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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A REVIEW OF OBSERVATIONAL studies1-4 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.5-9

The African American Study of Kidney Disease (AASK)10 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.10

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 low 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 1 125 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 obtained 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 measure-

RESULTS

BASELINE

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,
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 baseline 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.
(P<.001 for both baseline factors) (Table 2). 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 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 to 6 months. When the analysis was conducted in all 810 participants, the baseline level and the initial change in proteinuria were independent predictors of GFR slope and risk of ESRD. For a given level of the baseline UP:Cr, a doubling of UP:Cr in the first 6 months associated with a mean±SE 0.63±0.10–mL/min per 1.73 m² per year greater decline in GFR and a relative risk of ESRD of 2.11 (95% confidence interval, 1.89-2.36) for the remainder of follow-up. Similar results are presented graphically in Figure 3, which displays the relative risks of ESRD during follow-up for different subgroups defined by changes in proteinuria (UP:Cr) from baseline to 6 months.

The absolute magnitudes of the effects of the baseline level and Δ UP:Cr to 6 months on GFR slope were approximately twice as large in the baseline UP:Cr greater than 0.22 subgroup as in the subgroup with lesser proteinuria (Table 3). These relationships, however, remained statistically significant even in the subgroup with baseline UP:Cr of 0.22 or less. Moreover, the magnitudes of the relationships were similar in the 2 baseline proteinuria strata when expressed as proportions of the respective mean GFR slopes (approximately –1.4 mL/min per 1.73 m²/year in the baseline UP:Cr ≤0.22 subgroup vs –4.0 mL/min per 1.73 m² per year in the baseline UP:Cr >0.22 subgroup). The relative risks of ESRD associated with doubling of UP:Cr from baseline to 6 months were 1.55 and 1.86 in the UP:Cr of 0.22 or less and UP:Cr greater than 0.22 subgroups, respectively.

ASSOCIATION OF PROGRESSION WITH BASELINE AND Δ UP:CR WITHIN EACH DRUG GROUP

As reported previously,10 the geometric mean of the UP:Cr increased from baseline to 6 months in the amlo- dipine drug group compared with the ramipril and metoprolol groups and decreased in the low BP group compared with the usual BP group. However, although these effects of the AASK interventions were statistically significant, because of the large interpatient variability in the Δ UP:Cr, they accounted for only 8.6% of the total variation in the change of log-transformed UP:Cr from baseline to 6 months.

Table 4 presents the analysis from Table 3 separately for the 3 drug groups. The results for the ESRD outcome were similar in each group. The directions of the relationships for the GFR slope outcome were the same for each drug group, but the magnitude of the association of the Δ UP:Cr to 6 months with GFR slope was greater in the amlo- dipine group (a mean±SE 1.38±0.26–mL/min per 1.73 m² per year greater decline in GFR per doubling of UP:Cr) than in either the ramipril (mean±SE 0.47±0.16 mL/min per 1.73 m² per year per doubling) or metoprolol (mean±SE 0.49±0.15 mL/min per 1.73 m² per year per doubling) groups.

ESRD OR DEATH OUTCOME AND SENSITIVITY ANALYSES FOR COVARIATE ADJUSTMENT

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.

COMMENT

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. 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. Conversely, such renal outcome benefits have not been universally described with reductions in microalbuminuria. 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 diabetic and nondiabetic 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, 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 proteinuria for any given level of baseline GFR but not to the level of baseline GFR once the level of baseline proteinuria was taken into account. One interpretation of this result is that although participants

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**Table 2. Rates of ESRD Throughout Follow-up**

<table>
<thead>
<tr>
<th>Baseline UP:Cr Group</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>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.08</td>
<td>-0.66 (0.06)</td>
<td>2.11 (1.89-2.36)</td>
</tr>
<tr>
<td>0.08-0.22</td>
<td>-0.63 (0.10)</td>
<td>1.72 (1.49-1.97)</td>
</tr>
<tr>
<td>0.23-0.66</td>
<td>-0.41 (0.11)</td>
<td>1.94 (1.38-2.71)</td>
</tr>
<tr>
<td>&gt;0.66</td>
<td>-0.52 (0.14)</td>
<td>1.35 (1.24-1.93)</td>
</tr>
<tr>
<td>All</td>
<td>-0.91 (0.23)</td>
<td>2.20 (1.75-2.76)</td>
</tr>
<tr>
<td></td>
<td>-0.85 (0.14)</td>
<td>1.86 (1.52-2.27)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline GFR Group, mL/min per 1.73 m²</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>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;45</td>
<td>-0.66 (0.06)</td>
<td>2.11 (1.89-2.36)</td>
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<tr>
<td>40 to ≤48</td>
<td>-0.63 (0.10)</td>
<td>1.72 (1.49-1.97)</td>
</tr>
<tr>
<td>30 to ≤40</td>
<td>-0.41 (0.11)</td>
<td>1.94 (1.38-2.71)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>-0.52 (0.14)</td>
<td>1.35 (1.24-1.93)</td>
</tr>
<tr>
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<td></td>
<td>-0.85 (0.14)</td>
<td>1.86 (1.52-2.27)</td>
</tr>
</tbody>
</table>

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

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

<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>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>-0.66 (0.06)</td>
<td>2.11 (1.89-2.36)</td>
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</tbody>
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Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; GFR, glomerular filtration rate; UP:Cr, urine protein–urine creatinine ratio.

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Figure 3. Association of the risk of end-stage renal disease (ESRD) with initial change in proteinuria. The relative risks of ESRD during follow-up for different subgroups defined by the change in the urine protein–urine creatinine ratio (UP:Cr) from baseline to 6 months controlling for randomized treatment group and the initial level of proteinuria is shown. The reference group ranges from a 20% reduction in UP:Cr to a 25% increase. The cutoff values that define the change in proteinuria subgroups correspond to percentage changes that are symmetrical on the log scale. Error bars represent standard errors.
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, 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 intervention trials.

Mechanisms by which proteinuria may contribute to declines in renal function have been postulated. Large leakage of protein by the kidney is indicative of a diffuse disease process in the vasculature of the kidney and the body. Leakage of large quantities of protein into the interstitium has been shown to stimulate cytokines and oxidant stress associated with interstitial fibrosis. 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. 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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