Other Therapies for Reducing Low-Density Lipoprotein Cholesterol: Medications in Development

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• LDL cholesterol • Apo B antisense • MTP inhibitors
• Squalene synthase inhibitors • PCSK9 inhibitors

It has been more than 2 decades since lovastatin (Mevacor), the first of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), was approved on September 1, 1987, for general use for lowering of low-density lipoprotein cholesterol (LDL-C). Since that time, the statins repeatedly have been shown to significantly and substantially reduce all forms of atherosclerotic disease, especially coronary heart disease (CHD) and stroke, no matter what the starting levels of LDL-C and the underlying absolute risk for CHD was in the population in the trial.[1–4] Over the past 20 years there have been more effective statins developed and approved and higher doses of the original statins[5–7] used, such that with the most effective of these agents at their highest dose, an average reduction in LDL-C of close to 55% from baseline is achievable.[7] The efficacy and safety of this class of compounds has resulted in their becoming the largest therapeutic class of medications used today and in history.

Despite the success of the statins, a second class of agents, cholesterol absorption transport inhibitors, also has been developed and approved in the past decade for LDL-C lowering, although there is only one representative, ezetimibe, currently available.[8] This agent also has excellent tolerability and safety along with moderate reductions in LDL-C of approximately 18%, given alone or added to a statin. Thus,

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there is a potential for achieving average LDL-C reductions of up to 65% with combination therapy.[9]

Why, therefore, would there be a need for additional LDL-lowering agents?

1. Many clinical endpoint trials have confirmed that more LDL-C reduction results in more cardiovascular disease risk reduction.[10–12]
2. Clinical practice guidelines[13–15] from the National Cholesterol Education Program, American Heart Association, and American College of Cardiology and European guidelines continue to lower LDL-C goals for high-risk and even lower-risk patients who have CHD, with target goals in patients who have existing CHD and additional risk factors now set at less than 70 mg/dL in the United States and less than 2 mmol/L in Europe and Asia. Recent studies have shown that even with current therapies, many patients, especially those considered at high and very high risk, are not achieving these goals.[16]
3. Special populations, such as those with familial hypercholesterolemia (FH) and other forms of severe hypercholesterolemia, do not achieve even old goals and often require significantly greater LDL-C reductions than the 65% achievable by combining the highest dose of the most effective statin, rosuvastatin (40 mg), and ezetimibe.[9]
4. Perhaps the largest need, however, is for the growing number of patients who are statin adverse,[17] for whom there are limited alternatives to achieving significant LDL-C reductions if even low-dose statin cannot be tolerated.[18] Although in the first 2 decades of statin development and general use the focus on statin toxicity was rare, severe and life-threatening rhabdomyolysis, mild nonspecific myalgias, and other muscle-related side effects (MRSEs) have become major impediments to instituting successful lipid-lowering therapy in everyday medical practice. The magnitude of the problem recently has been evaluated (**Table 1**),[17] demonstrating an approximate prevalence of 5% to 10% of patients affected by MRSEs. Thus, with more than 20 million patients requiring more than 35% LDL-C reduction, there are a projected 1 to 2 million patients who are unable to tolerate statins and need effective LDL-C lowering currently unachievable with nonstatin therapy.

There remains, therefore, a medical need for new, effective, and safe medications to reduce LDL-C.

Table 1
PRIMO: risk for muscular symptoms with individual statins

Statin	Dosage	Patients who have Muscular Symptoms[a]	Odds Ratio (95% CI)[b]	*P* Value[c]
Pravastatin	40 mg/d	10.9%	—	—
Atorvastatin	40–80 mg/d	14.9%	1.421 (1.171–1.723)	<0.001
Simvastatin	40–80 mg/d	18.2%	1.812 (1.463–2.245)	<0.001
Fluvastatin	80 mg/d	5.1%	0.437 (0.352–0.542)	<0.001

[a] Percentage values relative to the total number of patients who had or did not have muscular symptoms.
[b] Odds ratios were calculated using pravastatin as the reference.
[c] *P* values were determined by Pearson's chi-square test.
From Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. Cardiovasc Drugs Ther 2005;19:403–14; with permission.