

## ■ REVERSAL

**Results.** For patients with coronary heart disease (CHD), intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared to pravastatin. Baseline low-density lipoprotein cholesterol level was reduced to 2.6 mmol/L in the pravastatin group and to 2.0 mmol/L in the atorvastatin group. C-reactive protein decreased 5.2% with pravastatin and by 36.4% with atorvastatin. The primary endpoint (percentage change in atheroma volume) showed a significantly lower progression rate in the atorvastatin group and similar differences between groups were observed for secondary efficacy parameters, including change in total atheroma volume, change in percentage atheroma volume and change in atheroma volume in the most severely diseased 10-mm vessel subsegment. For the primary endpoint, progression of coronary atherosclerosis occurred in the pravastatin group compared to

## ■ PROVE-IT

**Results.** Patients receiving a standard dose of pravastatin achieved a median low-density lipoprotein cholesterol (LDL-C) level of 2.46 mmol/L compared to an LDL-C level of 1.60 mmol/L achieved by patients receiving a high dose of atorvastatin ( $p < 0.001$ ). Kaplan-Meier estimates of the rates of the primary endpoint at two years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, reflecting a 16% reduction in the hazard ratio in favour of atorvastatin ( $p = 0.005$ ). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.

**Methods.** This study enrolled 4,162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared 40 mg/day

## ■ ANTITHROMBOTIC TRIALISTS' COLLABORATION

**Results.** Among high-risk patients, allocation to antiplatelet therapy reduced the combined outcome of any serious vascular event by about one quarter; non-fatal myocardial infarction (MI) was reduced by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth, with no apparent adverse effect on other deaths. Absolute reductions in the risk of having a serious vascular event were 36 (SE 5) per 1,000 treated for two years among patients with previous MI; 38 (SE 5) per 1,000 treated for one month among patients with

baseline, but progression did not occur in the atorvastatin group compared to baseline.

**Methods.** REVERSAL was a double-blind, randomized, active-control, multi-control-center trial performed at 34 community and tertiary care centers in the United States comparing the effects of two different statins administered for 18 months. Intravascular ultrasound was used to measure progression of atherosclerosis. Between June 1999 and September 2001, 654 patients were randomized and received a study drug; 502 had evaluable intravascular ultrasound examinations at baseline and after 18 months of treatment. Patients were randomly assigned to receive a moderate lipid-lowering regimen, consisting of 40 mg of pravastatin, or an intensive lipid-lowering regimen, consisting of 80 mg of atorvastatin.

Nissen SE, Tuzcu EM, Shoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004; 291(9):1071-80.

of pravastatin (standard therapy) with 80 mg/day of atorvastatin (intensive therapy). The primary endpoint was a composite of death from any cause, myocardial infarction, unstable angina requiring hospitalization, revascularization (performed at least 30 days after randomization) and stroke. The study was designed to establish the noninferiority of pravastatin compared to atorvastatin with respect to the time to an endpoint event. Follow-up lasted 18 to 36 months, with the mean being 24 months.

Cannon CP, Braunwald E, McCabe CH, et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350(15):1495-1504.

acute MI; 36 (SE 6) per 1,000 treated for two years among those with previous stroke or transient ischemic attack; 9 (SE 3) per 1,000 treated for three weeks among those with acute stroke; and 22 (SE 3) per 1,000 treated for two years among other high-risk patients (with separately significant results for those with stable angina ( $p = 0.0005$ ), peripheral arterial disease ( $p = 0.004$ ), and atrial fibrillation ( $p = 0.01$ )).

**Methods.** The objective was to determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events.

The inclusion criteria for this meta-analysis were: randomized trials of an antiplatelet regimen vs. control or of one antiplatelet regimen vs. another in high-risk patients (with acute or previous vascular disease or some other predisposing condition) from which results were available before September 1997. Trials had to use a method of randomization that precluded prior knowledge of the next treatment to be allocated and comparisons had to be unconfounded—that is, have study

groups that differed only in terms of antiplatelet regimen. There were 287 studies reviewed, involving 135,000 patients in comparisons of antiplatelet therapy vs. control and 77,000 in comparisons of different antiplatelet regimens.

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324:71-86.

### ■ CAPRIE

**Results.** There were 1,960 first events included in the outcome cluster on which an intention-to-treat analysis showed that patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, myocardial infarction (MI), or vascular death compared to 5.83% with ASA. These rates reflect a statistically significant ( $p = 0.043$ ) relative-risk reduction of 8.7% in favor of clopidogrel (95% CI 0.3-16.5). Corresponding on-treatment analysis yielded a relative risk reduction of 9.4%. There were no major differences in terms of safety. Reported adverse experiences in the clopidogrel and ASA groups judged to be severe included rash (0.26% vs. 0.10%, respectively), diarrhea (0.23% vs. 0.11%), upper gastrointestinal discomfort (0.97% vs. 1.22%), intracranial hemorrhage (0.33% vs. 0.47%), and gastrointestinal hemorrhage (0.52% vs. 0.72%). There were 10 patients (0.10%) in the clopidogrel group with significant reductions

in neutrophils ( $< 1.2 \times 10^9/L$ ) compared to 16 (0.17%) in the ASA group.

**Methods.** CAPRIE was a randomized, blinded, international trial designed to assess the relative efficacy of clopidogrel (75 mg/day) and ASA (325 mg/day) in reducing the risk of a composite outcome cluster of ischemic stroke, MI, or vascular death; relative safety was also assessed. The population studied comprised subgroups of patients with atherosclerotic vascular disease manifested as either recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease. Patients were followed for one to three years. CAPRIE consisted of 9,185 patients, with more than 6,300 in each of the clinical subgroups, recruited over three years, with a mean follow-up of 1.91 years.

CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348(9038):1329-39.

### ■ HOPE

**Results.** A total of 651 (14.0%) patients who were assigned to receive ramipril reached the primary endpoint, as compared with 826 (17.8%) patients who were assigned to receive placebo (RR 0.78; 95% CI, 0.70-0.86;  $p < 0.001$ ). Treatment with ramipril reduced the rates of death from cardiovascular causes (6.1% compared to 8.1% in the placebo group; RR 0.74;  $p < 0.001$ ), myocardial infarction (9.9% vs. 12.3%; RR 0.80;  $p < 0.001$ ), stroke (3.4% vs. 4.9%; RR 0.68;  $p < 0.001$ ), death from any cause (10.4% vs. 12.2%; RR 0.84;  $p = 0.005$ ), revascularization procedures (16.3% vs. 18.8%; RR 0.85;  $p < 0.001$ ), cardiac arrest (0.8% vs. 1.3%; RR 0.62;  $p = 0.02$ ), [corrected] heart failure (9.1% vs. 11.6%; RR 0.77;  $P < 0.001$ ), and complications related to diabetes (6.4% vs. 7.6%; RR 0.84;  $p = 0.03$ ).

**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. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The trial was a two-by-two factorial study evaluating both ramipril and vitamin E. The effects of vitamin E are reported in a companion paper.

Yusuf S, Sleight P, Pogue J, et al. for the Heart Outcomes Prevention Evaluation (HOPE) study investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342(3):145-53.