Cardiovascular Innovations and Applications

Vol. 7 (2022) 2
ISSN 2009-8618
DOI 10.15212/CVIA.2022.0011

RESEARCH ARTICLE

Effects of Loading-Dose Statins Combined with PCSK9 Inhibitor Pre-Treatment before Primary Percutaneous Coronary Intervention on the Short-Term Prognosis in Patients with ST-Segment Elevation Myocardial Infarction

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Received: 28 April 2022; Revised: 21 June 2022; Accepted: 29 June 2022; Published Online: 17 August 2022

Abstract

Objective: This study was aimed at investigating the effects of preoperative treatment with a loading dose of statins combined with a PCSK9 inhibitor on coronary blood perfusion and short-term cardiovascular adverse events in patients with ST-segment elevation myocardial infarction (STEMI).

Method: Sixty-five patients with STEMI who had visited the Shanxi Cardiovascular Disease Hospital between May 2018 and May 2021 were enrolled in the study. The enrolled patients had no history of oral statins or antiplatelet therapy. The patients were divided into a combined treatment group (loading dose of statins combined with PCSK9 inhibitors, 35 patients) and a routine treatment group (loading dose of statins only, 30 patients). The primary endpoints were thrombolysis in myocardial infarction (TIMI) blood flow grading, corrected TIMI frame count (CTFC), and TIMI myocardial perfusion grading (TMPG), immediately after and 30 days after the operation. The secondary endpoint was a composite endpoint of cardiovascular death, nonfatal myocardial infarction, and target vessel revascularization 30 days after the operation.

Results: The combined treatment group had significantly lower CTFC (14.09 ± 8.42 vs 26 ± 12.42, $P=0.04$) and better TMPG (2.74 ± 0.61 vs 2.5 ± 0.73, $P=0.04$) than the routine treatment group immediately after the operation. Similarly, the combined treatment group had a significantly lower CTFC (16.29 ± 7.39 vs 26.23 ± 11.53, $P=0.04$) and significantly better TMPG (2.94 ± 0.24 vs 2.76 ± 0.43, $P=0.01$) than the routine treatment group 1 month after the operation.

Conclusion: Preoperative treatment with a loading dose of high-intensity statins combined with PCSK9 inhibitors increased coronary blood flow and myocardial perfusion after emergency thrombus aspiration in patients with STEMI. However, the treatment did not significantly decrease the incidence of cardiovascular death, nonfatal myocardial infarction, or target vessel revascularization.

Keywords: PCSK9 inhibitor; ST-segment elevation myocardial infarction; thrombus aspiration

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Introduction

ST-segment elevation myocardial infarction (STEMI) is a severe stenosis/occlusion of the lumen

caused by acute thrombosis of the coronary artery, thus resulting in myocardial ischemia and necrosis. Preoperative intensive dose statin therapy and thrombus aspiration can effectively avoid the occurrence of slow blood flow and an absence of reflow in infarct-associated coronary arteries during primary percutaneous coronary intervention (PPCI) [1]. Unfortunately, nearly 10% of patients cannot achieve thrombolysis in myocardial infarction (TIMI) 3 blood flow even after receiving PPCI. Coronary blood flow in patients with STEMI is closely correlated with short- and long-term prognosis.

Recently, several studies on lipid-lowering mechanisms have focused on a class of drugs that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9), because they have shown good lipid-lowering effects [2]. Previous studies have suggested that a combination of PCSK9 inhibitors with the maximum tolerated statin dose improves the outcomes of atherosclerotic cardiovascular disease [3]. In addition, PCSK9 inhibitors have been found to improve endothelial cell function in patients at high risk of cardiovascular disease by regulating low-density lipoprotein cholesterol (LDL-C) [4]. Therefore, PCSK9 inhibitors can play major roles in improving myocardial perfusion, because they have effects in lipid lowering, plaque stabilization and endothelial function improvement [5]. Because of the relatively limited number of similar studies in China, the aim of this study was to determine the effects of preoperative administration of high dose statins in combination with PCSK9 inhibitors on coronary blood flow, myocardial perfusion and short-term prognosis in patients with STEMI without a history of statin therapy.

Data and Methods

Participants

Sixty-five patients with STEMI who underwent emergency thrombus aspiration at Shanxi Cardiovascular Disease Hospital between May 2018 and May 2021 were enrolled in this study. The inclusion criteria were as follows: patients with acute STEMI who had undergone emergency thrombus aspiration; and men or non-pregnant women over 18 years of age (inclusive) and under 80 years of age with no history of statin therapy. All enrolled patients provided signed informed consent to participate in the trial after approval by the ethics committee. The exclusion criteria were as follows: combined cardiogenic shock; severe valvular heart disease; cardiomyopathy; antithrombotic contraindications including bleeding tendency, active peptic ulcers, a history of hemorrhagic stroke and ischemic stroke within 6 months; multiple organ failure; advanced tumors; contrast agent allergies; and patient inability to follow the study protocol.

Research Methods

The patients providing signed informed consent were divided into a group receiving high-intensity statins (routine treatment group) and a group receiving high-intensity statins combined with PCSK9 inhibitors (combined treatment group), according to whether they received pretreatment with PCSK9 inhibitor before the emergency intervention. Thirty patients in the routine treatment group received preoperative doses of 40 mg atorvastatin calcium tablets (Lipitor, Pfizer Inc.) or 20 mg rosuvastatin calcium tablets (Cordine, Astra Zeneca Inc.). In the combined treatment group, 35 patients were injected with 140 mg evolocumab (Repatha, Amgen Manufacturing Limited; same below) and received preoperative doses of 40 mg atorvastatin calcium tablets (Lipitor, Pfizer Inc) or 20 mg rosuvastatin calcium tablets (Cordine, Astra Zeneca Inc.). Both groups were given atorvastatin calcium tablets (20 mg/day) or rosuvastatin calcium tablets (10 mg/day) postoperatively.

All patients were given a loading dose of 300 mg aspirin and 300–600 mg clopidogrel or 180 mg ticagrelor before PPCI. Bivalirudin was administered intravenously at 1.75 mg/kg/h during the operation, whereas platelet glycoprotein IIb/IIIa receptor antagonist (tirofiban) was applied according to the specific conditions, such as the patient has severe coronary thrombus burden. All patients who underwent thrombus aspiration had less than 30% coronary artery stenosis immediately after the operation, and optical coherence tomography indicated that the coronary artery dissection was not deep in the tunica media. Balloon dilation and stent implantation were not performed during the operation.

(1) Detailed baseline clinical data, angiographic information, and the nosocomial prognosis of the

enrolled patients were collected, and coronary angiography findings were reviewed 30 days after the operation. The primary endpoints were TIMI blood flow grading, corrected TIMI frame count (CTFC), and TIMI myocardial perfusion grading (TMPG), both immediately after the operation and 30 days after the operation. Assessment of the primary endpoints was performed by two observers who were blinded to the study and followed methods previously described in the literature [6, 7]. Patients with TIMI blood flow grade≤2 and CTFC>40 were considered to have no reflow or to have slow flow. Patients with normal blood flow had TIMI blood flow grade 3 and CTFC<40.

(2) The secondary endpoints were major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal myocardial infarction, and revascularization of the culprit artery at 30 days after the operation. Nonfatal myocardial infarction was defined as recurrent ischemic chest pain with at least three observations of re-elevation of myocardial markers above the upper normal limit, or new ST-segment elevation or pathological Q waves after PPCI. Revascularization of the culprit artery was defined as all unexpected revascularization of the culprit artery.

Statistical Methods

SPSS 22.0 software was used for statistical analysis of the data. Data are presented as mean ± standard deviation, and T tests were used to compare the means of normally distributed data between groups. Count data are expressed as frequencies (rates). The chi-square revised test was used when $1 \leq T < 5$, whereas Fisher's exact probability method was used when $T < 1$ or $n < 40$. Rank variables were tested with rank sum tests. $P < 0.05$ was considered statistically significant.

Results

1. Basic clinical characteristics of the study participants: A total of 65 patients with STEMI were enrolled in the study, including 30 patients in the routine treatment group and 35 patients in the combined treatment group. The basic information for patients in the two groups is shown in Table 1.
2. History of antithrombotic therapy in the patients in both groups: No patients had received prior antiplatelet lipid-lowering therapy. In emergency interventional treatment, all patients were given an aspirin load in perioperative treatment except for one patient with digestive hemorrhage. Clopidogrel bisulfate load therapy was administered to 35 patients, ticagrelor tablet load therapy was administered to 30 patients, and preoperative thrombolysis treatment was administered to 20 patients. All patients were given bivalirudin for anticoagulant therapy intraoperatively, whereas 28 patients were given tirofiban injection intraoperatively (Table 2).
3. Results of laboratory assays in the two groups. Laboratory assays were performed for hemoglobin, platelets, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, fasting blood glucose, endogenous creatinine clearance, and glutamic-pyruvic transaminase. The results of the assays are shown in Table 3. The levels of perioperative total cholesterol, triglycerides, and low-density lipoprotein were significantly lower in the combined treatment group than the routine treatment group. One month after operation, total cholesterol was significantly lower in the combined treatment group than the routine treatment group, but no significant differences were observed in triglycerides, high-density lipoprotein, and low-density lipoprotein between groups (Table 4).
4. Characteristics and interventions for coronary artery lesions in the two groups: Among the 65 patients, 26 had single vessel lesions, 19 had double vessel lesions, and 19 had triple vessel lesions. Classification based on the culprit artery revealed 34 cases of anterior descending artery disease, six cases of circumflex artery disease, and 25 cases of right coronary artery disease. In preoperative TIMI blood flow grading, we identified 28 cases of TIMI0, three cases of TIMI1, 13 cases of TIMI2, and 21 cases of TIMI3. The thrombus suction device was used in all patients, without balloon dilation or stent implantation. The coronary artery lesions and interventions for patients in both groups are shown in Table 5.
5. Experimental results: In terms of myocardial blood perfusion during interventional operation, 54 of the 65 patients had postoperative blood flow

Table 1 General Clinical Characteristics of Patients in the Two Groups.

Project	Routine treatment group (n=30)	Combined treatment group (n=35)	P
Age/(years, ±s)	44.67±12.51	48.34±12.2	0.94
Men (n, %)	29 (96.7)	30 (85.7)	0.13
Hypertension (n, %)	10 (33.3)	7 (20)	0.22
Type 2 diabetes (n, %)	2 (6.7)	4 (11.4)	0.51
Cerebrovascular disease (n, %)	1 (3.3)	1 (2.9)	0.91
Anemia (n, %)	0 (0)	1 (2.9)	0.35
Thrombocytosis (n, %)	0 (0)	1 (2.9)	0.35
Hyperlipidemia (n, %)	1 (3.3)	3 (8.6)	0.38
Smoking (n, %)	26 (86.7)	29 (82.9)	0.67
Family history (n, %)	4 (13.3)	5 (14.3)	0.89
Myocardial infarction Killip grading (n, %)			
Degree I	26 (86.7)	34 (97.1)	0.14
Degree II	4 (13.3)	1 (2.9)	
Degree III	0 (0)	0 (0)	
Degree IV	0 (0)	0 (0)	
Site of myocardial infarction			
Antetheca (n, %)	15 (50)	19 (54.3)	0.52
Inferior wall (n, %)	4 (13.3)	3 (8.6)	
Posterior inferior wall (n, %)	3 (10)	8 (22.9)	
Inferior wall with right ventricular (n, %)	3 (10)	2 (5.7)	
Posterior inferior wall with right ventricular (n, %)	5 (16.7)	3 (8.6)	

Table 2 Use of Antithrombotic Drugs in the Two Groups [n (%)].

Drug use	Routine treatment group (n=30)	Combined treatment group (n=35)	P
Aspirin (n, %)	29 (96.7)	35 (100)	0.84
Clopidogrel bisulfate (n, %)	16 (53.3)	19 (54.3)	0.01
Ticagrelor (n, %)	14 (46.7)	16 (45.7)	0.01
Thrombolytic therapy (n, %)	10 (33.3)	10 (28.6)	0.17
Tirofiban (n, %)	15 (51.7)	13 (37.1)	1.37

Table 3 Perioperative Laboratory Test Data for Patients in the Two Groups ($\bar{x}\pm s$).

Project	Routine treatment group (n=30)	Combined treatment group (n=35)	P
Body mass index ($\bar{x}\pm s$)	26±2.9	26±3.1	0.75
White blood cell count/(10^9, ±s)	11.5±3.2	11.5±2.8	0.28
Hemoglobin/(g/L, ±s)	145.8±18.8	144.6±20.7	0.55
Thrombocyte/(10^9, ±s	241.47±59.64	265.17±123.37	0.15
Alanine aminotransferase/(U/L, ±s)	70.08±49.24	57.18±37.13	0.21
Blood glucose/(mmol/L, ±s)	6.2±1.95	6.4±2.09	0.58
Total cholesterol/(mmol/L, ±s)	4.73±0.86	4.35±1.41	0.02
Triglycerides/(mmol/L, ±s)	2.16±1.51	1.76±0.79	0.01
High-density lipoprotein/(mmol/L, ±s)	0.97±0.21	0.95±0.25	0.28
Low-density lipoprotein/(mmol/L, ±s)	2.74±0.51	2.64±0.91	0.003
Endogenous creatinine clearance rate/(mL/min, ±s)	122.61±29.24	124.06±37.81	0.21

Table 4 Laboratory Test Data for Patients in the Two Groups 1 month after Operation ($\bar{x} \pm s$).

Project	Routine treatment group (n=30)	Combined treatment group (n=35)	P
White blood cell count/(10^9, ±s)	8.67±2.28	7.17±2.01	0.53
Hemoglobin/(g/L, ±s)	123.81±18.41	136.94±12.69	0.08
Thrombocyte/(10^9, ±s	234.81±56.52	230.97±91.79	0.42
Alanine aminotransferase/(U/L, ±s)	51.92±19.79	38.16±24.28	0.31
Blood glucose/(mmol/L, ±s)	5.27±1.53	4.77±1.06	0.61
Total cholesterol/(mmol/L, ±s)	3.62±1.05	2.91±0.76	0.03
Triglycerides/(mmol/L, ±s)	1.93±1	1.47±0.74	0.19
High-density lipoprotein/(mmol/L, ±s)	0.84±0.22	0.93±0.24	0.32
Low-density lipoprotein/(mmol/L, ±s)	2.01±0.51	1.45±0.39	0.18

Table 5 Coronary Artery Lesions and Interventions in the Two Groups [n(%)].

Project	Routine treatment group (n=30)	Combined treatment group (n=35)	P
Single/double/triple-vessel disease (n, %)			
Single	13 (44.8)	13 (37.1)	0.39
Double	8 (27.6)	11 (31.4)	
Triple	8 (27.6)	11 (31.4)	
Culprit artery (n, %)			
Anterior descending coronary artery	16 (53.3)	18 (51.4)	0.09
Left circumflex artery	3 (10)	3 (8.6)	
Right coronary artery	11 (36.7)	14 (40)	
Preoperative TIMI grading (n, %)			
0	13 (43.3)	15 (42.9)	0.61
1	1 (3.3)	2 (5.7)	
2	7 (23.3)	6 (17.1)	
3	9 (30)	12 (34.3)	

TIMI grade 3. The combined treatment group had significantly lower CTFT (14.09±8.42 vs 26±12.42, P=0.04) and significantly better TMPG (2.74±0.61 vs 2.5±0.73, P=0.04) than the routine treatment group immediately after the operation. Coronary angiography 1 month after the operation showed that the CTFC was significantly lower (16.29±7.39 vs 26.23±11.53, P=0.04), and the TMPG was significantly better (P=0.04), in the combined treatment group than the routine treatment group (Table 6). At 30 days after emergency thrombus aspiration, two patients in the routine treatment group showed substantial progression in the degree of coronary artery stenosis of the culprit vessels and were further treated with PCI (P=0.12) (Table 7).

Discussion

Prior studies have investigated the role of PCSK9 inhibitors in lowering blood lipids. The FOURIER trial provided the first demonstration that the combination of PCSK9 inhibitors with high-intensity statin drugs significantly decreases LDL-C and effectively and safely decreases the incidence of major cardiovascular events [8]. The subsequent ODYSSEY study has also demonstrated that a combination of PCSK9 inhibitors and statins has a clear effect on lowering blood lipids [9]. However, the two studies studied patients in a relatively stable period for acute coronary syndromes (ACS), and PCSK9 inhibitors were used when the control of LDL-C was still not ideal after treatment with high-potency

Table 6 Blood Perfusion Evaluation After Interventional Therapy in the Two Groups [$\bar{x}\pm s$, n(%)].

Project	Routine treatment group (n = 30)	Combined treatment group (n = 35)	P
Immediate postoperative			
TIMI blood flow level 3 (n, %)	23 (76.7)	31 (88.6)	0.82
CTFC ($\bar{x}\pm s$)	26±12.42	14.09±8.42	0.04
TMPG (n, %)			
I	4 (13.3)	3 (8.6)	0.04
II	7 (23.3)	3 (8.6)	
III	19 (63.3)	29 (82.9)	
One month after operation			
CTFC ($\bar{x}\pm s$)	26.23±11.53	16.29±7.39	0.04
TMPG (n, %)			
I	0	0	
II	7 (23.3)	2 (5.7)	0.04
III	23 (76.7)	33 (94.3)	

CTFC: corrected TIMI frame count, TMPG: TIMI myocardial perfusion grade.

Table 7 Incidence of Adverse Reactions after Interventional Therapy in both Groups.

Project	Routine treatment group (n = 30)	Combined treatment group (n = 35)	P
MACE (n, %)	2 (6.7)	0	0.12
Death	0	0	
Nonfatal myocardial infarction	0	0	
Ischemia driving revascularization of the culprit artery	2 (6.7)	0	0.12

MACE: major adverse cardiovascular events.

statins. According to a study by Thorsten, early treatment with evolocumab significantly decreases LDL-C levels in patients with ACS within 24 hours, and most patients with ACS keep continuous qualified serum lipid level, including LDL-C, at discharge and after 30 days [10]. Findings from our study confirmed that PCSK9 inhibitors had significant blood lipid lowering effects in patients with acute STEMI. In addition, we observed that the patients treated with high-intensity statins combined with PCSK9 inhibitors had significantly lower levels of total cholesterol, triglycerides, and low-density lipoprotein than patients treated with high-intensity statins alone, at 24 hours after the operation. One month after interventional treatment, patients who had been perioperatively administered PCSK9 inhibitors combined with statins had significantly lower levels of total cholesterol. However, no difference was observed in triglycerides, high-density lipoprotein and low-density lipoprotein between groups. These findings might be attributable to the 11–20 day elimination half-life of PCSK9 inhibitors. However, the patients in our study were treated with PCSK9 inhibitors only in the perioperative period [11]. Therefore, PCSK9 inhibitors and lipid-lowering therapy administration should be repeated 2 weeks after surgery.

No studies have reported the effects of PCSK9 inhibitors on improving coronary blood flow and myocardial tissue perfusion after thrombus aspiration in patients with acute STEMI. In this study, the patients treated with a combination of the PCSK9 inhibitors and high-intensity statins showed significantly improved coronary blood flow and myocardial tissue perfusion either immediately or 1 month after surgery. Previous studies have shown that the expression of PCSK9 is upregulated on the second day after the first administration of statins, and that

the degree of upregulation is dose-dependent [12]. The early increase in PCSK9 may be directly associated with the decrease in intracellular cholesterol biosynthesis and subsequent activation of SREBP-2, rather than the decrease in circulating LDL-C levels [13]. The mechanism of slow blood flow and no reflow is highly complex and is currently believed to be associated with microembolization, cholesterol crystal-induced coronary artery spasm, microcirculation disorders, ischemia-reperfusion injury, inflammatory response, platelet activation, and other factors [14]. According to previous animal studies, the PCSK9 enzyme activates platelets and promotes epinephrine-induced platelet aggregation and thrombogenesis [15]. Simultaneously, the PCSK9 enzyme regulates inflammatory responses and promotes the expression of a variety of pro-inflammatory factors [16]. The increase in PCSK9 expression levels enhances the phagocytosis of LDL-C by macrophages and accelerates the formation of foam cells, thus promoting the occurrence and development of atherosclerosis [17]. Recent studies have shown that the inhibition of the PCSK9 pathway not only decreases LDL-C levels but also affects various metabolic pathways, inflammatory responses, thrombosis, and the mediation of endothelial cell apoptosis. In addition, PCSK9 inhibitors reverse the formation of atherosclerotic plaques. According to the GLAGOV study, evolocumab combined with high-intensity statins decreases LDL-C to 36.6 mg/dL on average in patients with ACS [18]. Moreover, the synergistic effects of APO-A1, HDL, and ABCAl/G1 decrease cholesterol inflow from the artery wall and increase outflow, thus resulting in reverse cholesterol transport; ameliorating atherosclerotic vascular dense calcification, tissue fibrosis, lipid fibrosis, and core necrosis; and contributing to plaque reversal [19].

Currently, PSCK9 inhibitors are rarely used in patients with acute myocardial infarction in the perioperative period. The combination of PSCK9 inhibitors with statin intensification therapy before surgery may improve coronary perfusion in patients with STEMI, owing to the synergistic pleiotropic effects of PCSK9 inhibitors and statins rather than their lipid regulatory effects. PCSK9 inhibitors combined with statins further stabilize plaques, decrease distal thromboembolism and microvasospasm, and improve coronary blood flow and myocardial perfusion [20]. These effects are attributable to PCSK9 inhibitor-induced improvements in endothelial function, and anti-oxidant and anti-inflammatory activity, and a decrease in platelet activation and aggregation [21]. The PCSK9 inhibitors and statins were administered to patients within 1 hour after the beginning of the operation, and the interaction between drugs might have shortened the onset of pleiotropic effects, thus resulting in rapid onset of action. However, whether the effect of combining PCSK9 inhibitors with statins can occur within a short period must be determined, and the specific mechanisms involved must be identified.

This study has several limitations. The sample size of the study was small, and the participants were from a single center; thus, the comparison of clinical endpoints such as MACE between groups was inadequate. The findings from this study must be validated in a large-sample randomized controlled study with multi-center participation. Differences in the complexity of underlying diseases and the effects of interventional therapy on prognosis might have increased the bias to some extent. In addition, the short follow-up time might have affected judgments regarding MACE. In the acute phase of myocardial infarction and during regular follow-up, the lack of continuous monitoring of serum inflammatory indicators prevented further elucidation of the role of inflammation in the recovery of acute myocardium infarction.

In summary, findings from this study demonstrated that the preoperative combination of loading doses of high-intensity statins with PCSK9 inhibitors improved myocardial perfusion in patients with acute STEMI without a history of antiplatelets and statin lipid-lowering therapy. This preoperative treatment effectively reduces occurrence of the coronary slow flow and no-reflow phenomenon in patients undergoing emergency thrombus aspirations. Moreover, we observed no significant effects on cardiovascular MACE 30 days after the operation.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Lev EI, Kornowski R, Vaknin-Assa H, Ben-Dor I, Brosh D, Teplitsky I, et al. Effect of previous treatment with statins on outcome of patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol 2009;103:165–9.
2. Rosenson RS, Hegele RA, Fazio S, Cannon CP. The evolving future of PCSK9 inhibitors. J Am Coll Cardiol 2018;72:314–29.
3. Steg PG, Szarek M, Bhatt DL, Bittner VA, Brégeault M-F, Dalby AJ, et al. Effect of alirocumab on mortality after acute coronary syndromes. Circulation 2019;140:103–12.
4. Maulucci G, Cipriani F, Russo D, Casavecchia G, Di Staso C, Di Martino L, et al. Improved endothelial function after short-term therapy with evolocumab. J Clin Lipidol 2018;12:669–73.
5. Dixon DL, Pamulapati LG, Bucheit JD, Sisson EM, Smith SR, Kim CJ, et al. Recent updates on the use of PCSK9 inhibitors in patients with atherosclerotic cardiovascular disease. Curr Atheroscler Rep 2019;21:16.
6. van't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle myocardial infarction study group. Circulation 1998;97:2302–6.
7. Gibson CJC. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–88.
8. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.
9. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–107.
10. Leucker TM, Blaha MJ, Jones SR, Vavuranakis MA, Williams MS, Lai H, et al. Effect of evolocumab on atherogenic lipoproteins during the peri- and early postinfarction period: a placebo-controlled, randomized trial. Circulation 2020;142:419–21.
11. Wang Y, Liu ZP. PCSK9 inhibitors: novel therapeutic strategies for lowering LDLCholesterol. Mini Rev Med Chem 2019;19:165–76.
12. Stoekenbroek RM, Lambert G, Cariou B, Hovingh GK. Inhibiting PCSK9 - biology beyond LDL control. Nat Rev Endocrinol 2018;15:52–62.
13. Zhang Y, Liu J, Li S, Xu RX, Sun J, Li JJ. Impact of currently prescribed lipid-lowering drugs on plasma PCSK9 concentration: single or in combination study in rats. Lipids Health Dis 2014;13:35–5.
14. Donato M, Ferri N, Lupo MG, Faggin E, Rattazzi M. Current evidence and future perspectives on pharmacological treatment of calcific aortic valve stenosis. Int J Mol Sci 2020;21:8263.
15. Navarese EP, Kolodziejczak M, Winter MP, Alimohammadi A, Lang IM, Buffon A, et al. Association of PCSK9 with platelet reactivity in patients with acute coronary syndrome treated with prasugrel or ticagrelor: The PCSK9-REACT study. Int J Cardiol 2017;227:644–9.
16. Ding Z, Pothineni NVK, Goel A, Lüscher TF, Mehta JL. PCSK9 and inflammation: role of shear stress, pro-inflammatory cytokines, and LOX-1. Cardiovasc Res 2020;116:908–15.
17. Melendez QM, Wooten CJ, Krishnaji ST, Knagge K, Kirchner D, Lopez D. Identification of novel proteins interacting with proprotein convertase Subtilisin/Kexin 9. Int J Biomed Investig 2020;3:123.
18. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV Randomized Clinical Trial. J Am Med Assoc 2016;316:2373–84.
19. Nicholls SJ, Puri R, Ballantyne CM, Jukema JW, Kastelein JJP, Koenig W, et al. Effect of infusion of high-density lipoprotein mimetic containing recombinant apolipoprotein A-I milano on coronary disease in patients with an acute coronary syndrome in the MILANO-PILOT trial: a randomized clinical trial. JAMA Cardiol 2018;3:806–14.
20. Roth EM, Davidson MH. PCSK9 inhibitors: mechanism of action, efficacy, and safety. Rev Cardiovasc Med 2018;19:S31–46.
21. Behr PEB, Moriguchi EH, Castro I, Bodanese LC, Dutra OP, Leães PE, et al. Indications of PCSK9 inhibitors for patients at high and very high cardiovascular risk. Arq Bras Cardiol 2018;111:104–8.