

Original Article

Effects of intensive pitavastatin therapy on glucose control in patients with non-ST elevation acute coronary syndrome

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Abstract: *Objective:* This study aimed to investigate the effects of intensive pitavastatin therapy on glucose control in patients with non-ST elevation acute coronary syndrome (ACS). *Methods:* Patients who had ACS with significant stenosis on initial coronary angiography and received successful percutaneous coronary intervention (PCI) in the Second Hospital of Hebei Medical University, Shijiazhuang, China from August 2015 to January 2016 were enrolled in this study. The patients were randomized to receive pitavastatin (4 mg daily) or atorvastatin (20 mg daily). PCI was performed within 72 hours after admission according to the current clinical practice at the physician's discretion. The examinations of blood lipid levels and blood markers of glucose metabolism were performed at baseline and after 6-month follow-up using standard techniques. The inflammatory markers, including white blood cell, high-sensitivity C-reactive protein (hs-CRP) and fibrinogen, were also assessed before PCI and 24 hours after PCI. An independent adverse event assessment committee evaluated major adverse cardiovascular events (MACE) and any other adverse events. *Results:* A total of 132 patients were enrolled and randomly divided into the pitavastatin group (n = 65) or the atorvastatin group (n = 67), which had similar baseline characteristics and PCI procedural characteristics. For the inflammatory biomarkers at 24 hours after PCI, the fibrinogen level was significantly increased in the atorvastatin group; the hs-CRP levels were significantly increased in both groups, however, the hs-CRP level in the pitavastatin group was lower than that in the atorvastatin group. In addition, the blood lipid parameters (e.g., TC, LDL-C, TG, non-HDL-C and Apo B) were significantly decreased in both groups after 6-month follow-up ($P < 0.01$), but these parameters between the two groups had no significant difference. After 6-month follow-up, the FPG, IRI, HOMA-IR and HbA_{1c} levels were significantly decreased in the pitavastatin group ($P < 0.05$) but slightly increased in the atorvastatin group, indicating that the glucose homeostasis was improved in patients in the pitavastatin group but not in the atorvastatin group. Furthermore, the incidence of MACE was not significantly different between the two groups ($P > 0.05$). After 6-month antiplatelet treatment, the PAR value was significantly decreased in both groups ($P < 0.01$), but the PAR value in the pitavastatin group was lower than that in the atorvastatin group. *Conclusion:* Pitavastatin therapy may improve the glucose homeostasis for patients with ACS undergoing PCI and has more favorable outcomes than atorvastatin therapy.

Keywords: Intensive pitavastatin therapy, glucose metabolism, non-ST elevation acute coronary syndrome, percutaneous coronary intervention

Introduction

Acute coronary syndrome (ACS) is a clinical manifestation of coronary artery disease (CAD), and patients with ACS are at a very high risk of life-threatening cardiovascular events [1]. Now the percutaneous coronary intervention (PCI) is a recommended approach for the treatment of ACS and optimized medical therapies are imminently required for ACS patients [2]. The

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) decrease the level of low-density lipoprotein cholesterol (LDL-C), and have anti-inflammatory and immunomodulatory effects on atherosclerotic plaque [3, 4]. Previous studies found that intensive statin therapy had been proven to be superior in improving cardiovascular outcomes as compared to mild statin therapy [5]. Current guidelines, therefore, recommend a more aggressive

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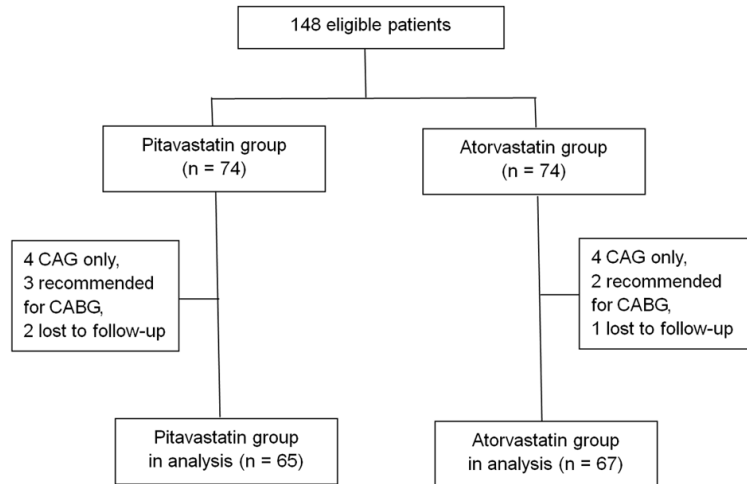


Figure 1. Patients enrolled in the present study.

LDL-C target of 70 mg/dL (< 1.8 mmol/L) for ACS patients or a $> 50\%$ reduction in LDL-C level from baseline [6-8]. Up to now, it has been proved that atorvastatin, pitavastatin and rosuvastatin have intensive LDL-C lowering effects in clinical practice. However, several statins have been shown to increase insulin resistance, glucose level and glycosylated hemoglobin (HbA_{1c}), which may lead to an increased risk of new-onset diabetes [9-11]. The exact effect of pitavastatin on glycemic control remains controversial [12] and has not been evaluated as the primary endpoint in previous clinical studies. Thus, the objective of the present study was to investigate the effects of intensive pitavastatin therapy on glucose control in patients with non-ST elevation acute coronary syndrome.

Subjects and methods

Study population

All the patients who suffered from ACS with significant stenosis on initial coronary angiography and received successful PCI in the Second Hospital of Hebei Medical University from August 2015 to January 2016 were eligible for inclusion in the present study. The diagnosis of ACS was made based on the fulfillment of at least two of the following three criteria: (1) the evidence of coronary ischemia on ECG, (2) the increase (≥ 2 fold) of serum creatinine kinase (CK) or CK-MB levels and/or troponin-I positivity, and (3) the presence of symptoms suggestive of ACS. Diabetes mellitus (DM) and

other complications were diagnosed by attending physicians. Exclusion criteria included failed PCI, diseased bypass graft, recommended CABG, cardiogenic shock, hepatic insufficiency, renal insufficiency, and administration of lipid-lowering drugs (statin, clofibrate, probucol or analog, nicotinic acid, or other prohibited drugs) before enrollment.

When being admitted to the Department of Cardiology, all eligible patients were randomly divided into the pitavastatin (4 mg daily) group or the atorvastatin (20 mg daily) group.

Patient enrollment was carried out according to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Second Hospital of Hebei Medical University. The written informed consent was obtained from each patient before his/her participation. The registration number is ChiCTR-IPR-15007035.

Percutaneous coronary intervention and medical therapies

PCI was performed within 48 hours after admission according to the current clinical practice at the physician's discretion. For all patients, aspirin (300 mg/day) and clopidogrel (300 mg/day) were loaded before the procedure, and aspirin (100 mg/day) and clopidogrel (75 mg/day) were prescribed as maintenance dosages for at least 1 year. An intravenous bolus of 5,000 U of unfractionated heparin was administered, and then additional heparin was administered to maintain an activated clotting time greater than 300 s during the procedure. Platelet glycoprotein IIb/IIIa inhibitor (GPI) tirofiban was administered according to the operator's preference. Other drugs were administered according to the current guidelines.

Blood sample tests

The examinations of blood lipid levels and blood markers of glucose metabolism (including HbA_{1c}) were performed at baseline and after 6-month follow-up using standard techniques.

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Table 1. Baseline characteristics of the two groups

	Pitavastatin group (n = 65)	Atorvastatin group (n = 67)	P value
Age (yr.)	65.8±10.5	65.3±9.3	0.7724
Male-n (%)	40 (61.5)	43 (64.2)	0.8936
BMI (kg/m ²)	24.2±3.4	24.5±3.7	0.6287
Waist circumference (cm)	87.1±8.8	86.4±9.5	0.6615
History			
Hypertension-n (%)	43 (66.2)	40 (59.7)	0.5572
Family history of CAD-n (%)	14 (21.5)	15 (22.4)	0.9264
Smoking-n (%)	32 (50.8)	34 (50.7)	1.0000
Alcohol drinker-n (%)	33 (50.8)	29 (43.3)	0.4920
Diabetes-n (%)	29 (44.6)	28 (41.8)	0.8794
Types of ACS			
Unstable angina-n (%)	35 (53.8)	38 (56.7)	0.8756
NSTEMI-n (%)	30 (46.2)	29 (43.3)	
GRACE score	167±37	170±40	0.6556
CRUSADE score	34.7±10.2	33.8±8.1	0.4548
SBP (mmHg)	127±5.8	129±7.6	0.0923
Heart rate (bpm)	74±3.5	73±3.2	0.0841
Hemoglobin (g/L)	140.6±12.2	141.8±13.4	0.5918
Hs-CRP (mg/L)	10.3±5.5	10.5±6.1	0.8436
eGFR- (mL/min/1.73 m ²)	74.5±16.1	72.6±15.2	0.4868
LVEF (%)	54.2±7.1	54.9±8.3	0.6040
Drug administration			
Aspirin-n (%)	65 (100)	66 (98.5)	1.000
Clopidogrel-n (%)	61 (93.8)	60 (89.6)	0.5313
β-blocker-n (%)	59 (90.8)	59 (88.1)	0.8399
Calcium blocker-n (%)	30 (46.2)	28 (41.8)	0.7418
Diuretics-n (%)	11 (16.9)	12 (17.9)	0.9363
ACEI/ARB-n (%)	54 (83.1)	58 (86.6)	0.7517
Insulin-n (%)	3 (4.6)	4 (6.0)	1.000
Nitrate-n (%)	23 (35.4)	26 (38.8)	0.8207
Sulfonylurea-n (%)	8 (12.3)	7 (10.4)	0.9503
α-glucosidase inhibitor-n (%)	9 (13.8)	8 (11.9)	0.9466

Note: BMI: body mass index; CAD: coronary artery disease; ACS: acute coronary syndrome; NSTEMI: non-ST segment elevated myocardial infarction; SBP: systolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; LVEF: left ventricle ejection fraction; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Blood samples were obtained between 08:00 am and 10:00 am after overnight fast. The inflammatory markers, including white blood cell (WBC), high-sensitivity C-reactive protein (hs-CRP) and fibrinogen, were also assessed before PCI and 24 hours after PCI. Safety was evaluated at 6 months after enrollment. An independent event assessment committee evaluated major adverse cardiovascular events (MACE) and any other adverse events. MACE included recurrent angina, target vessel revas-

cularization, sudden death, and/or heart failure.

Statistical analysis

SPSS 19.0 statistical software was used for all calculations. The continuous variables were reported as means ± SD and were compared using the unpaired t-test for normally distributed values and the Mann-Whitney U test for non-normally distributed variables. The categorical variables were expressed as absolute or relative frequencies and were compared using chi-square test or the Fisher's exact test, as appropriate to the cell frequencies. To compare the changes in the levels of lipid, glucose and inflammatory biomarkers before and after PCI, a paired t-test was used. $P < 0.05$ was considered statistically significant.

Results

In this study, a total of 148 patients met the inclusion criteria and 16 patients were excluded after CAG (8 patients underwent CAG only, 5 patients were recommended to receive CABG, and 3 patients lost to follow-up). Therefore, a total of 132 patients were enrolled finally and randomly divided into the pitavastatin group (n = 65) or the atorvastatin group (n = 67) (see **Figure 1**).

Baseline characteristics between the two groups

Baseline clinical characteristics were shown in **Table 1**. There were no significant differences in baseline clinical characteristics between the two groups, including age, gender, body mass index (BMI), risk factors of CAD, cardiac functions, as well as initial medications ($P > 0.05$).

Procedural characteristics between the two groups

The coronary angiography (CAG) and PCI procedures were performed via the radial artery in all

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Table 2. Procedural characteristics between the two groups

	Pitavastatin group (n = 65)	Atorvastatin group (n = 67)	P value
Multivessel disease-n (%)	34 (52.3)	33 (49.3)	0.8599
Target vessel			0.9163
LM-n (%)	1 (1.5)	2 (3.0)	
LAD-n (%)	34 (52.3)	32 (47.8)	
LCX-n (%)	13 (20.0)	14 (20.9)	
RCA-n (%)	17 (26.2)	19 (23.4)	
Stent per person	1.4±0.8	1.5±0.8	0.4741
Length of stent (mm)	40±24	41±23	0.8073
Diameter of stent (mm)	3.2±0.3	3.2±0.4	1.0000
Time from symptom onset (h)	45 (23, 65)	47 (21, 68)	0.7582
GP IIb/IIIa inhibitor-n (%)	14 (21.5)	17 (25.4)	0.7533

Note: LM: left main; LAD: left anterior descending coronary artery; LCX: left circumflex branch; RCA: right coronary artery.

Table 3. Changes of inflammatory biomarkers 24 hours after PCI

	Pitavastatin group (n = 65)		Atorvastatin group (n = 67)	
	Before PCI	24 h after PCI	Before PCI	24 h after PCI
WBC (×10 ⁹ /L)	8.4±2.5	8.5±2.7	8.2±2.0	8.4±2.6
Fibrinogen (g/L)	2.98±0.76	3.15±0.89	3.03±0.80	3.39±0.94*
hs-CRP (mg/L)	10.3±5.5	13.6±8.4*,#	10.5±6.1	16.8±9.7*

Note: WBC: white blood cell; hs-CRP: high-sensitivity C-reactive protein; *: compared with baseline, $P < 0.01$; #: compared with atorvastatin group, $P < 0.05$.

Table 4. Changes of lipid parameters 6 months after PCI

	Pitavastatin group (n = 65)		Atorvastatin group (n = 67)	
	Before PCI	6 months	Before PCI	6 months
TC (mmol/L)	5.52±0.91	4.10±0.67*	5.55±0.96	4.09±0.71*
LDL-C (mmol/L)	3.46±0.76	1.96±0.62*	3.49±0.80	1.98±0.69*
HDL-C (mmol/L)	1.17±0.29	1.45±0.33*	1.16±0.25	1.43±0.31*
TG (mmol/L)	1.95±0.73	1.53±0.58*	1.98±0.84	1.51±0.62*
LDL-C/HDL-C	2.95±0.55	1.35±0.47*	3.01±0.52	1.38±0.46*
Non-HDL-C (mmol/L)	4.35±0.88	2.65±0.74*	4.39±0.83	2.66±0.79*
Apo A1 (mmol/L)	3.02±0.45	3.61±0.66*	3.05±0.41	3.49±0.52*
Apo B (mmol/L)	2.74±0.56	2.25±0.44*	2.73±0.50	2.31±0.49*
Apo A1/Apo B	0.91±0.24	0.62±0.18*	0.90±0.22	0.66±0.20*

Note: TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; Apo A1: apolipoprotein A1; Apo B: apolipoprotein B; *: compared with baseline, $P < 0.01$.

patients. There were no significant differences in the distributions of target vessels, PCI procedures and drug medications between the two groups ($P > 0.05$). The procedural characteristics were shown in **Table 2**.

The baseline levels of fasting plasma glucose (FPG), insulin resistant index (IRI), HOMA-insulin resistance (HOMA-IR) and HbA_{1c} were comparable between the two groups. After 6-month follow-up, the levels of FPG, IRI, HOMA-IR and

Changes of inflammatory biomarkers after PCI

Levels of WBC, fibrinogen and hs-CRP were measured before PCI and 24 hours after PCI. The baseline levels of WBC, fibrinogen and hs-CRP were similar between the two groups. No significant difference was observed in the level of WBC after PCI. The level of fibrinogen was significantly increased in the atorvastatin group, but no significant change was observed in the pitavastatin group. The hs-CRP levels were significantly increased 24 hours after PCI in both groups ($P < 0.01$); however, the level of hs-CRP in the pitavastatin group was lower than that in the atorvastatin group ($P < 0.05$) (see **Table 3**).

Changes of lipids parameters 6 months after PCI

The lipid parameters before PCI and 6 months after PCI were shown in **Table 4**. Both the lipid parameters at baseline and after 6-month follow-up had no significant difference between the two groups. However, after 6-month follow-up, the TC, LDL-C, TG, non-HDL-C and Apo B levels were significantly decreased and the HDL-C and Apo A1 levels were significantly increased ($P < 0.01$) from baseline in both groups. The ratios of LDL-C/HDL-C and Apo A1/Apo B were also decreased 6 months after PCI ($P < 0.01$).

Changes of blood markers of glucose metabolism 6 months after PCI

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Table 5. Changes of blood markers of glucose metabolism 6 months after PCI

	Pitavastatin group (n = 65)		Atorvastatin group (n = 67)	
	Before PCI	6 months	Before PCI	6 months
FPG (mmol/L)	6.02±0.84	5.78±0.72#	5.99±0.78	6.23±0.92
IRI (μU/mL)	8.70±5.32	7.56±4.86#	8.68±5.41	9.67±6.15
HOMA-IR	2.3±1.4	1.9±0.8&,#	2.2±1.2	2.5±1.6
HbA _{1c} (%)	5.8±0.7	5.8±0.5#,&	5.8±0.6	6.1±0.9

Note: FPG: fasting plasma glucose; IRI: insulin resistant index; HOMA-IR: HOMA-insulin resistance; &: compared with baseline, $P < 0.05$; #: compared with atorvastatin group, $P < 0.05$.

HbA_{1c} were decreased significantly in the pitavastatin group ($P < 0.05$) but increased slightly in the atorvastatin group. The level of HbA_{1c} in the pitavastatin group was significantly lower than that in the atorvastatin group ($P < 0.05$) (see **Table 5**).

Incidence of MACE during 6-month follow-up

No significant difference was observed between the two groups in the incidence of MACE, which included recurrent angina, target vessel revascularization, sudden death, and heart failure ($P > 0.05$) (see **Table 6**).

Comparisons of liver function, renal function and platelet aggregation rate

The changes of liver function, renal function and platelet aggregation rate (PAR) were shown in **Table 7**. The baseline levels were similar between the two groups. After 6-month follow-up, the changes of liver and renal functions in the two groups had no significant difference. However, the PAR value was significantly decreased in both groups after 6 months of antiplatelet treatments ($P < 0.01$), and the PAR value in the pitavastatin group was lower than that in the atorvastatin group ($P < 0.05$).

Discussion

In this study, the intensive pitavastatin therapy in ACS patients showed more favorable effects in serum glucose levels and PAR value than the atorvastatin treatment.

Coronary artery disease, including ACS, is the leading cause of death globally. The association between elevated LDL-C and increased risk of CAD has been well established.

Therefore, intensive statin therapy is recommended in current guidelines in order to decrease the level of LDL-C. As atorvastatin, pitavastatin and rosuvastatin, which are known as strong statins, have intensive LDL-C lowering effects in clinical practice, they are suitable for the treatments of ACS. In Asian patients, atorvastatin 10 mg/day, pitavastatin 2 mg/day and rosuvastatin 2.5 mg/day showed similar effects in LDL-C reduction [13]. Our study showed that the lipid lowering effects of pitavas-

tatin and atorvastatin were similar, which was consistent with the results of previous studies. Despite the beneficial effects of statins on cardiovascular disease, a recent meta-analysis of 13 randomized studies showed that statin therapies significantly increased the incidence of new-onset diabetes by 9% [14]. In particular, some reports indicated that atorvastatin could adversely affect glycemic control, as what was observed in our study in **Table 5**. Pitavastatin is a new statin marginally metabolized by cytochrome P450 isoenzymes with potent LDL cholesterol-lowering effect similar to atorvastatin and particularly low potential for drug-drug interactions [15]. However, data on the potential impact of statin treatment on glucose homeostasis in patients with ACS are controversial. With regard to blood glucose control, a recent study reported that pitavastatin was neutral, whereas atorvastatin caused deterioration of glycemic control in patients with type 2 diabetes [16]. In contrast, some studies did not show such favorable effects of pitavastatin compared with atorvastatin [17].

In this study, we found that the levels of FPG, IRI, HOMA-IR and HbA_{1c} were significantly decreased in the pitavastatin group and slightly increased in the atorvastatin group after 6-month follow-up. The level of HbA_{1c} in the pitavastatin group was significantly lower than that in the atorvastatin group (see **Table 5**). The results indicated that intensive pitavastatin therapy could improve the glucose homeostasis in patients with ACS, but atorvastatin treatment had no such effect. The mechanisms by which some statins may exert diabetogenic effects currently remain unclear. It was reported that atorvastatin could attenuate expression of the glucose transporter GLUT-4 in adi-

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Table 6. Incidence of MACE during 6 months of follow-up

	Pitavastatin group (n = 65)	Atorvastatin group (n = 67)	P value
Total incidence of MACE-n (%)	6 (9.2)	8 (11.9)	0.8237
Recurrent angina-n (%)	3 (4.6)	4 (6.0)	1.000
Target vessel revascularization-n (%)	2 (3.1)	2 (3.0)	1.000
Sudden death-n (%)	0 (0)	0 (0)	-
Heart failure-n (%)	1 (1.5)	2 (3.0)	1.000

Note: MACE: major adverse cardiovascular event.

Table 7. Comparison of liver function, renal function and platelet aggregation rate before PCI and 6 months after PCI

	Pitavastatin group (n = 65)		Atorvastatin group (n = 67)	
	Before PCI	6 months	Before PCI	6 months
ALT (U/L)	35±7	37±8	36±6	38±11
AST (U/L)	34±7	36±8	36±7	38±10
SCr (μmol/L)	79.3±13.5	82.6±18.1	76.8±10.4	80.5±16.7
eGFR (mL/min/1.73 m ²)	74.5±16.1	72.4±14.9	72.6±15.2	70.6±14.2
PAR (%)	73.8±20.3	51.4±12.7*,#	72.4±21.2	57.5±14.8*

Note: ALT: alanine aminotransferase; AST: aspartate aminotransferase; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; PAR: platelet aggregation rate; *: compared with baseline, $P < 0.01$; #: compared with atorvastatin group, $P < 0.05$.

pocytes, thus impairing glucose tolerance [18], while elevated level of ceramide transported in LDL appeared to be correlated with increased insulin resistance [19]. Moreover, changes in the expression of insulin-sensitive glucose transporters, or the dysregulation of cellular cholesterol pathways leading to accumulation of triglycerides in pancreatic beta cells, might be involved in lipotoxicity and apoptosis of insulin-secreting beta cells [20]. On the other hand, the neutral effect of high-dose pitavastatin on the parameters of glucose homeostasis seen in the PREVAIL-US validation subset was similar to the effect seen in the PREVAIL-US comparison subset treated with pravastatin. This finding is important given that pravastatin has been consistently associated with the lowest diabetogenic risk of all members of the statin class. Intensive pitavastatin therapy may be a safer option for glucose control in ACS patients.

Another finding of this study was that the PAR value in the pitavastatin group was lower than that in the atorvastatin group, which indicated that there might be less interaction between pitavastatin and clopidogrel. This effect may be beneficial to ACS patients who accepted

clopidogrel therapy after PCI. The reason for this may be that pitavastatin is minimally metabolized by cytochrome P4-50 (CYP) isoenzymes and the possibility of interaction with drugs metabolized by inhibiting or inducing CYP enzymes is low [21].

This is a small scale study. Therefore, further adequately-powered studies will be needed to determine whether these physiological observations can be translated to patient outcome improvement and to assess the safety of this treatment strategy.

In conclusion, pitavastatin therapy may improve the glucose homeostasis

for patients with ACS undergoing PCI and has more favorable outcomes than atorvastatin therapy.

Disclosure of conflict of interest

None.

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