Daytime Systolic Ambulatory Blood Pressure With a Two-Step Switch From Candesartan to Olmesartan Monotherapy and the Fixed-Dose Combination of Olmesartan/Amlodipine in Patients With Uncontrolled Essential Hypertension (SEVICONTROL-2)

Peter Bramlage, MD, PhD;[1] Claudia Zemmrich, MD;[1] Andrea Gansz, MS;[1] Claus-Dieter Sturm, PhD;[1,†] Rolf Fimmers, PhD;[2] Jennifer Nadal, MS;[2] Roland E. Schmieder, MD, PhD;[3] Joachim Schrader, MD, PhD;[4] Stephan Lüders, MD, PhD[4]

From the Institut für Pharmakologie und präventive Medizin, Mahlow, Cloppenburg, Germany;[1] Institut für Medizinische Biometrie, Informatik und Epidemiologie, Universitätsklinikum Bonn, Germany;[2] Medizinische Klinik 4, Universitätsklinikum Erlangen, Germany;[3] and St. Josephs Hospital, Cloppenburg, Germany[4]

The objective of this study was to investigate the efficacy of the fixed-dose combination olmesartan/amlodipine 40/10 mg in patients with moderate essential hypertension not controlled on candesartan 32 mg. This was a prospective, single-arm, phase IV study. The primary endpoint was the change in mean daytime systolic blood pressure (BP). A total of 77 of 89 screened patients started candesartan 32 mg, 62 olmesartan 40 mg, and 57 olmesartan 40 mg/amlodipine 10 mg. Mean daytime systolic BP was reduced by 9.8±15.2 mm Hg ($P<.001$) vs candesartan monotherapy. Office BP reduction was 9.2±18.8/5.0±8.9 mm Hg ($P<0.001$). Treatment goals (<140/90 mm Hg for office and <135/85 mm Hg for ambulatory BP) were achieved in 58.2% and 78.4% of patients, respectively. There was one drug-related adverse event (edema) and no serious adverse events. Patients of Caucasian ethnicity with moderate essential hypertension uncontrolled on candesartan experienced a further drop in BP using olmesartan and amlodipine. *J Clin Hypertens (Greenwich).* 2014;16:41–46.

Despite a growing number of effective antihypertensive drugs, blood pressure (BP) in hypertensive patients is largely uncontrolled.[1,2] Angiotensin receptor blockers (ARBs) are generally perceived to be effective and particularly tolerable first-line antihypertensive drugs but usually have to be combined with additional drugs to achieve guideline-recommended treatment targets.[3–5] The combination of ARBs with calcium channel blockers (CCBs) has proven to be particularly effective mitigating the side effect profile (edema) of CCBs.[6] Their use has increased after the publication of the results from the Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, in which benazepril was combined with amlodipine.[7,8]

Since fixed-dose combinations (FDCs) with CCBs are available only for a subset of ARBs (but not candesartan, for example), treatment escalation using FDCs may require first switching the ARB and then escalating treatment. This is because labels of FDCs usually suggest that either of the components was previously used and failed to achieve BP control.

The aim of the present study was to determine the incremental BP-lowering effects of olmesartan 40 mg/amlodipine 10 mg FDC over prior monotherapy with candesartan 32 mg. To stay within label we chose a two-step design where candesartan was first exchanged for olmesartan and then escalated treatment using the FDC.

METHODS

Design

The study was a multicenter, prospective, open-label, single-arm, phase IV study according to the International Conference on Harmonisation guidelines of Good Clincal Practice and was approved by the ethics committee of the Lower Saxony State Chamber of Physicians in Hannover, Germany and the responsible health authority (BfArM, Federal Institute for Drugs and Medical Devices). It was performed between December 2011 and July 2012. Patients' written informed consent was obtained. The study was registered at clinicaltrials.gov with the identifier NCT01611077.

The study consisted of 3 phases (Figure 1): After a washout of 2 weeks, there was a 6-week treatment phase I using candesartan 32 mg, a subsequent 6-week treatment phase II using olmesartan 40 mg, and a treatment phase III with the FDC olmesartan 40 mg/amlodipine 5 mg for 2 weeks, followed by 4 weeks of olmesartan 40 mg/amlodipine 10 mg. Patients were eligible to enter the next study phase if BP targets were not achieved during the previous study phase.

Patient Population

Men and women aged at least 18 years with uncontrolled systolic grade II hypertension defined as systolic

†Deceased.

Address for correspondence: Priv.-Doz. Dr. Peter Bramlage, Institut für Pharmakologie und präventive Medizin, Menzelstrasse 21, 15831 Mahlow, Cloppenburg, Germany
E-mail: peter.bramlage@ippmed.de

Manuscript received: August 12, 2013; **revised:** October 4, 2013; **accepted:** October 6, 2013
DOI: 10.1111/jch.12227

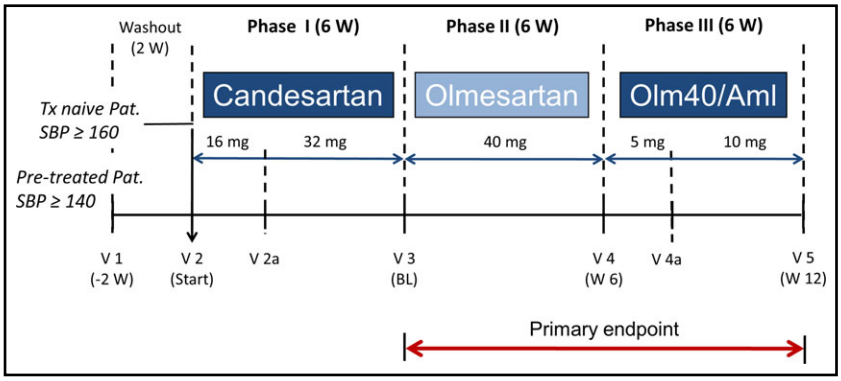

FIGURE 1. Study design. Aml indicates amlodipine; BL, baseline; Olm, olmesartan; SBP, systolic blood pressure; Tx, treatment; V, visit; W, week.

BP of at least 140 mm Hg with antihypertensive pretreatment and at least 160 mm Hg at the end of the washout phase OR at least 160 mm Hg when being treatment-naive were eligible for the study.

Patients who were excluded were those with a systolic office BP >180 mm Hg at the screening visit, known hypertensive retinopathy grade III or IV, myocardial infarction within the last 4 weeks or planned coronary or peripheral artery revascularization procedure, diabetes mellitus (type 1 or poorly controlled type 2 diabetes with glycated hemoglobin of at least 8 mmol/L), New York Heart Association class III or IV heart failure, history of stroke, transient ischemic attack, significant mitral or aortic valve disease of at least grade II or hypertrophic cardiomyopathy, significant hepatic or renal disease (alanine and aspartate aminotransferase, bilirubin >2-fold increase, creatinine clearance <60 mL/min or after renal transplantation), pregnant or nursing women as well as women of child-bearing potential not using an effective method of contraception, black patients and patients receiving lithium or other strong CYP3A4 inducers or inhibitors, patients with anticipated poor study compliance because of severe psychiatric or other comorbidity or limited life expectancy <6 months, night shift workers, and the inability to safely discontinue all antihypertensive medications for a washout period of 2 weeks.

Endpoints

The primary efficacy criterion was the change in mean daytime systolic BP assessed by 24-hour ambulatory BP measurement (ABPM) between visit 3 and 5. This corresponds to the end of the olmesartan 40 mg/amlodipine 10 mg treatment phase vs the initial candesartan treatment phase.

Secondary endpoints included mean night, mean 24-hour systolic and diastolic BP reduction, as well as office BP reduction between visits 3 and 5 and BP target achievement (defined as office BP <140/90 mm Hg; mean daytime BP using ABPM <135/85 mm Hg).

Safety endpoints included cardiovascular events as well as type and frequency of adverse events (AEs) or serious AEs (SAEs) during treatment with (1) candesartan, (2) olmesartan, and (3) the FDC olmesartan/amlodipine. Serum potassium and serum creatinine levels were obtained at screening visit 1, 7 to 10 days after visit 2 (start of treatment phase I), and visit 3 (start of treatment phase II).

BP Measurement

ABPM was performed over 24 hours within 2 days prior to visits 3, 4, and 5. Sitting office BP was recorded at each visit.[9] For this purpose, BP was taken with a standard sphygmomanometer with an appropriate cuff size after 5 minutes of rest with the higher baseline value supported at the level of the heart.

Statistical Analyses

The sample size was based on an estimated mean daytime BP reduction using an ABPM of 8 mm Hg and a standard deviation of 16 mm Hg. At an intended power of 90%, this corresponded to the documentation of 44 evaluable patients. Because of an anticipated substantial drop-out rate based on the expected number of patients reaching BP targets within the different treatment phases and/or AEs, we estimated that 80 patients would have to be included into the study.

Data were documented on a paper case report form and entered in duplicate into a Microsoft Access database. Analyses were conducted with SPSS 17.0 (SPSS, Inc, Chicago, IL). For the primary endpoint, the mean change in systolic mean daytime BP (ABPM) between visit 3 and visit 5 was calculated and tested against the null hypothesis of no change using a 2-sided *t* test at a 2-sided α of 0.05.

For the safety analysis, absolute and relative frequencies for AEs and SAEs were calculated and a potential causal relationship to the study drug assessed.

RESULTS

A total of 89 patients were screened, of which 77 patients entered treatment phase I. These patients had a mean age of 56±15 years, 49% were women, and had

a mean body mass index of 29±5 kg/m^2 and office BP of 160±12 mm Hg systolic/94±9 mm Hg diastolic (Table I). Figure 1 displays the study design with the 3 study phases. Candesartan was discontinued during or at the end of phase I in 15 patients (Figure 2): 7 patients were lost to follow-up, 4 patients achieved BP targets, and 2 were dropped because of adverse events and 2 withdrew consent. Overall, 62 patients entered treatment phase II. Five patients discontinued olmesartan during this phase: 4 achieved BP target and 1 withdrew consent. The remaining 57 patients entered treatment phase III. At the end of phase III, a total of 33 patients were available for the primary efficacy analysis (visit 3 vs visit 5).

TABLE I. Patient Baseline Characteristics

	Phase I	Phase II	Phase III
Patient, No.	77	62	57
Age, mean±SD, y	56±15	56±15	55±15
Women, %	49	45	44
BMI, mean±SD, kg/m^2	29±5	29±5	29±5
Heart rate, mean±SD, beats per min	76±9	76±9	76±15
Office BP, mean±SD, mm Hg			
Systolic	160±12	141±17	140±18
Diastolic	94±9	85±10	84±11
Hypertension pretreated, %	61	66	65
Diabetes, %	18	21	21
Laboratory values			
Creatinine, mg/dL±SD	77±15	80±15	80±15
Potassium, mmol/L±SD	4.7±0.8	4.8±0.9	4.8±1.0

Abbreviations: BMI, body mass index; BP, blood pressure; SD, standard deviation.

BP Reduction

The primary efficacy endpoint was the change in mean daytime systolic ambulatory BP at the end of treatment with the fixed combination olmesartan 40 mg/amlodipine 10 mg compared with candesartan monotherapy. Mean systolic BP decreased by 9.8±15.2 mm Hg from a baseline value of 136.9±11.2 mm Hg (*P*=.0008) (Figure 2).

Consistent with this, the mean daytime diastolic BP was decreased by 5.2±11.3 mm Hg (*P*=.012) as was the mean 24-hour BP (7.8±14.7 mm Hg systolic; 5.1±9.8 mm Hg diastolic; *P* value for both <.01). The nominal reduction of nighttime BP (4.8±15.9/2.6±10.1 mm Hg) did not reach statistical significance (*P*=.10; *P*=.15).

In parallel with the drop in ambulatory BP, office BP was reduced by 9.2±18.8 mm Hg systolic (*P*=.0006) and 5.0±8.9 diastolic (*P*=.0001) (Figure 3).

BP Target Achievement

BP target achievement rates for ABPM (<135/85 mm Hg) were 34.0%, 63.8%, and 78.4% at the end of the 3 treatment phases, respectively. For office BP measurements (<140/90 mm Hg), target achievement rates were 40.6% with candesartan monotherapy, 43.6% with olmesartan monotherapy, and 58.2% with FDC treatment (Figure 4).

Safety

Adverse events were experienced by 1 patient during washout, 2 patients in treatment phase I, 3 patients in phase II, and 1 patient in phase III. There was 1 drug-related AE during phase III (edema) (Table II). No SAEs were observed during the study and no

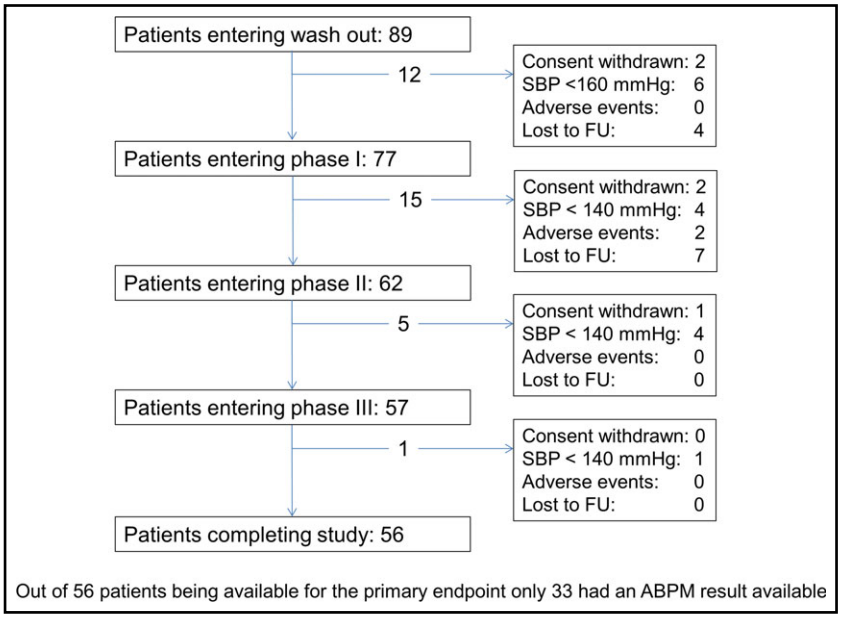

FIGURE 2. Patient flow. SBP indicates systolic blood pressure; FU, follow-up.

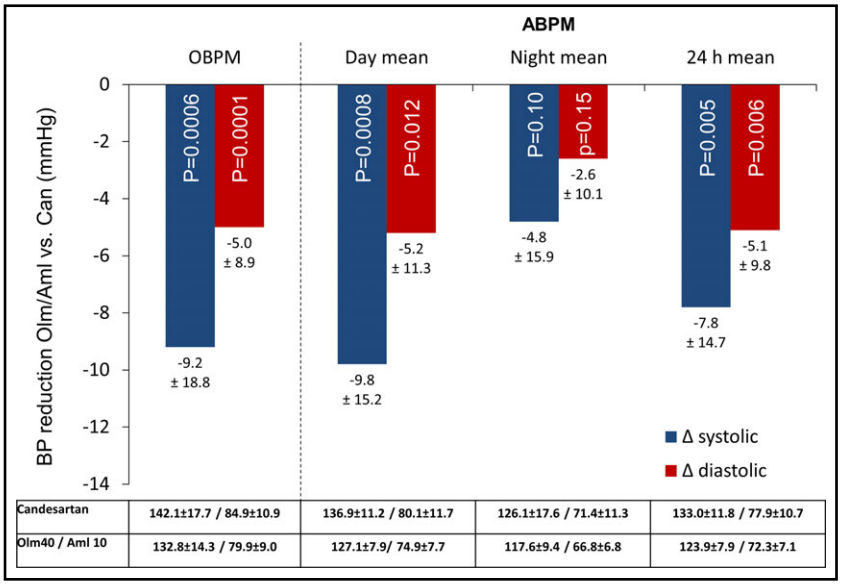

FIGURE 3. Blood pressure (BP) change after 12 weeks by olmesartan 40 mg and following olmesartan 40 mg/amlodipine 10 mg (visit 5) in comparison to prior candesartan 32 mg monotherapy (visit 3). Aml indicates amlodipine; ABPM, ambulatory blood pressure monitoring; OBPM, office blood pressure measurement; Can, candesartan; Olm, olmesartan.

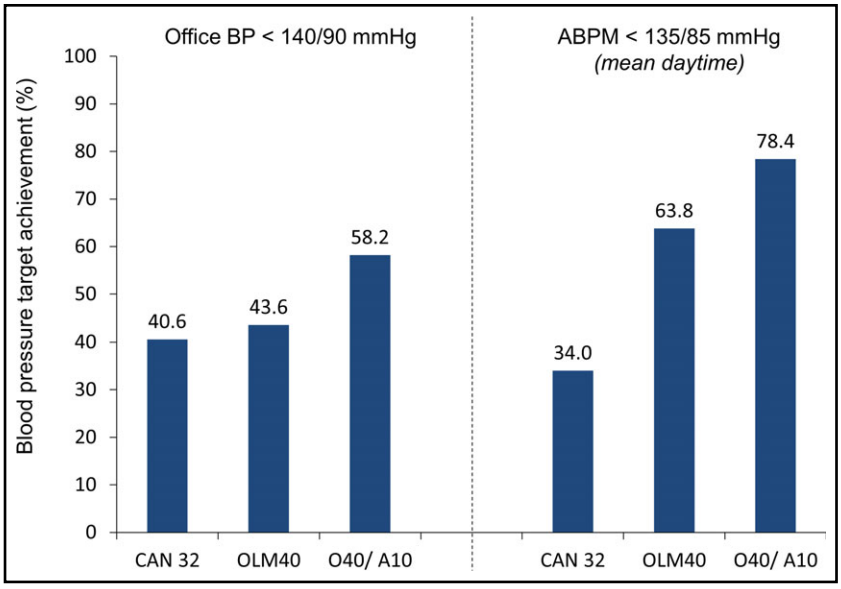

FIGURE 4. Blood pressure (BP) target achievement per treatment phase. ABPM indicates ambulatory blood pressure monitoring; A, amlodipine; Can, candesartan; O/OLM, olmesartan.

increased serum creatinine or potassium levels reported.

DISCUSSION

Patients being uncontrolled using 32 mg of candesartan experienced a further drop of BP when switched to an FDC of olmesartan and amlodipine. Treatment escalation was associated with edema in 1.8% (1) of patients. In a phase IIIb study (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]) in the same issue of this *Journal*,[10] we demonstrated that the direct switch from candesartan to olmesartan in FDC with amlodipine is effective.

TABLE II. Patient Safety

	Phase I (n=77)	Phase II (n=62)	Phase III (n=57)
Any AE	2 (2.6)	3 (4.8)	1 (1.8)
Drug discontinuation because of AE	1 (1.3)	0	1 (1.8)
Hypotension	1 (1.3)		
Peripheral edema		1 (1.6)	1 (1.8)
Muscle pain	1 (1.3)		
Other		2 (2.3)	

Abbreviation: AE, adverse event. Values are expressed at number (percentage).

BP-Lowering Effect in Comparison

The efficacy of olmesartan/amlodipine has been evaluated in 3 randomized, double-blind trials: the Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) compared the efficacy of the dual combination with its component monotherapies,[6,11] and 2 further trials evaluated the combination in patients with inadequate response to amlodipine or olmesartan monotherapy[12,13] but used the lower dose combination of olmesartan 20 mg and amlodipine 5 mg, making a direct comparison difficult.

In the COACH trial, combination of olmesartan 40 mg/amlodipine 10 mg led to a further 13.1 mm Hg systolic BP reduction compared with olmesartan 40 mg monotherapy using office measurement (8.5 mm Hg diastolic BP reduction). Office BP target achievement (BP <140/90 mm Hg) in that trial was 54% with olmesartan 40 mg/amlodipine 10 mg and thus comparable to our own data presented here. Other trials with olmesartan and valsartan showed similar results regarding BP reductions with combination therapies in comparison to the component monotherapies.[14–17] Smith and colleagues 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.[17] Reduction in office systolic/diastolic BP from baseline was 22.8/18.1 mm Hg for a high-dose regimen vs placebo in that study. Overall target achievement rates (<140/90 mm Hg in nondiabetic and <130/80 mm Hg in diabetic patients) were 49.1%. The following differences in trial design vs our own study appear noteworthy: (1) the trial duration was 2 weeks longer in the COACH study than in our own, (2) they used office measurements instead of ABPM, (3) the trial was substantially larger with about 160 patients per treatment group, (4) it was randomized and used placebo control while we had a sequential trial design, (5) we used the threshold of <140/90 mm Hg for all patients during office BP measurement. Taken together these differences may explain why the BP reduction in COACH was larger than in our own observations.

ABPM vs OBPM

None of the above-mentioned studies used ABPM for efficacy analysis of different antihypertensive treatment strategies. Study results substantially differ if single measurements are compared.[18,19] In our study, a comparable BP-lowering effect was seen throughout all measurements in the ambulatory and office setting with a slightly higher rate of BP target achievement using ABPM compared with OBPM. Differences between the two methods are of specific interest since ABPM is not prone to the white-coat effect and related BP elevations frequently seen during office measurement, and therefore may not translate into persistently elevated BP values.[19] We observed only minor numerical differences in the treatment effect between ABPM and OBPM. This may be explained by the OBPM-obtaining technique, which was used to generate BP values. An average value of 3 measurements taken after at least 5 minutes of rest had to be recorded, not only one random measurement. This approach minimizes BP differences between both techniques.[20]

Safety and Tolerability

In the aforementioned COACH trial,[6,11] 26.9% of patients experienced a drug-related treatment-emergent AE. Peripheral edema was the most common adverse event affecting 385 of the 1940 patients (19.8%). Other reported AEs were headache (6.7%), dizziness (3.9%), and fatigue (3.2%). Edema in particular was less frequent in patients receiving the combination treatment compared with amlodipine alone. Smith and colleagues[17] reported that frequent AEs in the low- and high-dose regimen were peripheral edema (9.7% and 17.1%), nasopharyngitis (8.1% and 7.2%), and dizziness (5.2% and 7.0%), respectively. Incidence of SAEs was 3.7% with the low-dose and 4.1% with the high-dose regimen. Our own data support these previous data. Our sample size, however, was not sufficient to finally evaluate safety of this approach and might have been too small to detect less frequent side effects of the treatment switch.

Limitations

The study was an open-label, single-arm study within the current labeling of most FDCs that require BP being not sufficiently controlled on one of the components of the later FDC therapy. The absence of a control group, however, only allows to compare sequential BP values and these may be prone to bias. Because of the setting in Germany, we were not able to enroll black hypertensive patients (excluded) and thus the results only apply to patients of Caucasian ethnicity.

We determined our sample size (44 evaluable patients) based on the estimated mean systolic daytime BP using ABPM, and although we enrolled more patients, only 33 were finally available for the analyses. This does not, however, compromise the study results, but may have resulted in the inability to verify the reduction in nighttime BP (a secondary endpoint), which did not reach statistical significance (Figure 3).

CONCLUSIONS

Patients of Caucasian ethnicity with moderate essential hypertension, uncontrolled on candesartan monotherapy, experienced a further drop in BP when receiving an FDC of olmesartan and amlodipine.

Authors Contributions: All authors made substantial contributions to conception and design or 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.

Conflict of Interest: SL, RS, JS, and PB have received consultancy fees, attended advisory boards, and have held lectures for a number of pharmaceutical companies that produce antihypertensive drugs, including Daiichi Sankyo Deutschl and GmbH. CZ, AG, CDS, RF, and JN and have no conflict of interests to declare.

Acknowledgments: We are indebted to Kerstin Plate, IPPMed – Institut für Pharmakologie und präventive Medizin GmbH Cloppenburg, for the trial organization and management. The authors acknowledge the cooperation and commitment of all investigators and their staff who contributed to the trial conduct.

Sponsorship/Funding: The Institut für Pharmakologie und präventive Medizin sponsored the study and received unrestricted research funding from Daiichi Sankyo Germany.

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