An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function

Frank A. Holtkamp¹, Dick de Zeeuw¹, Merlin C. Thomas², Mark E. Cooper², Pieter A. de Graeff¹, Hans J.L. Hillege³, Hans-Henrik Parving⁴, Barry M. Brenner⁵, Shahnaz Shahinfar⁶ and Hiddo J. Lambers Heerspink¹

¹Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ²Diabetes & Metabolism Division, Baker IDI Heart and Diabetes Research Institute, Melbourne, Victoria, Australia; ³Department of Cardiology/Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands; ⁴Department of Medical Endocrinology, University Hospital of Copenhagen, Copenhagen, Denmark; ⁵Renal Division, Department of Medicine, Brigham and Women’s Hospital, and Harvard School of Medicine, Boston, Massachusetts, USA and ⁶Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Intervention in the renin-angiotensin-aldosterone-system (RAAS) is associated with slowing the progressive loss of renal function. During initiation of therapy, however, there may be an acute fall in glomerular filtration rate (GFR). We tested whether this initial fall in GFR reflects a renal hemodynamic effect and whether this might result in a slower decline in long-term renal function. We performed a post hoc analysis of the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial. Patients assigned to losartan had a significantly greater acute fall in estimated (eGFR) during the first 3 months compared to patients assigned to placebo, but a significantly slower long-term mean decline of eGFR thereafter. A large interindividual difference, however, was noticed in the acute eGFR change. When patients were divided into tertiles of initial fall in eGFR, the long-term eGFR slope calculated from baseline was significantly higher in patients with an initial fall compared to those with an initial rise. When eGFR decline was calculated from 3 months to the final visit, excluding the initial effect, patients with a large initial fall in eGFR had a significant lower long-term eGFR slope compared to those with a moderate fall or rise. This relationship was independent of other risk markers or change in risk markers for progression of renal disease such as blood pressure and albuminuria. Thus, the greater the acute fall in eGFR, during losartan treatment, the slower the rate of long-term eGFR decline. Hence, interpretation of trial results relying on slope-based GFR outcomes should separate the initial drug-induced GFR change from the subsequent long-term effect on GFR.

Diabetic nephropathy is the most common cause of end-stage kidney disease (ESRD). Agents that block the renin-angiotensin-aldosterone-system (RAAS) can prevent the onset and progression of nephropathy, attenuate deterioration of kidney function, and improve survival in patients with diabetes.¹⁻⁴

Data from small-scale studies have suggested that treatment with blood pressure-lowering medication, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs), is associated with an initial fall in glomerular filtration rate (GFR) or increase in serum creatinine levels, most likely resulting from a reduction in intraglomerular pressure.¹⁻² In daily practice, a rise in serum creatinine may inappropriately raise safety concerns that prevent clinicians from using sufficiently high doses of ACE inhibitors or ARBs or from continuing treatment altogether. A systematic review showed that a rise in serum creatinine of up to 30% of baseline levels is no reason for concern, provided serum electrolytes (principally potassium) remain within normal limits.¹⁻⁹ A small-scale study in patients with chronic kidney disease even indicates that the magnitude of initial fall in GFR is inversely related to the long-term slope of GFR decline and is reversible after termination of RAAS blockade.⁹ These data do not only show that the initial fall in GFR is hemodynamic rather than structural, but also suggest that the decline can, in fact, serve as an early marker of subsequent slower decline of long-term renal function obtained from RAAS inhibitor treatment. Evidence from large-scale placebo-controlled trials to support this hypothesis is, however, lacking.

The Reduction in Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin-II Antagonist Losartan
RENAAL trial investigated the effects of the ARB losartan versus placebo. The presence of a baseline period without RAAS inhibitor treatment and the availability of serum creatinine values on baseline and every 3 months during therapy allows us to study the associations between treatment-induced short-term responses in estimated GFR (eGFR) on one hand and its long-term renal function decline on the other.

RESULTS
Course of eGFR in losartan- and placebo-treated individuals
The eGFR course during the RENAAL trial is shown in Figure 1. The fall in eGFR at 3 months after the start of treatment was greater in losartan-treated individuals compared with placebo (2.3 (95% confidence interval (CI) 2.7–1.8) vs 1.6 (2.0–1.1) ml/min per 1.73 m², respectively, $P = 0.031$). The initial fall in eGFR was inversely associated with the long-term eGFR slope, such that the long-term eGFR slope in the losartan group was significantly smaller compared with placebo (−4.2 (95% CI −3.9 to −4.6) vs −5.0 (−4.7 to −5.4) ml/min per 1.73 m² per year; $P<0.001$, respectively).

Predictors of an acute fall in eGFR
The initial change in eGFR in the losartan group showed a wide variability: mean −2.3 ml/min per 1.73 m² (min −18.3; max +14.7). In univariate analysis, urinary albumin/creatinine ratio (UACR) and the month 3 change in UACR showed the strongest associations with the degree of the initial eGFR fall (Table 1). In multivariable analysis, male gender, a higher baseline eGFR, UACR, and diastolic blood pressure, a lower hemoglobin, and a larger month 3 decline in UACR were statistically significantly associated with a larger acute fall in eGFR.

Effect of acute fall in eGFR on long-term renal function decline
To assess whether a more pronounced acute fall in eGFR during losartan therapy was associated with a more stable long-term eGFR course, patients assigned to losartan were stratified in tertiles according to the initial change in eGFR. The baseline characteristics of the losartan participants with available baseline and month 3 eGFR values are shown in Table 2. Patients with a larger acute fall in eGFR had a significantly higher UACR, eGFR, and systolic blood pressure at baseline and had greater reduction in UACR and systolic blood pressure after 3 months compared with those with a moderate fall or rise in eGFR.

In participants allocated to losartan, the mean eGFR at the median time (month 33) was lower in patients with an initial decline compared with those with an initial rise in eGFR (28.7 (95% CI 26.3–31.0) vs 33.0 (30.9–35.2 ml/min per 1.73 m²; $P = 0.007$; Figure 2). In addition, when the eGFR slope was calculated from baseline, eGFR decline was higher in subjects with an initial fall compared with those with an initial rise in eGFR (−5.2 (95% CI −5.8 to −4.7) vs −3.6 (−4.1 to −3.0 ml/min per 1.73 m² per year; $P<0.001$).

A different pattern emerged when the initial eGFR effect was excluded and long-term eGFR decline was calculated from 3 months to the final visit. In unadjusted analyses, patients with a large initial fall in eGFR showed a more stable long-term eGFR course compared with patients with a moderate fall or an increase in initial eGFR (−3.8 (95% CI −4.4 to −3.2) vs −4.1 (−4.7 to −3.6) vs −4.8 (−5.4 to −4.3) ml/min per 1.73 m², respectively, $P = 0.0094$ for tertile 1 vs 3). A multivariable analysis, adjusting for baseline characteristics and response parameters, demonstrated that an initial steeper
fall in eGFR remained statistically significantly associated with a more stable long-term eGFR course (Figure 3). This correlation between the initial eGFR fall and long-term eGFR decline was exclusively observed in losartan-treated patients. No correlation was observed between the acute fall in eGFR and long-term eGFR decline in placebo-treated subjects nor was there any association between an acute fall in eGFR and long-term eGFR slope other than defined by a fall from baseline to month 3. The results of a sensitivity analysis using serum creatinine instead of eGFR were similar to the primary analysis.

Instead of looking at eGFR changes over time, we could also analyze the data on hard outcomes (doubling of serum creatinine or ESRD). When the overall population was divided in tertiles, the rate of renal events was higher in those with an initial fall compared with those with an initial rise in eGFR. However, in patients with an initial fall in eGFR, the rate of renal events was profoundly attenuated in losartan-treated patients compared with placebo. In contrast, in those with an initial rise in eGFR, renal event rate was almost similar between both treatment groups (Table 3).

**DISCUSSION**

In this study we demonstrated that initiation of antihypertensive therapy with an ARB induces an acute fall in eGFR that is inversely correlated with renal function decline during long-term follow-up. Specifically, the greater the acute eGFR fall, the slower the rate of long-term eGFR decline. This relationship is independent of other risk markers or changes in risk markers for progression of renal disease such as blood pressure and albuminuria.

---

**Table 2 | Baseline characteristics of losartan-assigned patients by tertiles of initial change in eGFR**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tertiles of initial change in eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ eGFR (ml/min per 1.73 m²)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>239</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.1 (7.5)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>154 (64.4)</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>41.1 (12)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>153.6 (20)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>82.7 (11)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.8 (0.3)</td>
</tr>
<tr>
<td>UACR (mg/g) (median; IQR)</td>
<td>1525 (587-3417)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>12.4 (1.9)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>232.3 (62)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4 (1.6)</td>
</tr>
<tr>
<td>Diuretic (% n)</td>
<td>142 (59.4)</td>
</tr>
<tr>
<td>β-Blocker (% n)</td>
<td>51 (21.3)</td>
</tr>
<tr>
<td>Calcium antagonist (% n)</td>
<td>172 (72.0)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BP, blood pressure; eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio.

*There were no marked differences in other blood pressure-lowering therapies between losartan-treated subjects during long-term follow-up.

Values are expressed as mean with s.d. UACR and change in UACR is expressed as median with interquartile range (IQR).
The pharmacological effects of RAAS blockers on the GFR course can be best explained by a two-slope model of an acute fall in GFR up to 3 months and an attenuation of the long-term GFR slope until end of treatment. The acute fall in GFR could be of structural origin, because of a treatment-induced reduction in the number of functioning nephrons, or of hemodynamic origin. If the acute GFR fall induced by RAAS blockade is a hemodynamic response, treatment withdrawal should lead to an increase in GFR in the same order of magnitude as the initial fall. Indeed, a couple of studies demonstrated that after withdrawal of antihypertensive therapy, the GFR increased in the majority of patients and correlated with the initial GFR fall. These data support the notion that the initial fall in GFR during RAAS blockade is of hemodynamic and not of structural origin.

The opposite hemodynamic and structural effects on GFR provide an ambiguous picture of the relationship between angiotensin receptor blockade and the rate of renal function decline. The acute reversible hemodynamic effect creates a pattern in which the long-term slope starting several months after randomization differs from the mean slope determined from baseline to study end. Indeed, we observed that within losartan-treated subjects, the long-term renal function slope determined from month 3 differed from the slope assessed from baseline to month 39. It should be remembered that the aim of renoprotective therapies is to delay or prevent changes in renal structural function. Therefore, renoprotective therapies focus on attenuating the long-term structural renal function decline, excluding the early hemodynamic effect. In this respect, losartan-treated subjects with a larger fall in eGFR during the first 3 months had indeed a subsequent slower rate of long-term renal function decline. However, when the eGFR slope was calculated from baseline, eGFR decline was significantly higher in patients with an initial fall compared with those with an initial rise in eGFR. This may be attributed to the large initial hemodynamic effect that may have negated the long-term beneficial effect and obscured the effect on structural renal function. It is tempting to speculate that after a longer follow-up, this becomes apparent in a crossing of the long-term slopes as we also observed for the losartan-placebo comparison. However, the relatively short follow-up period precludes the verification of this possibility. Because of the opposite reversible hemodynamic effects that many drugs and dietary interventions exert, we recommend that clinical trials using GFR-based slopes as outcome should report the slope of (long-term) renal function decline starting several months after randomization and verify the reversibility of the initial (hemodynamic) effect by determining eGFR several months after treatment discontinuation.

Similar opposite short-term and long-term effects of different interventions on GFR decline have been observed in past clinical trials. In the Modification of Diet in Renal Disease (MDRD) study, non-diabetic patients assigned to a low-protein diet had a faster mean decline in GFR during the first 4 months but a slower mean GFR decline thereafter. Because the opposite directions of a low-protein diet on GFR balanced each other, the primary comparison of the MDRD study was judged to be inconclusive.

Apperloo et al. showed in non-diabetic renal patients that patients treated with an ACE inhibitor showed an acute initial fall in GFR. Again this fall was highly variable among the different patients. Those patients with a greater initial fall in GFR had a significant less steep GFR slope during long-term follow-up. A systematic review of 12 randomized (small) clinical trials demonstrated that the acute fall in eGFR or rise in serum creatinine was inversely related with the subsequent rate of renal function decline. The finding of our study substantiates the inverse association within the acute fall and chronic eGFR slope in losartan-treated patients. This study is thus the first large study in diabetes demonstrating the inverse association between initial GFR changes and long-term renal function decline.

The principle analyses were based on eGFR decline over time and not on the available hard renal end points like doubling of serum creatinine or ESRD. Selecting patients based on the initial change in serum creatinine (eGFR) directly influences the doubling of serum creatinine end point. It is therefore of no surprise that if we select those with an initial rise in serum creatinine (fall in eGFR), the renal event rate (doubling of serum creatinine or ESRD) is higher compared with patients with an initial fall in serum creatinine (rise in eGFR). However, if we take this into account and look at the group that has an initial fall in eGFR, we do see that the renal protective effect of losartan compared with placebo is much higher than in the patients who had a rise in eGFR. This indicates that a fall in eGFR on losartan is less worse than on placebo with respect to hard renal outcomes as well.

### Table 3 Renal events (doubling of serum creatinine or ESRD) according to tertiles of initial change in eGFR in losartan- and placebo-allocated patients

<table>
<thead>
<tr>
<th>Mean (s.d.) initial eGFR change (ml/min per 1.73 m²)</th>
<th>Losartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td>Event rate (per 100 patient year)</td>
<td>Events (%)</td>
</tr>
<tr>
<td>−8.3 (2.7)</td>
<td>98 (39.2)</td>
<td>15.6</td>
</tr>
<tr>
<td>−2.1 (1.3)</td>
<td>73 (29.7)</td>
<td>10.8</td>
</tr>
<tr>
<td>+4.6 (4.8)</td>
<td>46 (20.6)</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage kidney disease.

The mean initial eGFR changes in each tertile differ from those presented in Table 2 as the tertiles of initial eGFR change presented in Table 3 were created in the overall population (losartan and placebo groups).
What could be the mechanism for this hemodynamic acute fall in GFR and its relationship with long-term GFR decline? First of all, it could be possible that these effects are caused by a regression to the mean phenomenon. However, the fact that no correlation was observed between the acute fall in eGFR and long-term eGFR decline in the placebo group and the fact that no correlation was observed when the initial change in eGFR was calculated from baseline to month 6 or month 9 in losartan-assigned patients make this assumption less likely. A physiological explanation is that in the presence of diabetes and hypertension, a dysfunction of the autoregulation of the afferent renal artery leads to increased transmission of the systemic blood pressure into the glomerular capillary network. This results in increased intraglomerular pressure and flow and eventually contributes to glomerular sclerosis and proteinuria. Evidence that increased glomerular pressure and flow initiate this injury comes from animal studies demonstrating that reversing these hemodynamic processes, by means of ACE inhibitor treatment or low-protein diet, confer protection against structural damages. In other words, control of intraglomerular pressure, even in the presence of continued systemic hypertension, contribute to the long-term stability of kidney function. RAAS blockade causes efferent renal vasodilation that in turn causes a reduction in intraglomerular pressure, a reduction in filtration fraction, and an acute fall in GFR. Thus, the reduction in intraglomerular pressure may be the link between RAAS blockade-induced acute reductions in GFR and the ability of this therapeutic strategy to delay long-term renal function decline. Furthermore, the variability in response may be reflection of the difference in intraglomerular pressure and/or the difference in the drug effect.

Some limitations need to be addressed when interpreting our findings. This is a post hoc analysis of a large randomized controlled trial. Analyses according to the change in eGFR are no longer randomized; thus, although we adjusted for a range of clinical characteristics between groups, residual confounding cannot be excluded. The results can therefore only be interpreted as hypothesis generating. Second, no data on eGFR slope are available in individual patients before enrollment in the RENAAL trial. Therefore, we are not able to verify that patients with an acute eGFR fall had a less steep slope before initiation of therapy. We were therefore not able to distinguish between patients who respond to therapy compared with those who have progressive renal function loss. It must therefore be emphasized that a fall in eGFR can be the result of treatment or progressive renal function loss. One should therefore always interpret the eGFR fall in the context of other clinical conditions. Finally, we used the MDRD formula to calculate eGFR. It is known that such estimations suffer from both bias and imprecision. Because of this imprecision, our results likely convey an underestimation of the strength of the association between the acute fall in GFR and its correlation with long-term renal function decline.

This study has several clinical implications. First, our data suggest that a fall in eGFR after start of RAAS inhibitor may be an indicator of the responsiveness to therapy instead of a safety issue, in particular in the context when albuminuria and blood pressure are reduced as well. This can be interpreted as an encouragement to continue treatment, as long as other causes contributing to the fall in eGFR, such as renal artery stenosis or diminished arterial blood volume or safety issues such as hyperkalemia, can be excluded. Second, our data have important consequences for the design and interpretation of clinical trials investigating the effects of drugs on GFR course. Calculation of the eGFR slope during antihypertensive treatment is based on the assumption that the slope is constant during follow-up. Our results, demonstrating a two-slope model of an acute hemodynamic eGFR response and a long-term eGFR decline, show that this assumption does not hold true. This highlights our recommendation to analyze and report the initial and long-term eGFR decline separately when determining the effects of antihypertensive agents on renal function. However, reports on the effects of antihypertensive agents on renal function still analyze and report the GFR from baseline to end of study. Interpretation of changes in renal function in such reports is then based on both the hemodynamic and structural effects of the agent and provide a misleading picture of the effect of the antihypertensive agent on structural renal function.

In conclusion, an initial fall in eGFR during ARB treatment is independently inversely associated with less renal function loss during continued treatment. These opposite effects warrant caution in interpreting the results of clinical trials using slope outcomes defined by GFR. We recommend separate reporting of the drug-induced short-term and long-term effect on GFR.

MATERIALS AND METHODS

RENAAL study design

The RENAAL study was a double-blind, randomized, placebo-controlled trial that was designed to evaluate the renoprotective effects of a losartan-based antihypertensive regimen compared with a traditional blood pressure-lowering regimen in patients with type 2 diabetes, hypertension, and nephropathy. The study design, inclusion and exclusion criteria, and results have been reported elsewhere. In brief, participants were considered to have type 2 diabetes if they were >30 years old at the time of diagnosis of diabetes, had no history of ketoacidosis, and did not use insulin therapy within 6 months after diagnosis. A serum creatinine between 1.3 and 3.0 mg/dl (1.5–3.0 mg/dl for males >60 kg), UACR from a first morning specimen of at least 300 mg/g, HbA1c <12%, and age between 31 and 70 years were part of the inclusion criteria. After a 6-week screening phase, patients were randomly assigned to either losartan 50 mg (titrated to 100 mg after 4 weeks) or placebo. Additional antihypertensive medications (calcium channel blockers, β-blockers, centrally acting agents, and diuretics, excluding ACE inhibitors or other ARBs) were permitted during follow-up to reach the blood pressure goal of <140/90 mm Hg (systolic/diastolic). The mean follow-up duration was 3.4 years with a range of 2.3 to 4.6 years. The RENAAL trial was conducted according to the Declaration of Helsinki Principles. All patients signed informed consent. The protocol was approved by all relevant ethics committees.
Study visits, measurements, and outcomes
Participants were seen at a screening visit, randomization visit, at 1 and 3 months after randomization, and subsequently at 3 months intervals. At each visit, serum creatinine and electrolytes were measured. The MDRD equation was used to estimate GFR.22 The dose of losartan was titrated toward the maximum recommended dose of 100 mg at the first month visit. The acute change in eGFR was assessed from baseline to month 3, 2 months after institution of the maximum recommended dose of losartan.21 Renal events were defined as a confirmed doubling in serum creatinine from baseline or ESRD, which was defined as chronic dialysis or renal transplantation. All end points were adjudicated by an independent outcome committee.

Statistical analyses
The difference in short-term and long-term eGFR change between placebo and losartan was calculated from baseline to month 3 and from month 3 to month 39. The difference in long-term eGFR slope between both treatment groups was estimated by a linear mixed effects model with random intercepts and random slopes. As an acute fall in eGFR was only observed in individuals assigned to losartan, we investigated which factors predicted an initial fall in eGFR during losartan therapy. A multivariable model was used for this purpose. The following covariates were included in the model: age, gender, body mass index, log-transformed UACR, systolic and diastolic blood pressure, hemoglobin, total cholesterol, diuretic use at baseline, and change from baseline to month 3 in log-transformed UACR, and systolic and diastolic blood pressure. Baseline characteristics that were statistically significantly associated with an acute fall in eGFR were selected for the multivariable regression model. Baseline characteristics not associated with eGFR decline in univariate analyses were step-wise added to the multivariable model to test their inclusion for statistical significance. Subsequently, we questioned whether those individuals with a more pronounced acute fall in eGFR showed a more stable course during long-term follow-up. Therefore, we compared the long-term eGFR slope for losartan-treated individuals within subgroups (tertiles) of acute fall in eGFR. This approach was aimed at identifying subgroups with identical number of patients to increase the power of the analysis while minimizing the risk of bias. The long-term eGFR slope in each tertile of acute fall in eGFR was estimated by a linear mixed effects model with random intercepts and random slopes. To assess whether the long-term slope correlated with the acute eGFR fall independently of other patient characteristics or response parameters, the initial fall in eGFR was controlled for various covariates including baseline eGFR, diastolic blood pressure, hemoglobin, gender, log-transformed UACR, and month 3 change in log-transformed UACR. In a sensitivity analysis eGFR was replaced for serum creatinine. Means and s.d. are provided for continuous variables, whereas number of patients and percentages are provided for class variables. A two-sided P-value ≤0.05 was used to indicate statistical significance. All analyses were conducted with SAS version 9.1 software (SAS Institute, Cary, NC).

DISCLOSURE
The RENAAL study was funded by Merck. BMB, MEC, DdZ, and H-HP have received financial support from Merck for their participation in the Steering Committee. All the other authors declared no competing interests.

ACKNOWLEDGMENTS
We acknowledge the supportive role of all RENAAL investigators, support staff, and participating patients.

REFERENCES
18. Freedberg DE. To eGFR or not to eGFR: here is an intern’s answer. Kidney Int 2009; 76: 129–130.