Effect of Cholesterol-Lowering Therapy on Coronary Endothelial Vasomotor Function in Patients With Coronary Artery Disease

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Background—Improved endothelial function may contribute to the beneficial effects of cholesterol-lowering therapy.

Methods and Results—In this randomized, double-blind study, we compared the effect of 6 months of simvastatin (40 mg/d) treatment with that of placebo on coronary endothelial vasomotor function in 60 patients with coronary artery disease. Simvastatin lowered LDL-cholesterol by 40±12% from 130±28 mg/dL (P<0.001). Peak intracoronary acetylcholine infusion produced epicardial coronary constriction at baseline in both the simvastatin (−17±13%) and placebo (−24±16%) groups. After treatment, acetylcholine produced less constriction in both groups (−12±19% and −15±14%, respectively, P=0.97). The increase in coronary blood flow during infusion of the peak dose of substance P was blunted at baseline in both the simvastatin (42±50%) and placebo (55±71%) groups, reflecting impaired endothelium-dependent dilation of coronary microvessels. After treatment, the flow increase was 82±81% in the simvastatin group and 63±53% in the placebo group (P=0.16).

Conclusions—Six months of cholesterol-lowering therapy has no significant effect on coronary endothelial vasomotor function in the study population of patients with coronary artery disease and mildly elevated cholesterol levels. These findings suggest that the effects of cholesterol lowering on endothelial function are more complex than previously thought. (Circulation. 2000;102:846-851.)

Key Words: endothelium ■ lipids ■ coronary disease

The endothelium controls vascular homeostasis through the elaboration of paracrine factors, including nitric oxide. Endothelium-dependent vasodilation is impaired in epicardial coronary arteries1 and in the coronary microcirculation2 of patients with coronary artery disease (CAD). The loss of endothelium-derived nitric oxide (EDNO) promotes vasoconstriction, platelet aggregation, and inflammation in atherosclerotic coronary arteries and thus contributes to the clinical expression of CAD.3,4

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Recent studies have conclusively shown that cholesterol-lowering therapy reduces cardiovascular events5-7 and total mortality rates8 in patients with CAD, but the exact mechanisms of benefit remain unknown. Although statistically significant reductions in lesion severity have been demonstrated, the extent of improvement is modest, suggesting that alternative mechanisms are operative, including plaque stabilization and improved endothelial function.3

Several prior studies8-11 examined the effect of cholesterol-lowering therapy on coronary endothelial function in patients with hypercholesterolemia, CAD, or both. In those studies, cholesterol-lowering therapy reduced coronary artery constriction8-11 and increased coronary blood flow responses during intracoronary acetylcholine infusion,9 reflecting improved EDNO action in conduit coronary arteries and coronary microvessels, respectively. Improved endothelium-dependent dilation after cholesterol-lowering therapy has also been shown in the forearm circulation.12,13 Some of those prior coronary studies were not well controlled,8,9 and a relatively small number of subjects were enrolled. The study that examined the coronary microvasculature9 was not randomized. Therefore, the purpose of the present study was to examine the effect of cholesterol-lowering therapy on coro-
Coronary Vasomotor Studies
Coronary vasomotor function was assessed after diagnostic catheterization or before coronary angioplasty. Nitrites, calcium channel blockers, β-adrenergic blockers, and ACE inhibitors were withheld for 18 hours. Additional heparin was administered (total dose 10,000 U), and a 3F infusion catheter and an 0.018-inch Doppler flow wire (Cardiometrics Inc) were positioned in the index vessel via a 7F or an 8F guiding catheter. Serial infusions (0.8 mL/min) were made as follows: (1) 2-minute vehicle infusion of 5% dextrose with 1 U/mL heparin, (2) 3 two-minute infusions of acetylcholine (Michel: CIBA Vision) at 0.14, 1.4, and 14 μg/min, yielding estimated intracoronary concentrations of 10−4, 10−3, and 10−2 mol/L with the assumption of a flow rate of 80 mL/min, (3) 5-minute vehicle infusion, (4) three 2-minute infusions of substance P (Sigma Chemical Co) at 5, 20, and 40 pmol/min, (5) 5-minute vehicle infusion, and (6) 2-minute adenosine infusion (Sigma Chemical Co) at 2.2 mg/min. The order of acetylcholine and substance P administration was randomized. At the end of each infusion, arterial blood pressure and blood flow velocity were recorded, and angiography was performed with nonionic contrast medium and a power injector.
Both acetylcholine and substance P dilate epicardial and microvessels via EDNO-dependent mechanisms. Substance P at 20 pmol/min increases coronary flow by 150% in normal subjects. Adenosine-induced vasodilation is largely independent of EDNO synthesis.

Treatment and Follow-Up
On the day after catheterization, patients started the American Heart Association cholesterol-lowering Phase I diet and study medication (40 mg/d simvastatin or placebo). They returned after 8, 16, and 26 weeks for a reassessment of lipid profile and safety markers. At the final visit, patients underwent repeat research catheterization. Care was taken to replicate time when medications were held, angiographic views, tube height, catheter and flow wire positions, and order of infusions used in the baseline study. Lipid profiles were measured at a Centers for Disease Control and Prevention/National Heart, Lung, and Blood Institute–certified core laboratory (Medical Research Laboratories). LDL-cholesterol was calculated according to the Friedewald formula.

Assessment of Coronary Artery Diameter and Flow
Quantitative angiography was performed at a core laboratory (Emory University). An end-diastolic frame from each infusion was digitized (~10 pixels/mm), and the diameter of the index vessel was measured with CAAS II software (Pie Medical). Analysis was begun at a proximal landmark and continued distally for a maximum of 5 cm. Films from the baseline and follow-up studies were examined in parallel (blinded to chronological sequence) to ensure analysis of the identical portion of the vessel. The analysis software divided the vessel into contiguous 5-mm segments and determined the diameter of each segment.

Epicardial responses were expressed as percent change in diameter compared with those for the preceding dextrose infusion. We examined both the mean response for all measured segments and the response of the single 5-mm segment that was the site of maximal abnormal vasoactivity (SMAV). For acetylcholine, the SMAV was defined as the segment that demonstrated the most severe constriction, and for substance P, the SMAV was the segment that demonstrated the least vasodilation. The SMAV of the baseline study was identified, and the same segment was reexamined at follow-up, even if that segment no longer showed the most abnormal response.
Coronary blood flow velocity was determined by averaging the mean velocity for 6 consecutive beats at the end of each infusion. Flow was estimated as the product of velocity and the cross-sectional area of a 2-mm segment centered 5 mm distal to the flow wire tip. Flow responses were expressed as percent change relative to the preceding dextrose infusion.

Statistical Analysis
The primary end point was the effect of treatment (simvastatin or placebo) on the change in the diameter response of the SMAV to the maximal dose of acetylcholine. The study was planned to have 80% power to detect a difference of 14 percentage points for this end point with a sample size of 80 patients (α=0.05, 2-tailed), with an assumed within-group SD of change in diameter of 22%.

Other end points included (1) coronary blood flow responses to the maximal doses of acetylcholine and adenosine, (2) diameter responses to the maximal doses of substance P and adenosine, (3) diameter responses to the maximal doses of all 3 agonists with the average of all analyzed segments used for the analysis, rather than the SMAV, and (4) dose response for substance P–mediated changes in coronary blood flow. The dose responses to acetylcholine could not be examined because some patients did not receive all 3 doses due to severe constriction at a submaximum dose.

ANOVA was used to compare the treatment groups for the primary, key secondary, and first 3 other end points. The model included terms for treatment group, investigator, and response to the agonist at the baseline visit. The effect of treatment on the dose response to substance P at the follow-up visit was examined with an analysis of repeated measures with use of the mixed model that included dose of substance P, the treatment, and the interaction of dose and treatment. The effect of treatment on lipid profile was compared by ANOVA with treatment group and investigator in the model. The analysis was performed with SAS statistical software. A 2-tailed P value of <0.05 was considered to be statistically significant. All data are expressed as mean±SD unless otherwise indicated.

Results
Clinical Characteristics and Adverse Events
A total of 83 patients were enrolled. Twenty-three patients were withdrawn (simvastatin group n=11, placebo group n=12). Two patients in the simvastatin group had an adverse
TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n=26)</th>
<th>Simvastatin Group (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>55 (41–71)</td>
<td>55 (39–73)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>23 (88)</td>
<td>28 (82)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>83 ±13</td>
<td>84 ±12</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128±21</td>
<td>131±11</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79±12</td>
<td>79±9</td>
</tr>
<tr>
<td>Atherosclerosis rating, n (%)</td>
<td>Grade II (luminal irregularities)</td>
<td>14 (54)</td>
</tr>
<tr>
<td></td>
<td>Grade III (stenosis &gt;50%)</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Concurrent treatment with, n (%)</td>
<td>ACE inhibitor</td>
<td>4 (15)</td>
</tr>
<tr>
<td></td>
<td>Vitamin E or C</td>
<td>6 (25)</td>
</tr>
<tr>
<td></td>
<td>Estrogen</td>
<td>1 (4)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>24 (92)</td>
</tr>
</tbody>
</table>

Values are mean±SD or number (percent of total).

Drug experience (muscle cramps n=1, urticaria n=1). The remaining patients were withdrawn due to unwillingness to undergo the second catheterization (simvastatin n=6, placebo n=4); protocol violation (placebo n=1); non–medication-related adverse experience, including the development of unstable angina (simvastatin n=2, placebo n=3); or other reasons, including the exacerbation of preexisting non–CAD conditions (simvastatin n=1, placebo n=4). In 1 subject, the follow-up catheterization was complicated by acute myocardial infarction (peak creatine kinase 1300 U/L) due to failure to administer heparin before instrumentation and thrombus formation on the infusion catheter. The subject was treated with heparin and intracoronary urokinase and was discharged in stable condition with a mild hypokinesis in the involved territory (lateroinferior wall) on echocardiography. Thus, a total of 60 patients were available for analysis. The demographic and clinical characteristics of the evaluable patients are given in Table 1.

Lipid Effects

Lipid results are shown in Table 2. The effect of simvastatin treatment was significantly different from that for placebo for total cholesterol (P<0.001) and LDL-cholesterol (P<0.001) levels. At follow-up, LDL-cholesterol was <100 mg/dL in 30 of 34 patients in the simvastatin group and 4 of 25 patients in the placebo group.

Epicardial Vasomotor Function

As shown in Table 3, blood pressure, heart rate, and baseline coronary diameter were similar in both groups and were unaffected by either treatment. Coronary diameter and flow returned to baseline during the vehicle infusion before the next agonist.

The effect of acetylcholine infusion on coronary diameter is shown in Figure 1. The 10⁻⁴ mol/L dose of acetylcholine was omitted in 6 patients in the simvastatin group and 8 patients in the placebo group due to excessive vasoconstriction at 10⁻⁷ mol/L. The maximal dose of acetylcholine produced coronary constriction at the SMAV at baseline in both groups (−17±13% and −24±16%, respectively). After 6 months, acetylcholine produced less severe constriction in both groups (−12±19% and −15±14%, respectively). Because the baseline constricor responses for the 2 groups were different, the change was adjusted for baseline response with ANCOVA. The adjusted changes in the response to acetylcholine were 6±15 percentage points for the simvastatin group and 6±15 percentage points for the placebo group (P=0.97). Adjustment for investigator site, age, extent of atherosclerosis, and baseline LDL level did not alter the findings.

When epicardial function was assessed with the average response of all analyzed segments rather than the 5-mm segment with maximal constriction (SMAV), the extent of coronary constriction was still greater in the placebo group than in the simvastatin group at baseline (−11% versus −5%, respectively) and at follow-up (−12% versus −9%, respectively). The adjusted changes in acetylcholine response between baseline and follow-up were equivalent for the simvastatin group (−3±14 percentage points) and the placebo group (−3±14 percentage points, P=0.95).

The maximal dose of substance P produced modest vaso-dilation at the SMAV at baseline in both the simvastatin (12±10%) and placebo (1±10%) groups. After 6 months, the dilator response to substance P was increased in both groups (11±11% and 13±13%, respectively). The changes in substance P–induced dilation were equivalent in the 2 groups (P=0.53). The findings were similar when the average response of all segments was used for the analysis rather than the SMAV (data not shown).

Intracoronary adenosine induced coronary dilation at baseline for the simvastatin (4±12%, n=27) and placebo (5±10%, n=19) groups. After 6 months, the dilator response was greater in both groups (20±19% and 16±23%, respectively). The changes in adenosine-induced dilation were equivalent in the 2 groups (P=0.45).

Microvessel Vasomotor Function

Coronary blood flow responses to substance P infusion are displayed in Figure 2. The maximal dose of substance P increased coronary blood flow at baseline in both the simvastatin (42±50%) and placebo (55±71%) groups. After 6 months, the response was greater in both groups (82±81% and 63±53%, respectively). The unadjusted improvement was greater in the simvastatin group (39±79 percentage points) than the placebo group (8±79 percentage points). Blood flow responses differed according to participating center, and after adjustment for investigator site and baseline response, the change was 57±70 percentage points for the simvastatin group and 33±67 percentage points for the placebo group (P=0.16). Adjustment for age, extent of atherosclerosis, and baseline LDL level did not alter the findings.

When the entire dose response to substance P was considered, the flow response to substance P improved significantly in the simvastatin group (P=0.03 by analysis of repeated measures) but not in the placebo group (P=0.69) (see Figure 2). However, there was no significant difference...
between groups in the degree of improvement for all 3 doses of substance P ($P=0.21$).

The maximal dose of acetylcholine increased coronary blood flow at baseline in both the simvastatin (63±100%) and placebo (33±76%) groups. After 6 months, acetylcholine increased coronary blood flow by 49±87% in the simvastatin group and 35±85% in the placebo group. The change in acetylcholine response was equivalent in the 2 groups (−14±105 and 1±118 percentage points, respectively, $P=0.49$).

The intracoronary infusion of adenosine increased coronary blood flow at baseline in both the simvastatin (327±183%) and placebo (387±296%) groups. After 6 months, the increase was 388±269% and 353±223%, respectively. Thus, the change in adenosine-induced increase in coronary blood flow was 61±264 percentage points for the simvastatin group and 33±334 percentage points for the placebo group ($P=0.36$).

**Discussion**

In these patients with mild CAD and mildly elevated cholesterol levels, acetylcholine infusion produced epicardial coronary vasoconstriction, and there was a blunted blood flow response to substance P. Adenosine, which primarily acts on vascular smooth muscle in the coronary vasculature, produced epicardial dilation and expected increases in coronary blood flow. These findings suggest the presence of endothelial vasomotor dysfunction at baseline. Six-month treatment with simvastatin markedly improved the lipid profile, whereas placebo had no effect. At follow-up, the severity of acetylcholine-induced vasoconstriction was less in both treatment groups, but there was no difference in the extent of improvement. There also was no significant difference between groups in the degree of improvement in the coronary blood flow response to peak substance P dose ($P=0.16$), although the analysis of all 3 doses of substance P raised the possibility of a beneficial effect in the simvastatin group ($P=0.03$). Overall, cholesterol-lowering treatment for 6 months failed to improve coronary endothelial vasomotor function in this patient population.

The present study has a number of strengths. More patients were enrolled than in any prior study of this issue. The investigators were experienced, and the study was rigorously controlled with centralized blinding and core laboratories. In this study, patients with isolated hypercholesterolemia were examined, and thus, the potentially confounding effects of other risk factors were avoided. In addition to acetylcholine, substance P was also used, which permitted an examination of microvascular endothelial function without the simultaneous constriction of epicardial arteries. These features all suggest that the findings are reliable.

**Prior Studies**

Four previous studies examined the effects of cholesterol-lowering therapy on coronary endothelial vasomotor function (Table 4). In an uncontrolled study, Leung et al$^8$ reported that cholestyramine lowered total cholesterol by 29% and converted acetylcholine-induced constriction to vasodilation in hypercholesterolemic men with normal coronary arteries. In an open-label study, Egashira et al$^9$ reported improved epicardial and microvascular responses to acetylcholine after pravastatin treatment in patients with 1-vessel CAD and no change in a nonrandomized control group. In a randomized, double-blind placebo-controlled study, Treasure et al$^{10}$ examined the epicardial coronary responses to acetylcholine in patients with 1-vessel CAD. Lovastatin plus diet reduced total cholesterol by 31% and improved acetylcholine-induced coronary constriction (−16% to 0%), whereas placebo plus diet had no effect (−19 to −18%). Like in the present study, Treasure et al$^{10}$ examined the SMAV and used the same

**TABLE 2. Fasting Serum Lipid Levels**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Plus Diet</th>
<th>Simvastatin Plus Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 mo</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>203±28</td>
<td>200±28</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>41±10</td>
<td>41±9</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>131±24</td>
<td>129±28</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>152±87</td>
<td>147±93</td>
</tr>
</tbody>
</table>

* $P<0.001$, † $P<0.01$ compared with baseline. Values are mean±SD.

**TABLE 3. Hemodynamics and Resting Coronary Diameter**

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin Plus Diet</th>
<th>Placebo Plus Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 mo</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>133±14</td>
<td>129±13</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78±8</td>
<td>75±9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±12</td>
<td>64±12</td>
</tr>
<tr>
<td>Coronary diameter, mm*</td>
<td>Before ACh</td>
<td>2.11±0.48</td>
</tr>
<tr>
<td></td>
<td>Before substance P</td>
<td>2.05±0.47</td>
</tr>
</tbody>
</table>

*Average of all analyzed segments. Data are mean±SD.
quantitative angiography core laboratory. Finally, Anderson et al11 randomized patients with CAD to treatment with diet alone, lovastatin plus cholestyramine, or lovastatin plus the antioxidant/cholesterol-lowering agent probucol. Lovastatin plus cholestyramine reduced total cholesterol by 23%, and there was a trend for a reduction in the constrictor response to acetylcholine (P=0.08). Notably, the combination of cholesterol-lowering and antioxidant therapy produced a significant improvement in endothelial vasomotor function.

In contrast to those prior studies, the present study demonstrated no effect of cholesterol-lowering therapy on the response to acetylcholine. Several factors might explain these apparently discrepant findings. One possibility is a difference in the study population, and it is notable that baseline total and LDL-cholesterol levels were higher in all 3 studies8 –10 that showed a beneficial effect with cholesterol-lowering therapy alone (Table 4). The finding in the present study that there was no relation between baseline LDL-cholesterol and the response to therapy, at least within the limited range of cholesterol values in the study, argues somewhat against this potential explanation. Likely related to the modest LDL elevation is the relatively mild degree of endothelial dysfunction at baseline in the present study (average 5% constriction), which may also be attributable to the exclusion of patients with other coronary risk factors. Furthermore, the extent of atherosclerosis was relatively mild in the present study (half had no stenosis of >50%), whereas in the previous controlled studies,9 –11 nearly all patients had at least 1-vessel coronary disease. The duration of therapy might also be a factor. Although baseline lipid levels in the study by Anderson et al11 were similar to those of the present study, the duration of therapy was twice as long. Thus, it is possible that more prolonged treatment is required to demonstrate improved coronary endothelial function in patients with lower baseline cholesterol levels.

The present study has certain limitations. First, despite the randomized design, there were significant group differences in baseline vasomotor function. For example, the constrictor response to acetylcholine was more severe in the placebo group than in the simvastatin group. It also is unclear whether the basal tone was equivalent in the initial and follow-up studies, because the adenosine-induced vasodilation of epicardial arteries was higher during the follow-up study for both groups. Second, the use of the Doppler flow wire to assess coronary flow was relatively new at the time of the study. It is possible that there were unplanned methodological differences among sites. Third, the placebo group demonstrated sizable improvement in the epicardial response to acetylcholine, a finding that likely represents “regression to the mean.” This phenomenon was not observed when the vasomotor response of the entire segment was considered, indicating a limitation of the SMAV analysis for intervention studies. However, the overall findings of the study were the same by either approach to analysis. Finally, the study may have lacked sufficient power to demonstrate an effect of

### TABLE 4. Previous Studies of Cholesterol-Lowering and Coronary Artery Endothelial Function

<table>
<thead>
<tr>
<th>Study</th>
<th>n*</th>
<th>Randomized Control Group</th>
<th>Baseline Total Cholesterol, mg/dL</th>
<th>Baseline LDL Cholesterol, mg/dL</th>
<th>Treatment Duration, mo</th>
<th>Improvement Demonstrated</th>
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<tbody>
<tr>
<td>Leung et al8</td>
<td>25</td>
<td>No</td>
<td>275±31</td>
<td>220±34</td>
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<tr>
<td>Egashira et al9</td>
<td>9</td>
<td>No</td>
<td>272±8</td>
<td>195±25</td>
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<tr>
<td>Treasure et al10</td>
<td>11</td>
<td>Yes</td>
<td>230±33</td>
<td>148±23</td>
<td>5.5</td>
<td>+</td>
</tr>
<tr>
<td>Anderson et al11</td>
<td>21</td>
<td>Yes</td>
<td>209±33</td>
<td>139±38</td>
<td>12</td>
<td>±</td>
</tr>
<tr>
<td>Present study</td>
<td>34</td>
<td>Yes</td>
<td>204±32</td>
<td>130±28</td>
<td>6</td>
<td>–</td>
</tr>
</tbody>
</table>

*No. of subjects in active treatment group. Lipid data are mean±SD.
therapy on the microvascular response to substance P given that fewer than the planned number of patients were enrolled and the variability was greater than expected. If the planned number of subjects had been studied, the observed changes in microvascular function might have reached statistical significance.

Clinical Implications and Conclusions

It has been suggested that improvement of coronary endothelial function contributes to the reduction in CAD events associated with long-term cholesterol-lowering therapy.3 In the CAREa and LIPID7 studies, which involved patients with CAD and lipid levels comparable to those of the patients in the present study, there were no reductions in cardiovascular disease events during the first 2 to 3 years of treatment. The finding in the present study that endothelial function remained unimproved after only 6 months of treatment is consistent with the results of those clinical trials. It is possible that more prolonged treatment is associated with an improvement in coronary endothelial function that might contribute to the observed reduction in events.

In the present study, there was a suggestion that cholesterol-lowering therapy improved microvascular endothelial function (Figure 2), although the group difference did not reach statistical significance. Recent studies have shown that short-term cholesterol-lowering therapy (3 to 5 months) reduces ambulatory18 and stress-induced 19 ischemia in patients with CAD and higher total cholesterol levels than those in the present study (238 to 297 mg/dL). Because endothelial vasomotor function in coronary microvessels is relevant to metabolic regulation of coronary blood flow,20 it is possible that improved microvascular endothelial function contributes to the reduction in myocardial ischemia in these patients. However, the present study does not provide conclusive evidence to support this speculation.

In summary, this relatively large, well-controlled study demonstrated that 6 months of cholesterol-lowering therapy has no significant effect on coronary endothelial function in a group of patients with mildly elevated cholesterol levels, no concomitant coronary risk factors, and mild CAD. These findings suggest that the effects of cholesterol lowering on endothelial function are more complex than previously thought.

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References


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