Management of Hypertension in Patients With Diabetes Using an Amlodipine-, Olmesartan Medoxomil-, and Hydrochlorothiazide-Based Titration Regimen

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The safety and efficacy of an amlodipine/olmesartan medoxomil (OM)-based titration regimen was assessed in patients with type 2 diabetes mellitus and hypertension. After a 2- to 3-week placebo run-in period, 207 patients received amlodipine 5 mg and were uptitrated to amlodipine/OM 5/20, 5/40, and 10/40 mg and then amlodipine/OM 10/40 mg plus hydrochlorothiazide 12.5 and 25 mg in a step-wise manner at 3-week intervals if the seated blood pressure (BP) remained ≥120/70 mm Hg. The primary end point was the change from baseline in the mean 24-hour ambulatory systolic BP after 12 weeks of treatment. The baseline mean ± SD seated cuff systolic/diastolic BP was 158.8 ± 13.1/89.1 ± 10.1 mm Hg and the mean ± SD 24-hour ambulatory systolic/diastolic BP was 144.4 ± 11.7/81.6 ± 9.8 mm Hg. At week 12, the change from baseline in the mean ± SEM 24-hour ambulatory systolic/diastolic BP was −19.9 ± 0.8/−11.2 ± 0.5 mm Hg ($p < 0.0001$ vs baseline), and 70% of patients had achieved a 24-hour ambulatory BP target of <130/80 mm Hg. At the end of 18 weeks of active treatment in patients uptitrated to amlodipine/OM 10/40 mg plus hydrochlorothiazide 25 mg, the change from baseline in the mean ± SEM seated BP was −28.0 ± 1.5/−13.7 ± 1.0 mm Hg ($p < 0.0001$ vs baseline), with 62% of patients reaching the guideline-recommended seated BP goal of <130/80 mm Hg. Drug-related treatment-emergent adverse events occurred in 19.3% of patients. The most frequent events were peripheral edema (6%), dizziness (3%), and hypotension (2%). In conclusion, this amlodipine/OM-based titration regimen was well tolerated and effectively lowered BP throughout the 24-hour dosing interval in patients with hypertension and type 2 diabetes. **(Am J Cardiol 2011;107:1346–1352)**

The AZOR Trial Evaluating Blood Pressure Reductions and Control (AZTEC) study showed that an amlodipine/olmesartan medoxomil (OM)-based titration regimen controlled blood pressure (BP) for a 24-hour period in patients with hypertension.[1] The present study is a Prospective, open-label, ambulatory BP monitoring study to evaluate the safety and Efficacy of an olmesartan medoXomil- and amlodipine-based treatment regimen in patients with type 2 diabetes and hypertension (APEX). The efficacy and tolerability were evaluated after 12 weeks of treatment. In addition, the effect of adding hydrochlorothiazide (HCTZ) to the regimen for an additional 6 weeks was assessed.

Methods

The present phase IV, open-label, multicenter, single-arm, titration study consisted of a 3- to 14-day screening period, a 2- to 3-week placebo run-in period, and an 18-week active treatment phase (Figure 1). At each clinic visit, the seated BP and heart rate were determined in triplicate from the patient's nondominant arm using an automated Omron device. A Spacelabs Healthcare 90207 Oscillometric device (Issaquah, WA) was used to perform 24-hour ambulatory BP monitoring at baseline and after 12 weeks of active treatment. The monitoring was started at 8 A.M. ± 2 hours immediately before dosing. The same time window was monitored at baseline and week 12. The present study was conducted in accordance with the institutional review boards' committee regulations and the Declaration of Helsinki. The institutional review board oversaw the study at each site. All patients provided informed consent before study participation.

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This study was supported by Daiichi Sankyo, Inc., Parsippany, New Jersey.

C.V. Ram is a member of the speakers' and/or consultants' bureaus for AHM, Advanced Health Media (Bridgewater, New Jersey), and The Peer Group, Inc. (Edison, New Jersey), which conduct educational and interactive programs for various pharmaceutical and medical devices companies. R. Sachson is a member of the speakers' bureaus for Abbott Laboratories (Abbott Park, Illinois), Amgen (Thousand Oaks, California), Amylin Pharmaceuticals (San Diego, California), Eli Lilly (Indianapolis, Indiana), Genentech (South San Francisco, California), GlaxoSmithKline (Research Triangle Park, North Carolina), Novartis (Basel, Switzerland), Novo Nordisk (Princeton, New Jersey), Solvay (Brussels, Belgium), and Takeda Pharmaceuticals (Deerfield, Illinois). T. Littlejohn has nothing to disclose. C. Qian, A. Shojaee, and K.A. Stoakes are all employees of Daiichi Sankyo, Inc (Parsippany, New Jersey). J.M. Neutel is a member of the speakers' bureau for Boehringer Ingelheim (Ridgefield, Connecticut), Daiichi Sankyo, Inc. (Parsippany, New Jersey), Forest (New York, New York), Novartis (Basel, Switzerland), Pfizer (New York, New York), and Sanofi-aventis/Bristol-Myers Squibb (Bridgewater, New Jersey and Princeton, New Jersey).

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doi:10.1016/j.amjcard.2010.12.045

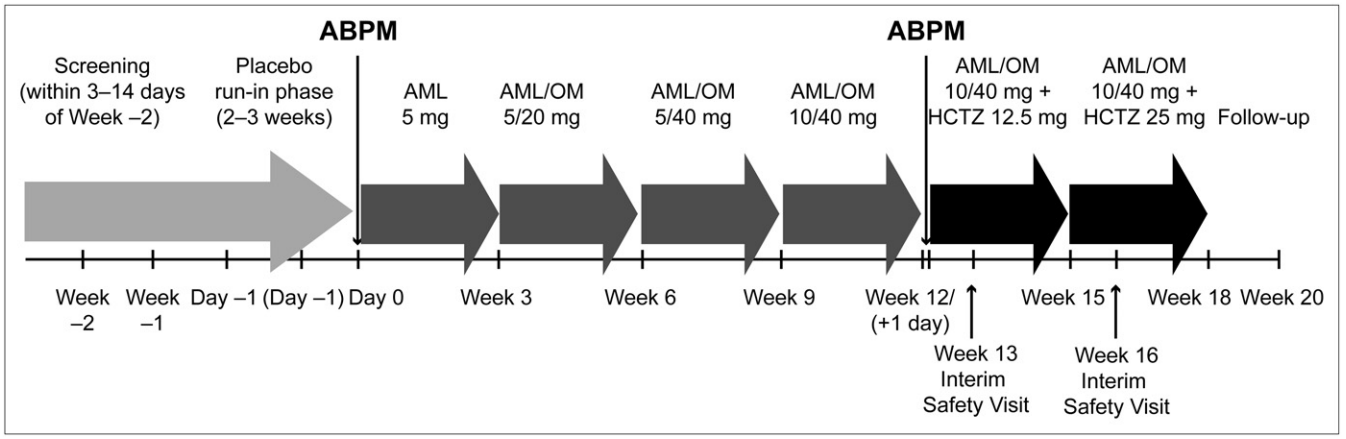

Figure 1. Study design. ABPM = ambulatory blood pressure monitoring; AML = amlodipine.

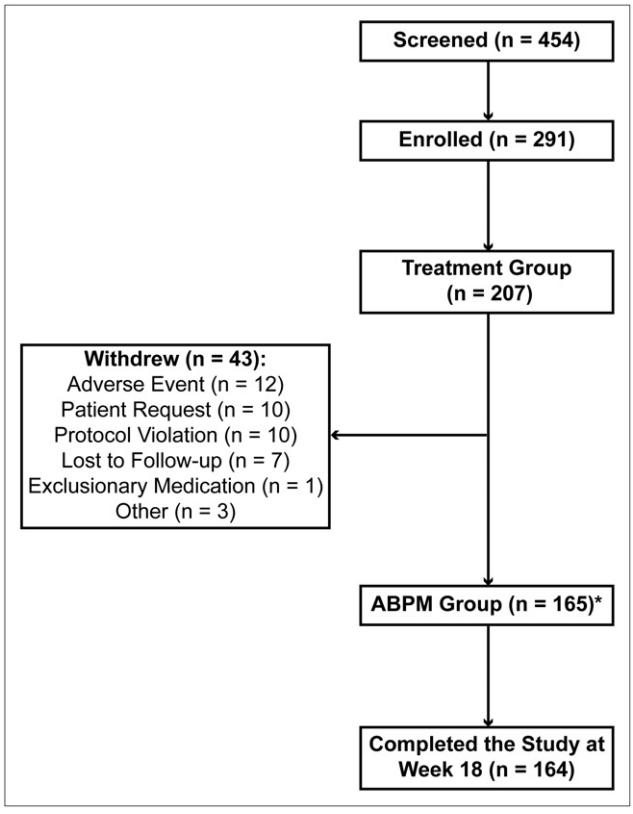

Figure 2. Patient disposition throughout study. *Ambulatory blood pressure monitoring (ABPM) group included patients with baseline and week 12 ABPM readings.

Table 1
Baseline patient characteristics*

Characteristic	Treated Group (n = 207)
Age at screening (years)	59.1 ± 9.5
Age <65 years	145 (70%)
Gender	
Men	122 (59%)
Women	85 (41%)
Race	
Caucasian	163 (79%)
Black	35 (17%)
Asian	8 (4%)
Other	2 (1%)
Hispanic or Latino ethnicity	54 (26%)
Weight (kg)	94.3 ± 20.2
Hemoglobin A1c (%) (n = 206)	6.9 ± 0.8
Body mass index (kg/m^2)	32.8 ± 5.9
Obesity	49 (24%)
Dyslipidemia	31 (15%)
Hypercholesterolemia	61 (30%)
Hyperlipidemia	50 (24%)
Mean interval from diabetes diagnosis to screening (years)	6.4
Seated BP (mm Hg)	158.8 ± 13.1/89.1 ± 10.1
Baseline cuff BP (mm Hg)	
140–159/90–99	115 (56%)
≥160/≥100	92 (44%)
24-Hour ambulatory BP (mm Hg)	144.4 ± 11.7/81.6 ± 9.8

* Data are presented as mean ± SD or n (%).

Noninstitutionalized men or women aged 18 to 80 years with type 2 diabetes mellitus were eligible for the present study if they were undergoing stable treatment with any oral antidiabetic agent for ≥3 months. The patients not receiving oral antidiabetic agents were required to have a fasting plasma glucose level of ≥126 mg/dl (7.0 mmol/L) at screening and a documented history of type 2 diabetes according to the American Diabetes Association criteria (i.e., fasting plasma glucose ≥126 mg/dl [7.0 mmol/L]; hyperglycemia symptoms, and a casual plasma glucose level ≥200 mg/dl [11.1 mmol/L]; or 2-hour plasma glucose level ≥200 mg/dl [11.1 mmol/L] during an oral glucose tolerance test). Patients with newly diagnosed or uncontrolled hypertension (i.e., current antihypertensive medication) were identified at screening if the mean systolic BP was >130 mm Hg and/or the diastolic BP was >80 mm Hg. The patients entered the active treatment phase if they had taken ≥80% of the study medication and had a mean seated systolic BP of ≥140 and ≤199 mm Hg and a mean seated diastolic BP of ≤114 mm Hg at 2 consecutive study visits during the placebo run-in period, with a difference in the seated systolic BP of ≤15 mm Hg between the 2 qualifying study visits. Additional inclusion criteria determined by ambulatory BP monitoring were a mean daytime (8 A.M. to

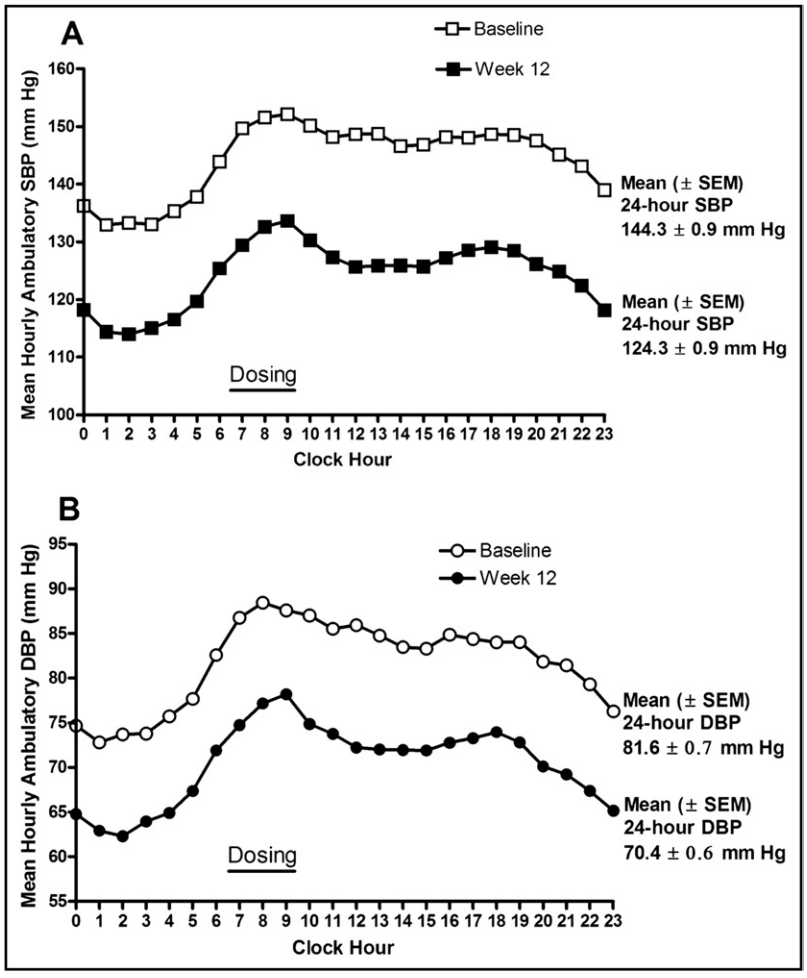

Figure 3. Hourly mean 24-hour ambulatory *(A)* systolic blood pressure (SBP) and *(B)* diastolic blood pressure (DBP) at baseline and 12 weeks.

4 P.M.) systolic BP of ≥130 and ≤199 mm Hg and diastolic BP of ≤114 mm Hg after the placebo run-in.

Patients with uncontrolled hypertension with multiple antihypertensive therapies, type 1 or 2 diabetes requiring insulin, type 2 diabetes with a glycosylated hemoglobin level of ≥9.0%, proteinuria of >1+ on the dipstick, serum creatinine >1.7 mg/dl, or fasting serum glucose level of >300 mg/dl at screening were excluded. A nondominant arm circumference of <24 or >42 cm or serious disorders that could have limited the ability to evaluate the efficacy or safety of OM (e.g., cardiovascular and renal disease) were also exclusionary. Women were eligible only if they were not pregnant or planning to become pregnant, were not breastfeeding, and were practicing protocol-approved birth control. The use of antihypertensive agents other than OM, amlodipine, or HCTZ was prohibited.

All patients started active treatment with amlodipine 5 mg/day at approximately 8.00 A.M. The medication was uptitrated at 3-week intervals if the patients' mean seated BP was greater than the titration threshold of ≥120/70 mm Hg. The titration schedule was amlodipine/OM 5/20, 5/40, and 10/40 mg/day, followed by the addition of HCTZ 12.5 and 25 mg/day. The patients with a mean seated systolic BP of ≥130 mm Hg were immediately uptitrated to HCTZ 12.5 and 25 mg/day. An amendment was added to the study design for patients who required uptitration to HCTZ after week 12. The patients with a mean seated systolic BP of ≥120 and <130 mm Hg underwent orthostatic BP and heart rate assessments before the initiation or uptitration of HCTZ. If these patients had an orthostatic systolic BP reduction of >10 mm Hg but were not taking HCTZ, they maintained their current therapy (amlodipine/OM 10/40 mg). Patients with an orthostatic systolic BP reduction of ≤10 mm Hg received HCTZ but underwent an additional safety assessment 1 week later. Patients receiving HCTZ 12.5 or 25 mg with an orthostatic decrease in systolic BP of >10 mm Hg at these interim safety assessments were withdrawn from the present study. Throughout the active treatment period, the patients with a mean seated BP of <120/70 mm Hg at any visit maintained their current therapy but were uptitrated to the next dose level if their seated systolic BP had increased to ≥130 mm Hg and/or their seated diastolic BP had increased to ≥80 mm Hg at any subsequent visit. The patients with a mean seated systolic BP of ≥200 mm Hg or seated diastolic BP ≥115 mm Hg or seated systolic BP of <120 mm Hg or seated diastolic BP of <70 mm Hg with symptomatic hypotension at any visit were required to withdraw from the study.

The primary efficacy variable was the change from baseline in the mean 24-hour ambulatory systolic BP after 12

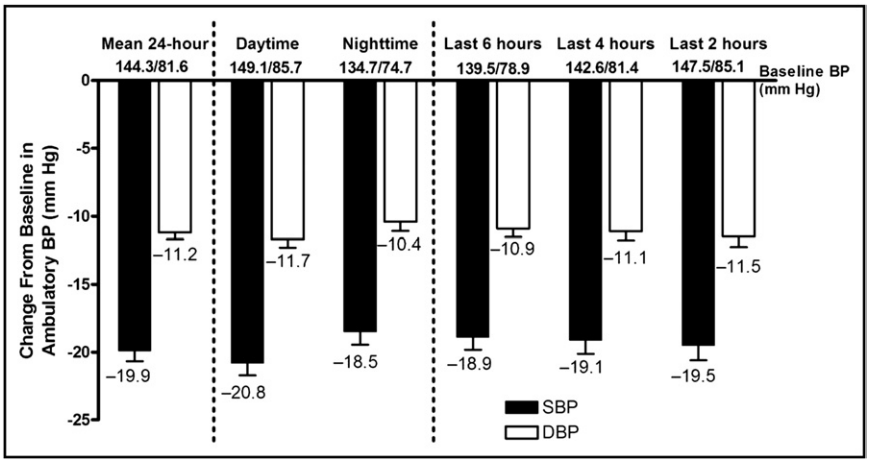

Figure 4. Mean changes from baseline to week 12 in ambulatory systolic blood pressure (SBP) (primary end point) and diastolic blood pressure (DBP) during 24-hour dosing interval, daytime, nighttime, and last 6, 4, and 2 hours of dosing (n = 165). All changes p <0.0001 versus baseline.

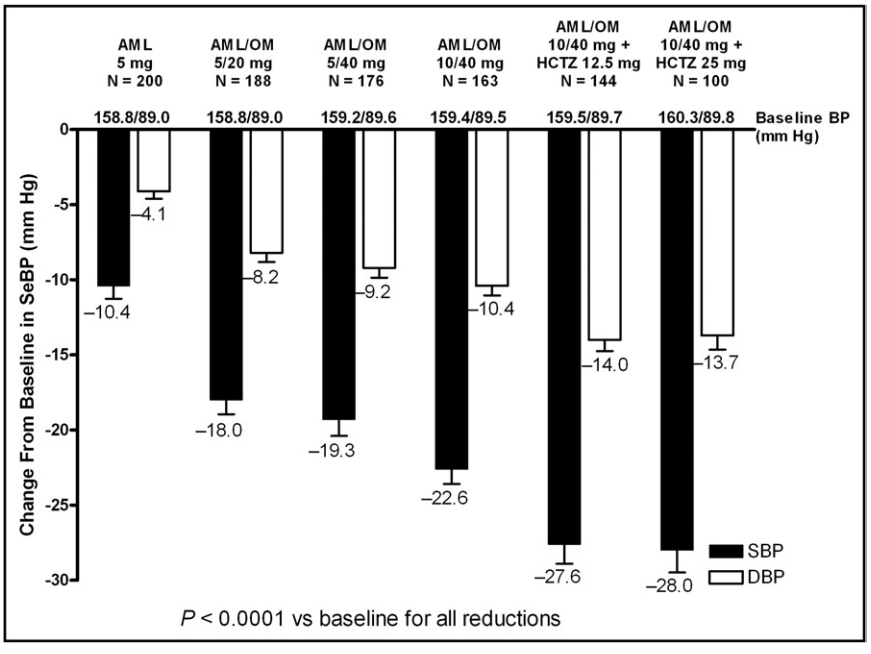

Figure 5. Changes from baseline in mean seated BP (SeBP) during each titration period (LOCF). All changes p <0.0001 versus baseline. AML = amlodipine; DBP = diastolic blood pressure; LOCF = last observation carried forward; SBP = systolic blood pressure.

weeks of treatment. The secondary ambulatory BP efficacy variables included the change from baseline in the mean 24-hour ambulatory diastolic BP, the change from baseline in the mean daytime (8.00 A.M. to 4.00 P.M.) and nighttime (12.00 A.M. to 6.00 A.M.) ambulatory BP, and the change from baseline in the mean ambulatory BP during the last 6, 4, and 2 hours of the 24-hour dosing interval after 12 weeks of treatment. These variables also included the proportions of patients achieving the prespecified ambulatory BP targets for these same periods and the proportion of patients who were "nondippers" at baseline and converted to "dippers" after 12 weeks of treatment. Ambulatory BP "dippers" were defined as patients with a nocturnal ambulatory systolic BP and/or diastolic BP reduction of ≥10% of their mean daytime ambulatory systolic and/or diastolic BP. Other secondary efficacy variables included changes from baseline in the mean seated BP at each titration step up to week 18, the proportion of patients achieving the prespecified ambulatory and seated systolic and diastolic BP reductions, and the proportion of patients achieving the seated BP goals during the study.

The adverse events reported by patients or observed by the investigators at any visit during the 18-week active treatment period and through 14 days after the last dose was taken were recorded and graded as mild, moderate, or severe and unrelated, unlikely related or possibly, probably, or definitely treatment-related. Serious adverse events were any events that resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or were an important medical event. Safety was also assessed by monitoring the laboratory values and physical examination findings at screening, week 12, and week 18.

The treated group included all subjects who had received one or more doses of active study medication. All efficacy (except ambulatory BP monitoring analysis) and safety analyses were based on the treated group. All ambulatory BP monitoring analysis was based on the ambulatory BP monitoring group, which consisted of all treated subjects having both valid baseline and week 12 ambulatory BP monitoring data. Summary statistics were calculated for the continuous variables, and the numbers and percentages of patients were calculated for the categorical variables. For the number of patients achieving certain BP goals by titration dose, the cumulative achievement rate (the percentage of patients achieving their goal at any point on or before the specified dose was taken) was calculated. The primary efficacy variable was analyzed using a one-sample *t* test, and the mean, 2-sided 95% confidence interval, and standard error of the mean were provided. The statistical test had a 2-sided significance level of 5%. It was estimated that a sample size of 200 patients would provide 99% power for a significant change from baseline in mean 24-hour ambulatory systolic BP at 12 weeks. This sample size was expected to allow approximately 150 patients to complete the first 12 weeks of the active treatment period.

Results

The study was conducted at 33 centers in the United States. The patient disposition is presented in Figure 2. All 207 patients who entered the active treatment phase received one or more doses of the study medication, and 164 (79%) completed the study. The main reasons for study withdrawal were adverse events (n = 12), patient request (n = 10), protocol violation (n = 10), and lost to follow-up (n = 7).

The baseline characteristics of the treated group (n = 207) are listed in Table 1. Before the placebo run-in, 183 patients of the treated group were undergoing antihypertensive therapy. The mean study drug exposure was 112.9 days (range 1 to 158). At week 18, 7 patients were receiving amlodipine/OM 5/20 mg, 5 amlodipine/OM 5/40 mg, 14 amlodipine/OM 10/40 mg, 38 amlodipine/OM 10/40 mg plus HCTZ 12.5 mg, and 101 amlodipine/OM 10/40 mg plus HCTZ 25 mg.

The baseline and week 12 data for 24-hour ambulatory BP were available for 165 patients. The mean 24-hour ambulatory BP was 144.3/81.6 mm Hg at baseline and 124.3/70.4 mm Hg at week 12 (Figure 3). At week 12, the overall change from baseline in the mean 24-hour ambulatory systolic BP (primary efficacy variable) was −19.9 mm Hg ($p < 0.0001$; Figure 4). The reduction in the mean ± SEM 24-hour ambulatory diastolic BP was −11.2 ± 0.5 mm Hg ($p < 0.0001$; Figure 4). The ambulatory BP was also significantly reduced in the daytime and nighttime and during the last 6, 4, and 2 hours of the dosing interval at week 12 (all $p < 0.0001$ vs baseline; Figure 4). After 12 weeks of treatment, 70%, 46%, and 36% of patients had achieved the prespecified 24-hour ambulatory BP targets of <130/80, <125/75, and <120/80 mm Hg, respectively. During the daytime, 50%, 29%, and 26% of the patients had achieved these thresholds compared to 83%, 72%, and 68% of the patients during the nighttime.

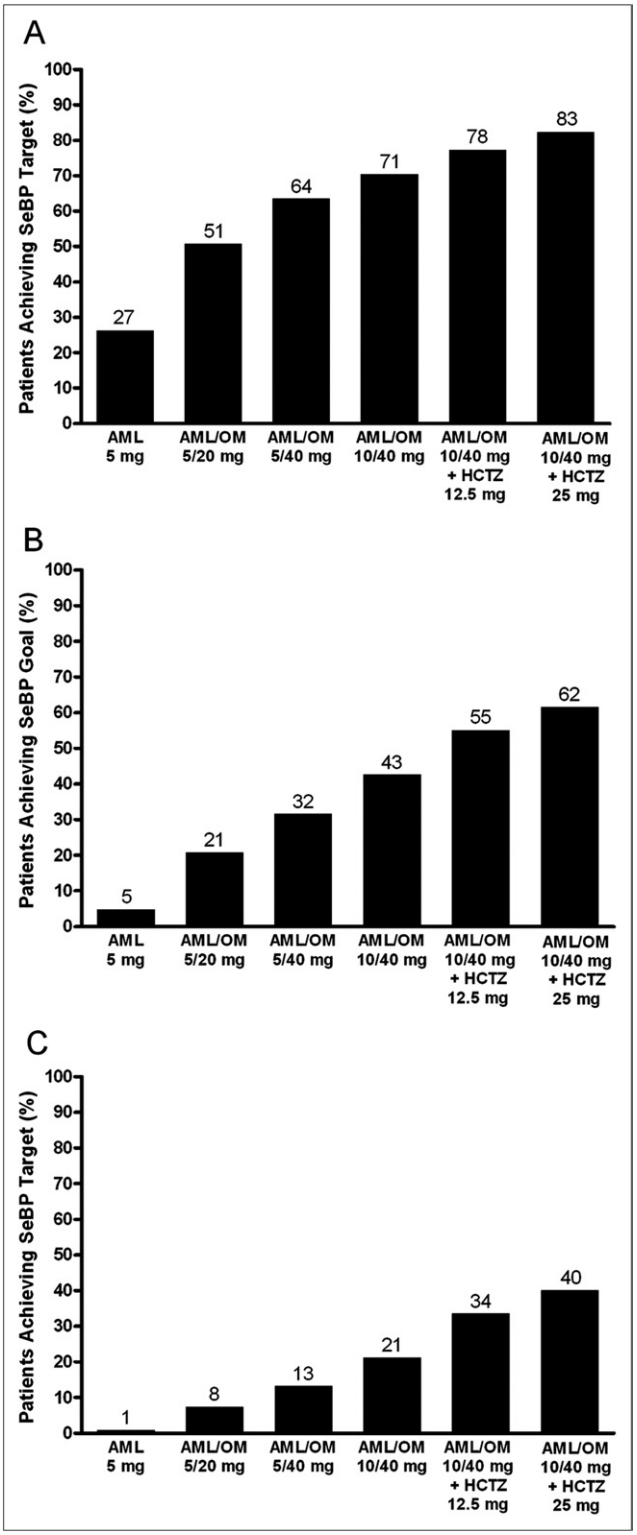

Figure 6. Cumulative proportions of patients achieving seated BP (SeBP) *(A)* target of <140/90 mm Hg, *(B)* goal of <130/80 mm Hg, and *(C)* target of <120/80 mm Hg at any time point by titration dose period. AML = amlodipine.

The mean seated BP at baseline was 158.8/89.1 mm Hg and was, in general, progressively reduced during each titration step (Figure 5). All seated BP reductions from

Table 2
Adverse events in safety group*

Adverse Event, n (%)	AML 5 mg (n = 207)	AML/OM 5/20 mg (n = 195)	AML/OM 5/40 mg (n = 177)	AML/OM 10/40 mg (n = 167)	AML/OM 10/40 + HCTZ 12.5 mg (n = 146)	AML/OM 10/40 + HCTZ 25 mg (n = 101)	Total* (n = 207)
Subjects with any treatment-emergent adverse event	30 (15%)	39 (20%)	27 (15%)	33 (20%)	26 (18%)	12 (12%)	117 (57%)
Subjects with any drug-related treatment-emergent adverse event	9 (4%)	10 (5%)	6 (3%)	7 (4%)	12 (8%)	2 (2%)	40 (19%)
Drug-related treatment-emergent adverse events of interest							
Peripheral edema	5 (2%)	3 (2%)	2 (1%)	4 (2%)	0	0	12 (6%)
Dizziness	0	0	2 (1%)	1 (1%)	4 (3%)	0	6 (3%)
Headache	1 (1%)	0	0	1 (1%)	0	1 (1%)	3 (1%)
Presyncope	0	0	0	0	1 (1%)	1 (1%)	2 (1%)
Hypotension	0	1 (1%)	0	0	2 (1%)	0	4 (2%)
Orthostatic hypotension	0	1 (1%)	0	0	0	0	1 (1%)

* Included treatment-emergent adverse events experienced during active treatment period and 14-day follow-up period.
AML = amlodipine.

baseline were statistically significant during each dosing period ($p < 0.0001$). The change from baseline in the mean seated BP ± SEM at the end of each titration period for the patients receiving monotherapy (amlodipine), dual therapy (amlodipine/OM), and triple therapy (amlodipine/OM plus HCTZ) was −10.4 ± 0.9/−4.1 ± 0.5 mm Hg, −23.0 ± 1.0/−10.8 ± 0.6 mm Hg, and −30.1 ± 1.3/−14.9 ± 0.8 mm Hg, respectively (all $p < 0.0001$ vs baseline). Intensifying treatment from amlodipine monotherapy to amlodipine/OM dual therapy produced a reduction in the mean seated BP ± SEM of 12.5 ± 1.0/6.7 ± 0.6 mm Hg. The observed titration effect of adding HCTZ to amlodipine/OM was 8.5 ± 1.0/4.8 ± 0.6 mm Hg. The cumulative proportions of patients achieving a seated BP target of <140/90 mm Hg, a goal of <130/80 mm Hg, and a target of <120/80 mm Hg at any time point by titration period is presented in Figure 6. The amlodipine/OM plus HCTZ-based titration regimen facilitated the cumulative achievement of the recommended seated BP goal of <130/80 mm Hg at any time point in 62% of the patients.

Overall, 117 patients (57%) treated with one or more doses of the study medications experienced a treatment-emergent adverse event during the study, and 40 patients (19%) experienced a drug-related treatment-emergent adverse event (Table 2). The incidence of individual drug-related treatment-emergent adverse events reported at each titration step is listed in Table 2. Five serious adverse events were reported during the study; four occurred during treatment with amlodipine/OM plus HCTZ (2 cases of syncope and 1 case each of hyperkalemia and pneumonia) and one occurred during amlodipine/OM therapy (exacerbation of chronic obstructive pulmonary disease). During the 14 days after active treatment, 1 case of pitting edema was identified. No deaths occurred during the study. Twelve patients (6%) discontinued the study treatment because of treatment-emergent adverse events, including 2 receiving amlodipine 5 mg, 4 receiving amlodipine/OM 5/20 mg, 1 receiving amlodipine/OM 5/40 mg, 1 receiving amlodipine/OM 10/40 mg, and 4 receiving amlodipine/OM 10/40 mg plus HCTZ 12.5 mg. The most commonly reported reason for discontinuation was peripheral edema (n = 3).

No significant changes in serum potassium, creatinine, or uric acid levels were seen during active treatment. Elevated serum potassium after treatment with amlodipine/OM 10/40 mg was reported as a drug-related treatment-emergent adverse event in 1 patient (0.5%).

Discussion

The results of the present trial have demonstrated that a titrate-to-goal treatment regimen comprising amlodipine, OM, and HCTZ was effective and well tolerated in patients with type 2 diabetes and hypertension. The strengths of the present study were the use of ambulatory BP monitoring to assess the level of BP-lowering efficacy during the 24-hour dosing interval and aggressive BP criteria for dose titration.

It is important for antihypertensive therapy to help maintain BP control throughout the 24-hour dosing interval. This might reduce the potential effect of the morning BP surge to trigger cardiovascular events.[2–4] This sustained BP control can be provided by a long-acting angiotensin receptor blocker such as OM. In the present study, significant reductions from baseline in ambulatory BP were also seen during the last 6, 4, and 2 hours of the 24-hour dosing interval. These data have reinforced the efficacy demonstrated in the AZTEC study[1] and have confirmed that this amlodipine/OM-based treatment algorithm may provide a useful treatment option for patients with type 2 diabetes and hypertension.

Although there are no generally accepted target values for ambulatory BP goals, the American Heart Association has suggested normal 24-hour, daytime, and nighttime ambulatory BP levels for adults of <130/80, <135/85, and <120/70 mm Hg, respectively.[5] In the present study, amlodipine/OM-based therapy enabled 70% of patients to achieve a 24-hour ambulatory BP target of <130/80 mm Hg. This compares favorably with the results of the BENIcar safety and efFICcacy evaluatIon: An open-label, single-ARm, titration study in patients with hypertension and tYpe 2 diabetes (BENIFICIARY) study in which an OM/HCTZ-based titration algorithm enabled 62% of patients with diabetes to achieve this goal.[6]

The current treatment guidelines are based on seated cuff BP measurements, and a consensus has been reached that the aim of antihypertensive treatment in patients with diabetes should be to attain a goal of <130/80 mm Hg.[7] However, the BP control in these patients has been suboptimal, highlighting the need for effective treatment regimens that comprise ≥2 antihypertensive agents to improve BP goal attainment.[7–9] In the present study, the titration algorithm was expanded to allow the addition of a third class of antihypertensive agents at week 12. The seated BP goal of <130/80 mm Hg was achieved by 62% of patients at the end of the titration scheme (i.e., when HCTZ 25 mg was added as needed). The reasons patients failed to reach the seated BP goal are unknown, although it is possible that patients who did not reach the goal had resistant hypertension. In clinical practice (i.e., outside the scope of the present protocol), spironolactone, clonidine, or a clonidine-like drug would likely be added to the treatment regimen to help patients achieve the recommended BP goal. The relevance of the seated BP goal of <130/80 mm Hg has recently been questioned because no outcomes data are available to support the potential benefit of this target.[10,11]

No unexpected adverse events occurred during the present study, and those related to the study drug were infrequent. The incidence of drug-related peripheral edema was low (1.5% to 2.4%) and, similar to previous studies,[12,13] was absent in patients uptitrated to HCTZ. The addition of HCTZ increased the incidence of dizziness and hypotension but not the risk of metabolic side effects often associated with thiazide diuretic therapy.[14]

The main limitations of the present study were the open-label, noncomparative study design, the recruitment of a relatively healthy population of patients with type 2 diabetes, and the inability to determine the long-term efficacy and tolerability of the treatment algorithm. Despite these limitations, the study is an important reflection of real-world clinical practice and provides important insights into how such a treatment algorithm can be implemented in difficult-to-treat patient populations such as those with diabetes. Furthermore, the availability of amlodipine/OM and amlodipine/OM/HCTZ fixed-dose combinations could improve adherence because the complex nature of diabetes and its concomitant co-morbidities require patients to take many pills per day.

Acknowledgment: We thank Christopher J. Jones, PhD, and Alan J. Klopp, PhD, of *in*Science Communications, a Wolters Kluwer business, for providing medical writing support funded by Daiichi Sankyo, Inc.

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