or cine imaging[25] and therefore may be more sensitive for detecting patients at risk for important cardiac events. While the burden of diabetes has been predicted to reach an epidemic level in the next decades affecting 12-15% of the United States population,[26] our results highlights that LGE imaging may provide a noninvasive risk-stratifying tool for moderate-high risk diabetics.

As a corollary finding, diabetic patients in our cohort without evidence of MI by history or LGE imaging enjoyed an initial 2-year period of relatively low rate of hazards increase for cardiac events. These findings are consistent with the temporal pattern of cardiac events experienced by diabetic patients enrolled in large epidemiologic studies.[27] However, we found that the rate of developing MACE steeply increased after the first 2 years in patients without history of MI who had negative LGE imaging. We postulate that some patients in this group who had no LGE at the time of CMR remained at ongoing risk for progressive coronary disease and may have developed subsequent subclinical myocardial scarring sometime after 2 years with an associated increased cardiac event rate. Thus it appears that in diabetic patients without clinical evidence of MI who have negative CMR studies for scar there is a limited 2-year "warranty period". Such a limited warranty has also been described with normal stress nuclear perfusion or dobutamine stress echocardiography, especially in populations of patients with known CAD or with diabetes.[28-31] In these patients without evidence of myocardial ischemia, the annual cardiac death or MI rate is very low (0.5-0.9% per year) for the first 3-5 years and then increases by 80-160% over the next 3 years.[30] The current study, however, characterized the presence and extent of LGE indicative of MI undetected by clinical evaluation. With a higher sensitivity for small subendocardial MI than cine[25] or nuclear methods[7,24], LGE by CMR may provide improved risk stratification of diabetic patients complementary to current methods for evaluating myocardial ischemia.

Limitations

A number of limitations exist in our study. First, since CMR is a new and costly imaging modality amongst other available noninvasive modalities, it is possible that selection bias exists from clinicians' referral at our institution. The STUDY group demonstrated high prevalence of coronary risk factors, evident by a history of hypertension in 71% of patients, hypercholesterolemia in 70%, and a long duration of diabetes (average 11, range 1-49 years). We postulate that selection bias likely has sampled high-risk diabetics with a high prevalence of sub-clinical coronary disease and thus an elevated mortality rate of 17% at 4.7 years follow-up. While we reported strong association of LGE with MACE and death in the current STUDY patients, whether any prognostic association of LGE with MACE exists in diabetics at lower pretest likelihood of CAD, requires future study. Furthermore, our study involved patients presenting with recent symptoms and likely represented a higher risk population; whether the

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current results apply to asymptomatic diabetic patients is unclear. A second study limitation relates to selection of the CONTROL patients based on evidence of prior MI. As a result, some characteristics such as age and history of prior coronary intervention were not matched between the STUDY and CONTROL groups. However, it is intriguing that STUDY group patients, despite being younger and with less frequent history of coronary intervention, had a markedly reduced event-free survival when LGE was present, comparable to CONTROL patients (Figure 4). The small patient numbers may have limited the power of the log-rank test in detecting a statistical difference between these 2 groups. We believe these patients represent a high-risk group who had suffered a silent MI undetected by clinical examination and ECG, but characterized by CMR. Finally, no conclusion can be drawn regarding prognostic value of CMR compared to other imaging or diagnostic techniques for risk-stratification of diabetic patients. We believe that as a noninvasive technique capable of concurrent stress perfusion or cine function in the same imaging session, CMR offers a strong potential for risk stratification and treatment guidance of diabetic patients at high risk of adverse outcomes.

Conclusions

Diabetic patients without clinical evidence of MI have a high prevalence of myocardial scar consistent with MI detected by CMR that is associated with a significant risk of important cardiac events, including death. Furthermore, LGE by CMR provides incremental prognostic information to MACE or all-cause mortality, beyond clinical and LV function variables combined, and may serve as a valuable non-invasive risk-stratifying tool in these patients with a known high prevalence of coronary artery disease.

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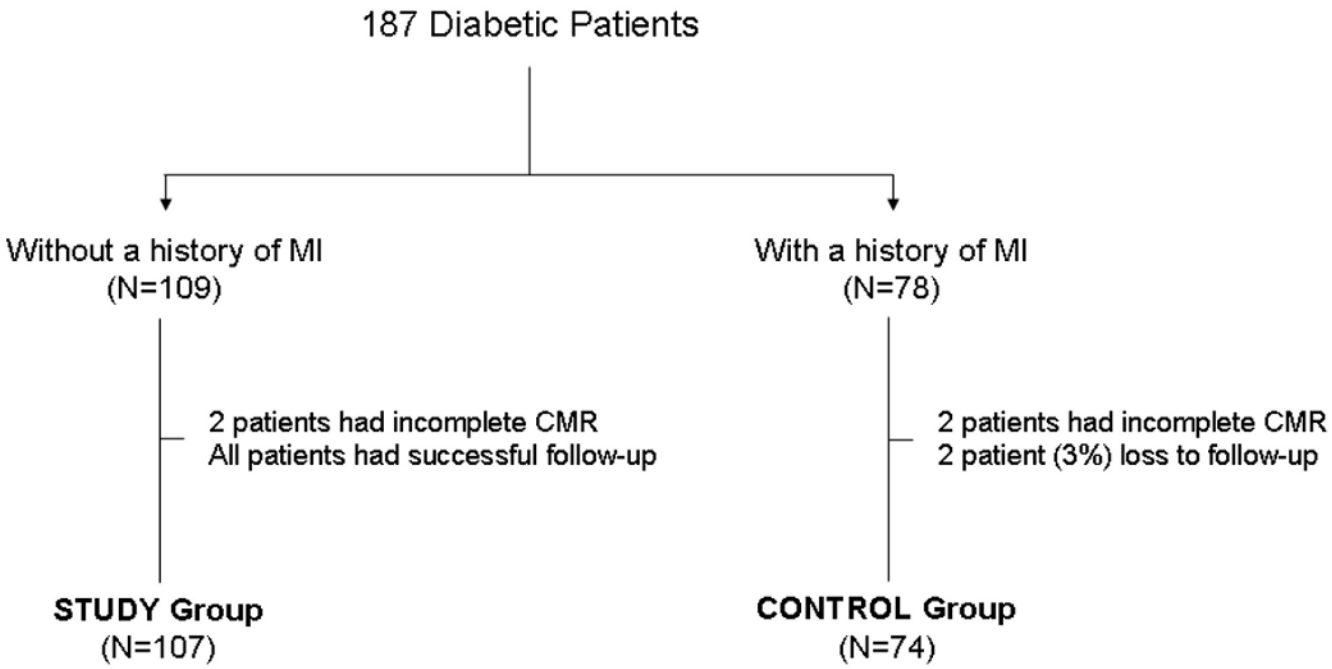

Figure 1.
Composition of the STUDY and the CONTROL Groups

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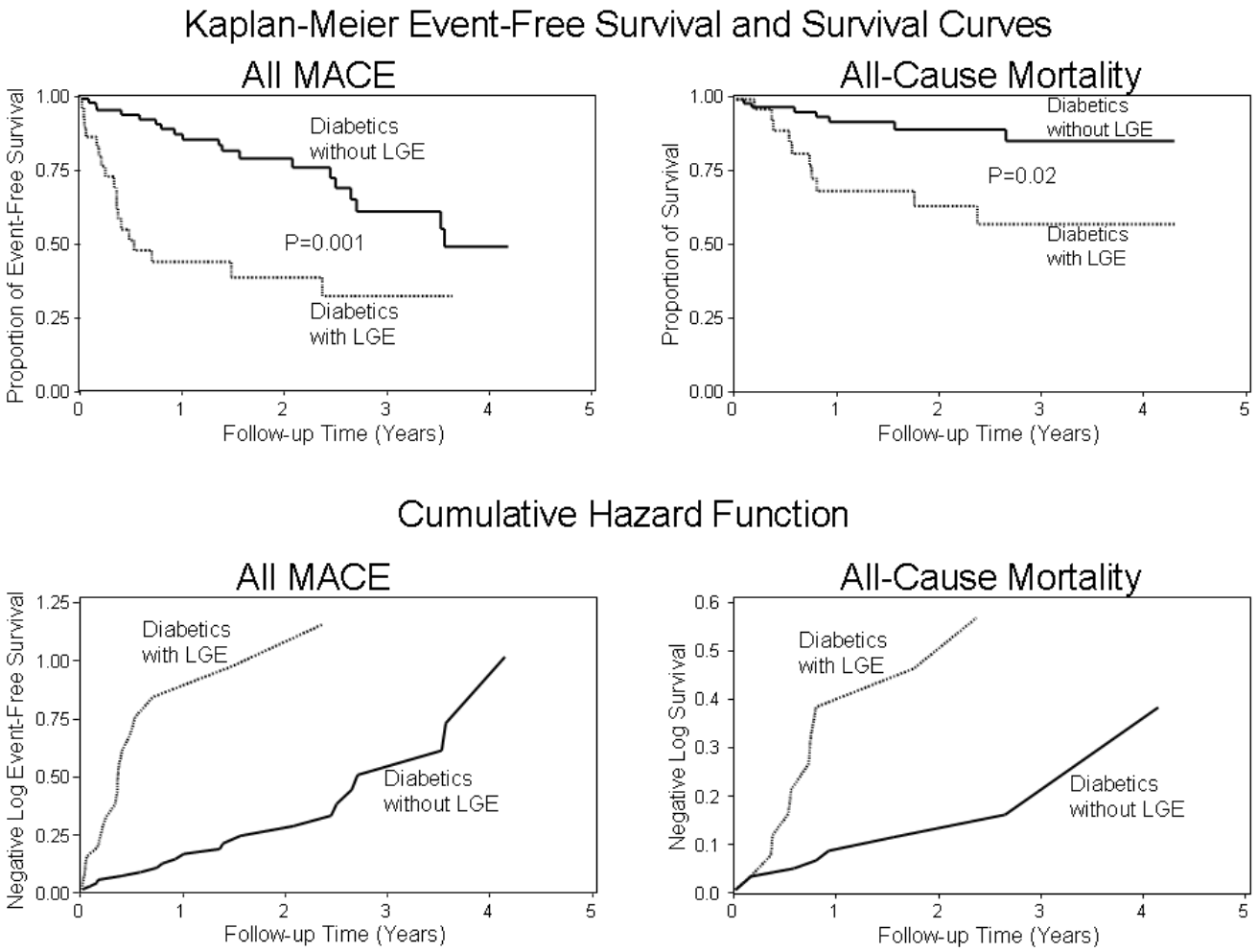

Figure 2.

A) Kaplan-Meier Event-Free Survival and Survival Curves and B) Cumulative Event-free Survival and Survival Functions of the STUDY Group

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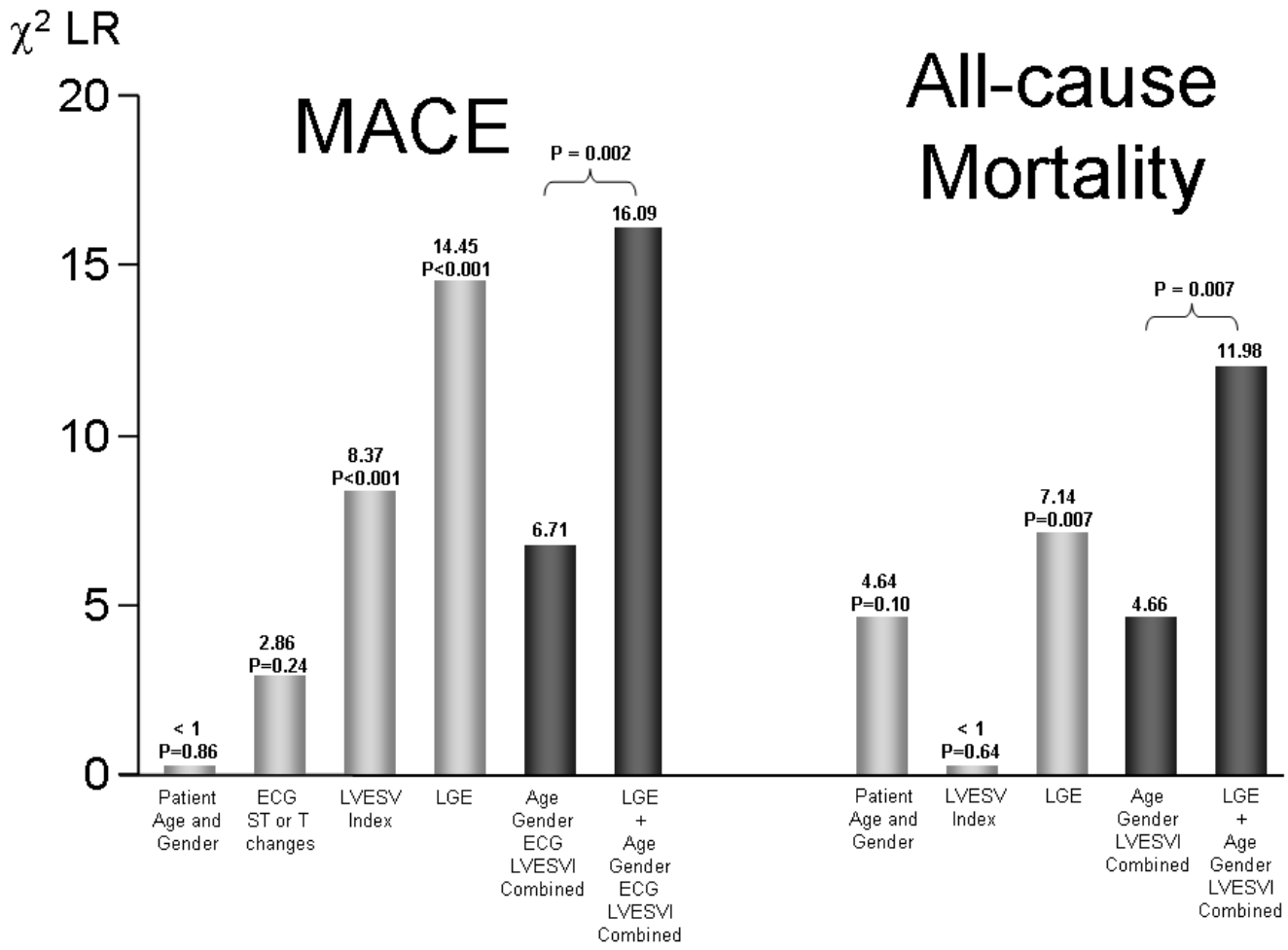

Figure 3.
Comparison of Univariable (light-colored bar) and Incremental Multivariable (dark-colored bar) Model Chi-Square Likelihood Ratio (χ^2 LR) for MACE and All-cause Mortality in the STUDY Group.

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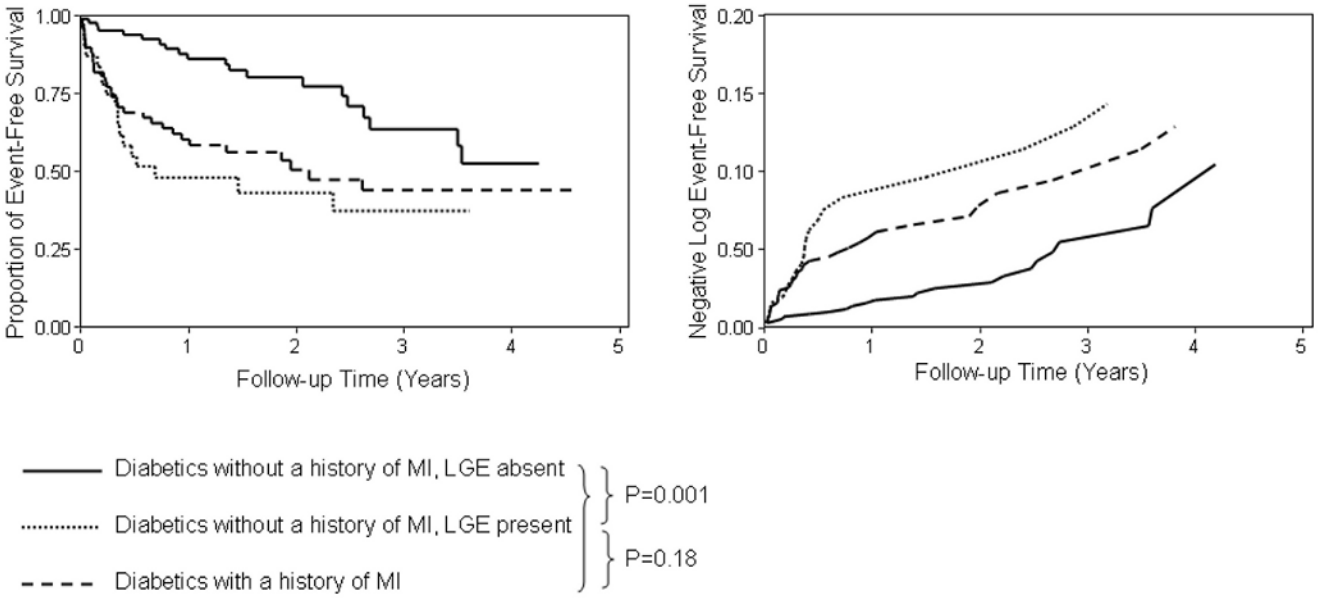

Figure 4.
Kaplan-Meier Event-Free Survival Curves and Log Event-Free Survival of Patients from Both STUDY and CONTROL Groups Combined.

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Table 1

Demographic Characteristics

	STUDY Group (n = 107)	LGE Absent (n= 77)	LGE Present (n=30)	P-value*	CONTROL Group (n = 74)	P-value¥
Clinical Characteristics						
Age (years)	59 ± 13	57 ± 12	63 ± 13	0.06	64 ± 10	0.002
Female Gender (%)	40 (37)	32 (42)	8 (27)	0.19	25 (34)	0.64
Race (Caucasian) (%)	56 (52)	36 (47)	20 (67)	0.09	28 (38)	0.07
High Body Mass Index (≥ 30 kg/m^2) (%)	57 (55)	43 (58)	14 (47)	0.38	28 (41)	0.09
Presenting Symptoms at Time of CMR						
Chest Pain	42 (39)	30 (39)	12 (40)	0.99	31 (42)	0.99
Dyspnea	35 (33)	21 (27)	14 (47)	0.07	27 (36)	0.07
Syncope/Arrhythmia/ECG Abnormality	30 (28)	26 (34)	4 (13)	0.05	16 (22)	0.05
Duration of Diabetes Diagnosis (Years)	10.7 ± 8.5	10.6 ± 9.0	11.0 ± 7.1	0.86	11.0 ± 8.3	0.85
HgA_{1c} (%)	7.3 ± 1.6	7.4 ± 1.6	7.2 ± 1.7	0.73	7.6 ± 2.0	0.22
Resting SBP (mmHg)	142 ± 27	142 ± 24	142 ± 34	0.99	131 ± 25	0.003
Resting Heart Rate > 100 beats/min (%)	7 (7)	7 (9)	0 (0)	0.19	4 (5)	0.99
Hx. of Hypertension (%)	76 (71)	55 (71)	21 (70)	0.99	57 (77)	0.40
Hx. of Hypercholesterolemia (%)	75 (70)	53 (69)	22 (73)	0.81	61 (82)	0.08
Total Cholesterol Level (mg/dL)	158 ± 37	161 ± 32	151 ± 47	0.24	148 ± 33	0.08
HDL Cholesterol Level (mg/dL)	41 ± 10	42 ± 10	40 ± 10	0.44	38 ± 7	0.03
Total/HDL Cholesterol Ratio	3.9 ± 1.0	4.0 ± 0.9	3.9 ± 1.3	0.66	4.0 ± 1.0	0.81
Heavy Tobacco Use (%)	25 (23)	17 (22)	8 (27)	0.62	22 (30)	0.39
Family Hx. of CAD (%)	15 (14)	12 (16)	3 (10)	0.55	17 (23)	0.16
Hx. of Peripheral Vascular Disease (%)	11 (10)	9 (12)	2 (7)	0.72	11 (15)	0.36
Hx. of Percutaneous Coronary Intervention (%)	9 (8)	4 (5)	5 (17)	0.11	20 (27)	0.002
Hx. of Cardiac Bypass Surgery (%)	13 (12)	6 (8)	7 (23)	0.04	20 (27)	0.02
UKPDS 5-year probability of MACE	0.08 ± 0.08	0.07 ± 0.07	0.11 ± 0.10	0.02	0.11 ± 0.07	0.04
Medication						
Beta-blocker (%)	62 (58)	42 (55)	20 (67)	0.28	64 (86)	< 0.001
Calcium Blocker (%)	24 (22)	15 (19)	9 (30)	0.30	12 (16)	0.35
Angiotensin-converting enzyme inhibitor (%)	60 (56)	43 (56)	17 (57)	0.99	52 (70)	0.06
Aspirin (%)	60 (57)	39 (51)	21 (70)	0.09	66 (89)	< 0.001
Rest Electrocardiogram						
Non-sinus rhythm	6 (6)	4 (6)	2 (7)	0.67	4 (5)	0.99

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	STUDY Group (n = 107)	LGE Absent (n= 77)	LGE Present (n=30)	P-value*	CONTROL Group (n = 74)	P-value¥
LV Hypertrophy on ECG	4 (4)	1 (1)	3 (11)	0.07	4 (5)	0.73
QRS duration (ms)	97 ± 20	94 ± 18	105 ± 22	0.01	102 ± 20	0.09
Left bundle branch block	7 (7)	3 (4)	4 (14)	0.10	5 (7)	0.99
Right bundle branch block	5 (5)	3 (4)	2 (7)	0.62	4 (5)	0.99
ST depression ≥ 1 mm	11 (11)	5 (7)	6 (21)	0.07	21 (29)	0.005
T inversion in > 2 contiguous leads	21 (21)	12 (17)	9 (32)	0.11	36 (49)	< 0.001
Corrected QT interval† (ms)	439 ± 32	436 ± 29	448 ± 37	0.10	436 ± 42	0.60
CMR						
Total LV Mass (gram)	142 ± 49	136 ± 44	154 ± 55	0.08	148 ± 43	0.37
Average LVEF (%)	56 ± 15	60 ± 12	47 ± 18	< 0.001	42 ± 18	< 0.001
LVEDV index (ml/m^2)	82 ± 26	74 ± 17	102 ± 34	< 0.001	114 ± 43	< 0.001
LVESV index (ml/m^2)	39 ± 26	30 ± 14	61 ± 37	< 0.001	73 ± 46	< 0.001
Presence of Wall Motion Abnormality (%)	30 (28)	8 (10)	22 (73)	< 0.001	58 (79)	< 0.001

*Comparing Within the STUDY Group: LGE Absent vs. LGE Present;

¥Comparison Between the STUDY and the CONTROL Groups.

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Table 2

Univariable Association with MACE and Mortality of Patients in the STUDY Group

	MACE			All-cause Mortality		
	HR	HR 95% CI	P value	HR	HR 95% CI	P value
Patient Age (years)	1.00	0.98 1.03	0.81	1.05	1.00 1.09	0.04
Female Gender	0.84	0.42 1.67	0.61	1.08	0.40 2.95	0.88
Body Mass Index > 30 kg/m^2	0.66	0.34 1.27	0.22	0.44	0.16 1.19	0.11
Years of Diabetes Diagnosis	0.98	0.94 1.02	0.39	0.99	0.93 1.05	0.70
Hemoglobin A_{1c} (%)	0.87	0.67 1.12	0.27	0.91	0.62 1.33	0.61
Resting Heart Rate > 100 beats/min	0.95	0.29 3.12	0.93	0.75	0.10 5.71	0.78
Hx. of PCI	2.41	1.00 5.81	0.05	2.00	0.58 6.94	0.28
Hx. of CABG	1.43	0.56 3.71	0.46	0.46	0.06 3.49	0.45
Hx. of Hypertension	0.65	0.32 1.29	0.22	0.61	0.23 1.66	0.34
Hx. of Hypercholesterolemia	0.63	0.33 1.23	0.18	0.48	0.19 1.23	0.13
Total Cholesterol Value (mg/dL)	1.00	0.99 1.00	0.32	0.99	0.97 1.00	0.06
HDL Cholesterol (mg/dL)	1.00	0.97 1.03	0.81	1.01	0.97 1.05	0.62
Total/HDL Cholesterol Ratio	0.83	0.55 1.23	0.34	0.42	0.22 0.81	0.009
Heavy Tobacco Use	1.16	0.58 2.33	0.67	1.94	0.75 5.03	0.17
Family Hx. of CAD	0.57	0.18 1.87	0.35	0.82	0.19 3.59	0.79
Systolic Blood Pressure at Rest (mmHg)	1.00	0.98 1.01	0.55	1.00	0.98 1.02	0.80
UKPDS 5-year Probability of MACE	0.22	0.01 15.53	0.49	7.38	0.06 986.72	0.42
Beta-blocker	0.89	0.47 1.71	0.74	0.87	0.34 2.20	0.76
Calcium Blocker	1.18	0.58 2.39	0.64	0.84	0.27 2.54	0.75
Angiotensin-converting enzyme inhibitor	0.75	0.40 1.42	0.37	0.71	0.28 1.81	0.50
Cholesterol Lowering Medication	0.80	0.41 1.54	0.50	0.37	0.15 0.95	0.04
Aspirin	1.20	0.63 2.31	0.57	1.22	0.47 3.16	0.68
Non-sinus rhythm	1.71	0.60 4.91	0.32	1.62	0.37 7.11	0.99
LVH on ECG	1.13	0.27 4.70	0.87	--	-- --	--
Left bundle branch block	1.77	0.62 5.05	0.28	2.31	0.66 8.04	0.19
Right bundle branch block	--	-- --	--	--	-- --	--
QRS duration (ms)	1.00	0.98 1.02	0.90	1.01	0.98 1.03	0.65
Corrected QT interval[†] (ms)	0.99	0.98 1.00	0.24	0.99	0.97 1.01	0.22
ST depression ≥ 1 mm	1.99	0.82 4.84	0.13	1.72	0.49 5.98	0.40

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	MACE				All-cause Mortality			
	HR	**HR 95% CI**		**P value**	**HR**	**HR 95% CI**		**P value**
T inversion in > 2 contiguous leads	1.80	0.89	3.64	0.10	2.10	0.81	5.44	0.12
LV Mass (grams)	1.01	1.00	1.01	0.09	0.99	0.98	1.00	0.23
LVEDD (per mm)	1.00	0.95	1.05	0.91	0.97	0.91	1.04	0.38
LVEDV index (per 10 ml/m^2)	1.19	1.05	1.34	0.006	1.02	0.86	1.21	0.79
LVESV index (per 10 ml/m^2)	1.18	1.07	1.31	<0.001	1.04	0.89	1.21	0.63
LVEF (per 10%)	0.79	0.65	0.96	0.02	0.96	0.72	1.30	0.81
Resting Wall Motion Abnormality	1.91	0.99	3.67	0.05	1.90	0.75	4.83	0.18
Presence of LGE	3.71	1.93	7.12	<0.001	3.61	1.42	9.19	0.007
LGE (% of LV Mass, per 10%)	1.63	1.12	2.38	0.01	1.60	0.87	2.92	0.13
TE_{Mean}	2.04	0.72	5.75	0.18	3.97	1.09	14.48	0.04
TE_{Max}	1.26	0.99	1.61	0.06	1.32	0.96	1.82	0.09
TE_{Max} (LAD territory)	0.98	0.61	1.56	0.92	1.22	0.76	1.96	0.42
TE_{Max} (RCA territory)	1.51	1.15	1.98	0.003	1.51	1.08	2.12	0.02
TE_{Max} (LCx territory)	1.08	0.47	2.47	0.85	1.47	0.44	4.84	0.53
No. of Seg with LGE	1.14	0.96	1.36	0.14	1.26	1.02	1.56	0.03
No. of Seg with LGE (LAD)	1.11	0.62	2.00	0.73	1.61	0.86	2.99	0.14
No. of Seg with LGE (RCA)	1.59	1.11	2.29	0.01	1.50	1.03	2.17	0.03
No. of Seg with LGE (LCx)	1.25	0.65	2.41	0.50	1.67	0.77	3.64	0.20

PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Grafting; ACE=Angiotensin Converting Enzyme; LVH=Left Ventricular Hypertrophy; TE=Transmural Extent of Late Gadolinium Enhancement; LAD=Left Anterior Descending Artery; RCA=Right Coronary Artery; LCx=Left Circumflex Artery; -- events too low for HR estimation.

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