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.

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.10 The combination of statin plus extended-release nicotinic acid clearly
improves atherogenic dyslipidemia more than does a statin alone, particularly by raising HDL-C.11

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.12 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 al12 has the advantage over previous imaging studies in which combina-
tion of nicotinic acid plus statin was used but not compared with a statin alone.13,14

A major question raised by the report of Taylor et al12 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.1 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 anti-
platelet 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 prob-
ably 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,12 are more affordable and
manageable and thus are increasingly attractive. They may
come 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%.1 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 combin-
ing 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 com-
bination 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.15 Such deterioration often
occurs with higher doses of nicotinic acid.15 A recent study16
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,12 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 treat-
ment 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 al-
ready on statin therapy.1,6 The study by Taylor et al12 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


Key Words: Editorials ■ atherosclerosis ■ lipoproteins ■ statins ■ trials
Atherosclerosis Imaging and the Future of Lipid Management
Scott M. Grundy

Circulation. 2004;110:3509-3511
doi: 10.1161/01.CIR.0000151100.28000.B3
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/110/23/3509

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/