


Hypertension Control and Kidney Disease

Some Questions Answered, Many Remain

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The African American Study of Kidney Disease and Hypertension (AASK) compared renal outcomes at different blood pressure goals with alternate antihypertensive drugs in patients with hypertensive nephrosclerosis. The primary end point was change in the glomerular filtration rate (GFR) with a secondary clinical composite end point composed of end-stage renal disease (ESRD), a threshold decline in GFR, and all-cause mortality. The results of this trial, reported in this issue of THE JOURNAL, are unlikely to satisfy physicians caring for patients like those in AASK.¹

Therapeutic guidelines now recommend blood pressure reduction to 130/85 mm Hg in patients with hypertension and renal insufficiency and to 125/75 mm Hg for those with proteinuria of more than 1 g per 24 hours.² The AASK was conceived as an experimental response to the virtual absence of data in support of such a recommendation, a recognition of the disproportionate burden of ESRD in black patients whose risk of ESRD is roughly 6 times that of white patients, and in the belief that hypertensive nephrosclerosis was the most common determinant of ESRD in black patients.³

To address these issues, 1094 participants were randomized at 21 US sites to either conventional or lower mean arterial pressure goals (102 to 107 mm Hg or 92 mm Hg or less, respectively). In-treatment blood pressures were 127/77 and 140/85 mm Hg, respectively, for the 2 groups. Although a lower pressure was associated with reduced proteinuria, the mean decline in GFR was nearly identical at the 2 blood pressure levels and, as expected in these hypertensive patients, was roughly twice the rate (mean [SE], 2.11 [0.16] and 2.32 [0.17] mL/min per 1.73 m² per year) observed in individuals without renal disease.⁴ Of greater relevance to patients and physicians, however, was the lack of a difference between the lower and higher pressure groups in the clinical composite outcome (an outcome that included at least 50% or 25 mL/min per 1.73 m² reduction in GFR, ESRD, or death).

Wright et al¹ conclude that these findings alone do not support current recommendations for a lower than conventional blood pressure goal. However, that conclusion should be tempered by the fact that both the primary and secondary end point in AASK largely depended on GFR, a surrogate end point for which the relation to health outcomes is, at best, uncertain. Modern methods can readily detect significant statistical differences, particularly in continuous variables such as GFR and blood pressure, that may or may not have clinically meaningful consequences. The AASK was not powered to detect differences in ESRD or in morbidity and mortality. However, if analysis is limited to the clinical end points of ESRD (n = 171), death (n = 80), or both, point estimates actually favored the higher blood pressure group, although confidence intervals are wide and include the possibility of either a positive or a negative effect of lower blood pressure.

As is usually the case with hypertensive patients, the decline in renal function was slow.⁵ Of patients who had compromised renal function at baseline, less than 10% developed ESRD during the 4 years of the trial, while even more sustained a cardiovascular event. Although cardiovascular outcomes were not a study end point, it is noteworthy that cardiovascular mortality and hospitalizations were 18% more likely among those assigned to the higher than lower blood pressure goal. Over the long term, most morbidity and mortality in patients with renal disease and hypertension are due to stroke and myocardial infarction.

In short, the end points for which this study was powered do not provide the information necessary to establish blood pressure goals for these (or other) patients with hypertension. Those physicians who believe that, particularly for high-risk patients such as those in AASK, lower blood pressure levels are better are unlikely to be persuaded by these findings. More cautious patients and physicians may well continue to try to attain 140/90 mm Hg, a more easily achieved blood pressure level for which there is solid clinical trial support for preventing morbidity and mortality.⁶

In contrast, the AASK results are more clinically useful in choice of antihypertensive therapy. A clear advantage for metoprolol for reducing ESRD, death, or both had already led to early termination of the amlodipine arm of this study.⁷ It is noteworthy that patients in the amlodipine group had significantly lower systolic blood pressure than those in the metoprolol and ramipril groups; however, the angiotensin-converting enzyme inhibitor ramipril was superior to amlodipine (38%-59% risk reduction) and metoprolol

(21%-22% risk reduction) in the overall secondary clinical end point as well as the individual components. Specifically, ESRD and death were significantly less frequent with both ramipril and metoprolol than amlodipine but were similar for metoprolol and ramipril.

The limitations of the use of surrogate end points is also confirmed by the finding that, in the face of more frequent progression to ESRD, amlodipine provided greater preservation of GFR and greater blood pressure reduction than metoprolol. Wright et al¹ convincingly argue that interpretation of the GFR results is complicated by the differing short-term and long-term effects of amlodipine. In the acute phase, amlodipine increased GFR through its short-term hemodynamic effects, which have little long-term impact. Nonetheless, in a relatively short study, even a transient effect can play a disproportionately large role. Thus, the chronic or post 3-month phase may provide the best gauge of long-term GFR effect. By this criterion, ramipril did not differ from metoprolol, and both were more renoprotective than amlodipine.

For these high-risk patients with hypertension, cardiovascular morbidity and mortality are likely to be more of a burden than renal events. Although the study was not powered to assess the impact of drugs on cardiovascular events, the rate was lowest in the amlodipine group. Because the cardiovascular protective ability of agents that block the renin angiotensin system, as do both ramipril and metoprolol, has been widely confirmed elsewhere, these nonsignificant cardiovascular findings can be safely ignored.⁸

The positive clinical results for ramipril strengthen the case for use of an angiotensin-converting enzyme inhibitor in patients similar to those in AASK and reinforce the view that effects widely demonstrated in white patients probably apply to black patients as well.⁹ Recent data suggest that when an angiotensin-converting enzyme inhibitor is unsuitable, an angiotensin-receptor blocker may be an appropriate substitute.¹⁰

How can these new findings be integrated into clinical practice? For the lower blood pressure goal, most patients were treated with 2 drugs, although about one third required use of at least a third drug. Because the most common second drug in AASK was a diuretic, the combination of an antirenin drug and a diuretic fits nicely with current practice. But what about patients who had effective blood pressure control with a single agent? No antihypertensive agent has yet produced cardiovascular protection superior to a diuretic. Thus, in the absence of clinical trial data to the contrary, particularly in patients with fairly well-maintained renal function (serum creatinine, <2 mg/dL [176.8 μ mol/L], about half of the AASK participants), initiation of therapy with a thiazide seems most reasonable, albeit with a low threshold for the addition of an angiotensin-converting enzyme inhibitor and a change to furosemide.²

What about patients who need 3 or more drugs for adequate blood pressure control? Because patients in the metoprolol group had lower rates of ESRD and death than those in the amlodipine group, and metoprolol has proven cardioprotective in other studies (although recently less effective than angiotensin-receptor blockers in patients with hypertension and left ventricular hypertrophy),¹⁰ β -blockers would seem an appropriate third choice. Few data describe the relative usefulness of reserpine, addition of an angiotensin-receptor blocker to an angiotensin-converting enzyme inhibitor, hydralazine, or minoxidil. At the same time, available data suggest that both α -blockers¹¹ and calcium antagonists¹² should be reserved for situations in which other options have been exhausted.

It is also important to consider how widely these findings may be generalized. It seems that participants in AASK, who were self-described black patients, most likely do not differ biologically from white patients with regard to hypertensive nephrosclerosis, and that these findings also may apply to all otherwise phenotypically similar patients.¹³ Moreover, the criteria for classification of hypertensive nephrosclerosis in AASK were more rigorous than those usually applied, and therefore may have defined a group far smaller than is generally categorized as having hypertensive nephrosclerosis.¹⁴ Indeed, it is possible that AASK diagnostic criteria would exclude most black patients currently identified as having hypertensive nephrosclerosis. Routinely ascribing progressive renal disease in black patients with hypertension to hypertensive nephrosclerosis may cause treatable underlying renal disease to be overlooked.

The AASK serves as an important reminder of the need to make therapeutic decisions on the basis of clinical outcomes. Precise design and elegant implementation help to explain both the strengths and limitations of AASK. The results reported provide important information about renal function and blood pressure control during antihypertensive care in patients with hypertensive nephrosclerosis but insufficient data on both clinical renal effects and cardiovascular outcomes. Even though knowledge of physiological functions is useful for patients with hypertensive nephrosclerosis, it is not the whole story. Patients and physicians are

best served when clinical decisions can be based on evidence of benefit measured by the duration and quality of life.

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