Differences in Action of Atorvastatin and Ezetimibe in Lowering Low-Density Lipoprotein Cholesterol and Effect on Endothelial Function
– Randomized Controlled Trial –

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Background: The aim of this study was to compare the effect on endothelial function of increasing statin dose to add-on ezetimibe in patients with coronary artery disease (CAD) already treated with statin.

Methods and Results: Two-hundred and forty-three patients with CAD and low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dl even after treatment with atorvastatin (10 mg) were prospectively randomized to the ezetimibe addition (10 mg) group (A10E10; n=117) or to the double atorvastatin dose (to 20 mg; A20; n=133) group for 12 weeks. Primary endpoint was change in endothelial function measured by logarithmic-scale reactive hyperemia index (L_RHI). After treatment, high-sensitivity C-reactive protein (hs-CRP) and all lipids except triglyceride and high-density lipoprotein cholesterol were significantly reduced in both groups. The mean percent changes in LDL-C for the A10E10 and A20 groups were −25.8% and −9.1%, respectively (P<0.001). L_RHI increased from 0.47 to 0.62 in the A20 group (P<0.001), but not in the A10E10 group (from 0.45 to 0.48, P=0.399). Absolute change in L_RHI was significantly higher in the A20 than A10E10 group (0.02±0.29 vs. 0.16±0.27, P<0.001).

Conclusions: Statin and ezetimibe have different effects on endothelial function independent from LDL-C-lowering effects. (Circ J 2013; 77: 1791–1798)

Key Words: Coronary artery disease; Endothelial function; Statin

Lipids are intimately involved in the atherogenic process leading to coronary artery disease (CAD). Therapeutic interventions aimed at favorable alterations of lipoprotein metabolism, particularly lowering low-density lipoprotein cholesterol (LDL-C), are the cornerstone of treatment for primary and secondary cardiovascular disease.

3-Hydroxy-3-methylglutarlyl coenzyme A inhibitors (statins) are essential drugs for patients with CAD to reduce the risk of adverse cardiovascular events via their LDL-C-lowering effect. Indeed, there is considerable evidence for a clear relationship between LDL-C level and cardiovascular event rate, supporting the “lower the better” hypothesis.1–3 In addition, many studies have suggested that statins have beneficial pleiotropic effects unrelated to their LDL-C-lowering effect, including anti-inflammatory effects,4 antioxidative effects,5 and improvement of endothelial function.6

Recently, the National Cholesterol Education Program Adult Treatment Panel recommended an optical LDL goal of <70 mg/dl for individuals with higher risk, including cardiovascular disease patients with additional high-risk factors: diabetes mellitus, multiple cardiovascular risk factors, multiple risk factors of metabolic syndrome, or severe or poorly controlled risk factors, especially smoking.7

Although statins are now accepted as first-line drugs for lowering LDL-C in patients with cardiovascular disease, statins alone are often insufficient to achieve the current guideline-recommended serum LDL-C level. In the Treating to New Targets (TNT) trial, less than half of the patients in the atorvastatin arm achieved LDL-C <70 mg/dl.8 In addition, a comparative study showed that most of the LDL-C-lowering effect of statins occurs at the starting dose, and doubling the dose of statin results in only a 6% increased reduction in LDL-C level.9

Ezetimibe is the first of a new class of cholesterol absorption inhibitor that impairs dietary and biliary cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides (TG) or fat-soluble vitamins.10

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Some studies have shown that ezetimibe can reduce LDL-C to a significantly greater extent than statin monotherapy when added to the standard dose of statin.\textsuperscript{11–13} The effect of statin and ezetimibe other than the LDL-C lowering effect, however, seems to be different when taking into account the results of recent large-scale trials.\textsuperscript{14,15}

Therefore, the aim of the present study was to investigate the difference between increasing the dose of statin and adding ezetimibe in terms of the pleiotropic effects for patients with CAD who have already been prescribed statins.

\textbf{Methods}

\textbf{Subjects and Study Site}

The Human Research Committee at Kameda Medical Center approved this study. All subjects provided written informed consent. The trial was registered as a randomized controlled trial titled “Randomized study in patients with CAD to compare the effect of atorvastatin with ezetimibe to endothelial function: ESSENTIAL study” with the University hospital Medical Information Network (UMIN) registration no. UMIN000002297.

Men and women aged >20 years with clinically evident CAD and LDL-C >70 mg/dl despite use of 10 mg of atorvastatin for >1 month were assessed for eligibility. CAD was defined as previous myocardial infarction (MI), previous or present angina with objective evidence of atherosclerotic CAD (at least 1 coronary stenosis >50%), and previous coronary revascularization procedure. Major exclusion criteria included any of the following: hypersensitivity to atorvastatin or ezetimibe; active liver disease or hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase >3.0-fold the upper limit of normal; women who were pregnant or breastfeeding; uncontrolled diabetes mellitus defined as hemoglobin A\textsubscript{1C} (HbA\textsubscript{1C}) >\textit{9.0}%; MI, coronary revascularization procedure, or severe/unstable angina within 1 month of screening; any planned surgical procedure for treatment of atherosclerosis; gastrointestinal disease limiting drug absorption or partial ileal bypass; any malignancy; concurrent therapy with long-term immunosuppressants; or familial hypercholesterolemia. The study was conducted at the Kameda Clinic of Kameda Medical Center in Chiba, Japan. Kameda Medical Center consists of a 965-bed inpatient facility and a comprehensive freestanding outpatient facility as its core functions in Kamogawa City, Chiba Prefecture.

\textbf{Study Design}

This was a prospective, randomized, parallel-group, open-labeled clinical trial conducted between September 2009 and November 2012 in a single center.

At screening (visit 0), the patients with LDL-C >70 mg/dl despite treatment with 10 mg of atorvastatin were assessed for eligibility, and informed consent was obtained. At visit 1, blood samples were collected from all patients who agreed to enroll in the study, and subjects in whom LDL-C was >70 mg/dl even at this time were randomly assigned to add 10 mg of atorvastatin (A20) or 10 mg of ezetimibe (A10E10) daily in the morning for 12 weeks. Randomization was performed by computer-based randomization system through an Internet navigation system. This system was constructed and operated by Internet Data and Information Center for Medical Research (INDICE). Endothelial function was also evaluated as reactive hyperemia index (RHI) by Endo-PAT2000 (Itamar Medical, Caesarea, Israel) after randomization as baseline. At visit 2, blood samples were collected from all patients and endothelial function was re-evaluated. Patients were not permitted to be treated with any lipid-modifying agent other than the study drug after randomization.

Patients were instructed to fast overnight for a minimum of 8h before all visits (visits 0, 1, and 2). Patients were also advised to continue their current medication and lifestyle for the duration of the study. The patients were not allowed any caffeine-containing drinks or tobacco consumption on the day of a visit.

Before starting the present study, we conducted a pilot study to evaluate the reproducibility of RHI, and estimate the standard deviation of natural logarithmic-scale RHI (L\_RHI). The subjects consisted of 23 CAD patients, and RHI was measured twice with an interval of 12 weeks. The Bland-Altman plot is shown in Figure 1, and L\_RHI showed good reproducibility.
Ezetimibe Does Not Improve Endothelial Function

Assessment of Endothelial Function

Endothelial function was measured via RHI according to the principle described previously. Briefly, this system consists of a finger probe to assess digital volume changes accompanying pulse waves. All patients were instructed to avoid eating or drinking, taking only water, for 8 h before measuring RHI. The same dim room maintained at a temperature of 26.5°C was used for measurement of RHI in all patients. Before commencing measurement of RHI, patients remained in bed for 15 min.

The reactive hyperemia peripheral artery tonometry (RH-PAT) probe was positioned on the middle finger of each hand and set by computer to inflate to 70 mmHg, and then the baseline pulse amplitude was recorded from both fingers. After this procedure, the blood pressure cuff was inflated on 1 arm to 200 mmHg or 60 mmHg plus systolic blood pressure for 5 min and released.

Throughout the period of inflation and release, recordings were taken simultaneously from both fingers. The increase in pulse amplitude in the hyperemic finger was recorded digitally and analyzed using an automated operator-independent proprietary algorithm as RHI, and L_RHI was calculated for use in subsequent analyses.

Endpoints

The predefined primary endpoint was the between-group difference in absolute change in L_RHI. The secondary endpoints were the changes in lipid profiles, malondialdehyde-modified low-density lipoprotein (MDA-LDL), MDA-LDL/LDL-C ratio, and adiponectin.

Biochemistry

A venous blood sample was obtained after overnight fast. Plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TG levels were measured using an automated analyzer. LDL-C was calculated using the Friedewald formula. Serum high-sensitive C-reactive protein (hs-CRP) concentration was measured on high-sensitive immunoturbidimetry (Roche Diagnostics, Tokyo, Japan). MDA-LDL was measured via commercially available sandwich ELISA for MDA-LDL (Sekisui Medical, Tokyo, Japan). Plasma concentration of adiponectin was determined using a commercially available ELISA kit (Otsuka Pharmaceutical, Tokyo, Japan).

Statistical Analysis

Continuous variables are expressed as mean±SD unless otherwise specified. Continuous variables of 2 groups were compared using Student’s t-test or Mann-Whitney U-test. Two-sided P<0.05 was considered significant. Distribution was tested with the Kolmogorov-Smirnov test. Categorical variables were compared using the chi-square test or Fisher’s exact test. The number of patients in each group needed to detect a difference in L_RHI of 0.1 with a power of 80% and 2-tailed t-test at the 5% level was approximately 115, assuming that standard deviation of L_RHI is 0.28.

Figure 2. Flow chart of randomization.

CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol.
Subjects

A total of 536 patients were initially assessed for eligibility, and finally 250 patients were randomly assigned to the A10E10 group or A20 group after exclusion of 286 patients: 259 did

rate of 8% in a recent study, and finally decided on a sample size of 125 for each group in a 1:1 randomized fashion. Data were analyzed in the intention-to-treat group, defined as the existence of 2 valid RHI measurements. All statistical analysis was performed using R version 2.14.

Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>A10E10 (n=115)</th>
<th>A20 (n=128)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>83 (72.2)</td>
<td>96 (75)</td>
<td>0.72</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.2±9.3</td>
<td>70.3±9.9</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3±3.5</td>
<td>24.7±3.8</td>
<td>0.42</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>131.4±18.5</td>
<td>132.6±17.7</td>
<td>0.60</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75.1±11.5</td>
<td>76.5±13.7</td>
<td>0.40</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>90 (78.3)</td>
<td>104 (81.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42 (36.5)</td>
<td>52 (40.6)</td>
<td>0.60</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20 (17.4)</td>
<td>22 (17.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>4 (3.5)</td>
<td>8 (6.2)</td>
<td>0.48</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>6 (5.2)</td>
<td>6 (4.7)</td>
<td>0.92</td>
</tr>
<tr>
<td>Heart failure</td>
<td>20 (17.4)</td>
<td>24 (18.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>History of CAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic CAD</td>
<td>1 (0.8)</td>
<td>1 (0.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Angina with documented ischemia</td>
<td>44 (38.3)</td>
<td>48 (37.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>70 (60.9)</td>
<td>79 (61.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Percutaneous coronary revascularization</td>
<td>85 (73.9)</td>
<td>102 (79.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>CABG</td>
<td>26 (22.6)</td>
<td>24 (18.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>40 (34.8)</td>
<td>36 (28.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>ARB</td>
<td>43 (37.4)</td>
<td>58 (45.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>β-blocker</td>
<td>72 (63.7)</td>
<td>80 (62.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>CCB</td>
<td>47 (40.9)</td>
<td>57 (44.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>Aspirin</td>
<td>115 (100)</td>
<td>128 (100)</td>
<td></td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>31 (27)</td>
<td>35 (27.3)</td>
<td>0.94</td>
</tr>
<tr>
<td>L_RHI</td>
<td>0.45±0.25</td>
<td>0.47±0.23</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). A10E10, atorvastatin 10-mg+ezetimibe 10-mg group; A20, atorvastatin 20-mg group; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; L_RHI, logarithmic-scaled reactive hyperemia index.

Table 2. Change in Lipids, Inflammatory Markers, and Adiponectin

<table>
<thead>
<tr>
<th></th>
<th>A10E10 (n=115)</th>
<th>A20 (n=128)</th>
<th>P-value (before vs. after)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>168.9±22.1</td>
<td>141.2±19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>110.7±35.7</td>
<td>98.8±43.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>52.4±11.9</td>
<td>51.8±10.8</td>
<td>0.292</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>94.4±16.8</td>
<td>69.6±15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RLP-C (mg/dl)</td>
<td>5.1±3.6</td>
<td>3.8±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MDA-LDL (U/L)</td>
<td>101.5±35.1</td>
<td>86.3±23.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP (ng/ml)</td>
<td>1,082.1±1,655</td>
<td>641.7±982.3</td>
<td>0.006</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.0±0.8</td>
<td>6.0±0.7</td>
<td>0.263</td>
</tr>
<tr>
<td>Adiponectin (μg/ml)</td>
<td>12.5±9.8</td>
<td>11.8±7.5</td>
<td>0.445</td>
</tr>
</tbody>
</table>

hs-CRP, high-sensitivity C-reactive protein; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein; RLP-C, remnant like particles cholesterol; TC, total cholesterol; TG, triglyceride. Other abbreviations as in Table 1.
Ezetimibe Does Not Improve Endothelial Function

Discussion

The present results indicate that atorvastatin can improve endothelial function, while ezetimibe does not, despite greater reduction in LDL-C. These observations suggest that atorvastatin, but not ezetimibe, has pleiotropic effects in patients with CAD. Moreover, the LDL/MDA-LDL ratio did not change significantly after treatment in the atorvastatin group, but increased significantly in the ezetimibe group.

A series of recent clinical studies compared the effects of statin and ezetimibe therapy on endothelial function.

Lipid-independent effects of statin on endothelial function were suggested in patients with dyslipidemia, heart failure,

not meet the inclusion criteria, 22 had LDL-C <70 mg/dl at visit 1, and 5 refused to participate in the study. The final intention-to-treat group consisted of 243 patients (Figure 2).

The baseline characteristics of the 243 patients who had completed the trial are listed in Table 1. The 2 groups of patients did not differ with respect to age, gender, comorbidity, or baseline L_RHI.

Lipids, Inflammatory Markers, and Others

Pre- and post-treatment lipid profiles, hs-CRP, HbA1c, and adiponectin levels are listed in Table 2. There were no significant differences between the groups in these biomarkers at baseline. After treatment, TC, LDL-C, MDA-LDL, and hs-CRP were significantly reduced in both groups. TG was significantly reduced in the A10E10 group, and slightly reduced in the A20 group but did not reach statistical significance. Adiponectin and HDL-C levels were not significantly different between the 2 groups. HbA1c did not change in the A10E10 group. In the A20 group, however, HbA1c increased from 6.0% to 6.1% (P=0.058) but did not reach statistical significance.

Percent changes of lipid profiles are compared in Figure 3. The mean percent changes in LDL-C for the A10E10 group and A20 group were –25.8% and –9.1%, respectively (P<0.001). The percent decreases in TC and MDA-LDL were significantly greater in the A10E10 group than the A20 group. We also analyzed the MDA-LDL/LDL-C ratio before and after treatment in both groups as an exploratory analysis. The ratio did not change significantly in the A20 group (1.09 vs. 1.10, P=0.659), but there was a significant increase in the A10E10 group after treatment (1.09 vs. 1.26, P<0.001; Figure 4).

Endothelial Function

Baseline L_RHI was similar in the 2 groups. Following 12 weeks of treatment, L_RHI increased from 0.47 to 0.62 in the A20 group, but it did not change significantly in the A10E10 group (from 0.45 to 0.48, P=0.399; Figure 5). The absolute change of L_RHI was significantly different between the A10E10 and A20 groups (0.02±0.29 vs. 0.16±0.27, P<0.001; Figure 5). The standardized effect size was calculated as 0.50 (95% confidence interval: 0.24–0.75).

Figure 3. Percent changes in lipid profiles. Data given as mean±SE. Percent changes before and after treatment in the atorvastatin 10-mg + ezetimibe 10-mg group (A10E10) and atorvastatin 20-mg group (A20). HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein; RLP-C, remnant like particles cholesterol; TC, total cholesterol; TG, triglycerides.

Figure 4. Change in MDA-LDL/LDL-C ratio before and after treatment in (blue) atorvastatin 10-mg + ezetimibe 10-mg group (A10E10) and (red) atorvastatin 20-mg group (A20). Data given as median±quartile. LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein.
All of these studies noted preferable effects of statin on endothelial function, but these previous studies did not include those with CAD who failed to achieve target LDL-C despite statin treatment. Thus we included such patients with insufficient treatment to critically examine the importance of lowering LDL-C in CAD patients after statin treatment. Given that “the lower the better” is robust in CAD patients, investigations in these patients are very important. The present results suggest the beneficial effects of increasing the dose of statin as a further step, and there may be differences in the effects between statin and ezetimibe even though both of these drugs decrease LDL-C in CAD patients.

Moreover, some previous studies compared statin to a combination of ezetimibe and statin (simvastatin). This design could not exclude the possibility that statin in combination with ezetimibe may affect the outcome of the study. In the present study, we compared the pure effect of statin to ezetimibe on endothelial function, and we have demonstrated the pleiotropic effects of statin on endothelial function independent of its LDL-C-lowering effect in the largest number of patients with adequate power.

In contrast, a few studies have demonstrated the beneficial effects of ezetimibe on endothelial function. In 1 study, changes in brachial artery flow-mediated vasodilatation (FMD) were examined in rheumatic arthritis patients, and improvements were observed in both the statin group and ezetimibe group compared to baseline. In another study, 39 patients with either diabetes or impaired fasting glucose, stable CAD, and without lipid-lowering therapy in the previous 3 months were examined with regard to the effects of simvastatin at 80 mg/day and combination therapy with ezetimibe 10 mg + simvastatin 10 mg/day on brachial artery FMD.

These studies, however, may not be applicable to CAD patients because it was performed exclusively in subjects with rheumatoid arthritis, a condition that is in itself highly associated with inflammation and endothelial dysfunction. In the latter study, as described, the sole effect of simvastatin at 10 mg on endothelial function was not evaluated, and the study design was insufficient to conclude that the effects of statin and ezetimibe on endothelial function are comparable. Recently, Nochioka et al showed that ezetimibe improved the endothelial function in a cross-over manner with a 4-week washout interval. That study, however, recruited and randomized only healthy subjects.

In the A20 group, increase in HbA1c nearly reached statistically significant difference, but not in the A10E10 group. This finding is consistent with recent study results concerning the effect of statin on glucose metabolism and insulin sensitivity. Some studies and meta-analyses have shown that statin is associated with worsening of glycemic control, decrease in insulin sensitivity, and increase in the incidence of diabetes.

One meta-analysis of 5 randomized trials (n=32,752) showed that approximately 1 additional case of diabetes is observed for every 500 patients treated with intensive rather than moderate statin therapy. Given the robust evidence of statin in secondary prevention, the beneficial effects of statin on CAD patients outweigh the slight worsening of glycemic control and decrease in insulin sensitivity.

Another important finding of the present study was that the ratio of MDA-LDL/LDL-C was not changed significantly after treatment in the statin group, but increased significantly in the ezetimibe addition group despite the lack of significant reductions in serum LDL-C and MDA-LDL. If the correlation between MDA-LDL and LDL-C ratio is maintained even after treatment with ezetimibe, this ratio must not change even after treatment. This suggests that the LDL-C-lowering effect of ezetimibe is different from that of atorvastatin with regard to lowering oxidized stress, and this may be why ezetimibe could not improve endothelial function. Indeed, Noma et al. reported that MDA-LDL was correlated with coronary endothelial function.
with Rho-associated kinase activity, which has been shown to be a contributing factor in endothelial dysfunction and vascular disease. In another study, MDA-LDL/LDL-C ratio was shown to be correlated with carotid intima-media thickness (IMT) in CAD patients. These results and the failure of ezetimibe to have a beneficial effect on IMT in 2 large-scale randomized studies (ENHANCE and ARBITER 6-HALTS) support the present findings. The importance of MDA-LDL/LDL-C, however, is supported only by cross-sectional studies with no prospective studies. Moreover, the present finding concerning MDA-LDL/LDL-C ratio is exploratory and was not a predefined analysis. Therefore, the implications of this finding need to be carefully interpreted with regard to prognostic meaning and should be elucidated in future large-scaled studies.

Study Limitations
First, this study was based on a small number of patients in a single center. Second, we compared the effects of atorvastatin and ezetimibe as an additional drug, but LDL-C was not a predefined analysis. Therefore, the implications of this study may have affected the primary outcome of the present study. Third, treatment duration was 12 weeks in the present trial, and this may not be sufficient for improvement in endothelial function by ezetimibe. A previous study, however, investi-gated the effect of ezetimibe on LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: A double-blind randomized trial. Lancet 2010; 376: 1658–1669.

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