

Which Antihypertensive Agents in Chronic Kidney Disease?

Hypertension is common in chronic kidney disease and is a risk factor for progressive loss of kidney function and kidney failure, as well as cardiovascular disease (CVD) (1, 2). In this issue, Rahman and colleagues (3) report the outcomes of CVD in a subgroup of patients with chronic kidney disease from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The outcomes of kidney disease in the same subgroup were previously reported (4). These reports are important because 17% of ALLHAT participants had chronic kidney disease, making it the largest study of hypertension treatment in patients with this disorder. In this editorial, we compare Rahman and colleagues' results with those of previous studies in patients with chronic kidney disease that looked at the efficacy of antihypertensive agents that interrupt the renin-angiotensin system.

PREVIOUS STUDIES OF CHRONIC KIDNEY DISEASE

Previous studies of chronic kidney disease included patients with recognized kidney disease and hypertension who were recruited primarily from nephrologists' practices (1). Authors often excluded elderly patients and those with CVD. The studies usually compared an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB), generally in combination with a diuretic, with other antihypertensive agents or placebo. Treating physicians were allowed to use additional antihypertensive agents in both groups to achieve a blood pressure of less than 140/90 mm Hg. The mean follow-up times ranged from 2 to 4 years. The authors ascertained progression of kidney disease from a composite outcome of doubling of baseline serum creatinine levels (approximately equivalent to a halving of glomerular filtration rate [GFR]) or kidney failure. Most trials showed that the ACE inhibitor- or ARB-based regimens reduced proteinuria, slowed the decrease in GFR, and delayed the onset of kidney failure more than other regimens, even though all comparison groups achieved equivalent levels of blood pressure. Point estimates for the relative risk for progression of kidney disease were generally in the range of 0.6 to 0.8 for the ACE inhibitor or ARB groups compared with the control groups (5, 6). In nondiabetic kidney disease, beneficial effects were stronger in patients with proteinuria (defined as approximately equivalent to spot urine total protein-to-creatinine ratio of 200 mg/g or greater) (6). Event rates for CVD and death were generally low in these studies, precluding definitive conclusions about the effect of ACE inhibitors or ARBs on these outcomes.

ALLHAT SUBGROUP OF PATIENTS WITH CHRONIC KIDNEY DISEASE

In ALLHAT, 33 357 patients were primarily recruited from the offices of family physicians, general internists, and

hypertension specialists. The patients were 55 years of age or older with hypertension and 1 or more risk factors for coronary heart disease (CHD) (7). The protocol excluded patients with baseline serum creatinine levels greater than 176.8 $\mu\text{mol/L}$ (>2.0 mg/dL), and proteinuria was not measured. The study compared regimens containing the ACE inhibitor lisinopril, the dihydropyridine calcium-channel blocker amlodipine, or the thiazide-type diuretic chlorthalidone. All 3 regimens included other agents to achieve a target blood pressure of less than 140/90 mm Hg. A composite of fatal CHD or nonfatal myocardial infarction was the primary outcome. The Table summarizes the main results for 5662 diabetic and nondiabetic participants with chronic kidney disease (an estimated GFR of <60 mL/min per 1.73 m²) over a 4.9-year mean follow-up interval (3, 4). The findings were as follows: Coronary heart disease occurred more frequently than kidney failure; lisinopril was not more effective than chlorthalidone in slowing the progression of kidney disease; and lisinopril was not more effective than chlorthalidone in preventing CHD. These findings are similar to those observed in the entire ALLHAT study population (7).

In previous studies, an ACE inhibitor slowed progression of kidney disease; in ALLHAT, it did not. How can we explain the differences between the previous chronic kidney disease studies and the ALLHAT chronic kidney disease subgroup?

DIFFERENCES IN POPULATIONS AND ANTIHYPERTENSIVE REGIMENS

The differences in design and results between ALLHAT and other hypertensive trials have been extensively reviewed (8). Two features are particularly important for comparison with the chronic kidney disease studies: different study populations and different antihypertensive regimens.

Because of differences in entry criteria and recruitment strategies, patients selected for previous chronic kidney disease studies had a higher risk for kidney disease progression and lower risk for CHD, and patients for ALLHAT had a higher risk for CHD and lower risk for kidney disease progression. It may be possible that ACE inhibitors are less effective in slowing kidney disease progression in patients with a lower risk for that outcome. Alternatively, the ALLHAT study population, with its lower risk for progression of kidney disease, may have had too few events to show a beneficial effect on halving of estimated GFR or kidney failure. In fact, the wide CIs for the effect of ACE inhibitors in ALLHAT include the point estimates observed in some of the previous studies of chronic kidney disease.

Angiotensin-converting enzyme inhibitors and ARBs

Table. Outcomes of Chronic Kidney Disease and Coronary Heart Disease in Patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) with Estimated Glomerular Filtration Rates of Less than 60 mL/min per 1.73 m²*

Variable	Entire Subgroup with GFR < 60 mL/min per 1.73 m ²			Diabetic Subgroup with GFR < 60 mL/min per 1.73 m ²			Nondiabetic Subgroup with GFR < 60 mL/min per 1.73 m ²		
	Chlorthalidone	Amlodipine	Lisinopril	Chlorthalidone	Amlodipine	Lisinopril	Chlorthalidone	Amlodipine	Lisinopril
Baseline									
Randomly assigned, n	2613	1516	1533	881	506	501	1732	1010	1032
GFR, mL/min per 1.73 m ²	50	51	50	50	50	49	50	51	51
Outcomes of chronic kidney disease									
Events for kidney failure or halving of GFR, n (%)	180 (6.9)	90 (5.9)	106 (6.9)	96 (10.9)	56 (11.1)	61 (12.1)	84 (4.8)	34 (3.4)	45 (4.4)
RR (95% CI) for kidney failure or halving of GFR, compared with chlorthalidone	1.00 (referent)	0.85 (0.66–1.11)	1.00 (0.78–1.29)	1.00 (referent)	1.02 (0.72–1.44)	1.13 (0.81–1.60)	1.00 (referent)	0.68 (0.46–1.03)	0.89 (0.62–1.30)
Events for kidney failure, n (%)	124 (4.7)	65 (4.3)	70 (4.6)	68 (7.7)	44 (8.7)	41 (8.2)	56 (3.2)	21 (2.0)	29 (2.8)
Mean 6-year rates/100 for kidney failure	6.2	5.7	6.0	10.1	11.6	11.1	4.4	2.8	3.6
RR (95% CI) for kidney failure, compared with chlorthalidone	1.00 (referent)	0.92 (0.68–1.24)	0.98 (0.73–1.31)	1.00 (referent)	1.11 (0.77–1.63)	1.07 (0.73–1.58)	1.00 (referent)	0.66 (0.40–1.09)	0.88 (0.56–1.38)
Outcomes of CHD									
Events for CHD, n (%)	318 (12.2)	194 (12.8)	184 (12.0)	132 (15.0)	83 (16.4)	76 (15.2)	186 (10.7)	111 (10.8)	108 (10.5)
Mean 6-year rates/100 for CHD	15.2	16.0	15.1	19.3	21.1	18.3	13.2	13.3	13.6
RR (95% CI) for CHD, compared with chlorthalidone	1.00 (referent)	1.06 (0.89–1.27)	1.00 (0.84–1.20)	1.00 (referent)	1.07 (0.81–1.41)	1.03 (0.78–1.37)	1.00 (referent)	1.05 (0.83–1.33)	1.00 (0.79–1.26)

* Kidney failure is defined as initiation of dialysis or transplantation or death due to kidney disease. Coronary heart disease is defined as fatal CHD or nonfatal myocardial infarction. CHD = coronary heart disease; GFR = glomerular filtration rate; RR = relative risk.

were usually combined with diuretics in the chronic kidney disease studies but without diuretics in ALLHAT. Thus, ALLHAT did not directly compare the regimens used in the previous chronic kidney disease studies. Patients in the chronic kidney disease studies required, on average, 2 to 3 antihypertensive agents to achieve the target blood pressure; patients in ALLHAT required an average of 1 to 2 agents. More agents probably would be required to reach the lower blood pressure goals recommended by recent guidelines. Thus, in clinical practice, many patients will require an ACE inhibitor or ARB and a diuretic.

These differences lead us to conclude that the results of ALLHAT do not invalidate conclusions from previous chronic kidney disease studies that ACE inhibitors or ARBs, generally in combination with a diuretic, slow the progression of kidney disease more than do other antihypertensive agents.

IS PROTEINURIA THE MISSING EXPLANATION?

We speculate that lower levels of proteinuria may explain why ALLHAT outcomes differed. First, the level of proteinuria in ALLHAT was probably lower than in the studies of kidney disease (ALLHAT did not measure proteinuria). Proteinuria was an entry criterion for most of the

studies of diabetic kidney disease and for some of the studies of nondiabetic kidney disease. However, among people in the general population with an estimated GFR of 30 to 59 mL/min per 1.73 m², only approximately 65% with diabetes and 30% without diabetes have proteinuria (as defined by albuminuria) (9, 10). Second, proteinuria is an important risk factor for progression of kidney disease. In particular, kidney disease associated with higher blood pressure progresses more rapidly in patients with proteinuria (11, 12). The lower risk for kidney disease progression reported in ALLHAT may have been due to lower levels of proteinuria. Third, ACE inhibitors are more effective in slowing progression of nondiabetic kidney disease in patients with proteinuria (6). Again, the lesser effect of ACE inhibitors in ALLHAT compared with the kidney studies could be due to lower levels of proteinuria. Future clinical trials of antihypertensive therapy should characterize the study population by the level of proteinuria, in addition to the level of estimated GFR (13).

WHAT SHOULD CLINICIANS DO?

The prevalence of chronic kidney disease among U.S. adults is approximately 11% and is higher among those with hypertension. Clinicians should evaluate all patients

with hypertension for chronic kidney disease (1, 2, 14, 15). A spot urine albumin-to-creatinine ratio greater than 30 mg/g or an estimated GFR less than 60 mL/min per 1.73 m² for 3 months or more indicates chronic kidney disease. Recent initiatives by clinical laboratories to report estimated GFR whenever serum creatinine levels are measured should facilitate detection of chronic kidney disease (16).

Current guidelines recommend a target blood pressure less than 130/80 mm Hg for all patients with chronic kidney disease and selection of antihypertensive agents based on the cause of kidney disease and level of proteinuria (1, 14, 17, 18). These recommendations are consistent with the results from the previous studies of chronic kidney disease and the ALLHAT chronic kidney disease subgroup. Although some uncertainty remains, patients with diabetic kidney disease or nondiabetic kidney disease with a total protein-to-creatinine ratio of 200 mg/g or greater are probably similar to those enrolled in the chronic kidney disease studies and should be treated with an ACE inhibitor or ARB; a diuretic and other agents should be added as necessary to reach the target blood pressure. Patients with nondiabetic kidney disease and spot urine total protein-to-creatinine ratio less than 200 mg/g may be more similar to those enrolled in ALLHAT and should be treated with a diuretic and additional agents as necessary to reach the target blood pressure.

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