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Effects of statin on atherosclerosis of ascending aorta in patients undergoing coronary artery bypass grafting

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ABSTRACT

Background: Atherosclerosis is a chronic inflammatory process characterized by thickening and hardening of the vascular walls. In many studies, the effect of statin therapy on atherosclerosis has been investigated. The effect of statins on slowing the atherosclerotic process and its clinical results have been revealed. **Aims and Objective:** The aims of the study was to investigate the protection of statin in the ascending aorta. **Materials and Methods:** The current study examined the presence of atherosclerosis by means of histopathologic evaluation of the tissues which sampled from ascending aorta during the CABG. These two groups of patients were evaluated in terms of the laboratory tests and the presence of atherosclerosis. **Results:** There were 43 male (89.6%), and 5 female (10.4%) patients between 39 and 81 years of age were included in the study. There were no statistically significant difference between the patients' preoperative cardiovascular risk assessments. It was observed that the LDL value of the group using statin was 56 ± 13.66 mg / dl, and the group that did not use was 57 ± 12.97 mg / dl. There were 6 patients (30%) in the statin group and 8 patients (28.6%) in the other group that did not use statin. There were no statistically significant difference in term of atherosclerosis between two groups. **Conclusion:** We evaluated the atherosclerosis of ascending aorta in patients using and not using statin. Even though there were no difference in atherosclerosis in large-scale vascular structures with higher flow rates such as ascending aorta, we think that statin reduces possible aortic pathologies by stabilizing the atherosclerotic plaque and reducing the shear stress.

Key words: Lipoproteins; atheriosclerosis; statins; rosuvastatin

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INTRODUCTION

There are many cardiovascular risk factors (CVRF). The most important of these are diabetes mellitus (DM), smoking, body mass index (BMI), high blood pressure and atherosclerosis.[1] Even if there is no other cardiovascular risk factor or the total risk is low, the number of patients with atherosclerosis who suffers from cardiovascular diseases is still quite high. In middle-age asymptomatic patient groups without other risk factors, atherosclerosis is an important risk factor for coronary artery disease and peripheral vascular diseases.[2,3]

Atherosclerosis is a chronic inflammatory process characterized by thickening and hardening of the vascular walls.[4] Local vascular damage, inflammation and oxidative stress are respectively plays a role in this pathology. Vascular endothelial injury is the first step of the process. After that,

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platelet and leukocyte adhesion and lipid accumulation initiates in the damaged area. These adhesive cells cause endothelial-induced growth factor release and so smooth muscle cell proliferation.[5]

In many studies, the effect of statin therapy on atherosclerosis has been investigated. The effect of statins on slowing the atherosclerotic process and its clinical results have been revealed.[6,7] At the same time, with the moderate or high dose statin therapy, there was a significant decrease in the levels of lipoproteins which cause atherosclerosis, especially low-density lipoprotein cholesterol (LDL-C).[8]

Role of statin on atherosclerosis has been a popular research topic. There are studies investigate this role using intravascular ultrasound (IVUS). In a study where patients with statin therapy has been compared to control group (no statin therapy) with IVUS imaging after emergency PTCA.[9] There is another study that investigates the effects of moderate (20mg) or high (40mg) doses of statin (provastatin / atorvastatin) therapies with patients who have no history of PTCA or non-invasive coronary disease.[10] We have done a histopathologic evaluation on a large-scale artery such as ascending aorta. In our study, we aim to understand the role of statin on atherosclerosis with two groups of patients depending on whether patient uses statin or not.

MATERIALS AND METHODS

Study design

Ethics committee approval for our study was approved from Istanbul University - Cerrahpasa ethics committee in 2019. Informed consent forms were obtained from the patients included in the study. Patients who underwent coronary artery bypass grafting (CABG) between June and August 2019 due to isolated coronary artery disease were evaluated. Elective cases and patients older than 18 years who had statin therapy for a minimum of 6 months were included in the study. On the other hand, patients with full arterial grafting and emergency cases were excluded. Patients using target dose of rosuvastatin (LDL <70mg / dl) due to hyperlipidemia and patients with no history of hyperlipidemia who also have a level of LDL <70 mg/dL were divided into two groups with very high-risk group. According to "2019 ESC / EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk"; Patients with ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures) were considered as very high risk.[11] We examined the presence of atherosclerosis by means of histopathologic evaluation of the tissues, which sampled from ascending aorta during the CABG. In this study, we separated two groups of patients with CABG, whether using statins or not. These two groups of patients were evaluated in terms of the laboratory tests, biomarkers and most importantly the presence of atherosclerosis.

Ascending aorta tissue sampling

The proximal anastomoses of saphenous vein grafts are performed on the aorta while coronary artery bypass grafting (CABG). We must prefer a region for anastomoses after manual examining of the presence or absence of hard plaque in the aortic tissue. While aortic side or cross clamping during the CABG, a small incision was made on the aorta using No: 11 scalpel. After that, aortic tissue samples were taken by using aortic punch (Aortic Punch size: 4.0mm).

Pathology evaluation

The aortic tissue samples stored with gluteraldehyde solutions under sterile conditions and taken to the pathology laboratory. Tissue samples were processed by routine clinical laboratory methods, being fixed in 10% formaldehyde and embedded in paraffin wax. Tissue sections were cut, using a microtome, at 5 micrometer thickness, placed onto glass slides, and the sections were stained with hematoxylin and eosin (H&E) and examined under the light microscope. Histochemical evaluation was done with orcein.

Vascular atherosclerosis was classified as AHA lesion type I, II, III, IV, V or VI plaques by two independent reviewers blinded to histopathology[12] (Figure 1; Table 1). In histopathologic examination, the evaluation of type 3,4,5 and 6 was considered significant in terms of atherosclerosis in our study and was selected into atherosclerosis group.

Statistical analysis

SPSS v21.0 and Microsoft Office Excel 2016 were used for data collection and analysis. Categorical variables are

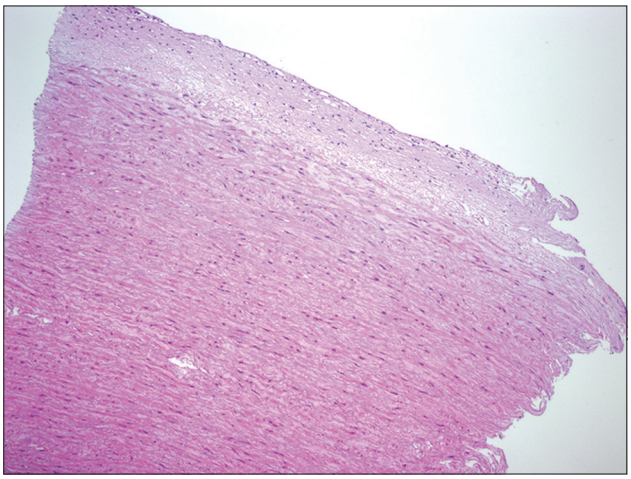

Figure 1: Foam histiocyts in intima

Table 1: Atherosclerotic lesions in histological classification (appearance with the eyes)[10]

Type 1	Initial lesion (isolated macrophage foam cells)
Type 2a	Type prone to progression of atherosclerosis (mainly intracellular lipid accumulation)
Type 2b	Type resistant to progression of atherosclerosis
Type 3	Pre-Atheroma (type 2+small extracellular lipids pool)
Type 4	Atheroma (type 2+core of extracellular lipid)
Type 5a	Fibro atheroma (lipid core+fibrotic layer or multiple lipid core)
Type 5b	Calcific lesion (fibrotic layer, mainly calcific)
Type 5c	Fibrotic lesion (fibrotic layer, mainly fibrotic)
Type 6	Lesion with surface defect, and/or hematoma-hemorrhage, and/or thrombotic deposit (surface defect, hematoma-hemorrhage, thrombus)

expressed in frequency (n) and percentage (%), while continuous variables were expressed as mean ± standard deviation and median (smallest-largest value). The suitability of the data to normal distribution was evaluated by the coefficient of variation, histogram curves and Shapiro Wilk Test. While chi-square test and fisher's exact test are used to evaluate the difference between groups for categorical variables; Independent groups t test was used if normal distribution conditions were provided in evaluating the difference between two independent groups for continuous variables. In cases where normal distribution conditions are not met, Mann Whitney U test was used. Statistical significance value was taken as $p < 0.05$ in the analyzes.

RESULTS

There were 48 cases in our study. All of these patients had an elective isolated CABG. All of the subjects were in the high-risk patient group according to the 2019 ESC / EAS dyslipidemia guidelines for the management of dyslipidemias. 43 male (89.6%), and 5 female (10.4%) patients between 39 and 81 years of age were included in the study. No significant difference was observed between the patients' preoperative cardiovascular risk assessments. Even there was no significant difference in preoperative echocardiography (ascending aorta diameter, ejection fraction). Preoperative biomarkers were examined in all patients. WBC and neutrophil values were statistically significant between two groups. We only included patients with the LDL value <70 mg / dl. It was observed that the LDL value of the group using statin was 56 ± 13.66 mg / dl, and the group that did not use was 57 ± 12.97 mg / dl (no statistically difference). When it comes to comparing the number of grafted vessels in CABG, it was 3.39 ± 1.03 in the no-statin group and 2.85 ± 0.59 in the statin group. It was found statistically significant (p: 0.037; Table 2).

Aortic tissue samples were examined histopathologically. The findings of extracellular fat cells (atheroma plaque) in aortic tissue were evaluated as atheroma. In total, 14 patients had atheroma plaque. Among these, there were 6 patients (30%) in the statin group and 8 patients (28.6%) in the other group that did not use statin. There were no statistically significant difference in term of atherosclerosis between two groups. However, after the histopathological evaluation of each individual samples, we have not found any type Vb, Vc or VI (Table 3).

After histopathological examination, it was observed that there were various levels of atherosclerotic lesions in all groups. However, when it comes to subgroup examination of atherosclerosis, 18 patients (37.5%) were evaluated as Type I, 16 patients (33.3%) as Type II, 10 patients (20.8%) as Type III, and 4 patients (8.3%) as Type IV. No statistically significant difference was found in either group (Table 4).

DISCUSSION

In this study, we evaluated atherosclerosis in ascending aorta with two groups of patients who were divided according to whether the patient uses statin or not. It is known that statin reduces cardiac mortality, as observed in many studies. Studies have also observed in which atherosclerosis were evaluated with computed tomography (CT) and intravascular ultrasound (IVUS). However, in this study, we aim to demonstrate the effect of statin by evaluating the atherosclerosis histopathologically in a large-scale artery such as an ascending aorta.

In the study of Hattori et al,[13] the effect of pitavastatin treatment on plaque character was evaluated with IVUS during the 9 months follow-up. LDL-C value was 134 ± 40mg / dl in the pitavastatin group and 122 ± 25mg / dl in the diet-only group. After 9 months, the LDL-C value in the pitavastatin group was 89 ± 23mg / dl and 121 ± 30mg / dl in the diet-only group. The decrease in the pitavastatin group was statistically significant (P: 0.001). HDL-C value was 46 ± 11mg / dl in the pitavastatin group and 59 ± 16mg / dl in the diet-only group. After 9 months, it was 58 ± 16mg / dl in the pitavastatin group and 53 ± 14mg / dl in the diet- only group. The increase in HDL-C in the pitavastatin group was also statistically significant (p.0004). When the patients were evaluated with IVUS, it was observed that the ratio of plaque volume index (PVI) to vascular volume index (VVI) decreased from 48.5 ± 10.4% to 42.0 ± 11.1% in the pitavastatin group (P:0.33). However, it increased from 48.7 ± 10.4% to 50.4 ± 11.8% in the diet-only group (p: 0.670). This decline in the pitavastatin group was statistically significant. In our study, while the LDL value was 56 ± 13.66 mg / dl in the statin

Table 2: Baseline characteristics and laboratory tests of study population

Characteristic	All patients	No Statin (n: 28)	Statin (n: 20)	p value
	Mean±STD	Mean±STD	Mean±STD	
Age	63.33±9.63	64.18±10.51	62.15±8.36	0.478*
	65 (39-83)	65 (39-83)	61.5 (47-77)	
Ejection Fraction(%)	53.27±8.42	54.43±9.2	51.65±7.09	0.059‡
Ascending Aorta (mm)	35.27±3.85	35.75±3.61	34.6±4.16	0.312*
Sinus Valsalva (mm)	34.83±2.64	35.32±2.42	34.15±2.83	0.130*
Vessels in CABG	3.17±0.91	3.39±1.03	2.85±0.59	0.037‡
BMI (kg/m^2)	27.05±4.3	26.91±4.95	27.28±3.3	0,653
Biomarkers (pre-op)				
RBC	4.51±0.47	4.52±0.48	4.48±0.47	0.790*
WBC	8.23±2.31	8.93±2.42	7.25±1.76	0.013‡
Lymphocyte	2.05±0.89	2.28±1.05	1.74±0.47	0.061‡
Neutrophils	5.34±2.06	5.92±2.13	4.52±1.68	0.015‡
Hematocrit	38.24±3.95	38.48±4.0	37.9±3.97	0.623*
Platalets	220.69±66.76	228.39±67.4	209.9±66.03	0.350*
BUN	16.58±4.86	16.04±5.35	17.35±4.08	0.15‡
Creatinin	0.91±0.25	0.86±0.18	0.98±0.32	0.3‡
ALT	30.58±28.13	28.71±29.96	33.2±25.88	0.396‡
AST	26.23±17.62	26.46±19.79	25.9±14.53	0.875‡
TSH	1.85±1.63	1.46±0.61	2.39±2.34	0.188‡
Free T3	3.04±0.45	2.97±0.3	3.14±0.6	0.271*
Fasting glucose	139.6±58.28	153.04±69.77	120.8±29.1	0.161‡
Total Cholesterol	169.19±39.98	176.04±42.88	159.6±34.28	0.163*
HDL-C	42.54±13.12	43.79±15.67	40.8±8.47	0.754‡
LDL-C	56±13.66	57±12.97	56±13.66	0.593‡
Triglycerides	148±77.14	153.21±88.9	140.7±58.26	0.754‡

*: Independent Groups t test ‡: Mann-Whitney U Test
RBC: Red Blood Cells, WBC: White Blood Cells, BMI: body mass index, HDL-C: High-density lipoprotein-Cholesterol, LDL-C: Low-density lipoprotein-Cholesterol, TSH: Thyroid-stimulating hormone

Table 3: Comparison in terms of atheroma plaque

Features	All groups	No Statin (n: 28)	Statin (n: 20)	p value
Atheroma plaque				
Yes (+)	34(%70.8)	20(%71.4)	14(%70)	0.915*
No (-)	14(%29.2)	8(%28.6)	6(%30)	

*: Chi-Square Test

Table 4: Histopathological classification of atherosclerosis in patients with statin and no statin use

	No Statin (n=28)	Statin (n=20)	%
Tip I (foam cells)	10 (35,7%)	8 (40%)	37.5
Tip II (intracellular lipid accumulation)	10 (35,7%)	6 (30%)	33.3
Tip III (pre-aterom)	6 (21.4%)	4 (20%)	20.8
Tip IV (aterom)	2 (7,2%)	2 (10%)	8.4
Tip V (fibroaterom	-	-	

group, it was 57 ± 12.97 mg/ dl in the patients without statin. No statistically significant difference was observed among the two groups. Six patients from statin group and 8 patients from non-statin group had atheroma plaques and but the differences was statistically not significant.

Kitagawa et al,[14] has evaluated the statin effect on non-calcific coronary plate with CT. They had 3 groups of patients: 64 patients with no-statin, 26 patients with moderate statin treatment (10-20mg pravastatin), 24 patients with intensive statins treatment (10-20mg atorvastatin). LDL-C value was 93.3 ± 17.9mg / dl in the intensive statin group, 115.2 ± 29.6mg / dl in the moderate statin group, and 124.4 ± 33.5mg / dl in the non-statin group. Although the difference between three groups was statistically significant, there were no significant difference in terms of the location of the plaque in the coronary artery. They also evaluated the density of plaque with CT and there was a statistically significant difference between the intensive statin and the no-statin group. However, there were no statistically significant difference between the moderate statin and no-statin group. In our study, there were no significant difference in terms of LDL-C values since we only included patients with LDL-C value below 100mg / dl. We also standardized the statin dose as 40mg rosuvastatin.

In the study of Adams et al,[15] while 1000 patients were using statin, 5700 patients were not. When the BMI of these two groups was compared, the group using statin was 28.9 kg / m2, and it was 28.2 kg / m2 in the other group. The LDL-C value was 104 mg / dl in the group using statin and 120 mg / dl in the other. Both results were statistically significant. In our study, BMI was 27.28 ± 3.3 kg / m2 in

patients using statin and 26.91 ± 4.9 kg / m2 in patients not using statin. There was also no significant difference between the LDL-C value because we have designed this study with patients who have LDL-C values below 70 mg/dl at the start with.

In the study of Zeb et al,[16] patients using statin (n = 60) and patients not using (n = 40) were followed-up for 406 ± 92 days. They were evaluated with coronary CT and evaluated in term of non-calcific plaque and low attenuation plaque. While the LDL-C value was 97.2 ± 30.6 mg / dl in the non-statin group, it was 99.1 ± 33.5 mg / dl in the statin group. However, when the plaque changes were taken into consideration, non-calcific plaque area had decreased (-47.7 ± 71.9 mm^3) in the statin group, while it was 13.8 ± 76.6 mm3 in the no-statin group. They also evaluated the low attenuation plaque areas that it was 5.9 ± 23.1 mm3 in the group using statin, while it had decreased (-12.2 ± 19.2 mm^3) in the no-statin group. The difference in these two parameters were statistically significant. In our study, considering the region that was sampled, there were no difference between the two groups in terms of any plaque formation by palpation. When histopathological images of the patients were evaluated individually, there were no type Vb, Vc, VI in both groups. The most important reason for this is that we prefer the region for anastomoses after manual examining of the presence or absence of hard plaque in the aortic tissue.

Shin et al.[17] divided the patients with coronary artery lesions into two groups as patients using simvastatin (n=24) and rosuvastatin (n=24). They evaluated the atherosclerotic plaques by using IVUS after 1 year. There was a significant decrease in LDL-C values in both groups after 1-year follow-up (from 100.0 ± 41.5mg / dl to 57.0 ± 21.2 mg / dl). After IVUS evaluation, it was observed that fibrosis plaque had volume decreased from 41.1 ± 23.6 mm3 to 23.8 ± 12.2 mm3 and fibro fatty volume had also decreased from 5.7 ± 4.3 mm3 to 2.1 ± 2.2 mm3 in the simvastatin group. On the other hand, in the Rosuvastatin group, the fibrosis plaque volume had decreased from 33.0 ± 13.0 mm3 to 24.2 ± 11.4 mm3, and the fibro fatty volume from 4.6 ± 3.3 mm^3 to 2.4 ± 1.8mm^3. These decreases in both groups are statistically significant. In our study, all patients used rosuvastatin for a minimum of 6 months. In the no-statin group foamy cells were presented in 10 patients, and also in 6 patients in the statin group. The number of patients with atheroma were 2 in each groups. Fibro atheroma was not presented in both groups. It was thought that taking the tissue samples from a relatively soft areas, as it required in the CABG, may hide the real plaque burden.

In the study of Saremi et al,[18] patients with type 2 diabetes were followed up for 5 years and coronary artery calcification (CAC) and abdominal aortic calcification were evaluated by CT for patients who continued to use statin during this period and those who did not receive statin or whose dose was reduced. At the end of the study, CAC had decreased from 7.9 ± 0.8 to 3.5 ± 1.0mm3, and this decrease was found to be statistically significant. Calcification in the abdominal aorta had also decreased from 11.9 ± 1.3 to 7.6 ± 1.6, but it was not statistically significant. In our study, there were 6 patients with pre-atheroma or atheroma plaques on ascending aorta in the group who used statin, and 6 patients in the group that did not. Although it seems to be low in number, it was not statistically significant.

van Meij et al.[19] evaluated 63 patients with statin (20mg / 40mg) and abdominal aortic aneurysm (AAA). Patients who used statin for at least 6 weeks before surgery were included in the study. Abdominal aortic diameters were measured as 63 ± 12mm in the patient group (n = 25) who did not use statin, 61 ± 10mm in the group using 20mg statin (n = 28) and 55 ± 9mm in the group using 40mg statin (n = 10). These results were not statistically significant. The effects of statins on AAA progression has been investigated but no significant effect has been revealed (p: 0.337). In our study, ascending aortic aneurysm was 35.75 ± 3.61mm in the group that did not use statin, while it was 34.6 ± 4.16mm in the group using statin (p: 0.312). When we compared the sinus valsalva diameters, it was 35.32 ± 2.42mm in no-statin group while it was 34.15 ± 2.83mm in the statin group (p: 0.130). Similarly, there were no significant effect observed in our study.

In a study with 91 patients, the relationship between LDL-C values and the diameter of the ascending aorta was investigated.[20] In this study, diameter of ascending aorta was measured as 40.5 ± 7.3 mm. In our study it was measured as 34.6 ± 4.16mm in the group using statin, while it was 35.32 ± 2.42 mm in the no-statin but they were statistically not significant.

In the ASTEROID study,[21] patients with coronary artery disease were given rosuvastatin treatment at 40mg / day, and patients were evaluated by IVUS at the end of 2 years. It was observed that the stenosis rate decreased from 37.3 ± 8.4% to 36.0 ± 10.1%. In our study, no significant difference was found between the statin and no-statin group. The reason for this can be the LDL-C values of all patients included in our study were below 100mg/dl.

Youn et al. examined the carotid intima media layers thickness in 1700 subjects and it appeared to be associated with increased body mass index (BMI) and high LDL-C cholesterol in healthy individuals.[22] The LDL-C value was 113.1 ± 31.9 in the male patients and 117.3 ± 32.2

in the female. In our study, LDL-C mean ± std value was 80±13.66 in the statin group and 81.89±13.02mg in the no-statin group. No statistically significant difference was found between both LDL-C and BMI values and presence of atherosclerosis (p: 0.221). The reason for this can be that Youn et al. have studied on relatively smaller vessels however we have sampled from aorta and all patients in our study has LDL-C values below 70 mg/dl.

In a study with 1779 subjects by Fernández-Friera et al,[23] (PESA Study), patients were examined by doppler USG or CT. More than 0.5 mm thickening in the intima media or 1.5 mm intima thickness towards the lumen in the carotid arteries or infrarenal aorta was considered as atherosclerosis. BMI was 24.5 ± 3.3 kg/m^2 in the non-atherosclerosis group and 25.3 ± 3.4 kg/m^2 in the group with atherosclerosis. There were no statistical difference. Total cholesterol values were 187.0 ± 24.4 mg/dl in the non-atherosclerosis group and 194.6 ± 22.9 mg/dl in the group with atherosclerosis. The LDL-C was 125.7 ± 20.1 mg/dl versus 117.4 ± 21.7 mg/dl. The HDL-C value was 53.5 ± 10.1 mg/dl versus 55.4 ± 10.6 mg/dl. The triglyceride was 63 (50–83) mg/dl versus 68 (53–92) mg/dl. In our study, the triglyceride was 140.7±58.26 mg/dl in the statin group, while it was 153.21±88.9 mg/dl in the no-statin group. Total cholesterol was 159.6±34.28 mg/dl versus 176.04±42.88 mg/dl. Although it was numerically low, there were no statistically significant difference. HDL-C value was 40.8 ± 8.47mg/dl in the group using statin, while it was 43.79 ± 15.67mg/dl in no-statin group. In our study, there were no statistically significant difference between the lipid profiles.

This study has several limitations; the fact that it was performed in a relatively small number of patients and that the ascending aorta was sampled from the plate-free area in accordance with the CABG procedure requirements. Therefore, since this region was avoided in the presence of relatively hard plaques, the plaque volumes may be considered less then it could have been. In addition, while selecting our patients, we ended up chosen the group of patients with relatively low atherosclerosis burden by including patients with the LDL-C value below <70mg/dl.

CONCLUSION

This study evaluated the atherosclerosis of ascending aorta in patients using and without statin, various levels of atherosclerosis were observed in all patient groups. No significant difference was observed between the patient groups with pre-atheroma and atheroma. Even though there were no difference in atherosclerosis (histopathologically significant) in large-scale vascular structures with higher flow rates such as ascending aorta. The anti-lipid effect should be investigated in small and medium-scale arteries, although no effect on large vessels was observed.

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