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Jackson T. Wright, Jr; George Bakris; Tom Greene; et al.

JAMA. 2002;288(19):2421-2431 (doi:10.1001/jama.288.19.2421)

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Effect of Blood Pressure Lowering and Antihypertensive Drug Class on Progression of Hypertensive Kidney Disease

Results From the AASK Trial

Jackson T. Wright, Jr, MD, PhD

George Bakris, MD

Tom Greene, PhD

Larry Y. Agodoa, MD

Lawrence J. Appel, MD, MPH

Jeanne Charleston, RN

DeAnna Cheek, MD

Janice G. Douglas-Baltimore, MD

Jennifer Gassman, PhD

Richard Glascock, MD

Lee Hebert, MD

Kenneth Jamerson, MD

Julia Lewis, MD

Robert A. Phillips, MD, PhD

Robert D. Toto, MD

John P. Middleton, MD

Stephen G. Rostand, MD

for the African American Study of
Kidney Disease and Hypertension
Study Group

HYPERTENSION IS REPORTED TO be the second leading cause of end-stage renal disease (ESRD).¹ African Americans are 6 times more likely to develop ESRD from hypertension than whites.² Observational studies show a direct relationship between the level of blood pressure (BP) and renal disease progression.^{3,4} Post hoc analyses of clinical trials also suggest that lowering BP may retard pro-

See also p 2466 and Patient Page.

Context Hypertension is a leading cause of end-stage renal disease (ESRD) in the United States, with no known treatment to prevent progressive declines leading to ESRD.

Objective To compare the effects of 2 levels of blood pressure (BP) control and 3 antihypertensive drug classes on glomerular filtration rate (GFR) decline in hypertension.

Design Randomized 3 × 2 factorial trial with enrollment from February 1995 to September 1998.

Setting and Participants A total of 1094 African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m²) were recruited from 21 clinical centers throughout the United States and followed up for 3 to 6.4 years.

Interventions Participants were randomly assigned to 1 of 2 mean arterial pressure goals, 102 to 107 mm Hg (usual; n=554) or 92 mm Hg or less (lower; n=540), and to initial treatment with either a β -blocker (metoprolol 50-200 mg/d; n=441), an angiotensin-converting enzyme inhibitor (ramipril 2.5-10 mg/d; n=436) or a dihydropyridine calcium channel blocker, (amlodipine 5-10 mg/d; n=217). Open-label agents were added to achieve the assigned BP goals.

Main Outcome Measures Rate of change in GFR (GFR slope); clinical composite outcome of reduction in GFR by 50% or more (or ≥ 25 mL/min per 1.73 m²) from baseline, ESRD, or death. Three primary treatment comparisons were specified: lower vs usual BP goal; ramipril vs metoprolol; and amlodipine vs metoprolol.

Results Achieved BP averaged (SD) 128/78 (12/8) mm Hg in the lower BP group and 141/85 (12/7) mm Hg in the usual BP group. The mean (SE) GFR slope from baseline through 4 years did not differ significantly between the lower BP group (-2.21 [0.17] mL/min per 1.73 m² per year) and the usual BP group (-1.95 [0.17] mL/min per 1.73 m² per year; $P=.24$), and the lower BP goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower BP group=2%; 95% confidence interval [CI], -22% to 21%; $P=.85$). None of the drug group comparisons showed consistent significant differences in the GFR slope. However, compared with the metoprolol and amlodipine groups, the ramipril group manifested risk reductions in the clinical composite outcome of 22% (95% CI, 1%-38%; $P=.04$) and 38% (95% CI, 14%-56%; $P=.004$), respectively. There was no significant difference in the clinical composite outcome between the amlodipine and metoprolol groups.

Conclusions No additional benefit of slowing progression of hypertensive nephrosclerosis was observed with the lower BP goal. Angiotensin-converting enzyme inhibitors appear to be more effective than β -blockers or dihydropyridine calcium channel blockers in slowing GFR decline.

JAMA. 2002;288:2421-2431

www.jama.com

Author Affiliations, Financial Disclosures, and Members of the African American Study of Kidney Disease and Hypertension Study Group are listed at the end of this article.

Corresponding Author and Reprints: Jackson T. Wright, Jr, MD, PhD, Case Western Reserve

University, Departments of Medicine, University Hospitals of Cleveland and the Louis Stokes Cleveland Department of Veterans Affairs Medical Center, 11000 Euclid Ave, Horwitz Tower, Suite 7311, Cleveland, OH 44106-5014 (e-mail: jxw20@po.cwru.edu).

gression of renal disease and reduce cardiovascular risk.⁵⁻¹⁰ African Americans, however, were not well represented in the aforementioned studies.^{5-7,9,11}

Several studies document that African Americans with chronic kidney disease have faster declines in renal function compared with whites with similar BPs.¹²⁻¹⁴ In the first trial to randomize patients to different BP levels and examine the outcome on kidney disease progression, the Modification of Diet in Renal Disease trial, a benefit of the lower BP goal (≤ 92 mm Hg) was suggested in the small subgroup of 53 African Americans.¹⁵ However, whether a lower BP goal actually retards progression of renal disease in African Americans is uncertain.¹⁶⁻²⁰

In trials that enrolled individuals with renal disease from diabetes and other

etiologies, angiotensin-converting enzyme inhibitors significantly reduce progression of kidney disease. However, few African Americans were included in such trials.²¹⁻²⁴

Angiotensin-converting enzyme inhibitor use is lower in African Americans with hypertension and chronic kidney disease compared with whites. This is a consequence of many factors including a lack of clinical end point and safety data and lower antihypertensive potency when they are used as monotherapy compared with other classes of antihypertensive agents.

The African American Study of Kidney Disease and Hypertension (AASK) prospectively addressed 2 questions in patients with hypertensive nephrosclerosis.²⁵ First, does very aggressive

lowering of BP result in slower declines in kidney function? Second, does the type of antihypertensive agent used to initiate BP lowering matter with regard to kidney disease outcomes?

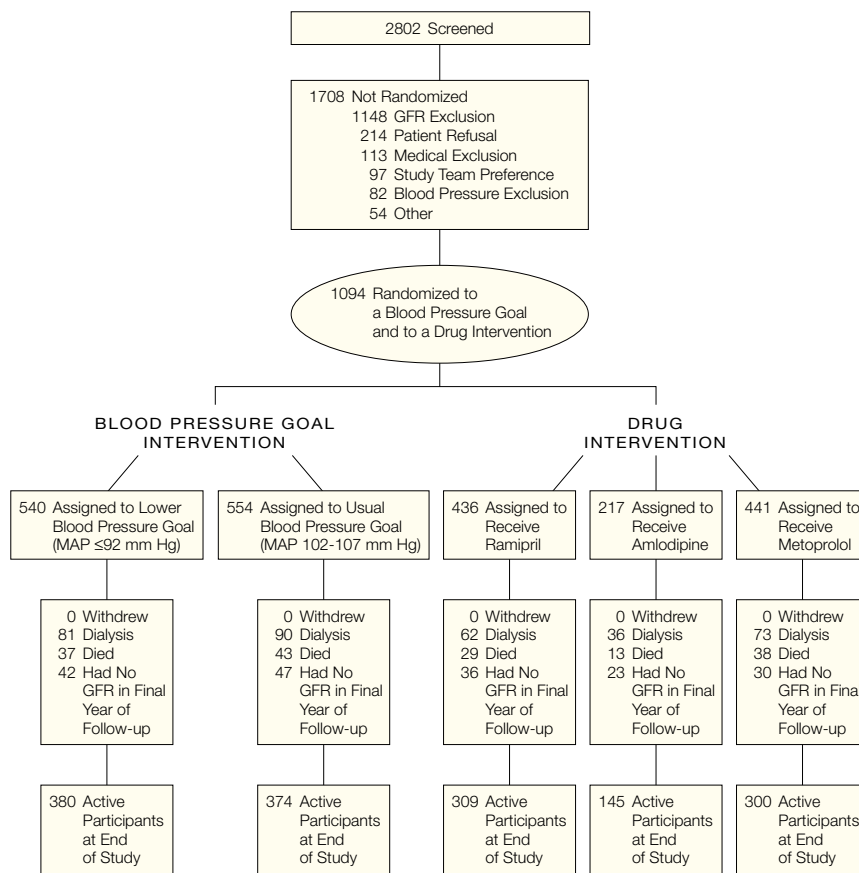
METHODS

Participants

The study design has been previously described.^{25,26} Briefly, participants were self-identified African Americans with hypertension (n=1094) who were aged 18 to 70 years with a glomerular filtration rate (GFR) between 20 and 65 mL/min per 1.73 m² and no other identified causes of renal insufficiency. Exclusion criteria included diastolic BP of less than 95 mm Hg, known history of diabetes mellitus (fasting glucose, ≥ 140 mg/dL or random glucose, >200 mg/dL), urinary protein to creatinine ratio of more than 2.5, accelerated or malignant hypertension within 6 months, secondary hypertension, evidence of non-BP-related causes of chronic kidney disease, serious systemic disease, clinical congestive heart failure, or specific indication for or contraindication to a study drug or study procedure. The protocol and procedures were approved by the institutional review board at each center, and all participants gave written informed consent. An independent data and safety monitoring board was also established by the National Institute of Diabetes and Digestive and Kidney Diseases.

Participant enrollment began in February 1995 and ended in September 1998. FIGURE 1 summarizes the numbers of participants recruited, randomized, and followed up. Planned follow-up to the end of the study in September 2001 was 3 to 6.4 years. On the recommendation of the data and safety monitoring board, the amlodipine arm was halted in September 2000,²⁵ at which point patients randomized to amlodipine were switched to open-label medication. The study's visit schedule, including GFR measurements, was continued and patients in all 3 drug groups remained on their randomly assigned BP goals through the end of the trial.

Figure 1. Participant Recruitment and Follow-up Flow Diagram



GFR indicates glomerular filtration rate; MAP, mean arterial pressure. All deaths were prior to dialysis and the number of participants who were alive and not receiving dialysis and who did not have a GFR were measured in the final year of follow-up. In all treatment groups combined, 96.7% of patients had at least 1 follow-up GFR.

Study Design

Based on a 3 × 2 factorial design, participants were randomized equally to a usual mean arterial pressure goal of 102 to 107 mm Hg or to a lower mean arterial pressure goal of 92 mm Hg or lower, and to treatment with 1 of 3 antihypertensive drugs (a sustained-release β -blocker, metoprolol, 50 to 200 mg/d; an angiotensin-converting enzyme inhibitor, ramipril, 2.5 to 10 mg/d; or a dihydropyridine calcium channel blocker, amlodipine, 5 to 10 mg/d). If the BP goal could not be achieved by the randomized drug, additional open-labeled antihypertensives (furosemide, doxazosin, clonidine, and hydralazine or minoxidil) were added sequentially.²⁷ A 2:2:1 randomization ratio for the metoprolol, ramipril, and amlodipine groups was used because comparisons involving amlodipine had increased power because of a projected early increase in GFR from this medication.^{25,26} Participants and investigators were masked to randomized drug but not BP goal.

Three primary treatment comparisons were specified: lower vs usual BP goal, ramipril vs metoprolol, and amlodipine vs metoprolol. Results of ramipril vs amlodipine, which was a secondary comparison, have been presented previously.²⁵

Measurement of BP and Kidney Function

At each visit, 3 consecutive seated BP readings were measured using a Hawksley random zero sphygmomanometer after at least 5 minutes rest,^{25,27} with the mean of the last 2 readings recorded. The baseline BP readings were those obtained at the screening visits prior to randomization. The follow-up BP measurements reported represent the mean of all BPs measured within a given visit window, including those at interim visits. The GFR was assessed by renal clearance of iodine 125 iothalamate at baseline twice, then at 3, 6, and every 6 months thereafter.²⁸ Serum and urinary levels of creatinine and protein were measured by a central laboratory at 6-month intervals.

Trial Outcomes

The primary analysis is based on the rate of change in GFR (GFR slope). The GFR slope was determined separately during the first 3 months following randomization (acute slope) and after 3 months (chronic slope). The acute and chronic phases were distinguished because previous studies indicated that the AASK interventions have acute effects on GFR that may differ from their long-term effects on disease progression.^{25,29-35} The chronic slope and the mean total slope from baseline (includes both the acute and chronic phases) were designated as coprimary outcomes. The analysis plan stipulated that a definitive benefit of a treatment intervention would be inferred if it is shown to reduce the magnitude of both the chronic and total mean slopes. The total slope assesses effects of interventions on kidney function during the study period, while the chronic slope may better reflect long-term progression.

The protocol also designated a main secondary clinical composite outcome, which included any of the following¹: a confirmed reduction in GFR by 50% or by 25 mL/min per 1.73 m² from the mean of the 2 baseline GFRs; ESRD (dialysis or transplantation); or death. The clinical composite outcome provided the principal assessment of patient benefit. In contrast with the analysis of GFR slope, which addresses the mean change in kidney function in all patients, including those with little or no progression, the analysis of the clinical outcome is based on events of major clinical relevance, either large declines in kidney function or death.

Urinary protein excretion, expressed as the urinary protein to creatinine ratio from a 24-hour urine collection, was a secondary outcome. All cardiovascular events including cardiovascular deaths and hospitalizations for myocardial infarctions, strokes, heart failure, revascularization procedures, and other hospitalized cardiovascular events were reviewed and classified by a blinded end points committee according to a prespecified protocol.

Statistical Methods

Because of acute changes in GFR at discontinuation of amlodipine, data from participants assigned to amlodipine were censored at termination of this arm in September 2000. This required slightly different strategies for each treatment group comparison. The BP group comparison retained all data through the end of the study in the 80% of patients in the ramipril or metoprolol groups but censored data on September 2000 for patients randomized to amlodipine (giving a median GFR follow-up of 3.8 years). Data was retained to the end of the study in both groups for the ramipril vs metoprolol comparison (median GFR follow-up, 4.1 years), and data was censored in September 2000 in both groups for the amlodipine vs metoprolol comparison (median GFR follow-up, 3.0 years).

The primary renal function analysis was based on a mixed-effects model^{36,37} with random intercepts, acute slopes, and chronic slopes, and with fixed effects for 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 urinary protein to creatinine ratio), history of cardiovascular disease, mean arterial pressure, sex, and age. The mean total slopes were computed as time-weighted averages of the mean acute and chronic slopes, and expressed from baseline to 3 years for the amlodipine vs metoprolol comparison and from baseline to 4 years for the lower vs usual BP and ramipril vs metoprolol comparisons. Because the effects of the BP and drug interventions were similar at each level of the other intervention for both the chronic and total GFR slopes (ie, no interaction between the BP groups and drug interventions), we report analyses of the main effects for both interventions. Thus, the BP group comparisons are averaged across the 3 drug groups according to the 2:2:1 randomization ratio, and the drug group comparisons are averaged equally across the 2 BP groups.

The relationships of the treatment comparisons with baseline proteinuria were investigated by adding con-

tinuous interaction terms between ln (urinary protein to creatinine ratio) and the treatment groups.^{21,25} If a statistically significant interaction was detected, the results were then illustrated by subgroup analyses in participants with baseline urinary protein to creatinine ratio of higher than 0.22 (n=357) and 0.22 or less (n=733). The value of 0.22 corresponds to a urine protein excretion of approximately 300 mg/d and divides the two thirds of patients with the lowest proteinuria from the one third with highest proteinuria in accordance with a heavy positive skewness of the urinary protein to creatinine ratio. Since proteinuria was inversely associated with GFR at baseline, the interaction of the treatment groups with baseline GFR was also tested.

The effects of the interventions on the clinical composite outcome, specific re-

nal events, mortality, and secondary cardiovascular events were each analyzed by Cox proportional hazards regression model with adjustment for the same 5 covariates as the analysis of GFR slope. Baseline GFR was included as an additional covariate in Cox proportional hazards regression models of time to ESRD and time to ESRD or death. Participants were administratively censored at loss-to-follow-up (9 patients) or else at the end of the study or September 2000 by the same strategy used for the primary renal function analysis. Because fewer participants were randomized to amlodipine than to the other 2 groups, numbers of events are expressed as rates per patient-year. Proportions of participants reporting symptoms during follow-up were compared between treatment groups by logistic regression controlling for reported symptoms at baseline.

All analyses are intent-to-treat and were performed using SAS versions 6.12 and 8 (SAS Institute Inc, Cary, NC). Two-sided *P* values and 95% confidence intervals (CIs) are reported. This is conservative for the primary analysis because both the chronic and total slopes comparisons needed to reach significance for a definitive conclusion. To simplify the presentation and maintain comparability of risk ratios, comparisons of amlodipine with metoprolol are expressed as risk reductions for metoprolol relative to amlodipine, although metoprolol was the reference group in the study design.

Based on 1094 patients and assuming a mean GFR slope of -4 mL/min per 1.73 m² per year in the usual BP group, the study was projected to have 99%, 79%, and 87% power to detect a 30% reduction in GFR slope for the BP comparison for analyses of the chronic slope, total slope, and clinical composite out-

Table 1. Baseline Characteristics by Randomized Group*

Characteristic	Blood Pressure Goal Intervention		Drug Intervention		
	Lower (n = 540)	Usual (n = 554)	Ramipril (n = 436)	Amlodipine (n = 217)	Metoprolol (n = 441)
Age, mean (SE), y	54.5 (10.9)	54.7 (10.4)	54.4 (10.9)	54.5 (10.7)	54.9 (10.4)
Female, No. (%)	205 (38.0)	219 (39.5)	168 (38.5)	86 (39.6)	170 (38.6)
Blood pressure, mean (SE), mm Hg					
Systolic	152 (25)	149 (23)	151 (23)	150 (25)	150 (24)
Diastolic	96 (15)	95 (14)	96 (15)	96 (14)	95 (14)
Mean arterial pressure	115 (17)	113 (15)	115 (16)	114 (17)	113 (16)
GFR, mean (SE), mL/min per 1.73 m ²	46.0 (12.9)	45.3 (13.2)	45.4 (12.8)	45.8 (12.9)	45.8 (13.4)
Serum creatinine, mean (SE), mg/dL†					
Male	2.17 (0.75)	2.20 (0.77)	2.18 (0.74)	2.28 (0.83)	2.14 (0.75)
Female	1.72 (0.55)	1.81 (0.57)	1.76 (0.59)	1.74 (0.55)	1.80 (0.55)
Urine protein/creatinine ratio, mean (SE)					
Male	0.33 (0.50)	0.32 (0.52)	0.34 (0.51)	0.30 (0.48)	0.33 (0.53)
Female	0.28 (0.48)	0.37 (0.58)	0.32 (0.52)	0.30 (0.55)	0.35 (0.54)
Urine protein, mean (SE), g/24 h					
Male	0.61 (1.01)	0.61 (1.08)	0.61 (1.01)	0.57 (0.99)	0.63 (1.11)
Female	0.36 (0.63)	0.46 (0.81)	0.41 (0.75)	0.38 (0.73)	0.44 (0.72)
With urinary protein to creatinine ratio of at least 0.22, No. (%)	181 (33.5)	176 (31.8)	144 (33.0)	71 (32.7)	140 (31.8)
Antihypertensive medications, No. (%)					
Diuretics	337 (62.4)	342 (61.7)	275 (63.1)	138 (63.6)	266 (60.3)
ACE inhibitors	205 (38.0)	210 (37.9)	174 (39.9)	90 (41.5)	151 (34.2)
β-Blockers	153 (28.3)	155 (28.0)	113 (25.9)	61 (28.1)	134 (30.4)
Calcium channel blocker	350 (64.8)	342 (61.7)	274 (62.8)	133 (61.3)	285 (64.6)
Dihydropyridine calcium channel blocker	268 (49.6)	243 (43.9)	203 (46.6)	97 (44.7)	211 (47.9)
Any antihypertensive	525 (97.2)	540 (97.5)	426 (97.7)	209 (96.3)	430 (97.5)

*GFR indicates glomerular filtration rate; ACE, angiotensin-converting enzyme. There are no significant differences between the lower and usual blood pressure groups or between either the ramipril and amlodipine groups vs the metoprolol group for any of the indicated baseline characteristics.

†To convert creatinine values to μmol/L, multiply values by 88.4.

come, respectively. Assuming a mean GFR slope of -4 mL/min per 1.73 m² per year in the metoprolol group, the projected power was 88%, 99%, and 98% for these same 3 outcomes to detect a 30% reduction in GFR slope for amlodipine vs metoprolol, and 97%, 69%, and 79% for ramipril vs metoprolol, respectively. Based on the AASK pilot study and other studies, the power calculations assumed a 2 mL/min per 1.73 m² greater acute GFR decline for the lower vs the usual BP goal, a 2 mL/min per 1.73 m² greater acute GFR increase for amlodipine vs metoprolol, and a 2 mL/min per 1.73 m² per year greater acute decline for ramipril vs metoprolol.^{29,30,32,34}

RESULTS

Baseline and Treatment Characteristics

Baseline patient characteristics were similar in the 2 BP groups and the 3 drug groups (TABLE 1). Baseline GFR was inversely associated with proteinuria (Spearman R , -0.46 ; $P < .001$).

After randomization, BP decreased from 152/96 to 128/78 mm Hg in the lower BP group and from 149/95 to 141/85 mm Hg in the usual blood BP goal group (TABLE 2). A mean separation of approximately 10 mm Hg mean arterial pressure was maintained throughout most of the follow-up period. Participants were prescribed more antihypertensives for the lower than the usual BP goal, but there were no significant differences between drug groups in the total number of antihypertensives or in the percentage of participants receiving the highest doses of the randomized study drug.

Follow-up systolic BP was 2 mm Hg lower for amlodipine than for the other drug groups; otherwise BP measurements were similar between the drug groups. There was a slightly lower use of the fifth-line agent (minoxidil) in the amlodipine group than in the metoprolol group, but the results of all drug group comparisons of the primary and secondary outcomes were essentially unchanged after controlling for follow-up mean arterial pressure and mean number of add-on (levels 2 to 5) drugs as covariates.

Primary Analysis

Lower vs Usual BP. During the acute phase, the mean (SE) GFR decline was 1.82 (0.54) mL/min per 1.73 m² per 3 months greater in the lower BP than the usual BP group ($P < .001$) (FIGURE 2 and TABLE 3). However, mean GFR decline did not differ significantly between the lower and usual BP groups during either the chronic phase (2.11 [0.16] vs 2.32 [0.17] mL/min per 1.73 m² per year; $P = .33$) or the total follow-up period from baseline to 4 years (2.21 [0.17] vs 1.95 [0.17] mL/min per 1.73 m² per year; $P = .24$). The 95% CIs for the differences in mean GFR slope between the BP groups were -0.21 to 0.64 mL/min per 1.73 m² per year for the chronic slope and -0.68 to 0.17 mL/min per 1.73 m² per year for the total slope.

Ramipril vs Metoprolol. The mean GFR decline was slower in the ramipril

than the metoprolol group during the acute phase (0.23 [0.44] vs 1.73 [0.40] mL/min per 1.73 m² per 3 months; $P = .01$) and the total follow-up period from baseline to 4 years (1.81 [0.17] vs 2.42 [0.17] mL/min per 1.73 m² per year; $P = .007$). However, the mean chronic GFR slopes did not differ significantly between the 2 groups (1.87 [0.17] vs 2.12 [0.17] mL/min per 1.73 m² per year; $P = .26$).

Amlodipine vs Metoprolol. GFR declined faster in the amlodipine than the metoprolol group during the chronic phase (3.22 [0.33] vs 2.33 [0.20] mL/min per 1.73 m² per year; $P = .02$), but during the acute phase GFR increased faster in the amlodipine vs the metoprolol group (4.03 [0.64] vs -1.73 [0.40] mL/min per 1.73 m² per 3 months; $P < .001$). Due to this acute effect, the total GFR decline to 3 years was significantly

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

	Blood Pressure Goal Intervention		Drug Intervention		
	Lower	Usual	Ramipril	Amlodipine	Metoprolol
Mean arterial pressure, mean (SE), mm Hg†	95 (8)	104 (7)	100 (9)	99 (8)	100 (9)
Systolic blood pressure, mean (SE), mm Hg†	128 (12)	141 (12)	135 (14)	133 (12)	135 (13)
Diastolic blood pressure, mean (SE), mm Hg†	78 (8)	85 (7)	82 (9)	81 (8)	81 (9)
Visits with mean arterial pressure in goal, %†	51.6	39.2	44.1	48.9	44.7
Visits with mean arterial pressure of <107 mm Hg, %†	81.3	64.3	71.5	76.5	72.0
Visits with systolic/diastolic blood pressure of $<140/90$, %†	68.6	35.5	51.2	54.9	50.8
Visits with systolic/diastolic blood pressure of $<125/75$, %†	24.7	6.2	16.2	14.4	14.9
Visits with assigned primary drug, %‡	81.7	80.1	76.8	83.4	83.6
Visits with high dose, %‡	62.8	45.0	53.5	54.6	53.6
Visits with crossover to 1 of other 2 classes, %‡	9.3	8.1	10.9	6.4	7.6
Total No. of drug classes, mean (SE)‡	3.04 (1.14)	2.39 (1.18)	2.66 (1.23)	2.65 (1.24)	2.79 (1.15)
Visits with level 2 (furosemide), %‡	82.2	66.6	74.0	70.8	76.4
Visits with level 3 (doxazosin), %‡	55.2	34.4	42.0	46.3	46.6
Visits with level 4 (clonidine), %‡	40.5	27.3	34.4	34.4	33.1
Visits with level 5 (minoxidil), %‡	34.9	22.7	27.5	24.1	32.3
Protocol visits held, %	90.3	87.5	88.0	88.7	89.8
GFRs performed, %	83.2	80.0	80.9	81.9	82.0

*GFR indicates glomerular filtration rate.

†Blood pressure summaries include visits after 3 months and exclude GFR visits.

‡Medication summaries include all visits starting at month 1 and are censored on September 22, 2000, for the calcium channel blocker (amlodipine) group only.

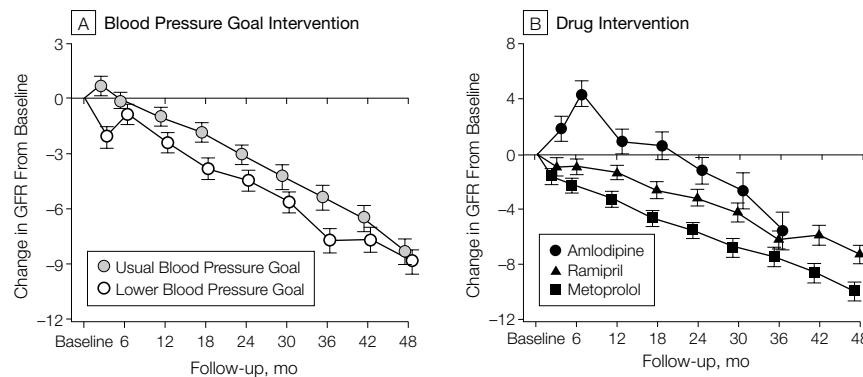
slower in the amlodipine group than the metoprolol group (1.60 [0.34] vs 2.68 [0.20] mL/min per 1.73 m² per year; *P* = .004).

Clinical Composite Outcome Analysis
Lower vs Usual BP. The numbers of events (rate/participant year) for the

main clinical composite outcome (declining GFR events, ESRD, or death) were 173 (rate, 0.081) and 167 (rate, 0.076) in the lower and usual BP groups. After adjustment for the prespecified covariates, there were no significant differences between the BP groups in the risk of the clinical composite outcome (risk reduction for lower BP goal, 2%; 95% CI, -22% to 21%; *P* = .85), the combined kidney end points of a declining GFR event or ESRD, the combined hard clinical end points of ESRD or death, or ESRD alone (TABLE 4).

Ramipril vs Metoprolol. A total of 126 (rate, 0.069) and 155 (rate, 0.087) patients in the ramipril and metoprolol groups reached the main clinical composite outcome during the full follow-up period. The risk reduction for ramipril vs metoprolol was 22% (95% CI, 1%-38%; *P* = .04). Similar risk reductions of 21% to 22%, which were not statistically significant, were seen for

Figure 2. Mean Change in Glomerular Filtration Rate by Randomized Group



Shown are the estimated mean changes (SE) in glomerular filtration rate (GFR) (mL/min per 1.73 m²) from baseline through follow-up in the 2 blood pressure goal interventions (A) and in the 3 drug interventions (B). The plot is based on a multislope generalization of the 2-slope mixed-effects model in which different mean slopes are estimated within each treatment group for each interval between scheduled GFR measurements. Numbers of patients with GFRs at years 0, 1, 2, 3, 4, and 5 in all treatment groups combined were 1094, 953, 837, 731, 469, and 262, respectively.

Table 3. Comparison of Mean Glomerular Filtration Rate Slopes Between Drug Groups*

Comparison	Acute Slope (mL/min per 1.73 m ² per 3 months)		Chronic Slope (mL/min per 1.73 m ² per year)†		Total Slope (mL/min per 1.73 m ² per year)†	
	Δ Mean (SE)	<i>P</i> Value	Δ Mean (SE)	<i>P</i> Value	Δ Mean (SE)	<i>P</i> Value
Lower vs usual blood pressure	-1.82 (0.54)	<.001	+0.21 (0.22)	.33	-0.25 (0.22)	.24
Ramipril vs metoprolol	+1.50 (0.59)	.01	+0.25 (0.22)	.26	+0.61 (0.22)	.007
Metoprolol vs amlodipine	-5.76 (0.76)	<.001	+0.89 (0.38)	.02	+1.08 (0.38)	.004
Ramipril vs amlodipine‡	-4.19 (0.79)	<.001	+1.16 (0.38)	.002	-0.34 (0.38)	.38

*Shown are differences in mean slopes between the randomized treatment groups, adjusted for clinical center and 5 prespecified covariates: baseline proteinuria, mean arterial pressure, sex, history of heart disease, and age. Plus signs indicate slower mean slope in the first than the second treatment group listed. Glomerular filtration rates censored in September 2000 for both treatment groups in the comparisons involving the amlodipine group and for the patients in the amlodipine group for the lower vs usual blood pressure group comparison. Additional information on the mean glomerular filtration rate slopes within the 6 cells of the 2 × 3 factorial design is available from the author upon request.
 †Total slope estimated over 4 years for the lower vs usual blood pressure and ramipril vs metoprolol comparisons, and over 3 years for comparisons involving amlodipine.
 ‡Secondary comparison described in previous publication.²⁵

Table 4. Analyses of Clinical Event Composite Outcomes*

Outcome§	Lower vs Usual Blood Pressure Goal Intervention		Drug Intervention					
	% Risk Reduction (95% Confidence Interval)‡	<i>P</i> Value	Ramipril vs Metoprolol		Metoprolol vs Amlodipine		Ramipril vs Amlodipine‡	
			% Risk Reduction (95% Confidence Interval)‡	<i>P</i> Value	% Risk Reduction (95% Confidence Interval)‡	<i>P</i> Value	% Risk Reduction (95% Confidence Interval)‡	<i>P</i> Value
GFR event, ESRD, or death	2 (-22 to 21)	.85	22 (1 to 38)	.04	20 (-10 to 41)	.17	38 (14 to 56)	.004
GFR event or ESRD	-2 (-31 to 20)	.87	22 (-2 to 41)	.07	24 (-9 to 47)	.13	40 (14 to 59)	.006
ESRD or death	12 (-13 to 32)	.31	21 (-5 to 40)	.11	42 (17 to 60)	.003	49 (26 to 65)	<.001
ESRD alone	6 (-29 to 31)	.72	22 (-10 to 45)	.16	59 (36 to 74)	<.001	59 (36 to 74)	<.001

*GFR indicates glomerular filtration rate; ESRD, end-stage renal disease.
 †Secondary comparison described in previous publication.²⁵
 ‡All risk reductions adjusted for prespecified covariates: baseline proteinuria, mean arterial pressure, sex, history of heart disease, and age. Risk difference for ESRD or death composite and ESRD alone also adjusted for baseline GFR.
 §GFR event, ESRD, or death: main secondary composite clinical outcome with 340 events, including 179 declining GFR events, 84 additional participants with ESRD events, and 77 deaths; GFR event or ESRD: composite end point with 263 events, including 179 declining GFR events and 84 additional participants with ESRD events; ESRD or death: composite end point with 251 events, including 171 ESRD events and 80 deaths; and ESRD alone: end point with 171 events and deaths censored in this analysis.

ESRD alone and for the combined end points of declining GFR events or ESRD, and ESRD or death.

Metoprolol vs Amlodipine. A total of 117 (rate, 0.079) and 59 (rate, 0.082) patients in the metoprolol and amlodipine groups reached the main clinical composite outcome by September 2000. There was no significant difference between the amlodipine and metoprolol groups in the main clinical composite outcome (risk reduction for metoprolol vs amlodipine, 20%; 95% CI, -10% to 41%; $P=.17$) or in declining GFR events or ESRD combined. However, the metoprolol group had a significantly lower risk than amlodipine for ESRD or death ($P=.003$) and for ESRD alone ($P<.001$).

Effects of Baseline Proteinuria and GFR

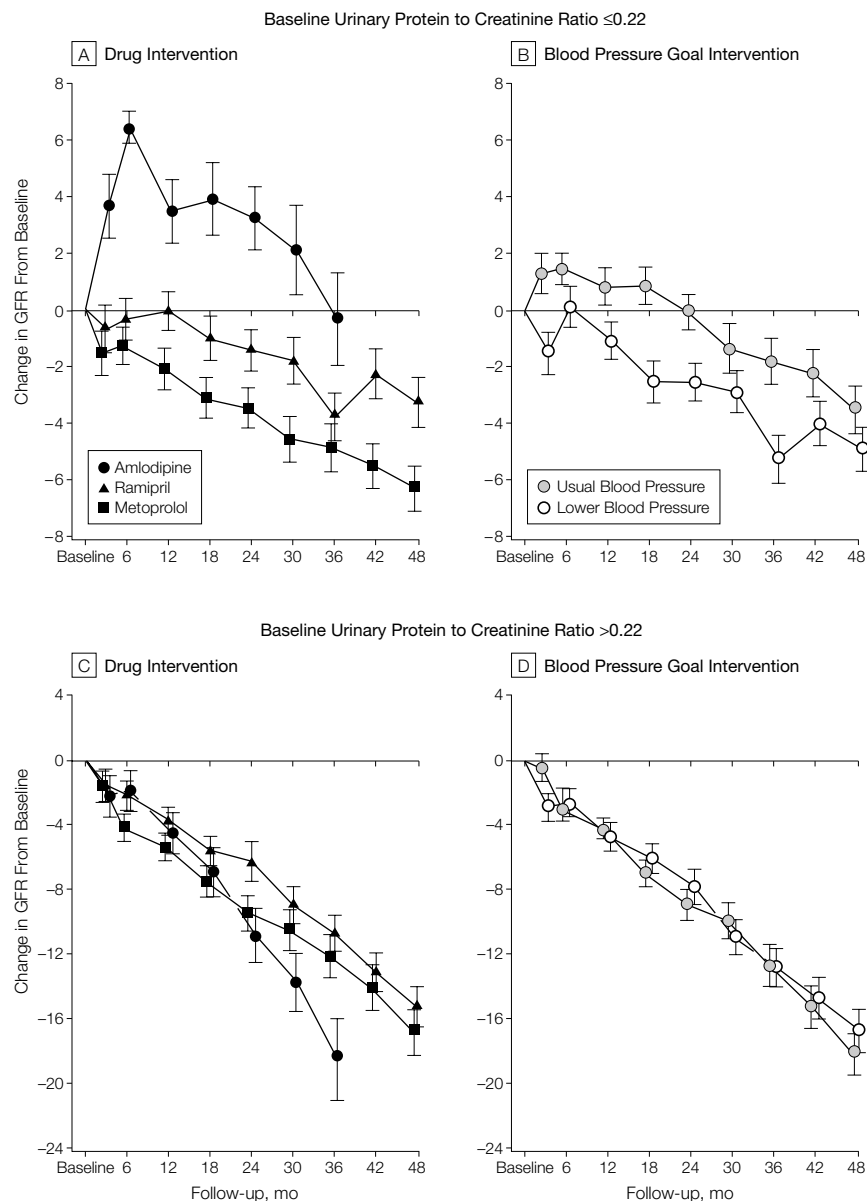
Baseline proteinuria was a strong predictor of GFR decline. For all treatment groups combined, the mean (SE) chronic slope was -1.35 (0.15) mL/min per 1.73 m² per year if baseline urinary protein to creatinine ratio was 0.22 or less compared with -4.09 (0.25) mL/min per 1.73 m² per year if baseline urinary protein to creatinine ratio was higher than 0.22 ($P<.001$).

Drug Group Comparisons. The difference in mean GFR decline between the amlodipine and metoprolol groups was significantly related to baseline proteinuria for the acute and total GFR slope (FIGURE 3A and 3C). These interactions reflect the presence of a large acute increase in GFR with amlodipine for participants with baseline urinary protein to creatinine ratio of 0.22 or less but not in participants with urinary protein to creatinine ratio higher than 0.22. The total decline in GFR to 3 years was 1.98 (SE, 0.43) slower for amlodipine than metoprolol if baseline urinary protein to creatinine ratio was 0.22 or less, but was 1.29 (SE, 0.75) mL/min per 1.73 m² per year faster for amlodipine than metoprolol if baseline urinary protein to creatinine ratio was higher than 0.22. The interaction of baseline proteinuria with the amlodipine vs metoprolol comparison was not significant for either the chronic

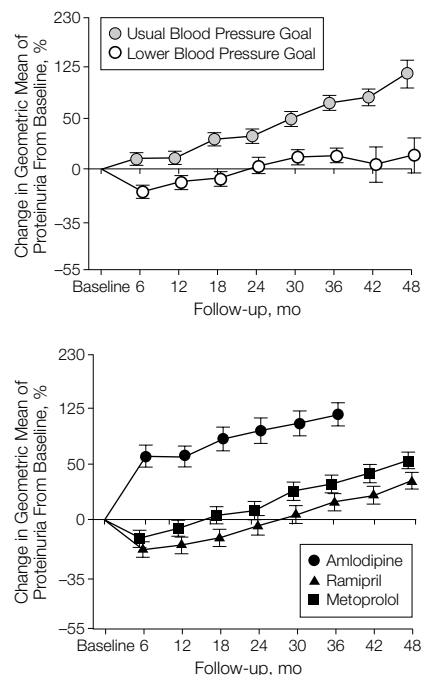
GFR slope or the clinical composite outcomes, although the effects favoring metoprolol over amlodipine tended to be

larger for higher baseline proteinuria. For participants with baseline urinary protein to creatinine ratio of higher than 0.22,

Figure 3. Mean Change in Glomerular Filtration Rate by Randomized Group for Proteinuria Subgroups



Presented are the mean changes (SE) in glomerular filtration rate (GFR) (mL/min per 1.73 m²) from baseline through follow-up in the 3 drug interventions (A and C) and in the 2 blood pressure goal interventions (B and D) for patients with baseline urinary protein to creatinine ratio of 0.22 or less (A and B) and higher than 0.22 (C and D) based on the multislope spline model (see legend of Figure 2). A urinary protein to creatinine ratio of 0.22 corresponds approximately with proteinuria of 300 mg/d. The GFRs after September 2000 were censored for the amlodipine group. For the 2-slope model, the results of the comparison of amlodipine with metoprolol and ramipril differed significantly depending on the level of baseline proteinuria for the acute slope ($P=.002$ and $P<.001$, respectively) and total slopes ($P=.001$ and $P<.001$, respectively) but not for the chronic slope ($P=.21$ and $P=.24$, respectively). The results of the blood pressure comparison differed significantly depending on the level of baseline proteinuria for the acute slope ($P=.008$) and total slopes ($P=.004$) but not for the chronic slope ($P=.16$).

Figure 4. Percentage Changes in Proteinuria by Randomized Group

Shown are the estimated percentage changes in the urine protein/creatinine ratio (geometric mean [SE]) from baseline throughout follow-up by blood pressure and drug intervention. The plot is based on the multislope spline model (see legend of Figure 2). Based on the 2-slope linear spline model for log(urinary protein to creatinine ratio), the percentage change in geometric mean proteinuria to 4 years was significantly lower for the lower blood pressure goal than the usual blood pressure goal ($P < .001$), and was significantly higher in the amlodipine group than the other 2 drug groups ($P < .001$).

the metoprolol group had risk reductions compared with amlodipine of 38% (95% CI, 6%-59%; $P = .03$) for the main composite outcome and 46% (95% CI, 15%-66%; $P = .008$) for ESRD or death.

Consistent with the association of higher GFR with lower proteinuria at baseline, there were also significant interactions between baseline GFR and the amlodipine vs metoprolol comparison for the acute ($P = .003$) and total GFR slopes ($P < .001$), such that the amlodipine group had smaller mean GFR declines compared with metoprolol for patients with higher baseline GFR but larger mean GFR declines compared with metoprolol for patients with lower baseline GFR.

The level of baseline proteinuria did not influence the comparison of ramipril

to metoprolol (interaction $P = .51$, $.32$, and $.61$ for the chronic slope, total slope, and main clinical composite outcome, respectively).

BP Group Comparison. The BP group comparison also depended significantly on the level of baseline proteinuria for the acute slope, total slope, and main clinical composite outcome ($P = .007$) but not for the chronic slope (Figure 3B and 3D). For each outcome, there were slight trends that tended to favor the lower BP goal over the usual goal in participants with higher proteinuria and opposite trends in participants with little or no proteinuria. However, with the exception of the acute slope, the BP comparison for the aforementioned outcomes was not significantly different within either the lower (baseline urinary protein to creatinine ratio ≤ 0.22) or higher (baseline urinary protein to creatinine ratio > 0.22) proteinuria strata. There was a corresponding trend for an interaction of the BP-group comparison with baseline GFR for the total GFR slope ($P = .07$) favoring the usual goal over the lower goal for patients with higher baseline GFR with the opposite pattern for patients with lower baseline GFR (data not shown).

Change in Proteinuria

Proteinuria (geometric mean urinary protein to creatinine ratio) increased by 58% for the amlodipine group and declined by 14% in the metoprolol group between baseline and 6 months ($P < .001$) (FIGURE 4). Proteinuria increased by 7% in the usual BP group and decreased by 17% in the lower BP group during the first 6 months. These differences between treatment groups persisted throughout the study. Follow-up proteinuria was slightly lower in the ramipril than the metoprolol group but not significantly ($P = .06$ for the comparison of total change over 4 years).

Adverse Events

There were no significant differences in all-cause mortality, cardiovascular mortality, or first cardiovascular events (defined as cardiovascular mortality or first cardiovascular hospitalizations) be-

tween the treatment groups (TABLE 5). Proportions of patients reporting adverse symptoms (including hypotensive symptoms) were similar in the 2 BP groups. The proportions of participants reporting angioedema and cough were highest in the ramipril group, although the proportion reporting edema was higher in the amlodipine group. Hyperkalemia was reported for 3 participants randomized to the ramipril group and 1 randomized to metoprolol.

COMMENT

The AASK is the first published large-scale trial to our knowledge that examines both the effect of 3 different antihypertensive regimens as well as the effect of 2 BP goals on decline in kidney function in a population with chronic kidney disease attributed to hypertensive nephrosclerosis.³⁸

Blood Pressure

Treatment of study participants to a lower than usual mean BP of 128/78 mm Hg did not significantly reduce either the mean rate of GFR decline or the risk of the clinical composite outcome compared with usual BP goal with a mean achieved BP of 141/85. The AASK, with its larger sample size and wider BP separation, extends previous negative findings regarding the level of BP reduction and change in GFR observed in smaller samples of both African Americans and non-African Americans with nonproteinuric kidney disease.^{7,39,40}

The average rate of decline in GFR in both treatment groups was approximately 2 mL/min per 1.73 m² per year. This average rate of GFR decline is similar to or slower than earlier trials of hypertensive nephrosclerosis⁴⁰ and slower than other common progressive kidney diseases.^{7,41,42} The relatively slow mean GFR decline reduced the power of the primary analysis of GFR slope. Nonetheless, the upper limits of the 95% CIs for the BP comparison exclude a risk reduction for the lower BP goal larger than 21% for the clinical composite outcome and 31% for ESRD alone. While a benefit smaller than these limits can-

not be excluded, the upper confidence limits are substantially smaller than the effects that would be estimated from observational studies given the large separation in BP that was achieved between the AASK BP groups.⁴³ Because randomized comparisons more accurately evaluate causal relationships,^{44,45} this discrepancy suggests that relationships observed between BP level and rates of ESRD in nonrandomized studies have overestimated the effect of lowering BP.

Mean BP during follow-up in the usual BP group was 141/85 mm Hg, which is similar to the level recommended to prevent cardiovascular target organ damage and is less than that achieved by more than 70% of individuals being treated for hypertension.⁴⁶ This study's finding of a failure to further slow progression of kidney disease by reducing BP below this level does not diminish the importance of maintaining BP in accordance with the current guidelines.¹⁸ We do not interpret the apparent lack of an effect of the lower BP goal to slow decline in GFR (and reduce risk for clinical end points) to illustrate that BP lowering is not important for preserving kidney function. Our study did not test the hypothesis that treatment vs no treatment of hypertension preserves kidney function. Nevertheless, our data suggest that once BP is lowered to a given level, additional risk factors are important in patients with chronic kidney disease resulting from hypertension.

Although there was no significant effect of the BP intervention on GFR slope or clinical events in all patients or in subgroup analyses by baseline proteinuria strata, there were significant interactions with a trend favoring the lower BP goal in participants with higher baseline proteinuria and an opposite trend in participants with little or no proteinuria. This is consistent with the Modification of Diet in Renal Disease results that showed a favorable trend for the lower BP goal in participants with baseline proteinuria of higher than 1 gram per day but not at lower levels of proteinuria.⁸ However, because proteinuria was inversely cor-

related with GFR at baseline, it is possible that the dependence of the BP comparison on baseline proteinuria in the AASK reflects a larger hemodynamic effect in patients with higher baseline GFR rather than true differences in clinically relevant outcomes. This study was not powered to detect differences in the rate of myocardial infarction, stroke, or death. However, we found no evidence of differences in the rates of these events between the randomized BP groups.

Antihypertensive Agents

The primary analysis of GFR slope did not establish a definitive difference among the 3 drug regimens. However, significant benefits of ramipril vs metoprolol (reported here) and amlodipine²⁵ on the main clinical composite outcome and the results of other secondary analyses suggest that ramipril slows hypertensive kidney disease progression compared with the other 2 regimens. Secondary analyses also suggest that metoprolol may improve renal outcome compared with amlodipine, particularly in participants with higher proteinuria.

Comparisons of amlodipine with the other drug groups were complicated by a large acute increase in GFR for amlodipine in the 3 months after randomization. Due to this acute effect, which was likely a hemodynamic response without clinical significance, beneficial effects of ramipril and metoprolol vs amlodipine on GFR decline after 3 months did not lead to corresponding beneficial effects on the total mean slope from baseline to the end of the study (Figures 2 and 3). However, compared with amlodipine, ramipril significantly reduced the risk of the main clinical composite,²¹ and both ramipril and metoprolol reduced the risk of ESRD and of ESRD and death combined (Table 4). The latter 2 outcomes were probably less sensitive to the acute effect, because they are based on clinical end points independent of GFR measurement. In the subgroup of patients with baseline urinary protein to creatinine ratio of more than 0.22 (urinary protein, 300 mg/d), the acute effect was negligible and each of the slope-based and time-to-event outcomes were in agreement, indicating consistent advantages for ramipril and metoprolol vs amlodipine.

Table 5. Rates of Adverse Events or Symptoms During Follow-up*

	Blood Pressure Goal Intervention, %		Drug Intervention, %		
	Lower	Usual	Ramipril	Amlodipine	Metoprolol
Adverse event					
All-cause mortality	1.6	1.9	1.5	1.7	2.0
Cardiovascular mortality	0.6	0.7	0.5	0.9	0.8
Cardiovascular event†	2.3	2.7	2.5	1.7	2.9
Symptom					
Hyperkalemia	0	0.7	0.7	0	0.2
Angioedema	3.5	5.4	6.4§	2.3	2.7
Shortness of breath‡	48.4	45.8	43.0	44.4	45.8
Syncope‡	6.3	5.2	6.7	2.3§	6.3
Dizziness‡	53.4	49.0	50.1	46.7	47.8
Lightheadedness‡	51.2	49.2	49.2	48.1	47.8
Edema	55.1	54.2	46.0	59.8§	51.0
Cough	54.6¶	47.0	54.9§	46.3	41.5
Sexual dysfunction	29.6	27.1	29.4	25.7	25.2

*Reported are the percentages of patients experiencing the adverse event per patient year of follow-up through the end of the study in the ramipril and metoprolol groups, and through September 2000 in the amlodipine group and the percentages of patients reporting the symptom at least once during follow-up.

†Composite of cardiovascular mortality or first cardiovascular hospitalization.

‡Participants were specifically asked about these symptoms at each protocol visit.

§Percentage reporting symptom significantly different from metoprolol group ($P < .05$).

||Percentage reporting symptom significantly different between ramipril and amlodipine groups ($P < .05$).

¶Percentage reporting symptom significantly different between lower and usual blood pressure groups ($P < .05$).

The AASK was designed to compare 3 active drug regimens and did not have a placebo control. In a placebo controlled trial of participants with diabetic nephropathy and proteinuria that included an amlodipine arm, however, no difference was noted between placebo and amlodipine on ESRD, death, or doubling of serum creatinine, and trends in proteinuria change were the same as AASK for amlodipine.^{47,48}

In contrast with the comparisons involving amlodipine, the evidence for benefit of ramipril vs metoprolol was noted in the full AASK cohort, irrespective of baseline proteinuria. However, the conclusion of the beneficial effect of ramipril compared with metoprolol is less definitive because the chronic slope was not significant. Several clinical trials of participants with proteinuria and primary glomerular disease show beneficial effects of ramipril.⁴⁹ Data from AASK^{23,50} extend these results to participants with hypertensive glomerulopathy and minimal proteinuria.^{51,52} Evidence that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers lower BP to a lesser extent in African Americans than others, when used as monotherapy, taken together with the paucity of prospective clinical end point data, has resulted in less use of such agents in African Americans.^{2,51,52} The AASK is the first outcome trial to demonstrate a renoprotective effect of angiotensin-converting enzyme inhibitor in an African American population.

We conclude that although BP reduction to levels below current guidelines for cardiovascular risk reduction are achievable, our results do not support additional reduction as a strategy to prevent progression of hypertensive nephrosclerosis. Our results do support recommendations that angiotensin-converting enzyme inhibitors should be considered as first line therapy over β -blockers and dihydropyridine calcium channel blockers in these patients. Moreover, β -blockers may be more effective than dihydropyridine calcium channel blockers in slowing progression among patients with proteinuria.

Author Affiliations: Departments of Medicine, University Hospitals of Cleveland and the Louis Stokes Cleveland Department of Veterans Affairs Medical Center (Dr Wright), Department of Biostatistics, Cleveland Clinic Foundation (Drs Greene and Gassman), and Department of Medicine, Case Western Reserve University (Dr Douglas-Baltimore), Cleveland, Ohio; Department of Preventive Medicine, Rush-Presbyterian-St Luke's Medical Center, Chicago, Ill (Dr Bakris); National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md (Dr Agodoa); Department of Preventive Medicine, Johns Hopkins University, Baltimore, Md (Dr Appel and Ms Charleston); Department of Medicine, Medical University of South Carolina, Charleston (Dr Cheek); Department of Medicine, University of California, Los Angeles (Dr Glasscock); Department of Medicine, Ohio State University, Columbus (Dr Hebert); Department of Medicine, University of Michigan, Ann Arbor (Dr Jamerson); Department of Medicine, Vanderbilt University, Nashville, Tenn (Dr Lewis); Mt Sinai School of Medicine, New York, NY (Dr Phillips); University of Texas Southwestern Medical Center, Dallas (Drs Toto and Middleton); and University of Alabama, Birmingham (Dr Rostand).

Financial Disclosure: Dr Wright has no stock ownership but has received research grants, honoraria, and consult fees from Astra, Bayer, Bristol-Myers Squibb, Eli Lilly and Co, Merck & Co, Novartis Pharma AG, Pharmacia, Pfizer, Sankyo Inc, GlaxoSmithKline, and Solvay/Unimed. Dr Appel has received honoraria from Astra and Novartis Pharma AG. Dr Cheek is a speaker for Wyeth, Novartis, and Sanofi-Synthelabo, and investigator for Abbott Laboratories. Dr Middleton is a speaker for Merck and a consultant for King Pharmaceuticals.

Author Contributions: Dr Wright, as principal investigator of the AASK study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Study concept and design: Wright, Bakris, Greene, Agodoa, Appel, Cheek, Gassman, Glasscock, Hebert, Jamerson, Lewis, Phillips, Toto, Rostand.

Acquisition of data: Wright, Bakris, Greene, Appel, Charleston, Cheek, Douglas-Baltimore, Hebert, Jamerson, Lewis, Phillips, Toto, Middleton, Rostand. **Analysis and interpretation of data:** Wright, Bakris, Greene, Agodoa, Appel, Douglas-Baltimore, Gassman, Glasscock, Hebert, Jamerson, Lewis, Phillips, Toto, Middleton.

Drafting of the manuscript: Wright, Bakris, Greene, Agodoa, Charleston, Cheek, Douglas-Baltimore, Gassman, Glasscock, Hebert, Lewis, Toto.

Critical revision of the manuscript for important intellectual content: Wright, Bakris, Greene, Agodoa, Appel, Douglas-Baltimore, Gassman, Glasscock, Hebert, Jamerson, Lewis, Phillips, Toto, Middleton, Rostand. **Statistical expertise:** Greene, Gassman.

Obtained funding: Wright, Agodoa, Appel, Lewis, Toto, Rostand.

Administrative, technical, or material support: Wright, Bakris, Agodoa, Appel, Gassman, Glasscock, Phillips, Middleton.

Study supervision: Wright, Bakris, Appel, Douglas-Baltimore, Gassman, Hebert, Jamerson, Lewis, Toto.

The African American Study of Kidney Disease and Hypertension (AASK) Study Group: Case Western Reserve University, principal investigator, J. Wright, study coordinator, Y. Hall, R. Haynie, C. Mbanefo, M. Rahman, M. Smith, B. Crenshaw, R. Dancie, L. Jaen; Emory University, principal investigator, J. Lea, A. Chapman, L. Dean, study coordinator, M. Douglas, D. Watkins, B. Wilkening, L. Williams, C. Ross; Harbor-UCLA Medical Center, principal investigator, J. Kopple, study coordinator, L. Miladinovich, P. Oleskie; Harlem Hospital Center, principal investigator, V. Pogue, study coordinator, D. Dowie, H. Anderson, L. Herbert, R.

Locko, H. Nurse, J. Cheng, G. Darkwa, V. Dowdy, B. Nicholas; Howard University, principal investigator, O. Randall, G. Ali, T. Retta, study coordinator, S. Xu, T. Alexander, M. Ketete, E. Mathew, D. Ordor, C. Tilghman; Johns Hopkins University, principal investigator, L. Appel, study coordinator, J. Charleston, C. Diggs, C. Harris, P. Miller, T. Shields, M. Sotomayer, P. Whelton; Martin Luther King, Sr, Charles R. Drew Medical Center, principal investigator, K. Norris, H. Ward, D. Martins, study coordinator, M. Miller, H. Howell; Medical University of South Carolina, principal investigator, D. Cheek, C. Gadegbeku, D. Ploth, study coordinator, D. Brooks, N. Monestime, S. Murner, S. Thompson; Meharry Medical College, principal investigator, M. Faulkner, O. Adeyeye, study coordinator, K. Phillips, G. Sanford, C. Weaver; Morehouse School of Medicine, principal investigator, W. Cleveland, A. Howard, K. Chapman, S. Plater, study coordinator, W. Smith; Mt Sinai School of Medicine, principal investigator, R. Phillips, M. Lipkowitz, study coordinator, A. Gabriel, A. Travis, J. Williams; Ohio State University, principal investigator, L. Hebert, M. Falkenhain, S. Ladson-Wofford, N. Nahman, K. Osei, study coordinator, L. Hiremath, A. Dodley, J. Parks, D. Veley; Rush-Presbyterian-St Luke's Medical Center, principal investigator, G. Bakris, J. Lash, study coordinator, L. Fondren, study coordinator, L. Bagnuolo, study coordinator, J. Cohen, study coordinator, M. Powell, A. Smith, D. White, G. Henry, A. Johnson, T. Collins, S. Koshy, E. Afante; University of Alabama, Birmingham, principal investigator, S. Rostand, D. Thornley-Brown, R. Gay, study coordinator, C. Johnson, B. Key; University of California, San Diego, principal investigator, D. O'Connor, F. Gabbai, R. Parmer, F. Rao, J. Little, T. Makrogiannis, study coordinator, J. Mount, A. Ogundipe, A. Stephenson; University of Florida, principal investigator, C. Tisher, D. Allen, study coordinator, L. Burgin, A. Diaz, C. Sarmiento; University of Miami, principal investigator, J. Bourgoignie, G. Contreras, D. Florence-Green, study coordinator, A. Doss, J. Junco, D. Merrill, J. Vassallo, A. de Velasco; University of Michigan, principal investigator, K. Jamerson, F. Port, M. Keshishian, A. Ojo, S. Steigerwalt, study coordinator, D. Cornish-Zirker, T. Graham, A. Johnson, J. Layne, S. Nesbitt, K. Manchester, W. Bloembergen; University of Southern California, principal investigator, S. Massry, V. Campese, M. Smogorzewski, study coordinator, A. Richardson; University of Texas Southwestern Medical Center, Dallas, principal investigator, J. Middleton, E. Kuo, S. Leach, R. Toto, K. Jones, K. Hart, study coordinator, T. Lightfoot, L. Littmon, B. McNeill, C. Ying; Vanderbilt University, principal investigator, J. Lewis, G. Schulman, S. McLeroy, study coordinator, N. Rogers, M. Sika; National Institute of Diabetes and Digestive and Kidney Diseases: L. Y. Agodoa, J. P. Briggs, J. W. Kusek; steering committee chair, J. Douglas; Data Coordinating Center (Cleveland Clinic Foundation): J. Gassman, G. Beck, V. Dennis, T. Greene, M. Kutner, study coordinator, K. Brittain, S. Sherer, R. Stewart, L. Tuason, S-R. Wang, X. Wang, W. Zhang; Central Biochemistry Laboratory, F. Van Lente, J. Waletzky, C. O'Laughlin, C. Peck; Central GFR Laboratory, P. Hall, D. Pexa, H. Rolin; Blood Pressure Consultant, R. Byington; Psychological Consultant, P. Greene; Data and Safety Monitoring Committee: R. Luke, V. Chinchilli, C. Cook, B. Falkner, C. Ford, R. Glasscock, T. Karrison, T. Kotchen, E. Saunders, M. Secundy, D. Wesson.

Funding/Support: In addition to funding under a cooperative agreement from National Institute of Diabetes and Digestive and Kidney Diseases, this work was supported in part by the following institutional General Clinical Research Center and other National Institutes of Health grants: M01 RR-00080, 5M01 RR-00071, M0100032, P20-RR11145, M01 RR00827, M01 RR00052, 2P20 RR11104, and DK 2818-02. We gratefully acknowledge support from the Office of Re-

search in Minority Health and the donation of drug and some financial support to NIDDK by Pfizer Inc, AstraZeneca Pharmaceuticals, and King Pharmaceuticals Inc.

Previous Presentation: Presented in part at the American Heart Association Annual Scientific Session, Anaheim, Calif, November 13, 2001.

Acknowledgment: We thank the AASK participants for their time and commitment to the trial.

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Paul M Ridker, MD
 pridker@partners.org
 Brigham and Women's Hospital
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Table 2. Antihypertensive Therapy and Blood Pressure During Follow-up*

	Blood Pressure Goal Intervention		Drug Intervention		
	Lower	Usual	Ramipril	Amlodipine	Metoprolol
Arterial pressure, mean (SD), mm Hg†	95 (8)	104 (7)	100 (9)	99 (8)	100 (9)
Systolic blood pressure, mean (SD), mm Hg†	128 (12)	141 (12)	135 (15)	133 (12)	135 (13)
Diastolic blood pressure, mean (SD), mm Hg†	78 (8)	85 (7)	82 (9)	81 (8)	81 (9)
Visits with mean arterial pressure in goal, %†	51.6	39.2	44.1	49.0	44.7
Visits with mean arterial pressure of <107 mm Hg, %†	81.3	64.1	71.4	76.5	71.8
Visits with systolic/diastolic blood pressure of <140/90, %†	68.5	35.3	51.1	54.5	50.8
Visits with systolic/diastolic blood pressure of <125/75, %†	24.6	6.1	16.1	14.2	14.8
Visits with assigned primary drug, %‡	82.7	80.9	78.0	84.7	84.1
Visits with high dose, %‡	63.6	45.4	54.3	55.3	54.0
Visits with crossover to 1 of other 2 classes, %‡	9.3	8.0	10.9	6.5	7.6
Total No. of drug classes, mean (SD)‡	3.07 (1.11)	2.42 (1.17)	2.69 (1.21)	2.69 (1.22)	2.81 (1.15)
Visits with level 2 (furosemide), %‡	83.2	67.4	74.9	72.0	77.1
Visits with level 3 (doxazosin), %‡	55.8	35.0	42.6	47.1	46.9
Visits with level 4 (clonidine), %‡	41.0	27.5	35.0	34.6	33.2
Visits with level 5 (minoxidil), %‡	35.4	22.9	27.8	24.4	32.5
Protocol visits held, %	90.3	87.4	88.0	88.6	89.8
GFRs performed, %	83.2	80.0	80.9	81.9	82.0

*GFR indicates glomerular filtration rate.

†Blood pressure summaries include visits after 3 months and exclude GFR visits.

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