Atherosclerosis Imaging and the Future of Lipid Management

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Lowering low-density lipoproteins (LDL) by statin therapy to reduce the risk for major clinical events in patients with established atherosclerotic cardiovascular disease (ASCVD) represents a therapeutic triumph of modern medicine. With standard doses of statins, the risk for CVD events falls by approximately one third. Additional risk reduction occurs by adding other therapeutic modalities to statin therapy—antiplatelet drugs, antihypertensive agents, smoking cessation, and healthy lifestyle changes. Most of the benefit from these combined treatments appears to result from the stabilization of vulnerable plaques in patients who have advanced atherosclerotic disease; in other words, they reduce the likelihood of plaque ruptures that cause acute cardiovascular syndromes.

Although novel nonlipid therapies may well be developed in the future, persistent aberrations in lipid metabolism in the face of standard doses of statins remain attractive targets of therapy. Two of these potential lipid targets are residually elevated low-density lipoprotein cholesterol (LDL-C) and atherogenic dyslipidemia. Additional LDL lowering can be achieved either by yet higher doses of statins or by combining standard doses of statins with other LDL-lowering drugs (eg, bile acid sequestrants or ezetimibe). Atherogenic dyslipidemia consists of elevations of serum triglycerides, apolipoprotein B, and small LDL particles plus low levels of high-density lipoprotein cholesterol (HDL-C). Alternative therapies for atherogenic dyslipidemia available for combination with statins include fibrates and nicotinic acid.

For many patients with ASCVD, enhanced LDL lowering beyond that obtained with standard doses of statins may further reduce CVD events. Current guidelines for cholesterol management in these patients set an LDL-C goal of <100 mg/dL. The recent Heart Protection Study (HPS) findings strongly suggest that high-risk patients with a baseline LDL-C <100 mg/dL will still benefit when LDL-C levels are reduced to well below 100 mg/dL by drug therapy. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, carried out in patients with recent acute coronary syndromes, tested a high dose of statins that lowered LDL-C levels to 62 mg/dL and compared it with a standard dose that reduced levels to 95 mg/dL. Over a 2-year period, this lower LDL-C level accounted for 16% fewer major CVD events than did the higher level. In the A-to-Z trial, a similar design used in patients with acute coronary syndromes resulted in a strong trend toward fewer CVD events in a group receiving a high-dose statin (compared with a standard dose).

The data base on ASCVD patients that suggests incremental risk reduction by lowering LDL-C to a very low range is not strong enough to go beyond “therapeutic option” and mandate a very low goal. Three major trials with clinical end points are being carried out to test whether high-dose statins will lessen risk more than standard doses do and still have acceptable safety. When these trials are published over the next few months or years, the value, if any, of lowering LDL-C levels beyond those attained by standard doses of statins should become evident.

Many ASCVD patients manifest the metabolic syndrome and atherogenic dyslipidemia, with or without type 2 diabetes mellitus. It is tempting to speculate that treating atherogenic dyslipidemia (high triglyceride/low HDL-C) will cut risk more than can be obtained by LDL-C lowering alone. A series of clinical trials indicate that both fibrates and nicotinic acid do in fact reduce the risk for CVD events, albeit seemingly less than with statins. This benefit has been more apparent in patients with the metabolic syndrome, type 2 diabetes mellitus, or both. Unfortunately, one fibrate, gemfibrozil, conveys an increased danger of severe myopathy when combined with a statin. This myopathy risk may be reduced considerably by replacing gemfibrozil with fenofibrate because the latter does not interfere with statin catabolism. The combination of statin plus fenofibrate clearly improves the lipoprotein profile when compared with statin alone in patients with atherogenic dyslipidemia.

Nicotinic acid has not been used as much as have fibrates in clinical practice. This preference is in no small part the result of the side effects of high doses of nicotinic acid (ie, flushing and itching of the skin, liver function abnormalities,
raised glucose levels, and higher uric acid levels). Newer formulations and lower doses nevertheless have opened the door to the treatment of atherogenic dyslipidemia with fewer side effects. In particular, an extended-release preparation of nicotinic acid lessens the frequency of flushing. The combination of statin plus extended-release nicotinic acid clearly improves atherogenic dyslipidemia more than does a statin alone, particularly by raising HDL-C.

The report by Taylor et al in this issue of Circulation examines whether a statin combined with a low dose of extended-release nicotinic acid (1 g/d) will retard atherosclerosis in carotid arteries more than will a statin alone when patients manifest established coronary heart disease. The progression of atherosclerosis was assessed by changes in carotid intimal-medial thickness (CIMT). When nicotinic acid was added to statin therapy, progression of CIMT was retarded more than when a statin was tested alone. Rates of progression of CIMT overall were relatively small, but the finding of a significant difference in a blinded trial strongly supports a slowing of the progression of carotid thickening by combination therapy. The study by Taylor et al has the advantage over previous imaging studies in which combination of nicotinic acid plus statin was used but not compared with a statin alone.

A major question raised by the report of Taylor et al is whether a favorable change in intermediate atherosclerosis end points will faithfully predict a subsequent reduction in CVD events. In general, the finding of retardation in lesion progression by statin therapy, whether in carotid or coronary arteries, foreshadowed a reduction in CVD events in large statin trials. Although changes in lesion size reported in other imaging studies with CIMT or coronary angiography likewise were small, they nonetheless coincided with a substantial reduction in CVD events by similar therapies in large-scale clinical trials. The reasons why these surrogate end points seemingly “predict” clinical end points are not entirely clear. One possibility is that lipid-lowering therapies stabilize vulnerable lesions more than they change lesion size. Hence, any favorable change in lesion size may signify a stabilizing influence on plaque morphology. If so, the critical question becomes whether this phenomenon can be generalized. In other words, can any therapy that retards (or reverses) arterial lesion size, as determined by imaging techniques, be assumed to reduce clinical CVD risk?

The development of new therapies for the reduction of ASCVD events is at a crossroads. Any new therapies will not likely replace existing modalities such as statins and antiplatelet drugs. When statins and antiplatelet drugs are used in combination, clinical events appear to be reduced by ~50% or even more. Therefore, any newly developed agents probably can be employed only in combination with these standard drugs. Moreover, new modalities may well yield lesser reductions in subsequent events, perhaps in the range of 15% to 20%. To demonstrate such efficacy in clinical end point trials, larger numbers of patients will be required than in previous monotherapy trials with statins or antiplatelet drugs. Obtaining incremental risk reduction in the range of 15% to 20% would be clinically meaningful but more difficult to document. If trials are underpowered for practical or financial reasons, then potentially useful therapies could be discarded. A poor clinical end point trial is worse than no clinical trial at all. For all of these reasons, trials with surrogate end points, such as the study by Taylor et al, are more affordable and manageable and thus are increasingly attractive. They may become the future of new drug testing for the prevention of ASCVD. The US Food and Drug Administration will be faced with the decision whether to register new drugs on the basis of atherosclerosis imaging studies without clinical end point trials.

Two fundamental problems haunt investigations with new combination therapies that use surrogate end points alone. First, even if a positive result is obtained, the absolute benefit attributable to the second drug cannot be defined. Second, the safety of long-term therapy with any new drug combination cannot be ensured if the study recruits too few patients. With regard to the first problem, previous clinical trials suggest that both fibrates and nicotinic acid reduce major CVD events in the range of 15% to 20%. Therefore, retarding lesion progression by adding nicotinic acid to statin therapy is reassuring. It suggests enhanced clinical efficacy. It may require setting a higher bar for entirely new agents, in which the absolute efficacy of monotherapy is unknown. For any new agents, therefore, a clinical end point trial may be required for registration by the Food and Drug Administration.

Even if enhanced risk reduction appears likely by combining nicotinic acid or fibrate with statin therapy, the question of side effects still exists. Clearly, a large database of experience defines safety profiles during monotherapy with these drugs. Considerable experience suggests that the combination of statins plus nicotinic acid does not produce side effects beyond those from monotherapy with either. The major concern about nicotinic acid treatment of patients who have the metabolic syndrome and type 2 diabetes mellitus is deterioration of glycemic control. Such deterioration often occurs with higher doses of nicotinic acid. A recent study in patients with type 2 diabetes mellitus demonstrated that extended-release nicotinic acid (1 g/d) does not significantly worsen glycemic control in most patients. In the article by Taylor et al, average glycemic control appeared to decline somewhat after the addition of nicotinic acid to statin therapy. Hemoglobin A1c percentages were not reported, however. This is unfortunate; monitoring hemoglobin A1c is probably the preferred way to assess glycemic response during treatment with nicotinic acid. Reported data and our clinical experience warn that some patients are sensitive to treatment with nicotinic acid and will show some deterioration in glycemic control; many others seemingly are resistant to elevations in glucose level. At present it is not possible to predict who will respond adversely to even low doses of nicotinic acid; hence, monitoring with regular measurements of hemoglobin A1c appears to be indicated for patients with any degree of elevated glucose.

Current cholesterol management guidelines permit the optional use of fibrates or nicotinic acid for the treatment of atherogenic dyslipidemia in high-risk patients who are already on statin therapy. The study by Taylor et al supports this option in such patients. The finding of carotid plaque
retardation by an imaging technique is reassuring and offers a greater rationale for exercising this therapeutic option in high-risk patients with low HDL-C levels, such as those with the metabolic syndrome or type 2 diabetes mellitus.

References


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