Benefits of Losartan over Atenolol for Hypertension in High-risk Patients

Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995–1003.

Study Overview

Objective. To compare long-term outcomes of antihypertensive therapy with losartan versus atenolol in patients at increased risk for cardiovascular events.

Design. Randomized double-blind trial.

Setting and participants. 9222 hypertensive patients aged 55 to 80 years with electrocardiographic evidence of left ventricular hypertrophy (LVH) from multiple sites in Scandinavia, Britain, and the United States were included. 25% had preexisting vascular disease. Mean age was 66.9 years.

Intervention. Patients were randomized to receive titrated therapy for hypertension starting with losartan or atenolol. Hydrochlorothiazide and other antihypertension drugs could be added until systolic blood pressure less than 140 mm Hg and diastolic blood pressure of 90 mm Hg were achieved.

Main outcome measures. The primary endpoint was the composite of cardiovascular death, myocardial infarction (MI), and stroke. Other pre-specified endpoints included cardiovascular and total mortality; stroke, MI, angina, or heart failure requiring hospital admission; revascularization procedures; resuscitated cardiac arrest; and new diagnosis of diabetes mellitus.

Main results. Data from 9193 patients were available for analysis. The dropout rate was about 2% in each group. Mean follow-up was 4.8 years. Achieved blood pressures were similar, with mean follow-up blood pressures of 144.1/81.3 mm Hg and 145.4/80.9 mm Hg in the losartan and atenolol groups, respectively. The composite endpoint was reached in 11.0% of the losartan group and 12.8% of the atenolol group (hazard ratio [HR], 0.85 [95% confidence interval {CI}, 0.76 to 0.96]). The reduction in cardiovascular death was not significant (HR, 0.87 [95% CI, 0.72 to 1.05]). The losartan group had fewer strokes (HR, 0.74 [95% CI, 0.63 to 0.88]), and fewer new cases of diabetes (HR, 0.75 [95% CI, 0.63 to 0.88]). Adverse events were more common in the atenolol group.

Conclusion. Losartan- and atenolol-based antihypertensive therapy achieved similar blood pressure control, but there were fewer cardiovascular events and drug side effects in the losartan group.

Commentary

Antihypertensive therapy based on angiotensin II (AT II)–receptor blockade with losartan performed better than treatment based on atenolol in this study group. This is important news for physicians choosing therapy for high-risk older patients because it adds additional strength to the observation that β blockers, while beneficial following MI, may not be the best choice for other hypertensive, elderly patients [1]. This study also lends credence to the hypothesis that AT II has detrimental effects on the cardiovascular system above and beyond its role in hypertension and that these effects can be countered with drugs that antagonize the renin-angiotensin system. This theory has also been supported by the HOPE [2] trial that added the angiotensin-converting-enzyme (ACE) inhibitor ramipril to standard therapy for nonhypertensive adults at high risk.

Major questions, however, remain unanswered. Diuretics were not compared directly to losartan. There is evidence that therapy based on thiazide-type diuretics leads to better outcomes than β blocker–based therapy in older patients [1]. While the current study suggests that treatment with diuretics combined with β blockers is less desirable than losartan plus diuretics (since the majority of patients in both arms received hydrochlorothiazide), we do not know how well diuretics along with other drugs would compare with losartan. Most importantly, we do not know how the outcomes would compare for therapy with ACE inhibitors versus AT II–receptor blockers. This latter question is important for economic reasons because the patents on ACE inhibitors in the United States have begun to expire and, therefore, they

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are considerably more affordable than AT II blockers. Soon-to-be available results from the ALLHAT study [3] will provide a direct comparison of therapy based on a diuretic, an ACE inhibitor, and a calcium channel blocker. These results will help us determine whether blocking the effects of AT II provides a special advantage over several other therapies, but will not provide a direct comparison with an AT II–receptor blocker and an ACE inhibitor [3].

Finally, it is not clear if these findings are applicable to younger adults. The respective roles of cardiac output and vascular tone in hypertension change during the course of the disease, with the latter playing a much more important role with advancing age. Drugs that reduce vascular tone, such as ACE inhibitors, AT II blockers, or thiazide diuretics, may have more of an advantage over β blockers in the elderly compared with younger patients. This may be why the CAPP trial [4] did not demonstrate an advantage of treatment with the ACE inhibitor captopril over β blocker and diuretic-based treatment in adults with a mean age of 53 years.

Applications for Clinical Practice

Losartan appears to be a better choice than atenolol for hypertension in older high-risk adults. Whether it offers an advantage over diuretics, ACE inhibitors, or other antihypertensive treatments is unknown.

–Review by Stephen D. Persell, MD

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