

Effect of Xuezhikang Combined with Rosuvastatin on Lipid Regulation in Patients with Atherosclerotic Cardiovascular Disease: A Real-World Study

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Research

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Abstract

Background Lipid control in atherosclerotic cardiovascular disease(ASCVD)patients has always been a focus, and the combination of lipid-regulating drugs has become a major trend. To evaluate the effects of Xuezhikang combined with rosuvastatin on the degree, time, rate and safety of lipid regulation in ASCVD patients.

Methods ASCVD patients were randomly divided into Xuezhikang group(group A),rosuvastatin group(group B)and combination group(groupC). Plasma total cholesterol, triglyceride, high density lipotein cholesterol and low density lipoprotein cholesterol were measured at various points of observation even the side effects were monitored. Compared carotid intima-media thickness (IMT),Crouse score,

plaque stability before and after treatment and calculated the LDL-C success rate. Use appropriate statistical descriptions and analyses based on data characteristics.

Results Except HDL-C,TC,TG and LDL-C decreased.

There were differences in the regulation of TC and LDL-C among the three groups.The effect of group C on reducing TC was similar to group B and better than group A($P_{A:B}=0.001,P_{A:BC}=0.001,P_{B:C}=0.175$).The effects of reducing LDL-C in group C, group B, and group A decreased successively ($P_{A:B}=0.001,P_{A:BC}=0.001,P_{B:C}=0.014$).After treatment between groups IMT, Crouse score, plaque stability are improved. The time of reaching the standard of LDL-C in the group C was earlier than that in the group A and group B($P_{A:B}=0.824,P_{A:C}=0.030,P_{B:C}=0.011$) and all treatment groups were safe and reliable($p=0.799,p\geq 0.05$).

Conclusion Xuezhikang combined with rosuvastatin can significantly reduce plasma TC,TG and LDL-C in ASCVD patients which shorten the time for plasma LDL-C to reach the standard and improve the success rate with both medication safety and the ability to stabilize plaque. It provides a new choice for the combination of lipid-regulating drugs.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a major global public health problem, which reduces people's quality of life and seriously endangers human health. ¹In recent years, studies have shown that hyperlipidemia, atherosclerosis and hypertension are closely related to the occurrence of cardiovascular and cerebrovascular diseases, especially the increase of serum low-density lipoprotein cholesterol (LDL-C) level is an important risk factor for coronary heart disease. ²Active lipid-lowering intervention measures can effectively reduce the progression of atherosclerosis and the occurrence of cardiovascular events.³ As the cornerstone of the treatment of ASCVD, statins can effectively inhibit the synthesis of cholesterol in vivo but some patients are intolerant of them. When the treatment dose is doubled, the decrease of LDL-C is only about 6%, at the same time the side effects are significantly increased and the benefits are cut down.^{4,5} Xuezhikang Capsule is a Chinese patent medicine fermented from red yeast rice and has the effect of lowering blood lipid.⁶ In addition, many studies have shown that Xuezhikang has apart from lipid regulating effects, such as inhibiting inflammatory reaction, inhibiting endoplasmic reticulum oxidative stress and cell apoptosis, reducing arterial stiffness, improving cardiac and vascular endothelial function, regulating blood glucose and insulin resistance.⁷⁻¹¹ China secondary prevention of coronary heart disease (CCSPS) shows that Xuezhikang can reduce the total risk of death, coronary heart disease mortality and fewer adverse reactions in patients with ASCVD.¹² Rosuvastatin is a medium and high-intensity lipid-lowering drug which is recommended in the guideline. Compared with other statins, rosuvastatin has stronger lipid-lowering effect, and the incidence of adverse events is similar or even less than that of similar drugs.¹³ Studies have shown that statins combined with Xuezhikang can better regulate lipid and improve blood pressure and blood glucose of patients. At present, the concept of cholesterol management has changed and sublimated from "strengthening statins" to "strengthening lipid-lowering". According to the "LDL principle", combined lipid-lowering therapy will be the focus of blood lipid management .¹⁴

Materials And Methods

Research Objects

Approved by the ethics Committee of the hospital (Ethics approval Number: QYFYWZLLZ5800), 80 males and 100 female patients with ASCVD were selected from the Affiliated Hospital of Qingdao University from May 2019 to December 2019, with an average age of (63.49±9.51) years old.

Inclusion criteria

Age 18-79 years old, without gender restriction; In line with the diagnosis of ASCVD disease in 2016 Guidelines for prevention and Treatment of Dyslipidemia in Chinese Adults; No lipid-regulating drugs were used in recent 2 weeks, total cholesterol (TC):4.40-6.47mmol/l (170-250mg/dl);triglyceride (TG)≤4.52mmol/l (400mg/dl);All kinds of chronic diseases were in stable stage without adjusted drug plan;Signed the informed consent form.

Exclusion criteria

Homozygous familial hypercholesterolemia or familial dyslipoproteinemia; Have a history of allergy or serious adverse reactions to statins; Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)≥3 times of normal upper limit (ULN); Creatinine (CREA)≥1.5 times ULN; Patients with uncontrolled severe hypertension;Hypothyroidism;History of alcohol and/or drug abuse;Use other lipid-regulating drugs;Failure to comply with lifestyle changes.

Research Methods

According to the method of random number table, the subjects were randomly divided into Xuezhikang group (group A), rosuvastatin group (group B) and combined medication group (Group C). On the basis of lifestyle change (low salt and low-fat diet, smoking cessation, walking 3-5 times a week, 30 minutes each time, etc.), Xuezhikang group: Xuezhikang 0.3g/capsule, 2 capsules a time, twice a day; Rosuvastatin group: rosuvastatin 10mg/tablet, one tablet each time, once a night; Combined medication group: rosuvastatin 10mg / tablet, half tablet each time, once a night + Xuezhikang Capsule 0.3g/tablet, 2 capsules a time, twice a day, and completed the follow-up for 6 months (Fig. 1).

Determination of blood lipid and other biochemical indexes

Total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-C), high density lipoprotein (HDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CR), urea nitrogen (UA), creatine kinase (CK) and creatine kinase isoenzyme MB (CKMB) were detected by automatic biochemical analyzer before(d0) and after treatment of 1 week(1W), 2 weeks(2W),1 month(1M), 3 months(3M) and 6 months(6M).Determination method: all patients were required to fasting for 8-12 hours, sitting rest for 5 minutes, the biochemical laboratory staff took peripheral blood samples, immediately on the machine test.

Cervical vascular ultrasound examination

Before treatment (d0) and 6 months after treatment (6m), Philips IU22 color doppler ultrasound with 8-12 MHZ linear array probe frequency was used to measure the vertical distance from the inferior intima of the longitudinal long axis section of the far lateral wall to the outer surface of the middle membrane at the initial expansion of bilateral common carotid artery which 10mm from the proximal end.Each side was measured for 3 times, and the bilateral average value was taken as the intima-media thickness (IMT) of the carotid artery(IMT).Atherosclerotic plaque is formed when $IMT \geq 1.2mm$ or the localized intima thickness exceeds 50% of the peripheral intima; $1.0mm \leq IMT < 1.2mm$ indicates intima thickening; $IMT < 1.0mm$ is considered normal. The sum of the maximum thickness of bilateral carotid plaques was crouse score to evaluate the degree of atherosclerosis. Unstable plaques and the number of stable plaques were recorded according to the echo

characteristics of cervical vascular plaques. Unstable plaques included hypoechoic and mixed echogenic plaques, and stable plaques included isoechoic and strong echogenic plaques.

Plasma LDL-C target

According to the 2016 Chinese Guidelines for the Prevention and Treatment of Dyslipidemia in adults, patients with ASCVD belong to the extremely high-risk population, and LDL-C < 1.8mmol/L (70mg/dl) is considered to reach the target; if the baseline LDL-C is high and cannot reach the target value, the LDL-C reduction of $\geq 50\%$ from the baseline is also considered to reach the target value.

Follow-up events

Adverse reactions include flatulence, loss of appetite, nausea, vomiting, abdominal pain, diarrhea, myalgia, fatigue, joint swelling, rhabdomyolysis, elevated transaminase, elevated creatine kinase, sore throat, insomnia, dreaminess and rash, etc.

Statistical methods

All the data were analyzed by SPSS 22.0 software to verify the normality of the data. The measurement data in line with the normal distribution were expressed as mean \pm standard deviation ($\bar{x} \pm s$). For three or more groups of data, analysis of variance was used for homogeneity of variance; LSD-t test was used for comparison between groups with significant difference; paired t test was used for intra group comparison before and after comparison; chi square test was performed for counting data expressed by rate or constituent ratio; repeated measurement data were analyzed by ANOVA of repeated measurement data of general linear model, and univariate analysis was used when spherical test was not obeyed. The correction part of the results was the criterion. The conservative Tukey test was used to reduce the type I error. $P < 0.05$ was considered as the difference.

Results

General information of patients

The study included 186 ASCVD cases, according to random number table method were randomly divided into Xuezhikang group (group A, $n=61$), rosuvastatin group (group B, $n=62$), and combined group (group C, $n=63$). During the follow-up period, 6 patients withdrew from observation, 2 cases (1.08%) had drug intolerance to stop their own medication, 1 case (0.54%) had increased their creatine after taking the Chinese medicine leech powder, and 3 cases (1.61%) had been lost due to the COVID-19. Finally, 180 patients completed the follow-up, 60 cases in each group. There were no significant differences in gender ratio, BMI, age, hypertension, coronary heart disease, cerebrovascular disease and diabetes history among the three groups ($P < 0.05$). The follow-up results of each group were comparable (Table 1).

Blood lipids

Blood lipids were detected before and 1 week, 2 weeks, 1 month, 3 months and 6 months after treatment, the changes of blood lipid at each observation point of the three groups were visible. Except HDL-C, TC, TG, LDL-C showed a downward trend. Analysis of variance of repeated measurement data showed that TG, TC, LDL-C and HDL-C were not subject to Mauchly's spherical test ($P < 0.05$), and the corrected part of Greenhouse-Geisser was the standard, TG ($F = 1.888$, $P = 0.120$), HDL-C ($F = 1.490$, $p = 0.195$, $P > 0.05$), there was no significant difference in the levels of TG and HDL-C in the three groups at the same observation point, and the effects of each group on TG and HDL-C were similar; TC ($F = 41.114$, $P < 0.001$), LDL-C ($F = 14.809$, $P < 0.001$), $P < 0.05$, the levels of TC and LDL-C in the three groups were not equal at the same observation point, and the difference was statistically significant. The comparison between TC groups showed that group A: group B, $P < 0.001$; group A: group C, $P < 0.001$; group B: group C, $P = 0.175$. It can be seen that rosuvastatin group and combined group have the similar effect on reducing TC and are better than Xuezhikang group. LDL-C comparison between

groups showed that group A: group B, $P = 0.001$; group A: group C, $P < 0.001$; group B: group C, $P = 0.014$. Obviously, the effect of combination group, rosuvastatin group and Xuezhikang group on reducing LDL-C in turn decreased (Table 2).

Carotid intima-media thickness and plaque total score

The carotid intima-media thickness of group A, group B and group C decreased from $1.17 \pm 0.17\text{mm}$, $1.18 \pm 0.19\text{mm}$, $1.17 \pm 0.16\text{mm}$ to $1.13 \pm 0.16\text{mm}$, $1.09 \pm 0.18\text{mm}$ and $1.06 \pm 0.14\text{mm}$ before and after treatment, and the total plaque score decreased from 3.63 ± 2.22 , 3.90 ± 3.17 , 4.07 ± 3.25 to 3.28 ± 2.05 , 3.16 ± 2.74 and 3.29 ± 2.73 , respectively, $P < 0.05$, the IMT and crouse scores of the latter groups were improved. The comparison of carotid intima-media thickness of each group showed that group B: group A, $P = 0.003$ ($P < 0.05$); group C: group A, $P < 0.001$; group C: group B, $P = 0.111$ ($P > 0.05$). The combined group and rosuvastatin group had similar improvement effect on IMT and were superior to the Xuezhikang group. The comparison between groups on the total plaque score (crouse score) showed that group B: group A, $P = 0.047$ ($P < 0.05$); group C: group A, $P = 0.027$ ($P < 0.05$); group C: group A, $P = 0.810$ ($P > 0.05$). The effect of combined group and rosuvastatin group in improving IMT was similar and better than Xuezhikang group (Table 3).

Cervical vascular plaque

The cervical vascular stable plaques in group A, Group B and group C before treatment were 118 (54.63%), 137 (60.09%) and 126 (53.85%) respectively, and 141 (65.28%), 166 (72.81%) and 171 (73.08%) respectively after treatment; the unstable plaques were 98 (45.37%), 91 (39.91%), 108 (46.15%) before treatment, and 75 (34.72%), 62 (27.19%) and 63 (26.92%) after treatment respectively. P value of each group before and after treatment were all < 0.05 , the difference was statistically significant, that is, plaque stability could be improved in each group. Among groups, before treatment $X^2 = 2.143$, $P = 0.342$; after treatment $X^2 = 4.163$, $P = 0.125$, $P > 0.05$, the difference was not statistically significant, it can be considered that the ability of plaque stability in each group is equal (Table 3).

Blood lipid success rate and time

The LDL-C level of group A began to reach the standard at 2W after administration, while that of group B and group C gradually reached the standard of LDL-C from 1W after medication. The cumulative number of persons reaching the target at each observation point in Group A was 0 (0.00%), 0 (0.00%), 2 (3.33%), 5 (8.33%), 14 (23.33%) and 19 (31.67%); 0 (0.00%), 2 (3.33%), 9 (15.00%), 15 (25.00%), 30 (50.00%) and 43 (71.67%) in group B; 0 (0.00%), 8 (13.33%), 17 (28.33%), 28 (46.67%), 50 (83.33%) and 56 (93.33%) in group C, respectively (Figure 2). Taking 6M observation point as an example, the success rate of each group was compared, among the groups, $X^2 = 52.012$, $P < 0.001$, the rate is not all the same. Further comparison shown that group A: group B, group A: Group C, $P < 0.001$, group B: group C, $P = 0.002$ ($P < 0.017$), indicating that the LDL-C success rate of group C, group B and group A decreased in turn after 6 months' medication (Table 3). In group A, group B and group C, the time to reach the standard of blood lipid was (96.21 ± 58.75) days, (92.61 ± 65.61) days, (62.07 ± 53.25) days, $F = 4.363$, $P = 0.015$ ($P < 0.05$). Further comparison shown that group A: group B, $P = 0.824$ ($P > 0.05$); group A: Group C, $P = 0.030$ ($P < 0.001$), group B: Group C, $P = 0.011$ ($P < 0.05$). The time for reaching the standard of LDL-C in the treatment groups was earlier than that in the rosuvastatin group and Xuezhikang group. It was not considered that there was difference in the target time between rosuvastatin group and Xuezhikang group in the LDL-C reaching patients in this observation (Table 3).

Adverse reactions

During the treatment, 1 (1.67%) patient had dizziness and headache in group A, 1 (1.67%) patient had fatigue symptoms, and 1 (1.67%) patient presented liver function injury in group B, 1 (1.67%) patient occurred elevated CK/CKMB in group C. There was no statistically significant difference, and the treatment scheme is safe and reliable, no difference among groups (Table 4).

Discussion

Summary

In this study, low-dose rosuvastatin combined with Xuezhikang can significantly reduce the level of blood lipid (except HDL) in patients with ASCVD, shorten the time to reach the standard of LDL-C, increase the success rate, improve arteriosclerosis, stabilize plaque and have safety at the same time.

Strengths and limitations

The main risk factor for atherosclerotic cardiovascular disease is the sustained damage of hypercholesterolemia to the vascular endothelium, and the control of Low-density lipoprotein level is a therapeutic target for ASCVD risk reduction. At present, lipid-regulating methods mainly include diet and exercise control and drug therapy. As a typical representative of lipid-lowering drugs, statins have become the cornerstone of prevention and treatment of cardiovascular diseases. Studies have shown that there is a causal relationship between myalgia, temporary elevation of alanine aminotransferase and new onset diabetes mellitus and the use of statins. The side effects limit the use of statins, especially the use of high-dose statins in special populations.¹⁵⁻¹⁷ Even with good statin treatment compliance, 30–70% of patients still fail to meet the standard LDL-C level according to different risk levels.¹⁸ Short term supplementation of monacolin-K can improve blood lipid and lipid metabolism in patients with low cardiovascular risk and hypercholesterolemia.¹⁹ Therefore, western countries take monascus fermentation extract (such as red yeast rice) and other nutritional preparations as a beneficial supplement of lipid-lowering therapy for people with statin intolerance or high-dose statins, but do not think that nutritional agents can be used as lipid-lowering drugs alone.^{15,20} Xuezhikang is a biological preparation refined from red koji, which is rich in monacolins, especially cholesterol synthase inhibitor (HMC-CoA). Different from western countries, Chinese guidelines for the prevention and treatment of dyslipidemia in adults (2016 revision) include Xuezhikang (1.2 g/d) as a moderate-intensity lipid-regulating drug.

A real-world study is the main advantage of this study, which reduces the influence of some miscellaneous factors in retrospective analysis. Another advantage is reflected in the choice of combined drugs, Xuezhikang is a compound component, ergosterol, unsaturated fatty acids and other components assist in lipid regulation and they also have an impact on improving cardiovascular outcomes, further more, in combination therapy, the dose of rosuvastatin was small with few side effects, which provides a new idea for combined lipid-lowering. The limitations of this study include the following: (1) The small sample size of this study has a certain influence on the extrapolation of the results. (2) The follow-up time of this study is short, and it has some limitations to observe the changes of carotid artery plaque. (3) In the use of drugs, compliance with combination drugs needs to be considered.

Comparison with existing literature

In this study, ASCVD patients after the treatment of Xuezhikang, rosuvastatin, small dose rosuvastatin combined with Xuezhikang for 6 months, TC, TG, LDL-C in each group decreased significantly. The effect of combined group on TC reduction was similar to rosuvastatin group and better than that of Xuezhikang group. There was no significant difference in the effect of TG between the combined group, rosuvastatin group and Xuezhikang group, while the effect of LDL-C was decreased in turn. Different from most previous studies, HDL of ASCVD patients in this study did not increase significantly, and there was no significant difference among the groups. This is similar to Wang TJ, Lien AS, Chen JL, et al. in the randomized clinical study on the treatment of hyperlipidemia patients with red yeast rice (RyR), the HDL did not rise, which may be related to the increase of plasma levels of mir-33a and mir-33b, and the inhibition of cell cholesterol output.^{21,22} In terms of time efficiency, reaching the target time of the combined group was earlier than the other two groups, and there was no significant difference between rosuvastatin group and Xuezhikang group in reaching the standard of LDL-C. The difference in standard reaching time of LDL-C in each group is out of sync with the difference in plasma LDL-C level, which

may be related to the fact that the calculation of the standard reaching time is based on the time node, lack of data continuity, and there may have a bias. In terms of plaque benefit, the effect of combination group and rosuvastatin group in improving IMT and Crouse score were similar and better than Xuezhikang group. Each group could improve the stability of carotid artery plaque, but there was no statistical difference among the three groups. It can be seen that the time of LDL-C reaching the standard was not synchronized with the improvement of IMT, Crouse score and plaque stability, which could not deny the existence of bias and needed to be further verified. Studies have shown that the red yeast rice extract can lower cholesterol levels and increase cardiovascular benefits, but the benefit is not dependent on the initial cholesterol level, and high-dose rosuvastatin can increase the level of ATP binding cassette A1 protein (ATP binding cassette A1 transporter) in macrophages in atherosclerotic plaque, and inhibit the outflow of ATP binding cassette A1 mediated cholesterol from apolipoprotein carrying macrophages.²³ IBIS-4 study, Reversal study, ASTEROID study and SATURN study have showed that the plaque can be reversed when LDL-C decreased to 1.8–2.1 mmol/L (70–80 mg/dl) and HDL increased significantly at the same time during intensive statin treatment. The observation time of these studies ranges from 13 months to 24 months.^{24–27}

The time of ARTMAP study and COSMOS study were relatively short (6–19 months) and the plaque reversion was also achieved under the conventional dose of statins.^{28,29} In addition to LDL-C control and HDL maintenance, plaque improvement may also be related to race. During the treatment, there were adverse reactions in all three groups, mainly liver function damage, followed by CK/CKMB increase, dizziness, headache, fatigue. There was no significant difference in adverse reactions among the three groups. Many studies have shown that Xuezhikang alone or Xuezhikang combined with low-dose rosuvastatin has good tolerance and safety.^{30,31} Combined with this study, it can be further seen that Xuezhikang combined with low dose rosuvastatin does not significantly increase the adverse reactions in patients, which is relatively safe.

Conclusion

In clinical practice, patients who have been treated with statins but still have poor lipid control or other conditions that require combination therapy, Xuezhikang combined with low-dose rosuvastatin is a good option, but the compliance and economic cost of combination therapy need to be further considered.

Abbreviations

TC: Total cholesterol; TG: Triglyceride; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; IMT: Intima-media thickness

Declarations

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Authors' contributions

Conceived: Xuejuan Zhang, Xiaozi Guo. Wrote the paper: Liyan Zhang. Data collection and follow-up: Liyan Zhang, Tong Chen, Lifang Zhang, Zhuyu Xue, Wei Ding. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Approved by ethics Society of the Affiliated Hospital of Qingdao University.

(Ethics approval Number: QYFYWZLLZ5800;Time of approval: April 23, 2019)

Consent for publication

Consent was obtained from the enrolled patients

Competing interests

The authors declare that they have no competing interests.

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Tables

		Group A n=60	Group B n=60	Group C n=60	p
Gender	Male,n(%)	22(36.67)	27(45.00)	31(51.67)	0.253
	female,n(%)	38(63.33)	33(55.00)	29(48.33)	
HP,n(%)		45(75.00)	37(61.67)	46(76.67)	0.139
CHD,n(%)		51(85.00)	46(76.67)	53 (88.33)	0.210
CVD,n(%)		39(65.00)	42(70.00)	40(66.67)	0.838
DM,n(%)		18(30.00)	30(50.00)	26(43.33)	0.077
Smoking,n(%)		24(40.00)	31(51.67)	35(58.33)	0.127
Age(Yr) $\bar{x} \pm s$		64.40±8.47	63.45±9.88	62.63±10.17	0.598
BMI kg/m ²		23.86±2.95	25.12±4.01	24.95±3.09	0.088

Note :HP: Hypertension; CHD: Coronary Heart Disease; CVD: Cerebral Vascular disease; DM: Diabetes Mellitus

Table 2 Changes of blood lipid at each observation point in three groups ($\bar{x} \pm s$, mmol / L)

Group	BL	d0	W1	W2	M1	M3	M6
A	TC	5.27±0.46	4.85±0.54*	4.63±0.55*#	4.38±0.51*#△	4.10±0.49*#△※	3.84±0.44*#△※□
	TG	1.77±0.65	1.52±0.46*	1.28±0.46*#	1.14±0.37*#△	1.07±0.36*#△※	1.00±0.31*#△※□
	LDL-C	3.31±0.43	2.74±0.42*	2.54±0.40*#	2.34±0.39*#△	2.11±0.36*#△※	1.93±0.36*#△※□
	HDL-C	1.39±0.50	1.44±0.33	1.47±0.22	1.50±0.26	1.50±0.25△	1.51±0.23△
B	TC	5.41±0.55	4.59±0.68*	4.20±0.59*#	3.81±0.47*#△	3.46±0.42*#△※	3.13±0.41*#△※□
	TG	1.82±0.91	1.59±0.68*	1.47±0.51*	1.34±0.59*#	1.28±0.53*	1.17±0.52*#△※□
	LDL-C	3.43±0.44	2.57±0.47*	2.31±0.45*#	2.02±0.36*#△	1.80±0.31*#△※	1.62±0.30*#△※□
	HDL-C	1.28±0.42	1.47±0.47*	1.53±0.37*#	1.52±0.33*	1.49±0.29*	1.48±0.28*
C	TC	5.60±0.65	4.36±0.70*	3.92±0.64*#	3.60±0.61*#△	3.35±0.52*#△※	3.05±0.50*#△※□
	TG	1.96±0.97	1.50±0.51*	1.31±0.48*#	1.25±0.40*#△	1.13±0.39*#△	1.02±0.30*
	LDL-C	3.47±0.58	2.51±0.61*	2.16±0.59*#	1.85±0.51*#△	1.48±0.36*#△※	1.35±0.30*#△※□
	HDL-C	1.21±0.33	1.38±0.32*	1.42±0.36*	1.44±0.35*	1.45±0.34*	1.44±0.32*
TC		P _{A:B} □0.001▲		P _{A:C} □0.001▲		P _{B:C} =0.175	
TG		P _{A:B} =0.070		P _{A:C} =0.447		P _{B:C} =0.291	
LDL-C		P _{A:B} =0.001▲		P _{A:C} □0.001▲		P _{B:C} =0.014▲	
HDL-C		P _{A:B} =0.907		P _{A:C} =0.141		P _{B:C} =0.174	

Note: BL:Blood lipids; d0:Before taking medicine; W1,W2,M1,M,M6:1week,2weeks,1month,3 months and 6months after taking the medicine;TC,total cholesterol;TG: triglycerides;HDL-C : High-density lipoprotein-cholesterol;LDL-C:low-density lipoprotein-cholesterol.In the same group, *:compared with d0,P<0.05; #:compared with W1,P<0.05;△:compared with W2 p<0.05; ※:compared with M1,p<0.05;⊠:compared with M3,p<0.05.Comparison between groups,▲:P<0.05.

Table 3:Changes of other indexes in each group						
	Group A	Group B	Group C	P _{B:A}	P _{C:A}	P _{C:B}
IMT $\bar{x} \pm s$,mm						
Pre-therapy	1.17±0.17	1.18±0.19	1.17±0.16			
Post-therapy	1.13±0.16	1.09±0.18	1.06±0.14			
t/P	7.60/0.001*	5.79/0.001*	9.361/0.001*	3.145/0.003*	4.763/0.001*	1.625/0.111
Crouse score $\bar{x} \pm s$,score						
Pre-therapy	3.63±2.22	3.93±3.16	4.07±3.25			
Post-therapy	3.28±2.05	3.16±2.74	3.29±2.73			
t/P	5.59/0.001*	3.97/0.001*	5.947/0.001*	2.026/0.047*	2.267/0.027*	0.241/0.810
Stability of cervical vascular plaque before and after treatment [n(%)]						
Pre-therapy						
Stable plaque	118/54.63	137/60.09	126/53.85	2.143/0.342		
Unstable plaque	98/45.37	91/39.91	108/46.15			
Post-therapy						
Stable plaque	141/65.28	166/72.81	171/73.08	4.163/0.125		
Unstable plaque	75/34.72	62/27.19	63/26.92			
X ² /p	5.100/0.024*	8.272/0.004*	18.660/0.001*			
LDL-C achievement after 6 months' treatment(n)						
Reach standard	19	43	56	19.221/0.001*	48.676/0.001*	9.755/0.002*
Substandard	41	17	4			
The time of reaching the standard of LDL-C($\bar{x} \pm s$, day)						
Time	96.211±58.746	92.605±65.614	62.069±53.246	0.223/0.824	2.197/0.030*	2.581/0.011*
Note:*p<0.05						

Table 4 Comparison of adverse reactions in each treatment group

	Group A N=60	Group B N=60	Group B N=60
Dizziness or Headache n/n%	1 1.67	0 0.00	0 0.00
Nausea or Vomiting n/n%	0 0.00	0 0.00	0 0.00
Bellyache n/n%	0 0.00	0 0.00	0 0.00
Feeble n/n%	0 0.00	1 1.67	0 0.00
Myalgia or increased CK / CKMB n/n%	0 0.00	0 0.00	1 1.67
Impaired liver function n/n%	0 0.00	1 1.67	1 1.67
Total n/n%	1 1.67	2 3.33	2 3.33
X ²	0.488		
p	0.799		

Figures

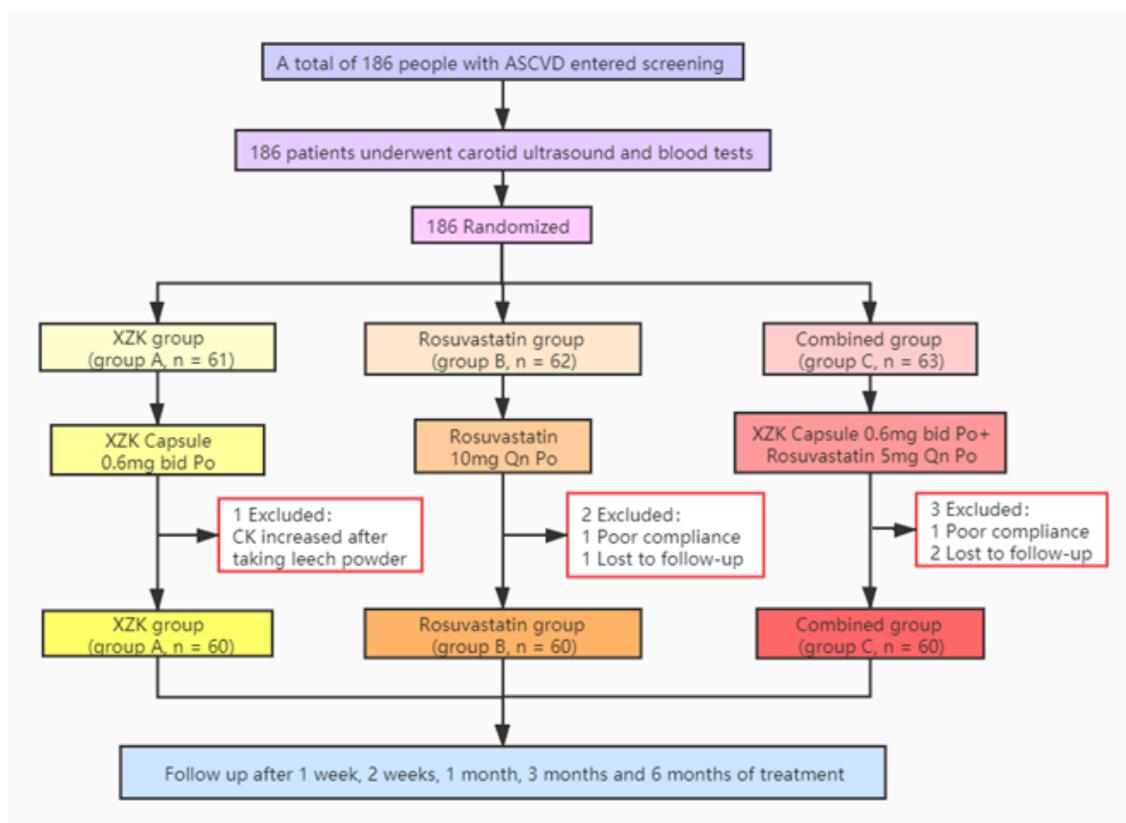


Figure 1

Flowchart of the participants through the trial

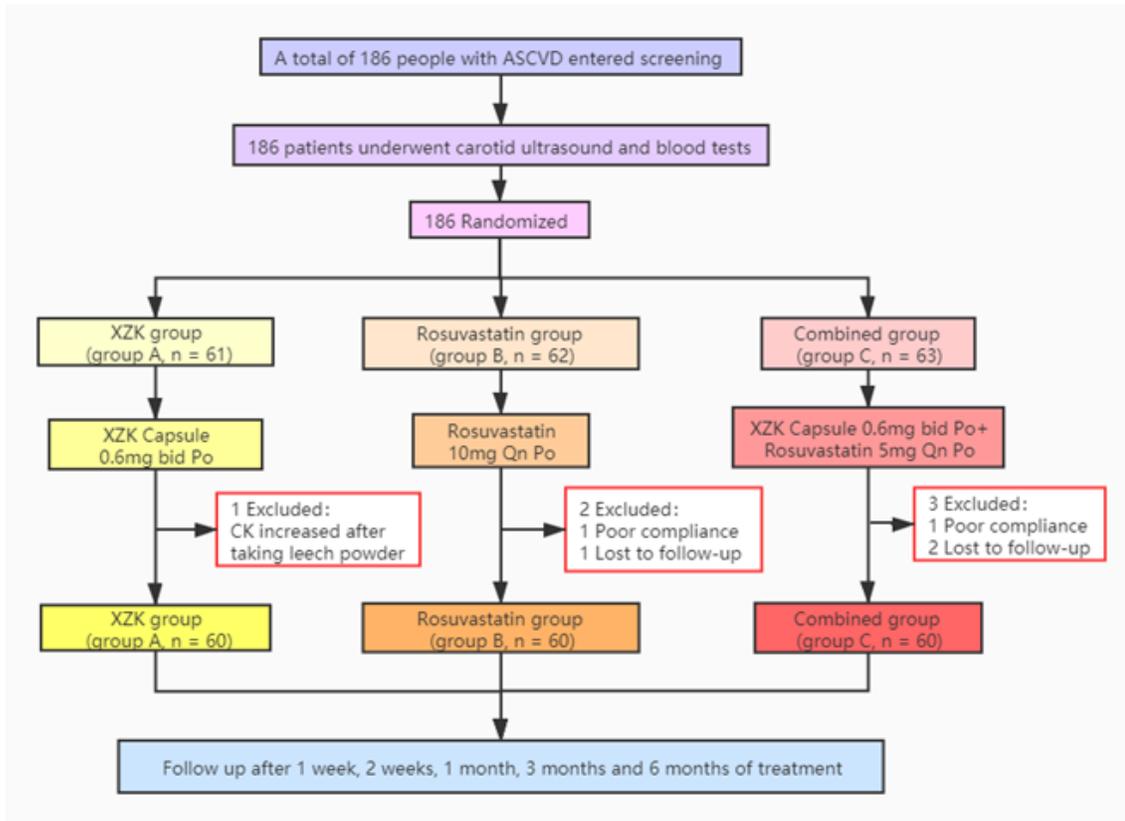


Figure 1

Flowchart of the participants through the trial

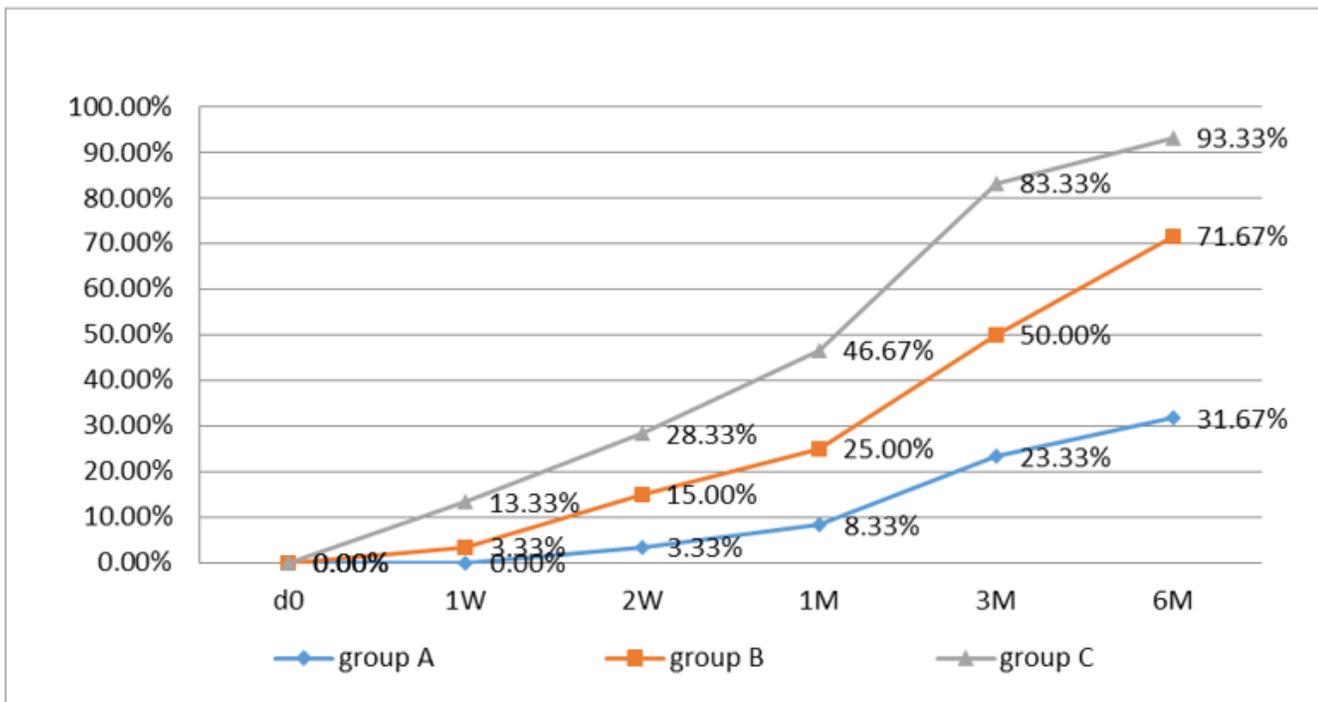


Figure 2

Cumulative LDL-C standard-reaching rate of each observation point in each treatment group

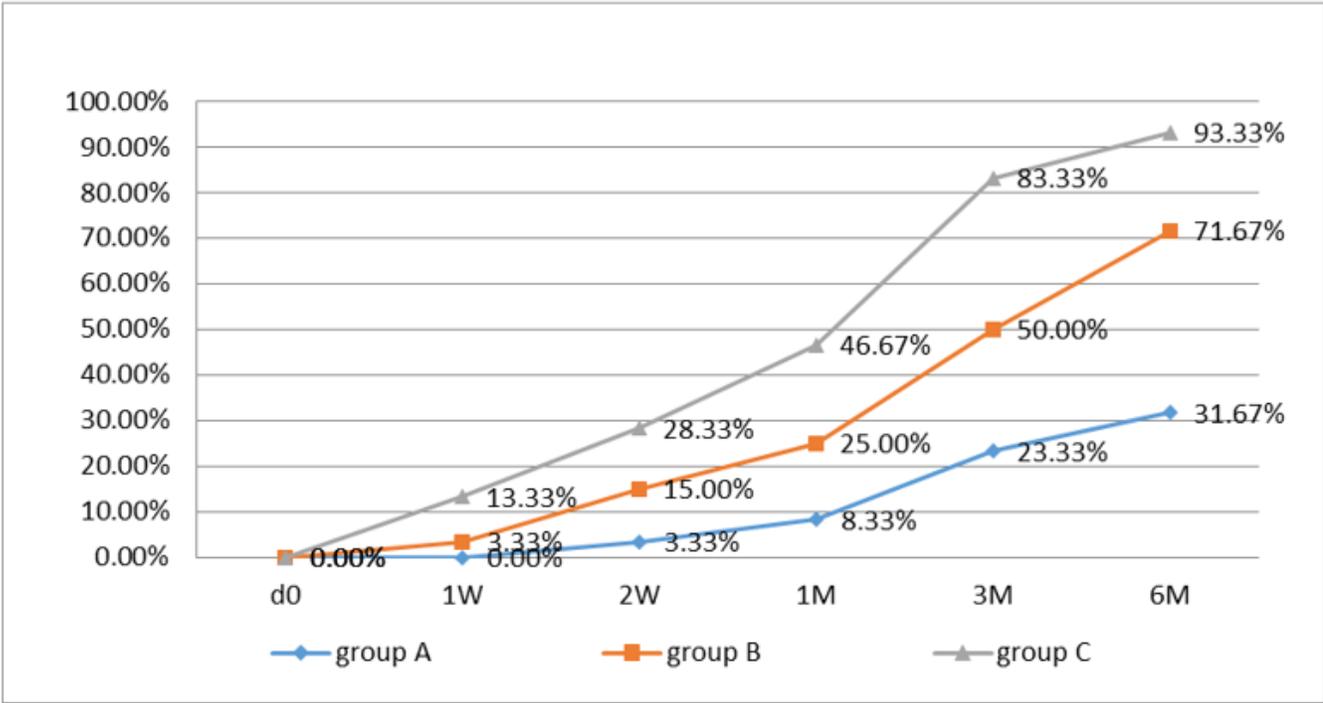


Figure 2

Cumulative LDL-C standard-reaching rate of each observation point in each treatment group