Antiproteinuric effects of angiotensin receptor blockers: telmisartan versus valsartan in hypertensive patients with type 2 diabetes mellitus and overt nephropathy

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Abstract

Background. Renin–angiotensin system blockade reduces proteinuria and prevents nephropathy progression in patients with type 2 diabetes mellitus (T2D). Experimental evidence demonstrates that angiotensin receptor blockers (ARBs) possess anti-inflammatory potential, which might contribute to reducing proteinuria and providing renoprotection.

Methods. We conducted a multicentre, double-blind, prospective, parallel-group non-inferiority study of 885 hypertensive [systolic blood pressure/diastolic blood pressure (SBP/DBP) >130/80 mmHg] patients with T2D, proteinuria (≥900 mg/24 h) and serum creatinine (≤3.0 mg/dl) who were randomized to once-daily telmisartan 80 mg or valsartan 160 mg; additional antihypertensive therapy was permitted. The primary endpoint was the change from baseline in the 24-h proteinuria after 12 months. Secondary endpoints included changes in 24-h albuminuria, estimated glomerular filtration rate (eGFR) and inflammatory parameters asymmetrical dimethylarginine (ADMA), high-sensitivity C-reactive protein (CRP) and urinary 8-iso-prostaglandin F2α (8-iso-PGF2α).

Results. Telmisartan and valsartan produced comparable reductions in 24-h urinary protein excretion rates: geometric mean reduction (95% confidence interval) [telmisartan, 33% (27–39%); valsartan, 33% (27–38%)]. No significant differences between treatments were seen in changes from baseline in 24-h proteinuria after 12 months. Secondary endpoints included changes in 24-h albuminuria, estimated glomerular filtration rate (eGFR) and inflammatory parameters asymmetrical dimethylarginine (ADMA), high-sensitivity C-reactive protein (CRP) and urinary 8-iso-prostaglandin F2α (8-iso-PGF2α).

Conclusions. In patients with T2D, hypertension and overt nephropathy, the renoprotection afforded by telmisartan and valsartan appears similar, and the study was unable to show any effect beyond that due to blood pressure control. At doses used to treat hypertension, there is no evidence of inflammatory parameters being modified by ARBs in patients with more advanced kidney disease due to T2D.

Keywords: angiotensin receptor blockers; diabetic nephropathy; proteinuria; telmisartan; valsartan

Introduction

High systemic blood pressure leads to increased intraglomerular pressure, which in turn brings about mesangial cell hypertrophy and extracellular matrix production, basement membrane thickening and growth-factor production [1]. Hence, reduction of blood pressure is essential to prevent progression of renal damage [2]. In patients with renal disease, including those with diabetes, meta-analysis of clinical trials has demonstrated a direct and continuous relationship between blood pressure and the decline in the glomerular filtration rate [3].

The renin–angiotensin system (RAS) plays a central role in the pathophysiology of diabetic nephropathy, with angiotensin II being a pro-inflammatory mediator [4]. Agents that target the RAS are the antihypertensive agents of choice in all patients with a spot protein/creatinine ratio ≥200 mg/g or with diabetic kidney disease, regardless of their blood pressure [5]. The National Kidney Foundation recommends angiotensin receptor blockers (ARBs) for type 2 diabetes mellitus (T2D) nephropathy [5]. This is based on strong evidence for the renoprotective efficacy of ARBs in patients with T2D and either microalbuminuria [6,7] or macroalbuminuria [8,9]. This study was designed to evaluate the non-inferiority of telmisartan in comparison with valsartan, an ARB with proven effect on albuminuria [7].

There is still, however, considerable debate as to whether or not the renoprotective effect of ARBs is exclusively

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due to blood pressure control. In particular, the anti-inflammatory role of ARBs has been proposed based largely on cell culture [10] and animal studies of atherosclerosis [11]. Whatever be the mechanism, the benefit of ARBs is clear: recent post hoc analysis of data from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study has demonstrated that lowering albuminuria using losartan improves cardiovascular outcomes over a 2-year period compared with atenolol-based therapy, despite similar blood pressure control [12].

In order to gain a more detailed insight into possible renoprotective mechanisms of ARBs that may occur in addition to blood pressure lowering in overt nephropathy, and in view of the paucity of long-term clinical data on the effects of ARBs on oxidative stress and pro-inflammatory parameters, we studied changes in levels of established markers of oxidative stress and inflammation: plasma asymmetric dimethylarginine (ADMA) [13,14], serum high-sensitivity C-reactive protein (hs-CRP) [15] and the urinary 8-isoprostaglandin F$_2$ α (8-iso-PGF$_2$ α) [16,17].

**Patients and methods**

**Study population**

Patients of either gender in the age range 30–80 years with a clinical history of T2D [glycosylated haemoglobin (HbA$_1$c) ≤10%] and overt nephropathy were eligible for inclusion. Overt nephropathy was defined as serum creatinine ≤3.0 mg/dl and proteinuria >900 mg/24 h in accordance with the previously defined criteria [9]. All patients were hypertensive, with mean cuff systolic blood pressure/diastolic blood pressure (SBP/DBP) >130/80 mmHg or in receipt of antihypertensive therapy at enrolment. Pre-menopausal women who were not surgically sterile, using an acceptable form of contraception, or who were pregnant or breast feeding were not eligible. Other exclusion criteria were a recent acute cardiovascular event, congestive heart failure, receipt of metformin in patients with elevated serum creatinine levels, non-diabetic renal disease, >30% increase in serum creatinine during run-in, secondary hypertension, hepatic dysfunction, biliary obstructive disorders, renal arterial stenosis, chronic immunosuppressive therapy, history of drug or alcohol dependency and SBP >180 mmHg and/or DBP >110 mmHg on two consecutive visits during run-in. All patients provided written informed consent.

**Study design**

The prospective, randomized, double-blind, double-dummy, forced-titration, multicentre, parallel-group study to investigate the efficacy of telmisartan versus valsartan in hypertensive type 2 diabetic patients with overt nephropathy (VIVALDI; NCT00153023; Figure 1) was performed according to the principles of the Declaration of Helsinki and approved by the institutional ethics committee of each study centre. The study was conducted between April 2003 and December 2005. Prior to randomization, there was a 2-week screening period and a further 2-week placebo run-in period to wash out any prior treatment with angiotensin-converting enzyme (ACE) inhibitors or ARBs. During this period, patients were allowed to receive alternative antihypertensive therapy, other than direct vasodilators, for the control of blood pressure. Thereafter, patients were randomly assigned in a 1:1 ratio to once-daily treatment with telmisartan 40 mg or valsartan 80 mg. After 2 weeks, doses of telmisartan and valsartan were increased in all patients to 80 mg and 160 mg, respectively, for the remaining 50 weeks. Patients were requested to take their study medication with water in the morning and at approximately the same time each day. Additional antihypertensive treatment, other than any ACE inhibitor or ARB, was permitted if SBP/DBP >130/80 mmHg. Treatment compliance was monitored at each visit. All blood pressures, which were measured using a standard mercury sphygmomanometer or electronic device, were a mean of three values obtained 2 min apart in patients who had been seated quietly for 3 min.

**Renal function evaluation**

Routine urinalysis, conducted by a central laboratory (MDS Pharma Services Central Lab GmbH, Hamburg, Germany), was performed at baseline and after 12 months' randomized treatment. The 24-h urinary protein excretion rate (UPER), based on a single collection at each time point, was calculated from the amount of protein measured in 24-h urine samples and urine volumes collected during this time. The change in 24-h UPER from baseline was the primary endpoint. Other parameters determined were urinary albumin excretion, serum creatinine, creatinine clearance and estimated glomerular filtration rate (eGFR). Creatinine clearance was calculated from creatinine excretion in 24-h urine (Jaffe reaction) and from the serum creatinine concentration. Estimated GFR was calculated using the short Modification of Diet in Renal Disease (MDRD) formula [18]. Changes from baseline after 12 months' treatment were determined.

**Pro-inflammatory parameters**

Serum hs-CRP was determined using a particle-enhanced immunonephelometric assay (Dade Behring, Marburg, Germany); patients with CRP >10 mg/l at some time point during the study were excluded as such values were considered to be caused by acute infection or tissue damage [19]. Plasma ADMA and 8-iso-PGF$_2$α in the 24-h urine samples were measured at a specialist laboratory (University Hospital Hamburg-Eppendorf, Germany), using validated ELISA (DLD Diagnostics, Hamburg, Germany) and gas chromatography/mass spectroscopy methods, respectively [20,21]. All plasma and urine samples were frozen and stored at −20°C and despatched to the assay laboratories on dry ice.

**Outcomes evaluation**

The primary endpoint was the change from baseline in the 24-h proteinuria after 12 months. Secondary endpoints included changes in 24-h albuminuria, eGFR and inflammatory parameters asymmetrical dimethylarginine (ADMA), hs-CRP and urinary 8-iso-PGF$_2$α. The occurrence of a
composite of doubling of serum creatinine, end-stage renal disease (defined as need for long-term dialysis, renal transplantation or serum creatinine $\geq 6.0$ mg/dl) and all-cause death was recorded. In addition, the incidence of a composite cardiovascular event (defined as myocardial infarction, stroke, or hospitalization for heart failure or unstable angina, coronary or peripheral revascularization) was determined.

**Safety evaluation**

The incidence, severity and considered relationship to study medication of all adverse events occurring during the study were recorded.

**Statistical analysis**

A sample size of 340 patients per treatment arm was established using an estimate of standard deviation (SD) of 2 g/day and a non-inferiority margin of 0.5 mg/day as suggested by the Irbesartan in Diabetic Nephropathy Trial (IDNT) [9] as having 90% power at the 2.5% (one-sided) level to demonstrate the non-inferiority of telmisartan for the primary endpoint of the change from baseline in UPER after 12 months’ treatment. Due to non-normality of UPER data, and use of log-transformed data, an SD of 0.82 from analysis of covariance (ANCOVA) and a non-inferiority margin of log $(1.25) = 0.223$, with 327 patients per treatment group, there was 93% power. For ADMA, it was anticipated that the SD of changes from baseline would be $\sim 0.3 \, \mu\text{mol/l}$; thus, a sample size of 340 patients per treatment arm would have a 20% power to detect treatment differences in the magnitude of 0.075 $\mu\text{mol/l}$. For analysis using log-transformed data, a sample size of 375 patients per treatment arm would have 90% power to detect treatment differences in the magnitude of 0.38. It was assumed that 15% of randomized patients would discontinue prematurely; thus, the total number of randomized patients required was 800.

Analysis of the changes in renal function parameters (except for GFR), because of non-normality, was based on log-transformed data in the full-analysis set with the last observation carried forward. Treatment effects were compared using ANCOVA that included terms for treatment and centre as main effects, and baseline function as a covariate, and expressed as geometric mean and 95% confidence interval (CI). ANCOVA was not to include effects of gender, HbA1c, prior ACE inhibitor/ARB treatment or smoking if these parameters were comparable in the two treatment groups. The same approach was used for the analysis of pro-inflammatory parameters.

Descriptive analysis was performed for the two composite outcome endpoints: doubling of serum creatinine, end-stage renal disease or all-cause mortality, and morbidity and mortality from cardiovascular causes (myocardial infarction, stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, cardiovascular death). The study was not powered to evaluate the time to the composite endpoints.

**Results**

**Demographic and clinical characteristics**

A total of 1372 patients were enrolled at 128 centres in 11 countries in Europe and three countries in Asia (Taiwan, Korea, Malaysia), and South Africa. Of the enrolled patients, 885 were randomized to treatment; 487 were not randomized because of failure to meet the inclusion criteria or withdrawal of consent. In the telmisartan and valsartan groups, 362 and 354 patients, respectively, completed the study (Figure 2). The two treatment groups were well matched regarding demographics and baseline characteristics (Table 1). Use of medication other than antihypertensives was comparable in the two treatment groups prior to the study (Table 2). Similar proportions of patients in the two treatment groups had been treated with ARB monotherapy (telmisartan, 17.6%; valsartan, 16.3%), ACE inhibitor monotherapy (telmisartan, 45.4%; valsartan, 45.5%), ARB plus diuretic combination therapy (telmisartan, 8.8%; valsartan, 8.6%), ACE inhibitor plus diuretic combination therapy (telmisartan, 3.6%; valsartan, 5.0%) and ACE inhibitor plus calcium channel blocker combination therapy (telmisartan, 3.6%; valsartan, 4.5%). The small numbers of patients who continued or started ACE inhibitor/ARB therapy other than telmisartan or valsartan during randomized
Fig. 2. CONSORT diagram.

Table 1. Demographics and baseline characteristics (mean ± SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Telmisartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>443</td>
<td>442</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63.0</td>
<td>65.2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.9 ± 9.2</td>
<td>61.4 ± 9.1</td>
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<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>20.1</td>
<td>18.1</td>
</tr>
<tr>
<td>Black</td>
<td>2.0</td>
<td>1.6</td>
</tr>
<tr>
<td>White</td>
<td>77.9</td>
<td>80.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.0 ± 5.2</td>
<td>30.4 ± 5.6</td>
</tr>
<tr>
<td>Urinary protein excretion rate [geometric mean (%)] (g/24 h)</td>
<td>2.70 (103.8)</td>
<td>2.86 (94.9)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate [geometric mean (%)] (ml/min/1.72 m²)</td>
<td>56.7 (26.3)</td>
<td>56.5 (25.4)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>147.6 ± 15.9</td>
<td>148.5 ± 15.5</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.6 ± 9.6</td>
<td>82.4 ± 10.0</td>
</tr>
<tr>
<td>Glycosylated haemoglobin (%)</td>
<td>7.8 ± 1.4</td>
<td>7.7 ± 1.3</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>18.1</td>
<td>18.3</td>
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<tr>
<td>Duration of hypertension (years)</td>
<td>11.1 ± 9.5</td>
<td>11.6 ± 9.7</td>
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<tr>
<td>Duration of type 2 diabetes (years)</td>
<td>13.9 ± 8.1</td>
<td>14.4 ± 8.4</td>
</tr>
<tr>
<td>Duration of diabetic nephropathy (years)</td>
<td>2.7 ± 3.4</td>
<td>2.8 ± 3.5</td>
</tr>
<tr>
<td>Concomitant medication other than antihypertensives (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>45.1</td>
<td>44.6</td>
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<tr>
<td>Lipidlowering agents other than statins</td>
<td>8.4</td>
<td>10.9</td>
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<tr>
<td>Oral antidiabetic agents</td>
<td>58.2</td>
<td>57.0</td>
</tr>
<tr>
<td>Insulin</td>
<td>58.7</td>
<td>56.8</td>
</tr>
<tr>
<td>Other drugs</td>
<td>81.3</td>
<td>84.8</td>
</tr>
</tbody>
</table>

*aLong Modification of Diet in Renal Disease formula [21]*
treatment period were considered important deviators from the protocol and were excluded from the efficacy analysis.

**Blood pressure changes**

During treatment, SBP and DBP were reduced in both treatment groups (baseline and end of treatment values, respectively, telmisartan 147.7 ± 16.0/81.7 ± 9.6 mmHg and 142.3 ± 18.0/79.2 ± 10.3 mmHg; valsartan 148.7 ± 15.2/82.5 ± 10.1 mmHg and 142.2 ± 17.2/78.4 ± 9.9 mmHg); there were no significant differences between telmisartan and valsartan after 12 months’ treatment. At 2 weeks, adjusted mean changes in SBP with telmisartan were −3.7 mmHg versus −1.7 mmHg with valsartan (P = 0.021). At subsequent visits, no clear differences between treatments were noted. With the use of additional antihypertensive therapy, during the study, 44.7% of telmisartan-treated patients and in 20.7% of valsartan-treated patients.

**Renal function**

In the full-analysis set, 24-h UPER (95% CI) was reduced by a geometric mean (95% CI) of 33% (27–39%) of the baseline value with telmisartan 80 mg (n = 404) and 33% (27–38%) with valsartan 160 mg (n = 411) after 12 months’ treatment, thus demonstrating non-inferiority of telmisartan (P = 0.849). At 6 months, 24-h UPER fell by 0.69 g/24 h from a baseline value of 2.75 (0.56, 13.60) g/24 h in the telmisartan group and by 0.75 g/24 h from a baseline of 2.89 (0.61, 13.78) g/24 h in the valsartan group.

Although macroalbuminuria was not an inclusion criterion, all but seven patients displayed macroalbuminuria at baseline (urinary albumin excretion rate [UAER] >300 mg/24 h). At the end of the study, 44 (13.5%) of patients in the telmisartan group and 32 (9.8%) were microalbuminuric (UAER 30–299 mg/24 h), and a further 4 (1.2%) patients in each treatment group were normoalbuminuric (<30 mg/24 h).

With the exception of a significant difference in creatinine clearance in favour of valsartan (P = 0.001), no significant differences in other renal function parameters were noted between the telmisartan and the valsartan treatment groups (Table 3). When patients were divided into tertiles according to the final SBP, DBP and HbA1c enhanced efficacy in terms of the reduction of the UPER was seen in both treatment groups in patients who exhibited better blood pressure control and better diabetes control at the end of treatment, and who had not previously received an ARB or ACE inhibitor (Table 4). There were no significant differences between the treatment groups, but this could be attributed to small patient numbers in the subgroups.

**Pro-inflammatory markers**

In the analysis of hs-CRP, 99 patients in the telmisartan group and 105 patients in the valsartan treatment group were excluded because serum CRP was >10 mg/l at some time point during the study. Changes from baseline in plasma ADMA, serum hs-CRP and urinary 8-iso-PGF2α are summarized in Table 5. There were no significant differences in changes in ADMA or hs-CRP between treatment groups. However, urinary excretion of 8-iso-PGF2α decreased by 14% with telmisartan and by 7% with valsartan (P = 0.040). There was no correlation between changes in pro-inflammatory markers and changes in the urinary albumin excretion rate.

**Outcomes**

The frequency of the composite endpoint of doubling of serum creatinine, end-stage renal disease and all-cause death was 5.1% with telmisartan and 4.2% with valsartan (P = 0.562). Cardiovascular morbidity or mortality was recorded in 7.2% and 7.7% in the telmisartan and valsartan groups, respectively (P = 0.739). The frequency of components of the composite endpoints is reported in Table 6.

**Safety**

Median duration of exposure to study drug was 363 days for telmisartan and 364 days for valsartan. During the study,
### Table 3. Comparison of the effect of telmisartan and valsartan on the percentage change from baseline after 12 months' treatment [geometric mean (95% confidence interval)] in renal function parameters

| Parameter                        | Telmisartan          | Valsartan            | P-value  
|---------------------------------|----------------------|----------------------|---------
| Urinary protein excretion rate (mg/24 h) | 2750 (556, 13,601) | 1800 (215, 15,039) | 0.883   
| Urinary albumin excretion rate (mg/24 h) | 1658 (258, 10,664) | 970 (74, 12,672) | 0.433   
| Urinary sodium excretion (mmol/24 h) | 188.1 (65.4, 541.3) | 180.2 (61.6, 526.8) | 0.296   
| Serum creatinine (mg/dl) | 1.37 (0.62, 3.04) | 1.57 (0.58, 4.28) | 0.101   
| Creatinine clearance (ml/min/1.73 m²) | 57.8 (19.2, 174.1) | 45.2 (11.9, 171.4) | 0.001   
| Estimated GFR (ml/min/1.73 m²) | 48.4 ± 23.0 | 45.8 ± 22.7 | 0.268   

*Geometric mean (%).  
*Mean ± SD.  
*P-value.

### Table 4. Comparison of the effect of telmisartan and valsartan on the percentage change in UPER (log-transformed) according to final blood pressure, final pulse pressure, final HbA₁c, baseline UPER and prior treatment with an ARB or ACE inhibitor

| Parameter                        | Telmisartan          | Valsartan            | P-value  
|---------------------------------|----------------------|----------------------|---------
| SBP (mmHg) ≤ 133               | 1.40 (0.19, 10.28) | -44 (−52, −34) |        
| 134–148                        | 1.73 (0.18, 16.28) | -37 (−46, −28) |        
| > 140                          | 2.48 (0.34, 17.89) | -16 (−28, −2) |        
| DBP (mmHg) ≤ 75                | 1.68 (0.21, 13.20) | -38 (−47, −28) |        
| 76–82                          | 1.61 (0.18, 14.23) | -37 (−46, −26) |        
| > 82                           | 2.16 (0.26, 17.67) | -24 (−33, −11) |        
| Pulse pressure (mmHg) ≤ 56     | 1.58 (0.19, 13.02) | -37 (−45, −27) |        
| 57–68                          | 1.73 (0.21, 13.95) | -40 (−48, −30) |        
| > 68                           | 2.17 (0.26, 18.42) | -23 (−34, −11) |        
| HbA₁c (%) ≤ 7                  | 1.59 (0.16, 15.66) | -39 (−45, −27) |        
| 7.1–8.5                       | 1.61 (0.27, 14.97) | -29 (−38, −19) |        
| > 8.5                          | 1.81 (0.23, 14.11) | -31 (−42, −19) |        
| UPER at baseline               | 0.64 (0.13, 3.09) | -31 (−43, −27) |        
| < 1.5 g/24 h                   | 0.66 (0.13, 3.09) | -31 (−43, −27) |        
| 1.5–2.9 g/24 h                 | 1.53 (0.38, 6.16) | -29 (−39, −19) |        
| ≥ 3 g/24 h                     | 3.42 (0.81, 14.42) | -39 (−46, −31) |        
| ACE inhibitor/ARB prior treatment | 1.96 (0.24, 15.71) | -31 (−38, −23) |        
| Yes                            | 1.96 (0.24, 15.71) | -31 (−38, −23) |        
| No                             | 1.57 (0.18, 13.58) | -37 (−46, −27) |        

*Mean ± SD.  
*P-value.
adverse events were recorded in 72.3% of telmisartan patients and 71.6% of valsartan patients, the majority (~55% in each group) being mild in intensity. In 28 (6.2%) telmisartan group patients and in 30 (6.7%) valsartan group patients, events were considered to be treatment related. Hyperkalaemia/increased serum potassium occurred in 2.2% and 2.9%, respectively, of patients treated with telmisartan and valsartan. All other adverse events were considered treatment related occurred at a frequency of <1%. Treatment was discontinued due to an adverse event (telmisartan, 3.2%; valsartan, 2.0%), mainly due to a worsening of diabetic nephropathy, hypertension or T2D. Serious adverse events occurred in 116 and 104 patients treated with telmisartan and valsartan, respectively. Serious adverse events occurring at a frequency of >2% in either treatment group were cardiac disorders (telmisartan, 5.5%; valsartan, 7.6%); infections (telmisartan, 6.9%; valsartan, 4.0%); renal and urinary disorders (telmisartan, 4.0%; valsartan, 3.8%); nervous system disorders (telmisartan, 4.0%; valsartan, 3.3%); metabolism and nutrition disorders (telmisartan, 2.7%; valsartan, 1.6%); neoplasms (telmisartan, 1.5%; valsartan, 2.2%); vascular disorders (telmisartan, 1.5%; valsartan, 2.4%); and respiratory, thoracic and mediastinal disorders (telmisartan, 2.4%; valsartan, 1.1%). Death while in receipt of active treatment occurred in 19 patients (telmisartan, 14; valsartan, 5), and a further 9 (telmisartan, 5; valsartan, 4) died during the post-study phase. The majority of these deaths were due to cardiovascular disease (telmisartan, 9; valsartan, 4), but none were considered by investigators to be treatment related.

Discussion

The present study confirms the antiproteinuric efficacy of ARBs in patients with hypertension, T2D and overt nephropathy. The reductions in proteinuria observed at 6 and 12 months were comparable to that recorded in the Reduction in Endpoints in Non-insulin-dependent Diabetes with Angiotensin II Antagonist Losartan (RENAAL) study [22], which showed that reducing albuminuria in the first 6 months of therapy affords cardiovascular protection. Comparable beneficial changes in other parameters of renal function were found, the only exception being a significant difference in creatinine clearance between the two treatment groups. However, creatinine clearance measurements are often inaccurate [23], and, indeed, when using the generally recommended calculation according to the MDRD formula [18] no difference was detected.

A previous study of 24 weeks’ duration has shown that valsartan 80–160 mg lowered the urinary albumin excretion rate more effectively than amlodipine 5–10 mg in patients with microalbuminuria [7]. The comparable reductions in blood pressure observed with the two treatments added fuel to the argument that the renoprotective effect of valsartan was, at least in part, independent of blood pressure control. Also, it has been recently reported that telmisartan reduced the transmission to overt nephropathy in Japanese patients with T2D but who were normotensive, thus implying that telmisartan has a blood pressure-independent effect [24]. This conclusion was further supported by the observation that transition rates were maintained when adjustment was

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Table 5. Comparison of the effect of telmisartan and valsartan on [geometric mean (95% confidence interval)] in pro-inflammatory parameters from baseline after 12 months’ treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Telmisartan</th>
<th>Valsartan</th>
<th>P-valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMA (µmol/L)a</td>
<td>0.71 (0.48, 1.05)</td>
<td>0.74 (0.48, 1.13)</td>
<td>1 (0, 3)</td>
</tr>
<tr>
<td>hs-CRP (mg/l)a, b</td>
<td>2.16 (0.31, 15.03)</td>
<td>2.11 (0.28, 15.82)</td>
<td>−7 (−4, 19)</td>
</tr>
<tr>
<td>8-Iso-PGF2α (µg/24 h)a</td>
<td>219 (61, 790)</td>
<td>188 (46, 767)</td>
<td>−14 (−19, −8)</td>
</tr>
</tbody>
</table>

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Table 6. Frequency of components of the composite outcome endpoints

<table>
<thead>
<tr>
<th>Outcome endpoint</th>
<th>Telmisartan (n = 428)</th>
<th>Valsartan (n = 429)</th>
</tr>
</thead>
</table>
made for the reduction in SBP [24]. We have shown that, using the maximum doses approved for the treatment of hypertension, the renoprotective efficacy of telmisartan 80 mg is comparable to that of valsartan 160 mg in improving parameters of renal function, as well as reducing proteinuria, in patients with hypertension, T2D and overt nephropathy. Importantly, it should be noted that the dose-response curves for reduction of BP and proteinuria are different: higher doses of ARBs (and ACE-inhibitors) are required to optimize tissue protection and reduce proteinuria than those required for blood pressure control [25].

It is noteworthy that, in both treatment groups of our study, the improvement in the UPER tended to be greater in the subgroups of patients that displayed greater blood pressure control and better diabetes control, and in those who had not previously received antihypertensive therapy that targeted the RAS. This finding suggests the importance of RAS blockade for renoprotection and underlines the predominant role of blood pressure control.

In our study, we were especially interested in determining whether there was any relationship between the decline in proteinuria and changes in endothelial function, as has been suggested by animal studies [26] and clinical studies of early renal damage [27]. The endothelium plays a major role in vascular homeostasis, and impaired function is implicated in the pathophysiology of hypertension, cardiovascular disease and renal impairment [28]. Endothelial dysfunction and disturbed oxidative balance is often observed in patients with T2D [29]. Our study evaluated plasma ADMA and urinary 8-iso-PGF2α, which are widely regarded as reliable markers of endothelial dysfunction and oxidative stress [13,14,16,17]. Elevated circulating ADMA may contribute to the increased cardiovascular morbidity and mortality occurring in early diabetic nephropathy [30]. In our patients with well-established renal damage, circulating levels of ADMA were within the reference range found in healthy volunteers [31,32] and remained stable in both treatment groups for the duration of the study. The larger decrease in 8-iso-PGF2α that we observed with telmisartan may, in part, be attributed to the lower creatinine clearance with telmisartan, but the accuracy of creatinine clearance estimations may be suspect in patients with impaired renal function [23]. Theoretically, a sampling error could be responsible for a lower creatinine clearance; however, in a relatively large trial as the VIVALDI study, it is highly unlikely that there was a systematic sampling error affecting one group (telmisartan) more than the other (valsartan). Alternatively, the difference between treatments may be explained by telmisartan’s longer duration of action, based on its longer half-life compared with valsartan [33].

CRP is another pro-inflammatory biomarker [34]. As a measure of inflammation, hs-CRP predicts cardiovascular risk and may foretell long-term cardiovascular risk in individuals with no prior evidence of cardiovascular disease [15]. Elevated levels of hs-CRP are associated with increased risk of hypertension, stroke and myocardial infarction. The recent Val-MARC study showed that valsartan monotherapy reduced plasma levels of hs-CRP, whereas no reduction was noted when hypertension was effectively treated with a combination of valsartan and hydrochlorothiazide [35]. Anti-inflammatory effects of an ARB have also been demonstrated in hypertensive patients with microinflammation [36]. Thus, angiotensin receptor blockade may have anti-inflammatory effects that, in the long term, may lower the risk of cardiovascular morbidity and mortality. In our study, comparable changes in hs-CRP were observed in the telmisartan and valsartan groups, and any differences were not considered to be of clinical relevance. Thus, telmisartan may confer comparable cardiovascular protection to valsartan.

The absence of changes in pro-inflammatory stress markers may be partly explained by the fact that many of the patients in this study were not naïve to treatment with agents targeting the RAS: prior to enrolment, nearly half had received ACE inhibitors and ∼20% ARBs. Hence, baseline values could have been favourably affected. Alternatively, the preclinical evidence of the anti-inflammatory effects of ARBs may not be extrapolated to clinical situations. The inclusion of a control group that received neither ACE inhibitors nor ARBs could have provided further insight into the inflammatory changes. However, this would have been unethical in these high-risk patients considering the proven renoprotection afforded by agents targeting the RAS [5].

The importance of controlling blood pressure in the management of diabetic patients with nephropathy is well recognized [37]. To achieve this, a single antihypertensive drug is usually insufficient. In our study, various combinations of antihypertensive agents in addition to the study drug were given in both treatment groups in an attempt to achieve the rigorous blood pressure targets now advocated [38]. There was a tendency for the patients in the valsartan group to require additional antihypertensive therapy, although not statistically significant, to achieve acceptable levels of blood pressure control. This is consistent with studies that have shown that valsartan is less effective than telmisartan in the control of blood pressure in the last hours of the dosing interval [39,40].

The dose of an antihypertensive agent used in the treatment of nephropathy may be particularly crucial. The maximum dose approved for the treatment of hypertension was used in our study. However, a pilot study has found that in patients with diabetic and non-diabetic renal disease increasing the dose of an ARB, in that case candesartan, too far in excess of that approved for the treatment of essential hypertension resulted in a dose-dependent reduction in proteinuria, but with no further reduction in blood pressure [41]. This additional clinical benefit with higher doses has been confirmed in the DROP trial [25].

It has also been proposed that more complete blockade of the RAS using a combination of an ARB and an ACE inhibitor provides additional renoprotection, and there is some short-term clinical evidence to support this suggestion [42–44]. The large-scale ONTARGET trial, in which the effects of a combination of ramipril and telmisartan are being compared with either monotherapy over a follow-up period of 5 years, should provide a large database to identify the long-term benefit of dual blockade on cardiovascular outcomes and renoprotection [45].

We conclude from the findings of our study in patients with hypertension, T2D and overt nephropathy that the
renoprotection afforded by the ARBs telmisartan and valsartan was comparable, and was consistent with reductions that confer cardiovascular protection. However, the study does not allow us to show any effect beyond blood pressure control. At the doses used to treat hypertension, we were unable to provide any evidence of inflammatory parameters being modified in patients with more advanced kidney disease due to diabetes.

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