Blood Pressure Control, Drug Therapy, and Kidney Disease

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Abstract—The African American Study of Kidney Disease and Hypertension examined the effect on renal function decline of 2 blood pressure (BP) goals (low mean arterial pressure [MAP] ≤92 versus usual MAP 102 to 107 mm Hg) and 3 antihypertensives (ramipril versus amlodipine versus metoprolol). We previously reported that in all drug groups combined the BP intervention had similar effects on the primary outcome of glomerular filtration rate (GFR) slope or the main secondary clinical composite outcome of end-stage renal disease (ESRD), death, or GFR decline by 50% or 25 mL/min per 1.73 m². This report examines the effect of the BP intervention separately in the 3 drug groups. The BP effect was similar among the drug groups for either GFR slope or the main clinical composite. However, the BP effect differed significantly among the drug groups for the composite of ESRD or death (P=0.035) and ESRD alone (P=0.021). Higher event rates for amlodipine patients assigned to the usual BP goal (0.087 per patient-year for ESRD or death and 0.064 per patient-year for ESRD) were seen compared with the remaining groups of the factorial design (range, 0.041 to 0.050 for ESRD or death; and range, 0.027 to 0.036 for ESRD). The low BP goal was associated with reduced risk of ESRD or death (risk reduction 51%; 95% confidence interval, 13% to 73%) and ESRD (54%; 8% to 77%) for amlodipine patients, but not for patients assigned to the other drug groups. These secondary analyses suggest a benefit of the low BP goal among patients assigned to amlodipine, but they must be interpreted cautiously.

(Hypertension. 2005;46:44-50.)

Key Words: angiotensin converting enzyme ■ calcium channel blockers ■ hypertension ■ renal disease

The African American Study of Kidney Disease and Hypertension (AASK) used a 2 × 3 factorial design to examine the effect on decline in renal function of 2 blood pressure (BP) goals, defined by a mean arterial pressure (MAP) ≤92 mm Hg or 102 to 107 mm Hg, and of 3 different first-line antihypertensive agents, ramipril, amlodipine, and metoprolol, in African-Americans with chronic kidney disease (CKD) attributed to hypertensive nephrosclerosis.1,2 The AASK study demonstrated a significant overall benefit of the use of ramipril compared with amlodipine or metoprolol in reducing the rate of the main secondary clinical composite outcome including end-stage renal disease (ESRD), death, or declining glomerular filtration rate (GFR) events. There was no significant overall benefit of lowering MAP to ≤92 mm Hg.1,2 However, a plausible physiological hypothesis is that reducing BP may have different effects on progression to ESRD among the antihypertensive regimens of the AASK trial. The rationale for this hypothesis comes from animal3 and human data,4 suggesting that renal disease progression and proteinuria reduction may differ between angiotensin-converting enzyme inhibitors (ACEIs) and dihydropyridine calcium channel blockers (DHP-CCB) at higher blood pressure levels but are similar at lower blood pressures corresponding to those achieved in the low goal of the AASK Study. The factorial design of the AASK trial provides a unique opportunity to address this hypothesis for a wide range of outcomes.5 The primary purpose of this investigation is to evaluate the effect of the BP intervention on the clinical composite outcome and its specific components separately within each of the 3 drug groups. In addition, this investigation compares amlodipine versus ramipril or metoprolol within each of the 2 BP groups.

Methods

Population
The AASK study population has been previously described.1,2 Briefly, participants were self-identified African-Americans with hypertensive renal disease (n=1094), aged 18 to 70 years, with a
The primary analysis of renal function is based on the rate of change described previously.\textsuperscript{1,2} Blood pressure and renal function measurements were conducted as usual BP goal (MAP 102 to 107 mm Hg, n = 215) or to a lower BP goal (MAP ≤92 mm Hg lower, n = 554) or to a double-blinded treatment with 1 of 3 first-line antihypertensive drugs, a sustained-release beta blocker (BB), metoprolol (n = 441), 50 to 200 mg/d, an ACEI, ramipril (n = 436), 2.5 to 10 mg/d, or a DHP-CCB, amlodipine (n = 217), 5 to 10 mg/d. If the BP goal was not achieved while the participants were taking the highest tolerated dose of randomized drug, additional unblinded drugs (furosemide, doxazosin, clonidine, hydralazine, minoxidil) were added sequentially. A 2:2:1 randomization ratio for the metoprolol, ramipril, and amlodipine groups was used because of an expected acute increase in GFR in the amlodipine group.\textsuperscript{6–8}

Measurement of BP and Renal Function

Blood pressure and renal function measurements were conducted as described previously.\textsuperscript{1,2}

**Trial Outcomes**

**Primary Renal Function Analysis**

The primary analysis of renal function is based on the rate of change in GFR (GFR slope), which was evaluated separately during the first 3 months after randomization (acute phase) and after 3 months (chronic phase). The chronic slope and the mean total slope from baseline (including both the acute and chronic phases) were designated as co-primary outcomes.

**Clinical Outcome Analysis**

The main clinical secondary outcome was a composite including ESRD, death, or declining GFR events defined by a 50\% or 25 mL/min per 1.73 m$^2$ reduction in GFR from baseline. Additional secondary endpoints included a renal composite outcome of the declining GFR events and ESRD (while censoring deaths before ESRD), a hard endpoint composite outcome including ESRD and death, ESRD alone (censoring death), and death alone (censoring ESRD). Urinary protein excretion, expressed as urine protein to creatinine ratio (UP/Cr) from a 24-hour urine collection, was also a secondary outcome.

**Statistical Methods**

Glomerular filtration rate slope was analyzed using a mixed-effects model,\textsuperscript{3} which included terms for the estimation of the mean acute, chronic, and total slopes within each of the 6 cells in the 2x3 factorial design, adjusting for clinical center and 5 prespecified baseline covariates: proteinuria (log UP/Cr), history of cardiovascular disease, mean arterial pressure, sex, and age. We present here the differences in the mean GFR slopes between the cells corresponding to the usual and lower BP interventions separately for each of the 3 drug groups and compare the differences in mean slope between the 2 BP interventions among the 3 drug groups to evaluate the interaction of the BP and drug interventions.

The effects of the drug and BP interventions on the main clinical composite outcome including declining GFR events, ESRD, or death, and on components of this outcome were analyzed by Cox regression analysis. Each Cox regression model included appropriate indicator variables for the randomized treatment groups and the same
Results

Baseline and Treatment Characteristics

Baseline participant characteristics were similar in the 2 BP groups within each of the 3 drug groups (Table 1). After randomization, the difference in mean achieved MAP between BP groups was maintained at ≈10 mm Hg in all 3 drug groups, although mean MAP for the lower BP goal was 94 mm Hg in the amlodipine group versus 95 mm Hg in the other 2 groups. Participants were prescribed more antihypertensives for the lower than usual BP goal (Table 2). Those participants assigned to the low MAP goal were more commonly on the highest dose of the randomized drug compared with those assigned to the usual MAP goal. There was no difference in the percentage of participants remaining on the assigned randomized drug during follow-up (Table 2).

Primary Analysis of GFR Slope

As reported previously, the mean chronic and total GFR slopes decline did not differ significantly between the lower and usual BP goal groups when averaged across the 3 drug groups, and the differences in mean slopes between the BP groups did not differ among the 3 drug groups (interaction \( P = 0.64 \) for the chronic slope, \( P = 0.61 \) for the total slope) (Figure 1).

Clinical Outcome Analysis

As reported previously, the overall effect of the BP intervention on the main clinical composite outcome (including ESRD, death, or GFR decline by 50% or by 25 mL/min per 1.73 m^2) was not statistically significant when all 3 drug groups were combined, and the BP effect on the clinical composite did not differ significantly among the 3 drug groups (interaction \( P = 0.17 \)) (Figure 2A). However, the rate of the ESRD or death composite was higher for patients in the amlodipine group assigned to the usual BP goal (0.087 per patient-year) than for the amlodipine patients assigned to the...
low BP goal (0.046 per patient-year), or for patients assigned to either BP goal in the metoprolol or ramipril groups (with event rates ranging from 0.041 to 0.050 per patient-year). A similar pattern can be seen for ESRD alone (Table 3). Hence, the effect of the BP intervention differed significantly among the 3 drug groups for the composite of ESRD or death (interaction \( P = 0.035 \)) and for ESRD alone (\( P = 0.021 \)) (Table 4). For participants in the amlodipine group, there was a significantly lower risk of ESRD or death (risk reduction 51%; 95% CI, 13% to 73%) and of ESRD alone (54%; 95% CI, 8% to 77%) in those assigned to the lower BP goal. By contrast, there was no significant difference in outcomes between BP groups within the metoprolol or ramipril groups. Figure 2B and 2C illustrate the cumulative incidence of participants reaching ESRD or death and ESRD alone.

As reported previously, among both BP goals combined, the ramipril group had a significantly reduced risk of the main clinical composite outcome compared with the amlodipine group, and both the ramipril and metoprolol groups had significantly reduced rates of ESRD or death and of ESRD alone compared with amlodipine. Consistent with the effects noted, the differences between amlodipine and the other 2 drug groups were larger for the composite of ESRD or death and for ESRD alone compared with amlodipine. Consistent with the effects noted, the differences between amlodipine and the other 2 drug groups were larger for the composite of ESRD or death and for ESRD alone compared with amlodipine. Consistent with the effects noted, the differences between amlodipine and the other 2 drug groups were larger for the composite of ESRD or death and for ESRD alone compared with amlodipine. Consistent with the effects noted, the differences between amlodipine and the other 2 drug groups were larger for the composite of ESRD or death and for ESRD alone compared with amlodipine. Consistent with the effects noted, the differences between amlodipine and the other 2 drug groups were larger for the composite of ESRD or death and for ESRD alone compared with amlodipine.

Figure 1. Mean change in GFR during follow-up. Shown are the mean changes (SE) in glomerular filtration rate (GFR) (mL/min per 1.73 m²) from baseline throughout follow-up in the 6 cells of the 2x3 factorial design. Red indicates amlodipine, green ramipril, black metoprolol, solid low BP goal, and dashed usual BP goal. Mean changes were estimated using a mixed effects model, allowing separately linear mean rates of decline during each successive interval between scheduled GFR visits. *to 36 months for Amlodipine, 48 months for Ramipril and Metoprolol.

Figure 2. Cumulative incidence of clinical events. Shown are cumulative incidence curves for designated clinical events for the six cells of the 2x3 factorial design. Red indicates amlodipine, green ramipril, black metoprolol, solid low BP goal, and dashed usual BP goal. A. Cumulative incidence of the main clinical composite outcome of declining GFR event, ESRD, or death. B. Hard clinical composite of ESRD or death or (C) of ESRD alone, censoring death. *to 36 months for Amlodipine, 48 months for Ramipril and Metoprolol.

significant differences in the rates of the outcome of death alone between the 2 BP groups or among the 3 drug groups

Proteinuria
Within each drug group, the risk reductions for any secondary clinical outcome of the low versus usual BP goal were not
significantly different between patients with baseline UP/Cr \( \leq 0.22 \) and \( > 0.22 \) (\( P=\text{not significant} \)). Effects of the BP intervention within each drug group on the change in proteinuria during follow-up are illustrated in Figure 3.

**Discussion**

Using the factorial design of the AASK trial, we have investigated whether reducing BP level has different effects on the progression of hypertensive renal disease depending on the type of first-line antihypertensive used. No significant differences were observed among the 3 AASK drug groups in the effect of the BP intervention on several key outcomes, including GFR slope, the main clinical composite, all-cause mortality, and change in proteinuria. However, the low BP intervention appeared to reduce the incidence of primarily ESRD in those participants assigned to amlodipine as the first-line antihypertensive, but not for participants assigned to ramipril or metoprolol. The low BP intervention in participants assigned to amlodipine also reduced significantly the proteinuria during follow-up.

The differential effects of antihypertensive drugs on glomerular microcirculation provide a plausible biological basis to better understand why the effects on progression to ESRD of BP control might differ by type of antihypertensive drug. In the setting of systemic hypertension, autoregulation of blood flow protects against glomerular hypertension by increasing afferent arteriolar tone and thus preventing the transmission of high systemic pressure to the glomerular capillary circulation. DHP-CCBs impair the autoregulatory vasoconstrictor response of the afferent arteriole in experimental models.\(^3,10\) Impairment in this protective mechanism by a DHP-CCB could theoretically exaggerate the glomerular capillary exposure to systemic hypertension and result in glomerular capillary hypertension, hyperfiltration, accelerated glomerulosclerosis, and progression of kidney disease.\(^11,12\) There is some evidence that in rats with experimental hypertensive kidney disease, the risk of glomerulosclerosis attributed to hypertension, is similar between DHP-CCB and ACEIs when systolic BP is lowered to a level \(< 120 \text{ mm Hg}.\)\(^3,13\) In the AASK, lowering systemic BP to only 140/86 mm Hg in the usual BP goal/amlodipine group may not have been protective against transmission of high BP to the glomerular capillary circulation. In contrast, lowering systemic BP to 126/77 mm Hg in the low BP goal/amlodipine group would be expected to mitigate the pressure load to the glomerular capillaries and theoretically mitigate glomerular injury.

ACEIs and angiotensin II receptor blockers (ARBs) preferentially dilate the postglomerular vasculature and should have a salutary effect because of a proportionally greater reduction in glomerular capillary pressure for any given

**TABLE 3. Numbers Clinical Events for Low and Usual BP Groups**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metoprolol</th>
<th>Ramipril</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR event, ESRD, or death*</td>
<td>61 (0.084)</td>
<td>50 (0.070)</td>
<td>26 (0.070)</td>
</tr>
<tr>
<td>GFR event or ESRD</td>
<td>46 (0.063)</td>
<td>41 (0.057)</td>
<td>21 (0.056)</td>
</tr>
<tr>
<td>ESRD or death*</td>
<td>36 (0.047)</td>
<td>36 (0.048)</td>
<td>18 (0.046)</td>
</tr>
<tr>
<td>ESRD alone</td>
<td>21 (0.027)</td>
<td>27 (0.036)</td>
<td>13 (0.033)</td>
</tr>
<tr>
<td>Death alone*</td>
<td>15 (0.019)</td>
<td>9 (0.012)</td>
<td>5 (0.013)</td>
</tr>
</tbody>
</table>

Event rates (per patient-year) given in parentheses. All groups censored on Sept 22, 2000.

GFR indicates glomerular filtration rate; ESRD, end-stage renal disease.

**TABLE 4. Relative Risk Reduction for Low vs Usual BP Groups for Clinical Event Composite Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metoprolol</th>
<th>Ramipril</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR event or ESRD</td>
<td>269</td>
<td>7% (4% to 12%)</td>
<td>11% (9% to 22%)</td>
</tr>
<tr>
<td>ESRD alone</td>
<td>130</td>
<td>11% (6% to 20%)</td>
<td>21% (16% to 25%)</td>
</tr>
</tbody>
</table>

% Risk Reduction (95% CI) | P Value | % Risk Reduction (95% CI) | P Value | % Risk Reduction (95% CI) | P Value |
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<tbody>
<tr>
<td>GFR event, ESRD or death*</td>
<td>269</td>
<td>4% (3% to 33%)</td>
<td>0.84</td>
<td>28% (19% to 38%)</td>
<td>0.04</td>
</tr>
<tr>
<td>GFR event or ESRD</td>
<td>209</td>
<td>7% (4% to 12%)</td>
<td>0.74</td>
<td>42% (26% to 57%)</td>
<td>0.04</td>
</tr>
<tr>
<td>ESRD or death*</td>
<td>192</td>
<td>11% (9% to 22%)</td>
<td>0.61</td>
<td>32% (22% to 43%)</td>
<td>0.04</td>
</tr>
<tr>
<td>ESRD alone</td>
<td>130</td>
<td>11% (6% to 20%)</td>
<td>0.70</td>
<td>6% (2% to 14%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

% Death Alone | 62 | 1% (0% to 9%) | 0.97 | 21% (16% to 25%) | 0.04 |

GFR indicates glomerular filtration rate; † ESRD, end-stage renal disease.

All risk reductions were adjusted for the prespecified baseline covariates: proteinuria, mean arterial pressure, sex, history of heart disease, and age. Risk reductions for ESRD or death composite or ESRD alone were also adjusted for baseline GFR. All groups censored on Sept 22, 2000.

*Deaths prior to dialysis.
reduction in systemic BP.\textsuperscript{14} Several multicenter trials in CKD patients have demonstrated that blockade of the renin-angiotensin system with ACEIs and ARBs reduced the progression of kidney disease to a greater extent than any other antihypertensive drug and its benefit is beyond their effect of reduction in systemic BP.\textsuperscript{1,2,15-20} Consistent with these findings, in the Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy due to Type 2 Diabetes (IDNT) study,\textsuperscript{16} irbesartan treatment reduced the incidence of doubling of the serum creatinine concentration (risk reduction 37\%; \(P=0.001\)) and ESRD (risk reduction 23\%; \(P=0.07\)) compared with amlopidine treatment. These differences were not explained by differences in the BPs that were achieved. Evidence of a renoprotective effect of angiotensin blockade independently of BP control was also seen in the overall drug group comparisons of the AASK trial, in which assignment to the ramipril group significantly reduced the risk of the main composite clinical outcome compared with the amlopidine and metoprolol groups.\textsuperscript{1,2} In the IDNT, there were no significant differences between the amlopidine and placebo groups in the rate of doubling of the serum creatinine concentration and ESRD (\(P=\text{not significant}\)). In that study, achieved mean BP of 141/77 mm Hg in the amlopidine group was similar to achieved BP in the usual BP goal/amlopidine group in the AASK study.

We view the secondary analyses suggesting a benefit of the low BP goal for participants in the amlopidine group as potentially important but as hypothesis-generating. The implications of these findings are limited by several factors. First, this was a post hoc analysis stemming from the hypothesis that the BP effect is different specifically in the amlopidine group compared with the other 2 groups. However, as described previously, this analysis is based on a biologically plausible mechanism and is consistent with findings in some animal models as noted. Second, the interaction test between the BP and drug group interventions did not approach statistical significance for any outcome including GFR measurements. It is possible that effects on GFR were obscured by the initial effects of the interventions on GFR during the acute phase, especially those of amlopidine, which were likely hemodynamic effects without clinical significance (Figure 1).\textsuperscript{2} However, this hypothesis does not appear to be able to account for the absence of a difference in the effect of the BP intervention on the chronic GFR slope among the drug groups. One could argue that the AASK follow-up time from 3 to 6.4 years was short to show possible difference in outcomes including GFR measurements. This is an important question undergoing study in the AASK cohort study, an ongoing National Institutes of Health-sponsored follow-up to the AASK trial. Third, the multiple comparisons of the various combinations of the main secondary clinical composite outcome between different treatment groups caution conservative interpretation of the nominally significant probability values caused by the risk of type I error. Finally, hypertensives patients with renal disease who might receive a DHP-CCB must also be receiving an ACEI (or an ARB), and the protocol precluded evaluation of this combination. Thus, it is unclear whether the interaction of BP goal and amlopidine on the progression to ESRD is evident in patients using an appropriate renoprotective antihypertensive regimen.

In conclusion, the secondary analyses presented in this report raise the possibility that the effects of BP control differ by class of antihypertensive medication in the AASK study population. The results do not alter the main conclusions from the AASK trial, namely that there was a significant overall benefit of the use of ramipril compared with amlopidine (risk reduction 38\%; \(P=0.004\)) or metoprolol (risk reduction 22\%; \(P=0.04\)) in reducing the rate of the main clinical composite outcome, but no significant overall benefit of lowering MAP to \(\leq 92\text{ mm Hg}\).\textsuperscript{1,2}

**Perspectives**

Hypertension is an independent risk factor for progressive CKD\textsuperscript{21} and is the second leading cause of ESRD in African-Americans\textsuperscript{22,23} in whom the risk of ESRD is graded as a function of BP level.\textsuperscript{22} The AASK trial simultaneously compared 3 classes of antihypertensive agents (ACEI, DHP-CCB, and BB) and 2 levels of BP control (usual BP and low BP) on the progression of CKD. The AASK trial previously documented its main results, namely, that an ACEI was more effective than either DHP-CCB or BB in reducing the risk for rapidly declining renal function, ESRD, or death from any cause and that the low BP goal had the same effects on GFR decline as the usual (traditional) BP goal. This article explored the possibility that the drug effects (ACEI, DHP-CCB, and BB) might differ by BP goal. In secondary analyses that focused on the occurrence of ESRD or death, it appeared that among patients assigned to amlopidine, those randomized to the low BP goal had fewer ESRD or death events than those randomized to the usual BP goal. This intriguing finding, while biologically plausible, should be interpreted cautiously, in part because the analyses were post-hoc (not specified in the protocol) and because parallel analyses with other outcomes were inconsistent.
Acknowledgments

This work was supported in part by an National Institutes of Health grant (5K24DK0281802) awarded to R.D.T. For AASK Study Acknowledgement, see online supplement (http://hyper.ahajournals.org).

References


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Hypertension. 2005;46;44-50: originally published online May 16, 2005;
doi: 10.1161/01.HYP.0000166746.04472.60

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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