UNMET NEEDS IN THE TREATMENT OF ATHEROSCLEROSIS: WHY ARE WE NOT DONE YET?

Evan A. Stein, MD, PhD†

ABSTRACT

Heart disease remains the leading cause of death in the United States. Despite advances in surgical, interventional, and pharmacologic therapies for heart disease, prevention remains paramount in reducing morbidity and mortality. Almost 15 years of clinical experience with statin-based lipid-lowering therapy, including data from multiple large, evidence-based clinical trials, has brought about major changes in the approach to prevention of coronary heart disease. However, even with the gains of effective lipid-lowering therapy, a majority of at-risk individuals continue to experience clinical events, even with treatment.

Statin trials have provided a strong basis for prevention of coronary disease and associated events; however, it is time to take the next step toward eradication of the disease. A number of approaches are being evaluated, such as intensified reduction of low-density lipoprotein cholesterol and increasing levels of high-density lipoprotein cholesterol. Combination lipid-lowering therapy, using existing agents or a combination of existing and new drugs, represents one promising approach to coronary risk reduction. Combination therapy offers the opportunity to explore new and emerging treatments in the reduction of coronary risk, including inflammation.

ADVANCED STUDIES IN MEDICINE

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ABSTRACT

Coronary artery disease remains the leading cause of death among men and women in the United States. Approximately 14 million Americans have a history of myocardial infarction (MI) or angina. Each year, 1.1 million people have MIs; one third of these patients die from the MI, and one fourth of these patients will die within 1 hour of experiencing the MI. Thus, almost half of all coronary heart disease (CHD) deaths occur outside of a hospital, emphasizing that prevention of a first or repeated CHD event represents the best option for managing coronary disease risk. Among men, mortality from CHD decreased steadily from the mid-1980s to the mid-1990s, but has since begun to increase. There has also been a relative increase in CHD in women, such that morbidity and mortality from CHD is approaching that of males. The continuing morbidity and mortality trends clearly indicate a need for further improvement in strategies to reduce CHD risk. However, results of large, randomized, placebo-controlled trials of lipid-lowering therapy on CHD have provided the evidence base and should lead to the alteration of clinical practice that will contribute to substantial reductions in CHD mortality. The following discussion reviews the progress to date, the challenges of the future, and the potential strategies and options in lipid management to prevent CHD events.

WHAT HAS BEEN ACHIEVED?

Beginning with the Scandinavian Simvastatin Survival Study (4S) in 1994, results of 6 major clinical trials of various statin-based lipid-lowering therapy have now reported consistent and powerful evidence in over 50,000 people that low-density lipoprotein

* This article is based on a presentation given by Dr Stein at a satellite symposium held during the 75th Annual Scientific Sessions of the American Heart Association.
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cholesterol (LDL-C) therapy leads to a 25% to 35% reduction in the relative risk (RR) for CHD morbidity and mortality. Moreover, the trials showed consistent benefits regardless of the baseline LDL-C level. With respect to RR reduction, virtually every population studied has benefited from lowering of LDL. Collectively, results of the trials have shown that statins currently offer the most effective approach for reducing CHD2-7 (Table 1).

The benefits of statin-based lipid-lowering therapy have extended to every major subgroup of patients examined. In the 4S trial, diabetic patients, who had a substantially higher event rate compared with nondiabetic patients, reduced their future risk of CHD after receiving simvastatin therapy to that of nondiabetic patients who had not received the statin. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) demonstrated the benefits of treating low-risk patients with a statin. Overall, the risk in AFCAPS/TexCAPS for a new coronary event, which averaged approximately 1% per year, was significantly reduced during 5 years of treatment with lovastatin. As in the other statin trials, the benefits of treatment emerged early, after about 6 months of follow-up.5

Until recently, even with 5 major trials completed, the data had a few gaps that left room for controversy about the benefits of statin therapy. In particular, relatively little data existed with respect to the effects of statin therapy in women, in the elderly, and in patients with low LDL-C levels. Of the approximate 20 000 patients included in the Heart Protection Study (HPS) population, roughly one fourth of the participants were women and almost half of the patients were between the ages of 65 and 80 years.7 Almost one third of the HPS population had a baseline LDL-C level of less than 115 mg/dL. Overall, treatment with simvastatin resulted in a 24% reduction in the RR for vascular events, and the benefits were consistent in women, the elderly, and in patients who had low baseline LDL-C levels.

The major clinical trials have also shown a surprising beneficial effect of cholesterol reduction on stroke risk, which was not anticipated when the trials were designed. Originally observed in unplanned post-hoc analyses of the data from 4S, the stroke reduction has since been confirmed in trials that included stroke a priori as an endpoint. The overall reduction in stroke risk has ranged between 11% and 40%, being primarily seen in secondary prevention trials.8

What More Can Be Achieved?

Clearly, the ideal objective would be to eliminate all CHD events. In terms of lipid-lowering therapy, what magnitude would be required to achieve that goal? Based on results from the major secondary prevention trials, extrapolation shows an LDL-C of approximately 30 mg/dL might produce an event rate of zero. Extrapolation from primary prevention trials, which have involved a lower absolute risk, have indicated that an LDL-C level of approximately 50 mg/dL might result in total elimination of CHD events.

Such extrapolation from clinical trial results raises 2 obvious questions: will increasingly greater reductions in LDL-C levels result in additional benefits, and is it feasible to attain those LDL-C levels? Data from the 4S trial suggest that greater reductions in LDL-C do translate into greater reductions in event rates. A comparison of patients whose LDL-C levels declined by <34% versus 34% to 44% showed a 5.6% absolute reduction in event rate and those whose LDL-C levels declined by 44% to 70% with simvastatin therapy had a further 2.3% reduction in absolute risk.9 While these data suggest that greater reductions in LDL-C levels

<table>
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<tr>
<th>Clinical Events Trials</th>
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<td>4S</td>
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<td>LIPID</td>
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<td>WO SCO PS</td>
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<td>AFCAPS</td>
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*Nonfatal MI or CHD death in WO SCO PS, CARE, LIPID; nonfatal or fatal MI, unstable angina, or sudden cardiac death in AFCAPS; nonfatal MI, coronary death, or resuscitated cardiac arrest in 4S.
†vs placebo
do correlate with greater risk reduction, they do not provide a definitive answer.

The Effects of Atorvastatin and Simvastatin on Atherosclerosis Progression (ASAP) trial also provides data on the relationship between LDL-C reduction and cardiac risk.10 The trial compared aggressive lipid-lowering and conventional lipid-lowering therapy in a population of patients with familial hypercholesterolemia (average baseline LDL-C level nearly 300 mg/dL). The patients began therapy with atorvastatin 40 mg/day or simvastatin 20 mg/day, and the starting doses were doubled after 4 weeks. The primary endpoint was change in carotid intimal-medial thickening (IMT) after 2 years of treatment, as assessed by B-mode ultrasound. Participating patients randomized to aggressive lipid-lowering therapy had an overall reduction in carotid IMT, whereas patients treated conventionally had an increase in IMT ($P = .001$).

The ASAP investigators noted that aggressive cholesterol-lowering therapy induced regression of carotid IMT despite a mean LDL-C level of 150 mg/dL on treatment (after a 51% reduction in baseline LDL-C levels). The investigators concluded that future trials that have clinical, rather than anatomical, endpoints are necessary to demonstrate the benefits of aggressive cholesterol lowering on cardiovascular morbidity and mortality.

Several ongoing trials might provide more definitive answers regarding the benefits of aggressive versus conventional cholesterol-lowering therapy. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial involves 12 000 CHD patients treated with simvastatin 20 mg/day or 80 mg/day with or without folate/vitamin B$_{12}$ supplementation. Patients are being followed for 5 years, and the primary endpoints are cardiovascular death and non-fatal MI. LDL-C targets for the trial are 100 mg/dL in patients receiving 20 mg of simvastatin and 70 mg/dL in patients receiving the higher dose of the statin.

The Treat to New Targets (TNT) study involves 10 000 CHD patients randomized to atorvastatin 10 mg/day or 80 mg/day. The Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial includes 8888 patients randomized to simvastatin 20-40 mg/day or to atorvastatin 80 mg/day. The follow-up and primary endpoints in both trials are the same as in the SEARCH trial, and the TNT trial has the same LDL-C goals as SEARCH.

### Table 2. Lipid Therapy: Enhanced Efficacy

<table>
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<tr>
<th>Combination</th>
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<tr>
<td>LDL cholesterol</td>
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<td>- More effective</td>
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<td>- Statin + BAS (bile acid sequestrants)</td>
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<td>- Statin + IBAT (bile acid transport inhibitors)</td>
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<td>- Statin + MTPI (microsomal triglyceride transport inhibitors)</td>
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<td>- Statin + PPAR (peroxisome proliferator-activated receptor)</td>
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<td>- Statin + niacin</td>
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<td>LDL + triglycerides + HDL Cholesterol</td>
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<tr>
<td>Triglycerides + HDL Cholesterol</td>
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LDL = low-density lipoprotein; HDL = high-density lipoprotein.
greater lipid-lowering effects compared with a higher statin dose alone. Such findings demonstrate that drugs with different mechanisms of action work well when added to a statin base.

A particularly promising new approach is to combine a statin with a cholesterol absorption inhibitor. For example, adding 10 mg of ezetimibe to 10 mg of simvastatin leads to an additional 15% decrease in LDL-C compared with 10 mg of simvastatin alone. Furthermore, in 1 therapeutic step, the combination achieves the same results as 3 dose escalations or an 8-fold increase of simvastatin (from 10 mg to 20, 40, and 80 mg). Moreover, the combination of a low-dose statin and ezetimibe is well tolerated and avoids potential concerns about high-dose statin monotherapy (Figure).

The combination of a statin and niacin has been used for years in the United States. Niacin adds a relatively modest effect to a statin's LDL-C lowering ability. The primary impact of the combination is on triglycerides and HDL-C. One small placebo-controlled clinical trial demonstrated that the combination of niacin and simvastatin reduced the RR of a clinical event by 90% in a few years, and the overall event rate fell to 3% in patients who received the combination in a secondary prevention setting. The question remains as to whether we can utilize this combination in a large clinical trial and, by also lowering triglycerides and raising HDL-C combined with significant LDL-C reduction, achieve the same results.

If after appropriate use of a statin to reduce LDL-C there is need to reduce triglycerides and improve HDL-C, a logical therapeutic strategy would be the combination of simvastatin with niacin. However, given the patient and physician acceptance of niacin, fibrates are more commonly used in these patients. The combination with a fibrate remains controversial, and there is no outcome evidence of the combination at all to guide clinicians as to either the added effectiveness for CHD prevention over either drug alone, or the safety of the combination. The Veterans Affairs HDL-C Intervention Trial (VA-HIT) demonstrated that a fibrate can significantly reduce the risk of acute coronary events in high-risk patients who have existing CHD.

On the horizon are other potential combinations that await testing in clinical trials. These include a fibrate and a cholesteryl ester transfer protein (CETP), a PPAR-alpha agonist and a CETP inhibitor, a PPAR-alpha agonist and a statin, and others. We already know that we can improve lipoprotein profiles with these agents. However, if we “beautify” the lipid profile, will this translate into a greater reduction in clinical events?

**Antiatherosclerotic Therapy**

Several options exist for antiatherosclerotic therapy. Aspirin reduces the risk of clinical events, so the addition of aspirin to a statin should lead to additional benefits. Other agents with proven benefits for reducing clinical events include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers. Adding 1 or more of these agents to a statin makes sense, but the additional benefits have yet to be proven, or even evaluated in some instances, in large, well-designed clinical trials. On the horizon is the possibility of combining a statin with an acyl CoA:cholesterol acyltransferase (ACAT) inhibitor, a drug that is designed to reduce lipid uptake by the macrophage but has little if any effect on plasma lipid levels.

Future improvements in reducing CHD risk will be incremental. Perhaps giving patients higher doses of...
statins to achieve greater reductions in LDL-C will reduce the clinical event rate, as is being tested in the SEARCH, TNT, and IDEAL trials. Once these trials are completed, attention will turn to combination therapy in the hopes of achieving even greater reductions in clinical events. A statin might be studied in combination with niacin, a cholesterol absorption inhibitor, or a newer class of drug. Not to be overlooked is the emerging potential for therapeutic agents that target inflammation, which is the next step in atherosclerosis after apparent initiation by LDL-C entering the vascular wall. Investigation into the role of inflammation has uncovered numerous potential therapeutic targets. Also not to be overlooked are the contributions of thrombosis and fibrinolysis to acute coronary events. Various clot-related targets for reducing cardiovascular morbidity and mortality already are being explored.

Finally, the quest for better therapies should not obscure the progress that has been made toward reducing cardiovascular morbidity and mortality. With currently available therapies, lowering LDL-C alone can prevent 30% to 35% of coronary events. Failure to implement current knowledge into clinical practice represents one of the biggest obstacles to reductions in coronary risk. Perhaps no more than 20% of patients with CHD actually achieve the National Cholesterol Education Program LDL-C target of less than 100 mg/dL.

SUMMARY

Heart disease remains the leading cause of death in the United States. A high proportion of these deaths occur suddenly and out of the hospital, emphasizing that prevention offers the best option for reducing cardiovascular morbidity and mortality. Existing statins have been shown to reduce the risk of coronary events by 30% to 35%. More aggressive treatment can lead to greater reductions in LDL-C, but the impact on cardiac morbidity and mortality remains to be proven. Potential strategies to achieve greater reductions in clinical event rates include high-dose statin therapy, combination therapy with a statin and other classes of lipid-lowering agents, nonstatin combinations that primarily target triglycerides and HDL-C, and antiatherosclerotic therapy that combines lipid and nonlipid therapies.

REFERENCES