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ASCOT EASES THE HEART

The lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) with atorvastatin showed a significant reduction in the risk of major cardiovascular events in hypertensive patients with cholesterol values less than 6.5 mmol/L. This finding adds to the body of evidence that statins are vascular protective.

The trial was presented at the American College of Cardiology 2003 Scientific Sessions and published online in the *Lancet*.[1]

Study Design

The trial is made up of two studies with hypertensive patients; a comparison of two antihypertensive regimens (still ongoing), and a lipid-lowering study. The lipid part of the ASCOT trial involved 10,305 hypertensive patients aged 40 to 80 (average age 63) with at least three other cardiovascular risk factors, and with total cholesterol below 6.5 mmol/L. They were randomized to 10 mg atorvastatin or placebo. Followup was planned for five years, but treatment was stopped after 3.3 years due to significant benefits in the atorvastatin group.

This benefit emerged in the first year of followup. As well as a reduction in the primary end point, fatal and non-fatal stroke, total cardiovascular events, and total coronary events were also significantly lowered (Tables 1-3). Atorvastatin lowered total serum cholesterol by approximately 1.3 mmol/L compared with placebo at 12 months and by 1.1 mmol/L after three years of followup.

Study Results

These patients were at moderately high risk of cardiovascular disease (three or more risk factors, and high blood pressure). The primary end point was death from coronary heart disease, and non-fatal heart attack. Treatment was stopped after 3.3 years when it became clear that atorvastatin had benefits over placebo (100 primary events compared with 154, respectively; a relative risk reduction of 36%). Treatment with atorvastatin also reduced the risk of stroke, and total cardiovascular events. The benefits could have been larger with longer followup.

In the discussion section of the *Lancet* paper, the authors note that after one year of followup in ASCOT, total cholesterol and low-density lipoprotein cholesterol (LDL-C) among patients taking atorvastatin were 24% and 35% lower, respectively, than among those taking placebo. The dose of atorvastatin was not titrated up in ASCOT, although higher doses would have resulted in greater reductions in total cholesterol and LDL-C concentrations, and would probably have produced even larger reductions in cardiovascular events.

Comparison with ALLHAT

ASCOT is similar to the recently reported U.S. Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), which also looked at both antihypertensive and lipid-lowering treatments in hypertensive patients. In the lipid arm

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of ALLHAT, 10,355 hypertensive patients were randomized to 40 mg pravastatin or usual care. No significant benefits in terms of all-cause mortality or coronary and stroke events were apparent with statin use in ALLHAT. This finding has been explained by substantial use of statins in the usual-care group, leading to differences in total cholesterol and LDL-C of only 9% and 17% respectively between the two groups. In ASCOT, only 9% of patients in the placebo group were using statins by three years of followup. In addition, only 13% of patients assigned to atorvastatin dropped out of this treatment group at three years, thus maintaining the integrity and power of the original study design.

Physician's perspective

ASCOT is obviously an important study and should have a marked influence on clinical practice. The reduction in all-cause mortality in ASCOT (13%) and primary end point of 35% was seen in addition to good blood pressure control. We do a poor job with blood pressure in hypertensive patients, and lipid management provides another way to protect our patients. Better ways to treat all risk factors are a challenge, and we must work harder to achieve them.

References
1. Sever PS, Dahlöf B, Poulter NR, et al: 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 multicenter randomized controlled trial. 2003; 1149-1158. Available at: www.lancet.com.
2. Lindholm LH, Samuelsson O: What are the odds at ASCOT today? Lancet 2003; 1144-1145. Available at: www.lancet.com.

Table 1
Ascot primary end point

End point	Atorvastatin (%)	Placebo (%)	Hazard Ratio	P
Myocardial ischemia/fatal coronary heart disease	1.9	3.0	0.64	0.0005

p=probability

Table 2
Ascot secondary end points

End point	Atorvastatin (%)	Placebo (%)	Hazard Ratio	P
Total cardiovascular events/procedures	7.5	9.5	0.79	0.0005
Total coronary events	3.4	4.8	0.71	0.0005
All-cause mortality	3.6	4.1	0.87	0.16
Cardiovascular mortality	1.4	1.6	0.90	0.50
Fatal/Non-fatal stroke	1.7	2.4	0.73	0.02
Fatal/Non-fatal coronary heart failure	0.8	0.7	1.13	0.58

p=probability

Table 3
Ascot tertiary end points

End point	Atorvastatin (%)	Placebo (%)	Hazard Ratio	P
Silent myocardial ischemia	0.3	0.3	0.82	0.58
Unstable angina	0.4	0.5	0.87	0.64
Chronic stable angina	0.6	1.1	0.59	0.013
Peripheral artery disease	0.8	0.8	1.02	0.92
Life-threatening arrhythmia	0.2	0.1	3.31	0.05
Development of diabetes	3.0	2.6	1.15	0.24
Development of renal impairment	0.06	0.5	1.29	0.35

p=probability