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Original Article

Clinical benefits of evolocumab in diabetic patients with STEMI undergoing PCI: a retrospective study

Wei Li, Yi Li, Chen Liu, Jinghao Yuan, Weize Fan, Qing Miao, Xinshun Gu

Cardiovascular Department, The Second Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei, P. R. China

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Abstract: Objective: It was unclear whether the clinical benefit of evolocumab extended to diabetic patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI) in China. In this study, the safety and efficacy of evolocumab in treating diabetic patients with STEMI undergoing PCI was assessed. Methods: A retrospective study was conducted involving 184 diabetic patients with STEMI PCI. The patients were assigned to either the evolocumab group or the control (Ctrl) group based on whether they were treated with evolocumab. After six months of treatment and 12 months of follow-up, the primary efficacy endpoint, blood lipid levels, and adverse events were evaluated. Additionally, a prognostic model was developed to examine the relationship between evolocumab intervention and primary efficacy endpoint. Results: Blood lipid levels and intima-media thickness decreased significantly and the LVEF levels increased significantly in patients after treatment with evolocumab compared to those in patients after administering a standard therapy. Treatment with evolocumab also led to a significant reduction in the primary efficacy endpoint. Moreover, no difference in the incidence of adverse reactions was recorded between the groups. The prognostic model constructed showed that evolocumab intervention was a protective factor for the primary efficacy endpoint. Conclusions: Administering evolocumab had greater benefits for diabetic patients with STEMI undergoing PCI. Our findings might encourage doctors to consider use evolocumab to reduce the risk of future cardiovascular events in diabetic patients with STEMI.

Keywords: Evolocumab, primary efficacy endpoint, ST-segment elevation myocardial infarction (STEMI), blood lipid, adverse events

Introduction

Several studies have shown that low-density lipoprotein cholesterol (LDL-C) was an independent risk factor for cardiovascular disease [1, 2]. Genetic studies have shown that the presence of proprotein convertase subtilisin/kexin type 9 (PCSK9) loss-of-function alleles was associated with lower LDL-C levels and a reduced risk of myocardial infarction [1, 3]. Therefore, lowering LDL-C levels can significantly aid in the treatment of patients with acute coronary syndrome. Evolocumab was a fully human monoclonal antibody that targets the PCSK9 protein [4]. In the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk), researchers demonstrated that supplementing evolocumab with statin therapy reduces the risk of the primary composite outcome by 15% and the key secondary composite outcome by 20% in patients with atherosclerotic cardiovascular disease [5]. Additionally, another FOURIER trial conducted with 22,351 patients who had previously experienced myocardial infarction (MI). The study showed a decrease in risk after they were treated with evolocumab; specifically, their primary endpoint tended to be greater in the high-risk subgroups, with reductions of 20% (HR, 0.80; 95% CI, 0.71-0.91), 18% (HR, 0.82; 95% CI, 0.72-0.93), and 21% (HR, 0.79; 95% CI, 0.69-0.91) for patients with more recent MI, multiple prior MIs, and residual multivessel coronary artery disease [6]. However, the efficacy, safety, and feasibility of the supplementation of evolocumab to statin treatment in subtypes of acute coronary syndromes (ACS) patients undergoing PCI were unclear. Exploring the safety and efficacy of evolocumab for ST-segment elevation myocardial infarction (STEMI) patients

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undergoing PCI in China will help further clarify the clinical efficacy of evolocumab and encourage healthcare professionals to use it during the statin therapy.

A study found that STEMI was the most dangerous type of coronary heart disease [7]. In STEMI, patient's coronary artery, which provides blood to the heart, suffered from acute thrombosis, resulting in complete blockage of blood vessels. This led to a portion of the myocardium losing blood perfusion, resulting in acute myocardial necrosis and various clinical symptoms of the disease [8, 9]. Although there were many evidence-based therapeutic strategies available, patients with STEMI undergoing PCI had a consistently high risk of experiencing recurrent ischemic cardiovascular events, especially in the acute phase following the index event [10-12]. The occurrence of diabetes mellitus in patients was rapidly increasing worldwide [13]. Studies had shown that patients with diabetes were 3-5 times more likely to experience an acute myocardial infarction (AMI) than those without diabetes. Patients with diabetes and MI usually have a higher mortality rate, with about 80% of diabetic patients dying from cardiovascular disease [14]. The incidence rate of STEMI patients with diabetes was 32.2% [15]. Therefore, it was crucial to reduce the incidence and mortality of STEMI patients with diabetes. The total number of patients with diabetes mellitus (DM) was expected to increase to nearly 600 million by 2035 [16]. As DM was a critical risk factor for coronary artery disease, it typically presented with diffuse comorbid atherosclerosis and multiple-vessel stenosis, which were poor prognostic indicators for revascularization strategies [17].

In this study, we validated the efficacy, safety, and feasibility of supplementating statins with evolocumab in diabetic patients with STEMI. We conducted a retrospective study to test the hypothesis that supplementing statin treatment with evolocumab can more effectively decrease recurrent cardiovascular events in diabetic patients with STEMI undergoing PCI.

Patients and methods

Study design

A retrospective study was conducted involving diabetic patients with STEMI. This clinical study was conducted at the Second Hospital of Hebei Medical University and was approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (Shijiazhuang, China, NO.2020-R683-R01).

Participants

From March 2019 to June 2023, a total of 204 patients receiving treatment in the Fifth Cardiovascular Department of our hospital were assessed for eligibility, with 184 meeting the inclusion criteria. The participants were screened for STEMI by specialists in the field following the diagnostic criteria of STEMI as per the 2017 "ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation" [18]. The diagnostic criteria for STEMI included an increase in the cardiac marker levels exceeding the upper limit of the normal reference level at least once. Additionally, the diagnostic criteria also required the presence of at least one of the following conditions: (a) elevated ST-segment on electrocardiography; (b) presence of ischemic symptoms; (c) detection of pathological Q waves; (d) new onset ST-T change or left bundle branch block; (e) coronary artery thrombosis found by angiography; (f) new evidence of local cardiac wall motion abnormality or new loss of viable myocardium, determined by imaging. Furthermore, the participants met the diagnostic criteria of "Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance" for diabetes [19]. The diagnostic criteria included at least one of the following conditions: (a) for impaired fasting glucose: fasting glucose ≥ 6.11 to < 7 mmol/L and post glucose (if measured) < 11.1 mmol/L; (b) for impaired glucose tolerance: fasting glucose (if measured) < 7 mmol/L and post glucose ≥ 7.8 to 11.1 mmol/L; (c) for diabetes mellitus: fasting glucose ≥ 7 mmol/L and/or post glucose ≥ 11.1 mmol/L.

The inclusion criteria were as follows: (a) patients who were 40 to 68 years old; (b) patients who were administered coronary intervention therapy within 24 h of onset; (c) patients with high LDL-C levels at the time of visit (serum LDL-C ≥ 1.8 mmol/L); (d) patients who were administered statin lipid-lowering treatment; (e) patients with diabetes.

The exclusion criteria were as follows: (a) presence of severe non-cardiovascular disease; (b) malignancy within the last five years; (c) prior use of PCSK9 inhibitors; (d) intolerance to statin; (e) uncontrolled ventricular tachycardia; (f) New York Heart Association class III or IV; (g) severe renal or hepatic dysfunction; (h) allergic to the drugs under investigation; (i) pregnant or lactating women.

Power analysis

The Prescription Automatic Screening System (PASS) software (Version: 21.03; NCSS, LLC; Utah, USA) was used to calculate the sample size. For a take-effect value of 0.25, $\alpha = 0.05$, $1 - \beta = 0.8$, a total of two groups, and measurements conducted twice, a sample size of 52 cases was required. With the consideration of 20% sample attrition, the minimum sample size required was found to be 66 cases.

Interventions

Patients in the two groups were administered maximally-tolerated statin treatment (rosuvastatin ≥ 10 mg or atorvastatin ≥ 20 mg per day) after admission. If the patients did not attain the target LDL-C levels after 4-6 weeks of statin therapy, a medium-intensity statin plus ezetimibe was recommended by the treating physician. Other cardiovascular medications could be administered following professional guidelines. Decisions about the arterial access site, used of an intra-aortic balloon pump, revascularization strategy, and type of stent were made by the attending interventional cardiologist.

For STEMI patients in the evolocumab group, the first dose was administered at the prior to revascularization. Evolocumab was injected subcutaneously at a dose of 140 mg every two weeks for six months.

Outcome measures

Follow up with patients using outpatient clinic, telephone, and online services. Cardiologists evaluated the presence (or absence) of the primary efficacy endpoint, including cardiogenic death, recurrent myocardial infarction, hospitalization for unstable angina pectoris, coronary target vessel revascularization, composite cardiogenic death, recurrent myocardial infarction, and coronary target vessel revascularization (MACE), all-cause mortality rate, and heart failure [20].

The safety endpoints, with reflect drug safety, included reaction at the site of injection, allergic reactions, myalgia, rhabdomyolysis, neurocognitive impairment, alanine aminotransferase (ALT) > 3× upper limit of normal (ULN), creatine kinase (CK) > 5× ULN, liver function, renal function, hemorrhagic stroke, and other adverse events during the follow-up period.

Blood samples were collected the morning after admission to assess blood lipid levels at admission, and after three and six months of intervention. The parameters assessed included total cholesterol (TC), triacylglycerol (TG), LDL-C, and lipoprotein (a) (LP(a)). Additionally, the left ventricular ejection fraction (LVEF) was evaluated at admission and after three and six months of intervention using the real-time three-dimensional echocardiography (SONOS 7500, Philips Medical Systems, Best, Netherlands). The middle intimal thickness of the carotid artery was measured at admission, and after three and six months of intervention, using a Doppler ultrasound detector (KR-S60, Kaier Medical Instruments Co., Ltd., Tianjin, China).

Establishment of the nomogram score for prognostic evaluation

The prognostic factors were initially calculated by conducting a univariate logistic analysis. Subsequently, a least absolute shrinkage and selection operator (LASSO) logistic regression analysis was performed to identify the risk factors for the primary efficacy endpoint. Using the “rms” and “survival” packages in R (version 4.0.2) [21], the nomogram score was determined, and calibration plots were constructed. Furthermore, a receiver operating characteristic (ROC) curve analysis was conducted using the R package “survival ROC”. The “survival” package was used to determine Harrell’s C index. Finally, using the “rmda” package, a decision curve analysis (DCA) was performed to assess the clinical utility of the nomogram score.

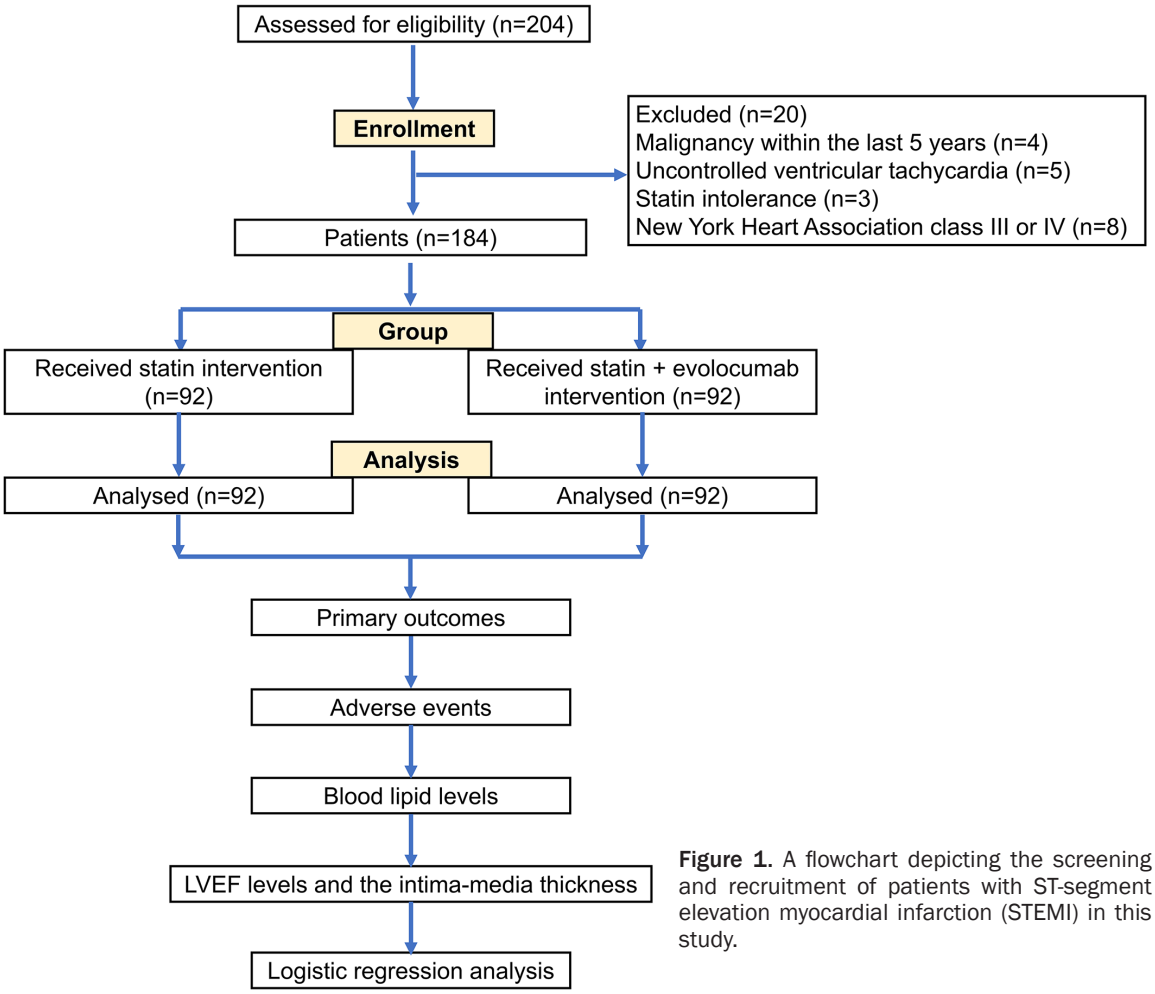

Figure 1. A flowchart depicting the screening and recruitment of patients with ST-segment elevation myocardial infarction (STEMI) in this study.

Statistical analysis

All statistical analyses were performed using SPSS (version 22.0; SPSS Inc., Chicago, USA). The Shapiro-Wilk test was performed to determine whether the data followed a normal distribution. The Chi-square test or Fisher's exact test was performed to assess the differences in count data between groups. The data that followed a normal distribution were analyzed using the Student's t-test to determine differences in various parameters between the groups. The data that did not follow a normal distribution were analyzed using the Wilcoxon test or Mann-Whitney U test to determine differences between the two groups. Repeated measures ANOVA was performed to compare the data of the two groups after intervention. All differences were considered to be statistically significant at $P < 0.05$.

Results

Demographics and clinical characteristics of the participants

In this study, we included 204 diabetic patients with STEMI who were admitted to the hospital between March 2019 and June 2023. Of these, 184 patients met the inclusion criteria and were assigned to the two groups: the Ctrl group (n = 92) and the evolocumab group (n = 92) (**Figure 1**). The baseline characteristics of both groups were provided in **Table 1**. There were no significant differences in the distributions of gender, age, body mass index (BMI), and blood routine index in the two groups (all $P > 0.05$). Most participants in both groups were smokers. Hypertension was the most common comorbidity; more than 60% of diabetic patients with STEMI having hypertension. More than 90% of participants had single-ves-

Table 1. The baseline characteristics of both groups

Characteristic	Ctrl group (n = 92)	Evolocumab group (n = 92)	t/Z value	*P* value
Age (year)	61.5 (56.25-68)	63 (55-68)	0.301	0.764
Gender			0.229	0.632
Male	65 (70.65%)	62 (67.39%)		
Female	27 (29.35%)	30 (32.61%)		
BMI (kg/m^2)	24.67±2.55	24.44±2.78	0.585	0.559
Smoking	60 (65.22%)	57 (61.95%)	0.211	0.646
Drink	50 (54.35%)	54 (58.70%)	0.354	0.552
Hypertension	59 (64.13%)	65 (70.65%)	0.890	0.345
CK-MB (U/L)	223.13±30.95	228.39±26.59	1.237	0.218
NT-proBNP (pg/ml)	346.53±58.21	349.92±51.8	0.417	0.677
Single vessel lesion	89 (96.74%)	87 (94.57%)	0.523	0.470
Number of stents	1 (1-1)	1.5 (1-2)	0.721	0.471
ALT (U/L)	42.22 (35.77-51.89)	44.57 (36.59-50.91)	0.291	0.771
AST (U/L)	197.21±31.79	198.8±25.43	0.375	0.709
CK (U/L)	2303.24±336.03	2296.61±349.92	0.131	0.896
Hospital time (day)	7 (6-8)	7 (6-8)	0.119	0.905

Note: BMI: body mass index; CK-MB: creatine kinase-MB; NT-proBNP: N-terminal proBNP; ALT: alternative lengthening of telomeres; AST: androgen suppression treatment; CK: creatine kinase.

Table 2. Primary outcome of both groups

Outcome	Ctrl group (n = 92)	Evolocumab group (n = 92)	x^2 value	*P* value
Cardiogenic death	2 (2.17%)	1 (1.09%)		1
Recurrent myocardial infarction	2 (2.17%)	1 (1.09%)		1
Hospitalization due to unstable angina pectoris	4 (4.35%)	2 (2.17%)	0.689	0.406
Coronary target vessel revascularization	3 (3.26%)	1 (1.09%)		0.621
Heart failure	2 (2.17%)	1 (1.09%)		1
Stroke	0	0		/
Composite MACE	8 (8.70)	4 (4.35%)	1.426	0.232
All-cause death rate	7 (7.61%)	3 (3.26%)	1.692	0.193
Total	19 (20.65)	7 (7.61%)	6.45	0.011

Note: MACE: major cardiovascular adverse events.

sel lesions. The average number of scaffolds was 1.05±0.23 in the evolocumab group and 1.03±0.18 in the Ctrl group (all P > 0.05). Furthermore, the differences in the distributions of creatine kinase-MB (CK-MB), N-terminal proBNP (NT-proBNP), alternative lengthening of telomeres (ALT), androgen suppression treatment (AST), and creatine kinase (CK) between the two groups were not significant (all P > 0.05). The hospitalization time for both groups of patients was similar (P > 0.05).

Primary outcomes

During the 12-month follow-up, evolocumab addition was associated with a significant reduction in the occurrence of the primary efficacy endpoint compared to standard therapy (P < 0.05). This reduction was mainly due to lower rates of all-cause death and composite MACE. However, there was no significant differences between the two groups in terms of the other components of the primary efficacy endpoint (all P > 0.05, **Table 2**).

Adverse events

The adverse events were mild-to-moderate in both groups. During the intervention, muscle soreness was a common adverse event (1.63%). In the evolocumab group, the adverse events included muscle pain, liver injury, and hemorrhagic stroke (2.17%, 1.09%, and 1.09%, respectively). In the Ctrl group, the

Table 3. Adverse events of both groups

Adverse event	Ctrl group (n = 92)	Evolocumab group (n = 92)	t/x^2 value	*P* value
Injection site reaction	0	0		/
Allergic reactions	0	0		/
Myalgia	1 (1.09%)	2 (2.17%)		1
Rhabdomyolysis	0	0		/
Neurocognitive impairment	0	0		/
ALT > 3* ULN	1 (1.09%)	0		1
CK > 5* ULN	0	1 (1.09%)		1
Abnormal liver function	1 (1.09%)	0		1
Abnormal renal function	0	0		/
Hemorrhagic stroke	0	1 (1.09%)		1
Total	3 (3.26%)	4 (4.35%)	0.149	0.700

Note: ALT: alternative lengthening of telomeres; CK: creatine kinase; ULN: upper limit of normal.

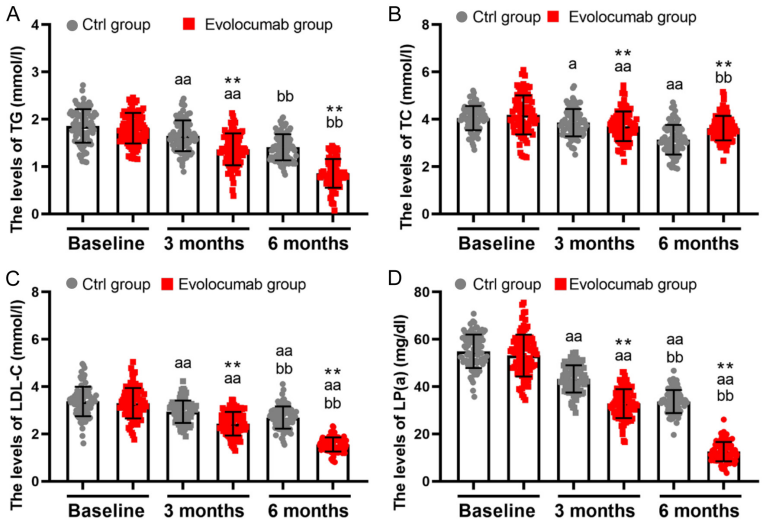

Figure 2. The blood lipid levels were determined at admission and after three and six months of intervention; (A) total cholesterol (TC), (B) triacylglycerol (TG), (C) low-density lipoprotein cholesterol (LDL-C), and (D) lipoprotein(a) (LP(a)). Statistically significant differences were considered **P < 0.01 (Evolocumab group vs. Control group), ^{aa}P < 0.01 (Baseline vs. 3 months or 6 months), ^{bb}P < 0.01 (3 months vs. 6 months).

adverse events included muscle pain and liver injury (1.09% and 2.17%, respectively). The differences in the incidence of adverse reactions between the two groups were not significant (4.35% for the evolocumab group vs. 3.26% for the Ctrl group, P > 0.05) (**Table 3**).

Effect of the addition of evolocumab on blood lipid levels

The results of within-group comparisons showed that the TG levels decreased significantly after three or six months of intervention compared to the baseline values in both groups (all P < 0.01). The TG levels at baseline were not significantly different between the two groups (P > 0.05). After three months of intervention, the TG levels in the evolocumab group were significantly lower than those in the Ctrl group (P < 0.01); the difference remained significant after six months of intervention (P < 0.01) (**Figure 2A**).

Treatment with evolocumab resulted in a 13.43% reduction in the TC levels after three months of intervention and a 24.70% reduction after six months of intervention, compared to baseline levels. After six months of intervention, but not after three months of intervention, the TC levels in the Ctrl group also decreased significantly compared to the baseline (P < 0.01). The baseline TC levels in the two groups were similar, and the TC levels in the evolocumab group decreased significantly compared to that in the Ctrl group after six months of intervention but not after three months of intervention (P < 0.01, **Figure 2B**). There was no significant difference in the LDL-C levels at baseline between the two groups (P > 0.05, **Figure 2C**). Additionally, the LDL-C levels after three months of intervention in the Ctrl and evolocumab groups were 2.94±0.47 and 2.43±0.5, respectively, and they were significantly lower than the baseline LDL-C levels (P < 0.01). The LDL-C lev-

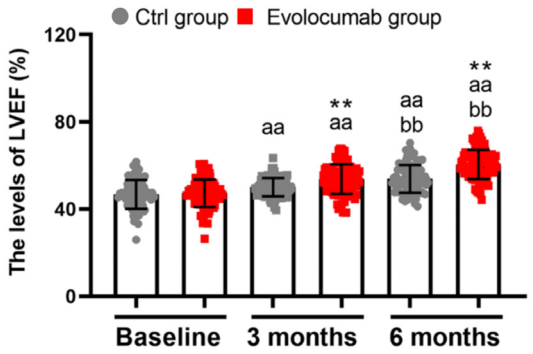

Figure 3. The changes in left ventricular ejection fraction (LVEF) at admission and after three and six months of intervention. Statistically significant differences were considered $^{**}P < 0.01$ (Evolocumab group vs. Control group), $^{aa}P < 0.01$ (Baseline vs. 3 months or 6 months), $^{bb}P < 0.01$ (3 months vs. 6 months).

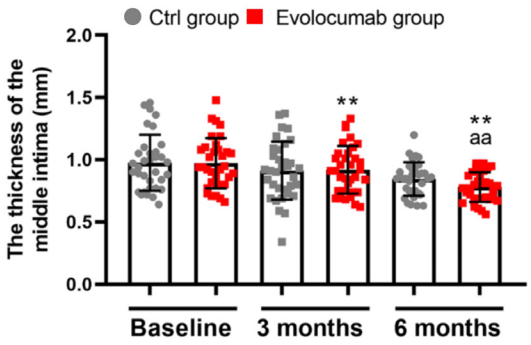

Figure 4. The changes in the middle intimal thickness of the carotid artery at admission and after three and six months of intervention. Statistically significant differences were considered $^{**}P < 0.01$ (Evolocumab group vs. Control group), $^{aa}P < 0.01$ (Baseline vs. 3 months or 6 months).

els after six months of intervention in the Ctrl and evolocumab groups were 2.7±0.47 and 1.56±0.3, respectively, and they were significantly lower than the LDL-C levels recorded after three months of intervention ($P < 0.01$). Moreover, the LDL-C levels were significantly decrease in the evolocumab group than those in the Ctrl group after three months of intervention ($P < 0.01$). Similar results were also found after six months of intervention ($P < 0.01$). The comparison with each groups showed that the LP(a) levels decreased significantly after three months of intervention, and this decrease in LP(a) levels became even more pronounced after six months of intervention, compared to the baseline LP(a) levels ($P < 0.01$). Moreover, evolocumab addition resulted in a more significant decrease in LP(a) levels after three months of intervention compared to the LP(a) levels in the Ctrl group, and after six months of intervention, the difference in the LP(a) levels between the two groups remained significant ($P < 0.01$) (**Figure 2D**).

Changes in LVEF levels and the intima-media thickness of the carotid artery

The effect of evolocumab on cardiac function was evaluated by measuring the LVEF levels. The baseline LVEF levels were not significantly different between the two groups ($P > 0.05$). The LVEF levels increased significantly in both groups after three months of intervention (all $P < 0.05$) and remained significant after six months (all $P < 0.05$). Further analysis demonstrated that evolocumab had greater effects on the LVEF levels after three and six months of intervention compared to the LVEF levels in the Ctrl group (all $P < 0.01$) (**Figure 3**).

We further evaluated the effect of evolocumab on the intima-media thickness of the carotid artery. Among all participants, 34 patients in each group underwent carotid artery testing. The intima-media thickness in the patients of the Ctrl group showed no significant changes during the treatment period ($P > 0.05$) (**Figure 4**); however, the intima-media thickness in the evolocumab group decreased after six months of intervention compared to the baseline thickness. While the intima-media thickness was similar at baseline in both groups, it was significantly lower in the evolocumab group than that in the Ctrl group after three and six months of intervention (both $P < 0.01$).

Independent prognostic factors in diabetic patients with STEMI

We conducted a logistic regression analysis to demonstrate the association between evolocumab intervention and the primary efficacy endpoint. Based on the results of the univariate logistic regression analysis, we identified that age, LVEF, and evolocumab were linked to the primary efficacy endpoint (**Figure 5A**). Then, LASSO regression was performed using three primary efficacy endpoint-related factors from the univariate logistic regression. These three factors with non-zero coefficients were

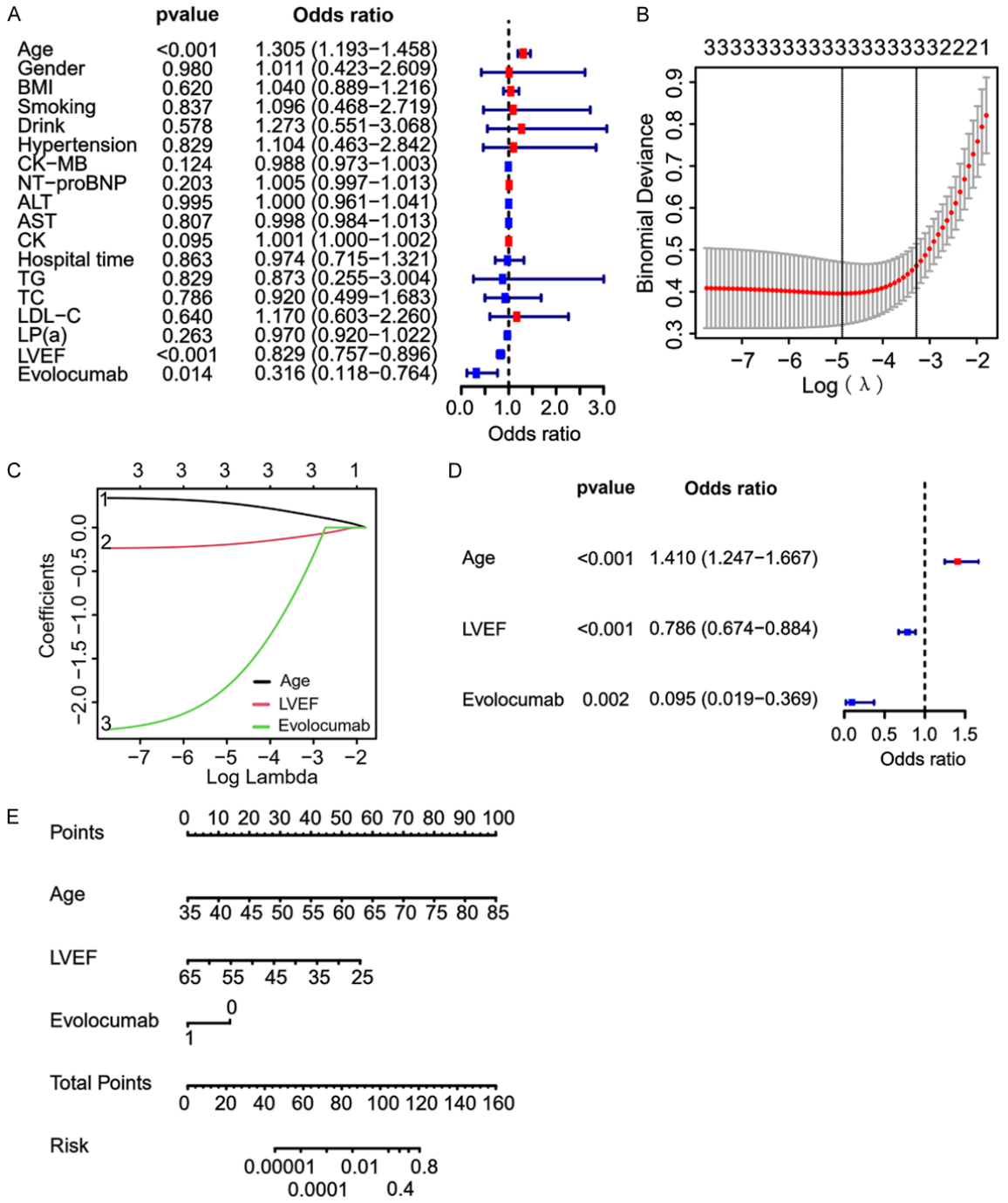

Figure 5. Selection of the risk factors associated with primary efficacy endpoint in diabetic patients with ST-segment elevation myocardial infarction (STEMI). A: A univariate logistic regression analysis was performed to determine the risk factors associated with the primary efficacy endpoint. A forest plot was constructed to visualize the results of the univariate logistic regression analysis. B: The tuning parameter (lambda) selection using least absolute shrinkage and selection operator (LASSO)-type penalized logistic regression with ten-fold cross-validation using minimum criteria. C: LASSO coefficient profiles of the primary efficacy endpoint-associated variables of the radiomic features. D: The forest plot shows the results of the multivariate logistic analysis. The risk factors associated with the primary efficacy endpoint in the multivariate logistic analysis were screened using $P < 0.05$ as the threshold. E: A nomogram was constructed to predict the primary efficacy endpoint in diabetic patients with STEMI based on the result of the multivariate logistic regression analysis.

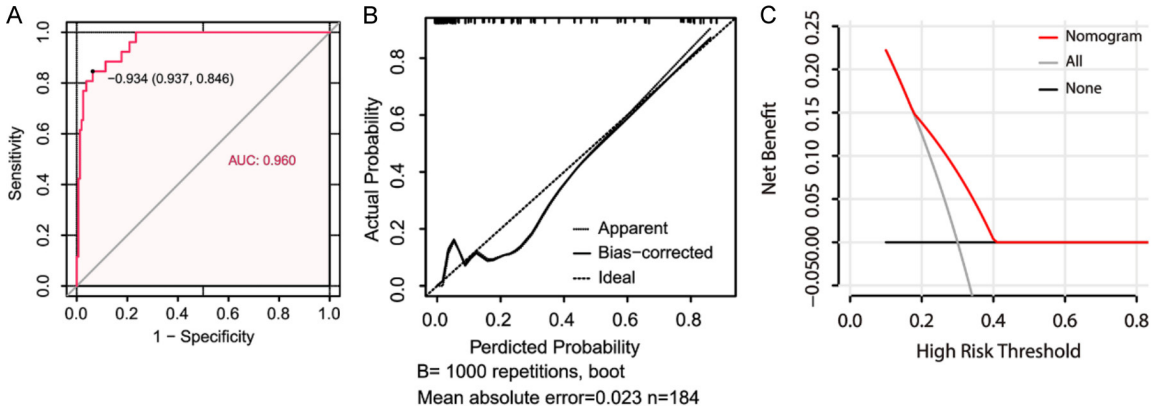

Figure 6. Evaluation of the performance of the nomogram score in predicting the primary efficacy endpoint for diabetic patients with ST-segment elevation myocardial infarction (STEMI). A: A receiver operating characteristic (ROC) curve analysis was conducted to determine the prediction accuracy of the nomogram score. B: The calibration curve plotted was used to examine the performance characteristics of the nomogram score. C: The decision curve analysis (DCA) curve was plotted to assess the clinical utility of the nomogram score.

chosen according to the minimum criteria (**Figure 5B** and **5C**). Subsequently, a multivariate logistic regression analysis was performed, and the age, LVEF, and evolocumab were ultimately identified as independent prognostic factors (**Figure 5D**). Using these independent prognostic factors, we constructed a nomogram score for diabetic patients with STEMI to predict the 12-month primary efficacy endpoint. By adding up the total score of all variables, we could determine the 12-month probability of the primary efficacy endpoint (**Figure 5E**).

After constructing the nomogram, we validated the nomogram score using several metrics. A high C-index (0.960) of the nomogram score indicated good ability to separate patients with different outcomes. Additionally, the ROC curve showed that the value of AUC reached 0.960, which indicated that the score had a good distinguishing ability (**Figure 6A**). The calibration curves in **Figure 6B** depicted the calibration of the nomogram score in terms of the agreement between the observed outcomes and predicted probabilities. The DCA graphically showed the significant net benefits of the nomogram score for predicting the 12-month primary efficacy endpoint to verify its clinical utility and impact on practical decision-making (**Figure 6C**).

Discussion

The evidence supporting the ability of evolocumab to significantly reduce clinical risk among diabetic patients with STEMI undergoing PCI was lacking. This retrospective study was conducted to evaluate the effect of adding evolocumab to statin treatment for reducing cardiovascular events in diabetic patients with STEMI undergoing PCI. During the 12 months of follow-up, the combination treatment with evolocumab and statins resulted in a significant decrease in the incidence of the primary efficacy endpoint. Furthermore, the combination treatment did not significantly increase the incidence of adverse events throughout the follow-up period. Regarding blood lipid levels, evolocumab addition led to a decrease in the TC, TG, LDL-C, and LP(a) levels, which had a beneficial effect. Compared to statin treatment alone, the combination treatment with evolocumab and statins increased the LVEF levels, and reduced the intima-media thickness of the carotid artery to a greater extent. Evolocumab was shown to mitigate heart function damage through lipid lowering, anti-inflammation and plaque stabilization [22-24]. By developing a prognostic model with the primary efficacy endpoint as the outcome, we found that evolocumab acted as a protective factor against poor prognosis in diabetic patients with STEMI. These findings suggested that the combination of evolocumab with statin therapy might be associated with the reduction of cardiovascular events in diabetic patients with STEMI.

Inhibiting PCSK9 was a key therapeutic strategy for reducing the risk of cardiovascular disease [25, 26]. Several studies had shown that

evolocumab, a human monoclonal antibody targeting the PCSK9 protein, could reduce LDL-C by approximately 65% over the dosing interval and by approximately 60% at the end of the dosing interval [27-29]. A large meta-analysis showed that evolocumab addition was associated with a decrease in relative risk of myocardial infarction, ischemic stroke and coronary revascularization [30]. Considering the prevalence of diabetes in patients with MI and the effect of diabetes on the clinical outcomes of such patients [31, 32], we retrospectively analyzed the clinical data of 184 diabetic patients with STEMI from China. We found that evolocumab substantially decreased the occurrence of the primary efficacy endpoint, which was similar to the results of Zhang et al. [8]. In the early addition of evolocumab to statin treatment in patients with ACS and MD who underwent PCI [33]. However, we did not observe any difference in the rate of all-cause death between the two groups, which was different from the findings of Zhang [8]. This disparity occurred probably because of insufficient sample size. PCSK9 could modulate the activity of lipid-uptake receptors of macrophages, vascular inflammation, plaque formation, and platelet thrombosis [33]. Therefore, in diabetic patients with STEMI undergoing PCI, evolocumab in combination with statin treatment could significantly decrease the risk of recurrent cardiovascular events. Specifically, for the safety endpoints, there was not significant difference in the overall occurrence of adverse events between the evolocumab plus statin group and statin group. This finding highlighted that adding evolocumab to statins can significantly improve the cardiovascular outcomes in patients with STEMI. Furthermore, logistic regression analysis confirmed that age, LVEF, and evolocumab were independent prognostic factors for the primary efficacy endpoint, which further confirms the benefits of evolocumab in improving the clinical outcomes of diabetic patients with STEMI undergoing PCI. Our study provided substantial evidence that evolocumab administration can help prevent negative outcomes in STEMI patients, further supporting our conclusion. Interestingly, the study of Haller et al. showed that increasing age independently influenced short- and long-term mortality in patients with STEMI [34]. STEMI damage triggers a host of biochemical, cellular, and molecular reactions that result to concurrent dynamic processes of remodeling and healing over several weeks. At the same time, oxidative stress, angiotensin II, and other factors lead to cardiac enlargement, cardiomyocyte slippage, heart failure, and cardiac dysfunction [35, 36]. Previous studies have shown that impaired and/or defective healing with aging can, in turn, augment or accelerate maladaptive remodeling, thereby leading to progressive cardiac enlargement, fibrosis, disability and/or death [35, 37]. Recent studies in the mouse model of reperfusion myocardial infarction displayed that the older the age, the more delayed the repair, the less infarction collagen and the more obvious adverse remodeling [38]. In addition, with the increase of age, patients are exposed to risk factors for a longer time, and the severity and scope of coronary artery disease are further increased. Meanwhile, the symptomology of the acute event may differ for elderly than non-elderly STEMI patients. It is not uncommon for elderly patients to present with atypical symptoms [39]. Obviously, elderly STEMI patients need more attention and active treatment.

Reducing LDL-C levels was a key strategy for evolocumab to improve cardiovascular events. Some studies had shown that the inhibition of PCSK9 by evolocumab can increase the extracellular membrane density of LDL receptors, thus reducing the levels of circulating LDL-C [40]. Several studies had shown that evolocumab plus statin therapy can decrease LDL-C levels [41, 42]. Our study showed a similar result. Additionally, we found that the levels of other blood lipid indicators, including TC, TG, and LP(a), decreased significantly. Evolocumab considerably decreased the LDL-C levels in patients with STEMI, which suggested that evolocumab might be used for clinical application of evolocumab in patients with different subtypes of acute coronary syndrome.

Evolocumab combined with statin can more effectively stabilize and regress coronary atherosclerosis, compared to using statins alone. This was indicated by a significant increase in the minimum fibrous cap thickness and a reduction in the maximum lipid arc and macrophage index [43]. Due to the limitation of the equipment and insufficient funding for the detection of aortic plaques, we examined carotid artery plaques, which was a simpler and more convenient approach to assess the impact of

evolocumab on plaques. Our results revealed that the intima-media thickness was significantly lower in the evolocumab group than in the Ctrl group after three and six months of intervention. Evolocumab was an inhibition directed that targets the PCSK9 protein. Interestingly, animal studies have shown that PCSK9 knockout mice showed a reduction of FeCl3 injury-induced carotid artery thrombosis, with the formation of unstable non-occlusive thrombi [44, 45], suggesting an impaired platelet function. Furthermore, in PCSK9 knockout mice the activation of circulating platelets provoked by arterial injury, shown by increased glycoprotein IIb/IIIa activation, P-selectin expression and circulating platelet - leukocyte aggregates, was strikingly reduced as compared with control mice [44, 45]. This also explains why evolocumab can reduce the intima-media thickness of carotid artery plaques in patients with STEMI. These findings suggested that administering evolocumab might be an effective strategy for treating patients with STEMI undergoing PCI.

Limitations

This study had several limitations that should be addressed in future studies. First, it was conducted at a single-center (one hospital), and thus, the results represent only the population in China. Therefore, multicenter and large-scale studies are needed to confirm our conclusions. Additionally, while our findings were credible, the follow-up lasted only one year. Thus, studies with follow-up for a longer duration are needed to validate the clinical benefits of evolocumab for STEMI. Subgroup analysis was typically conducted to evaluate the consistency between the results and the overall trial, such as for different ages and genders. A highly accurate subgroup analysis cannot be performed with a small sample size; thus, in the future, analysis of STEMI patients with different clinical characteristics is necessary.

Conclusions

Patients with STEMI were at a higher risk of major adverse cardiovascular events. In this retrospective study, we found that adding evolocumab to statin therapy in diabetic patients with STEMI can decrease the risk of recurrent cardiovascular events. The use of evolocumab was also found to be safe and well-tolerated by patients. These findings might encourage healthcare professionals to consider using evolocumab alongside statin treatment to lower the risk of future cardiovascular events in diabetic patients with STEMI.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xinshun Gu, Cardiovascular Department, The Second Hospital of Hebei Medical University, 215 Heping West Road, Shijiazhuang 050000, Hebei, P. R. China. E-mail: guxishhmu@163.com

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