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Original Article

Effects of early PCSK9 inhibitor application on inflammation levels and microcirculatory function after PCI in patients with NSTE-ACS

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Abstract: Objective: To investigate inflammation levels and microcirculatory function following the early application of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor after percutaneous coronary intervention (PCI) in patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS). Methods: This is a retrospective study. Between December 2019 and December 2021, 120 patients with NSTE-ACS admitted to the People's Hospital of Henan University of Traditional Chinese Medicine for PCI were randomized via a web-based randomization system into a control group (60 cases) treated with atorvastatin or a PCSK9 inhibitor group (60 cases) treated with atorvastatin + evolocumab. After 6 months of treatment, between-group differences were assessed for the following measures: triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) [Lp(a)], high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), index of microcirculatory resistance (IMR), Thrombosis in Myocardial Infarction myocardial perfusion grading (TMPG), major adverse cardiovascular events (MACEs), and adverse reactions. Results: After 6 months of treatment, TG (P=0.037), TC (P<0.001), LDL-C (P<0.001), Lp(a) (P<0.001), hs-CRP (P<0.001), TNF-α (P<0.001), and IL-6 (P<0.001) levels and IMR values (P<0.001) were significantly lower in the PCSK9 inhibitor group than in the control group. TMPG grade 3 (P=0.04) was noted to occur significantly more frequently in the PCSK9 inhibitor group than in the control group. No significant between-group differences in MACEs (P>0.05) or adverse reactions (P>0.05) were observed. Conclusions: Compared with statins alone, a PCSK9 inhibitor combined with statins improves inflammation levels and microcirculatory function after PCI in patients with NSTE-ACS, and this strategy deserves clinical attention.

Keywords: Proprotein convertase subtilisin/kexin 9, non-ST segment elevation acute coronary syndrome, inflammation levels, microcirculatory function

Introduction

Acute coronary syndrome (ACS), characterized by sudden onset and rapid changes, is a severe type of coronary heart disease [1]. Although patients with ACS are treated with intensive anti-platelet, anti-lipidemic, cardiac remodeling, and revascularization therapies as early as possible, the risk of major adverse cardiovascular events (MACEs) remains high [2]. After 1 year, the mortality rate of patients with ACS was approximately 15%, which increases to 25% after 3 years and to 39% after 4 years, while being potentially associated with persistent residual lipid and inflammatory risk factors [3, 4]. In addition, good coronary microcirculatory perfusion after PCI is associated with good clinical prognosis [5]. Therefore, anti-inflammatory and anti-lipidemic therapies are important for preventing the occurrence of MACEs [3, 4]. Recently, the Association for Acute Cardiovascular Care, in collaboration with the European Association of Preventive Cardiology and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy, issued a consensus statement proposing a "strike early and strike strong" lipid-lowering strategy and recommending immediate lipid management for all patients with ACS, including the reduction of low-density lipoprotein cholesterol (LDL-C) levels to <1.4 mmol/L and a ≥50% reduction in LDL-C levels relative to baseline levels [6]. The inhibition of proprotein convertase subtilisin/kexin 9 (PCSK9) represents a

novel anti-lipid strategy that has been recommended by these proposed guidelines. PCSK9 inhibitors stabilize vulnerable plaques, diminish inflammatory responses and prevent thrombosis by directly antagonizing PCSK9 [7, 8]. A recent study found that even after receiving the maximum tolerated statin dose, approximately half of patients with ACS required the addition of a PCSK9 inhibitor to achieve the LDL-C target [9]. However, whether the early addition of a PCSK9 inhibitor to statin therapy could achieve the LDL-C target sooner and result in a clinical benefit remains unknown. Many studies have reported that the addition of PCSK9 inhibitors to statin therapy after PCI in patients with ST-segment elevation ACS significantly improves compliance with LDL-C reduction therapies and clinical prognosis [10, 11]; however, fewer studies have examined the effects of PCSK9 inhibitors in patients with non-ST segment elevation (NSTE)-ACS. This study investigated inflammation levels and microcirculatory function following early PCSK9 inhibitor application after PCI in patients with NSTE-ACS.

Material and methods

Subjects

This is a retrospective study. Patients with NSTE-ACS admitted to the People's Hospital of Henan University of Traditional Chinese Medicine for PCI between December 2019 and December 2021 were recruited for this study. Patients who satisfied the following inclusion criteria were recruited: ① met the diagnostic criteria for NSTE-ACS [12]; ② were aged <80 years; ③ received PCI within 12 h of NSTE-ACS onset; and ④ had no prior history of PCSK9 inhibitor use. Patients who met the following exclusion criteria were not included: ① were diagnosed with severe cardiopulmonary, hepatic, or renal insufficiency; ② experienced mechanical complications during the perioperative period; ③ had any prior history of any lipid-lowering drug use; ④ displayed evidence of contraindication or intolerance for the drugs used in this study; ⑤ met the diagnostic criteria for familial hypercholesterolemia; or ⑥ experienced any infection or trauma within 2 weeks prior to hospitalization.

Ethics approval and consent to participate

This study strictly adhered to the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Fifth Clinical School of Henan University of Traditional Chinese Medicine (No. 20220125). Informed consent was obtained from patients or their families for all treatments.

Sample size estimation

The sample size was estimated using the international PASS10 software, with α=0.05 and β=0.20, based on clinical experience and with reference to data reported in the literature [13]. A total of 50 cases in each group were estimated to achieve an expected mean index of microcirculatory resistance (IMR) value of 23.63, with a standard deviation of 9.91, for the control group and a mean IMR value of 18.05, with a standard deviation of 9.98, for the PCSK9 inhibitor group. To ensure a sample size of 100, considering a projected dropout rate of 20%, 120 patients were recruited for this study, divided into two groups of 60 patients. In the control group, 2 patients were excluded due to hemodynamic instability and high-degree atrioventricular block during PCI, 1 patient required surgical coronary artery bypass grafting, and 2 patients were lost to follow-up, resulting in the inclusion of 55 patients in the final study group. In the PCSK9 inhibitor group, 2 patients were excluded due to missing measurements for relevant indices and 3 patients were lost to follow-up, resulting in the inclusion of 55 patients in the final study group (**Figure 1**).

Grouping

The 120 patients who met the inclusion criteria were randomly divided into a control group (60 patients) and a PCSK9 inhibitor group (60 patients) according to a random number table method. Data were collected for age, sex, body mass index (BMI), previous medical history, oral medication, biochemical index, and cardiac ultrasound. To ensure the accuracy of the original data entry, all data were collected by two independently trained investigators.

Randomization, allocation concealment, and blinding

The web-based randomization system used in this study was provided by the Independent Academic Data Management Center of Henan University of Traditional Chinese Medicine. The treating physician identified eligible patients based on established inclusion and exclusion

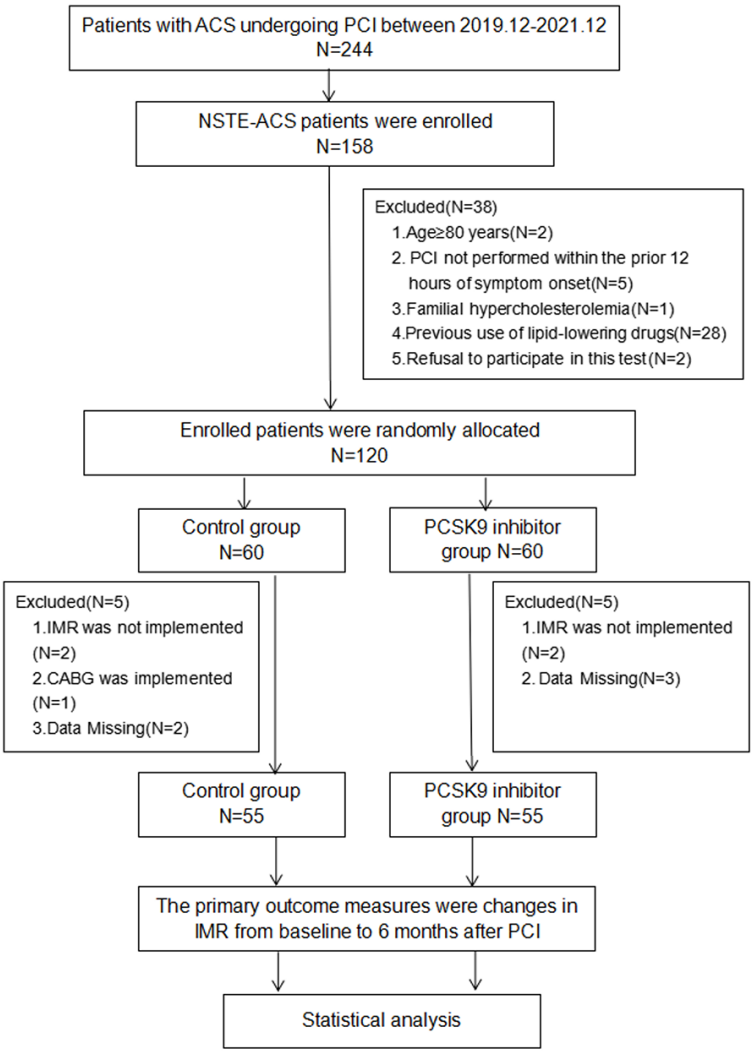

Figure 1. Project flow chart.

criteria. The attending physician obtained informed consent from participants, after which participants were referred to the study coordinator, who randomly assigned them to either the control group or the PCSK9 inhibitor group. The randomization list was retained by the biostatistician and study coordinator until the end of the study to ensure allocation concealment and blinding of data analysts to patient allocation. Participants were requested not to share their allocation with the treating physician.

Treatment method

Patients in both groups were treated with dual anti-platelet agents (enteric-coated aspirin tablets 100 mg once daily, clopidogrel 75 mg once daily, or ticagrelor 90 mg twice daily) before and after PCI. In addition, nitrates, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers were administered according to each patient's individual condition. The control group was given 20 mg/d atorvastatin (Pfizer Inc., New York, USA), and the PCSK9 inhibitor group was given 20 mg/d atorvastatin + 140 mg evolocumab (Amgen Pharmaceuticals Inc., California, USA) by subcutaneous injection every 2 weeks. The first injection was administered within 24 h of stent implantation for criminal lesions. The treatment course was 6 months for both groups, after which relevant indices and coronary angiographies were assessed. Evolocumab is available at hospital pharmacies with a clinical study-specific prescription signed by an authorized physician.

For lipid management in patients with NSTE-ACS, current guidelines recommend progressive lipid-lowering regimens [14]. However, the HPS2-THRIVE study [15] showed that Chinese patients had significantly higher risks of experiencing myopathy (0.24% per year vs. 0.02% per year, respectively) and liver function abnormalities (0.13% per year vs. 0.04% per year, respectively) than European patients in response to high-intensity statin therapy. Therefore, Chinese patients with NSTE-ACS have poor tolerance for and poor adherence to high-intensity statins. The current study explored the early initiation of an intensive lipid-lowering strategy using evolocumab combined with the routine application of moderate-strength statins during the early stages of NSTE-ACS onset. This approach differs from the approaches used in similar studies and is more relevant to the current reality of Chinese patients with coronary heart disease.

Biochemical indices

Relevant indices were compared between groups before and after 6 months of treatment. Fasting venous blood was collected within 24 h of admission, and a fully automated biochemical instrument (HITACHI 7080, Hitachi Ltd, Tokyo, Japan) was used to measure TG, TC, HDL-C, LDL-C, LP(a), cardiac troponin I (cTnI), and hs-CRP using a latex immunoturbidimetric method (Beijing Sainuopu Biotechnology Co., Ltd, Beijing, China). N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) was detected by electrochemiluminescence immunoassay (Beijing Sainuopu Biotechnology Co., Ltd, Beijing, China). TNF-α and IL-6 levels were determined by enzyme-linked immunosorbent assay (Shanghai Jianglai Biotechnology Co., Ltd, Shanghai, China).

Coronary angiography and PCI

Coronary angiography was performed by a qualified and experienced interventional cardiologist using GE Innova 3100 digital subtraction angiography machine (General Electric Company, Boston, USA). The radial or femoral artery was punctured using the Seldinger puncture method to fully expose all segments of the coronary artery, and other positions were added if necessary. Stents were selected according to the degree of coronary stenosis, and the door-to-balloon time, number of implanted stents, and Thrombosis in Myocardial Infarction (TIMI) myocardial perfusion grade (TMPG) were recorded before and after the procedure.

The index of microcirculatory resistance

The IMR is a quantitative index of microcirculatory function calculated by combining a coronary pressure-measuring guidewire with a temperature-measuring guidewire. After PCI, a pressure guidewire with a receptor at its tip was inserted into a distal vessel in a state of maximum coronary artery congestion, and intravascular pressure (Pd) was measured by rapidly injecting 3 mL room-temperature saline into the catheter artery to obtain a thermodilution curve. This procedure was repeated three times to measure the mean conduction time (Tmn), and IMR was calculated as IMR = Pd × Tmn.

Cardiovascular events and safety evaluation

MACE occurrences within 6 months of discharge were recorded, including cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for unstable angina, and unplanned revascularization. All cardiovascular events were adjudicated independently by two cardiovascular physicians who were unaware of the study parameters. Adverse event occurrences were also recorded, including gastrointestinal symptoms, rash, muscular symptoms, alanine aminotransferase levels ≥3 times the upper limit of normal, and upper respiratory tract symptoms.

Main outcome measure

The primary outcome measures were changes in microcirculatory functional parameters (IMR) from baseline to 6 months after PCI. Secondary outcomes included changes in TG, TC, HDL-C, LDL-C, Lp(a), hs-CRP, TNF-α, and IL-6 levels and the occurrence of any MACEs or adverse reactions from baseline to 6 months after PCI.

Statistical analysis

SPSS 25.0 software (IBM, Armonk, New York) was used for statistical processing. Continuous variables with normal distributions and variables with approximately normal distributions are expressed as the mean ± standard deviation. Between-group comparisons were assessed by independent-sample t-tests, whereas paired-sample t-tests were used to evaluate within-group comparisons. The Wilcoxon signed-rank test was used for comparisons of ordered categorical variables. Count data are expressed as the number (percentage), and differences were evaluated using the Chi-square test or Fisher's exact test. Differences were considered significant at $P<0.05$, and all statistical tests were performed as two-sided tests.

Results

General clinical data

Table 1 shows a comparison of clinical data between groups. No significant differences were noted between groups in age, sex, BMI, past medical history, cTnI levels, NT-proBNP lev-

Table 1. Comparison of general clinical data between groups

Variable	Control group (n=55)	PCSK9 inhibitor group (n=55)	χ^2/t	P
Age (years)	61.23±10.34	60.45±11.67	0.371	0.711
Male	36 (65.4)	38 (69.1)	0.165	0.685
BMI (kg/m^2)	25.31±1.74	24.93±1.68	1.165	0.247
Past medical history				
Hypertension	25 (45.5)	28 (50.9)	0.328	0.567
Diabetes	4 (7.3)	6 (10.9)	0.440	0.507
Smoking	23 (41.8)	21 (28.2)	0.152	0.697
cTnI (ng/L)	5.51±2.33	5.64±2.17	-0.303	0.763
NT-proBNP (ng/L)	546.34±72.23	524.65±69.77	1.602	0.112
Creatinine (μmol/L)	65.64±8.69	67.78±7.78	-1.361	0.176
Culprit vessel				
Left main stem	1 (1.8)	1 (1.8)	-	1
Left anterior descending	19 (34.5)	20 (36.4)	0.040	0.841
Left circumflex	10 (18.2)	9 (16.4)	0.064	0.800
Right	17 (30.9)	18 (32.7)	0.042	0.838
Branch lesions	8 (14.5)	7 (12.7)	0.077	0.781
Stent number	1.62±0.55	1.56±0.59	0.552	0.582
D-to-B time (min)	63.45±5.67	62.87±5.48	0.546	0.587
Postoperative medication use				
Aspirin	55 (100)	55 (100)	-	1
Clopidogrel	11 (20)	13 (23.6)	0.213	0.644
Ticagrelor	44 (80)	42 (76.4)	0.213	0.644
β-blockers	53 (96.4)	52 (94.5)	0.210	0.647
ACEI/ARB	36 (65.5)	37 (67.3)	0.041	0.840

Note: All data are presented as n (%) or mean ± SD; - indicates data not obtained. Abbreviations: ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro b-type natriuretic peptide.

els, creatinine levels, vascular offenders, or postoperative medication use (P>0.05 for all comparisons).

Comparison of blood lipid levels before and after treatment

Before treatment, no significant differences were observed in TG, TC, HDL-C, LDL-C, or Lp(a) levels between groups (P>0.05 for all comparisons). After treatment, TG (P=0.037), TC (P<0.001), LDL-C (P<0.001), and Lp(a) (P< 0.001) levels were significantly lower in the PCSK9 inhibitor group than in the control group. Compared with pre-treatment levels, HDL-C levels increased in both groups after treatment, but the differences were not significant (P>0.05 for both groups). Compared with pre-treatment levels, Lp(a) levels decreased in the control group after treatment, but the difference was not significant (P>0.05, **Table 2**).

Comparison of inflammation levels before and after treatment

Before treatment, no significant differences were observed between groups for the levels of hs-CRP, TNF-α, or IL-6 (P>0.05 for all comparisons). Compared with pre-treatment levels, the levels of hs-CRP (P<0.001), TNF-α (P<0.001), and IL-6 (P<0.001) were significantly reduced after treatment for both groups, with significantly larger decreases observed for the PCSK9 inhibitor group than for the control group (P<0.001 for all comparisons, **Table 3**).

Comparison of IMR values before and after treatment

Before treatment, no significant difference in IMR values was observed between groups (P>0.05). After treatment, the IMR values for both groups were significantly higher (P<0.001)

Table 2. Comparison of blood lipid levels between groups before and after treatment

Variable		Control group (n=55)	PCSK9 inhibitor group (n=55)	t	P
TG (mmol/L)	Before treatment	1.86±0.87	1.84±0.96	0.115	0.909
	After treatment	1.52±0.73	1.21±0.81	2.108	0.037
	t	2.220	3.719		
	P	0.029	<0.001		
TC (mmol/L)	Before treatment	5.78±1.15	5.81±1.35	-0.126	0.900
	After treatment	4.61±1.04	3.67±1.03	4.7627	<0.001
	t	5.596	9.346		
	P	<0.001	<0.001		
HDL-C (mmol/L)	Before treatment	1.04±0.27	1.05±0.29	-0.187	0.852
	After treatment	1.15±0.24	1.21±0.25	-1.284	0.202
	t	-2.258	-3.099		
	P	0.026	0.003		
LDL-C (mmol/L)	Before treatment	3.94±0.76	3.87±1.17	0.372	0.711
	After treatment	2.51±0.86	1.82±0.97	3.947	<0.001
	t	9.240	10.003		
	P	<0.001	<0.001		
Lp(a) (mg/L)	Before treatment	321.23±102.43	320.78±100.96	0.023	0.982
	After treatment	318.87±97.23	241.93±94.45	4.210	<0.001
	t	0.124	4.230		
	P	0.902	<0.001		

Note: All data are presented mean ± SD. Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin 9; TC, total cholesterol; TG, triglycerides.

Table 3. Comparison of inflammation levels between groups before and after treatment

Variable		Control group (n=55)	PCSK9 inhibitor group (n=55)	t	P
hs-CRP (mg/L)	Before treatment	4.49±0.45	4.43±0.42	0.723	0.471
	After treatment	3.53±0.34	3.01±0.26	9.010	<0.001
	t	12.623	21.3194		
	P	<0.001	<0.001		
TNF-α (ng/L)	Before treatment	124.56±23.45	126.87±22.46	-0.528	0.599
	After treatment	58.89±15.12	32.36±10.03	10.844	<0.001
	t	17.455	28.4946		
	P	<0.001	<0.001		
IL-6 (pg/L)	Before treatment	37.56±3.46	36.23±3.64	1.964	0.052
	After treatment	20.39±2.09	17.72±1.45	7.784	<0.001
	t	31.501	35.035		
	P	<0.001	<0.001		

Note: All data are presented mean ± SD. Abbreviations: hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; PCSK9, proprotein convertase subtilisin/kexin 9; TNF-α, tumor necrosis factor-alpha.

Table 4. Comparison of IMR values between groups before and after treatment

Variable		Control group (n=55)	PCSK9 inhibitor group (n=55)	t	P
IMR	Before treatment	22.56±3.13	22.86±3.03	-0.511	0.611
	After treatment	27.98±2.87	25.45±2.66	4.795	<0.001
	T	-9.465	-4.764		
	P	<0.001	<0.001		

Note: All data are presented mean ± SD. Abbreviations: IMR, index of microcirculatory resistance; PCSK9, proprotein convertase subtilisin/kexin 9.

Table 5. Comparison of TMPG between groups before and after treatment

Variable	Preoperative		Immediate postoperative period		6-month postoperative	
	Level 0-2	Level 3	Level 0-2	Level 3	Level 0-2	Level 3
Control group (n=55)	49 (89.1)	6 (10.9)	9 (16.4)	46 (83.6)	6 (10.9)	49 (89.1)
PCSK9 inhibitor group (n=55)	50 (90.9)	5 (9.1)	8 (14.5)	47 (85.5)	1 (1.8)	54 (98.2)
X^2	0.101		0.07		4.131	
P	0.751		0.791		0.04	

Note: All data are presented as n (%). Abbreviations: PCSK9, proprotein convertase subtilisin/kexin 9; TMPG, Thrombosis in Myocardial Infarction (TIMI) Myocardial Perfusion Grade.

Table 6. Comparison of the occurrence of MACEs between groups

Variable	Control group (n=55)	PCSK9 inhibitor group (n=55)	χ^2	P
Cardiovascular death	0	0	-	-
Nonfatal myocardial infarction	5 (9.1)	2 (3.6)	1.373	0.241
Nonfatal ischemic stroke	4 (7.3)	3 (5.5)	0.153	0.696
Hospitalization for unstable angina	8 (14.5)	3 (5.4)	2.525	0.112
Unplanned revascularization	7 (12.7)	4 (7.3)	0.909	0.340
Target lesion revascularization	2 (3.6)	0	2.037	0.154
Revascularization of other lesions	3 (3.4)	1 (1.8)	1.038	0.308

Note: All data are presented as n (%). Abbreviations: MACEs, major adverse cardiovascular events; PCSK9, proprotein convertase subtilisin/kexin 9.

Table 7. Comparison of the occurrence of adverse reactions between groups

Variable	Gastrointestinal symptoms	Rash	Muscular symptoms	ALT ≥3 × ULN	Upper respiratory tract symptoms	Total incidence n (%)
Control group (n=55)	6	2	4	2	1	15 (9.5)
PCSK9 inhibitor group (n=55)	1	2	0	1	1	5 (8.9)
χ^2	0.529	1.198	1.445	0.081	0.593	0.016
P	0.467	0.274	0.229	0.776	0.441	0.899

Note: All data are presented as n (%). Abbreviations: ALT, alanine aminotransferase; PCSK9, proprotein convertase subtilisin/kexin 9; ULN, upper limit of normal.

than those before treatment, and the IMR value was significantly (P<0.001) lower for the PCSK9 inhibitor group than for the control group (**Table 4**).

Comparison of TMPG before and after treatment

No differences were observed between groups in TMPG values either pre-treatment or during the immediate postoperative period (P>0.05 for both comparisons). However, at 6 months postoperative, TMPG grade 3 was observed at a significantly higher frequency in the PCSK9 inhibitor group than in the control group (P=0.04, **Table 5**).

Comparison of MACE occurrences between groups

After 6 months of treatment, no significant differences were observed between groups in the occurrence of nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for unstable angina, or unplanned revascularization (P>0.05 for all comparisons, **Table 6**).

Comparison of adverse reaction occurrences between groups

A total of 15 adverse events (9.5%) occurred in the control group, and 5 adverse events (8.9%) occurred in the PCSK9 inhibitor group. This difference was not significant (P>0.05, **Table 7**).

Discussion

Dyslipidemia, especially altered LDL-C levels, is a well-known cause of atherosclerosis, and lipid-lowering strategies are the treatments of choice for arteriosclerotic cardiovascular disease (ASCVD). Studies have shown that inflammation plays crucial roles in atherosclerosis onset and development, and atherosclerosis requires both dyslipidemia and inflammation [16]. Chellan et al. found that ASCVD is an inflammatory disease of the arteries, in which immune malfunction promotes atherogenesis, and a disordered and inhibited lipid metabolism promotes atherosclerosis and enhances the inflammatory response, activating a series of signaling pathways that "fuse" lipids with other traditional atherosclerosis risk factors [17]. Recent studies have found that residual cholesterol risk, the presence of persistent inflammation, and microcirculatory dysfunction are important causes of MACEs following revascularization in patients with ACS [18-20]. Therefore, the early initiation of lipid-lowering and anti-inflammatory therapies is particularly important for improving patient prognosis.

The novel lipid-lowering target PCSK9 is a serine protease synthesized in the endoplasmic reticulum and the ninth identified member of the K subfamily of chymotrypsin proteases. PCSK9 consists of 692 amino acid residues, plays an important role in the regulation of lipid metabolism through the PCSK0-LDL receptor (LDLR) axis, and is widely involved in the pathogenesis of atherosclerotic plaques [21, 22]. By directly neutralizing serum PCSK9, PCSK9 inhibitors upregulate LDLR density, reduce LDL-C levels, stabilize vulnerable plaques, diminish inflammatory responses, improve microcirculation, and trigger other pleiotropic effects that enhance lipid control and reduce the residual risk of adverse cardiovascular events [23]. In this study, we found that TG, TC, LDL-C, and Lp(a) levels were significantly lower in the PCSK9 inhibitor group than in the control group after treatment. The early combination of a PCSK9 inhibitor with a statin was more effective in reducing lipid levels in patients with ACS than the statin alone, consistent with the findings of Su et al. [24].

Studies have shown that PCSK9 plays a pro-inflammatory role in atherosclerosis development by activating the Toll-like receptor 4-nuclear factor kappa B signaling pathway to increase expression of inflammatory factors, as an imbalance between pro-inflammatory and anti-inflammatory pathways may contribute to the onset and development of atherosclerosis [25]. Englert et al. found that human liver microvascular endothelial cells produce a variety of reactive oxygen species under inflammatory conditions, which ultimately contribute to coronary microvascular dysfunction [26, 27]. In this study, we found that hs-CRP, TNF-α, and IL-6 levels were significantly lower in the PCSK9 inhibitor group than in the control group after treatment. PCSK9 inhibitors reduce the expression of inflammatory factors, improving the inflammatory environment and weakening the response to pro-inflammatory stimuli, including diminishing the arterial inflammatory response, which inhibits atherosclerosis progression and enhances the anti-atherosclerotic capacity.

In this study, we found that IMR values were lower and the frequency of TMPG grade 3 was significantly increased in the PCSK9 inhibitor group compared with the control group after 6 months of treatment, indicating that the early use of PCSK9 inhibitors combined with statins improves coronary microcirculatory perfusion. Previous studies have found that the vast majority of NSTE-ACS is triggered by plaque erosion, and PCI can lead to coronary microcirculation impairment due to the dislodgment of atheromatous plaque debris or microthrombosis, with a higher incidence of distal microembolism reported when the plaque lipid load or target lesion thrombus load is high [28]. PCSK9 inhibitors improve myocardial perfusion at the cardiomyocyte level by reducing arterial plaque volume and inhibiting platelet activation and thrombosis [29, 30]. Previous studies have found that mice in an inflammatory state have dysfunctional microvascular endothelial cells that produce various inflammatory mediators, leading to microcirculatory disorders and indicating that inflammation is also involved in the development of microcirculatory disorders [31]. A study showed that in patients with ASCVD, PCSK9 inhibitor treatment effectively improved vascular endothelial function and ventricular remodeling, which were positively correlated with the degree of LDL-C reduction [32]. In summary, PCSK9 inhibitors induce lipid-lowering, anti-inflammatory, and anti-thrombotic effects that further improve coronary microcirculation function and inhibit ventricular remodeling in

patients with NSTE-ACS myocardial infarction following PCI.

Limitations

This study was a single-center study with a small sample size, and PCSK9 levels were not monitored. Therefore, limiting factors may exist that affect the conclusions that can be drawn from this study, and these conclusions require validation in multicenter studies with expanded sample sizes and additional observation indicators. In addition, the results of this study may not be applicable to all patients with ACS, and current ASCVD treatment recommendations should be adjusted according to individual differences in patient parameters.

Conclusions

In conclusion, despite the current high success rate of PCI, some patients fail to achieve microcirculatory reperfusion. The early administration of PCSK9 inhibitors combined with conventional anti-atherosclerotic therapies in patients with NSTE-ACS can reduce the circulatory inflammatory response after myocardial infarction and improve vascular endothelial function, microcirculatory disorders, and ventricular remodeling. Therefore, early identification of inflammation and PCSK9 inhibitor intervention can increase clinical benefits following PCI.

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Disclosure of conflict of interest

None.

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