OBJECTIVE — The objective of this study was to evaluate the safety and short-term effect of adding spironolactone to conventional antihypertensive treatment including diuretics and maximally recommended doses of an ACE inhibitor or an angiotensin II receptor blocker (ARB) on albuminuria and blood pressure in type 2 diabetic patients with nephropathy.

RESEARCH DESIGN AND METHODS — Twenty-one type 2 diabetic patients with nephropathy were enrolled in a randomized, double-masked, cross-over study. Patients were treated in random order with spironolactone 25 mg once daily and matched placebo for 8 weeks, respectively, in addition to ongoing antihypertensive treatment including diuretics and maximally recommended doses of an ACE inhibitor and/or an ARB. At the end of each treatment period, albuminuria, 24-h ambulatory blood pressure (ABP), and glomerular filtration rate (GFR) were determined.

RESULTS — During the addition of placebo, values were as follows: albuminuria (geometric mean [range]) 1,566 [655–7,762] mg/24 h, ABP (mean ± SE) 138 ± 3/71 ± 1 mmHg, and GFR (mean ± SE) 74 ± 6 ml/min per 1.73 m². During the addition of spironolactone, albuminuria was reduced by 33% (95% CI 25–41) (P < 0.001), fractional clearance of albumin by 40% (24–53) (P < 0.001), and 24-h ABP by 6 mmHg (2–10) for systolic and 4 mmHg (2–6) for diastolic (P < 0.001 for both). The change in albuminuria did not correlate with the change in systolic 24-h ABP (r = 0.19, P = 0.42) or diastolic 24-h ABP (r = 0.01, P = 0.96). Spironolactone treatment induced an insignificant reversible reduction in GFR of 3 ml/min per 1.73 m² (–0.3 to 6) (P = 0.08). One patient was excluded from the study due to hyperkalemia. Otherwise treatment was well tolerated.

CONCLUSIONS — Our study suggests that spironolactone safely adds to the renoprotective benefits of treatment with maximally recommended doses of ACE inhibitor and ARB by reducing albuminuria and blood pressure in type 2 diabetic patients with nephropathy.

Diabetes Care 28:2106–2112, 2005

Aldosterone, the end product of the renin-angiotensin-aldosterone system (RAAS), has attracted renewed attention as an important mediator of both cardiovascular and renal disease (1,2). Accumulating experimental evidence suggests that circulating aldosterone per se contributes directly to renal and cardiovascular disease by inducing inflammation, fibrosis, and necrosis in end-organ tissues such as the heart, brain, and kidney (3). Moreover, aldosterone blockade has been shown to greatly improve survival in patients with chronic heart failure (4,5).

Angiotensin II has long been considered the main mediator of the pathophysiological effects of the RAAS, and in diabetic nephropathy the renoprotective effects of treatment with an ACE inhibitor or an angiotensin receptor blocker (ARB) are well established (6–9). Both ACE inhibitor and ARB treatments initially suppress plasma aldosterone. Eventually, however, plasma aldosterone may return to pretreatment levels, i.e., the aldosterone escape phenomenon. Aldosterone escape occurs in ~20% of patients with chronic heart failure (10) and nearly 40% of patients with diabetic nephropathy (11,12). The clinical importance of the unsuppressed actions of aldosterone during treatment with an ACE inhibitor or ARB in diabetic nephropathy is emphasized by enhanced proteinuria and a faster rate of decline in renal function among patients with aldosterone escape (11,12). Furthermore, short-term open-labeled and nonrandomized clinical studies in patients with chronic renal disease including some with diabetic nephropathy have indicated that aldosterone blockade may have beneficial effects in reducing albuminuria when added to treatment with an ACE inhibitor (11,13–15). However, limitations in the design of these studies warrant an overall assessment of the anti-
proteinuric and blood pressure–lowering effects of spironolactone.

The aim of the present randomized double-masked study was therefore to evaluate the short-term antiproteinuric and blood pressure–lowering efficacy of a low dose of spironolactone added to treatment with an ACE inhibitor and/or an ARB in maximally recommended doses in type 2 diabetic patients with nephropathy.

**RESEARCH DESIGN AND METHODS** — At the Steno Diabetes Center, we consecutively enrolled 21 type 2 diabetic patients with nephropathy (albuminuria persistently >300 mg/24 h), who were all receiving the maximally recommended dose of an ACE inhibitor and/or an ARB. Important exclusion criteria were clinical or laboratory evidence of nondiabetic renal disease, GFR <30 ml/min per 1.73 m², or plasma potassium concentration >4.5 mmol/l. A criterion for termination from the study was an increase in plasma potassium concentration to >5.5 mmol/l during the study.

The study was conducted as a randomized, double-masked, placebo-controlled, cross-over trial with two treatment periods. Each patient received 8 weeks of treatment with spironolactone 25 mg once daily and 8 weeks with matching placebo tablets in random order. The study medication was given in the morning and was added to the patient’s previous antihypertensive treatment. In addition to ACE inhibitor and ARB treatment, all patients received diuretics in individualized doses before entry into the study to treat and prevent fluid retention and hyperkalemia. After inclusion previous antihypertensive medication including diuretics was kept unchanged throughout the study.

Clinical end points were evaluated at the end of each treatment period. The primary end point was albuminuria. Secondary end points included 24-h ambulatory blood pressure (ABP), fractional clearance of albumin, and GFR.

For safety reasons, blood pressure and plasma potassium, plasma sodium, and creatinine concentrations were determined 1, 2, and 4 weeks after the beginning of each treatment period. All patients were given written and oral information on how to lower potassium intake in the diet. Randomization was concealed with computer-generated envelopes. The code was not broken until all data were entered into a database, which was locked for editing. Drug compliance was assessed by tablet counts. The study was performed according to the principles of the Declaration of Helsinki and approved by the ethical committee of Copenhagen County. All patients gave their informed consent.

**Laboratory procedures**

Albuminuria was determined from three consecutive 24-h urine collections, completed immediately before the end of each treatment period (Turbidimetry, Hitachi 912 system; Roche Diagnostics, Mannheim, Germany). From 24-h urine samples, sodium, potassium, creatinine, and urea excretions were determined (Hitachi 912 system). Fractional clearance of albumin (θ_ab) was determined as urinary albumin excretion/(plasma albumin concentration × GFR), where urinary albumin excretion was measured in the 4-h urine collection during determination of GFR.

ABP was measured by the Takeda-TM02421 device (A & D Medical, Tokyo, Japan). Blood pressure was measured at 15 min during the day (7:00 A.M. to 11:00 P.M.) and every 30 min during the night (11:00 P.M. to 7:00 A.M.). Values were averaged for each hour before calculating day, night, and 24-h ABP.

Office blood pressure was measured at ~8:30 A.M. using an appropriate cuff with a sphygmomanometer (Hawksley random zero device) after at least 10 min of rest in the sitting position. The average of three readings was used.

GFR was measured after a single intravenous injection of 3.7 MBq 51Cr-EDTA at 8:30 A.M. by determining the radioactivity in venous blood samples taken 180, 200, 220, and 240 min after injection (16). The results were standardized for 1.73 m² body surface area, using the patient’s surface area at the start of the study. In our laboratory the mean day-to-day coefficient of variation is 4%

From venous samples, hemoglobin concentration (Sysmex SF3000; Sysmex, Kobe, Japan) and plasma potassium, sodium, creatinine, and cholesterol concentrations were determined (Hitachi 912 system), and HbA1c (A1C) was measured by high-performance liquid chromatography (normal range 4.1–6.4%) (Tosoh automated glycohemoglobin analyzer; Tosoh Bioscience, Minato, Japan). Blood samples for plasma renin activity and aldosterone concentrations were taken after 30 min of supine rest. Plasma renin activity was measured by a method based on determining by radioimmunoassay the amount of angiotensin I generated; normal range is 1–12 ng angiotensin I ml⁻¹ h⁻¹ (17). Plasma aldosterone was measured with a radioimmunoassay (Coat-ACount; Diagnostic Products, Los Angeles, CA); normal range was 50–250 pg/ml.

**Statistics**

A sample-size calculation showed a necessary minimum of 16 patients to detect a 25% change in urinary albumin excretion rate when based on three 24-h urinary collections (α = 0.05, β = 0.80), as described in detail previously (18). Normally distributed variables are expressed as means and changes upon treatment as mean difference with 95% CIs. Albuminuria, plasma renin activity, plasma aldosterone, and θ_ab were logarithmically transformed owing to their skewed distribution and are given as geometric means with interquartile range or range as indicated, and changes upon treatment are expressed as relative changes with 95% CIs. Comparisons of clinical end points including albuminuria, ABP, and GFR between each treatment period were performed using linear mixed models with repeated measurements for albuminuria (19). The adapted model was one with fixed effects of treatment level, visit and carryover (i.e., treatment level in the previous period), and a random effect of person included to account for the person dependencies in data. Tests for the presence of effects were performed as likelihood ratio tests, and final estimates were reported as restricted maximum likelihood estimates (19). Linear regression analysis (least-squares method) was used to analyze for correlations. P < 0.05 was considered significant. Data were evaluated using SPSS version 13.0 (SPSS, Chicago, IL) and the freely available software R (available from http://www.r-project.org).

**RESULTS** — A total of 21 patients with type 2 diabetes and nephropathy were included in the study. One patient was excluded due to hyperkalemia as described under SAFETY below. The baseline characteristics of the remaining 20 patients who completed the study and were available for analysis are shown in Table 1. Previous antihypertensive treatment was continued unchanged throughout the study.
Spironolactone in diabetic nephropathy

Table 1—Baseline clinical data and baseline antihypertensive treatment in 20 type 2 diabetic patients with diabetic nephropathy

| Age (years) | 58 ± 10 |
| Sex (male/female) | 17/3 |
| Duration of diabetes (years) | 12 ± 6 |
| BMI (kg/m²) | 34.9 |
| Retinopathy (none/background/proliferative) | 5/14/1 |
| Nonsmokers/smokers | 12/8 |
| Total number of antihypertensive drug (1/2/3/4/5) | 0/2/5/9/4 |
| Ongoing RAAS blocking agents* | 11 |
| ARB | 4/1 |
| Irbesartan (300 mg) | 6 |
| ACE inhibitor | 4 |
| Enalapril (40 mg) | 2 |
| Trandolapril (4 mg) | 2 |
| Both ARB and ACE inhibitor | 5 |
| Irbesartan (300 mg) and ramaipril (10 mg) | 3 |
| Irbesartan (300 mg) and enalapril (40 mg) | 1 |
| Losartan (100 mg) and enalapril (40 mg) | 1 |
| Diuretics (thiazide/furosemide)* | 5/16 |
| Dihydropyridines† | 16 |
| β-Blockers | 13 |
| Statins | 18 |
| Low-dose aspirin | 20 |

Data are means ±SD or n. *One patient received both a loop diuretic and a thiazide. †Mainly 10 mg amloidipine once daily.

and included diuretics and maximally recommended doses of an ACE inhibitor and/or an ARB in all patients (Table 1). All patients had received an ACE inhibitor and/or an ARB for at least 1 year before entry to the trial. The median number of antihypertensive agents per patient was four (range two to five). The median (range) dose of loop diuretics corresponded to 210 mg (30–750) daily of long-acting furosemide, and all patients treated with a thiazide received bendroflumethiazide 5 mg once daily.

Efficacy
Albuminuria, fractional clearance of albumin, and arterial blood pressure were all significantly reduced during treatment with spironolactone 25 mg once daily as compared with placebo (Table 2). No carryover effect or time period effect was observed for any of these end points.

Albuminuria was demonstrated in 17 of the 20 patients. Fractional clearance of albumin was reduced by 40% (24–53) during addition of spironolactone compared with placebo (P < 0.001) (Table 2).

In general, renal function was well preserved with a mean (range) GFR of 74 ml/min per 1.73 m² (31–118) during the placebo period. Six patients had a GFR between 30 and 59 ml/min per 1.73 m², nine patients had a GFR between 60 and 89 ml/min per 1.73 m², and five patients had a GFR >90 ml/min per 1.73 m². During spironolactone treatment there was a tendency toward a slight decrease in GFR of 3 (−0.3 to 6) ml/min per 1.73 m² (P = 0.08) (Table 2), and there was a significant increase in plasma creatinine from 121 to 132 µmol/l (P < 0.01) (Table 2).

Arterial blood pressure
Morning blood pressure in the physician’s office was significantly reduced by 10 mmHg (5–16) for systolic and 5 mmHg (1–9) for diastolic during treatment with spironolactone compared with placebo (P < 0.01 for both) (Table 2). The 24-h ABP was reduced by 6 mmHg (2–10) for systolic and 4 mmHg (2–6) for diastolic by spironolactone treatment compared with placebo (P < 0.01 for both) (Table 2). Spironolactone treatment significantly reduced daytime blood pressure whereas the blood pressure reduction was not sustained during the night (Table 2). Changes in 24-h systolic and diastolic ABP in patients receiving spironolactone versus placebo did not correlate to changes in albuminuria (r = 0.19, P = 0.42 and r = 0.01, P = 0.96, respectively).

Laboratory parameters
There was a significant increase in plasma aldosterone concentration and renin activity during spironolactone treatment (Table 2). Baseline (placebo) levels and changes upon spironolactone treatment of plasma aldosterone and renin activity did not correlate significantly in linear regression analysis to changes in albuminuria. Both higher baseline levels of aldosterone and the increase in aldosterone upon spironolactone treatment correlated significantly to changes in 24-h systolic ABP (r = 0.55, P = 0.01 and r = 0.49, P = 0.03, respectively) but not to 24-h diastolic blood pressure.

There was a significant decrease in body weight of 1.4 kg (0.2–2.5) (P = 0.02) during treatment with spironolactone. Changes in body weight during spironolactone treatment did not correlate to changes in albuminuria or changes in arterial blood pressure. Plasma cholesterol, hemoglobin, albumin, and sodium concentrations as well as urinary sodium and K/Na excretion were unchanged during spironolactone treatment (Table 2).

Secondary analysis of factors associated with enhanced treatment response
Comparison of patients with reductions in albuminuria above and below the median reduction of 33% upon spironolactone treatment revealed no difference with respect to age, sex, and placebo levels of 24-h systolic and diastolic ABP, albuminuria, plasma potassium concentration, urinary sodium excretion rate, urinary K-to-Na ratio, plasma aldosterone concentration, and renin activity.

A total of eight patients had albuminuria in the nephrotic range (>2,500 mg/24 h) before entry to the trial. Albuminuria was 4,656 mg/24 h (range 3,162–7,762) during placebo treatment in these patients. During treatment with spironolactone albuminuria was reduced by 35% (15–50) compared with placebo (P < 0.01), and blood pressure was re-
duced in this subgroup of patients to an extent similar to that seen in the entire group of patients.

Among the five patients receiving concomitant treatment with an ACE inhibitor and an ARB, both in maximally recommended doses, albuminuria was reduced by 22% (−4 to 42) (P = 0.09) and 24-h ABP was reduced by 8 mmHg (0.5–16) for systolic (P = 0.04) and by 5 mmHg (−1 to 10) for diastolic (P = 0.09). During the placebo period aldosterone levels were similar among the 5 patients who received both an ACE inhibitor and an ARB to those of the remaining 15 patients who received either drug alone (35 [13–95] vs. 40 pg/ml [28–58], P = 0.71). However, during spironolactone treatment, aldosterone levels tended to be lower among patients receiving both agents than in patients receiving either drug alone (58 [28–117] vs. 100 pg/ml [76–132], P = 0.05).

**Safety**

One patient was excluded due to development of severe hyperkalemia upon spironolactone treatment. In this patient plasma potassium concentration increased from 4.5 mmol/l before treatment to 5.4 mmol/l after 1 week and to 7.1 mmol/l after 2 weeks when the patient was excluded from the study. Normalization of plasma potassium concentration was obtained within hours by intravenous insulin and glucose infusion with continuous electrophysiological monitoring at a cardiology unit. The patient was discharged from hospital without complications on the following day. The patient had a moderately reduced GFR of 41 ml/min per 1.73 m² and received a rather low dose of long-acting furosemide of 30 mg once daily. There was no other incidence of hyperkalemia (plasma potassium concentration >5.5 mmol/l). In general, the plasma potassium concentration was increased by 0.3 mmol/l (0.04–0.5) during spironolactone treatment (P < 0.01) (Table 2), and there was a slight increase in A1C from 7.8 to 8.1% (P = 0.03) (Table 2).

**CONCLUSIONS**— Our randomized, double-masked cross-over study of type 2 diabetic patients with nephropathy in whom an ACE inhibitor and/or an ARB were titrated to the recommended maximum doses demonstrates that addition of a low dose of spironolactone provides additional reno- and cardiovascular protection, as reflected by substantial short-term reductions in albuminuria and...
arterial blood pressure. Furthermore, our study suggests that changes in albuminuria do not correlate with changes in arterial blood pressure and GFR. We also observed that beneficial effects of spironolactone are obtained even in patients with very advanced proteinuria as indicated by the reduction in albuminuria and blood pressure among eight patients with nephrotic range albuminuria. Apart from one patient who developed severe hyperkalemia, which emphasizes the need for close monitoring of plasma potassium concentrations, therapy was well tolerated.

The antiproteinuric effect of spironolactone seen in our study confirms and extends findings in previous nonrandomized (11,13,14) and open-labeled clinical studies (15) of patients with various chronic renal diseases including some with diabetic nephropathy. Previous studies have exclusively evaluated the effect of adding spironolactone to treatment with an ACE inhibitor. We have extended these findings by showing that antiproteinuric effects are also obtained when spironolactone is added to treatment with an ARB as received by 80% of the patients in our study. This result emphasizes that the deleterious actions of aldosterone are incompletely suppressed during treatment with both an ACE inhibitor and an ARB. Recent studies in diabetic renal disease have demonstrated that a more complete blockade of the RAAS can be obtained by combined treatment with both an ACE inhibitor and an ARB (dual RAAS blockade) (20–22). Both aldosterone and albuminuria are reduced more effectively by combined therapy compared with single-agent therapy (23). Thus, it is of particular interest that we observed a reduction in albuminuria and blood pressure when spironolactone was added to the subset of patients who received dual RAAS blockade. This finding points toward a potential benefit of triple RAAS blockade as a new treatment strategy to effectively reduce the deleterious actions of both angiotensin II and aldosterone in diabetic nephropathy.

In our study aldosterone escape could not be established, as patients were receiving long-term (at least 1 year) RAAS blockade before entry to the trial, and the aldosterone concentration was not determined before initiation of RAAS treatment. However, albuminuria was reduced in 17 of 20 patients who completed the study, and therefore our study suggests that the antiproteinuric effect is not restricted to patients with aldosterone escape, which has been reported to occur in ~40% of patients receiving chronic ACE inhibitor or ARB treatment (11,12).

Previous clinical studies of patients with chronic renal disease have not found any effect on arterial blood pressure as evaluated by office blood pressure by adding spironolactone to conventional antihypertensive treatment (11,13,14). This is in contrast to the substantial reduction of arterial blood pressure observed in our study. The discrepancy is probably due to the fact that previous studies have been limited to patients with well-controlled blood pressure during conventional antihypertensive treatment, whereas patients in our study had higher blood pressure. Because in our study, in which spironolactone was taken in the morning, the reduction in blood pressure was not fully sustained during the night, administration of spironolactone twice daily may lead to even further effects. Even though we did not find any significant correlation between reduction in 24-h blood pressure and albuminuria upon spironolactone treatment, the observed reduction in blood pressure has most likely contributed to the reduction in albuminuria.

We observed a slight decrease in body weight of ~1% during spironolactone treatment, which may be a consequence of the diuretic properties of spironolactone. However, it is unlikely that the blood pressure-lowering effect of spironolactone in our study is merely a consequence of decreased plasma volume, as there was no change in plasma albumin and hemoglobin concentrations during spironolactone treatment. Furthermore, changes in body weight did not correlate to changes in arterial blood pressure. It also seems unlikely that a reduction in blood pressure could have been obtained simply by increasing the dose of diuretics because patients received rather high doses during the study.

The classic genomic aldosterone effects are characterized by salt and water retention, systemic and renal vasoconstriction, hypertension, and potassium wasting together with renal- and cardiovascular damage (1,2). In addition, non-genomic aldosterone effects have been described and are characterized by their rapid onset of action (within minutes), an insensitivity to inhibitors of transcription, protein synthesis, and antagonists of the type 1 mineralocorticoid receptor [e.g., spironolactone, as reviewed by Falkenstein et al. (24)]. In the microcirculation of isolated and microperfused rabbit glomeruli the nongenomic actions of aldosterone have been demonstrated to include a dose-dependent constriction of both the afferent and efferent arterioles but with a higher sensitivity in the efferent arterioles, leading to elevated glomerular capillary pressure (25). Such unopposed nongenomic actions of aldosterone are likely to reduce the therapeutic benefits of spironolactone. However, if these nongenomic effects on glomerular microcirculation dominated the genomic effects one would anticipate that spironolactone, by elevating circulating aldosterone concentration, leads to kidney damage. On the contrary, spironolactone reduces proteinuria and kidney damage in chronic models of experimental renal diseases (26,27) and in accordance our clinical study demonstrated an overall renoprotective effect characterized by lowering of albuminuria and a small reversible GFR decline after 8 weeks of spironolactone treatment.

The nonhemodynamic actions of aldosterone blockade include reduced production of prosclerotic growth factors such as transforming growth factor-β1 and plasminogen activator inhibitor 1 and decreased macrophage infiltration leading to reduced renal fibrosis and albuminuria (14,28). Such nonhemodynamic factors may, in addition to specific lowering of intraglomerular capillary blood pressure, contribute to reduction of albuminuria independent of changes in systemic blood pressure.

There is a substantial risk of hyperkalemia during aldosterone blockade in patients with reduced renal function, in particular when patients are treated with other compounds that increase potassium such as ACE inhibitors and ARBs. As the risk of hyperkalemia is clearly dose dependent (29), we used a low dose of spironolactone to minimize the risk of hyperkalemia. In addition, all patients received oral and written information about a potassium-sparing diet. Furthermore, patients with GFR <30 ml/min were excluded from the study. Finally, plasma potassium concentrations were monitored regularly. Within this regimen spironolactone was generally well tolerated, except for one patient who developed se-
vere hyperkalemia. The incidence of hyperkalemia may have been prevented by increasing the relatively low dose of the loop diuretics received by the patient. There were no complaints of dizziness or antiandrogen side effects in our study, but exposure time was short. The antiandrogen side effects can be avoided by using the newer selective aldosterone receptor antagonist eplerenone, which has shown promising short-term effects in type 2 diabetic patients with albuminuria (30).

We observed a slight increase in A1C of 0.3% upon spironolactone treatment. This is in agreement with a recent study of diabetic patients without nephropathy, which, surprisingly, suggested that the increase in A1C during spironolactone treatment correlated with a worsening in endothelial dysfunction (31). It has not been determined whether spironolactone impairs endothelial dysfunction in diabetic patients with nephropathy. However, when we look at the impact of risk factors for progression of renal disease and cardiovascular disease among type 2 diabetic patients with nephropathy, the potential deleterious effects of a slight increase in A1C upon spironolactone treatment seems outweighed by the substantial reduction in blood pressure and albuminuria.

The long-term clinical effect of spironolactone cannot be established from our short-term study. However, both elevated blood pressure and albuminuria are well-established risk factors for progression of diabetic nephropathy (32,33). Furthermore, several clinical trials have consistently demonstrated that the short-term reduction of albuminuria when antihypertensive treatment is initiated is a strong predictor of the long-term outcome; i.e., the greater the short-term reduction in albuminuria, the lower the long-term cardiovascular risk and the slower the progression of renal disease (34–37). A recent analysis of the Reduction in End Points in Noninsulin-Dependent Diabetes with the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated that every 50% reduction in proteinuria after initiation of antihypertensive therapy reduced the risk of development of end-stage renal disease by 45% (36). When we extrapolate from these data, the 33% reduction in albuminuria seen in our study would imply a relative risk reduction of 29% for progression to end-stage renal disease. In the U.K. Prospective Diabetic Study Group study tight blood pressure control led to a reduction in office blood pressure of 10 mmHg systolic and 5 mmHg diastolic compared with less tight control. This blood pressure reduction was associated with a risk reduction of 32% in deaths related to diabetes, 44% in deaths related to stroke, and 56% in deaths related to heart failure (38). The reduction in office blood pressure was 10/5 mmHg in our long-standing type 2 diabetic patients with nephropathy. Because the absolute risk of cardiovascular events is much higher in our patients than in the U.K. Prospective Diabetic Study Group study, such patients may benefit even more if the blood pressure reduction can be sustained for years.

In summary, our short-term study suggests that 25 mg spironolactone daily added to recommended antihypertensive treatment including ACE inhibitors and/or ARBs is well tolerated and may offer beneficial reno- and cardiovascular protection as reflected by reductions in blood pressure and albuminuria in type 2 diabetic patients with nephropathy. A note of caution should, however, be made regarding the importance of close monitoring of plasma potassium concentration to avoid severe hyperkalemia during aldosterone blockade. Studies are needed to establish the long-term beneficial clinical effects of aldosterone blockade.

Acknowledgments — This study was supported by The Danish Diabetes Association. The study medication was kindly provided by Durascan Medical Products, which is supported by The Danish Diabetes Association.

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Spironolactone in diabetic nephropathy

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