Amlodipine and Losartan: Reaction to Comparison

In the recent comparison of losartan to amlodipine in patients with mild to moderate hypertension by Phillips et al.,[1] the authors conclude that amlodipine, losartan, and losartan/hydrochlorothiazide combination therapy are effective and safe treatments for hypertension. They further conclude from their analysis that amlodipine demonstrated better efficacy because sitting diastolic blood pressure (DBP) and systolic blood pressure (SBP) were lower. This conclusion reflects their primary end point, but there are other data from within this study that support a different conclusion. Furthermore, there was no reference to previous studies that compared these two agents with notably different results.

Although Phillips and colleagues' study[1] demonstrated differences in the primary end point, the 24-hour ambulatory blood pressures were similar between the two groups. Ambulatory blood pressure has been linked to clinical outcomes, so the potential importance of this similarity should not be understated. In addition, a number of other studies have compared the efficacy of these agents. Wilson et al.,[2] in a study of 302 hypertensive patients, 97 of whom where monitored for 24 hours, concluded that observed changes in office DBP were less for losartan monotherapy than with amlodipine or combination therapy with losartan/hydrochlorothiazide, but 24-hour monitoring did not confirm this difference. Ankle edema was more frequent with amlodipine.

In a 12-week, double-blind, randomized, parallel-group, multicenter study, Dahlof et al.[3] studied 898 patients with DBPs ranging from 95 to 115 mm Hg. In that study, 50 mg losartan plus 12.5 mg hydrochlorothiazide, as necessary, or 5 mg amlodipine increased to 10 mg, as necessary, lowered blood pressure as well as or better than losartan monotherapy. There was no difference in blood pressure between the amlodipine group and the losartan/hydrochlorothiazide group, but drug-related adverse events and withdrawals were more common for the amlodipine group. Oparil et al.,[4] adding hydrochlorothiazide as necessary to primary treatments of losartan or amlodipine, found no difference in sitting DBP or SBP at four, eight, and 12 weeks of therapy. They also concluded that superior tolerability was observed in the losartan-based group. A separate study demonstrated that left ventricular mass decreased significantly in mild-to-moderate hypertensive patients treated for 16 weeks with 50 mg losartan/12.5 mg hydrochlorothiazide but not in patients treated with up to 10 mg amlodipine.[5]

In hypertensive patients with impaired renal function, losartan-based therapy with added hydrochlorothiazide, as necessary, lowered sitting DBP and SBP more than amlodipine-based therapy titrated up to 10 mg, as necessary, at 12 weeks. Further, albuminuria decreased with losartan-based therapy but increased with amlodipine-based therapy, and the differences were statistically significant.[6]

Treatment of hypertension is based on the knowledge that lowering blood pressure will prevent serious clinical pathology or death. As Phillips and colleagues[1] conclude, it is difficult to extrapolate their results to outcomes. That is in contrast to experience with losartan. In the Reduction in Endpoints in Patients with non–Insulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial, losartan (plus conventional antihypertensive therapy, including calcium channel blockers) was shown to be superior to placebo (plus conventional antihypertensive therapy, including calcium channel blockers) in type II diabetics with nephropathy in preventing the composite end point of end-stage renal disease, doubling of serum creatinine, or death.[7] The Losartan Intervention For Endpoint Reduction In Hypertension (LIFE) study of hypertensives with left ventricular hypertrophy demonstrated a statistically significant 13% reduction in the composite end point of cardiovascular death, stroke, and myocardial infarction in the losartan-based therapy group compared with the atenolol-based therapy group. Most benefit related to a 25% reduction in one of the most serious adverse outcomes of hypertension: stroke.[8] Thus, in two large studies (combined >10,000 patients studied over 49,000 patient-years of treatment), hypertension treatment based on losartan therapy, usually with a diuretic, has been shown to be superior to calcium channel blocker- or β-blocker based treatment regimens in preventing some of the serious outcomes related to hypertension.

In today's age of evidence-based medicine, the data suggest that losartan-based therapy is as effective as amlodipine-based therapy in lowering blood pressure and is consistently better tolerated. Amlodipine therapy is an effective means of lowering blood pressure, but clinicians should be confident that losartan-based treatment is equally effective, better tolerated, and has demonstrated unequivocal benefit for clinical outcomes.

—*Gilbert W. Gleim, PhD, Merck Research Labs, West Point, PA, and Ronald D. Smith, PhD, Merck & Co., Inc., Whitehouse Station, NJ*

References

1 Phillips RA, Kloner RA, Grimm RH Jr, et al. The effects of amlodipine compared to losartan in patients with mild to moderately severe hypertension. *J Clin Hypertens (Greenwich).* 2003; 5:17–23, 30.

2 Wilson TW, Lacourciere Y, Barnes CC. The antihypertensive efficacy of losartan and amlodipine assessed with office and ambulatory blood pressure monitoring. Canadian Cozaar Hyzaar Amlodipine Trial Study Group. *CMAJ.* 1998;159(5):469–476.

3 Dahlof B, Lindholm LH, Carney S, et al. Main results of the losartan versus amlodipine (LOA) study on drug tolerability and psychological general well-being. *J Hypertens.* 1997;15(11):1327–1335.

4 Oparil S, Barr E, Elkins M, et al. Efficacy, tolerability, and effects on quality-of-life of losartan, alone or with hydrochlorothiazide, versus amlodipine, alone or with hydrochlorothiazide, in patients with essential-hypertension. *Clin Ther.* 1996;18(4):608–625.

5 Martina B, Dieterle T, Weinbacher M, et al. Effects of losartan titrated to losartan/hydrochlorothiazide and amlodipine on left ventricular mass in patients with mild-to-moderate hypertension. A double-blind randomized controlled study. *Cardiology.* 1999;92(2):110–114.

6 Fernandez-Andrade C, Russo D. Comparison of losartan and amlodipine in renally impaired hypertensive patients. *Kidney Int.* 1998;54(suppl 68):S120–S124.

7 Brenner, BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with Type 2 diabetes and nephropathy. *N Engl J Med.* 2001; 335(12):861–869.

8 Dahlof 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.

Authors' response

We appreciate Gleim and Smith's review of studies comparing antihypertensive efficacy of amlodipine and losartan. However, we disagree with the assertion that notably different results were obtained in patient populations similar to those studied in our report.[1] Indeed, Wilson et al.,[2] found, as we did, that although ambulatory blood pressure was reduced to the same degree, trough sitting blood pressure was more effectively reduced by amlodipine than with losartan-based therapy. We agree that ambulatory blood pressure may be a better measure of risk, yet decisions in routine clinical practice about drug efficacy are made on the basis of the seated office blood pressure. Although we did not measure left ventricular (LV) mass regression, we believe the study cited by Gleim and Smith that compared the LV mass reduction by losartan and amlodipine is invalid.[3] At baseline, the losartan group had LV mass that was 20% greater than the amlodipine group, and at the end of the study the amlodipine group still had lower LV mass. Greater LV mass reduction in the losartan arm most likely represents regression to the mean for the losartan group, rather than a true biologically different effect of treatments on LV mass.[3] Furthermore, amlodipine has been shown to be quite effective in reversing LV hypertrophy.[4]

We agree that evidence-based medicine should guide clinical practice, and we were careful to point out in our conclusions that differences in drug efficacy may be found in different patient populations. In the recently published Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), where the demographics of the patients were similar to our study, amlodipine was as effective as the angiotensin-converting enzyme inhibitor and diuretic in preventing the primary outcome of cardiovascular death and nonfatal myocardial infarction.[5] Furthermore, in ALLHAT the angiotensin-converting enzyme inhibitor, but not amlodipine, was associated with more stroke than chlorthalidone. We also acknowledge that in patients with impaired renal function, blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy should be the basis of antihypertensive therapy[6,7] and that in patients with ECG evidence of left ventricular hypertrophy, losartan reduced stroke more effectively than atenolol.[8] In our study, patients with renal dysfunction were excluded, and ECG evidence of left ventricular hypertrophy was not an inclusion criteria.

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References

1 Phillips RA, Kloner RA, Grimm RH Jr, et al. The effects of amlodipine compared to losartan in patients with mild to moderately severe hypertension. *J Clin Hypertens (Greenwich).* 2003;5:17–23.

2 Wilson TW, Lacourciere Y, Barnes CC. The antihypertensive efficacy of losartan and amlodipine assessed with office and ambulatory blood pressure monitoring. *CMAJ.* 1998;159(5):469–476.

3 Martina B, Dieterle T, Weinbacher M, et al. Effects of losartan titrated to losartan/hydrochlorothiazide and amlodipine on left ventricular mass in patients with mild-to-moderate hypertension. A double-blind randomized controlled study. *Cardiology.* 1999;92(2):110–114.

4 Kloner RA, Sowers JR, DiBona GF, et al. Effects of amlodipine on left ventricular mass in the Amlodipine Cardiovascular Community Trial. *J Cardiovasc Pharmacol.* 1995;26:471–476.

5 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2002;288(23):2981–2997.

6 Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345(12):861–869.

7 Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA.* 2002;288(19):2421–2431.

8 Dahlof 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.