Impact of Telmisartan Versus Ramipril on Renal Endothelial Function in Patients With Hypertension and Type 2 Diabetes

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OBJECTIVE — One of the earliest signs of vascular change is endothelial dysfunction, which is also known to provoke albuminuria and to predict cardiovascular prognosis. The aim of this study was to analyze the effects of renin-angiotensin system (RAS) blockade on renal endothelial function.

RESEARCH DESIGN AND METHODS — In a multicenter, prospective, double-blind, forced-titration, randomized study, 96 patients with type 2 diabetes, hypertension, glomerular filtration rate >80 ml/min, and normo- or microalbuminuria were treated once daily with 40/80 mg telmisartan or 5/10 mg ramipril for 9 weeks.

RESULTS — The mean ± SE fall in renal plasma flow (RPF) in response to intravenous N^G-monomethyl-L-arginine (L-NMMA), reflecting the magnitude of nitric oxide (NO) activity, increased with telmisartan from 71.9 ± 9.0 ml/min before therapy to 105.2 ± 9.7 ml/min at the end of treatment ($P < 0.001$). With ramipril, RPF response to L-NMMA increased from 60.1 ± 12.2 to 87.8 ± 9.2 ml/min ($P = 0.018$). The adjusted difference between treatments was −17.1 ± 13.7 ml/min ($P = 0.214$). In accordance, telmisartan increased RPF at rest (i.e., without L-NMMA) from 652.0 ± 27.0 to 696.1 ± 31.0 ml/min ($P = 0.047$), whereas ramipril produced no significant changes in RPF. The more the basal NO activity improved, the greater was the vasodilatory effect on renal vasculature ($r = 0.47$, $P < 0.001$).

CONCLUSIONS — In patients with type 2 diabetes, telmisartan and ramipril both increased NO activity of the renal endothelium significantly, which in turn may support the preservation of cardiovascular and renal function.

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The close link between cardiovascular and renal changes due to cardiovascular risk factors, such as arterial hypertension and diabetes, has stimulated increasing interest (1–3). Albuminuria and decreased renal function, which are both primarily known to predict renal outcome, have now been identified as excellent predictors of cardiovascular morbidity and mortality (2–4). Most surprisingly, their predictive power surpasses that of classic risk markers of cardiovascular and atherosclerotic disease (5). Albuminuria is related to intrarenal hydraulic pressure, podocyte function, electric charge, and increased permeability, provoked by endothelial dysfunction (6). Prospective studies have demonstrated the predictive value of endothelial dysfunction for future cardiovascular morbid events when assessed in the peripheral and coronary circulation (7–9) and most likely, although not yet proven, in the renal circulation.

The endothelium is a major regulator of vascular homeostasis, with functional integrity being essential for the maintenance of blood flow and antithrombotic activity (10). Nitric oxide (NO), formed from L-arginine in the presence of NO synthase, is released by the vascular endothelial cells and brings about relaxation of vascular tissue and inhibition of platelet aggregation and adhesion (11). Endothelial dysfunction occurs as a result of impairment of NO synthesis or increased NO degradation and has been detected in patients with hypertension, peripheral arterial occlusive disease, and chronic renal failure (12–15). Angiotensin II, which is widely implicated in endothelial dysfunction, increases oxidative stress, which causes stimulation of NO breakdown (16). In the long term, endothelial dysfunction results in atherosclerosis and subsequent target-organ damage, leading to overt cardiovascular disease and chronic kidney disease (9). Studies in the forearm vasculature of hypertensive patients have shown that increased blood pressure correlates with decreased NO activity (13,15,17) and normalization of blood pressure with increased NO activity (18).

In view of the pathogenetic role of the imbalance between angiotensin II and NO in target-organ damage, it is a logical approach to target the renin-angiotensin system (RAS). ACE inhibitors prevent the formation of angiotensin II from angiotensin I, whereas the angiotensin II receptor blockers (ARBs) specifically prevent the binding of angiotensin II to type 1 receptors (19). All of the antihypertensive agents used in this study have been shown to exert target-organ protection (20–22), but their pharmacologic profiles differ substantially. ACE inhibitors lead to accu-

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Abbreviations: ARB, angiotensin II receptor blocker; DBP, diastolic blood pressure; GFR, glomerular filtration rate; L-NMMA, N^G-monomethyl-L-arginine; MAP, mean arterial pressure; RAS, renin-angiotensin system; RPF, renal plasma flow; SBP, systolic blood pressure.

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

mulation of bradykinin, known to improve endothelial function, whereas ARBs elicit stimulation of the angiotensin II AT_2 receptors and modulate peroxisome proliferator–activated receptor-γ receptors. The clinical relevance of these additional effects of ACE inhibitors and ARBs is controversial. So far, the effects of ACE inhibitors and ARBs have been examined mainly in the peripheral circulation. Although small sample sizes have been used, significant improvement of endothelial function has been observed for both compounds used in the current trial. Ramipril significantly improved renal endothelial function in normotensive, normoalbuminuric men with type 1 diabetes (23), and telmisartan increased endothelial function in treatment-naive hypertensive patients (24). However, to date, there have been no studies and no head-to-head comparisons examining the effects of RAS blockade on renal endothelial function in patients with type 2 diabetes and hypertension, who are known to have a very high risk of cardiovascular and renal morbidity (25,26).

RESEARCH DESIGN AND METHODS

— Adult (age range 30–80 years) patients of either sex with type 2 diabetes who either were not taking metformin or had been receiving a stable dose for a minimum of 12 weeks before enrollment were eligible for inclusion in the study. Other inclusion criteria were normoalbuminuria or microalbuminuria; glomerular filtration rate (GFR), determined using the Cockcroft-Gault formula (27), >80 ml/min; and arterial hypertension (mean seated systolic blood pressure [SBP] 130–179 mmHg and/or diastolic blood pressure [DBP] 80–109 mmHg or receipt of antihypertensive treatment at stable doses) with mean seated SBP <180 mmHg and/or DBP <110 mmHg. Patients were excluded if any of the following applied: A1C >9%, receipt of thiazolidinediones, and/or initiation of statins in the 4 weeks before randomization; proliferative retinopathy; symptomatic cardiovascular disease; secondary hypertension; hepatic dysfunction; renal artery stenosis; electrolyte imbalance; and/or previous intolerance of ACE inhibitors or ARBs.

In this prospective, multicenter, parallel-group, double-blind, forced-titration, randomized study, there was an initial 2-week open-label, placebo run-in period. During this time, hydrochlorothiazide and, if required, metoprolol or atenolol were permitted to avoid uncontrolled blood pressure (mean SBP ≥180 mmHg and/or DBP ≥110 mmHg). At the end of this period, there was double-blind randomization to once-daily telmisartan or ramipril. For the first 3 weeks of the double-blind, double-dummy treatment, the lower dose of the assigned study drug (40 mg telmisartan or 5 mg ramipril) was administered. For the subsequent 6 weeks, patients received double-blind, double-dummy treatment with either 80 mg telmisartan or 10 mg ramipril. Add-on therapy was permitted if blood pressure was inadequately controlled (mean SBP ≥160 mmHg and/or DBP ≥95 mmHg) at the end of the forced-titration period. The overall goal was to reach a target blood pressure of <130/80 mmHg. In fact, in one patient of each group, 12.5 mg hydrochlorothiazide was added. The study was approved by the local ethic committees in each country, and written informed consent was obtained.

Assessment of renal endothelial function

The change in renal plasma flow (RPF) in response to N^G-monomethyl-L-arginine (L-NMMA) served as a measure of basal NO activity in the renal circulation (28–30). The magnitude of the vasoconstrictive response to the blockade of NO synthesis mirrors the vasodilatory effect of NO at baseline in the renal endothelium. Thus, a greater vasoconstrictive response after L-NMMA application indicates a greater blockade of NO. The evaluation of the change in this response between the end of the placebo phase and the end of the 9 weeks' treatment was the primary objective.

Renal hemodynamic parameters were determined by the constant-infusion input-clearance technique with inulin (Inutest; Fresenius, Linz, Austria) and sodium *p*-aminohippurate (Clinalpha, Basel, Switzerland) for GFR and RPF, respectively, as previously outlined (28). Briefly, after bolus infusion of inulin and sodium *p*-aminohippurate over 15 min and a subsequent constant infusion over 105 min, a steady state between input and renal excretion of the tracer substances was reached, and the administration of experimental substances was started in addition. Systemic hemodynamic parameters (i.e., blood pressure and heart rate) were monitored in parallel by means of an oscillometric device (Dinamap 1,846 SX; Critikon, Norderstedt, Germany). Filtration fraction was calculated by dividing GFR by RPF. Renal vascular resistance was calculated as mean arterial pressure (MAP) × (1 − hematocrit)/RPF.

L-NMMA was administered intravenously as a bolus infusion (3 mg/kg over 5 min) followed by constant infusion (2 mg/kg over 40 min). Thus, the total dose of L-NMMA was 5 mg/kg (29). Then, L-arginine (L-arginine hydrochloride 6%; University Hospital Pharmacy, Erlangen, Germany) was administered intravenously at a dose of 100 mg/kg over 45 min (30). Blood samples to determine inulin and *p*-aminohippurate concentrations were drawn at 0, 120, 165, and 210 min. During the last 5 min of each infusion step, blood pressure was measured twice, and the mean of these measurements was used for analysis.

Blood samples for the determination of plasma angiotensin II concentrations were collected from patients in the supine position after 1 h of complete rest. For plasma angiotensin II measurements, blood was collected into prechilled 10-ml syringes prepared with 1.25 mmol EDTA and 26 mmol phenanthrolene to inhibit ACE. Immunoreactive angiotensin II was measured by radioimmunoassay as described in detail previously (31).

Statistical analysis

The primary objective was to determine whether ACE inhibitors or/and ARBs increase basal NO activity relative to baseline after 9 weeks of treatment. The sample size was calculated to be $n = 50$ per group. The secondary objective was to compare these two treatment arms with respect to their effect on basal NO activity. The analysis was conducted using an ANCOVA with pooled center and treatment as main effects and RPF in response to L-NMMA at baseline as covariate in the per protocol set. Adjusted mean ± SE treatment group differences were determined.

RESULTS

Baseline characteristics

A total of 96 patients were randomly assigned to treatment, of whom 93 completed the study. Premature discontinuation was due to an adverse event in one patient, loss to follow-up after 38 days of treatment in another, and elevated lipid levels due to withdrawal of statin therapy after 11 days of treatment in a third patient; all these patients were in the ramipril treatment group. Table 1 summarizes the baseline characteristics of the per protocol set; there were no

Table 1—*Baseline characteristics*

	Telmisartan	Ramipril
n	45	42
Male (%)	68.1	71.4
Age (years)	59.6 ± 1.3 (37–75)	58.80.0 ± 1.4 (35–74)
Weight (kg)	86.8 ± 2.5	91.3 ± 2.7
BMI (kg/m^2)	29.4 ± 0.9	30.7 ± 0.9
Smokers (%)	19.1	22.3
Duration of hypertension (years)	10.0 ± 1.3 (0–9.6)	8.9 ± 1.0 (0–8.4)
Duration of diabetes (years)	6.8 ± 1.1 (0.2–29)	5.4 ± 0.8 (0.1–30)
SBP (mmHg)	148.0 ± 2.4	150.0 ± 1.9
DBP (mmHg)	85.8 ± 1.3	87.9 ± 1.5
A1C (%)	6.92 ± 0.15	6.62 ± 0.11
Previous ACE inhibitor or ARB use (%)	72.3	63.3
Concomitant therapy (%)		
α-Blockers	10.6	4.1
β-Blockers	31.3	36.7
Calcium channel blockers	42.6	28.6
Diuretics	59.6	58.2
Other cardiovascular drugs	25.5	34.2
Oral antiglycemic drugs	74.5	73.6
Fibrates	6.4	2.0
Other drugs	55.3	63.3

Data are means ± SE (range) or %. No significant differences ($P > 0.20$) were observed between the two groups.

significant differences between the two treatment groups. After excluding, in total, nine patients with protocol violations (two in the telmisartan group and seven in the ramipril group, e.g., administration of glitazone or a statin, which was the case in one patient each), the per protocol set comprised 45 patients in the telmisartan treatment group and 42 patients in the ramipril treatment group.

Primary efficacy end point

At the end of the placebo phase, RPF decreased in response to L-NMMA by 71.9 ± 9.0 ml/min in the telmisartan group and by 60.1 ± 12.2 ml/min in the ramipril group. After 9 weeks' active treatment, RPF decreased in response to L-NMMA by 105.2 ± 9.7 ml/min in the telmisartan group and by 87.8 ± 9.2 ml/min in the ramipril group, without any significant difference between the two groups. In the telmisartan group, the adjusted mean change from end of placebo to end of treatment in response to L-NMMA of −43.2 ± 10.7 ml/min was significant ($P < 0.001$) (Fig. 1). Similarly, in the ramipril group, the adjusted change of −26.1 ± 10.8 ml/min was significant ($P = 0.018$). The difference between the two groups of −17.1 ± 13.7 ml/min was not different. The corresponding values in percent change were for telmisartan −3.3 ± 9.5% ($P = 0.027$) and for ramipril −3.1 ± 11.5% ($P = 0.105$), respectively. No sex-based differences were present with respect to the primary objective. No clear relation between a fall in SBP or glycemic control (A1C) and treatment effects on NO activity was found in univariate and multivariate analyses (data not shown).

Secondary efficacy end points

Before treatment, resting RPF, measured before L-NMMA infusion, was comparable in the telmisartan and ramipril groups (Table 2). After 9 weeks' treatment, resting RPF measured before L-NMMA infusion increased significantly ($P = 0.047$) by an adjusted mean of 52.1 ± 25.8 ml/min in the telmisartan group, whereas in the ramipril group there was a nonsignificant increase ($P = 0.221$) of 31.0 ± 25.1 ml/min, without any significant difference between the two groups.

MAP before L-NMMA infusion decreased significantly with both telmisartan and ramipril (telmisartan −6.02 ± 9.3 mmHg and ramipril −4.75 ± 8.2 mmHg, both $P < 0.001$ vs. before treatment). Although numerically greater with telmisartan, the difference between the two groups was not significant. Nevertheless, we analyzed the relation of changes in L-NMMA response with changes in MAP after treatment: No significant correlation was found ($r = 0.13$, $P = 0.232$). After adjustment for the decrease in blood pressure, the change of RPF from end of placebo to end of treatment in response to L-NMMA was −40 ± 11 ml/min for telmisartan and – 30 ± 14 ml/min for ramipril (both $P < 0.01$), without any difference between the two groups.

GFR did not change significantly at the end of the 9-week treatment period, and values were similar between the two groups (Table 2). As a consequence of the increased RPF, renal vascular resistance decreased in the telmisartan group (Table

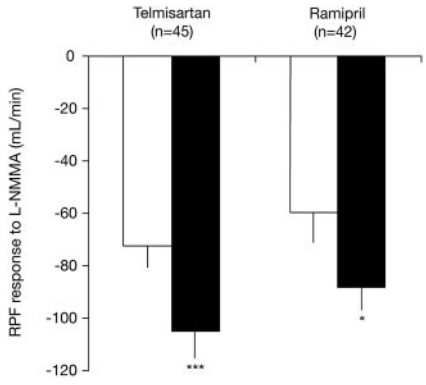

Figure 1—*Effects of 40/80 mg telmisartan and 5/10 mg ramipril for 9 weeks on the mean ± SE RPF in response to 5 mg/kg L-NMMA infusion compared with pre–L-NMMA infusion values. □, baseline; ■, end of treatment.* *P = *0.018 vs. baseline;* ***P < *0.001 vs. baseline.*

Table 2—*Effects of 80 mg telmisartan and 10 mg ramipril on secondary renal end points and MAP*

Parameter*	Telmisartan: before treatment	Ramipril: after treatment	*P* value	Before treatment	After treatment	*P* value
RPF (ml/min)	652 ± 27.0	696 ± 31.0	0.047	631 ± 27.3	658 ± 28.2	0.221
GFR (ml/min)	136.3 ± 3.1	136.4 ± 3.4	0.212	134.3 ± 3.7	133.7 ± 3.8	0.558
Filtration fraction (%)	22.0 ± 0.8	20.6 ± 0.7	0.020	22.2 ± 0.7	21.4 ± 0.7	0.154
MAP (mmHg)	100.0 ± 10.4	93.3 ± 10.8	<0.001	100.1 ± 9.2	95.4 ± 11.0	0.009
Renal vascular resistance (RU)	96.2 ± 4.2	87.1 ± 4.2	0.010	99.3 ± 4.7	93.7 ± 5.1	0.119

Data are means ± SE. *No significant differences in the changes due to treatment were observed between telmisartan and ramipril. RU, resistance unit.

2). The filtration fraction also decreased significantly with telmisartan but remain unchanged with ramipril.

The increase in resting RPF observed after 9 weeks' treatment with telmisartan was related to improved NO activity ($r = 0.47$, $P < 0.001$). This positive relationship between change in RPF and NO activity was found in the whole study cohort, as well as in both of the two treatment groups, and demonstrates the functional consequences of improved NO activity.

The increase in MAP after L-NMMA infusion was similar at the end of the placebo phase and at the end of 9 weeks' treatment, as well as between the two treatment groups. The adjusted mean differences of MAP response to L-NMMA before versus after therapy were 0.2 ± 1.1 mmHg ($P = 0.891$) for telmisartan and −0.2 ± 1.1 mmHg ($P = 0.884$) for ramipril.

L-Arginine infusion increased the RPF at baseline by 6.4 ± 13.7 ml/min compared with the pre–L-NMMA infusion value in the telmisartan group, whereas the increase was 1.3 ± 13.3 ml/min in the ramipril group. After 9 weeks' treatment, there was a significant adjusted mean increase in the RPF response to L-arginine in the telmisartan group of 22.0 ± 22.8 ml/min ($P = 0.024$), whereas the adjusted mean increase of 12.3 ± 23.8 ml/min was not significant in the ramipril group ($P = 0.075$).

The adjusted geometric mean albumin excretion decreased from 9.0 to 7.2 mg/24 h at week 9 in the telmisartan group ($P = 0.022$) and changed from 11.7 to 10.7 mg/24 h in the ramipril group ($P = 0.961$), without any clear difference between the two groups ($P = 0.074$). In the subset of patients with albumin excretion >10 mg/24 h at the end of placebo phase, telmisartan and ramipril both decreased albumin excretion significantly to the same extent (telmisartan, $P \leq 0.05$; ramipril, $P < 0.05$).

Mean serum angiotensin II concentrations were similar at the end of placebo phase in the telmisartan (3.2 pg/ml) and ramipril (3.4 pg/ml) groups. In the telmisartan group, there was a significant increase in angiotensin II concentrations to 7.0 pg/ml ($P < 0.001$), whereas in the ramipril group the angiotensin II concentration was halved to 1.6 pg/ml after treatment ($P < 0.001$). The results confirm the mechanism of action of both drugs and similar angiotensin II levels before therapy.

Adverse events were reported by 12 patients (25.5%) while receiving telmisartan and by 12 patients (24.5%) while receiving ramipril. The majority of these events were mild in intensity (nine telmisartan patients and seven ramipril patients). Adverse events considered to be drug related (headache, cough, and two cases of dizziness) were recorded in four patients treated with ramipril. There were no drug-related adverse events in the telmisartan group.

CONCLUSIONS — The impact of RAS blockers on endothelial function has been repeatedly examined in hypertensive patients. With respect to the ACE inhibitors and ARBs, an improvement in endothelium-dependent flow-mediated vasodilation has been observed (32,33). The enhancement of endothelial function has been related to improved cardiovascular prognosis (34,35). Similarly, a reduction in albuminuria, which is also linked to the integrity of the endothelium, results in improved cardiovascular and renal prognosis (36,37). So far, the assessment of endothelial function has been mainly carried out in the peripheral circulation (7,13,17,38). However, it is now apparent that the cardiovascular prognosis is clearly reflected by renal parameters, such as GFR, albuminuria, and, potentially, renal endothelial function (2–4). Moreover, head-to-head comparisons of ARBs and ACE inhibitors on endothelial function have not yet been reported. Thus, this is the first study to analyze the NO activity in renal circulation in type 2 diabetes and to compare directly the effects of two different classes of agents that target the RAS. Endothelial function was determined by the effect of NO activity on renal perfusion in patients with type 2 diabetes and hypertension, which reflects NO production and release, as well as the effects of oxidative stress on NO breakdown.

The significant increase in RPF in response to L-NMMA at the end of treatment with the ARB telmisartan or the ACE inhibitor ramipril shows that targeting the RAS increases NO activity. Although numerically greater with telmisartan, there was no statistically significant difference between the effects of telmisartan and ramipril. Under resting conditions (pre–L-NMMA infusion), RPF increased significantly in the telmisartan group but not in the ramipril group, and the greater the improvement of NO activity the greater was the increase of renal perfusion under resting conditions. This indicates that the increase of NO activity after the blockade of the RAS is functionally relevant because vasodilation became evident in the renal vasculature. Because the effect of L-NMMA on systemic MAP did not change significantly after therapy compared with before therapy with either of the study drugs and because the decrease of blood pressure after treatment was not related to the RPF response to L-NMMA, changes in renal perfusion pressure do not appear to explain our results.

Our findings in patients with type 2 diabetes and hypertension are consistent with previous observations on the effects of enalapril, eprosartan, and valsartan in hypertensive patients (30,39). In contrast, opposite effects have been observed with amlodipine in humans, which was associated with reduced NO activity in the renal vessels (39). Inhibition of NO in the kidneys has been found to increase

glomerular sclerosis, tubular interstitial fibrosis, osteopontin expression, macrophage infiltrations, and proteinuria (40,41). In accordance with these experimental data in the kidneys, NO is considered the ideal antiatherosclerotic substance, and increased NO activity is thought to be likely to counteract profibrotic, inflammatory, and proliferative processes in the whole vascular system. Hence, the increased NO activity of the endothelium, as now documented in type 2 diabetes, might in the long term reduce the development of cardiovascular complications.

Infusion of L-arginine after the inhibition of NO synthase with L-NMMA reversed the effects of L-NMMA on RPF. The relationship between the L-arginine effect and NO release has previously been demonstrated by Schlaich et al. (42). Analysis of the reaction to L-arginine showed that, at the end of treatment, there was a vasodilatory effect that overshot the vasoconstriction produced by L-NMMA. This suggests that the capability of the renal vasculature to produce NO upon stimulation was improved by targeting the RAS. A previous study performed in hypertensive patients has shown the beneficial effect of ACE inhibition (43). Telmisartan improved the renal response to L-arginine infusion measured in terms of RPF, whereas ramipril did not. This observation could be biased by the prolonged effect of the previous L-NMMA infusion, but the infused dose of L-NMMA was similar in both treatment arms. Clearly, our data on L-arginine infusion do not reflect the true L-arginine–mediated vasodilation repeatedly examined in other trials and, therefore, do not allow any comparison with these previously published trials.

Microalbuminuria, a sign of impaired endothelial function, is a frequent observation in patients with type 2 diabetes and can be considered an early manifestation of generalized endothelial dysfunction (15,18,44). Both drugs used in the current trial were effective in reducing albumin excretion in patients with low-grade albuminuria, which has been found to predict cardiovascular complications in the Framingham Heart Study (4). Previous studies have shown that ACE inhibitors and ARBs reduced urinary albumin excretion in patients with upper normal to low-level microalbuminuria (35,37). These studies also demonstrated that the reduction in albuminuria was associated with a reduction in cardiovascular risk (36,45).

In summary, targeting the RAS in patients with type 2 diabetes and hypertension with ACE inhibitors and ARBs showed similar effects on renal endothelial function, demonstrated by increased NO activity.

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