

# Single-Pill Combination of Telmisartan/Amlodipine Versus Amlodipine Monotherapy in Diabetic Hypertensive Patients: An 8-Week Randomized, Parallel-Group, Double-Blind Trial

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## ABSTRACT

**Background:** Hypertensive patients with diabetes often require combination therapy to achieve a blood pressure (BP) goal, and evidence suggests that time to BP goal is crucial to decrease cardiovascular risk.

**Objective:** The aim of the study was to investigate whether the single-pill combination of telmisartan and amlodipine was superior to amlodipine alone as initial antihypertensive therapy in patients with diabetes and hypertension.

**Methods:** An 8-week, randomized, parallel-group, double-blind international trial comparing the once-daily single-pill combination of telmisartan 80 mg and amlodipine 10 mg (T/A; n = 352) with once-daily amlodipine 10 mg (A; n = 354) in patients with type 2 diabetes mellitus and stage 1 or 2 hypertension (systolic BP [SBP] >150 mm Hg).

**Results:** Patient demographics were similar between treatment groups, with an mean (SD) age of 60.5 (10.1) years; 51.7% were male, the mean (SD) body mass index was 32.0 (6.1) and the mean (SD) duration of hypertension was 8.8 (7.9) years. After 8 weeks (primary end point) as well as after 1, 2, and 4 weeks (key secondary end points), significantly greater decreases in the in-clinic mean seated trough cuff SBP with T/A versus A were achieved (−29.0 mm Hg vs −22.9 mm Hg at 8 weeks;  $P < 0.0001$ ). After 8 weeks, 71.4% versus 53.8% of patients achieved the BP goal (<140/90 mm Hg) with T/A versus A, with mean SBPs of 131.9 and 137.9 mm Hg, respectively. Similar results were observed in the obese (metabolic syndrome) subpopulation. The more stringent goal (<130/80 mm Hg) was achieved by 36.4%

and 17.9% patients in the T/A and A groups, respectively. The most common adverse events were peripheral edema, headache, and dizziness.

**Conclusions:** In this selected population of patients with diabetes and hypertension, T/A provided prompt and greater BP decreases compared with A monotherapy, with the majority of patients achieving the BP goal (<140/90 mm Hg). (*Clin Ther.* 2012;34:537–551) © 2012 Elsevier HS Journals, Inc. All rights reserved.

**Key words:** hypertension, metabolic syndrome, obesity, single-pill combination, telmisartan/amlodipine, type 2 diabetes mellitus.

## INTRODUCTION

Hypertension, a major risk factor for cardiovascular (CV) and cerebrovascular morbidity and mortality,<sup>1</sup> is a highly prevalent disease in all age groups.<sup>2,3</sup> Epidemiologic studies and clinical trials have provided clear evidence in support of rigorous control of blood pressure (BP), and national/international guidelines are in general agreement regarding their recommendations, although differences do exist.<sup>4–7</sup> However, in the United States, Canada, and many European countries, despite clear rec-

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ommended BP targets, patients remain untreated, or, if treated, their BP is poorly controlled.<sup>5,8–11</sup>

The management of hypertension is often complicated by the presence of additional CV risk factors or comorbidities such as type 2 diabetes mellitus (T2DM) and obesity.<sup>6</sup> Evidence from the United Kingdom Prospective Diabetes Study (UKPDS) showed that decreases in BP lowered the rate of diabetes-related mortality and morbidity,<sup>12</sup> and, therefore, more aggressive BP targets have traditionally been recommended for patients with T2DM.<sup>4,6</sup> However, more recent trial results have led to a reappraisal of the limited clinical trial evidence.<sup>13</sup> Revised European recommendations now state that systolic BP (SBP) should be lowered to well below 140 mm Hg in patients with diabetes<sup>7</sup> rather than trying to reach the goal of <130/80 mm Hg previously recommended. These recommendations have been supported by the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial.<sup>14</sup>

Although treatment for hypertension is often initiated with a single agent, it is now generally accepted that the majority of patients will require combination therapy to reach their BP goal quickly.<sup>7</sup> Both the time to BP goal and the BP goal itself are considered independent CV risk factors; therefore, fast and sustained attainment of BP goal is of the utmost importance to decrease CV risk. Indeed, US and European guidelines now recommend initial combination therapy for patients whose BP is substantially higher than the goal BP or those with lower BP targets.<sup>4,6,7</sup> By combining drugs with complementary mechanisms of action, more patients may reach their BP goal earlier, which decreases their individual CV risk.<sup>7</sup> Combining 2 drugs, such as telmisartan and amlodipine with well-established 24-hour BP efficacy<sup>15</sup> as well as clinical evidence of CV risk decrease independent of BP,<sup>16</sup> should be considered in added-risk hypertensive patients, such as those patients with diabetes, obesity, or a combination of the 2, ie, metabolic syndrome (MS).

Telmisartan, an angiotensin II receptor blocker (ARB), decreases BP by selectively blocking the AT<sub>1</sub> receptor of the renin-angiotensin system (RAS). Telmisartan has a favorable pharmacokinetic profile with a long plasma elimination half-life and highest lipophilicity in its class, thus determining deep penetration in tissues, ie, a high volume of distribution.<sup>17</sup> It has been reported not only to decrease BP effectively,<sup>18–20</sup> but also to lower the CV risk independent of BP.<sup>16</sup>

Telmisartan, in combination with the calcium channel blocker (CCB) amlodipine, has been reported to be superior to respective monotherapy in a wide range of patients at all stages of hypertension, as well as in subpopulations such as added-risk patients with obesity, diabetes, or MS,<sup>15,21–28</sup> and better tolerated than high-dose amlodipine monotherapy.<sup>27</sup>

The aim of this current clinical trial, the Telmisartan/Anlodipine Single-Pill Study Versus Amlodipine as first-line therapy in patients with stage 1 or 2 hypertension and T2DM (TEAMSTA diabetes), was to investigate the efficacy and safety profile of telmisartan/amlodipine (T/A) single-pill combination (SPC) in added-risk patients with diabetes and hypertension compared with amlodipine (A) monotherapy.

## MATERIALS AND METHODS

### Study Design

This was an 8-week, randomized, parallel-group, double-blind, international trial that evaluated the efficacy and safety profile of the T/A SPC compared with A (trial registration: NCT00877929). Patients were recruited from 64 trial centers in 9 countries (Argentina, Republic of Korea, Mexico, the Netherlands, Slovakia, South Africa, Spain, Sweden, and the United States). The trial was approved by each participating country's health authority and institutional review board or an independent ethics committee and conducted in accordance with the principles laid down in the Declaration of Helsinki. Each patient or their legally accepted representative provided written informed consent at screening, before any study procedures were undertaken.

After screening, all patients underwent a 14- to 21-day, single-blind, placebo run-in period, and eligible patients were then randomized to 1 of 2 treatment groups in a 1:1 ratio, either T/A SPC or A alone. Patients were initially treated with SPC T 80 mg/A 5 mg once daily or A 5 mg for the first 2 weeks and were then up-titrated to T 80 mg/A 10 mg once daily or A 10 mg once daily for an additional 6 weeks of treatment. The trial drug was provided as 2 tablets and 2 capsules to be administered orally, once daily with water, in the morning at 9 AM ( $\pm$ 1 hour), and it could be taken with or without food. If the patient missed a dose, he or she was instructed to skip that dose and take the next dose as scheduled. The study included an ambulatory BP monitoring (ABPM) substudy.

## Patients

The study participants were men and women  $\geq 18$  years of age with diagnosed T2DM and stage 1 or 2 hypertension based on a mean in-clinic seated cuff SBP  $> 150$  mm Hg. Patients with type 1 diabetes mellitus or in whom diabetes was not stable and controlled for at least the previous 3 months ( $\text{HbA}_{1\text{C}} > 10\%$ ), prespecified renal or hepatic disorders, congestive heart failure (New York Heart Association functional class III or IV), clinically relevant cardiac arrhythmias as determined by the investigator, severe obstructive coronary artery disease (CAD), or any other condition that would not allow safe completion of the protocol were excluded, as were nightshift workers and pregnant or nursing women or women of childbearing age not using a medically approved means of contraception. Patients with a contraindication to a placebo run-in period, patients treated with any investigational drug therapy within 1 month of signing the informed consent, those who had previously experienced symptoms characteristic of angioedema during treatment with angiotensin-converting enzyme (ACE) inhibitors or ARBs, those with a history of drug or alcohol dependency within 6 months before signing the informed consent form, and those with known hypersensitivity to any component of the study drugs were excluded from the study. Patients with a history of noncompliance or inability to comply with prescribed medications or protocol procedures and any other clinical condition that, in the opinion of the investigator, would not allow safe completion of the protocol and safe administration of telmisartan and amlodipine were not permitted to enter the study.

A protocol amendment, approved on September 25, 2009, included the addition of an ABPM substudy to provide a better understanding of the 24-hour BP profile and goal attainment of this patient population. All patients admitted into the trial after the protocol amendment was approved participated in the ABPM substudy. These patients met the same inclusion and exclusion criteria as patients previously admitted into the trial.

## Medication Restrictions

Concomitant administration of any medication known to affect BP was not permitted during the trial.

## Efficacy Assessments

Seated trough cuff BP was measured before randomization (screening). Seated and standing trough cuff BP was measured at randomization (baseline measurement) and after 1, 2, 4, 6, and 8 weeks. BP was taken at 9 AM ( $\pm 1$  hour) and before administration of the study drug. BP was measured with standard calibrated BP measuring equipment and recorded to the nearest 2 mm Hg. BP measurements were performed on the same arm and preferably by the same person at all study visits. After a 5-minute rest in the seated position, 3 BP measurements were taken 2 minutes apart. Patients then had their BP taken within 1 minute of quiet standing. Only 1 standing BP measurement was taken.

ABPM equipment was provided by Medifacts International Inc. (Rockville, Maryland). Starting in the morning at 9 AM ( $\pm 1$  hour), 24-hour BP measurements were taken at baseline and at day 57 using the validated and calibrated SpaceLabs Model 90207 monitor (SpaceLabs Medical Equipment Inc., Issaquah, Washington). Measures were taken every 20 minutes throughout the day and night and analyzed using Web-Heart ABPM software (CoreLab Partners Inc., Princeton, New Jersey).

The primary end point was the change from baseline in mean seated trough cuff SBP after 8 weeks of treatment. The key secondary efficacy end point was a change from baseline in mean seated trough cuff SBP after 1, 2, 4, 6, and 8 weeks of treatment.

Additional secondary end points included a change from baseline in mean seated trough cuff diastolic BP (DBP) after 1, 2, 4, 6, and 8 weeks of treatment as well as SBP and BP goal attainment ( $< 140$  mm Hg,  $< 140/90$  mm Hg,  $< 130/80$  mm Hg), response rates (130 mm Hg or a decrease of  $\geq 10$  mm Hg or 140 mm Hg or a decrease of  $\geq 10$  mm Hg), and a change from baseline in the urine albumin: creatinine ratio (UACR), measured in spot urine) after 8 weeks of treatment. For the ABPM substudy, the secondary end points included (1) a change from baseline in the 24-hour ABPM mean (relative to dose time) for SBP after 8 weeks of treatment; (2) changes from baseline in DBP and SBP hourly means over the 24-hour dosing interval as measured by ABPM after 8 weeks of treatment; and (3) proportion of patients achieving 24-hour study targets of mean SBP/DBP  $< 130/80$  mm Hg and  $< 120/80$  mm Hg as assessed by ABPM after 8 weeks of treatment. Prespecified subgroup analyses of SBP by sex, age, race,

body mass index (BMI), and baseline SBP category were conducted.

### Safety Profile and Tolerability

All adverse events that occurred after the patient signed the informed consent were recorded. Any adverse events that were present at the time that the patient discontinued participation in the trial were followed until the event was resolved or for a period of time agreed on by the investigator and the Boehringer Ingelheim clinical monitor. Pulse rate was measured as beats per minute in the clinic at every visit along with the BP measurements. Laboratory tests, including hematology, serum chemistry, and urinalysis, were conducted at screening in a nonfasted state and in a fasted state at randomization and at the end-of-trial visit or at early termination. All specimens were analyzed by a central laboratory to ensure standardization in laboratory parameters. Laboratory samples were obtained at the study site, packaged, and transferred to the central laboratory in accordance with instructions provided in the country-specific laboratory manual. All discrepancies were queried, and policies were specified to ensure that accurate, timely, and consistent clinical data were transmitted. Laboratory data were transmitted directly from the central laboratory and uploaded to the Boehringer Ingelheim trial database. The central laboratory trial data manager identified and documented the study data transmittal process requirements. Twelve-lead standard electrocardiography was performed on all patients at screening and at the end-of-trial visit. All incidences of peripheral edema were recorded as adverse events. Orthostatic changes in SBP and DBP were measured at randomization through to the end-of-trial visit (calculated for both SBP and DBP as the mean seated BP at a particular visit subtracted from the first standing BP at the same visit). Patients were instructed to bring all study drugs to each clinic visit, and compliance was assessed by physical count of returned study drug at each visit.

### Statistical Analysis

The primary and key secondary end points were analyzed using a restricted maximum likelihood-based repeated-measures approach, using all available longitudinal observations at each visit during the maintenance phase. Significance tests were based on least squares means using a 2-sided 0.05 level of significance.<sup>29</sup> The 2-sided 95% CIs for the least squares

mean differences in between-treatment effects evaluated as the changes from baseline for each of the respective time points were computed based on the *t* distribution and presented along with the level of significance (*P* value).<sup>29</sup>

The primary and key secondary analyses of the change from baseline in mean seated trough cuff SBP were performed on the treated set, which included all randomized patients who took at least 1 dose of study drug. Summary statistics were calculated for each of the secondary response variables of BP control, SBP control, SBP response, and normal BP after 1, 2, 4, 6, and 8 weeks of treatment. However, no formal significance testing was planned to evaluate the treatment effects on the results for these response variables. The comparison of obese and nonobese subpopulations was performed in a prespecified subgroup analysis.

Evaluation of the safety profile was performed on all patients who received at least 1 dose of randomized treatment. In general, safety profile analyses were descriptive in nature.

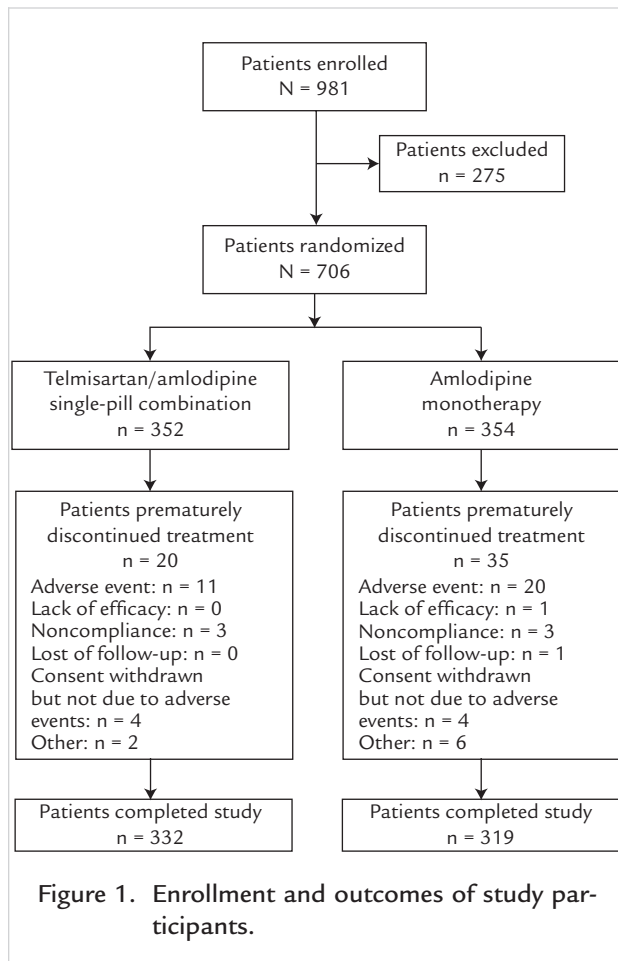
## RESULTS

### Patients

A total of 981 patients were enrolled in the study from February 2009 to May 2010, with 706 being randomized to 1 of 2 treatment groups: 352 to receive T/A SPC and 354 to receive A (Figure 1). There were no significant differences between the 2 treatment groups at baseline (Table I). The baseline BP was 160.8/91.0 mm Hg and 57.5% of patients were obese. The efficacy and safety profile analyses were performed on the treated set, which consisted of all patients who took at least 1 dose of the randomized treatment (*n* = 706). The ABPM dataset consisted of 132 patients (18.7%): 68 (19.3%) in the T/A SPC group and 64 (18.1%) in the A group. The mean treatment compliance rate was 98.1%, with no appreciable differences between the 2 treatment groups. A total of 55 patients (7.8%) discontinued the study treatment prematurely: 20 (5.7%) in the T/A SPC group and 35 (9.9%) in the A group. The main reason for premature treatment discontinuation in both groups was adverse events (overall, 4.4%; T/A, 3.1%; A, 5.6%). A total of 651 patients (92.2%) completed the 8-week trial.

### Efficacy Assessments

Treatment with T/A SPC for 8 weeks provided a significantly greater decrease in the primary efficacy



end point of in-clinic mean seated trough cuff SBP compared with A monotherapy ( $-29.0$  vs  $-22.9$  mm Hg;  $P < 0.0001$ ). Significant decreases were evident from week 1 ( $P < 0.0001$ ) and continued throughout the study (Figure 2).

Patients treated with T/A SPC in each of the baseline SBP categories had greater decreases in in-clinic mean seated trough cuff SBP from baseline to week 8 than those treated with A monotherapy (Figure 3).

A greater proportion of patients achieved the BP ( $<140/90$  mm Hg) and SBP ( $<140$  mm Hg) goal with T/A SPC compared with A 10 mg alone. At week 2, 54.6% and 57.3% of patients treated with T 80 mg/A 5 mg compared with 30.2% and 32.8% of patients treated with A 5 mg achieved the BP goal and SBP goal, respectively. At week 8, 71.4% and 73.2% of patients treated with T/A SPC compared with 53.8% and 56.8% of patients treated with A monotherapy achieved the BP goal and SBP goal, respectively. In terms of the more stringent BP goal of  $<130/80$  mm Hg, 17.2% of

patients treated with T 80 mg/A 5 mg compared with 6.7% of patients treated with A 5 mg achieved this goal by week 2. At week 8, the rates were greater: 36.4% of patients treated with T/A SPC compared with 17.9% of patients treated with A monotherapy. After 2 weeks of treatment with T 80 mg/A 5 mg, 88.1% of patients achieved an SBP response ( $<140/90$  mm Hg or  $\geq 10$  mm Hg decrease) compared with 72.1% of patients treated with A 5 mg. After 8 weeks of treatment with T/A SPC, 93.1% of patients achieved an SBP response ( $<140/90$  mm Hg or  $\geq 10$  mm Hg decrease) compared with 87.5% of patients treated with A alone.

Patients treated with T/A SPC for 8 weeks experienced greater decreases in DBP from baseline than those treated with A monotherapy ( $-12.5$  vs  $-10.5$  mm Hg, respectively). The differences between the 2 treatment groups were evident after week 1 ( $-7.1$  vs  $-5.0$  mm Hg), and the effect was maintained over the 8-week treatment period.

Patients in the T/A SPC group had a geometric mean decrease in UACR from 2.00 to 1.60 mg/g (baseline vs end of trial [8 weeks]), approximately 70% of baseline, whereas those in the A monotherapy group remained at a similar level (2.10–2.14 mg/g).

The 24-hour ABPM substudy was conducted in 132 patients (68 patients in the T/A SPC group and 64 patients in the A group). A 24-hour profile of mean SBP and DBP at baseline and at the end of study for both groups is presented in Figure 4A. At baseline, the mean 24-hour SBP was 144.7 mm Hg in the T/A SPC group and 145.8 mm Hg in the A 10 mg group. After 8 weeks of treatment, the mean 24-hour SBP had decreased to 128.3 mm Hg in the T/A SPC group and to 134.1 mm Hg in the A group. For DBP, the 24-hour mean at baseline was 81.6 mm Hg in the T/A SPC group compared with 85.0 mm Hg in the A group. After 8 weeks of treatment, the mean 24-hour DBP had decreased to 72.8 mm Hg in the T/A SPC group and to 78.3 mm Hg in the A group. The mean change in BP from baseline to week 8, when adjusted for baseline, was statistically greater in the T/A SPC group for both SBP ( $P = 0.0044$ ) and DBP ( $P = 0.0004$ ) compared with A alone. The proportion of patients who achieved a mean 24-hour BP of  $<130/80$  mm Hg was greater in the T/A SPC group than in the A group (52.9% vs 39.1%, respectively). Similar patterns were seen for mean daytime and nighttime BP.

The majority of patients were overweight or obese, with 33.6% ( $n = 237$ ) and 57.5% ( $n = 406$ ) having a BMI of 25 to  $<30$  kg/m<sup>2</sup> and  $\geq 30$  kg/m<sup>2</sup>,

Table 1. Baseline demographics and clinical characteristics of the patient population (N = 706) randomized to receive either 8 weeks of treatment with T/A or A alone.

	T/A	A	Total
No. of patients	352	354	706
Sex, n (%)			
Male	180 (51.1)	185 (52.3)	365 (51.7)
Female	172 (48.9)	169 (47.7)	341 (48.3)
Age, y, mean (SD)	60.5 (10.4)	60.5 (9.7)	60.5 (10.1)
<65	214 (60.8)	235 (66.4)	449 (63.6)
≥65	138 (39.2)	119 (33.6)	257 (36.4)
Ethnicity, n (%)			
Black	43 (12.2)	41 (11.6)	84 (11.9)
Non-black	309 (87.8)	313 (88.4)	622 (88.1)
BMI, kg/m <sup>2</sup> , mean (SD)	32.1 (6.0)	31.8 (6.1)	32.0 (6.1)
<25	32 (9.1)	31 (8.8)	63 (8.9)
25 to <30	114 (32.4)	123 (34.7)	237 (33.6)
≥30	206 (58.5)	200 (56.5)	406 (57.5)
Smoking history, n (%)			
Never smoked	221 (62.8)	222 (62.7)	443 (62.7)
Ex-smoker	91 (25.9)	89 (25.1)	180 (25.5)
Currently smokes	40 (11.4)	43 (12.1)	83 (11.8)
Duration of hypertension, y, mean (SD)	8.8 (7.8)	8.9 (8.1)	8.8 (7.9)
Previous antihypertensive therapy, n (%)			
0	21 (6.0)	23 (6.5)	44 (6.2)
1	123 (34.9)	119 (33.6)	242 (34.3)
2*	131 (37.2)	132 (37.3)	263 (37.3)
3*	58 (16.5)	65 (18.4)	123 (17.4)
≥4*	19 (5.4)	15 (4.2)	34 (4.8)
Duration of diabetes, y, n (%)			
<1	48 (13.6)	45 (12.7)	93 (13.2)
1-5	163 (46.3)	160 (45.2)	323 (45.8)
6-10	75 (21.3)	87 (24.6)	162 (22.9)
>10	66 (18.8)	62 (17.5)	128 (18.1)
Baseline BP, mm Hg, mean (SD) <sup>†</sup>			
SBP	160.7 (7.8)	160.8 (7.9)	160.8 (7.8)
DBP	90.5 (8.3)	91.4 (7.8)	91.0 (8.0)

A = amlodipine 10 mg; BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; T/A = telmisartan 80 mg plus amlodipine 10 mg.

\*Combination medications were counted once for each active ingredient in the combination.

<sup>†</sup>T/A, n = 344; A, n = 345; overall, N = 689 for baseline BP measurements.

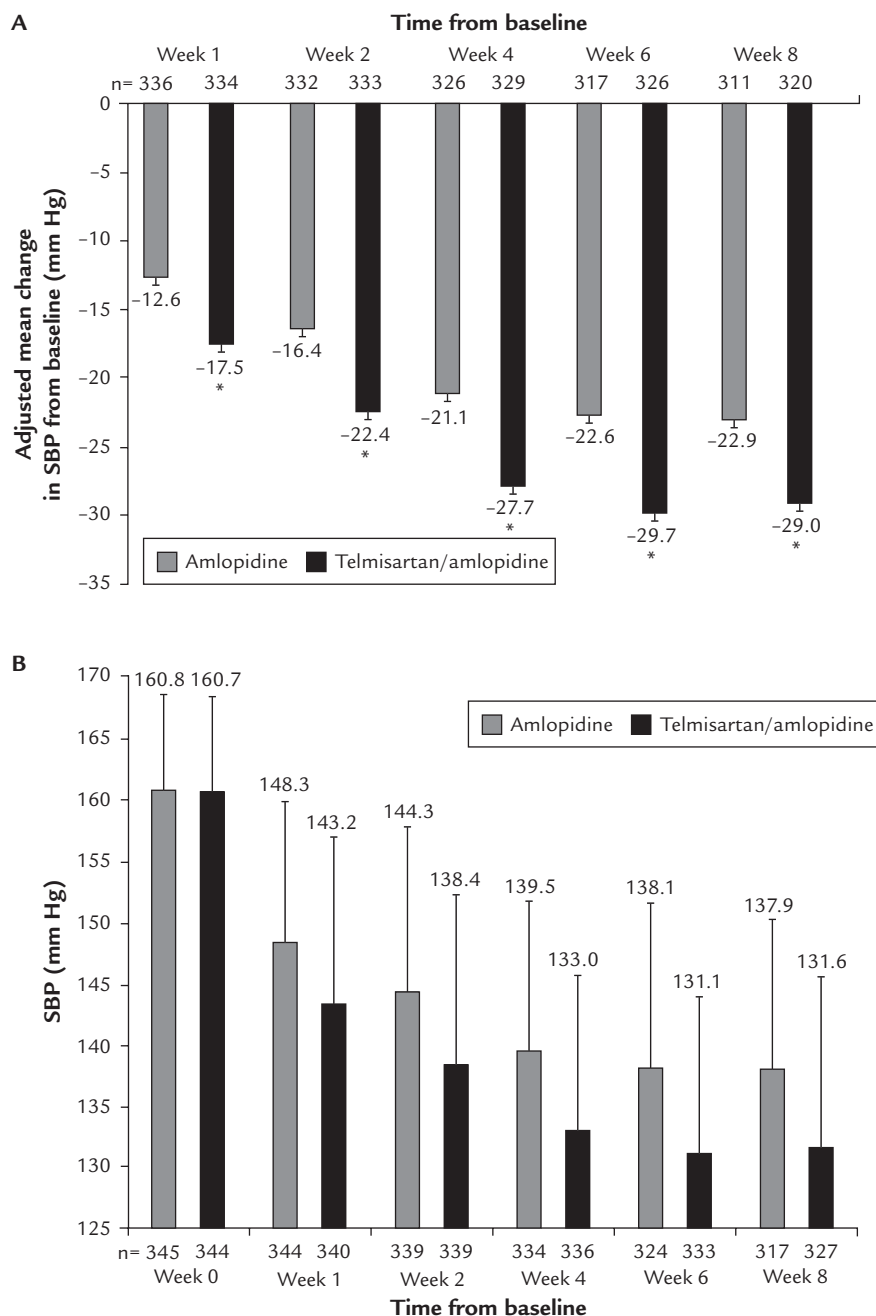


Figure 2. The least squares mean decreases in the in-clinic seated trough cuff systolic blood pressure (SBP) (mm Hg) over 8 weeks of treatment with telmisartan 80 mg plus amlodipine 10 mg compared with amlodipine 10 mg alone. (A) Reduction from baseline (SE). (B) In-clinic seated trough cuff mean (SD) SBP. Mean is adjusted for baseline as a covariate. Amlodipine 5 mg and telmisartan 80 mg/amlodipine 5 mg for the first 2 weeks. \* $P < 0.0001$  for amlodipine 10 mg versus telmisartan 80 mg/amlodipine 10 mg at each point.

respectively (Table I). When patients were stratified as nonobese (BMI  $< 30$  kg/m<sup>2</sup>) or obese (BMI  $\geq 30$  kg/m<sup>2</sup>) to treatment with T/A SPC for 8 weeks, mean

SBP decreases were significantly greater than with A alone in both groups of patients (Table II) (obese,  $P < 0.0001$ ; nonobese,  $P = 0.0002$ ). BP goal

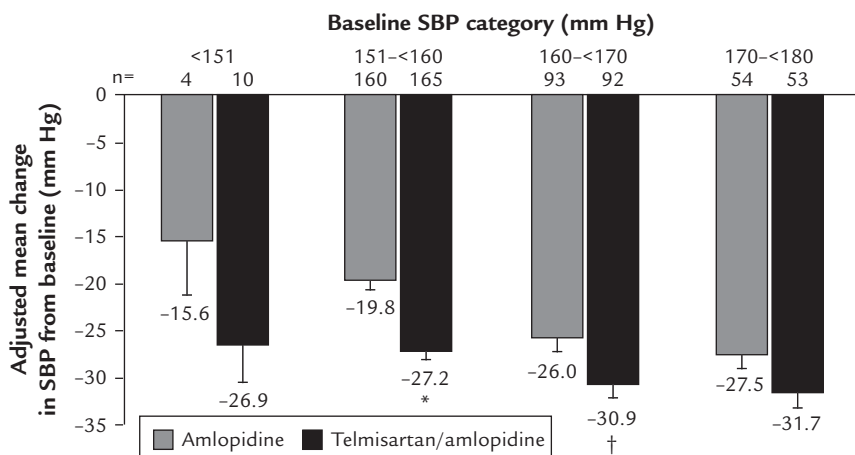


Figure 3. The least squares mean decreases in the in-clinic seated trough cuff systolic blood pressure (SBP) (mm Hg) over 8 weeks of treatment with telmisartan 80 mg plus amlodipine 10 mg compared with amlodipine 10 mg alone. (A) Reduction from baseline (SE). (B) In-clinic seated trough cuff mean (SD) SBP. Mean is adjusted for baseline as a covariate. Amlodipine 5 mg and telmisartan 80 mg/amlodipine 5 mg for the first 2 weeks.

Adjusted for baseline as a covariate.

\* $P < 0.0001$  for amlodipine versus telmisartan/amlodipine.

† $P < 0.01$ .

(BP <140/90 mm Hg), SBP goal (SBP <140 mm Hg), and an SBP response (<140/90 mm Hg or  $\geq 10$  mm Hg decrease) was achieved by a greater proportion of patients treated for 8 weeks with T/A SPC compared with A monotherapy in both the obese and nonobese groups (Table II).

### Safety Profile Assessments

A total of 293 patients (41.5%) experienced an adverse event: 147 (41.8%) in the T/A SPC group and 146 (41.2%) in the A monotherapy group. The majority of adverse events were mild or moderate in intensity. Severe adverse events, as determined by the investigator, were reported in 4 patients (1.1%) and 10 (2.8%) patients in the T/A SPC and the A groups, respectively. These were dyslipidemia, peripheral edema, hyponatremia, and flank pain in the T/A SPC group and severe cardiac failure, peripheral edema, myocardial infarction, bronchitis, nasopharyngitis, pneumonia, hypokalemia, back pain, muscle spasms, and major depression in the A group.

The most common adverse events in both treatment groups were peripheral edema (T/A, 17.6%; A, 20.1%), headache (T/A, 2.0%; A 10 mg, 2.5%), and dizziness (T/A, 2.3%; A, 1.1%). Patients reported the

first onset of peripheral edema twice as frequently when they were being treated with A 10 mg than with A 5 mg, either as monotherapy or in combination with telmisartan. The majority of cases of peripheral edema were mild (T/A, 15.9%; A 10 mg, 15.5%) and most patients who prematurely discontinued the study did so because of peripheral edema (T/A, 1.4%; A, 2.8%). Hypotension and orthostatic hypotension were each reported in 2 patients in the T/A group (0.6% each) compared with none treated with A alone (Table III).

A total of 141 patients (20.0%) experienced drug-related adverse events: 69 (19.6%) in the T/A SPC group and 72 (20.3%) in the A monotherapy group. Peripheral edema (17.6% and 20.1%) and joint swelling (0.3% and 1.1%) were the only drug-related adverse events that were reported in  $\geq 1\%$  of patients in the T/A and A groups, respectively. There was a numerical difference between the 2 groups in the incidence of drug-related peripheral edema (14.2% and 15.3% in T/A and A groups, respectively).

The incidence of serious adverse events was rare; 3 (0.9%) in the T/A group compared with 4 (1.1%) in the A group. These were ulcer, lower limb fracture, hyperglycemia, and arteriosclerosis in the T/A SPC group and anemia, cardiac failure, myocardial



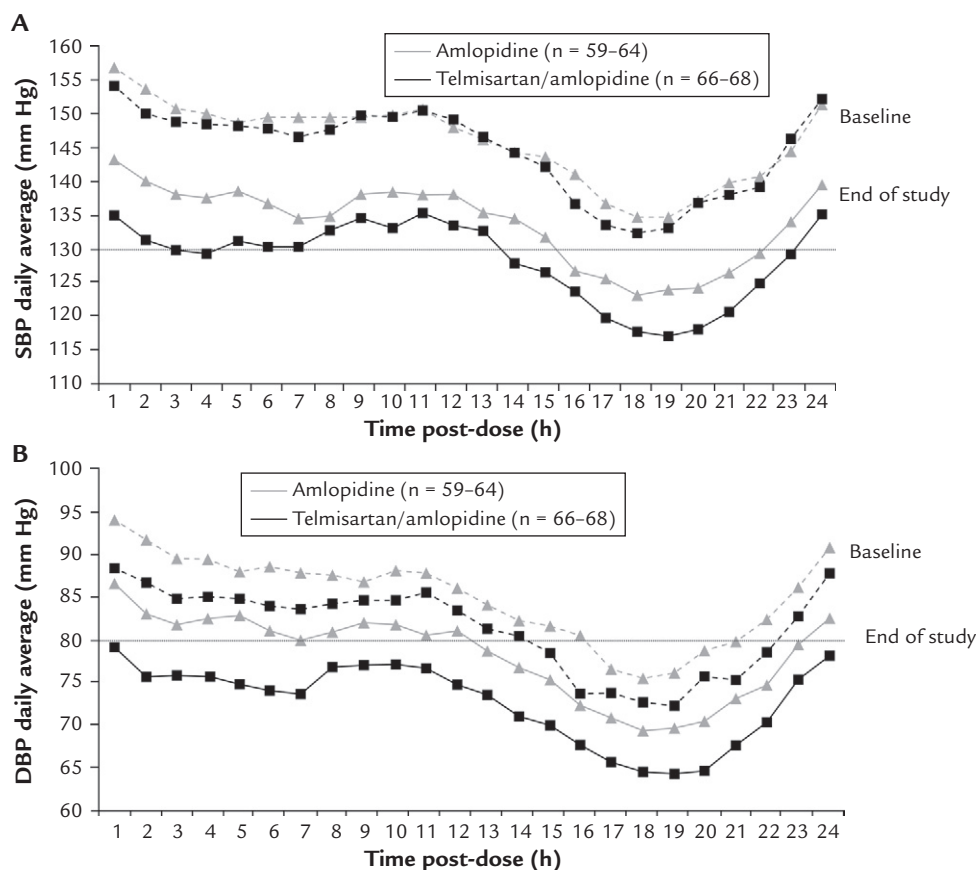


Figure 4. The 24-hour blood pressure (BP) profiles from the ambulatory BP monitoring substudy: systolic BP (SBP) (A) and diastolic BP (DBP); (B) telmisartan 80 mg plus amlodipine 10 mg.

infarction, hepatitis alcoholic, hypokalemia, T2DM, and depression and major depression. Two patients discontinued study treatment due to 1 or more serious adverse events. None of the serious adverse events were considered to be related to the study drug. One female patient in the A group died as a result of hypokalemia associated with a previously undiagnosed bronchus carcinoma, but it was not considered to be related to the study drug.

There were no clinically relevant changes on electrocardiography, in pulse rate, or in routine laboratory test results from baseline to study end; any laboratory test result changes were consistent with this patient population.

## DISCUSSION

In this double-blind, randomized, controlled study, we observed significant in-clinic mean seated trough SBP

decreases after 8 weeks of treatment with the T/A SPC in a population of 706 patients with T2DM and stage 1 or 2 hypertension ( $-29.0$  mm Hg vs  $-22.9$  mm Hg for A alone;  $P < 0.0001$ ). Our findings were consistent with those observed in a previous large randomized  $4 \times 4$  factorial study of the T/A combinations, in which 8 weeks of treatment with T/A resulted in a significant mean decrease in SBP of  $-26.4$  mm Hg compared with both monotherapies in patients with stage 1 or 2 hypertension ( $P < 0.05$ ).<sup>22</sup> In addition, a predefined subanalysis of this large factorial study indicated that the T/A combination was as effective in the T2DM subpopulation compared with the nondiabetic population (mean seated trough SBP decrease of  $-29.1$  mm Hg compared with  $-25.1$  mm Hg, respectively).<sup>24,28</sup> Similar changes were observed for the mean seated trough DBP in the diabetic and nondiabetic subpopulations (mean seated trough DBP

Table II. Outcomes for the prespecified analysis of the subpopulation obese versus nonobese patients.

	Obese (BMI $\geq 30$ kg/m <sup>2</sup> )		Nonobese (BMI $< 30$ kg/m <sup>2</sup> )	
	T/A	A	T/A	A
No.	198	183	134	146
Mean change in SBP, mm Hg*	-28.4 <sup>†</sup>	-21.7	-29.9 <sup>‡</sup>	-24.5
BP goal, %	68.2	48.1	76.1	61.0
SBP goal, %	71.2	51.4	76.1	63.7
SBP response, %	92.9	86.9	93.3	88.4

A = amlodipine 10 mg; BMI = body mass index; BP = blood pressure; SBP = systolic blood pressure; T/A = telmisartan 80 mg plus amlodipine 10 mg.

BP goal  $< 140/90$  mm Hg; SBP goal  $< 140$  mm Hg; SBP response = SBP  $< 140$  mm Hg or  $\geq 10$  mm Hg decrease.

\*Adjusted for baseline as a covariate.

<sup>†</sup> $P < 0.0001$  for T/A versus A.

<sup>‡</sup> $P = 0.0002$  for T/A versus A.

decrease of  $-20.2$  mm Hg compared with  $-19.4$  mm Hg, respectively).<sup>24,28</sup>

Significant decreases were observed in the in-clinic mean seated trough SBP and DBP as early as week 1 ( $P < 0.0001$ ), suggesting a prompt onset of action by the SPC. This is highly relevant because several outcome trials<sup>30-32</sup> reported that regimens lowering BP more rapidly are more effective in decreasing the risk of major CV events, and the time to BP control is considered an independent CV risk factor.

Although decreasing the BP lowers CV risk, it is also important to reach and maintain the appropriate BP target for the respective patient.<sup>7</sup> Although, for the time being, some guidelines still recommend lower trough cuff office BP targets of  $< 130/80$  mm Hg for hypertensive patients with diabetes, there is increasing evidence that not all of these patients benefit from such lower targets.<sup>13,14</sup> In this study, more patients treated with T/A SPC achieved the BP goal ( $< 140/90$  mm Hg) and SBP goal ( $< 140$  mm Hg) compared with patients

Table III. Summary of the adverse events experienced by study participants treated with either 8 weeks of treatment with T/A or A alone.

	T/A (n = 352)	A (n = 354)	Total (N = 706)
Any adverse event, n (%)	147 (41.8)	146 (41.2)	293 (41.5)
Severe adverse events, n (%)	4 (1.1)	10 (2.8)	14 (2.0)
Drug-related adverse events, n (%)	69 (19.6)	72 (20.3)	141 (20.0)
Peripheral edema, n (%)	62 (17.6)	71 (20.1)	133 (18.8)
Mild	56 (15.9)	55 (15.5)	111 (15.7)
Moderate	5 (1.4)	14 (4.0)	19 (2.7)
Severe	1 (0.3)	2 (0.6)	3 (0.4)
Adverse events leading to discontinuation, n (%)	10 (2.8)	19 (5.4)	29 (4.1)
Discontinuations due to peripheral edema, n (%)	5 (1.4)	10 (2.8)	15 (2.1)
Serious adverse events, n (%)	3 (0.9)	4 (1.1)	7 (1.0)

A = amlodipine 10 mg; T/A = telmisartan 80 mg plus amlodipine 10 mg.

treated with A monotherapy. Approximately one third of patients achieved a target BP of <130/80 mm Hg with T/A SPC. These findings are similar to those of the previously mentioned factorial study,<sup>22</sup> with 76.5% of patients with stage 1 or 2 hypertension achieving their BP goal of <140/90 mm Hg with T/A after 8 weeks. In patients with diabetes, the goal rate achievement (<140/90 mm Hg) was 87%, although the number of patients with diabetes in this study was limited.<sup>24,28</sup>

As a consequence of the lack of incontrovertible trial evidence that aggressively decreasing BP to <130/80 mm Hg in patients with diabetes lowers CV risk,<sup>33</sup> the European Society of Hypertension-European Society of Cardiology (ESH-ESC) reappraised their guidelines and now recommend decreasing SBP to well below 140 mm Hg, ie, approaching the old target of 130/80 mm Hg but not necessarily going below it.<sup>7</sup> These recommendations are supported by the findings of the ADVANCE-ON (Action in Diabetes and Vascular Disease Preterax and Diamicron-MR Controlled Evaluation) study, which reported that decreasing SBP to <135 mm Hg in patients with T2DM was associated with macrovascular and microvascular benefits compared with placebo-treated patients with an SBP of ~140 mm Hg.<sup>13</sup> More recently, the validity of the widespread recommendations to apply more stringent BP targets in patients with T2DM and hypertension<sup>4,6</sup> has been further called into question after the results of the ACCORD study<sup>14</sup> and an additional analysis of the INVEST (International Verapamil SR-Trandolopril) study.<sup>34</sup> The ACCORD study showed that targeting an SBP of <120 mm Hg in patients with T2DM at high risk for CV events rather than using a target of <140 mm Hg did not lower the risk of fatal and nonfatal major CV events.<sup>14</sup> A subgroup analysis of the INVEST study reported that the relationship between the primary outcome (first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke) and the mean follow-up SBP and DBP was in the form of a J-shaped curve in previously revascularized patients,<sup>34</sup> supporting the theory that decreasing BP too aggressively can result in decreased blood flow to vital organs, which may increase CV risk.

Patients with T2DM are often overweight or obese, and this was true for our study population, with 57.5% being in the obese category (BMI  $\geq$ 30 kg/m<sup>2</sup>). Obese diabetic patients such as these, often classed as having MS, are typically difficult to treat<sup>35</sup> and are at added risk for CV events.<sup>10</sup> They have a similar or

increased CV risk profile to that of diabetic patients, and, therefore, patients with obesity or MS similarly benefit from treatment. When we stratified our patients according to their BMI, we observed that the SPC T/A remained more effective than A alone in both nonobese and obese patients, which is reassuring considering the difficulty in treating this population. Our findings support those of a recent subanalysis of the large factorial study by Littlejohn et al,<sup>22</sup> which reported consistent decreases in mean seated trough SBP and DBP in both the obese and nonobese subpopulations, with the greatest decreases being achieved with the T/A combination.<sup>24</sup> It must be noted, however, that patient numbers in the subanalysis of the factorial study were limited.

In the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) trial, BP decreases in both treatment arms were similar, and the BP goal (<140/90 mm Hg) was achieved in 75.4% and 72.4% in the benazepril plus amlodipine combination arm and the benazepril hydrochlorothiazide (HCTZ) combination arm, whereas antihypertensive add-on medication was allowed to achieve this BP goal. Approximately 60% of the patients in the ACCOMPLISH trial had comorbid diabetes, and almost half were obese (BMI, 31.0 [6.2] kg/m<sup>2</sup>). In addition, the majority presented with established CAD. Despite similar trough cuff office BP decreases, also confirmed by 24-hour ABPM and BP goal rates in the 2 treatment arms of the ACCOMPLISH trial, the amlodipine combination was significantly more effective than the HCTZ combination in decreasing CV events.<sup>36,37</sup> In addition, evidence from the CAMELOT (Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis) study<sup>38</sup> and PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial)<sup>39</sup> revealed that amlodipine is effective in CAD as well as in hypertension. Evidence from the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) suggested that telmisartan prevents 1 in 5 CV events in CV risk patients with or without hypertension.<sup>16</sup> Telmisartan and amlodipine can therefore be considered to be logical combination partners. No outcome data are available yet; however, the free combination is currently being investigated in an outcome study (Effects of Angiotensin II Receptor Blocker Compared With Diuretics in High-Risk Hypertensive Patients [CHIEF] trial).<sup>40</sup>

This study showed a 70% decrease in UACR in those patients treated with T/A SPC compared with amlodipine monotherapy. A possible explanation for this could be the synergistic dilatatory effect of T/A on the vas afferens and vas efferens of the glomerula. Therefore, hyperfiltration, induced by amlodipine due to dilation of the vas afferens, is decreased by telmisartan due to vasodilation of the vas efferens.<sup>41</sup> In the ACCOMPLISH trial, it was found that an RAS blocker plus CCB combination was superior to an RAS blocker plus diuretic combination (benazepril plus amlodipine or HCTZ) in renal parameters, such as progression to chronic kidney disease (2.0% vs 3.7%, respectively).<sup>42</sup> This indicates that the beneficial renal effect seen with RAS blockers such as telmisartan are preserved in a combination with a CCB, such as amlodipine.

The 24-hour ABPM is considered to be a gold standard measurement for BP.<sup>43</sup> Analysis of the 24-hour ABPM substudy showed that the T/A SPC was significantly more effective in decreasing 24-hour SBP and DBP and achieving the 24-hour BP goal of <130/80 mm Hg than A monotherapy. This confirms results from the factorial design study, in which patients treated with T/A achieved a significantly higher 24-hour BP goal rate compared with those treated with A (82.7% vs 37.9%;  $P < 0.0001$ ).<sup>15</sup>

The tolerability analysis showed that comparable numbers of patients in the 2 treatment groups experienced adverse events, and the majority of these were mild or moderate. With no comparator placebo arm, the reported adverse events should not be ignored; however, these adverse event rates were similar to those previously observed for the T/A combination.<sup>22</sup> Patient retention in the study was high (92.2%), similar to that of an earlier study of this treatment combination (92%), suggesting a high treatment adherence.<sup>22</sup>

The most common adverse events (peripheral edema, headache, and dizziness) are all known adverse events for such kind of treatments.<sup>44</sup> Headache is common in patients with hypertension, and its incidence was previously reported to be lower with telmisartan than with placebo.<sup>44</sup> The onset of peripheral edema was apparently related to the use of amlodipine and dose dependent, and the overall incidence was numerically decreased when amlodipine was used in combination with telmisartan. These findings were in line with results suggesting low rates of peripheral edema when an ARB such as telmisartan is combined with

amlodipine.<sup>22,23,45,46</sup> CCB-induced peripheral edema is caused by capillary hypertension in the upright position,<sup>47</sup> and RAS blockade with ACE inhibitors and ARBs is known to decrease the effect by venous dilation.<sup>47,48</sup> However, the decrease in peripheral edema observed in diabetic patients appears to be not as prominent as in the hypertensive patient population in the factorial design study.<sup>22,23</sup> The reason for this remains speculative and deserves further investigation. It might be due to impaired microcirculation in T2DM patients resulting from microvascular damage, which is characteristic of T2DM often already in early stages of the disease.<sup>49</sup> However, the severity grade of peripheral edema in the 2 treatment arms is different, with more patients experiencing moderate to severe peripheral edema and more patients discontinuing treatment due to peripheral edema with A monotherapy than with T/A SPC.

## CONCLUSIONS

In this 8-week study, initial treatment with T/A SPC was an effective and well-tolerated treatment in this selected group of hypertensive patients with diabetes. Clinical evidence suggests that such a combination is beneficial to decrease CV risk in this type of added-risk patients and may be considered a preferred treatment option in patients with metabolic disorders such as diabetes, MS, and obesity.

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## CONFLICTS OF INTEREST

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## REFERENCES

- Ezzati M, Oza S, Danaei G, Murray CJ. Trends and cardiovascular mortality effects of state-level blood pressure and uncontrolled hypertension in the United States. *Circulation*. 2008;117:905-914.
- Ostchega Y, Dillon CF, Hughes JP, et al. Trends in hypertension prevalence, awareness, treatment, and control in older U.S. adults: data from the National Health and Nutrition Examination Survey 1988 to 2004. *J Am Geriatr Soc*. 2007;55:1056-1065.
- Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA*. 2010;303:2043-2050.
- Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206-1252.
- Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension*. 2004;43:10-17.
- Mancia G, De 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.
- Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009;27:2121-2158.
- Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. *Arch Intern Med*. 2007;167:141-147.
- Falaszetti E, Chaudhury M, Mindell J, Poulter N. Continued improvement in hypertension management in England: results from the Health Survey for England 2006. *Hypertension*. 2009;53:480-486.
- Kotseva K, Wood D, De Backer G, et al, for the EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet*. 2009;373:929-940.
- Antikainen RL, Kastarinen MJ, Jousilahti P, et al. Despite evidence-based guidelines, systolic blood pressure remains inadequately controlled in older hypertensive adults. *J Hum Hypertens*. 2010;24:439-446.
- Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*. 2000;321:412-419.
- ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829-840.
- The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575-1585.
- White WB, Littlejohn TW, Majul CR, et al. Effects of telmisartan and amlodipine in combination on ambulatory blood pressure in stages 1-2 hypertension. *Blood Press Monit*. 2010;15:205-212.
- Yusuf S, Teo KK, Pogue J, et al, for the ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547-1559.
- Burnier M. Telmisartan: a different angiotensin II receptor blocker protecting a different population? *J Int Med Res*. 2009;37:1662-1679.
- Littlejohn T, Mroczek W, Marbury T, et al. A prospective, randomized, open-label trial comparing telmisartan 80 mg with valsartan 80 mg in patients with mild to moderate hypertension using ambulatory blood pressure monitoring. *Can J Cardiol*. 2000;16:1123-1132.
- Sharma AM, Hollander A, Köster J, for the Efficacy and Safety in Patients with Renal Impairment; treated with Telmisartan (ESPRIT) Study Group. Telmisartan in patients with mild/moderate hypertension and chronic kidney disease. *Clin Nephrol*. 2005;63:250-257.
- Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angioten-

- sin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008;372:1174–1183.
21. 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.
  22. Littlejohn TW, Majul CR, Olvera R, et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. *J Clin Hypertens (Greenwich)*. 2009;11:207–213.
  23. Littlejohn TW, 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 × 4 factorial study. *Postgrad Med*. 2009;121:5–14.
  24. Guthrie R, Dahlöf B, Jamerson K, et al. Efficacy and tolerability of telmisartan plus amlodipine in added-risk hypertensive patients. *Curr Med Res Opin*. 2011;27:1995–2008.
  25. Neutel J, Mancia G, Black H, et al. Single-pill combination of telmisartan 80 mg/amlodipine 10 mg provides superior blood pressure reductions in patients with severe hypertension: TEAMSTA severe HTN study: HT.1.04. *J Hypertens*. 2010;28:e46.
  26. Neldam S, Lang M, Jones R, for the TEAMSTA-5 Investigators. Telmisartan and amlodipine single-pill combinations versus amlodipine monotherapy for superior blood pressure lowering and improved tolerability in patients with uncontrolled hypertension: results of the TEAMSTA-5 Study. *J Clin Hypertens*. 2011;13:459–466.
  27. Neldam S, Lang M. Fixed-dose combination therapy with telmisartan and amlodipine 5 mg in non-responders to amlodipine 5 mg provides superior blood pressure reductions to, and is better tolerated than, amlodipine 10 mg. *J Clin Hypertens*. 2009;11(Suppl A):A129.
  28. Oigman W, Neves MF, Gismondi RA. Combination of telmisartan plus amlodipine in the treatment of hypertension: review of results. *Expert Rev Cardiovasc Ther*. 2010;8:1509–1517.
  29. Mallinckrod CH, Lane PW, Schnell D, et al. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. *Drug Information J*. 2008;42:303–319.
  30. Julius S, Kjeldsen SE, Weber M, et al, for the VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031.
  31. Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet*. 2004;363:2049–2051.
  32. Dahlöf B, Sever PS, Poulter NR, et al, for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.
  33. Cooper-DeHoff RM, Egelund EF, Pepine CJ. Blood pressure lowering in patients with diabetes—one level might not fit all. *Nat Rev Cardiol*. 2011;8:42–49.
  34. Denardo SJ, Messerli FH, Gaxiola E, et al. Coronary revascularization strategy and outcomes according to blood pressure (from the International Verapamil SR-Trandolapril Study [INVEST]). *Am J Cardiol*. 2010;106:498–503.
  35. Tomlinson JW, Owen KR, Close CF. Treating hypertension in diabetic nephropathy. *Diabetes Care*. 2003;26:1802–1805.
  36. Jamerson K, Weber MA, Bakris GL, et al, for the ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.
  37. Jamerson KA, Devereux R, Bakris GL, et al. Efficacy and duration of benazepril plus amlodipine or hydrochlorothiazide on 24-hour ambulatory systolic blood pressure control. *Hypertension*. 2011;57:174–179.
  38. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292:2217–2226.
  39. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. *Circulation*. 2000;102:1503–1510.
  40. Effects of Angiotensin II Receptor Blocker Compared With Diuretics in High-risk Hypertensive Patients (CHIEF) trial. <http://clinicaltrials.gov/ct2/show/NCT01011660>. Accessed February 27, 2012.
  41. Peti-Peterdi J, Toma I, Vargas SL, Koo J. P648: improved renal hemodynamics in diabetic rats treated with Telmisartan and Amlodipine. *Eur Heart J*. 2010;31(Abstract Suppl):88.
  42. Bakris G, Sarifidis P, Weir M, et al, for the ACCOMPLISH Trial Investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet*. 2010;375:1173–1181.
  43. Parati G, Faini A, Valentini M. Blood pressure variability: its measurement and significance in hypertension. *Curr Hypertens Rep*. 2006;8:199–204.

44. Schumacher H, Mancia G. The safety profile of telmisartan as monotherapy or combined with hydrochlorothiazide: a retrospective analysis of 50 studies. *Blood Press Suppl.* 2008;1:32–40.
45. Kreutz R. Olmesartan/amlodipine: a review of its use in the management of hypertension. *Vasc Health Risk Manag.* 2011;7:183–192.
46. Kostis JB. Antihypertensive therapy with CCB/ARB combination in older individuals: focus on amlodipine/valsartan combination. *Am J Ther.* 2010;17:188–196.
47. Makani H, Bangalore S, Romero J, et al. Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema. *Am J Med.* 2011;124:128–135.
48. Frishman WH, Ram CV, McMahon FG, et al. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study. The Benazepril/Amlodipine Study Group. *J Clin Pharmacol.* 1995;35:1060–1066.
49. McGill JB. Improving microvascular outcomes in patients with diabetes through management of hypertension. *Postgrad Med.* 2009;121:89–101.

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