Daytime Systolic Ambulatory Blood Pressure With a Direct Switch Between Candesartan Monotherapy and the Fixed-Dose Combination Olmesartan/Amlodipine in Patients With Uncontrolled Essential Hypertension (SEVICONTROL-1)

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A direct switch of candesartan to the fixed-dose combination olmesartan/amlodipine in uncontrolled hypertension is a frequent clinical requirement but is not covered by current labeling. An open-label, prospective, single-arm phase IIIb study was performed in patients with 32 mg candesartan followed by olmesartan/amlodipine 40/10 mg. The primary endpoint was change in mean daytime systolic blood pressure (BP). Mean daytime systolic BP was reduced by 9.2±12.6 mm Hg ($P<.0001$) after substituting candesartan for olmesartan/amlodipine (baseline BP 140.2±9.7 mm Hg). The reduction in office BP was 9.4±18.4/4.0±9.6 mm Hg; $P<.002$). Overall, 61.3% of patients achieved a target BP <140/90 mm Hg using office BP and <135/85 mm Hg using ambulatory BP measurement. There were 8 adverse events with a possible relation to study drug and 1 unrelated serious adverse events. In conclusion, patients with uncontrolled moderate arterial hypertension being treated using candesartan monotherapy achieve a further reduction of BP when switched directly to a fixed-dose combination of olmesartan 40 mg/amlodipine 10 mg. *J Clin Hypertens (Greenwich).* 2013;15:815–819. ©2013 Wiley Periodicals, Inc.

There is an increasing need for effective blood pressure (BP)–lowering using fixed-dose combination (FDC) treatment. Blockers of the angiotensin receptor (ARBs) were recently found to provide good BP control at a good tolerability level in combination with the calcium channel blocker (CCB) amlodipine.[1–4] In a phase IV study (Efficacy and Safety of a Therapy Change From Candesartan 32 mg to Fixed Combination of Olmesartan 40 mg/Amlodipine 10 mg [SEVICONTROL-2]) described in the same issue of this *Journal*,[5] we demonstrated that the stepwise switch from candesartan to olmesartan monotherapy and finally olmesartan in FDC with amlodipine is effective. The aim of the present SEVICONTROL-1 study was to demonstrate the efficacy and tolerability of a direct switch between candesartan monotherapy and the FDC. This is because substituting monotherapy with a renin-angiotensin system (RAS)–blocking agent (eg, candesartan) for a fixed combination of a CCB with another RAS blocker (eg, amlodipine/olmesartan) is a frequent clinical requirement, but is not covered by specific clinical trial results and the respective registrations.

METHODS

SEVICONTROL-1 was a multicenter, open-label, prospective, single-arm phase IIIb study. It was conducted in parallel with another phase IV study (SEVICONTROL-2). Readers are referred to this publication for a detailed methodology shared by either trial.[5] The study was conducted between December 2011 and September 2012.

Treatment

The study consisted of 3 treatment phases (Figure 1). In phase I, eligible patients received candesartan 16 mg in the morning for 2 weeks followed by candesartan 32 mg for 4 weeks. Patients with uncontrolled BP taking 32 mg of candesartan (systolic office BP ≥140 mm Hg) were switched to phase II and received a FDC of olmesartan 40 mg/amlodipine 5 mg in the morning for 2 weeks followed by olmesartan 40 mg/amlodipine 10 mg for 4 weeks. Patients with a mean nighttime systolic BP of at least 120 mm Hg or a nighttime dipping <10% entered phase III and were switched from morning to bedtime administration of olmesartan 40 mg/amlodipine 10 mg treatment. Details on reasons for dropouts according to the different treatment phases are given in Figure 1.

Endpoints

The primary efficacy measure was the change in mean daytime systolic BP assessed by 24-hour ambulatory BP measurement (ABPM) between candesartan 32 mg monotherapy (phase I) and olmesartan 40 mg/amlodipine 10 mg FDC, administered in the morning (phase II).

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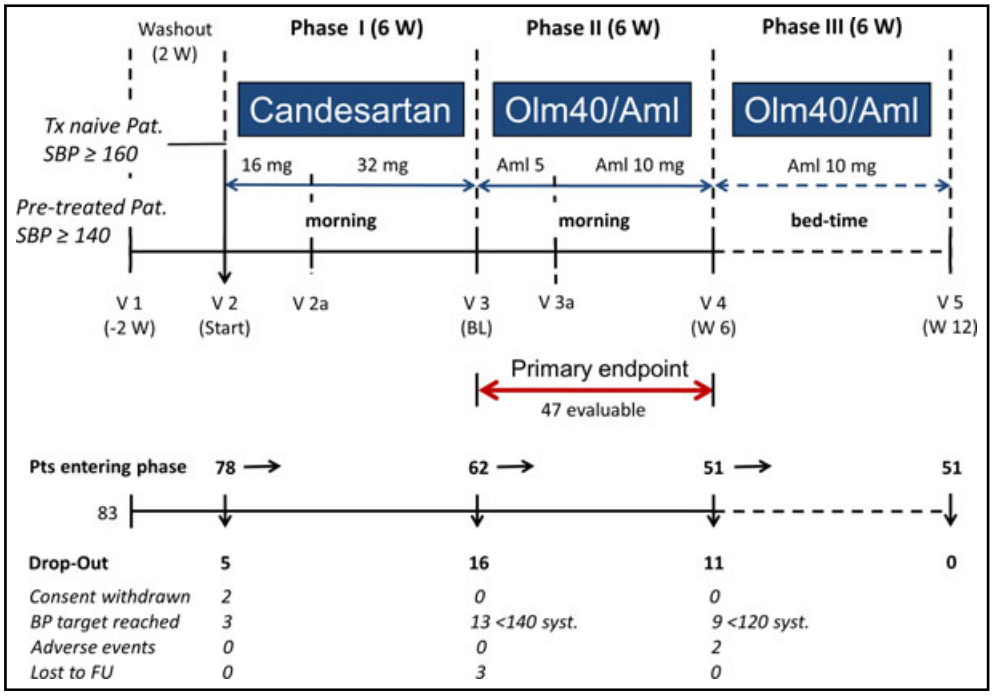

FIGURE 1. Study design. Aml indicates amlodipine; BL, baseline; FU, follow-up; Olm, olmesartan; V, visit; W, week.

Further secondary endpoints are identical to SEVICONTROL-2. An additional exploratory secondary endpoint was a change in the dipping pattern after switching the FDC from morning to bedtime administration during a 6-week follow-up.

RESULTS

A total of 83 patients were screened, of which 78 remained eligible after the washout phase and received candesartan (phase I). Phase II was entered by 62 patients (Figure 1), and 51 patients entered treatment phase III. Baseline characteristics of patients by phase are listed in Table I. Mean office BP at the end of the washout phase was 170.4±8.8/94.1±10.0 mm Hg.

BP Reduction

The primary evaluation criterion was the change in mean daytime systolic ambulatory BP between candesartan monotherapy (phase I) and the fixed combination of olmesartan 40/amlodipine 10 mg morning administration (phase II). Compared with a baseline BP of 140.2±9.7 mm Hg at the end of phase I, BP was reduced by 9.2±12.6 mm Hg (P<.001; Figure 2).

Mean daytime diastolic ambulatory BP decreased (from 81.8±8.4 mm Hg) by 4.6±8.4 mm Hg (P<.005), mean 24-hour systolic/diastolic BP by 9.2/4.6 mm Hg (P<.001), and mean nighttime BP by 9.9/4.7 mm Hg (P<.001/.005). The reduction in office BP was comparable, with a reduction of 9.4±18.4/4.0±9.6 mm Hg (P<.001/.005).

After 6 weeks of treatment with olmesartan 40/amlodipine 10 mg (phase II), systolic and diastolic BP targets were achieved in 77.6% of patients according to ABPM (<135/85 mm Hg). The rate of office BP target achievement (<140/90 mm Hg) was 61.3% (Figure 3).

TABLE I. Patient Baseline Characteristics

	Patients Starting Phase I	Patients Starting Phase II	Patients Starting Phase III
Patients, No.	78	62	51
Age, mean±SD, y	59±12	59±11	60±11
Women, %	46	47	45
BMI, mean±SD, kg/m^2	30±6	30±6	30±6
Diabetes mellitus, %	13	13	16
Heart rate, mean±SD	75±9	75±10	75±10
Office BP, mean±SD, mm Hg			
Systolic	170.4±8.8	145±16.7	137.8±14.4
Diastolic	94.1±10.0	85.6±9.7	81.9±9.7
Antihypertensive pretreatment, %	71	83	82
Laboratory values[a]			
Creatinine, μmol/L±SD	76.6±16.2	77.7±15.3	NA
Potassium, mmol/L±SD	4.6±0.5	4.7±0.4	NA

Abbreviations: BMI, body mass index; BP, blood pressure; bpm, beats per minute; NA, not applicable; SD, standard deviation.

[a]Visit 2a: 7–10 days after visit 2 (n=73).

Bedtime Administration

No further ambulatory BP reduction was achieved by switching the FDC from morning to bedtime administration in treatment phase III. Office BP showed a

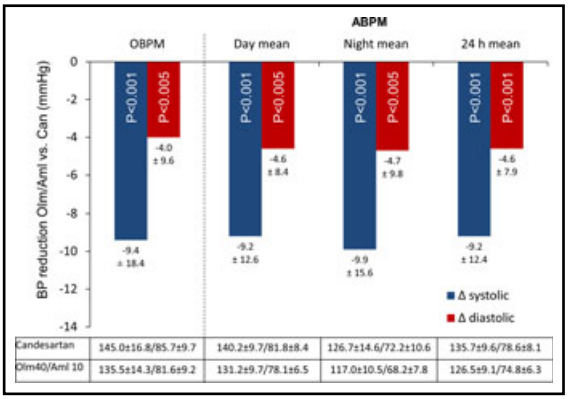

FIGURE 2. Blood pressure (BP) change after 6 weeks by olmesartan 40 mg/amlodipine 10 mg (visit 4) in comparison to prior candesartan 32 mg monotherapy (visit 3). Aml indicates amlodipine; ABPM, ambulatory BP monitoring; Can, candesartan; Olm, olmesartan.

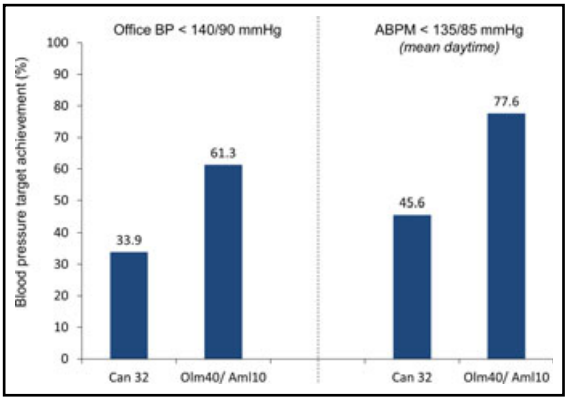

FIGURE 3. Blood pressure (BP) target achievement after 6 weeks of olmesartan/amlodipine (visit 4) compared with 6 weeks of candesartan monotherapy (visit 3). ABPM indicates ambulatory BP monitoring; Aml, amlodipine; Can, candesartan; Olm, olmesartan.

further decrease of 4.5/2.5 mm Hg (P=.03/.01; Figure 4). The percentage of nondippers decreased from 44% to 31%. In parallel, the group of normal dippers increased to 51% after switch to evening administration (Figure 5).

Safety

In total, 4 patients during washout, 9 during phase I, and 4 patients in phase II experienced at least 1 adverse event (AE). Eight of these were classified as possibly related to the study drug. There were 3 cases of edema, 3 cases of vertigo/decrease of BP, and 1 case each of excessive BP values and drug intolerability. No AE was recorded during phase III. The frequencies of clinically relevant AEs are listed in Table II.

In total, 1 patient experienced a severe AE. This was in phase II and was a coronary revascularization after dyspnea caused by worsening of pre-existing coronary

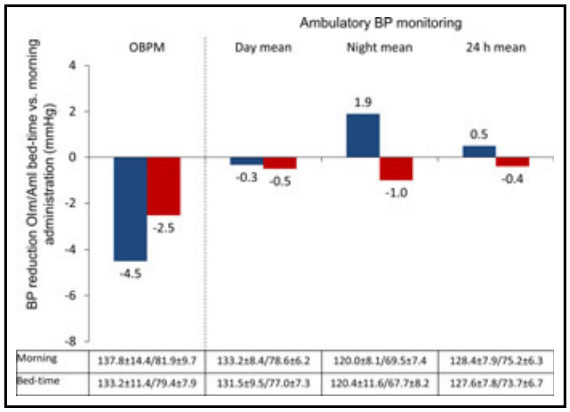

FIGURE 4. Blood pressure (BP) changes after 6 weeks of olmesartan 40 mg/amlodipine (Aml) 10 mg administered at bedtime (visit 5) compared with prior olmesartan (Olm) 40 mg/amlodipine 10 mg administered in the morning (visit 4). OBPM indicates office blood pressure measurement.

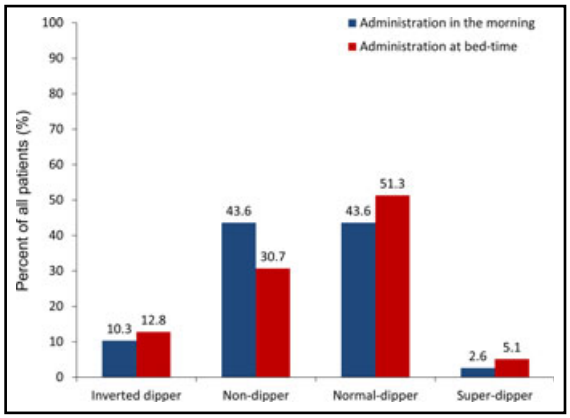

FIGURE 5. Non-normal and normal dipper rates according to morning and bedtime administration. Normal dippers were defined as patients with a reduction of ≥10% and <20% of the daytime mean during the night. Nondippers were defined as those with a reduction between ≥0% and <10% of the daytime mean. Inverted dippers were defined as those with a reduction <0% of the mean during daytime or an increase at night. Super (extreme) dipping was defined as a reduction at night that exceeded 20% of the values during the day.

artery disease. It was classified as not drug related by the treating physician. Study drug discontinuation due to an AE occurred in 2 patients in phase II. No increases in creatinine or potassium blood levels were documented.

DISCUSSION

Patients with uncontrolled arterial essential hypertension on candesartan 32 mg monotherapy experienced a further drop of both ambulatory and office BP when directly switched to treatment with the FDC olmesartan 40 mg/amlodipine 10 mg. There were 8 AEs with potential relation to the study drug (mostly edema), and 1 patient had a severe AE not classified as drug related.

TABLE II. Patient Safety

	Washout (n=83)		Phase I (n=78)		Phase II (n=62)		Phase III (n=51)	
Type of AE	No.	%	No.	%	No.	%	No.	%
Any AE, No. (%)	4	4.8	10	12.8	6	9.2	0	0.0
Serious AE[a]	0		0		1	1.5	0	0
Adverse drug reactions	0		0		1	1.5	0	0
Drug discontinuation because of AE	0		0		2	3.1	0	0
Cough/flushing	0		0		0		0	
Dizziness	0		1	1.3	0		0	
Hypotension	0		1	1.3	1	1.5	0	
Peripheral edema	0		1	1.3	2	3.1	0	
Other	4	4.8	7	9.0	3	4.6	0	

Abbreviation: AE, adverse event.

[a]Coronary revascularization.

Our results are in line with data supporting FDC treatment strategies in general and a combination of an ARB and a CCB in particular. Our results match those of the recent Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High BP (COACH) trial results, which compared efficacy and safety of an olmesartan/amlodipine combination with the component monotherapies.[1] Other trials with olmesartan and valsartan showed similar results regarding BP reductions with combination therapies in comparison to the component monotherapies.[6–9] Smith and colleagues[9] reported a significant and persistent reduction in BP over 52 weeks for the combination of amlodipine and valsartan and optional addition of hydrochlorothiazide with forced titration up to amlodipine 10 mg and valsartan 160 mg.

Switching Within and Off Label

In SEVICONTROL-1, we directly switched from candesartan monotherapy treatment to the FDC of olmesartan and amlodipine, a step not covered by the current labeling. That is why, in addition and in parallel to this, SEVICONTROL-2[5] was performed with a switch from candesartan to olmesartan monotherapy first and treatment escalation to olmesartan/amlodipine FDC in a second step, in order to stay within the current labeling. Both approaches, however, demonstrated a similar outcome. The daytime systolic BP reduction with the direct switch was 9.2±12.7 mm Hg while it was 9.8±15.2 mm Hg with the stepwise approach.

A few differences deserve note: (1) Although being largely comparable with respect to their BP-lowering effect, the different time to achieve the desired BP reduction was substantially shorter (6 vs 12 weeks) with the direct switch; (2) BP reduction was nominally higher with the stepwise approach, but the prolonged duration of the therapy with olmesartan 40 mg in the stepwise approach (6 weeks in monotherapy + 6 weeks in combination) may have favored this result; (3) the reduction of mean nighttime BP was 9.6/4.6 mm Hg with the direct switch and was 4.8/2.6 mm Hg with the stepwise approach. This difference was unforeseen and the loss of significance for the stepwise approach can only partially be explained by the lower patient number (33 for the stepwise evaluation and 47 for the direct switch); (4) although there was no safety concern with either approach, the sample size of both trials is limited to ascertain the safety of a direct switch in clinical practice; and (5) we acknowledge that a direct comparison of the direct and stepwise switching approach in a randomized controlled comparison would have been important and should be considered for future research.

Bedtime Administration

The potential benefit of a bedtime vs morning administration of olmesartan 40/amlodipine 10 mg was explored in (pilot) phase III of the present study. This was because another study by Hermida and colleagues[10] reported that a fixed combination of valsartan 150 mg/amlodipine 5 mg given at bedtime instead of in the morning resulted in a mean BP reduction of 4.3 mm Hg systolic and 0.8 mm Hg diastolic during the day (using ABPM) and 13.7 mm Hg systolic and 4.5 mm Hg diastolic during the night, resulting in pronounced dipping. For olmesartan monotherapy (20 mg), on the other hand, it was reported that the bedtime administration resulted in no further BP reduction during the day but during the night (systolic BP/diastolic BP 4.0/2.8 mm Hg). For amlodipine monotherapy, a total of 3 studies[11–13] reported no effect on the circadian rhythm when amlodipine was given at bedtime instead of in the morning. These results support the known sufficient long half-life of olmesartan and amlodipine resulting in a real 24-hour lasting efficacy.

There was a favorable trend in the reduction of nondippers, but, finally, the number of patients for these analyses was too low to statistically verify a significant effect. Interestingly, and this is in agreement with previous observations,[14] the proportion of patients with edema was reduced with bedtime administration. This administration time seems to be a particularly favorable

alternative for patients with prevalent edema caused by venous insufficiency or lymphedema.

CONCLUSIONS

Patients with uncontrolled moderate arterial hypertension treated with candesartan monotherapy experience a further reduction of BP when switched directly to an FDC of olmesartan 40 mg/amlodipine 10 mg. The safety of this approach has to be verified in a larger trial.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data. CZ and PB drafted the manuscript. The other authors revised the manuscript for important intellectual content, and all authors granted final approval of the manuscript to be published.

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Disclosures: SL, RS, JS, and PB received consultancy fees, attended advisory boards, and have held lectures for a number of pharmaceutical companies producing antihypertensive drugs, including Daiichi Sankyo Deutschland GmbH. CZ, AG, CDS, RF, and JN have no conflict of interest to declare.

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