Effect of Ramipril vs Amlodipine on Renal Outcomes in Hypertensive Nephrosclerosis

A Randomized Controlled Trial

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Context Incidence of end-stage renal disease due to hypertension has increased in recent decades, but the optimal strategy for treatment of hypertension to prevent renal failure is unknown, especially among African Americans.

Objective To compare the effects of an angiotensin-converting enzyme (ACE) inhibitor (ramipril), a dihydropyridine calcium channel blocker (amlodipine), and a β-blocker (metoprolol) on hypertensive renal disease progression.

Design, Setting, and Participants Interim analysis of a randomized, double-blind, 3×2 factorial trial conducted in 1094 African Americans aged 18 to 70 years with hypertensive renal disease (glomerular filtration rate [GFR] of 20-65 mL/min per 1.73 m^2) enrolled between February 1995 and September 1998. This report compares the ramipril and amlodipine groups following discontinuation of the amlodipine intervention in September 2000.

Interventions Participants were randomly assigned to receive amlodipine, 5 to 10 mg/d (n=217), ramipril, 2.5 to 10 mg/d (n=436), or metoprolol, 50 to 200 mg/d (n=441), with other agents added to achieve 1 of 2 blood pressure goals.

Main Outcome Measures The primary outcome measure was the rate of change in GFR; the main secondary outcome was a composite index of the clinical end points of reduction in GFR of more than 50% or 25 mL/min per 1.73 m^2, end-stage renal disease, or death.

Results Among participants with a urinary protein to creatinine ratio of >0.22 (corresponding approximately to proteinuria of more than 300 mg/d), the ramipril group had a 36% (2.02 [SE, 0.74] mL/min per 1.73 m^2/y) slower mean decline in GFR over 3 years (P=.006) and a 48% reduced risk of the clinical end points vs the amlodipine group (95% confidence interval [CI], 20%-66%). In the entire cohort, there was no significant difference in mean GFR decline from baseline to 3 years between treatment groups (P=.38). However, compared with the amlodipine group, after adjustment for baseline covariates the ramipril group had a 38% reduced risk of clinical end points (95% CI, 13%-56%), a 36% slower mean decline in GFR after 3 months (P=.002), and less proteinuria (P<.001).

Conclusion Ramipril, compared with amlodipine, retards renal disease progression in patients with hypertensive renal disease and proteinuria and may offer benefit to patients without proteinuria.

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THE MORTALITY FROM HYPERTENsive 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.[1] In certain age groups, the risk of hypertensive ESRD for African Americans is 20-fold greater than in whites.[1,2] The optimal strategy for treatment of hypertension to prevent renal failure has remained elusive. Recent data in participants with diabetic and proteinuric nondiabetic kidney dis-

ease have suggested significant benefits with angiotensin-converting enzyme inhibitors (ACEIs).[3-7] 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.[8,9] Although animal studies have demonstrated prevention of glomerulosclerosis by calcium channel blockers (CCBs),[10-12] human studies have not consistently confirmed their renoprotective effects.[5,12-16]

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).[17] To date, AASK is the largest comparative drug intervention trial that has focused on renal outcomes conducted in any population and the first clinical end point 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 m^2 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.[17] 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, hydralazine hydrochloride, 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.[18] 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 after at least 5 minutes rest,[17,19] 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 ^{125}iothalamate clearance at baseline twice, then at 3, 6, and every 6 months thereafter.[20] 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.[5,21-25] 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 clinical 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[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.[4,6,7,14,15,25] 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 ≤ 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 ≤ 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,[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 assigment 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-CCB 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 m^2.

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.

Table 1. Baseline Characteristics*

	All		Baseline UP/Cr >0.22†	
	Ramipril (n = 436)	Amlodipine (n = 217)	Ramipril (n = 144)	Amlodipine (n = 69)
Age, y	54.2 (10.9)	54.4 (10.7)	49.8 (11.2)	50.9 (10.3)
Women, %	38.8	40.1	34.7	34.8
Blood pressure, mm Hg				
Systolic	151.0 (23.3)	150.0 (25.3)	156.0 (21.8)	157.3 (26.0)
Diastolic	96.0 (14.5)	95.7 (14.1)	99.8 (14.9)	100.3 (14.4)
Mean arterial pressure, mm Hg	114.6 (15.9)	114.0 (16.7)	118.7 (15.6)	119.5 (17.2)
Glomerular filtration rate, mL/min per 1.73 m^2	46.1 (13.6)	46.8 (13.2)	37.7 (12.2)	40.1 (13.3)
Serum creatinine, mg/dL‡				
Men	2.18 (0.74)	2.27 (0.83)	2.62 (0.81)	2.76 (0.93)
Women	1.76 (0.59)	1.75 (0.56)	2.13 (0.66)	1.98 (0.53)
Urine protein, g/d‡				
Men	0.61 (1.01)	0.57 (0.99)	1.55 (1.24)	1.50 (1.25)
Women	0.40 (0.75)	0.38 (0.73)	1.18 (1.01)	1.17 (1.02)
UP/Cr†				
Men	0.34 (0.51)	0.30 (0.48)	0.84 (0.58)	0.77 (0.56)
Women	0.32 (0.52)	0.30 (0.55)	0.93 (0.63)	0.93 (0.74)
History of heart disease, %	50.5	54.8	50.7	53.6
Years of hypertension	13.3 (9.9)	14.6 (10.0)	12.6 (9.0)	11.7 (9.2)
Antihypertensive use, %				
Angiotensin-converting enzyme inhibitor	39.9	41.5	36.8	40.6
β-Blocker	25.9	28.1	25.7	23.2
Calcium channel blocker	62.8	61.3	72.9	63.8
Dihydropyridine calcium channel blocker	46.6	44.7	54.2	55.1

*Values are expressed as mean (SD) unless otherwise indicated. None 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 creatinine mg/dL to μmol/L, multiply by 88.4. To convert urine protein g/d to mg/d, multiply by 1000.

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 m^2/y in the ramipril and amlodipine groups, respectively. The mean decline was 1.15 mL/min per 1.73 m^2/y (95% CI, 0.41-1.90) or 36% slower in the ramipril group (*P*=.002). However, during the 3-month acute phase, GFR increased 4.19 mL/min per 1.73 m^2/y (95% CI, 2.64-5.73) more 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 m^2 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 mean slopes=0.34 mL/min per 1.73 m^2/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

($P<.001$). The mean (SE) total decline in GFR to 3 years (FIGURE 2A) was 1.22 (0.44) mL/min per 1.73 m^2/y faster in the ramipril group than in the amlodipine group among participants with baseline UP/Cr ≤ 0.22 (~300 mg/d) ($P=.006$) (mean [SE] total slopes were −1.02 [0.25] and 0.20 [0.39] mL/min per 1.73 m^2/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 m^2/y, or 36%, slower in the ramipril group ($P=.006$) (mean [SE] total slopes were −3.60 [0.34] and −5.62 [0.65] mL/min per 1.73 m^2/y in the ramipril and amlodipine groups) (Figure 2B).

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 m^2/y less in the ramipril group than in the amlodipine group in participants with baseline UP/Cr >0.22 ($P=.003$) (mean [SE] declines of 3.55 [0.41] and 5.92 [0.69] mL/min per 1.73 m^2/y in the ramipril and amlodipine groups, respectively). 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 m^2/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 m^2/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 m^2 (mean [SE] declines of 1.53 [0.26] and 0.55 [0.42] mL/min per 1.73 m^2/y in the ramipril and amlodipine groups) (Figure 2C). However, it was 1.61 (0.62) mL/min per 1.73 m^2/y faster in the amlodipine group for subjects with baseline GFR less than 40 mL/min per 1.73 m^2 (mean [SE] declines of 2.73 [0.32] and 4.33 [0.54] mL/min per 1.73 m^2/y in the ramipril and amlodipine groups) (Figure 2D).

Figure 1. Trial Profile

Asterisk indicates those seen at a screening visit but not the participants prescreened by chart review or telephone screening. Dagger indicates the number of participants who were alive and not receiving dialysis and who did not have a GFR measured in the final year. Double dagger indicates the number of participants who were alive, were not receiving dialysis, and who had at least 1 GFR in the final year of follow-up prior to September 22, 2000.

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

	Ramipril			Amlodipine		
	Baseline (n = 436)	Month 3 (n = 375)	Follow-up After 3 Months (n = 418)	Baseline (n = 217)	Month 3 (n = 189)	Follow-up After 3 Months (n = 209)
Blood pressure, mean, mm Hg						
Systolic	151.0	134.4	134.5	150.0	134.0	132.9
Diastolic	96.0	84.0	82.2	95.7	83.1	81.4
Mean arterial pressure, mm Hg	114.6	101.0	99.8	114.0	100.3	98.8
Total No. of drugs	2.40	2.80	2.75	2.48	2.64	2.75
Assigned therapy, %	NA	91.2	78.5	NA	91.7	83.5
Crossover, %	NA	5.77	11.6	NA	5.07	7.1

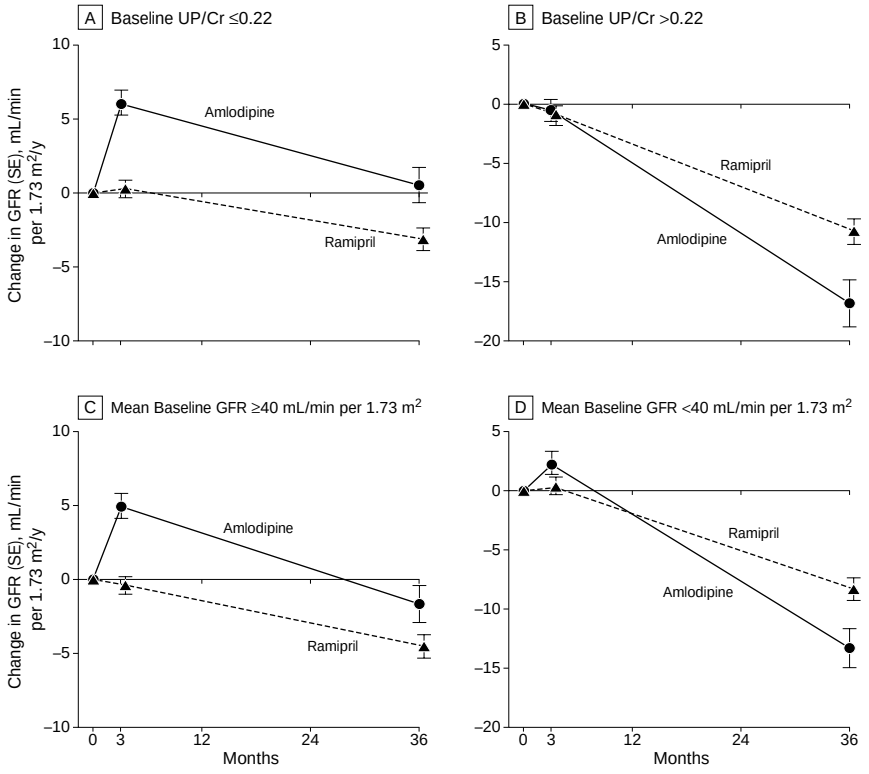
*No. of patients with blood pressure measurements at indicated times. NA indicates not applicable.

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 provides 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 UP/Cr >0.22 (approximately 300 mg/d) since 90 (62.9%) of these 143 events occurred in this group. Among participants with UP/Cr >0.22, the risk reduction was 48% (95% CI, 20%-66%; $P=.003$).

Figure 2. Mean Change in Glomerular Filtration Rate (GFR) Under 2-Slope Model



UP/Cr indicates urinary protein to creatinine ratio. Baseline UP/Cr of 0.22 corresponds approximately to proteinuria of 300 mg/d.

Table 3. Rates and Numbers of Clinical Events*

Event	Events per Person-Year (No. of Events)		% Relative Risk Reduction (95% CI)†	*P* Value
	Ramipril (n = 436)	Amlodipine (n = 217)		
GFR	0.028 (44)	0.038 (29)	41 (5 to 63)	.03
ESRD	0.030 (47)	0.043 (32)	44 (13 to 65)	.01
Death‡	0.011 (18)	0.016 (13)	31 (−41 to 66)	.31
GFR or ESRD	0.047 (70)	0.059 (43)	38 (10 to 58)	.01
ESRD or death	0.042 (65)	0.060 (45)	41 (14 to 60)	.007
GFR, ESRD, or death§	0.058 (87)	0.077 (56)	38 (13 to 56)	.005

*CI indicates confidence interval; GFR, glomerular filtration rate; and ESRD, end-stage renal disease.
†Adjusted for baseline levels of log transformed urine protein–creatinine ratio, history of heart disease, mean arterial pressure, sex, and age.
‡Includes only deaths prior to ESRD. Three additional patients died in each group after ESRD.
§Prespecified clinical composite outcome.

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 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 amlodipine group.

COMMENT

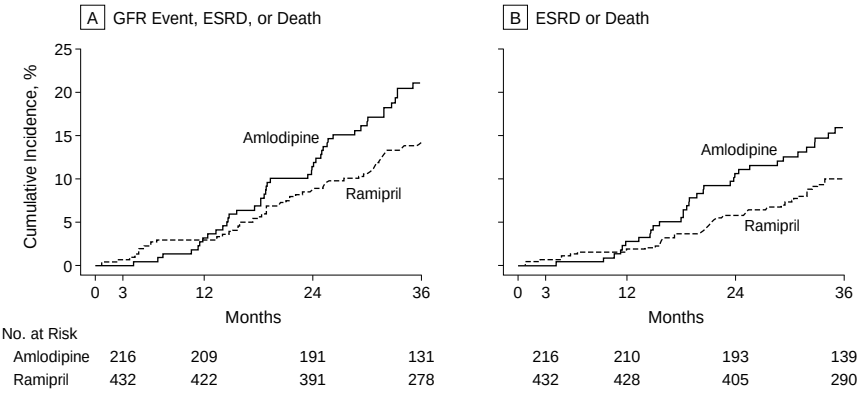
This report suggests that initial antihypertensive therapy with ramipril, an ACEI, offers greater benefit in slowing deterioration of renal function than amlodipine, a DHP-CCB, in participants with mild-to-moderate chronic renal insufficiency associated with hypertensive nephrosclerosis. This conclusion is supported by 3 findings based on analyses of the entire cohort in this trial. Participants randomized to the ramipril group experienced significant reductions compared with those in the amlodipine group in (1) risk of the important clinical end points, that is, marked decline of renal function, ESRD, or death; (2) mean chronic decline in GFR from 3 months postrandomization; 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 stratified by level of baseline urine protein excretion.[3-6,10,14,22,25-28] Participants with protein excretion greater than 2.5 g/d were not included in AASK, but one third of participants had baseline protein excretion with UP/Cr >0.22 or approximately 300 mg/d, a value that defines clinically significant proteinuria. Participants with protein excretion above this level showed the greatest benefit of ramipril compared with those receiving amlodipine in all outcome parameters, including the combined clinical end point, the mean GFR slope from baseline and from 3 months, and urinary protein excretion. Consistent with other reports, proteinuria was a strong predictor of GFR decline, and the majority of participants 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 excretion did not extend to those participants without proteinuria. Because treatment with a DHP-CCB–based antihypertensive 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 compared with the amlodipine regimen for either the subgroup without proteinuria or the entire cohort. There is some evidence that increases in GFR observed 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 pressure typically rises, even when systemic arterial pressure falls.[30,32] In contrast, ACEIs generally reduce intraglomerular pressure and do not interfere with autoregulation.[30,32] These observations, taken together with clinical studies showing increases in proteinuria with DHP-CCBs, raise the possibility that pressure-mediated glomerular injury could contribute to the greater increase in proteinuria and more rapid decline in GFR observed in AASK participants receiving these agents.[10,14,16,22,33,34]

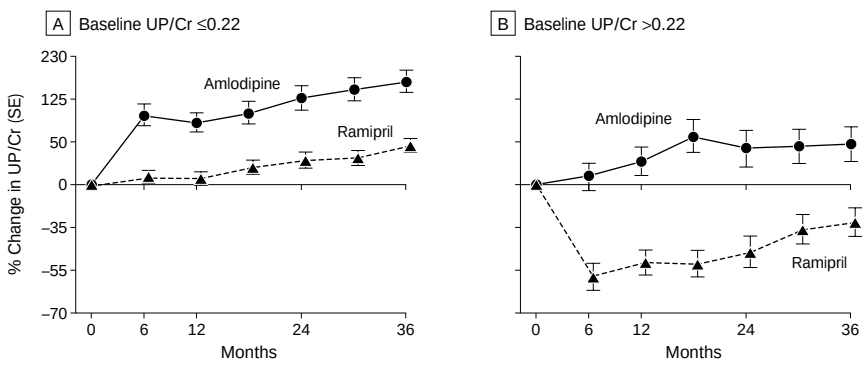
While the total change in GFR during the study period did not differ significantly between treatment groups,

Figure 3. Cumulative Incidence of Renal Events and Death



GFR indicates glomerular filtration rate; ESRD, end-stage renal disease. The adjusted risk reduction for ramipril vs amlodipine for the GFR event, ESRD, or death composite outcome was 38% (95% confidence interval [CI], 13%-56%; $P = .005$) (A) and for ESRD or death was 41% (95% CI, 14%-60%; $P = .007$) (B). The risk reductions are adjusted for baseline levels of log transformed urine protein–creatinine ratio, history of heart disease, mean arterial pressure, sex, and age.

Figure 4. Percent Changes in Proteinuria From Baseline



UP/Cr indicates urinary protein to creatinine ratio. Shown are the estimated percentage changes from baseline in the geometric mean UP/Cr. Baseline UP/Cr of 0.22 corresponds approximately to proteinuria of 300 mg/d. Error bars represent SE.

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 amlodipine 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.[35] However, the results of the GFR slope analyses changed little under alternative models for the missing GFRs[36] (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 baseline 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 also was 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 diabetic and nondiabetic renal disease that ACEIs have a renoprotective effect[3,4,6,28] and that treatment with a DHP-CCB increases proteinuria and may not slow the progression of established renal disease despite substantial reductions in BP.[10,14-16,22,25,28,33,34] 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.[3-6,14,27] These 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.

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