Single-Pill Combination of Telmisartan/Amlodipine in Patients With Severe Hypertension: Results From the TEAMSTA Severe HTN Study

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This 8-week, randomized, double-blind, controlled study compared efficacy and tolerability of telmisartan/amlodipine (T/A) single-pill combination (SPC) vs the respective monotherapies in 858 patients with severe hypertension (systolic/diastolic blood pressure [SBP/DBP] ≥180/95 mm Hg). At 8 weeks, T/A provided significantly greater reductions from baseline in seated trough cuff SBP/DBP (−47.5 mm Hg/−18.7 mm Hg) vs T ($P<.0001$) or A ($P=.0002$) monotherapy; superior reductions were also evident at 1, 2, 4, and 6 weeks. Blood pressure (BP) goal and response rates were consistently higher with T/A vs T or A. T/A was well tolerated, with less frequent treatment-related adverse events vs A (12.6% vs 16.4%) and a numerically lower incidence of peripheral edema and treatment discontinuation. In conclusion, treatment of patients with substantially elevated BP with T/A SPCs resulted in high and significantly greater BP reductions and higher BP goal and response rates than the respective monotherapies. T/A SPCs were well tolerated. *J Clin Hypertens (Greenwich).* 2012;14:206–215. ©2012 Wiley Periodicals, Inc.

Based on evidence from a number of large antihypertensive trials,[1–9] most guidelines acknowledge that combination therapy is needed to reduce blood pressure (BP) successfully to goal in the majority of patients; only a minority of patients achieve their BP goal with a single agent.[10–14] Also, the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) study showed a significant reduction of cardiovascular (CV) events and death in hypertensive patients at high CV risk treated with a combination of an angiotensin-converting enzyme (ACE) inhibitor and a calcium channel blocker (CCB).[15] Nevertheless, despite rigorous and comprehensive guidelines, and a trend towards an increase in the use of combination therapy in treatment practice,[16] several studies have demonstrated the persistence of poor BP goal rates in treated patients.[17–19] The impact of poor BP control is compounded by the often high prevalence of other CV risk factors in hypertensive patients (eg, hypercholesterolemia, obesity, type 2 diabetes mellitus [T2DM], and smoking).[13] Therefore, an urgent need still remains to improve the management of hypertension. One logical approach would be to use 2 drugs from different classes and complementary mechanisms of action in combination. Such combinations may result in additional BP decreases and improved goal rates, compared with either agent used alone.[20–23] Furthermore, single-pill combinations (SPCs) are known to increase treatment adherence and reduce health care costs.[24–27]

A combination of a CCB and an angiotensin II receptor blocker (ARB) is a rational approach for managing hypertension and there is increasing evidence that this combination is effective.[11,13,28,29] The aim of the current study was to compare the efficacy and tolerability of the SPC of telmisartan 80 mg/amlodipine 10 mg (T80/A10) with that of its respective monotherapy components (T80 or A10 alone) in patients with severe hypertension (ie, systolic BP [SBP]/diastolic BP [DBP] ≥180/95 mm Hg).

MATERIALS AND METHODS

Study Design

This was an 8-week randomized, double-blind, forced-titration, parallel-group, multicenter, multinational study to compare the efficacy and tolerability of the SPC of T80/A10 with that of its respective monotherapy components (T80 and A10) in patients with SBP/DBP ≥180/95 mm Hg (ClinicalTrial.org registration: NCT00860262). Patients were recruited from 114 centers in 11 countries (Bulgaria, Czech Republic, France, Hungary, Romania, Russia, Slovakia, South Korea, Spain, Ukraine, and the United States) between March 2009 and December 2009. 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 boards or independent ethics committees in each participating

*Details of the TEAMSTA Severe HTN Study Investigators (see Appendix).

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country. Written informed consent (in accordance with Good Clinical Practice and local legislation) was provided by all patients prior to any trial-specific investigations.

Following screening and a 1- to 14-day, single-blind, placebo run-in period, eligible patients were randomized (2:1:1) to 1 of 3 treatments: the SPC of T80/A10, T80 monotherapy, or A10 monotherapy. All patients assigned to the T/A or A groups received the lower 5-mg dose of amlodipine (ie, T80/A5 or A5) for the first 2 weeks and were then uptitrated to the target T80/A10 or A10 for the remaining 6 weeks of treatment; patients in the T80 group started and remained on the same treatment for the entire 8 weeks. Trial medication was to be taken once daily in the morning at approximately the same time each day. Other antihypertensive or concomitant medications known to affect BP were not permitted during the study.

Patients

Male or female patients aged 18 years or older with mean seated cuff SBP $\geq$180 mm Hg and DBP $\geq$95 mm Hg who were able to stop current antihypertensive therapy without unacceptable risks (at the investigator's discretion) were eligible for randomization.

Patients with suspected/known secondary hypertension, mean seated cuff SBP $\geq$200 mm Hg and/or mean seated cuff DBP $\geq$120 mm Hg and those with symptomatic congestive heart failure (New York Heart Association functional class III or IV), clinically relevant cardiac arrhythmias (eg, ventricular tachycardia, atrial fibrillation, or atrial flutter), 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), unstable or uncontrolled diabetes (hemoglobin $A1_c$ $\geq$10% within the 3 months prior to the study), or any other condition that would not allow for the safe completion of the protocol were excluded, as were pregnant, nursing, or premenopausal women, or women of childbearing potential not using adequate birth control. Patients with previous symptoms characteristic of angioedema during treatment with ACE inhibitors or ARBs, those with a contraindication to a placebo run-in period (eg, stroke within the past 6 months prior to the study, myocardial infarction, cardiac surgery, percutaneous transluminal coronary angioplasty, unstable angina, or coronary artery bypass graft within the past 3 months prior to the study), those with a history of drug or alcohol dependency within the 6 months prior to the study, or those with a history of noncompliance or inability to comply with prescribed medications or protocol procedures, were also excluded.

Assessments

BP was recorded at the end of the run-in treatment period prior to randomization (ie, at baseline) and after 1, 2, 4, 6, and 8 weeks of double-blind treatment (at approximately 24 hours after the last drug dose). BP measurements were performed using standard BP measuring equipment, consisting of a cuff with an inflatable bladder with a cloth sheath. All of the BP devices used in the trial were identical and shipped from the same manufacturer (A&D Medical, Inc; model UA-787EJ, Canton, GA). 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 recordings.

The primary end point was change from baseline in mean seated in-clinic trough cuff SBP after 8 weeks of treatment. The key secondary end points were change from baseline in mean seated in-clinic trough cuff SBP after 1, 2, 4, and 6 weeks of treatment. Other secondary end points after 1, 2, 4, 6, and 8 weeks of treatment (all mean seated in-clinic trough cuff) included SBP control (SBP <140 mm Hg or <130 mm Hg) or DBP control (DBP <90 mm Hg or <80 mm Hg) and overall BP goal achievement (SBP <140 and DBP <90 mm Hg). Prespecified subgroup analyses of baseline SBP categories in 5-mm Hg thresholds are supplemented in this report by analyses in 10-mm Hg increments ($\geq$180 mm Hg to <190 mm Hg and $\geq$190 mm Hg to <200 mm Hg). Similarly, prespecified subgroup analyses according to age, presence of T2DM, body mass index (BMI), and race are supplemented with an analysis according to the presence or absence of the metabolic syndrome (ie, patients with T2DM and BMI $\geq$30 kg/m^2).

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 12.1. A physical examination was carried out and vital signs assessed at screening (ie, at start of study). Laboratory parameters were assessed at screening, at baseline (ie, at randomization), and at the end of the study. Twelve-lead electrocardiographic assessment was performed at screening and at the end of the study.

Statistical Analyses

A restricted maximum likelihood–based repeated-measures approach was applied to analyze changes from baseline to each post-baseline time point. The model included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, with the continuous covariates of baseline mean seated trough cuff SBP (at visit 3) and baseline-by-visit interaction. One model, using baseline and all available post-baseline data, was used to make inferences for weeks 8, 6, and 4. A second model, using baseline and

post-baseline data for weeks 1 and 2, was used to make inferences for weeks 1 and 2. Subgroup analyses were conducted using this model, with the addition of terms for the respective subgroup and the treatment-by-subgroup interaction. Response rates for SBP and DBP control rates were evaluated using logistic regression.

Power calculations based on an expected standard deviation of 15 mm Hg for trough SBP showed that a total sample size of 720 evaluable patients would deliver 95% power to detect a 5.0-mm Hg difference between treatments in the reduction from baseline mean seated in-clinic trough cuff SBP with a 0.05 significance level in a 2-sided test.

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

RESULTS

Patient Disposition and Baseline Characteristics

A total of 1315 patients were enrolled in the study and 858 were randomized to treatment. Of these 858 patients, 60 (7.0%) were prematurely discontinued (Figure 1). Patient baseline demographics and clinical characteristics were comparable between treatment groups and are shown in Table I. Half (50.7%) of the patients had a baseline SBP between 180 mm Hg and 185 mm Hg, almost half (47.6%) were obese (ie, BMI $\geq$30 kg/m^2) and 15.0% had concomitant T2DM. The efficacy analyses were performed on 830 patients and the safety analyses on 858 patients (Figure 1). Compliance with trial medication was high, with no difference between treatment groups. At the end of the study, the mean compliance was 97.3% with 835 patients taking $\geq$80% to $\leq$120% of their allocated trial medication throughout the study.

Reductions in BP

At 8 weeks, greater reductions from baseline in mean$\pm$standard deviation (SD) seated trough cuff SBP were observed with the T80/A10 SPC (−47.5$\pm$13.4 mm Hg; from 185.4$\pm$4.6 to 137.9$\pm$12.8 mm Hg), compared with either T80 (−36.9$\pm$13.1 mm Hg; from 185.6$\pm$4.5 to 149.6$\pm$18.1 mm Hg) or A10 monotherapy (−43.2$\pm$9.1 mm Hg; from 185.1$\pm$4.5 to 141.9$\pm$12.9 mm Hg) (Figure 2a and 2c). The difference in adjusted means achieved with T80/A10 compared with T80 at 8 weeks (−10.6 mm Hg; 95% confidence interval [CI], −12.9 to −8.3) was statistically significant (P<.0001). Similarly, the difference between the adjusted means achieved with T80/A10 compared with A10 at 8 weeks (−4.4 mm Hg; 95% CI, −6.7 to −2.1) was statistically significant

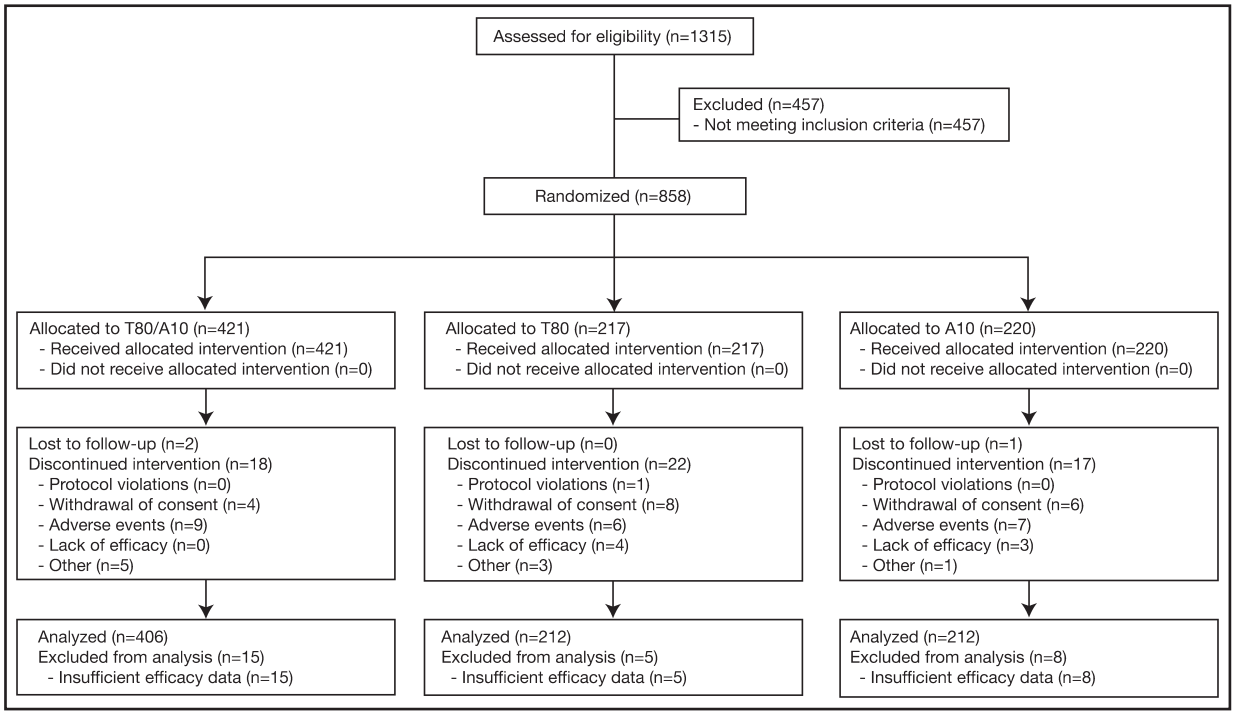

FIGURE 1. Patient disposition.

TABLE I. Baseline Characteristics

	T80/A10 SPC	T80	A10	Overall
Patients, No.	421	217	220	858
Age, y[a]	58.0±10.4	58.1±10.2	58.6±10.5	58.2±10.3
Age ≥65 y, No. (%)	112 (26.6)	59 (27.2)	64 (29.1)	235 (27.4)
Sex (male), No. (%)	219 (52.0)	108 (49.8)	118 (53.6)	445 (51.9)
Current smoker, No. (%)	79 (18.9)	42 (19.4)	38 (17.3)	159 (18.5)
Baseline trough BP, mm Hg[a]				
SBP	185.4±4.6	185.6±4.5	185.2±4.5	185.4±4.5
DBP	103.2±6.3	103.4±6.8	103.5±6.2	103.3±6.4
Race, No. (%)				
White	362 (86.0)	186 (85.7)	190 (86.4)	738 (86.0)
Black	34 (8.1)	15 (6.9)	15 (6.8)	64 (7.5)
Asian	20 (4.8)	14 (6.5)	14 (6.4)	48 (5.6)
Other	5 (1.2)	2 (0.9)	1 (0.5)	8 (0.9)
BMI, kg/m^2[a]	30.6±5.9	30.2±5.2	30.7±6.3	30.6 (5.8)
BMI 25 to <30 kg/m^2, No. (%)	160 (38.0)	79 (36.4)	82 (37.3)	321 (37.4)
BMI ≥30 kg/m^2, No. (%)	198 (47.0)	107 (49.3)	103 (46.8)	408 (47.6)
Duration of hypertension, y[a]				
<1 y	38 (9.0)	25 (11.5)	20 (9.1)	83 (9.7)
1–5 y	124 (29.5)	64 (29.5)	72 (32.7)	260 (30.3)
6–10 y	103 (24.5)	61 (28.1)	54 (24.5)	218 (25.4)
>10 y	156 (37.1)	67 (30.9)	74 (33.6)	297 (34.6)
Previous antihypertensive therapy, No. (%)				
0	49 (11.6)	37 (17.1)	26 (11.8)	112 (13.1)
1	133 (31.6)	67 (30.9)	78 (35.5)	278 (32.4)
2	136 (32.3)	59 (27.2)	71 (32.3)	266 (31.0)
≥3	103 (24.5)	54 (24.9)	45 (20.5)	202 (23.5)
Concomitant T2DM, No. (%)	72 (17.1)	34 (15.7)	23 (10.5)	129 (15.0)

Abbreviations: A10, amlodipine 10 mg; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SPC, single-pill combination; T2DM, type 2 diabetes mellitus; T80, telmisartan 80 mg; T80/A10, telmisartan 80 mg/amlodipine 10 mg. [a]Mean±standard deviation.

(*P*=.0002). These reductions from baseline in mean seated trough cuff SBP at 8 weeks with the T80/A10 SPC were sustained irrespective of baseline SBP category (Figure 3). Patients with a baseline SBP of ≥180 mm Hg to <185 mm Hg, ≥185 mm Hg to <190 mm Hg, ≥190 mm Hg to <195 mm Hg, and ≥195 mm Hg to <200 mm Hg achieved SBP reductions of 47.0 mm Hg, 48.3 mm Hg, 48.7 mm Hg, and 49.5 mm Hg, respectively. Overall, patients with baseline SBP levels of ≥180 mm Hg to <190 mm Hg and ≥190 mm Hg to <200 mm Hg achieved substantial mean reductions in SBP of 47.5 mm Hg and 48.9 mm Hg, respectively, with the SPC (Figure 3).

At all time points at which BP was measured, the differences in the adjusted mean SBP in the T80/A10 SPC group were significantly greater than found in either monotherapy group (overall, *P*<.0001, compared with T80; *P*≤.0077, compared with A10) (Figure 2a and 2c). The significantly greater reduction in the adjusted mean SBP with the SPC (T80/A5) was evident after 1 week of treatment, compared with either monotherapy (−6.4 mm Hg compared with T80 [*P*<.0001] and −3.3 mm Hg compared with A5 [*P*=.0077]) and maintained throughout the study. Mean reductions (±SD) from baseline in seated trough cuff SBP with T80/A10 at 1, 2, 4, and 6 weeks were −31.9 (14.6), −38.0 (13.7), −44.6 (13.3), and −47.0 (12.3) mm Hg, respectively. At 1, 2, 4, and 6 weeks, the adjusted mean (±SD) SBP reductions achieved with T80/A10 were −31.9 (14.2), −37.9 (14.1), −44.5 (14.5), and −46.9 (14.4) mm Hg, respectively. Furthermore, 80% of maximum effect (ie, −37.9±14.1 [SD] mm Hg) was achieved after 2 weeks; a reduction in the adjusted means SBP of −7.8 mm Hg compared with T80 (*P*<.0001) and −4.6 mm Hg compared with A5 (*P*=.0001). By weeks 4, 6, and 8, combination therapy with T80/A10 resulted in a >10-mm Hg reduction (−10.2 mm Hg, −10.6 mm Hg, and −10.6 mm Hg, respectively) in mean SBP, compared with T80 monotherapy (*P*<.0001 for all time points) and nearly a 5-mm Hg reduction (−4.8 mm Hg, −4.8 mm Hg, and −4.4 mm Hg, respectively) compared with A10 monotherapy (*P*=.0001 at weeks 4 and 6; *P*=.0002 at week 8).

Similar results were obtained for changes in seated trough cuff DBP from baseline. At 8 weeks, reductions from baseline in mean±SD seated trough cuff DBP were observed with the T80/A10 SPC (−18.7±8.0 mm Hg),

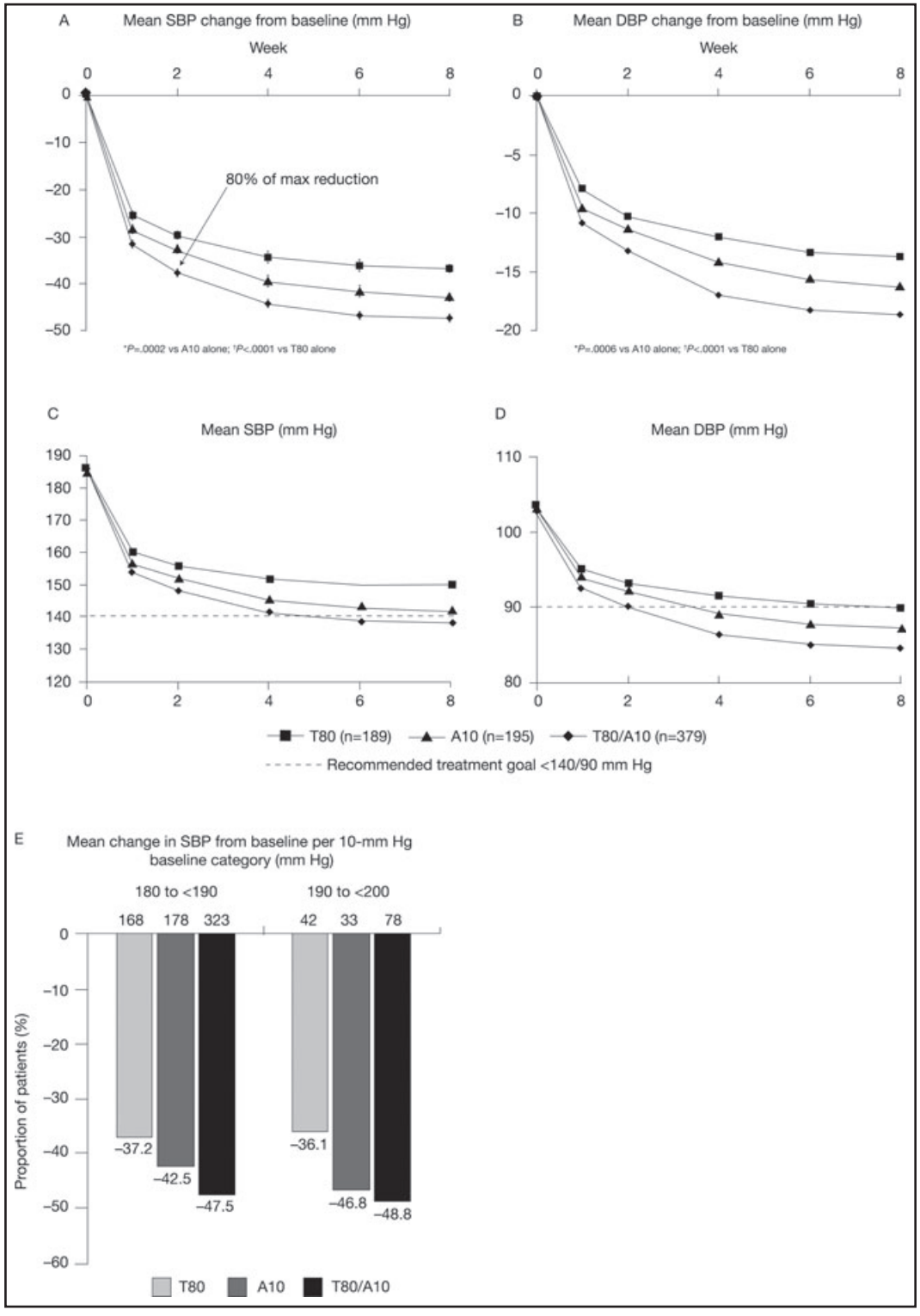

FIGURE 2. Mean reductions (±standard error of mean [SEM]) from baseline in seated trough cuff systolic blood pressure (SBP) (panel A) and diastolic blood pressure (DBP) (panel B) by treatment week (note that some SEMs may not be visible as they are too small to reach beyond the border of the symbol), mean seated trough cuff SBP (panel C) and DBP (panel D) by treatment week, and patients assigned to the telmisartan/amlodipine (T/A) or amlodipine (A) groups received telmisartan 80 mg (T80)/ amlodipine 5 mg (A5) or A5 for the first 2 weeks, then T80/amlodipine 10 mg (A10) or A10 for the remaining 6 weeks; patients in the T80 group remained on the same treatment for the entire 8 weeks.

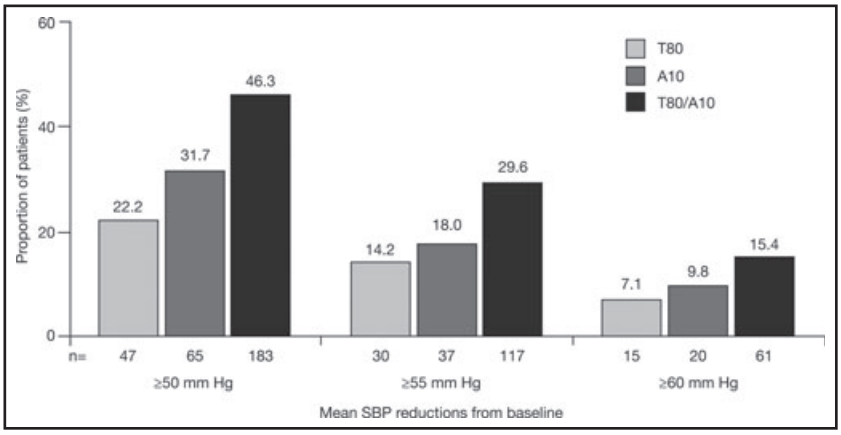

FIGURE 3. Mean reductions in mean seated trough cuff systolic blood pressure (SBP) from baseline to end of study (week 8) per baseline SBP category; 10-mm Hg increments. Patients assigned to the telmisartan/amlodipine (T/A) or amlodipine (A) groups received telmisartan 80 mg (T80)/amlodipine 5 mg (A5) or A5 for the first 2 weeks, then T80/amlodipine 10 mg (A10) or A10 for the remaining 6 weeks; patients in the T80 group remained on the same treatment for the entire 8 weeks. DBP indicates diastolic blood pressure.

compared with either T80 (−13.8±8.0 mm Hg) or A10 monotherapy (−16.3±8.1 mm Hg) (Figure 2b and 2d). The differences in adjusted means for T80/A10, compared with T80 (−5.0 mm Hg; 95% CI, −6.4, −3.6) and A10 (−2.4 mm Hg; 95% CI, −3.8, −1.0), were consistent with those observed in SBP ($P<.0001$ and $P=.0006$, respectively). At all other time points, starting from week 1, the differences in adjusted mean DBP in the T80/A10 group were greater than in either monotherapy group (overall, $P<.0001$ compared with T80; $P\leq.008$ compared with A10).

Subgroup analyses by age, race group, BMI, T2DM status, and presence of metabolic syndrome, supported the findings of the primary analyses: greater reductions in SBP in patients who received the SPC treatment compared with the SBP reductions recorded with either monotherapy were observed (Figure 4). There were no treatment-by-subgroup interactions, except in patients with T2DM ($P=.0164$).

BP Goal Attainment and Response Rates

The proportion of patients who reached the BP goals was consistently higher with the T80/A10 SPC compared with either monotherapy (Figure 5). The SBP/DBP response rates were higher with the T80/A10 SPC compared with either monotherapy. Overall, 99.7% of the T80/A10 group had an SBP response (<140-mm Hg or a ≥10-mm Hg reduction), compared with 91.5% and 98.5% of patients in the T80 and A10 monotherapy groups, respectively. Looking at the more stringent SBP response criteria of <140-mm Hg or a ≥15-mm Hg reduction, 99.0% of patients in the T80/A10 SPC group compared with 88.7% and 98.5% of patients in the T80 and A10 monotherapy groups achieved SBP response, respectively. For DBP response (mean seated DBP <90 mm Hg or a reduction of ≥10 mm Hg): 91.4% of patients in the T80/A10 group achieved DBP response, compared with 69.3% and 83.9% in the T80 and A10 groups, respectively.

Safety

T/A SPC was safe and well tolerated, with similar rates of adverse events to those reported with T80 or A10 monotherapy (32.8% vs 33.2% and 33.2%) (Table II). The most frequently reported adverse events across all treatment groups were peripheral edema (11.2%), headache (5.4%), dizziness (2.1%), and dyspepsia (1.4%); peripheral edema occurred at a rate of 13.1%, 3.7% and 15.0% in the T80/A10, T80, and A10 groups, respectively. The majority of adverse events (98.5%) were of mild to moderate intensity.

Treatment-related adverse events were reported in 12.6% of patients in the T80/A10 group, 6.9% in the T80 group, and 16.4% in the A10 group, and the respective incidence of treatment-related peripheral edema was 9.3%, 2.3%, and 13.2%. Headache was reported in 1.0%, 2.3%, and 0.5% and dizziness in 0.5%, 0.5%, and 0.9% in the T80/A10, T80, and A10 groups, respectively.

Treatment discontinuation due to adverse events was 2.1% with T80/A10, compared with 2.8% with T80 and 3.2% with A10. The incidences of serious adverse events (0.7% vs 0.9% and 0.9%, respectively) were comparable and low for all treatments. Most were a result of hospitalization (6 patients; 0.7%) and none were fatal. Three serious adverse events were considered to be related to study medication: one ischemic stroke in the T80/A10 group, one transient ischemic attack in the T80 group, and one second-degree atrioventricular block in the A10 group (during the first 2 weeks on A5).

DISCUSSION

More than 70% of treated hypertensive patients may have uncontrolled BP,[18] and it is generally acknowledged

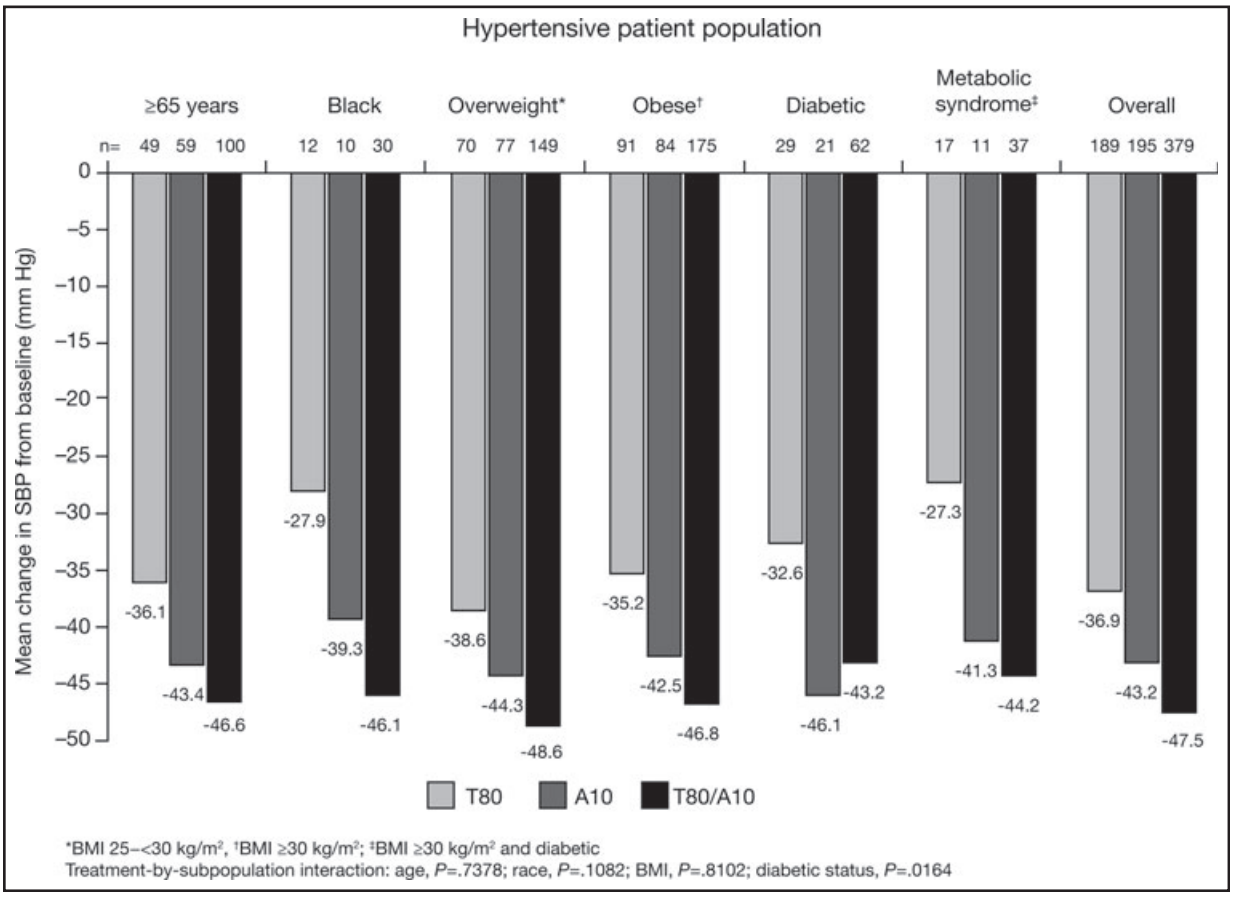

FIGURE 4. Mean reductions from baseline in seated trough cuff systolic blood pressure across hypertensive patient subpopulations.

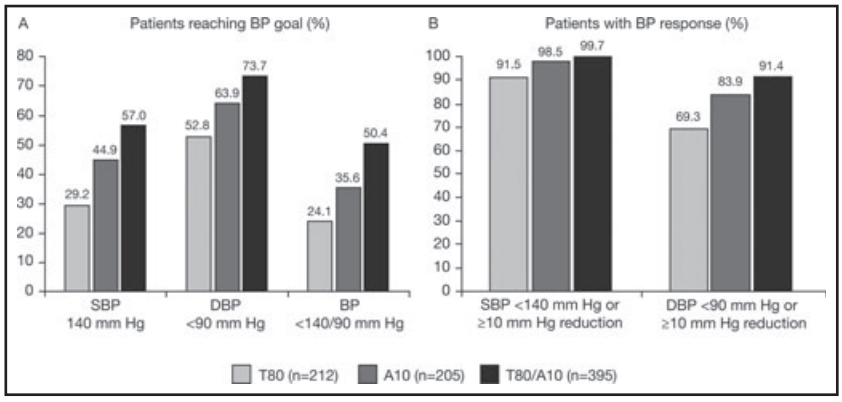

FIGURE 5. Proportion of patients (%) achieving systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood pressure (BP) goal at study end (week 8).

that the majority need >1 antihypertensive treatment to reach their BP target.[10–14,17] In the current study, treatment of patients with severe hypertensive (ie, BP ≥180/95 mm Hg) with an SPC of T80/A10 resulted in significantly greater BP reductions (−47.5/−8.7 mm Hg) than with either T80 (−36.9/−13.8 mm Hg) or A10 monotherapy (−43.2/−16.3 mm Hg), irrespective of the baseline severity of hypertension. It is worth noting that 60% of patients in this population had hypertension for more than 5 years and 31% had previously received 2 antihypertensive medications. With this combination treatment, almost all patients

TABLE II. Incidence of Adverse Events

	T80/A10 SPC (n=421)	T80 (n=217)	A10 (n=220)
Any adverse event, No. (%)	138 (32.8)	72 (33.2)	73 (33.2)
Severe adverse events, No. (%)	8 (1.9)	1 (0.5)	4 (1.8)
Drug-related adverse events, No. (%)	53 (12.6)	15 (6.9)	36 (16.4)
Other significant adverse events, No. (%)[a]	7 (1.7)	5 (2.3)	6 (2.7)
Adverse events leading to discontinuation, No. (%)	9 (2.1)	6 (2.8)	7 (3.2)
Serious adverse events, No. (%)	3 (0.7)	2 (0.9)	2 (0.9)

Abbreviations: A10, amlodipine 10 mg; SPC, single-pill combination; T80, telmisartan 80 mg; T80/A10, telmisartan 80 mg/amlodipine 10 mg.
[a]Adverse events that resulted in dose reductions or withdrawal of study treatment that were not serious adverse events.

(99.7%) had an SBP response and, importantly, more than 50% of patients with SBP/DBP ≥180/95 mm Hg achieved the BP target of <140/90 mm Hg after 6 weeks with the high-dose combination of T80/A10. More patients reached target SBP and/or DBP goals with the T80/A10 SPC than with either T or A monotherapy (where 24% and 36% reached BP <140/90 mm Hg).

The significant difference between the combination and monotherapies, in terms of mean change in seated trough cuff SBP, was observed within 1 week of treatment, which is crucial to reduce CV risk in patients with substantially elevated BP (ie, SBP/DBP ≥180/95 mm Hg). Significant reductions with the combination compared with monotherapy were maintained throughout the study, with 80% of the maximum effect achieved after 2 weeks of treatment with T80/A5. The importance of rapid BP reductions in terms of improving CV outcome was shown in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) study, where amlodipine was more effective in reducing BP in the early phases of treatment and where higher odds ratios in favor of amlodipine were noted for all end points during the first 6 months of the study.[30,31]

Hypertension is particularly prevalent in some patient populations, such as elderly, obese, or black patients.[32–34] It is also associated with a greater CV risk in patients with diabetes or renal disease.[2–4] Thus, subgroup analyses have been performed to investigate whether the treatment effect in these subpopulations is consistent with the overall treatment effect. Efficacy with T/A SPC tended to be greater than the monotherapies in all subgroups but the differences were not large enough to reach significance. However, as the study was not powered for subgroup analysis, no definite conclusions can be drawn. No treatment-by-subgroup interaction in any at-risk subpopulation was found, except in patients with T2DM (P=.0164), which may be due to the small number of patients in this subgroup. These results suggest that the T/A SPC is similarly effective across relevant subpopulations.

The findings from the current study are in line with previous studies with T plus A combinations in other hypertensive populations. Littlejohn and colleagues found that using a combination of T40–80/A5–10 was associated with statistically and clinically significantly greater reductions in SBP/DBP than either monotherapy alone, in patients with stage 1 and 2 hypertension.[35,36] In addition, the incidence of peripheral edema was shown to be lower with the combination compared with amlodipine monotherapy. Furthermore, 24-hour ambulatory BP goal (<130/80 mm Hg) achievement was significantly higher in patients treated with T80/A10 than with A10 (82.7% of vs 37.9%; P<.0001).[37] The T/A combination also resulted in similar BP reductions to those seen with triple therapy with valsartan/amlodipine/hydrochlorothiazide.[38] The large and prompt BP reductions observed with T/A SPC will help patients achieve target BP and reduce the risk for CV morbidity and mortality.

The safety profile of the T80/A10 SPC was comparable to that of its respective components and was similar to those reported in previous T80/A10 combination studies.[35,36] In the current study, the T80/A10 SPC was associated with peripheral edema rates of 9.3%, compared with 13.2% with A10 monotherapy and an incidence of headaches of 1.0% (compared with 2.3% with T80 alone). Although 3 serious adverse events (one in each treatment group) were felt to be treatment related, these may in part have been caused by the underlying condition of hypertension.

CONCLUSIONS

The study shows that the T/A SPC is superior in reducing trough cuff BP after 1 week of treatment, an effect that was maintained throughout the 8-week study as compared with the respective monotherapies. In severe hypertensive patients, mean BP reductions were 47.5 mm Hg, with 80% of the maximum effect achieved after 2 weeks. Overall, 99% of patients responded to the combination therapy and, importantly, >50% achieved a BP goal of <140/90 mm Hg after 8 weeks of treatment. The safety and tolerability profiles of the T/A SPC in patients with severe systolic hypertension (SBP/DBP ≥180/95 mm Hg) were similar to that seen in previous studies in other populations with this combination and is consistent with the well-established safety profile of the individual components. In conclusion, T/A is an effective treatment option in this rather difficult-to-treat population and may contribute to the principle long-term objective

of antihypertensive therapy and prevention of CV morbidity and mortality.

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Appendix

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