Telmisartan and Amlodipine Single-Pill Combinations vs Amlodipine Monotherapy for Superior Blood Pressure Lowering and Improved Tolerability in Patients With Uncontrolled Hypertension: Results of the TEAMSTA-5 Study

Steen Neldam, MD;[1] Margreet Lang, PhD;[2] Russell Jones, MSc;[3] On behalf of the TEAMSTA-5 Investigators*

From the Rødovre Centrum, Rødovre, Denmark;[1] the Boehringer Ingelheim bv, Alkmaar, the Netherlands;[2] and the Biometrics and Data Management, Boehringer Ingelheim Ltd, Bracknell, UK[3]

An 8-week, randomized, double-blind, controlled study with single-pill combinations of telmisartan 40 mg or 80 mg/amlodipine 5 mg (T40/A5 or T80/A5) vs monotherapy with amlodipine 5 mg or 10 mg (A10) in 1097 patients with uncontrolled hypertension (diastolic blood pressure [BP] $\geq$90 mm Hg). T40/A5 and T80/A5 resulted in significantly greater ($P<.0001$) reductions in seated trough systolic/diastolic BP vs A5 (–7.4 mm Hg/–3.6 mm Hg; –8.8 mm Hg/–4.9 mm Hg) and a significantly greater ($P<.001$) proportion of patients achieving systolic/diastolic BP goal rate (60.0%/56.7%; 65.7%/63.8%) vs A5 (39.2%/42.0%). Superior BP reductions were also seen with T40-T80/A5 vs A10, with BP goal rates at least as high as with A10; however, there was significantly more peripheral edema with A10 (27.2% vs 4.3% for pooled T40-T80/A5; $P<.0001$). Switching patients with uncontrolled BP to a single-pill combination of T40/A5 or T80/A5 is a better treatment option than up-titration to full-dose monotherapy with A10. *J Clin Hypertens (Greenwich).* 2011;13:459–466.

Current European and US guidelines emphasize the need for aggressive pharmacologic treatment of hypertension to reduce cardiovascular (CV) risk.[1,2] Large clinical studies suggest that more than 50% of hypertensive patients receiving monotherapy with amlodipine 5 mg do not have their blood pressure (BP) controlled adequately,[3,4] and the 2007 guidelines from the European Society of Hypertension/European Society of Cardiology (ESH/ESC) emphasizes that the ability of any antihypertensive agent used alone to achieve target BP values (<140/90 mm Hg) does not exceed 20% to 30% of the overall hypertensive population except in patients with grade 1 hypertension.[1] When initial monotherapy with an antihypertensive agent does not have the desired BP-lowering effect, the dose of the antihypertensive agent is often increased. Up-titrating amlodipine from 5 mg to 10 mg may improve BP response rates but typically also increases the incidence of side effects such as edema, which, in turn, may lead to reduced patient compliance and possibly to treatment discontinuation. To achieve the specified BP goals and to reduce the risk of CV morbidity and mortality, the majority of patients with hypertension will require $\geq$2 antihypertensive medications.[1,2]

Two drugs from different classes with complimentary mechanisms of action may result in additional BP decreases compared with either agent used alone.[5] In a recent meta-analysis, Wald and colleagues[6] showed that the combination of drugs from two different antihypertensive drug classes was up to 5 times more effective in lowering BP than increasing the dose of one drug. Hypertensive patients whose BP is not controlled adequately by monotherapy amlodipine 5 mg may therefore benefit from combination therapy by adding an antihypertensive agent with a distinct and complementary mechanism of action. There are published data suggesting that the combination of a calcium channel blocker (CCB) with an angiotensin II receptor blocker (ARB) is beneficial.[5,7–17] Furthermore, such a combination approach involving adding a blocker of the renin-angiotensin system (RAS) to a CCB appears to be associated with a reduction in the incidence of CCB-related edema;[18] the exact mechanism for this attenuation of edema remains to be established but appears to involve the ability of RAS blockers to counteract the microcirculatory changes induced by CCBs and dilate venous capacitance vessels.[19,20]

The aim of the current study was to evaluate the efficacy and safety of two different strengths of single-pill combinations (SPCs) of telmisartan 40 or 80 mg (T40 or T80) and amlodipine 5 mg (A5) compared with that of monotherapy with A5 and amlodipine 10 mg (A10) in a hypertensive patient population whose BP is not controlled by A5 alone.

METHODS

Study Design

This was a multicenter, multinational, 8-week randomized, double-blind, parallel-group study that evaluated the efficacy and safety of two SPCs of

*See Appendix for details.

Address for correspondence: Steen Neldam, MD, Rødovre Centrum 294, 2610 Rødovre, Denmark
E-mail: neldam@dadlnet.dk

Manuscript received November 2, 2010; **Revised:** January 14, 2011; **Accepted:** January 15, 2011
DOI: 10.1111/j.1751-7176.2011.00468.x

telmisartan/amlodipine (T/A) compared with amlodipine monotherapy in patients with uncontrolled hypertension (ClinicalTrial.org registration: NCT00558428). Patients were recruited from 129 centers in Belgium, Canada, Denmark, Finland, France, Korea, The Netherlands, Norway, The Philippines, South Africa, Sweden, and Taiwan between October 2007 and October 2008. The trial was conducted in accordance with the Declaration of Helsinki (1996) and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and was approved by the health authority and institutional review board or independent ethics committee in each participating country.

Following screening and a 6-week open-label, run-in treatment period with A5, eligible patients were randomized (1:1:1:1) to 1 of 4 treatment groups: the SPC of T40/A5, the SPC of T80/A5, A5 monotherapy, or A10 monotherapy for 8 weeks. Trial medication was taken orally once daily every morning between 8 AM and 10 AM. If a dose was missed, the patient was instructed to take the next dose as originally scheduled.

Patients

Men and women aged 18 years or older with essential hypertension (defined as seated diastolic BP [DBP] $\geq$95 mm Hg in patients receiving antihypertensive treatment, or DBP $\geq$100 mm Hg in treatment-naïve patients) who failed to respond adequately to treatment with amlodipine monotherapy at baseline were included (defined as diastolic BP $\geq$90 mm Hg after a 6-week run-in treatment with A5). Written informed consent (in accordance with GCP and local legislation) was provided by all patients prior to participation.

Patients with suspected or known secondary hypertension, mean seated systolic BP $\geq$200 mm Hg and/or mean seated DBP $\geq$120 mm Hg at screening or at start of the run-in period, or mean seated systolic BP (SBP) $\geq$180 mm Hg and/or mean seated DBP $\geq$120 mm Hg at the end of the run-in period; those with symptomatic congestive heart failure (New York Heart Association functional class III or IV), clinically significant hepatic impairment (eg, clinically significant cholestasis, biliary obstructive disorder, or hepatic insufficiency), severe renal impairment (eg, serum creatinine $>$3.0 mg/dL or $>$265 μmol/L, known creatinine clearance $<$30 mL/min, or clinical markers of severe renal impairment), or any other condition that would not allow for the safe completion of the protocol; and pregnant, nursing, or premenopausal women, or women of childbearing potential not using adequate birth control were excluded. Patients with previous symptoms characteristic of angioedema during treatment with angiotensin-converting enzyme inhibitors or ARBs, those with a history of drug or alcohol dependency within the 6 months prior to the study, or those who were noncompliant with study medication (defined as $<$80% or $>$120%) during the run-in treatment period were also excluded. Any antihypertensive or concomitant medications known to affect BP, other than the trial medication, were not permitted during the study.

Assessments

Seated in-clinic BP was to be measured using a standard manual cuff sphygmomanometer at screening, at the start of the open-label run-in treatment period, at the end of the run-in treatment period prior to randomization (ie, at baseline), and after 4 and 8 weeks of double-blind treatment (at approximately 24 hours after the last drug dose). In sites where no sphygmomanometer was allowed or the staff was not experienced in its use, alternative equipment, validated according to regulatory standards, could be used. Pulse rate was measured at these same times. The BP was recorded as the mean of 3 consecutive measurements, taken approximately 2 minutes apart. Pulse rate was recorded during the 2-minute interval between the second and third BP recording. Efficacy end points were assessed after 8 weeks of treatment or at last trough observation during the double-blind treatment period (ie, last trough observation carried forward).

The primary end points were change from baseline in seated trough DBP and the incidence of edema adverse events (defined as peripheral edema, edema, or generalized edema). Secondary efficacy end points included change from baseline in seated trough systolic BP, the proportion of patients achieving DBP response (defined as mean seated DBP $<$90 mm Hg or DBP reduction $\geq$10 mm Hg) and systolic BP (SBP) response (defined as mean seated SBP $<$140 mm Hg or SBP reduction $\geq$15 mm Hg) after 8 weeks' treatment, and the proportion of patients achieving DBP goal (defined as mean seated DBP $<$90 mm Hg), SBP goal (defined as mean seated SBP $<$140 mm Hg), and BP goal (defined as mean seated SBP $<$140 mm Hg and DBP $<$90 mm Hg) after 8 weeks' treatment.

All adverse events, including reported or diagnosed edema, that occurred throughout the entire study period (ie, from screening to end of study) were recorded. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 11 (Reston, VA). A physical examination was carried out and vital signs assessed at the start of the study (ie, at screening). Laboratory parameters were assessed at screening, at randomization (ie, baseline), and at the end of the double-blind treatment period. Twelve-lead electrocardiography (ECG) was performed at screening and at the end of the double-blind treatment period. Study drug compliance was assessed by physical count of returned trial medication at each visit.

Statistical Analysis

BP changes from baseline to end of study were tested for differences between treatment with T/A SPCs vs amlodipine monotherapies using an analysis of covariance adjusted for country and baseline BP. Response rates and BP goal rates were evaluated using the

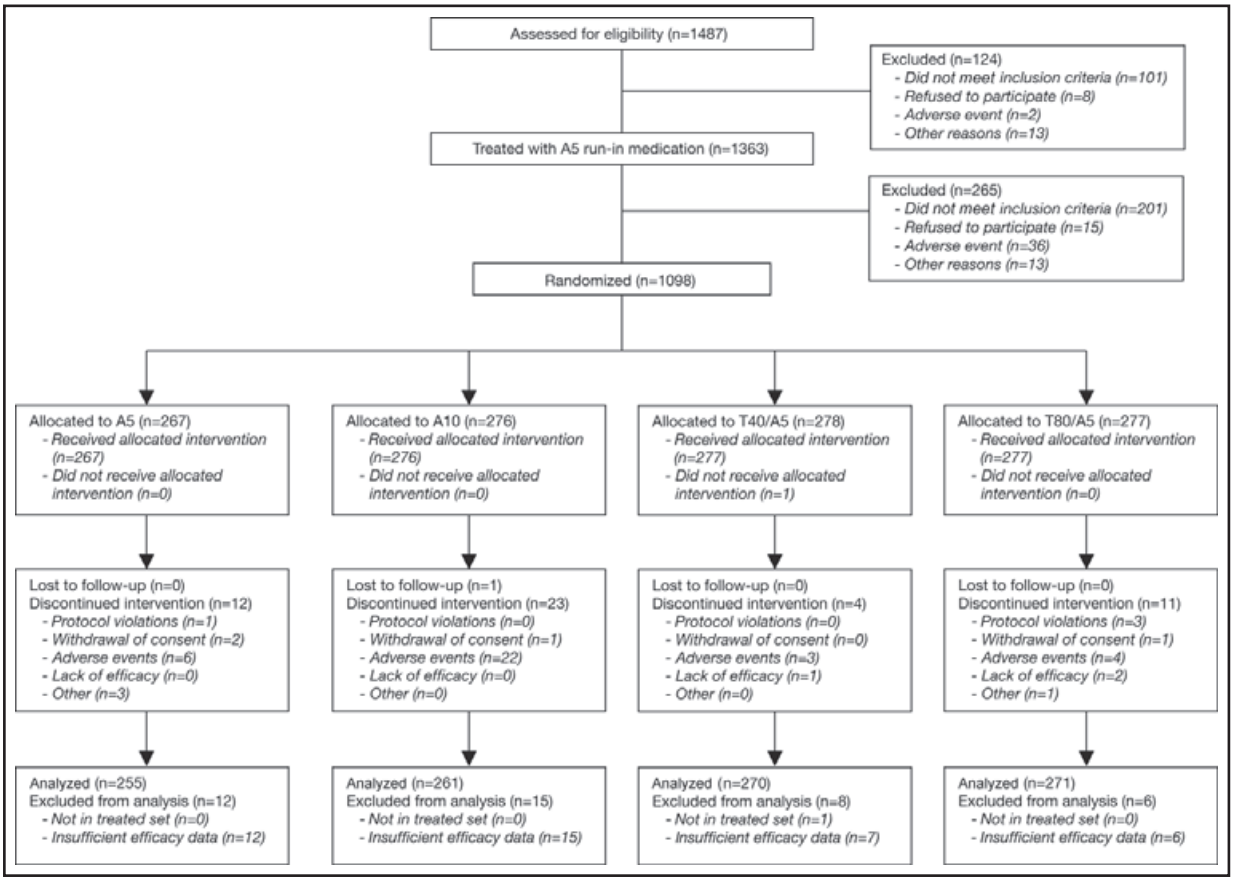

FIGURE 1. Patient disposition. A5 indicates amlodipine 5 mg; A10, amlodipine 10 mg; T40, telmisartan 40 mg; T80, telmisartan 80 mg.

Mantel-Haenszel test, expressed as odds ratios (ORs) and associated 95% confidence intervals (CIs) for achieving goal with the T/A SPCs vs the amlodipine monotherapies. Rates of edema adverse events were evaluated using the Mantel-Haenszel test as above for the pooled T/A SPCs vs A10 monotherapy. Superiority testing was performed for all primary and secondary efficacy analyses of T/A SPCs vs A5 and for the comparison of edema rates for the pooled T/A SPCs vs A10. Inferiority testing was performed for all primary and secondary efficacy analyses of T/A SPCs vs A10.

Power calculations, based on the findings of a recent study with SPCs with telmisartan/hydrochlorothiazide[21] and estimates of edema showed that a sample size of 240 evaluable patients per treatment group would deliver 90% power to detect a 2.0-mm Hg difference between treatments in the reduction from baseline in trough seated DBP and a 96% power to detect a difference in edema incidence rates between the pooled SPCs of T/A (estimated to 2.1%) and A10 (estimated to 10.3%), both with a .05 significance level in a 2-sided log-rank test.

The primary and secondary efficacy analyses were performed on the full analysis set, which consisted of all randomized patients who took at least one dose of double-blind trial medication and for whom a baseline measurement and at least one postdose trough efficacy measurement during the double-blind treatment period were available (last observation carried forward). The safety evaluation was performed on all patients who received at least one dose of any trial treatment.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 1487 patients were enrolled in the study, 1363 patients entered the open-label run-in treatment, and 1098 patients were randomized to double-blind treatment for up to 8 weeks; one randomized patient did not receive any treatment (Figure 1). Patient baseline demographics and clinical characteristics were comparable between treatment groups and are shown in Table I. The efficacy analyses were performed on 1057 patients, and the safety analyses on 1097 patients.

Of the 1097 patients receiving double-blind treatment, 51 (4.6%) were prematurely discontinued from the study due to adverse events (n=35), protocol violations (n=4), withdrawal of consent (n=4), lack of efficacy (n=3), lost to follow-up (n=1), and other reasons

TABLE I. Baseline Demographics and Clinical Characteristics of Randomized Population

	Amlodipine 5 mg	Amlodipine 10 mg	Telmisartan 40 mg/Amlodipine 5 mg	Telmisartan 80 mg/ Amlodipine 5 mg	Overall
Patients, No.	267	276	277	277	1097
Age, y	54.0±10.6	54.3±10.6	53.9±11.0	54.5±10.2	54.2±10.6
Sex (male)	163 (61.0)	176 (63.8)	160 (57.8)	183 (66.1)	682 (62.2)
Screening BP (ie, pre-amlodipine run-in), mm Hg					
Systolic BP	159.9±14.5	158.8±13.9	158.2±14.2	156.9±13.6	158.4±14.1[a]
Diastolic BP	101.8±5.4	101.8±5.1	101.6±5.3	101.3±5.2	101.6±5.2[a]
Baseline trough BP (ie, post-amlodipine run-in), mm Hg					
Systolic	150.5±13.4	149.3±12.0	150.0±12.5	148.6±11.7	149.6±12.4
Diastolic	96.4±5.3	96.5±4.7	96.4±4.9	96.5±5.0	96.6±5.0
Race					
Caucasian	207 (77.5)	213 (77.2)	213 (76.9)	216 (78.0)	849 (77.4)
Asian	56 (21.0)	55 (19.9)	60 (21.7)	56 (20.2)	227 (20.7)
Black	4 (1.5)	6 (2.2)	3 (1.1)	4 (1.4)	17 (1.5)
Other	0 (0.0)	2 (0.8)	1 (0.4)	1 (0.4)	4 (0.4)
Body mass index, kg/m^2	29.9±5.2	28.6±5.0	29.4±5.5	29.6±5.5	29.2±5.3
Duration of hypertension, y					
<1	69 (25.8)	80 (29.0)	89 (32.21)	73 (26.4)	311 (28.4)
1–5	100 (37.5)	88 (31.9)	97 (35.0)	89 (32.1)	374 (34.1)
6–10	53 (19.9)	52 (18.8)	42 (15.2)	57 (20.6)	204 (18.6)
>10	45 (16.9)	56 (20.3)	49 (17.7)	58 (20.9)	208 (19.0)
Concomitant diabetes	24 (9.0)	24 (8.7)	32 (11.5)	18 (6.5)	98 (8.9)
Smoking history					
Never smoker	162 (60.7)	175 (63.4)	172 (62.1)	180 (65.0)	689 (62.8)
Ex-smoker	57 (21.3)	61 (22.1)	65 (23.5)	58 (20.9)	241 (22.0)
Current smoker	48 (18.0)	40 (14.5)	40 (14.4)	39 (14.1)	167 (15.2)

Abbreviation: BP, blood pressure. [a]n=1093. Values are expressed as mean ± standard deviation or number (percentage).

(n=4) (Figure 1). Compliance with trial medication was high, with no difference between treatment groups (1048 [98.7%] patients took ≥80% to ≤120% of their trial medication at each visit).

Efficacy Assessment

BP Reductions. Both T/A SPCs resulted in significantly greater reductions from baseline in seated trough SBP and DBP compared with continuation of A5 alone (Figure 2). For the SPCs of T40/A5 and T80/A5, the adjusted mean differences (and associated 95% CI) in SBP/DBP reductions compared with A5 were −7.4 mm Hg (−9.3, −5.5; $P<.0001$)/−3.6 mm Hg (−4.9, −2.4; $P<.0001$) and −8.8 mm Hg (−10.7, −6.9; $P<.0001$)/−4.9 mm Hg (−6.2, −3.7; $P<.0001$), respectively. Both SPCs also resulted in superior reductions in seated trough SBP and DBP compared with the higher dose (10 mg) of amlodipine monotherapy (Figure 2). For the SPCs of T40/A5 and T80/A5, the adjusted mean differences in SBP/DBP reductions compared with A10 were −2.4 mm Hg (−4.3, −0.6; $P=.010$)/−1.4 mm Hg (−2.7, −0.1; $P=.029$) and −3.9 mm Hg (−5.7, −2.0; $P<.0001$)/−2.7 mm Hg (−3.9, −1.4; $P<.0001$), respectively.

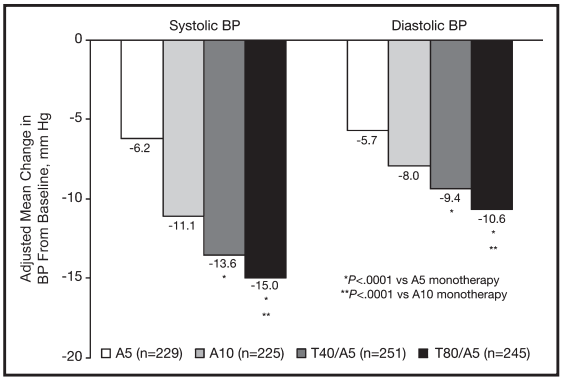

FIGURE 2. Effect of 8 weeks of treatment with single-pill combinations of telmisartan 40 mg/amlodipine 5 mg (T40/A5) or telmisartan 80 mg/amlodipine 5 mg (T80/A5) compared with monotherapy with A5 or amlodipine 10 mg (A10) on the change from baseline in seated trough systolic blood pressure (BP) (mm Hg) or diastolic BP (mm Hg).

BP Response. Both T/A SPCs resulted in a significantly greater proportion of patients achieving BP response (SBP <140 mm Hg or SBP reduction ≥15 mm Hg and DBP <90 mm Hg or DBP reduction ≥10 mm Hg) compared with A5 alone (Figure 3). For the SPCs of T40/A5 and T80/A5, the ORs (and associated 95% CIs) for achieving SBP/DBP response compared with A5 were 2.80 (1.94–4.04; $P<.001$)/2.41 (1.67–3.46; $P<.001$), and 3.44 (2.36–5.02; $P<.001$)/2.77

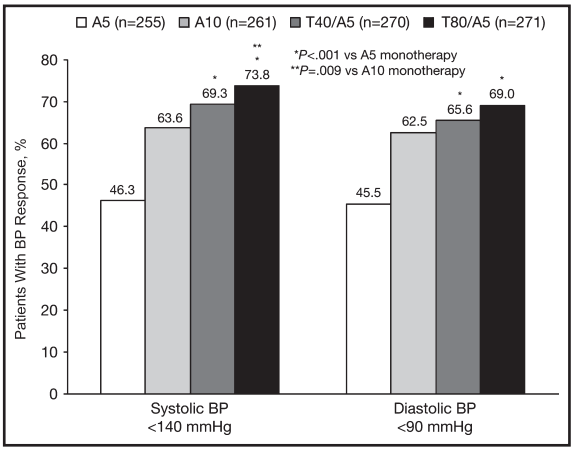

FIGURE 3. Effect of 8 weeks of treatment with single-pill combinations of telmisartan 40 mg/amlodipine 5 mg (T40/A5) or telmisartan 80 mg (T80)/A5 compared with monotherapy with A5 or amlodipine 10 mg (A10) on the proportion of patients who achieved blood pressure (BP) response (ie, systolic BP <140 mm Hg or systolic BP reduction ≥15 mm Hg; diastolic BP <90 mm Hg or diastolic BP reduction ≥10 mm Hg) (%).

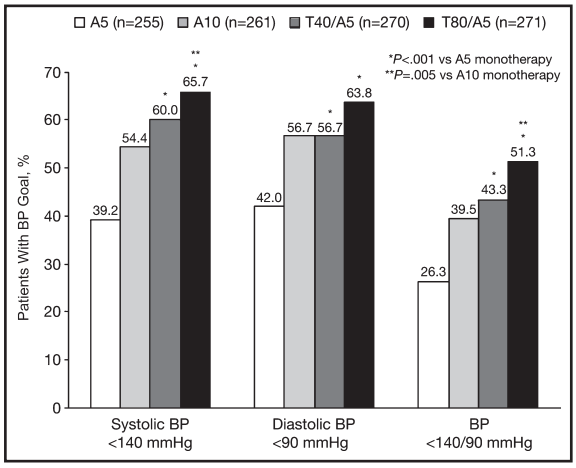

FIGURE 4. Effect of 8 weeks of treatment with single-pill combinations of telmisartan 40 mg/amlodipine 5 mg (T40/A5) or telmisartan 80 mg (T80)/A5 compared with monotherapy with A5 or amlodipine 10 mg (A10) on the proportion of patients with blood pressure (BP) goal (ie, systolic BP <140 mm Hg; diastolic BP <90 mm Hg; BP <140/90 mm Hg) (%).

(1.92–4.00; *P*<.001), respectively. Both T/A SPCs also resulted in BP response rates at least as good as those observed with the higher dose (10 mg) of amlodipine monotherapy (Figure 3). ORs (and associated 95% CI) for achieving SBP/DBP response compared with A10 were 1.32 (0.91–1.90; *P*=.142)/1.15 (0.80–1.66; *P*=.452) and 1.67 (1.14–2.44; *P*=.009)/1.36 (0.94–1.96; *P*=.107), respectively.

BP Goal Rates. Both T/A SPCs resulted in a significantly greater proportion of patients achieving BP goal (DBP <90 mm Hg and SBP <140 mm Hg) compared with A5 alone (Figure 4). For the SPCs of T40/A5 and T80/A5, the ORs (and associated 95% CI) for achieving SBP/DBP goal compared with A5 were 2.53 (1.75–3.64; *P*<.001)/1.87 (1.32–2.67; *P*<.001), and 3.24 (2.23–4.71; *P*<.001)/2.50 (1.75–3.58; *P*<.001), respectively. Both T/A SPCs also resulted in significantly more patients reaching BP goal compared with A5. T80/A5 SPC resulted in significantly higher BP goal rates than those observed with the higher dose (10 mg) of amlodipine monotherapy (Figure 4). ORs (and associated 95% CI) for achieving SBP/DBP goal compared with A10 were 1.29 (0.90–1.84; *P*=.150)/1.00 (0.70–1.42; *P*=.994), and 1.71 (1.18–2.48; *P*=.005)/1.37 (0.96–1.95; *P*=.092), respectively. The overall BP goal rates were also significantly higher for the T/A SPCs compared with amlodipine monotherapy (Figure 4).

Safety Assessment

A total of 123 (11.2%) patients reported at least one incidence of edema during the 8-week double-blind study period. Both the SPCs of T40/A5 and T80/A5 were associated with a significantly lower incidence of

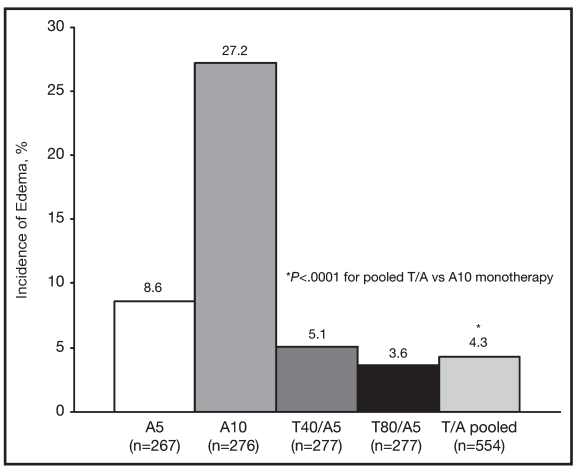

FIGURE 5. Effect of 8 weeks of treatment with single-pill combinations of telmisartan 40 mg/amlodipine 5 mg (T40/A5) or telmisartan 80 mg (T80)/A5 compared with monotherapy with A5 or amlodipine 10 mg (A10) on the proportion of patients on the rate of incidence of edema (%).

edema compared with A10 alone (Figure 5). In the pooled T/A SPCs treatment groups, 4.3% (n=24) of patients experienced at least one incidence of edema compared with 27.2% (n=75) in the A10 treatment group (OR, 0.12; 95% CI, 0.07–0.19; *P*<.0001). Both the SPCs were also associated with a lower incidence of edema than A5 (Figure 5).

A total of 422 (38.5%) patients reported at least one adverse event during the 8-week study. The incidence of adverse events with the T/A SPCs (35.4% [n=98] and 33.6% [n=93], respectively) were similar to that observed with A5 alone (37.1%; n=99) and

TABLE II. Adverse Events Leading to Discontinuation of Study Medication

	Amlodipine 5 mg	Amlodipine 10 mg	Telmisartan 40 mg/Amlodipine 5 mg	Telmisartan 80 mg/Amlodipine 5 mg
Patients, No.	267	276	277	277
Total adverse events	6 (2.2)	22 (8.0)	3 (1.1)	4 (1.4)
Edema adverse events	2 (0.7)	18 (6.5)	1 (0.4)	0 (0.0)
Other adverse events	4 (1.5)	4 (1.4)	2 (0.7)	4 (1.4)

Values are expressed as number (percentage).

lower than that with A10 alone (47.8%; n=132). Edema was the most commonly reported adverse event (5.1% [n=14] with T40/A5 and 3.6% [n=10] with T80/A5 vs 8.6% [n=23] with A5 and 27.9% [n=77] with A10). The number of discontinuations due to adverse events (n=35) was comparable between the treatment groups, with the exception of discontinuations due to edema, which were higher with A10 monotherapy (n=18) (Table II).

Drug-related adverse events were reported in 157 (14.3%) patients. Both the SPCs of T40/A5 and T80/A5 were associated with a lower incidence of drug-related adverse events (7.9% [n=22] and 8.7% [n=24], respectively) than A5 alone (12.1%; n=34) and A10 alone (27.9%; n=77).

Serious adverse events were reported in 6 (0.5%) patients, none of which were considered related to the study drug. There were no clinically relevant changes in ECG, pulse rate, or routine laboratory measures from baseline to end of study.

DISCUSSION

Clinical evidence and guidelines suggest the use of combination treatments to provide additional antihypertensive efficacy in patients who are not controlled with monotherapy. There are indications that combination treatments may not only result in more patients achieving BP target, but may also result in a more rapid BP-lowering effect.[22] In the present study, we demonstrate the antihypertensive efficacy of SPC of the ARB telmisartan and the CCB amlodipine compared with low-dose and up-titrated dose of amlodipine monotherapy. We found that the SPC of T80/A5 resulted in significantly greater double-digit reductions in in-clinic SBP/DBP (−15.0 mm Hg/−10.6 mm Hg; $P<.0001$) compared with continuation of low-dose A5 monotherapy. BP reductions were greater than those achieved by up-titration of amlodipine to 10 mg. The SPC of T40/A5 also resulted in SBP/DBP reductions (−13.6 mm Hg/−9.4 mm Hg; $P<.0001$) that were significantly greater than those seen with A5 monotherapy and at least as good as those seen with A10 monotherapy. Importantly, the SPC was associated with a better safety profile than the amlodipine monotherapy. The greater antihypertensive efficacy of the SPC of T80/A5 resulted in a significantly greater proportion of patients achieving SBP/DBP response (73.8%/69.0%; $P<.001$) and SBP/DBP and overall BP goal (65.7%/63.8% and 51.3%; $P<.001$) compared with monotherapy with A5. Overall, the SBP/DBP response and goal rates seen with the SPC of T80/A5 were at least as good as those seen with A10, with the SBP response and goal figures being significantly greater ($P=.009$ and $P<.005$, respectively).

Our findings are consistent with recent studies of initial therapy with a combination of telmisartan and amlodipine. In patients with moderate to severe hypertension, the combination of telmisartan and amlodipine provided significantly better BP lowering than the respective monotherapies.[7,8,23]

In addition to BP-lowering efficacy, the tolerability of antihypertensive therapy is crucial as it affects patient compliance. Improved tolerability may potentially increase treatment adherence and thereby help attain the ultimate long-term goal of BP lowering, such as protecting patients from CV morbidity and mortality. In this study, we found that treatment with the SPCs of T/A were associated with significantly lower rates of peripheral edema compared with treatment with the up-titrated 10-mg dose of amlodipine monotherapy (4.3% vs 27.2%; $P<.0001$). The edema rates seen with the SPCs (5.2% [T40/A5] and 3.7% [T80/A5]) were even reduced compared with that observed in patients continuing on the lower 5-mg dose of amlodipine monotherapy (8.2%). Furthermore, the SPCs of T/A were generally well tolerated with lower rates of adverse events compared with amlodipine monotherapy.

Amlodipine is a potent antihypertensive drug with a long half-life (approximately 30–50 hours). Of the available ARBs, telmisartan has a unique pharmacokinetic profile with the longest plasma elimination half-life (approximately 24 hours) and longest dissociation half-life from the angiotensin II type 1 (AT_1) receptor and the strongest binding affinity to the AT_1 receptor.[2,24–27] Telmisartan has been shown to provide long-acting BP reductions throughout the 24-hour dosing period, including during the critical early morning hours when compared with other ARBs.[28,29] Taken together with the significant increase in antihypertensive

efficacy and the reduced incidence of edema observed with this combination it would seem that in hypertensive patients who are not controlled by amlodipine monotherapy, the addition of telmisartan over other ARBs may be particularly well suited to provide the additional BP reductions needed to reach BP treatment targets.

CONCLUSIONS

The findings of our study show that in patients who do not achieve target BP with A5, SPCs with T40/A5 or T80/A5 are the better treatment option than continuation of A5 or up-titration to A10. The SPCs provide superior SBP/DBP reductions compared with A5 or A10 monotherapy and significantly improve SBP/DBP goal and response rates to A10; however, the SPCs are better tolerated, with significantly lower rates of peripheral edema and fewer discontinuations from therapy. Additionally, an SPC may also help simplify treatment regimens and thereby also favor compliance and treatment adherence. These findings demonstrate the advantages of switching patients who fail to achieve target BP with A5 to a BP-lowering treatment using an SPC containing T40/A5 or T80/A5 instead of increasing the dose of amlodipine monotherapy to 10 mg.

Acknowledgments and Disclosures: Writing and editorial assistance was provided by Anne Jakobsen of PAREXEL, which was contracted by Boehringer Ingelheim GmbH for these services. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE), were fully responsible for all content and editorial decisions, and were involved at all stages of manuscript development. The authors received no compensation related to the development of the manuscript. The study reported was funded and sponsored by an educational grant from Boehringer Ingelheim. Steen Neldam has no conflicts of interest. Margreet Lang is the responsible study manager at Boehringer Ingelheim.

REFERENCES

1. Mancia G, Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension. The Task Force for the management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25:1105–1187.
2. Chobanian AV, Bakris GL, Black HR, et al. 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.
3. Dahlöf B, Lindholm LH, Carney S, et al. Main results of the losartan versus amlodipine (LOA) study on drug tolerability and psychological general well-being. LOA Study Group. *J Hypertens*. 1997; 15:1327–1335.
4. Phillips RA, Kloner RA, Grimm RH Jr, et al. The effects of amlodipine compared to losartan in patients with mild to moderately severe hypertension. *J Clin Hypertens (Greenwich)*. 2003;5:17–23.
5. Tedesco MA, Natale F, Calabro R. Effects of monotherapy and combination therapy on blood pressure control and target organ damage: a randomized prospective intervention study in a large population of hypertensive patients. *J Clin Hypertens (Greenwich)*. 2006;8:634–641.
6. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300.
7. Littlejohn TW III, Majul CR, Olvera R, et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. *J Clin Hypertens (Greenwich)*. 2009;11:207–213.
8. Littlejohn TW III, Majul CR, Olvera R, et al. Telmisartan plus amlodipine in patients with moderate or severe hypertension: results from a subgroup analysis of a randomized, placebo-controlled, parallel-group, 4 x 4 factorial study. *Postgrad Med*. 2009;121:5–14.
9. Poldermans D, Glazes R, Kargiannis S, et al. Tolerability and blood pressure-lowering efficacy of the combination of amlodipine plus valsartan compared with lisinopril plus hydrochlorothiazide in adult patients with stage 2 hypertension. *Clin Ther*. 2007;29:279–289.
10. Volpe M, Brommer P, Haag U, et al. Efficacy and tolerability of olmesartan medoxomil combined with amlodipine in patients with moderate to severe hypertension after amlodipine monotherapy: a randomized, double-blind, parallel-group, multicentre study. *Clin Drug Investig*. 2009;29:11–25. doi: 10.2165/0044011-200929010-00002
11. Allemann Y, Fraile B, Lambert M, et al. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure After Single Therapy (EX-FAST) study. *J Clin Hypertens (Greenwich)*. 2008;10:185–194.
12. Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo- controlled, 8-week factorial efficacy and safety study. *Clin Ther*. 2008;30:587–604.
13. Chrysant SG, Oparil S, Melino M, et al. Efficacy and safety of long-term treatment with the combination of amlodipine besylate and olmesartan medoxomil in patients with hypertension. *J Clin Hypertens (Greenwich)*. 2009;11:475–482.
14. Andreadis EA, Tsourous GI, Marakomichelakis GE, et al. High-dose monotherapy vs low-dose combination therapy of calcium channel blockers and angiotensin receptor blockers in mild to moderate hypertension. *J Hum Hypertens*. 2005;19:491–496.
15. Weir MR. Targeting mechanisms of hypertensive vascular disease with dual calcium channel and renin-angiotensin system blockade. *J Hum Hypertens*. 2007;21:770–779.
16. Barrios V, Brommer P, Haag U, et al. Olmesartan medoxomil plus amlodipine increases efficacy in patients with moderate-to-severe hypertension after monotherapy: a randomized, double-blind, parallel-group, multicentre study. *Clin Drug Investig*. 2009;29:427–439.
17. Schunkert H, Glazer RD, Wernsing M, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on amlodipine monotherapy. *Curr Med Res Opin*. 2009;25:2655–2662.
18. Fogari R, Malamani G, Zoppi A, et al. Effect on the development of ankle edema of adding delapril to manidipine in patients with mild to moderate essential hypertension: a three-way crossover study. *Clin Ther*. 2007;29:413–418.
19. Kohlmann O, Oigman W, Mion D, et al. Estudo 'LOTHAR': avaliacao de eficacia e tolerabilidade da combinacao fixa de amlodipino e losartana no tratamento da hipertensao arterial primaria. *Arq Bras Cardiol*. 2006;86:39–51.
20. Fogari R, Zoppi A, Derosa G, et al. Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. *J Hum Hypertens*. 2007;21:220–224.
21. Neldam S, Edwards C; Telmisartan/hydrochlorothiazide Investigators. Results of increasing doses of hydrochlorothiazide in combination with an angiotensin receptor blocker in patients with uncontrolled hypertension. *J Clin Hypertens (Greenwich)*. 2008; 10;612–618.
22. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm (ASCOT-BPLA): a mulicentre randomised controlled trial. *Lancet*. 2005;366:895–906.
23. Sharma A, Bagchi A, Kinagi SB, et al. Results of a comparative, phase III, 12-week, multicenter, prospective, randomized, double-blind assessment of the efficacy and tolerability of a fixed-dose combination of telmisartan and amlodipine versus amlodipine monotherapy in Indian adults with stage II hypertension. *Clin Ther*. 2007; 29:2667–2676.
24. Costa FV. Telmisartan standing out in a crowded contest? *High Blood Press Cardiovasc Prev*. 2006;13:85–94.
25. Burnier M. Telmisartan: a different angiotensin II receptor blocker protecting a different population? *J Int Med Res*. 2009;37:1662–1679.
26. Kakuta H, Sudoh K, Sasamata M, et al. Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor: comparison with other angiotensin II type 1 receptor blockers. *Int J Clin Pharmacol Res*. 2005;25:41–46.
27. Lewington S, Clarke R, Qizilbash N, et al.; Prospective Studies Collaboration. 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.

28. Lacourcière Y, Krzesinski JM, White WB, et al. Sustained antihypertensive activity of telmisartan compared with valsartan. *Blood Press Monit*. 2004;9:203–210.
29. 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 (Greenwich)*. 2003;5:58–63.

Appendix

TEAMSTA-5 Study Investigators

Belgium: van de Borne P, Bruxelles; De Cort P, Tienen; Elshot S, Mol; Burette P, Aywaille; Bekaert I, Turnhout; van Dhelzen G, Seraing; Balthazar Y, Natoye; Maury O, Linkebeek; Erpicum L, Tavier; De Meulemeester M, Gozée; Henry G, Dour. *Canada*: Carlson B, Coquitlam; Conter H, Halifax; Lacourciére Y, Sainte-Foy; Cliché L, Montreal; O'Keefe D, Mount Pearl; O'Mahony M, Sarnia; Powell C, Bay Roberts; Ramjatten B, St. John's; Tan KW, Ottawa; Tytus R, Hamilton; Lai J, Vancouver; Dzongowski P, London; O'Mahony W, Corunna; Kanani S; Etobicoke. *Denmark*: Neldam S, Rødovre; Garne S, Birkerød; Sørensen T, Værløse; Johannsen JA, Haderslev; Saaby Jensen G, Rødovre; Brun Egeberg B, Vildebjerg; Veng-Christensen I, Herning; Fly G, Hinnerup. *Finland*: Kantola I, Turku; Järveläinen V, Turku; Icen R, Joensuu; Kekki S, Joensuu. *France*: Pineau-Valencienne D, Nantes; Lemoine T, Nevers; Lemoine C, Vannes; Lochet Goarant S, La Fresnais; Lemarié B, Bourg Des Comptes; Boucher L, Murs-Erigné; Marty J, Murs-Erigné; Schaupp T, Vihiers; Hodebourg de Verbois F, Beaucouze; Richter D, Jarny. *Korea*: Seung HH, Junggu; Hyo-Soo K, Seoul; Dong HC, Seoul; Jung-han Y, Gangwon-Do; Hyuck Moon K, Seoul; Sahng L, Daejon; Doo-il K, Busan; Myung HJ, Gwangju. *Netherlands*: Feis WL, Oude Pekela; Prak H, Musselkanaal; de Jong A, Hoogwoud; van Mierlo HFCM, Roelefarendsveen; Rol H, Bennebroek; van Soest JA, Nijverdal; glas WO, Beerzerveld; de Backer WA, Rijswijk; Costongs RJMG, Voerendaal. *Norway*: Løland Jacobsen K, Ålesund; Aaserud E, Bergen; Høye K, Hamar; Aarskog D, Oslo. *Philippines*: Castillo R, Manila; Que W, Manila; Durante M, Quezon City; Ramos EJ, Pasig City; Lapitan R, Makati City; Sibulo A, Jr, Quezon City; Bravo P, Pasay City; Chua Alabang E,, Muntinlupa City. *South Africa*: Jurgens J, Krugersdorp; Ne lP, Pretoria; Bernhardi D, Boksburg North; Vawda Z, Durban; Lakha D, Lenasia South; Patel P, Cape Town; Fouche L, Florida Park; Kahanovitz C, Sandton; David N, Cape Town; Janari E, Cape Town. *Sweden*: Östergren J, Stockholm; Bokemark L, Göteborg; Berglund T, Göteborg; Larnefeldt H, Rättvik; Lundgren M, Luleå. *Taiwan*: Wen-Ter L, Kaohsiung; Ju-Pin P, Taipei; Pei-Ying P, Taichung; Meng-Tin T, Taipei; Ching-Pei C, Changhua; Jyh-Hong C, Tainan; Wei-Chuan T, Douliu City; Ji-Hung W, Hualien City.