Chapter 3

The angiotensin II receptor antagonist telmisartan reduces urinary albumin excretion in patients with isolated systolic hypertension: results of a randomized, double-blind, placebo-controlled trial

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Objective—To examine the effect of telmisartan or hydrochlorothiazide (HCT) on the control of urinary albumin excretion (UAE) in patients with isolated systolic hypertension (ISH) and unselected for albuminuria in a pre-planned substudy of a large, multicentre, double-blind, placebo-controlled, randomized study. Methods—The Angiotensin II Receptor Antagonist Micardis in Isolated Systolic hypertension (ARAMIS) study compared the antihypertensive efficacy after 6 weeks of once-daily fixed doses of telmisartan 20, 40 or 80 mg versus HCT 12.5 mg or placebo in patients (n = 1039, age 35-84 years) with ISH (seated blood pressure (BP) 150-179/< 90 mmHg). The prospective substudy analysed UAE using spot morning samples. Results—Urinary albumin (> 2.2-901.6 mg/L) was detected at baseline in 614/918 patients, who were included in the substudy analysis. In the telmisartan group (n = 354, all doses combined), a median reduction in UAE from baseline of 14.1% (95% confidence intervals 7.3, 21.8) was observed versus 1.1% (-13.5, 16.0) and 2.7% (-0.9, 19.9) in the HCT (n = 140) and placebo (n = 120) groups, respectively. The difference between telmisartan and HCT was significant (p = 0.017). Reductions in UAE with telmisartan were observed in patients with baseline normoalbuminuria, microalbuminuria or macroalbuminuria. Telmisartan and HCT produced comparable reductions in systolic BP in these patients. Conclusion—In patients with ISH and unselected for baseline albuminuria, telmisartan 20-80 mg after 6 weeks’ treatment afforded significantly greater lowering of UAE than HCT 12.5 mg, irrespective of the baseline UAE, and despite comparable reductions in systolic BP with both drugs.

Isolated systolic hypertension (ISH) is an important treatment target, recognized as a dominant risk factor for heart disease, stroke and renal failure (1,2). Microalbuminuria and macroalbuminuria are also widely accepted risk factors for cardiovascular and renal disease in patients with diabetes (3,4) and hypertension (5-7). In patients with urinary albumin excretion (UAE) below the definition of microalbuminuria (< 20 mg/L), increased cardiovascular and renal risk still exists (8), and epidemiological studies show that such individuals are at increased risk of cardiovascular death (9) and all-cause mortality (9,10). Moreover, in hypertensive patients with left ventricular hypertrophy, elevated UAE results in heightened cardiovascular risk without any thresholds for albuminuria (11). In patients with ISH, macroalbuminuria is predictive of cardiovascular mortality and cardiovascular and renal morbidity (12), but the relationship between slightly elevated UAE in these patients and cardiovascular risk has not been studied.

Antihypertensive treatment should ideally not only lower the risk associated with high blood pressure, but also lower UAE and thus reduce its associated risk (13). Agents targeting the renin-angiotensin-aldosterone system (RAAS) lower blood pressure and are
particularly effective in reducing microalbuminuria and macroalbuminuria (14). This reduction of UAE contributes independently to improved cardiovascular and renal outcomes in many different patient groups (15-21).

Until now there has been no information on the effects of different antihypertensive agents on UAE in hypertensive patients with UAE below microalbuminuric levels. Data in the present report are derived from a pre-planned substudy of a large-scale, multicentre study—Angiotensin II Receptor Antagonist telmisartan (Micardis) in Isolated Systolic hypertension (ARAMIS) (22). The purpose of the main study was to identify telmisartan doses that are more effective than placebo and non-inferior to hydrochlorothiazide (HCT) in lowering systolic blood pressure (SBP) in patients with ISH and that are well tolerated. The primary objective of this substudy was to evaluate the effect of different once-daily telmisartan doses (20, 40 and 80 mg) on UAE in patients with ISH and with UAE of any degree (including below the threshold for microalbuminuria), compared with once-daily HCT 12.5 mg or placebo. To determine whether any effect on UAE is independent of blood pressure control, efficacies of the different telmisartan doses on the reduction in SBP and diastolic blood pressure (DBP) were compared with those of HCT and placebo.

PATIENTS AND METHODS

Study population
A total of 1039 patients with ISH (seated SBP/DBP 150-179/< 90 mmHg) were randomized to treatment in the ARAMIS study, which was conducted in 17 countries in Europe, Australia and South Africa (22). Participants of either sex and between 35 and 84 years of age were recruited from primary-care or specialist hypertension centres. Patients receiving antihypertensive medication immediately prior to the study could only be enrolled if it was considered that withdrawal of that treatment and the possible receipt of up to 10 weeks’ placebo would not compromise their health. Exclusion criteria comprised secondary hypertension, hepatic and/or renal dysfunction (defined as serum creatinine > 159 µmol/L (> 1.8 mg/dL)), clinically relevant hypo- or hyperkalaemia, uncorrected volume or sodium depletion, primary aldosteronism, symptomatic cardio- or cerebrovascular disease, previous percutaneous transluminal angioplasty or coronary artery bypass grafting, inadequately controlled or recently stabilized type 2 diabetes mellitus, type 1 diabetes mellitus, hypersensitivity to telmisartan or HCT, or gout. Women who were pregnant, nursing or of childbearing potential were not eligible. Patients from Australia (n = 65) were excluded from the substudy because correct collection of urine was not possible for UAE assessment. All patients gave written, informed consent.
Study design
Local institutional review boards approved the protocol for the randomized, double-blind, placebo-controlled, parallel-group substudy. After screening, eligible patients entered a single-blind run-in period before randomization. If a patient was not receiving antihypertensive treatment at the time of enrolment, placebo was administered for 2 weeks. For patients who had received antihypertensive treatment immediately prior to enrolment, the placebo washout period was extended to 4 weeks. Thereafter, patients were randomized to 6 weeks’ double-blind, once-daily treatment with telmisartan 20, 40 or 80 mg, HCT 12.5 mg or placebo. Patients were instructed not to take their trial medication on the clinic visit days, which were always in the morning at approximately the same time and within 23-26 h of the most recent study medication intake.

Determination of UAE, renal function and blood pressure
Patients were evaluated at baseline and after 6 weeks’ double-blind treatment. UAE was measured as the urinary albumin concentration in a morning urine sample (first micturition after getting out of bed) determined by a commercial immunoturbidimetry assay (BNII, Bade Behring Diagnostica), lower limit of quantification 2.2 mg/L and inter- and intra-assay coefficients of variation 4.4% and 4.3%, respectively. Microalbuminuria was defined as a UAE of 20-200 mg/L and macroalbuminuria as UAE > 200 mg/L (23).

Urinary creatinine was determined in spot urine sample and serum creatinine was analysed. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine according to the Cockcroft formula (24).

Seated trough blood pressure was measured three times at every clinic visit, with at least 2 min. between measurements, after the patient had been seated for 5 min. A manual cuff sphygmomanometer was used, with measurements to the nearest 2 mmHg. SBP was recorded as Korotkoff phase I and DBP as phase V.

Statistics analysis
For the pre-planned substudy, the analysis was performed on the per-protocol population, comprising all randomized patients in whom UAE was measured at baseline and after 6 weeks’ treatment and who met the substudy inclusion criteria. Based on our previous clinical experience, we assumed a 15% UAE reduction (log-transformed change 0.4 mg/L) to be clinically relevant. Based on data from the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) (25), the mean UAE is 31.3 mg/L (log 2.87) with a standard deviation (SD) of 85.5 (log 0.93) for patients with ISH. Using the log-transformed values of 2.8 mg/L (SD = 0.9), a 0.4 mg/L (15%)
change could be detected with 5% error probability and 80% power using a two-sided $t$-test in a population of 81 patients per group. Baseline values are expressed as means and 95% confidence intervals (CI), except for UAE which is expressed as median and 95% CI of the median range. Effects of treatment on UAE, expressed as percentage and absolute changes from baseline, and UAE-to-creatinine ratios were analysed by the non-parametric Kruskal-Wallis test. In case of significance, pair-wise post-hoc comparisons between the separate groups were performed using the Mann-Wilcoxon-Whitney test. Blood pressure effects between the different treatment groups were analysed by a general linear model of covariance, adjusting for treatment and country effects with baseline as covariates.

**RESULTS**

Of the 1039 patients included in the ARAMIS study, spot morning urine samples were available both before and after the 6-week intervention and UAE was determined in 918 patients (figure 1). There was a wide baseline distribution of UAE (> 2.2-901.6 mg/L, figure 2), with UAE detectable (i.e., above lower level of quantification of 2.2 mg/L) in 614 patients (66.9%); these patients were included in the substudy analysis. Microalbuminuria (20-200 mg/L) was present in 70 (7.6%) patients and macroalbuminuria (> 200 mg/L) in 86 (9.4%). All treatment groups were comparable with regard to the number of patients with detectable UAE and baseline characteristics (table 1).

**Efficacy of different telmisartan doses**

After 6 weeks’ telmisartan treatment, the median (95% CI) reductions in UAE with telmisartan 20, 40 and 80 mg were 0.8 mg/L (0.5, 1.8), 1.2 mg/L (0.6, 2.1) and 0.3 mg/L.
Table 1. Demographic and baseline values (mean (SD)) for patients with detectable urinary albumin excretion (UAE)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>HCT 12. mg (n = 120)</th>
<th>Telmisartan All doses (n = 354)</th>
<th>Telmisartan 20 mg (n = 117)</th>
<th>Telmisartan 40 mg (n = 119)</th>
<th>Telmisartan 80 mg (n = 118)</th>
</tr>
</thead>
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<tr>
<td>Male (%)</td>
<td>41.7</td>
<td>46.4</td>
<td>44.6</td>
<td>46.2</td>
<td>42.9</td>
<td>48.3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.0 (10.5)</td>
<td>63.6 (11.5)</td>
<td>62.6 (11.3)</td>
<td>62.7 (12.2)</td>
<td>62.2 (11.2)</td>
<td>62.8 (10.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 (4.0)</td>
<td>27.5 (4.3)</td>
<td>28.0 (4.5)</td>
<td>28.0 (4.4)</td>
<td>27.8 (4.3)</td>
<td>28.1 (4.9)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>164.3 (7.8)</td>
<td>162.5 (8.3)</td>
<td>163.7 (8.0)</td>
<td>162.9 (7.9)</td>
<td>164.5 (8.2)</td>
<td>163.5 (8.0)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83.3 (5.6)</td>
<td>83.5 (4.4)</td>
<td>83.4 (4.8)</td>
<td>83.7 (4.7)</td>
<td>83.5 (4.5)</td>
<td>83.1 (5.1)</td>
</tr>
<tr>
<td>Pulse (bpm)</td>
<td>72.3 (9.8)</td>
<td>71.9 (9.5)</td>
<td>73.5 (10.0)</td>
<td>73.4 (9.5)</td>
<td>73.4 (10.0)</td>
<td>73.6 (10.4)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>95 (32)</td>
<td>102 (40)</td>
<td>106 (38)</td>
<td>103 (37)</td>
<td>105 (35)</td>
<td>109 (41)</td>
</tr>
<tr>
<td>UAE (mg/L)</td>
<td>5.1</td>
<td>4.8</td>
<td>5.2</td>
<td>5.2</td>
<td>5.7</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>(4.1–6.0)</td>
<td>(4.0–5.6)</td>
<td>(4.6–5.7)</td>
<td>(4.2–6.3)</td>
<td>(4.6–6.6)</td>
<td>(3.9–5.5)</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>7.5</td>
<td>10.7</td>
<td>11.3</td>
<td>11.1</td>
<td>12.6</td>
<td>10.2</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>10.0</td>
<td>9.3</td>
<td>12.7</td>
<td>14.5</td>
<td>8.4</td>
<td>15.3</td>
</tr>
</tbody>
</table>

*Cockcroft formula (24). *Median (95% CI), *UAE 20-200 mg/L. BMI, body mass index.

(0.0, 1.0), respectively. Mean (95% CI) reductions in seated trough SBP in the 20-, 40- and 80-mg treatment groups were 15.1 mmHg (12.8, 17.4), 17.6 mmHg (15.3, 19.9) and 16.9 mmHg (14.4, 19.5), respectively. Since no true dose–response was observed for either UAE or SBP, the values of the three telmisartan groups were combined (n = 354) for comparison with HCT and placebo.

**Efficacy of telmisartan compared with HCT and placebo on UAE**

The effects of the different treatments on absolute UAE values are shown in figure 3. Baseline UAE (median (95% CI)) in the total telmisartan group was 5.2 mg/L (4.2, 6.3). After treatment, median (95% CI) UAE was reduced significantly from baseline by 14.1% (7.3, 21.8) in the telmisartan group, where as non-significant reductions from baseline of 1.1% (-13.5, 16.0) and 2.7% (-0.9, 19.9) were observed in the HCT and placebo groups, respectively. The reduction in the telmisartan group differed significantly from that in the HCT group (p = 0.0165).

Correcting for the urinary creatinine excretion revealed the same pattern: in the telmisartan group, UAE-to-creatinine ratio was significantly reduced by 12.7% (5.4, 21.8). In the placebo groups, the median reduction was 8.0% (-7.9, 22.0) whereas there was a 1.8% (-25.3, 20.1) increase in the HCT group. Again, the difference between telmisartan and HCT was significant (p = 0.0378).
In the telmisartan group, when the response was analysed based on baseline UAE (> 2.2-20 mg/L (normoalbuminuria), > 20-200 mg/L (microalbuminuria) and > 200 mg/L (macroalbuminuria/overt proteinuria)), UAE reductions after 6 weeks’ telmisartan treatment of 10.2% (1.5, 16.3), 55.4% (3.9, 77.0) and 50.4% (-371.7, 81.1), respectively, were detected.

**Antihypertensive efficacies**

The effects of treatment on blood pressure (adjusted mean) are depicted in figure 4. Baseline (mean (95% CI)) SBP in the total telmisartan group was 163.7 mmHg (162.8, 164.5); this was comparable to the SBP in the HCT and placebo groups of 162.5 mmHg (161.1, 163.9) and 164.3 (162.9, 165.8) mmHg, respectively. After 6 weeks, SBP was significantly reduced from baseline by 6.7% (5.4, 8.0) in the placebo group. Telmisartan treatment resulted in a larger reduction in SBP of 10.1% (11.0, 9.3). With HCT, a 9.1% (10.4, 7.7) reduction from baseline was detected. At baseline, the DBP in the total telmisartan group was 83.4 mmHg (95% CI 82.9, 83.9) and this was reduced by 2.7% (95% CI 2.0, 3.5) after 6 weeks’ treatment. In the placebo group, DBP did not change significantly from a baseline of 83.3 mmHg (82.2, 84.3), whereas a 2.0% (0.9, 3.1) reduction from a baseline value of 83.5 mmHg (82.8, 84.2) was detected in the HCT group. The differences in SBP and DBP reductions between HCT and telmisartan were not statistically significant.

**Safety**

Incidences of all-cause adverse events in the per-protocol population ($n = 918$) were 17.6%, 14.0% and 16.9%, respectively, for telmisartan 20, 40 and 80 mg. By
Figure 3.
Adjusted mean (95% confidence intervals) urinary albumin excretion (ΔUAE) after 6 weeks’ treatment with placebo (n = 120), hydrochlorothiazide (HCT) 12.5 mg (n = 140); and telmisartan 20, 40 or 80 mg (n = 354); ‡ p < 0.02.

Figure 4.
Adjusted mean (95% confidence intervals) changes in (a) systolic blood pressure (ΔSBP), (b) diastolic blood pressure (ΔDBP) and (c) urinary albumin excretion (ΔUAE) after 6 weeks’ treatment with placebo (n = 120), hydrochlorothiazide (HCT) 12.5 mg (n = 140) or telmisartan 20, 40 or 80 mg (n = 354); * p < 0.0001; † p < 0.005; ‡ p < 0.02.
Table 2. The five most frequent reported adverse events after 6 weeks’ treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 183)</th>
<th>HCT 12.5 mg (n = 185)</th>
<th>Telmisartan 20 mg (n = 180)</th>
<th>Telmisartan 40 mg (n = 187)</th>
<th>Telmisartan 80 mg (n = 183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4 (2.2%)</td>
<td>4 (2.1%)</td>
<td>3 (1.6%)</td>
<td>4 (2.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (1.6%)</td>
<td>2 (1.1%)</td>
<td>4 (2.2%)</td>
<td>3 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (2.7%)</td>
<td>1 (0.5%)</td>
<td>4 (2.2%)</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (0.5%)</td>
<td>3 (1.6%)</td>
<td>3 (1.6%)</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>1 (0.5%)</td>
<td>2 (1.1%)</td>
<td>2 (1.1%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

In comparison, in the HCT and placebo groups, 19.8% and 18.7%, respectively, experienced an adverse event. The five most frequently reported events in any of the treatment groups are summarized in Table 2. The total incidence of drug-related events was 3.0%, being comparable in the different treatment groups.

No significant changes from baseline in clinical laboratory parameters were detected during the study. The mean (95% CI) calculated creatinine clearance decreased by 3.6 mL/min (1.3, 5.8) after 6 weeks’ treatment with telmisartan. A reduction of 2.1 mL/min (-1.6, 5.7) was observed in the HCT group and an increase of 0.6 mL/min (-3.1, 4.3) was detected in the placebo group.

**DISCUSSION**

This study demonstrates that, in patients with ISH and unselected for the degree of albuminuria at baseline, UAE was effectively reduced after telmisartan treatment, but not after treatment with HCT. This was despite similar reductions in SBP and DBP with the two treatments. Further analysis showed that this reduction in UAE was not only observed in patients with microalbuminuria or macroalbuminuria, but also in those with UAE within the range generally considered to be normal.

Based on the outcomes of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) (26), Systolic Hypertension in the Elderly Program (SHEP) (27) and Systolic Hypertension in Europe trial (Syst-Eur) (28), The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure proposes the use of a diuretic as first-choice therapy for the treatment of ISH, with a long-acting calcium channel blocker as an alternative (29). However, it is noted that the choice of the initial agent is of less importance than the degree of blood pressure reduction achieved (29). The results of ARAMIS provide a different perspective, with telmisartan proving non-inferior to hydrochlorothiazide in the control of SBP (22). The results of our subsstudy show that telmisartan could have an additional benefit as it reduced UAE, whereas HCT did not. To our knowledge, there
have been no previous studies comparing the effect of an angiotensin II receptor blocker with that of HCT on UAE. However, there is evidence that targeting the RAAS using an angiotensin-converting enzyme inhibitor, as well as reducing blood pressure, decreased UAE in hypertensive diabetic patients, whereas HCT was ineffective despite comparable antihypertensive efficacy (30). Another study showed that, in normotensive diabetic patients, an angiotensin-converting enzyme inhibitor, but not HCT, reduced microalbuminuria (31).

The reduction in UAE we observed in the short term among patients with varying degrees of albuminuria may confer clinically significant long-term cardiovascular benefit. Data from 40 000 individuals in PREVEND demonstrated that, after adjustment for other well-recognized risk factors, UAE is predictive of cardiovascular death in the general population (9). An individual with a UAE of 10-20 mg/L is reported to have 28% higher risk of cardiovascular death than one with a UAE of 0-10 mg/L (9). Findings of the Heart Outcomes Prevention Evaluation (HOPE) study also demonstrated that any degree of albuminuria is a risk factor for cardiovascular events (19). A similar relationship exists between UAE and the development of renal damage, patients with high-normal UAE being at higher risk of developing microalbuminuria and macroalbuminuria (32).

Whether or not a reduction in UAE, as a consequence of antihypertensive treatment—even when established within baseline ranges below the threshold for microalbuminuria—contributes to a risk reduction still needs to be established. Nevertheless, data from studies performed in both diabetic and non-diabetic microalbuminuric or macroalbuminuric patients show that a reduction in albuminuria using antihypertensive treatment favourably impacts on the incidence of end-organ damage (16-18,33). In particular, the beneficial effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular and renal risk are predicted by their antiproteinuric activity (34). Currently, there are no data on changes in UAE from comparative studies conducted in patients with very low levels of UAE. Given that over 80% of the patients in our study had levels of UAE lower than the criteria for microalbuminuria, the significantly greater reduction in UAE with telmisartan compared with placebo is all the more striking. The effect on cardiovascular and renal risk reduction is uncertain at present, but deserves further examination.

In the interpretation of our results, we acknowledge deficiencies. Firstly, although the reduction in UAE with telmisartan compared with placebo exceeded our prespecified limit for clinical significance, it did not reach statistical significance. Furthermore, SBP was also significantly reduced by placebo, although to a lesser extent than the two active treatments. It is, therefore, not feasible to distinguish between possible favourable effects of telmisartan or the more detrimental effect of HCT.
Secondly, our patient population displayed a marked variation in baseline UAE, ranging from < 2.2 mg/L to 901.6 mg/L. After treatment, the changes of UAE varied greatly in the three treatment groups. This wide distribution can be partly explained by the use of spot sampling, as opposed to 24-h collection of urine, and the collection of only one sample at baseline and one at the end of treatment. Nevertheless, correction of UAE for the creatinine excretion, which would allow for confounding factors, did not affect the overall pattern of our results. Thirdly, we did not observe a dose-response effect on UAE reduction with telmisartan. By contrast, in macroalbuminuric patients, uptitration of doses of RAAS-targeting agents may bring about additional UAE reduction (35). Since optimal blood pressure reduction is of great importance for optimizing outcome, it is interesting that no dose-response effect on SBP and DBP was detected with telmisartan. This suggests that telmisartan doses used in our study were at the plateau of the dose–response curve, both for the reduction of UAE and for blood pressure control. A previous study was unable to detect any significant linear trend in blood pressure reduction among telmisartan doses in the range 40-120 mg (36).

In conclusion, treatment of ISH with the angiotensin II receptor antagonist telmisartan reduced UAE. In contrast, hydrochlorothiazide did not affect UAE, despite bringing about a similar reduction in blood pressure. With respect to optimal risk management, the telmisartan-induced reduction in UAE could be of additional benefit, although no cause-effect relationship has been demonstrated so far. Future studies should be directed at aggressive treatment of risk factors to establish the cardiovascular and renal benefit.

REFERENCES
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ACKNOWLEDGEMENTS
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Elements of this study were presented at the American Society of Nephrology 2002 Annual Meeting in Philadelphia (abstract J Am Soc Nephrol 2002; 13: 241A)