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## INITIAL FINDINGS OF THE AASK

# African Americans with hypertensive kidney disease benefit from an ACE inhibitor

**ACE inhibitors protect the kidneys in diabetic and proteinuric renal disease**

## ■ ABSTRACT

Experts have long thought that African Americans were less responsive to ACE inhibitors than other racial or ethnic groups. The African American Study of Kidney Disease and Hypertension (AASK) provides the first evidence of a beneficial effect of ACE inhibition on renal function in African American patients, in addition to excellent blood pressure control.

**I**N AFRICAN AMERICANS with hypertensive nephrosclerosis and proteinuria, ramipril (Altace), an angiotensin-converting enzyme (ACE) inhibitor, slowed the decline of renal function better than amlodipine (Norvasc), a calcium channel blocker.

These are the preliminary findings of the African American Study of Kidney Disease and Hypertension (AASK).<sup>1</sup>

Sponsored by the National Institutes of Health, this prospective, randomized, double-blind study refutes the notion that African Americans might not derive the same benefit as white patients from ACE inhibitor therapy. It also reinforces the concept that ACE inhibitors can protect kidney function in hypertensive kidney disease, as they do in diabetic nephropathy and other chronic proteinuric renal diseases.

\*The author has indicated that he has received honoraria for speaking engagements from the Solvay, Abbott, and Pfizer companies.

This paper summarizes the rationale, design, preliminary findings, and implications of this important study.

## ■ RATIONALE FOR THE AASK

The AASK is much needed, for several reasons.

**Kidney disease is increasing.** The incidence of end-stage renal disease has been increasing at approximately 8% per year over the last decade.<sup>2</sup> With its associated morbidity, mortality, and costs, this disease has become a major public health problem in this country.

**African Americans are particularly at risk.** While constituting 12% of the US population, African Americans account for 32% of cases of end-stage renal disease. In fact, African Americans ages 25 to 44 have a 20-fold higher risk of end-stage renal disease compared with other racial or ethnic groups.<sup>2</sup>

Hypertension is an important cause of end-stage renal disease in African Americans, and appropriate treatment of hypertension may slow the decline in renal function in these patients.

**African Americans have not been well studied.** The optimal drug therapy and the level of blood pressure that is most effective in this population are not known.<sup>3</sup> Most large hypertension studies before the AASK had few African American patients.

In addition, although ACE inhibition has been shown to be renoprotective in diabetic nephropathy and proteinuric renal disease, it has not been well studied in patients with



hypertensive renal disease, particularly in African Americans.<sup>4</sup>

## ■ STUDY DESIGN

The AASK was designed to evaluate the effect of two different blood pressure goals (low and usual) and three different treatment regimens on the progression of hypertensive kidney disease in African Americans.

With 1,094 patients, it is the largest comparative drug intervention trial to focus on renal outcomes in any population, and it is the first trial with sufficient sample size to evaluate the effects on clinical end points of inhibition of the renin-angiotensin-aldosterone system in African Americans.

### Inclusion criteria

All patients in the study had to fulfill all of the following inclusion criteria:

- African American
- Age 18 to 70 years
- Hypertension
- Mild to moderate renal insufficiency (a glomerular filtration rate [GFR] of 20–65 mL/minute/1.73 m<sup>2</sup>).

### Exclusion criteria

No one could participate who had any of the following:

- Diastolic blood pressure < 95 mm Hg
- Diabetes
- A ratio of urinary protein to creatinine greater than 2.5
- Accelerated or malignant hypertension
- Secondary hypertension
- Evidence of causes of kidney disease other than hypertension (In the pilot study, kidney biopsies were performed to confirm the diagnosis of hypertensive nephrosclerosis, and histopathologic findings were consistent with hypertensive nephrosclerosis in most patients with this clinical picture.)
- Serious systemic disease
- Congestive heart failure
- A specific indication for or contraindication to any of the study drugs or procedures.

### Treatment

Participants were randomized to two blood pressure goals:

- Usual (mean arterial pressure 102–107 mm Hg)
- Low (mean arterial pressure ≤ 92 mm Hg). They were also randomized to treatment with three antihypertensive drugs:
- Sustained-release metoprolol (Lopressor, Toprol), a beta-blocker, 50–200 mg/day
- Ramipril, an ACE inhibitor, 2.5–10 mg/day
- Amlodipine, a dihydropyridine calcium channel blocker, 5–10 mg/day.

If the assigned study drug did not lower the blood pressure to the goal level, additional drugs were added in unblinded fashion in the following order: furosemide, doxazosin, clonidine, hydralazine, and minoxidil. The GFR was assessed by iothalamate sodium I 125 clearance at baseline twice, then at 3 and 6 months and every 6 months thereafter.

### Patient characteristics

- Mean age: 54 years
- Women: approximately 40%
- Mean arterial blood pressure at baseline: 151/96 mm Hg
- Mean GFR: 46 mL/minute/1.73 m<sup>2</sup>.

Patients randomized to amlodipine (n = 217) and ramipril (n = 436) did not differ significantly at baseline with regard to any of these characteristics.

### Outcomes measured

The primary outcome evaluated was the rate of change in GFR over time (the GFR slope). The secondary outcome was a composite clinical outcome of a significant decline in GFR (a decline of 50% or 25 mL/minute/1.75 m<sup>2</sup>), development of end-stage renal disease (need for dialysis or transplantation), or death.

## ■ RESULTS: AMLODIPINE-RAMIPRIL ARM TERMINATED EARLY

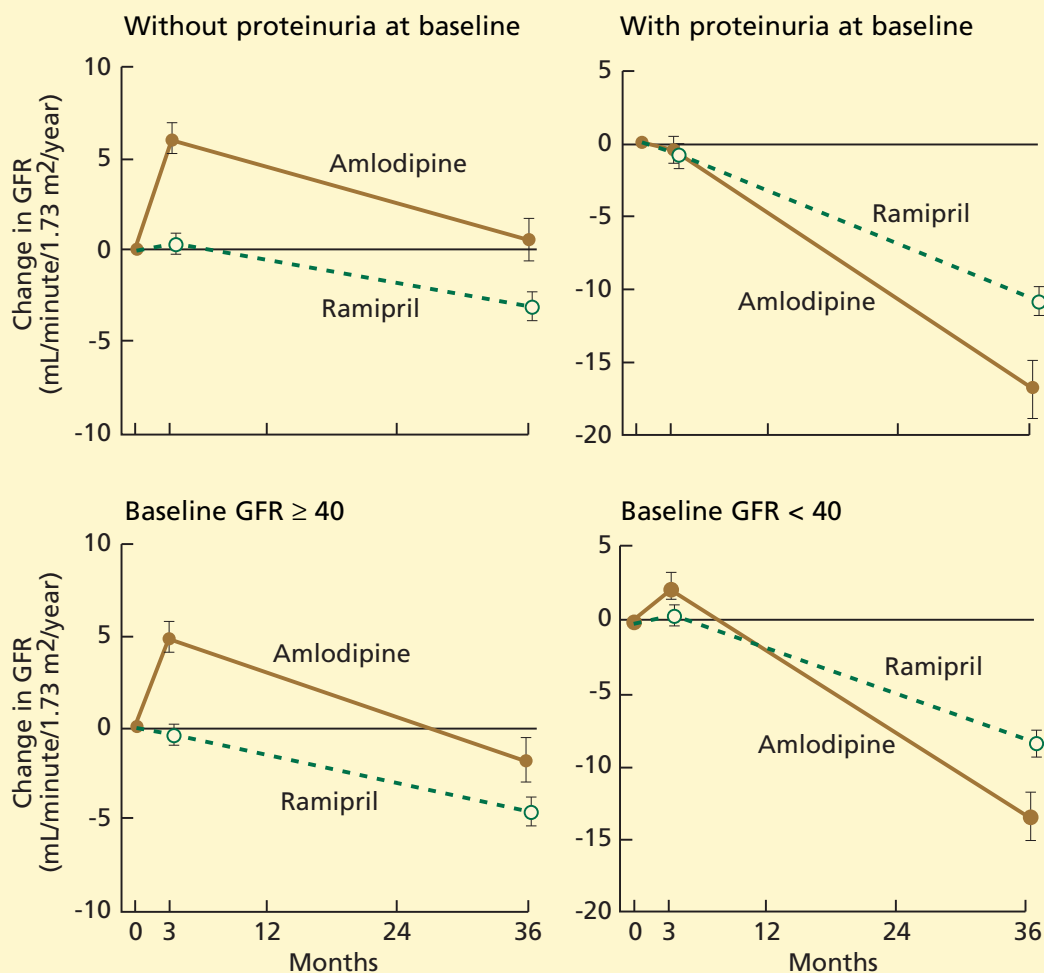
Though the trial was scheduled to end in 2001, the amlodipine-ramipril arm was terminated in September 2000 upon the recommendation of an independent Data Safety and Monitoring Board, and the results of the amlodipine-ramipril comparison were published. These data are reviewed below.

The results of the metoprolol-amlodipine comparison and the effect of the two levels of

**African Americans ages 25 to 44 have a 20-fold higher risk of end-stage renal disease**



**AASK data: Effect of ramipril vs amlodipine on GFR**



**FIGURE 1.** Mean change in glomerular filtration rate (GFR) in the African American Study of Kidney Disease and Hypertension (AASK); two-slope model, ie, the first 3 months of therapy and the last 30 months of therapy. **Top,** subgroup analysis based on proteinuria at baseline (urinary protein-creatinine ratio > 0.22). **Bottom,** subgroup analysis based on baseline GFR. Error bars are standard errors of the mean.

FROM AGODOA LY, APPEL L, BAKRIS GL, ET AL. EFFECT OF RAMIPRIL VS AMLODIPINE ON RENAL OUTCOMES IN HYPERTENSIVE NEPHROSCLEROSIS. A RANDOMIZED CONTROLLED TRIAL. JAMA 2001; 285:2719-2728.

**Most patients with renal insufficiency require more than one BP drug**

blood pressure control on decline in renal function are expected to be published later.

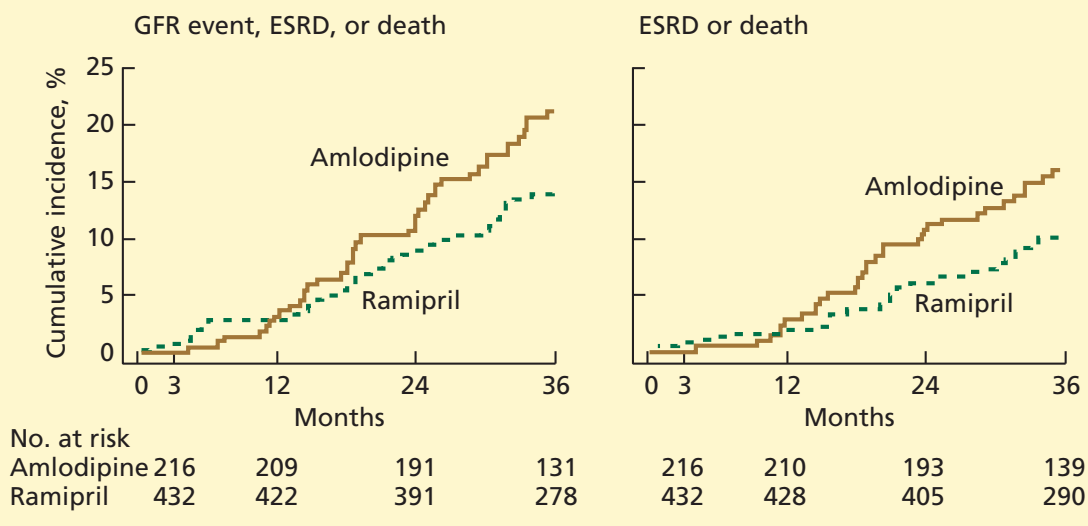
The GFR was followed for a median of 36 months in the amlodipine group and 37 months in the ramipril group. Blood pressure during follow-up was, as expected, substantially lower than at baseline, but did not differ significantly between the treatment groups. After the 3-month visit, there was no significant difference between the two groups either

in the number of antihypertensive drugs prescribed or in the percentage of participants receiving the highest doses of ramipril (57.4%) or amlodipine (56.7%).

**Primary outcome: GFR decline 36% slower in ramipril group**

Analyzing the rate of change in GFR was complex, because the GFR initially rose in the first 3 months in the amlodipine group (FIGURE 1).

### AASK data: Effect of ramipril vs amlodipine on renal events or death



**FIGURE 2.** Cumulative incidence of renal events and death in the African American Study of Kidney Disease and Hypertension (AASK). GFR event: a 50% or 25 mL/minute/1.73 m<sup>2</sup> decline in glomerular filtration rate from baseline; ESRD: end-stage renal disease, defined as need for dialysis or transplantation.

FROM AGODOA LY, APPEL L, BAKRIS GL, ET AL. EFFECT OF RAMIPRIL VS AMLODIPINE ON RENAL OUTCOMES IN HYPERTENSIVE NEPHROSCLEROSIS. A RANDOMIZED CONTROLLED TRIAL. JAMA 2001; 285:2719-2728.

### Proteinuria had an important influence on outcomes

Therefore, two different phases of the GFR slope could be identified: an “acute” phase within the first 3 months, and a “chronic” phase from 3 months onward until the end of follow-up. The “total” slope compared the GFR at baseline to that at the last follow-up period.

In the entire cohort, in the chronic phase, the decline in GFR was 36% slower in the ramipril group compared with the amlodipine group. However, there was no difference in the total slope.

**Impact of proteinuria on outcome.** Proteinuria had an important influence on outcomes. About one third of patients (144 of 436 in the amlodipine group and 69 of 217 in the ramipril group) had significant proteinuria, defined as a ratio of urinary protein to creatinine of greater than 0.22, which roughly corresponds to 300 mg/day.

Even though analysis stratified by proteinuria was not prespecified in the protocol, it is rational, given the accumulating evidence about the role of proteinuria as a risk factor for renal and cardiovascular disease.

In the subgroup with proteinuria, the rate

of decline in GFR was significantly slower in the ramipril group than in the amlodipine group in both the total and chronic slopes. However, in patients with no baseline proteinuria or with a GFR of at least 40 mL/minute/1.73 m<sup>2</sup>, there was no difference in the decline of GFR between the two treatment groups.

### Clinical outcomes showed benefit of ramipril

The secondary outcomes (a significant decline in GFR, end-stage renal disease, or death), which may bear a more direct relevance to the clinician, showed a beneficial effect of ramipril (FIGURE 2). In the entire cohort, the risk reduction for the ramipril vs amlodipine groups in the clinical composite outcome was 38% (95% CI 13%–56%;  $P = .005$ ).

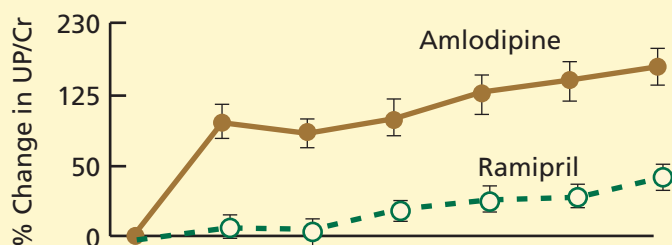
This risk reduction, however, was influenced by the subgroup of patients with baseline proteinuria; this subgroup contributed 63% of the events, although it represented only 33% of the cohort (213 of 653 patients).

Proteinuria, ie, the mean urinary protein-creatinine ratio, increased by 58% in the

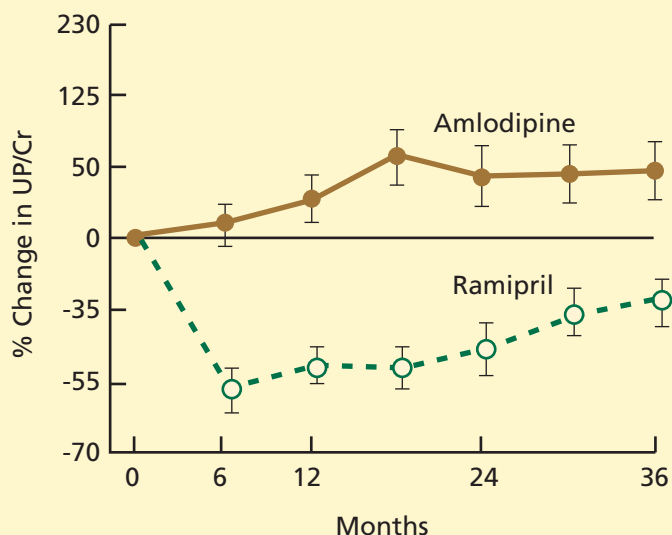


## AASK data: Effect of ramipril vs amlodipine on proteinuria

Without proteinuria at baseline



With proteinuria at baseline



**FIGURE 3.** Percent changes in proteinuria from baseline in the African American Study of Kidney Disease and Hypertension (AASK). Subgroup analysis based on proteinuria at baseline (urinary protein-creatinine ratio > 0.22). Error bars are standard errors of the mean.

FROM AGODOA LY, APPEL L, BAKRIS GL, ET AL. EFFECT OF RAMIPRIL VS AMLODIPINE ON RENAL OUTCOMES IN HYPERTENSIVE NEPHROSCLEROSIS. A RANDOMIZED CONTROLLED TRIAL. JAMA 2001; 285:2719-2728.

amlodipine group and declined by 20% in the ramipril group during the first 6 months of the study (FIGURE 3). This difference between treatment groups was significant ( $P < .001$ ) and persisted throughout the follow-up period, with moderate increases in proteinuria in both groups.

### ■ IMPORTANCE FOR CLINICIANS

Most patients with chronic renal insufficiency require more than one antihypertensive drug to achieve blood pressure control. The preliminary results of the AASK support the initial use of an ACE inhibitor as a part of a multi-drug regimen in African American patients with hypertensive nephrosclerosis.

Final results of this landmark study are expected to report the effect of different levels of blood pressure control, and to compare the efficacy of a beta-blocker vs an ACE inhibitor as the basis of an antihypertensive regimen aimed at preventing decline of renal function. These data will be important in developing improved therapeutic strategies to slow decline in renal function in hypertensive nephrosclerosis.

Experts have long thought that African Americans were less responsive to ACE inhibitors than other racial or ethnic groups. Moreover, studies of patients with congestive heart failure suggest that African American patients might not derive the same benefits as white patients do from ACE inhibitor therapy.

More recent studies, however, show that increasing the dose or adding a diuretic significantly reduces blood pressure, and now the AASK provides the first evidence of a beneficial effect of ACE inhibition on renal function in African American patients, in addition to excellent blood pressure control. ■

### ■ REFERENCES

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