

Effect of diabetes mellitus on long-term outcomes of surgical revascularization in patients with ischemic heart failure: a propensity score-matching study

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Abstract

Background: Diabetes mellitus (DM) is an important risk factor in the long-term outcomes of surgical revascularization. However, few studies have focused on patients with ischemic heart failure (IHF) and DM, and the results are controversial. This study aimed to evaluate the effect of DM on the long-term outcomes of IHF patients undergoing coronary artery bypass grafting (CABG).

Methods: In this propensity-matched study, data of IHF patients who underwent CABG in our hospital from January 2007 to December 2017 were analyzed. With a mean 73-month follow-up time, the patients were divided into two groups according to whether they had DM. The primary endpoint was all-cause death, and the secondary endpoint was a composite of all-cause death, stroke, recurrent myocardial infarction, and revascularization.

Results: There was no significant difference in all-cause mortality between the two groups (5.8% vs. 4.1%, $P = 0.216$). The incidence of main adverse cardiovascular and cerebrovascular events (MACCE) in the secondary endpoint was significantly higher in the DM group than that in the non-DM group (10.4% vs. 8.1%, $P = 0.023$).

Conclusions: DM can negatively affect the long-term outcomes of IHF patients undergoing CABG by significantly increasing the overall incidence of MACCE, though the long-term survival does not show a significant difference between the DM and non-DM patients.

Keywords: Coronary artery bypass grafting; Diabetes mellitus; Ischemic heart failure

Introduction

Ischemic heart disease (IHD), diabetes mellitus (DM), and heart failure (HF) are serious public health disorders around the world. Among them, IHD is the leading cause of HF^[1] while DM plays a critical role in the occurrence, development, and long-term outcome of HF caused by IHD.^[2,3] Coronary artery bypass grafting (CABG) has been widely accepted as the standard treatment of IHD. For patients with ischemic heart failure (IHF) which means the HF caused by IHD, CABG shows better outcomes than percutaneous intervention and oral medication therapy and was recommended by the current guidelines as the first treatment of choice.^[4,5] DM has been demonstrated as an independent risk factor for long-term outcomes of CABG by a series of studies.^[6] However, previous studies on the effect of DM on patients with IHD and IHF undergoing CABG were controversial.^[7,8] In recent years, with the

improvement of treatment strategy and patients' compliance with glucose control, the long-term survival of patients with DM and cardiovascular disease has been significantly improved.^[9] Additionally, improvement of the CABG technique and the popularity of the optimal medical therapy after CABG have significantly improved the long-term outcomes of IHF patients.^[10] Therefore, we conducted this single-center retrospective study aiming to re-evaluate the effect of DM on the long-term outcomes of IHF patients undergoing CABG, and trying to provide contemporary evidence for daily clinical practice.

Methods

Ethical approval

The present study involved an analysis of historical de-identified data; thus, it was exempt from the PLA General Hospital Ethics Committee approval. Pre-operatively,

Access this article online

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DOI:

10.1097/CM9.0000000000001421

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Chinese Medical Journal 2021;134(10)

Received: 25-05-2020 Edited by: Li-Shao Guo

Table 1: Baseline characteristics of patients with ischemic heart failure undergoing surgical revascularization before and after matching.

Items	Before matching				After matching			
	Diabetes (n = 183)	Non-diabetes (n = 256)	Statistics	P value	Diabetes (n = 173)	Non-diabetes (n = 173)	Statistics	P value
Female	23 (12.6)	29 (11.3)	0.157 [†]	0.69	21 (12.1)	18 (10.4)	0.260 [†]	0.61
Age (years)	62.14 ± 8.50	62.08 ± 9.23	0.069 [*]	0.95	62.02 ± 8.60	62.25 ± 9.05	-0.244 [*]	0.81
Height (cm)	167.22 ± 8.29	167.12 ± 7.23	0.144 [*]	0.89	167.17 ± 8.29	167.70 ± 6.84	-0.651 [*]	0.52
Weight (kg)	71.83 ± 10.22	71.33 ± 11.64	0.471 [*]	0.64	71.70 ± 10.39	70.83 ± 11.67	0.736 [*]	0.46
BMI (kg/m ²)	25.72 ± 3.81	25.48 ± 3.39	0.694 [*]	0.49	25.70 ± 3.89	25.13 ± 3.41	1.446 [*]	0.15
LVEF (%)	42.78 ± 6.34	41.72 ± 6.62	1.683 [*]	0.09	42.73 ± 6.39	41.90 ± 6.09	1.239 [*]	0.22
LVEDD (mm)	52.46 ± 5.78	53.27 ± 6.83	-1.306 [*]	0.18	52.49 ± 5.87	53.86 ± 6.92	-1.982 [*]	0.05
MVR	63 (34.4)	78 (30.5)	0.767 [†]	0.38	59 (34.1)	62 (35.8)	0.114 [†]	0.74
Pulmonary disease	16 (8.7)	19 (7.4)	0.254 [†]	0.61	16 (6.3)	10 (5.8)	1.497 [†]	0.22
Cerebrovascular disease	41 (22.4)	32 (12.5)	7.551 [†]	<0.01	31 (18.5)	29 (16.8)	0.081 [†]	0.78
Renal disease	17 (9.3)	14 (5.5)	2.374 [†]	0.12	14 (8.1)	10 (5.8)	0.716 [†]	0.40
Symptomatic heart failure	60 (32.8)	82 (32.0)	0.028 [†]	0.87	58 (33.5)	56 (32.4)	0.052 [†]	0.82
Smoker current	43 (23.5)	73 (28.5)	1.382 [†]	0.24	43 (24.9)	48 (27.8)	0.373 [†]	0.54
Smoker ever	63 (34.4)	96 (37.5)	0.436 [†]	0.51	58 (33.5)	60 (34.7)	0.051 [†]	0.82
Dialysis	0	0	-	-	0	0	-	-
Hypertension	122 (66.7)	144 (56.3)	4.849 [†]	0.03	114 (65.9)	114 (65.9)	<0.001 [†]	1.00
Hyperlipidemia	56 (30.6)	63 (24.6)	1.939 [†]	0.16	51 (29.5)	41 (23.7)	1.481 [†]	0.22
Liver/gastrointestinal disease	8 (4.4)	6 (2.3)	1.421 [†]	0.23	6 (3.5)	6 (3.5)	<0.001 [†]	1.00
Peripheral vascular disease	13 (7.1)	28 (10.9)	1.852 [†]	0.17	12 (6.9)	19 (10.9)	1.736 [†]	0.19
Prior PCI	23 (12.6)	24 (9.4)	1.138 [†]	0.29	22 (12.7)	15 (8.7)	1.483 [†]	0.22
Prior CABG	1 (0.5)	0	-	-	1 (0.6)	0	-	-
MI history	101 (55.2)	149 (58.2)	0.395 [†]	0.53	97 (56.1)	101 (58.4)	0.189 [†]	0.66
MI in 3 months	50 (27.3)	68 (26.6)	0.031 [†]	0.86	46 (26.6)	49 (28.3)	0.131 [†]	0.72
Stable angina	5 (2.7)	14 (5.5)	1.930 [†]	0.17	4 (2.3)	12 (6.9)	- [‡]	0.05
Unstable angina	133 (72.7)	186 (72.7)	<0.001 [†]	1.00	127 (73.4)	118 (68.2)	1.133 [†]	0.29
Malignancy	3 (1.6)	2 (0.8)	- [‡]	0.65	3 (1.7)	1 (0.6)	- [‡]	0.62

Data are expressed as n (%) or mean ± standard deviation. *t-test; †Chi-square test; ‡Fisher exact test. BMI: Body mass index; CABG: Coronary artery bypass grafting; LVEDD: Left ventricular end-diastolic dimension; LVEF: Left ventricular ejection fraction; MVR: Mitral regurgitation; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; -: Not applicable.

written consent for potential treatment, post-operative follow-up, and use of the medical record for future research was obtained from all the patients.

General clinical data

From January 2007 to December 2017, a total of 439 IHF patients underwent isolated CABG in our center. Pre-operative coronary angiography of the entire group of patients confirmed significant left main disease and/or triple vessel disease involving the left anterior descending coronary artery. Pre-operative echocardiography showed that the left ventricular ejection fraction (LVEF) was ≤50%. The criteria for DM including patients whose glycated hemoglobin levels were >6.5%, patients who were diagnosed with type 2 diabetes and have received treatment with hypoglycemic drugs or insulin since then. Patients were divided into two groups according to whether they had DM. There were 183 patients in the DM group and 256 in the non-DM group. All patients in the DM group received oral medication, insulin, or both before the procedure. Patients who underwent emergency CABG or concurrent procedures (eg, mitral or aortic valve replacement or left ventricular aneurysm resection) were excluded. Using the propensity score-matching method, pre-operative echocardiographic parameters (LVEF, left ventricular end-diastolic dimension)

were used as the primary matching index, and patients with DM and those without DM were initially selected. Logistic regression models were used to estimate the propensity score. We chose the nearest neighbor matching to balance the differences between groups. The risk factors of the Euroscore (age, sex, etc) were used as the secondary matching index, and 173 pairs of patients were selected according to the ratio of a 1:1 match, and the baseline characteristics were listed in Table 1.

Treatment modalities

All the operations were performed under general anesthesia and median sternotomy approach with or without cardiopulmonary bypass according to the patients' condition and surgeons' preference. Left internal mammary artery (LIMA) was always grafted to the left anterior descending artery if possible and the great saphenous vein was anastomosed to other lesions. All patients received standard dual antiplatelet therapy consisting of 100 mg/d of aspirin and 75 mg/d of clopidogrel for at least 1 year and then changed to aspirin or clopidogrel either. This therapy was combined with statins, angiotensin-converting enzyme inhibitors, β-blocker depending on the patient's blood pressure and heart rate. Patients in the DM group were administered oral hypoglycemic agents or hypodermic

insulin or both to control blood glucose levels. The DM group had a mean history of DM for 8.0 ± 5.5 years, a mean glycated serum protein level of 200.0 ± 40.5 $\mu\text{mol/L}$ (reference value: 125–240 $\mu\text{mol/L}$), and a mean glycated hemoglobin level of $6.40\% \pm 0.72\%$ (reference value: 4.1%–6.5%) at admission. Based on a diabetic diet, patients in the DM group received oral hypoglycemic drugs (84.9%) or subcutaneous insulin injection (41.6%) or both to control blood glucose levels at 6 mmol/L (5.28 ± 1.06 mmol/L) before surgery. All patients were followed up by the out-patient clinic, telephone, or mail.

Outcomes

The primary endpoint was all-cause death, and the secondary endpoint was a composite endpoint of cardiovascular and cerebrovascular adverse events, including death, stroke, myocardial infarction (MI), and revascularization. MI included ST-segment elevation MI or non-ST-segment elevation MI at readmission. Stroke was defined as a neurological diagnosis of cerebral hemorrhage or cerebral infarction. Revascularization was defined as revascularization at the time of readmission, including CABG and percutaneous coronary intervention (PCI).

Statistical analysis

SPSS 19.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used for analysis. All continuous variables are shown as mean \pm standard deviation. Student’s *t* test was used to compare the normally distributed data, non-parametric Wilcoxon test was used for comparison of non-normally distributed data. Categorical variables were tested by the Chi-square test. Propensity score matching was performed by using SPSS 19.0 statistical software. Primary and secondary outcomes were analyzed by the Kaplan-Meier method, and Kaplan-Meier curves were drawn. The confidence interval (CI) was 95% and a statistical difference was considered as $P < 0.05$.

Results

Perioperative outcomes

Patients in the DM group also received continuous insulin infusion at the early post-operative period in the intensive care unit to control blood glucose levels at 6 to 8 mmol/L

(6.77 ± 1.21 mmol/L). There was no significant difference in the proportion of on-pump CABG and extracorporeal bypass time in on-pump CABG between the DM and non-DM groups (81.5% *vs.* 78.0%, $P = 0.422$, $\chi^2 = 0.645$; 101.99 ± 32.44 min *vs.* 101.05 ± 30.99 min, $P = 0.768$, t -value = 0.295, respectively). There was no significant difference in the loss of blood and the number of target lesions that were treated between the DM and non-DM groups (305.43 ± 116.70 mL *vs.* 294.44 ± 116.28 mL, $P = 0.382$, t -value = 0.875; 2.96 ± 0.92 *vs.* 3.03 ± 0.82 , $P = 0.096$, t -value = -0.742, respectively). There were also no significant differences in the rates of in-hospital death, severe ventricular arrhythmia, post-operative renal failure, low cardiac output, and respiratory insufficiency between the two groups [Table 2].

Primary outcome

Kaplan-Meier analysis showed that the cumulative incidence of all-cause death was not different between the DM and non-DM groups at 5 years (5.8% *vs.* 4.1%, $P = 0.216$ by log-rank test $\chi^2 = 1.318$).

Secondary outcomes

Kaplan-Meier analysis showed that the incidence of composite endpoint events was significantly higher in the DM group than in the non-DM group at 5 years (10.4% *vs.* 8.1%, $P = 0.023$ by log-rank test $\chi^2 = 5.203$) [Figure 1]. Cox regression analysis showed that the non-DM group was associated with a significantly lower risk for composite endpoint events compared with the DM group (hazard ratio = 0.605; 95% CI 0.39 to 0.94, $P = 0.024$, Exp[B] = 0.605). There were no significant differences in the other components of composite endpoint events, including stroke (2.3% *vs.* 3.5%, $P = 0.135$ by log-rank test $\chi^2 = 2.230$), MI (0% *vs.* 1.2%, $P = 0.520$ by log-rank test $\chi^2 = 0.414$), and the incidence of revascularization (2.9% *vs.* 0.6%, $P = 0.251$ by log-rank test $\chi^2 = 1.320$) at 5 years between the DM and non-DM groups. There were no significant differences in the Kaplan-Meier curves between the groups [Figure 2].

Discussion

The main findings of this study are as follows. First, DM significantly increased the overall composite adverse events

Table 2: Perioperative adverse events of patients with ischemic heart failure undergoing surgical revascularization after matching ($n = 173$), n (%).

Adverse events	Diabetes	Non-diabetes	Statistics	P value
In-hospital death	2 (1.2)	0	–	–
Respiratory failure	1 (0.6)	0	–	–
Ventricular arrhythmia	1 (0.6)	1 (0.6)	–	1.000*
Post-operative renal failure	4 (2.3)	3 (1.7)	–	1.000*
Low output syndrome	11 (6.4)	10 (5.8)	0.051	1.000†
Pericardial tamponade	1 (0.6)	2 (1.2)	–	1.000*
Deep wound infection	2 (1.2)	1 (0.6)	–	1.000*
Re-exploration for hemorrhage	3 (1.7)	1 (0.6)	–	0.623*

*Fisher exact test; †Chi-square test; –: Not applicable.

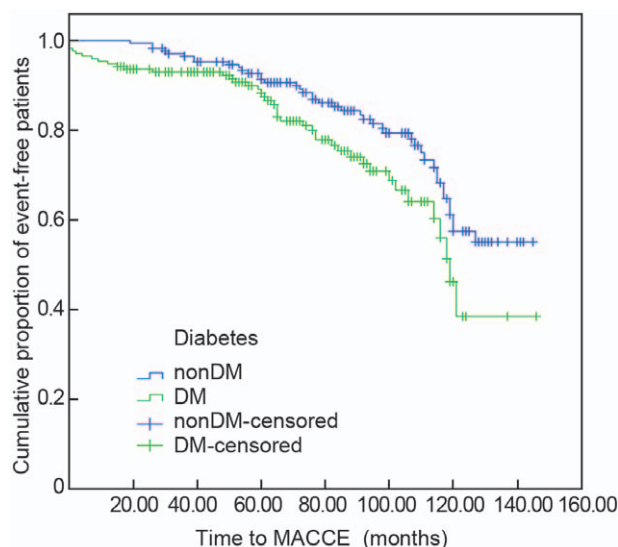


Figure 1: DM group associated with worse long-term outcomes. The non-DM group was associated with a significantly lower risk for composite endpoint events compared with the DM group (hazard ratio = 0.605, 95% CI 0.39–0.94, $P = 0.024$). CI: Confidence interval; DM: Diabetes mellitus; MACCE: Main adverse cardiovascular and cerebrovascular events.

in patients with IHF undergoing CABG. Second, the long-term survival between the DM and non-DM groups had no significant difference.

DM has become a high-risk factor for HF because it is associated with high glycosylated hemoglobin levels, a high body mass index, use of insulin, and combined coronary artery disease and diabetic nephropathy.^[11–13] Meanwhile, DM is closely associated with the occurrence, progress, and prognosis of IHD. It is recorded that almost 30% of patients admitted with the acute coronary syndrome were complicated with DM and this ratio reached 40% for patients undergoing CABG.^[4] Framingham study showed that DM can increase the incidence of death and HF in patients with IHD by two to four times.^[14] The Finnish National Diabetes Registration Study^[15] showed that DM significantly increased the risk of MI in patients with IHD, and MI was the leading cause of chronic HF in these patients. The SOLVD trial^[16] also showed that DM significantly increased the mortality rate and incidence of HF in patients with IHF compared with those of non-IHF. CABG has been widely accepted as the standard treatment for patients with IHD. However, previous studies of the effect of DM on the long-term outcomes of CABG in treating patients with IHF are relatively remote and the results are controversial. Therefore, further research in this field needs to be performed.

The effect of DM on long-term outcomes of patients with IHF undergoing CABG was mainly investigated from the 1980s to 2000. The primary endpoint in these investigations was long-term survival. Trachiotis *et al*^[7] reported that DM significantly reduced the long-term survival of IHF patients undergoing CABG. However, other studies reported that there was no significant difference in long-term survival between patients with DM and non-DM in this subgroup.^[18,17] The CABG PATCH trial,^[18] which was the largest trial during that period, included 900 patients with

the LVEF <35%. The patients were divided into the DM group with 344 patients and the non-DM group with 556 patients. There was no significant difference in survival between the two groups at a 32-month follow-up; however, the incidence of readmission was significantly lower in the non-DM group. Compared with these studies, our study was somewhat different both in patient's inclusion and study design. In the patient's inclusion, most of our patients were moderate IHF with a mean LVEF of 42% which was higher than the patients included in previous studies with a mean LVEF $\leq 35\%$. In the study design, our study used propensity score matching to eliminate the baseline characteristics bias which were common in previous studies due to the nature of the controlled study. Besides, we chose the composite main adverse cardiovascular and cerebrovascular events (MACCE) as a secondary outcome except for the all-cause death. In a mean 73-month follow-up, the secondary outcome showed a significant difference between the DM and non-DM patient groups. Therefore, our study further extended previous studies from the severe IHF patient population to the moderate IHF patient population.

Great progress has been made in the comprehensive prevention and treatment of DM in the past 20 years, and mortality from cardiovascular causes in patients with DM has been significantly reduced.^[19–22] However, DM as a high-risk factor affecting the long-term outcomes of CABG has remained unchanged. Two meta-analyses and a large-scale, controlled study have suggested that DM is an important risk factor that affects long-term survival and adverse events of CABG.^[6,23,24] Studies have shown^[25,26] that DM mainly affects the outcomes of CABG from anatomical and metabolic aspects. With regard to anatomical aspects, DM can deteriorate the endothelium of the vascular system, including the coronary arteries, and accelerate the progression of atherosclerosis and change the microvascular structure. DM also increases the burden of atherosclerosis and the number of lipid-rich plaques, which are more likely to rupture.^[25,26] Thus, the severity and extent of diffuse coronary lesions are significantly worse in patients with DM and IHD than in those without DM.^[27] With regard to metabolic aspects, long-term abnormal glucose metabolism leads to energy metabolism disorders, hypertrophy, degeneration, apoptosis, focal necrosis and fibrosis, and finally, irreversible myocardial remodeling. Additionally, high blood glucose levels increase the activity of the myocardial sympathetic nervous system, activate the renin-angiotensin system, and promote the proliferation of fibrosis, which leads to myocardial hypertrophy and induces diabetic cardiomyopathy (DCM) by various factors.^[28] DCM is an independent risk factor for HF in addition to IHD and hypertension. Therefore, the coronary anatomy of IHD patients with DM is more complicated, and cardiac function reserve is worse than IHD patients without DM, and this situation is more serious for patients with IHF. Although CABG can effectively improve myocardial blood supply, it may not be able to compensate for coronary artery and myocardial damage caused by DM. As the result, CABG probably cannot achieve the same effect in patients with DM as that in patients without DM in improving cardiac function and preventing post-operative adverse events. Despite this, there were no significant differences in perioperative mortality and long-term survival between the DM and non-DM groups. This

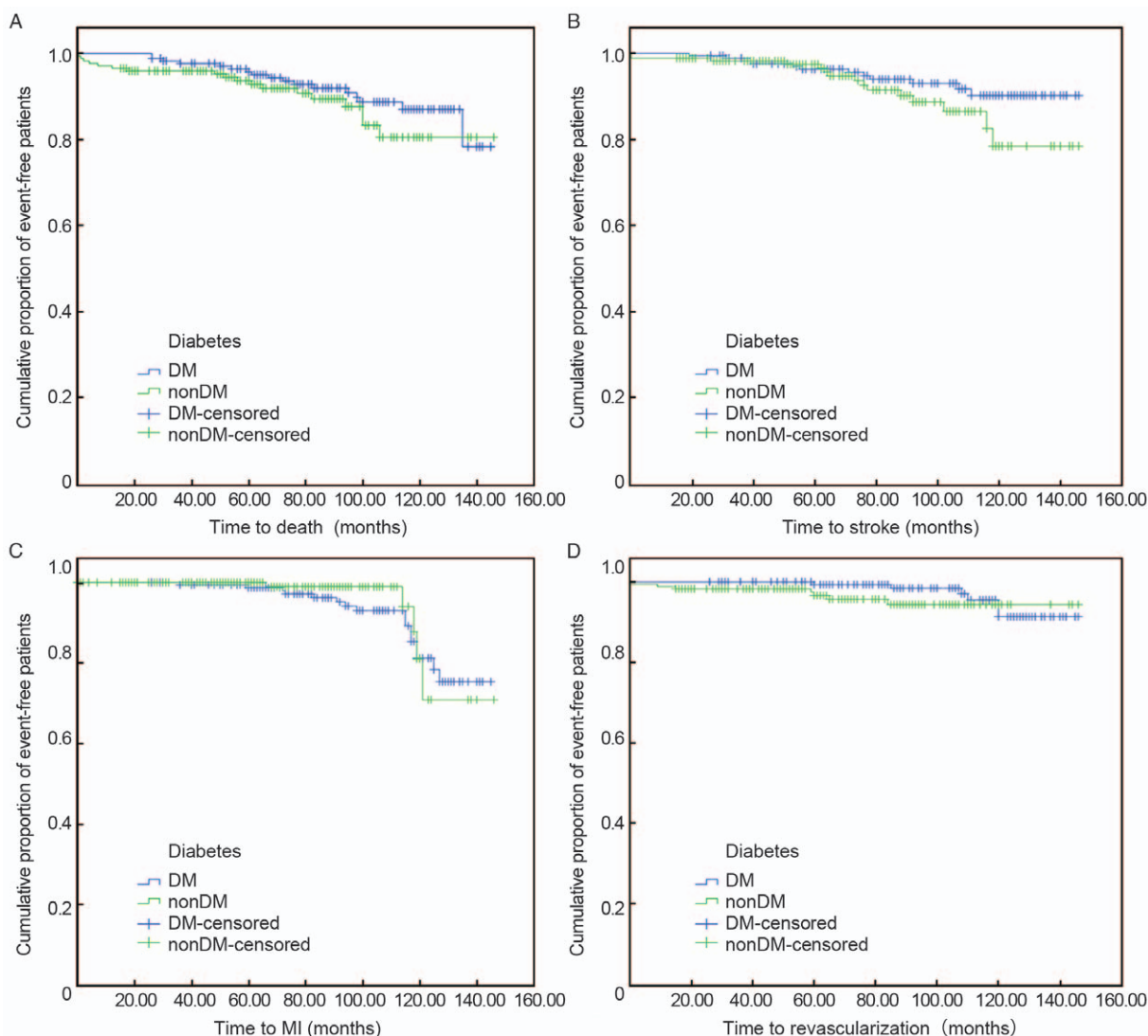


Figure 2: Kaplan-Meier curves of primary outcome and components of the composite endpoint event. There was no significant difference between the DM and the non-DM groups in the incidence of death (A), stroke (B), MI (C), and revascularization (D). DM: Diabetes mellitus; MI: Myocardial infarction.

finding suggests that CABG is still a standard treatment for patients with IHF and DM. This group of patients can obtain relatively good clinical benefits through meticulous pre-operative evaluation and perioperative management.

Although our study used the propensity score-matching method to balance the differences in baseline characters, the fact that it was a single-center retrospective study and it had a small sample size may affect the final results. Additionally, the degree of IHF in the enrolled patients was different from that in previous studies. Therefore, we could not compare our study with previous studies. What is more, we have no complete information about the level of HbA1c during follow-up. Large-scale, multicenter studies or randomized, controlled trials are required to further evaluate the effect of DM on the long-term outcomes of CABG in patients with IHF.

DM can negatively affect the long-term outcomes of patients with IHF undergoing CABG by significantly

increasing the overall incidence of MACCE, though the long-term survival does not show a significant difference between the DM and non-DM patients.

Conflicts of interest

None.

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How to cite this article: Liu M, Zhang HJ, Song H, Cheng N, Wu YB, Wang R. Effect of diabetes mellitus on long-term outcomes of surgical revascularization in patients with ischemic heart failure: a propensity score-matching study. *Chin Med J* 2021;134:1146–1151. doi: 10.1097/CM9.0000000000001421