

## ■ CARDS

**Results.** The trial was terminated two years earlier than expected because the prespecified early stopping rule for efficacy had been met. Median duration of follow-up was 3.9 years. A total of 127 patients allocated placebo (2.46 per 100 person-years at risk) and 83 allocated atorvastatin (1.54 per 100 person-years at risk) had at least one major cardiovascular event (rate reduction 37% [95% CI, 52% to 17%],  $p = 0.001$ ). Treatment would be expected to prevent at least 37 major vascular events per 1,000 such people treated for four years. Incidence of any cardiovascular disease endpoint was reduced with atorvastatin therapy by 32% (95% CI, 45% to 15%,  $p = 0.001$ ), rate of stroke was reduced by 48% (95% CI, 69% to 11%,  $p = 0.016$ ) and all cause mortality rate was reduced by 27% (95% CI, 48% to -1%,  $p = 0.059$ ). No excess of adverse events was noted in the atorvastatin group.

## ■ UKPDS 66

**Results.** Patients with fatal MI had higher HbA<sub>1c</sub> than those with nonfatal MI (odds ratio 1.17 per 1% HbA<sub>1c</sub>,  $p = 0.014$ ). Patients with fatal stroke had higher HbA<sub>1c</sub> than those with nonfatal stroke (odds ratio 1.37 per 1% HbA<sub>1c</sub>,  $p = 0.007$ ). Other risk factors for MI case fatality included increased age, blood pressure, and urine albumin level.

**Methods.** Analyses were based on 674 cases of MI (351 fatal) that occurred in 597 of 5,102 United Kingdom Prospective Diabetes Study (UKPDS) patients for whom covariate data were available

## ■ ASCOT-LLA DIABETES SUBSTUDY

**Results.** In the prespecified subgroup of patients with type 2 diabetes mellitus, among those allocated to atorvastatin, LDL-cholesterol was lowered by an average of about 1.0 mmol/L compared to placebo, and there was a 23% reduction in the number of total cardiovascular events (hazard ratio 0.77,  $p = 0.036$ ).

The analysis was not sufficiently powered to detect reductions in individual components of the composite endpoint. All coronary events were reduced with atorvastatin therapy by 17% and fatal and non-fatal stroke by 33%. These reductions were not significant, however, there was no significant heterogeneity among subgroups of

**Methods.** A total of 2,838 patients aged 40 to 75 years in 132 centres in the United Kingdom and Ireland were randomized to placebo ( $n = 1,410$ ) or atorvastatin 10 mg daily ( $n = 1,428$ ). Study entrants had no documented previous history of cardiovascular disease, an LDL-cholesterol concentration of 4.14 mmol/L or lower, a fasting triglyceride level of 6.78 mmol/L or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension. The primary endpoint was time to first occurrence of the following: acute coronary heart disease events, coronary revascularization, or stroke. Analysis was by intention to treat.

Colhoun HM, Betteridge DJ, Durrington PN, et al., for the CARDS investigators. 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.

during a median follow-up of seven years. Multivariate logistic regression was used to examine differences in risk factors, measured within two years of diagnosis of diabetes, between fatal and nonfatal MI. Similar analyses were performed for 234 strokes (48 fatal) that occurred in 199 patients.

Stevens RJ, Coleman RL, Adler AI, et al. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. *Diabetes Care* 2004; 27(1):201-7.

patients in the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA). These results, in a lower risk diabetic population than studied in the Heart Protection Study, extend the evidence for cardiovascular benefits from lipid-lowering with statins in patients with type 2 diabetes mellitus.

**Methods.** In ASCOT-LLA, the investigators sought to assess the benefits of cholesterol lowering in the primary prevention of CHD in hypertensive patients not conventionally considered to have dyslipidemia. Of 10,305 patients randomized to either atorvastatin (10 mg) or placebo in ASCOT-LLA, approximately 25% ( $n = 2,532$ ) fulfilled predefined criteria

for a diagnosis of type 2 diabetes mellitus. All patients were hypertensive (aged 40 to 79 years) with at least two additional risk factors for cardiovascular disease, and had non-fasting total cholesterol levels of 6.5 mmol/L or less.

ASCOT-LLA was stopped early after a median follow-up period of 3.3 years, owing to a 36% reduction in non-fatal myocardial infarction and fatal

coronary heart disease ( $p = 0.0005$ ) and a 27% reduction in fatal and non-fatal stroke ( $p = 0.02$ ) in the atorvastatin group.

Sever PS, Dahlöf B, Poulter NR, et al, for the ASCOT Investigators. Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA): Results in the Subgroup of Patients With Diabetes. Presented at the American College of Cardiology 53rd Annual Scientific Session. March 7-10, 2004. New Orleans, Louisiana.

## ■ MICRO-HOPE

**Results.** The study was stopped six months early (after 4.5 years) by the independent data safety monitoring board because of a consistent benefit of ramipril compared to placebo. After adjustment for the changes in systolic (2.4 mmHg) and diastolic (1.0 mmHg) blood pressure, ramipril still lowered the risk of the combined primary outcome by 25%, myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, total mortality by 24%, revascularization by 17%, and overt nephropathy by 24%.

**Methods.** A total of 9,297 high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive ramipril (10 mg/day) or matching placebo for a mean of five years in the original Heart

Outcomes Prevention Evaluation (HOPE) study. Treatment with ramipril reduced the rates of death from cardiovascular causes, myocardial infarction, stroke, death from any cause, revascularization procedures, cardiac arrest, and complications related to diabetes. In MICRO-HOPE, 3,577 of those patients who were diabetic, had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and who were not taking ACE inhibitors, were randomly assigned ramipril (10 mg/day) or placebo, and vitamin E or placebo, according to a two-by-two factorial design. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death.

HOPE Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355(9200):253-9.

## ■ HPS

**Results.** Compared to placebo, simvastatin therapy was associated with a significantly lower rate of all-cause mortality in adults aged 40 to 80 years with coronary disease, other occlusive arterial disease or diabetes. This 13% relative reduction was due to a highly significant 18% proportional reduction in coronary death rate, a marginally significant reduction in other vascular deaths and a non-significant reduction in nonvascular deaths with simvastatin. Highly significant reductions were also observed with simvastatin in terms of first-event rates for nonfatal myocardial infarction, coronary death, nonfatal and fatal stroke, and coronary or noncoronary revascularization. The benefits of simvastatin therapy were significant in all subcategories of participants studied, and were additional to those of other cardioprotective treatments.

**Methods.** The HPS included 20,536 patients, randomized to receive simvastatin (40 mg/day) or matching placebo, in an effort to assess the cardioprotective effect of lowering low-density lipoprotein cholesterol. Primary outcomes were mortality (overall analyses) and fatal and nonfatal vascular events (subcategory analyses). Analyses were of the first occurrence of particular events among all simvastatin-allocated vs. all placebo-allocated participants. Subsidiary assessments were made of cancer and other major morbidity.

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002; 360:7-22.