

Original Article



Effect of Rosuvastatin on Coronary Flow Reserve in Hypertensive Patients at Cardiovascular Risk

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OPEN ACCESS

Received: Dec 28, 2020

Revised: Feb 1, 2021

Accepted: Feb 3, 2021

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Funding

This research was supported by a grant from Dong-a ST Cooperation, Seoul, Korea

ABSTRACT

BACKGROUND: It has been unclear whether statin therapy directly improves coronary flow reserve (CFR) in hypertensive patients at cardiovascular risk, independent of lifestyle modification and antihypertensive medications.

METHODS: In this double-blind, randomized controlled trial, we randomly assigned 95 hypertensive patients at cardiovascular risk to receive either rosuvastatin 10 mg or placebo for 12 months, in addition to antihypertensive therapy and lifestyle modification for hypercholesterolemia. Using Doppler echocardiography, coronary flow velocity in the distal left anterior descending artery was measured and CFR was calculated as the ratio of hyperemic to basal averaged peak diastolic flow velocity. The primary end point was change in CFR from baseline to 12 months follow-up.

RESULTS: Low-density lipoprotein-cholesterol was changed from 157 ± 23 to 84 ± 16 mg/dL in the rosuvastatin group ($p < 0.001$) and from 152 ± 19 to 144 ± 22 mg/dL in the control group ($p = 0.041$, but there were no significant differences between the treatment groups in the changes in C-reactive protein, high-density lipoprotein cholesterol, and blood pressures. CFR was changed from 3.03 ± 0.44 to 3.25 ± 0.49 in the rosuvastatin group ($p < 0.001$) and from 3.15 ± 0.54 to 3.17 ± 0.56 in the control group ($p = 0.65$). The primary end point of change in CFR was significantly different between the rosuvastatin group and the control group (0.216 ± 0.279 vs. 0.015 ± 0.217 ; $p < 0.001$).

CONCLUSIONS: Compared with lifestyle modification alone, addition of rosuvastatin significantly improved CFR in hypertensive patients at cardiovascular risk.

Keywords: Coronary circulation; Coronary atherosclerosis; Rosuvastatin; Hypertension

INTRODUCTION

Statin therapy improves coronary flow reserve (CFR) in patients with coronary atherosclerosis.¹⁻³ Statins also decrease the risk of cardiovascular events among hypertensive patients with average levels of serum total cholesterol and intermediate-risk persons without cardiovascular disease.^{4,5} Improvements in CFR may be related to the beneficial effects of statins in such patients, but measurement of CFR was rarely performed in hypertensive patients without coronary artery disease (CAD), because CFR could be invasively

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kang DH; Data curation: Lee S, Kang DH; Formal analysis: Yang Y; Funding acquisition: Kang DH; Investigation: Lee S, Song JM, Kang DH; Methodology: Hwang E, Lee SA, Kang DH; Project administration: Lee SA, Kim DH, Song JM, Kang DH; Resources: Kim DH, Kang DH; Software: Lee SA, Kim DH, Kang DH; Supervision: Kang DH; Visualization: Yang Y; Writing - original draft: Yang Y, Kang DH; Writing - review & editing: Kang DH.

measured using Doppler guide wire in a cardiac catheterization laboratory. Advances in echocardiographic imaging techniques have made it feasible to measure CFR noninvasively, which highly correlates with the CFR measured by invasive means,⁶⁻⁸⁾ and we previously reported that CFR was significantly improved after 12 months of rosuvastatin therapy in a clinical trial of hypertensive patients with cardiovascular risk factors.⁹⁾ However, the absence of a placebo group in our previous trial made it difficult to exclude the possibility that lifestyle modification and antihypertensive medication also played a role in improving CFR.

We hypothesized that the addition of statins to lifestyle modification would improve CFR in hypertensive patients at cardiovascular risk, and tried to examine this hypothesis by comparing the changes in CFR after 1-year treatment with rosuvastatin or placebo in a prospective, double-blinded, randomized trial.

Methods

Study design

The principal investigator designed this placebo-controlled, double-blinded, randomized trial and oversaw the conduct of the trial and data analyses. The study protocol was approved by the Asan Medical Center Institutional Review Board (2015-0610), and all patients provided written informed consent.

Patient selection

Eligibility criteria at screening included an age from 35 to 80 years, controlled hypertension, hypercholesterolemia, and presence of cardiovascular risk factors. Controlled hypertension was defined as treated systolic blood pressure (BP) < 140 mmHg and diastolic BP < 90 mmHg, and hypercholesterolemia was defined as a low-density lipoprotein (LDL) cholesterol \geq 130 mg/dL without receiving statin therapy for > 6 months. Cardiovascular risk factors included smoking, age \geq 55 years (men) or \geq 65 years (women), type 2 diabetes, peripheral arterial disease, previous stroke, premature family history of CAD, or high-density lipoprotein (HDL) cholesterol < 40 mg/dL. Exclusion criteria were current use or medication history of statins within 6 months, history of intolerance to statins, uncontrolled hypertension, secondary hypertension, currently treated angina, previous myocardial infarction, stroke, or transient ischemic attack within the previous 3 months, left ventricular hypertrophy, heart failure, uncontrolled arrhythmia, fasting triglycerides > 500 mg/dL, or concomitant clinically important gastrointestinal, hepatic, renal, hematological, or other disease.

Study procedures

At an initial screening visit, BP was measured by standard procedures and fasting blood samples for total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, and high sensitivity C-reactive protein (CRP) were obtained. Eligibility was determined after each patient underwent a thorough evaluation of BPs, medical records and results of blood test. Patients were randomly assigned in a 1:1 ratio to receive either rosuvastatin (10 mg) or placebo in addition to standard antihypertensive therapy and lifestyle modification for hypercholesterolemia with the use of a computerized randomization system involving concealed study-group assignments. The interactive web response system assigned a randomization number to each patient that linked the patient to a treatment group and specified a unique medication number for study drug to be dispensed. Study medications

were identical in appearance. After randomization, rosuvastatin 10 mg or placebo q.d. was given to study patients and continued for 1 year without further dose titration. Patients were educated about dietary modifications to lower cholesterol and advised to exercise regularly. Follow-up was performed at 2, and 6 months and 1 year, and patients were asked to follow lifestyle modification during the study period and continued taking their antihypertensive medication, which was unchanged during the entire follow-up period. At 1-year follow-up, we collected fasting blood samples and performed echocardiographic follow-up measurement of CFR. Study investigators, responsible pharmacists and patients were masked to treatment allocation for the duration of the trial.

Echocardiographic evaluation was performed at randomization and at the 12-month follow-up. Experienced sonographers who were unaware of the patients' clinical characteristics and treatment assignments, performed a standard 2-dimensional and Doppler echocardiographic examination on all patients using a commercial echocardiography system. Coronary flow velocity was recorded by an experienced sonographer (Hwang) who was also blinded to the patient data. Echocardiographic examinations were performed by placing a high-frequency (5 MHz) transducer at the 4th or 5th intercostal space in the midclavicular line in the left decubitus position. After obtaining the longitudinal cross-section of the lower interventricular sulcus, the distal left anterior descending coronary artery was visualized under the guidance of color flow imaging and the coronary flow velocity was recorded using a pulsed wave Doppler. The diastolic coronary flow velocity was obtained for 5 heart beats at baseline and during the maximum hyperemic period while adenosine was intravenously infused at the rate of 0.14 mg/kg/min. The primary echocardiographic efficacy analyses were done on off-line digital computerized review system by an investigator who was blinded to treatment allocation and previous echocardiographic measures. CFR was calculated as the ratio of hyperemic to basal averaged peak diastolic flow velocity.

End points

The primary end point was change in CFR from baseline to 12 months follow-up. Secondary end points included changes in CRP and LDL cholesterol.

Statistical analysis

We assumed a baseline mean CFR of 3.1 and a common standard deviation of 0.4.⁹⁾ Given these assumptions, we calculated that a sample size of 128 patients randomly assigned to 2 groups, would provide 80% power to detect a difference of 0.2 in the CFR between groups, using a 2-sided *t*-test with an alpha level of 0.05. The null hypothesis was that there would be no between-group difference regarding the change in CFR from baseline to 12-month follow-up. This hypothesis was tested in an intention-to-treat analysis. The primary analysis was prespecified as measurement of a change between baseline and 12-month follow-up, and included all randomized patients who had a baseline and a follow-up assessment, according to the intention-to-treat principle. Baseline clinical and echocardiographic characteristics were compared in the 2 treatment groups with the use of the Student *t*-test or the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables as appropriate. For the primary and secondary end points, we used the *t*-test methods for differences between groups as described in the protocol. All reported *p*-values were 2 sided, and a *p*-value < 0.05 was considered statistically significant.

RESULTS

Between November 2016 and November 2018, we enrolled a total of 95 patients; 46 patients were randomly assigned to receive rosuvastatin and 49 to placebo. While enrollment period of the present trial was extended due to a lower than expected rate of patient recruitment, the major guidelines for management of hypercholesterolemia were revised to recommend statins for patients at cardiovascular risk, independent of their LDL-cholesterol level. On the basis of the revised guidelines, the Institutional Review Board suggested early termination of the trial and investigators decided to stop enrollment in November 2018 and pursue follow-up evaluation of all patients.

The numbers of patients who were randomly assigned to a treatment group and included in the primary analysis are shown in **Figure 1**. The baseline clinical, laboratory, and echocardiographic characteristics of the study patients are listed in **Table 1**. The mean age of the patients was 61.1 ± 8.1 years and 81% were men. Mean total cholesterol and LDL cholesterol was 217 ± 26 mg/dL and 154 ± 21 mg/dL, respectively. Mean systolic BP/diastolic BP was $127 \pm 15/77 \pm 11$ mmHg, and mean CFR at baseline was 3.07 ± 0.49 . An angiotensin receptor blocker or angiotensin-converting enzyme inhibitor had been used in eighty-four patients (88%) and calcium channel blocker used in 60 (63%). There were no significant differences in any baseline characteristics between treatment groups.

Follow-up clinical and echocardiographic examination was performed on 83 patients (87%) and not performed on 12 (13%) who withdrew from therapy. Ten patients withdrew consent and 2 withdrew because of serious adverse event; 1 patient in the rosuvastatin group underwent percutaneous coronary intervention due to development of angina and 1 in the placebo control group underwent direct percutaneous coronary intervention due to acute myocardial infarction.

Hemodynamic, laboratory, and echocardiographic measures at baseline and 12 months follow-up, and changes in measures are shown in **Table 2**. CFR was changed from 3.03 ± 0.44 to 3.25 ± 0.49 in the rosuvastatin group ($p < 0.001$) and from 3.15 ± 0.54 to 3.17 ± 0.56 in the control group ($p = 0.65$) (**Figure 2**). The primary end point of change in CFR was significantly different between the rosuvastatin group and the control group (0.216 ± 0.279 vs. 0.015

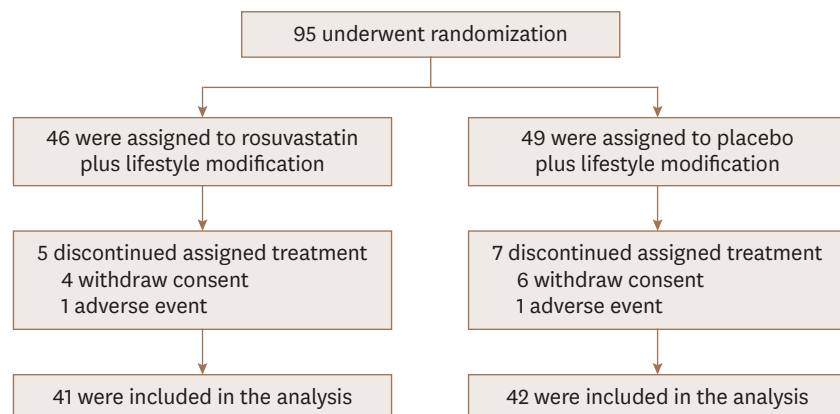


Figure 1. Randomization and follow-up. Of the 95 patients who underwent randomization, 46 were assigned to rosuvastatin group and 49 to the placebo control group; follow-up clinical and echocardiographic examination was not performed on 12 who withdrew from therapy, and 83 were included in the analysis.

Table 1. Baseline clinical, laboratory and echocardiographic characteristics of the study patients

Variables	Rosuvastatin group (n = 46)	Control group (n = 49)
Age (years)	61.2 ± 7.3	61.0 ± 9.0
Male	39 (84.8)	42 (85.7)
Systolic BP (mmHg)	127 ± 15	127 ± 14
Diastolic BP (mmHg)	77 ± 11	77 ± 10
Heart rate (bpm)	68 ± 12	66 ± 11
Antihypertensive medication		
ACE inhibitor	1 (2.2)	1 (2.0)
ARB	40 (87.0)	42 (85.7)
Calcium-channel blocker	30 (65.2)	30 (61.2)
Beta-blocker	4 (8.7)	6 (12.2)
Diuretic	3 (6.5)	3 (6.1)
Laboratory measurements		
Hemoglobin (g/dL)	14.7 ± 1.1	14.5 ± 0.9
Glucose (mg/dL)	106.8 ± 14.7	110.4 ± 16.0
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2
Total cholesterol (mg/dL)	218 ± 26	217 ± 26
LDL cholesterol (mg/dL)	155 ± 23	153 ± 20
HDL cholesterol (mg/dL)	48 ± 10	49 ± 11
Triglycerides (mg/dL)	168 ± 59	183 ± 107
C-reactive protein (mg/L)	0.14 ± 0.17	0.16 ± 0.20
Echocardiographic variables		
LV end-systolic dimension (mm)	30.0 ± 3.4	30.0 ± 4.5
LV end-diastolic dimension (mm)	48.7 ± 4.0	48.7 ± 4.1
LV mass (g)	168.5 ± 29.2	169.5 ± 35.4
Ejection fraction (%)	63.0 ± 2.3	62.0 ± 5.5
E/e' ratio	10.1 ± 2.6	9.5 ± 1.7
Coronary flow velocity (cm/s)		
Baseline	20 ± 5	20 ± 6
Hyperemia	61 ± 17	62 ± 19
Coronary flow reserve	3.03 ± 0.43	3.10 ± 0.54

Values are mean ± standard deviation or number (%)

ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, LV: left ventricle, E: early diastolic mitral inflow velocity, e': early diastolic mitral annular velocity.

± 0.217; $p < 0.001$). LDL-cholesterol was changed from 157 ± 23 to 84 ± 16 mg/dL in the rosuvastatin group ($p < 0.001$) and from 152 ± 19 to 144 ± 22 mg/dL in the control group ($p = 0.041$), and the change in LDL-cholesterol was significantly greater in the rosuvastatin group than in the control group (-73 ± 22 vs. -8 ± 23 mg/dL; $p < 0.001$). The rosuvastatin group also had a significantly greater decrease in triglycerides than the control group (-46 ± 50 vs. -3 ± 100 mg/dL; $p = 0.015$). There were no significant differences between the treatment groups in the changes in CRP ($p = 0.94$), HDL cholesterol ($p = 0.52$), glucose ($p = 0.14$), systolic and diastolic BPs ($p = 0.95$ and 0.98), and left ventricular mass ($p = 0.10$).

DISCUSSION

We found that addition of rosuvastatin to lifestyle modification and antihypertensive medications was associated with improvement of CFR in hypertensive patients with cardiovascular risk factors.

Statin therapy decreases cardiac morbidity and mortality in patients with CAD and hypercholesterolemia via pleiotropic effects of statins, including regression of atheroma and stabilization of atherosclerotic plaques.¹⁻³⁾¹⁰ Improvements in endothelial dysfunction

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Table 2. Hemodynamic, laboratory, and echocardiographic data at baseline, 12 months, and changes between treatment groups

Variables	Baseline			12 months			Change		
	Rosuvastatin (n = 41)	Control (n = 42)	p-value	Rosuvastatin (n = 41)	Control (n = 42)	p-value	Rosuvastatin (n = 41)	Control (n = 42)	p-value
Systolic BP (mmHg)	127 ± 15	127 ± 15	0.853	125 ± 12	125 ± 16	0.911	-1.9 ± 19.5	-2.1 ± 17.9	0.949
Diastolic BP (mmHg)	77 ± 11	77 ± 10	0.928	76 ± 9	76 ± 14	0.957	-0.8 ± 13.6	-0.8 ± 13.1	0.979
Heart rate (bpm)	68 ± 12	66 ± 10	0.348	68 ± 11	64 ± 9	0.155	-0.3 ± 9.4	-1.1 ± 9.1	0.675
Total cholesterol (mg/dL)	220 ± 26	213 ± 23	0.210	140 ± 21	208 ± 27	< 0.001	-80 ± 22	-5.3 ± 16.0	< 0.001
LDL cholesterol (mg/dL)	157 ± 23	152 ± 19	0.256	84 ± 16	144 ± 22	< 0.001	-73 ± 22	-7.6 ± 23.2	< 0.001
HDL cholesterol (mg/dL)	48 ± 9	48 ± 12	0.793	48 ± 9	48 ± 11	0.846	0.5 ± 6.8	-0.6 ± 7.6	0.517
Triglycerides (mg/dL)	172 ± 60	176 ± 102	0.820	125 ± 46	173 ± 93	0.004	-46 ± 50	-3.0 ± 100	0.015
C-reactive protein (mg/L)	0.14 ± 0.17	0.15 ± 0.20	0.833	0.15 ± 0.28	0.15 ± 0.20	0.999	0.01 ± 0.33	0.00 ± 0.29	0.942
Glucose (mg/dL)	106 ± 15	111 ± 17	0.152	113 ± 20	114 ± 21	0.822	7.4 ± 12.0	2.9 ± 14.9	0.142
Creatinine (mg/dL)	0.86 ± 0.15	0.91 ± 0.16	0.189	0.85 ± 0.14	0.89 ± 0.15	0.166	-0.02 ± 0.07	-0.01 ± 0.08	0.982
LV ESD (mm)	30.2 ± 3.5	29.8 ± 4.7	0.614	30.2 ± 6.3	30.0 ± 4.9	0.876	-0.07 ± 5.1	0.19 ± 3.5	0.784
LV EDD (mm)	48.5 ± 4.0	48.6 ± 4.2	0.863	48.6 ± 3.8	48.8 ± 4.5	0.786	0.10 ± 2.2	0.19 ± 2.4	0.856
LV mass (g)	168 ± 30	168 ± 37	0.968	164 ± 31	171 ± 34	0.296	-4 ± 18	3.4 ± 21	0.098
Ejection fraction (%)	63 ± 2	62 ± 6	0.134	63 ± 2	63 ± 3	0.315	0.3 ± 2.5	1.2 ± 5.5	0.329
E/e' ratio	10.2 ± 2.8	9.7 ± 1.7	0.494	9.2 ± 2.5	8.6 ± 2.1	0.458	-1.0 ± 2.6	-1.1 ± 1.9	0.945
Coronary flow reserve	3.03 ± 0.44	3.15 ± 0.54	0.260	3.25 ± 0.49	3.17 ± 0.56	0.501	0.22 ± 0.28	0.02 ± 0.22	< 0.001

Values are mean ± standard deviation.

BP: blood pressure, ESD: end-systolic dimension, EDD: end-diastolic dimension, HDL: high-density lipoprotein, LDL: low-density lipoprotein, LV: left ventricle, E: early diastolic mitral inflow velocity, e': early diastolic mitral annular velocity.

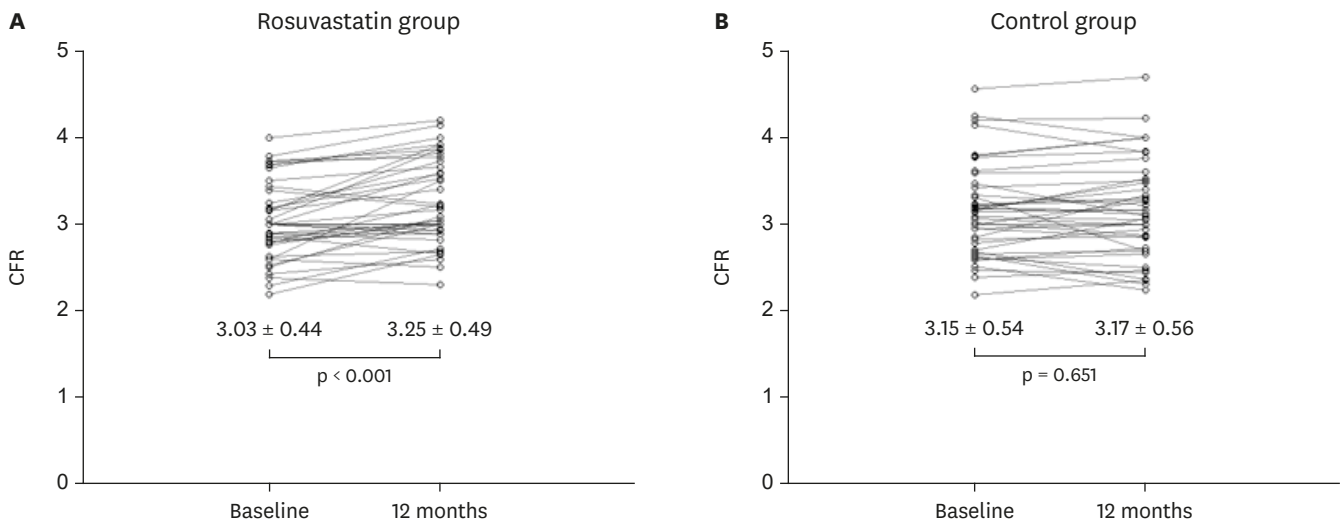


Figure 2. CFR at baseline and after 12 months of treatment with rosuvastatin (A) or placebo (B). CFR: coronary flow reserve.

and CFR may be related to the beneficial effects of statins in hypertensive patients without hypercholesterolemia. Because activation of the renin-angiotensin-aldosterone system and sympathetic nervous system may cause endothelial dysfunction, and hypertensive load results in left ventricular hypertrophy,¹¹⁴³ it is possible that antihypertensive medications may play a role in improving CFR. CFR was significantly improved after 12 months of rosuvastatin therapy in our previous study that enrolled 56 hypertensive patients with cardiovascular risk factors,⁹ but there might be confounding effects of lifestyle modification and antihypertensive medications, and direct effect of statins on CFR could not be assessed in our previous single-arm trial that did not include placebo-control group. Although CFR was not improved significantly in the control group, CFR was significantly improved after 12 months of rosuvastatin therapy in the present study. Because increase in CFR was significantly

greater in the rosuvastatin group than in the control group in a double-blinded, randomized, controlled trial, we suggest that rosuvastatin improves CFR in hypertensive patients at cardiovascular risk, independent of lifestyle modification and antihypertensive medications.

In the Heart Outcomes Prevention Evaluation (HOPE)-3 trial, there was a significant reduction in the risk of cardiovascular event with the use of rosuvastatin at a dose of 10 mg per day in an intermediate-risk population without cardiovascular disease.⁵⁾ The HOPE-3 trial included men 55 years of age or older and women 65 years of age or older who had at least one of cardiovascular risk factors. Because baseline characteristics of our study patients are similar to those of patients enrolled in HOPE-3 trial, effect of rosuvastatin on improvement of CFR demonstrated in the present study, may partly mediate the significant clinical benefits observed in the HOPE-3 trial. Although the same, low dose of rosuvastatin was used, mean reduction of LDL-cholesterol (65 mg/dL) in the present study was greater than mean reduction of 35 mg/dL observed in the HOPE-3 trial. Because statin-naïve patients with a LDL cholesterol \geq 130 mg/dL were enrolled in the present study, such differences in the baseline characteristics and racial or ethnic backgrounds might affect the response to low dose of rosuvastatin.

The limitations of this trial included early termination for safety of patients assigned to the control group, thereby resulting in an underpowered study. We tried to perform follow-up echocardiographic evaluation on all of the 95 patients who underwent randomization, but 12 who withdrew from therapy refused to undergo follow-up assessment and primary analysis included only 83 patients with follow-up echocardiographic measurement of CFR done.

In this double-blind, randomized controlled trial, increase in CFR was significantly greater in the rosuvastatin group than in the control group, and these findings suggest that statin directly improves CFR in hypertensive patients at cardiovascular risk.

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