Sudden Cardiac Death After Myocardial Infarction in Type 2 Diabetic Patients With No Residual Myocardial Ischemia

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OBJECTIVE—Diabetes mellitus (DM) is a well-established risk factor for coronary artery disease. Nonetheless, it remains unclear whether DM contributes to sudden cardiac death in patients who survive myocardial infarction (MI). The objective of this study was to compare the incidence of sudden cardiac death post-MI in diabetic and nondiabetic patients with no residual myocardial ischemia.

RESEARCH DESIGN AND METHODS—A total of 610 consecutive post-MI patients referred to a cardiac rehabilitation program with negative exercise stress test were studied.

RESULTS—Of these, 236 patients had DM at baseline. Over a mean follow-up of 5 years, 67 patients with DM (28.4%) and 76 of 374 patients without DM (20.2%) had died with a hazard ratio (HR) of 1.74 (95% CI: 1.28–2.56; $P < 0.001$). Patients with DM also had a higher incidence of cardiac death (1.84 [1.16–3.21]; $P = 0.01$), principally due to a higher incidence of sudden cardiac death (2.14 [1.22–4.23]; $P < 0.001$). Multiple Cox regression analysis revealed that only DM (adjusted HR: 1.9 [95% CI: 1.04–3.40]; $P = 0.04$), left ventricular ejection fraction (LVEF) ≤30% (3.6 [1.46–8.75]; $P < 0.01$), and New York Heart Association functional class >II (4.2 [1.87–9.45]; $P < 0.01$) were independent predictors for sudden cardiac death. Among patients with DM, the 5-year sudden cardiac death rate did not differ significantly among those with LVEF ≤30%, LVEF 31–50%, or LVEF >50% (8.8 vs. 7.8 vs. 6.8%, respectively; $P = 0.83$).

CONCLUSIONS—Post-MI patients with DM, even in the absence of residual myocardial ischemia clinically, were at higher risk of sudden cardiac death than their non-DM counterparts.

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Diabetes mellitus (DM) is a common metabolic disorder that has been recognized as an emerging epidemic in the developed world (1) as well as in less-developed countries in the Asia Pacific region, with a prevalence of ≥10% (2,3). DM is associated with increased morbidity and mortality, predominantly due to associated cardiovascular complications such as coronary artery disease. In addition to a higher risk of coronary artery disease among patients with DM, those who suffer an acute myocardial infarction (MI) also have a poorer prognosis than nondiabetic patients. Specifically, it has been previously reported that post-MI patients with DM have a higher incidence of heart failure (4), a higher risk of recurrent myocardial ischemic events (5), and higher short- (6) and long-term mortality (7–9). A recent analysis of two prospective post-MI cohorts demonstrated that the presence of DM increases the risk of sudden cardiac death (10), consistent with early epidemiological data that proposes DM as an independent underlying risk factor (11). It is conceivable that post-MI patients with DM are more likely to have more severe coronary artery disease than nondiabetic patients, and the accompanying residual myocardial ischemia may contribute to their higher risk of sudden cardiac death (12). It nonetheless remains unclear whether DM confers a higher risk of sudden cardiac death post-MI to patients without residual ischemia. Alternative mechanisms such as autonomic dysfunction (13), coexisting microvascular complications (14), as well as clinical and/or subclinical hypoglycemic episodes secondary to tight blood glucose control (15) may also contribute to sudden cardiac death in post-MI patients. Although sudden cardiac death secondary to lethal ventricular tachyarrhythmia can be effectively prevented by an automatic implantable cardioverter-defibrillator (AICD), its use is often limited by financial constraints and potential complications associated with such devices (16,17). Thus, the ability to identify patients at high risk of sudden cardiac death using clinical parameters in addition to standard indications for AICD and appropriate triage of such patients for AICD therapy may have important clinical implications. The purpose of this study was to investigate the effects of DM on cardiovascular mortality in a cohort of Chinese patients who survived an ST-segment elevation MI with no inducible ischemia.

RESEARCH DESIGN AND METHODS

Patients

From January 1998 to December 2005, 617 consecutive patients who recently survived an ST-segment elevation MI (>40 days) were referred to the Cardiac Rehabilitation and Prevention Center of Tung Wah Hospital (18,19). This is the largest rehabilitation facility in Hong Kong and serves a population of about half a million. During this study period, coronary revascularization was performed in those who survived ST-segment elevation MI and who experienced chest pain or ischemia inducible on treadmill testing. Patients were excluded from this study if they had a positive exercise stress test suggestive of residual myocardial ischemia, documented ventricular tachyarrhythmia that necessitated

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AICD implantation for secondary prevention, New York Heart Association (NYHA) functional class IV, and/or other terminal illness. In Hong Kong, prophylactic implantation of AICD to prevent sudden cardiac death based on the Second Multicenter Automatic Defibrillator Implantation Trial II criteria (20) is not reimbursable and thus is not available in public hospitals (16). As a result, 610 eligible patients were recruited and classified according to their DM status. Informed consent was obtained from all patients.

Study design

This was a single-center, prospective observational study, and the local research ethics committee approved the study protocol. Following recruitment to the Cardiac Rehabilitation Program, data pertaining to the index MI, demographics, cardiovascular risk factors, and medications were entered into the Tung Wah Hospital Cardiac Rehabilitation Program Database. Diagnosis of DM was based on medical records or prescription of diabetic medication. All patients underwent baseline exercise stress tests and echocardiography and were prospectively followed up in our cardiac outpatient clinic. All of the patients were followed up in our Cardiac Rehabilitation Program once every 3 months. Deaths within the follow-up period were retrieved from the medical records and discharge summaries and classified according to the Modified Hinkle-Thaler scheme (21,22). Specifically, sudden cardiac death was defined as a death that occurs within 1 h of onset of cardiac symptoms in a person without any previous condition that would explain the fatality. Patients who failed to attend the clinic were contacted by phone. Survival data were also obtained from the Hong Kong Births and Deaths General Register Office. The survival rate, cause of death, and clinical characteristics were compared between patients with and without DM.

Statistical analysis

Continuous variables are expressed as mean ± SD. Statistical comparisons were performed using Student *t* test or Fisher exact test, as appropriate. Kaplan-Meier survival analysis with the log-rank test and simple Cox regression analysis were used for cumulative incidences of all-cause death, cardiovascular death, sudden cardiac death, and nonsudden cardiac death. Multiple Cox regression analyses were performed with an enter regression model in which each variable with a P value ≤0.1 (based on the univariate analysis) was entered into the model. Calculations were performed using SPSS software (version 12.0; SPSS Inc.). A P value <0.05 was considered statistically significant.

RESULTS—A total of 610 post-MI patients with negative exercise stress test were recruited, of whom 236 patients (38.7%) had DM at the time of MI, and 374 did not (61.3%). Table 1 summarizes their clinical characteristics. Compared with nondiabetic patients, patients with DM were older (66.2 ± 9.9 vs. 64.1 ± 12.2 years; $P = 0.02$) and more likely to be female (31.8 vs. 21.7%; $P < 0.01$), hypertensive (63.6 vs. 45.2%; $P < 0.01$), have significant renal impairment as defined by serum creatinine level ≥2 times the upper limit of normal (14.1 vs. 5.1%; $P < 0.01$), and on statin (78.8 vs. 71.1%; $P = 0.04$). With regard to the index MI, there was no significant difference in the site of MI, peak creatine kinase level, or proportion of patients undergoing revascularization (percutaneous coronary intervention or coronary artery bypass grafting). Nonetheless, post-MI patients with DM had a lower left ventricular ejection fraction (LVEF) (44.6 ± 10.5 vs. 46.2 ± 10.0%; $P = 0.04$), and a lower proportion was classified as NYHA function class I (39.8 vs. 53.5%; $P < 0.01$) compared with post-MI patients without DM. All patients had a negative exercise stress test prior to enrolment.

After a mean follow-up of 62.7 ± 43.9 months (range 0.2–148.6 months), 67 patients with DM (28.4%, 6.2%/year) and 76 patients without DM (20.2%, 3.6%/year) had died. Figure 1*A* depicts the Kaplan-Meier curves for the percentage of patients with and without DM who

Table 1—*Baseline characteristics of patients with and without DM*

	DM	No DM	*P* value
n	236	374	
Age (years)	66.2 ± 9.9	64.1 ± 12.2	0.02*
Female sex [*n* (%)]	75 (31.8)	81 (21.7)	<0.01*
Hypertension [*n* (%)]	150 (63.6)	169 (45.2)	<0.01*
Current or past smoker [*n* (%)]	114 (48.3)	208 (55.6)	0.08
Hypercholesterolemia [*n* (%)]	135 (57.2)	209 (55.9)	0.75
Lung disease [*n* (%)]	16 (6.8)	42 (11.2)	0.07
AF at enrollment [*n* (%)]	5 (2.1)	5 (1.3)	0.52
Significant renal impairment [*n* (%)]	34 (14.4)	19 (5.1)	<0.01*
NYHA class [*n* (%)]			<0.01*
I	94 (39.8)	200 (53.5)	
II	127 (53.8)	160 (26.2)	
III	15 (6.4)	14 (3.7)	
Site of MI			0.84
Anterior MI [*n* (%)]	105 (44.5)	171 (45.7)	
Anterolateral MI [*n* (%)]	14 (5.9)	19 (5.1)	
Lateral MI [*n* (%)]	17 (7.2)	21 (5.6)	
Inferior MI [*n* (%)]	82 (34.8)	138 (36.9)	
Other [*n* (%)]	18 (7.6)	25 (6.7)	
Peak creatinine kinase (μmol/L)	2,532 ± 2,372	2,639 ± 2,166	0.60
LVEF (%)	44.6 ± 10.5	46.2 ± 10.0	0.046*
Revascularization			
PCI [*n* (%)]	108 (45.8)	161 (43.0)	0.51
CABG [*n* (%)]	8 (3.4)	6 (1.6)	0.15
Medications			
Aspirin [*n* (%)]	221 (93.6)	353 (94.4)	0.71
ACEI [*n* (%)]	193 (81.8)	288 (77.0)	0.16
β-Blockers [*n* (%)]	175 (74.2)	269 (71.9)	0.55
Statin [*n* (%)]	186 (78.8)	266 (71.1)	0.04*
CCB [*n* (%)]	23 (9.7)	26 (7.0)	0.22
Amiodarone [*n* (%)]	7 (3.0)	20 (5.3)	0.16
Digoxin [*n* (%)]	4 (1.7)	7 (1.9)	0.87

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; CABG, coronary artery bypass surgery; CCB, calcium channel blocker; PCI, percutaneous coronary intervention. *$P < 0.05$.

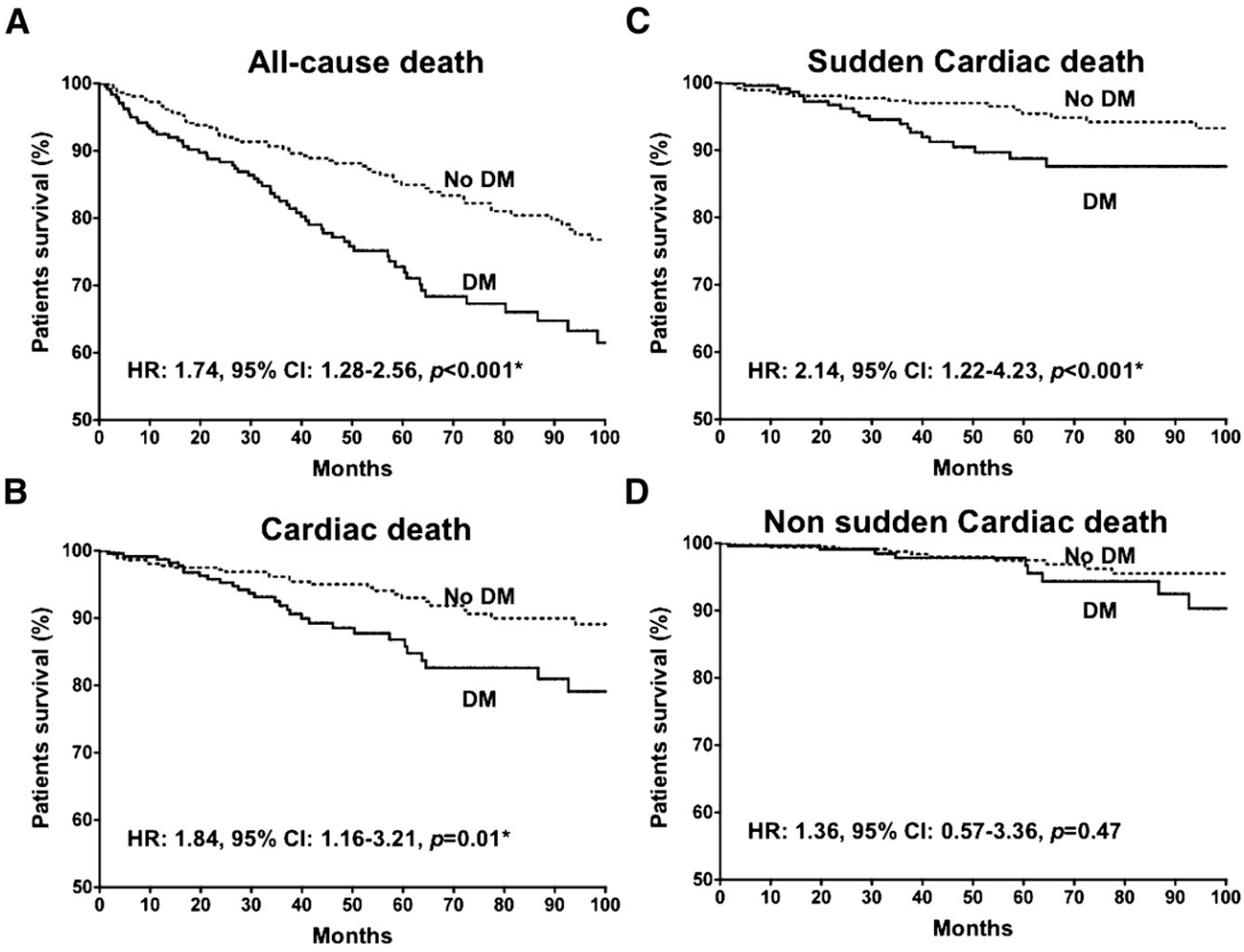

Figure 1—*Kaplan-Meier curves of all-cause death* (A)*, cardiac death* (B)*, sudden cardiac death* (C)*, and nonsudden cardiac death* (D) *in patients with and without DM.*

survived. For those patients with DM, the proportion that died during follow-up was significantly higher than for those without DM: hazard ratio (HR) 1.74 (95% CI: 1.28–2.56; $P < 0.001$). Of these 143 deaths, 66 (46.2%) were attributed to a cardiac cause, of which sudden cardiac death accounted for 66.7%. The proportion of patients with DM who died resulting from a cardiac cause was higher than for those without DM (32 of 236 [3.0%/year] vs. 34 of 374 [1.6%/year], HR: 1.84 [95% CI: 1.16–3.21]; $P = 0.01$) (Fig. 1*B*). Likewise, and more importantly, the incidence of sudden cardiac death was also higher in patients with DM (23 of 236 [2.1%/year] vs. 21 of 374 [1.0%/year], 2.14 [1.22–4.23]; $P < 0.001$) (Fig. 1*C*). There was no statistically significant difference in the nonsudden cardiac death rate between the two groups (9 of 236 [0.8%/year] vs. 13 of 374 [0.6%/year], 1.36 [0.57–3.36]; $P = 0.47$) (Fig. 1*D*).

To identify risk factors that could predict sudden cardiac death, patients were categorized as follows: *1*) those with sudden cardiac death ($n = 44$) or 2) those without sudden cardiac death ($n = 566$). Table 2 summarizes their baseline clinical characteristics. There were no statistically significant differences in age and sex between the two groups. In the sudden cardiac death group, there was a higher proportion of patients with DM (52.3 vs. 37.6%; $P = 0.05$), a lower proportion of hypercholesterolemia defined as fasting LDL cholesterol level ≥2.6 mmol/L or already on pharmacological treatment for hypercholesterolemia (40.9 vs. 57.6%; $P = 0.03$), and a lower proportion of patients with NYHA class I (22.7 vs. 50.2%; $P < 0.01$); they were also less likely to have received percutaneous coronary intervention (29.5 vs. 58.0%; $P < 0.01$) or statin therapy (59.1 vs. 75.3%; $P = 0.02$). Nonetheless, there were no significant differences in other demographics, medications, or site of index MI. Multiple Cox regression analysis revealed that only DM (adjusted HR: 1.9 [95% CI: 1.04–3.40]; $P = 0.04$), LVEF ≤30% (3.6 [1.46–8.75]; $P < 0.01$), and NYHA class >II (4.2 [1.87–9.45]; $P < 0.01$) were independent predictors for sudden cardiac death.

Risk of sudden cardiac death across different LVEF

As LVEF was a major determinant of future sudden cardiac death in this cohort, and current guidelines are based largely on LVEF for AICD prescription (23), we further evaluated the effect of DM on sudden cardiac death in patients with different levels of LVEF. Among patients with LVEF ≤30% ($n = 68$), there was no statistically significant difference in the proportion of sudden cardiac death between those with and without DM (HR:

Table 2—*Baseline characteristics of patients with or without sudden cardiac death*

	SCD	No SCD	*P* value
n	44	566	
Age (years)	67.9 ± 11.6	64.6 ± 11.4	0.07
Female sex [*n* (%)]	13 (29.5)	143 (25.3)	0.53
DM [*n* (%)]	23 (52.3)	213 (37.6)	0.047*
Hypertension [*n* (%)]	23 (52.3)	296 (52.3)	1.00
Current or past smoker [*n* (%)]	21 (47.7)	301 (53.2)	0.49
Hypercholesterolemia [*n* (%)]	18 (40.9)	326 (57.6)	0.03*
Lung disease [*n* (%)]	3 (6.8)	55 (9.7)	0.79
AF at enrollment [*n* (%)]	0 (0)	10 (1.8)	1.00
Significant renal impairment [*n* (%)]	5 (11.4)	48 (8.5)	0.57
NYHA class [*n* (%)]			<0.01*
I	10 (22.7)	284 (50.2)	
II	26 (59.1)	261 (46.1)	
III	8 (18.2)	21 (3.7)	
Site of MI			0.78
Anterior MI [*n* (%)]	20 (45.5)	256 (45.2)	
Anterolateral MI [*n* (%)]	2 (4.5)	31 (5.5)	
Lateral MI [*n* (%)]	2 (4.5)	36 (6.4)	
Inferior MI [*n* (%)]	20 (45.5)	200 (35.3)	
Other [*n* (%)]	0 (0)	43 (7.6)	
Peak creatinine kinase (μmol/L)	2,366 ± 2,400	2,616 ± 2,236	0.50
LVEF (%)	39.6 ± 10.9	46.1 ± 10.0	<0.01*
Revascularization			
PCI [*n* (%)]	13 (29.5)	328 (58.0)	<0.01*
CABG [*n* (%)]	1 (0.0)	14 (2.5)	0.61
Medications			
Aspirin [*n* (%)]	39 (88.6)	535 (94.5)	0.17
ACEI [*n* (%)]	35 (79.5)	446 (78.8)	0.91
β-Blockers [*n* (%)]	29 (65.9)	415 (73.4)	0.29
Statin [*n* (%)]	26 (59.1)	426 (75.3)	0.02*
CCB [*n* (%)]	5 (11.4)	44 (7.8)	0.40
Amiodarone [*n* (%)]	3 (6.8)	24 (4.2)	0.43
Digoxin [*n* (%)]	1 (2.3)	10 (1.8)	0.56

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; CABG, coronary artery bypass surgery; CCB, calcium channel blocker; PCI, percutaneous coronary intervention; SCD, sudden cardiac death. *$P < 0.05$.

0.34 [95% CI: 0.13–1.14], $P = 0.09$) (Fig. 2*A*). Figure 2*A* depicts the Kaplan-Meier curves for these patients. On the contrary, among patients with LVEF between 31 and 50% ($n = 348$) and those with LVEF >50% ($n = 194$), there was a higher proportion of sudden cardiac death among those with DM (12 of 129 vs. 10 of 219; HR: 2.30 [95% CI: 1.08–6.91]; $P = 0.03$ [Fig. 2*B*]; and 8 of 73 vs. 1 of 121; 14.90 [2.75–42.90]; $P < 0.01$ [Fig. 2*C*]). Overall, the 5-year sudden cardiac death rates in patients with DM did not differ significantly in relation to LVEF: LVEF ≤30%, LVEF 31–50%, and LVEF >50% (8.8 vs. 7.8 vs. 6.8%, respectively; $P = 0.83$).

CONCLUSIONS—We show that despite the lack of residual myocardial ischemia, post-MI patients with DM had a higher incidence of all-cause mortality, cardiac death, and sudden cardiac death, but not nonsudden cardiac death, compared with post-MI patients without DM. Sudden cardiac death was the main contributor to cardiac death in patients with DM. The presence of DM independently predicted sudden cardiac death. This was in addition to the two most recognized risk factors for sudden cardiac death in post-MI patients: low LVEF and poor functional class. More importantly, the increased risk of sudden cardiac death post-MI in patients with DM remained across different levels of LVEF.

Sudden cardiac death is presumably related to lethal cardiac arrhythmia. Published data concerning the contribution of DM to sudden cardiac death nonetheless remain conflicting. In previous epidemiological studies, patients with DM but no previously documented coronary artery disease appeared to be at higher risk of sudden cardiac death, with an HR ranging from 1.82– to 4.22 (11,24–26). In contrast, among studies that did not exclude patients with pre-existing coronary artery disease (27–30), the association between DM and sudden cardiac death remained equivocal. This could be partly related to the heterogeneity in the study populations: it has been postulated that the competing risks for sudden cardiac death related to coronary artery disease and other associated factors in these populations outweighed the increased risk related to DM (31). Recently, Junttila et al. (10) reported the outcome following 5-year follow-up of a cohort of 3,267 patients who survived acute MI. The incidence of sudden cardiac death was higher in patients with DM than those without DM, with an adjusted HR of 2.3 (10). This increased risk of sudden cardiac death remained in multiple logistic regression analysis. Nonetheless, because the study did not exclude patients with residual myocardial ischemia, it remained unclear whether the increased sudden cardiac death in patients with DM was the result of an arrhythmic event, residual ischemia, or both. This is because, although sudden cardiac death can be considered primarily an arrhythmic event, post-MI patients with DM may have significant residual ischemia even after revascularization therapy (32) that is conducive to developing a life-threatening ventricular tachyarrhythmia. In the current study, all patients had a negative treadmill exercise test at baseline. This indicated the absence of significant residual myocardial ischemia; nonetheless, the risk of sudden cardiac death remained higher in these post-MI patients with DM compared with those without. More importantly, the risk of sudden cardiac death was remarkably consistent with the study by Junttila et al. (HR: 2.3) (10) and the current study (2.14). This further supports the undeniable risk of sudden cardiac death post-MI associated with DM. These results may have important clinical implications. The effectiveness of prophylactic AICD therapy to reduce sudden cardiac death in post-MI patients without a history of cardiac arrest or ventricular tachyarrhythmias has been established by major clinical trials (20). Current guidelines thus recommend the therapy for primary prevention of sudden cardiac death in post-MI patients with low LVEF (23). Unfortunately, most post-MI patients who fulfill these criteria

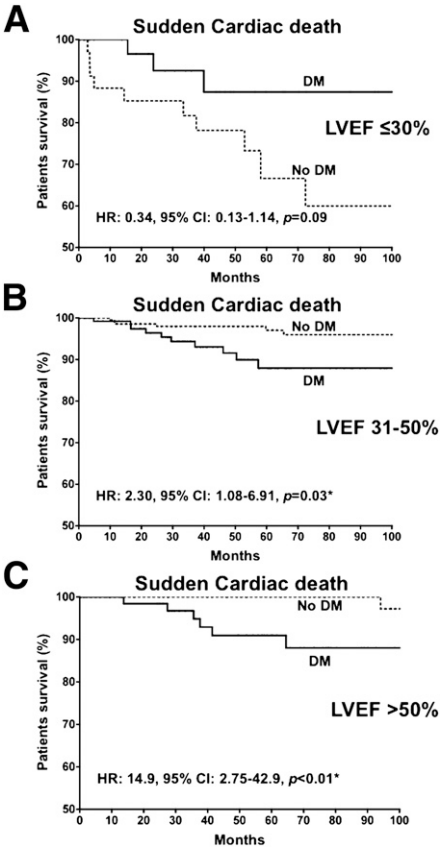

Figure 2—*Kaplan-Meier curves of sudden cardiac death among patients with and without DM and with LVEF ≤30%* (n = *68*) (A)*, LVEF 31–50%* (n = *348*) (B)*, and LVEF >50%* (n = *194*) (C).

for AICD therapy will not receive AICD implantation in most countries due to reimbursement difficulties (16). The ability to triage patients at high risk of sudden cardiac death using clinical parameters in addition to standard indications for AICD therapy may allow for more cost-effective use of such therapy. More importantly, although low LVEF is the major criteria for prophylactic AICD therapy in post-MI patients, our study and that of Junttila et al. (10) have demonstrated that the risk of sudden cardiac death remains substantial in diabetic patients with LVEF well above the conventional threshold for prophylactic AICD therapy. Additional methods of risk stratification for sudden cardiac death are clearly needed.

Limitations

The study had several limitations. First, it was limited by the relatively small sample size and a single-centered observational design. Second, given the nature of the study, plausible mechanisms for DM-related sudden cardiac death such as cardiac autonomic dysfunction (13,28,33), QT prolongation (34,35), as well as severe hypoglycemia secondary to stringent glycemic goal (15,36) were not addressed. Third, the development of new coronary lesions and their identification during the study period was not specifically addressed. Ideally, the coronary artery disease severity should have been assessed both at baseline and throughout the study period in all of the participants, using, for example, a modified Gensini index. Unfortunately, in the current study, reevaluation of coronary angiography would only be performed on a clinical basis in patients with recurrence ischemic symptom rather than on a routine basis. Finally, newer risk stratifiers were not assessed routinely. This study nonetheless demonstrates that baseline DM state predicted incident sudden cardiac death following MI in a cohort of Chinese patients who were free of significant myocardial ischemia. Further studies are needed to define the recommendations for risk stratification and therapy, including implantation of a cardioverter defibrillator device, in this particularly high-risk group.

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C.-Y.Y. and C.-W.S. drafted the manuscript and analyzed and interpreted the data. S.-W.L. and C.-W.S. collected the data. C.-Y.Y., K.S.-L., S.-W.L., H.-F.T., and C.-W.S. conceived the study design. K.-F.L. reviewed statistical analysis and interpreted the data. All authors critically revised the manuscript for important intellectual content and were involved in approving and critiquing the final manuscript for publication. C.-W.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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