Effect of diabetes mellitus on long-term outcomes of patients with ischemic heart disease and left ventricular dysfunction undergoing surgical revascularization: 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 left ventricular dysfunction (LVD) and DM, and the results are controversial. This study aimed to evaluate the effect of DM on the long-term outcomes of patients with ischemic heart disease (IHD) and LVD undergoing coronary artery bypass grafting(CABG).

Methods

In this propensity-matched study, patients with IHD and LVD who underwent CABG in our hospital from January 2007 to December 2017 were enrolled. 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 re-revascularization.

Results

There was no significant difference in all-cause mortality between the two groups(5.78%vs.4.05%,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 in the non-DM group (10.40% vs. 8.09%, P=0.023).

Conclusions

DM can negatively affect the long-term outcome of patients with IHD and LVD undergoing CABG by significantly increasing the overall incidence of MACCE, though the long-term survival doesn't show significant difference between the DM and non-DM patients.

Background

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 the critical role in the occurrence, development and long-term outcome of IHD and HF[2]. Coronary artery bypass grafting (CABG) has been widely accepted as the standard care of treating IHD. For patients with IHD and left ventricular dysfunction (LVD), CABG shows better outcomes than percutaneous intervention and oral medication therapy, and was recommended by the current guidelines as the first treatment choice[3, 4]. DM has been demonstrated as an independent risk factor for long-term outcomes of CABG by a series of studies[5]. However, previous studies on the effect of DM on patients with IHD and LVD undergoing CABG were relatively remote and controversial[6, 7]. In recent years, with the improvement of patients' compliance of glucose control and the treatment strategy, the long-term survival of patients with DM and cardiovascular disease has been significantly improved[8]. Additionally, improvement of the CABG technique and the popularity of optimal medical therapy after CABG have significantly improved the long-term outcome of patients with IHD and LVD[9]. Therefore, we conducted this single center retrospective study aiming to re-evaluate the effect of DM on the long-term outcomes of patients with IHD and LVD undergoing CABG, and trying to provide contemporary evidence for daily clinical practice.

1. Materials And Methods

1.1 Patients

From January 2007 to December 2017, a total of 439 patients with IHD and LVD underwent isolated CABG in our center. Preoperative coronary angiography of the entire group of patients confirmed significant triple vessel disease involving the left anterior descending coronary artery and/or left main disease. Preoperative echocardiography showed that the left ventricular ejection fraction (LVEF) was ≤ 50%. 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 (e.g., mitral or aortic valve replacement or left ventricular aneurysm resection) were excluded. Using the propensity score-matching method, preoperative echocardiographic parameters (LVEF, left ventricular end-diastolic dimension LVEDD) were used as the primary matching index, and patients with DM and those without DM were initially selected. 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.

1.2 Methods

All the operations were performed under general anesthesia and median sternotomy approach with or without cardiopulmonary bypass according to the surgeons’ preference and patients’ condition. 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. 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. All patients were followed up by the out-patient clinic, telephone, or mail.

1.3 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 was defined as a 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. Repeated revascularization was defined as revascularization at the time of readmission, including CABG and percutaneous intervention.

1.4 Statistical Analysis

SPSS 19.0 statistical software (SPSS, Inc, Chicago, IL) was used for analysis. All continuous variables are shown as mean ± SD. Student's t-test was used to compared normal distributed data, non-parametric wilcoxon test was used for comparsion of innormal 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 $P < 0.05$.

2. Results

2.1 Perioperative outcomes

The DM group had a mean history of DM for 8 ± 5.5 years, a mean glycated serum protein level of 200 ± 40.5 μmol/L (reference value: 125–240 μmol/L), and a mean glycated hemoglobin level of 6.40%±0.72% (reference value: 4.1–6.5%) at admission. On the basis of 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) during the preoperative period. Patients in the DM group also received continuous insulin infusion at the early postoperative period in the intensive care unit to control blood glucose levels at 6–8 mmol/L (6.77 ± 1.21 mmol/L). There was no significant difference in the proportion of on-pump CABG between the DM and non-DM groups (81.5% vs. 78.0%). There was no significant difference in the number of target lesions that were treated between the DM and non-DM groups (2.96 ± 0.92 vs. 3.03 ± 0.82).There were also no significant differences in the rates of surgical death, severe ventricular arrhythmia, postoperative renal failure, low cardiac output, respiratory insufficiency, perioperative use of intra-aortic balloon pump(IABP), and cerebrovascular complications between the two groups.(Table 2)

2.2 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 (5.78% vs. 4.05% $P = 0.216$). (Fig. 2)

2.3 Secondary Outcomes

Kaplan–Meier analysis showed that the incidence of composite endpoint events was significantly higher in the DM group than in non-DM group at 5 years (10.40% vs. 8.09%, P = 0.023)(Fig. 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). There were no significant differences in the other components of composite endpoint events, including stroke (2.31% vs. 3.47%), MI (0% vs. 1.16%), and the incidence of re-revascularization (2.89% vs. 0.58%) at 5 years between the DM and non-DM groups. There were no significant differences in the Kaplan–Meier curves between the groups. (Fig. 2)

3. Discussion

The main findings of this study are as follows. Firstly, DM significantly increased the overall composite adverse events in patients with IHD and LVD undergoing CABG. Secondly, the long-term survival between the DM group and non-DM group had no significant difference.

DM has become a high risk factor for heart failure because it is associated with high glycated hemoglobin levels, a high body mass index, use of insulin, and combined coronary artery disease and diabetic nephropathy.[10–12] Meanwhile,DM is closely associated with the occurrence, progress and prognosis of IHD. It is recorded that almost 30% patients admitted with acute coronary syndrome were complicated with DM and this ratio reached 40% for patients undergoing CABG.[3] Framingham study showed that DM can increase the incidence of death and HF in patients with IHD by two to four times[13]. The Finnish National Diabetes Registration Study[14] showed that DM significantly increased the risk of myocardial infarction (MI) in patients with IHD, and MI was the leading cause of chronic HF in these patients. The SOLVD trial also showed that[15] DM significantly increased the mortality rate and incidence of HF in patients with ischemic heart failure compared with those non-ischemic heart failure. CABG has been widely accepted as the standard care for patients with IHD. However, previous studies of the effect of DM on the long-term outcome of CABG in treating patients with IHD and LVD 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 IHD and LVD undergoing CABG was mainly investigated from the 1980s to 2000. The primary endpoint in these investigations was long-term survival. Morris and Trachiotis et al. reported that DM significantly reduced long-term survival of patients with IHD and LVD undergoing CABG [6, 16]. However, other studies reported that there was no significant difference in long-term survival between patients with DM and non-DM in this subgroup[7, 17, 18]. The CABG PATCH trial, which was the largest trial during that period, included 900 patients with the LVEF < 35%. The patients were divided to DM group with 344 patients and non-DM group with 556 patients.[19] 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. [19]. Compared with these studies, our study was somewhat different both in patient's inclusion and in study design. In patient's inclusion, most of our patients were moderately impaired LVD with a mean LVEF 42% which was higher than the patients included in previous studies with mean LVEF ≤ 35%. In study design, our study used propensity score matching to eliminate the baseline characteristics bias which were common in previous studies due to the controlled study design. Besides, we set the composite MACCE as the second endpoint except with the all cause death as the primary endpoint. In an average 5-year follow-up, the secondary endpoint did show significant difference between the DM and non-DM patient group. Therefore, our study further extended previous study from the severe LVD patient population to moderate LVD patient population supported by a more reliable statistical approach.

Great progress has been made in comprehensive prevention and treatment of DM in the past 20 years, and mortality from cardiovascular causes in patients with DM has been significantly reduced[20–23]. 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 with CABG and increases adverse events[5, 24, 25]. Studies have shown[26, 27]that DM mainly affects the outcome 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 progression of atherosclerosis and change microvascular structure. DM also increases the burden of atherosclerosis and the number of lipid-rich plaques, which are more likely to rupture[26, 27]. Thus, the severity and extent of diffuse coronary lesions are significantly worse in patients with DM and IHD than in those without DM[28]. 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 proliferation of fibrosis, which lead to myocardial hypertrophy[29] and induce diabetic cardiomyopathy(DCM) by various factors. DCM is an independent risk factor for HF in addition to IHD and hypertension. Therefore, the coronary anatomy of patients with IHD and DM is more complicated and cardiac function reserve is worse than IHD patients without DM, and this situation is more serious for patients with LVD. 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 can not achieve the same effect in patients with DM as that in patients without DM in improving cardiac function and preventing postoperative adverse events. Despite of this, there were no significant differences in perioperative mortality and in long-term survival between the DM and non-DM groups. This finding suggests that CABG is still a standard treatment for patients with IHD and DM and LVD. This group of patients can obtain relatively good clinical benefits through meticulous preoperative evaluation and perioperative management.

4. Limitations

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 LVD in the enrolled patients was different to that in previous studies. Therefore, we could not compare our study with previous studies. 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 IHD and LVD.

5. Conclusion

DM can negatively affect the long-term outcome of patients with IHD and LVD undergoing CABG by significantly increasing the overall incidence of MACCE, though the long-term survival doesn't show significant difference between the DM and non-DM patients.

Declarations

Ethics approval and consent to participate

The present study involved analysis of historical de-identified data; thus, it was exempt from Institutional Review Board approval.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Department of Cardiovascular Surgery, PLA General Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Department of Cardiovascular Surgery, PLA General Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ML and HJZ collected and analyzed the data and drafted the manuscript together. These two authors have equal contribution to the completion of this study. HS provided expert statistical advice and reviewed all the statistical results. NC and YBW provided research advice and were involved in the patient's follow-up. All authors were involved in editing of the manuscript, and read and approved the final version.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

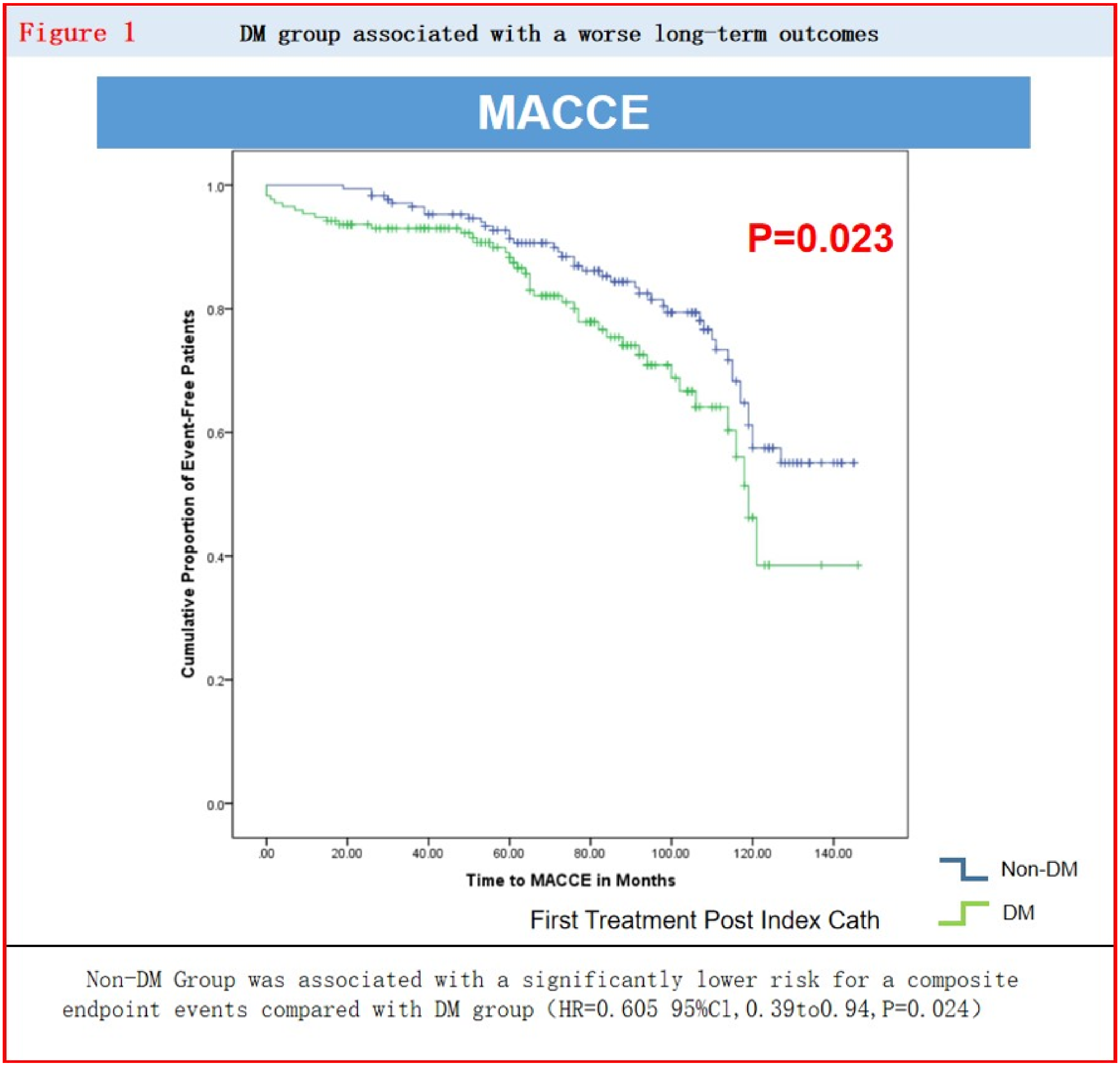
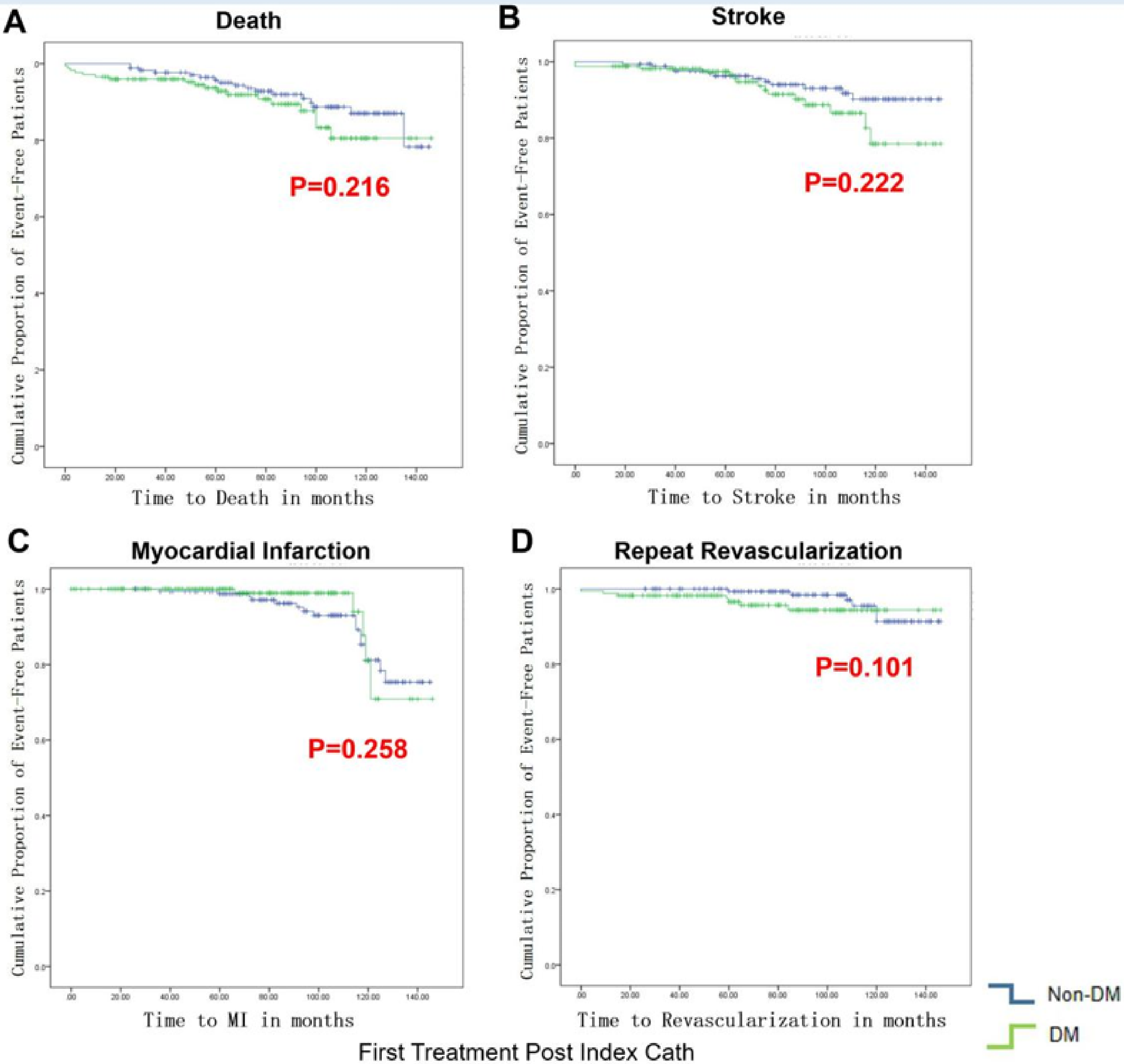


Figure 2

DM group associated with a worse long-term outcomes

Figure2 KM curves of primary outcome and components of the composite end point event



There was no significant difference between DM group and non-DM group in the incidence of Death（A）， Stroke（B）， MI（C）and revascularization（D）

Figure 4

KM curves of primary outcome and components of the composite end point event.

Supplementary Files

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