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Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

Hans-Henrik Parving, M.D., D.M.Sc., Frederik Persson, M.D., Julia B. Lewis, M.D., Edmund J. Lewis, M.D.,
and Norman K. Hollenberg, M.D., Ph.D., for the AVOID Study Investigators*

ABSTRACT

BACKGROUND

Diabetic nephropathy is the leading cause of end-stage renal disease in developed countries. We evaluated the renoprotective effects of dual blockade of the renin–angiotensin–aldosterone system by adding treatment with aliskiren, an oral direct renin inhibitor, to treatment with the maximal recommended dose of losartan (100 mg daily) and optimal antihypertensive therapy in patients who had hypertension and type 2 diabetes with nephropathy.

METHODS

We enrolled 599 patients in this multinational, randomized, double-blind study. After a 3-month, open-label, run-in period during which patients received 100 mg of losartan daily, patients were randomly assigned to receive 6 months of treatment with aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months) or placebo, in addition to losartan. The primary outcome was a reduction in the ratio of albumin to creatinine, as measured in an early-morning urine sample, at 6 months.

RESULTS

The baseline characteristics of the two groups were similar. Treatment with 300 mg of aliskiren daily, as compared with placebo, reduced the mean urinary albumin-to-creatinine ratio by 20% (95% confidence interval, 9 to 30; $P < 0.001$), with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared with 12.5% of those who received placebo ($P < 0.001$). A small difference in blood pressure was seen between the treatment groups by the end of the study period (systolic, 2 mm Hg lower [$P = 0.07$] and diastolic, 1 mm Hg lower [$P = 0.08$] in the aliskiren group). The total numbers of adverse and serious adverse events were similar in the groups.

CONCLUSIONS

Aliskiren may have renoprotective effects that are independent of its blood-pressure–lowering effect in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended renoprotective treatment. (ClinicalTrials.gov number, NCT00097955.)

From the Department of Medical Endocrinology, Rigshospitalet, Copenhagen (H.-H.P.); the Faculty of Health Science, Aarhus University, Aarhus, Denmark (H.-H.P.); Steno Diabetes Center, Gentofte, Denmark (F.P.); Vanderbilt University School of Medicine, Nashville (J.B.L.); Rush University Medical Center, Chicago (E.J.L.); and Brigham and Women's Hospital and Harvard Medical School, Boston (N.K.H.). Address reprint requests to Dr. Parving at the Department of Medical Endocrinology, Rigshospitalet, University Hospital of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark, or at hparving@dadlnet.dk.

*The investigators who participated in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study are listed in the Appendix.

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THE PATHOGENESIS OF DIABETIC NEPHROPATHY is multifactorial, and the renin–angiotensin–aldosterone system plays an important role.^{1,2} Persistent proteinuria is the hallmark of diabetic nephropathy, a condition that is characterized by a progressive rise in blood pressure, a declining glomerular filtration rate, and a high risk of fatal or nonfatal cardiovascular events. The degree of proteinuria is closely associated with the rates of renal and cardiovascular events.^{3,4} Furthermore, a reduction in proteinuria is associated with a slowing of both the decline in the glomerular filtration rate⁵ and the progression to end-stage renal disease.⁶ In addition, decreasing proteinuria is associated with improved cardiovascular outcomes in patients with diabetic nephropathy⁷ and arterial hypertension.⁸ As a result, a reduction in proteinuria has been widely used as a surrogate end point for renoprotection.

During the past two decades, the outlook for patients with diabetes who have microalbuminuria or macroalbuminuria has improved, probably owing to early aggressive lowering of blood pressure and blocking of the renin–angiotensin–aldosterone system.^{3,4,9–12} However, there is still a large, unmet need to develop strategies for the prevention of diabetic nephropathy and its progression to end-stage renal disease. Diabetic nephropathy remains the leading cause of end-stage renal disease in the developed world.

The aim of this trial was to evaluate the potential renoprotective capacity of direct renin inhibition with aliskiren in patients with hypertension, type 2 diabetes, and proteinuria who were already receiving the maximal recommended renoprotective treatment with losartan (100 mg daily) and optimal treatment for hypertension. In addition, the safety of dual blockade of the renin–angiotensin–aldosterone system was monitored and recorded.

METHODS

PATIENTS

We enrolled patients with hypertension who were 18 to 85 years of age and who had type 2 diabetes and nephropathy (defined by an early-morning urinary albumin-to-creatinine ratio of >300 mg per gram, or >200 mg per gram in patients receiving therapy targeted at blockade of the renin–angiotensin–aldosterone system). The criteria for exclusion were known nondiabetic kidney disease, a urinary albumin-to-creatinine ratio of more

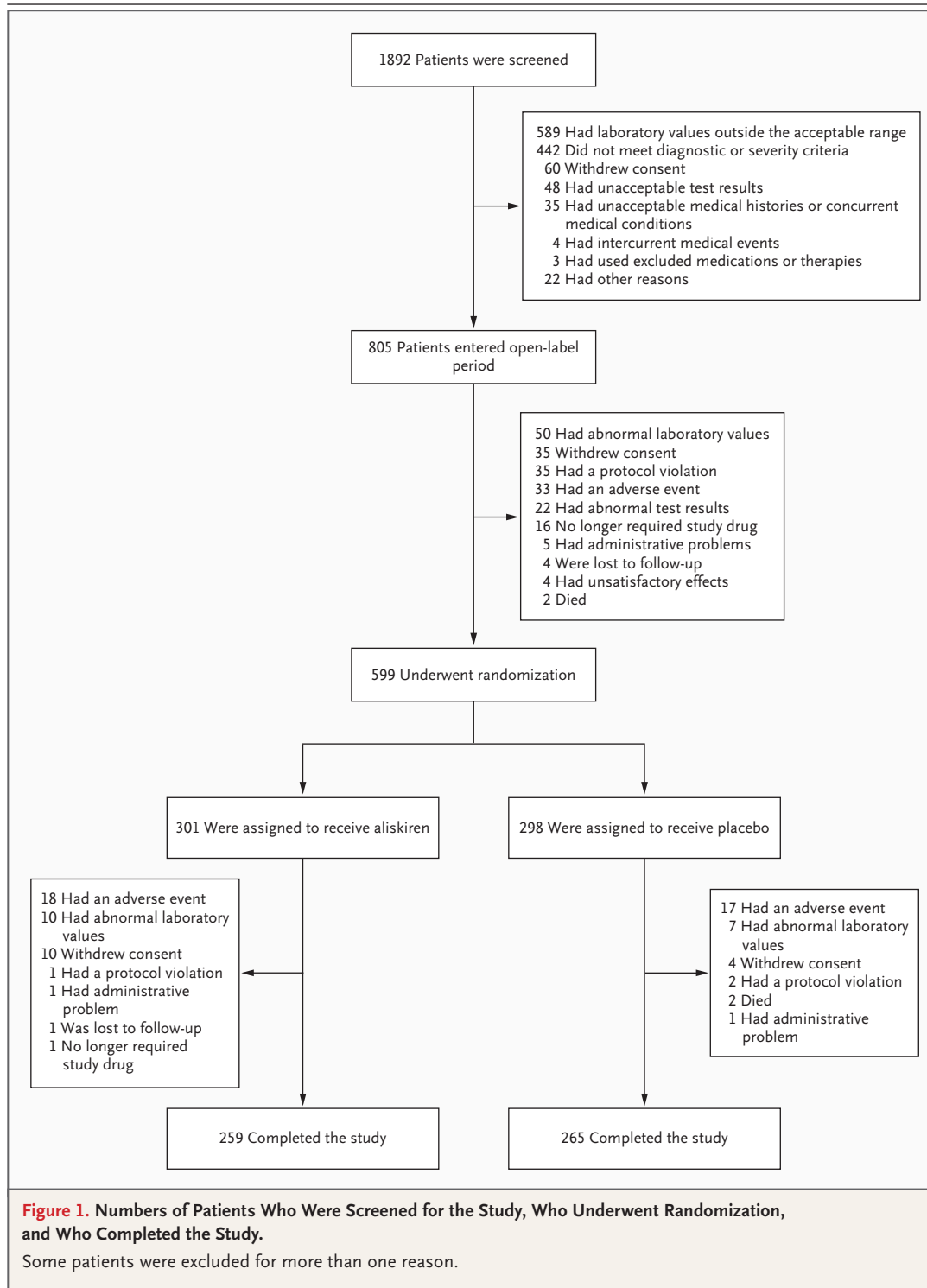
than 3500 mg per gram, an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m² of body-surface area,¹³ chronic urinary-tract infection, a serum potassium level greater than 5.1 mmol per liter at the time of randomization, severe hypertension, or major cardiovascular disease within the previous 6 months.

STUDY DESIGN

In a randomized, double-blind, placebo-controlled study that was conducted in 15 countries and 150 centers worldwide, we evaluated the possible renoprotective effect of aliskiren in 599 patients with hypertension, type 2 diabetes, and nephropathy. We screened 1892 eligible patients at an enrollment visit (Fig. 1). A total of 805 patients entered a 3-month open-label period during which all drugs that the patients had been taking that block the renin–angiotensin–aldosterone system were discontinued, except for beta-blockers, and treatment was initiated with the maximal recommended renoprotective dose of losartan (100 mg daily) plus additional antihypertensive therapy that was aimed at achieving an optimal target blood pressure (i.e., <130/80 mm Hg). During the 3-month open-label treatment period, 206 patients were excluded, leaving 599 patients who underwent randomization and were followed for a median of 6 months (Fig. 1). Patients were randomly assigned to receive 150 mg of aliskiren once daily for 3 months, followed by 300 mg of aliskiren daily for another 3-month period, or matching placebo once daily for 6 months. The randomization list was generated by a validated system that automated the random assignment of treatment groups to randomization numbers. 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 study was overseen by a steering committee that included nonvoting members from the sponsor, Novartis. The steering committee oversaw the design of the study, the conduct of the trial, and the management and analysis of all data. The sponsor was also involved in the design of the study and in the collection and analysis of the data. All authors had access to all study data and vouch for the accuracy and completeness of the data reported.

PROCEDURES, MEASUREMENTS, AND OUTCOME

The patients were examined 13, 12, 8, 4, and 2 weeks before randomization; at the time of ran-



domization; and 1, 4, 8, 11, 12, 16, and 24 weeks after randomization. To account for the delay in obtaining results of laboratory tests, the baseline urinary albumin-to-creatinine ratio, which was based on the median values in three early-morn-

ing urine collections, was calculated 2 weeks before randomization. Blood pressure and pulse, adverse events, concomitant medications, and adherence to medication regimens were assessed at each visit. Three early-morning spot urine speci-

Table 1. Baseline Characteristics of the Randomized Population.*			
Characteristic	Aliskiren Group (N=301)	Placebo Group (N=298)	P Value
Demographic			
Age — yr	59.8±9.6	61.8±9.6	0.009
Male sex — no. (%)	206 (68.4)	221 (74.2)	0.11
Race — no. (%)†			0.39
White	259 (86.0)	261 (87.6)	
Black	24 (8.0)	26 (8.7)	
Asian	5 (1.7)	6 (2.0)	
Other	13 (4.3)	5 (1.7)	
Clinical			
Body-mass index‡	33±7	32±6	0.08
Known duration of diabetes — yr	13.2±8.4	14.9±8.7	0.02
Mean sitting blood pressure — mm Hg			
Systolic	135±12	134±12	0.38
Diastolic	78±8	77±9	0.18
Medical history — no. (%)			
Angina pectoris	24 (8.0)	20 (6.7)	0.55
Coronary artery disease	24 (8.0)	25 (8.4)	0.85
Myocardial infarction	19 (6.3)	15 (5.0)	0.50
Stroke	9 (3.0)	12 (4.0)	0.49
Diabetic neuropathy	55 (18.3)	49 (16.4)	0.56
Diabetic retinopathy	65 (21.6)	82 (27.5)	0.09
Dyslipidemia	74 (24.6)	72 (24.2)	0.90
Current smoking	61 (20.3)	53 (17.8)	0.48
Urinary albumin-to-creatinine ratio§	513 (463–569)	553 (502–609)	0.29
Urinary albumin excretion rate — µg/min¶	495 (440–557)	520 (469–576)	0.52
Serum creatinine — mg/dl¶¶			
Men	1.3±0.5	1.3±0.4	0.62
Women	1.1±0.4	1.1±0.4	0.28
Estimated glomerular filtration rate — ml/min/1.73 m²¶¶	68.5±25.7	66.8±24.5	0.41
Hemoglobin — g/liter	135.4±17.8	133.6±15.8	0.55
Glycated hemoglobin — %	8.0±1.4	7.9±1.4	0.16
Triglycerides — mg/dl	203.5±156.6	177.0±144.2	0.42
Cholesterol — mg/dl			
Total	181.5±43.6	177.6±44.8	0.88
Low-density lipoprotein	104.2±36.3	104.2±36.7	0.77
High-density lipoprotein	42.5±11.6	42.5±12.4	0.60
Serum potassium — mmol/liter	4.5±0.5	4.5±0.5	0.88
Glucose-lowering therapies — no. (%)			
Insulin and insulin analogues	162 (53.8)	158 (53.0)	0.84
Biguanides	145 (48.2)	141 (47.3)	0.83
Sulfonylureas	113 (37.5)	119 (39.9)	0.55
Thiazolidinediones	33 (11.0)	38 (12.8)	0.50

Table 1. (Continued.)

Characteristic	Aliskiren Group (N=301)	Placebo Group (N=298)	P Value
Lipid-lowering therapies — no. (%)			
Statins	169 (56.1)	169 (56.7)	0.89
Fibrates	24 (8.0)	22 (7.4)	0.79
Aspirin — no. (%)	122 (40.5)	123 (41.3)	0.85

* Plus-minus values are means \pm SD. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259.

† Race was determined by investigator report.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Values are geometric means, with 95% confidence intervals in parentheses.

¶ Data are for 205 men in the aliskiren group and 221 men in the placebo group and for 95 women in the aliskiren group and 77 women in the placebo group.

|| The glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease (MDRD) formula.

mens were collected on 3 sequential days 13 weeks and 2 weeks before randomization and 4, 8, 12, 16, and 24 weeks after randomization. Three overnight urine specimens were obtained on 3 sequential nights 2 weeks before randomization (baseline) and 12 and 24 weeks after randomization. All assessments of urine and blood were performed by the same company (CRL.Medinet) in a central laboratory in Europe or the United States. The urinary albumin concentration was determined by immunoturbidimetry,¹⁴ and the serum creatinine concentration was determined by means of the Jaffe reaction (with the use of a Roche kit).¹⁵ The Modification of Diet in Renal Disease (or MDRD) formula was used to estimate the glomerular filtration rate.¹³ Glycated hemoglobin was measured by means of high-performance liquid chromatography (Bio-Rad).¹⁶ All the other laboratory variables were also measured centrally with the use of conventional laboratory techniques.

Blood pressure, measured while the patient was seated, was assessed after at least 5 minutes of rest with the use of standard mercury sphygmomanometers and an appropriately sized cuff. Three measurements were obtained, 2 minutes apart at each time point, and the average of the three was used for the calculation of the 24-hour trough level (i.e., the level 24 hours after administration of the drug). The target blood pressure during the open-label and double-blind periods was less than 130/80 mm Hg for both groups. Consequently, further adjustments, as needed, in the dosing of blood-pressure-lowering medication were recommended after random assignment to bring the patient's blood pressure closer to the target. All

classes of blood-pressure-lowering drugs were allowed, except for drugs that block the renin-angiotensin-aldosterone system. Patients continued to receive their usual care for diabetes and cardiovascular protection (Table 1). No restriction on dietary salt or protein was mandated. The primary efficacy measure was the percentage reduction in the early-morning urinary albumin-to-creatinine ratio from baseline to the end of the study (24 weeks) among patients who received aliskiren, as compared with patients who received placebo.

STATISTICAL ANALYSIS

Our target sample size for patients completing the study was approximately 396 patients (198 per treatment group). Assuming a dropout rate of 20%, we planned to randomly assign 496 patients. This sample size would have provided 90% power to detect, at a two-sided level of significance of 0.05, a treatment difference of 18% in the primary end point — the change in the urinary albumin-to-creatinine ratio from baseline to week 24 — between the group that received aliskiren and the group that received placebo (assuming a standard deviation of 55%). However, 599 patients were enrolled, mainly as a result of a long screening and run-in period, an increased rate of enrollment at the end of the recruitment phase, and a decreased rate of screening failure toward the end of the enrollment phase. With 599 patients enrolled, and with the same assumptions as stated above, the power was approximately 94%.

Changes in the log-transformed urinary albumin-to-creatinine ratio from baseline (2 weeks

before randomization) to weeks 4, 12, and 16 and to week 24 (end point) were assessed for the intention-to-treat population with the use of an analysis of covariance (ANCOVA) model, with treatment and region as factors and baseline log-transformed albumin-to-creatinine ratio as the covariate. To adjust for differences in the change in systolic blood pressure from baseline, the log-transformed urinary albumin-to-creatinine ratio was also analyzed with the use of an ANCOVA model in which treatment and region were variables, with the baseline urinary albumin-to-creatinine ratio and the change from baseline in systolic blood pressure as covariates. For patients with missing albumin-to-creatinine ratio values for week 24 (13% and 9.7% in the aliskiren and placebo groups, respectively), the last post-baseline urinary albumin-to-creatinine ratio was carried forward for the week-24 end-point analysis. Patients who had an adverse event or an abnormal value on a laboratory test but who remained in the study were followed for its duration and included in the analysis of efficacy at 24 weeks. Patients who withdrew from the study were monitored for adverse events or abnormal values on laboratory tests for the duration of the study. Treatment comparisons between the patients who received aliskiren and those who received placebo were performed with the use of a two-sided test with a significance level of 0.05. Least-squares mean differences between the groups (aliskiren vs. placebo) for the change from baseline in the urinary albumin-to-creatinine ratio (and associated 95% confidence intervals) were back-transformed to provide aliskiren-to-placebo ratios. In addition, a mixed-effects model with the use of the appropriate procedure of the SAS package (SAS PROC MIXED) was implemented for the primary end point. The model included study group, visit, and the interaction term for these two factors, as well as region and baseline urinary albumin-to-creatinine ratio, as fixed effects and visits as repeated measurements. A common correlation structure for albumin-to-creatinine ratio was assumed for each patient.

Changes from baseline in the urinary albumin excretion rate, blood pressure, and estimated glomerular filtration rate were analyzed with the use of an ANCOVA model, with treatment, region, and baseline proteinuria classification as factors and respective baseline values for the urinary albumin excretion rate, blood pressure, and glomerular fil-

tration rate as covariates. Analyses of the urinary albumin excretion rate and the estimated glomerular filtration rate were performed with the use of log-transformed data. Correlations between changes from baseline in blood pressure and changes from baseline in the urinary albumin-to-creatinine ratio were assessed by linear regression analysis. All statistical analyses were performed with SAS software, version 8.2 or higher (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

Baseline demographic, clinical, and biochemical characteristics and the number of patients who were receiving glucose-lowering and lipid-lowering therapies and aspirin (≤ 325 mg daily) were balanced between the two groups, except that the patients in the placebo group were slightly older ($P=0.009$) (Table 1). The mean glycosylated hemoglobin values remained unchanged, at 8.0%, in the aliskiren group and rose to 8.1% in the placebo group, and the numbers of severe hypoglycemic episodes were zero and one, respectively. Additional blood-pressure-lowering drugs that were taken by patients in the two groups are shown in Table 2.

PRIMARY AND SECONDARY OUTCOMES

By the end of the study period, treatment with aliskiren (150 mg daily for 3 months, followed by 300 mg daily for another 3 months) had reduced the mean urinary albumin-to-creatinine ratio by 20%, as compared with placebo (95% confidence interval [CI], 9 to 30; $P<0.001$) (Fig. 2A). The mixed-effects model yielded an identical reduction of 20% in the mean urinary albumin-to-creatinine ratio (95% CI, 11 to 29; $P<0.001$). After adjustment for the change from baseline in systolic blood pressure, the reduction was 18% (95% CI, 7 to 28; $P=0.002$). By week 12, 150 mg of aliskiren daily, as compared with placebo, had decreased the urinary albumin-to-creatinine ratio by 11% (95% CI, 2 to 20; $P=0.02$). At week 24, the overnight urinary albumin excretion rate showed a similar pattern, with a reduction of 18% in the aliskiren group (95% CI, 5 to 30; $P=0.009$ for the comparison with the placebo group) (Fig. 2B). After adjustment for the change from baseline in systolic blood pressure, the reduction was 17% (95% CI, 4 to 29; $P=0.02$). Mean blood pressure, measured while the

Table 2. Concomitant Antihypertensive Therapies Received at Baseline and during the Double-Blind Period among Patients with Type 2 Diabetes and Nephropathy.

Drug	Aliskiren Group (N=301)	Placebo Group (N=298)
	<i>no. of patients (%)</i>	
Antihypertensive drugs received at baseline		
Calcium-channel blocker	154 (51.2)	173 (58.1)
Beta-blocker	104 (34.6)	108 (36.2)
Thiazide diuretic	103 (34.2)	104 (34.9)
Loop diuretic	78 (25.9)	85 (28.5)
Alpha-blocker	46 (15.3)	34 (11.4)
Centrally acting agent	25 (8.3)	17 (5.7)
Angiotensin-receptor blocker	2 (0.7)	1 (0.3)
Angiotensin-converting–enzyme inhibitor	0	1 (0.3)
Antihypertensive drugs received during double-blind period		
Calcium-channel blocker	157 (52.2)	180 (60.4)
Beta-blocker	109 (36.2)	121 (40.6)
Thiazide diuretic	99 (32.9)	102 (34.2)
Loop diuretic	93 (30.9)	99 (33.2)
Alpha-blocker	46 (15.3)	38 (12.8)
Centrally acting agent	28 (9.3)	21 (7.0)
Angiotensin-receptor blocker	1 (0.3)	0
Angiotensin-converting–enzyme inhibitor	0	0
Antihypertensive drugs started during double-blind period		
Calcium-channel blocker	23 (7.6)	32 (10.7)
Beta-blocker	12 (4.0)	21 (7.0)
Thiazide diuretic	9 (3.0)	16 (5.4)
Loop diuretic	29 (9.6)	32 (10.7)
Alpha-blocker	9 (3.0)	10 (3.4)
Centrally acting agent	6 (2.0)	5 (1.7)
Angiotensin-receptor blocker	0	0
Angiotensin-converting–enzyme inhibitor	0	0
Antihypertensive drugs stopped during double-blind period		
Calcium-channel blocker	20 (6.6)	25 (8.4)
Beta-blocker	7 (2.3)	8 (2.7)
Thiazide diuretic	13 (4.3)	18 (6.0)
Loop diuretic	14 (4.7)	18 (6.0)
Alpha-blocker	9 (3.0)	6 (2.0)
Centrally acting agent	3 (1.0)	1 (0.3)
Angiotensin-receptor blocker	1 (0.3)	1 (0.3)
Angiotensin-converting–enzyme inhibitor	0	1 (0.3)
No. of concomitant antihypertensive drugs received during double-blind period		
0	7 (2.3)	4 (1.3)
1	45 (15.0)	51 (17.1)
2	69 (22.9)	43 (14.4)
≥3	180 (59.8)	200 (67.1)

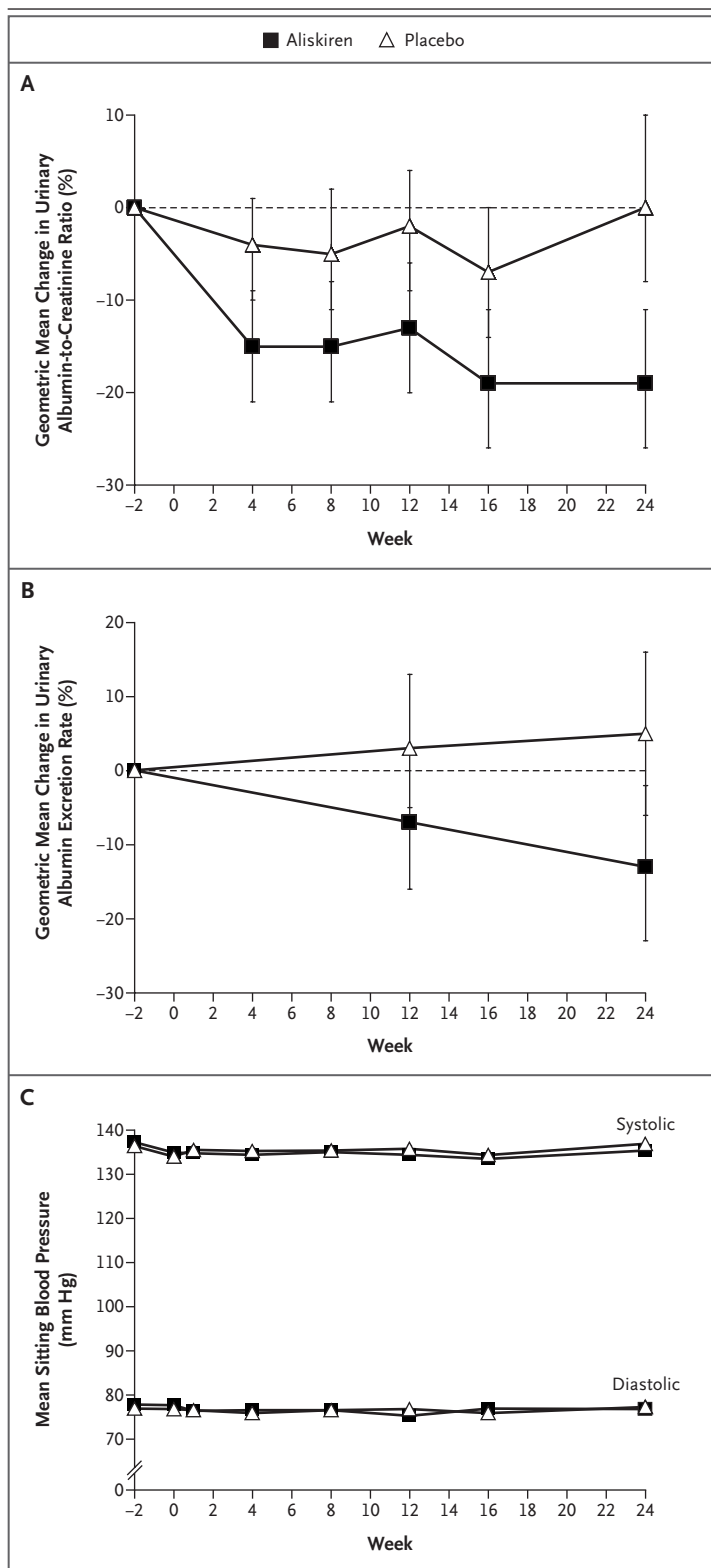


Figure 2. Changes from Baseline in the Urinary Albumin-to-Creatinine Ratio, Urinary Albumin Excretion Rate, and Blood Pressure According to Study Group.

The percentage change from baseline (2 weeks before randomization), in the geometric mean, with 95% confidence intervals, is shown for the ratio of urinary albumin to creatinine (Panel A), overnight urinary albumin excretion rate (Panel B), and mean blood pressure, measured while the patient was seated (Panel C). The data show a dose-dependent effect of aliskiren on albuminuria.

aliskiren group was 2/1 mm Hg lower than that in the placebo group ($P=0.07$ for systolic pressure, $P=0.08$ for diastolic pressure) (Fig. 2C).

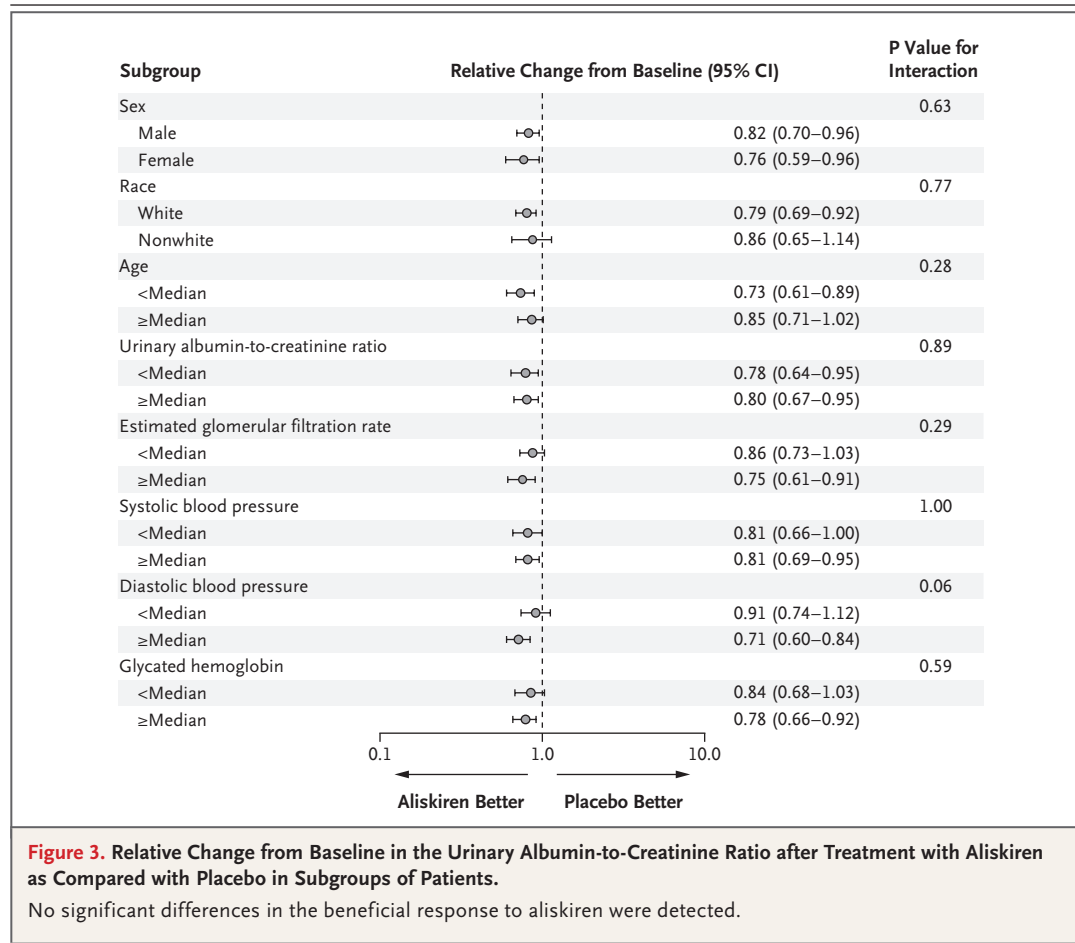
A reduction of 50% or more in albuminuria was seen in 24.7% of the patients who received aliskiren, as compared with 12.5% of the patients who received placebo ($P<0.001$). A comparison of baseline characteristics between patients who had a heightened response (a reduction of 50% or more in albuminuria) and those who had a normal response (a reduction of less than 50% in albuminuria) did not reveal any significant differences.

There were no significant differences in the response to aliskiren among subgroups of patients (Fig. 3). Even though aliskiren appeared to have a beneficial effect or trend in all subgroups, the effect was not always significant. The mean rate of decline in the estimated glomerular filtration rate during the 24-week study period was 2.4 ml per minute per 1.73 m² (95% CI, 1.1 to 3.7) in the aliskiren group and 3.8 ml per minute per 1.73 m² (95% CI, 2.5 to 5.1) in the placebo group ($P=0.07$).

ADVERSE EVENTS

There was no difference in the overall incidence of adverse events between the aliskiren group and the placebo group (66.8% and 67.1%, respectively) (Table 3). The rate of serious adverse events was also similar (9.0% and 9.4%, respectively), as was the percentage of patients who withdrew from the study owing to adverse events (5.6% and 6.4%, respectively). There were no deaths in the aliskiren group and two deaths in the placebo group. Hypertension was reported in 5.0% of the patients in the aliskiren group and in 5.7% of the patients in the placebo group. A total of 14 patients (4.7%) in the aliskiren group had at least one value for the serum potassium level that was 6.0 mmol per liter or more, as compared with 5 patients (1.7%) in the placebo group ($P=0.06$). A total of 9 of the

patient was seated, was nearly identical at baseline in the two groups. By the end of the study period (week 24), the mean blood pressure in the



14 aliskiren-treated patients had had a serum potassium level of 5.1 mmol per liter or more at baseline, a level that should have led to the exclusion of the patients from the study, according to the exclusion criteria described earlier. Of these 9 patients, 3 were excluded from the study when the laboratory value became available. One of the remaining 11 patients withdrew from the study because a subsequent laboratory test showed a serum potassium level of 6.3 mmol per liter. The mean (\pm SD) serum creatinine level in the aliskiren group at baseline was 1.4 ± 0.6 mg per deciliter (123.76 ± 53.04 μ mol per liter). Only half of the patients in the two study groups who had at least one value for serum potassium that was 6.0 mmol per liter or more (a total of 16 patients) received a diuretic. None of the five patients in the placebo group had a serum potassium level of 5.1 mmol per liter or more at baseline, and the mean value for these five patients was 4.7 ± 0.2 mmol per liter at baseline. The hyperkalemia was transient, and none of the five patients stopped taking the study medication.

DISCUSSION

The present trial shows that treatment with 300 mg of aliskiren daily reduces albuminuria in patients with hypertension, type 2 diabetes, and proteinuria who are receiving the recommended maximal renoprotective treatment with losartan and optimal antihypertensive therapy. Furthermore, a 50% reduction in albuminuria was seen twice as often in the group that received 300 mg of aliskiren daily as in the group that received placebo. The benefits of aliskiren appear to be independent of the systemic blood pressure; average trough systolic and diastolic blood pressures during the study were only marginally lower in the aliskiren group than in the placebo group, and an analysis that adjusted for these small differences confirmed the renoprotective effect of aliskiren. In addition, the decline in kidney function tended to be smaller among the patients who received aliskiren than among those who received placebo.

The benefit of blocking the renin–angiotensin–

Table 3. Serious Adverse Events, Adverse Events, and Prespecified Abnormal Laboratory Values during Double-Blind Treatment (Safety Population).

Adverse Event or Abnormal Laboratory Value	Aliskiren Group (N=301)	Placebo Group (N=298)
	number (percent)	
Any adverse event	201 (66.8)	200 (67.1)
Any serious adverse event	27 (9.0)	28 (9.4)
Death	0	2 (0.7)
Discontinuation of study medication due to adverse event	17 (5.6)	19 (6.4)
Discontinuation of study medication due to serious adverse event	9 (3.0)	8 (2.7)
Serious adverse events occurring in more than one patient		
Pneumonia	2 (0.7)	3 (1.0)
Peripheral edema	2 (0.7)	1 (0.3)
Congestive cardiac failure	2 (0.7)	1 (0.3)
Limb abscess	2 (0.7)	0
Gastroenteritis	2 (0.7)	0
Acute renal failure	2 (0.7)	0
Angina pectoris	1 (0.3)	2 (0.7)
Cellulitis	1 (0.3)	2 (0.7)
Adverse events in $\geq 2\%$ of either group		
Headache	18 (6.0)	11 (3.7)
Nasopharyngitis	18 (6.0)	15 (5.0)
Dizziness	15 (5.0)	10 (3.4)
Hyperkalemia	15 (5.0)	17 (5.7)
Edema, peripheral	13 (4.3)	23 (7.7)
Back pain	13 (4.3)	12 (4.0)
Anemia	12 (4.0)	5 (1.7)
Hypotension	12 (4.0)	3 (1.0)
Diarrhea	9 (3.0)	8 (2.7)
Influenza	9 (3.0)	7 (2.3)
Nausea	8 (2.7)	5 (1.7)
Upper respiratory tract infection	8 (2.7)	4 (1.3)
Urinary tract infection	8 (2.7)	11 (3.7)
Gastroenteritis	7 (2.3)	1 (0.3)
Pain in extremity	7 (2.3)	7 (2.3)
Asthenia	6 (2.0)	3 (1.0)
Cough	5 (1.7)	7 (2.3)
Dyspnea	5 (1.7)	6 (2.0)
Fatigue	5 (1.7)	6 (2.0)
Angina pectoris	4 (1.3)	6 (2.0)
Arthralgia	4 (1.3)	7 (2.3)
Abdominal pain, upper	3 (1.0)	6 (2.0)
Myalgia	3 (1.0)	7 (2.3)
Laboratory abnormalities*		
Serum potassium		
<3.5 mmol/liter	15 (5.0)	11 (3.7)
>5.5 mmol/liter	41 (13.7)	32 (10.8)
≥ 6.0 mmol/liter	14 (4.7)	5 (1.7)
Creatinine >2.0 mg/dl (176.8 μ mol/liter)	37 (12.4)	54 (18.2)
Blood urea nitrogen >40.0 mg/dl (14.28 mmol/liter)	65 (21.7)	66 (22.2)

* Data were available for 299 patients in the aliskiren group and 297 patients in the placebo group.

aldosterone system in patients with diabetes who are at risk for end-stage renal disease is now well established.^{3,4,10-12} However, most studies to date also show that renal disease progresses in many patients despite treatment with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II-receptor blockers.^{3,4,10-12} Consequently, alternatives that optimize the blockade of the renin-angiotensin-aldosterone system are being explored in the hope that a more complete blockade will lead to a better therapeutic outcome.¹⁷ New renoprotective strategies include dual blockade of the renin-angiotensin-aldosterone system with the use of ACE inhibitors and angiotensin II-receptor blockers, very high doses of angiotensin II-receptor blockers,¹⁸⁻²⁰ aldosterone blockade,^{21,22} and, as in the present study, direct renin inhibition.

Aliskiren, the renin inhibitor used in our study, has a 40-hour half-life and reduces both blood pressure and plasma renin activity. It is well established that a dose of 300 mg of aliskiren is optimal for the reduction of blood pressure.²³ Further information concerning the development of oral renin inhibitors and their pharmacokinetic and pharmacodynamic properties, with a focus on aliskiren, is available in a recent review.²⁴

In a study reported in 2000 that involved patients with type 2 diabetes, hypertension, and microalbuminuria, Mogensen et al.²⁵ showed that treatment with a combination of submaximal doses of candesartan and lisinopril was more effective in reducing blood pressure (reductions in systolic pressure of approximately 10 mm Hg and in diastolic pressure of approximately 6 mm Hg) than therapy with only one agent; however, the effectiveness of the combined therapy in reducing albuminuria was not firmly established. Since then, numerous small studies, often using submaximal doses of ACE inhibitors in patients with diabetic nephropathy, have shown a significant reduction in blood pressure and albuminuria with this treatment strategy.²⁶ In contrast, a large, randomized, controlled trial involving patients with type 2 diabetes, hypertension, and albuminuria who received the maximal recommended doses of ramipril and irbesartan failed to show a significant effect of combination therapy, as compared with monotherapy, on albuminuria,²⁷ despite a significant reduction in systemic blood pressure. However, this study may have been underpowered, owing to a more marked variability in the urinary albumin excretion rate than antici-

pated. Our study was larger and adequately powered, and the results clearly support a specific renoprotective effect of aliskiren — namely, a beneficial effect on kidney function beyond the effect on hypertension. However, we cannot completely rule out the possibility that changes in antihypertensive medications after randomization might have confounded the results of our study.

Glomerular proteinuria is determined by four factors: the mean transcapillary hydraulic-pressure difference, the glomerular surface area, and the size selectivity and charge selectivity of the glomerular filter. In diabetic nephropathy several of these variables are abnormal, and blockade of the renin-angiotensin-aldosterone system has been shown to normalize directly measured or estimated glomerular hydraulic pressure,²⁸⁻³⁰ to reduce the shunt-like defects in the membrane, at least in part,^{31,32} and to restore the charge-selectivity properties of the glomerular membrane.³³

In our study, the estimated glomerular filtration rate was nearly identical in the two groups at baseline, whereas the decline in the glomerular filtration rate tended to be smaller among the patients who were treated with aliskiren for 6 months than among the patients who were given placebo. Long-term studies (more than 2 years' duration) must be conducted to elucidate whether the beneficial effect on the kidney that is seen in the short term is sustained.

Previous studies with antihypertensive drugs have usually shown an initial drop in the glomerular filtration rate that is steeper than the sustained decline.^{11,34} Recently, a study of healthy people on a low-sodium diet has shown that renal vasodilatation with aliskiren far exceeds that seen with ACE inhibitors and angiotensin II-receptor blockers.³⁵ These results indicate that aliskiren may provide greater and thus more effective blockade of the renin system in the kidney. Since the renin system is enhanced in patients with diabetes, as compared with controls,³⁶ a more pronounced difference in renal vasodilatation may be expected during aliskiren therapy.

During the course of the trial, the average difference in blood pressure was only 2 mm Hg systolic and 1 mm Hg diastolic in favor of the dual blockade of the renin-angiotensin-aldosterone system. Studies of the same treatment approach (300 mg of aliskiren combined with 320 mg of valsartan³⁷ or 10 mg of ramipril³⁸) in patients with essential hypertension have shown at least a doubling of the difference in blood pressure in the

combination-therapy groups as compared with the monotherapy groups. A likely explanation for this finding is that the patients in these two trials had a much higher average baseline blood pressure than the patients in our study, whose baseline blood pressure was well controlled. Even though many of the patients in both of our study groups received three or more antihypertensive agents, our systolic blood-pressure goal of 130 mm Hg was reached in less than half the patients, whereas our diastolic blood-pressure goal of 80 mm Hg was reached in the majority of patients in both groups. Previous studies among patients with diabetic nephropathy have also shown that ideal control of systolic blood pressure is very difficult to attain in patients with diabetes, probably owing to the presence of diabetic macroangiopathy.^{2-4,11}

It is possible that aliskiren also differs from ACE inhibitors or angiotensin II-receptor blockers in other ways that might explain these results. In 2002, Nguyen et al.³⁹ discovered a (pro)renin receptor that was detected in the brain, heart, liver, and kidney. Prorenin, when bound to the (pro)renin receptor, displayed enzymatic activity and activation of intracellular signaling pathways without proteolytic removal of the prosegment. Recent studies in animals with diabetes^{40,41} and in *in vitro* conditions with high glucose⁴² have shown that aliskiren reduces the number of (pro)renin receptors in the kidney, mitigates profibrotic activity in the kidney, and nearly abolishes the apoptotic effects on cultured podocytes. Furthermore, data from transgenic (mRen-2)²⁷ rats with diabetes suggest that aliskiren has a greater renoprotective capacity than ACE inhibitors.⁴³

These findings are consistent with the observation that an elevated plasma prorenin level is associated with the development of diabetic nephropathy.¹

The combination therapy consisting of the maximal recommended doses of aliskiren and losartan had similar tolerability to therapy with placebo and losartan, consistent with findings in an earlier study of the combination of aliskiren and valsartan.³⁷ Hyperkalemia was reported in 5.0% of the patients in the aliskiren group and in 5.7% of the patients in the placebo group. The number of patients with a serum potassium level of 6.0 mmol per liter or more was higher with the combined drugs than with placebo, although the occurrence of such cases, after adjustment for the nine patients who were mistakenly enrolled in the trial, was low.

In conclusion, aliskiren appears to have a renoprotective effect that is independent of its blood-pressure-lowering effect in patients with type 2 diabetes who are receiving the maximal recommended renoprotective treatment and optimal antihypertensive therapy.

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APPENDIX

The following investigators participated in the study: **Canada** — M. Lebel, M. Agharazi (Quebec, QC); N. Muirhead, A. House, F. Rehman (London, ON); V. Pichette, M. LeBlanc, A. Bomardeaux, M. Houde (Montreal); G. Pylpichuk, A. Ahmed, J. Barton (Saskatoon, SK); S. Jolly (Kitchener, ON); **Greece** — K. Siamopoulos, I. Theodorou (Ioannina); E. Pagkalos, M. Gavra, A. Klitsas, K. Soulis (Thessaloniki); **Portugal** — M.J. Pais, L. Parreira, A. Ribeiro da Cunha, P. Carmo (Carnaxide); A. Gomes da Costa, S. Morgado da Silva (Lisbon); D. Carvalho, Â. Magalhães, A. Oliveira, J. Queirós (Porto); **Turkey** — A. Oguz, A. Erenmemisoglu, S. Seker, C. Muderrisoglu, E. Altinoglu, A. Erenmemisoglu, T. Eder, H. Yazici (Istanbul); M. Arici, A. Erenmemisoglu, R. Yilmaz (Ankara); K. Dilek, A. Erenmemisoglu, S. Kahvecioglu, I. Akdag (Bursa); **Denmark** — H.-H. Parving, F. Persson, K. Schjødt, L. Tarnow (Gentofte); O.L. Svendsen, T. M. Christensen, M.-B. Tanderup Petersen, H. Perrild (Copenhagen); T. Almdal (Hvidovre); B. Thorsteinsson, O. Snørgård (Hillerød); H. Juhl, H. Hansen (Slagelse); J. Henriksen, B. Vind (Odense); O. Østergaard, E. Christiansen (Roskilde); **France** — G. Choukroun, N. El Esper, C. Presne (Amiens); J. Aldigier (Limoges); P. Bataille, D. Nour (Boulogne-sur-Mer); J.-P. Fauvel (Lyon); P. Zaoui, P. Malvezzi (Grenoble); J.-M. Halimi, P. Lecomte (Tours); G. Charpentier, B. Boucherie (Corbeil); **Germany** — T. Jung, N. Jung (Deggingen); J. Jordan, H. Mehling, P. Budziarek, S. Engeli (Berlin-Buch); H. Haller, J. Menne, S. Niescken, A. Herrmann, S. Hellweg, S. David, A. Deines (Hannover); R. Schmieder, B. Schmidt, T. Schäufole (Nuremberg); J. Simon (Fulda); E. Oerter (Wuerzburg); M. Rambauek, M. Schoemig, M. Stephan (Heilbronn); E. Austenat, C. Grothe, T. Lederer, B. Al-Masry (Berlin); G. Blume (Quedlinburg); C. Hohberg, R. Butzer, T. Forst, P. Musholt, B. Wilhelm (Mainz); A. Gruenerbel, M. Gruenerbel, C. Richter (Munich); **Italy** — A. Santoro, M. Federico, M. Mandreoli, L. Stalteri (Bologna); G. Remuzzi, P. Ruggenenti, E. Perticucci, S. Rota (Bergamo); L. Gesuaido, M. Ktena, E. Pallotta (Foggia); S. David, C. Grasselli (Parma); C. Zoccali, F.M. Cambareri, G. Parlongo (Reggio Calabria); A. Balducci, M. Gamerini, G. Sorbo (Rome); E. Fanciulli, P. Freddi, E. Balestra (Torrette di Ancona); F. Quarello, R. Boero, S. Borsa, C. Mossara (Turin); A. Fabbri, E. degli Esposti, C. Baraccani, A. Sturani, M. Gentile (Ravenna); A. Baraldi, M.R. Federico (Carpì); **the Netherlands** — A. van den Mei-

racker, J. Rutten, J. Wijberga (Rotterdam); H.A.H. Kaasjager, L.J. Reichert (Arnhem); J. Breed (Weert); A. Hollander, P. van Meurs, F. Ciggaar, P. van Hoek (*s-Hertogenbosch); P.J. Smak Gregoor (Dordrecht); S. Landewé-Cleuren (Maastricht); P. Viergever, R. Timmerman (Den Helder); R.P. Verhoeven, J. Barendregt, R. Lieverse, J. Smit, S. Radema, M.A. van Dijk, T. van Bemmel (Apeldoorn); A.J. Woittiez, F. Visser (Almelo); **Spain** — J. Alegre Martin, C. Aleman Llano, M. Duran Tabena, J. Recio Iglesias, T. Soriano Sanchez, L. Comas, X. Farres, A. Ledesma Casteltort, M. Terns, P. Fernandez, F. Gonzales-N, F. Ortiz-Herbener, A. Oliveras, S. Vazquez, A. Martinez Castelao, F. Moreso Mateos, M.T. Gonzalez Alvarez (Barcelona); J. Redon, A. Casanova, J. Gorriz, P. Molina Vila, A. Priego (Valencia); L. Ruilope, C. Roldan, J. Segura, C. Campo, A. Calle Pascual, J. Garcia Honduvilla, F. de Alvaro, O. Costero Fernandez, S. Garcia de Vinvera, M. Goicoechea, J. Luño (Madrid); J. Olivan, J. Pizarro Nunez, E. Gonzales-Serna, A. Rodriguez Botaro (Seville); P. Gomez, M. Eady Alonso (Cadiz); L. De Teresa Parreno, P. Garcia Hermosa, J. Gomez Gomez, S. Fuentes Luri, J. Blazquez (Alicante); P. Aranda (Málaga); C. Calvo, M. Rodriguez Fernandez, J. Lopez Paz (Coruña); **United Kingdom** — G. Viberti, J. Karalliedde, V. Miranda, L. Gnudi (London); A. Rees, A. Roberts (Cardiff); J. Reckless, A. Robinson, R.Y. Mukhtar, J. Vora, A. Joshi, H. White, J. Franklin (Bath); J. Walker, T. Sandeep, A. Mukhtar, R. Gray (Livingston); S. Heller, A. Mackie, S.H. Song (Sheffield); J. O'Hare, M.V. Chittari, K. Kos, M. Pierides (Rugby); **Romania** — M. Voiculescu, N. Caceaune, L. Iliescu, R. Bobeica, C. Ionescu, G. Ismail, L. Luca, G. Tatu-Chitriu, S. Cronaci, R. Jumata, D. Zamfir (Bucharest); M. Stefanescu, D. Muntui, D. Dobreanu, D. Cromos, G. Dogaru, C. Caldaru (Tg. Mures); D. Zdrenghea, C. Roman, A. Malai, M. Cebanu, M. Ostace, D. Pop, R. Rosu (Cluj-Napoca); R. Mihaila, R. Mihaila, E. Rezi, M. Strugariu, M. Deac (Sibiu); **Russia** — V. Zadiionchenko, T. Adasheva, O. Demicheva, M. Antsiferov, O. Koteschkova, I. Sretenskaya, K. Tsipturia, E. Vasilieva, I. Fomina, A. Tazimanova, A. Vasileva, S. Martsevich, J. Semenova, A. Serazhim, V. Voronina, N. Dmitrieva (Moscow); O. Ershova, P. Kumzerov, N. Borisova, E. Ohapkina, E. Bolshakova (Yaroslavl); O. Lantseva, L. Strezhova, T. Terentieva, I. Karpova, E. Ostrovskaya, V. Panina (Saint Petersburg); **Argentina** — C. Majul, O. Paez, P. Puleio, M. Visser, I. Sinay, M. Nepote, A. Elbert, H. Beresan (Buenos Aires); L. Juncos, N. Garcia, M. Orias, M. Belen Barron, P. Novoa (Cordoba); **United States** — A. Wynne, J. Conrow (Topeka, KS); M. Rendell, J. Lane (Omaha); D. Robertson (Atlanta); R. Solomon (Burlington, VT); E. Himot (Marietta, GA); S. Schmidt (Philadelphia); W. Spisak (Portland, OR); J. Mossberg (Eugene, OR); R. Graf (Tacoma, WA); R. Cooper (Tempe, AZ); R. Ouseph (Louisville, KY); J. Liljquist (Idaho Falls, ID); M. Seidner (Lansdale, PA); R. Culpepper, F. Lester (Mobile, AL); B. Wood, R. Butin (Kansas City, MO); V. Ram, R. Sachson, R. Toto, B. Zamora (Dallas); R. Busch (Albany, NY); K. Cohen (Golden, CO); A. Barreto (Oklahoma City); K. Hillner (Bryan, TX); N.P. Kopyt (Allentown, PA); R. Lipetz (Spring Valley, CA); J. LaSalle (Excelsior Springs, MO); J. Robertson (Riverside, CA); J. Mageli (St. Paul, MN); R. Cherlin (Los Gatos, CA); P. Snell (Greer, SC); E. Dyess (Jackson, MS); N. Sapin (Glendale, AZ); M. Reeves (Chattanooga, TN); P. Suchinda (Sumter, SC); T. Fagan, M. Parker (Tucson, AZ); D. Martinez (Moreno Valley, CA); R. Arakaki (Honolulu); N. Bohannon (San Francisco); M. Moustafa (Orangeburg, SC); A. Chen (Pensacola, FL); E. Barranco (Ponce, PR).

REFERENCES

- Luetscher JA, Kraemer FB, Wilson DM, Schwartz HC, Bryer-Ash M. Increased plasma inactive renin in diabetes mellitus: a marker of microvascular complications. *N Engl J Med* 1985;312:1412-7.
- Parving H-H, Mauer M, Ritz E. Diabetic nephropathy. In: Brenner BM, ed. *Brenner & Rector's the kidney*. 8th ed. Vol. 2. Philadelphia: Elsevier, 2008:1265-98.
- Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9.
- Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60.
- Rossing P, Hommel E, Smidt UM, Parving H-H. Reduction in albuminuria predicts a beneficial effect on diminishing the progression of human diabetic nephropathy during antihypertensive treatment. *Diabetologia* 1994;37:511-6.
- de Zeeuw D, Remuzzi G, Parving H-H, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int* 2004;65:2309-20.
- de Zeeuw D, Remuzzi G, Parving H-H, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 2004;110:921-7.
- Ibsen H, Olsen MH, Wachtell K, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension* 2005;45:198-202.
- Parving H-H, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1983;1:1175-9.
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-62. [Erratum, *N Engl J Med* 1993;330:152.]
- Parving H-H, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870-8.
- Gæde P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383-93.
- 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. *Ann Intern Med* 1999;130:461-70.
- Multizentrische Erprobung von Tinaquant-Albumin im Urin und β -N-Acetylglucosaminidase (β -NAG) im Urin. *Wien Klin Wochenschr Suppl* 1991;189:1-66.
- Bartels H, Böhmer M, Heierli C. Serum kreatininbestimmung ohne enteiweissen. *Clin Chim Acta* 1972;37:193-7.
- Rohlfing CL, Little RR, Wiedmeyer HM, et al. Use of GHb (HbA1c) in screening for undiagnosed diabetes in the U.S. population. *Diabetes Care* 2000;23:187-91. [Erratum, *Diabetes Care* 2000;23:876.]
- Hollenberg NK. Is there a pharmacologic basis for combination renin axis blockade? *Kidney Int* 2005;68:2901-3.
- Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving H-H. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. *Kidney Int* 2005;68:1190-8.
- Hollenberg NK, Parving H-H, Viberti G, et al. Albuminuria response to very high-dose valsartan in type 2 diabetes mellitus. *J Hypertens* 2007;25:1921-6.
- Burgess E, Muirhead N, De Cotret P. A double-blind randomized controlled trial of high dose candesartan cilexetil in proteinuric renal disease — results from SMART (Supra Maximal Atoral Renal Trial). *J Am Soc Nephrol* 2007;18:57A.
- Schjoedt KJ, Rossing K, Juhl TR, et al. Beneficial impact of spironolactone in diabetic nephropathy. *Kidney Int* 2005;68:2829-36.
- Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2006;1:940-51.
- Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, Bedigian MP.

- Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 2005;111:1012-8.
24. Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet* 2006;368:1449-56. [Erratum, *Lancet* 2006;368:2124.]
25. Rossing K, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the Candesartan and Lisinopril Microalbuminuria (CALM) study. *BMJ* 2000;321:1440-4.
26. Rossing K. Progression and remission of nephropathy in type 2 diabetes: new strategies of treatment and monitoring. *Dan Med Bull* 2007;54:79-98.
27. Bakris GL, Ruilope L, Locatelli F, et al. Treatment of microalbuminuria in hypertensive subjects with elevated cardiovascular risk: results of the IMPROVE trial. *Kidney Int* 2007;72:879-85.
28. Hostetter TH, Troy JL, Brenner BM. Glomerular hemodynamics in experimental diabetes mellitus. *Kidney Int* 1981;19:410-5.
29. Trevisan R, Tiengo A. Effect of low-dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin-dependent diabetic patients. *Am J Hypertens* 1995;8:876-83.
30. Imanishi M, Yoshioka K, Konishi Y, et al. Glomerular hypertension as one cause of albuminuria in type II diabetic patients. *Diabetologia* 1999;42:999-1005.
31. Andersen S, Blouch K, Bialek J, Deckert M, Parving H-H, Myers BD. Glomerular permselectivity in early stages of overt diabetic nephropathy. *Kidney Int* 2000;58:2129-37.
32. Remuzzi A, Ruggenti P, Mosconi L, Pata V, Viberti GC, Remuzzi G. Effect of low-dose enalapril on glomerular size-selectivity in human diabetic nephropathy. *J Nephrol* 1993;6:36-43.
33. Langham RG, Kelly DJ, Cox AJ, et al. Proteinuria and the expression of the podocyte slit diaphragm protein, nephrin, in diabetic nephropathy: effects of angiotensin converting enzyme inhibition. *Diabetologia* 2002;45:1572-6.
34. Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med* 2002;347:1256-61.
35. Fisher ND, Hollenberg NK. Unprecedented renal responses to direct blockade of the renin-angiotensin system with aliskiren, a novel renin inhibitor. *Circulation* 2007;116:Suppl II:II-556. abstract.
36. Hollenberg NK, Price DA, Fisher ND, et al. Glomerular hemodynamics and the renin-angiotensin system in patients with type 1 diabetes mellitus. *Kidney Int* 2003;63:172-8.
37. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007;370:221-9. [Erratum, *Lancet* 2007;370:1542.]
38. Uresin Y, Taylor AA, Kilo C, et al. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. *J Renin Angiotensin Aldosterone Syst* 2007;8:190-8.
39. Nguyen G, Delarue F, Burcklé C, Bouzahir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 2002;109:1417-27.
40. Nguyen G, Contrepas A, Mueller DN, et al. Effect of the direct renin inhibitor aliskiren on (pro)renin receptor and profibrotic gene expression in kidneys of diabetic TG(mRen-2)27 rats. *J Am Soc Nephrol* 2007;18:60A.
41. Feldman DL, Jin L, Xuan H, Miserindino-Molteni R. Effect of the direct renin inhibitor (DRI) aliskiren on renal gene expression of pro-fibrotic molecules in experimental hypertensive diabetic nephropathy. *J Am Soc Nephrol* 2007;18:168A.
42. Phillips L, Dai T, Feldman DL, LaPage J, Adler SG. Aliskiren attenuates high-glucose induced extracellular matrix and protects against cell death in cultured podocytes (Pods). *J Am Soc Nephrol* 2007;18:169A.
43. Kelly DJ, Zhang Y, Moe G, Naik G, Gilbert RE. Aliskiren, a novel renin inhibitor, is renoprotective in a model of advanced diabetic nephropathy in rats. *Diabetologia* 2007;50:2398-404.

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