The Nature of the Statins

To the Editor:

In his editorial,1 Furberg cites CURVES2 as demonstrating that atorvastatin “unfavorably influences” HDL cholesterol (HDL-C) concentrations. In fact, atorvastatin 10 to 40 mg/d increased HDL-C 4.8% to 5.5%, typical for a statin. In a much smaller group, atorvastatin 80 mg/d did not affect HDL-C levels.2 The sample size (10 patients) raises questions, because HDL-C response with statins as a class can vary; larger trials of atorvastatin 80 mg/d demonstrated significant increases (7% to 26%).3,4 Furberg also states that with proper dose titration, the “natural statins” achieve LDL cholesterol (LDL-C) reductions similar to those of atorvastatin. In CURVES, atorvastatin 10 mg once daily was better at LDL-C lowering than any single daily dose of fluvastatin, lovastatin, pravastatin, or simvastatin except simvastatin 40 mg. Atorvastatin 20 mg once daily was better than all single daily doses of the other agents.

I believe the term “natural statins” is inexact and should not be adopted. Although lovastatin and pravastatin are fungal derivatives, simvastatin is semisynthetic. While one might call any plant-derived compound “natural,” one should carefully define the meaning to avoid misinterpretation. There may be the implication, as exploited by the alternative medicine industry, that synthetic drugs have detrimental effects that would not be expected from “natural” products. “Natural” may also imply that over-the-counter products such as Colestipol, which contains lovastatin, may be taken without physician supervision.

Furberg emphasizes that the “natural statins” were the agents used in the published clinical end-point trials. More exactly, lovastatin, pravastatin, and simvastatin are the first- and second-generation statins (Food and Drug Administration approval 1987–1991) and so were the first available for use in long-term trials. Available data—from the secondary-prevention Atorvastatin Versus Revascularization Treatment trial (36% decrease in ischemic events) and Lipoprotein and Coronary Atherosclerosis Study (reduced coronary lesion progression and beneficial clinical event trends with fluvastatin therapy)—suggest that clinical outcomes are beneficial with newer-generation statins as well.

All the approved statins have a common mechanism of LDL-C lowering. Extensive published data demonstrate safety regardless of agent derivation. Data do not support clinically important differences among the statins concerning effects on lesion stability or vascular function. The message the medical community needs to hear and understand, in particular because many patients are not receiving the therapy they need, is that the degree of LDL-C lowering enabled by this breakthrough class of drugs is remarkably consistent in benefit and has established LDL-C lowering as fundamental to preventive cardiology.

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Response

Dr Jones raises several important issues in his letter. My comment on atorvastatin and HDL cholesterol was also based on the knowledge of a recently published large comparative trial involving 842 patients.1 Atorvastatin 40 mg daily was less than half as effective as simvastatin 80 mg daily in raising HDL cholesterol levels. This dose of atorvastatin had no effect on apolipoprotein A-I. Particularly troubling was the observation that these findings were most pronounced in those with low baseline levels of HDL cholesterol.

A careful comparison of the LDL-lowering potential of the 6 statins from many sources shows a well-known but moderate difference in potency. At the recommended initial dose and the highest dose, atorvastatin lowers LDL cholesterol by 37% and 55%, simvastatin by 35% and 47%, and lovastatin by 26% and 40%, respectively. These lipid-lowering effects are sufficient in the large majority of patients to bring LDL cholesterol below 125 mg/dL. There are no clinical trial data to suggest that a further reduction is beneficial.

The AVERT trial (Atorvastatin Versus Revascularization Treatments) had a total of 11 major events (death, nonfatal myocardial infarction, or stroke) evenly distributed between atorvastatin (n=5) and placebo (n=6). There is no available documentation that any of the synthetic statins reduces major cardiovascular events in a manner repeatedly shown for the fermentation-derived statins.

The falacy of relying on surrogate outcomes, such as LDL cholesterol reduction, for regulatory approval and clinical decision making is illustrated by the findings from large trials of clofibrate2 and hormone replacement therapy.3 The fundamental principle of preventive cardiology is to reduce cardiovascular events, not just surrogate outcomes. Medicine should be evidence based.

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