Impact of Baseline Renal Function on the Efficacy and Safety of Aliskiren Added to Losartan in Patients With Type 2 Diabetes and Nephropathy

Frederik Persson, md[1]
Julia B. Lewis, md[2]
Edmund J. Lewis, md[3]
Peter Rossing, dmsc[1]

Norman K. Hollenberg, phd[4]
Hans-Henrik Parving, dmsc[5]
for the AVOID Study Investigators*

OBJECTIVE — Proteinuric diabetic patients with reduced glomerular filtration rate (GFR) are at high risk of renal and cardiovascular disease progression and treatment-related adverse events. This post hoc analysis assessed the efficacy and safety of aliskiren added to the maximal recommended dose of losartan according to baseline estimated GFR (eGFR) (stage 1–3 chronic kidney disease [CKD]).

RESEARCH DESIGN AND METHODS — In the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study, 599 hypertensive patients with type 2 diabetes and nephropathy received 6 months of aliskiren (150 mg daily titrated to 300 mg daily after 3 months) or placebo added to 100 mg losartan and optimal antihypertensive therapy. Exclusion criteria included eGFR <30 ml/min per 1.73 m^2 and serum potassium >5.1 mmol/l.

RESULTS — Baseline characteristics were similar between treatment groups in all CKD stages. The antiproteinuric effects of aliskiren were consistent across CKD stages (19, 22, and 18% reduction). In the stage 3 CKD group, baseline serum creatinine levels were equal, but renal dysfunction, prespecified as a postrandomization serum creatinine elevation >176.8 μmol/l (2.0 mg/dl) occurred more frequently in the placebo group (29.2 vs. 13.6%, $P = 0.032$). Serum potassium elevations >5.5 mmol/l (based on a single measurement) were more frequent with aliskiren (22.5 vs. 13.6%) in stage 3 CKD. Adverse event rates were similar between treatments, irrespective of CKD stage.

CONCLUSIONS — Aliskiren added to losartan reduced albuminuria and renal dysfunction and was well tolerated, except for hyperkalemia (stage 3), independent of baseline CKD stage in patients with type 2 diabetes, hypertension, and nephropathy.

Diabetes Care 33:2304–2309, 2010

R enin inhibition is a new treatment modality that blocks the renin-angiotensin-aldosterone system (RAAS) at the first rate-limiting step of the cascade. Because the direct renin inhibitor aliskiren recently was approved for the treatment of hypertension, it seemed a reasonable assumption that this drug would also possess antiproteinuric qualities. In theory, renin inhibition will decrease plasma renin activity and levels of circulating angiotensin I and angiotensin II, leading to more efficient RAAS blockade. A previous study from our group has suggested a higher degree of RAAS blockade by the use of the combination of aliskiren and the angiotensin II receptor blocker irbesartan (1). Whereas this hypothesis was formerly proven only in small studies (1,2), the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study (3) was the first double-blind, randomized controlled trial to demonstrate the antiproteinuric ability of aliskiren (300 mg once daily) as an add-on to standard treatment, including the recommended dose of an angiotensin II receptor blocker (losartan), in patients with type 2 diabetes, hypertension, and nephropathy.

There is an evident unmet need for improved renoprotective therapies because this patient group constitutes the majority of patients requiring dialysis in the western world (4). Reduction in proteinuria from RAAS blockade has been shown to be associated with improved renal and cardiovascular prognosis (5,6), and although its use remains controversial, albuminuria is the best available surrogate marker for renal protection. Combination treatment with renin inhibition and angiotensin II receptor blockade is evolving as a new antiproteinuric treatment, but not much is known about the impact of underlying renal function on the safety and efficacy of this treatment. The aim of this post hoc analysis was to investigate the efficacy and safety of add-on treatment with aliskiren in the AVOID study across different stages of estimated glomerular filtration rate (eGFR) at baseline.

RESEARCH DESIGN AND METHODS — The trial enrolled hypertensive patients, ranging in age from 18 to 85 years, with type 2 diabetes and nephropathy (early morning urinary albumin-to-creatinine ratio [UACR]) >300 mg/g or >200 mg/g in patients receiving blockade of the RAAS). The criteria for exclusion were known nondiabetic kid-

ney disease, UACR >3,500 mg/g, eGFR <30 ml/min per 1.73 m^2 (7), chronic urinary tract infection, serum potassium >5.1 mmol/l at time of randomization, severe hypertension, or major cardiovascular disease within the last 6 months.

In a randomized, double-blind, placebo-controlled study conducted in 15 countries and 150 centers worldwide, we evaluated the possible renoprotective effect of aliskiren in 599 hypertensive patients with type 2 diabetes and nephropathy. The methods have been described in detail in the main publication (3). In brief, we screened 1,892 eligible patients at an enrollment visit. Subsequently 805 patients entered a 3-month open-label period during which all previous drugs that block the RAAS were discontinued, except for β-blockers, and treatment was initiated with the maximal recommended renoprotective dose of losartan (100 mg daily) plus additional antihypertensive therapy aiming for an optimal target blood pressure, i.e., <130/80 mmHg. During the 3-month open-label treatment period, 206 patients were excluded, leaving 599 randomly assigned patients who were followed for a median of 6 months. Patients were randomly assigned to receive aliskiren at a dose of 150 mg once daily for 3 months, followed by aliskiren at 300 mg daily for another 3-month period or matching placebo once daily. The study protocol was in accordance with the Declaration of Helsinki (2002) and was approved by local and central review boards. All patients provided written informed consent.

The patients were examined 13, 12, 8, 4, and 2 weeks before randomization, at randomization, and 1, 4, 8, 11, 12, 16, and 24 weeks after randomization. Blood pressure and pulse, adverse events, concomitant medications, and adherence to medications were assessed at each visit. Three early morning spot urine samples were collected on three sequential days at 13 and 2 weeks before randomization and at 4, 8, 12, 16, and 24 weeks after randomization. Three overnight urine collections were performed on three sequential nights 2 weeks before randomization (baseline) and 12 and 24 weeks after randomization. The urinary albumin concentration was determined by immunoturbidimetry (8) and the serum creatinine concentration by Jaffe reaction (Roche kit) (9). The Modification of Diet in Renal Disease (MDRD) formula was used to estimate the glomerular filtration rate (GFR) (7). A1C was measured by Bio-

Rad high-performance liquid chromatography (10). All of the remaining laboratory variables were also measured centrally by applying conventional laboratory techniques.

Seated blood pressure was assessed by standard mercury sphygmomanometers with an appropriate cuff size after at least 5 min of rest. Three measurements were obtained, 2 min apart at each time point, and the average of the three was used for calculation of the 24-h trough level (24 h postdose). The target blood pressure during the open-label and double-blind period was less than 130/80 mmHg for both groups. Consequently, further adjustments in blood pressure–lowering medication were recommended

after randomization. All classes of blood pressure–lowering drugs were allowed, except for drugs blocking the RAAS.

In this post hoc analysis, we compared the effect of aliskiren versus placebo across the patients according to baseline stage 1–3 of chronic kidney disease (CKD). In these albuminuric type 2 diabetic patients, the stage 1 group is defined as having eGFR ≥90 ml/min per 1.73 m^2, the stage 2 CKD group contains patients with eGFR ≥60–>90 ml/min per 1.73 m^2, and the stage 3 CKD group is defined as having eGFR <60 ml/min per 1.73 m^2.

The primary end point comparing the efficacy of aliskiren treatment versus placebo was the reduction in UACR, based

Table 1—Baseline characteristics of the randomized population according to stage 1–3 CKD

	Aliskiren	Placebo	P value
eGFR <60 ml/min per 1.73 m^2	129	119	
Age (years)	63.1 ± 8.2	65.4 ± 8.5	0.030
Male sex (%)	83 ± 64.3	84 ± 70.6	0.295
Systolic blood pressure (mmHg)	136 ± 12	135 ± 12	0.550
Diastolic blood pressure (mmHg)	77 ± 9	75 ± 9	0.165
UACR (mg/g)	628 (89–3,175)	670 (103–3,393)	0.788
Serum creatinine (μmol/l)	141.1 ± 37.1	146.7 ± 33.3	0.213
eGFR (ml/min per 1.73 m^2)	47.1 (22.8–59.9)	44.7 (24.6–59.7)	0.116
Serum potassium (mmol/l)	4.6 ± 0.54	4.5 ± 0.51	0.436
A1C (%)	8.2 ± 1.5	7.7 ± 1.4	0.004
Medical history (combined cardiovascular disease, %)	32 ± 24.8	26 ± 21.8	0.583
eGFR >60–< 90 ml/min per 1.73 m^2	104	122	
Age (years)	59.8 ± 8.3	60.7 ± 9.2	0.450
Male sex (%)	74 ± 71.2	96 ± 78.7	0.191
Systolic blood pressure (mmHg)	134 ± 11	133 ± 10	0.966
Diastolic blood pressure (mmHg)	78 ± 8	78 ± 8	0.748
UACR (mg/g)	410 (105–2,984)	484 (110–3,097)	0.167
Serum creatinine (μmol/l)	91.5 ± 13.6	94.3 ± 13.9	0.126
eGFR (ml/min per 1.73 m^2)	73.6 (60.8–89.9)	72.4 (60.0–89.7)	0.605
Serum potassium (mmol/l)	4.5 ± 0.49	4.5 ± 0.48	0.297
A1C (%)	7.8 ± 1.3	8.0 ± 1.4	0.320
Medical history (combined cardiovascular disease, %)	20 ± 19.2	24 ± 19.7	0.933
eGFR >90 ml/min per 1.73 m^2	64	51	
Age (years)	53.0 ± 10.7	55.3 ± 9.5	0.232
Male sex (%)	47 ± 73.4	35 ± 68.6	0.571
Systolic blood pressure (mmHg)	135 ± 12	133 ± 13	0.387
Diastolic blood pressure (mmHg)	80 ± 8	78 ± 10	0.422
UACR (mg/g)	530 (103–2,770)	405 (101–3,103)	0.929
Serum creatinine (μmol/l)	69.3 ± 10.6	68.2 ± 10.1	0.570
eGFR (ml/min per 1.73 m^2)	102.5 (90.4–171.2)	100.4 (90.7–155.8)	0.776
Serum potassium (mmol/l)	4.4 ± 0.46	4.4 ± 0.38	0.906
A1C (%)	8.0 ± 1.5	8.1 ± 1.6	0.865
Medical history (combined cardiovascular disease, %)	8 ± 12.5	7 ± 13.7	0.846

Data are *n*, mean ± SD, or median (range). Patients with missing values were not included in the baseline comparison.

on the early morning urine samples, from randomization to week 24, compared across the eGFR subgroups. Secondary efficacy end points were between-treatment comparisons of urinary albumin excretion rate reduction, based on overnight samples, change in eGFR from baseline, and comparison of the proportion of patients with ≥50% reduction in UACR from randomization to week 24.

For evaluation of safety across eGFR subgroups, we compared occurrences of hyperkalemia (single measures of serum potassium >5.5 and >6.0 mmol/l) and investigator-reported incidences of hypotension. In addition, development of renal dysfunction (prespecified as serum creatinine >176.8 μmol/l [2.0 mg/dl]) was investigated.

Statistics

The following subgroups were defined based on baseline renal function: moderate to severe renal dysfunction, eGFR <60 ml/min per 1.73 m^2 (stage 3 CKD), mild renal dysfunction, eGFR ≥60–<90 ml/min per 1.73 m^2 (stage 2 CKD), and no renal dysfunction, eGFR ≥90 ml/min per 1.73 m^2 (stage 1 CKD).

Log-transformed eGFR at week 24 was analyzed using ANCOVA. Subgroup, treatment, subgroup by treatment interaction, region, and baseline proteinuria classification were fitted as factors. Log-transformed baseline eGFR was fitted as a covariate.

For between-treatment comparison of rate of change in eGFR (milliliters per minute per 1.73 m^2) by eGFR subgroup with adjustment for covariates, an ANCOVA model was fitted to the rate of change in eGFR, with baseline UACR, baseline systolic blood pressure, baseline A1C, baseline total cholesterol, and baseline hemoglobin as covariates, with treatment, region, age, sex, and eGFR subgroup as factors and eGFR subgroup by treatment as an interaction term.

For analyses of associations, a linear regression model was fitted to change from baseline in eGFR with change from baseline in log-transformed UACR as an explanatory variable, treatment as a factor, and treatment by change from baseline in log-transformed UACR as an interaction term. The change from baseline in eGFR was also analyzed using linear regression with change from baseline in systolic blood pressure in the model and treatment by change from baseline in systolic blood pressure as the interaction term.
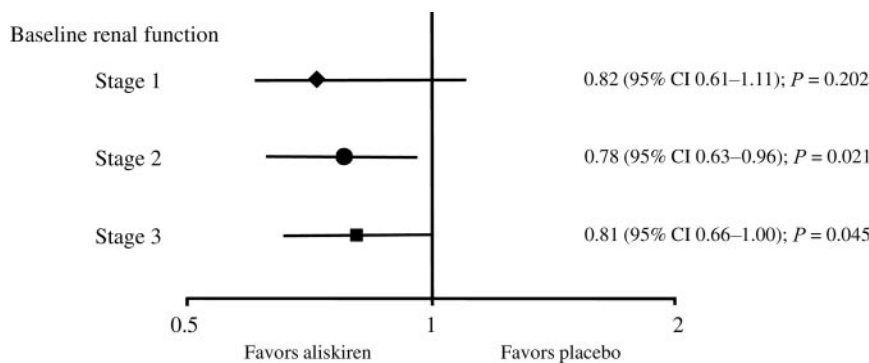

Figure 1—*Difference in UACR after 24 weeks compared with baseline after treatment with aliskiren or placebo as add-on to standard treatment including an optimal dose of the angiotensin II receptor blocker losartan in type 2 diabetic patients with albuminuria. Groups according to baseline CKD stage.*

RESULTS — Patient characteristics in the three eGFR groups at baseline can be seen in Table 1. The two treatment groups were similar in all eGFR subgroups, except for a difference in age and in baseline A1C in the CKD stage 3 group. However, this imbalance did not have an impact in the subsequent statistical analysis. We found a consistent UACR reduction in the aliskiren treatment groups, with a 19% (95% CI 34−0) reduction in the stage 3 CKD group (*P* = 0.045), a 22% (34−4) reduction in the stage 2 CKD group (*P* = 0.021), and an 18% (39 to −11) reduction compared with placebo (*P* = 0.202) in the stage 1 CKD group (Fig. 1).

Table 2—*End points*

	Aliskiren	Placebo	*P* value
eGFR <60 ml/min per 1.73 m^2	128	118	
UACR change at 24 weeks (%)	−9 (−21 to 6)	13 (−3 to 31)	0.045
UACR reduction ≥50 (%)	25/122 (20.2)	11/115 (9.6)	0.019
Change in eGFR (ml/min per 1.73 m^2) per 6 months	−1.7 (−6.2 to 2.9)	0.25 (−4.5 to 5.0)	0.552
Serum creatinine elevation >176.8 μmol/l*	15/110 (13.6)	28/96 (29.2)	0.032
Blood pressure change SBP/DBP (mmHg)	2.4 (1.3)/−1.0 (0.7)	4.7 (1.3)/0.6 (0.8)	0.166/0.094
eGFR >60–<90 ml/min per 1.73 m^2	104	122	
UACR change at 24 weeks (%)	−23 (−34 to −10)	−1 (−14 to 15)	0.021
UACR reduction ≥50 (%)	28/101 (27.7)	17/118 (14.4)	0.012
Change in eGFR (ml/min per 1.73 m^2) per 6 months	−2.7 (−7.6 to 2.3)	−4.8 (−9.3 to −0.2)	0.536
Serum creatinine elevation >176.8 μmol/l*	1 (1.0)	3 (2.5)	0.627
Blood pressure change SBP/DBP (mmHg)	0.7 (1.4)/0.3 (0.8)	1.8 (1.3)/0.5 (0.8)	0.547/0.843
eGFR >90 ml/min per 1.73 m^2	63	51	
UACR change at 24 weeks (%)	−27 (−40 to −10)	−11 (−29 to 12)	0.202
UACR reduction ≥50 (%)	18/62 (29.0)	8/50 (16.0)	0.132
Change in eGFR (ml/min per 1.73 m^2) per 6 months	−5.6 (−11.8 to 0.66)	−9.5 (−16.5 to −2.5)	0.410
Serum creatinine elevation >176.8 μmol/l*	0	0	NA
Blood pressure change SBP/DBP (mmHg)	−1.4 (1.8)/−0.6 (1.0)	0.9 (1.9)/1.2 (1.1)	0.352/0.218

Data are *n*, mean (SD), or median (range). Patients with missing values were not included in the analysis. DBP, diastolic blood pressure; NA, not applicable; SBP, systolic blood pressure. *Development of serum creatinine >176.8 μmol/l after randomization.

The proportions of patients achieving ≥50% reduction in UACR were consistently higher in the aliskiren-treated patients, reaching 29.0, 27.7, and 20.5% in stages 1, 2, and 3, respectively, compared with 16.0, 14.4, and 9.6% in the corresponding placebo groups (between-treatment differences $P = 0.132$, $P = 0.012$, and $P = 0.019$, respectively) (Table 2).

The changes in eGFR over the 6-month duration of the study can be seen in Table 2. Notably, there were no statistically significant differences between treatments in changes in eGFR, but in the stage 1 group the change in eGFR in the aliskiren group was -5.6 (-11.8 to 0.66) ml/min per 6 months, numerically lower than that in the placebo group, changing -9.5 (-16.5 to -2.5) ml/min per 6 months. Adjustment of the changes in eGFR for clinical covariates in the ANCOVA model did not significantly alter the results. Overall, a reduction in systolic blood pressure was associated with a change in eGFR in both treatment groups, and (although not significant) the tendency remained in the eGFR subgroups, except in the placebo group in the eGFR >90 ml/min per 1.73 m^2 subgroup (data not shown).

Adverse event rates were highest in the stage 3 CKD group (68.1–72.9%) and lowest in the stage 1 CKD group (59.4–60.8%); there were no notable differences between treatments in any subgroup (Table 3). In the stage 3 CKD group, hyperkalemia, based on a single measurement of serum potassium >5.5 mmol/l, was more frequent in the aliskiren-treated patients (22.5%) compared with that in the placebo group (13.6%), although this value was not statistically significant ($P = 0.07$). There were no differences between the other treatment groups (Table 3). Severe hyperkalemia (serum potassium >6.0 mmol/l) in the stage 3 group was registered in 11 aliskiren-treated patients (8.5%) compared with 4 placebo-treated patients (3.4%) ($P = 0.113$). However, 9 of the 11 aliskiren-treated patients displayed serum potassium levels >5.1 mmol/l at baseline and should have been excluded from randomization according to the study protocol. Four of these patients left the study shortly after randomization.

Symptoms of hypotension (investigator defined) were not a frequent adverse event, with no differences between treatments in any eGFR subgroup (Table 3).

In the stage 3 CKD group there was a significant difference in development of renal dysfunction (prespecified as development of serum creatinine >176.8 μmol/l after randomization) during the course of the study (excluding patients who already had serum creatinine >176.8 μmol/l at the time of randomization). In the placebo-treated group, 29.2% developed renal dysfunction compared with 13.6% in the aliskiren group ($P = 0.032$) (Table 3).

CONCLUSIONS — In this post hoc analysis of the results of the AVOID study, we demonstrate that the reduction in UACR from add-on aliskiren treatment was independent of baseline renal function, and, thus, aliskiren can be of added benefit to standard treatment (including the optimal dose of the angiotensin receptor blocker losartan) in patients with stage 1–3 CKD. In addition, the proportion of aliskiren-treated patients achieving a 50% reduction in UACR was similar in all three stages, approximately twice the proportion of placebo-treated patients. There were no significant differences in systolic or diastolic blood pressure change from baseline in any eGFR subgroup, but overall the reduction in systolic blood pressure was associated with a reduction in eGFR in both aliskiren- and placebo-treated groups.

From a safety point of view, we found that hyperkalemia, based on a single measurement of serum potassium, was more common in aliskiren-treated patients with stage 3 CKD. This result represents a side effect to this therapy that must be considered, given the above-noted benefit. It is possible that more frequent serum potassium control and concomitant use of loop diuretics in these patients would ameliorate this. We were not able to investigate in detail the influence of other concomitant medications on the levels of potassium, but the use of potassium-sparing diuretics and ACE inhibitors was not allowed in the study. Severe hyperkalemia, defined as a single serum potassium result >6.0 mmol/l, was also more common in stage 3 CKD; however, 9 of the 11 aliskiren-treated patients in stage 3 CKD with severe hyperkalemia were randomly assigned despite violating the exclusion limit of serum potassium >5.1 mmol/l stated in the study protocol.

Importantly, however, we also found that aliskiren-treated patients with stage 3 CKD had a lower incidence of development of renal dysfunction, underlining the improved renal prognosis in these patients, provided that other safety measures are taken into consideration. Of note, in the overall study population there was a low incidence of death or acute re-

Table 3—*Adverse events according to stage 1–3 CKD*

	Aliskiren	Placebo	P value
eGFR <60 ml/min per 1.73 m^2	129	119	
Serum potassium >6.0 mmol/l	11 ± 8.5	4 ± 3.4	0.113
Serum potassium >5.5 mmol/l	29 ± 22.5	16 ± 13.6	0.070
Any adverse event	94 ± 72.9	81 ± 68.1	0.407
Any serious adverse event	12 ± 9.3	11 ± 9.2	0.987
Discontinuations due to an adverse event	10 ± 7.8	7 ± 5.9	0.561
Hypotension	5 ± 3.9	1 ± 0.8	0.215
eGFR >60–<90 ml/min per 1.73 m^2	104	122	
Serum potassium >6.0 mmol/l	3 ± 2.9	1 ± 0.8	0.336
Serum potassium >5.5 mmol/l	10 ± 9.6	14 ± 11.5	0.651
Any adverse event	67 ± 64.4	83 ± 68.0	0.567
Any serious adverse event	13 ± 12.5	10 ± 8.2	0.286
Discontinuations due to an adverse event	7 ± 6.7	7 ± 5.7	0.758
Hypotension	5 ± 4.8	1 ± 0.8	0.097
eGFR >90 ml/min per 1.73 m^2	64	51	
Serum potassium >6.0 mmol/l	0	0	NA
Serum potassium >5.5 mmol/l	2 ± 3.2	2 ± 3.9	1.000
Any adverse event	38 ± 59.4	31 ± 60.8	0.878
Any serious adverse event	2 ± 3.1	6 ± 11.8	0.136
Discontinuations due to an adverse event	0	5 ± 9.8	0.015
Hypotension	2 ± 3.1	0	0.502

Data are *n* or mean ± SD. Patients with missing values were not included in the analysis. NA, not applicable.

nal failure, with no significant difference between the groups (0.7% in both groups).

Despite the differences in overall rates of renal dysfunction (new development of serum creatinine >176.8 μmol/l/2.0 mg/dl), ΔeGFR in the two treatment groups in patients with stage 3 CKD did not differ significantly. When ΔGFR is small, with a substantial portion of patients having no detectable eGFR decline, a time-to-event analysis has greater statistical power to detect a treatment effect than a slope-based effect (11). The Ramipril in Non-Diabetic Renal Failure (REIN) and MDRD studies support the validity of this analysis in nondiabetic nephropathies (12,13).

The efficacy and safety of aliskiren treatment has been assessed in a few studies. In a short-term double-blind crossover study (1), we investigated aliskiren treatment compared with and in combination with irbesartan in patients with type 2 diabetes and albuminuria, with baseline levels of GFR as low as 40 ml/min per 1.73 m^2. We found no sign of reduced efficacy or safety of the drug in patients with impaired renal function. In a pharmacokinetic study of 17 men with mild, moderate, or severe renal impairment (creatinine clearance 50–80, 30–49, and <30 ml/min, respectively) and matched control subjects, aliskiren was found to be well tolerated when administered alone or with irbesartan (14).

A study of healthy people consuming a low-sodium diet has shown that renal vasodilation with aliskiren far exceeds that seen with ACE inhibitors and angiotensin II receptor blockers (15). The increase in renal plasma flow may be a response to AT_1 receptor-dependent reduction of the vascular tone in the efferent arteriole. These results indicate that aliskiren may provide greater and thus more effective blockade of the renin system in the kidney. Because the activity of the renin-angiotensin system is enhanced in patients with diabetes, compared with that in control subjects (16), a more pronounced difference in renal vasodilatation may be expected during aliskiren therapy. Studies in patients with uncomplicated type 1 diabetes consuming a normal salt diet have demonstrated that aliskiren enhances renal plasma flow and GFR, independent of glycemic control (17). Both studies (15,17) found a reduction in filtration fraction and a GFR dependency of renal plasma flow, supporting the presence of a filtration pressure equilibrium in humans (i.e., filtration stops along the glomerular capillaries as oncotic pressure equals hydrostatic pressure). It is suggested that with an increase in renal plasma flow there is a shift to the right of this equilibrium, leading to a greater surface area available for filtration, as filtration stops at a later point. The concomitant decrease in intraglomerular pressure will lead to a reduction in albuminuria.

The change in eGFR from baseline to 6 months was more pronounced in patients with well-preserved kidney function (stage 1 and 2 CKD) compared with reduced eGFR (stage 3 CKD). Hyperfiltration and regression to the mean may contribute to these findings. Observational studies (18) and treatment trials applying completely different interventions have resulted in similar findings in proteinuric type 2 diabetic patients (D. de Zeeuw, personal communication).

When the results of our analysis are interpreted, the post hoc nature of the analysis must be taken into consideration. Statistical comparisons were made without adjustment for multiple testing, but all analyses were prespecified and results were consistent between groups. It must be remembered that the reported changes in eGFR were recorded over only 6 months. Optimally, studies of at least 2 years duration are needed to properly assess changes in eGFR in relation to outcome. This will be possible, along with assessment of the effect of renin inhibition on cardiorenal hard end points, in the ongoing Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study (19). In addition, we were not able to assess the effect of treatment in patients with stage 4 and 5 CKD, as such patients were not included in the AVOID study owing to safety concerns.

In summary, aliskiren as add-on treatment to standard therapy including the optimal dose of the angiotensin II receptor blocker losartan, in the AVOID study, reduced albuminuria and slowed development of renal dysfunction more than placebo across different levels of eGFR in patients with type 2 diabetes, hypertension, and nephropathy. Hyperkalemia is more frequent in the aliskiren-treated patients with stage 3 CKD.

References
1. Persson F, Rossing P, Reinhard H, Juhl T, Stehouwer CD, Schalkwijk C, Danser AH, Boomsma F, Frandsen E, Parving HH. Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. Diabetes Care 2009;32: 1873–1879
2. Persson F, Rossing P, Schjoedt KJ, Juhl T, Tarnow L, Stehouwer CD, Schalkwijk C, Boomsma F, Frandsen E, Parving HH: Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. Kidney Int 2008;73:1419–1425
3. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;358: 2433–2446
4. National Institute of Diabetes and Digestive and Kidney Diseases. *United States Renal Data System: USRDS 2008 Annual Data Report*. Bethesda, MD, National Institutes of Health, 2009
5. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 2004;65:2309–2320
6. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation 2004;110:921–927
7. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration

rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470

8. Multizentrische Erprobung von Tina-quant-Albumin im Urin und ß-N-Acetyl-glucosaminidase (ß-NAG) im Urin. Wien Klin Wochenschr 1991;Suppl. 189:1–66

9. Bartels H, Böhmer M, Heierli C. Serum creatinine determination without protein precipitation. Clin Chim Acta 1972;37: 193–197 [in German]

10. Rohlfing CL, Little RR, Wiedmeyer HM, England JD, Madsen R, Harris MI, Flegal KM, Eberhardt MS, Goldstein DE. Use of GHb (HbA$_{1c}$) in screening for undiagnosed diabetes in the U.S. population. Diabetes Care 2000;23:187–191

11. Greene T, Lau J, Levey AS: Interpretation of clinical studies of renal disease. In *Immunological Renal Diseases.* Neilson EG, Couser WG, eds. Philadelphia, Lippincott-Raven, 1997, p. 887–911

12. Levey AS, Greene T, Beck GJ, Caggiula AW, Kusek JW, Hunsicker LG, Klahr S. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. J Am Soc Nephrol 1999;10:2426–2439

13. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP, Remuzzi G. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999;354:359–364

14. Vaidyanathan S, Bigler H, Yeh C, Bizot MN, Dieterich HA, Howard D, Dole WP. Pharmacokinetics of the oral direct renin inhibitor aliskiren alone and in combination with irbesartan in renal impairment. Clin Pharmacokinet 2007;46:661–675

15. Hollenberg NK. Direct renin inhibition and the kidney. Nat Rev Nephrol 2010;6: 49–55

16. Hollenberg NK, Price DA, Fisher ND, Lansang MC, Perkins B, Gordon MS, Williams GH, Laffel LM. Glomerular hemodynamics and the renin-angiotensin system in patients with type 1 diabetes mellitus. Kidney Int 2003;63:172–178

17. Cherney DZ, Lai V, Scholey JW, Miller JA, Zinman B, Reich HN. The effect of direct renin inhibition on renal hemodynamic function, arterial stiffness and endothelial function in humans with uncomplicated type 1 diabetes mellitus: a pilot study. Diabetes Care 2010;33:361–365

18. Rossing K, Christensen PK, Hovind P, Tarnow L, Rossing P, Parving HH. Progression of nephropathy in type 2 diabetic patients. Kidney Int 2004;66: 1596–1605

19. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Ghadanfar M, Weissbach N, Xiang Z, Armbrecht J, Pfeffer MA. Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design. Nephrol Dial Transplant 2009;24:1663–1671