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Safety of Telmisartan in Patients with Arterial Hypertension

An Open-Label Observational Study

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Abstract

Objective: To determine whether age, gender, concomitant disease and/or previous or present antihypertensive medication affect the safety or antihypertensive efficacy of telmisartan in the treatment of arterial hypertension.

Study Design and Methods: In this large-scale, open-label postmarketing surveillance study, German physicians systematically documented their observations concerning patients with essential hypertension on case report forms. Patients were treated for 6 months with telmisartan (40–80mg once daily). Data were analysed using direct group comparisons and multiple linear regression analysis.

Results: A total of 19 870 patients (52.3% males, mean age 59.1 years) were evaluated, of whom 47.6, 18.3, 13.2 and 2.1%, respectively, had concomitant hypercholesterolaemia, diabetes mellitus, congestive heart failure and renal insufficiency. In the overall group, adverse events were reported in 1.9% of patients. Global tolerability was rated as very good, good, moderate or poor, respectively, in 74.7, 22.1, 0.7 and 0.5% of patients; tolerability was similar across all subgroups of patients. Telmisartan treatment did not increase serum creatinine or potassium in any subgroup, including >400 patients with impaired renal function (basal creatinine 1.73 mg/dL). Telmisartan had no adverse effects on glucose, triglyceride or cholesterol levels. In the overall group, telmisartan reduced mean ± SD systolic blood pressure from 171.3 ± 16.4mm Hg to 141.3 ± 12.0mm Hg and diastolic blood pressure from 99.0 ± 9.4mm Hg to 83.4 ± 6.9mm Hg. Reductions were very similar between genders, age groups and patients with and without comorbidities, and not dependent on prior or concomitant treatment with other antihypertensive drugs.

Conclusion: The safety and efficacy of telmisartan found in controlled studies is maintained in a large postmarketing population that included sizeable patient subgroups potentially at higher risk for adverse events.

Chronically elevated blood pressure causes major morbidity and mortality, and a variety of drug classes are now available to treat arterial hypertension and at least partly normalise that risk.[1] With all drug classes, the extent of blood pressure lowering appears to be the most important contributor to the

reduction of hypertension-associated morbidity and mortality.[2-5] However, the hypertensive population is heterogeneous with regard to age, gender, concomitant morbidity and concurrent medications, and it remains difficult to predict which medication will lower blood pressure most safely and effectively in a given patient, and hence improve the long-term prognosis. Therefore, the initial choice of therapy is directed by additional effects of certain drugs and/or their specific adverse-effect profiles in relation to defined patient subgroups.

Angiotensin II receptor blockers (ARBs) are the latest drug class to be introduced for the treatment of hypertension. Recent data indicate that ARBs may have benefits beyond blood pressure reduction and, at least in specific subgroups of patients such as those with diabetes mellitus[3,5-8] or myocardial hypertrophy,[4,9] may reduce cardiovascular risk to a greater extent than drugs not directly acting on the renin-angiotensin system (RAS). The overall tolerability of ARBs is excellent with even fewer adverse effects then other inhibitors of the RAS, such as angiotensin-converting enzyme (ACE) inhibitors.[10] Theoretically, the ARBs could have adverse effects on serum creatinine or potassium concentrations based upon their mechanism of action.[11] This may become particularly relevant in certain patients, such as those with impaired renal function, who are more prone to creatinine and/or potassium elevations. However, until now, ARBs have only been tested for short periods in relatively small groups of patients with renal impairment.[12-14]

Telmisartan is an ARB that is characterised by a long duration of action, yielding consistent blood pressure control over 24 hours when administered once daily.[15] The safety and efficacy of telmisartan in the treatment of hypertension have been documented in >60 controlled clinical studies in hypertensive patients comparing it with placebo and a variety of other antihypertensive drugs, including the diuretic hydrochlorothiazide, the β-blocker atenolol, the calcium channel blocker amlodipine, the ACE inhibitors enalapril and lisinopril, and the ARBs losartan and valsartan.[16]

Controlled clinical studies are performed using predefined protocols in specific patient populations established by the means of specific inclusion and exclusion criteria; hence, these studies may not always reflect the situation in day-to-day medical practice. Against this background, the drug regulatory authority of the European Union – the European Agency for the Evaluation of Medicinal Products (EMEA) – requested a large-scale evaluation of the safety and efficacy of telmisartan under real-life conditions. We report here the findings of the resultant study, in which almost 20 000 hypertensive patients were exposed to telmisartan for a period of 6 months. This database allows a more detailed analysis of the tolerability and safety of telmisartan in patients who may be at greater risk of adverse events than in previous studies. Since it can be reasoned that certain comorbidities or concurrent medications may interfere with the activity of the RAS, and thus affect the ability of ARBs to lower blood pressure and improve long-term prognosis, we have also analysed the effect of such factors on the efficacy of telmisartan treatment.

Patients and Methods

Study Design and Treatment

In the open-label, observational study, physicians (office-based general practitioners, internists and cardiologists) in Germany were asked to document systematically on case report forms their observations for five consecutive essential hypertensive patients who were to receive telmisartan based on the physician's medical judgement. They received a compensation of Deutschmark (DM) 200 per patient (≈US$100 at that time) for documenting a total of four visits. In accordance with regulatory guidelines patient consent was not obtained as this was a purely observational study.

Patient Selection

There were no specific inclusion or exclusion criteria for patients other than a minimum age of 18 years. Inclusion was at the discretion of the prescribing physician. All physicians were asked to record concomitant diseases and concurrent medication.

Treatment

The patients were to receive telmisartan as monotherapy or as part of a combination therapy, based on the physician's medical judgement. In accor-

dance with the package insert, telmisartan 40 or 80mg administered once daily was recommended. The planned duration of treatment was 6 months.

Patient Evaluation

Visits were scheduled at the time of the initial prescription and after 2–4 weeks, 6–8 weeks and 6 months of treatment. At the initial consultation, a medical history including existing cardiovascular risk factors, concomitant diseases and current medication was recorded. This information was used to stratify the patient population for all further analyses. At all follow-up visits, each patient was asked about treatment-emergent adverse events. Patients were also requested to provide an evaluation of tolerability, which could be rated as very good, good, moderate or poor, and changes in medication including adjustments of the telmisartan dose were documented. Vital signs were recorded at each visit. Laboratory evaluation of serum creatinine, potassium, glucose, triglycerides and/or total cholesterol was optional. Clinical chemistry values were included only for patients where at least one post-treatment value was available. Moreover, laboratory values that were implausible were excluded from the analysis (i.e. creatinine <0.2 mg/dL and >15 mg/dL, potassium <2.56 mEq/L and >10 mEq/L, glucose <40 mg/dL and >230 mg/dL, triglycerides <50 mg/dL and >700 mg/dL, cholesterol <70 mg/dL and >570 mg/dL).

The efficacy analysis was based primarily on changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with baseline. In line with previous placebo-controlled studies of telmisartan in hypertensive patients,[16] a 'full response' to treatment was defined as a final DBP of ≤90mm Hg or a reduction in DBP of ≥10mm Hg from the start of telmisartan treatment. 'Inadequate response' was defined as reduction in DBP of <7mm Hg with a final DBP of >90mm Hg, based on EMEA recommendations. To establish the quality of the data documentation, source data were verified in a randomly selected sample of about 5% of the patients.

Statistical Analysis

Baseline parameters and treatment effects were initially analysed by descriptive statistics according to age (≤60 years versus >60 years), gender (male/female) and presence of comorbidity (diabetes, hypercholesterolaemia, coronary heart disease, congestive heart failure, renal insufficiency, none of the above). Since some of these variables can be related, multivariate analyses (logistic regression or multiple linear regressions) were performed to determine the contribution of each explanatory variable to the observed outcome upon telmisartan treatment. All patients with at least one assessment following telmisartan exposure were included in the analysis on an intention-to-treat basis with the last observation carried forward. All statistical calculations were performed with the SAS program package (version 8.02). Data are shown as means ± SD unless otherwise indicated.

Results

Patient Characteristics

Patient enrolment started in January 1999 and the last patient completed the study in May 2000. A total of 3842 physicians participated, and between them they recruited 19 870 patients, 52.3% of whom were male (table I). Mean age, height and weight in male and female patients were 57.4 ± 11.1 years and 61.1 ± 12.0 years (range 18–99 years), 176.2 ± 6.9cm and 164.8 ± 6.3cm (range 90–210cm), and 85.0 ± 12.0kg and 74.3 ± 12.6kg (range 50–188kg), respectively. Although ethnicity was not recorded in this study, the vast majority of hypertensive patients in Germany are Caucasian. Based on the case report forms provided by the physicians and relying on the individual physician's judgement rather than using defined criteria, the following concomitant diseases related to the cardiovascular system were present: diabetes (18.3%), hypercholesterolaemia (47.6%), coronary heart disease (19.9%), congestive heart failure (13.2%) and renal insufficiency (2.1%) [table I]. Comorbidities not related to the cardiovascular system included gastrointestinal complaints (10.8%), rheumatic complaints (9.7%), obstructive airway disease (8.1%) and a variety of other concomitant diseases (19.1% combined).

Table I. Baseline characteristics of patient subgroups[a]

	Mean age (y)	Gender	Previous antihypertensive medication				Number
		(% males)	none	1	2	≥3	(% of total)
≤60y	50.5 ± 7.5	58.2	42.8	34.7	15.5	6.9	10426 (52.5)
>60y	69.2 ± 6.6	45.4	20.8	36.2	27.3	15.6	9005 (45.3)
Males	57.4 ± 11.1		35.6	34.3	20.0	10.0	10384 (52.3)
Females	61.1 ± 12.0		29.3	36.5	22.3	11.9	9443 (47.5)
No comorbidity	54.7 ± 11.6	37.5	47.2	34.8	13.1	5.0	7390 (37.2)
Diabetes	62.8 ± 10.4	49.2	19.5	32.6	28.9	19.0	3643 (18.3)
Hypercholesterolaemia	60.3 ± 10.6	53.1	26.4	35.6	24.6	13.4	9450 (47.6)
Coronary heart disease	66.9 ± 9.7	53.2	10.1	30.4	33.9	25.6	3948 (19.9)
Congestive heart failure	69.5 ± 9.8	41.4	8.4	26.5	37.7	27.4	2626 (13.2)
Renal insufficiency	67.5 ± 11.8	52.2	10.6	22.2	30.4	36.7	414 (2.1)
Total (% of total)		52.3	6481 (32.6)	7023 (35.3)	4193 (21.1)	2173 (10.9)	19870 (100.0)

a Data are means ± SD for age and percentage of patients within group for gender and the number of antihypertensive medications.

Approximately one-third of all patients (n = 6452) received telmisartan monotherapy without having had previous antihypertensive medication, 6463 received telmisartan monotherapy as a replacement for existing antihypertensive medication and the remainder (n = 6877) received telmisartan in addition to previous antihypertensive medication (which in approximately half of all cases was modified to some extent). Among patients in whom telmisartan had been added to an existing antihypertensive treatment, more than 100 patients each had previously received monotherapy with a diuretic, a β-blocker, a calcium channel blocker or an ACE inhibitor. The percentage of patients previously receiving other antihypertensive medications differed considerably between subgroups, ranging from about 50% in patients without comorbidity to >90% in patients diagnosed with congestive heart failure (table I). Patients in the substituted or added medication groups were slightly older than those in the group who had not previously received treatment and exhibited a greater prevalence of hypercholesterolaemia, diabetes, heart failure and renal insufficiency (data not shown). The following concurrent medications (other than antihypertensives) were recorded as being prescribed in the indicated percentage of patients: digitalis (7.3%), nitrates (12.3%), aspirin (21.9%), oral antidiabetics (12.2%), nonsteroidal antirheumatics (9.6%), β_2-adrenoceptor agonists (3.5%) and a variety of other medications (26.6% combined).

The study was completed as planned by 91.7% of patients; 4.3% of patients discontinued prematurely and an additional 4.0% were lost to follow-up for unknown reasons. Documented premature discontinuation was due to adverse events in 0.9% of patients, insufficient blood pressure reduction in 1.8% and non-medical reasons in 1.8%.

Telmisartan Dose

At the beginning of treatment, 76.6% of patients were treated with telmisartan 40mg, and the higher dose of 80mg was prescribed to the remaining 23.3% of patients. During the course of the 6-month treatment period, the dose was lowered in 2.2% of patients because it was deemed too potent and raised in 24.1% of patients because of insufficient reductions of blood pressure with the low dose. As expected, based on previous studies,[16] dose-escalation yielded additional blood pressure lowering in patients with a previously insufficient reduction (data not shown).

Safety

In the overall group of 19 870 patients, 576 treatment-emergent adverse events (254 classified as drug related) were reported in 382 patients (1.9%). The most frequent adverse events were headache (0.3%), dizziness (0.2%), nausea (0.2%), abdominal pain (0.1%), diarrhoea (0.1%), back pain (0.1%), bronchitis (0.1%), tachycardia (0.1%), fatigue (0.1%), coughing (0.1%) and sleep disorders

(0.1%); all other events occurred in fewer than ten patients. Serious adverse events were defined as death or congenital anomaly, events that were immediately life-threatening, severely or permanently disabling, the result of an overdose, events that required hospitalisation or extension of hospitalisation, or that caused inability to work (according to the observational plan). Such events were reported in 11 patients (0.06%). Among the 12 serious events there were six deaths, which were due to pancreatic carcinoma, pulmonary oedema, colon cancer, generalised lymphogranuloma, myocardial infarction or cerebral haemorrhage. None of the deaths was classified as drug related.

In the overall group of patients, global tolerability was rated as very good, good, moderate or poor in 74.7, 22.1, 0.7 and 0.5% (data missing for 2% of patients) of patients, respectively. Global tolerability was similar in male and female patients, those aged ≤60 years and >60 years, and those with diabetes, hypercholesterolaemia, coronary heart disease, congestive heart failure or renal insufficiency relative to those without any of these comorbidities (figure 1).

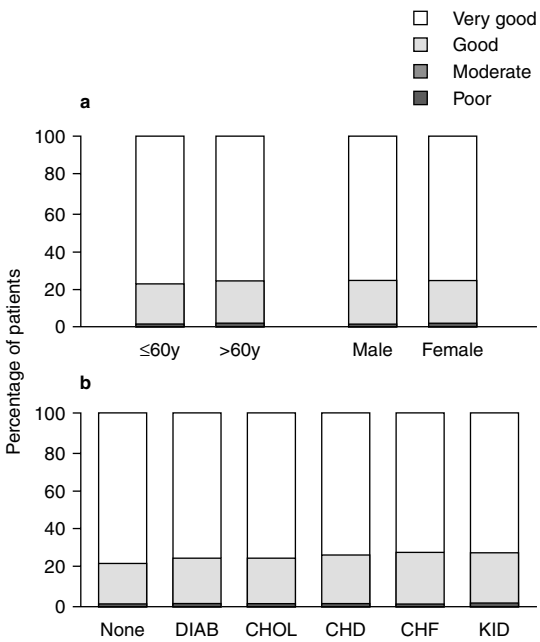

Fig. 1. Effects of (**a**) age and gender and (**b**) presence of comorbidities on the global tolerability of telmisartan. A logistic regression for all variables is shown in table II. Note that the combined 'moderate' and 'poor' groups accounted for no more than 2% of all patients, which is less than the smallest possible bar size. **CHD** = coronary heart disease; **CHF** = congestive heart failure; **CHOL** = hypercholesterolaemia; **DIAB** = diabetes; **KID** = renal insufficiency.

Table II. Logistic regression of effects of age, gender and comorbidities on global tolerability of telmisartan treatment[a]

Variable	Odds ratio[a]	95% CI (lower and upper limit)
Age	1.003	0.999, 1.006
Gender (male)	0.999	0.933, 1.096
Diabetes	1.005	0.920, 1.097
Hypercholesterolaemia	1.062	0.992, 1.136
Coronary heart disease	1.122	1.025, 1.229
Congestive heart failure	1.141	1.026, 1.268
Renal insufficiency	1.110	0.885, 1.391

a A value significantly smaller than 1 indicates a poorer tolerability associated with the respective variable. With regard to age this was calculated per year, with regard to gender the odds ratio for males relative to females is shown and with regard to comorbidities those for their presence relative to the absence of comorbidities is shown. Raw data for all groups are shown in figure 1.

Logistic regression demonstrated that none of the investigated explanatory variables (age, gender or comorbidity with diabetes, hypercholesterolaemia, coronary heart disease, congestive heart failure or renal insufficiency) was associated with a statistically significant reduction in global tolerability (table II). Patients with coronary heart disease or congestive heart failure tended to report a slightly greater global tolerability than those without comorbidity.

In the present study, telmisartan treatment produced no or only minor alterations of serum creatinine in the overall study group (table III). This lack of adverse effects on serum creatinine, and on potassium, was maintained in all subgroups of patients, including those with impaired renal function (table III and table IV). In addition, telmisartan exhibited no adverse effects on glucose, triglycerides or cholesterol concentrations. Again, this beneficial profile was maintained in all patient subgroups (table III and table IV).

Efficacy

In the overall study population, 6 months' telmisartan treatment was associated with the reduction of SBP from 171.3 ± 16.4mm Hg to 141.3 ± 12.0mm Hg, of DBP from 99.0 ± 9.4mm Hg to 83.4 ± 6.9mm

Table III. Effects of age and gender on serum creatinine, potassium and metabolic parameters associated with telmisartan treatment (mean ± SD)

	Creatinine (mg/dL) [n = 7549]		Potassium (mEq/L) [n = 5390]		Glucose (mg/dL) [n = 7141]		Triglycerides (mg/dL) [n = 5580]		Cholesterol (mg/dL) [n = 7452]	
	baseline	Δ	baseline	Δ	baseline	Δ	baseline	Δ	baseline	Δ
Age ≤60y	1.00 ± 0.55	−0.02 ± 0.40	4.37 ± 0.48	−0.02 ± 0.50	105.6 ± 29.1	−4.0 ± 18.1	198.2 ± 76.9	−19.8 ± 29.1	237.6 ± 45.4	−18.2 ± 34.4
Age >60y	1.04 ± 0.43	−0.00 ± 0.47	4.40 ± 0.51	−0.02 ± 0.46	112.4 ± 32.6	−4.2 ± 19.9	190.5 ± 76.4	−14.4 ± 54.1	237.7 ± 42.2	−14.4 ± 33.2
Males	1.05 ± 0.47	−0.02 ± 0.50	4.38 ± 0.49	−0.03 ± 0.42	108.7 ± 29.8	−4.0 ± 18.7	202.6 ± 79.7	−22.0 ± 57.1	237.0 ± 43.3	−17.8 ± 33.4
Females	0.98 ± 0.51	−0.01 ± 0.56	4.39 ± 0.51	−0.02 ± 0.45	109.1 ± 32.4	−4.1 ± 19.4	185.0 ± 72.0	−11.8 ± 53.4	238.7 ± 44.8	−11.8 ± 33.2
Total	1.02 ± 0.49	−0.01 ± 0.53	4.38 ± 0.50	−0.02 ± 0.43	108 ± 31.0	−4.0 ± 19.0	194.6 ± 76.0	−17.4 ± 55.7	237.8 ± 44.0	−16.4 ± 34.0

Hg and of heart rate from 78.0 ± 10.3 beats/min to 73.8 ± 7.4 beats/min. Blood pressure data in the 996 patients selected for source data verification were very similar to the overall patient population (data not shown). A full response was achieved in 76.2% of patients, whereas an inadequate response was observed in 22.1% of patients.

In a multiple linear regression analysis using baseline blood pressure, age, gender and the cardiovascular-related comorbidities as explanatory variables, baseline blood pressure had by far the dominating effect on blood pressure lowering (data not shown). Blood pressure reductions were similar in male and female patients (table V), whereas the effect of age on the blood pressure lowering by telmisartan revealed a complex relationship. Greater age was associated with higher baseline blood pressure, but in a multiple regression analysis higher baseline pressure was associated with greater reductions upon treatment. By contrast, greater age (after adjustment for the higher baseline values) was associated with somewhat smaller reductions (data not shown). The net effect of these opposing factors, however, was small and not considered clinically relevant (table V).

In a univariate analysis, age, gender and the investigated comorbidities, including heart failure and renal insufficiency, had little if any effect on telmisartan-induced blood pressure lowering (table V). Accordingly, age, gender and comorbidities did not appear to have any statistically significant association with treatment-associated blood pressure reductions in a multiple linear regression analysis, i.e. yielding partial correlation coefficients of <0.03 in all cases (data not shown).

The baseline blood pressure in the groups that received telmisartan as a replacement for, or in addition to, previous antihypertensive medication was only marginally lower than in patients without previous antihypertensive therapy (SBP 169.8 ± 16.2mm Hg and 171.8 ± 17.4mm Hg versus 172.2 ± 15.3mm Hg; DBP 98.5 ± 9.3mm Hg and 98.1 ± 8.9mm Hg versus 100.5 ± 8.8mm Hg). Telmisartan-induced blood pressure lowering was similar in all three groups (data not shown), indicating a similar incremental benefit of telmisartan in all three patient groups.

Table IV. Effects of comorbidity on serum creatinine, potassium and metabolic parameters associated with telmisartan treatment (mean ± SD)

	Creatinine (mg/dL) [n = 7549]		Potassium (mEq/L) [n = 5390]		Glucose (mg/dL) [n = 7141]		Triglycerides (mg/dL) [n = 5580]		Cholesterol (mg/dL) [n = 7452]	
	baseline	Δ	baseline	Δ	baseline	Δ	baseline	Δ	baseline	Δ
No comorbidity	0.98 ± 0.49	−0.02 ± 0.61	4.38 ± 0.53	−0.02 ± 0.47	94.1 ± 16.1	−0.6 ± 14.2	172.3 ± 65.2	−9.1 ± 48.9	211.6 ± 35.4	−0.51± 25.8
Diabetes	1.07 ± 0.54	−0.03 ± 0.50	4.39 ± 0.49	−0.02 ± 0.42	147.1 ± 32.4	−13.0 ± 26.9	215.5 ± 85.7	−22.7 ± 62.2	240.3 ± 45.1	−17.4 ± 37.2
Hypercholesterolaemia	1.02 ± 0.46	−0.01 ± 0.50	4.39 ± 0.49	−0.03 ± 0.42	111.6 ± 32.3	−4.9 ± 19.3	207.9 ± 80.0	−22.7 ± 57.9	254.6 ± 40.8	−23.8 ± 35.8
Coronary heart disease	1.07 ± 0.49	−0.00 ± 0.41	4.40 ± 0.53	−0.03 ± 0.46	115.4 ± 33.2	−5.5 ± 21.5	200.1 ± 78.8	−17.6 ± 54.1	239.0 ± 45.3	−17.2 ± 35.7
Congestive heart failure	1.10 ± 0.50	−0.01 ± 0.42	4.40 ± 0.47	−0.02 ± 0.41	118.4 ± 35.9	−5.7 ± 24.2	201.4 ± 83.5	−17.2 ± 58.3	237.8 ± 44.9	−15.5 ± 35.7
Renal insufficiency	1.73 ± 1.30	−0.04 ± 0.42	4.59 ± 0.55	−0.05 ± 0.45	122.4 ± 41.1	−9.1 ± 25.4	204.1 ± 91.4	−12.4 ± 50.8	242.8 ± 53.1	−18.6 ± 39.2

Due to the large variety of agents used in previous or continued antihypertensive regimens, we restricted the analysis of whether the type of previous and/or continued antihypertensive medication affected the blood pressure response to telmisartan to subgroups with at least 100 patients. Across all subgroups, at the start of the study, blood pressures were similarly high. Blood pressure levels following 6 months of telmisartan treatment were very similar in all subgroups (figure 2).

Discussion

There is growing evidence for the use of ARBs in comparison with other classes of antihypertensive agents. Their clinical efficacy is acknowledged in the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and their use in hypertensive patients with end-stage heart disease, diabetes or chronic renal disease is recommended based on favourable outcome data from clinical trials.[17]

The present study covering more than 10 000 patient-years confirms the tolerability data from controlled studies with telmisartan (covering more than 5300 patients, including 1758 in placebo-controlled studies) which demonstrated that adverse events are generally mild and transient and occurred at a similar incidence as in those patients who received placebo.[16] Although postmarketing surveillance studies generally tend to report lower incidences of adverse events than controlled studies, the occurrence of treatment-emergent adverse events in only 1.9% of patients in the present study is in line with the findings of the controlled studies. Back pain, diarrhoea and upper respiratory tract infection, which previously were the only adverse events observed more frequently with telmisartan than with placebo,[16] were reported in only ≤0.1% of the present study population. The incidence of treatment discontinuation due to adverse events was 2.8% in the controlled studies[16] and 0.9% in the present analysis. Taken together, our data confirm the excellent tolerability of telmisartan, which is similar to that of placebo in controlled studies.[16]

Postmarketing surveillance studies have distinct limitations but also definite advantages, which must be considered in the interpretation of the findings. In contrast to a randomised controlled trial, the present

study lacked a control group and had no specific inclusion or exclusion criteria. This results in lower internal validity of the data than those of a controlled study. A second limitation of postmarketing surveillance studies is that they are often less vigorously controlled for data quality, but in the present study this was assured by source data verification in a randomly selected, sizeable subset of patients.

On the other hand, postmarketing surveillance studies put patient and physician in a less artificial situation than controlled trials. Moreover, the lack of inclusion and exclusion criteria results in a patient population that is typical of everyday medical practice. Thus, despite their lower internal validity, observational studies may have high external validity. This is important because the hypertensive population is very heterogeneous, specifically with regard to age, gender, concomitant diseases, concurrent medication and the use of antihypertensive medication either in the past or concurrently. Since controlled trials are powered to detect equivalence or superiority of one treatment relative to another, they typically lack the statistical power to look at such subgroups of patients, particularly when the characteristics of these subgroups are interrelated. Large studies in specific subgroups are rarely performed. In line with the specific strengths and weaknesses of an observational study relative to a controlled trial, our analysis has focused on the relative comparison of patient subgroups rather than on absolute safety and efficacy.

Since the overall incidence of adverse events was very low, we have used patient assessment of global tolerability to determine whether subgroups of patients potentially at higher risk of adverse events may experience reduced tolerability. Univariate and multiple linear regression analyses demonstrated that age, gender and comorbidity with diabetes, hypercholesterolaemia, coronary heart disease, congestive heart failure or renal failure did not significantly impair tolerability. This beneficial profile is even more remarkable when it is considered that subgroup sizes of 400–9450 patients gave the present study large statistical power to detect possible effects of the above factors on tolerability.

Some classes of antihypertensive drugs such as diuretics or β-blockers can have adverse effects on the metabolic profile,[18] whereas others such as ACE inhibitors do not.[19] Placebo-controlled studies with telmisartan have not demonstrated any such effects,[16] and the present analysis confirms the absence of adverse metabolic effects associated with telmisartan. Moreover, our data establish that this beneficial profile is maintained across all patient subgroups, including those with diabetes and hypercholesterolaemia.

The reduction of aldosterone due to RAS inhibition may lead to increases in serum potassium concentrations.[20] A previous 8-week, double-blind study of >800 hypertensive patients did not detect telmisartan effects on potassium excretion, whereas another study reported slight increases in serum potassium ranging between 0.005–0.131 mEq/L.[16] Pre- and post-treatment serum potassium values were available for >5000 patients in the present study; analysis of these data did not identify any

Table V. Effects of age, gender and comorbidities on blood pressure (mean ± SD)

	Number	Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
		baseline	Δ	baseline	Δ
Age ≤60y	10369	170.0 ± 15.6	−30.0 ± 16.4	100.3 ± 8.9	−16.5 ± 9.7
Age >60y	8938	172.7 ± 17.0	−29.4 ± 17.8	97.5 ± 9.8	−14.2 ± 10.3
Males	10315	170.7 ± 15.9	−29.4 ± 16.8	99.4 ± 9.3	−15.8 ± 9.9
Females	9385	171.9 ± 16.9	−30.1 ± 17.5	98.6 ± 9.6	−15.1 ± 10.2
No comorbidity	7325	170.0 ± 15.8	−29.9 ± 16.7	99.5 ± 9.1	−16.1 ± 9.9
Diabetes	3634	173.2 ± 16.9	−29.8 ± 17.1	98.1 ± 10.1	−14.5 ± 10.4
Hypercholesterolaemia	9468	172.0 ± 16.5	−29.8 ± 17.2	99.2 ± 9.4	−15.4 ± 10.0
Coronary heart disease	3933	172.6 ± 17.4	−29.5 ± 17.7	97.5 ± 9.9	−14.1 ± 10.3
Congestive heart failure	2611	173.0 ± 17.6	−28.8 ± 17.7	97.3 ± 10.3	−13.9 ± 10.4
Renal insufficiency	409	173.2 ± 18.8	−29.1 ± 19.2	96.4 ± 11.9	−13.3 ± 12.1
Total	19743	171.3 ± 16.4	−29.7 ± 17.1	99.0 ± 9.4	−15.5 ± 10.1

increases in serum potassium. More importantly, patients with impaired renal function, who can have elevated baseline values and are particularly at risk for elevated serum potassium,[21] did not exhibit telmisartan-induced hyperkalaemia.

Inhibition of the RAS can also elevate serum creatinine levels in some patients, particularly in those with impaired renal function and particularly during the early phase of treatment.[3,6,22] In the present study, no adverse effects on serum creatinine were detected for the overall group of patients or for any of the subgroups, including those with impaired renal function, following 6 months of telmisartan treatment. Taken together, the present study indicates that telmisartan does not cause adverse effects on serum creatinine or potassium and maintains its beneficial metabolic profile in various subgroups of patients, including those with impaired renal function.

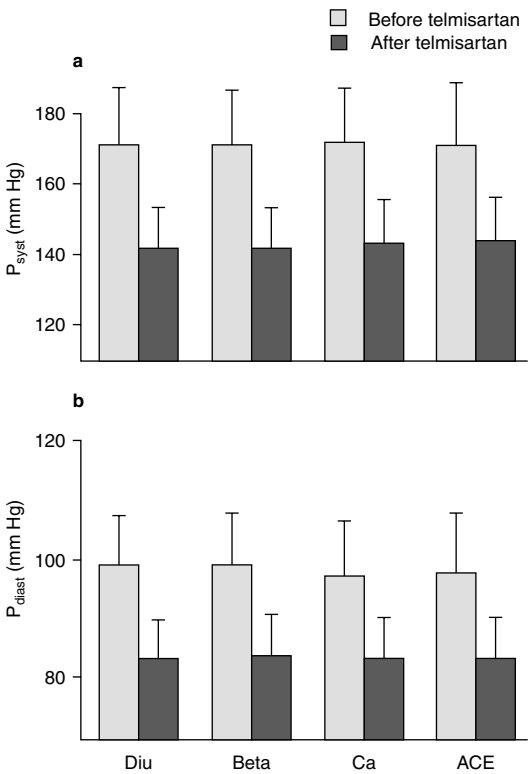

Fig. 2. Incremental benefit of adding telmisartan to existing antihypertensive medication of patients with inadequate blood pressure control. Data are means ± SD for (**a**) systolic blood pressure and (**b**) diastolic blood pressure prior to addition of telmisartan and after 6 months of telmisartan treatment. The number of patients with existing treatment with diuretics (Diu), β-blockers (Beta), calcium channel blockers (Ca) or ACE inhibitors (ACE) was 389, 874, 455 and 174, respectively.

To consider the tolerability of a drug in isolation does not provide an overall measure of its suitability for day-to-day clinical use. The efficacy of an antihypertensive agent can have an important impact on the long-term prognosis; an agent of choice should be both well tolerated and highly effective. The secondary aim of the present study was to compare the antihypertensive efficacy of telmisartan in subgroups of patients, many of whom could be regarded as being at increased risk of cardiovascular morbidity and mortality. The reduction in SBP and DBP of 30 and 16mm Hg, respectively, and a responder rate of 76%, is somewhat greater than in previous controlled randomised trials,[16] a situation that is not unusual for a postmarketing surveillance study. Although our study does not allow relating blood pressure measurements and their alterations upon treatment to time of day relative to time of telmisartan administration, it should be noted that previous studies have established that the long-acting ARB telmisartan, in contrast to some shorter acting ARBs, provides continuous 24-hour blood pressure control.[15]

Our analysis focused on relative differences between groups of patients. In confirmation of the findings of considerably smaller controlled studies,[16] the antihypertensive effect of telmisartan was very similar in the present study in male and female patients, and similar effects were recorded in younger and older patients. According to the present data, comorbidities that are prevalent in the hypertensive population, such as hypercholesterolaemia, or in which ARBs may have specific benefits, such as diabetes,[3,5-8] were not associated with clinically relevant differences in the blood pressure lowering ability of telmisartan. Comorbidities such as congestive heart failure[23] or renal insufficiency[24] and certain antihypertensive pretreatments such as diuretics[25] can be associated with increased RAS activity. Concomitant antihypertensive medication with a diuretic, which would be expected to activate the RAS, an ACE inhibitor or a β-blocker, both of which would be expected to reduce RAS effects,[26] or a calcium channel blocker, which would expected

to be neutral,[27] yielded blood pressure reductions that were very similar to each other and also very similar to those seen in patients without any previous antihypertensive treatment. The present data, therefore, suggest that from a day-to-day practice point of view telmisartan (and perhaps also other ARBs) may be expected to lower similarly an insufficiently controlled blood pressure regardless of concomitant diseases, or previous or present antihypertensive medication.

Taken together, the present data clearly demonstrate that the excellent tolerability of telmisartan is independent of age, gender and a variety of comorbidities. Moreover, the magnitude of its blood pressure-lowering effect is also largely independent of these factors, as well as of previous or present antihypertensive therapy.

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