The Relationship Between Magnitude of Proteinuria Reduction and Risk of End-stage Renal Disease

Results of the African American Study of Kidney Disease and Hypertension

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Background: The magnitude of proteinuria is associated with a graded increase in the risk of progression to end-stage renal disease and cardiovascular events. The objective of this study was to relate baseline and early changes in proteinuria and glomerular filtration rate (GFR) to long-term progression of hypertensive nondiabetic kidney disease.

Methods: Post hoc analysis of a randomized 3 × 2 factorial trial. A total of 1094 African Americans with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m²) were followed up for a median of 3.8 years. Participants were randomized to a mean arterial pressure goal of 102 to 107 mm Hg (usual) or 92 mm Hg or less (lower) and to initial treatment with a β-blocker (metoprolol), an angiotensin-converting enzyme inhibitor (ramipril), or a dihydropyridine calcium channel blocker (amlodipine).

Results: Baseline proteinuria and GFR predicted the rate of GFR decline. For each 10–mL/min per 1.73 m² lower baseline GFR, an associated mean±SE 0.38±0.08–mL/min per 1.73 m² per year greater mean GFR decline occurred, and for each 2-fold higher proteinuria level, a mean±SE 0.54±0.05–mL/min per 1.73 m² per year faster GFR decline was observed (P < .001 for both). In multivariate analysis, the effect of baseline proteinuria GFR decline persisted. Initial change in proteinuria from baseline to 6 months predicted subsequent progression, with this relationship extending to participants with baseline urinary protein levels less than 300 mg/d.

Conclusions: The change in the level of proteinuria is a predictor of subsequent progression of hypertensive kidney disease at a given GFR. A prospective trial is needed to confirm this observation.

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Review of Observational studies demonstrates that the magnitude of urinary protein excretion is associated with a linear increase in the risk of cardiovascular events and progression to end-stage renal disease (ESRD). During the past decade, there has been speculation that interventions that reduce proteinuria are more likely to slow the progression of renal disease in diabetic and nondiabetic patients.

The African American Study of Kidney Disease (AASK) evaluated 2 different blood pressure (BP) goals and 3 different treatment regimens (a β-blocker [metoprolol succinate], a dihydropyridine calcium channel blocker [amlodipine besylate], and an angiotensin-converting enzyme [ACE] inhibitor [ramipril]) in African Americans with nondiabetic kidney disease. In this trial, the magnitude of proteinuria reduction differed among the antihypertensive treatment groups in the context of renal outcomes. The interpretation of these results depended on the level of baseline proteinuria, expressed as the ratio of urine protein to urine creatinine (UP:Cr) assessed from a 24-hour urine collection sample. Approximately two thirds of the participants had a UP:Cr of 0.22 or less (approximately 300 mg/d) or microalbuminuria, and one third had a UP:Cr greater than 0.22 or proteinuria.

In this study, we evaluate the relationship of the baseline proteinuria level and its change in the first 6 months on subsequent longer-term progression of renal disease during follow-up.
PARTICIPANTS

The 1094 randomized participants in the AASK were self-identified African Americans with hypertension, aged 18 to 70 years, with glomerular filtration rates (GFRs) of 20 to 65 mL/min per 1.73 m² and no other identified causes of renal insufficiency. The exclusion criteria consisted of a UP:Cr greater than 2.5 and various conditions associated with severe cardiovascular disease. Additional details regarding participants and the design of the trial are provided elsewhere.10,11

STUDY DESIGN

Participants were randomized according to a 3 × 2 factorial design 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 less and to treatment with 1 of 3 antihypertensive drugs: a sustained-release β-blocker (metoprolol succinate, 50-200 mg/d), an ACE inhibitor (ramipril, 2.5-10.0 mg/d), or a dihydropyridine calcium channel blocker (amlodipine besylate, 5-10 mg/d). If the randomized drug could not achieve the BP goal, additional open-label antihypertensive agents (furosemide, doxazosin mesylate, clonidine, and hydralazine hydrochloride or minoxidil) were added sequentially.

The GFR was assessed by iothalamate sodium I 125 clearance twice during baseline, at 3 and 6 months, and every 6 months thereafter during follow-up. Proteinuria was expressed as the UP:Cr ratio derived from a 24-hour urine collection once during baseline and at 6-month intervals thereafter. All GFR and proteinuria measurements were performed at Cleveland Clinic Laboratories.

Participants were randomized during a 3-year recruitment period, with planned follow-up ranging from 3.0 to 6.4 years. For this study, follow-up was censored 1 year before the scheduled end of the trial for participants randomized to the amlopidine group, when this intervention was terminated on the recommendation of the Data Safety and Monitoring Board. The median duration of GFR follow-up was 3.8 years.

OUTCOMES AND PREDICTOR VARIABLES

Two renal outcomes were considered: (1) the mean GFR slope throughout follow-up, starting with the GFR observed at the 6-month follow-up visit, and (2) the occurrence of ESRD. The GFR slope outcome expresses the average rate of change of the GFR in all patients, whereas the ESRD outcome represents the clinical end point of most direct relevance. The GFR slope was computed starting at 6 months to reflect changes in the GFR after the 6-month assessment of proteinuria (see the following paragraph).

The primary predictor variables include (1) baseline proteinuria, defined as the log-transformed baseline UP:Cr; (2) baseline GFR, defined as the mean of the 2 iothalamate GFR measurements before randomization; and (3) initial change in proteinuria, defined as the difference between the log 6-month follow-up UP:Cr and the log baseline UP:Cr (Δ UP:Cr). Throughout this article, GFR is expressed after standardization for body surface area in milliliters per minute per 1.73 m².

ANALYSIS PLAN

The first set of analyses investigated the relationships of the renal outcome variables with baseline proteinuria and baseline GFR in 1090 patients with a valid baseline UP:Cr measurement. Baseline proteinuria and baseline GFR were analyzed individually and then jointly to assess the independent association of each factor with progression after controlling for the other factor. The following categories were defined to describe dose-response relationships: for proteinuria, UP:Cr less than 0.08, 0.08 to less than or equal to 0.22, greater than 0.22 to less than or equal to 0.66, and greater than 0.66; and for GFR, greater than 48, greater than 40 to less than or equal to 48, greater than 30 to less than or equal to 40, and less than or equal to 30 mL/min per 1.73 m². We then examined the relationship of the long-term outcomes with the initial changes in proteinuria by relating the outcome variables to the baseline level and the initial changes in log UP:Cr from baseline to 6 months in multivariable analyses. These analyses were performed in the subset of 810 participants for whom 6-month follow-up UP:Cr measurements and at least 1 GFR at or after the 6-month visit were obtained and were repeated in the subgroups with baseline UP:Cr of 0.22 or less and greater than 0.22 to determine whether the association of the long-term outcomes with initial change in proteinuria depended on the baseline level of proteinuria. The multivariable analyses were also performed separately in the 3 drug groups to examine whether changes in proteinuria that resulted from different medication classes may have different relationships with long-term outcomes.

STATISTICAL ANALYSIS

All analyses of the GFR slope outcome were performed using a single-slope mixed-effects model with a random slope and intercept.12 Separate covariance matrices were fit for the subgroups of participants with baseline GFRs less than 40 mL/min per 1.73 m² and 40 mL/min per 1.73 m² or greater to account for greater variability in the individual GFR measurements for participants with higher baseline GFRs. Indicator variables for the randomized treatment groups were included in all analyses so that the reported coefficients represent averages of the indicated relationships that were observed within the respective treatment groups.

Analyses of time to ESRD were performed using Cox proportional hazards regression analysis. As in the analysis of GFR slope, indicator variables for the randomized treatment groups were included as covariates in the Cox models. Participants were administratively censored at loss to follow-up (12 participants), in September 2000 if randomized to the amlopidine group, and at study completion if randomized to the other drug groups.

The study analyses were conducted without adjustment for baseline patient factors other than proteinuria and GFR. However, in sensitivity analyses, all the analyses presented in this article were repeated after adjustment for age, sex, history of heart disease, and baseline mean arterial pressure. All analyses are intent-to-treat. Comparison-wise P values and 95% confidence intervals are reported.

RESULTS

Table 1 summarizes the levels of GFR and proteinuria at baseline for the 1094 randomized participants. The level of 24-hour urine protein excretion was positively associated with male sex, younger age, and higher body mass index. The dependence of proteinuria level on these factors was eliminated or substantially weakened when proteinuria was expressed as the UP:Cr ratio. For example,
median 24-hour urine protein excretion was substantially higher in males (143 mg/d) compared with females (89 mg/d), whereas the UP:Cr ratio was similar in males (0.082) and females (0.080). There was an inverse relationship between baseline GFR and proteinuria, and UP:Cr ratios greater than 1.0 were seen almost exclusively in participants with GFRs less than 40 mL/min per 1.73 m² (Figure 1).

**ASSOCIATION OF PROGRESSION WITH BASELINE LEVELS OF PROTEINURIA AND GFR**

The overall mean±SE GFR slope after 6 months was −1.83±0.12 mL/min per 1.73 m² per year. Considered individually, higher levels of baseline proteinuria and lower levels of baseline GFR were associated with faster progression. Across the GFR range in the AASK, each 10–mL/min per 1.73 m² lower GFR was associated with a mean±SE 0.04±0.08–mL/min per 1.73 m² per year greater decline in GFR (P<.001) and with more than a 2-fold greater risk of ESRD (relative risk, 2.70; 95% confidence interval, 2.33-3.13; P<.001). Across the range of proteinuria, for every 2-fold higher level in baseline UP:Cr, an associated mean±SE 0.54±0.05–mL/min per 1.73 m² per year greater decline in GFR (P<.001) was noted, with a 1.80 relative risk (95% confidence interval, 1.66-1.95) of ESRD (P<.001). The effects of baseline GFR and doubling of baseline proteinuria on the GFR slope of 0.38 and 0.54 mL/min per 1.73 m² per year represent approximately 21% and 30%, respectively, of the overall mean rate of decline of 1.83 mL/min per 1.73 m² per year.

When baseline GFR and baseline proteinuria were considered jointly in a multivariable model, the relationship of GFR slope with proteinuria persisted, with each 2-fold higher UP:Cr associated with a mean±SE 0.57±0.06–mL/min per 1.73 m² per year faster mean GFR decline (P<.001). However, after controlling for baseline proteinuria, the relationship between GFR slope and baseline GFR was eliminated, with a 10–mL/min per 1.73 m² lower GFR associated with a mean±SE 0.04±0.08–mL/min per 1.73 m² per year slower mean GFR slope (P = .61). This joint relationship between GFR slope and baseline GFR and proteinuria is illustrated in Figure 2. The mean GFR slopes become steeper as the degree of proteinuria increases at any given baseline GFR, but they were not related to the baseline GFR within fixed baseline proteinuria subgroups.

The risk of ESRD increased with higher baseline proteinuria and lower baseline GFR even when both factors were considered jointly in a multivariate analysis.
To reach ESRD sooner because they started from a lower GFR, participants who progressed faster at a given level of proteinuria, they tended to reach ESRD sooner because they started from a lower baseline GFR. The persistence of the relationship of baseline GFR with risk of ESRD after controlling for baseline proteinuria indicates that although participants with lower GFRs did not progress faster at a given level of proteinuria, they tended to reach ESRD sooner because they started from a lower baseline GFR.

ASSOCIATION OF PROGRESSION WITH BASELINE UP:CR AND Δ UP:CR

There was substantial variability between participants when evaluating the percentage Δ UP:Cr between baseline and 6 months. In all treatment groups combined, approximately equal proportions of participants registered increases (47.6%) and decreases (52.2%) in UP:Cr. The 10th, 25th, 50th, 75th, and 90th percentiles for the percentage Δ UP:Cr were −73%, −43%, −2%, 73%, and 301%, respectively.

Table 3 provides multivariate analyses relating GFR slope and risk of ESRD after 6 months to the baseline level and Δ UP:Cr within each drug group. The results were observed for ESRD alone and for the composite outcome including ESRD and death. Similar results were reported previously herein were also conducted for the composite outcome of ESRD and death for each analysis. Because analyses of ESRD alone may be biased by the competing risk of death, each of the analyses for risk of ESRD reported previously herein were also conducted for the composite outcome including ESRD and death. Similar results were observed for ESRD alone and for the composite of ESRD and death for each analysis.

The results presented in this article were essentially unchanged after controlling for age, sex, history of heart disease, and baseline mean arterial pressure.

This article presents evidence that changes in low levels of proteinuria are predictive of ESRD development and the annual rate of decline in GFR in people with non-diabetic kidney disease. Although it is well known that
higher levels of proteinuria are associated with increased risk of ESRD and that reductions in proteinuria are associated with reduced risk of ESRD development, the distinctive role of a given level or change in proteinuria level on rate of decline in kidney function has not been clarified.2,3,7,10 This is the first article to present evidence that in nondiabetic kidney disease, changes in low levels of proteinuria are predictive of ESRD development and the annual rate of decline in the GFR.

Many clinical trials in the past decade define kidney disease progression as the time to doubling of the serum creatinine level or halving of the GFR, ESRD, or death. All these trials have reported significant relationships between slower rates of kidney disease progression and early reductions in proteinuria in secondary analyses.2,3,6,7 Conversely, such renal outcome benefits have not been universally described with reductions in microalbuminuria.13,14 The AASK examines a cohort of exclusively nondiabetic participants with hypertensive nephrosclerosis where the renal outcome benefit was associated with reductions in proteinuria across all levels of baseline proteinuria.

Consistent with previous studies of diabetic2,3,15 and nondiabetic6,7,16 persons with chronic kidney disease, our data show that the level of proteinuria at baseline was associated with a greater mean decline in GFR and a higher rate of ESRD. Unlike some previous studies,17 a lower GFR at baseline was also associated with a faster subsequent average decline in GFR. However, in multivariate analysis, the rate of decline in the GFR remained significantly related to baseline UP:Cr for a given level of baseline GFR and to the level of baseline GFR for a given level of proteinuria.

Abbreviations: UP:Cr, urine protein–urine creatinine ratio.

<table>
<thead>
<tr>
<th>Baseline GFR Group</th>
<th>All participants</th>
<th>Participants with baseline UP:Cr (\leq 0.22)</th>
<th>Participants with baseline UP:Cr (&gt;0.22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UP:Cr Group</td>
<td>GFR Slope After 6 mo, Mean (SE), mL/min per 1.73 m² per Year</td>
<td>ESRD Relative Risk (95% CI)</td>
<td>GFR Slope After 6 mo, Mean (SE), mL/min per 1.73 m² per Year</td>
</tr>
<tr>
<td>(&lt;0.08)</td>
<td>–0.66 (0.06)</td>
<td>2.11 (1.89-2.36)</td>
<td>–0.41 (0.11)</td>
</tr>
<tr>
<td>(0.08-0.22)</td>
<td>–0.63 (0.10)</td>
<td>1.72 (1.49-1.97)</td>
<td>–0.52 (0.14)</td>
</tr>
<tr>
<td>(0.23-0.66)</td>
<td>–0.41 (0.11)</td>
<td>1.94 (1.38-2.71)</td>
<td>–0.52 (0.14)</td>
</tr>
<tr>
<td>(&gt;0.66)</td>
<td>–0.85 (0.14)</td>
<td>1.86 (1.52-2.27)</td>
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</tr>
</tbody>
</table>

Table 3. Joint Effect of Baseline UP:Cr and Initial Change (\(\Delta\)) in UP:Cr to 6 Months*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All participants</th>
<th>Participants with baseline UP:Cr (\leq 0.22)</th>
<th>Participants with baseline UP:Cr (&gt;0.22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline UP:Cr</td>
<td>–0.66 (0.06)</td>
<td>2.11 (1.89-2.36)</td>
<td>–0.41 (0.11)</td>
</tr>
<tr>
<td>Initial (\Delta) UP:Cr</td>
<td>–0.63 (0.10)</td>
<td>1.72 (1.49-1.97)</td>
<td>–0.52 (0.14)</td>
</tr>
<tr>
<td>Baseline UP:Cr</td>
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<td>–0.52 (0.14)</td>
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<tr>
<td>Initial (\Delta) UP:Cr</td>
<td>–0.85 (0.14)</td>
<td>1.86 (1.52-2.27)</td>
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</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; UP:Cr, urine protein–urine creatinine ratio.

* \(P<.001\) for all.
with higher proteinuria tend to have lower GFRs at a given cross-sectional assessment and thus may progress faster, it is the level of proteinuria, and not the GFR, that is most relevant for determining the future course of decline in renal function.

Also consistent with previous studies of cohorts with chronic kidney disease, for any given level of proteinuria at baseline, the early change in proteinuria from baseline to the 6-month point predicts the subsequent rate of decline in the GFR and the incidence of ESRD across a 3- to 6-year period. In the AASK, the association of the initial change in proteinuria with subsequent kidney disease progression was seen in the entire cohort studied regardless of baseline levels of UP:Cr.

As described in a previous article,18 the amlodipine intervention led to a substantial increase in the average level of proteinuria during the first 6 months of the trial. However, the interindividual variability of the percentage change in proteinuria was large, and only a small proportion of the variation in the change of log-transformed proteinuria was accounted for by the AASK interventions. It will be useful to determine the extent to which this finding of change in proteinuria and renal outcome in the AASK is observed in other interventional trials.

Mechanisms by which proteinuria may contribute to declines in renal function have been postulated.10 Large leakage of protein by the kidney is indicative of a diffuse disease process in the vasculature of the kidney and the body.14,20 Leakage of large quantities of protein into the interstitium has been shown to stimulate cytokines and oxidant stress associated with interstitial fibrosis.10 Reduction of BP reduces proteinuria by decreasing systemic and consequently intraglomerular pressure. However, certain antihypertensive agents, such as dihydropyridine calcium channel blockers, fail to reduce membrane permeability in the glomerulus and vasculature, whereas others, such as ACE inhibitors and angiotensin receptor blockers, reduce permeability.20-22 The mechanisms that mediate these changes are not fully characterized.

In summary, the baseline level and the initial change from baseline to 6 months in proteinuria were predictors of subsequent progression of hypertensive kidney disease in African Americans. The relationship between the initial change in proteinuria and subsequent progression extended to participants with normoalbuminuria to microalbuminuria. The level of baseline GFR was not predictive of the subsequent rate of GFR decline after accounting for baseline proteinuria. The association of the early change in proteinuria with subsequent renal outcomes suggests that effects of antihypertensive agents on proteinuria should be considered when selecting agents for their potential to slow the progression of renal disease. However, because the AASK randomized patients to antihypertensive drug regimens and BP targets, it does not provide a direct randomized comparison of the effect of titrating to different levels of proteinuria. Additional investigations that involve multiple studies are needed to address the question of whether the ability of an intervention to reduce proteinuria is sufficient to conclude that the intervention will delay progression to ESRD.

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REFERENCES


Table 4. Joint Effect of Baseline UP:Cr and Initial Change (Δ) in UP:Cr to 6 Months by Randomized Drug Group*

<table>
<thead>
<tr>
<th>Variable</th>
<th>GFR Slope After 6 mo, Mean (SE), mL/min per 1.73 m² per Year</th>
<th>ESRD Relative Risk (95% CI)</th>
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</thead>
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<tr>
<td>Participants randomized to ramipril</td>
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<tr>
<td>Baseline UP:Cr</td>
<td>−0.65 (0.09)</td>
<td>2.17 (1.80-2.63)</td>
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<tr>
<td>Initial Δ UP:Cr</td>
<td>−0.47 (0.16)</td>
<td>1.75 (1.39-2.21)</td>
</tr>
<tr>
<td>Participants randomized to metoprolol</td>
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<td></td>
</tr>
<tr>
<td>Baseline UP:Cr</td>
<td>−0.53 (0.08)</td>
<td>2.12 (1.75-2.55)</td>
</tr>
<tr>
<td>Initial Δ UP:Cr</td>
<td>−0.49 (0.15)</td>
<td>1.66 (1.34-2.04)</td>
</tr>
<tr>
<td>Participants randomized to amlodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline UP:Cr</td>
<td>−0.88 (0.17)</td>
<td>2.12 (1.70-2.65)</td>
</tr>
<tr>
<td>Initial Δ UP:Cr</td>
<td>−1.38 (0.26)</td>
<td>1.88 (1.36-2.61)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; GFR, glomerular filtration rate; UP:Cr, urine protein–urine creatinine ratio.

*P<.001 for all.


