Do hypertensive patients with average cholesterol levels benefit from atorvastatin therapy?

ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo–Scandinavian Cardiac Outcomes Trial — Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-58.

Background: Cholesterol lowering with statins effectively reduces cardiovascular event rates in a broad array of individuals at high risk of vascular disease. There is limited information, however, on the benefits of statins in patients with well-controlled hypertension and average or low cholesterol levels.

Question: Does treatment with atorvastatin improve cardiovascular outcomes in patients with hypertension and additional vascular risk factors?

Design: The trial was a substudy of a large randomized controlled trial comparing 2 antihypertensive treatment strategies in 19 342 hypertensive outpatients 40 to 79 years of age with at least 3 additional cardiovascular risk factors. Patients included in the lipid-lowering arm had a total serum cholesterol level of 6.5 mmol/L or less. Exclusion criteria included previous myocardial infarction, currently treated angina, recent cerebrovascular event, fasting serum triglyceride level exceeding 4.5 mmol/L, symptomatic heart failure, uncontrolled arrhythmias or significant renal, hepatic or hematologic disease. The study design was double-blind, and end-point analyses were performed on an intention-to-treat basis. The trial was stopped early after an interim analysis showed clear evidence of efficacy.

Results: In all, 10 305 patients were randomly assigned to receive either atorvastatin (10 mg/d) or placebo and were followed up for a median of 3.3 years. Most participants were white (95%) and male (81%), with a mean age of 63 years. The mean serum total cholesterol level was 5.5 mmol/L in both groups; at the end of follow-up, it was 1.0 mmol/L lower in the atorvastatin group. The mean blood pressure was reduced from 164/95 mm Hg to 138/80 mm Hg in both groups by the end of the study.

The primary end point (incidence of nonfatal myocardial infarction and fatal coronary artery disease) was reduced by 36% in the atorvastatin group (95% confidence interval [CI] 17% to 50%; $p < 0.001$). The incidence of fatal and nonfatal strokes was reduced by 27% (95% CI 4% to 44%) and total coronary events by 29% (95% CI 14% to 41%), with a nonsignificant reduction in all-cause mortality of 13% (95% CI –6% to 29%). The incidence of chronic stable angina was reduced by 41% (95% CI 10% to 62%). The benefit of atorvastatin emerged in the first year of follow-up. The rate of serious adverse events did not differ significantly between the 2 groups.

Commentary: The positive findings of this trial are in keeping with those of a number of previous clinical trials showing the benefit of statins in patients at heightened vascular risk.[1,2] However, the ASCOT-LLA extends this paradigm to patients with well-controlled hypertension and additional vascular risk factors. Several aspects of the ASCOT-LLA may have even underestimated the degree of benefit conferred by this therapy: crossover between the 2 groups was 21% after 3 years of follow-up, the study was stopped nearly 2 years earlier than most previous statin trials, blood pressure was being aggressively treated in both patient groups, and the dose of atorvastatin was not titrated from the starting dose of 10 mg/d. Higher doses would have resulted in substantially greater reductions in total cholesterol and low-density-lipoprotein (LDL) cholesterol levels, which in turn, given the current evidence, might well have led to even greater reductions in cardiovascular event rates.[3]

Practice implications: The mean total and LDL cholesterol levels in the ASCOT-LLA (5.5 and 3.4 mmol/L respectively), although comparable to those seen in Western countries, were substantially higher than those in many Asian populations. This may be one reason why the latter enjoy significantly lower rates of coronary artery disease and ischemic stroke.[4] Even with intensive blood pressure control, high-risk patients with average or below-average cholesterol levels appear to derive significant additional benefit from statin therapy. The results of the ASCOT-LLA, therefore, reinforce the concept that initiating statin therapy should be informed more by consideration of the patient's global vascular risk than by the numeric value of an individual risk factor, such as systolic blood pressure or serum cholesterol level.

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