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

Received for publication 27 July 2006 and accepted in revised form 19 February 2007.

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Statement of funding: TRENDY (Telmisartan versus Ramipril on Renal Endothelium Function in Type 2 Diabetes) is a stand-alone trial and part of the ongoing PROTECTION (Programme of Research to show Telmisartan End-organ proteCTION) study programme (co-sponsored by Boehringer Ingelheim, Bayer AG and GlaxoSmithKline)
ABSTRACT

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

Methods: In a multicenter, prospective, double-blind, forced-titration, randomized study, 96 patients with type 2 diabetes, hypertension, GFR >80 mL/min, and normo- or microalbuminuria were treated once daily with telmisartan 40/80 mg or ramipril 5/10 mg for 9 weeks.

Results: The (mean ± SE) fall in renal plasma flow (RPF) in response to intravenous NG-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 end of treatment (p < 0.001). With ramipril, RPF response to L-NMMA increased from 60.1 ± 12.2 mL/min to 87.8 ± 9.2 mL/min (p = 0.018). The adjusted mean ± SE 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 mL/min 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 that in turn may support the preservation of cardiovascular and renal function.
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). Angiotensin-converting enzyme (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 I receptors (19). Each of the antihypertensive agents used in this study have been shown to exert target-organ protection (20–22), but their pharmacologic profile differs substantially. ACE inhibitors lead to accumulation of bradykinin, known to improve endothelial function, whereas ARBs elicit stimulation of the AT2-receptors and modulate PPARγ receptors. The clinical relevance of these additional effects of ACE-inhibitors and ARBs are controversial. So far, the effects of ACE-inhibitors and ARBs have been mainly examined 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 (23) normotensive, normoalbuminuric men with type 1 diabetes, and telmisartan increased endothelial function in treatment-naïve 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).

Methods

Study Population

Adult (age range 30 to 80 years) patients of either gender with non-insulin dependent type 2 diabetes that either were not taking metformin or had been on 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 to 179 mm Hg and/or diastolic blood pressure [DBP] 80 to 109 mm Hg or receipt of antihypertensive treatment at stable doses) with mean seated SBP <180 mm Hg and/or DBP <110 mm Hg. Patients were excluded if any of the following applied: glycosylated hemoglobin >9%, receipt of thiazolidinediones and/or initiation of statins in the 4 weeks prior to randomization; proliferative retinopathy; symptomatic cardiovascular disease; secondary hypertension; hepatic dysfunction; renal artery stenosis; electrolyte imbalance; and/or previous intolerance of ACE inhibitors or ARBs.

Study Design

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 $\geq 180$ mm Hg and/or DBP $\geq 110$ mm Hg). At the end of this period, there was double-blind randomization to once-daily telmisartan or ramipril. For the first 3 weeks of double-blind, double-dummy treatment, the lower dose of the assigned study drug (telmisartan 40 mg or ramipril 5 mg) was administered. For the subsequent 6 weeks, patients received double-blind, double-dummy treatment with either telmisartan 80 mg or ramipril 10 mg. Add-on therapy was permitted if blood pressure was inadequately controlled (mean SBP $\geq 160$ mm Hg and/or DBP $\geq 95$ mm Hg) at the end of the forced-titration period. The overall goal was to reach a target blood pressure of $<130/80$ mm Hg. In fact, in 1 patient of each group 12.5mg HCTZ was added. The study was approved by the local ethic committees in each country and informed consent was obtained in written manner.

**Assessment of Renal Endothelial Function**

The change in renal plasma flow (RPF) in response to $\text{N}^\text{G}$-monomethyl-$\text{L}$-arginine ($\text{L}$-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, greater vasoconstrictive response following $\text{L}$-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 $\text{p}$-aminohippurate (Clinalpha, Basel, Switzerland) for GFR and RPF, respectively, as previously outlined (28). Briefly, after bolus infusion of inulin and sodium $\text{p}$-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 1846 SX®; Critikon, Norderstedt, Germany). Filtration fraction (FF) was calculated by dividing GFR by RPF. Renal vascular resistance (RVR) was calculated as mean arterial pressure (MAP) x (1-hematocrit)/RPF.

$\text{L}$-NMMA was administered intravenously (iv) 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 $\text{L}$-NMMA was 5 mg/kg (29). Then, $\text{L}$-arginine ($\text{L}$-arginine hydrochloride 6% [University Hospital Pharmacy, Erlangen, Germany]) was administered iv at a dose of 100 mg/kg over 45 min (30). Blood samples to determine inulin and $\text{p}$-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 phenantrolin to inhibit ACE. Immunoreactive angiotensin II was measured by radio-immunoassay as previously described in detail (31).

**Statistical Analysis**

The primary objective was 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 analysis of covariance with pooled center and treatment as main effects and RPF in response to $\text{L}$-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 randomized 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 patient were in the ramipril treatment group. Table 1 summarizes the baseline characteristics of the per protocol set; there were no significant differences between the two treatment groups. After excluding, in total, 9 patients with protocol violations (2 in the telmisartan group and 7 in the
ramipril group, for example administration of glitazone or statin which was the case in 1 patient each), the per protocol set comprised 45 patients in the telmisartan treatment group and 42 patients in the ramipril treatment group.

Primary Efficacy Endpoint

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, the 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; Figure 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 for telmisartan are -3.3 ± 9.5 % (p=0.027) and for ramipril -3.1 ± 11.5 %, (p=0.105) respectively. No gender-based differences were present with respect to the primary objective. No clear relation between fall in systolic blood pressure or glycemic control (HbA1c) and treatment effects on NO activity was found in an univariate and multivariate analysis (data not shown).

Secondary Efficacy Endpoints

Before treatment, resting RPF, measured prior to L-NMMA infusion, was comparable in the telmisartan and ramipril groups (Table 2). After 9 weeks’ treatment, resting RPF measured prior to 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 non-significant increase (p = 0.221) of 31.0 ± 25.1 mL/min, without any significant difference between the two groups.

MAP prior to L-NMMA infusion decreased significantly with both telmisartan and ramipril (telmisartan: -6.02 ± 9.3 mm Hg and ramipril - 4.75 ± 8.2 mm Hg, 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, RVR decreased in the telmisartan group (Table 2). FF 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 either of the two treatment groups, and demonstrates the functional consequences of improved NO activity.

The increase in MAP following L-NMMA infusion was similar at the end of 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 mm Hg (p = 0.891) for telmisartan and −0.2 ± 1.1 mm Hg (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/24h at Week 9 in the telmisartan group (p = 0.022) and changed from 11.7 to 10.7 mg/24h 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 < 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 following 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 in receipt of telmisartan and by 12 patients (24.5%) while in receipt of ramipril. The majority of these events were mild in intensity (9 telmisartan patients and 7 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.

**Discussion**

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, 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 that 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 following the blockade of the RAS is functionally relevant, since vasodilation became evident in the renal vasculature. Since the effect of L-NMMA on systemic MAP did not change significantly after compared with before therapy with either of the study drugs, and since 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 of 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 a 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 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 following 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 that 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).

Conclusions
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.
References
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blocker, improves endothelial function in patients with chronic heart failure (abstract no. 3536). J Am Coll Cardiol 2002;39(Suppl B):266B.


Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan (n = 45)</th>
<th>Ramipril (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>68.1</td>
<td>71.4</td>
</tr>
<tr>
<td>Age, mean ± SE, y range</td>
<td>59.6±1.3 (37-75)</td>
<td>58.8±1.4 (35-74)</td>
</tr>
<tr>
<td>Weight, mean ± SE, kg</td>
<td>86.8 ± 2.5</td>
<td>91.3 ± 2.7</td>
</tr>
<tr>
<td>BMI, mean ± SE, kg/m²</td>
<td>29.4 ± 0.9</td>
<td>30.7 ± 0.9</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>19.1</td>
<td>22.3</td>
</tr>
<tr>
<td>Duration of hypertension, mean ± SE, y range, y</td>
<td>10.0 ± 1.3</td>
<td>8.9 ± 1.0</td>
</tr>
<tr>
<td>Duration of diabetes, mean ± SE, y range, y</td>
<td>6.8 ± 1.1</td>
<td>5.4 ± 0.8</td>
</tr>
<tr>
<td>SBP, mean ± SE, mm Hg</td>
<td>148.0 ± 2.4</td>
<td>150.0 ± 1.9</td>
</tr>
<tr>
<td>DBP, mean ± SE, mm Hg</td>
<td>85.8 ±</td>
<td>87.9 ± 1.5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.92 ± 0.15</td>
<td>6.62 ± 0.11</td>
</tr>
<tr>
<td>Previous ACE inhibitor or ARB use, %</td>
<td>72.3</td>
<td>63.3</td>
</tr>
</tbody>
</table>

Concomitant therapy, %
- Alpha-blockers: 10.6%
- Beta-blockers: 31.3%
- Calcium channel blockers: 42.6%
- Diuretics: 59.6%
- Other cardiovascular drugs: 25.5%
- Oral antiglycemic drugs: 74.5%
- Fibrates: 6.4%
- Other drugs: 55.3%

BMI indicates body mass index; SBP systolic blood pressure; DBP diastolic blood pressure; ACE angiotensin-converting enzyme; ARB angiotensin II receptor blocker.

No significant differences (p > 0.20) were observed between the two groups.
Table 2. Effects of telmisartan 80 mg and ramipril 10 mg on mean (± SE) secondary renal endpoints and mean arterial pressure.

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Telmisartan Before treatment</th>
<th>Telmisartan After treatment</th>
<th>p-value</th>
<th>Ramipril Before treatment</th>
<th>Ramipril After treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal plasma flow (ml/min)</td>
<td>652 ± 27.0</td>
<td>696 ± 31.0</td>
<td>0.047</td>
<td>631 ± 27.3</td>
<td>658 ± 28.2</td>
<td>0.221</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>136.3 ± 3.1</td>
<td>136.4 ± 3.4</td>
<td>0.212</td>
<td>134.3 ± 3.7</td>
<td>133.7 ± 3.8</td>
<td>0.558</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>22.0 ± 0.8</td>
<td>20.6 ± 0.7</td>
<td>0.020</td>
<td>22.2 ± 0.7</td>
<td>21.4 ± 0.7</td>
<td>0.154</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>100.0 ± 10.4</td>
<td>93.3 ± 10.8</td>
<td>&lt;0.001</td>
<td>100.1 ± 9.2</td>
<td>95.4 ± 11.0</td>
<td>0.009</td>
</tr>
<tr>
<td>Renal vascular resistance (RU)</td>
<td>96.2 ± 4.2</td>
<td>87.1 ± 4.2</td>
<td>0.010</td>
<td>99.3 ± 4.7</td>
<td>93.7 ± 5.1</td>
<td>0.119</td>
</tr>
</tbody>
</table>

* No significant differences in the changes due to treatment were observed between telmisartan and ramipril.
Figure 1. Effects of telmisartan 40/80 mg and ramipril 5/10 mg for 9 weeks on the mean ± SE renal plasma flow (RPF) in response to $N\&$-monomethyl-$L$-arginine (l-NMMA) 5 mg/kg infusion compared with pre-l-NMMA infusion values.