

Statin Treatment in Diabetic Subjects: What the Heart Protection Study Shows

Reviewed by Ronald B. Goldberg, MD

STUDY

Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled trial. *Lancet* 361:2005–2016, 2003

SUMMARY

Objective. To assess the effects on vascular mortality and morbidity of a substantial LDL cholesterol reduction maintained for several years in a large cohort of diabetic individuals.

Design. A multicenter, randomized placebo-controlled clinical trial conducted in the United Kingdom.

Subjects and Methods. A total of 5,963 adults aged 40–80 years, known to have diabetes, with and without cardiovascular disease (CVD), and with total and LDL cholesterol levels not considered by their general practitioners to warrant statin therapy were randomized to simvastatin, 40 mg/day, or placebo. Rates of major cardiovascular events were assessed over a 5-year period and compared between active-treatment and placebo-treated groups.

Results. Simvastatin reduced LDL cholesterol from a mean baseline value of 125 mg/dl to a mean of 86 mg/dl. This effect was associated with a significant 22% reduction of major cardiovascular events compared to the placebo-allocated group, in which the absolute incidence was 25.1% in the 5-year period of follow-up. There was also a significant 33% reduction in events associated with

simvastatin treatment among diabetic subjects without evident cardiovascular disease at entry and a 27% reduction among those with a baseline LDL cholesterol < 116 mg/dl.

Conclusion. Statin treatment is beneficial for people with diabetes irrespective of whether they have evident cardiovascular disease and even in those with below-average LDL cholesterol levels.

COMMENTARY

Past studies of statin intervention trials^{1–4} demonstrated approximately equal benefit for CVD event reduction in the small subgroups of diabetic subjects who had been included in these trials to that observed in their predominantly nondiabetic study cohorts. However, there were very few participants with diabetes in the primary prevention statin trials, and thus evidence for benefit of cholesterol-lowering therapy in the large group of diabetic subjects without cardiovascular disease was lacking.

This deficiency badly needed clarification for several reasons. First, the National Cholesterol Education Program Adult Treatment Panel III⁵ recommended that diabetes should be considered a coronary heart disease (CHD) equivalent for the purpose of assigning LDL cholesterol cutpoints for drug treatment initiation (≥ 130 mg/dl) and goal-targeting (< 100 mg/dl). This was based on observational data of incident CHD event rates in diabetic and nondiabetic populations.⁶ Such an assignment, however, does not necessarily mean that the benefits of LDL cholesterol-lowering would also be equivalent in diabetic subjects

without CHD compared to nondiabetic subjects with CHD. Second, people with diabetes do not have elevated LDL cholesterol levels compared to the general population,⁶ which meant that about half of all diabetic subjects (those with LDL cholesterol ≥ 130 mg/dl)—a sizable population—would now require statin therapy where benefit was largely unproven. In contrast, subjects with diabetes are more likely than those without diabetes to have a dyslipidemic profile for which other agents, such as fibrates, may be beneficial, creating a dilemma for clinicians regarding how to initiate lipid-lowering therapy, particularly in diabetic subjects with average LDL cholesterol levels.

The Heart Protection Study (HPS) has provided critical information in this area. The investigators are to be complimented for their decision to recruit a very large number of diabetic subjects with and without CVD, as well as an even larger group of nondiabetic subjects all of whom had CVD. As a result, it was possible to demonstrate in the 2,912 diabetic subjects without evident CVD at entry and with average LDL cholesterol levels that simvastatin treatment reduced the first major cardiovascular event by 33% ($P < 0.001$); in diabetic subjects with CVD, there was a significant 18% reduction in first events ($P < 0.002$). The apparent difference in effect in these two diabetic groups may simply reflect the play of chance in these relatively small subgroups. More importantly, the rate of first events in the placebo-treated group without CVD was 13% over 5 years, which strongly supports the contention that diabetic subjects (at least those with

mean age 62 years as in the HPS) without CVD should be considered to have an NCEP CHD risk equivalent (> 20% event rate/10 years).

For diabetic subjects with CVD, the placebo group event rate for a first event in the study was 36% over 5 years, emphasizing the seriousness of established CVD in diabetic subjects. Simvastatin treatment significantly reduced by about one-fourth 1) major coronary events, 2) ischemic stroke, 3) revascularizations, 4) peripheral vascular events, and 5) recurrent events in those having their first CVD event during the study. Similar results were observed in the nondiabetic cohort with CVD.

A second, key observation in this HPS report was the finding that the relative benefit of statin therapy in those with diabetes whose LDL cholesterol level was < 116 mg/dl at entry was similar to that obtained in individuals with baseline LDL values > 116 mg/dl (27 vs. 20% reduction in placebo group event rates, $P < 0.001$). Although this could not be further separated for those with or without CVD, it strongly suggests that in diabetic subjects, statins provide benefit at LDL levels less than the current NCEP recommendation of ≥ 130 mg/dl).

The American Diabetes Association guidelines in fact recommend pharmacotherapy for those with LDL cholesterol levels > 100 mg/dl if they have CVD, but not universally for those without CVD. Indeed, among the entire cohort of diabetic and nondiabetic subjects, there were sufficient individuals with an entry LDL value < 100 mg/dl to show that these subjects had a relative benefit from statin treatment equivalent to those with baseline LDL levels ≥ 130 mg/dl. These findings led the investigators to conclude that "statin therapy should now be considered routinely for all diabetic subjects at sufficiently high risk of (such) major vascular events, irrespective of their initial cholesterol concentrations."

What then constitutes "sufficiently high risk for major vascular events"? In subgroup analyses, the benefit derived

from statin therapy was significant irrespective of age, sex, BMI, diabetes duration, serum creatinine, hemoglobin A_{1c} (A1C), triglyceride level, HDL cholesterol value, or the presence or absence of hypertension. We are not told what forms of treatment the diabetic subjects were being given for their hyperglycemia, but since 54% of them had A1C levels < 7%, and the laser treatment rate was a low 1.3% over 5 years, they presumably had relatively mild hyperglycemia.

Of importance, too, was the group of 615 subjects diagnosed as having type 1 diabetes using Early Treatment Diabetic Retinopathy Study criteria (insulin use within 1 year of diagnosis before 30 years of age or before 40 years with normal body weight), in whom statin treatment was associated with a 24% event rate reduction (nonsignificant, but underpowered). This is the first evidence that type 1 diabetic subjects (> 30/40 years of age) without elevated LDL cholesterol levels will benefit from statin therapy. Intriguingly, there was also a suggestion that statin treatment reduced the 5-year increase in serum creatinine level noted in the placebo group, but no evidence that statin treatment reduced the occurrence of new diabetes among the nondiabetic cohort.

Thus, other than the restriction of the study's lower age limit of 40 years, the HPS results suggest a strong likelihood that most diabetic subjects will benefit from statin therapy. The important questions of how low to go in treatment for LDL cholesterol and what the role of fibrates should be if most subjects are to be treated with statins remain unanswered for now and will continue to challenge us therapeutically. However, the most important task we now face is to ensure that statin therapy constitutes a central feature in the management of our own patients with diabetes.

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