Elevated serum cholesterol level is an important risk factor for cardiovascular disease, and cholesterol lowering by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins has been shown to reduce cardiovascular events. The reduction in cardiovascular risks with statin therapy, whether for primary or secondary prevention, correlates almost linearly with the reduction in serum cholesterol levels. Indeed, for every 30 mg/dL decrease in low-density lipoprotein-cholesterol (LDL-C), there is a concomitant 30% decrease in cardiovascular events. For patients presenting with acute coronary syndrome, or in patients with stable coronary artery disease, intensive lipid-lowering therapy provides even greater clinical benefits, implying that the lower the LDL-C, the better the outcome is, especially for high-risk patients. Because most of the US adult population with coronary heart disease has serum LDL-C levels between 135 and 145 mg/dL, to achieve an Adult Treatment Panel III/National Cholesterol Education Panel guideline for LDL-C target goal of <100 mg/dL with an optional goal of <70 mg/dL, most high-risk patients with coronary heart disease will likely require at least a 40% to 50% reduction in LDL-C.

Depending on the dose used, most statins can reduce serum cholesterol by 30% to 58%. This is compared with bile acid sequestrants or intestinal cholesterol absorption inhibitors, which tend to lower serum cholesterol by only 15% to 18%. Thus, it is not surprising that statins have emerged as the principal cholesterol-lowering therapy for patients at risk for cardiovascular disease. However, most statins, with the exception of the more potent statins, such as atorvastatin and rosuvastatin, will require near-maximum dosages to achieve a 40% to 50% LDL-C reduction. This is because the majority of statins’ LDL-C-lowering efficacy occurs at the starting dose with only a modest 4% to 6% further LDL-C reduction with doubling of the dose. However, titrating statins to higher doses to achieve LDL-C target goals increases their costs and potential side effects. Because of these issues, most of the patients who begin statin therapy remain on their initial dose, and <30% of patients with coronary heart disease achieve a LDL-C target of <100 mg/dL. Thus, there is a need for additional therapy to lower serum cholesterol levels, if treatment targets, especially for high-risk patients, are to be met.

By blocking the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, statins inhibit the early rate-limiting step in cholesterol biosynthesis (Figure). This leads to the upregulation of LDL receptors in the liver and increased clearance of serum cholesterol. However, by inhibiting cholesterol biosynthesis at such an early step, statins also decrease the production of mevalonate and isoprenoid intermediates such as isopentenylpyrophosphate, farnesylpyrophosphate, and geranylgeranylpyrophosphate. Some of these isoprenoids serve as lipid attachments for signaling molecules belonging to the family of Ras and Rho GTPases, the inhibition of which could mediate some of the noncholesterol or pleiotropic effects of statins. However, these isoprenoid intermediates are also important precursors for signaling molecules that regulate protein synthesis (isopentenyl adenine), mitochondrial respiration (ubiquinone, coenzyme Q10), and glycosylation (dolichol). Thus, inhibition of isoprenoid synthesis by statins could be a double-edged sword. On the one hand, the inhibition of Rho GTPases may provide additional benefits beyond cholesterol reduction. Indeed, further cholesterol lowering by use of an intestinal cholesterol absorption inhibitor, ezetimibe, failed to decrease atherosclerosis progression in patients with familial hypercholesterolemia compared with statins, suggesting that cholesterol lowering alone may not contribute to all of the clinical benefits observed with statin therapy. This issue will hopefully be addressed in terms of clinical outcomes in the ongoing Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), which will determine whether further cholesterol lowering by ezetimibe is beneficial compared with statin alone in patients at high risk for cardiovascular events. On the other hand, some of the unwanted side effects of statin therapy may be due to the inhibition of isoprenoid synthesis in skeletal muscle. Indeed, some in vitro studies suggest that myotoxicity induced by statins could be alleviated by the addition of isoprenoid intermediates, farnesol and geranylgeraniol. Because statin-induced myopathy and rhabdomyolysis are real safety concerns, whereas statin pleiotropy remains a theoretical consideration, there is a need for therapeutic agents that could decrease cholesterol biosynthesis without affecting isoprenoid metabolism. These newer therapies could also be used to determine whether there are any beneficial effects of statins beyond cholesterol lowering.
Squalene synthase catalyzes the first committed step, which leads exclusively to the formation of cholesterol by converting and dimerizing farnesylpyrophosphate to squalene (Figure). In animal studies, squalene synthase inhibitors (SSIs) reduce hepatic cholesterol biosynthesis and upregulate LDL receptors, without depleting cellular levels of isoprenoids. Indeed, cellular levels of isoprenoids, such as farnesylpyrophosphate, are usually elevated because of higher 3-hydroxy-3-methylglutaryl coenzyme A reductase activity from the lack of feedback inhibition and increased backup of isoprenoid intermediates that leads to squalene. Furthermore, SSIs do not cause myotoxicity, and when they are coadministered with statins, they decrease statin-induced myotoxicity.

These initial findings provide the basis for the clinical development of SSIs as monotherapy or adjunctive therapy to statins for patients who cannot achieve cholesterol target goals because of either statin intolerance, lack of sufficient statin potency, or both. However, it should be noted that most of the SSIs in clinical development have not progressed beyond clinical phase I/II trials and many have been abandoned because of hepatotoxicity. Only one SSI, lapaquistat acetate, has progressed to phase II/III clinical trials, and has accumulated sufficient efficacy and safety data for comparison with placebo and statins.

In the current issue of Circulation, Stein et al summarize the phase II/III results from a lapaquistat clinical program that was halted because of safety concerns and lack of commercial viability. Although pooling of the data from 12 different clinical trials that range from 6 to 96 weeks in duration could lead to unforeseen bias and random errors, the analysis of the trials taken together consisted of >6000 patients, most of whom were given the 50- and 100-mg daily dose of lapaquistat acetate, with or without statin therapy. Furthermore, for easier comparison, the efficacy for 3 monotherapy and 5 statin coadministration studies were reported separately. The trials included patients with heterozygous or

**Figure.** Cholesterol biosynthesis. Diagram of cholesterol biosynthesis pathway showing the chemical structure of some of the intermediates. Inhibition of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase by statins and inhibition of squalene synthase by lapaquistat are shown. Isoprenoids (isopentenyl-PP, geranyl-PP, farnesyl-PP, and geranylgeranyl-PP) are important modulators of various signaling pathways involving Rho GTPases (RhoA, Rac1, and Cdc42). Note that squalene synthase is the first committed step toward cholesterol biosynthesis, which would not deplete cellular levels of isoprenoids. PP indicates pyrophosphate; eNOS, endothelial nitric oxide synthase; t-PA, tissue-type plasminogen activator; ET-1, endothelin-1; and PAI-1, plasminogen activator inhibitor-1.
homozgyous familial hypercholesterolemia, and all patients had LDL-C of >100 mg/dL and triglyceride of <400 mg/dL on entry. With the exception of one study, where LDL-C was calculated, the LDL-C was directly measured using ultracentrifugation, which is especially important in patients with elevated triglyceride where calculated LDL-C could be erroneous. In addition, patients were excluded who have baseline alanine aminotransferase or aspartate aminotransferase levels of >1.5 times the upper limit of normal or a creatinine phosphokinase level of >3 times the upper limit of normal. The overall completion rate was ≈90% for both the placebo and lapaquistat acetate groups.

Compared with placebo, lapaquistat acetate 50 mg and 100 mg decreased LDL-C by 18% and 23%, respectively, at 12 weeks, and when coadministered with statins, decreased LDL-C by an additional 14% and 19%, respectively, at 24 weeks. Lapaquistat also significantly reduced non–high-density lipoprotein-cholesterol, total cholesterol, apolipoprotein B, very-low-density lipoprotein-cholesterol, and triglyceride when compared with placebo or with coadministration with statins. It is interesting that high-sensitivity C reactive protein, a nonspecific inflammatory marker, was also reduced by lapaquistat acetate in a dose-dependent manner, suggesting that changes in serum cholesterol or triglyceride levels may somehow modulate inflammatory status. The incidence of adverse events leading to withdrawal was fairly similar for all treatment groups, with the statin monotherapy group being slightly lower overall. This was somewhat surprising, given that lapaquistat acetate was expected to cause fewer muscle-related side effects. However, the lack of difference in adverse events between the treatment groups could be simply caused by the overall low rate of adverse events observed in the statin group, with or without lapaquistat acetate. Nevertheless, from an adverse event or muscle-related side effect perspective, there was no particular advantage of lapaquistat acetate compared with statin therapy.

Hepatotoxicity was the primary reason for halting the late-stage clinical development of lapaquistat 100 mg. In contrast, patients receiving lapaquistat 50 mg did not exhibit any signs of hepatotoxicity compared with patients receiving placebo. However, lapaquistat 50 mg was considered not commercially viable when compared with existing therapies, such as bile acid sequestrants or intestinal cholesterol absorption inhibitors that could lower LDL-C to a comparable extent. The incidence of elevated transaminases (alanine aminotransferase and aspartate aminotransferase >3×the upper limit of normal on 2 successive occasions) in patients taking lapaquistat 100 mg was between 2% and 3%, which was substantially higher compared with those taking placebo or statin monotherapy (<0.3%). In 2 patients, the elevation of alanine aminotransferase was accompanied by increases in total bilirubin levels, thereby fulfilling the Food and Drug Administration-defined Hy’s Law for the likelihood of progression to hepatic failure.16 Thus, the decision to terminate further clinical development of lapaquistat acetate for the treatment of hypercholesterolemia was based on the findings that, in comparison with statin monotherapy, lapaquistat’s LDL-C–lowering efficacy was quite modest, the incidence of hepatotoxicity exceeded that of any commercially available statins at their highest dose,8 and there was no observable reduction in the incidence of muscle-related side effects. It is likely that the failure of lapaquistat acetate will end further clinical development of SSIs for the treatment of hypercholesterolemia. There are still several early-phase candidates in on-going clinical development that target more distal pathways in cholesterol biosynthesis, such as squalene monoxygenase, oxidosqualene cyclase, and lanosterol synthase.17 However, some of these agents, which inhibit oxidosqualene cyclase and lanosterol synthase, are associated with the development of cataracts. Thus, it remains to be determined whether any of these candidates will have efficacy and safety advantages over lapaquistat acetate, and more importantly, over statins. This begs the question as to whether there is a need for further development of inhibitors of cholesterol biosynthesis. Despite the inability to reach cholesterol target goals in some patients, the overwhelming clinical benefits and the overall safety profile of statins make it hard to justify using any other agents as the first-line therapy for cholesterol reduction in patients at risk for cardiovascular disease. If adjunctive therapy is required to reach LDL-C target goals, perhaps the addition of fibrates or niacin, which have been shown to reduce cardiovascular events, could be used.18,19 For patients who are intolerant of statin therapy because of potential side effects, adjunctive or monotherapy with bile acid sequestrants, or intestinal cholesterol absorption inhibitors may offer the best strategy for achieving targeted LDL-C goals. However, it is not known whether achieving further LDL-C reduction by nonstatins, alone or in combination with statins, will result in further decrease in cardiovascular events. For example, is reaching LDL-C target goals by any means with nonstatins more important in terms of cardiovascular risk reduction than how one achieves LDL-C target goals with statins? If not, then this would suggest that statin therapy is hard to beat when it comes to cardiovascular risk reduction. Whether this is due to cholesterol lowering, statin pleiotropy, or both, remains to be determined. Unfortunately, because of safety concerns, the clinical development of lapaquistat acetate did not progress far enough to address this issue.

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References


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