Secondary prevention of cardiovascular events in patients with documented coronary artery disease is an unmet need. Current guidelines recommend tight control of cardiovascular risk factors (1). In this context, lowering of low-density lipoprotein cholesterol (LDL-C) remains crucial, because it has been associated with better prognosis and stabilization, or even regression of coronary atherosclerosis as assessed by intravascular ultrasound (IVUS). Many studies have suggested that targeting LDL-C to levels to <70 mg/dl should be the goal of statin therapy in high-risk patients. In the meta-analysis by the Cholesterol Treatment Trialists’ Collaboration, which included 5 trials that compared more versus less intensive statin therapy, on-treatment LDL-C levels were reduced 39 to 77 mg/dl by the more intensive regimens, which is an average of approximately 20 mg/dl lower than the less intensive regimens (2). This further LDL-C reduction was associated with a highly significant 15% decrease in major cardiovascular events, without increasing the risk of cancer or noncardiovascular mortality.

For the many patients who do not achieve guideline-driven LDL-C targets with statin monotherapy, guidelines recommend either increasing the statin dose or initiating statin therapy in combination with another lipid-lowering agent. In particular, the new American College of Cardiology/American Heart Association guidelines (3) recommend that the maximum tolerated statin dose be used in high-risk individuals, and that the addition of a nonstatin cholesterol-lowering drug may be considered if the risk-reduction benefit outweighs the safety risk in patients with a less than adequate therapeutic response to statins.

The beneficial effects of intensive statin treatment are attributed to the slowing of atherosclerotic plaque progression, and more importantly, to plaque stabilization, as suggested by large IVUS studies of more versus less intensive statin therapy (4,5). In this issue of the Journal, Tsujita et al. report the results of the PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial (6). Briefly, patients with stable angina or an acute coronary syndrome were randomized to either atorvastatin alone (monotherapy group) or atorvastatin plus ezetimibe (combination therapy group), with the atorvastatin dosage up-titrated to achieve an LDL-C <70 mg/dl. IVUS was performed at baseline and at 9- to 12-month follow-up. Patients randomized to combination therapy experienced a greater reduction in percent atheroma volume (PAV) than those randomized to monotherapy; the prevalence of side effects was similar in the 2 groups.

At first glance, the lower mean LDL-C level achieved with combination therapy than with monotherapy (63.2 mg/dl vs. 73.3 mg/dl) seems to account for the enhanced regression associated with the former. However, linear regression analysis failed to show an association between achieved LDL-C levels and PAV changes. Furthermore, in the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) trial, rosuvastatin 40 mg achieved lower levels of LDL-C (mean 62.6 mg/dl) versus atorvastatin 80 mg (mean 70.2 mg/dl), which were values very similar to those observed in PRECISE-IVUS but had no detectable PAV reduction (7). Thus, cholesterol lowering itself does not seem to explain the greater reduction.
of PAV with combination therapy versus monotherapy observed in the PRECISE-IVUS trial.

This difference is unlikely to be accounted for by the anti-inflammatory effect of ezetimibe. In the PRECISE-IVUS trial, reduction of C-reactive protein levels was similar in the 2 treatment groups. This finding is in keeping with previous studies that suggested no further reduction of inflammatory biomarkers when ezetimibe was added to statin therapy (8).

We would like to offer a possible explanation for the greater reduction of PAV observed with combination therapy, which might stimulate further research in this field.

Ezetimibe acts at the brush border of the small intestine, where it selectively inhibits both cholesterol and plant sterol absorption from the intestinal lumen into the enterocytes by selective blockage of the sterol transporter, the Niemann-Pick C1-like 1 protein, thus eventually reducing their serum levels (9). Accordingly, in PRECISE-IVUS, sterols (lathosterol, campesterol, and sitosterol) and their ratio to cholesterol decreased with the combination therapy, but increased with monotherapy. Interestingly, the campesterol-to-cholesterol ratio reduction was significantly and positively related to a reduction in PAV, which suggested a possible role for sterols other than cholesterol. The genetic disease sitosterolemia, which is characterized by elevated plasma levels of plant sterol, is associated with premature atherosclerosis, although the relationship between plant sterols and atherosclerosis is not clear. The largest prospective trials and genome-wide association studies have suggested that high plasma levels of plant sterols are associated with increased risk, but other studies have reported no such association or even an inverse relationship (10). Thus, available data cannot confirm an increased cardiovascular risk with plant sterols, but cannot rule it out either (11). Only a prospective interventional trial to analyze the effects of plant sterol–enriched food on the incidence of cardiovascular events can exclude a potential cardiovascular risk linked with their excess.

Other pleiotropic effects unrelated to cholesterol lowering might also be involved in ezetimibe-related potentiation of plaque regression, including modulation of genes related to inflammation and/or oxidative stress (12), inhibition of monocyte and/or macrophage differentiation by altering microribonucleic acid expression (13), and inhibition of smooth muscle cell proliferation (14). Furthermore, ezetimibe inhibits platelet aggregation and activation (15), and seems to modulate atherosclerotic plaque composition with reduction of cholesterol crystals that, in turn, are associated with inflammasome activation, plaque growth, and vulnerability (16,17). Ezetimibe and statins might have additive effects on cholesterol crystallization (18) (Figure 1).

In conclusion, the investigators of the PRECISE-IVUS trial should be congratulated for this excellent study, which provides a solid pathophysiological foundation for the modest, albeit statistically significant, clinical benefit observed with ezetimibe plus simvastatin versus simvastatin alone in the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (19). The molecular mechanisms driving the additional benefit of ezetimibe on plaque progression compared with statin monotherapy need to be further investigated. In particular, it would be interesting to establish the clinical relevance of the potential pleiotropic effects of ezetimibe that operate beyond cholesterol lowering.

The reality is always more complex than we tend to believe, in line with the wise words of Isaac Newton: “What we know is a drop, what we ignore is an ocean.”

**FIGURE 1 Effects of Statins and Ezetimibe**

<table>
<thead>
<tr>
<th>Statins</th>
<th>Ezetimibe</th>
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<tbody>
<tr>
<td>LDL-C reduction</td>
<td>LDL-C reduction</td>
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<tr>
<td>Anti-oxidant effects</td>
<td>Anti-oxidant effects</td>
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<tr>
<td>Anti-inflammatory effects</td>
<td>Sterol reduction</td>
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<tr>
<td>Anti-thrombotic effects</td>
<td>vSMC proliferation inhibition</td>
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<tr>
<td>CC dissolution</td>
<td>CC reduction</td>
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Various mechanisms mediate the beneficial effects of statins and ezetimibe on plaque growth. CC = cholesterol crystals; LDL-C = low-density lipoprotein cholesterol; vSMC = vascular smooth muscle cells.

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REFERENCES


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