

What Do the Statin Trials Tell Us?

Based on a presentation by David D. Waters, MD

Presentation Summary

The results of 5 major placebo-controlled trials evaluating the effects of statins in approximately 31,000 individuals with and without known coronary disease have demonstrated the following: statins reduce the incidence of coronary events, the reduction in relative risk for coronary events increases with the duration of therapy, the reduction in coronary events is proportional to the reduction in low-density lipoprotein cholesterol (LDL-C) levels, and lower LDL-C levels are associated with lower event rates. The studies have also shown that statins are safe and effective in reducing the incidence of coronary events in women, individuals with diabetes, and patients older than 65 years of age and in reducing the risk of stroke and transient ischemic attacks in patients with coronary disease. Finally, studies indicate that statins ameliorate a variety of pathophysiologic processes that are associated with increased risk for atherosclerosis.

Although we have known for almost a century that cholesterol is important in the pathophysiology of atherosclerosis, we have only in the past decade been able to demonstrate that cholesterol-lowering therapy is of benefit to a wide spectrum of patients. As recently as 1992, it was still possible to claim that lowering serum cholesterol concentrations did not reduce mortality or prevent coronary disease.¹ However, beginning with the publication of the Scandinavian Simvastatin Survival Study (4S) in 1994, compelling evidence has accumulated to document

that lowering cholesterol levels with a statin reduces mortality, prevents coronary heart disease, and provides other clinical benefits.

For the first time, the 4S trial demonstrated that use of a statin affected a highly statistically significant reduction in mortality in 4444 patients with hypercholesterolemia and documented coronary disease.² Two years later, the Cholesterol and Recurrent Events (CARE) trial demonstrated similar results—a 25% reduction in low-density lipoprotein cholesterol (LDL-C) produced a 24% reduction in the combined primary endpoint of nonfatal myocardial infarction (MI) or coronary death. The CARE trial studied 4159 post-MI patients with average cholesterol levels who were treated with 40 mg of pravastatin or placebo for 5 years.³

In 1998, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, in which 9014 Australians and New Zealanders with documented coronary disease and a broad range of initial cholesterol levels were treated with 40 mg of pravastatin (n = 4512) or placebo (n = 4502) and followed for 7 years, showed a 25% reduction in LDL-C and a 24% reduction in the combined primary endpoint of nonfatal MI or coronary death.⁴

In 1995 and 1998, 2 primary prevention trials found that statin therapy reduced LDL-C and the risk of coronary death plus nonfatal MI. The first of these trials, the West of Scotland Coronary Prevention Study (WOSCOPS), involved

more than 6595 men with hyperlipidemia who were treated with 40 mg of pravastatin or placebo. After an average follow up of nearly 6 years, the investigators found a 25% reduction in LDL-C and a 31% reduction in the combined primary endpoint of nonfatal MI or coronary death.⁵

The Air Force/Texas Coronary Atherosclerosis Prevention Study involved 5608 men and 997 women with total cholesterol, LDL-C, and triglyceride levels that were at the mean for the American population and slightly low high-density lipoprotein cholesterol (HDL-C) levels. After 5 years of treatment with lovastatin (n = 3304) or placebo (n = 3301), study investigators found a 37% risk reduction in the primary endpoint, first acute major coronary event.⁶ An important element of this study was that it included women, Hispanics, African-Americans, and individuals older than 65 years of age, thus expanding the knowledge base to a wider segment of the population.

Key Findings and Conclusions

Together, these 5 primary and secondary prevention trials have compared statin therapy with placebo in nearly 31,000 individuals with and without known coronary disease. Although the trials evaluated different statins in different patient populations, they all demonstrated that statin therapy reduced mortality and risk for new or recurrent coronary events. They also share several key findings (Table) and permit a number of statements to be made about statin therapy in general.

Statins Reduce the Incidence of Coronary Events. All 5 trials demonstrated that statins reduce the incidence of coronary events in patients with and without known coronary disease. In the treatment of our patients with coronary disease, the data supporting the use of statins are at least as strong as the data supporting the use of beta-blockers and angiotensin-converting enzyme inhibitors.

Risk Reduction Increases with Duration of Therapy. The reduction in

relative risk for mortality and coronary events increases with the duration of therapy. This point is illustrated most convincingly by data from the 4S trial. In years 1 and 2, there was a 29% reduction in coronary mortality in the group receiving simvastatin compared with the group receiving placebo. In years 3 and 4, there was a 36% reduction in coronary death, and in years 5 and 6, a 58% reduction in the simvastatin group compared with the placebo group.⁷

The continued reduction in risk with increasing duration of therapy is an important clinical point because many patients who begin statin therapy discontinue it within the first year, even if they do not have to pay for it out of pocket and even if they are not experiencing adverse effects. By discontinuing statin therapy relatively early, these patients are not

Table. Key Findings and Conclusions of Statin Trials

- Statins reduce the incidence of coronary events in patients with and without known coronary disease
- The reduction in relative risk increases with the duration of statin therapy
- The reduction in coronary events is proportional to the reduction in LDL-C levels
- Across the range of LDL-C levels studied to date, lower levels are associated with lower event rates
- Statins are safe
- Statins reduce the incidence of coronary events in women
- Statins are associated with lower coronary event rates in patients with diabetes and impaired glucose tolerance
- Statins reduce mortality and coronary event rates in older patients as well as in younger patients
- Statins reduce the risk of stroke and transient ischemic attacks in patients with coronary disease
- Statins ameliorate a variety of pathophysiologic processes that are associated with increased risk for atherosclerosis

Source: References 2-4,6-8,10,12,13.

LDL-C = low-density lipoprotein cholesterol.

giving themselves the chance to realize the fullest clinical benefits.

Coronary Event Reduction Is Proportional to LDL-C Lowering. The statin trials and other studies evaluating nonstatin lipid-lowering drugs and strategies have clearly demonstrated that the reduction in coronary events is proportional to the reduction in LDL-C and total cholesterol (which is largely a reflection of LDL-C lowering). In the LIPID study, the reduction in coronary events was 22% (total cholesterol levels were reduced by 39 mg/dL),⁴ and in the Lipid Research Clinics Coronary Primary Prevention Trial, which evaluated the effects of cholestyramine in patients with high baseline levels of total cholesterol and LDL-C, the reduction in coronary events was 18% (the reduction in LDL-C was 20.3%).⁸

Similarly, the Program on the Surgical Control of the Hyperlipidemias, which evaluated only the effects of ileal bypass surgery on cholesterol lowering, found that the reduction in coronary events was proportional to the reduction in LDL-C.⁹

Thus, despite the different cholesterol-lowering strategies and the different patient populations, the relationship between coronary event reduction and LDL-C lowering in these trials was robust.

Lower LDL-C Levels, Better Results. Across the range of LDL-C levels in the primary and secondary prevention trials, it appears that lower LDL-C levels are associated with better outcomes. Although the event rates were higher in the secondary prevention trials than in the primary prevention trials, lower event rates were associated with lower LDL-C levels in both.

Statins Are Safe. Statins are safe drugs, as demonstrated primarily by the 4S trial, for which there is now an 8-year follow-up period.¹⁰ These drugs do not increase the rates of death or cancer, and they do not increase the risk of cataracts. When the statins were first introduced, patients receiving the drugs

were required to have a lens examination every 3 months. Indeed, over the past decade, many of the complications originally considered potentially related to statin use have not occurred.

Statins Reduce Coronary Events in Women. Except for WOSCOPS, which studied men only, the major statin trials included women in their study populations, in proportions ranging from 15% to 19%.^{2-4,6} In each of these 4 trials, women benefited at least as much as men in terms of reduction in coronary events.

This is an important finding because many physicians presuppose that hormone replacement therapy (HRT) is better than statin therapy for postmenopausal women with coronary disease. However, the results of the randomized, placebo-controlled, double-blind Heart and Estrogen/progestin Replacement Study, which involved approximately 3000 postmenopausal women with documented coronary heart disease, have shown that HRT has no beneficial effect on coronary events and mortality.¹¹ Although HRT produced a 15% reduction in LDL-C and an 8% increase in HDL-C, it also produced an unwanted 10% increase in triglycerides and no beneficial effect on clinical endpoints after 4.1 years of treatment. It should be noted, however, that most women in the study have continued with their assigned treatments and that 7-year outcome data are expected sometime in 2001.

Statins Reduce Event Rates in Patients with Diabetes. At present, the data supporting an association between tight glucose control and improved cardiovascular outcomes in patients with diabetes are fairly weak. By contrast, the data supporting an association between statin therapy and improved cardiovascular outcomes in patients with diabetes are fairly strong.

In the 4S trial, individuals receiving simvastatin and those receiving placebo were divided into 3 groups according to their blood glucose levels: normal glucose

levels, impaired fasting glucose levels, and diabetic levels. Although event rates increased with increasing glucose levels in both the treatment and placebo groups, individuals receiving simvastatin had lower coronary event rates than those receiving placebo.¹²

Statins Reduce Mortality and Event Rates in Older Patients. The statin trials have demonstrated that treatment reduces mortality and event rates not only in patients younger than age 65 years but also in patients older than age 65, an important finding in light of the growing population of older people in the United States.

As demonstrated in the 4S trial, individuals older than age 65 years who received simvastatin had a 34% risk reduction in total mortality, a 43% risk reduction in coronary mortality, and a 48% risk reduction in the need for revascularization procedures compared with patients randomized to placebo.² This, too, is an important finding because older patients generally have poorer outcomes after revascularization than do younger patients.

Statins Reduce Stroke/Transient Ischemic Attack Rates. The statin trials have demonstrated that treatment with these agents reduces the risk of stroke and transient ischemic attacks in patients with coronary disease. This is particularly relevant to the management of older patients, who often fear the disability resulting from a stroke more than they fear death. As demonstrated in the 4S, CARE, and LIPID trials, those receiving statin therapy had statistically significant reductions in stroke risk compared with individuals receiving placebo.

Statins Ameliorate Pathophysiologic Processes Related to Atherogenesis. Recent studies with statins have also shown that the cholesterol-lowering properties of these agents can rapidly ameliorate a variety of pathophysiologic processes that increase the risk associated with atherosclerosis. Among these deleterious

processes are endothelial dysfunction, increased platelet thrombogenicity, and low-grade inflammation. Whether

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—David D. Waters, MD

statin therapy results in early risk reduction in patients with an acute coronary event is an area of active investigation.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Trial¹³ is the first of several trials to investigate potential early benefits of statins in patients with acute coronary syndromes. Among 3086 patients with unstable angina or non-Q wave MI randomized to placebo or atorvastatin 80 mg/day, recurrent coronary events over the 16-week follow-up period were reduced by 16% in the atorvastatin group, in association with an LDL-C reduction to 72 mg/dL. Future studies are likely to more clearly define the benefits of statins in acute coronary syndromes and in other clinical conditions.

QUESTION-AND-ANSWER SESSION

Question from the Audience: Is there any evidence from the statin trials that indicates a risk associated with lowering LDL-C to very low levels, and what would you consider to be a dangerous level? Is there some level at which you would decrease the statin dose or stop the drug?

Dr. Waters: We are born with an LDL-C level of approximately 35 mg/dL and

don't suffer adverse consequences. Rare patients with hereditary defects live comfortably with very low LDL-C levels. We do not have much data on long-term follow up of patients whose LDL-C has been reduced to very low levels. However, we have data on short- to medium-term follow up in patients with LDL-C levels in the range of 50 to 70 mg/dL or even lower from studies evaluating atorvastatin 80 mg. If a patient has an LDL-C of 50 mg/dL and has no symptoms, there is no known reason to lower the statin dose. We don't know yet if there is any additional benefit in reducing levels to 50 mg/dL, but there doesn't appear to be any harm.

Question from the Audience: *Is the patient who has had a coronary event and has an LDL-C of 50 or 70 mg/dL in a different category than someone who is on a statin and has had the level reduced?*

Dr. Waters: That's a difficult question. A patient who has had a coronary event with a low LDL-C probably has other factors driving the atherosclerosis. Some factors may be detectable, such as smoking or diabetes; some require special tests for detection, such as lipoprotein A and homocysteine; and some of them may be things that we don't yet know anything about.

In my experience, these patients do very poorly, more poorly than someone whose LDL-C level has been lowered to that level. Studies that compare the outcome of patients whose LDL-C levels have been lowered with statins with the outcome of patients whose LDL-C is naturally lower are intrinsically biased. Such studies have been used to suggest that there are non-cholesterol-lowering benefits with statins, but that type of analysis is not reasonable.

Question from the Audience: *Why were differences seen in recent studies looking at the effects of statins on osteoporosis and Alzheimer's disease?*

Dr. Waters: There were 2 papers published in *Lancet*, which described obser-

vational studies in which patients who took statins, but not other cholesterol-lowering drugs, had a lower risk of osteoporotic fractures.^{14,15} This finding is corroborated by studies in rats showing increased bone formation after treatment with a statin. In the subset of patients with dementia or Alzheimer's disease that is vascular or atherosclerotic in origin, cholesterol-lowering therapy might have a preventive effect. At least one recent observational study has reported a decreased risk of developing dementia in patients receiving statins.¹⁶

Question from the Audience: *Would you comment on the post hoc pravastatin pooling analysis of the lack of benefit of reducing LDL-C if the baseline level is 125 mg/dL or less?*

Dr. Waters: In an editorial comment that accompanied one of these analyses, the old adage "the data can be tortured until they confess" was used.¹⁷ Subset analyses such as this should be viewed as hypothesis generating and should not be used as a basis for deciding on treatment. The current guidelines from the National Cholesterol Education Program recommend the lowering of LDL-C to less than 100 mg/dL in patients with atherosclerosis. Several trials are currently assessing whether or not treating to lower levels will produce additional benefit.

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