Long-term statin use before primary percutaneous coronary intervention improves treatment outcomes of acute myocardial infarction

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Abstract. Numerous studies have reported that high-dose statin loading therapy prior to primary percutaneous coronary intervention (PPCI) improves the clinical outcomes of patients following acute myocardial infarction (AMI). However, little is known about the effects of long-term statin use prior to PPCI on such outcomes. Therefore, the aim of the present analysis was to clarify the effects of long-term statin use before PPCI on the treatment outcomes of patients following AMI. The records of 213 patients who had AMI and met the inclusion criteria were retrospectively reviewed. Patients were divided into two groups: A control group (n=178) who had received no statin pretreatment before AMI onset, and a statin group (n=35) who had received statin treatment for ≥1 month before AMI onset. All patients received a standard treatment regimen for the secondary prevention of coronary artery disease after PPCI. Baseline clinical variables, details of the PPCI procedure and clinical outcomes within 3 months after treatment were reviewed. Patients in the statin group were significantly older than those in the control group (P=0.003). Compared with the control group, there was a greater proportion of patients with hyperlipidemia and previous angina pectoris in the statin group. There were no differences in the use of other drugs (aspirin, β-blockers and angiotensin-converting enzyme inhibitors) prior to PPCI between the two groups. The corrected TIMI frame count (cTFC) was significantly lower in the statin group than in the control group (24.1±12.8 vs. 29.4±14.3, respectively; P=0.043). Multivariable linear regression analysis showed that long-term statin use before AMI was a significant predictor of cTFC after PPCI (P=0.012). Furthermore, the incidence of major adverse cardiac events within 3 months after PPCI was higher in the control group than in the statin group (16.8 vs. 2.9%, respectively; P=0.032). Logistic regression analysis showed that previous statin use was associated with the incidence of major adverse cardiac events within 3 months after treatment (P=0.012). The results of the present study demonstrate that long-term statin use prior to PPCI improved treatment outcomes after AMI in actual clinical practice.

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Introduction

Treatment outcomes of patients after acute myocardial infarction (AMI) have greatly improved following the introduction of primary percutaneous coronary intervention (PPCI) (1). However, major adverse cardiac events (MACEs) continue to occur at markedly higher rates in patients after AMI as compared with those with stable coronary artery disease, particularly within the first 3 months after PPCI (2).

It is well established that statin treatment is beneficial for the primary and secondary prevention of coronary artery diseases (3,4). In addition to lowering serum lipid levels, statins have been shown to convey favorable effects on endothelial function, coagulation activation, nitric oxide bioavailability and stimulation of the inflammatory response. Collectively, these effects are known as the 'pleiotropic effects' of statins (5). Recently, the 'pleiotropic effects' of statins have also been shown to modulate platelet adhesion and activation, inhibit inflammation, and attenuate thrombosis, all of which may contribute to the preservation of microvascular function during ischemia and reperfusion following ST-elevation myocardial infarction (STEMI) (6-8). Several studies have demonstrated that high-dose statin loading therapy prior to PPCI may be more efficacious in patients with STEMI than in other clinical situations because STEMI is characterized by extreme inflammation (9-11). However, little is known about the long-term effects of statin loading prior to PPCI on treatment outcomes of patients after AMI.

A recent meta-analysis indicated a time-related impact of statin therapy on the clinical outcomes of patients with acute coronary syndrome (ACS) undergoing PPCI: The earlier the

administration before PPCI, the greater the benefits. Earlier statin administration was found to be significantly correlated with a lower risk of AMI, MACEs and major adverse cardiac and cerebrovascular events within 30 days after treatment (12). Previous observational studies of patients after STEMI have suggested that previous chronic statin use may improve coronary blood flow and is associated with reduced short-term mortality (13). Based on the findings of these studies, it may be hypothesized that long-term statin use prior to PPCI could improve the treatment outcomes of patients after AMI. Therefore, the present retrospective study was performed to clarify the effects of long-term statin use prior to PPCI on the treatment outcomes of patients after AMI.

Materials and methods

Study population. The medical records of 268 patients who underwent PPCI for AMI at the Kunming General Hospital of Chengdu Military Command (Kunming, China) from January 2014 to March 2015 were retrospectively reviewed. Of these, 55 patients were excluded because of incomplete follow-up data; thus, the study population consisted of 213 patients. For the purposes of the present study, patients were divided into two groups according to statin treatment for at ≥1 month prior to AMI onset. A total of 35 patients received statin treatment (20 mg atorvastatin/day or 10 mg rosuvastatin/day) before AMI onset because of hyperlipidemia or coronary artery disease (statin group). The other 178 patients did not receive statin pretreatment before AMI onset (control group). All patients received standard treatment for secondary prevention of coronary artery diseases after PPCI, including treatment with aspirin, clopidogrel, ACE inhibitors, beta blockers and statins. The following patient information was collected: i) Patient age; ii) gender; iii) risk factors for cardiovascular disease, including diabetes (fasting plasma glucose and two-hour plasma glucose value of ≥126 mg/dl and ≥200 mg/dl, respectively), hypertension (a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg), hyperlipidemia (a total cholesterol level ≥240 mg/dl), smoking history and previous angina pectoris; iv) previous medications prior to PPCI; v) the time from chest pain to balloon dilation (PTB) were measured according to inquiry and standard procedure; vi) details of PPCI treatment; and vii) myocardial infarct outcomes within 3 months after treatment. All patients provided informed consent, and the study protocol was approved by the Medical Ethics Committee of Kunming General Hospital of Chengdu Military Command (approval no. 2015067).

PPCI procedure. After angiography, the PPCI procedure was performed using standard techniques by an experienced operator. Prior to the procedure, 300 mg aspirin (Bayer AG, Leverkusen, Germany) and 600 mg clopidogrel (Sanofi S.A., Paris, France) were administered to all patients. An intravenous bolus of 5,000 units heparin (Kunming Jida Pharmaceutical Co., Ltd, Kunming, China) was administered to maintain an activated clotting time of >300 sec during PPCI. Culprit vessel blood flow was evaluated using thrombolysis in myocardial infarction (TIMI) grade and corrected TIMI frame count (cTFC). Specific details regarding TIMI flow grades and cTFC have been described previously (14). TIMI flow grades and cTFC were evaluated following the completion of PPCI.

Study end point. The primary end point of the study was the incidence of MACEs within 3 months after treatment, including all-cause mortality rates, the incidence of new myocardial infarction, and target vessel revascularization (TVR). New myocardial infarction and TVR were defined as previously described (15). Only the first MACE was considered. The secondary end points included TIMI flow grade and cTFC after PPCI.

Statistical analysis. Continuous variables are presented as means ± standard deviations and were compared using the t-test in cases of two independent groups with parametric data. Categorical variables are presented as frequencies with percentages, and comparisons were made using the Pearson chi-squared test. Multiple linear regression analysis was performed to determine the influence of previous statin treatment on cTFC after PPCI. The following variables were entered into the model: Age, gender, hypertension, diabetes, hypercholesterolemia, smoking history, previous angina pectoris, drugs given before AMI onset, PTB time, multivessel disease, and stent length and diameter. A multivariable logistic regression model was constructed to predict the occurrence of MACEs within 3 months after PPCI. The following variables were selected and inserted into the logistic regression analysis: Age, gender, hypertension, diabetes, hypercholesterolemia, smoking history, previous angina pectoris, peak creatine kinase concentration, drugs given before AMI onset, PTB time, multivessel disease, stent length and diameter, and cTFC. A two-tailed probability (P)-value of <0.05 was considered to indicate a statistically significant difference. All analyses were performed using SPSS version 19.0 software (IBM SPSS, Armonk, NY, USA).

Results

Baseline characteristics. The key baseline characteristics of patients eligible for the study are listed in Table I. A total of 35 patients received long-term statin administration (28 patients with 20 mg atorvastatin/day and 7 patients with 10 mg rosuvastatin/day) for >1 month before AMI onset. Of these patients, 34 received long-term statin administration to treat hyperlipidemia and the other received this treatment because of previous angina pectoris. Patients in the statin group were significantly older than those in the control group (67.3±4.9 vs. 61.8±10.4 years, respectively; P=0.003). Compared with the control group, hyperlipidemia and previous angina pectoris were more prevalent in the statin group (97.1 vs. 29.2%, respectively; P<0.001; and 25.7 vs. 10.1%, respectively; P=0.011). There were no significant differences in gender, diabetes, hypertension, smoking history, PTB time or peak creatine kinase concentrations between the groups. Furthermore, there were no differences in the frequency of administration of other drugs (i.e., aspirin, B-blockers and angiotensin-converting-enzyme inhibitors) prior to PPCI between the two groups.

PPCI procedure and clinic outcomes within 3 months. All patients underwent angiography and PPCI. Clinical outcomes of PPCI are listed in Table II. Glycoprotein IIb/IIIa platelet inhibitors and thrombectomy devices were used when a

Table I. Baseline clinical characteristics.

Characteristic	Control group (n=178)	Statin group (n=35)	P-value
Age, years[a]	61.8±10.4	67.3±4.9[b]	0.003
Male, n (%)	131 (73.6)	25 (71.4)	0.791
Peak creatine kinase (U/l)	1,794.1±1072.1	1,670.6±890.1	0.523
Risk factor, n (%)			
Diabetes	48 (27.0)	13 (37.1)	0.796
Hypertension	62 (34.5)	14 (40.0)	0.560
Hyperlipidemia	52 (29.2)	34 (97.1)[b]	<0.001
Smoking history	47 (26.4)	12 (34.3)	0.341
Previous angina pectoris	18 (10.1)	9 (25.7)[b]	0.011
Previous medications, n (%)			
Aspirin	26 (14.6)	7 (20.0)	0.420
β-blocker	7 (3.9)	3 (8.6)	0.236
ACEI	13 (7.3)	6 (17.1)	0.062
PTB time (h)	9.1±3.3	19.6±4.2	0.584

[a]Values presented as mean ± standard deviation; [b]P<0.05 vs. the control group. ACEI, angiotensin-converting enzyme inhibitor; PTB, pain-to-balloon.

Table II. Primary percutaneous coronary intervention management and clinical outcomes.

Management and outcomes	Control group (n=178)	Statin group (n=35)	P-value
Multivessel disease, n (%)	68 (38.2)	19 (54.3)	0.077
Culprit vessel			
Left main	1 (0.6)	0 (0.0)	0.657
Left anterior descending	79 (44.4)	15 (42.9)	0.868
Left circumflex	26 (14.6)	6 (17.1)	0.701
Right coronary artery	72 (40.4)	14 (40.0)	0.960
Use of glycoprotein inhibitor, n (%)	23 (12.3)	6 (17.1)	0.506
Use of thrombectomy devices, n (%)	10 (5.6)	4 (11.4)	0.205
Length of stents (mm)[a]	27.6±8.0	25.9±8.8	0.255
Diameter of stents (mm)[a]	3.3±0.3	3.2±0.3	0.193
Final TIMI 3 flow, n (%)	161 (90.4)	32 (91.4)	0.856
cTFC[a]	29.4±14.3	24.1±12.8[b]	0.043
Clinical outcome at 3 months, n (%)			
All cause mortality	8 (4.5)	1 (2.9)	0.660
New myocardial infarction	6 (3.4)	1 (2.9)	0.876
TVR	22 (12.3)	1 (2.9)	0.088
MACEs	30 (16.8)	1 (2.9)[b]	0.032

[a]Values presented as mean ± standard deviation; [b]P<0.05 vs. the control group. MACEs includes all-cause mortality, new myocardial infarction and TVR. TIMI, thrombolysis in myocardial infarction; cTFC, corrected TIMI frame count; TVR, target vessel revascularization; MACEs, major adverse cardiac events.

large number of thrombi were observed. The cTFC value was significantly lower in the statin group than in the control group (24.1±12.8 vs. 29.4±14.3, respectively; P=0.043). There were no significant differences in other angiographic or procedural outcomes between groups. The 3-month clinical outcomes are listed in Table II. There were no significant differences in all-cause mortality rates (P=0.660) or in the incidence of new myocardial infarction (P=0.876) between the two groups. However, there was tendency toward a higher rate of TVR among patients in the control group (12.3 vs. 2.9%, respectively; P=0.088). This tendency may underlie the higher prevalence of major adverse cardiac events in the

Table III. Multivariate linear regression determinants of cTFC after PCI.

Determinant	B	t	95% CI	P-value
Previous statin use	7.920	2.547	1.787-14.054	0.012
Age	0.267	2.552	0.610-0.474	0.011
Diabetes	4.802	2.210	0.443-9.161	0.031
PTB times	0.631	0.244	0.149-1.112	0.011

Variables entered for the multivariate linear regression analyses were age, gender, hypertension, diabetes, hypercholesterolemia, smoking, previous angina pectoris, drugs given before the onset of acute myocardial infarction, PTB times, multivessel disease, and the length and diameter of stents. cTFC, corrected thrombolysis in myocardial infarction frame count; PCI, percutaneous coronary intervention; PTB, pain-to-balloon; CI, confidence interval.

Table IV. Multivariate logistic regression determinants of 3-month MACEs after PCI.

Determinant	B	OR	95% CI	P-value
Previous statin use	2.694	14.788	1.023-213.870	0.048
Age	0.100	1.105	1.027-1.190	0.008
Diabetes	-1.896	0.150	0.030-0.744	0.020
Hypertension	-1.646	0.193	0.048-0.769	0.020
Smoking history	1.652	5.216	1.525-17.840	0.008
PTB times	0.149	1.543	0.261-9.141	0.033
Peak creatine kinase	0.001	1.001	1.000-1.001	0.007
Diameter of stent	-2.238	0.107	0.014-0.795	0.029
cTFC	0.070	1.073	1.034-1.113	<0.001

Variables entered for the multivariable logistic regression analyses were age, gender, hypertension, diabetes, hypercholesterolemia, smoking, previous angina pectoris, peak creatine kinase, drugs given before the onset of acute myocardial infarction, PTB times, multivessel disease, length and diameter of stents, and cTFC. MACEs, major adverse cardiac events; PCI, percutaneous coronary intervention; PTB, pain-to-balloon; cTFC, corrected thrombolysis in myocardial infarction frame count; CI, confidence interval; OR, odds ratio.

control group compared with the statin group (16.8 vs. 2.9%, respectively; P=0.032).

Association between long-term statin use before AMI and cTFC. Multivariable linear regression analysis was performed to assess the effects of long-term statin use before AMI on cTFC after PPCI. The multivariate regression determinants of cTFC during PPCI are shown in Table III. The regression model showed that long-term statin use before AMI was a significant predictor of cTFC after PPCI (P=0.012). Other independent predictors of cTFC after PPCI were patient age (P=0.011), presence of diabetes (P=0.031), and PTB time (P=0.011).

Association between long-term statin use before AMI and MACEs within 3 months after treatment. Multivariate logistic regression analysis showed that previous statin use was associated with MACEs within 3 months (Table IV; P=0.048). Other factors significantly associated with MACEs within 3 months after treatment included patient age (P=0.008), diabetes (P=0.020), hypertension (P=0.020), smoking history (P=0.008), PTB time (P=0.033), peak creatine kinase concentration (P=0.007), stent diameter (P=0.029) and cTFC (P<0.001).

Discussion

Statin use is acknowledged to be beneficial to patients after AMI through 'pleiotropic mechanisms' additional to the ability of the treatment to lower low-density lipoprotein cholesterol levels (4,5). The results of the present study demonstrated that long-term statin use prior to AMI improves clinical outcomes after PPCI, despite a substantially higher risk profile in the statin group. In addition, the improved coronary reflow after PPCI, as assessed by cTFC, may be attributable to the beneficial outcomes observed in the statin group. These conclusions are based on several lines of evidence. First, the cTFC value was significantly lower in the statin group than in the control group. Second, the regression model showed that long-term statin use before AMI was a significant predictor of cTFC after PPCI. Third, multivariate logistic regression analysis showed that previous statin use was also associated with the occurrence of MACEs within 3 months. In addition, some predictors of clinical outcomes within 3 months after PPCI were identified.

The results of this retrospective study revealed significantly greater risk factors among patients in the statin group, specifically, age, hyperlipidemia and previous angina pectoris. These results are in accordance with those of some previous

trials (16-18). The main reason for a greater risk of MACEs in older people is that the risk of coronary heart disease is greater among the elderly and those patients at greater risk are more likely to reject statin treatment due to associated liver toxicity. In order to analyze the effects of long-term statin use before AMI after PPCI, cTIMI frame count was employed in this study because it is a simple clinical tool for the assessment of quantitative indices of coronary blood flow (19). In addition, cTFC is closely associated with the clinical outcomes of patients after AMI (20). The results of the present study showed that cTFC values were significantly lower in the statin group than in the control group, and the regression model indicated that long-term statin use before AMI was a significant predictor of cTFC following PPCI. Celik *et al* (6) also reported that prior statin use may improve coronary blood flow after PPCI in patients after AMI, possibly due to its beneficial effects on microvascular function. However, another study reported that atorvastatin loading may not convey protective effects on endothelial function or against inflammatory responses in patients with STEMI undergoing primary PPCI (5). These results indicate that long-term statin use may have favorable effects on microvascular function. Another previous study showed that chronic statin administration preserved coronary microvascular integrity independent of lipid-lowering effects (21).

There is considerable evidence to indicate that statin therapy improves the clinical outcomes of patients with ACS undergoing PPCI. The ARMYDA-ACS trial, which was the first randomized study to assess the efficacy of statin therapy prior to PPCI in patients with ACS, showed that loading with 80 mg atorvastatin 12 h before PPCI reduced the elevation in post-procedural biomarkers and the incidence of MACEs within 30 days after treatment (22). The Euro Heart Survey trial reported a reduction in all-cause 7-day mortality in patients with ST-elevation ACS who received statin treatment within 24 h after admission, as compared with patients who did not receive statins within the first 24 h (23). The current study also evaluated the effect of long-term statin use prior to PPCI on the clinical outcomes of patients after AMI. The results of multivariate logistic regression analysis revealed that previous statin use was associated with a lower incidence of MACEs within 3 months after treatment. Moreover, Lev *et al* (16) also reported that previous statin therapy in patients who underwent PPCI after STEMI may be associated with reduced short-term mortality. Lee *et al* (24) demonstrated that early and continuous statin therapy can improve the early outcomes of STEMI patients following PPCI in actual clinical practice. Since these cited reports were retrospective studies, a large prospective study is required to confirm the effect of long-term statin use prior to PPCI on the clinical outcomes of patients after AMI.

There were several limitations to the present study that should be addressed. First, this study was retrospective and there were large differences in baseline clinical characteristics between the two patient groups, particularly age and risk profiles. Second, there was no control for statin properties or dosage among patients prior to PPCI. Third, this study was a single-center study; thus the data may not be representative of other institutions. In addition, the sample size of the study was relatively small. Therefore, a larger cohort is needed to confirm the study findings.

In conclusion, the results of the present study demonstrated that long-term statin use prior to PPCI improved the treatment outcomes of patients after AMI in actual clinical practice.

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