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Original Article

Rosuvastatin combined with ezetimibe decreases myocardial injury in acute coronary syndrome patients receiving percutaneous coronary intervention

Xin Wang, Donghui Zhao, Jian Wang, Ze Zheng

Department of Cardiology, 28th Division, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, P. R. China

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Abstract: Background: High-sensitivity C-reactive protein (hs-CRP) and pregnancy-associated plasma protein-A (PAPP-A) are potential biomarkers for acute coronary syndrome (ACS). Statins are effective in preventing elevation of biomarkers of myocardial infarction (MI) after elective coronary stent implantation. In this paper, we report the dual effect of rosuvastatin with ezetimibe in patients after percutaneous coronary intervention (PCI) by measuring the levels of myocardial biomarkers and inflammation factors. Methods: After PCI in patients with ACS, the effects on levels of cardiac troponin I was examined. The hs-CRP and PAPP-A levels at baseline and after a 12-week course of rosuvastatin (Rosuva) with ezetimibe (Ez) (10/10 mg qN; 70 patients) versus rosuvastatin alone (10 mg qN; 70 patients) were evaluated. Peripheral blood samples were taken within 24 h of admission to hospital and after 12 weeks of drug administration. Results: Elevations of cTnI >5 times ULN after PCI procedure occurred in 17 (24.3%) patients in the Rosuva/Ez group and 23 (32.9%) in the Rosuva group (pearson Chi-Square value =100.9, P=0.0001). The hs-CRP levels were significantly reduced in both groups, but the reductions were not significantly different between the Rosuva/Ez and Rosuva alone group (5.72±1.38 mg/L to 5.26±0.81 mg/L, P>0.05) after 12 weeks compared with baseline levels. PAPP-A levels also decreased in both the Rosuva/Ez group (from 19.32±9.16 to 6.31±2.02 mIU/L) and the Rosuva group (from 20.24±8.73 to 10.21±3.07 mIU/L) after 12 weeks, compared with baseline levels. However, a greater reduction of PAPP-A levels was observed in the Rosuva/Ez group (13.51±4.77 mIU/L) compared with the Rosuva group (9.33±5.46 mIU/L). Conclusion: Rosuva/Ez treatment was more effective than treatment with Rosuva alone in decreasing myocardial injury and inflammatory factors after PCI.

Keywords: Rosuvastatin, ezetimibe, percutaneous coronary intervention, high-sensitivity C-reactive protein

Introduction

Acute coronary syndrome (ACS) accounts for a high percentage of advanced health risk and deaths. The rupture of atherosclerotic plaque and subsequent thrombosis is the pathological basis of ACS, and inflammation plays an important role in the onset and development of atherosclerosis which is the underlying cause of ACS [1, 2]. In recent years, studies have indicated that high-sensitivity C-reactive protein (hs-CRP) and pregnancy-associated plasma protein A (PAPP-A) are potential biomarkers to assess the stability of plaque [1, 3].

Percutaneous coronary intervention (PCI) is an alternative option for ACS treatment to improve life expectancy. However, 5% to 30% of patients who receive successful PCIs have an increase in cardiac biomarkers. It has been well demonstrated that the risk of subsequent adverse cardiac events is related to the degree of increase in cardiac biomarkers such as cardiac troponin [4]. The available data suggest that a high loading dose of statin is effective in preventing elevation of cardiac biomarkers of myocardial infarction (MI) after elective PCI. However, despite the current trend of aggressive lipid-lowering strategies, the majority of patients continue to experience cardiovascular (CV) events and remain exposed to high "residual risk" of future acute CV events. Furthermore, aggressive strategies may increase the risk of liver damage. Therefore, additional novel phar-

macologic strategies for the prevention of further CV events risk have emerged. In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) investigators compared simvastatin plus placebo with simvastatin plus ezetimibe. Both drugs reduce low-density lipoprotein cholesterol (LDL-C) levels, but in different ways. Ezetimibe (Ez) is a cholesterol transporter Niemann-Pick C1-Like 1 protein inhibitor which blocks the intestinal absorption of dietary and biliary cholesterol but does not affect the uptake of triglycerides (TG) or fat-soluble vitamins [5]. Compared with simvastatin plus placebo, simvastatin plus 10 mg of Ez daily led to a significantly lower incidence of the primary combined CV endpoint [6]. Several investigators have already reported that ezetimibe also has both anti-inflammatory [7] and pleiotropic effects [8]. The present study aimed to assess whether treatment with Rosuva/Ez is effective in preventing elevation of cardiac biomarkers of MI after elective PCI and decreasing inflammation biomarkers in ACS patients.

Materials and methods

Patient information

Our study was a prospective, randomized study to evaluate the effect of ezetimibe added to rosuvastatin in preventing elevation of biomarkers of MI and inflammatory factors in patients with CAD undergoing elective PCI. Patients were enrolled after having undergone successful coronary angiography (CAG) and satisfying the following criteria for inclusion: 1) provision of written informed consent; 2) age 18-80 years; 3) diagnosisof ACS; 4) undergoing PCI. The exclusion criteria were as follows: 1) familial hypercholesterolemia; 2) previous treatment with ezetimibe; 3) renal insufficiency (serum creatinine >2.0 mg/dL); 4) abnormal hepatic function (serum AST or ALT >3-fold standard value); 5) concurrent hemodialysis or peritoneal dialysis; 6) allergy or intolerance to rosuvastatin or ezetimibe; 7) myocarditis or cardiomyopathy, infectious diseases; 8) severe underlying disease.

Eligible patients were randomly assigned to receive either rosuvastatin (10 mg) alone (Rosuva group) or rosuvastatin (10 mg) plus ezetimibe (10 mg) daily (Rosuva/Ez group) in a 1:1 ratio. The drugs assigned to the group were prepared in numbered, opaque envelopes and chosen randomly. Rosuvastatin was increased by titration within the usual dose range with a treatment goal of LDL-C <70 mg/dl on the basis of published lipoprotein management guidelines. Lipid profiles and other biomarker levels were measured in our hospital at both baseline and follow-up at 12 weeks (analyzed by Beckman Coulter Co. Ltd., USA). Patients started statin and ezetimibe treatment ≥ 3 days before stent deployment. The study protocol was approved by the local ethics committee of Beijing Anzhen Hospital.

Study procedure

All the patients were enrolled in the study after hospitalization. Before PCI, all the patients received a single dose of 300 mg of clopidogrel and 300 mg of aspirin. PCI was performed in accordance with standard treatment procedure. Implantation of the stent was performed using Judkin's catheter stent technology, that is, through the right femoral artery or right radial artery pathway. Angiographic residual stenosis was defined as a final angiographic residual stenosis of less than 20%. Procedural success was considered to be angiographic success with no in-hospital major complication (including need for bypass surgery or repeat PCI, or death). After PCI, the patients received daily 75 mg of clopidogrel and 75 mg of aspirin along with rosuvastatin plus ezetimibe or rosuvastatin alone for 12 weeks. Stent angiographic success rates were based on no residual stenosis associated with distal coronary blood flow, and no acute complications. Vital signs of the patients were closely observed after PCI. The number of stents implanted in the patients was recorded and the Gensini score was calculated to analyze the coronary stenosis. Serum cardiac troponin I (cTnI) was assessed before, and 6 and 12 h after PCI, using a radioimmunoassay analyzer (Stratus CS-STAT Fluorometric Analyzer, Dade Behring Marburg GmbH, Marburg, Germany). The first endpoint was the rate of periprocedural MI which was assessed by the elevation of cardiac biomarkers after PCI. The upper limit of normal (ULN) levels of cTnI was 0.05 ng/ml (ranged from 0.00 to 0.05 ng/ml). The primary endpoint in our study was defined as an elevation of cTnI levels >5× ULN in patients with normal baseline values or a rise of cTnI values >20% if the baseline values were elevated but stable and falling. In addition, one of the following conditions had to be satisfied:

Table 1. Demographic and clinical pathological features of the patients with acute coronary syndrome who underwent PCI

	Rosuva/Ez group (n=70)	Rosuva group (n=70)
Sex (male/female)	37/33	38/32
Age (years, $\bar{x}\pm s$)	64.3±10.1	62.2±9.7
Systolic BP (mmHg, $\bar{x}\pm s$)	132.16±15.29	131.58±13.91
Diastolic BP (mmHg, $\bar{x}\pm s$)	84.25±8.13	83.70±7.52
Coronary stenosis (Gensini Score)	24.95±9.56	23.67±11.2
Number of stents implanted	1.60±0.97	1.62±1.26
Medication prior to dosage		
Aspirin	70 (100)	70 (100)
Clopidogrel	70 (100)	70 (100)
Beta blocker	36 (51.4)	32 (45.7)
ACE inhibitor/ARB	42 (60)	48 (68.6)
GPI	7 (10)	9 (12.6)
LMWH	50 (71.4)	48 (68.6)
Bivalirudin	6 (8.6)	5 (7.1)
Nitrates	54 (77.1)	44 (65.7)
Calcium blockers	21 (30)	24 (34.3)
Hypoglycemic agents	14 (20)	18 (25.7)

BP, blood pressure; LDL-C, low-density lipoprotein Cholesterol; HDL-C, high-density lipoprotein Ccholesterol; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GPI, glycoprotein IIb/IIIa inhibitor; LMWH, low molecular weight heparin.

1) symptoms suggestive of myocardial ischaemia; 2) new ischaemia ECG changes; 3) angiographic findings consistent with a procedural complication; 4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.

Biomarker assessment

The secondary endpoints were changes in the lipid and inflammatory profile (total cholesterol, LDL-C, triglyceride, HDL-C, PAPP-A and hs-CRP) during the study period. Peripheral blood samples were collected within 24 h of hospital admission and after 12 weeks of drug administration after PCI. Blood samples were collected under aseptic conditions and the serum was separated by centrifuging at 1500 rpm for 5 minutes and stored at -70°C in sealed tubes until further use. PAPP-A and hs-CRP were quantified by ELISA using Human PAPP-A Kit (DRG, Germany), and hs-CRP kit (DiaSys Diagnostic Systems GmbH, Germany) respectively, according to the manufacturer's instructions.

Statistical analysis

SPSS 11.0 software package was used for statistical analysis of all data. After the descriptive statistics, continuous variables were recorded (mean ± standard deviation and medians with interquartile ranges). The comparison between the 2 groups used the unpaired Student t test or the Mann-Whitney U test. Continuous variables between the baseline and follow-up were compared by 1-sample Student t tests or the Wilcoxon signed rank test according to their distributions. Categorical variables (frequencies) were compared using chi-square statistics or the Fisher exact test. All the patients were included in the safety analysis. The number of adverse events was assessed to determine safety profiles. $P<0.05$ was considered statistically significant.

Results

Basic characteristics of patients in both groups

From June 11, 2011 to August 22, 2013, a total of 141 patients were enrolled and randomly assigned to receive Rosuvastatin plus ezetimibe 10 mg/day (n=71) or Roruvastatin alone (n=70). One patient enrolled in the Rosuva/Ez group withdrew consent and was removed from the study. **Table 1** lists demographic and baseline characteristics of the patients and their cardiovascular medications received prior to enrollment. No significant differences in demographics or cardiovascular medication were observed between the Rosuva/Ez group and the Rosuva group.

Cardiac markers increase

Median peak of cTnI was 0.25 (0.07-4.82) ng/ml in the Rosuva group and 0.18 (0.05-3.45) ng/ml in the Rosuva/Ez group (P=0.019). Elevations of cTnI >5 times ULN after PCI procedure occurred in 17 (24.3%) patients in the Rosuva/Ez group and in 23 (32.9%) in the Rosuva group (pearson Chi-Square value =100.9, P=0.0001).

Table 2. Lipid levels of the two groups at baseline and after 12 weeks' drug treatment

	Baseline		Follow-up		
	Rosuva/Ez group (n=70)	Rosuva group (n=70)	Rosuva/Ez group (n=70)	Rosuva group (n=70)	*P* value
TC (mmol/L)	4.42±1.32	4.28±0.87	3.24±0.81	3.42±0.65	0.149
LDL-C (mmol/L)	2.52±1.07	2.48±0.66	1.65±0.43	1.91±0.52	0.002
HDL-C (mmol/L)	1.08±0.24	1.13±0.19	1.11±0.28	1.16±0.23	0.250

Data were shown as mean ± SD. TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 3. Angiographic characteristics of the patients enrolled in the two groups

	Rosuva/Ez group (n=70)	Rosuva group (n=70)	*P*
Normal (n, %)	4 (5.7)	3 (4.3)	>0.05
Single coronary artery (n, %)	34 (48.6)	36 (51.4)	>0.05
Double coronary arteries (n, %)	15 (21.4)	17 (24.3)	>0.05
Multiple coronary arteries (n, %)	15 (21.4)	12 (17.1)	>0.05
Left main (n, %)	4 (5.7)	5 (7.1)	>0.05
LAD (n, %)	46 (65.7)	50 (71.4)	>0.05
LCX (n, %)	16 (22.9)	17 (24.3)	>0.05
RCA (n, %)	20 (28.6)	24 (34.3)	>0.05

LAD, left anterior descending; LCX, left circumflex artery; RCA, right coronary artery.

Baseline and follow-up laboratory data

Baseline and follow-up laboratory data are shown in **Table 2**. Lipid profiles were similar at baseline, but differed significantly at the end of 12 weeks of follow-up. LDL-C level was significantly lower at 12 weeks in the Rosuva/Ez group than in the Rosuva group (P<0.001). In the combination group, an extra LDL-C reduction was achieved compared with the Rosuva alone group (1.65±0.43 vs. 1.91±0.52). The dual lipid-lowering strategy showed more marked reduction of LDL-C level than rosuvastatin monotherapy throughout the study (P<0.001).

Angiographic and procedural characteristics

Direct stenting was performed in 84.3% of cases in the Rosuva/Ez group and in 86.7% in the Rosuva group (P>0.05). All the other angiographic and procedural characteristics were similar in the two groups (**Table 3**). Coronary stenosis tended to be similar in both groups with respect to GensiniScore.

Serum inflammation factors levels at baseline and 12 weeks after PCI

The levels of hs-CRP were significantly lower in the Rosuva/Ez group after 12 weeks of treatment (5.67±1.12 mg/L; P<0.05) than baseline (11.57±3.12 mg/L) (**Table 4**). Similar trends were observed in the Rosuva group where the levels of hs-CRP were lower after 12 weeks (5.93±1.53 mg/L) than baseline (11.09±2.78 mg/L). Statistically, the decrease in the level of hs-CRP in the Rosuva/Ez group (5.72±1.38 mg/L) compared with the Rosuva group (5.26±0.81 mg/L) was not significant.

Significant reduction in PAPP-A levels was observed in the Rosuva/Ez group after 12 weeks of treatment (6.31±2.02 mIU/L; P<0.05) compared with baseline levels (19.32±9.16 mIU/L). PAPP-A levels in the control group (Rosuva group) followed a similar trend, showing reduction after 12 weeks (10.21±3.07 mIU/L) compared with baseline levels (20.24±8.73 mIU/L). However, the reduction was greater in the Rosuva/Ez group (13.51±4.77 mIU/L) than the Rosuva group (9.33±5.46 mIU/L).

Safety

The percentages of patients who had elevations in alanine aminotransferase levels >3 times the ULN were similar in both groups and the rates of muscle-related adverse events or cancer between the two groups had no significant difference (**Table 5**). There was no discontinuation of study medication owing to an adverse event in either group.

Discussion

This study demonstrated the cardioprotective effects of a statin combined with ezetimibe when administered as pre-treatment in patients undergoing elective stent implantation and the anti-inflammation effect in those patients during 12 weeks of follow-up. The incidence of

Table 4. Hs-CRP and PAPP-A concentration in the serum of the two groups at baseline and after 12 weeks drug treatment

	Baseline		Follow-up		*P* value
	Rosuva/Ez group (n=70)	Rosuva group (n=70)	Rosuva/Ez group (n=70)	Rosuva group (n=70)	
hs-CRP (mg/L)	11.57±3.12	11.09±2.78	5.67±1.12	5.93±1.53	0.331
PPAP (mIU/L)	19.32±9.16	20.24±8.73	6.31±2.02	10.21±3.07	0.000

Data were shown as mean ± SD. hs-CRP, high-sensitivity C-reactive protein; PPAP, pregnancy-associated plasma protein A.

Table 5. Safety endpoints

Endpoints	Rosuva/Ez group (n=70)	Rosuva group (n=70)	P
ALT, AST, or both ≥ 3× ULN	1 (1.4)	2 (2.8)	>0.05
Rhabdomyolysis	0 (0)	0 (0)	>0.05
Myopathy	0 (0)	0 (0)	>0.05
Myalgia with creatine kinase elevation ≥ 5× ULN	1 (1.4)	0 (0)	>0.05
Cancer	0 (0)	0 (0)	>0.05

periprocedural MI was significantly further lower in patients who received pre-treatment with statin combined with ezetimibe although statins alone can also exert the similar effect. It has been well demonstrated that periprocedural myocardial injury is associated with a worse long-term clinical outcome [4, 9]. In recent clinical studies, statin pre-treatment administered for at least 3 to 7 days or as a single high loading dose within 24 h before procedure resulted in a substantial reduction in the incidence of periprocedural MI [10, 11]. It has been demonstrated that the potential mechanisms of the cardioprotective effect of the statins are mostly related to their "pleiotropic effects". The pleiotropic effects encompass several mechanisms that include plaque stability, endothelial function, modification of inflammation responses, and thrombus formation. Pesaro et al. demonstrated that the pleiotropic effect of ezetimibe/low-dose simvastatin was more effective than high-dose simvastatin alone in inhibiting platelet aggregation [12]. Westerweel *et al.* demonstrated that treatment with either high-dose statin monotherapy or low-dose statin plus ezetimibe combination therapy has similar effects on reduced endothelial progenitor cell (EPC) levels [13]. This is important as EPCs are the contributor of endothelial regeneration and thereby protect against cardiovascular disease.

Recently the IMPROVE-IT investigators proved that levels of total cholesterol, TC, triglycerides non-HDL-C, apolipoprotein B, and hs-CRP were all significantly lower in the simvastatin/ezetimibe group than in the simvastatin/monotherapy group at 1 year. In previous studies [14] differences in CRP reduction were described between statins and the combination of ezetimibe/statin. In our study the inflammatory markers of CRP were reduced by either treatment strategy but the lack of significant difference between the two groups might be explained by the period of 12 weeks not being long enough to detect some of the anti-inflammatory effects of these treatments. PAPP-A is thought to be released when neovascularization occurs and its level has been shown to be elevated in unstable plaques and in circulation in patients with ACS [15]. PAPP-A has been shown to be a specific activator of IGF-I, a potent mediator of atherosclerosis. Studies in ACS patients have shown that elevated serum PAPP-A is a strong independent predictor of death or recurrent myocardial infarction [16]. Miedema et al. demonstrated that PAPP-A significantly increased in patients with ACS compared with those with stable coronary disease and high-dose atorvastatin significantly decreased PAPP-A at 1 month and hs-CRP at 6 months in patients with verified CAD [17]. Low-dose atorvastatin did not produce this effect. Stulc et al. found that atorvsastatin did not change the circulating PAPP-A levels significantly in patients with hyperlipidemia maybe PAPP-A was expressed in the unstable plaques and involved in the plaque inflammatory responses [18]. In the present study, the levels of PAPP-A were significantly higher at baseline than after the 12-week combination treatment. The reduction in levels of PAPP-A was significantly greater in the dual drug regimen of rosuvastatin with ezetimibe than in rosuvastatin alone. The study has shown that rosuvastatin with ezetimibe also

has a direct impact on the reduction of PAPP-A which is also an inflammatory marker.

There were no significant differences between the two study groups in any of the prespecified safety endpoints or in the rate of discontinuation of study medication owing to adverse events. This convincingly established the safety of combination treatment. According to best practice guidelines high-dose statin treatment before stent implantation may decrease the cardiac adverse events and protect the myocardia, but high-dose statins have raised the risk of elevations in alanine aminotransferase levels or muscle-related adverse events. The combination of low-dose statin and ezetimibe is promising in exerting similar effects as high-dose statins in several fields.

Rosuvastatin in combination with ezetimibe could reduce inflammatory factors and thereby inhibiting the inflammatory response in ACS patients who have undergone PCI and reduce periprocedural myocardial infarction so as to protect the myocardia. Further studies are needed with larger number of patients enrolled and evaluating more factors in this dual drug therapy in ACS patients after PCI.

Disclosure of conflict of interest

None.

Address correspondence to: Xin Wang, Department of Cardiology, 28th Division, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing 100029, P. R. China. Tel: +86-10-64456541; Fax: +86-0-64456541; E-mail: qwangxin45@aliyun.com

References

[1] Lodh M, Goswami B, Parida A, Patra S, Saxena A. Assessment of serum leptin, pregnancy-associated plasma protein A and CRP levels as indicators of plaque vulnerability in patients with acute coronary syndrome. Cardiovascular J Africa 2012; 23: 330-335.

[2] Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. J Intern Med 2008; 264: 295-314.

[3] Blake GJ, Ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. J Am Coll Cardiol 2003; 41 Suppl S: 37S-42S.

[4] Ellis SG, Chew D, Chan A, Whitlow PL, Schneider JP, Topol EJ. Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. Circulation 2002; 106: 1205-1210.

[5] Viigimaa M, Vaverkova H, Farnier M, Averna M, Missault L, Hanson ME, Dong Q, Shah A, Brudi P. Ezetimibe/Simvastatin 10/20 mg versus Rosuvastatin 10 mg in high-risk hypercholesterolemic patients stratified by prior statin treatment potency. Lipids Health Dis 2010; 9: 127.

[6] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372: 2387-2397.

[7] Pearson TA, Ballantyne CM, Veltri E, Shah A, Bird S, Lin J, Rosenberg E, Tershakovec AM. Pooled analyses of effects on C-reactive protein and low density lipoprotein cholesterol in placebo-controlled trials of ezetimibe monotherapy or ezetimibe added to baseline statin therapy. Am J Cardiol 2009; 103: 369-374.

[8] Kalogirou M, Tsimihodimos V, Elisaf M. Pleiotropic effects of ezetimibe: do they really exist? Eur J Pharmacol 2010; 633: 62-70.

[9] Kong TQ, Davidson CJ, Meyers SN, Tauke JT, Parker MA, Bonow RO. Prognostic implication of creatine kinase elevation following elective coronary artery interventions. JAMA 1997; 277: 461-466.

[10] Briguori C, Colombo A, Airoldi F, Violante A, Focaccio A, Balestrieri P, Paolo Elia P, Golia B, Lepore S, Riviezzo G, Scarpato P, Librera M, Bonizzoni E, Ricciardelli B. Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction. Eur Heart J 2004; 25: 1822-1828.

[11] Briguori C, Visconti G, Focaccio A, Golia B, Chieffo A, Castelli A, Mussardo M, Montorfano M, Ricciardelli B, Colombo A. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. J Am Coll Cardiol 2009; 54: 2157-2163.

[12] Pesaro AE, Serrano CV Jr, Fernandes JL, Cavalcanti AB, Campos AH, Martins HS, Maranhão RC, de Lemos JA, Souza HP. Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin. Int J Cardiol 2012; 158: 400-404.

[13] Westerweel PE, Visseren FLJ, Hajer GR, Olijhoek JK, Hoefer IE, de Bree P, Rafii S, Doevendans PA, Verhaar MC. Endothelial progenitor cell levels in obese men with the metabolic

syndrome and the effect of simvastatin monotherapy vs. simvastatin/ezetimibe combination therapy. Eur Heart J 2008; 29: 2808-2817.
[14] Koh KK, Oh PC, Sakuma I, Kim EY, Lee Y, Hayashi T, Han SH, Park YM, Shin EK. Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia. Int J Cardiol 2015; 199: 126-131.
[15] Bayes-Genis A, Conover CA, Overgaard MT, Bailey KR, Christiansen M, Holmes DR Jr, Virmani R, Oxvig C, Schwartz RS. Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. N Engl J Med 2001; 345: 1022-9.
[16] Heeschen C, Dimmeler S, Hamm CW, Fichtscherer S, Simoons ML, Zeiher AM; CAPTURE Study Investigators. Pregnancy-associated plasma protein-A levels in patients with acute coronary syndromes: comparison with markers of systemic inflammation, platelet activation, and myocardial necrosis. J Am Coll Cardiol 2005; 45: 229-37.
[17] Miedema MD, Conover CA, MacDonald H, Harrington SC, Oberg D, Wilson D, Henry TD, Schwartz RS. Pregnancy-associated plasma protein-A elevation in patients with acute coronary syndrome and subsequent atorvastatin therapy. Am J Cardiol 2008; 101: 35-39
[18] Stulc T, Malbohan I, Malík J, Fialová L, Soukupová J, Ceska R. Increased levels of pregnancy-associated plasma protein-A in patients with hypercholesterolemia: The effect of atorvastatin treatment. Am Heart J 2003; 146: e21.