

**International Task Force for the Prevention of Coronary
Heart Disease**

**Summary of the Expert Panel Meeting:
Cholesterol-lowering with statins – are they all the same?**

New Orleans, March 7 2004

Cholesterol lowering with statins – are they all the same?

Much interest has recently surrounded the question of whether all the available statins are basically the same – and therefore interchangeable – in terms of their clinical effects. To examine this question, the International Task Force for the Prevention of Coronary Heart Disease organized an Expert Symposium at the occasion of the American College of Cardiology meeting in New Orleans, Louisiana, on 6. March 2004. The participants at this meeting were: Dr. Gerd Assmann (organizer of the meeting), Dr. Alberto Corsini, Dr. Jean Davignon, Dr. Scott M. Grundy, Dr. Peter Libby, Dr. Winfried Maerz, Dr. R. Preston Mason, Dr. Steven E. Nissen, Dr. Terje R. Pederson, Dr. Paul M. Ridker, Dr. Walter Riesen, Dr. Ernst J. Schaefer and Dr. David Waters. The following document presents a summary of the proceedings of this meeting.

Since the discovery of the first statin, compactin, by Akiro Endo in the laboratories of the Sankyo corporation nearly 30 years ago, this class of drugs has advanced to become the mainstay of cholesterol-lowering therapy. More than twenty million people take statins world-wide, and the world market for this class of drugs is estimated at about 19 billion US Dollars.

Statins are a chemically and pharmacologically diverse group of drugs that share the ability to inhibit hydroxymethylglutaryl coenzyme A (HMGCoA) reductase, the enzyme that controls the rate-limiting step of cholesterol synthesis. The currently available statins are lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin and rosuvastatin.

In asking the question “are all statins basically the same?”, there are four distinct issues we need to address:

1. Are all statins the same in terms of their principal therapeutic effect, namely lowering of LDL cholesterol?
2. Lowering LDL cholesterol is not an aim in itself. Rather, the goal of LDL cholesterol-lowering is to prevent progression of atherosclerosis and its complications of myocardial infarction, stroke, peripheral vascular disease, and cardiovascular death. We must therefore ask the question: are all statins the same in terms of therapeutic end-point reduction?
3. In the past five years, statins have been shown to have a wide-range of secondary, so called pleiotropic effects. These range from effects on oxidation over a putative anti-inflammatory effect to possible effects on cell turnover. The third question therefore is: are all statins the same in terms of their pleiotropic effects?
4. Are all statins the same in terms of toxicity?

In the following, these questions will be addressed in turn.

Are all statins the same in terms of LDL cholesterol lowering?

The main action of statins is to specifically and reversibly inhibit the enzyme HMG CoA reductase, which controls the rate-limiting step in cholesterol synthesis. Faced with this drop in endogenous production, the cells of the body, in particular those of the liver, react by increasing their uptake of cholesterol from the bloodstream, thus lowering the circulating LDL cholesterol level. The CURVES study investigated the LDL cholesterol lowering effects of five statins at their usual therapeutic dose. At this dose, the effect on LDL cholesterol ranged from a lowering of 17% with fluvastatin at 20 mg/day to a lowering of 38% with 10 mg/day of atorvastatin (1). Similarly, in the STELLAR study, LDL cholesterol lowering ranged from 20% with pravastatin at 10 mg/day to a lowering of 55% with 40 mg/day of rosuvastatin (15). These differences in efficacy were confirmed in a meta-analysis of 164 studies published in 2003. Here also, the different statins showed a two- to three-fold difference in the extent of LDL cholesterol lowering across the dosage range (2). Thus the evidence is that statins are not the same in their ability to lower LDL cholesterol, but rather differ by a factor of at least two in this regard. Dr. David Waters of San Francisco General Hospital

concluded that the evidence of differences in efficacy between statins is so strong that there can no longer be justification for using weaker statins because they do not provide optimal risk reduction.

Are all statins the same in terms of end-point reduction?

Clinical end-points can be divided into two groups. “Soft” end-points include indices of atherosclerosis such as a change in the thickness of the arterial wall or in the volume of atherosclerotic tissue within the arteries. “Hard” end-points are the number of cardiovascular events such as myocardial infarction or stroke, or – the hardest end-point of all - the mortality rate from cardiovascular disease.

In terms of soft end-points, substantial differences have been found between the statins. For example, the Atorvastatin vs. Simvastatin on Atherosclerosis Progression (ASAP) study recently showed that at the highest therapeutic dose, two years of treatment with atorvastatin reduced the thickness of the arterial wall, while after two years of treatment with simvastatin the thickness of the arterial wall had continued to increase (3). Similar results were obtained in a comparison of atorvastatin and pravastatin (ARBITER) (4).

A newer means of assessing atherosclerotic burden is by measuring the volume of atherosclerotic tissue in the arteries by means of intravascular ultrasound. In a very recent study (REVERSAL), carried out by Dr. Steven Nissen of the Cleveland Heart Foundation, this index also showed improvement under 18 months of treatment with 80 mg/day atorvastatin while the volume of atherosclerotic plaque in the coronary arteries continued to increase under treatment with 40 mg/day of pravastatin. It is unclear at the present time, however, if this difference in coronary plaque development simply reflects the greater degree of cholesterol lowering seen with atorvastatin (mean LDL level on treatment 79 mg/dL vs. 110 mg/dL in the pravastatin group) or whether it is at least partly attributable to an intrinsic difference between the two drugs.¹

¹ Source: Nissen S. American Heart Association, Scientific Sessions 2003, Orlando Florida, Plenary Session XI: Late Breaking Trials, 12 Nov. 2003.

Turning to hard end-points, two issues need to be addressed. First, do all statins produce the same reduction in the hard end-points of myocardial infarction and mortality? Second, are all statins the same in the speed with which these benefits occur?

The bulk of evidence at the present time suggests that all statins reduce the hard end-point of myocardial infarction and that the extent to which they do this depends mainly on two factors. The first factor is the baseline risk of coronary heart disease, which differs widely among various studies. As a rule, the higher the baseline coronary heart disease risk, the greater the absolute risk reduction on statin treatment. The second factor is the extent of LDL cholesterol lowering. This also differs widely between studies. In general, the greater the degree of LDL cholesterol lowering, the greater the benefit in terms of end-point reduction. Since statins differ in their ability to lower LDL cholesterol, it is not surprising that they also show different effects on end-point reduction and that these differences cannot be entirely compensated for by adjustment of statin dosage.

Differences also appear to exist between the statins in the lag-time before a reduction in therapeutic end-points is observed. Thus, in the Cholesterol and Recurrent Events (CARE) trial of pravastatin (5), the West of Scotland Coronary Prevention Study (WOSCOPS) of pravastatin (6), the Heart Protection Study (hps) of simvastatin in high-risk individuals (7), the Scandinavian Simvastatin Survival Study (8), the Assessment of Lescol in Renal Transplantation (ALERT) study of fluvastatin (9), and the The Lescol Intervention Prevention Study (LIPS) of long-term fluvastatin use in patients with coronary heart disease (10), about a year passed before the cumulative incidence of end-points began to diverge between the treatment and placebo groups. By contrast, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA) study of atorvastatin (11) and in the Atorvastatin versus Revascularization Treatment (AVERT) trial (12), a divergence of the cumulative incidence curves for major coronary end-points for atorvastatin and placebo was observed from the very start of the trial. These differences may also be explained, however, as discussed by Dr. Terje Pedersen, by a lack of statistical power rather than reflecting real differences between the drugs studied.

Are all statins the same in terms of their pleiotropic effects?

In addition to their main therapeutic effect on LDL cholesterol, statins also exhibit a wide range of other biological effects. Because of their apparent unrelatedness, these effects are often termed “pleiotropic” (*Gr.* many turnings) and include actions on cell function and cell division, on oxidative processes, on inflammation, on coagulation and on vasomotor activity. Here also, important differences exist between the statins. For example, as noted by Dr. Preston Mason of Harvard Medical School, atorvastatin is present in the circulation primarily in the form of hydroxylated metabolites that are as active in inhibiting HMGCoA reductase as the parent compound, unlike other statins. He reported that the hydroxylated metabolite of atorvastatin has the unique effect at pharmacological levels of increasing the resistance of LDL to oxidation in humans (13). A further benefit of this property is to interfere with the formation of cholesterol crystalline domains in cell membranes under controlled experimental conditions, unlike vitamin E. Further, vitamin E failed to exhibit significant antioxidant activity under atherosclerotic conditions characterized by membrane cholesterol enrichment.

In rabbits, as reported by Professor Peter Libby, also of Harvard Medical School and the Brigham and Women’s Hospital, differences have been observed between pravastatin and fluvastatin in their effects on the collagen content of the atheromatous plaque. Dr. Walter Riesen from the Kantonspital in St. Gallen in Switzerland presented evidence of important differences between simvastatin and atorvastatin on activation of peripheral T cells, and suggested that these effects may have clinical implications in transplant patients and in certain infectious diseases. Dr. Jean Davignon of the Institut de Recherches Cliniques in Montreal pointed out that most of these effects are due to inhibition of the activity of small G proteins, an activity that also occurs downstream from mevalonate. In addition, in one instance (the interaction of integrin alpha-L/beta 2 with intercellular adhesion molecule-1), these differences in the pleiotropic effects of statins were due to a variation in the molecular structure at the non-pharmacophore moiety of the molecule, i.e. independently of the inhibition of cholesterol synthesis.

One effect of statins that has received much interest recently concerns their ability to lower the level of circulating C-reactive protein (CRP). While CRP is a marker of inflammation (including atherosclerotic burden), it is premature at present to conclude that lowering of CRP by statins necessarily reflects an anti-inflammatory effect of these drugs. It is possible, for example, that statins lower CRP by specifically altering sterol homeostasis in the liver, a hypothesis proposed by Dr. Winfried Maerz of the University of Graz in Austria. In support of this, Dr. Maerz pointed out that of the other well-established acute-phase markers of inflammation such as fibrinogen, interleukin 6 and white blood cell count, none has consistently been shown to be lowered by statin administration.

In addition, it is not possible to know if the differences in the CRP-lowering effects of the various statins were due to differences in drug properties or differences in drug dosages. In order to investigate these issues, Dr. Paul Ridker of Brigham and Women's Hospital, Harvard Medical School is carrying out the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, the results of which are expected in about three years from now.

Further, statins also profoundly affect serum triglycerides as well as LDL particle density and HDL metabolism. Dr. Ernst Schaefer of Tufts University in Boston, Massachusetts reported that atorvastatin in comparative studies was significantly more effective than all other statins – except simvastatin – in reducing fasting and postprandial triglyceride levels. Atorvastatin was also more effective than fluvastatin, pravastatin, lovastatin and simvastatin in raising large alpha HDL apoA-I levels. This subfraction of HDL has been noted to interact with the scavenger receptor B 1 on liver cells and thus to promote uptake of cholesterol by liver cells.

Although the importance of the pleiotropic effects of statins for their therapeutic benefit is unclear at the present time, here too potentially important differences exist between the members of this drug class.

Are all statins the same in terms of toxicity?

Of the questions dealt with so far, this one is the easiest to answer. The answer is clearly no, as was exhibited by the unfortunate occurrence of excessive muscle

toxicity under treatment with cerivastatin, an effect which led to the withdrawal of this drug from the market in 2001. While all other statins exhibited fewer than 2 cases of severe muscle toxicity (rhabdomyolysis) per 10 million prescriptions, 32 cases of rhabdomyolysis were observed for every 10 million prescriptions of cerivastatin (14). As a side-issue, it is worth noting that these figures in fact illustrate that statins are in general a remarkably safe class of drugs.

Equally, documentation from the Food and Drug Administration indicates that rosuvastatin, particularly at high doses may be associated with a somewhat greater incidence of proteinuria and hematuria than other statins.²

As pointed out by Dr. Alberto Corsini of the University of Milan in Italy, important pharmacological differences exist between the statins. Wide diversity exists in terms of the pharmacokinetic properties of these drugs that may explain differences in drug-drug interactions, safety, tolerability and compliance. These interactions are more common and of greater clinical relevance than is often appreciated. An extensive search of FDA documents on statin-associated rhabdomyolysis showed that among 3,339 reports of this complication, 58% were associated with the co-administration of other drugs including in particular the lipid-lowering drug gemfibrozil, the immunosuppressant cyclosporin, macrolide antibiotics, the anticoagulant warfarin, the heart drug digoxin and the azole antifungal drugs. For this reason, there was unanimous agreement among the participants at the meeting that co-administration of gemfibrozil and statins should be avoided because of the excessive risk of muscle damage. In patients requiring a combination of statins and fibrates, fenofibrate was universally recommended as the fibrate of choice. Dr. Corsini also emphasized that statins are generally metabolized in the liver. Exceptions to this are pravastatin and rosuvastatin. Between 20% and 40% of an administered dose of these two statins is excreted via the kidney. This may help to explain the occasional proteinuria seen in patients receiving high doses of rosuvastatin.

Summary

Since they share a common mode of action and certain structural features, all statins exhibit the same broad pharmacological effects. Nevertheless, important differences

exist between the statins in terms of LDL cholesterol lowering, end-point reduction, pleiotropic effects and toxicity. For this reason, it is incorrect to view all statins as being interchangeable as lipid lowering therapy. In addition, it should be remembered that perhaps the main difficulty in clinical practise today does not concern details of the differences between statins but rather the fact that in many studies long-term compliance has been shown to be only of the order of 30%.

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² www.fda.gov/ohrms/dockets/ac/03/slides/3968S1_03_FDA-Lubas.ppt

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Note added by Dr. Gerd Assmann on Monday, March 8 2004:

At the American College of Cardiology Meeting in New Orleans, the results of the important Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial were presented on March 7, 2004 (16). This study was performed in high-risk patients who had recently suffered acute coronary syndrome. The primary end-point was a composite of death from any cause, myocardial infarction, documented unstable angina pectoris requiring hospitalization, revascularization, and stroke. Contrary to the expectations of those who designed the study, intensive lipid lowering with 80 mg atorvastatin per day provided greater protection against death or major cardiovascular events than did a standard regimen of 40 mg/day pravastatin. The median LDL cholesterol achieved during treatment was 95 mg/dl in the pravastatin group and 62 mg/dl in the atorvastatin group ($p < 0.001$). Kaplan-Meier estimates of the rates of the primary end-point at two years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, reflecting a 16% reduction in the hazard ratio in favour of atorvastatin ($p = 0.005$, 95% confidence interval 5-26%). The major implication of this study, therefore, is that the use of statins to lower LDL cholesterol to an even greater extent than previously aimed at is associated with important clinical benefit. In line with the report of the Expert Panel, this study provides even more evidence for the selective use of only those statins that exhibit a high efficacy to safety ratio.

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