EDITORIAL

Intensive Statin Therapy — A Sea Change in Cardiovascular Prevention

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In the management of atherosclerotic vascular disease, statin drugs have already surpassed all other classes of medicines in reducing the incidence of the major adverse outcomes of death, heart attack, and stroke. A decade ago, their effectiveness was first demonstrated by the results of the Scandinavian Simvastatin Survival Study (4S), a trial that provided definitive evidence of the benefit of simvastatin, as compared with placebo, in improving survival.[1] By 1996, statins were dubbed "miracle drugs," and their underuse was duly noted.[2] Prominent scientists in the field even speculated that heart attacks might be "gone with the century."[3] For the most part, it was believed that the benefit of statins was due to the lowering of low-density lipoprotein (LDL) cholesterol levels.

In 2002, the Heart Protection Study not only confirmed the benefit of statins but raised new questions. This study, the largest trial of a statin, showed that an overall 25 percent reduction in the incidence of coronary events was associated with a reduction of 40 mg per deciliter (1.03 mmol per liter) in the LDL cholesterol level.[4] Equally important, patients with a "normal" base-line LDL cholesterol level — that is, below 100 mg per deciliter (2.59 mmol per liter) — according to the currently accepted National Cholesterol Education Program guidelines for therapy,[5] received just as much benefit as those with high LDL cholesterol levels. This surprising finding raised the question of whether the benefits of statins were fully attributable to their effects on LDL cholesterol.

The "pleiotropic" actions of statins — the term refers to their several distinct and seemingly unrelated effects, apart from lowering LDL cholesterol levels — have also been suggested by their salutary effects in a wide range of diseases, including multiple sclerosis, neurodegenerative disorders such as Alzheimer's disease, and nonischemic cardiomyopathy, in the prevention of bone fractures, and even in the reduction in the incidence of some types of cancer. More evidence is needed to prove the benefit of statins for these varied conditions, but the diverse effects of these drugs do not appear simply to be related to cholesterol lowering. For the most part, a generalized antiinflammatory action has been invoked as an explanation.

Virtually everything we understood about the effects of statins on atherosclerotic coronary disease had come from placebo-controlled trials until two new head-to-head randomized trials were completed. In the mechanistic Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial,[6] Nissen and colleagues compared atorvastatin with pravastatin to determine whether the extent of progression of atherosclerotic coronary disease could be differentiated between the two drugs with the use of intravascular ultrasonography. During 18 months of study-drug treatment, in a total of 502 patients with stable coronary disease who could be evaluated, atorvastatin was superior to pravastatin in terms of limiting the progression of atheroma. LDL cholesterol levels were lowered substantially more with atorvastatin, but careful analysis showed that "LDL-cholesterol reduction alone did not explain all of the differences in efficacy."[6] Even though this trial was not designed to detect differences in clinical outcomes, it attracted considerable attention because of the implication that more intensive lipid-lowering therapy was the preferred approach.[7-9]

In this issue of the *Journal*, Cannon and associates report on the Pravastatin or Atorvastatin Evalu-

ation and Infection Therapy (PROVE-IT) trial, a comparison of the effects on clinical outcomes of exactly the same daily doses of atorvastatin (80 mg) and pravastatin (40 mg) as used in REVERSAL.[10] In 4162 patients with acute coronary syndromes who were followed for a mean of 24 months, atorvastatin was superior to pravastatin, resulting in a 16 percent lower risk of the primary end point, a composite of major cardiovascular events.[10] The benefit of atorvastatin was evident very early, even in the first 30 days of therapy, and was consistent among all subgroups. Mortality from all causes was reduced by 28 percent, and every other individual outcome favored the use of atorvastatin — with the exception of stroke, for which there was little difference between the groups.

This result is a major surprise, for several reasons. First, the trial was designed to demonstrate the noninferiority of pravastatin, as compared with aforvastatin, and not its superiority. Second, the beneficial effect appeared extremely rapidly, whereas in the placebo-controlled trials, such as 4S[1] and the Heart Protection Study,[4] there was a lag of approximately 18 months before the event curves separated. Third, although PROVE-IT was an event-driven trial (that is, it was prospectively designed to end after a certain number of events had occurred), it was felt that the short duration of follow-up, the use of "soft" end points (those that do not cause irrevocable damage) in the composite measure, and the relatively small number of patients would make it impossible to discern differences between the effects of the two statins. In contrast, three other large trials comparing different statins or different doses of the same statin, with study populations ranging from 8888 to 12,000 patients and with five-year planned follow-up, are currently under way.

Taken together, the REVERSAL and PROVE-IT trials herald a shake-up in the field. Previously, it was considered optimal to lower the LDL cholesterol level to less than 100 mg per deciliter.[4] That axiom has now come under serious question, because we know that atherosclerotic progression and clinical outcomes will be ameliorated by much more aggressive use of statins. Indeed, the 80-mg dose of atorvastatin is the most intensive LDL-lowering regimen for which data on clinical outcomes are available. Unfortunately, we do not know the precise mechanism of action responsible for atorvastatin's superiority. The drug is lipophilic, whereas pravastatin is water-soluble, but this is just one feature of each drug's profile. Analysis is further complicated by the fact that lowering LDL cholesterol results in other antiinflammatory effects, such as reductions in the levels of high-sensitivity C-reactive protein (CRP) and soluble CD40 ligand. However, there is a lack of correlation between LDL cholesterol and inflammatory markers.

Even in these two trials, the results with respect to inflammatory markers are disparate. The patients in the REVERSAL trial, who had stable coronary disease, had a markedly different degree of reduction in the CRP level with the two drugs, but in PROVE-IT, in which patients with acute ischemic heart disease made up the study population, there was relatively little difference in the degree of reduction in CRP (Table 1). Clearly, more investigation is needed to disentangle the independent and interdependent effects of statins on LDL cholesterol levels and the process of arterial inflammation.

The implications of this turning point — that is, of the new era of intensive statin therapy — are profound. Even today, only a fraction of the patients who should be treated with a statin are actually receiving such therapy.[10] It is estimated on the basis of the criteria in current national guidelines that 36 million people in the United States should be taking a statin, but only 11 million are currently being treat-

Table 1. Key Findings in Two New Trials of Statin Drugs.*

Variable	REVERSAL	PROVE-IT
Clinical indication for therapy	Stable coronary disease	Acute coronary syndromes
Length of follow-up (mo)	18	24
LDL cholesterol†	150	106‡
Base-line (mg/dl)		
Atorvastatin group (mg/dl)	79	62
Percent decrease	46	42
Pravastatin group (mg/dl)	110	95
Percent decrease	26	10
High-sensitivity CRP		
Base-line (mg/liter)	2.9	12.3
Atorvastatin group (mg/liter)	1.8	1.3
Percent decrease	36	89
Pravastatin group (mg/liter)	2.9	2.1
Percent decrease	5	83

* REVERSAL denotes Reversing Atherosclerosis with Aggressive Lipid Lowering trial, PROVE-IT Pravastatin or Atorvastatin Evaluation and Infection Therapy trial, LDL low-density lipoprotein, and CRP C-reactive protein.
† To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
‡ One fourth of the patients were taking a statin drug at the time of enrollment.

ed.[11] Worldwide, the discrepancy is even more staggering; more than 200 million people meet the criteria for treatment, but fewer than 25 million take statins. One of the most important reasons for this degree of undertreatment is cost, and more aggressive use of statins may exacerbate the problem. The recommended starting dose of atorvastatin is 10 mg per day; the cost at this dosage in Cleveland pharmacies is $900 per year. The 80-mg dose costs $1,400 per year. The statin drugs already account for the largest prescription drug expenditure in the United States, at $12.5 billion per year.[12] Treatment based on the new data could cause the costs associated with statin therapy to skyrocket even further.

In addition to the likely changes in practice, the lessons of the new findings for clinical investigation are many. The combination of a clinical-outcomes trial (PROVE-IT) and an imaging study (REVERSAL), in which identical doses of the two drugs were used, yields a compelling validation of intravascular ultrasonography as a surrogate measure of the clinical benefits of antiatherosclerotic agents. This approach was presaged by comparative studies of statins in which B-mode ultrasonography was used to measure carotid-artery intimal–medial thickness. Furthermore, these two studies strongly reinforce the need to engage in more head-to-head trials of drugs within the same class, despite the recent assertion by a senior Food and Drug Administration official that "there is almost never a difference between active treatments."[13] We have long suffered from ignorance as a result of not having comparative data for similar agents, and it is well worth the resources and effort to illuminate such therapeutic choices.

There will soon be a sea change in the prevention and management of atherosclerotic vascular disease. The proportional reduction in major clinical outcomes that results from aggressive statin therapy is of the same order of magnitude as that seen when statins were compared with placebo in controlled trials. Intensive therapy with statins, monitored by means of measurements of LDL cholesterol or biologic markers of inflammation, is likely to result in even greater steps toward actualizing the full benefit of this remarkable class of medicines.

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