Effect of Ramipril vs Amlodipine on Renal Outcomes in Hypertensive Nephrosclerosis
A Randomized Controlled Trial

Lawrence Y. Agodoa, MD; Lawrence Appel, MD, MPH; George L. Bakris, MD; Gerald Beck, PhD; Jacques Bourgoinie, MD; Josephine P. Briggs, MD; Jeanne Charleston, RN; DeAnna Cheek, MD; William Cleveland, MD; Janice G. Douglas, MD; Margaret Douglas, MPH; Donna Dowie, MD; Marquetta Faulkner, MD; Avril Gabriel, RN; Jennifer Gassman, PhD; Tom Greene, PhD; Yvette Hall, RN; Lee Hebert, MD; Leena Hiremath, PhD; Kenneth Jamerson, MD; Carolyn J. Johnson, RN; Joel Kopple, MD; John Kusek, PhD; James Lash, MD; Janice Lea, MD; Julia B. Lewis, MD; Michael Lipkowitz, PhD; Shaul Massry, MD; John Middleton, MD; Edgar R. Miller III, MD; Keith Norris, MD; Daniel O’Connor, MD; Akinlou Ojo, MD; Robert A. Phillips, MD, PhD; Velvie Pogue, MD; Malboobh Rahman, MD, MS; Otelio S. Randall, MD; Stephen Rostand, MD; Gerald Schultman, MD; Winifred Smith, MPH; Denyse Thornley-Brown, MD; C. Craig Tisher, MD; Robert D. Toto, MD; Jackson T. Wright, Jr, MD, PhD; Shichen Xu, MD; for the African American Study of Kidney Disease and Hypertension (AASK) Study Group

Author Affiliations and Study Group Members and Financial Disclosures are listed at the end of this article. Corresponding Author and Reprints: Jackson T. Wright, Jr, MD, PhD, Case Western Reserve University, Clinical Hypertension Program, University Hospitals of Cleveland and the Louis Stokes Cleveland Veterans Affairs Medical Center, 10900 Euclid Ave, Wood Bldg Room W-165, Cleveland, OH 44106-4982 (e-mail: jxw20@po.cwru.edu).

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T HE MORTALITY FROM HYPERTENSION vascular disease has declined progressively over the past 2 decades in the United States, a decline ascribed in part to improved treatment of high blood pressure (BP). During the same period, the incidence of end-stage renal disease (ESRD) due to hypertension has increased steadily, particularly among African Americans. In certain age groups, the risk of hypertensive ESRD for African Americans is 20-fold greater than in whites. The optimal strategy for treatment of hypertension to prevent renal failure has remained elusive. Recent data in patients with diabetic and proteinuric nondiabetic kidney dis-
ease have suggested significant benefits with angiotensin-converting enzyme inhibitors (ACEIs). The impact of ACEIs on progression of renal disease in African Americans is unknown since all published trials had too few African Americans randomized to such agents. Although animal studies have demonstrated prevention of glomerulosclerosis by calcium channel blockers (CCBs), human studies have not consistently confirmed their renoprotective effects.

The African American Study of Kidney Disease and Hypertension (AASK) was designed to evaluate the impact on progression of hypertensive kidney disease of 2 different BP goals (low and usual), and treatment regimens initiated with 1 of 3 antihypertensive drug classes, a β-blocker (BB, metoprolol), a dihydropyridine (DHP) CCB (amlodipine), or an ACEI (ramipril). To date, AASK is the largest comparative drug intervention trial that has focused on renal outcomes conducted in any population and the first clinical endpoint trial with sufficient sample size to evaluate the effect of inhibition of the renin-angiotensin-aldosterone system in African Americans. Recruitment into the full-scale trial began in February 1995, with planned follow-up through September 2001.

The present report summarizes data obtained through September 2000, when, at the recommendation of the data and safety monitoring board (DSMB), the amlodipine arm was terminated. The DSMB recommendation was based on safety concerns that arose because interim analyses showed a slower decline in mean glomerular filtration rate (GFR) and a reduced rate of clinical end points (rapid decline in renal function, ESRD, or death) in the ramipril and metoprolol groups relative to the amlodipine group in participants with proteinuric nondiabetic kidney disease. Termination of the entire amlodipine arm, not just of participants with high levels of proteinuria, was recommended, partly because protein excretion increased significantly both in participants with proteinuria and without proteinuria and because conditional power calculations indicated key conclusions were unlikely to change with continuation of this arm. However, both the ramipril vs metoprolol comparison and the comparison of the 2 BP groups will continue until the scheduled end of the study. Since the study investigators must remain blinded to the ramipril vs metoprolol and low vs usual BP comparisons, this report compares only the amlodipine and ramipril arms, with all results averaged between the 2 BP groups.

**METHODS**

**Participants**

Participants were self-identified African Americans with hypertension (n=1094), aged 18 to 70 years, with GFR between 20 to 65 mL/min per 1.73 m² and no other identified causes of renal insufficiency. Exclusion criteria were as follows: (1) diastolic BP (DBP) less than 95 mm Hg, (2) known history of diabetes mellitus (fasting glucose ≥140 mg/dL [≥7.8 mmol/L] or random glucose >200 mg/dL [≥11.1 mmol/L]), (3) urinary protein to creatinine ratio (UP/Cr) greater than 2.5, (4) accelerated or malignant hypertension within 6 months, (5) secondary hypertension, (6) evidence of non-BP-related causes of renal disease, (7) serious systemic disease, (8) clinical congestive heart failure, or (9) specific indication for or contraindication to a study drug or study procedure. An antihypertensive washout period was believed to be unethical. Thus, potential participants were only required to have at least 1 DBP reading higher than 95 mm Hg or their antihypertensive medication dose tapered until they met the BP entry criteria. The protocol and procedures were approved by the institutional review board at each center, and all participants gave written informed consent. Participant enrollment began in February 1995 and ended in September 1998.

**Study Design**

AASK uses a 3×2 factorial design. Participants were randomized to a usual mean arterial pressure (MAP) goal of 102 to 107 mm Hg or to a low MAP goal of 92 mm Hg or lower and to treatment with 1 of 3 antihypertensive study drugs: a sustained-release BB, metoprolol; an ACEI, ramipril; or a DHP-CCB, amlodipine. Dosages were 50 to 200 mg/d, 2.5 to 10 mg/d, and 5 to 10 mg/d, respectively. If the BP goal was not achieved while the participants were taking the study drug, additional unmasked drugs were added in the following recommended order: furosemide, doxazosin mesylate, clonidine hydrochloride, hydrochlorothiazide, and minoxidil. The dosage of each drug was increased to the maximum tolerated dose before the addition of a subsequent agent. A randomization scheme that resulted in a 2:2:1 (metoprolol-ramipril-amlodipine) ratio was used because AASK pilot data revealed an early increase in GFR in the DHP-CCB group compared with the ACEI and BB groups. This increased the projected statistical power for the DHP-CCB vs BB comparison, allowing a smaller sample size for the amlodipine group. Study drug assignment but not BP goal was double masked.

**Measurement of BP and Renal Function**

Three consecutive seated BPs were measured using a Hawksley random zero sphygmomanometer at least 5 minutes rest, with the mean of the last 2 readings recorded. All personnel measuring BPs were centrally trained and certified annually. During the 6 months following randomization, antihypertensive drugs were adjusted at monthly protocol and interim visits to achieve the BP goal. Subsequent protocol visits occurred at 2-month intervals. Glomerular filtration rate was assessed by [125I]iothalamate clearance at baseline twice, then at 3, 6, and every 6 months thereafter. Serum and urinary levels of creatinine and protein were measured by a central laboratory at 6-month intervals.

**Trial Outcomes**

The primary analysis of renal function is based on the rate of change in GFR.
(GFR slope). The GFR slope was determined separately during the first 3 months after randomization (acute phase) and during the remainder of follow-up (chronic phase), because previous studies indicated that drug interventions could result in acute changes in GFR that differ from long-term effects on renal disease progression.\textsuperscript{1,21-25} The analytic plan called for determining both the mean chronic slope and the mean total slope from baseline to end of follow-up, including both phases, and for inferring a definitive beneficial effect on renal function of an intervention that significantly reduced the magnitude of both the chronic and total mean slopes. The mean total slope assesses the effect of interventions on renal function during the study period, while the chronic slope is interpreted as the parameter more likely to reflect long-term disease progression.

The protocol also designated a secondary clinical-outcome analysis, based on the time from randomization to any of the following end points: (1) a confirmed reduction in GFR by 50% or by 25 mL/min per 1.73 m\(^2\) from the mean of the 2 baseline GFRs; (2) ESRD, defined as need for renal replacement therapy; or (3) death. The clinical end point analysis was identified as the principal assessment of patient benefit. In contrast to the analysis of GFR slope, which addresses the mean drug effect on renal function in all participants, including those with little or no GFR decline, the chronic end point analysis is based on events of clear clinical impact, either large declines in renal function or death.

Urinary protein excretion, expressed as the urine protein–creatinine ratio (UP/Cr), was also specified as a secondary outcome variable.

**Statistical Methods**

The protocol specified 3 primary comparisons (ramipril vs metoprolol, amlodipine vs metoprolol, and low vs usual MAP goal). The ramipril vs amlodipine comparison was designated as a secondary rather than a primary comparison because the amlodipine and ramipril interventions were expected to produce acute changes in opposite directions, complicating the comparison of these 2 groups.

The primary renal function analysis was based on a mixed-effects model with random intercepts and random acute and chronic slopes. The mean acute, chronic, and total slopes were estimated by restricted maximum likelihood for each treatment group. Total mean slopes were estimated as time-weighted averages of the acute and chronic slopes. The effects of the treatment interventions were tested by comparing the mean slopes. The model included clinical center and the following prespecified baseline factors as covariates: proteinuria (expressed as the log transformed UP/Cr to account for positive skewness), history of heart disease, mean arterial pressure, sex, and age.

A formal stopping rule was constructed based on the primary renal function analysis with separate O'Brien-Fleming\textsuperscript{26} boundaries for the chronic and total mean slopes for each of the 3 primary treatment group comparisons. The stopping rule stipulated that a treatment arm should be discontinued at one of the study’s annual interim analyses if the stopping boundaries indicating faster progression were crossed in the same direction for both the chronic and total mean slopes.

During the trial, members of the steering committee became aware of external clinical studies, published after the initiation of the AASK, that suggested a slowing of the progression of renal disease by ACEIs in participants with elevated proteinuria, as well as studies suggesting DHP-CCBs may increase the level of proteinuria and not slow the progression of renal disease.\textsuperscript{6,7,14,15,25} Consequently, the steering committee (which was blinded to the AASK data) requested that the coordinating center provide the DSMB with data on the ramipril vs amlodipine comparison in relation to the level of proteinuria. Therefore, subsequent reports to the DSMB included an extension of the primary renal function model with interaction terms between log baseline UP/Cr and the ramipril vs amlodipine comparison. This analysis identified significant interactions with baseline proteinuria for the acute and total mean GFR slopes. After interactions were detected, subgroup analyses were performed in participants with baseline UP/Cr >0.22 and \leq 0.22 (a value corresponding approximately to the threshold of 300 mg/d for clinically significant proteinuria). The subgroup with baseline UP/Cr >0.22 includes one third of the study participants, with the remaining two thirds belonging to the subgroup with a baseline UP/Cr \leq 0.22. The UP/Cr cutpoint of 0.22 was post hoc but was selected because of clinical relevance and was independent of the AASK data.

Since UP/Cr was inversely associated with GFR at baseline, the interaction of the treatment groups with baseline GFR was also considered. For subgroup analyses, a cutpoint of baseline GFR of 40 mL/min per 1.73 m\(^2\) was used. This cutpoint matched the cutpoint of 0.22 for baseline UP/Cr by splitting the one third of participants with lowest baseline GFR from the two thirds with highest baseline GFR.

The DSMB’s recommendation to terminate the amlodipine arm was based primarily on results related to the interaction of the treatment interventions with baseline proteinuria and not on the original stopping rule, which was not triggered for any of the 3 primary comparisons. Because the decision to examine the treatment interventions in relation to baseline proteinuria was prompted by other studies of ACEI regimens,\textsuperscript{3,6,10,14,22,25-29} the DSMB recommended that comparison of the ramipril and amlodipine groups rather than the amlodipine and metoprolol groups be included in this report.

Analyses of the clinical outcome events and new occurrences of clinically significant proteinuria (defined by UP/Cr >0.22) were performed by Cox regression with adjustment for the same covariates as the analysis of GFR slope. All analyses are intent-to-treat, with participants analyzed according to their
randomized treatment assignment regardless of medications received or duration of follow-up. P values and 95% confidence intervals (CIs) are reported on a comparison-wise basis, without adjustment for multiple analyses. This strategy is conservative for the primary renal function analysis, since both the chronic and total slopes analyses needed to reach significance for a definitive conclusion. This report is based on the trial database as of September 22, 2000.

RESULTS

Baseline Characteristics

Table 1 displays selected baseline clinical and demographic characteristics of all participants randomized to ramipril and amlodipine and for the subgroups with baseline UP/Cr >0.22 (~300 mg/d). The mean baseline BP was 151/96 mm Hg for the 2 groups, with 46% of the participants receiving a DHP-CBB at entry. The urine protein excretion result was positively skewed, with a median of 112 mg/d. Proteinuria was inversely associated with renal function, with median UP/Cr equal to 0.47, 0.07, and 0.04, respectively, for GFR less than 30, 30 to 60, and greater than 60 mL/min per 1.73 m².

Treatment Characteristics

The median duration of GFR follow-up was 36 months in the amlodipine group and 37 months in the ramipril group. Additional details on recruitment and retention are provided in Figure 1. Follow-up BP results were substantially lower than baseline values but did not differ significantly between treatment groups (P >.10 for mean follow-up values of systolic BP, diastolic BP, and MAP after the 3-month visit) (Table 2). After the 3-month visit, there was no significant difference in the number of antihypertensive drugs prescribed or in the percentage of participants receiving the highest doses of ramipril or amlodipine (57.4% and 56.7%, respectively). There were also no significant differences between the ramipril and amlodipine groups in the percentage of visits for which each of the individual add-on antihypertensive classes were prescribed. At 32 months of follow-up, 80.1% of active participants in the ramipril group and 83.3% in the amlodipine group were still taking their study drug.

Renal Function Analysis

Overall. During the chronic phase, the mean (SE) decline in GFR was 2.07 (0.21) and 3.22 (0.33) mL/min per 1.73 m²/y in the ramipril and amlodipine groups, respectively. The mean decline was 1.15 mL/min per 1.73 m²/y (95% CI, 0.41–1.90) or 36% slower in the amlodipine than ramipril group (P <.001) (mean [SE] change in GFR was 0.16 ± [0.46] and 4.03 ± [0.64] mL/min per 1.73 m² in the ramipril and amlodipine groups, respectively); consequently, the mean total slope (including acute and chronic phases) did not differ significantly (P = .38) between the treatment groups (difference in total slope = 0.16 mL/min per 1.73 m²/y, 95% CI, −0.41 to 1.08). As described below, the different results for chronic and total slopes are clarified by taking into account the level of baseline proteinuria.

Effect of Baseline Proteinuria. The acute rise in GFR produced by amlodipine was confined to the participants with baseline UP/Cr =0.22 (approximate protein excretion of 300 mg/d or lower). As a consequence, there were highly significant interactions of the treatment regimen with baseline proteinuria for both the acute GFR slope (P <.001) and the total mean slope.

Table 1. Baseline Characteristics*  

<table>
<thead>
<tr>
<th></th>
<th>All (n = 436)</th>
<th>Amlodipine (n = 217)</th>
<th>Ramipril (n = 144)</th>
<th>Amlodipine (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.2 (10.9)</td>
<td>54.4 (10.7)</td>
<td>49.8 (11.2)</td>
<td>50.9 (10.3)</td>
</tr>
<tr>
<td>Women, %</td>
<td>38.8</td>
<td>40.1</td>
<td>34.7</td>
<td>34.8</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>151.0 (23.3)</td>
<td>150.0 (25.3)</td>
<td>156.0 (21.8)</td>
<td>157.3 (26.0)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>96.0 (14.5)</td>
<td>95.7 (14.1)</td>
<td>92.8 (14.9)</td>
<td>100.3 (14.4)</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>114.6 (15.9)</td>
<td>114.0 (16.7)</td>
<td>118.7 (15.6)</td>
<td>119.5 (17.2)</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.18 (0.74)</td>
<td>2.27 (0.83)</td>
<td>2.62 (0.81)</td>
<td>2.76 (0.93)</td>
</tr>
<tr>
<td>Women</td>
<td>1.76 (0.59)</td>
<td>1.75 (0.56)</td>
<td>2.13 (0.66)</td>
<td>1.98 (0.53)</td>
</tr>
<tr>
<td>Urine protein, g/d‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.61 (1.01)</td>
<td>0.57 (0.99)</td>
<td>1.55 (1.24)</td>
<td>1.50 (1.25)</td>
</tr>
<tr>
<td>Women</td>
<td>0.40 (0.75)</td>
<td>0.38 (0.73)</td>
<td>1.18 (1.01)</td>
<td>1.17 (1.02)</td>
</tr>
<tr>
<td>UP/Cr†‡</td>
<td>0.34 (0.51)</td>
<td>0.30 (0.48)</td>
<td>0.84 (0.58)</td>
<td>0.77 (0.56)</td>
</tr>
<tr>
<td>Men</td>
<td>0.32 (0.52)</td>
<td>0.30 (0.55)</td>
<td>0.93 (0.63)</td>
<td>0.93 (0.74)</td>
</tr>
<tr>
<td>History of heart disease, %</td>
<td>50.5</td>
<td>54.8</td>
<td>50.7</td>
<td>53.6</td>
</tr>
<tr>
<td>Years of hypertension</td>
<td>13.3 (9.9)</td>
<td>14.6 (10.0)</td>
<td>12.6 (9.0)</td>
<td>11.7 (9.2)</td>
</tr>
<tr>
<td><strong>Antihypertensive use, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>39.9</td>
<td>41.5</td>
<td>36.8</td>
<td>40.6</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>25.9</td>
<td>28.1</td>
<td>25.7</td>
<td>23.2</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>62.8</td>
<td>61.3</td>
<td>72.9</td>
<td>63.8</td>
</tr>
<tr>
<td>Dihydropyridine calcium channel blocker</td>
<td>46.6</td>
<td>44.7</td>
<td>54.2</td>
<td>55.1</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD) unless otherwise indicated. Of the variables considered differed significantly between the ramipril and amlodipine groups, either in the full study or in the subgroup with urine protein-creatinine (UP/Cr) levels >0.22. †Expressed as urine protein (mg/d) to urine creatinine (mg/d) ratio. UP/Cr of 0.22 corresponds approximately to proteinuria of 300 mg/d. ‡To convert urine protein (mg/d) to µmol/L, multiply by 88.4. To convert serum creatinine (mg/dL) to µmol/L, multiply by 88.4.

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group than the amlodipine group for participants with baseline GFR levels of at least 40 mL/min per 1.73 m² (mean [SE] declines of 1.53 [0.26] and 0.55 [0.42] mL/min per 1.73 m²/y in the ramipril and amlodipine groups) (Figure 2C). However, it was 1.61 (0.62) mL/min per 1.73 m²/y faster in the amlodipine group for subjects with baseline GFR less than 40 mL/min per 1.73 m² (mean [SE] declines of 2.73 [0.32] and 4.33 [0.54] mL/min per 1.73 m²/y in the ramipril and amlodipine groups) (Figure 2D).

During the chronic phase, mean GFR declined at a substantially faster rate in participants with higher baseline proteinuria (UP/Cr >0.22) than in participants without proteinuria (UP/Cr ≤0.22, P<.001). The rate of GFR decline during the chronic phase was 2.37 (0.80) mL/min per 1.73 m²/y, or 36%, slower in the ramipril group than in the amlodipine groups, respectively. However, among participants with baseline UP/Cr >0.22, the total decline to 3 years was 2.02 (0.74) mL/min per 1.73 m²/y, or 36%, slower in the ramipril group than in the amlodipine groups (P=.006) (mean [SE] total slopes were −1.02 [0.25] and 0.20 [0.39] mL/min per 1.73 m²/y in the ramipril and amlodipine groups, respectively). However, among participants with baseline UP/Cr >0.22, the total decline to 3 years was 2.02 (0.74) mL/min per 1.73 m²/y, or 36%, slower in the ramipril group than in the amlodipine groups (P=.006) (mean [SE] total slopes were −3.60 [0.34] and −5.62 [0.65] mL/min per 1.73 m²/y in the ramipril and amlodipine groups) (Figure 2B).

Among participants with baseline UP/Cr <0.22, the difference in mean chronic GFR slope between ramipril and amlodipine groups was slightly smaller (0.80 [0.43] mL/min per 1.73 m²/y; P=.07) (mean [SE] declines of 1.22 [0.25] and 2.02 [0.38] in the ramipril and amlodipine groups, respectively). However, the interaction of the drug regimens with baseline proteinuria was not significant (P=.21).

**Effect of Baseline GFR.** Consistent with the inverse association between GFR and proteinuria at baseline, significant interactions were also observed between baseline GFR and the treatment interventions on the acute slopes (P=.006) and total mean slopes (P=.003). The total mean GFR decline to 3 years was 0.97 (0.47) mL/min per 1.73 m²/y faster in the ramipril group than the amlodipine group for participants with baseline GFR levels of at least 40 mL/min per 1.73 m² (mean [SE] declines of 1.53 [0.26] and 0.55 [0.42] mL/min per 1.73 m²/y in the ramipril and amlodipine groups) (Figure 2C). However, it was 1.61 (0.62) mL/min per 1.73 m²/y faster in the amlodipine group for subjects with baseline GFR less than 40 mL/min per 1.73 m² (mean [SE] declines of 2.73 [0.32] and 4.33 [0.54] mL/min per 1.73 m²/y in the ramipril and amlodipine groups) (Figure 2D).

**Table 2. Antihypertensive Therapy and Blood Pressure During Follow-up**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>Month 3</th>
<th>Follow-up</th>
<th>Baseline</th>
<th>Month 3</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 436)</td>
<td>(n = 375)</td>
<td>After 3 Months</td>
<td>(n = 418)</td>
<td>(n = 189)</td>
<td>After 3 Months</td>
</tr>
<tr>
<td>Ramipril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>151.0</td>
<td>134.4</td>
<td>134.5</td>
<td>150.0</td>
<td>134.0</td>
<td>132.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>96.0</td>
<td>84.0</td>
<td>82.2</td>
<td>95.7</td>
<td>83.1</td>
<td>81.4</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of drugs</td>
<td>2.40</td>
<td>2.80</td>
<td>2.75</td>
<td>2.48</td>
<td>2.64</td>
<td>2.75</td>
</tr>
<tr>
<td>Assigned therapy, %</td>
<td>NA</td>
<td>91.2</td>
<td>78.5</td>
<td>NA</td>
<td>91.7</td>
<td>83.5</td>
</tr>
<tr>
<td>Crossover, %</td>
<td>NA</td>
<td>5.77</td>
<td>11.6</td>
<td>NA</td>
<td>5.07</td>
<td>7.1</td>
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Clinical End Point Analysis
The results of the analysis of clinical end points are presented in Table 3 and Figure 3. The top 2 rows of Table 3 provide the frequencies of GFR events and ESRD, irrespective of the order of the events. The 143 composite events in the ramipril and amlodipine groups included 73 GFR events, 40 additional participants who reached ESRD without a prior GFR event, and 30 additional participants who died without ESRD or a prior GFR event. Without covariate adjustment, the risk reduction for the ramipril vs amlodipine groups for the clinical composite outcome including all 3 end points was 26% (95% CI, –4% to 47%; \( P = .09 \)). After adjustment for the prespecified covariates as required by the study’s analysis plan, the risk reduction for the ramipril vs amlodipine groups in the clinical composite outcome was 38% (95% CI, 13%-56%; \( P = .005 \)); for the combined hard end points of ESRD or death (excluding GFR events), it was 41% (95% CI, 14%-60%; \( P = .007 \)); and for the 2 renal end points, major declines in GFR or dialysis, censoring death, it was 38% (95% CI, 10%-58%; \( P = .01 \)). The risk reduction in the clinical end points for the ramipril group was not significantly related to baseline proteinuria (\( P = .25 \)), but it was strongly influenced by the subgroup with baseline proteinuria \( \text{UP/Cr} > 0.22 \) (approximately 300 mg/d) since 90 (62.9%) of these 143 events occurred in this group. Among participants with \( \text{UP/Cr} > 0.22 \), the risk reduction was 48% (95% CI, 20%-66%; \( P = .003 \)).

Proteinuria
Proteinuria (geometric mean UP/Cr increased by 58% from 0.0997 to 0.1575 in participants in the amlodipine group and declined by 20% from 0.1147 to 0.0915 in the ramipril group during the first 6 months of the study. This difference between treatment groups was significant (\( P < .001 \)) and persisted throughout the follow-up period, with moderate increases in proteinuria in both groups. The percentage increase in proteinuria was significantly greater with amlodipine than ramipril in both baseline proteinuria strata (Figure 4). However, the magnitude of the difference between the ramipril and amlodipine groups in the median change in UP/Cr was larger for the baseline UP/Cr > 0.22 strata (difference in median change=0.35 mg of protein per mg of creatinine) than for the baseline UP/Cr ≤0.22 strata (difference in median change=0.02 mg of protein per mg of creatinine). Nonetheless, among those with baseline UP/Cr <0.22, the rate at which participants first developed UP/Cr ≥0.22 (~300 mg/d) was 56%
lower (95% CI, 37%-69%; P<.001) for the ramipril group than for the amlo-
dipine group.

**COMMENT**

This report suggests that initial anti-
hypertensive therapy with ramipril, an ACEI, offers greater benefit in slowing
deterioration of renal function than am-
lodipine, a DHP-CCB, in participants with mild-to-moderate chronic renal in-
sufficiency associated with hyperten-
sive nephrosclerosis. This conclusion is supported by 3 findings based on
analyses of the entire cohort in this trial. Participants randomized to the ramipril group experienced significant reduc-
tions compared with those in the am-
lodipine group in (1) risk of the im-
portant clinical end points, that is, marked decline of renal function, ESRD, or death; (2) mean chronic decline in
GFR from 3 months postrandomiza-
tion; and (3) proteinuria.

Because reports published during the
course of the trial suggested that ACEIs had a greater relative benefit in patients with proteinuria, analyses were strati-
fied by level of baseline urine protein ex-
cretion.3-6,10,14,22,25-28 Participants with pro-
tein excretion greater than 2.5 g/d were not included in AASK, but one third of
participants had baseline protein excre-
tion greater than 2.5 g/d and from 3 months, and urinary pro-
tein excretion. Consistent with other re-
ports, proteinuria was a strong predictor of GFR decline, and the majority of par-
ticipants who experienced a clinical end
point had baseline protein excretion of
UP/Cr >0.22.7,14

The benefit of ramipril on the total change in GFR observed in participants with higher baseline urine protein ex-
cretion did not extend to those partici-
pants without proteinuria. Because treatment with a DHP-CCB–based anti-
hypertensive drug regimen produced an
acute rise in GFR that was confined to participants without proteinuria, the ramipril regimen did not significantly
slow the total mean GFR decline com-
pared with the amlodipine regimen for either the subgroup without protein-
uria or the entire cohort. There is some
evidence that increases in GFR ob-
served after initiation of a DHP-CCB may not confer benefit on long-term renal outcome. In animal studies, DHP-
CCBs produce an acute rise in GFR by
causing afferent arteriolar vasodilation
and loss of renal autoregulation.30-32 As
a consequence, intraglomerular pres-
sure typically rises, even when systemic arterial pressure falls.30,32 In contrast,
ACEIs generally reduce intraglomeru-
lar pressure and do not interfere with au-
toregulation.30,32 These observations, taken together with clinical studies show-
ing increases in proteinuria with DHP-
CCBs, raise the possibility that pressure-
mediated glomerular injury could contribute to the greater increase in pro-
teinuria and more rapid decline in GFR observed in AASK participants receiving
these agents.10,14,16,22,33,34

While the total change in GFR during
the study period did not differ sig-
nificantly between treatment groups,
other AASK results suggest the benefit of ramipril over amlodipine may extend to individuals without proteinuria. The analysis of total GFR slope is strongly influenced by acute changes in participants with little overall disease progression, while both the clinical end points and chronic slope outcomes better reflect long-term disease progression. These outcomes demonstrate significant benefits of ACEI for the entire cohort. The benefit of ACEI in the clinical end point analysis is particularly compelling since it is based on events with direct patient impact.

The increase in proteinuria in the amlodipine group compared with the ramipril group was significant for both baseline proteinuria strata. Furthermore, in AASK participants with baseline UP/Cr <0.22, the time until the ratio first reached the 0.22 cutpoint was significantly shorter for the amlo-
dipine than for the ramipril group. Thus, treatment of a patient without proteinuria with a DHP-CCB may result in the development of proteinuria and potentially a greater risk of long-term renal disease. Nonetheless, the relatively low rates of renal disease progression in the participants without proteinuria and data suggesting that ACEIs have a larger benefit in participants with proteinuria than those without proteinuria make the evidence for a renoprotective benefit of ACEIs in these participants without proteinuria less definitive.25

A limitation of the analyses of GFR slope in this report is that the occurrence of ESRD, death, or patient dropout prevented observation of GFRs over the entire study period for a substantial fraction of participants (Figure 1). This could have biased our results depending on the relationship of the pattern of missing data with the GFR slopes.33 However, the results of the GFR slope analyses changed little under alternative models for the missing GFRs (data not shown), suggesting that the missed GFRs did not affect our conclusions. A second limitation is that the investigation of the ramipril vs amlodipine comparison in relation to base-
line proteinuria was not specified in the protocol prior to the study. However, the decision to investigate the influence of proteinuria on the treatment effects was made by study investigators who were blinded to AASK outcome data, reducing the risk of a spurious post hoc finding. The cutpoint of 0.22 used for stratification by baseline UP/Cr was also selected independently of the AASK data based on clinical and statistical considerations. However, the sample size of this study is not sufficient to determine a precise threshold where the advantage of ACEIs becomes definitive.7

In aggregate, our results are consistent with prior observations in participants with both diabetics and nondiabetic renal disease that ACEIs have a renoprotective effect7,14-28 and that treatment with a DHP-CCB increases proteinuria and may not slow the progression of established renal disease despite substantial reductions in BP.10,14-16,22,28,33-35 Interim results of the AASK trial, taken together with previous trials, support the use of an ACEI as initial therapy in a multidrug regimen over a DHP-CCB-based regimen in African American and white participants with mild-to-moderate chronic renal insufficiency and levels of proteinuria defined in this report.14 Interim results further provide documentation extending the renoprotective action of an ACEI-based regimen to African Americans with this disorder, a population previously thought to be less responsive to these agents. For participants with hypertension without proteinuria and those at low risk for progressive renal disease, the evidence is less conclusive. By design, only persons with hypertension and mild-to-moderate renal disease were studied in the AASK, and the effect of amlodipine and ramipril on renal function was the major focus of the study. The study was not designed to evaluate the effect of these agents on cardiovascular and cerebrovascular complications, the most frequent complications of hypertension. The risk of these complications has been shown to be lowered by DHP-CCBs in a number of clinical end point trials.37-40 However, clinicians should be aware that use of DHP-CCBs both in this and other trials not involving African Americans are associated with the development of proteinuria.7,10,14-16,22,28,33 Thus, measurement of urinary protein excretion is recommended to guide initial therapy selection.

Author Affiliations: National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md (Dr Agodoa, Briggs, and Kusek); Department of Preventive Medicine, Johns Hopkins University, Baltimore, Md (Dr Appel and Miller and Ms Charleston); Department of Preventive Medicine, Rush-Presbyterian-St Luke’s Medical Center, Chicago, III (Dr Bakris); Department of Biostatistics, Cleveland Clinic Foundation, Cleveland, Ohio (Dr Beck, Gassman, and Greene); Department of Medicine, University of Miami, Coral Gables, Fla (Dr Bourgoignie); Department of Medicine, Medical University of South Carolina, Charleston (Dr Cheek); Department of Medicine, Morehouse School of Medicine, Atlanta, Ga (Dr Cleveland and Mr Smith); Department of Medicine, Case Western Reserve University Hospitals, Cleveland, Ohio (Dr Douglas, Dr O’Connor, Dr Homer, and Dr Wright, and Ms Hall); Department of Medicine, Emory University Medical Center, Atlanta, Ga (Ms Douglas and Dr Lea); Department of Medicine, Harlem Hospital Center, New York, NY (Dr Dowie and Pogue); Department of Medicine, Meharry Medical College, Nashville, Tenn (Dr Faulkner); Department of Medicine, Mount Sinai School of Medicine, New York, NY (Ms Gabriel and Drs Lipkowitz and Phillips); Department of Medicine, Ohio State University, Columbus (Drs Hebert and Hirsemath); Department of Medicine, University of Michigan, Ann Arbor (Dr Jamer-
son and Ojo); Department of Medicine, Harbor Medical Center, University of California, Los Angeles (Dr Kopple); Department of Medicine, University of Illi-
ois, Chicago (Dr Lash); Department of Medicine, Vanderbilt University, Nashville, Tenn (Dr Lewis and Schulumn); Department of Medicine, University of Southern California, Los Angeles (Dr Massry); Department of Medicine, University of Texas Southwest-
ern Medical Center, Dallas (Drs McManus and Toto); Department of Medicine, University of California, San Diego (Dr O’Connor); Department of Medicine, Howard University, Washington, DC (Drs Randall and Xu); Department of Medicine, University of Alabama, Birmingham (Drs Rostand and Thornley-
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