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ORIGINAL ARTICLE

Effects of Combination of Ezetimibe and Rosuvastatin on Coronary Artery Plaque in Patients with Coronary Heart Disease

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Background In approximately 80% of cardiovascular disease-related deaths, patients suffer from coronary atherosclerotic heart disease. Ezetimibe is the first intestinal cholesterol absorption inhibitor. Its combination with statins for treating coronary atherosclerotic heart disease has attracted attention worldwide.

Methods The study group comprised 106 patients with coronary atherosclerotic heart disease and hyperlipidaemia. Each was randomly assigned to one of two groups: (1) Ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night) (n = 55) or (2) Rosuvastatin alone (10 mg, once a night) (n = 51). The primary endpoint was new or recurrent myocardial infarction, unstable angina pectoris, cardiac death, and stroke. Blood lipid, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) levels were measured before treatment and at one, six and 12 months after treatment. Coronary plaque size and compositional changes were determined using intravascular ultrasonography.

Results The combination of ezetimibe plus rosuvastatin decreased total cholesterol, low-density lipoprotein cholesterol, hsCRP, IL-6, and MMP-9 levels at six and 12 months after treatment. Statistical significance was detected between two groups. At 12 months, the plaque burden, plaque cross-sectional area, and percentage of necrotic plaque composition were significantly lower in the combination group than in rosuvastatin alone group ($P < 0.05$). And compared with rosuvastatin alone group, the primary endpoint decreased more effectively in combination group.

Conclusions The combination of ezetimibe and rosuvastatin apparently diminishes lipid levels and plaque burden and improves plaque stability, which may be associated with the potent inhibitory effects of ezetimibe and rosuvastatin on inflammatory cytokines.

Keywords Ezetimibe • Rosuvastatin • Coronary artery plaque • High-sensitivity C-reactive protein • Interleukin-6 • Matrix metalloproteinase-9

Introduction

In approximately 80% of cardiovascular disease-related death, patients suffer from coronary atherosclerotic heart disease [1]. Atherosclerosis is a complicated chronic inflammatory process whose primary essence includes an excessive inflammatory response and lipid accumulation [2]. At present, there are three main approaches to treating coronary atherosclerotic heart disease: drug therapy, percutaneous coronary intervention (PCI), and coronary artery bypass

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grafting. Drug therapy is a basis for all coronary heart disease patients. And it is the first choice for patients with borderline lesions, patients with severe coronary artery stenosis who cannot or are unwilling to undergo intervention, and/or coronary artery bypass grafting. Statins are effective medicine. Statins can effectively stabilise or reverse plaque, improve prognosis, and reduce mortality and morbidity by lowering blood lipid levels and inhibiting the inflammatory response within the already present atherosclerotic plaque [3]. So, in clinic statins are used to lower lipid levels and stabilise plaque for patients with coronary atherosclerotic heart disease. Some patients, however, react badly to the strongest statins even in the maximum doses. In those cases, it is necessary to combine statins with other kinds of lipid-lowering drugs. Ezetimibe is a newly developed lipid-lowering drug that can inhibit intestinal absorption of cholesterol. Its combination with statins for treating coronary atherosclerotic heart disease has attracted attention worldwide.

In this study, patients with borderline lesions and (or) severe coronary atherosclerotic heart disease combined with hyperlipidaemia, who cannot or are unwilling to undergo stenting or coronary artery bypass grafting, were administered a combination of ezetimibe and rosuvastatin or rosuvastatin alone. Intravascular ultrasonography (IVUS) and virtual histology were used to determine the coronary plaque size and compositional changes before and after treatment. This study observed the effects of potent lipid-lowering therapy on coronary lesions and inflammatory factors and analysed the possible mechanisms.

Methods

Subjects

All of the subjects in the study were inpatients at the Department of Cardiology, First Affiliated Hospital, Zhengzhou University, China, from January 2011 to January 2014. Inclusion criteria were that coronary angiography had revealed one or more atherosclerotic lesions near the middle of the coronary arteries; total cholesterol level was $\geq$ 5.2 mmol/L; and (or) low-density lipoprotein (LDL)-cholesterol level was $\geq$ 3.6 mmol/L. The atherosclerotic lesions were borderline lesions and (or) severe coronary atherosclerotic lesions. Borderline lesion was 40-70% stenosis demonstrated by quantitative coronary angiography. Severe lesion was more than 75% stenosis demonstrated by quantitative coronary angiography. Exclusion criteria were (1) contraindications for the intervention; (2) statin use is contraindicated, such as the patient has active hepatitis; (3) high (> two-fold normal) transaminase levels. The patients were randomly divided into two groups: (1) Ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night) (n = 55), paying attention to changes in lifestyle; and (2) Rosuvastatin alone (10 mg, once a night) (n = 51), paying attention to changes in lifestyle. The therapies administered were identical in the two groups. The primary endpoint was new or recurrence myocardial infarction, unstable angina pectoris, cardiac death, stroke. Blood lipid levels, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) were measured before treatment and at one, six, and 12 months after treatment. Coronary angiography and IVUS were conducted again at 12 months after treatment.

Ethics Approval of the Study Protocol

All experimental procedures were approved by the Clinical Trial Ethics Committee of Zhengzhou University (Zhengzhou, China). All patients signed informed consent forms for the interventional examination and treatment (including IVUS) and stated that their participation was voluntary.

Coronary Angiography

Conventional angiography was performed through the radial artery pathway. In case of failure, the right femoral artery was selected. Two experienced interventional cardiologists quantitatively analysed the extent of the coronary artery lesion. Blood vessels more than 2.5 mm in diameter were further examined.

Blood Analysis

All blood samples were obtained after an overnight fast. Serum levels of TC, TG, HDL-C, and LDL-C were measured by standard enzymatic methods in the laboratory of our hospital. High-sensitivity C-reactive protein was measured by immunoturbidimetric assay kit. Interleukin-6 and MMP-9 were measured by ELISA assay kit.

Intravascular Ultrasonography

After coronary angiography, IVUS was performed as follows. The probe (phased array, 20 MHz, 3.2 F) (Eagle Eye; Volcano Corp., San Diego, CA, USA) was placed in the distal end of a stenotic lesion with a coronary guidewire and then moved to the proximal end at a speed of 0.5 mm/s. Grayscale IVUS images and virtual histology–IVUS images (IVUS mainframe: Volcano S5; Volcano Corp.) were continuously recorded on a carved disk, and then analysed by two experienced physicians. Using grayscale IVUS images, some indexes were measured: External elastic membrane area (EEM), minimum lumen area (MLA), plaque cross-sectional area (EEM–MLA), and plaque burden—i.e., area stenosis rate (MLA/EEM $\times$ 100%). Ten consecutive images of most stenotic regions were selected for the above measurement, and the average value was calculated. Using virtual histology–IVUS images, plaque components were categorised into four colours. White represented calcified tissue, red represented the necrotic core, light green represented fat and fibrous tissue, and dark green represented fibrous tissue, which is recorded as the percentage of various components to the total area of the plaque.

Statistical Analysis

All data were analysed using SPSS 13.0 software (SPSS, Chicago, IL, USA). Numerical data were expressed as a rate. Measurement data were expressed as the mean $\pm$ SD. The means of the two groups were compared using an independent sample t-test. The means in a group before and after

Table 1 Clinical data for patients in the two treatment groups.

Item	Ezetimibe + rosuvastatin group	Rosuvastatin group	*P*
Number of patients	50	48	
Number of lesions	87	81	
Age (year, X±*S*)	63±10	65±12	0.371
Gender (male)	36(72%)	35(73%)	0.919
Acute coronary syndrome (%)	28(56%)	27(57%)	0.980
Vascular lesions			
LM/LAD/LCX/RCA	11/33/23/20	9/34/22/16	0.926
Hypertension	25(50%)	23(48%)	0.837
Smoking	31(62%)	29(60%)	0.872
Diabetes	18(36%)	17(35%)	0.952
Critical number of lesions	22(25%)	19(23%)	0.858
Number of severe stenosis lesions	65(75%)	62(77%)	0.858
Medicine			
Nitrate ester	42(84%)	39(81%)	0.719
Antiplatelet	50(100%)	48(100%)	1.000
β-Receptor blocker	39(78%)	35(73%)	0.641
Calcium channel blocker	15(30%)	13(27%)	0.749
Low molecular weight heparin	40(80%)	39(81%)	0.876
ACEI/ARB	18(36%)	16(33%)	0.782
Degree of coronary artery stenosis detected by QCA (%, X±*S*)	72±18	70±19	0.485

QCA: quantitative coronary angiography; LM: left main coronary artery; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

treatment were compared using the paired *t*-test. A value of $P < 0.05$ was considered statistically significant.

Results

Basic Data of the Patients

A total of 106 patients (168 lesions) were included in this study. There were 55 patients in the ezetimibe plus rosuvastatin group and 51 patients in the rosuvastatin group. Clinical data of patients in both groups are shown in Table 1. The baseline characteristics of the patients in the two study groups were well-matched. No significant differences were detected in baseline characteristics between the two groups ($P > 0.05$). In the rosuvastatin group, one patient was withdrawn due to adverse events, one patient was withdrawn because of poor compliance and one patient was lost to follow-up. In the combination of ezetimibe plus rosuvastatin group, two patients were withdrawn due to adverse events, one patient was withdrawn because of poor compliance and two patients were lost to follow-up. The distribution of these patients in the two groups is summarised in Figure 1.

The Primary Endpoint and Major Adverse Events

Compared with the rosuvastatin group, the primary endpoint decreased more effectively in the combination of ezetimibe and rosuvastatin group. There was one patient with new occurrence myocardial infarction and five patients had symptoms of unstable angina pectoris in the rosuvastatin group. But in the combination group, there was no new or recurrent myocardial infarction and two patients had symptoms of unstable angina pectoris ($P < 0.05$). The major adverse events were recorded during 12 months. Adverse events occurred in two groups: One case of abnormality of laboratory value AST or ALT > 3 × ULN; one case of myalgia in the rosuvastatin group; two cases of abnormality of laboratory value AST or ALT > 3 × ULN, one case of myalgia in the ezetimibe plus rosuvastatin group. Two cases of myalgia in the two groups occurred in older patients (Table 2).

Blood Lipid and Inflammatory Cytokine Levels

Fasting venous blood was extracted from patients of both groups in the morning before treatment and at one, six, and 12 months after treatment to detect blood lipid and inflammatory cytokine levels. Total cholesterol, LDL-cholesterol, hsCRP, IL-6, and MMP-9 levels were significantly lower after treatment in both groups compared with the levels before treatment. Moreover, the above noted levels were lower in the ezetimibe plus rosuvastatin group than in the rosuvastatin alone group ($P < 0.05$) (Tables 3, 4).

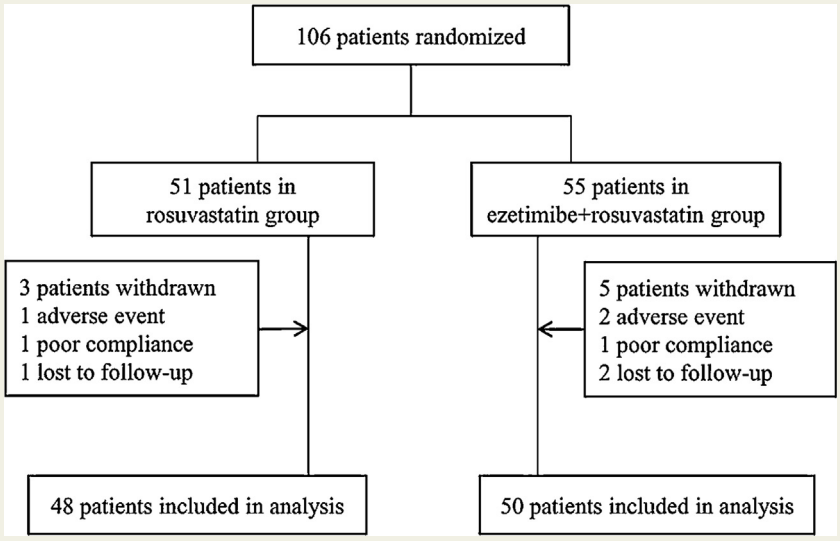

Figure 1 Flow chart of patients in two groups.

Grayscale IVUS Images and Virtual Histology Versus IVUS Images

As displayed in Figure 2 and Table 5, the EEM, MLA, plaque burden, plaque cross-sectional area, and the percentage of necrotic plaque composition were identical in the ezetimibe plus rosuvastatin and rosuvastatin alone groups before treatment, with no significant statistical difference ($P > 0.05$). At 12 months, the plaque burden, plaque cross-sectional area, and the percentage of necrotic plaque composition were significantly diminished in both groups but were lower in the ezetimibe plus rosuvastatin group than in the rosuvastatin alone group ($P < 0.05$). External elastic membrane area and MLA did not alter obviously after treatment (Figure 2, Table 5).

Table 2 **Primary endpoint and major adverse events in the two treatment groups.**

	Ezetimibe + rosuvastatin group	Rosuvastatin group
New myocardial infarction	0(0)	1(2.1)
Recurrent myocardial infarction	0(0)	0(2.1)
Unstable angina pectoris	2(4.0)	5(10.4)
Cardiac death	0(0)	0(0)
Stroke	0(0)	0(0)
Abnormality of laboratory value	2(4.0)	1(2.1)
AST or ALT > 3 × ULN		
Myalgia	1(2.0)	1(2.1)
Creatine kinase (CK) > 5 × ULN	0(0)	0(0)
Rhabdomyolysis	0(0)	0(0)

Discussion

Ezetimibe is the first intestinal cholesterol absorption inhibitor by binding to the Niemann-Pick C1-Like 1 (NPC1L1) protein, which leads to up-regulation of hepatic LDL-C receptors and increases clearance of circulating LDL-C. It mainly blocks exogenous cholesterol absorption, acts on the brush border of the intestinal cells, and inhibits the absorption of cholesterol and plant sterols. It can therefore reduce the supply of cholesterol to the liver, promote liver LDL receptor synthesis, and accelerate LDL metabolism. Numerous studies have confirmed that ezetimibe could reduce intestinal cholesterol absorption by 54–67% [4–6]. Another study verified that in patients treated with statins, whose LDL-cholesterol levels did not reach a normal level or target value, combining the statin with ezetimibe increased the standard-reaching rate, reduced LDL-cholesterol levels, increased high density lipoprotein cholesterol and apoprotein AI, and decreased triglyceride [7].

Statin is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibitor. Because ezetimibe and statins have different lipid-lowering mechanisms of action, this study hoped to combine them to achieve the strongest effects available on lowering lipids and stabilising plaque areas. The ENHANCE study explored the promoting effects of ezetimibe and simvastatin on atherosclerosis regression in patients with hypercholesterolaemia [8]. Its results demonstrated that the combination of ezetimibe and simvastatin obviously reduced LDL-cholesterol levels when compared with simvastatin alone and simultaneously seemed to reduce triglyceride and CRP levels [8]. Recently a new clinical trial

Table 3 Blood lipid levels in the two groups of patients before and after treatment (X±S).

Parameter	n	Total cholesterol (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	Triglyceride (mmol/L)
Ezetimibe + rosuvastatin group					
Pre-treatment	50	5.65±2.47	3.62±1.18	1.13±0.21	1.97±0.67
Post-treatment (month)					
1	50	5.01±0.98	3.05±0.79	1.15±0.28	1.88±0.79
6	50	3.93±0.79*#	1.95±0.61*#	1.23±0.45	1.51±0.25*#
12	50	3.21±0.82*#	1.37±0.83*#	1.26±0.41	1.19±0.32*#
Rosuvastatin group					
Pre-treatment	48	5.58±2.58	3.48±1.26	1.13±0.22	1.90±0.65
Post-treatment (month)					
1	48	5.25.±1.12	3.11±0.86	1.14±0.43	1.87±0.87
6	48	4.36.±1.07*	2.38±0.91*	1.18±0.50	1.83±0.61
12	48	4.02±0.91*	1.85±0.79*	1.30±0.49	1.76±0.38

*$P < 0.05$, *vs* pre-treatment in the same group; #$P < 0.05$, *vs* rosuvastatin group. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 4 Changes in inflammatory cytokines in patients in the two groups before and after treatment (X±S).

Parameter	n	hs-CRP (mg/L)	Interleukin-6 (ng/L)	MMP-9 (mg/L)
Ezetimibe + rosuvastatin group				
Pre-treatment	50	9.35 ±3.21	272.36±20.74	971.63±238.32
Post-treatment (month)				
1	50	5.62±1.71*#	198.21±18.69	684.76±189.54
6	50	3.02±1.65*#	163.81±17.42*#	425.69±135.82*#
12	50	2.04±1.71*#	112.36±14.58*#	210.38±110.75*#
Rosuvastatin group				
Pre-treatment	48	9.43±3.11	281.08±21.25	968.95±241.76
Post-treatment (month)				
1	48	7.18±1.26	236.73.±20.11	779.85±210.58
6	48	4.28±1.72*	192.87.±19.62*	596.42±178.67*
12	48	3.17±1.49*	159.35±17.82*	385.92±131.82*

hs-CRP: high-sensitivity C-reactive protein; MMP: matrix metalloproteinase.

about ezetimibe and statin therapy after acute coronary syndromes (IMPROVE-IT) evaluated whether ezetimibe could lower LDL cholesterol by approximately 24% and result in a significantly lower risk of cardiovascular events than statin monotherapy [9]. The event reduction was consistent with the predicted effects seen with statins, even in the range of low LDL cholesterol levels in this trial, and no offsetting adverse events or toxic effects were observed [9]. And a meta-analysis which evaluated the effect of naturally random allocation to lower LDL-C mediated by polymorphisms in the NPC1L1 gene (target of ezetimibe), the HMGCR gene (target of statins), or both (target of combination therapy) on the risk of CHD confirmed these results [10].

The present study showed that ezetimibe plus rosuvastatin further diminished total cholesterol and LDL-cholesterol, evidently reduced triglyceride levels, and strengthened lipid-lowering effects. No previous clinical report, however, has addressed the effects of ezetimibe plus rosuvastatin on coronary plaque areas. We observed that ezetimibe plus rosuvastatin for lipid lowering could further reduce plaque areas and stabilise plaque properties. The mechanisms may be associated with intensive lipid lowering and potent inhibition of inflammation. Ezetimibe combined with other statins has been shown to lower blood lipids and inflammatory markers. Inflammatory cytokines are involved in the occurrence and development of unstable plaque. A number of

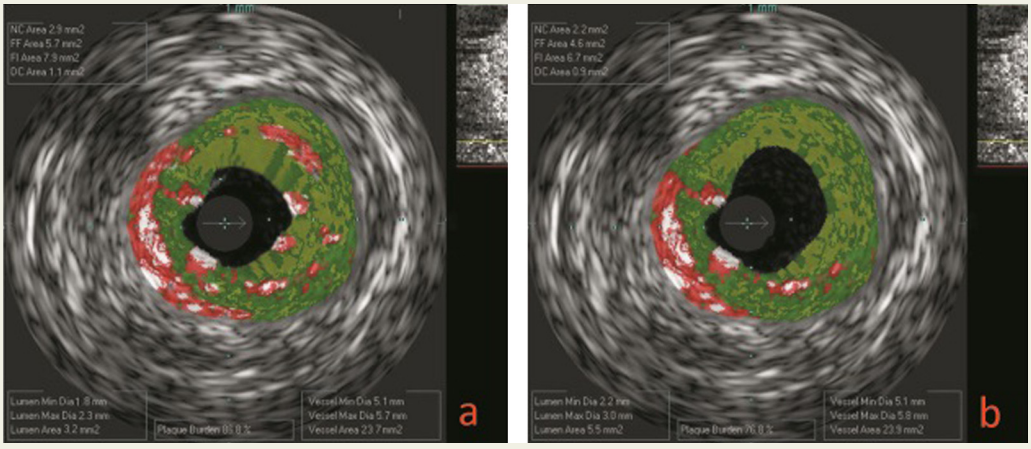

Figure 2 Virtual histology–intravascular ultrasonography images. (a) Image before combined treatment with ezetimibe + rosuvastatin. (b) Image after combined treatment with ezetimibe + rosuvastatin shows evident improvement in the plaque burden and necrotic plaque composition.

Table 5 **Analysis of grayscale IVUS images and virtual histology–IVUS images in the two groups of patients (X±*S*).**

	n	EEM (mm^2)	MLA (mm^2)	Plaque burden (%)	Plaque cross-sectional area (mm^2)	The percentage of necrotic plaque composition(%)
Ezetimibe + rosuvastatin group						
Pre-treatment	50	12.3±3.2	3.1±1.2	73.4±19.8	9.6±3.7	48±10
Post-treatment	50	11.9±3.5	4.0±0.7$^{*\#}$	62.1±7.2$^{*\#}$	5.2±1.4$^{*\#}$	26±5$^{*\#}$
Rosuvastatin group						
Pre-treatment	48	12.2±2.5	3.2±1.3	73.1±19.1	9.8±3.8	46±8
Post-treatment	48	11.3±3.3	3.6±0.6	68.2±8.3*	7.3±1.6*	31±7*

$^{*}P < 0.05$, *vs* pre-treatment in the same group; $^{\#}P < 0.05$, *vs* rosuvastatin group.
IVUS: intravascular ultrasonography; EEM: extravascular elastic membrane area; MLA: minimal lumen area.

studies have indicated that CRP is an independent risk factor for atherosclerotic cardiovascular disease. Interleukin-6 is also inextricably linked with this process, and it is involved in the inflammatory process in unstable plaque. The increased IL-6 concentration shows that plaques are prone to rupture. Matrix metalloproteinases, a group of endopeptidases that are dependent on zinc and calcium ions, can degrade extracellular matrix at neutral pH conditions. Matrix metalloproteinases' activities largely determine the fibrous cap thickness and collagen content. The synthesis and activity of MMP-9 obviously increase in unstable plaque, especially breakable plaque in the shoulder region. Excessive secretion of MMP-9 promotes atherosclerotic plaque rupture by degrading collagen within the fibrous cap [11]. Previous studies [12,13] confirmed that only ezetimibe combined with statins could significantly reduce levels of high-sensitivity CRP. The ENHANCE study found that ezetimibe plus statins could better reduce LDL-cholesterol and CRP levels than the statins alone, having twice the effect of statins alone on reducing CRP levels [8]. These findings are consistent with the results of our study. When LDL-cholesterol is lowered to a certain threshold in the body, ezetimibe reduces inflammatory markers by enhancing the inhibitory effects of statins on CRP in the liver [14].

This study included some patients with critical coronary lesions. Borderline lesions lead to less severe coronary stenosis but cause great damage. Studies have shown that acute coronary syndrome is often not due to coronary artery stenosis but mostly to borderline lesions of unstable plaque. Recently, IVUS and virtual histology–IVUS have been commonly used to assess the coronary atherosclerotic plaque burden and to judge whether it is vulnerable plaque. Many previous studies have observed the effects of statins on plaque and confirmed that statins can inhibit or reverse plaque formation by lowering LDL-cholesterol levels. In the present study, IVUS and virtual histology–IVUS were

utilised to evaluate the effects of the potent lipid-lowering drugs ezetimibe and rosuvastatin on plaque, which is more objective and direct, with a degree of innovation. Results from this study demonstrate that the combination of ezetimibe and rosuvastatin can effectively reduce blood lipid levels and inhibit expression of inflammatory cytokines, significantly reduce the plaque burden, and enhance the stability of the plaque. This study included patients with severe coronary artery disease, a population that often make doctors feel clinically helpless. Patients with severe coronary artery disease cannot undergo coronary stenting or coronary artery bypass grafting. This situation is more common in patients who also have diabetes mellitus. Intensive medical therapy is the first choice for these patients. Among the intensive medical therapies available today, intensive lipid-lowering therapy can provide the greatest benefit. If LDL-cholesterol levels are strictly controlled, an ezetimibe plus rosuvastatin strengthening program can decrease the plaque area and stabilise plaque properties. In this study, combination ezetimibe and rosuvastatin decreased effectively the occurrence of acute coronary syndrome.

Finally, ezetimibe is a new lipid-lowering drug. When combined with statins, they can achieve more-potent lipid-lowering benefits which significantly reduce inflammatory cytokines expression and the plaque burden and improve the stability of the plaque. These results are particularly beneficial for patients with coronary atherosclerotic heart disease. Nevertheless, which statin is best in combination with ezetimibe is still controversial, as is a suitable dose ratio. Nor is there definitive information on the adverse events of combination of ezetimibe and rosuvastatin. Thus, the clinical safety of their combined usage needs further observation.

Conclusion

The combination of ezetimibe and rosuvastatin apparently diminishes lipid levels and plaque burden and improves plaque stability, which may be associated with the potent inhibitory effects of ezetimibe and rosuvastatin on inflammatory cytokines.

Conflict of Interest

None.

Acknowledgements

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