

Cholesterol Lowering with Atorvastatin for the Primary Prevention of Cardiovascular Disease in Diabetic Adults

Collhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685-96.

Study Overview

Objective. To determine the effects of atorvastatin 10 mg daily for primary prevention of major cardiovascular events in diabetic patients with at least 1 other cardiovascular risk factor and low-density lipoprotein (LDL) cholesterol levels less than 160 mg/dL.

Design. Double-blind, randomized controlled trial.

Setting and participants. Eligible participants were men and women aged 40 to 75 years who had type 2 diabetes for at least 6 months and at least 1 of the following: hypertension, retinopathy, micro- or macroalbuminuria, or current smoking. Patients were excluded if they had clinically evident coronary artery disease, prior stroke, or severe peripheral arterial disease, or if baseline LDL cholesterol was above 160 mg/dL, triglycerides were above 600 mg/dL, serum creatinine was above 1.7 mg/dL, glycosylated hemoglobin was more than 12%, or adherence to placebo during the prerandomization phase was less than 80%.

Intervention. Patients were randomized to receive atorvastatin 10 mg daily or placebo.

Main outcome measures. Initial occurrence of myocardial infarction (symptomatic or silent), unstable angina, acute coronary heart disease death, cardiac arrest, coronary revascularization, or stroke. Secondary endpoints were total mortality and hospital-verified occurrence of the cardiovascular endpoint.

Main results. 4053 patients were screened, 3249 entered the baseline phase, and 2838 were ultimately randomized. Patients were predominantly white (94%) and male (68%). Mean baseline LDL cholesterol level was 117 mg/dL. 99% of patients who were randomized were assessed at the study's termination. The study was ended early because criteria were met for a prespecified stopping rule. The median observation period was 4 years. Mean LDL and total cholesterol levels at year 2 were 75 and 156 mg/dL in the atorvastatin

group and 117 and 206 mg/dL in the placebo group, respectively. The primary endpoint occurred in 9.0% of the placebo group and 5.8% of the atorvastatin group (hazard ratio [HR], 0.63 [95% confidence interval {CI}, 0.48-0.83]). There was a trend towards lower all-cause mortality in the atorvastatin group as compared with placebo (5.8% versus 4.3%; HR, 0.73 [95% CI, 0.52-1.01]). Acute coronary heart disease events and stroke were reduced in the atorvastatin group when assessed individually (by 36% and 48%, respectively). Adverse effects did not differ between treatment groups. By the end of the study, 9% of placebo and 85% of the atorvastatin group were taking some type of statin.

Conclusion. Atorvastatin 10 mg daily produced an important reduction in major cardiovascular events and was well tolerated in patients with diabetes without high LDL cholesterol.

Commentary

The 2001 report of the National Cholesterol Education Program (NCEP) recognizes the high cardiovascular disease risk associated with diabetes. This report set the target LDL cholesterol for diabetes patients at less than 100 mg/dL—the same target as for patients with established cardiovascular disease [1]. For individuals with LDL cholesterol between 100 mg/dL and 129 mg/dL, cholesterol-lowering medication was considered optional.

Recent clinical trial results challenge these recommendations. The Heart Protection Study (HPS) [2] demonstrated that patients with diabetes and a mean nonfasting LDL cholesterol of 123 mg/dL benefited substantially from lipid-lowering therapy with a statin. Diabetic adults in the HPS

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without diagnosed cardiovascular disease had a 4.2% absolute and 33% relative reduction in major cardiovascular events over 5 years. Subgroup analysis of the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) [3] showed a nonsignificant 16% reduction in cardiovascular events among diabetic patients (95% CI, 45% reduction to 29% increase). Given the low event rate in this group, this finding may reflect inadequate power, especially in light of the shortened follow-up period (the study was stopped early due to benefits seen with atorvastatin among the entire study group). The risk reduction seen in ASCOT-LLA among diabetic subjects was fairly consistent with the findings of HPS and the current study by Colhoun and colleagues.

A recent position statement updating the 2001 NCEP report acknowledges the findings of HPS and ASCOT-LLA and suggests that for the highest-risk patients, an LDL cholesterol goal of less than 70 mg/dL may be a more desirable target, and that medications should be initiated if the LDL cholesterol is 100 mg/dL or greater. For those at very high cardiovascular risk with LDL cholesterol levels 70 to 100 mg/dL, drug options should be considered [4].

Do the results of the current study push beyond the updated NCEP recommendations for diabetes patients? Given the fact that almost none of the patients had a pretreatment LDL cholesterol below 70 mg/dL, probably not. But, the findings in Colhoun et al's study do reinforce the NCEP suggestion to give strong consideration to medical cholesterol-lowering treatment for high-risk patients, such as those with diabetes, who have pretreatment LDL cholesterol 70 to 100 mg/dL. However, it is also clear that the absolute benefit of statin use is dependent on patients' pretreatment cardiovascular risk. Among diabetes patients at lower risk than those in this study (ie, those who are younger, who lack microvascular or large vessel complications, and who do not have hypertension or smoke cigarettes), more individuals will need to be treated to prevent 1 cardiovascular event. Unfortunately, how to best estimate cardiovascular risk among adults with diabetes across a range of ages and

cardiovascular risk factors is an unresolved question, and whether or not a truly low-risk subgroup of diabetic adults exists is still debatable.

When treating patients at lower risk we should bear in mind that while pharmacologically reducing the LDL cholesterol to very low levels appears to be safe over the course of a few years, patients may require these treatments for decades, and the long-term safety of using statin therapy to achieve very low cholesterol levels for prolonged periods of time is unknown.

Applications for Clinical Practice

Cholesterol reduction with atorvastatin 10 mg daily is effective for the primary prevention of cardiovascular events in high-risk patients with diabetes. Diabetes patients' pretreatment cardiovascular risk is a better guide in deciding who should receive statin therapy rather than their initial LDL cholesterol level.

—Review by Stephen D. Persell, MD, MPH

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