ORIGINAL RESEARCH

PCSK9 Inhibitors in Multi-Branch Lesions in Coronary Artery Disease with Substandard Lipid-Lowering Effects

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ABSTRACT

Objective • This study was carried out to evaluate the clinical efficacy of proprotein convertase chymotrypsin 9 (PCSK9) inhibitors in multi-branch lesions in coronary artery disease with substandard lipid-lowering effects.

Methods • This retrospective study collected the clinical data of 100 patients with multiple coronary artery diseases admitted to our hospital between May 2020 and August 2022 for analysis. The eligible patients were assigned to either a PCSK9 inhibitor group or a control group at a ratio of 1:1 by their dosing regimens, with 50 cases in each group. Outcome measures for the clinical efficacy of PCSK9 inhibitors included lipid levels, low-density lipoprotein cholesterol (LDL-C) changes, serum concentrations of coronary artery disease-related inflammatory factors, improvement of angina questionnaire scores, adverse reactions, and major cardiovascular adverse events.

Results • PCSK9 inhibitors resulted in significantly lower serum concentrations of total cholesterol (TC), LDL-C, and ApoB and higher high-density lipoprotein cholesterol (HDL-C) levels versus conventional lipid-lowering medication ($P < .05$). The two arms exhibited similar serum concentrations of triglyceride (TG) and ApoA1 after treatment ($P > .05$). With LDL-C<1.4 mmol/L as the cut-off for desirable blood lipid levels, 47 (94%) patients reached the standard after in the PCSK9 inhibitors group, while no eligible cases were reported in the control group ($P < .05$). PCSK9 inhibitors provided a marked reduction in the serum concentrations of high-sensitivity C-reactive protein in the patients. Patients had higher angina stability (AS), angina flare (AF), physical limitation (PL), and treatment satisfaction (TS) scores after PCSK9 inhibitor administration versus after conventional medication ($P < .05$). PCSK9 inhibitors were associated with a significantly lower incidence of adverse cardiovascular events (10%) versus conventional medication (42%) ($P < .05$).

Conclusion • PCSK9 inhibitors significantly improve the LDL-C concentrations of patients with multiple lesions of coronary artery disease who have failed to meet lipid-lowering targets, this enables physicians to more effectively manage patients' cholesterol levels, consequently reducing their cardiovascular risk. Moreover, these inhibitors have the potential to enhance patients' quality of life by alleviating relieve angina symptoms. These findings offer valuable insights into managing multi-branch coronary artery disease. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Cardiovascular disease represents a significant and pressing global public health issue, posing a substantial threat to human life and well-being. Research on the global burden of disease indicates that over the past two decades, the global burden of cardiovascular disease has continuously intensified. In 2019, the worldwide prevalence of cardiovascular disease reached 523 million cases, with cardiovascular disease-related deaths totaling 18.6 million. Cardiovascular disease is responsible for over 40% of all deaths in the Chinese population. Notably, atherosclerotic cardiovascular disease (ASCVD) stands as the leading cause of mortality among Chinese residents, accounting for over 60% of all cardiovascular disease-related deaths.[1] Studies have shown that elevated cholesterol levels are the main cause of increased mortality from ASCVD, with coronary artery disease combined with multivessel disease constituting the highest risk of cardiovascular diseases. Coronary artery bypass grafting or

percutaneous coronary intervention (PCI) is recommended for the clinical management of these patients. However, beyond surgical approaches, the judicious use of pharmacotherapy to alleviate clinical symptoms plays an indispensable role in enhancing patients' quality of survival.[2-4] Of notable significance is the observation that a substantial proportion of patients diagnosed with multiple vascular lesions in coronary artery disease also present with hyperlipidemia. Thus, effective control of dyslipidemia is of great significance for the prevention, control, and treatment of coronary heart disease.[5] At present, statins are the mainstay of lipid-lowering therapy in clinical practice, and ezetimibe therapy is also available when necessary. However, a substantial subset of patients exhibit an inadequate response to statins or develop statin intolerance due to adverse effects such as myalgia or elevated transaminases, resulting in suboptimal lipid control.[6] Addressing suboptimal lipid control is a priority in such cases, leading to the exploration of new therapies like proprotein convertase chymotrypsin 9 (PCSK9) inhibitors.

Low-density lipoprotein cholesterol (LDL-C) levels are closely linked to the low-density lipoprotein receptor (LDLR) expressed on the surface of hepatocytes. The binding of LDLR to LDL-C on the hepatocyte surface can form the LDL-R-LDL complex, which is subsequently translocated to the nuclear endosome for LDL-C degradation, and LDLR is then recycled back to the cell surface.[7,8] PCSK9 is a serine protease encoded by the PCSK9 gene and produced by the liver. PCSK9 binds to LDL receptors on the surface of hepatocytes, triggering LDLR degradation and raising plasma LDL-C levels, ultimately resulting in hypercholesterolemia, ultimately resulting in hypercholesterolemia. It has been shown that PCSK9 levels are significantly associated with cholesterol, ox-LDL, and TG. By leveraging the presence of PCSK9 in the bloodstream, the inhibition of PCSK9 from binding to LDLR is achieved, thereby impeding the PCSK9-mediated degradation of LDLR, this allows for the recycling of LDLR to the surface of hepatic cells, facilitating the binding and metabolic breakdown of LDL-C at the hepatic cell surface, thereby reducing the body's blood lipids.[9] Current findings suggest a potent cholesterol-lowering effect of PCSK9 inhibitors, which can significantly reduce LDL-C levels by 50% to 70%.[10] However, its application in patients with intractable hyperlipidemia complicated with coronary artery disease with multiple vascular lesions has been sporadically explored. To fill this research gap and evaluate the clinical effectiveness of PCSK9 inhibitors in cases of coronary artery disease featuring multi-branch lesions who exhibit suboptimal lipid control despite conventional treatments, this study was undertaken.

MATERIALS AND METHODS

Participants

This retrospective study collected the clinical data of 100 patients with multiple coronary artery diseases admitted to our hospital between May 2020 and August 2022 for analysis. The eligible patients were assigned to either a PCSK9 inhibitor group or a control group at a ratio of 1:1 by their dosing regimens, with 50 cases in each group.

Inclusion criteria: (1) The coronary angiography or coronary artery CT confirmed that multiple vessel stenosis was ≥50%. These blood vessels include the left main trunk, left anterior descending branch, left circumflex branch, and right coronary artery; (2) Taking a category drug or combined with ezetimibe tablets for at least 8-12 weeks, LDL-C ≥ 1.4 mmol/L.

Requiring a minimum duration of medication use (8-12 weeks) helps ensure that participants have a consistent baseline for evaluating the effects of the intervention. LDL-C levels serve as a biomarker for hyperlipidemia severity, with an LDL-C level of ≥1.4 mmol/L indicating increased risk of atherosclerosis and coronary artery disease. These criteria are central to the research objectives and expected outcomes.

Exclusion criteria: (1) incomplete clinical data; (2) other major diseases and severe hepatic and renal insufficiency; (3) poor compliance and allergy to the study medication during treatment; (4) pregnant or lactating women.

Treatment methods

All participants received conventional lipid-lowering treatment medication. The control group received atorvastatin (20 mg per tablet), administered orally once daily for a duration of 12 weeks. In addition to the standard treatment, the Patients in the PCSK9 inhibitor group additionally received 140mg of evolocumab subcutaneously in the abdomen, thigh, or upper arm every 2 weeks. The duration of treatment was 12 weeks.

Outcome measures

(1) The lipid levels, including total cholesterol (TC) levels, ApoA1, ApoB, and LDL-C and high-density lipoprotein cholesterol (HDL-C) levels, were recorded before and after 3 months of treatment. The LDL-C compliance rate [≥50% reduction in LDL-C levels from baseline and LDL-C levels < 1.4 mmol/L] was calculated for both groups. Fasting venous blood (2~3ml) was collected from the patients and centrifuged at 2,000r/min for 5min to obtain the serum. A fully automated biochemical analyzer (Beckman Coulter, USA) was used to determine the serum concentrations of TC, triglyceride (TG), LDL-C, HDL-C, ApoA1, and ApoB.

(2) The serum concentrations of high-sensitivity C reactive protein (hs-CRP) were recorded.

(3) The improvement of patients' Seattle Angina Questionnaire scores (SAQ) and quality of life scores before and after 3 months of treatment were recorded to evaluate the mitigation of patients' angina, which was divided into 5 items of angina stability (AS), angina flare (AF), physical limitation (PL), disease perception (DP), and treatment satisfaction (TS). The total score is 100, and the higher the score, the better the mitigation of angina pectoris and the functional status of the body.

(4) The adverse reactions and major cardiovascular adverse events of the patients were recorded.

Statistical analysis

SPSS 22.0 was used for data analyses, and GraphPad Prism 9 was used for imaging rendering. Normally distributed measures were expressed as mean ± standard deviation ($\bar{x} \pm s$), and non-normally distributed measures were expressed as median (quartiles) [M(Q1, Q3)]. Data that met the normal distribution by K-S normal distribution test were tested by independent samples t test, significant differences were indicated by $P < .05$. Non-normal data were tested by independent samples Mann-Whitney U-test. Count data were expressed as frequencies (%) and examined using the chi-square test, significant differences were indicated by $P < .05$.

RESULTS

Baseline patient profiles

The two arms were well-balanced in terms of baseline patient features, including age, gender, hypertension, diabetes, history of PCI, smoking, BMI, TC, TG, LDL-C, HDL-C, ApoA1, ApoB, SAQ score (points) ($P > .05$). (Table 1)

Blood lipids and LDL-C compliance rate

PCSK9 inhibitors resulted in significantly lower serum concentrations of TC, LDL-C, and higher HDL-C levels versus conventional lipid-lowering medication ($P < .05$). The two arms exhibited similar serum concentrations of TG after treatment ($P > .05$). With LDL-C<1.4 mmol/L as the cut-off for desirable blood lipid levels, 47 (94%) patients reached the standard after in the PCSK9 inhibitors group, while no eligible cases were reported in the control group ($P < .05$). (Table 2)

Apolipoproteins

No statistically significant differences were observed between the pre-treatment ApoA1 and ApoB levels of the two groups ($P > .05$). The levels of ApoA1 remained similar between the two groups after treatment ($P > .05$). PCSK9 inhibitors provided a more significant reduction in the ApoB levels than conventional medication ($P < .05$). (Table 3)

3.4 hs-CRP

PCSK9 inhibitors provided a marked reduction in the serum concentrations of hs-CRP in the patients ($P < .05$), while the hs-CRP levels showed no significant alterations after conventional medication ($P > .05$). (Table 4)

SAQ

Patients had higher AS, AF, PL, and TS scores after PCSK9 inhibitor administration versus after conventional medication ($P < .05$). (Figure 1)

Adverse cardiovascular events

The total incidence of adverse cardiovascular events in the PCSK9 inhibitor group during the follow-up was 10%. The total incidence of adverse cardiovascular events in the control group was 42%. PCSK9 inhibitors were associated

Table 1 Baseline patient profiles

Indices	PCSK9 inhibitor group (n = 50)	Control group (n = 50)	t/χ^2	P value
Age (year)	54.92±11.82	54.17±10.28	0.339	.736
Male [n, (%)]	27(54.00%)	29(58.00%)	0.162	.687
Hypertension [n, (%)]	28(56.00%)	27(54.00%)	0.040	.841
Diabetes[n, (%)]	30(60.00%)	23(46.00%)	1.967	.161
History of PCI [n, (%)]	11(22.00%)	14(28.00%)	0.480	.488
Smoking[n, (%)]	31(62.00%)	26(52.00%)	1.020	.3125
BMI(kg/m^2)	25.33±4.32	25.71±3.27	0.496	.621
TC(mmol/L)	4.80±1.61	4.91±1.65	0.337	.736
TG(mmol/L)	1.73±0.44	1.74±0.47	0.109	.913
LDL-C(mmol/L)	2.64±0.83	2.62±0.74	0.127	.899
HDL-C(mmol/L)	1.37±0.37	1.34±0.36	0.411	.682
ApoA1(mmol/L)	1.14±0.58	1.13±0.43	0.098	.922
ApoB(mmol/L)	0.95±0.29	0.97±0.31	0.333	.739
SAQ scores (points)				
AS	14.92±4.18	15.12±5.13	0.214	.831
AF	55.14±11.37	54.19±10.85	0.427	.670
PL	62.37±5.64	61.20±5.28	1.071	.287
DP	32.51±7.89	31.72±7.29	0.520	.604
TS	46.28±11.01	47.11±10.49	0.386	.700

Table 2 Blood lipid levels

Groups	n	TC(mmol/L)		TG(mmol/L)		LDL-C(mmol/L)		HDL-C(mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
PCSK9 inhibitor group	50	4.80±1.61	2.76±1.25	1.73±0.44	1.63±0.41	2.64±0.83	1.20±0.38	1.37±0.37	1.87±0.63
Control group	50	4.91±1.65	4.90±1.58	1.74±0.47	1.72±0.46	2.62±0.74	2.61±0.75	1.34±0.36	1.35±0.31
t		0.337	3.737	0.109	0.589	0.127	3.576	0.411	2.554
P value		.736	.001	.913	.557	.899	.001	.682	.012

Table 3 Apolipoproteins

Groups	n	A^{poA1}(mmol/L)		ApoB(mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
PCSK9 inhibitor group	50	1.14±0.58	1.11±0.34	0.95±0.29	0.48±0.30
Control group	50	1.13±0.43	1.19±0.51	0.97±0.31	0.72±0.28
t		0.098	0.923	0.333	4.135
P value		.922	.358	.739	.001

Table 4 hs-CRP level

Groups	n	hs-CRP(mg/L)	
		Before treatment	After treatment
PCSK9 inhibitor group	50	10.94±0.97	7.13±0.51
Control group	50	10.35±0.92	10.24±0.68
t		3.121	17.553
P value		.002	.001

Figure 1 Comparison of SAQ scores between the two groups before and after treatment. A: AS scores; B: AF scores; C: PL scores; D: DP scores; E: TS scores

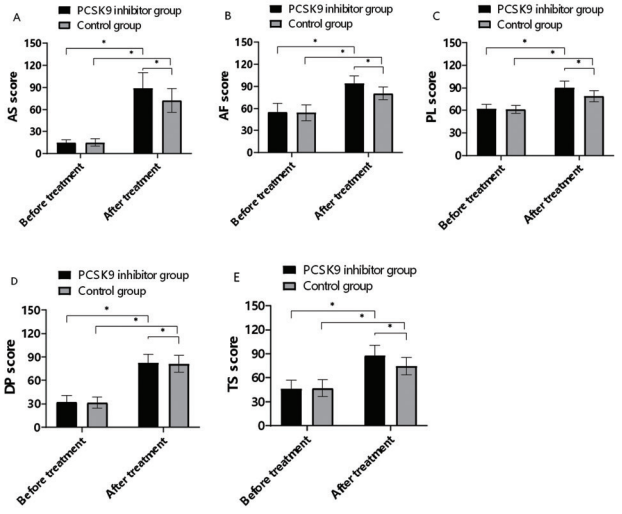

Table 5 Adverse cardiovascular events

Indices	PCSK9 inhibitor group (n = 50)	Control group (n = 50)	χ^2	*P* value
Cardiovascular death	0(0%)	0(0%)		
Myocardial infarction	0(0%)	1(2%)		
Heart failure	1(2%)	2(4%)		
Unstable angina	1(2%)	4(8%)		
Coronary revascularization	1(2%)	3(6%)		
Compound cardiovascular events	2(4%)	11(22%)	7.162	.007
Incidence of adverse cardiovascular event	5(10%)	21(42%)	13.306	.001

with a significantly lower incidence of adverse cardiovascular events versus conventional medication ($P < .05$). (Table 5)

DISCUSSION

Lipid-lowering therapy is the cornerstone of coronary artery disease treatment; however, around 80% of patients with acute coronary syndrome (ACS) fail to meet guideline lipid-lowering targets.[11] LDL-C and other atherogenic lipoproteins are the main cause of coronary heart disease, and altered lipid profiles due to elevated LDL-C levels are associated with an increased risk of atherosclerotic plaque formation and cardiovascular disease development. Clinical research has shown that the reduction of LDL-C concentrations after PCI lowers the risk of in-stent restenosis.[12] Furthermore, Pasta, A et al[13] showed that abnormal lipid levels are a risk factor for all-cause mortality and readmission rates 1 year after PCI in patients with coronary artery disease. Therefore, it is essential for patients with incomplete revascularization of multiple lesions in coronary artery disease combined with hyperlipidemia to obtain the standard lipid level. At present, statins are the mainstay of lipid-lowering therapy in clinical practice, and ezetimibe therapy is also available when necessary. Nonetheless, a significant number of patients exhibit poor responses to statins or become intolerant to statins due to myalgia or elevated transaminases, resulting in undesirable lipid control. Thus, conventional doses of statin plus an intensive lipid-lowering agent (eflornithine or ezetimibe) are usually recommended for lipid control.[14,15] Evolocumab is a new-generation lipid-lowering drug and a monoclonal antibody against PCSK9. It can block the degradation of LDLR by inhibiting PCSK9, thereby regulating plasma LDL-C metabolism.[16] Studies have shown that it can effectively mitigate dyslipidemia in patients with hyperlipidemia, and the combination of evolocumab with existing lipid-lowering drugs such as statins provides a 50% to 70% reduction in LDL-C levels. In the present study, PCSK9 inhibitors produced a marked reduction in the serum concentrations of TC, LDL-C, and hs-CRP, and the reduction of TC and LDL-C levels was more significant than conventional medication. Moreover, the LDL-C compliance rate of the PCSK9 inhibitor group was 94%, which was significantly better than that of the control group ($P < .001$), indicating that evolocumab can slow down the progression of coronary artery disease by inhibiting inflammatory mediators such as hs-CRP. Recent research has also confirmed the high drug safety of evolocumab, and no neutralizing antibodies were found in vivo.[17] The present study also found no statistically significant pre- and post-treatment differences in TG reduction with evolocumab, which is consistent with the lipid-lowering mechanism of evolocumab. The levels of apolipoproteins in the blood often follow the levels of cholesterol, ApoA1 tends to mirror the levels of HDL cholesterol and ApoB tends to mirror the levels of LDL cholesterol. However, in this study, no significant effect of evolocumab on ApoA1 levels was detected, but HDL-C levels were significantly increased after treatment, which was inconsistent with previous findings. The reason may be that ApoA1 is the main structural protein of HDL; HDL-C represents the metabolic state of HDL carrying cholesterol, ApoA1 reflects the particle number of HDL, and the changes of HDL-C are not necessarily proportional to the alterations of ApoA1.[18] Evolocumab, as a PCSK9 inhibitor, increases the number of LDL-C receptors in the liver by inhibiting PCSK9-mediated LDL-C receptor degradation and reducing the incidence of risk factors for coronary heart disease.[19] A prior study has shown the effectiveness of evolocumab, evolocumab is effective in reducing major cardiovascular events in secondary prevention in patients with clinically unspecified ASCVD or stable ischemic heart disease.[20] In the current study, PCSK9 inhibitors were associated with a significantly lower incidence of adverse cardiovascular events (10%) versus conventional medication (42%), indicating that lipid-lowering drugs plus evolocumab may synergistically produce lipid-lowering benefits and reduce the incidence of adverse cardiovascular events. In addition, in this study, the SAQ scores of all domains were significantly higher in the PCSK9 inhibitor group after treatment ($P < .05$), suggesting that the angina symptoms in the PCSK9 inhibitor group were significantly mitigated compared with those before treatment. These positive outcomes could be attributed to the administration of standardized antiplatelet aggregation, heart rate control to reduce oxygen consumption, coronary artery dilation, and lipid-lowering drugs to improve endothelial function and stabilize vulnerable coronary plaques. The levels of AS, AF, PL, and TS in the PCSK9 inhibitor group were significantly higher than those in the control group after treatment, suggesting that the alleviation of angina symptoms in the observation group was more significant than that in the control group, which was considered to be related to the more potent lipid-lowering effect of evolocumab, the higher LDL-C attainment rate, the more effective stabilization of vulnerable plaques, and the effective inhibition of inflammatory responses in the atherosclerotic process.[21,22] These findings emphasize the significance of incorporating PCSK9 inhibitors into the management of cardiovascular diseases, potentially as a complementary therapy alongside conventional medications. Moreover, the study underscores the importance of personalized treatment strategies to address individual patient needs in order to achieve better outcomes in the field of cardiovascular medicine.

This study presents several limitations that warrant consideration. Firstly, the relatively small sample size used in this research may raise questions about the generalizability of

our findings to larger and more diverse populations. So, the results observed in this study may not be directly applicable to broader patient demographics. Secondly, the follow-up period in this study was limited to 12 weeks. While the findings provide valuable insights into the short-term effects of evolocumab, it is important to recognize that the sustained effects of PCSK9 inhibitor therapy over longer periods are yet to be fully elucidated. Such investigations may reveal whether the initial improvements in lipid profiles and other relevant clinical parameters are sustained, and whether there are any delayed or cumulative effects that become evident with time. Additionally, the absence of coronary angiography data is a notable limitation. Further studies should include comprehensive angiographic assessments to better understand the impact of PCSK9 inhibitor therapy on coronary artery disease progression or regression. To gain a comprehensive understanding of PCSK9 inhibitor therapy, future investigations should address these limitations and explore its long-term implications in cardiovascular medicine, building upon the foundation laid by this study..

CONCLUSION

PCSK9 inhibitors significantly improve the LDL-C concentrations of patients with multiple lesions of coronary artery disease who have failed to meet lipid-lowering targets, this enables physicians to more effectively manage patients' cholesterol levels, consequently reducing their cardiovascular risk. Moreover, these inhibitors have the potential to enhance patients' quality of life by alleviating relieve angina symptoms. These findings offer valuable insights into managing multi-branch coronary artery disease. However, personalized and professional treatment decisions remain essential to address individual patient needs.

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