Renoprotective Effects of Adding Angiotensin II Receptor Blocker to Maximal Recommended Doses of ACE Inhibitor in Diabetic Nephropathy

A randomized double-blind crossover trial

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OBJECTIVE — We evaluated the renoprotective effects as reflected by short-term changes in albuminuria of dual blockade of the renin-angiotensin system (RAS) by adding an angiotensin II receptor blocker (ARB) to treatment with maximal recommended doses of an ACE inhibitor (ACEI) in patients with type 2 diabetes and nephropathy.

RESEARCH DESIGN AND METHODS — A total of 20 patients (17 men and 3 women) with type 2 diabetes along with hypertension and nephropathy were enrolled in this double-blind, randomized, two-period, crossover trial of 8 weeks of treatment with the ARB candesartan 16 mg daily and placebo added in random order to existing treatment with lisinopril/enalapril 40 mg daily or captopril 150 mg daily. At the end of each treatment period, we evaluated albuminuria in three 24-h urinary collections by turbidimetry, 24-h ambulatory blood pressure (ABP) using the Takeda-TM2420, and glomerular filtration rate (GFR) by the ^{51}Cr-EDTA plasma-clearance technique.

RESULTS — During monoblockade of the RAS by ACEI treatment, albuminuria was 706 (349−1,219) mg/24 h [geometric mean (IQR)]; 24-h ABP was 138 ± 3/72 ± 2 mmHg (mean ± SE); and GFR was 77 ± 6 ml · min^{-1} · 1.73 m^{-2} (mean ± SE). During dual blockade of the RAS by addition of candesartan 16 mg daily, there was a mean (95% CI) reduction in albuminuria of 28 (17−38) compared with ACEI alone ($P < 0.001$). There was a modest reduction in systolic/diastolic 24-h ABP of 3/2 mmHg (−2 to 8 systolic, −2 to 5 diastolic; NS). Changes in albuminuria did not correlate to changes in ABP. Addition of candesartan 16 mg daily induced a small, insignificant decrease in GFR of 4 (−1 to 9) ml · min^{-1} · 1.73 m^{-2}.

CONCLUSIONS — Dual blockade of the RAS provides superior short-term renoprotection independent of systemic blood pressure changes in comparison with maximally recommended doses of ACEI in patients with type 2 diabetes as well as nephropathy.

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Abbreviations: ABP, ambulatory blood pressure; ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; RAS, renin-angiotensin system; TGF-β, transforming growth factor-β.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetic nephropathy occurs in 30–40% of all diabetic patients and has become the leading cause of end-stage renal disease in the western world (1). In diabetic patients, albuminuria independently predicts poor renal and cardiovascular outcome (1). Several clinical studies have clearly demonstrated that blockade of the renin-angiotensin system (RAS), either by an ACE inhibitor (ACEI) or an angiotensin II receptor blocker (ARB), reduces albuminuria, retards the progressive loss in renal function, and improves survival (2–7). The antiproteinuric response upon blockade of the RAS has been demonstrated to predict the subsequent long-term rate of decrease in glomerular filtration rate (GFR), i.e., the greater the initial decrease in albuminuria, the less the long-term decrease in kidney function (8,9). Consequently, the short-term reduction in albuminuria may serve to monitor treatment efficacy and long-term prognosis in diabetic nephropathy, and it has previously been advocated that albuminuria should be reduced as far as possible to obtain maximal renoprotective effects (10).

Despite the proven benefit of RAS blockade by either ACEIs or ARBs, clinical studies to date have found that such treatment slows but does not completely arrest the progression of renal disease toward end-stage renal disease. Because ACEIs and ARBs antagonize the RAS at different sites, these agents may have additive effects that result in even greater renoprotection when used in combination. Such beneficial additive effects have previously been reported in diabetic patients with microalbuminuria (11) and macroalbuminuria (12,13). However, in these studies, the full renoprotective potential of the RAS blocking agents may not have been reached because either the ACEI or the ARB was not given in maximal recommended doses and the benefi-

cial effects of dual RAS blockade may have been overestimated. When combining two drugs working on the same hormone system, an additive effect specific for the combination can only be demonstrated when compared with monotherapy at the top of the dose response. Therefore, it remains unknown whether similar beneficial renoprotective effects can be obtained when adding an ARB to maximally recommended doses of an ACEI.

The objective of the present study was to evaluate the renoprotective effects, as reflected by short-term changes in albuminuria, of dual blockade of the RAS by adding an ARB at a maximally effective dose (14) to treatment with maximally recommended doses of an ACEI in patients with type 2 diabetes and nephropathy.

RESEARCH DESIGN AND METHODS

Subjects

From the Steno Diabetes Center, we included consecutively 20 Caucasian patients (17 men and 3 women) with type 2 diabetes (according to World Health Organization criteria) (15) as well as nephropathy (persistent albuminuria >300 mg/24 h) and elevated office blood pressure (>135 mmHg systolic and/or >85 mmHg diastolic). All patients included in the study had been on maximal dosage of an ACEI for at least 2 months before inclusion. Patients were excluded if they had a known nondiabetic kidney or renal tract disease, plasma potassium levels >4.6 mmol/l, and/or GFR <25 ml/min.

Design

The study was a randomized, double-blind, crossover trial consisting of two treatment periods, each lasting 2 months. In random order, patients received treatment with candesartan cilexetil 16 mg once daily and matching placebo tablets added to previous antihypertensive treatment. Throughout the study, all patients received ACEI treatment in maximally recommended doses (enalapril/lisinopril 40 mg daily or captopril 150 mg daily). All patients received diuretics in individual doses before entry into the study to treat edema formation or fluid retention. The type and dose of the diuretic used remained unchanged throughout the study.

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. None of the patients had their dietary intake of salt or protein restricted.

Patients attended the clinic for a total of five study visits: one screening visit and subsequently 2 and 8 weeks after the beginning of each treatment period. At the screening visit, blood pressure was measured three times after 10 min rest, and plasma potassium and plasma creatinine levels were measured. Blood pressure, plasma potassium level, and plasma creatinine level were measured 14 days after the beginning of each treatment period for safety reasons.

At the end of each treatment period, the primary end point, which was 24-h urinary albumin excretion, and the secondary end points, including 24-h blood pressure and GFR, were determined. When GFR was assessed, the patients arrived fasting at 8:00 A.M. and breakfast was given after the initial blood samples had been collected at ~8:30 A.M.

The local ethical committee approved the study, and all patients gave informed consent after the nature of the study had been explained. The study was performed in accordance with the Helsinki Declaration.

Laboratory procedures

Albuminuria was determined as the geometric mean of three consecutive 24-h urine collections, completed immediately before the visit at the end of each treatment period (turbidimetry, Cobas Mira Plus; Roche, Montclair, NJ). From 24-h urine samples, sodium, urea, and creatinine excretion in the urine were determined (Cobas Mira Plus). The urinary excretion of urea was used to calculate the protein intake (16). Blood pressure was measured by a 24-h ambulatory blood pressure device (Takeda TM2421; A & D Medical, Tokyo, Japan). A measurement of the blood pressure was performed every 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 the mean 24-h, day, and night blood pressures. Office blood pressure (phase I/V) was measured using an appropriate cuff with a sphygmomanometer in the sitting position after at least 10 min. Three readings, 2 min apart and read to the nearest 2 mmHg, were recorded and the average was used for calculation. GFR was measured after a single intravenous injection of 3.7 MBq ^{51}Cr-EDTA at 8:00 A.M. by determining the radioactivity in venous blood samples taken 180, 200, 220, and 240 min after the injection (17,18). Extra renal loss was corrected for by subtracting 3.7 ml/min (19). The small underestimation (10%) of ^{51}Cr-EDTA renal clearance versus renal clearance of insulin was corrected for by multiplying the EDTA clearance by 1.10 (20). The results were standardized for 1.73 m^2 body surface area. The mean day-to-day coefficient of variation in GFR is 4% in our laboratory.

From venous samples, plasma potassium, sodium, creatinine, and cholesterol concentrations were determined (Cobas Mira Plus) and HbA_{1c} was measured by high-performance liquid chromatography (normal range 4.1–6.1%) (Variant; Bio-Rad, Richmond, CA). Blood samples for renin concentration were taken after 30 min supine rest, and plasma renin concentration was determined using the principle of antibody trapping (21), as modified by Millar et al. (22).

Statistical analysis

Before the present study, we calculated the SD (log scale 0.1771) of the mean difference in urinary albumin excretion rate in three consecutive 24-h urine samples collected twice within 3 months in 36 patients with diabetic nephropathy. On the basis of these data, a sample-size calculation showed a necessary minimum of 16 patients to detect a 25% change in urinary albumin excretion rate ($\alpha = 0.05$, $\beta = 0.8$).

Normally distributed variables are expressed as mean (SE). Values for albuminuria and renin were logarithmically transformed and expressed as geometric mean (interquartile range) because of their positively skewed distribution. Changes in these variables during treatment with candesartan as compared with placebo are expressed in percent.

Comparisons of all clinical end points including albuminuria, blood pressure, and GFR between each treatment period were performed using linear mixed models (23). The software used was R version 1.51 (http://www.r-project.org). The adapted model was one with fixed effects of treatment level (placebo and candesartan 16 mg daily), visit (1 and 2) and carryover (i.e., treatment level in the previous

Table 1—*Effect of adding candesartan 16 mg o.d. to maximal recommended doses of ACEI (enalapril/lisinopril 40 mg daily) on kidney function and ABP in 20 patients with type 2 diabetes and diabetic nephropathy*

	ACEI + placebo	ACEI + candesartan 16 mg	Mean difference (95% CI)*	*P** value
Albuminuria (mg/24 h)†	706 (349–1,219)	508 (228–909)	28% (17–38)	<0.001
Blood pressure (mmHg)				
24-h	138 (3)/72 (2)	135 (3)/70 (2)	3 (−2 to 8)/2 (−2 to 5)	0.21/0.38
Day (7:00 a.m. to 11:00 p.m.)	142 (3)/74 (2)	139 (3)/72 (2)	3 (−2 to 7)/3 (−2 to 7)	0.32/0.31
Night (11:00 p.m. to 7:00 a.m.)	131 (4)/67 (2)	126 (4)/65 (3)	5 (−2 to 11)/2 (−3 to 7)	0.16/0.51
GFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	77 (6)	74 (5)	4 (−1, 9)	0.10
Plasma creatinine (μmol/l)	121 (10)	123 (10)	2 (−7 to 10)	0.66
Plasma renin (mU/l)	42 (1)	53 (1)	−24% (−60 to 12)	0.19
Plasma potassium (mmol/l)	4.0 (0.1)	4.2 (0.1)	−0.13 (−0.3 to 0.1)	0.13
HbA_{1c} (%)	7.9 (0.2)	8.1 (0.2)	−0.1 (−0.1 to 0.4)	0.31
Cholesterol (mmol/l)	4.5 (0.2)	4.6 (0.2)	−0.1 (−0.2 to 0.4)	0.60
Urinary sodium (mmol/24 h)	195 (13)	188 (12)	6 (−19 to 32)	0.63
Protein intake ($g \cdot kg^{-1} \cdot 24\ h^{-1}$)	0.92 (0.06)	0.93 (0.04)	−0.01 (−0.07 to 0.07)	0.94

Data are means (SE). *Mean difference of (ACEI + placebo) − (ACEI + candesartan 16 mg); †geometric mean (IQR).

period), and a random effect of person included to account for the person-dependencies in data. For the simplest models, the *P* value and effects correspond to results obtained from paired Student's *t* test and two-way ANOVA, but these models allow for more elaborate exploration of the material. Tests for presence of effects were performed as likelihood ratio tests, and final estimates were reported as restricted maximum likelihood estimates (23).

RESULTS

A total of 20 patients were randomized, all of whom completed the study. However, in one patient, the renin analysis failed. All patients included in the study were Caucasian and most were men (17 men and 3 women). The mean (SD) age of the patients was 62 (8) years, the known duration of diabetes was 15 (8) years, and the mean BMI was 31 (6) kg/m^2. A total of 18 patients had diabetic retinopathy, whereas two patients had no signs of retinopathy. Throughout the study, all patients received ACEI treatment in maximally recommended doses: enalapril ($n = 17$)/lisinopril ($n = 2$) 40 mg daily or captopril 150 mg daily ($n = 1$). In addition, all patients received diuretics; 10 patients received hydrochlorothiazide (median 25 mg daily; range 25–50) and 10 patients received long-acting furosemide 105 mg daily (30–300). A total of 13 patients received a calcium channel antagonist and 4 patients received a β-blocker. The median number of antihypertensive drugs in addition to the study medication was 3 (range 2–4). The median duration of treatment was 63 days (range 54–100) and compliance to treatment as assessed by tablet count was 100% (87–100) during addition of both placebo and candesartan 16 mg daily.

The statistical analysis showed no evidence of a carry-over or time sequence effect on the end points evaluated in the study, including albuminuria, 24-h ambulatory blood pressure (ABP), or GFR.

During dual blockade of the RAS by addition of candesartan 16 mg daily to maximally recommended doses of ACEI, albuminuria was significantly reduced by 28% (95% CI 17–38) compared with RAS blockade with ACEI alone ($P < 0.001$) (Table 1). GFR and plasma creatinine levels remained unchanged during the study (Table 1). However, there was a statistically insignificant trend toward a small decrease in GFR of 4 (−1 to 9) $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ by addition of candesartan 16 mg daily as compared with placebo.

There were no significant changes in 24-h, day, or night ABP during dual blockade of the RAS as compared with monoblockade with ACEI treatment alone (Table 1). However, there was a general tendency toward a modest decrease of 3–5 mmHg in 24-h systolic and 2–3 mmHg in 24-h diastolic ABP measurements during dual blockade of the RAS as compared with ACEI treatment alone (Table 1). Similarly, there was a general tendency toward a modest decrease in office blood pressure from 147 ± 5/77 ± 2 mmHg (mean ± SE) during placebo to 142 ± 3/75 ± 2 mmHg during addition of candesartan (NS; data not shown in Table 1).

Plasma renin concentration tended to increase by 24% (95% CI −12 to 60) during additional treatment with candesartan as compared with placebo; however, this increase was not statistically significant (Table 1). Plasma potassium, HbA_{1c}, cholesterol, urinary sodium excretion, and protein intake remained unchanged throughout the study (Table 1). There were no incidences of hyperkalemia, and the therapy was well tolerated without adverse symptoms related to the study medication.

In linear regression analysis, relative changes in albuminuria did not correlate to changes in 24-h systolic ABP ($R = 0.07$, $P = 0.8$) (Fig. 1*A*) or 24-h diastolic ABP ($R = 0.11$, $P = 0.6$). Furthermore, changes in albuminuria did not correlate to changes in renin concentrations ($R = 0.04$, $P = 0.9$). However, changes in renin concentrations were closely correlated to changes in 24-h systolic ABP ($R = 0.79$, $P < 0.001$) (Fig. 1*B*) and, to a lesser extent, to 24-h diastolic ABP ($R = 0.47$, $P = 0.04$).

Using linear regression analysis, we found no correlation between changes in albuminuria upon dual blockade of the RAS and baseline variables (ACEI + placebo) including age, BMI, albuminuria, plasma renin, total cholesterol, ABP, and salt intake.

CONCLUSIONS — Our double-blind, randomized, crossover study suggests that dual blockade of the RAS

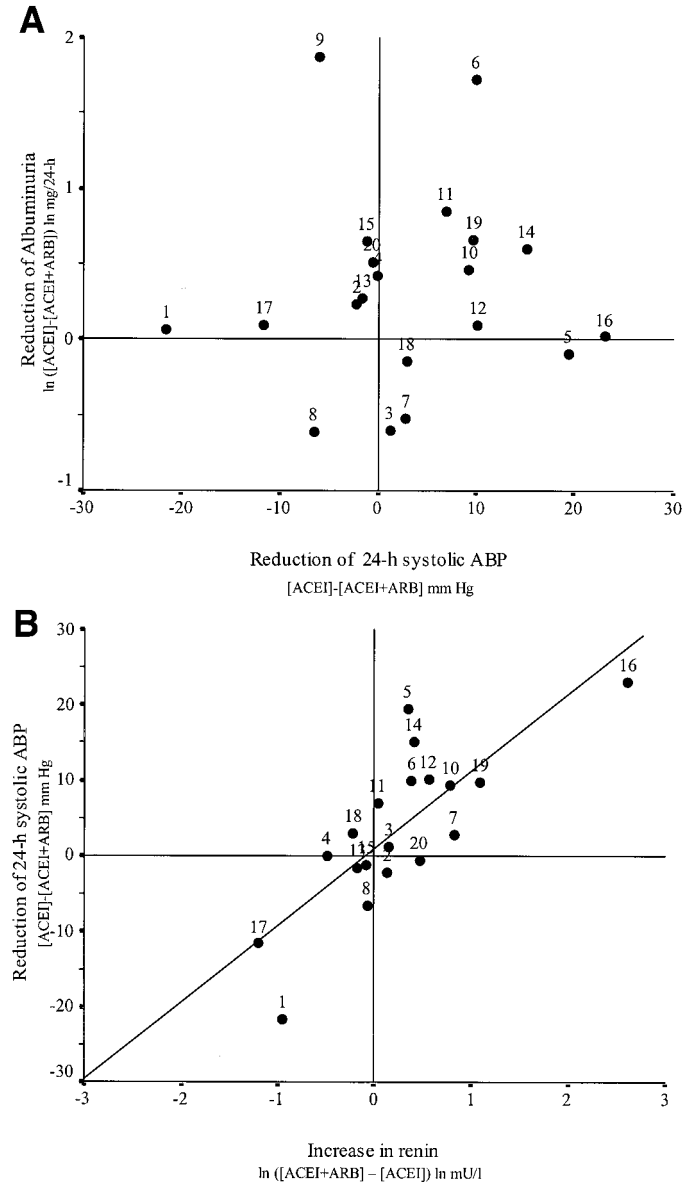

Figure 1—*Individual responses to addition of candesartan cilexetil 16 mg daily to maximal recommended doses of ACEI in 20 patients with type 2 diabetes and nephropathy.* A*: Linear regression between absolute reduction in 24-h systolic blood pressure (mmHg; placebo − candesartan) and relative reduction in albuminuria (ln mg/24 h; ln placebo − ln candesartan).* B*: Linear regression between relative increase in plasma renin (ln mU/l; ln candesartan − ln placebo) and absolute reduction in 24-h systolic blood pressure (mmHg; placebo − candesartan). Individuals are indicated by the same numbers in* A *and* B.

provides superior renoprotection, as reflected by short-term changes in albuminuria, compared with the maximal recommended dose of ACEI in type 2 diabetic patients with nephropathy. The reduction of albuminuria by dual blockade of the RAS was independent of changes in blood pressure, which was only modestly and insignificantly reduced. The therapy was generally well tolerated without associated adverse events, and no incidences of hyperkalemia were observed in these patients, who generally had normal or only moderately reduced kidney function.

The rationale for dual RAS blockade depends on the different sites of actions of ACEI and ARB leading to synergistic blockade of the RAS not obtainable by either drug alone. ACEIs decrease the formation of angiotensin II and the degradation of bradykinin, which is a powerful vasodilator (24). However, angiotensin II may be generated through ACE-independent pathways such as chymase, leading to incomplete blockade of the formation of angiotensin II upon ACEI (25). Such incomplete blockade may explain the observation that plasma angiotensin II levels return to normal after chronic ACEI treatment, the so-called "ACE-escape" phenomenon (26,27). Treatment with ARB may result in more complete blockade of the unfavorable actions of angiotensin II mediated through the angiotensin II type 1 receptor. However, new data from animal studies indicate that some of the deleterious effects of angiotensin II on glomerular cell migration, tubular cell proliferation, and development of urinary protein excretion may be mediated through the angiotensin II type 2 receptor (28–30), which is not blocked by currently used ARBs. Data supporting the evidence of more complete RAS blockade by combination ACEI/ARB therapy as compared with single agent therapy have come from an animal model in which treatment with captopril (1.7 mg/day) and losartan (0.7 mg/day) reduced renal tissue angiotensin II level significantly more than treatment with monoblockade using double and triple doses of either captopril or losartan (31). The mechanisms underlying the lower renal tissue angiotensin II during ARB treatment may involve decreased binding to the receptor and internalization of angiotensin II in the presence of a receptor blocker and/or increased degradation of angiotensin II.

In humans, beneficial effects of dual blockade of the RAS have been demonstrated previously in several short-term clinical studies of both diabetic patients with microalbuminuria (11) and macroalbuminuria (12,13) and nondiabetic nephropathy (32–35). However, in these studies, either the ACEI or the ARB was not given in maximal recommended doses, and as a consequence, the effect of monoblockade of the RAS may potentially be underestimated. The antiproteinuric dose-response of ACEI has been evaluated in a large meta-analysis from 10 randomized clinical trials in the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Disease (AIPRD) database, including 881 patients with nondiabetic chronic kidney disease followed for 2.2 years (36). Patients were treated with benazepril, cilazapril, ramipril, or enalapril, and doses were calculated as a time-

weighted average and converted into equivalent doses of enalapril. Increasing the ACEI dose (5–20 mg daily) was associated with a greater antiproteinuric effect independent of the blood pressure–lowering effect. Unfortunately, there are no data from large clinical studies on the antiproteinuric effects of ACEIs in doses higher than enalapril 20 mg daily (or equivalents). However, in a recent nonrandomized open-labeled study of nine patients with nondiabetic renal disease, the reduction in proteinuria was significantly higher with lisinopril 40 mg daily (70% reduction from baseline values of 4.5 g proteinuria/24 h) than with lisinopril 20 mg daily (50% reduction from baseline), suggesting that maximal recommended doses of the ACEI should be used to obtain maximal reduction in albuminuria (37). The antiproteinuric effects of ACEI in doses above current recommendations are unknown and further antiproteinuric effects of such doses cannot be excluded.

There are only limited data from clinical studies on the renoprotective effects of dual blockade of the RAS, as compared with maximal recommended doses of ACEI. In a heterogeneous group of 16 severely obese, hypertensive, proteinuric diabetic African Americans with advanced renal failure, addition of losartan 50 mg daily to lisinopril 40 mg daily had no short-term effect on blood pressure and proteinuria (38). However, subsequent analysis in the same patients of urinary excretion of the profibrotic growth factor transforming growth factor-β (TGF-β) showed elevated urinary TGF-β during monoblockade with maximal doses of ACEI and a 38% reduction during addition of losartan that was independent of changes in blood pressure or albuminuria (39). The lack of antiproteinuric effects of dual blockade in this study may be due to underdosing of the ARB, because 100 mg losartan is more effective than 50 mg in reducing both albuminuria and blood pressure in patients with diabetic and nondiabetic nephropathy (40,41). Furthermore, these findings cannot be extrapolated to other ethnic groups due to differences in RAS activity and response to RAS blockade (42,43). In the previously mentioned study of nine patients with nondiabetic renal disease, dual RAS blockade (40 mg lisinopril + 50–150 mg losartan) induced a significantly greater reduction in proteinuria compared with monoblockade (37). Recently, the combination of ACEI and ARB has also been shown to produce beneficial antiproteinuric effects independent of blood pressure in 45 patients with primary nondiabetic nephropathies followed for 6 months in an open, randomized, paralleled study (44).

The long-term effect of dual RAS blockade on principal renal end points in nondiabetic patients has recently been addressed in the COOPERATE trial (45). In this double-blind randomized study of 263 patients, only 11% of patients on dual blockade (100 mg losartan daily and 3 mg trandolapril daily) developed doubling of serum creatinine or reached end-stage renal disease during a median of 3 years of follow-up, whereas 23% reached the primary end points during treatment with either monotherapies ($P = 0.02$). The combination of ACEI and ARB was well tolerated in this study, in which patients had more severely reduced kidney function at baseline (estimated GFR ~40 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) as compared with our study. According to the authors of this study, the optimal dosage of trandolapril had been confirmed during the run-in period, during which no further antiproteinuric effects were seen by doses of trandolapril >3 mg daily (increased to 6 mg daily). Because losartan 100 mg daily has previously been demonstrated as the optimal effective dose for maximal reduction of proteinuria (40,41), the COOPERATE study suggests a beneficial additive effect of ACEI and ARB, even at maximal effective doses of both drugs. Unfortunately, there are no similar long-term studies in diabetic nephropathy.

The reduction in albuminuria by dual blockade of the RAS seen in our study did not correlate with changes in systemic blood pressure, which was only modestly and insignificantly reduced by addition of candesartan. This may suggest a blood pressure–independent reduction of albuminuria and, furthermore, that higher doses of RAS blocking agents are required to obtain maximal antiproteinuric effects as compared with the doses needed to maximally reduce systemic blood pressure. Furthermore, changes in circulatory renin did not correlate with changes in albuminuria but were highly correlated to changes in systemic blood pressure. This may indirectly suggest that local RAS activity in the kidneys requires higher RAS blockade than systemic RAS activity responsible for systemic blood pressure. The blood pressure–independent effect of additional therapy with candesartan in the present study seems in overall agreement with findings from large clinical trials in diabetic patients demonstrating intrinsic renoprotective effects in addition to the antihypertensive effect by ARB (5–7). Several mechanisms have been suggested for such blood pressure–independent antiproteinuric effects of RAS inhibition. First, it may be related to a reduction in intraglomerular blood pressure independent of systemic blood pressure by vasodilatation preferentially of the postglomerular arterioles (46). Second, RAS inhibition may improve charge and size selectivity of the glomerular membrane (47), which may be related, in part, to reduced loss of glomerular nephrin, a protein located at the slit-diaphragm of the glomerular podocyte, which is suggested to play a central role in the function of the glomerular filtration barrier (48).

In our study, there was a wide variation in the individual antiproteinuric response to dual blockade. However, we were not able to demonstrate any significant correlations between changes in albuminuria upon dual blockade and baseline (ACEI + placebo) variables such as age, BMI, albuminuria, plasma renin, blood pressure, and salt intake. This may be due to the relatively small number of patients included in the study, and future studies are needed to characterize responders versus nonresponders to dual RAS blockade to more specifically target treatment to the individual patient. The wide range in the duration of the treatment periods in the study (54–100 days) was due to one patient who was not able to attend the clinic at the scheduled visit after 2 months. Because all other patients were followed for 2 months ± 1 week, the differences in duration of treatment are not likely to affect the response to treatment in the study. Because only three female patients were included in the study, the results may mainly be applicable to male patients.

The present study design does not allow an evaluation of the placebo effect because end points (including three 24-h urinary collections, 24-h blood pressure readings, and GFR) were not evaluated at the screening visit. The study was designed to evaluate only placebo values versus ARB.

In conclusion, our short-term study supports the concept that treatment with both ACE-I and ARB offer synergistic renoprotection not obtainable with maximal recommended doses of ACEI in type 2 diabetic patients with nephropathy. Future trials are needed to characterize those individuals who are likely to benefit from dual blockade and to establish the long-term impact of dual blockade of the RAS.

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