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Ezetimibe and regression of carotid atherosclerosis: Importance of measuring plaque burden

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Ezetimibe and Regression of Carotid Atherosclerosis
Importance of Measuring Plaque Burden

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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 ± 39.57 mm^2 (SD); after addition of ezetimibe, despite the decline in high-density lipoprotein, plaque area decreased by $-3.05\pm$SD 38.18 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;43:1153-1155.)

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 therapy[2] 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.

Table. **Baseline Characteristics of the Subjects**

	Mean±SD
Age, y	68.40±9.79
Systolic blood pressure, mm Hg	140.56±18.91
Diastolic blood pressure, mm Hg	76.04±11.44
Total cholesterol, mmol/L	4.51±1.06
Triglycerides, mmol/L	1.65±1.24
High-density lipoprotein cholesterol, mmol/L	1.40±0.44
Low-density lipoprotein cholesterol, mmol/L	2.39±0.88
Smoking, pack-years	17.86±17.86
Body mass index, kg/m^2	27.83±4.96
	Percent, %
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.[5] IMT where there is no plaque does not truly represent atherosclerosis; it is mainly hypertensive medial hypertrophy,[1] 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[6]; notably in that study, there was no significant change in IMT.

Recent meta-analyses have shown that high-dose statins slightly increase the risk of incident diabetes.[7,8] 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.
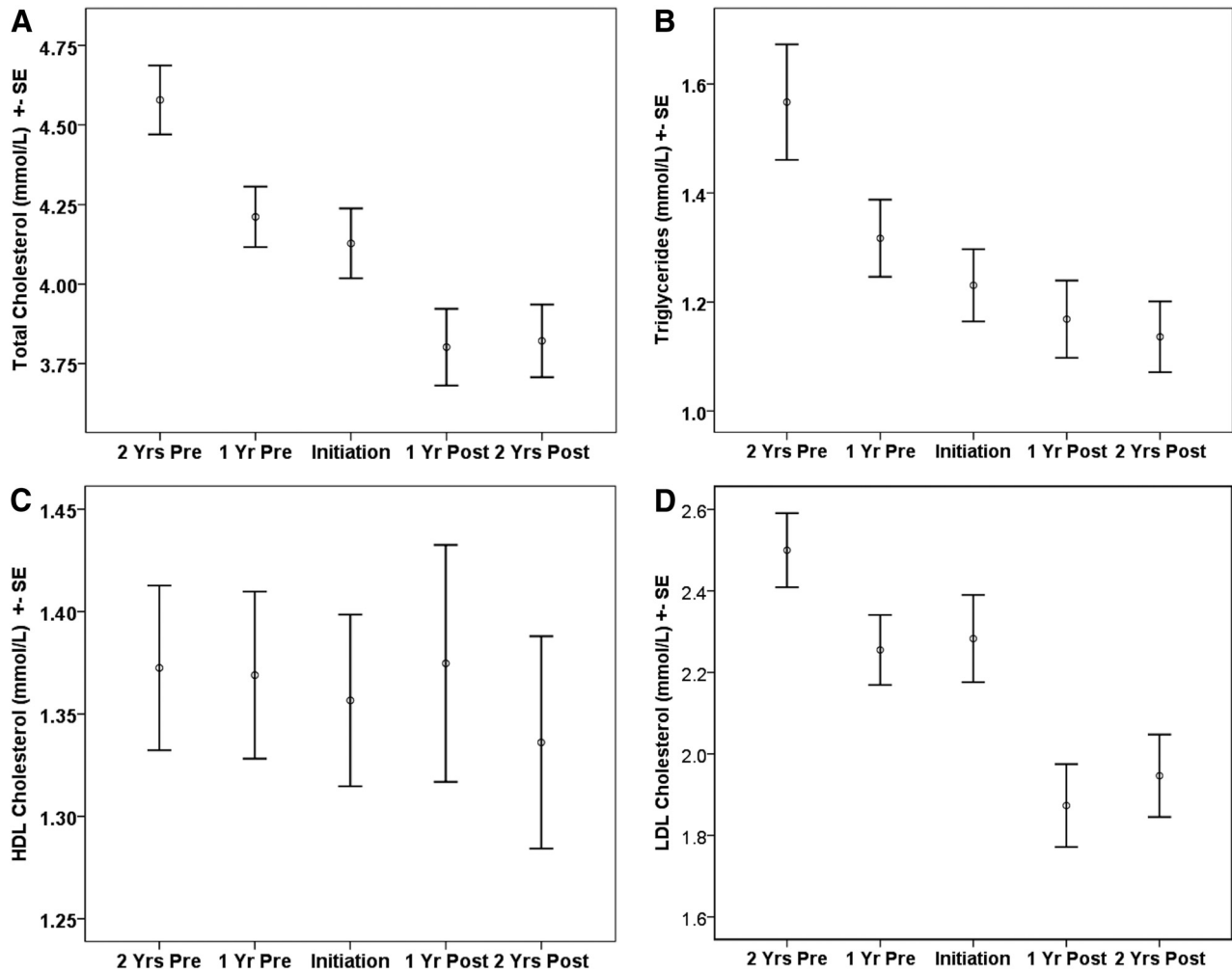
Disclosures

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).
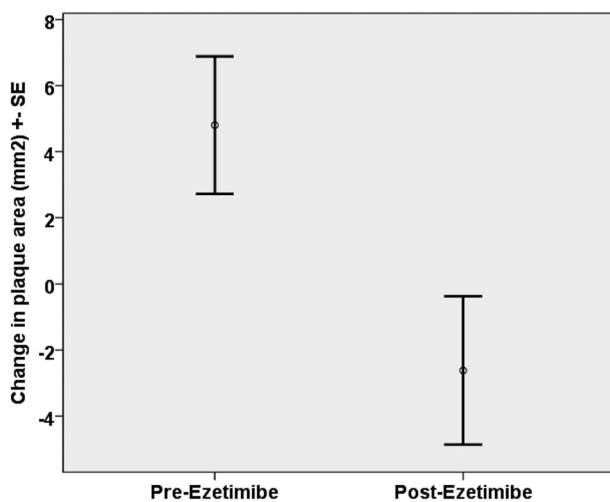

Figure 2. Progression of carotid plaque before and regression after initiation of ezetimibe. The change in within-individual plaque area in the 2 years before and after initiation of ezetimibe was significantly different ($P<0.01$) with progression before initiation of ezetimibe despite the decline in 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.

interest in any pharmaceutical company nor does any member of his family.

References

1. Finn AV, Kolodgie FD, Virmani R. Correlation between carotid intimal/medial thickness and atherosclerosis. A point of view from pathology. *Arterioscler Thromb Vasc Biol*. 2010;30:177–181.

2. Spence JD, Hackam DG. Treating arteries instead of risk factors. A paradigm change in management of atherosclerosis. *Stroke*. 2010;41:1193–1199.

3. Spence JD, Coates V, Li H, Tamayo A, Munoz C, Hackam DG, et al. Effects of Intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol*. 2010;67:180–186.

4. Spence JD, Eliasziw M, DiCicco M, Hackam DG, Galil R, Lohmann T. Carotid plaque area: a tool for targeting and evaluating vascular preventive therapy. *Stroke*. 2002;33:2916–2922.

5. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis*. Epub ahead of print June 18, 2011. DOI: 10.1016/j.atherosclerosis.2011.06.044.

6. Shai I, Spence JD, Schwarzfuchs D, Henkin Y, Parraga G, Rudich A, et al. Dietary intervention to reverse carotid atherosclerosis. *Circulation*. 2010; 121:1200–1208.

7. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–742.

8. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305:2556–2564.