Original Paper

Telmisartan Plus HCTZ vs. Amlodipine Plus HCTZ in Older Patients With Systolic Hypertension: Results From a Large Ambulatory Blood Pressure Monitoring Study

Steen Neldam, MD, PhD;[1] Colin Edwards, PhD;[2] on behalf of the ATHOS Study Group*
From Rodøvre Centrum, Denmark;[1] and Boehringer Ingelheim Ireland Ltd, Dublin, Ireland[2]
*ATHOS Study Group members are listed in the Appendix.
Address for correspondence: Steen Neldam, MD, Rodøvre Centrum 294, 2610 Rodøvre, Denmark
E-mail: neldam@dadlnet.dk
Manuscript received September 21, 2005; revised January 17, 2006; accepted February 10, 2006

Systolic hypertension often requires combination therapy. Few data exist comparing angiotensin receptor blocker plus diuretic therapy with other combinations in older patients. In a prospective, randomized, open-label, blinded-end point trial, patients (≥60 years of age) with predominantly systolic hypertension received telmisartan 40–80 mg or amlodipine 5–10 mg for 8 weeks, before the addition of hydrochlorothiazide (HCTZ) 12.5 mg for a further 6 weeks. Twenty-four-hour ambulatory blood pressure monitoring showed that telmisartan plus HCTZ (n=448) and amlodipine plus HCTZ (n=424) changed systolic blood pressure for the last 6 hours of the dosing interval by –18.3 and –17.4 mm Hg, respectively (p=0.2520). Over the 24-hour period, telmisartan plus HCTZ was superior (–19.3 and –17.2 mm Hg, respectively; p=0.001) and provided higher systolic control rates (65.9% and 58.3%, respectively; p=0.0175). Adverse events (41.2% and 53.7%, respectively) and discontinuations (5.0% and 11.3%, respectively) were lower (p<0.0001) with telmisartan than with amlodipine, mainly due to peripheral edema (1.2% and 24.3%, respectively). (AJGC. 2006;15:151–160) ©2006 Le Jacq Ltd.

Systolic hypertension (SH) in the absence of significant diastolic hypertension is a major health problem that predominantly affects older people. Approximately 65% of hypertensive patients ≥60 years old have systolic blood pressure (SBP) ≥140 mm Hg but diastolic blood pressure (DBP) <90 mm Hg,[1] a worrying statistic given that the Framingham Heart Study found that even this relatively moderate degree of SH was associated with a 1.57-fold increase in cardiovascular (CV) mortality.[1,2]

The fundamental pathophysiologic feature of SH is the loss of arterial recoil in the aorta and its branches that causes the full stroke volume to be delivered during systole, with minimal or no diastolic flow.[3] Both pulse pressure and pulse-wave velocity increase as a result. Increasing arterial stiffness is caused by structural and functional changes in the vascular wall, resulting in intimal thickening and fibrosis. Many factors can contribute to pathophysiology, including high sodium intake and activation of the renin–angiotensin system.[4]

The risk of CV morbidity is further increased by variations in the circadian rhythm of SBP. In a substudy[5] of the Systolic Hypertension in Europe (Syst-Eur) study, conventional cuff SBP, measured at a single time point in the morning, was only weakly associated with CV risk, whereas the 24-hour,

www.lejacq.com ID: 5219

daytime, and nighttime mean SBP measurements significantly predicted CV mortality, all CV end points, and fatal and nonfatal stroke.[5] In elderly patients with predominantly systolic hypertension, a high morning SBP surge was significantly associated with the risk of silent cerebral infarct and stroke.[6]

The reason for the relatively improved prognostic power of ambulatory blood pressure monitoring (ABPM) is likely due to the adverse CV effects of an abnormal circadian rhythm.[7] Such a mechanism is thought to underpin the higher incidence of CV events in the early morning period, when blood pressure (BP) increases markedly upon arising, compared with other periods of the day.[8] As a result, maintenance of antihypertensive efficacy throughout the day and night, including the final hours of the dosing period, may be important for reducing CV morbidity.

Lifestyle intervention, such as dietary modification, can reduce SH.[9] However, many patients will require antihypertensive therapy. Both diuretics and calcium channel blockers (CCBs) have been shown to reduce significantly the risk of stroke and CV disease in elderly patients with SH.[10,11] Amlodipine, a widely used dihydropyridine CCB, has demonstrated efficacy in improving SH, most notably in a meta-analysis of 85 studies enrolling >5000 patients that found an average decrease in SBP with amlodipine of 17.5 mm Hg.[9] Because SH is a consequence of decreased vascular compliance resulting from stiffening of the large arteries, therapies that reduce vascular stiffening and/or total peripheral resistance are likely to be beneficial.[12] Dihydropyridine CCBs activate the sympathetic nervous system, which could, in turn, increase arterial stiffness and may make arteries less suitable for treating SH,[13] although longer-acting agents such as amlodipine appear to display little activation.[14] More recently, however, it has been reported that daytime sympathetic activity is stimulated by amlodipine.[15] Furthermore, dihydropyridine CCBs are associated with a high incidence of peripheral edema.[16]

Angiotensin receptor blockers (ARBs) are a promising alternative for the treatment of SH, in part, at least because angiotensin II plays a prominent role in the development of arterial stiffness.[17] In patients with SH and left ventricular hypertrophy, losartan significantly reduced stroke compared with atenolol, despite similar reductions in BP.[18] Losartan provided clinical efficacy comparable to amlodipine in an 857-patient, 12-week trial.[19] Valsartan and amlodipine, with the option for additional hydrochlorothiazide (HCTZ), have also shown similar efficacy.[20]

Because diuretics and CCBs are the only antihypertensive classes that have been shown to reduce mortality in elderly patients with SH, they are currently the only classes recommended by the International Society of Hypertension for initial treatment of these patients.[21] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) proposes that diuretics should be the initial treatment for all hypertensive patients,[22] although the justification for this is open to question because of the potential for hypokalemia, resulting in cardioprotective benefit being lost.[23,24] For most patients with SH, monotherapy is insufficient, and most will require combination therapy to achieve SBP control.[25] The combination of a diuretic with CCB can provide greater SBP reduction, although there is no synergy between their mechanisms of action. For this reason, combinations of a diuretic or CCB with an agent that blocks the renin-angiotensin-aldosterone system may have greater potential.[23] The Valsartan in Systolic Hypertension (Val-Syst) trial[20] found that valsartan and amlodipine, alone and in combination with HCTZ, were similarly effective in lowering BP, although amlodipine was associated with a high rate of edema. However, intention-to-treat data from the subset of patients who received amlodipine plus HCTZ (A+H) in this trial have not been published.[20,26]

Telmisartan, the ARB with the longest plasma half-life,[27] produces reductions in 24-hour mean SBP that are comparable to those provided by amlodipine.[28,29] Unlike amlodipine, telmisartan does not induce sympathetic activation during the day, and instead increases parasympathetic activity.[15] Telmisartan was effective and well tolerated in a study of patients aged 36–84 years with SH,[30] and post-marketing surveillance has found the tolerability of telmisartan to be unaffected by old age (>60 years).[31] The combination of telmisartan with HCTZ (T+H) provides an additive reduction in SBP and DBP.[32] Data for the efficacy of T+H in older patients are limited to a trial in 35 elderly patients with mild-to-moderate hypertension, in whom the reduction of BP with the combination was around twice that of either monotherapy.[33]

No large-scale studies comparing combination therapy of an ARB plus HCTZ with a CCB plus HCTZ have yet been published. We therefore undertook this study using 24-hour ABPM to compare the antihypertensive efficacy of T+H with A+H in older patients with SH.

METHODS

Study Design. This multinational study employed a forced titration, prospective, randomized, open-label,

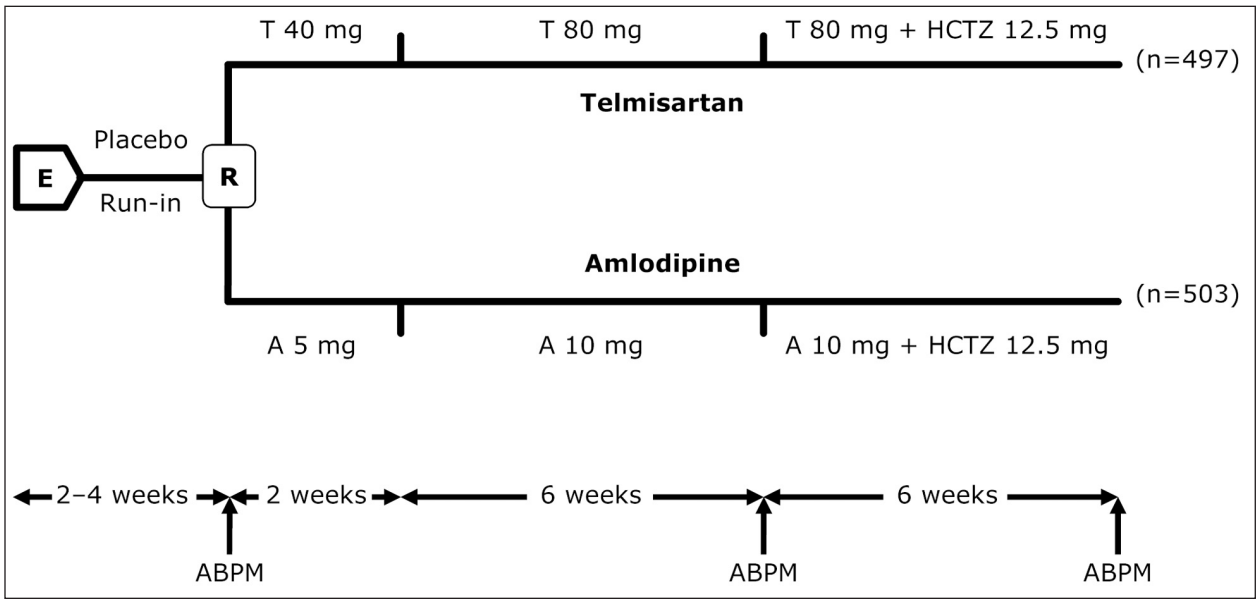

Figure 1. Study design. E=entry; R=randomization; T=telmisartan; HCTZ=hydrochlorothiazide; A=amlodipine; ABPM=ambulatory blood pressure monitoring

blinded end point design,[34] which is summarized in Figure 1. Eighty-four centers in Europe and five in South Africa participated. The study was conducted between December 2, 2002 and March 23, 2004, conformed to the Declaration of Helsinki, and was approved by each local ethics committee before initiation at any site.

There was an initial 2-week, single-blind, placebo run-in period, extended to 4 weeks for patients who had been receiving an ARB or angiotensin-converting enzyme (ACE) inhibitor before starting the study. The active treatment period lasted 14 weeks. Initial therapy was telmisartan 40 mg or amlodipine 5 mg, forced-titrated to telmisartan 80 mg or amlodipine 10 mg at Week 2, with the addition of HCTZ 12.5 mg for all patients at Week 8. Patients were not allowed other antihypertensive medication during the trial period. They were instructed to take their trial medications once daily in the morning with water (with or without food) at approximately the same time each day. When a clinical visit was scheduled, patients were instructed not to take their medicine until after BP measurement (which took place between 8 a.m. and 10 a.m.).

Patients. The study was conducted in outpatients aged 60 years and older who attended a general practitioner, cardiologist, geriatrician, or hypertension clinic with either a new diagnosis or a history of SH. Patients were required to have cuff SBP of 141–179 mm Hg, DBP ≤95 mm Hg, and 24-hour ABPM mean of SBP >125 mm Hg at the end of the 2–4-week placebo run-in. Patients had to be able to discontinue their current antihypertensive medication (if any) and had to provide written, informed consent before entry into the study. Patients with hepatic and/or renal dysfunction, or who had previously experienced symptoms characteristic of angioedema during treatment with ACE inhibitors or ARBs, or who had insulin-dependent diabetes mellitus that had not been stable and controlled for the previous 3 months, or who were noncompliant in the run-in period, were excluded from participation. In addition, night-shift workers (i.e., those who routinely sleep during the daytime and whose working hours include midnight to 4 a.m.) were excluded due to the potential for confounding the ABPM analysis.

Patient Evaluation. Patients were given a physical examination on study entry and at completion (or earlier, in the case of premature withdrawal). Trough BP, concomitant medication, and adverse events were recorded at each clinic visit. Twenty-four-hour BP was assessed by ABPM (Model 90207, Spacelabs Medical Data, Issaquah, WA) at baseline, Week 8 (at the end of the monotherapy phase), and at Week 14. Visits were scheduled so that the daytime and nighttime activities of the patient were similar on successive visits (e.g., always a workday). On these clinic visit days, patients arrived at approximately 8:30 a.m., and medication was dosed after application and initiation of the ABPM device at approximately 9 a.m. (and no later than 10:30 a.m.).

Ambulatory BP was measured every 20 minutes throughout the day and night. Patients were instructed to keep their arm stationary during each BP measurement, and were also instructed on repositioning of the cuff in case of slippage. The patients returned to the clinic after 24 hours, and ABPM data were uploaded to a central data management site (Spacelabs Medical Data, Issaquah, WA), which was not aware of the identity of the trial treatments.

The primary end point was the change from baseline in mean SBP during the last 6 hours of the dosing interval at Week 14. Secondary end points included the change from baseline in DBP and pulse pressure during the last 6 hours of the dosing interval at Week 14 and changes from baseline in BP over other time periods (24-hour mean, morning mean [6 a.m. to 11:59 a.m.], daytime mean [6 a.m. to 9:59 p.m.], and nighttime mean [10 p.m. to 5:59 a.m.]). These end points were also analyzed using changes from baseline at the end of the monotherapy period (Week 8). In addition to ABPM, trough SBP and DBP were analyzed between baseline, Week 8, and Week 14.

The proportion of patients who achieved SBP response (24-hour mean SBP, <130 mm Hg, and/or a decrease of ≥10 mm Hg from baseline) or SBP control (24-hour mean SBP, <130 mm Hg) at Week 14 was calculated, as was the proportion of patients who achieved normal BP (trough seated SBP/DBP, <130/85 mm Hg) or high-normal BP (trough seated SBP/DBP, <140/<90 mm Hg) at Weeks 8 and 14.

Safety was evaluated as the incidence, severity, and relationship to treatment of adverse events. Vital signs and adverse events were assessed at every visit, and heart rate monitoring was performed.

Statistical Analyses. The primary analysis was a noninferiority test of the primary end point with a noninferiority margin of 3 mm Hg (i.e., it was to be concluded that T+H is not inferior to A+H if the upper limit of the 95% confidence interval [CI] of the adjusted mean difference for [T+H] – (A+H) in mean SBP changes from baseline during the last 6 hours of the dosing interval was <3 mm Hg). If noninferiority of T+H vs. A+H was proved, superiority of T+H over A+H was to be shown (hierarchic procedure).

The primary analysis for noninferiority was performed using the per protocol dataset (after excluding patients with relevant protocol violations). All other primary and secondary analyses (with the exception of responder rates) were conducted on the full analysis set (FAS) of patients. The primary analysis was also tested using the per protocol dataset (after excluding patients with relevant protocol violations). Analysis of covariance was employed, using baseline and treatment center as covariates (pooling centers with fewer than four patients). Responder rates were evaluated using the Mantel-Haenszel test adjusted for center. All secondary analyses were tested at a two-sided α of 0.05.

The sample size was based on the expected SD of the primary end point (reduction in mean SBP during the last 6 hours of the dosing interval) of 12 mm Hg, as determined from the subgroup of patients older than 64 in a previous study of telmisartan.[35] With a two-sided α at the 5% level, a sample size of 340 patients per group had 90% power to demonstrate noninferiority of T+H vs. A+H at a margin of 3 mm Hg if both combinations were equal. Likewise, with 340 patients per group, the study had 90% power to detect a 3-mm Hg difference between treatments in the reduction from baseline in the mean SBP during the last 6 hours of the 24-hour dosing interval. The study aimed to enroll 1440 patients to allow for an anticipated failure rate to meet the ABPM entry criterion of approximately 48% and a drop-out rate of approximately 15%.

RESULTS

Patients. A total of 1265 patients were enrolled and 1000 randomized to study treatment, 497 to T+H and 503 to A+H. Baseline characteristics in the two treatment groups were comparable, as shown in Table I. The majority of the patients were female (58.2%) and Caucasian (99.1%). Approximately 60% of patients were aged 60–69 years, and 46.9% had a duration of diagnosed hypertension >5 years. There were 617 (61.7%) patients on antihypertensive therapy, which was discontinued before randomization. Therapy included ARBs (18.5%), ACE inhibitors (23.7%), diuretics (20.6%), CCBs (20.4%), and β blockers (18.3%). Many patients (20.9%) were on combination therapy, including ARBs plus diuretics (9.7%), ACE inhibitors plus diuretics (6.5%), β blockers plus diuretics (2.3%), calcium antagonists plus β blockers (1.9%), and ACE inhibitors plus calcium antagonists (0.5%).

The study was completed by 453 (91.1%) patients in the telmisartan group and 429 (85.3%) patients in the amlodipine group. Most discontinuations were due to adverse events (telmisartan 25, amlodipine 57). Six patients (telmisartan

2, amlodipine 4) were noncompliant, 21 withdrew consent (telmisartan 13, amlodipine 8), and three were lost to follow-up (telmisartan 1, amlodipine 2). Three patients in each group were withdrawn for other reasons. No patients were withdrawn due to lack of efficacy.

BP Changes. The change from baseline to Week 14 in SBP hourly means over the full 24-hour dosing interval in the FAS dataset is shown in Figure 2. Similar results were observed in the per-protocol dataset. At the primary end point, the adjusted mean change from baseline during the last 6 hours of the dosing interval was –18.3 mm Hg in the T+H group compared with –17.4 mm Hg in the A+H group for the FAS. The (T+H) – (A+H) difference (95% CI) was –0.8 (–2.2 to 0.6). The upper limit of the 95% CI was less than the prespecified 3 mm Hg (for the per protocol set as well as the FAS). Therefore, the noninferiority of T+H has been demonstrated, although the superiority of T+H over A+H on the primary end point could not be demonstrated (p=0.2520).

There was no significant interaction between age group (60–69 years, 70–79 years, >79 years) and treatment (p=0.37), indicating that the treatment effects were consistent across age groups. Likewise, there was no significant effect of gender on the response to treatment in either treatment group.

The adjusted mean changes (FAS) in SBP and DBP hourly means from baseline to Week 14 with T+H and A+H during different periods of the day are shown in Figure 3. T+H provided statistically superior (p≤0.05) reductions in mean SBP compared with A+H in the 24-hour, morning, and daytime intervals, but not at nighttime. The differences between T+H and A+H on DBP were statistically significant (p≤0.05) at 14 weeks over all time periods tested.

SBP control rates (measured by ABPM) at Week 14 were significantly greater (p=0.0175) with T+H (65.9%) than with A+H (58.3%). There was no significant difference between T+H and A+H in percentage of SBP responders (measured by ABPM, 86.4% vs. 85.1%, respectively) or in the proportion of patients achieving normal or high-normal BP (50.2% and 50.8%, respectively). Mean changes in pulse pressure were not significantly different in the two groups. Changes in trough cuff SBP (–22.8 and –23.4 mm Hg, for T+H and A+H respectively) and DBP (–8.9 and –8.4 mm Hg, for T+H and A+H respectively) were also statistically indistinguishable.

The ABPM end points were also assessed at 8 weeks, following the monotherapy phase.

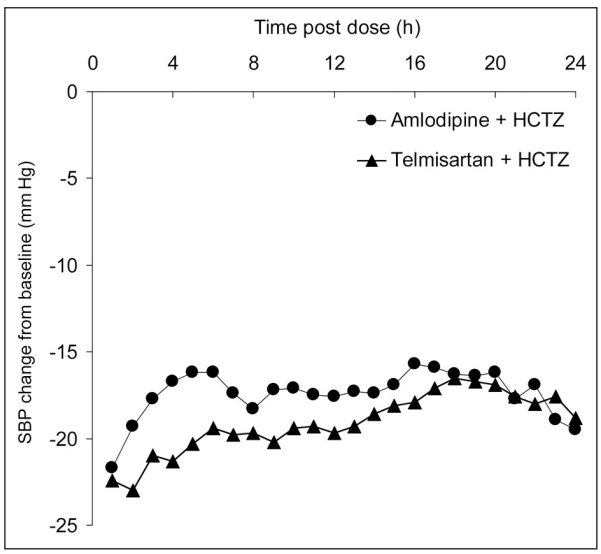

Figure 2. Hourly observed mean changes (full analysis set) in systolic blood pressure (SBP) with telmisartan 80 mg + hydrochlorothiazide (HCTZ) 12.5 mg (n=448) or amlodipine 10 mg + HCTZ 12.5 mg (n=424) from baseline to end of study (Week 14)

Amlodipine 10 mg was different from telmisartan 80 mg (p<0.0001) during the last 6 hours of the dosing interval (changes in SBP, –15.3 vs. –10.9 mm Hg, respectively; DBP, –7.4 vs. –5.6 mm Hg, respectively), and over the full 24-hour period (SBP, –15.2 vs. –11.8 mm Hg, respectively; DBP, –7.4 vs. –6.3 mm Hg, respectively). Reductions in other time periods similarly favored amlodipine monotherapy. Twenty-four-hour mean BP was controlled (<130 mm Hg) in only 43.8% of telmisartan-treated and 50.7% of amlodipine-treated patients; the difference was not statistically significant. The incidences of normal seated trough BP control (<130/85 mm Hg) were very low in both treatment groups: telmisartan, 10.8%; amlodipine, 10.5%.

Safety and Tolerability. There were marked differences between the two groups in the incidence of adverse events (Table II). The most frequently reported adverse event was peripheral edema, reported in 6 (1.2%) patients taking telmisartan (± HCTZ) compared with 122 (24.3%) patients taking amlodipine (± HCTZ) (p<0.0001). Most of the reported events occurred during monotherapy (amlodipine, 108 reports; telmisartan, six reports) as compared with combination therapy (amlodipine, 20 reports; telmisartan, no reports). There was also a higher incidence of associated symptoms such as edema and flushing in the amlodipine group. Adverse events considered to be related to study drug were correspondingly higher with amlodipine than with telmisartan (33.4% vs.

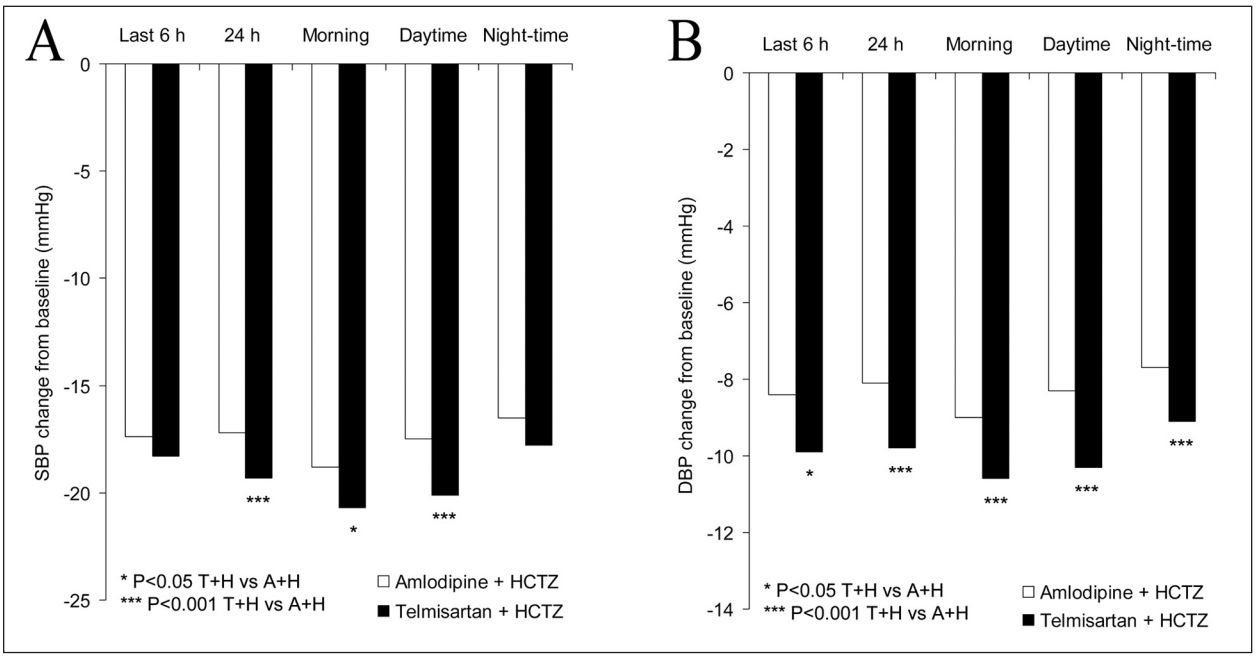

Figure 3. Adjusted mean changes (full analysis set) from baseline to the end of the study (Week 14) in (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) during different periods of the day with telmisartan 80 mg plus hydrochlorothiazide (HCTZ) 12.5 mg (T+H) (n=448) or amlodipine 10 mg plus HCTZ 12.5 mg (A+H) (n=424)

Table I. Patient Characteristics at Baseline

Characteristic	Telmisartan + HCTZ (n=497)	Amlodipine + HCTZ (n=503)	Total (N=1000)
Female	290 (58.4)	292 (58.1)	582 (58.2)
Caucasian	492 (99.0)	499 (99.2)	991 (99.1)
Age (yr)	68.6±6.2	69.1±6.3	68.8±6.3
60–69	299 (60.2)	294 (58.4)	593 (59.3)
70–79	171 (34.4)	167 (33.2)	338 (33.8)
≥80	27 (5.4)	42 (8.3)	69 (6.9)
Body mass index (kg/m^2)	27.9±4.9	27.9±4.6	27.9±4.8
Hypertension duration (yr)	7.0±8.0	7.6±8.2	7.3±8.1
24-hour ambulatory BP (mm Hg)			
Systolic	145.1±12.9	145.9±12.7	145.5±12.8
Diastolic	80.7±9.2	80.9±8.5	80.8±8.8
Last 6-hour ambulatory BP (mm Hg)			
Systolic	141.2±15.2	142.3±14.9	141.8±15.0
Diastolic	77.9±9.9	78.5±9.7	78.2±9.8
Seated cuff BP (mm Hg)			
Systolic	161.0±12.3	161.7±12.3	161.3±12.3
Diastolic	87.3±6.6	86.8±6.6	87.0±6.6

Data are presented as mean ± SD or n (%). HCTZ=hydrochlorothiazide; BP=blood pressure

8.0%, respectively; $p<0.0001$). This led to a higher overall discontinuation rate from adverse events in the amlodipine group as compared with the telmisartan group (11.3% vs. 5.0%, respectively).

Most adverse events were of mild or moderate intensity, although 11 patients in the telmisartan group and 23 in the amlodipine group experienced a severe adverse event. Serious adverse events were reported in 11 patients in the telmisartan group and in 13 patients in the amlodipine group during the active treatment phase. Serious adverse events resulted in discontinuation in five patients

in the telmisartan group and in four patients in the amlodipine group. Three deaths were reported during the trial (two in the telmisartan group and one in the amlodipine group). None were reported as related to trial treatment. There were no changes in heart rate during the study.

DISCUSSION

This study was designed to compare the BP-lowering effects of combination therapy with T+H or A+H in older patients with SH. ABPM was employed to compare effects at different periods in the dosing interval, and change in the last 6 hours of the dosing interval was selected as the primary outcome. In addition, seated trough BP was monitored.

During this study in older patients with SH, monotherapy with either telmisartan or amlodipine provided poor control of BP, with 24-hour mean SBP control being achieved in ≤50% of patients and normal response rates in only ≈10% of patients. When HCTZ was added to either monotherapy, BP control became more acceptable, although still not completely satisfactory. The results demonstrate that T+H brought about reductions in SBP during the last 6 hours of the dosing interval that are at least as great as the reductions with A+H. The significantly superior SBP reductions with T+H during the morning and daytime periods, together with a numeric superiority during the last 6 hours of the dosing interval, provided a significantly ($p<0.0001$) larger mean reduction with T+H for the 24-hour period as a whole. The addition of HCTZ to monotherapy also resulted in the percentage of patients with normal or high-normal trough seated BP increasing to 50% in both treatment arms. In patients receiving telmisartan-based therapy, the side effect profile was more favorable with respect to a significantly lower incidence of peripheral edema and other associated symptoms. In the Val-Syst study, both the valsartan- and amlodipine-based treatments effectively lowered mean 24-hour, daytime, and nighttime systolic ambulatory BP without any significant differences between the two regimens,[26] suggesting a possible distinction between T+H and valsartan plus HCTZ, although no direct comparison has been conducted in this patient population.

A reduction in early morning BP may translate into clinical benefit. In a study of 519 elderly Japanese patients (mean age, 72 years) with predominantly SH (mean clinic SBP/DBP, ≈164/91 mm Hg), the incidence of silent cerebral infarcts and stroke were significantly higher in those with a high early morning BP surge (EMBPS).[6] Those patients with a magnitude of EMBPS in the top 10% had a 2.7-fold greater risk of stroke over the 41-month follow-up, compared with the patients with a smaller EMBPS. Although it is not clear whether a reduction in early morning BP translates into a reduced EMBPS, it seems likely that the reduced BP afforded in this period by both study drugs will be beneficial.

Table II. Number of Patients (n [%]) With Adverse Events Reported With an Incidence of ≥2% in Either Group at Any Stage of the Trial

	Telmisartan (±HCTZ) (N=497)	Amlodipine (±HCTZ) (N=503)
Total	205 (41.2)	270 (53.7)*
Related to study drug	40 (8.0)	168 (33.4)*
Discontinued due to adverse events	25 (5.0)	57 (11.3)*
Adverse events reported		
Peripheral edema	6 (1.2)	122 (24.3)*
Edema	1 (0.2)	22 (4.4)
Headache	15 (3.0)	13 (2.6)
Dizziness	15 (3.0)	7 (1.4)
Vertigo	12 (2.4)	6 (1.2)
Bronchitis	8 (1.6)	10 (2.0)
Flushing	0 (0.0)	11 (2.2)

HCTZ=hydrochlorothiazide; *$p<0.0001$, telmisartan vs. amlodipine

Furthermore, the reduction in 24-hour mean SBP in this study (amounting to 19.3 mm Hg with T+H and 17.2 mm Hg with A+H in the FAS) is a clinically meaningful effect. In an 808-patient substudy of Syst-Eur,[5] each 10-mm Hg increase in 24-hour mean SBP was associated with a 23% increase in the risk of total mortality and a 34% increase in the risk of CV mortality, with patients with a smaller decrease in nighttime BP being most at risk. Patients in the Syst-Eur substudy had baseline characteristics (mean age, 69.6 years; mean 24-hour SBP, 145.8 mm Hg) similar to those in our study, which suggests that these data have direct relevance.

Since the risk due to raised SBP is continuous,[36] the goal of antihypertensive treatment should be to reduce SBP to the maximum extent possible without incurring side effects intolerable to the patient. For this reason, JNC 7 recommended initial combination therapy in all patients with cuff SBP ≥160 mm Hg, as well as for all patients who fail to achieve BP goal with monotherapy.[22]

Choice of combination therapy, therefore, depends on efficacy and tolerability in the target population. The greater reductions in BP seen in our study with T+H compared with A+H are likely due to differences between the mechanism of action of telmisartan and HCTZ.[37] CCBs, on the other hand, have intrinsic natriuretic properties and are thus less likely to provide additive benefits from combination with HCTZ.[38] Since the JNC 7 guidelines recommend diuretics for most patients,[22] combination of HCTZ with telmisartan rather than amlodipine is both theoretically appealing and supported by the results of our study. It is acknowledged that the patients in this study were predominantly Caucasian. Approaches to antihypertensive monotherapy for patients of African-American origin may vary from that for Caucasians. The 2003 guidelines of the International Society on Hypertension in Blacks[39] considered that thiazides and some CCBs may have greater BP-lowering abilities than β blockers or ACE inhibitors, but recommended that initial treatment should be with a β blocker, ARB, CCB, or diuretic and recognized that many patients would require combination therapy. Again, this supports the results of the present study. It should be noted that amlodipine should be used with caution in African-Americans with hypertension and even mild renal insufficiency.[40]

SH is frequently undertreated. A survey of British general practitioners[41] has found that, although most (84%) would treat isolated SH, the median threshold for them to commence treatment was a dangerously high 180 mm Hg (with a range of 140–240 mm Hg). In a cohort of military veterans being treated for hypertension, 76% had SH in 1999, an increase from the 57% prevalence in 1990–1995.[42] In part, this is due to the relatively high prevalence of SH among the elderly, whom general practitioners may be reluctant to treat intensively for fear of side effects.[43]

Noncompliance with medication is another major reason for failure to reach BP goals,[44] and so the relatively high rate of discontinuations in our study due to edema with amlodipine is a concern. Peripheral edema is a well known side effect of CCBs resulting from preferential precapillary dilation without commensurate postcapillary dilation.[14] Although it is not life threatening, many patients find it distressing and, as a result, stop their medication. Clinical trials of CCBs report discontinuation rates due to edema averaging 15%,[45] and our findings that the rate of discontinuation from amlodipine is greater than from telmisartan is supported by a meta-analysis that found that discontinuations due to adverse events are twice as high with CCBs as with ARBs.[46] Because the edema is not caused by sodium retention,[47] the coadministration of a diuretic is unlikely to explain the relative additional increase in rate we observed with A+H compared with amlodipine monotherapy. The mechanism of amlodipine-induced edema also means that initiating treatment with HCTZ therapy and adding amlodipine would not prevent this side effect. A pilot study[48] has shown that addition of HCTZ at a high dose of 25 mg in patients treated with amlodipine did not overcome lower extremity edema. The most likely explanation for the lower rates of edema with A+H is a survivor effect, which may also have implications for the results of our efficacy analysis.

In conclusion, this is the first large-scale comparison of combination therapy based on either an ARB or a CCB in older patients with predominantly SH. The results of this study indicate that telmisartan, in combination with HCTZ, offers comparable SBP reduction during the last 6 hours of the dosing interval, superior SBP reduction over the full 24-hour dosing period, and fewer discontinuations due to adverse events. Therefore, patients with isolated SH may benefit from initial treatment with T+H combination therapy.

Appendix: Additional members of the ATHOS Study Group: J.-M. Krzesinski, C.H.U. Liege, Esneux, Belgium; M. Huttunen, Diacor, Helsinki, Finland; V. Bernard, Hôpital d'Adultes de la Timone 264, Marseille, France; J. Schmidt, Arzt für Innere Medizin, Flörsheim, Germany; D. O'Brien, Birr Co., Offaly, Ireland; M. Santonastaso, U.O. di Medicina Ospedale Civile, Veneto, Italy; W.A. de Backer, Risjwijk, The Netherlands; P.C. Grey, Hazelwood, Pretoria, South Africa; P. Gómez, Hospital General de Jerez de la Frontera, Spain.

References

1 National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group Report on Hypertension in the Elderly. *Hypertension.* 1994;23:275–285.

2 Sagie A, Larson MG, Levy D. The natural history of borderline isolated systolic hypertension. *N Engl J Med.* 1993;329:1912–1917.

3 Izzo JL Jr, Shykoff BE. Arterial stiffness: clinical relevance, measurement, and treatment. *Rev Cardiovasc Med.* 2001;2:29–40.

4 Safar ME, Benetos A. Factors influencing arterial stiffness in systolic hypertension in the elderly: role of sodium and the renin-angiotensin system. *Am J Hypertens.* 2003;16:249–258.

5 Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs. ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA.* 1999;282:539–546.

6 Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation.* 2003;107:1401–1406.

7 Pringle E, Phillips C, Thijs L, et al. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens.* 2003;21:2251–2257.

8 Elliot WJ. Cyclic and circadian variations in cardiovascular events. *Am J Hypertens.* 2001;14:291S–295S.

9 Moore TJ, Conlin PR, Ard J, et al. DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. *Hypertension.* 2001;38:155–158.

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

11 Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet.* 1997;350:757–764.

12 Tonkin A, Wing L. Management of isolated systolic hypertension. *Drugs.* 1996;51:738–749.

13 Laurent S, Kingwell B, Bank A, et al. Clinical applications of arterial stiffness: therapeutics and pharmacology. *Am J Hypertens.* 2002;15:453–458.

14 Leenen FH, Fourney A. Comparison of the effects of amlodipine and diltiazem on 24-hour blood pressure, catecholamines, and left ventricular mass. *Am J Cardiol.* 1996;78:203–207.

15 Karas M, Lacourcière Y, Leblanc AR, et al. Effect of the renin-angiotensin system or calcium channel blockade on the circadian variation of heart rate variability, blood pressure and circulating catecholamines in hypertensive patients. *J Hypertens.* 2005;23:1251–1260.

16 Gustafsson D. Microvascular mechanisms involved in calcium antagonist edema formation. *J Cardiovasc Pharmacol.* 1987;10(suppl 1):S121–S131.

17 Volpe M. Treatment of systolic hypertension: spotlight on recent studies with angiotensin II antagonists. *J Hum Hypertens.* 2005;19:93–102.

18 Kjeldsen SE, Dahlöf B, Devereux RB, et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. *JAMA.* 2002;288:1491–1498.

19 Volpe M, Junren Z, Maxwell TP, et al. Comparison of the blood pressure-lowering effects and tolerability of losartan- and amlodipine-based regimens in patients with isolated systolic hypertension. *Clin Ther.* 2003;25:1469–1489.

20 Malacco E, Vari N, Capuano V, et al. A randomized, double-blind, active-controlled, parallel-group comparison of valsartan and amlodipine in the treatment of isolated systolic hypertension in elderly patients: the Val-Syst study. *Clin Ther.* 2003;25:2765–2780.

21 Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens.* 2003;21:1983–1992.

22 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289:2560–2572.

23 Dickerson LM, Gibson MV. Management of hypertension in older persons. *Am Fam Physician.* 2005;71:469–476.

24 Franse LV, Pahor M, Di Bari M, et al. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. *Hypertension.* 2000;35:1025–1030.

25 Chaudhry SI, Krumholz HM, Foody JM. Systolic hypertension in older persons. *JAMA.* 2004;292:1074–1080.

26 Palatini P, Mugellini A, Spagnuolo V, et al. Comparison of the effects on 24-h ambulatory blood pressure of valsartan and amlodipine, alone or in combination with a low-dose diuretic, in elderly patients with isolated systolic hypertension (Val-Syst study). *Blood Press Monit.* 2004;9:91–97.

27 Burnier M, Maillard M. The comparative pharmacology of angiotensin II receptor antagonists. *Blood Press Suppl.* 2001;1:6–11.

28 Lacourcière Y, Lenis J, Orchard R, et al. A comparison of the efficacy and duration of action of the angiotensin II receptor blocker telmisartan to amlodipine. *Blood Press Monit.* 1998;3:295–302.

29 Poirier L, de Champlain J, Larochelle P, et al. A comparison of the efficacy and duration of action of telmisartan, amlodipine and ramipril in patients with confirmed ambulatory hypertension. *Blood Press Monit.* 2004;9:231–236.

30 Manolis AJ, Reid JL, de Zeeuw D, et al. 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. *J Hypertens.* 2004;22:1033–1037.

31 Michel MC, Bohner H, Koster J, et al. Safety of telmisartan in patients with arterial hypertension. An open-label observational study. *Drug Saf.* 2004;27:335–344.

32 McGill JB, Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *Clin Ther.* 2001;23:833–850.

33 Fenton C, Keating GM, Scott LJ. Telmisartan/hydrochlorothiazide: in the treatment of essential hypertension. *Drugs.* 2003;63:2013–2026.

34 Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Blood Press.* 1992;1:113–119.

35 Smith DH, Cramer MJ, Neutel JM, et al. Comparison of telmisartan versus losartan: meta-analysis of titration-to-response studies. *Blood Press Monit.* 2003;8:111–117.

36 Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903–1913.

37 Schmieder RE. Telmisartan/hydrochlorothiazide combination therapy in the treatment of essential hypertension. *Expert Opin Pharmacother.* 2004;5:2303–2310.

38 Hansson L, Himmelmann A. Calcium antagonists in antihypertensive combination therapy. *J Cardiovasc Pharmacol.* 1991;18(suppl 10):S76–S80.

39 Douglas JG, Bakris GL, Epstein M, et al. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society of Hypertension in Blacks. *Arch Intern Med.* 2003;163:525–541.

40 Sica DA, Douglas JG. The African American Study of Kidney Disease and Hypertension (AASK): new findings. *J Clin Hypertens (Greenwich).* 2001;3:244–251.

41 Mead GE, Murray H, McCollum CN, et al. How do general practitioners manage patients at risk from stroke? *Br J Clin Pract.* 1996;50:426–430.

42 Borzecki AM, Wong AT, Hickey EC, et al. Hypertension control: how well are we doing? *Arch Intern Med.* 2003;163:2705–2711.

43 Ekpo EB, Shah IU, Fernando MU, et al. Isolated systolic hypertension in the elderly: survey of practitioners' attitude and management. *Gerontology.* 1993;39:207–214.
44 Neutel JM, Smith DH. Improving patient compliance: a major goal in the management of hypertension. *J Clin Hypertens (Greenwich).* 2003;5:127–132.
45 Weir MR. Incidence of pedal edema formation with dihydropyridine calcium channel blockers: issues and practical significance. *J Clin Hypertens (Greenwich).* 2003;5:330–335.
46 Ross SD, Akhras KS, Zhang S, et al. Discontinuation of antihypertensive drugs due to adverse events: a systematic review and meta-analysis. *Pharmacotherapy.* 2001;21:940–953.
47 Sica DA. Calcium channel blocker-related peripheral edema: can it be resolved? *J Clin Hypertens (Greenwich).* 2003;5:291–294, 297.
48 Weir MR, Rosenberger C, Fink JC. Pilot study to evaluate a water displacement technique to compare effects of diuretics and ACE inhibitors to alleviate lower extremity edema due to dihydropyridine calcium antagonists. *Am J Hypertens.* 2001;14:963–968.