A Comparison of Iothalamate-GFR and Serum Creatinine-Based Outcomes: Acceleration in the Rate of GFR Decline in the African American Study of Kidney Disease and Hypertension

JULIA LEWIS, TOM GREENE, LAWRENCE APPEL, GABRIEL CONTRERAS, JANICE DOUGLAS, JIM LASH, ROBERT TOTO, FREDRICK VAN LENTE, XUELEI WANG, and JACKSON T. WRIGHT, JR., FOR THE AASK STUDY GROUP

Vanderbilt University Medical Center, Nephrology Clinical Trials Center, Nashville, Tennessee

Abstract. In renal clinical trials, both slope-based and time-to-event renal outcomes have been used. These outcomes are typically based on estimates of GFR obtained using creatinine or iothalamate GFR (iGFR). The African American Study of Kidney Disease and Hypertension (AASK) was a trial in 1094 African Americans with hypertensive nephrosclerosis, which examined the effects of two levels of BP control and three antihypertensive regimens. This study compared the effects of the AASK interventions on outcomes based on serum creatinine with corresponding outcomes based on iGFR using 9742 matched pairs of iGFR and serum creatinine measurements. The iGFR-based outcomes included (1) a time-to-event composite outcome including a 50% GFR decline, ESRD, or death; (2) a composite outcome including a 50% GFR decline or ESRD; (3) mean decline in GFR in the first 3 mo after randomization (acute slope); (4) mean decline in GFR starting 3 mo after randomization (chronic slope); and (5) mean decline in GFR from baseline (total slope). The corresponding creatinine-based outcomes were (1) a composite of doubling of serum creatinine, ESRD, or death and (2) a composite of doubling of serum creatinine or ESRD and acute, chronic, and total slopes defined by the mean change in estimated GFR (eGFR), where eGFR was estimated from a regression equation for GFR depending primarily on serum creatinine and developed in AASK enrollees. Mean changes in iGFR and eGFR were also compared under extended models that allowed for the possibility that the rate of GFR decline may change over time during the chronic phase. An apparent acceleration in rate of decline of renal function over time was found. Subtle differences were observed between effects of the interventions on some of the creatinine and iGFR slope-based outcomes, but the main conclusions of the trial were similar for the serum creatinine and iothalamate-based measurements. This has important implications for the design of clinical trials with renal outcomes.

Choosing appropriate outcomes is critical to the success of clinical trials. In renal clinical trials to date, both slope-based and time-to-event renal outcomes have been used (1–5). In the slope-based analysis, GFR is estimated at multiple time points for all participants and curves constructed from these points that reflect the change in renal function over time. In most cases, constant slopes over time are assumed, and mean slopes are compared between the study groups to evaluate the effects of interventions on the rate of GFR decline. In time-to-event analysis, an event such as halving of GFR or ESRD is measured, and the time from randomization to the occurrence of these events is compared between the study groups.

Inulin clearance is arguably the gold standard for accurately measuring GFR (6). In large clinical trials, however, 125I-iothalamate has been used to estimate GFR because it can be given as a single injection. However, both of these techniques require (2–8) water loading, multiple blood draws, and 6 to 8 h of time. In large clinical trials that investigate therapeutic interventions, the absolute value of any given GFR is not as important as being able to detect a change in renal function over time. In addition, these methods are expensive. To reduce cost and time involved in clinical trials, simpler methods to estimate changes in renal function are desirable.

Estimation of GFR from serum creatinine measurements is now recommended by the National Kidney Foundation as a method for assessing kidney function in those who either are at risk for or have chronic kidney disease regardless of cause (9). This method is now being tested in longitudinal studies, including the Chronic Renal Insufficiency Cohort and African American Study of Kidney Disease and Hypertension (AASK) cohort studies to monitor changes in kidney function over time.
We use data from the recently completed AASK to evaluate whether use of serum creatinine measurements (or estimated GFR from equations based on serum creatinine measurements) would alter any of the primary conclusions of the study compared with the conclusions reached on the basis of direct measurements of $^{125}$I-iothalamate GFR (iGFR) $(10, 11)$. The comparison of iGFR with serum creatinine–based results was performed for three types of analysis. First, using the time-to-event approach, we compared the effects of the study interventions on the time to halving of iGFR with the time to doubling of serum creatinine. (Serum creatinine is approximately inversely proportional to GFR, so halving of GFR corresponds roughly to doubling of serum creatinine.) Second, using the slope-based approach, we compared the effects of the interventions on the mean rate of decline in iGFR with the mean rate of decline in estimated GFR (eGFR), where eGFR was estimated from an equation depending primarily on serum creatinine developed in the AASK enrollees at baseline $(12)$. This second approach corresponds to the primary analysis of the AASK and assumes a constant mean rate of GFR decline from 3 mo after randomization though the end of the 3- to 6-yr follow-up period of the trial. Third, we compared mean changes in iGFR and eGFR under extended models that allowed for the possibility that GFR decline may accelerate over time. Finally, in addition to these aggregate comparisons, we compared the precision of individual eGFR with iGFR values by investigating the variability in eGFR and iGFR within the same patients over time.

Materials and Methods

Study Design

Briefly, participants were self-identified African Americans who had hypertension ($n = 1094$), were aged 18 to 70 yr, and had a GFR between 20 and 65 ml/min per 1.73 m$^2$ and no other identified causes of renal insufficiency. The protocol and procedures were approved by the institutional review board at each center, and all participants gave written informed consent $(10, 11)$. On the basis of a 3 × 2 factorial design, participants were randomized to a usual mean arterial pressure goal of 102 to 107 mmHg or to a lower mean arterial pressure goal of 92 mmHg or lower and to treatment with one of three 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). When the BP goal could not be achieved by the randomized drug, additional open-labeled antihypertensives were added sequentially. On the recommendation of the Data Safety and Monitoring Board, the amlodipine intervention was terminated in 2000, ~1 yr before the scheduled end of the trial.

The GFR was assessed by renal clearance of $^{125}$I-iothalamate twice at baseline, at 3 and 6 mo, then every 6 mo thereafter $(10, 11)$. Serum creatinine was centrally measured using the rate-Jaffe method with an alkaline picrate assay (normal range, 0.7 to 1.4 mg/dl) $(13)$ twice during baseline and at 6-mo intervals during follow-up.

A total of 10,679 iGFR and 11,135 serum creatinine measurements were obtained during the trial (excluding those in the amlodipine group after September 2000). To facilitate comparisons between analyses on the basis of iGFR and serum creatinine, the data set for this report was restricted to 9742 matched pairs of iGFR and serum creatinine measurements that were obtained within 8 wk of each other.

 Trial Outcomes

The primary outcome for the trial was based on the rate of change in iGFR (iGFR slope). The GFR slope was determined separately during the first 3 mo after randomization (acute slope) and after 3 mo (chronic slope). The acute and chronic phases were distinguished because previous studies indicated that the AASK interventions have acute effects on iGFR that may differ from their long-term effects on disease progression $(14)$. The chronic slope and the mean total slope from baseline (includes both the acute and the chronic phases) were designated as co-primary outcomes. The analysis plan stipulated that a definitive benefit of a treatment intervention would be inferred when it was shown to reduce the magnitude of both the chronic and the total mean slopes.

The protocol also designated a main secondary clinical composite outcome that included any of the following: A confirmed reduction in iGFR by 50% or by 25 ml/min per 1.73 m$^2$ from the mean of the baseline iGFR, ESRD (dialysis or transplantation), or death. The clinical composite outcome provided the principal assessment of patient benefit. In contrast with the analysis of iGFR 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.

Outcomes Compared

For comparisons of slope-based analyses, the mean acute, chronic, and total slopes for iGFR were compared with the mean acute, chronic, and total slopes for eGFR, where eGFR was defined by the following equation obtained by multiple regression analysis of 1703 enrollees in the baseline phase of the AASK Study $(12)$:

$$eGFR = 329 \times (Scr)^{1.096} \times \text{age}^{-0.294} \times (0.736 \text{ if female})$$

For comparisons of time-to-event analyses, we defined the following composite events on the basis of iGFR: G1, time to a 50% decline in iGFR from the mean of the two baseline iGFR, ESRD, or death; and G2, time to a 50% decline in iGFR from the mean of the two baseline iGFR or ESRD, censoring death. The outcome G1 is similar to main time-to-event outcome in the trial design; we also consider G2 in this report to allow direct comparisons of the renal events excluding deaths. The effects of the treatment interventions on these two outcomes were compared with the corresponding effects on the serum creatinine–based composite outcomes: S1, time to a doubling of serum creatinine, ESRD, or death; and S2, time to doubling of serum creatinine or ESRD, censoring death. The outcome G1 is similar to main time-to-event outcome in the trial design; we also consider G2 in this report to allow direct comparisons of the renal events excluding deaths. The effects of the treatment interventions on these two outcomes were compared with the corresponding effects on the serum creatinine–based composite outcomes: S1, time to a doubling of serum creatinine, ESRD, or death; and S2, time to doubling of serum creatinine or ESRD, censoring death. Mathematically, when the serum creatinine doubles, the GFR (estimated by creatinine clearance) approximately halves. Note that G1 differs slightly from the main secondary time-to-event outcome in the trial design in that 25 ml/min per 1.73 m$^2$ reductions in iGFR are not counted as events in the absence of a 50% decline in iGFR, and confirmation of declining GFR events was not required (for either iGFR or eGFR). These deviations were made for the present analyses to simplify the comparisons of the iGFR-based analyses with the corresponding analyses based on doubling of serum creatinine, where confirmatory measurements were not obtained as part of the protocol.

For consistency with the study’s primary analysis plan, iGFR was factored by baseline body surface area in this report. However, sensitivity analyses indicated that the results of this report are essentially unchanged if iGFR is factored by the body surface area computed using the patient’s weight at the time of the GFR measurement.
Statistical Analyses

Time-to-Event Analyses. The effects of the BP and drug group interventions on the time-to-event outcomes (G1, G2, S1, and S2) were analyzed using Cox proportional hazards regression (15) with adjustment for the following five prespecified baseline covariates: Proteinuria (log urinary protein to creatinine ratio), history of cardiovascular disease, mean arterial pressure, gender, and age. The relative risks corresponding to the respective treatment group comparisons were compared between the corresponding iGFR and serum creatinine–based outcomes (S1 versus G1, and S2 versus G2) using robust sandwich estimates of the covariance between the associated Cox-regression coefficients (16).

Slope-Based Analyses with Constant Mean Slope after 3 Mo. The analysis of mean iGFR slope first was performed using a mixed effects model (17) 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 six cells in the 2 × 3 factorial design, adjusting for the same five prespecified baseline covariates as in the time-to-event analyses. A two-slope linear spline model was used for both the fixed and the random effects so that each patient’s estimated regression lines for the acute and chronic phases joined together at 3 mo (14). The total slope was defined as the weighted average of the acute and chronic slopes corresponding to the average rate of change of iGFR from baseline to 4 yr for comparisons of the low versus usual BP goals and for the comparison of the ramipril and metoprolol groups, and as the average of change of iGFR from baseline to 3 yr for the comparison of the amlodipine group with the other two drug groups. The same two-slope linear mixed-effects model was used to relate the mean eGFR slope to the treatment groups. Comparisons of the iGFR and eGFR slopes were conducted for each phase (acute, chronic, and total) using robust sandwich-type estimates (18) of standard errors for the differences between the corresponding slopes.

Slope-Based Analyses Incorporating Accelerated Decline. To investigate the possibility of nonlinear mean changes in iGFR and eGFR during the chronic phase, we considered two extensions of the basic two-slope model. The first extension included both linear and quadratic fixed-effects terms for each of the six cells of the study design during the chronic phase and is referred to as the quadratic extension of the two-slope model. The second extension was a three-slope spline model in which separate mean slopes were modeled within each treatment group for the first 3 mo (acute phase), months 3 to 24 (early chronic phase), and after 24 mo (late chronic phase). Finally, we also graphically summarized the pattern of mean change over time on the basis of a multislope linear spline model in which separate mean slopes were fit within each treatment group for each interval between scheduled measurements (baseline to 3 mo, 3 to 6 mo, 6 to 12 mo, and successive 6-mo intervals thereafter). As with the basic two-slope model, relevant parameters related to the mean changes of iGFR and eGFR were compared under the extended models using robust sandwich estimates of standard errors (18).

Assessment of Within-Patient Variability

Each of the analyses described above evaluates whether there is a systematic bias in the AASK treatment group comparisons for creatinine–based estimates of GFR compared with iGFR. The relative performance of the different methods for estimating GFR also depends on the precision of the estimates. To evaluate precision, we examined the variability in the measurements of iGFR and eGFR over time within the same patients. For this comparison to be meaningful, it was necessary first to remove from the analysis variations that resulted from the patients’ long-term GFR slopes so that the remaining variability that is analyzed reflects short-term fluctuations that are unlikely to represent true changes in renal function.

The variability of individual measurements of iGFR or of serum creatinine first was evaluated by estimating the within-patient variance components for the individual iGFR or eGFR measurements under the basic two-slope model. The within-patient variance describes the variation within the same patients over time after accounting for long-term systematic changes as reflected in the individual patient’s slopes during the acute and chronic phases. To remove in addition the effects of a gradual change in the rate of decline over time, we also estimated the within-patient variance components under the extended quadratic model. To improve interpretability, we report the within-patient variance components as SD (by taking the square roots of the variance components).

Results

The baseline characteristics of the 1094 randomized AASK patients have been presented elsewhere (10,11). Briefly, the mean (SD) iGFR was 46 ± 13 ml/min per 1.73m², serum creatinine was 2.2 ± 0.8 mg/dl in men and 1.7 ± 0.6 mg/dl in women, age was 55 ± 11 yr, 39% were female. The median (25th and 75th percentiles) 24-h urine protein/creatinine ratio was 0.08 (0.03, 0.36) mg protein/mg creatinine.

Time-to-Event Analysis

Table 1 presents the numbers of patients who reached the composite events G1 (GFR halving, ESRD, or death) and S1 (serum creatinine doubling, ESRD, or death) and G2 (GFR halving or ESRD, excluding deaths) and S2 (serum creatinine doubling or ESRD, excluding deaths) and the associated event rates per patient-year. For all 1094 patients combined, 309 (0.074 per patient-year) reached the composite G2 of a 50% reduction of iGFR or ESRD, compared with 224 (0.051 per patient-year) who reached the corresponding composite S2 of a doubling of serum creatinine or ESRD.

Table 2 presents the relative risks (RR) and 95% confidence intervals for comparisons of the randomized treatment interventions. The results were generally similar between the corresponding iGFR and serum creatinine–based outcomes, and none of the RR for the treatment group comparisons differed significantly between the outcomes S1 and G1 or between S2 and G2 (P > 0.05 in all cases). For the drug group comparisons, the RR were 0.80 for G1 versus 0.76 for S1, ramipril versus metoprolol; 0.92 for G1 versus 0.78 for S1, metoprolol versus amlodipine; and 0.69 for G1 versus 0.62 for S1, ramipril versus amlodipine. For the BP comparison, the RR were 1.05 for G1 versus 0.88 for S1. The same treatment group comparisons were also statistically significant at the 0.05 level for both G1 and S1 (ramipril versus metoprolol and ramipril versus amlodipine but not metoprolol versus amlodipine or low versus usual BP). Figures 1 and 2 indicate similar patterns in the cumulative incidence curves for the comparisons of BP groups and drug groups for S1 as for G1. The RR for the treatment group comparisons were also similar for the composite outcomes G2 and S2 excluding deaths, although the ramipril versus metoprolol comparison did reach statistical significance (P = 0.05) for S2 but not quite for G2 (P = 0.07). With this
minor exception, the conclusions regarding the comparisons of the BP goals or drug groups on the basis of the time-to-event analysis were unchanged irrespective of whether the outcomes were defined by halving of GFR or doubling of serum creatinine.

Slope Analysis under Two-Slope Linear Model

Figures 3 and 4 present the mean changes from baseline in iGFR and eGFR by randomized treatment group. Consistent with the higher rates of events for the outcomes defined by iGFR than serum creatinine, the overall mean (±SE) total slope for all groups combined through 4 yr was slightly steeper for iGFR (−1.92 ± 0.11 ml/min per yr/1.73 m²) than for eGFR (−1.64 ± 0.10 ml/min per yr/1.73 m²; *P* < 0.001 for difference in overall mean total slopes).

Under the two-slope model, each of the four treatment group comparisons produced equivalent results for the total mean slopes (Table 3). The same treatment group comparisons that had significant (*P* < 0.05) differences in mean iGFR slope also had significant differences in eGFR slope (amlodipine versus metoprolol and ramipril versus metoprolol), and the magnitude of the treatment effects was similar and did not differ significantly between iGFR and eGFR.

When the acute and chronic phases are considered separately, iGFR initially increased by a greater amount than eGFR in the amlodipine group compared with each of the other two drug groups during the acute phase (*P* < 0.05 for amlodipine versus ramipril and for amlodipine versus metoprolol). After 3 mo, iGFR tended to decline faster than eGFR in the amlodipine group compared with the ramipril group (*P* = 0.05) and also in the amlodipine group compared with the metoprolol group (*P* = 0.06). As a result, the mean chronic slope was significantly steeper in the amlodipine group compared with both of the other two drug groups for iGFR but not for eGFR. Otherwise, the same treatment group comparisons with significant differences for iGFR also had significant differences for eGFR for the acute and chronic slopes. Because the analysis plan required statistically significant differences in the same direction to conclude a definitive benefit of an intervention, the primary conclusions for the slope-based analyses would have been the same for eGFR as for iGFR despite these differences.

### Table 1. Event outcomes: Number of events (event rate)a

<table>
<thead>
<tr>
<th>BP Goal Drug Group</th>
<th>Low (Usual)</th>
<th>Ramipril</th>
<th>Amlodipine</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% reduction in GFR, ESRD, or death (G1)</td>
<td>196 (0.096)</td>
<td>183 (0.085)</td>
<td>104 (0.071)</td>
<td>62 (0.088)</td>
</tr>
<tr>
<td>Doubling of Scr, ESRD, or death (S1)</td>
<td>147 (0.067)</td>
<td>155 (0.069)</td>
<td>79 (0.052)</td>
<td>51 (0.069)</td>
</tr>
<tr>
<td>50% reduction in GFR or ESRD (G1)</td>
<td>164 (0.080)</td>
<td>145 (0.067)</td>
<td>87 (0.060)</td>
<td>50 (0.071)</td>
</tr>
<tr>
<td>Doubling of Scr or ESRD (S1)</td>
<td>110 (0.050)</td>
<td>114 (0.051)</td>
<td>60 (0.040)</td>
<td>38 (0.052)</td>
</tr>
</tbody>
</table>

a Scr, serum creatinine; iGFR, iothalamate GFR; eGFR, estimated GFR.

### Table 2. Comparison of event outcomes between randomized groupsa

<table>
<thead>
<tr>
<th>Low versus Usual</th>
<th>Ramipril versus Metoprolol</th>
<th>Metoprolol versus Amlodipine</th>
<th>Ramipril versus Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR 95% CI</strong></td>
<td><strong>RR 95% CI</strong></td>
<td><strong>RR 95% CI</strong></td>
<td><strong>RR 95% CI</strong></td>
</tr>
<tr>
<td>50% reduction in GFR, ESRD, or death (G1)</td>
<td>1.05 (0.86–1.29)</td>
<td>0.80b (0.64–0.998)</td>
<td>0.92 (0.68–1.25)</td>
</tr>
<tr>
<td>Doubling Scr, ESRD, or death (S1)</td>
<td>0.88 (0.70–1.10)</td>
<td>0.76b (0.59–0.98)</td>
<td>0.78 (0.55–1.10)</td>
</tr>
<tr>
<td>50% reduction in GFR or ESRD (G2)</td>
<td>1.11 (0.89–1.40)</td>
<td>0.78 (0.59–1.02)</td>
<td>0.76 (0.53–1.09)</td>
</tr>
<tr>
<td>Doubling of Scr or ESRD (S2)</td>
<td>0.90 (0.69–1.18)</td>
<td>0.75b (0.56–0.998)</td>
<td>0.70 (0.47–1.04)</td>
</tr>
</tbody>
</table>

a RR, relative risk; CI, confidence interval.

b *P* < 0.05.
in the acute and chronic phases for the comparisons of amlo-
dipine with the other two treatment groups.

Slope Analyses Considering Nonlinear Changes during the Chronic Phase

Inspection of Figures 3 and 4 suggests that the mean decline may be accelerating for some of the curves over time during the chronic phase. This issue is examined in Table 4. The column labeled “acceleration” summarizes the quadratic term in the extended quadratic model (see Materials and Methods section). This parameter evaluates the mean rate of change (per year) of the slope throughout the chronic phase. In all patients combined (Table 4), the mean iGFR decline accelerated (became more negative) by $-0.28 \pm 0.11 \text{ ml/min per yr/1.73 m}^2$ for each additional year of follow-up. The average rate of acceleration in eGFR decline was $-0.51 \pm 0.09 \text{ ml/min per yr/1.73 m}^2$ for each additional year of follow-up. Thus, the overall mean acceleration was greater for eGFR than for iGFR ($P = 0.02$). The subsequent columns of Table 4 show how this acceleration affects the average slope during months 3 to 24 (early chronic slope) and after month 24 (late chronic slope). The mean iGFR slope changed from $-1.69 \pm 0.20$ in the early chronic phase to $-2.34 \pm 0.16$ in the late chronic phase, whereas the mean eGFR slope almost doubled from $-1.30 \pm 0.18 \text{ ml/min per yr/1.73 m}^2$ during the early chronic phase to $-2.58 \pm 0.14$ during the later chronic phase.

When the BP groups are considered separately, it is apparent that the difference between the acceleration in iGFR and eGFR decline was primarily limited to the low BP group, as both iGFR and eGFR experienced a similar acceleration in their mean rate of decline in the usual BP group, whereas only eGFR had an accelerated decline in the low BP group. Despite this acceleration in decline for iGFR in the usual BP group, the mean iGFR slope still did not differ significantly between the two BP groups even when the analysis is restricted to the later chronic phase after 24 mo (difference in mean late iGFR slope
between low and usual BP goals = 0.92 ± 0.58 ml/min per yr/1.73 m²; P = 0.06). Because of the acute decline in iGFR during the acute phase (see Figure 3), the mean total slope from baseline to 4 yr still slightly favored the usual BP goal (difference in mean total iGFR slope between low and usual BP goals = −0.19 ± 0.22 ml/min per yr/1.73 m²; P = 0.38).

When the drug groups are considered individually, the acceleration in the decline of eGFR was significantly greater than that for iGFR in the metoprolol and ramipril groups but not in the amlodipine group. As a result, the mean eGFR slope after 24 mo was significantly steeper than the iGFR slope after 24 mo for the metoprolol and ramipril groups but significantly less steep than the iGFR slope after 24 mo for the amlodipine group.

Comparison of Residual Variances

If the two-slope model is assumed, then the SD of the differences between the individual eGFR measurements from each patient’s two-slope regression lines were 5.58 ml/min per 1.73 m². This is slightly smaller than the corresponding SD for the individual iGFR measurements of 6.45 ml/min per 1.73 m². Essentially identical SD for differences with the patient regression lines were obtained under the extended model, including both linear and quadratic mean changes during the chronic phase (5.55 ml/min per 1.73 m² for eGFR versus 6.42 for iGFR). The larger SD for the differences of the individual measurements from the patient regression lines for iGFR compared with eGFR indicates a slightly greater degree of longitudinal fluctuations of iGFR.

Discussion

The principal finding of this report is that serum creatinine– and iGFR-based measurements gave similar outcome results in the AASK. Conclusions based on the time-to-event analysis
were similar whether renal function decline was estimated from the halving of iGFR or the doubling of serum creatinine. Some subtle differences between the iGFR and eGFR results were observed for the mean slope and for the acceleration in the mean rate of decline when analyses were conducted specifically for the chronic phase starting 3 mo after randomization. However, there were no significant differences between the iGFR and eGFR results when the treatment effects were evaluated for the change in GFR (or eGFR) over the entire follow-up period, including both the acute and the chronic phases. Thus, estimating changes in renal function using the far less cumbersome and expensive serum creatinine–based measurements yielded the same conclusions about the efficiency of the interventions in the AASK as did the iGFR-based estimates. We previously assessed renal function measurements obtained in 1703 African Americans who had presumed hypertensive nephrosclerosis and were screened for entry into AASK (12). We documented in cross-sectional renal function measurements of this group of screenes that serum creatinine level was an imprecise measure of absolute GFR, with participants with any given serum creatinine having a wide range of absolute GFR (7). This is largely because serum creatinine is not only a function of excretion of creatinine (GFR) but also the production of creatinine that reflects muscle mass and varies with many factors such as age, gender, and race. This resulted in several creatinine-based estimates of GFR incorporating adjustments for some of these parameters. In addition, the excretion of creatinine is affected not just by the GFR but also by the tubular secretion of creatinine that is increased at lower GFR and can be influenced by diet and drugs (19–21). However, in the relatively short-term follow-up of renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change. In renal clinical trials (2 to 5 yr), these factors—muscle mass and tubular secretion of creatinine—are less likely to change.

Table 3. Comparison of AASK treatment effects on mean slope eGFR versus iGFR

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Method for Estimating GFR</th>
<th>Difference in Acute Slopes (ml/min per yr/1.73 m²; SE)</th>
<th>Difference in Chronic Slope (ml/min per yr/1.73 m²; SE)</th>
<th>Difference in Total Slopes (ml/min per yr/1.73 m²; SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine versus</td>
<td>iGFR</td>
<td>5.40 a (0.76)</td>
<td>−0.75 a (0.37)</td>
<td>1.11 a (0.38)</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>3.30 a,b (0.61)</td>
<td>−0.24 (0.35)</td>
<td>0.88 a (0.34)</td>
</tr>
<tr>
<td>Ramipril versus</td>
<td>iGFR</td>
<td>1.49 a (0.60)</td>
<td>0.21 (0.22)</td>
<td>0.57 a (0.23)</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>1.00 a (0.46)</td>
<td>0.26 (0.20)</td>
<td>0.49 a (0.20)</td>
</tr>
<tr>
<td>Amlodipine versus</td>
<td>iGFR</td>
<td>3.93 a (0.79)</td>
<td>−0.45 a (0.37)</td>
<td>0.44 (0.37)</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>2.28 a (0.61)</td>
<td>−0.42 (0.34)</td>
<td>0.37 (0.33)</td>
</tr>
<tr>
<td>Low BP versus</td>
<td>iGFR</td>
<td>−1.91 a (0.54)</td>
<td>0.25 (0.22)</td>
<td>−0.24 (0.22)</td>
</tr>
<tr>
<td>usual BP</td>
<td>eGFR</td>
<td>−1.19 a (0.43)</td>
<td>0.16 (0.20)</td>
<td>−0.15 (0.20)</td>
</tr>
</tbody>
</table>

* Significant difference in mean slopes between treatment groups for indicated outcome (P < 0.05).

* Comparison of mean slopes between treatment groups differs for eGFR versus iGFR (P < 0.05).

Table 4. Mean GFR slope in chronic phase under models for nonlinear change

<table>
<thead>
<tr>
<th>Group</th>
<th>Method for Estimating GFR</th>
<th>Early Chronic Slope (ml/min per yr/1.73 m²)</th>
<th>Late Chronic Slope (ml/min per yr/1.73 m²)</th>
<th>Total Mean Slope from Baseline (ml/min per yr/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean SE P Value</td>
<td>Mean SE</td>
<td>Mean SE</td>
</tr>
<tr>
<td>All</td>
<td>iGFR</td>
<td>−0.28 0.11 0.01</td>
<td>−1.69 0.20</td>
<td>−2.34 0.16</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>−0.51 a 0.09 &lt;0.001</td>
<td>−1.30 a 0.18</td>
<td>−2.58 0.14</td>
</tr>
<tr>
<td>Low BP</td>
<td>iGFR</td>
<td>−0.11 0.15 0.45</td>
<td>−1.85 0.28</td>
<td>−2.03 0.22</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>−0.51 a 0.13 &lt;0.001</td>
<td>−1.23 a 0.25</td>
<td>−2.52 a 0.18</td>
</tr>
<tr>
<td>Usual BP</td>
<td>iGFR</td>
<td>−0.46 0.16 0.004</td>
<td>−1.54 0.28</td>
<td>−2.64 0.24</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>−0.51 0.09 &lt;0.001</td>
<td>−1.30 0.18</td>
<td>−2.58 0.14</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>iGFR</td>
<td>−0.09 0.14 0.49</td>
<td>−1.91 0.29</td>
<td>−2.02 0.22</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>−0.40 a 0.12 0.001</td>
<td>−1.51 0.28</td>
<td>−2.67 a 0.19</td>
</tr>
<tr>
<td>Ramipril</td>
<td>iGFR</td>
<td>−0.33 0.14 0.02</td>
<td>−1.19 0.30</td>
<td>−2.13 0.23</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>−0.64 a 0.12 &lt;0.001</td>
<td>−0.83 0.26</td>
<td>−2.66 a 0.19</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>iGFR</td>
<td>−0.57 0.37 0.12</td>
<td>−2.28 0.54</td>
<td>−3.40 0.53</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>−0.44 0.29 0.13</td>
<td>−1.84 0.44</td>
<td>−2.24 a 0.42</td>
</tr>
</tbody>
</table>

* Indicated parameter differed significantly between eGFR and iGFR (P < 0.05).
than the absolute GFR. In comparing study groups, one seeks to determine whether one group is losing renal function more quickly than another (a faster rate of decline in renal function) or whether one group is having more renal events such as halving of GFR.

Our analysis also indicated that the within-patient variability over time in eGFR on the basis of serum creatinine was slightly smaller than the within-patient variability of iGFR. This suggests that in the context of a clinical trial, one can estimate the change in renal function with serum creatinine–based measurements with a similar or slightly greater precision as one does with 125I-iothalamate–based measurements in a clinical trial. This finding is consistent with the observation that the actual measurement of iGFR has a higher coefficient of variation than the measurement of serum creatinine (22). This has important implications for the future design of similar renal clinical trials. Serum creatinine–based measurements are far less expensive both in personnel time and in reagent cost and far less demanding for the participants.

It is important to recognize that this validation of the use of serum creatinine was provided in the setting of the AASK. The observations in the AASK may be unique to African Americans who had hypertensive nephrosclerosis with renal function in the GFR range enrolled in this trial. These observations may not be generalizable to other patient populations, other kidney diseases, or other levels of renal function. In studies that have a substantially longer duration, have more acutely ill patient populations, or are intended to evaluate factors (e.g., diet) that may affect creatinine independent of GFR, iGFR may prove to yield substantially different results than serum creatinine–based measurements.

When the linearity of the decline in renal function in the AASK over time was examined, we found an acceleration in the mean rate of decline of renal function using both iGFR and eGFR on the basis of serum creatinine. In previous studies in smaller numbers of participants, a linear rate of decline has been reported (23–26). In this large cohort, we found that as renal function declined, the rate of decline of renal function accelerated. Previous reported studies in addition to not including African Americans with hypertensive nephrosclerosis had fewer participants. Patients with hypertensive nephrosclerosis or African Americans may have more rapid progression of their renal disease as their renal function progressively declines.

The mechanism of this apparent acceleration is incompletely understood. The detection of an acceleration in the rate of decline of renal function may reflect that as fewer and fewer nephrons do more and more work, they sclerose or otherwise deteriorate more quickly. As renal function declines, the rate of renal function may accelerate because some other factor or factors associated with lower renal function such as anemia, renal osteodystrophy, or salt and water retention cause further damage to the kidney superimposed on the underlying disease process. Other large renal databases such as the MDRD and Chronic Renal Insufficiency Cohort databases should be examined for this phenomenon.

In conclusion, for renal clinical trials with an average follow-up of up to 4 yr comparing therapeutic interventions similar to those considered in the AASK, serum creatinine–based outcome measurements are likely to yield similar results to 125I-iothalamate–based outcome measurements. Also, by either method of measuring renal function, the rate of decline in renal function accelerates in African Americans with hypertensive nephrosclerosis as their renal function declines.

References