ESRD Progression in High-Risk Hypertensive Patients Treated with a Diuretic, Calcium Channel Blocker, or ACE Inhibitor


Study Overview

Objective. To determine if treatment with a calcium channel blocker (amlodipine) or an angiotensin-converting enzyme (ACE) inhibitor (lisinopril) reduces the incidence of renal disease outcomes compared with treatment with a diuretic (chlorthalidone).

Design. Post hoc subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

Setting and participants. Hypertensive participants aged 55 years or older with at least 1 other coronary heart disease risk factor were recruited from 623 North American centers. The study included 8126 participants with normal or increased glomerular filtration rate (GFR) (≥ 90 mL/min per 1.73 m²), 18,109 with mildly reduced GFR (60–89 mL/min per 1.73 m²), and 5662 with moderately to severely reduced GFR (< 60 mL/min per 1.73 m²).

Intervention. Participants were randomly assigned to initial treatment for hypertension with chlorthalidone, amloidipine, or lisinopril in a 1.7:1:1 ratio. If blood pressure was not below 140/90 mm Hg after titrating the study drug, open-label atenolol, clonidine, or reserpine could be added.

Main outcome measures. Onset of end-stage renal disease (ESRD) (ie, death due to kidney disease, kidney transplantation, or initiation of long-term renal dialysis) and the combination of ESRD or at least a 50% decline in GFR from baseline (estimated using the Modification of Diet in Renal Disease equation).

Main results. 448 patients developed ESRD. There were no significant differences in the incidence of ESRD in any of the 3 GFR groups by treatment type. Among participants with mildly reduced GFR, the relative risk (RR) of ESRD was 1.47 in the amloidipine group (95% confidence interval [CI], 0.97–2.23) and 1.34 in the lisinopril group (95% CI, 0.87–2.06) compared with the chlorthalidone group. Among participants with moderately to severely reduced GFR, the RR of ESRD was 0.92 in the amloidipine group (95% CI, 0.68–1.24) and 0.98 in the lisinopril group (95% CI, 0.73–1.31). In the subgroup with diabetes mellitus and mildly reduced GFR, there was a trend towards an increased risk of ESRD with amloidipine (RR, 1.72 [95% CI, 1.01–2.95]; P = 0.05) or lisinopril (RR, 1.74 [95% CI, 1.00–3.01]; P = 0.05). The composite renal outcome of ESRD or ≥ 50% decline in GFR was less common among participants with a normal baseline GFR who were assigned amloidipine (RR, 0.65 [95% CI, 0.46–0.92]) than among those assigned chlorthalidone, but there were no significant differences in this outcome among subgroups with reduced GFR.

Conclusion. For hypertensive patients with reduced GFR, treatment with lisinopril or amloidipine was not superior to the diuretic chlorthalidone. ESRD tended to occur more often in patients with diabetes and mildly reduced GFR who were assigned amloidipine or lisinopril versus chlorthalidone.

Commentary

Hypertension is a major risk factor for the development and progression of chronic renal disease. Multiple studies have demonstrated that drugs antagonizing the renin angiotensin-aldosterone system effectively delay the progression of both diabetic and nondiabetic renal disease. Studies of ALLHAT’s magnitude that directly compare the renal effects of an ACE inhibitor or angiotensin receptor blocker with a thiazide-type diuretic in patients with renal disease have not previously been performed.

Although this study is based on post hoc analyses of population subgroups, the groups with mild and moderate-to-severe renal insufficiency are large. Therefore, although ESRD occurred in only 1.3% of the study population, the CIs for drug comparisons in the subgroups with mildly decreased GFR are narrow enough to exclude a clinically meaningful advantage of the ACE inhibitor lisinopril over the diuretic chlorthalidone. In the case of the diabetic subgroup with mildly decreased GFR, chlorthalidone may be superior to lisinopril in preventing ESRD. The authors are correct to point out that the study’s selection criteria may...
have excluded many patients with glomerular renal disease. Because proteinuria was not measured, it is unclear if these findings can be applied to patients with all forms of mild and moderate renal disease.

The greater GFRs observed in the amlodipine group should not be interpreted to mean that using this drug as a first-line agent will produce more favorable renal outcomes. Dihydropyridine calcium channel blockers are known to increase glomerular pressure and raise GFR due to their effects on renal resistance vessels. However, these changes may not be renoprotective and may hasten the decline in glomerular function. Dihydropyridine calcium channel blockers should not be used as the sole antihypertensive agent in patients with renal disease because greater deterioration of renal function has been observed with these agents compared with other drugs [1].

Applications for Clinical Practice

For patients with hypertension and mildly reduced renal function, a thiazide diuretic is a reasonable first choice for treatment, especially in patients without albuminuria or other evidence of glomerular disease.

—Review by Stephen D. Persell, MD, MPH

Reference