Ezetimibe and Regression of Carotid Atherosclerosis
Importance of Measuring Plaque Burden

Chrysi Bogiatzi, MD; J. David Spence, BA, MBA, MD, FRCPC, FAHA

**Background and Purpose**—There has been recent controversy over failure of ezetimibe to reduce carotid intima-media thickness. Much of this is based on failure to understand important differences among ultrasound phenotypes of atherosclerosis.

**Methods**—We analyzed the effect of adding ezetimibe to the regimen of patients being followed in vascular prevention clinics where measurement of carotid plaque burden (total plaque area) is used to guide therapy.

**Results**—There were complete data in 231 patients with total plaque area for 2 years before and 2 years after initiation of ezetimibe. In the 2 years before and after initiation of ezetimibe, total cholesterol decreased significantly before \((P<0.0001)\) and after initiation of ezetimibe \((P<0.0001)\); low-density lipoprotein cholesterol declined significantly before \((P<0.0001)\) and after \((P=0.003)\) initiation of ezetimibe. Triglycerides declined significantly before ezetimibe \((P<0.0001)\) but did not change after addition of ezetimibe \((P=0.48)\). High-density lipoprotein cholesterol did not change significantly before \((P=0.87)\) but declined significantly after ezetimibe \((P=0.03)\). Despite the decline in low-density lipoprotein cholesterol before addition of ezetimibe, there was a significant mean increase in within-individual total plaque area in the 2 years before addition of ezetimibe by \(6.89\pm39.57\ mm^2\) (SD); after addition of ezetimibe, despite the decline in high-density lipoprotein, plaque area decreased by \(-3.05\pm38.18\ mm^2\) SD \((P<0.01)\).

**Conclusions**—Ezetimibe appears to regress carotid plaque burden. To assess effects of antiatherosclerotic therapies, it is important to measure plaque burden. These findings should be tested in a clinical trial. *(Stroke. 2012;43:00-00.)*

**Key Words:** atherosclerosis ■ ezetimibe ■ LDL cholesterol ■ plaque area ■ ultrasound

In recent years, there has been controversy and confusion over effects of ezetimibe on “atherosclerosis” (see Online Supplement for references; http://stroke.ahajournals.org). However, commentators did not seem to understand that intima-media thickness (IMT), although it represents a form of end-organ disease, is biologically and genetically distinct from plaque, which is true atherosclerosis.¹

In 2010, we showed that the proportion of patients with plaque regression had doubled since 2003 (from 25% to 50%) since using plaque measurements to guide therapy² and that among patients with asymptomatic carotid stenosis, intensive medical therapy based on plaque measurements significantly reduced microemboli and significantly reduced cardiovascular events.³ We suspected that much of the plaque regression, and much of the reduction of microemboli and cardiovascular events among patients with asymptomatic carotid stenosis after 2003, was due to addition of ezetimibe (which first became available in Canada in June 2003) in patients whose plaque was progressing despite already low levels of low-density lipoprotein (LDL) cholesterol.

In this study, we therefore analyzed carotid plaque progression and regression for 2 years before and 2 years after ezetimibe was added to the regimen of patients attending our vascular prevention clinics.

**Methods**

Patients were attending the Stroke Prevention Clinic, the Premature Atherosclerosis Clinic, or the Atherosclerosis Prevention Clinic at University Hospital, in London, Ontario, Canada. Due to reimbursement issues, the patients were mainly patients who were unable to take high doses of statins because of myalgia or myopathy. We analyzed patients who had signed a consent form approved by the University of Western Ontario ethics research board with measurements of carotid total plaque area for 2 years before and 2 years after initiation of ezetimibe for whom we also had data on plasma lipids and medications. Missing data were obtained from clinical records and entered into the database.

Carotid total plaque area was measured as previously described.⁴ Fasting lipids were measured in the Biochemistry Laboratory of the London Health Sciences Centre.

Analyses were performed using SPSS PASW Statistics Version 18. Differences between means were assessed by a paired \(t\) test.
Recent meta-analyses have shown that high-dose statins slightly increase the risk of incident diabetes. For this reason, addition of ezetimibe to lower doses of statins appears to be an attractive alternative to high-dose statins. Our findings provide some reassurance that this may be an appropriate strategy.

Conclusions
In clinical practice, ezetimibe appears to regress carotid plaque burden. This finding suggests that to study effects of antiatherosclerotic therapies, it is important to study patients with measurable plaque and to use measurements that assess plaque burden. A clinical trial should be done to confirm these findings.

Disclosures
Dr Spence has an interest in www.vascularis.com and received speakers’ fees from Merck, AstraZeneca, Boehringer-Ingelheim, Novartis, and Pfizer and consulting fees from A salary for a summer student to help with data collection for this study was donated by Merck Canada. The study was initiated by Dr Spence; Merck had no input into the design or reporting of the study. He has no financial

Table. Baseline Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.40±9.79</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140.56±18.91</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76.04±11.44</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.51±1.06</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.65±1.24</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>1.40±0.44</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>2.39±0.88</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>17.86±17.86</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.83±4.96</td>
</tr>
</tbody>
</table>

**Female** | 43.7  
**Diabetic** | 15.7  
**Smoking status**  
Never smoked | 29.7  
Former smoker | 58.6  
Current smoker | 11.6  
**History of myocardial infarction** | 12.6  
**History of stroke** | 28.5  
**History of transient ischemic attack** | 46.3  
**History of vascular surgery** | 24.2  

Mean and SD or percentages were computed for descriptive variables.

Results
There were 284 patients with measurement of plaque at all time points; 42 were excluded because they either had a carotid occlusion or a carotid endarterectomy or stenting during the 5 years, invalidating the measurement of plaque progression/regression. An additional 12 were excluded because they did not give consent or were unable to give consent (dead, moved away). This left 231 patients with data on plaque area at each time point for analysis. Baseline characteristics of the patients are shown in the Table. The participants were typical reasonably well-controlled elderly patients being followed in vascular prevention clinics. Supplemental Table I shows treatment with lipid-lowering drugs by year before and after addition of ezetimibe.

As shown in Figure 1, in the 2 years before and after initiation of ezetimibe, total cholesterol decreased significantly before ($P<0.0001$) and after initiation of ezetimibe ($P<0.0001$); LDL cholesterol declined significantly before ($P<0.0001$) and after ($P=0.003$) initiation of ezetimibe. Triglycerides declined significantly before ezetimibe ($P<0.0001$) but did not change after addition of ezetimibe ($P=0.48$). High-density lipoprotein cholesterol did not change significantly before ($P=0.87$) but declined significantly after ezetimibe ($P=0.03$). Blood pressure declined over the 5 years (Online Supplemental data). Despite the decline in LDL cholesterol before addition of ezetimibe, there was a significant increase in within-individual total plaque area in the 2 years before addition of ezetimibe by $6.89±SD$ 39.57 mm$^2$ SD; after addition of ezetimibe, despite the decline in high-density lipoprotein cholesterol, plaque area decreased by $-3.05±38.18$ mm$^2$ SD. As shown in Figure 2, the within-individual changes in progression/regression were significantly different before and after addition of ezetimibe ($P<0.01$). As shown in Online Supplemental data, total plaque area continued to progress in contemporaneous patients not receiving ezetimibe despite a decline in LDL over the 5-year period.

Discussion
In patients attending vascular prevention clinics, we found that carotid total plaque area progressed before addition of ezetimibe despite a decline in LDL and then regressed after addition of ezetimibe with a further decline of LDL cholesterol but despite a decline in levels of high-density lipoprotein cholesterol. An important limitation is that our findings were observational; a randomized trial would be required to establish this result.

To understand why carotid plaque regressed with addition of ezetimibe, whereas IMT did not in the 2 IMT studies referred to online, it is instructive to examine the differences between IMT and plaque burden as phenotypes of atherosclerosis.

Although IMT is predictive of cardiovascular events and in some studies responds to lipid-lowering therapy, a key issue that is not well enough understood is that there are different approaches to measuring IMT, with and without plaque thickness; these different approaches assess biologically different phenotypes, and neither predicts cardiovascular events as well as plaque area. IMT where there is no plaque does not truly represent atherosclerosis; it is mainly hypertensive medial hypertrophy, and because studies in which plaque thickness is included in some cases average the results with cases that have no plaque, neither should be called atherosclerosis.

Recently we showed regression of vessel wall volume with dietary weight loss in groups of 45 over 2 years; notably in that study, there was no significant change in IMT.

Recent meta-analyses have shown that high-dose statins appear to be an attractive alternative to high-dose statins. Our findings provide some reassurance that this may be an appropriate strategy.
interest in any pharmaceutical company nor does any member of his family.

References


Figure 1. Serum cholesterol (A), triglycerides (B), high-density lipoprotein (HDL; C), and low-density lipoprotein (LDL; D) by years before and after initiation of ezetimibe (mmol/L, mean±SE).

Figure 2. Progression of carotid plaque before and regression after initiation of ezetimibe. The change in within-individual plaque area in the 2 years before and after initiation of ezetimibe was significantly different (P<0.01) with progression before initiation of ezetimibe despite the decline in low-density lipoprotein (LDL) cholesterol shown in Figure 1 and regression after initiation of ezetimibe despite the decline in high-density lipoprotein (HDL) shown in Figure 1.
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Supplemental Material

Ezetimibe and regression of carotid atherosclerosis:
importance of measuring plaque burden
Supplemental Table 1. Concomitant lipid-lowering therapy before and after initiation of ezetimibe.
The number and percentage of patients taking lipid-lowering drugs is shown by year before, at the time of and after initiation of ezetimibe 10 mg. daily.

<table>
<thead>
<tr>
<th></th>
<th>2 years pre</th>
<th>1 year pre</th>
<th>Initiation of ezetimibe</th>
<th>1 year post</th>
<th>2 years post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>62 (31%)</td>
<td>74 (37%)</td>
<td>30 (15%)</td>
<td>58 (29%)</td>
<td>96 (48%)</td>
</tr>
<tr>
<td>Low dose*</td>
<td>106 (53%)</td>
<td>92 (46%)</td>
<td>116 (58%)</td>
<td>104 (52%)</td>
<td>77 (35%)</td>
</tr>
<tr>
<td>Medium dose**</td>
<td>30 (15%)</td>
<td>30 (15%)</td>
<td>47 (23.5%)</td>
<td>29 (14.5%)</td>
<td>19 (9.5%)</td>
</tr>
<tr>
<td>High dose***</td>
<td>1 (1%)</td>
<td>4 (2%)</td>
<td>7 (3/5%)</td>
<td>9 (4.5%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Niacin</td>
<td>10 (5%)</td>
<td>8 (4%)</td>
<td>15 (7.5%)</td>
<td>18 (9%)</td>
<td>18 (9%)</td>
</tr>
<tr>
<td>Fibrate</td>
<td>39 (19.5%)</td>
<td>37 (18.5%)</td>
<td>50 (25%)</td>
<td>44 (22%)</td>
<td>10 (5%)</td>
</tr>
</tbody>
</table>

* Low dose = 5-10 mg rosuvastatin, 10-20mg atorvastatin or simvastatin

** Medium dose = 20mg rosuvastatin, 40mg atorvastatin or simvastatin

*** High dose = 40mg rosuvastatin, 80mg atorvastatin or simvastatin

(It is recognized that the potency of these dose ranges overlap; the definition was according to the manufacturers’ recommended range of dosing.)
We have added results here on blood pressure by year in the patients on ezetimibe, and for comparison with the patients who were treated with ezetimibe, the lipid levels and plaque areas by year in the patients in the database (n=530) who were not taking ezetimibe, but had plaque measurements and lipid levels in the years that were contemporaneous with the ezetimibe patients. (Ezetimibe was introduced into the Canadian market in 2003).

Blood pressure declined over time in the patients on ezetimibe. However, in a multivariable model, plaque change from initiation to ezetimibe was not significantly explained by age, sex, smoking status, or the LDL level or systolic blood pressure 2 years after initiation of ezetimibe.

**Supplemental Figure 1. Blood pressure (mmHg) by year pre and post initiation of ezetimibe**

a) Systolic blood pressure  

![Systolic blood pressure graph](image)

b) Diastolic blood pressure  

![Diastolic blood pressure graph](image)
Supplemental Figure 2. Total plaque area by year in all patients in the database not on ezetimibe, with lipid levels

Supplemental Figure 3. Plasma lipid levels in all patients in the database not on ezetimibe by year N= 530

a) Total cholesterol

b) Triglycerides

c) HDL cholesterol
d) LDL cholesterol

Supplemental references:
