

Treatment of Normotensive Coronary Patients with Amlodipine or Enalapril: Effects on Cardiovascular Outcomes

Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA 2004;292:2217–25.

Study Overview

Objective. To compare the effects of amlodipine and enalapril with placebo on cardiovascular events in patients with coronary artery disease (CAD) and normal blood pressure.

Design. Randomized, double-blind, multicenter trial with 2 intervention groups and a placebo group.

Setting and participants. Men and women aged 30 to 79 years who required coronary angiography for chest pain or percutaneous coronary intervention were eligible if their diastolic blood pressure was less than 100 mm Hg with or without treatment and coronary angiography revealed 1 or more stenoses greater than 20%. Patients were excluded if they had left main coronary artery stenosis of more than 50%, ejection fraction of less than 40%, or moderate or severe congestive heart failure. Patients were taken off angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers over a 6-week period. 1991 patients were included in the analysis. A substudy ($n = 274$) measured atherosclerosis progression by intravascular ultrasound (IVUS).

Intervention. After a 2-week placebo run-in period, patients with at least 80% or greater compliance were randomly assigned to amlodipine 5 mg or enalapril 10 mg daily taken in the morning. If tolerated, amlodipine was increased to 10 mg or enalapril to 20 mg daily.

Main outcome measure. Two-year incidence of adverse cardiovascular events (ie, cardiovascular death, nonfatal myocardial infarction, cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke, transient ischemic attack, newly diagnosed peripheral vascular disease). The subgroup had serial IVUS of a vessel that had no more than 50% stenosis and had not undergone angioplasty to measure atheroma volume.

Main results. Cardiovascular events occurred in 23.1% of placebo-treated patients, 16.6% of amlodipine-treated patients (hazard ratio [HR], 0.69 [95% confidence interval

{CI}, 0.54–0.88]), and 20.2% of enalapril-treated patients (HR, 0.85 [95% CI, 0.67–1.07]). The difference between amlodipine and placebo groups was largely due to reductions in hospitalizations for angina and cardiac revascularization observed in the amlodipine group. The amlodipine group had fewer hospitalizations for angina than the enalapril group (HR, 0.59 [95% CI, 0.42–0.84]); other clinical outcomes were not significantly different between the 2 active treatment groups. The IVUS subgroup showed significant progression in atheroma volume in the placebo group only ($P < 0.001$), and there was a trend towards progression in the enalapril group ($P = 0.08$). In the overall population, mean baseline blood pressure was 129/78 mm Hg. During follow-up, blood pressure increased 0.7/0.6 mm Hg in the placebo group and declined 4.8/2.5 mm Hg and 4.9/2.4 mm Hg in the amlodipine and enalapril groups, respectively.

Conclusion. Addition of amlodipine reduced cardiovascular events in patients with CAD and normal blood pressure, and enalapril showed a nonsignificant trend towards beneficial treatment effects. Amlodipine appeared to slow progression of atherosclerosis.

Commentary

Few studies have examined if patients with CAD and blood pressure less than 140/90 mm Hg should be treated with additional blood pressure-lowering medication. Researchers examining this question have postulated special protective effects of ACE inhibitors, but it is also possible that some observed benefits of ACE inhibitors were due to blood pressure lowering. Two of 3 studies comparing an ACE inhibitor with placebo in normotensive patients at high risk of CAD events but without heart failure showed improvements in cardiovascular outcomes [1–3]. In these studies, ACE inhibitor groups had systolic blood pressure reductions of 3 to 5 mm Hg and diastolic reductions of 1 to 2 mm Hg compared with controls. These differences are too small to easily explain the reductions in cardiovascular events that were observed [1,2]. However, in 1 of the 2 positive studies [1], the 24-hour blood pressure difference may have been greater than what was detected by daytime office blood pressures measurements

because ramipril was taken at night [4].

In the trial by Nissen et al, both treatment groups experienced similar reductions in daytime office blood pressures compared with controls (amlodipine group, 5.5/3.1 mm Hg difference; enalapril group, 5.6/3.0 mm Hg difference), but the amlodipine group tended to have better outcomes. The longer half-life of amlodipine compared with enalapril may have produced a more consistent 24-hour blood pressure reduction. However, results to support this speculation have not been reported.

Another possible explanation for the observed differences may be that amlodipine (a calcium channel blocker) has better antianginal properties than enalapril, and therefore, the outcomes of hospitalization for angina and revascularization were disproportionately reduced. The results of the IVUS subgroup study, however, suggest that the benefits of amlodipine go beyond its antianginal properties. Whether these benefits are due to better 24-hour blood pressure control or other reasons remains to be determined.

Applications for Clinical Practice

Treating normotensive CAD patients with amlodipine is an effective way to reduce the incidence of hospitalization for angina and coronary revascularization and may reduce the progression of atherosclerosis. Enalapril produced a similar

reduction in daytime office blood pressure and tended to provide cardiovascular benefits, but the reduction in cardiovascular events was less pronounced and not statistically significant. Whether the differences between the 2 drugs are due to differences in 24-hour blood pressure control or their other properties warrants future investigation.

—Review by Stephen D. Persell, MD, MPH

References

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