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.

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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
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 m² 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, which included terms for the estimation of the mean acute, chronic, and total slopes within each of the 6 cells in the 2×3 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 groups.
between BP groups was maintained at randomization, the difference in mean achieved MAP be-
groups within each of the 3 drug groups (Table 1). After Baseline participant characteristics were similar in the 2 BP
Baseline and Treatment Characteristics

the amlodipine was terminated on the recommendation of the Data Safety and Monitoring Board,
 interventions.
 the 3 drug groups to evaluate the interaction of the BP and drug
each of the 3 drug groups and to compare these relative risks among
5 covariates as the analysis of GFR slope. Baseline GFR was
included as an additional covariate in Cox regressions of time to
ESRD and time to ESRD or death. These Cox regressions were used
to estimate relative risk of the lower versus the usual BP goals within
each drug intervention are expressed as risk reductions.

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 be-
tween 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 antihyper-
tensives 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,2 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=0.17) (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

Clinical Outcome Analysis
As reported previously,2 the overall effect of the BP inter-
vention on the main clinical composite outcome (including
ESRD, death, or GFR decline by 50% or by 25 mL/min per
1.73 m²) 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

<table>
<thead>
<tr>
<th>Table 2. Antihypertensive Therapy and Blood Pressure During Follow-Up (Mean±SD or %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ramiplril</strong></td>
</tr>
<tr>
<td><strong>Low Goal</strong></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
</tr>
<tr>
<td>% visits MAP in goal</td>
</tr>
<tr>
<td>% visits MAP&lt;107 mm Hg</td>
</tr>
<tr>
<td>% visits Sys/Dia&lt;140/90</td>
</tr>
<tr>
<td>% visits Sys/Dia&lt;125/75</td>
</tr>
<tr>
<td>% visits on assigned therapy</td>
</tr>
<tr>
<td>% visits on high dose</td>
</tr>
<tr>
<td>Total # of drug classes</td>
</tr>
<tr>
<td>Any other 2 classes</td>
</tr>
<tr>
<td>ACEi</td>
</tr>
<tr>
<td>BB</td>
</tr>
<tr>
<td>CCB</td>
</tr>
<tr>
<td>% visits on level 2</td>
</tr>
<tr>
<td>% visits on level 3</td>
</tr>
<tr>
<td>% visits on level 4</td>
</tr>
<tr>
<td>% visits on level 5</td>
</tr>
<tr>
<td>% protocol visits held</td>
</tr>
<tr>
<td>% GFRs done</td>
</tr>
</tbody>
</table>

All groups censored on September 22, 2000.
Blood pressure summaries include visits after three months and exclude GFR visits.
Medication summaries include all visits starting at month one.
GFR indicates glomerular filtration rate; BP, blood pressure; MAP, mean arterial pressure; Sys/Dia, systolic over diastolic blood pressure; ACEi, angiotensin-converting enzyme inhibitor; BB, β blocker; CCB, calcium channel blocker.
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. Significant differences in the rates of the outcome of death alone between the 2 BP groups or among the 3 drug groups were not

**Proteinuria**

Within each drug group, the risk reductions for any secondary clinical outcome of the low versus usual BP goal were not
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></td>
<td>% Risk Reduction (95% CI)</td>
<td>P Value</td>
<td>% Risk Reduction (95% CI)</td>
</tr>
<tr>
<td>GFR event, ESRD, or death*</td>
<td>269</td>
<td>4% (−39% to 33%)</td>
<td>0.84</td>
</tr>
<tr>
<td>GFR event or ESRD</td>
<td>209</td>
<td>7% (−42% to 39%)</td>
<td>0.74</td>
</tr>
<tr>
<td>ESRD or death*</td>
<td>192</td>
<td>11% (−40% to 44%)</td>
<td>0.61</td>
</tr>
<tr>
<td>ESRD alone</td>
<td>130</td>
<td>11% (−60% to 50%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Death Alone</td>
<td>62</td>
<td>−1% (−110% to 51%)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

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.
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 an ACEI or (an ARB), and the protocol precluded evaluation of this combination. Thus, it is unclear whether the interaction of BP goal and amlodipine on the progression to ESRD is evident in patients using an appropriate renoprotective antihypertensive regimen.

Perspectives
Hypertension is an independent risk factor for progressive CKD and is the second leading cause of ESRD in African-Americans in whom the risk of ESRD is graded as a function of BP level. 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 progression to ESRD. 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 components 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 amlodipine on the progression to ESRD is evident in patients using an appropriate renoprotective antihypertensive regimen.

We view the secondary analyses suggesting a benefit of the low BP goal for participants in the amlodipine 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 amlodipine 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 amlodipine, which were likely hemodynamic effects without clinical significance (Figure 1). 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 components 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 amlodipine on the progression to ESRD is evident in patients using an appropriate renoprotective antihypertensive regimen.

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Acknowledgments

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References


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