

## Statins—Similarities and Differences

*Based on a debate between Terje Pedersen, MD, PhD,  
and Allan Gaw, MD, PhD*

### **Debate Summary**

The number of statins available to physicians continues to grow, leading to the question: Are all statins alike? Comparisons of side effects and safety profiles and the dose-response relationship among the different drugs show similar results. The cholesterol-lowering action of each depends on its ability to lower low-density lipoprotein cholesterol (LDL-C). On the other hand, the molecular structures of the newer statins are not similar and could have an effect on the mechanism of action of the compounds. Differences in metabolism also suggest the possibility of serious drug-drug interactions, and differences in levels of lipid reduction at varying dosages among the statins point to clinical variation as well.

### **Dr. Pedersen:**

Except for minor pharmacologic differences, all currently available statins are the same. They share a common mechanism of action, similar efficacy, and a similar safety profile.

All statins lower cholesterol by inhibiting HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase, thus preventing the formation of the major building block of the cholesterol molecule. Although there may be some differences among the affinity of statins for the target molecule, such differences are of little consequence to clinicians, who simply have to increase the dose of the statins with lower affinity.

An elevated cholesterol level is widely considered to be a risk factor for coronary heart disease (CHD). High cholesterol

should, however, be considered a causative factor because it independently, consistently, and strongly predicts CHD. The relationship between elevated cholesterol and CHD events and mortality has been demonstrated in many epidemiologic studies, such as the Multiple Risk Factor Intervention Trial (MRFIT),<sup>1</sup> which showed a log-linear relationship over a wide range of cholesterol levels.

Clinical studies evaluating the cholesterol-lowering properties of various statins reflect the same dose-response relationship for each statin, with all statins falling along the same regression line. This underscores the premise that all statins are the same. If significant differences among the statins existed as a result of their ancillary properties, the dose-response relationship for trials evaluating a particular statin would not be on the regression line, but would instead have a point estimate for benefit falling below the regression line.

The cholesterol-lowering action of statins depends on their ability to lower low-density lipoprotein cholesterol (LDL-C). When statins were first developed in the 1980s and early 1990s, the companies manufacturing these drugs were cautious about dosage. Some waited considerable time before daring to market doses high enough to take advantage of the full potential of their statins. For example, it took the company that developed simvastatin 10 years to realize that doses above 40 mg, which was considered the maximal dose, would provide

even greater benefit in terms of reducing LDL-C levels and the risk for coronary events. Now another company is developing dosage formulations of its statin at 80, 160, and 320 mg.

An internal analysis of the relationship between the changes in various lipids and lipoproteins after 1 year of therapy, and the subsequent reduction in the coronary-event rate in the Scandinavian Simvastatin Survival Study (4S), revealed that a 1% reduction in the LDL-C level was associated with a 1.7% reduction in the risk of a coronary event, which is highly statistically significant.<sup>2</sup> In the same analysis, lowering LDL-C also reduced total cholesterol and non-high-density lipoprotein cholesterol (HDL-C). In contrast, the reduction in triglyceride levels seen with statin treatment had no significant impact on prognosis, and the increase in HDL-C levels was only marginally prognostically significant ( $P = 0.039$ ). Thus, virtually all of the reduction in coronary events in the 4S trial can be attributed to the reduction in LDL-C levels.

A comparison of the side-effect profiles of currently available statins revealed them to be remarkably similar, with no major differences in either the incidence or seriousness of side effects.<sup>3-5</sup> Moreover, all statins are generally well tolerated.<sup>6-8</sup>

In clinical trials using pravastatin,<sup>9-11</sup> lovastatin,<sup>12</sup> and simvastatin,<sup>13</sup> the incidence of abnormal liver-function tests was similar among the trials and also between the placebo and treated groups. The incidences of cancers, deaths from suicide or violence, total deaths, total noncardiovascular events, and study withdrawals because of adverse events were also remarkably similar in these trials.<sup>9-13</sup>

In brief, the currently available statins have the same mechanism of action and demonstrate similar efficacy and safety across a broad range of cholesterol levels. Statins differ only in dosage.

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**Dr. Gaw:**

New structural, pharmacologic, and clinical evidence indicate that all statins are not the same.

Although the molecular structures of lovastatin and pravastatin are very similar, the structures of the newer statins—fluvastatin, atorvastatin, cerivastatin, and rosuvastatin—are not similar. Some experts say that structural differences are of little clinical consequence, but that is simply not the case. Even small structural differences between compounds can have a huge impact on the mechanism of action of a compound and, ultimately, on physiology. For example, small structural differences in testosterone, estro-

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—Allan Gaw, MD, PhD

gen, and progesterone molecules account for some of the most major differences in physiology.

Structural differences also account for differences in pharmacology and pharmacokinetics. The overriding differences among the statins in pharmacology and pharmacokinetics are those concerning the relative lipophilicity and hydrophilicity of the statins (Table). For example, cerivastatin, simvastatin, fluvastatin, and atorvastatin are relatively lipophilic, while pravastatin and rosuvastatin are essentially hydrophilic. Clinically, these differences have a major impact on tissue penetration and metabolism of the compounds.

Although statins are predominantly metabolized by the cytochrome P450 system in the liver, they are metabolized by different isoenzymes within the system (Table). This metabolic difference has major clinical implications regarding drug-drug interactions. Atorvastatin, lovastatin, and simvastatin are predominantly metabolized by the P450 3A4

isoenzyme, resulting in the formation of a variety of metabolites. Fluvastatin and cerivastatin, by comparison, are metabolized by the P450 2C9 isoenzyme, also resulting in the formation of a variety of metabolites. Because of pravastatin's water solubility, however, it undergoes no significant hepatic metabolism and is excreted virtually intact.

Because atorvastatin, cerivastatin, lovastatin, and simvastatin are metabolized by the P450 3A4 isoenzyme, each has the potential to interact with other drugs, such as erythromycin and diltiazem, which are metabolized by the same pathway. Thus, if any 1 of these 4 statins is given together with another drug that is metabolized by the P450 3A4 pathway, the circulating level of the statin is likely to increase. This increases the possibility of a serious statin side effect, such as myopathy, or, at its most extreme, rhabdomyolysis. Not too long ago, mibefradil was withdrawn from the world market because of its adverse interaction with lovastatin and simvastatin, demonstrating that such an interaction is not a theoretical issue, but a very real one.

In addition to their structural and pharmacologic differences, statins also exhibit clinical differences. Although

statins all lower total cholesterol and LDL-C levels, they do so to varying extents. As demonstrated in the CURVES study—an 8-week randomized open-label trial in patients with hypercholesterolemia—atorvastatin at doses of 10, 20, and 40 mg/day reduced total and LDL-C levels to a significantly greater extent ( $P \leq 0.01$ ) than did milligram-equivalent doses of fluvastatin, lovastatin, pravastatin, or simvastatin.<sup>14</sup> When 10-mg doses of 3 of these statins were given, the LDL-C reductions were 19% with pravastatin, 28% with simvastatin, and 38% with atorvastatin. Furthermore, the start dose of atorvastatin, 10 mg/day, produced LDL-C reductions comparable to or greater than those produced by 10, 20, and 40 mg of simvastatin ( $P < 0.02$ ); 10, 20, and 40 mg of pravastatin; 20 and 40 mg of lovastatin; and 20 and 40 mg of fluvastatin. Similarly, a dose-ranging study with rosuvastatin found that a 10-mg dose of atorvastatin reduced LDL-C levels by 51%.<sup>15</sup> Clearly, statins differ where it matters most—in patients.

Are all statins the same? Based on the evidence of structural, pharmacologic, and clinical differences, the answer is clearly no.

## REBUTTAL

### *Dr. Pedersen:*

Although there are subtle differences among the statins with regard to their pharmacology and pharmacokinetics, the potential for adverse drug-drug interactions is virtually nonexistent. In the 4S, in which 2322 patients were treated with simvastatin for 5.5 years, there was only 1 case of myopathy.<sup>13</sup> In my personal clinical experience, I have prescribed statins for hundreds of patients and have never had a problem with drug-drug interactions. For the overwhelming majority of patients treated with statins, and for the clinicians who prescribe statin therapy for patients with CHD, the dif-

**Table.** Pharmacologic and Clinical Differences Among Statins

Statin	Hydrophilic/Lipophilic	Metabolism
Atorvastatin	Lipophilic	P450 3A4
Cerivastatin	Lipophilic	P450 2C9
Fluvastatin	Lipophilic	P450 2C9
Lovastatin	Lipophilic	P450 3A4
Pravastatin	Hydrophilic	Not extensively metabolized
Simvastatin	Lipophilic	P450 3A4
Rosuvastatin	Hydrophilic	P450 2C9, P450 2C19

ferences in pharmacokinetics are of absolutely no consequence.

What matters most are the observations from the 5 major clinical trials evaluating the efficacy of statin therapy.<sup>9-13</sup> However, it is impossible to compare these trials head to head because the researchers had recruited patients with very different baseline characteristics, including substantial differences in baseline LDL-C levels. Moreover, these trials did not use high dosages or equipotent dosages, as discussed in this debate. Therefore, the LDL-C-lowering effects of the 3 statins used in the 5 trials varied considerably.

To find clinically meaningful differences among the statins, it is necessary to do a head-to-head comparison, using equipotent dosages, in a randomized fashion. Only then can we determine whether the differences are clinically significant.

**Dr. Gaw:**

The 4S, the first of the 5 large-scale clinical trials evaluating statins, literally changed clinical practice throughout the world with regard to managing patients with hypercholesterolemia. As a group, the trials demonstrated consistent clinical benefits and a reduction in relative risk of approximately one third across the board.<sup>9-13</sup>

Despite compelling evidence of the linear relationship between the degree of cholesterol lowering and the reduction in coronary risk, the differing magnitudes of cholesterol reduction with equal doses of different statins argue against the premise that all statins are the same. When a 10-mg dose of different statins reduces LDL-C levels by 19% to 51%, and when an 80-mg dose of rosuvastatin tested in a dose-ranging study reduces LDL-C levels by 65%,<sup>16</sup> one can only conclude that all statins are not the same.

Clearly, the currently available statins provide clinicians with effective therapeutic choices. However, all statins are not the same; they differ in structure, in pharmacokinetics, and most importantly, in our patients.

## QUESTION-AND-ANSWER SESSION

### Elevated Liver Enzymes

**Question from the Audience:** *Dr. Pedersen, if a statin is discontinued because of abnormal liver function values, is it worth trying another statin? In other words, is the adverse-event profile always going to be the same?*

**Dr. Pedersen:** It appears that the effect of a statin on liver enzymes is largely related to the dose. Rather than trying another statin, it is worthwhile lowering the dose of the statin you are using. Cut the dose in half and then, at a later time, try increasing the dose again. In most cases, elevated liver enzymes during statin therapy are transient and often are caused by something else. In fact, the incidence of elevated liver enzymes in the statin trials was the same in both the treatment and placebo groups.<sup>9-13</sup>

### Effects on HDL-C

**Question from the Audience:** *Dr. Gaw, do you think the changes in HDL-C that occur during high-dose statin therapy are clinically meaningful? Also, if one statin increased HDL-C significantly better than another, would you prefer that statin? Is the ability of a statin to significantly raise HDL-C levels prima facie evidence for a different mechanism of action depending on the structure of the drug?*

**Dr. Gaw:** To answer the first question, I think the increase in HDL-C we see with statin therapy is extremely important; it is part of the overall risk correction, as is the reduction in triglyceride levels. We tend to focus on lowering LDL-C because that is the most impressive in terms of the percentages. However, we should not forget the favorable effects of the statins on HDL-C and triglycerides.

Some data have shown the HDL-C-raising effect is attenuated or even reversed with some higher doses of the newer statins. However, in the dose-ranging study of rosuvastatin, all of the tested

doses—from 1 to 80 mg—showed an increase in HDL-C levels ranging from 7% to 14%.<sup>17</sup>

Therefore, I don't think it's a general rule that a highly potent statin will automatically have a negative effect on HDL-C.

**Question from the Audience:** *Dr. Pedersen, based on your experience as a 4S investigator, what is your impression about statins and HDL-C?*

**Dr. Pedersen:** The alleged differences among statins in raising HDL-C levels are not borne out by the various clinical trials. Some trials using high doses of atorvastatin showed no increase in HDL-C levels, while others showed an increase of 13%.<sup>18</sup>

In our internal analysis of the 4S data, HDL-C was found to be a weak predictive factor, probably because LDL-C was such a strong predictive factor. That is not to say, however, that HDL-C is unimportant.

#### Rosuvastatin Studies

**Question from the Audience:** *Dr. Gaw, are there ongoing trials looking at the relationship between LDL-C reduction and cardiovascular events with rosuvastatin?*

**Dr. Gaw:** A large international clinical trial program is under way with rosuvastatin. Many of the trials in the program have been put in place to evaluate the clinical endpoints.

#### Anti-inflammatory Effects

**Question from the Audience:** *Is there any evidence in animals or in humans to support independent anti-inflammatory properties in one statin versus another? In other words, can we focus on the pleiotropic effects, particularly the anti-inflammatory effects, to help us choose a statin?*

**Dr. Gaw:** Many of the anti-inflammatory effects evaluated to date have been studied in great detail, particularly with pravastatin. I am thinking specifically of a subgroup analysis from the Cholesterol

and Recurrent Events (CARE) trial. However, no extensive surveys have been conducted to look at the mechanism of action for anti-inflammatory effects for different statins. Therefore, I am not sure that we are in a position to say whether a mechanism exists that is common to all statins or whether a mechanism exists that is specific to certain statins.

Clearly, if a common mechanism exists, it would probably be one of the key features of statins, particularly because we are beginning to understand that inflammatory processes play a very important role in the development of atherosclerotic disease, and in vascular disease in general. Perhaps a common mechanism would help explain how statins not only prevent coronary disease, but also reduce the risk for cerebrovascular disease and perhaps for other vasculopathies as well.

**Dr. Pedersen:** We looked at inflammatory markers in the 4S and the changes induced by simvastatin treatment. Our findings were the same as those of the pravastatin trials. Our explanation for these anti-inflammatory effects is that statins reduce oxidized LDL-C, which is a very potent inducer of inflammation. Thus, the anti-inflammatory effects of statins are mediated through the reduction of LDL-C levels.

**Question from the Audience:** *Were you able to see a correlation between the reduction in LDL-C and the reduction in the inflammatory marker? Or was it difficult to show that?*

**Dr. Pedersen:** We have not done that analysis yet, but the amount was in the same range as for pravastatin.

**Dr. Gaw:** In the CARE studies, the researchers found no strong relationship between the amount of LDL-C lowering and the amount of the anti-inflammatory effect. This prompted the CARE investigators to suggest that the anti-inflammatory effects of pravastatin were caused by an independent mechanism. I believe,

however, that definitive studies in this area still need to be done.

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