Angiotensin II receptor antagonist telmisartan in isolated systolic hypertension (ARAMIS) study: efficacy and safety of telmisartan 20, 40 or 80 mg versus hydrochlorothiazide 12.5 mg or placebo

Athanasios J. Manolis[a], John L. Reid[b], Dick de Zeeuw[c], Michael B. Murphy[d], Elke Seewaldt-Becker[e] and Jürgen Köster[f] on behalf of the ARAMIS Study Group

Objective **To identify telmisartan doses that are more effective than placebo and non-inferior to hydrochlorothiazide (HCTZ) 12.5 mg, and are well tolerated, in lowering systolic blood pressure (SBP) in patients with isolated systolic hypertension (ISH).**

Patients and methods **A 2–4-week single-blind placebo run-in was followed by randomization of 1039 patients (age 36–84 years) with ISH [seated SBP 150–179 mmHg and seated diastolic blood pressure (DBP) < 90 mmHg] to once-daily double-blind treatment with telmisartan 20, 40 or 80 mg, HCTZ 12.5 mg, or placebo. The change in seated trough SBP after 6 weeks compared with baseline was the primary end point. Secondary end points were the percentage achieving the target fall in SBP and the change from baseline in seated trough DBP. Incidence and severity of adverse events and physical examination and laboratory parameters were monitored for the safety evaluation.**

Results **Baseline demographics in telmisartan 20 mg ($n = 206$), 40 mg ($n = 210$), 80 mg ($n = 207$), HCTZ 12.5 mg ($n = 205$) and placebo ($n = 211$) treatment groups were comparable: (mean ± SD) age, 63.0 ± 10.9 years; SBP, 162.9 ± 8.1 mmHg; and DBP 83.4 ± 5.0 mmHg. No previous antihypertensive therapy had been received by 66% of the patients. Mean reductions in seated trough SBP (adjusted for baseline and country) were: telmisartan 20 mg, 15.6 mmHg ($n = 204$); 40 mg, 17.9 mmHg ($n = 209$); and 80 mg, 16.9 mmHg ($n = 205$), compared with placebo, 11.4 mmHg ($n = 208$), and HCTZ 12.5 mg, 15.7 mmHg ($n = 204$). The target fall in seated trough SBP (≤ 140 mmHg or reduction by ≥ 20 mmHg) was achieved in 46.6% (telmisartan 20 mg), 51.7% (telmisartan 40 mg), 53.9% (telmisartan 80 mg), 27.4% (placebo) and 42.7% (HCTZ 12.5 mg); the response rate was significantly higher for telmisartan 80 mg than for HCTZ 12.5 mg ($P = 0.03$). All-causality adverse events occurred in 19.9, 17.6 and 20.3% receiving telmisartan 20, 40 and 80 mg, respectively; 20.9% receiving placebo and 22.0% receiving HCTZ 12.5 mg. No drug-related serious adverse events occurred.**

Conclusions **All doses of telmisartan (20–80 mg) were significantly superior to placebo in reducing SBP in patients with ISH and clinically comparable to HCTZ 12.5 mg. Tolerability of telmisartan was similar to that of placebo. *J Hypertens* 22:1033–1037 © 2004 Lippincott Williams & Wilkins.**

Journal of Hypertension 2004, **22**:1033–1037

Keywords: telmisartan, angiotensin receptor blocker, isolated systolic hypertension, hydrochlorothiazide, efficacy

[a]Tzanio General Hospital, Piraeus, Greece, [b]Department of Medicine and Therapeutics, University of Glasgow, Glasgow, UK, [c]Department of Clinical Pharmacology, University of Groningen, Groningen, The Netherlands, [d]Department of Pharmacology and Therapeutics, University College, Cork, Ireland, [e]Clinical Research Department, Boehringer Ingelheim Pharma KG, Biberach, Germany and [f]Medical Data Services/Biostatistics, Boehringer Ingelheim Pharma KG, Ingelheim, Germany.

Sponsorship: This study was funded by Boehringer Ingelheim.

Correspondence and requests for reprints to Professor A.G. Manolis, Tzanio General Hospital, Piraeus, Greece.
Tel: +30 301 459 2184; e-mail: ajmanol@otenet.gr

Received 25 October 2002 **Revised** 13 January 2004
Accepted 13 January 2004

Introduction

Until recently, isolated systolic hypertension (ISH) was considered a physiological feature of ageing and of little clinical significance. Now, it is regarded as being a more important determinant of cardiovascular risk in the elderly than elevated diastolic blood pressure (DBP) [1]. Also, ISH plays an important role in stroke [2]. Defining ISH as a systolic blood pressure (SBP) > 140 mmHg and a DBP < 90 mmHg, 15% of people > 60 years have ISH [3] and, among subjects between 50 and 59 years of age, ISH accounts for 87% of cases of uncontrolled hypertension [4].

Presented as a poster at the 11th European Meeting on Hypertension, Milan, Italy, 15–18 June 2001.

0263-6352

DOI: 10.1097/01.hjh.0000098301.94994.d5

The Systolic Hypertension in the Elderly Program showed that a low-dose diuretic, with or without a β-blocker, reduced the incidence of stroke and other cardiovascular events [5] and the Systolic Hypertension in Europe trial [6] revealed the benefits of combining antihypertensive agents from different classes in reducing stroke in patients ⩾ 60 years with ISH. Thiazide diuretics, such as hydrochlorothiazide (HCTZ), have been used as first-line treatment of ISH in the elderly [7]. However, some physicians are hesitant to prescribe them because of the possible negative impact of side-effects [7]. Electrolyte imbalance, glucose intolerance, cardiac arrhythmias and gout may also restrict their use in the elderly [8]. The angiotensin-converting enzyme (ACE) inhibitors are an alternative treatment because of their ability to lower morbidity and mortality [9]. Angiotensin receptor blockers (ARBs), which like ACE inhibitors act on the renin–angiotensin system, should also prove effective. Two small-scale, double-blind studies have evaluated ARBs in patients with ISH: losartan was compared with atenolol, and valsartan with placebo [10,11]. Another larger-scale, open-label, uncontrolled study assessed the efficacy of candesartan cilexetil [12].

Telmisartan is a highly lipophilic ARB that binds insurmountably to the AT_1 receptor [13] and has a terminal elimination half-life of about 24 h [14]. Clinical studies using ambulatory blood pressure show that telmisartan provides blood pressure control at the end of the once-daily dosing interval [15]. Also, telmisartan significantly reduces pulse velocity by the carotid artery route [16].

This study was performed to identify telmisartan doses that are more effective than placebo and not inferior to HCTZ in lowering SBP in patients with ISH, and that are well tolerated.

Patients and methods

Study design

The multicentre, double-blind, parallel-group, randomized study received prior approval by local institutional review boards. During the initial single-blind run-in, patients received placebo for 2 weeks if not in receipt of antihypertensive therapy or for 4 weeks if treated at the time of enrolment (visit 1). At visit 2, the patients were randomized to 6 weeks' double-blind treatment with telmisartan 20, 40 or 80 mg, HCTZ 12.5 mg, or placebo. The patients were monitored at visits 3 (2 weeks' double-blind treatment) and 4 (end of treatment). Patients were instructed not to take their trial medication on the days of clinic visits, which were always in the morning at approximately the same time and within 23–26 h of the most recent intake of study medication. This ensured measurement of trough blood pressures. Seated cuff SBP and DBP, heart rate, use of concomitant medication and spontaneously reported adverse events were recorded. Compliance with medication (determined by counting returned tablets) was evaluated at visits 2 and 4. A physical examination and laboratory tests (haematology, clinical chemistry, urinalysis) were performed at visits 1 and 4, and a 12-lead ECG was obtained at visits 1, 2 and 4.

Patients

Patients were between 35 and 84 years old, with a mean seated cuff SBP/DBP of 150–179/< 90 mmHg at randomization. Patients receiving antihypertensive therapy immediately before the study were only eligible if withdrawal of the medication and possible administration of placebo for 10 weeks would not jeopardize their health. Patients with secondary hypertension, hepatic and/or renal dysfunction, clinically relevant electrolyte imbalance, symptomatic cardiovascular or cerebrovascular disease, or inadequately controlled or recently stabilized diabetes mellitus, or gout were excluded. Pregnant or nursing women or of childbearing potential were excluded.

Patient evaluation

Blood pressure was measured using a manual cuff sphygmomanometer. The primary efficacy end point was the change from visit 2 in seated trough SBP (i.e. 24 h post-dose) after 6 weeks' double-blind treatment (visit 4). Secondary end points were percentage of patients with mean seated trough SBP ⩽ 140 mmHg and/or ⩾ 20 mmHg SBP reduction, and the change from baseline in seated trough DBP. Safety was evaluated by physical examination, laboratory parameters, 12-lead electrocardiogram and adverse events.

Statistical analysis

Non-inferiority of telmisartan was defined as a SBP reduction that was ⩽ 5 mmHg of that achieved with HCTZ. Previous studies suggest that the standard deviation of the change from baseline in seated trough SBP may be ⩽ 16 mmHg. Thus, 151 patients per treatment group would have a 90% power to detect a 6.0 mmHg difference between telmisartan and placebo. At 80% power, and using a standard deviation of 16 mmHg, 161 patients would be required to establish non-inferiority. Combining the two calculations, and assuming a dropout rate of about 10%, 180 patients should be randomized to each treatment group.

The primary analysis was performed on the intent-to-treat population: all patients who took at least one dose of double-blind medication, and with baseline SBP and at least one SBP measurement during double-blind treatment. Analysis of covariance was performed with data adjusted for baseline and country, utilizing visit 2 as the covariate. Telmisartan was compared with placebo using a superiority hypothesis, and with HCTZ

using a non-inferiority hypothesis for the mean reductions from visit 2 in mean seated trough SBP. All treatment comparisons were performed at a one-sided $\alpha = 0.025$. Pairwise tests between selected treatment groups for percentages of patients achieving the target response were performed using Fisher exact tests. Analysis of covariance was carried out on adjusted mean changes in DBP. Safety and tolerability of telmisartan and HCTZ were determined in all patients receiving at least one dose of double-blind treatment and were presented descriptively.

Results

Demographics

In total, 1039 patients entered, were randomized at 100 centres in 17 countries in Europe, Australia and South Africa, and received at least one dose of study drug. Baseline characteristics in the treatment groups were comparable (Table 1). Previous antihypertensive treatment had been received by 34% of patients; drugs used were ACE inhibitors (10.5%), calcium antagonists (9.3%), β-blockers (7.9%), diuretics (6.4%), ARBs (4.5%), other monotherapies (3.2%) or combination therapy (2.7%).

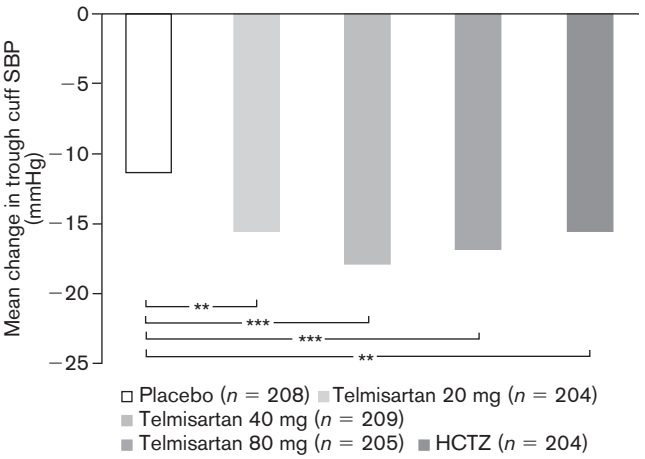
Clinical efficacy

At baseline, SBP was comparable in the five groups (Table 1). During double-blind treatment, compliance was 98–99%. After 6 weeks' placebo, the mean reduction in seated trough SBP was 11.4 mmHg (adjusted for baseline and country, Fig. 1). Adjusted mean SBP reductions with telmisartan 20, 40 and 80 mg were 15.6, 17.9 and 16.9 mmHg, respectively. The SBP reductions with telmisartan were all significantly greater compared with placebo: 20 mg, 4.2 mmHg ($P = 0.0042$); 40 mg, 6.5 mmHg ($P = 0.0001$) and 80 mg, 5.6 mmHg ($P = 0.0002$). The mean adjusted SBP reduction with HCTZ was 15.7 mmHg, which was superior to that achieved with placebo (4.3 mmHg, $P = 0.0038$). Statistical analysis showed that telmisartan was not inferior to HCTZ.

Subgroup analysis was performed on patients according to age (< 65 years and $\geqslant 65$ years). With patients aged < 65 years, baseline SBP in the five treatment groups was in the range 161–162 mmHg. Placebo produced an adjusted mean reduction in SBP of 12.0 mmHg. The adjusted reductions achieved with telmisartan 20, 40 and 80 mg of 17.1, 19.3 and 18.8 mmHg, respectively, compared with baseline, were significantly greater than those achieved with placebo ($P = 0.0141$, 0.0001 and 0.0002, respectively). The adjusted reduction of SBP with HCTZ of 14.5 mmHg was not superior to that of placebo ($P = 0.1750$).

In the subjects aged $\geqslant 65$ years, baseline SBP was in the range 163–165 mmHg. In placebo-treated patients, the adjusted reduction in SBP after 6 weeks' treatment was 7.9 mmHg. Adjusted mean reductions with telmisartan 20, 40 and 80 mg, compared with baseline, were 14.2, 17.7 and 16.5 mmHg; all doses of telmisartan were significantly superior to placebo ($P = 0.0314$, 0.0005 and 0.0003, respectively) in reducing SBP. In the HCTZ group, the adjusted reduction in SBP of 15.7 mmHg was significantly superior compared with that of placebo-treated patients ($P = 0.0001$).

Fig. 1



Adjusted mean changes in trough seated systolic blood pressure. HCTZ, hydrochlorothiazide; $^{**}P < 0.01$; $^{***}P < 0.001$.

Table 1 **Demographic and baseline characteristics**

Characteristic	Placebo ($n = 211$)	Telmisartan 20 mg ($n = 206$)	Telmisartan 40 mg ($n = 210$)	Telmisartan 80 mg ($n = 207$)	HCTZ 12.5 mg ($n = 205$)	Total ($n = 1039$)
Male (%)	90 (42.7)	87 (42.2)	87 (41.4)	91 (44.0)	94 (45.9)	449 (43.2)
Age (years)						
Mean (SD)	63.6 (10.2)	63.0 (11.5)	62.7 (10.8)	62.5 (10.9)	63.3 (11.2)	63.0 (10.9)
⩾ 65 years (%)	46.9	52.4	50.0	47.3	51.7	49.7
Duration of hypertension (years), mean (SD)	5.4 (7.0)	5.1 (6.3)	5.0 (6.5)	4.8 (7.1)	4.8 (7.2)	5.0 (6.8)
SBP[a] (mmHg), mean (SD)	163.3 (7.8)	163.5 (8.0)	162.7 (8.2)	162.4 (8.2)	162.5 (8.1)	162.9 (8.1)
DBP[a] (mmHg), mean (SD)	83.5 (5.1)	83.7 (5.2)	83.4 (4.6)	83.2 (5.1)	83.5 (5.0)	83.4 (5.0)
Pulse (bpm), mean (SD)	72.2 (9.9)	72.4 (10.0)	72.1 (9.9)	72.4 (9.9)	72.7 (9.8)	72.4 (9.9)

[a]Cuff measurements. SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Mean seated trough SBP of ⩽ 140 mmHg and/or SBP reduction of ⩾ 20 mmHg was achieved in 27.4% with placebo, in 46.6, 51.7 and 53.7%, respectively, with telmisartan 20, 40 and 80 mg ($P < 0.0001$) and in 42.0% with HCTZ ($P < 0.0001$). Telmisartan 80 mg produced a significantly higher response rate than HCTZ ($P = 0.03$).

Adjusted seated trough DBP was not reduced by placebo. Telmisartan 20, 40 and 80 mg, and HCTZ produced small reductions in DBP compared with placebo, of 2.4 ($P = 0.0002$), 3.3 ($P = 0.0001$), 3.0 ($P = 0.0001$) and 1.9 mmHg ($P = 0.0145$), respectively.

Safety

Incidences of all-causality adverse events were 19.9, 17.6 and 20.3%, respectively, for telmisartan 20, 40 and 80 mg, 20.9% for placebo and 22.0% for HCTZ. Treatment-related events were experienced by 37 (3.6%) patients, with comparable incidences in the different treatment groups. Most events were mild or moderate in intensity; severe events occurred in three patients treated with telmisartan 20 mg, three treated with telmisartan 40 mg, two treated with telmisartan 80 mg, two treated with HCTZ and two patients in receipt of placebo. In total, 15 serious adverse events occurred in 13 patients; none occurring during active treatment were thought to be related to treatment. Treatment was discontinued due to an adverse event in five placebo-treated patients; four, four and three patients, respectively, receiving telmisartan 20, 40 and 80 mg; and four patients receiving HCTZ.

No relevant changes from baseline in median laboratory values, pulse rate or ECG were detected.

Discussion

This large-scale, double-blind study showed that telmisartan 20, 40 or 80 mg is superior to placebo in controlling ISH, and produces clinically significant reductions in seated trough SBP after 6 weeks' treatment. In this study, placebo produced a relatively large reduction in SBP, which was comparable to that observed in other large-scale studies [5,6]. The findings of the present study are consistent with two previous smaller-scale studies conducted in patients with ISH, which found that the ARBs valsartan and candesartan are effective in reducing SBP [11,12].

The study comprised patients between the ages of 36 and 84 years, but the mean age of subjects in all groups was approximately 63 years, with approximately equal proportions < 65 years and ⩾ 65 years old. Subgroup analysis of the data suggests that the more elderly patients might benefit more from telmisartan treatment, with reductions compared with placebo of 5.9, 9.1 and 9.2 mmHg with doses of 20, 40 and 80 mg, respectively, as opposed to reductions of 5.1, 8.4 and 6.9 mmHg, respectively, in those aged < 65 years. One explanation may be that the placebo effect was greater in the younger patients. Another possibility is that the baseline values were higher in the elderly subgroup. This may lead to smaller room for improvement in younger patients.

A general practitioner questionnaire revealed that most only treat ISH in patients with a median SBP of 180 mmHg [17]. The reluctance to treat is confirmed in this study; the majority of patients had not received antihypertensives previously. Physicians' concerns about side-effects [7] are unjustified, as telmisartan was not associated with any higher incidence of side-effects than placebo. This is consistent with other studies evaluating the use of telmisartan in hypertensive patients of all ages [18]. This short-term study showed that low-dose HCTZ was also well tolerated. In long-term use, higher doses are often employed which may increase the incidence of adverse effects and laboratory abnormalities, especially in the elderly [7].

In the past, there has been concern that treating patients with ISH may result in a reduction in both SBP and DBP. In patients with coronary heart disease, a decline in DBP to < 80–85 mmHg may reduce coronary blood flow – the so-called 'J-curve phenomenon' [19]. In patients with coronary artery disease, this may lead to ischaemia. However, the results of the Hypertension Optimal Treatment (HOT) trial suggest that the J-curve phenomenon is not a problem [20]. The present study found that the DBP reductions in patients treated with telmisartan or HCTZ were small, although statistically significant, compared with placebo.

In conclusion, this large-scale, double-blind study in patients with ISH showed that once-daily telmisartan 20–80 mg produced significantly greater reductions in SBP than placebo, and was not inferior to HCTZ 12.5 mg. Telmisartan was well tolerated, with a side-effect profile no different to that of placebo.

References

1 Gifford RW Jr. Are systolic/diastolic and isolated systolic hypertension risk factors for the elderly? *Geriatrics* 1989; **44(suppl B)**:10–14.

2 Rigaud AS, Seux ML, Staessen JA, Birkenhager WH, Forette F. Cerebral complications of hypertension. *J Hum Hypertens* 2000; **14**:605–616.

3 Wang JG, Staessen JA. Improved outcomes with antihypertensive medication in the elderly with isolated systolic hypertension. *Drugs Aging* 2001; **18**:345–353.

4 Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension* 2001; **37**:869–874.

5 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA* 1991; **265**:3255–3264.

6 Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, *et al.* Randomised double-blind comparison of placebo and active

treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350**:757–764.
7 Ekpo EB, Shah IU, Fernando MU, White AD. Isolated systolic hypertension in the elderly: survey of practitioners' attitude and management. *Gerontology* 1993; **39**:207–214.
8 Prichard BN, Owens CW, Woolf AS. Adverse reactions to diuretics. *Eur Heart J* 1992; **13(suppl G)**:96–103.
9 Izzo JL, Levy D, Black HR. Importance of systolic blood pressure in older Americans. *Hypertension* 2000; **35**:1021–1024.
10 Farsang C, Garcia-Puig J, Niegowska J, Baiz AQ, Vrijens F, Bortman G, *et al*. The efficacy and tolerability of losartan versus atenolol in patients with isolated systolic hypertension. *J Hypertens* 2000; **18**:795–801.
11 Neutel JM, Bedigian MP. Efficacy of valsartan in patients aged ⩾ 65 years with systolic hypertension. *Clin Ther* 2000; **22**:961–969.
12 Neutel JM, Weir MR, Moser M, Harris S, Edwards D, Michelson EL, *et al*. The effects of candesartan cilexetil in isolated systolic hypertension: A clinical experience trial. *J Clin Hypertens* 2000; **2**:181–186.
13 Wienen W, Entzeroth M, van Meel JCA, Stangier J, Busch U, Ebner T, *et al*. A review on telmisartan: a novel, long-acting angiotensin II-receptor antagonist. *Cardiovasc Drug Rev* 2000; **18**:127–156.
14 Neutel JM, Smith DHG. Dose response and antihypertensive efficacy of the AT_1 receptor antagonist telmisartan in patients with mild to moderate hypertension. *Adv Ther* 1998; **15**:206–217.
15 Neutel J, Smith DH. Evaluation of angiotensin II receptor blockers for 24-hour blood pressure control: meta-analysis of a clinical database. *J Clin Hypertens* 2003; **5**:58–63.
16 Asmar R, Gosse P, Topouchian J, N'tela G, Dudley A, Shepherd GL. Effects of telmisartan on arterial stiffness in Type 2 diabetes patients with essential hypertension. *J Renin Angiotensin Aldosterone Syst* 2002; **3**:176–180.
17 Mead GE, Murray H, McCollum CN, O'Neill PA. How do general practitioners manage patients at risk from stroke? *Br J Clin Pract* 1996; **50**:426–430.
18 Neutel JM. Ambulatory blood pressure monitoring to assess the comparative efficacy and duration of action of a novel new angiotensin II receptor blocker –telmisartan. *Blood Press* 2001; **10(suppl 1)**:27–32.
19 Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet* 1987; **i**:581–584.
20 Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; **351**:1755–1762.