Cholesterol-Lowering Treatment Is Associated With Improvement in Coronary Vascular Remodeling and Endothelial Function in Patients With Normal or Mildly Diseased Coronary Arteries

Shuichi Hamasaki, Stuart T. Higano, Jassim Al Suwaidi, Rick A. Nishimura, Katsumi Miyauchi, David R. Holmes, Jr, Amir Lerman

Abstract—Coronary vascular remodeling and altered endothelial function have been described in the early stages of native atherosclerosis. The purpose of this study was to evaluate the association between cholesterol-lowering therapy and coronary vascular remodeling and endothelial function in patients with normal or mildly diseased coronary arteries. Patients (N=101) with normal or mildly diseased coronary arteries by coronary angiography underwent intravascular ultrasound examination of the left anterior descending coronary artery. Vessel and lumen area, atherosclerotic plaque area, and plaque morphology were evaluated. Vascular reactivity was examined with the use of intracoronary adenosine, acetylcholine, and nitroglycerin. Patients were divided into 3 groups based on the total cholesterol levels: group 1 (n=25), patients with a history of hypercholesterolemia adequately treated (total cholesterol <240 mg/dL); group 2 (n=26), patients with hypercholesterolemia not adequately controlled (total cholesterol ≥240 mg/dL); and group 3 (n=50), patients without hypercholesterolemia. Vessel area and lumen area were significantly greater in groups 1 and 3 than in group 2 (for respective values in groups 1, 2, and 3: vessel area 11.9±0.5, 10.6±0.4, and 11.8±0.4 mm², both P<0.05; lumen area 8.3±0.4, 6.9±0.3, and 8.9±0.3 mm², both P<0.01). However, plaque areas in groups 1 and 2 were similar. Furthermore, acetylcholine-induced percent increases in coronary blood flow were significantly greater in groups 1 and 3 than in group 2 (for respective values in groups 1, 2, and 3: 70.5±20.1%, 22.8±13.7%, and 68.6±14.8%, both P<0.05). Cholesterol-lowering treatment is associated with an improvement in coronary lumen area that results not from a decrease in plaque area but from an increase in vessel area, reflecting vascular remodeling. Additionally, this adaptive process may occur in association with an improvement of endothelium-dependent vasodilation of the resistance coronary artery. (Arterioscler Thromb Vasc Biol. 2000;20:737-743.)

Key Words: remodeling ■ hypercholesterolemia ■ cholesterol ■ endothelium ■ ultrasonics

Using histopathological techniques, Glagov et al1 examined the effects of plaque development on vessel and lumen area of the left main coronary artery and demonstrated that adaptive enlargement of the wall of diseased arterial segments occurs to compensate for the accumulation of atherosclerotic plaque. Several studies have reproduced these results in vivo by using epicardial or intravascular ultrasound techniques.2–6 These studies have shown that the increase in plaque area is apparently uniformly accompanied by an increase in total vessel area; in this way, luminal dimensions are preserved until the progressive accumulation of plaque exceeds the ability of the vessel to compensate.1 Thus, compensatory enlargement, reflecting vascular remodeling, is now recognized as an important adaptive process in early atherosclerosis.

Hypercholesterolemia is recognized as a risk factor for ischemic heart disease and coronary mortality.7–9 Several trials have demonstrated that cholesterol-lowering therapy markedly reduces cardiovascular mortality.10–12 It has been suggested that the reduction in coronary events seen in the angiographic trials is greater than would be expected for the degree of angiographic improvement induced by cholesterol lowering. Plaque stabilization that is due to a decrease in the lipid content of the lesions, improved endothelial function, and the reduction of thrombogenic risk are 3 mechanisms that could partly account for the reduction in coronary events with cholesterol lowering.13–16 Another associated mechanism may be a beneficial effect on coronary vascular remodeling. However, the association between cholesterol lowering and coronary vascular remodeling and endothelial function in humans is not fully defined.

Thus, the present study was designed to assess the association between hypercholesterolemia and cholesterol-lowering therapy on coronary vascular remodeling and endothelial function in humans.
Study Population
Patients (N=101) who had been referred for cardiac catheterization to exclude coronary artery disease were prospectively studied. Patients with an obvious history of variant angina, cardiomyopathy, previous myocardial infarction, previous coronary artery bypass graft, or coronary intervention were excluded from the present study. Long-acting nitrates or calcium channel–blocking agents were withheld for 36 to 48 hours before the study. The study was approved by the Mayo Clinic Institutional Review Board, and all patients agreed to participate in the study.

Patients were included in the present study if they had the following: (1) angiographically smooth arteries, (2) mild irregularities with no coronary artery lesion with >30% diameter stenosis by visual assessment in any major epicardial vessel, and (3) proximal coronary arteries ≥2.0 mm in diameter.

The 101 patients of the present study were divided into 3 groups according to their history of hypercholesterolemia and their total serum cholesterol level at the time of the study. Group 1 consisted of 25 patients who had been previously diagnosed with hypercholesterolemia and had reduced their total serum cholesterol levels to <240 mg/dL. Group 2 consisted of 26 patients who had been previously diagnosed with hypercholesterolemia and had failed to reduce their total serum cholesterol levels to <240 mg/dL. Patients who had not been diagnosed with hypercholesterolemia and were first diagnosed with hypercholesterolemia at the time of the study were also included in group 2. Group 3 consisted of 50 patients without hypercholesterolemia.

Definition of Hypercholesterolemia
A total cholesterol level of ≥240 mg/dL was used for the definition of hypercholesterolemia. Blood specimens from the subjects were analyzed in a Mayo Clinic medical laboratory. Venous blood specimens were obtained after an overnight 12-hour fast. Serum lipids were measured with use of the following techniques: cholesterol and triglycerides were determined by enzymatic methods, HDL cholesterol was isolated by dextran precipitation, and LDL cholesterol was calculated with use of the Friedewald formula.

Study Protocol
Diagnostic coronary angiography was performed by using a 6F Judkins catheter with a standard femoral percutaneous approach. Heparin (2500 U) was administered at the beginning of the procedure. Nonionic contrast material was used for all patients. No nitroglycerin was given before the diagnostic procedure. Vasomotor responses to acetylcholine and adenosine were studied according to a previously reported protocol. After control coronary angiograms had been obtained, a 0.014-in Doppler guide-wire (Endosonics) was introduced through an 8F guiding catheter (Advanced Cardiovascular Systems). Images were obtained after administration of intracoronary nitroglycerin. All images were performed by manual pullback from the second diagonal coronary artery to the bifurcation of the LAD with the circumflex artery, and segments were visualized. These selected vessel segments were visually divided to equal ~4 or 5 segments, and images were obtained accordingly. After optimization of the ultrasound image, continuous real-time images were recorded on 0.5-in videotape. Four or 5 segments of the LAD were identified on the videotape recording of the ultrasound images, and the exact position of the ultrasound catheter in relation to the artery was recorded on cine film at each position. The location of the catheter as seen on the cine film at each segment position was used to correlate the identified ultrasound imaging with the angiographic segment.

Quantitative Coronary Angiography
Analysis of artery diameter from the cine films was performed with a modification of the technique previously described. A diastolic still frame at each infusion (baseline, saline solution, 300 μg acetylcholine, and nitroglycerin) was selected from the cine film. The different segments of the artery selected at the time of intracoronary ultrasound imaging were identified on the radiograph. By use of the computer-interactive digitizing system, the outline of the contrast material within the lumen was digitized at each specific region of interest identified. The absolute diameter of the vessel lumen perpendicular to the long axis of the artery at the selected specific points of the artery was measured by using the guide catheter as the calibration standard. These measurements were taken by observers without knowledge of the ultrasound findings.

Assessment of Coronary Blood Flow
Doppler flow velocity spectra were analyzed on-line to determine time-averaged peak velocity. Coronary flow reserve was calculated as the ratio of hyperemic to basal average peak velocity of the distal vessel. Volumetric coronary blood flow (CBF) was determined from the following relation: CBF=cross-sectional area×average peak velocity×0.5.

Ultrasound Image Analysis
An off-line computer-interactive analysis system was used to digitize the intracoronary ultrasound video images onto a 256×256-bit matrix. Standard calibration markers directly from the ultrasound image were used for calibration of absolute measurements. Measurements of area stenosis and minimal lumen diameter were made of the most severely stenosed region at each specific segment of the artery that had been previously identified. With computer planimetry, the specific segment was assessed quantitatively. The external elastic membrane cross-sectional area, which represents the area within the border between the hypoechoic media and echoreflective adventitia, was a measure of total arterial cross-sectional area (vessel area, Figure 1). Because medial thickness cannot be measured accurately by intravascular ultrasound, plaque plus medial cross-sectional area (plaque area), which was calculated as external elastic membrane cross-sectional area (vessel area) minus lumen cross-sectional area (lumen area), was used as a measure of plaque mass. Percent area stenosis was calculated as the ratio of plaque plus media to external elastic membrane cross-sectional area. Morphological plaque fea-
TABLE 1. Patient Characteristics and Serum Lipids

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Hypercholesterolemia Adequately Treated, n=25)</td>
<td>(Hypercholesterolemia Inadequately Controlled, n=26)</td>
<td>(Without Hypercholesterolemia, n=50)</td>
</tr>
<tr>
<td>Men 13/25 (52%)</td>
<td>7/26 (27%)</td>
<td>22/50 (44%)</td>
</tr>
<tr>
<td>Age, y 54.8±2.4</td>
<td>55.8±1.9</td>
<td>52.1±1.6</td>
</tr>
<tr>
<td>BSA, mm² 1.93±0.04</td>
<td>1.88±0.03</td>
<td>1.88±0.04</td>
</tr>
<tr>
<td>Risk factor Hypertension 14/25 (56%)</td>
<td>12/26 (46%)</td>
<td>10/50 (20%)</td>
</tr>
<tr>
<td>Diabetes 2/25 (8%)</td>
<td>4/26 (15%)</td>
<td>5/50 (10%)</td>
</tr>
<tr>
<td>Smoking 16/25 (64%)</td>
<td>12/26 (46%)</td>
<td>29/50 (58%)</td>
</tr>
<tr>
<td>Family history 14/25 (56%)</td>
<td>14/26 (54%)</td>
<td>31/50 (62%)</td>
</tr>
<tr>
<td>Serum lipids Total cholesterol, mg/dL 203.2±4.8</td>
<td>273.3±4.4*</td>
<td>193.2±5.1</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL 171.3±5.9</td>
<td>178.5±5.6*</td>
<td>113.5±5.0</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL 50.3±3.1</td>
<td>55.0±3.7</td>
<td>55.7±3.8</td>
</tr>
<tr>
<td>Triglycerides, mg/dL 185.7±17.4</td>
<td>208.4±20.4†</td>
<td>133.0±11.2</td>
</tr>
</tbody>
</table>

Values are mean±SE or patients/group total (percentage of group total). BSA indicates body surface area.

*P<0.001 vs groups 1 and 3; †P<0.01 vs group 3.

Statistical Analysis

Continuous variables are presented as mean±1 SE. Differences in groups among baseline variables were tested by 1-way ANOVA. Discrete variables are presented as percentages. The Pearson χ² test was used to determine significant baseline differences. Appropriate transformations for vessel area, lumen area, and percent change in CBF were used to normalize the response distributions. Significant treatment differences in vessel area, lumen area, and percent change in CBF were adjusted for age, sex, and hypertension. To account for multiple observations of lumen and vessel area per subject, generalized estimating equations with exchangeable correlation structure were used to model the marginal distribution of these variables. Treatment parameters were then used for significance by using an approximation to the standard normal distribution with empirical standard errors. Treatment differences in percent change in CBF were determined with an F test.²⁸

Results

Segments (N=456) derived from the 101 patients with normal and mildly diseased coronary arteries were initially selected. Eleven angulated segments, 6 segments of bifurcated lesions, and 30 segments with a calcium arc >90° were excluded. Twelve segments with technical problems of video images were also excluded from analysis. Thus, a total of 397 segments from the 101 patients were evaluated.

Patient Characteristics

Sex distribution, age, and body surface area were comparable in the 3 groups. With regard to other coronary risk factors, there were no significant differences among the study group (Table 1).

Serum Lipids

Group 1 consisted of patients with a history of hypercholesterolemia that was adequately treated; their mean total cholesterol level was 203.2±4.8 mg/dL. The duration of cholesterol-lowering therapy was 27±1.0 months. Group 2 consisted of patients with hypercholesterolemia that was not adequately controlled; their mean total cholesterol level was 273.3±4.4 mg/dL. Group 3 consisted of patients without hypercholesterolemia; their mean total cholesterol level was 193.2±5.1 mg/dL. Total serum cholesterol and LDL cholesterol were significantly (P<0.001) elevated in group 2 compared with groups 1 and 3. HDL cholesterol was normal in all 3 groups and did not differ significantly between them. Triglyceride levels were significantly (P<0.01) elevated in group 2 compared with group 3 (Table 1).

Intravascular Ultrasound Data

The dimensions of vessel area, lumen area, and plaque area of the 3 groups are shown in Figure 2. Plaque areas in groups 1 and 2 were similar and significantly (P<0.05 and P<0.01, respectively) larger than plaque areas in group 3: 3.6±0.3 mm² (group 1), 3.7±0.2 mm² (group 2), and 2.9±0.2 mm² (group 3). However, lumen areas in the groups with total cholesterol <240 mg/dL (groups 1 and 3) were similar and significantly (P<0.01) larger than lumen areas in group 2: 8.3±0.4 mm² (group 1), 6.9±0.3 mm² (group 2), and
8.9±0.3 mm² (group 3). In addition, vessel areas in groups 1 and 3 were similar and significantly (P<0.05) larger than vessel areas in group 2: 11.9±0.5 mm² (group 1), 10.6±0.4 mm² (group 2), and 11.8±0.4 mm² (group 3). This significant difference persisted when measurements were adjusted for sex and indexed to body surface area: vessel area 6.06±0.2 mm/m² (group 1) and 6.38±0.2 mm/m² (group 3) versus 5.43±0.2 mm/m² (group 2), P<0.05 and P<0.01, respectively; lumen area 4.27±0.2 mm/m² (group 1) and 4.82±0.1 mm/m² (group 3) versus 3.53±0.1 mm/m² (group 2), P<0.01 and P<0.001, respectively. Furthermore, to adjust for the nonsignificant differences between the various groups in the incidence of diabetes, analyses were also performed after excluding diabetic patients, and these differences remained significant: vessel area 11.9±0.5 mm² (group 1), 10.5±0.4 mm² (group 2), and 11.9±0.4 mm² (group 3), P<0.05 and P<0.01 for groups 1 and 3 versus group 2; lumen area 8.3±0.4 mm² (group 1), 6.9±0.3 mm² (group 2), and 9.0±0.3 mm² (group 3), P<0.001 for groups 1 and 3 versus group 2.

The correlation between vessel area and plaque area is shown in Figure 3. Vessel area significantly increases with plaque area in all 3 groups. Vessel area in groups 1, 2, and 3 increased by 1.24, 1.08, and 1.35 mm², respectively, for every 1-mm² increase in plaque area, suggesting that the vessel enlarges in response to plaque accumulation (r=0.63, P<0.0001; r=0.68, P<0.0001; and r=0.61, P<0.0001, respectively).

Percent area stenosis, maximal thickness of plaque, and plaque composition are shown in Table 2. Percent area stenosis and maximal plaque thickness in both the hypercholesterolemic groups (1 and 2) were similar and significantly greater than those values in group 3, which had no history of hypercholesterolemia (P<0.01 and P<0.001, respectively). Groups 1 and 2 had a significantly higher percentage in composition of hard plaque and calcified plaque than group 3 (P<0.01 and P<0.05, respectively). However, groups 1 and 2 did not differ in any type of plaque. Even after adjustment with all other cardiovascular risk factors, the association between hypercholesterolemia, cholesterol-lowering therapy, and coronary artery remodeling remained significant.

The left main coronary artery vessels were used as the referenced vessels for the 3 groups, and there were no significant differences between the 3 groups (20.6±1.2 mm² in group 1, 23.7±1.3 mm² in group 2, and 22.6±1.3 mm² in group 3).

Changes in CBF
Baseline CBF did not differ among groups 1, 2, and 3 (51.4±6.8, 51.5±7.1, and 53.6±3.7 mL/min, respectively). With regard to calculated coronary flow reserve examined when adenosine was used, there was no significant difference between the 3 groups. Intracoronary acetylcholine induced similar increases in CBF in both groups with total cholesterol <240 mg/dL (groups 1 and 3); the increases were significantly greater than those in group 2 (P<0.05). This was associated with similar changes in coronary artery diameters. The percent increases in CBF induced by nitroglycerin were similar between the groups (Table 2).
The interobserver variability was 0.4±2.4% and 1.06±4.3% for the coronary diameter and area measurements, respectively, and the intraobserver variability was 0.8±1.9% and 1.5±3.3% for the coronary diameter and area measurements, respectively.

**Discussion**

The present study demonstrates that coronary vascular remodeling and coronary endothelial function are impaired in patients with hypercholesterolemia. Moreover, cholesterol-lowering treatment was associated with an increase in lumen area that was due to an increase in vessel area rather than a decrease in plaque area, reflecting vascular remodeling. These changes were associated with improvement in endothelial function.

Patients with hypercholesterolemia have an early and accelerated course of coronary atherosclerosis. Coronary angiography, which uses contrast medium to visualize the coronary artery lumen, is limited to the measurement of a reduction in lumen diameter rather than the extent of atherosclerosis. However, intracoronary ultrasound provides the opportunity to identify early atherosclerotic change in the coronary artery wall during the process of atherosclerosis.

Coronary remodeling may be defined as any change in artery size. It may be considered favorable (adaptive or outward expansion) or unfavorable (pathological or inward shrinkage). Thus, impaired or unfavorable coronary artery remodeling may contribute to the early and accelerated course of coronary atherosclerosis and may lead to greater luminal stenosis for the same amount of atherosclerotic plaque in patients with hypercholesterolemia. Plaque stabilization, improved endothelial function, and the reduction of thrombogenic risk are 3 mechanisms that could partly account for the reduction in coronary events with cholesterol-lowering therapy. Another mechanism may be the improvement of impaired coronary artery remodeling. Clarkson et al. have suggested that the failure of adaptive remodeling may be an important factor in the development of significant atherosclerotic lesions.

Our results are consistent with previous studies that demonstrated impairment of coronary endothelial function in patients with hypercholesterolemia. Moreover, cholesterol-lowering therapy was associated with an improvement in endothelial function in these patients. There were no significant differences between the groups in coronary artery diameter changes in response to acetylcholine, indicating that the response was mainly at the level of the resistance vessels. The CBF responses to the endothelium-independent vasodilator nitroglycerin and adenosine did not differ among the 3 groups. Thus, these findings suggest that an impairment of endothelium-dependent vasodilatation of the resistance coronary artery coincides with structural changes in the coronary arteries in patients with hypercholesterolemia and that normalization of these alterations is associated with effective cholesterol-lowering treatment.

**Mechanisms of Favorable Coronary Remodeling**

The mechanism of compensatory enlargement is not completely elucidated, but a number of hypotheses have been suggested, including bulging of the vessel wall because of degradation of the underlying media and adventitia in response to the development of plaque and/or intimal thickening and arterial dilatation initiated by increased shear stress secondary to increased velocity of flow in stenotic arteries. The small decreases in the lumen in response to the development of plaque produce a large

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**TABLE 2. Characteristics of Plaque and Coronary Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Hypercholesterolemia Adequately Treated, n=25)</th>
<th>Group 2 (Hypercholesterolemia Inadequately Controlled, n=26)</th>
<th>Group 3 (Without Hypercholesterolemia, n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of segments</td>
<td>86</td>
<td>107</td>
<td>179</td>
</tr>
<tr>
<td>Percent area stenosis, %</td>
<td>29.5±1.6*</td>
<td>33.2±1.6†</td>
<td>23.6±1.0</td>
</tr>
<tr>
<td>Maximal plaque thickness, mm</td>
<td>0.60±0.05*</td>
<td>0.64±0.04*†</td>
<td>0.45±0.03</td>
</tr>
<tr>
<td>Plaque composition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>26/86 (30%)</td>
<td>32/107 (30%)</td>
<td>67/179 (37%)</td>
</tr>
<tr>
<td>Soft</td>
<td>30/86 (35%)</td>
<td>36/107 (34%)</td>
<td>73/179 (41%)</td>
</tr>
<tr>
<td>Fibrous</td>
<td>13/86 (15%)</td>
<td>19/107 (18%)</td>
<td>28/179 (16%)</td>
</tr>
<tr>
<td>Hard</td>
<td>8/86 (9%)*</td>
<td>9/107 (8%)*</td>
<td>2/179 (1%)</td>
</tr>
<tr>
<td>Calcified</td>
<td>9/86 (10%†)</td>
<td>11/107 (10%‡)</td>
<td>7/179 (4%)</td>
</tr>
<tr>
<td>Coronary hemodynamics</td>
<td></td>
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<tr>
<td>Percent change of CBF from baseline, %</td>
<td></td>
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</tr>
<tr>
<td>Induced by acetylcholine</td>
<td>70.5±20.1§</td>
<td>22.8±13.7</td>
<td>68.6±14.8§</td>
</tr>
<tr>
<td>Induced by nitroglycerin</td>
<td>50.6±16.8</td>
<td>23.5±13.9</td>
<td>64.0±16.2</td>
</tr>
<tr>
<td>Percent change of coronary artery diameter from baseline, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induced by acetylcholine</td>
<td>−12.1±8.8</td>
<td>−16.0±5.7</td>
<td>−15.8±4.1</td>
</tr>
<tr>
<td>Induced by nitroglycerin</td>
<td>5.0±6.9</td>
<td>7.1±4.1</td>
<td>13.6±4.7</td>
</tr>
</tbody>
</table>

*Values are mean±SE or segments/group total of segments (percentage of segment total). *P<0.01, †P<0.001, and ‡P<0.05 vs group 3; §P<0.05 vs group 2.
increase in shear stress on the vessel wall. The artery normalizes the shear stress by expanding to normal lumen size. Langille and O’Donnell have demonstrated that this is probably an endothelium-dependent response to coronary flow abnormalities. Shircore et al have speculated that coronary artery remodeling might occur in response to changes in CBF reserve. In addition, we have recently demonstrated that experimental hypercholesterolemia is characterized by altered coronary endothelial function and vascular structural changes, suggesting an association between the 2 processes. Thus, the present study suggests that the improvement in the remodeling process in association with cholesterol-lowering therapy occurs not by changes in plaque area but rather by a combination of mechanisms that may affect the vessel wall structure.

Study Limitations
The limitations of intracoronary ultrasound imaging and Doppler flow velocity have been described in detail elsewhere. The present study is a cross-sectional study, and its findings may warrant confirmation through a prospective study.

Clinical Implications
Previous studies have demonstrated an improvement in lumen as detected by coronary angiography after cholesterol lowering. The present study extends these previous observations and demonstrates that the enlargement of the lumen may be the result of vascular remodeling, resulting in an increase in vessel area rather than a decrease in plaque area.

Previous investigators have demonstrated vascular remodeling in advanced coronary atherosclerosis. The present study focused on the early stage of coronary atherosclerosis and has demonstrated that even at this early stage of the disease, without significant luminal disease, there are significant functional and structural changes. Moreover, the present study suggests that lowering the cholesterol levels at an early stage of coronary atherosclerosis is associated with beneficial effects on coronary vascular function and structure.

Conclusions
A decrease in lumen area in patients with hypercholesterolemia may result from an attenuated compensatory enlargement of vessel area in response to an increase in plaque area. The associated improvement in lumen area in the cholesterol-lowering treatment group may result not from a decrease in plaque area but from an increase in vessel area, reflecting vascular remodeling. In addition, our results suggest that impairment of endothelium-dependent vasodilatation at the level of the resistance coronary artery in these patients may be normalized with effective cholesterol-lowering treatment. Therefore, this adaptive process in the epicardial coronary artery may occur in association with an improvement of endothelium-dependent vasodilation of the resistance coronary artery.

Acknowledgments
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