Effect of Telmisartan–Amlodipine Combination at Different Doses on Urinary Albumin Excretion in Hypertensive Diabetic Patients With Microalbuminuria

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Background: Aim of this study was to evaluate the effect of the telmisartan–amlodipine combination at different doses on urinary albumin excretion rate (UAER) in hypertensive diabetic patients with microalbuminuria.

Methods: After a 2-week placebo period, 300 hypertensive patients with type 2 diabetes and microalbuminuria were treated with the 40 mg of telmisartan and 2.5 mg of amlodipine combination. After 4 weeks 210 patients whose blood pressure (BP) was not controlled (BP >130/80 mm Hg) were randomized to two-dose titration regimens, one based on increasing doses of telmisartan (up to 160 mg daily) and fixed 2.5-mg dose of amlodipine, the other based on increasing doses of amlodipine (up to 10 mg daily) and fixed 40-mg dose of telmisartan. After 12 weeks the nonresponder patients were given transdermic clonidine (0.1mg/d). After 16 weeks the patients yet not controlled were discontinued, the others were followed for 48 weeks. Office BP, UAER, creatinine clearance, plasma potassium, fasting glycemia, and glycosylated hemoglobin were assessed at the end of the telmisartan (40 mg)/amlodipine (2.5 mg) treatment period and after 48 weeks of treatment.

Results: Similar decrease in systolic/diastolic BP values were obtained with both regimens (−24/−21, −23/−21, and −24/−21 mm Hg, all $P < .001$ *v* baseline, with increasing telmisartan; −25/−22, −25/−21, and −25/−22 mm Hg, all $P < .001$ *v* baseline with increasing amlodipine). Reductions of UAER were 47.5% ($P < .01$), 65.3% ($P < .001$), and 77% ($P < .0001$) for telmisartan 80, 120, and 160 mg/amlodipine 2.5 mg daily, respectively, whereas reductions of UAER were 34% ($P < .03$), 37% ($P < .03$), and 33% ($P < .03$) for amlodipine 5, 7.5, and 10 mg/telmisartan 40 mg daily, respectively, The difference between the two regimens was statistically significant ($P < .05$, $P < .01$, and $P < .001$, respectively).

Conclusions: These findings indicate that, at comparable levels of BP reduction, UAE decreased more in subjects treated with escalating doses of telmisartan.

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Key Words: Telmisartan amlodipine, microalbuminuria, hypertension, type 2 diabetes.

Microalbuminuria, defined as urinary albumin excretion rate (UAER) between 30 and 300 mg/24 h, is a major prognostic factor for both progressive diabetic renal disease and increased cardiovascular morbidity and mortality rates in diabetic patients.[1–3] In type 2 diabetes microalbuminuria is frequently associated with hypertension and this coexistence is associated with a more rapid progression of renal and cardiovascular damage.[4,5] Therefore therapy should be directed at decreasing both blood pressure (BP) and UAER.[6] With overwhelming evidence that earlier and more intensive BP control is renoprotective in hypertensive patients with diabetes, preferably achieving a BP of less than 130/80 mm Hg,[7,8] it is clear that these patients will require multiple medications to target these BP goal values.[6–8]

A clear general consensus has been reached regarding the usefulness of blocking the renin-angiotensin system (RAS) in reducing UAER, retarding the progressive loss in

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renal function, and improving survival.[9–13] Therefore to ensure renal protection, any combined therapy for progressive renal disease must include either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), or both. Recently, combined therapy with an ACE inhibitor and an ARB has been shown to provide a greater reduction in urinary albumin excretion (UAE) than monotherapy with either of these agents in patients with diabetic nephropathy.[14–17] However, such combinations may be associated with potential hazards, including increased serum potassium concentrations and worsening of renal anemia, especially in patients whose kidney function is mildly to moderately impaired.[18,19] Therefore, in type 2 diabetic hypertensive patients the use of a calcium channel blocker (CCB) plus an ARB may be an useful alternative to avoid these potential adverse effects. In addition, because CCBs per se yield a reliable reduction in BP whereas ARBs offer an assured antiproteinuric effect, such a combination may potentially provide renoprotection. To date, however, few data exist about combined antihypertensive therapy with an ARB plus a CCB in type 2 diabetic patients[19] and optimal dosage of both components to maximize proteinuria reduction remains to be established.

With this background, in the present study we evaluated the effect of a combination therapy with the ARB telmisartan and the long-acting CCB amlodipine on UAER in hypertensive patients with type 2 diabetes and microalbuminuria and examined whether two different dose regimens (high-dose telmisartan/low-dose amlodipine and vice-versa) offered different benefit in terms of reduction of proteinuria.

Methods

Outpatients of both genders, aged 35 to 70 years, with essential hypertension (diastolic BP and systolic BP), type 2 diabetes mellitus well controlled by diet or by oral antidiabetic drugs, and microalbuminuria (UAER >30 and <300 mg/24 h in two distinct 24-h urine collections during 7 days before enrolment) were considered for screening. Patients were excluded if they had secondary hypertension, history of myocardial infarction or stroke within 6 months before the start of the study, congestive heart failure, cancer or any severe disease likely to interfere with the conduct of the study, smoking habits, and body mass index (BMI) >30 kg/m^2. Patients with known intolerance to ARBs or CCB were likewise excluded.

The local ethical committee approved the study protocol and all patients gave their informed consent to participate in the study after the nature of the study had been explained.

After a 2-week placebo washout period, during which antihypertensive but not oral antidiabetic drugs were discontinued, patients fulfilling the inclusion criteria were treated with the telmisartan (40 mg)/amlodipine (2.5 mg) combination. After 4 weeks, patients whose BP was not

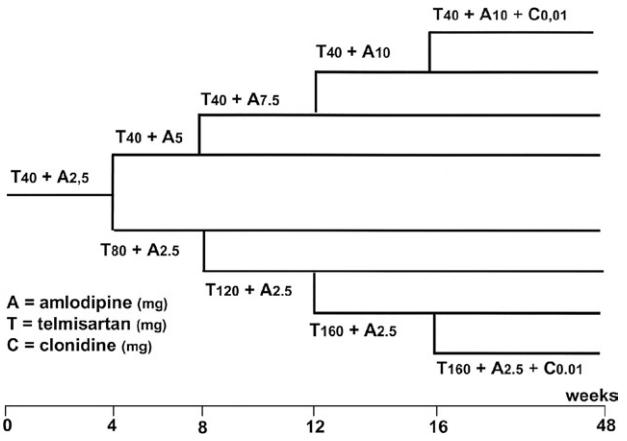


FIG. 1. Study design.

controlled (BP >130/80 mm Hg) were enrolled in the study and randomized to two different dose titration regimens: one based on increasing doses of telmisartan (40 mg every 4 weeks until 160 mg) and fixed 2.5-mg dose of amlodipine (group T), the other based on increasing dose of amlodipine (2.5 mg every 4 weeks until 10 mg) and fixed 40-mg dose of telmisartan (group A). After 16 weeks the nonresponder patients were given 0.1 mg/d transdermic clonidine (Fig. 1). After 20 weeks (end of titration period) patients who were yet not controlled were discontinued. The responder patients were followed for 48 weeks. All patients were maintained on a diet previously prescribed as part of their routine medical care. Oral antidiabetic treatment was maintained throughout the study and no other medication was administered.

At the end of the telmisartan (40 mg)/amlodipine (2.5 mg) treatment period, at the end of the 16-week titration period, and after 48 weeks office BP was evaluated. The UAER, creatinine clearance, plasma potassium, fasting glycemia, and glycosylated hemoglobin (HbA_{1c}) were evaluated at the end of telmisartan (40 mg)/amlodipine (2.5 mg) period and after 48 weeks.

The BP was measured in the morning before daily drug intake (ie, at trough, 22 to 24 h after dosing) by using a standard mercury sphygmomanometer (Korotkoff I and V) on the patient's same arm three times after a 5-min rest in the sitting position at consecutive 2-min intervals. The actual BP value considered was the average of the three measurements. The UAER was assessed by radioimmunoassay. Each reported UAER value represents the mean of two distinct 24-h urine collections within 1 week. Clear instructions were given on how to collect urine samples and patients were advised to have minimal physical activity. Data about 24-h urine creatinine levels and body weight (Table 1) confirmed adequate urine collection. Chemical analyses of serum and urine were performed by standard clinical laboratory tecnique. The HbA_{1c} concentrations were determined by high performance liquid chromatography (HPLC).

Table 1. Demographic and clinical characteristics of the study population

	Telmisartan	Amlodipine
Patients (*n*)	105	105
Sex (M/F)	52/53	54/51
Age (y)	56 ± 7	55 ± 8
Hypertension duration (y)	8 ± 4	7 ± 3
Diabetes duration (y)	6 ± 3	6 ± 4
BMI (kg/m^2)	27.3 ± 1.2	27.8 ± 1.5
Body weight (kg)	78.1 ± 6.4	78.4 ± 6.9
SBP (mm Hg)	150 ± 11	151 ± 11
DBP (mm Hg)	96 ± 5	96 ± 5
24-h urine creatinine (mg/24 h)	1357.2 ± 110.5	1388.7 ± 119.7
UAER (mg/24 h)	132.4 ± 68.2	135.5 ± 72.3
Creatinine clearance (mL/min)	92.4 ± 8.3	94.1 ± 9.2
Plasma K (mmol/L)	4.0 ± 0.3	4.1 ± 0.4
FPG (mg/dL)	133.6 ± 22.0	135.5 ± 24.0
HbA_{1c} (%)	6.8 ± 1.2	6.9 ± 1.1
FPI (μU/mL)	17.2 ± 3.1	17.8 ± 3.4
Total cholesterol (mg/dL)	193.3 ± 12.2	191.7 ± 10.9
HDL-cholesterol (mg/dL)	41.4 ± 3.6	42.2 ± 3.9
LDL-cholesterol (mg/dL)	124.4 ± 6.1	122.7 ± 5.8
Triglycerides (mg/dL)	129.7 ± 29.8	123.1 ± 27.5

P = not significant; all values are mean ± SD.

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; UAER = urinary albumin excretion rate; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; FPI = fasting plasma insulin.

Statistical Analysis

Data are expressed as means ± SD. The homogeneity check of patient distribution between the two treatment groups was performed using the χ^2 test. The results were analyzed statistically using analysis of variance and Student *t* test (paired–unpaired for intra/intergroup comparisons). All tests were two-tailed and statistical significance was defined as $P < .05$.

Results

Three hundred patients who fulfilled the inclusion criteria at the end of the placebo washout period were treated with the telmisartan (40 mg)/amlodipine (2.5 mg) combination for 4 weeks. Of them 210 patients whose BP was not controlled (BP >130/80 mm Hg) were enrolled in the study and randomized to the titration period, 105 in the T group and 105 in the A group. Their baseline demographic and clinical characteristics are shown in Table 1. There were no statistical differences between the two regimen groups for the analyzed parameters. As a result of dose titration, in the T group 36 patients needed to be treated with the highest telmisartan dose, 33 with 120 mg of telmisartan and 36 were maintained in treatment with 80 mg of telmisartan. In the A group 26 patients needed to be treated with the highest amlodipine dose, 33 were given 7.5 mg of amlodipine and 36, 5 mg of amlodipine. Due to insufficient BP control after 12 weeks of titration, 16 patients in the telmisartan (160 mg)/amlodipine (2.5 mg) group and 11 in the telmisartan (40 mg)/amlodipine (10 mg) group needed to be added 0.1 mg/d transdermic clonidine. Their clinical characteristics were similar in the two treatment groups. After 20 weeks (end of titration period) 6 patients (4 in the T and 2 in the A group) were yet not controlled and were withdrawn from the study. Their baseline characteristics, including UAER, were similar to those of the patients who continued the study; the only difference being uncontrolled BP (>130/80 mm Hg). Two patients in the T group and 1 patient in the A group were lost at follow-up, therefore 99 patients in the T group and 102 patients in the A group completed the 48-week study period.

The main results of the study are shown in Tables 2 and 3.

High-dose telmisartan/low-dose amlodipine and low-dose telmisartan/high-dose amlodipine combination produced similar reduction in systolic and diastolic BP values, with no significant difference between the two regimens at any time of the study. With increasing doses of telmisartan (from 40 to 80, 120, and 160 mg) systolic/diastolic BP values were reduced from baseline by 16/10 mm Hg ($P < .01$ *v* baseline), 24/21 mm Hg, 23/21 mm Hg, and 24/21 mm Hg (all $P < .001$ *v* baseline), respectively. With increasing dose of amlodipine (from 2.5 to 5, 7.5, and 10 mg) systolic/diastolic BP values were reduced from baseline by 16/10 mm Hg ($P < .01$ *v* baseline), 25/22 mm Hg, 25/21 mm Hg, and 25/22 mm Hg (all $P < .001$ *v* baseline), respectively.

The UAER was significantly decreased from baseline by both combination regimens, but such a decrease was significantly more marked in the T group (Fig. 2). Reductions of UAER from baseline were of 34.6 mg/24 h ($P <$

Table 2. Dosage and metabolic parameters in the telmisartan group

	Baseline	4 Weeks	48 Weeks		
Dosage (T/A)	—	40/2.5	80/2.5	120/2.5	160/2.5
Patients (*n*)	105	105	35	33	34
SBP (mm Hg)	150 ± 11	134 ± 10*	127 ± 9†	127 ± 9†	127 ± 8†
DBP (mm Hg)	96 ± 5	85 ± 6*	75 ± 5†	75 ± 5†	75 ± 5†
UAER (mg/24 h)	132.4 ± 68.2	97.8 ± 43.7‡	69.5 ± 32.1*‖	45.9 ± 25.9†#	30.3 ± 18.5**††
Creatinine clearance (mL/min)	92.4 ± 8.3	92.6 ± 8.4	92.9 ± 8.5	93.3 ± 8.9	91.5 ± 7.9
Plasma K (mmol/L)	4.0 ± 0.3	4.1 ± 0.4	4.1 ± 0.5	4.2 ± 0.7	4.3 ± 0.8
FPG (mg/dL)	133.6 ± 22.0	128.2 ± 20.5	126.4 ± 19.3	128.2 ± 21.1	125.4 ± 18.3
HbA_{1c} (%)	6.8 ± 1.2	6.6 ± 1.1	6.7 ± 1.2	6.5 ± 1.0	6.6 ± 1.1

T = telmisartan; A = amlodipine; abbreviations as in Table 1.
* $P < .01$ *v* baseline; † $P < .001$ *v* baseline; ‡ $P < .05$ *v* baseline; § $P < .0001$ *v* baseline; ‖ $P < .05$ *v* amlodipine; # $P < .01$ *v* amlodipine; ** $P < .001$ *v* amlodipine; †† $P < .05$ *v* telmisartan 80 mg.

.05 *v* baseline), 62.9 mg/24 h ($P < .01$ *v* baseline and $P < .05$ *v* A group), 86.5 mg/24 h ($P < .001$ *v* baseline and $P < .01$ *v* A group) and 102 mg/24 h ($P < .0001$ *v* baseline and $P < .001$ *v* A group) for telmisartan 40, 80, 120, and 160 mg/amlodipine 2.5 mg daily, respectively. Reductions of UAER from baseline were of 35.1 mg/24 h ($P < .05$ *v* baseline), 46.2 mg/24 h ($P < .03$ *v* baseline), 50.3 mg/24 h ($P < .03$ *v* baseline), and 45 mg/24 h ($P < .03$ *v* baseline) for amlodipine 2.5, 5, 7.5, and 10 mg/telmisartan 40 mg daily, respectively.

Body weight remained substantially unchanged in all patients. Creatinine clearance did not significantly change from baseline during the 48-week study period with both treatment regimens. Likewise, neither combination therapy significantly affected levels of plasma potassium and fasting glycemia. The HbA_{1c} levels were not significantly influenced by any treatment and no patient required substantial changes in hypoglycemic therapy.

Both treatment regimens were well tolerated. The number of patients who reported one or more adverse events were 10 in the T group (10%) and 15 (14%) in the A group, with no statistical difference between the two treatments. The reported side effects were dizziness ($n = 5$), nausea ($n = 3$), asthenia ($n = 2$), and headache ($n = 1$) in the T group; leg edema ($n = 7$), headache ($n = 3$), hot flushes ($n = 3$), and palpitations ($n = 2$) in the A group. No patient withdrew from the study because of a serious adverse experience.

Discussion

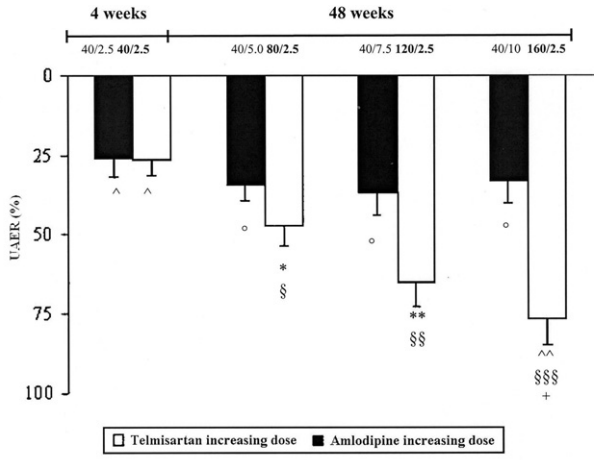
The results of this study demonstrated that in nonsmoking hypertensive patients with type 2 diabetes and microalbuminuria the high-dose telmisartan/low-dose amlodipine combination was as effective as low-dose telmisartan/high-dose amlodipine combination in reducing BP values during the 48-week study period without affecting glycemic control or electrolyte plasma levels. This confirms the usefulness and safety of a combination therapy with an ARB and a long-acting CCB to achieve required target BP levels in these high risk patients.

The most interesting findings of this study, however, regard the effects of the two different regimens on UAER. Although the telmisartan/amlodipine combination, both with high- and low-dose of telmisartan, produced a significant reduction in UAER, this effect was significantly more pronounced with the high-dose telmisartan combination, despite equivalent BP-lowering effect. Although

Table 3. Dosage and metabolic parameters in the amlodipine group

	Baseline	4 Weeks	48 Weeks		
Dosage (T/A)	—	40/2.5	40/5.0	40/7.5	40/10
Patients (*n*)	105	105	43	32	24
SBP (mm Hg)	151 ± 11	135 ± 10*	126 ± 8†	126 ± 8†	126 ± 8†
DBP (mm Hg)	96 ± 5	86 ± 6*	74 ± 5†	75 ± 5†	74 ± 5†
UAER (mg/24 h)	135.5 ± 72.3	100.4 ± 46.9‡	89.3 ± 40.3§	85.2 ± 36.2§	90.5 ± 42.1§
Creatinine clearance (mL/min)	94.1 ± 9.2	93.8 ± 8.6	94.5 ± 8.8	93.9 ± 8.7	94.2 ± 8.9
Plasma K (mmol/L)	4.1 ± 0.4	4.2 ± 0.5	4.1 ± 0.4	4.0 ± 0.4	4.2 ± 0.7
FPG (mg/dL)	135.5 ± 24.0	132.6 ± 23.0	129.2 ± 20.4	131.8 ± 21.7	129.1 ± 20.0
HbA_{1c} (%)	6.9 ± 1.1	6.7 ± 1.0	6.6 ± 0.9	6.9 ± 1.1	6.7 ± 0.9

Abbreviations as in Tables 1 and 2.
* $P < .01$ *v* baseline; † $P < .001$ *v* baseline; ‡ $P < .05$ *v* baseline; § $P < .03$ *v* baseline.



^p < 0.05, ^^p < 0.0001, ° p < 0.03 *p < 0.01, **p < 0.001, change from baseline;

§p < 0.05; §§p < 0.01, §§§p < 0.001, between treatment, + p < 0,05 vs 80/2,5

FIG. 2. Percentage of urinary albumin excretion rate (UAER) decrease with telmisartan–amlodipine combination at different doses.

increasing amlodipine from 7.5 to 10 mg daily did not produce a further decrease in UAER, increasing the telmisartan dose up to 160 mg once daily (ie, largely exceeding the currently recommended dose of 80 mg once daily) resulted in additional reduction of UAER (−26% *v* baseline with 40 mg of telmisartan, −47.5% with 80 mg, −65% with 120 mg, and −77% with 160 mg). Although in the present study the telmisartan dose was coupled to the BP response and further information could be provided by increasing the telmisartan dose above the level required for BP control, our results are in agreement with findings of previous dose–response studies of both ACE inhibitors and ARBs, which have demonstrated that higher doses provided greater antiproteinuric effects than lower doses.[20–24]

The greater reduction of UAER by higher doses of telmisartan was independent of reductions in systemic BP. Several mechanisms have been suggested to explain the BP independent effects of ARBs on UAER, including (1) reduction of intraglomerular hydraulic pressure by preferential vasodilation of the postglomerular arterioles[25]; (2) improvement of permselective properties of the glomerular membrane[26]; (3) reduction of the deficiency in glomerular nephrin expression, 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[27]; and (4) reduction of renal levels of prosclerotic cytokines such as transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF).[28] Increased RAS activity and augmented angiotensin II receptor density in the diseased renal tissue, together with possible reduced penetration of the drug, might explain that higher doses are needed for complete RAS blockade in the tissue responsible for antiproteinuric effect as compared to circulatory levels regulating systemic BP.[25] This also suggests that higher doses of RAS blocking agents are required to obtain maximal antiproteinuric effects as compared with the doses needed to reduce BP levels.[22]

The finding that the low-dose telmisartan/high-dose amlodipine combination provided a significantly less pronounced, although significant, antiproteinuric effect suggests that the reduction in UAER with this regimen occurred through different pathways, possibly involving mainly the antihypertensive action of amlodipine rather than other intrinsic effects of this drug. This is consistent with available data in the literature indicating that tight BP control in the early stage of diabetic nephropathy is an important factor in reducing UAER and preventing progression to macroalbuminuria.[29]

Improved glycemic control has also been demonstrated to decrease proteinuria in type 2 diabetic patients.[29] In the present study no combination regimen significantly modified fasting glycemia or HbA_{1c}. Therefore, it seems unlikely that the between treatment difference observed in UAER can be explained by differing degrees of metabolic control in the two treatment groups.

Because proteinuria in itself contributes to the progression of renal lesions, the reduction in UAER is likely to delay the onset of clinical proteinuria and decline of renal function in microalbuminuric subjects.[13] In our patients, renal function, assessed by creatinine clearance, showed no significant change with both high- and low-dose telmisartan/amlodipine combination and no difference between the two combination regimens was found. Forty-eight weeks, however, represent perhaps a too short observation period to detect possible changes in renal function due to the reduction in UAER in patients with incipient nephropathy.

The present study indicates that, at comparable levels of BP reduction, combined antihypertensive therapy with escalating doses of the ARB telmisartan produces a more profound reduction in UAER than that with escalating dose of the dihydropyridine CCB amlodipine in hypertensive patients with type 2 diabetes and microalbuminuria.

References

1. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. N Engl J Med 1984;310: 356–360.
2. Dinneen SF, Gerstein HC: The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. Arch Intern Med 1997;157:1413–1418.
3. Parving HH, Mauer M, Ritz E: Diabetic nephropathy, in Brenner BM (ed): Brenner and Rector's the Kidney, 7th ed. Philadelphia, Saunders, 2004, pp 1777–1818.
4. Schmitz A, Vaeth M, Mogensen CE: Systolic blood pressure relates to the rate of progression of albuminuria in NIDDM. Diabetologa 1994;37:1251–1258.
5. Sowers JR, Epstein M, Frohlic ED: Diabetes, hypertension and cardiovascular disease: an update. Hypertension 2001;37:1053–1059.

6. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J: Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 2000;36:646–661.
7. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351: 1755–1762.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, for the National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 Report. JAMA 2003;289:2560–2571.
9. Ravid M, Lang R, Rachmani R, Lishner M: Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. Arch Intern Med 1996;156: 286–289.
10. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, for the RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869.
11. Parving HH, Lehnert H, Brochner-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; 345:870–878.
12. Viberti G, Wheeldon NM: Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure independent effect. Circulation 2002;106:672–678.
13. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 2004;65: 2309–2320.
14. Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper ME: 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;321:1440–1444.
15. Rossing K, Christensen PK, Jensen BR, Parving HH: Dual blockade of the renin angiotensin system in diabetic nephropathy. A randomised double-blind crossover study. Diabetes Care 2002;25:95–100.
16. Doulton TWR, He FJ, MacGregor GA: Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. Hypertension 2005;45:880–886.
17. Sengul AM, Altuntas Y, Kurklu A, Aydin L: Beneficial effect of lisinopril plus telmisartan in patients with type 2 diabetes, microalbuminuria and hypertension. Diabetes Res Clin Pract 2006;71: 210–219.
18. Jacobsen P, Andersen S, Rossing K, Hansen BV, Pareving HH: Dual blockade of the renin-angiotensin system in type 1 patients with diabetic nephropathy. Nephrol Dial Transplant 2002;17:1019–1024.
19. Kuriyama S, Tomonari H, Tokudome G, Horiguchi M, Hayashi H, Kobayashi H, Ishikawa M, Hosoya T: Antiproteinuric effects of combined antihypertensive therapies in patients with overt type 2 diabetic nephropathy. Hypertens Res 2002;25:849–855.
20. Andersen S, Rossing P, Juhl TR, Deinum J, Parving HH: Optimal dose of losartan for renoprotection in diabetic nephropathy. Nephrol Dial Transplant 2002;17:1413–1418.
21. Laverman GD, Navis G, Henning RH, de Jong PE, de Zeeuw D: Dual renin-angiotensin system blockade at optimal doses for proteinuria. Kidney Int 2002;62:1020–1025.
22. Rossing K, Jacobsen P, Pietraszek L, Parving HH: Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy. A randomized double-blind cross-over trial. Diabetes Care 2003;26:2268–2274.
23. Rossing K, Schjoedt KJ, Jensen BR, Boomsa F, Parving HH: Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. Kidney Int 2005;68:1190–1198.
24. Schmieder RE, Klingbeil AU, Fleishmann EH, Veelken R, Delles C: Additional antiproteinuric effect of ultrahigh dose candesartan: a double-blind, randomized, prospective study. J Am Soc Nephrol 2005;16:3038–3045.
25. Imanishi M, Yoshioka K, Konishi Y, Okumura M, Okada N, Sato T, Tanaka S, Fujii S, Kimura G: Glomerular hypertension as one cause of albuminuria in type II diabetic patients. Diabetologia 1999;42: 999–1005.
26. Andersen S, Blouch K, Bialek J, Deckert M, Parving HH, Myers BD: Glomerular permselectivity in early stages of overt diabetic nephropathy. Kidney Int 2000;58:2129–2137.
27. Bonnet F, Cooper ME, Kawachi H, Allen TJ, Boner G, Cao Z: Irbesartan normalises the deficiency in glomerular nephron expression in a model of diabetes and hypertension. Diabetologia 2001; 44:874–877.
28. MacIsaac RJ, Jerums G, Cooper ME: New insights into the significance of microalbuminuria. Curr Opin Nephrol Hypertens 2004; 13:83–91.
29. United Kingdom Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. BMJ 1998;317:703–713.