Comparative study of the efficacy of olmesartan/amlodipine vs. perindopril/amlodipine in peripheral blood pressure after missed dose in type 2 diabetes

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Introduction: Combination therapy is needed to control blood pressure (BP) in a large number of hypertensive patients with diabetes mellitus. Adherence to treatment is a major clinical problem; therefore, the time duration of the antihypertensive action of a drug determines BP control when a dose is skipped.

Objectives: The aim was to determine whether the fixed-dose combination of olmesartan/amlodipine provides equal efficacy and safety as the perindopril/amlodipine combination when a drug dose is missed.

Methods: In this noninferiority trial with a randomized, double-blind, double-dummy parallel group, controlled design, 260 patients received either olmesartan 20–40 mg/amlodipine 5–10 mg or perindopril 4–8 mg/amlodipine 5–10 mg for 24 weeks. The main outcome was the sitting office DBP after 24 weeks of treatment at 48 h from last administration.

Results: The olmesartan/amlodipine combination reached noninferiority criteria in reduction of office DBP after 24 weeks of treatment and after the missed dose, compared with the perindopril/amlodipine combination (−11.7 and −10.5 mmHg, respectively). Office SBP and pulse pressure were significantly lower in both groups after 24 weeks of treatment and 48 h after the missed dose, observing a trend to greater SBP reduction in the olmesartan/amlodipine group.

Conclusions: The combination olmesartan/amlodipine is safe, well tolerated, and as effective as the combination of perindopril/amlodipine in the control of essential hypertension in patients with diabetes mellitus. A missed dose does not leave the patients unprotected in both treatments; however, a faster control with less dose increment is observed with olmesartan/amlodipine.

Keywords: amlodipine, antihypertensive agents, blood pressure, diabetes mellitus, olmesartan, perindopril

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; BP, blood pressure; FAS, full analysis set; HR, heart rate; LOCF, last observation carried forward; oDBP, office sitting DBP; oSBP, office sitting SBP; V, visit

INTRODUCTION

Antihypertensive treatment reduces cardiovascular morbidity and mortality. The main benefits of antihypertensive treatment are mediated by lowering peripheral blood pressure (BP) per se, and the reduction of cardiovascular risk followed by BP lowering is largely independent from the drugs employed [1]. However, combination treatment is needed to control BP in most patients and the addition of a drug from another class should thus be regarded as a recommended treatment strategy, unless the initial drug needs to be withdrawn [2–4]. This is especially the case in patients with high cardiovascular risk and diabetes mellitus. Diabetes mellitus leads to numerous changes of the vessel structure and function; as a consequence, diabetic patients frequently need more than one drug for adequate BP control. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers are two groups of antihypertensive medication recommended for first line treatment in diabetic patients, and combinations with diuretic or calcium channel blockers are recommended when monotherapy does not achieve the BP goals. Additive effect on BP lowering and reduction in side-effects have been described with the combination therapy [5].

One major problem in clinical practice is the patients' adherence to treatment, which is directly related to the number of pills to be taken [6–8]. Fixed-dose combinations have shown to improve adherence by reducing the total number of pills. Despite the improvement in adherence, patients frequently miss doses and, in this case, the lack of adherence affects concomitantly all the given treatment. The time duration of the antihypertensive action of a drug

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determines BP control when a dose is skipped. Patients might benefit from antihypertensive drugs that act for longer than 24 h, as a missed dose can partially be compensated by the long-acting drug effect, although information about the persistence of the antihypertensive efficacy of combination therapy has not been assessed.

Perindopril and olmesartan are two compounds frequently used for antihypertensive treatment that have shown antihypertensive efficacy, including 24-h BP reduction and good tolerability profile. Proven efficacy and safety in both monotherapy and combination with amlodipine have been described [9–15]. However, it is unclear whether the combination of perindopril or olmesartan with amlodipine provides equal efficacy and safety when a drug dose is missed. The primary objective of the present study is to determine whether the fixed-dose combination of olmesartan 20–40 mg/amlodipine 5–10 mg is at least as effective as the perindopril 4–8 mg/amlodipine 5–10 mg combination in reducing office sitting DBP (oDBP) after 24 weeks of treatment at 48 h from the last administration (missed dose). The efficacy on office sitting SBP (oSBP) and pulse pressure and safety issues were also assessed.

STUDY PARTICIPANTS AND METHODS

Design

The study design was a non-inferiority controlled trial with a randomized, double-blind, double-dummy, parallel group (EUDRA-CT No.: 2010-018774-2) (Fig. 1). Eligible patients started 1 or 2 weeks [visit 1 (V1)] of run-in period during which they were treated with amlodipine, 5 mg once a day in open-label conditions. At the end of the run-in period (V2), patients matching inclusion criteria were randomized to the first 12 weeks of randomized, double-blind, double-dummy treatment. During this period, patients received either a combination of olmesartan 20 mg + amlodipine 5 mg once a day, or perindopril 4 mg + amlodipine 5 mg once a day in 1 : 1 ratio. After 12 weeks (V4) of combined treatment in patients not normalized by the treatment, the dose of the treatment drug was uptitrated to olmesartan 40 mg + amlodipine 5 mg once a day or perindopril 8 mg + amlodipine 5 mg once a day. At week 18 (V5), in patients not normalized after 6 additional weeks of treatment, the dose of the drug was further uptitrated to olmesartan 40 mg + amlodipine 10 mg once a day or perindopril 8 mg + amlodipine 10 mg once a day. At V6a (week 24), patients received placebo treatment in a single-blind for 1 day (V6b).

Study population

Study participants 40–70 years old of both sexes with type 2 diabetes mellitus and hypertension were enrolled. An oSBP between 140 and 179 mmHg and an oDBP between 90 and 109 mmHg were required either in never treated patients or in the ones taking one or two antihypertensive medications, excluding test drugs combinations. In addition, inclusion criteria required diet or oral glucose lowering drugs for the treatment of diabetes and HbA1c $\leq$ 7.5% before randomization. Women of childbearing potential were required to have a negative urine pregnancy test and to use adequate contraceptive methods. The exclusion criteria are listed in supplementary Table 1, http://links.lww.com/HJH/A548. Protocol was approved by the ethics committees of the institutions including patients. Written informed consent prior to enrolment was required.

Methods

During clinical evaluations (visits), BP measurement, physical examination, recording of concomitant medications and adverse events, collection of unused drugs, and compliance check were performed. After the run-in with amlodipine, if eligible, the patients were randomized to receive one of the two treatments and the study

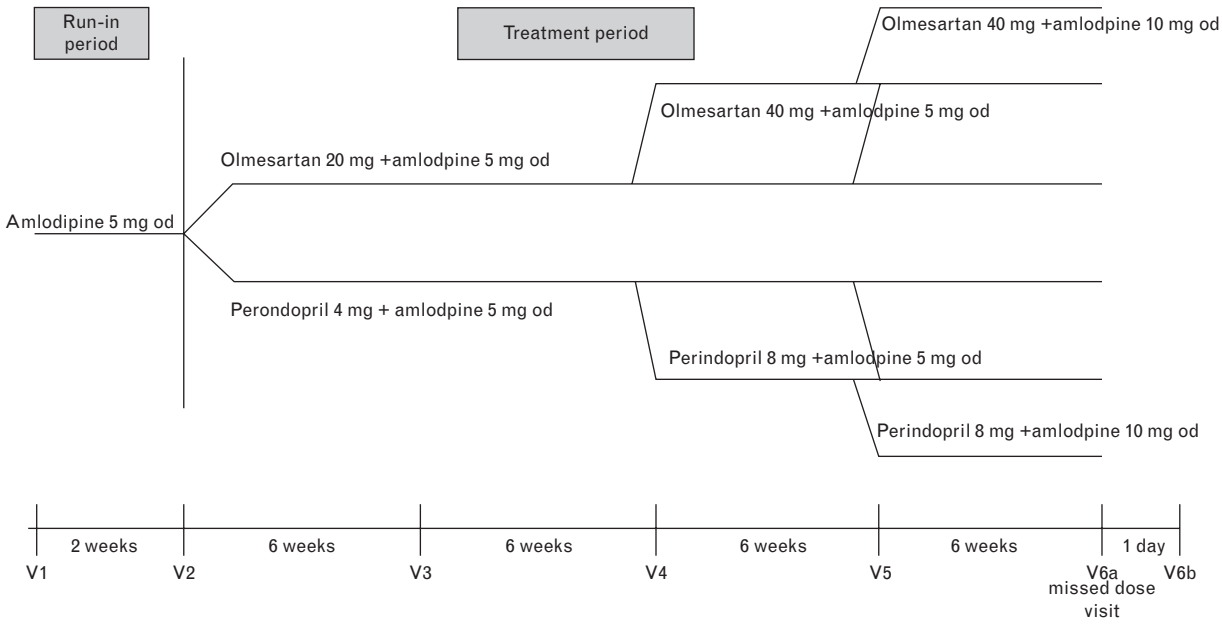

FIGURE 1 Study design.

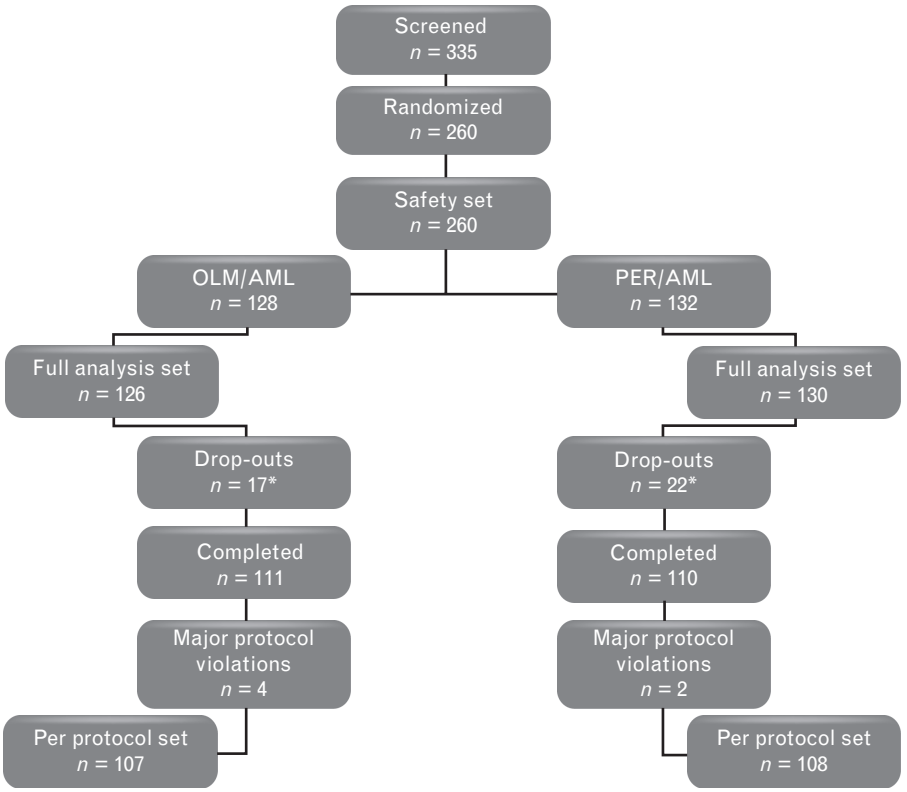

FIGURE 2 Flow chart of the patients included in the study.

medication was dispensed, and the first dose of double-blind medication administered. The measurement of office BP was performed in accordance with European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines. Office BP and heart rate (HR) were measured at brachial artery level or upper arm in triplicate at 2-min intervals by an automated electronic digital sphygmomanometer (Omron 705CP; Omron Healthcare, Lake Forest, Illinois, USA) after sitting for 5 min. The measurement was performed 24 ± 2 h after the last active drug intake at all visits, except at V6 (or early withdrawal), where it had to be measured at 24 ± 2 h and 48 ± 2 h after last drug intake. For safety purposes, after the sitting BP measurement was taken in triplicate, the patient was kept in a standing position for 1 min before standing BP evaluation was performed. The standing BP measurement was repeated after a further 4 min. For each patient, BP was measured in the nondominant arm at each visit. Treatment compliance was monitored from V2 to V6b in all patients by counting the number of tablets returned.

Safety

Secondary effects were collected at each visit by symptoms, physical examination, and HR. ECG abnormalities and laboratory parameters (haematology, blood chemistry, urinalysis) were assessed at baseline and at the end of the study period. The overall incidence of adverse events was recorded.

Statistical methods

The main outcome was the (brachial) sitting oDBP change after 24 weeks of treatment at 48 h from last administration (missed dose) (baseline minus V6b). The statistical analyses were designed to assess the noninferiority and safety of the olmesartan plus amlodipine combination, the experimental group, in comparison with the perindopril plus amlodipine combination, in the primary efficacy variable. Given the noninferiority design, the primary analysis was performed on both the full analysis set (FAS) and per-protocol sets, and results obtained on the FAS were carefully interpreted in light of those obtained on the per-protocol one. The analysis was performed by estimating the 95% confidence interval (two-sided) of the between-treatments difference in the changes in sitting oDBP (24 weeks or early withdrawal minus baseline). If the noninferiority was reached, then superiority was tested. In the case that the lower boundary of the 95% confidence interval was greater than zero, then an additional claim of superiority to the previous noninferiority conclusion was considered as met if obtained in the FAS. Mean changes from baseline were analysed using a maximum likelihood-based repeated measures approach, using a longitudinal mixed model for repeated measurements. Last observation carried forward (LOCF) method was applied to the FAS population. Secondary continuous variables were analysed according to similar methods described for the primary endpoint, whenever applicable. Fisher's exact test was used to compare categorical variables between treatment groups. The safety set included all randomized patients who took at least one dose of the study medication.

Sample size was calculated considering data coming from other antihypertensive studies based on the missed dose using ACEIs or AT1-antagonists, alone or in combination [16–18]. One hundred patients in each treatment

TABLE 1. General characteristics of the study population

	Olmesartan/amlodipine	Perindopril/amlodipine	*P* value
Study participants (*n*)	128	132	
Age (years)	58.91 ± 7.47	59.18 ± 7.29	0.764
Men/women, *n* (%)	87 (68)/41 (32)	85 (64.4)/47 (35.6)	0.600
Weight (kg)	82.44 ± 12.56	84.11 ± 12.09	0.275
Height (m)	169.24 ± 8.87	169.92 ± 8.84	0.535
BMI (kg/m^2)	28.69 ± 3.38	29.02 ± 3.16	0.409
Waist circumference (cm)	101.31 ± 8.62	102.58 ± 9.16	0.254
SBP (mmHg)	156.59 ± 10.62	156.04 ± 10.34	0.674
DBP (mmHg)	96.95 ± 4.11	96.94 ± 4.49	0.980
Heart rate (bpm)	74.46 ± 11.46	76.11 ± 10.84	0.235
Hypertension duration (months)	115 ± 91.80	118.15 ± 106.11	0.798
Hypertension treatment, *n* (%)			
Never treated	14 (10.9)	20 (15.2)	0.278
Treated but not normalized	114 (89.1)	112 (84.8)	
Diabetes mellitus II duration (months)	61.83 ± 54.93	66.25 ± 62.66	0.546
Control of diabetes mellitus II, *n* (%)			
Diet	50 (39.1)	50 (37.9)	0.899
Hypoglycaemic drug	78 (60.9)	82 (62.1)	
Fasting glucose (mg/dl)	113.41 ± 29.48	112.97 ± 25.04	0.897
HbA1c (%)	6.20 ± 0.72	6.14 ± 0.59	0.444
Creatinine (mg/dl)	0.90 ± 0.19	0.87 ± 0.19	0.207
Uric acid (mg/dl)	5.85 ± 1.35	5.98 ± 1.54	0.502
Total cholesterol (mg/dl)	197.24 ± 38.51	194.67 ± 38.73	0.591
LDL cholesterol (mg/dl)	118.38 ± 32.93	115.76 ± 31.72	0.513
HDL cholesterol (mg/dl)	47.97 ± 12.12	51.71 ± 14.24	0.024
Triglicerides (mg/dl)	158.49 ± 96.22	135.01 ± 63.52	0.022

Data are mean SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

group were required to have 80% power in a 0.025 one-sided *t*-test and to reject the null hypothesis with a lower margin of acceptance for the difference reference test in changes from baseline of −4 mmHg.

RESULTS

General characteristics of the study population

The population recruited in this study consisted of 260 patients (128 patients in the olmesartan/amlodipine group and 132 patients in the perindopril/amlodipine group, respectively) of both sexes, with a prevalence of men (68.0%) and with a wide age range (40–78 years) and similar median age in both groups (Fig. 2). General characteristics of the study population are shown in Table 1. On an average, the patients were overweight with a similar median BMI in both treatment groups. Most of the patients had a long-lasting hypertension history (duration in months: 115 and 118.15 in olmesartan/amlodipine and perindopril/amlodipine groups, respectively), 12.5% in the olmesartan/amlodipine group and 7.6% in the perindopril/amlodipine group had chronic kidney disease, and no previous cardiovascular event, myocardial infarction, stroke, or peripheral artery occlusion was present in the patients enrolled.

There were no significant differences between the two treatment groups at study entry in the percentage and/or kind of glucose lowering and antihypertensive drugs

TABLE 2. Blood pressure levels over study visits

	Baseline (Visit 2)	Visit 3	Visit 4	Visit 5	Visit 6a	Visit 6b	*P* overall[a]	*P* visit 6a[b]	*P* visit 6b[b]
SBP (mmHg)									
Olmesartan/amlodipine	155.17 ± 10.22	141.72 ± 13.16	140.47 ± 14.64	137.14 ± 12.78	135.65 ± 13.39	138.57 ± 13.77			
Perindopril/amlodipine	154.33 ± 9.59	145.43 ± 14.51	143.66 ± 14.90	139.25 ± 14.29	138.06 ± 13.49	141.54 ± 14.30	0.012	0.032	0.026
DBP (mmHg)									
Olmesartan/amlodipine	96.31 ± 4.99	85.76 ± 8.09	85.41 ± 8.56	84.13 ± 7.58	82.18 ± 7.82	84.61 ± 8.41			
Perindopril/amlodipine	96.28 ± 4.62	88.41 ± 8.44	87.72 ± 8.16	84.88 ± 9.22	83.08 ± 8.10	85.75 ± 8.27	0.058	0.387	0.296
Pulse pressure (mmHg)									
Olmesartan/amlodipine	58.86 ± 11.13	55.96 ± 11.49	55.06 ± 11.41	53.02 ± 9.70	53.47 ± 10.82	53.96 ± 10.98			
Perindopril/amlodipine	58.05 ± 9.80	57.02 ± 11.67	55.94 ± 11.17	54.38 ± 10.42	54.98 ± 11.86	55.78 ± 12.45	0.099	0.059	0.053
Heart rate (bpm)									
Olmesartan/amlodipine	74.83 ± 11.71	74.23 ± 11.38	75.49 ± 11.59	73.81 ± 10.69	74.59 ± 11.02	73.51 ± 10.18			
Perindopril/amlodipine	75.82 ± 9.88	75.43 ± 11.21	75.42 ± 10.95	73.75 ± 10.37	74.50 ± 11.01	72.24 ± 10.95	0.239	0.293	

Data are mean SD.
[a]*P* value for treatment effect after adjustment for country, visit, treatment by visit interaction, and baseline measure.
[b]*P* value at Student's *t* test comparing BP reductions with respect to baseline in the two treatments.

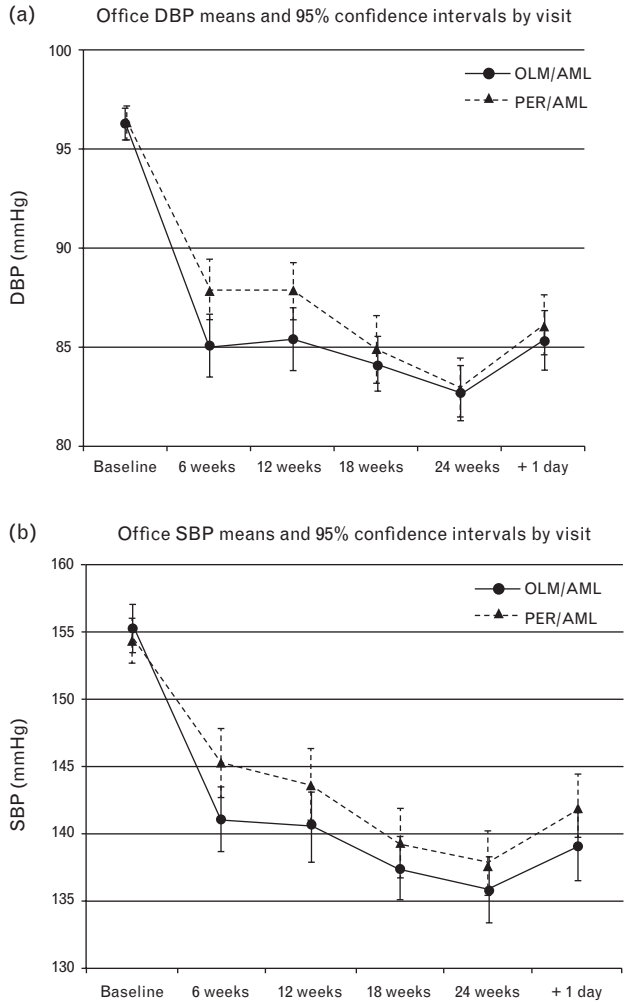

FIGURE 3 (a) Main outcome of the study: office DBP means and 95% CI at baseline and during the study visits. No significant differences were observed between olmesartan 20–40 mg/amlodipine 5–10 mg and perindopril 4–8 mg/amlodipine 5–10 mg. (b) Secondary outcome of the study: office SBP means and 95% CI at baseline and during the study visits. Significant differences were observed between olmesartan 20–40 mg/amlodipine 5–10 mg and perindopril 4–8 mg/amlodipine 5–10 mg at visit 6a ($P = 0.032$) and 6b ($P = 0.012$) (see text). CI, confidence interval.

(see Table 1). Baseline BP values are shown in Table 2, and the profile of change in SBP and DBP during the study is shown in Fig. 3a and b. Fig. 4 shows the DBP reduction in each of the visits during the trial.

Primary endpoint

In the FAS population, the decrease in oDBP after the missed dose, V6b, vs. baseline (V2) was −11.7 mmHg (12.2%) and −10.5 mmHg (10.9%), respectively, in olmesartan/amlodipine-treated patients and in perindopril/amlodipine-treated ones. The noninferiority, demonstrated since the lower limit of 95% confidence interval is higher than −4 mmHg (predefined not inferiority margin), was reached in the FAS and in PPS. The total treatment effect on oDBP reduction shows a positive trend (P value = 0.058) in favour of olmesartan/amlodipine in the FAS population. Moreover, the decrease in oDBP was consistent even after the missed dose, since the increase of oDBP values after missed dose was limited: +2.4 mmHg and of +2.7 mmHg, respectively, for olmesartan/amlodipine and perindopril/amlodipine groups. Similar results were obtained in PPS population and when the LOCF method was applied to the FAS population.

Secondary endpoints

Office SBP decreased significantly: the total treatments effect V6b vs. baseline was −16.35 and −12.32 mmHg, respectively, in olmesartan/amlodipine-treated patients and in the perindopril/amlodipine-treated ones ($P = 0.012$). Moreover, the decrease in oSBP was consistent even after the missed dose, V6b, compared with 24 weeks of treatment, V6a; indeed, the increase of sitting SBP values after the missed dose was limited: +2.92 and +3.48 mmHg, respectively, after missed olmesartan/amlodipine and perindopril/amlodipine administration.

In the FAS population, SBP change at V6a vs. baseline was −19.61 and −15.80 mmHg, respectively, in olmesartan/amlodipine-treated patients and in the perindopril/amlodipine-treated ones ($P = 0.032$). oDBP change at V6a vs. baseline was −14.15 and −13.18 mmHg, respectively, in

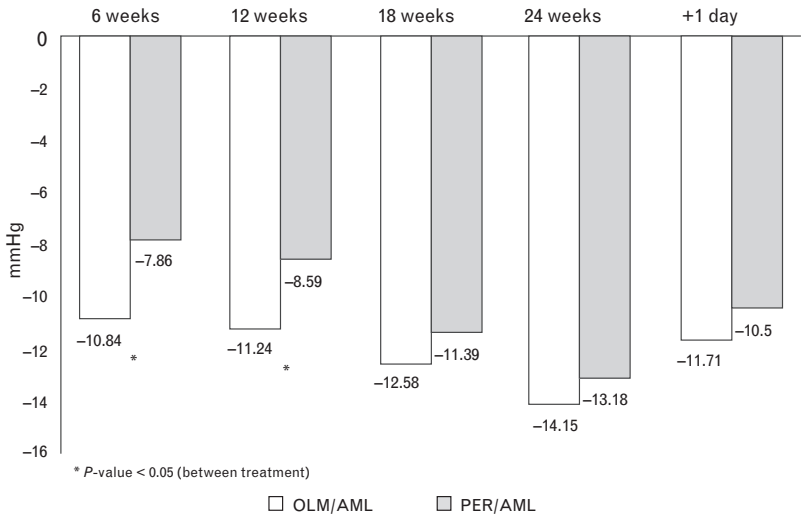

FIGURE 4 Reduction in DBP by treatment in each of the visits from the baseline in the FAS *P-value < 0.05 (between treatment).

olmesartan/amlodipine-treated patients and in the perindopril/amlodipine-treated ones (P = ns). Similar results were obtained when LOCF method was applied to FAS. Pulse pressure change at V6a vs. baseline was −5.46 and −2.62 mmHg, respectively, in olmesartan/amlodipine-treated patients and in perindopril/amlodipine-treated ones ($P = 0.059$).

Efficacy

In the FAS population, the rate of responders at V6a, considered with a reduction in oSBP > 10 mmHg and oDBP > 5 mmHg, was 79.51% (97 study participants) and 72.8% (91 study participants) in olmesartan/amlodipine-treated patients and in perindopril/amlodipine-treated ones, respectively. After the missed dose, the rate of responders was 64.2% (77 study participants) and 60.0% (75 study participants), respectively. Concerning normalization (BP < 130/80 mmHg) rates, 23.77% (29 study participants) and 20% (25 study participants) in olmesartan/amlodipine-treated patients and in perindopril/amlodipine ones, respectively, achieved the goal. After the missed dose, the rates were 7.5% (nine study participants) and 10.4% (13 study participants), respectively, in olmesartan/amlodipine-treated patients and in perindopril/amlodipine ones. Otherwise, considering a BP target of <140/90 mmHg, the control rates were 61.48% (75 study participants) and 58.4% (71 study participants) in the olmesartan/amlodipine and perindopril/amlodipine group, respectively. After the missed dose, the control rates were 56.67% (68 study participants) and 44.8% (56 study participants), respectively, in olmesartan/amlodipine-treated patients and in perindopril/amlodipine-treated ones.

The need for uptitration at V4 was 75.78 and 85.45% of the patients, respectively, in the olmesartan/amlodipine and in the perindopril/amlodipine group. Similarly, at V5, it was 58.56 and 66.36% of the patients, respectively, in olmesartan/amlodipine and perindopril/amlodipine group. Mean compliance assessed at each visit was high and with limited deviation in both treatment groups; considering both the therapies, it was 97.6 ± 4.24%, Table 3.

TABLE 3. Efficacy

	Olmesartan/ amlodipine	Perindopril/ amlodipine
Normalized study participants (BP < 130/80 mmHg), *n* (%)		
Visit 6a vs. baseline	29 (23.77)	25 (20.0)
Visit 6b vs. baseline	9 (7.5)	13 (10.4)
Normalized study participants (BP < 140/90 mmHg), *n* (%)		
Visit 6a vs. baseline	75 (61.4)	71 (58.4)
Visit 6b vs. baseline	68 (56.7)	56 (44.8)
Responder study participants, *n* (%)		
Visit 6a vs. baseline	97 (79.51)	91 (72.8)
Visit 6b vs. baseline	77 (64.2)	75 (60.0)
Uptitration study participants, *n* (%)		
Visit 4	84 (75.78)	94 (85.4)
Visit 5	65 (58.56)	73 (66.4)

TABLE 4. Safety

Type of event	Olmesartan/ amlodipine	Perindopril/ amlodipine
At least one side-effect	10 (7.8%)	13 (9.8%)
Discontinuation	4 (3.13%)	2 (1.52%)
Severe	1 (0.8%)	2 (1.5%)

Safety

The safety data collected in this study showed that both drug combinations were well tolerated in diabetic patients with hypertension treated with olmesartan/amlodipine or perindopril/amlodipine for 24 weeks. Two hundred and sixty patients were included in the safety set: 128 and 132 of which received olmesartan/amlodipine or perindopril/amlodipine, respectively. Sixty-nine patients, 32 (25.0%) in the olmesartan/amlodipine group and 37 (28.0%) in the perindopril/amlodipine group, reported at least one treatment-emergent adverse event with any relation to study medication. Twenty-three patients, 10 (7.8%) in the olmesartan/amlodipine group and 13 (9.8%) in the perindopril/amlodipine group, reported at least one adverse event related to study medication (i.e. classified by the investigator as certainly, probably, possibly related, or not assessable). Only four patients (3.13%) in the olmesartan/amlodipine group and two patients (1.52%) in the perindopril/amlodipine group discontinued because of an adverse effect with any relationship to study drug. Three serious adverse events were recorded in three patients during the study period, one patient (0.8%) in the olmesartan/amlodipine group and two patients (1.5%) in the perindopril/amlodipine group. None of them was considered by the investigators as related to the study treatments (Table 4).

DISCUSSION

The present study conducted in hypertensive and diabetic patients found that the combination of olmesartan/amlodipine was noninferior to the combination of perindopril/amlodipine in reducing oDBP after 24 weeks of treatment and at 48 h from the last administration (primary endpoint). Similarly, oSBP and per-protocol were significantly lower vs. baseline in both groups, either after 24 weeks of treatment and 48 h after the last active drug intake (missed dose), observing a trend to a greater SBP reduction in the olmesartan/amlodipine group. The percentage of responder study participantsand patients with normalized BP was similar between the two groups; both combinations were well tolerated and showed a good safety profile. The number of patients who reported at least one related treatment-emergent adverse event was inferior to 10% in both groups. However, the need for uptitration was significantly higher in the perindopril/amlodipine arm.

The study population included diabetic patients with a broad age spectrum and a long-lasting hypertension history, notoriously a group of study participants with difficult to control hypertension. All patients had diabetes without the need for insulin, representing a common population in daily clinical practice. Renal function

was preserved in a majority of patients and at least one additional cardiovascular risk factor was present. At study enrolment, there were no significant differences in clinical characteristics between the two groups, and the level of adherence to experimental treatment was very high allowing for comparison between the two experimental groups.

The 2013 ESH-ESC guidelines recommend BP control based on the assessment of office BP in all hypertensive patients, because of the strong relationship between BP and cardiovascular risk [19,20]. Diabetes mellitus is a strong independent cardiovascular risk factor in which BP control is even more crucial to reduce cardiovascular events. Moreover, hypertensive patients with diabetes mellitus frequently require antihypertensive combinations with more than two drugs, because of the diabetes-induced micro and/or macrovascular abnormalities that make BP goals more difficult to achieve [21]. Combined treatment with angiotensin II receptor blockers or ACEI and calcium channel blockers (CCB) is considered as one of the first-line combinations for BP management, since it has been demonstrated to be more efficacious vs. combinations of diuretics or beta blockers with CCB in terms of cardiovascular risk reduction in diabetic patients [22,23]. Combination of perindopril or olmesartan with amlodipine provide better BP control than either drugs in monotherapy and provide a good tolerability profile [24–27]. In addition, olmesartan in combination with amlodipine has been shown to improve the metabolic profile of hypertensive study participants [28] resulting in a reduction of fasting plasma glucose and insulin resistance as well as an improvement in insulin sensitivity parameters.

In the present study, the addition of olmesartan or perindopril to amlodipine resulted in a substantial and significant reduction in both SBP and DBP as well as in the per-protocol. The responders' rate was similar in both treatment groups. At the end of the study, 23.8 and 20% of the patients in the olmesartan and perindopril group, respectively, achieved BP normalization, defined as SBP values less than 130 mmHg and DBP values less than 80 mmHg. The latest National Health and Nutrition Examination Survey reported that an estimated 50% of all patients with hypertension achieve adequate BP below 140/90 mmHg [29], although the figures are lower for diabetic hypertensive patients. The rate of BP normalized study participants in the present study was 68% in the olmesartan/amlodipine group and 56% in the perindopril/amlodipine group.

The antihypertensive effect of a given drug after a missed dose is an important element to consider during the antihypertensive treatment, because of the fact that among the most compliant study participants, up to 20% of patients under BP treatment skip their antihypertensive medication 3 days a month with the resulting loss of protection in front of BP elevation particularly in the risky periods [1]. Moreover, the incidence of cardiovascular events like stroke or cardiac death is highest during the morning hours, coinciding with an increase in BP and HR as well as the activation of the renin–angiotensin–aldosterone system [30,31]. Patients might therefore benefit from antihypertensive drugs that act longer than 24 h because of partial BP control during the critical morning hours even after a missed dose. Up to now, missed dose studies have been conducted using monotherapies with several antihypertensive agents, including perindopril [32] but not olmesartan, and showed divergent results [33,34]. In contrast, studies of missed dose with combination therapy are lacking. In one study with a missed dose design and using ambulatory BP monitoring, a combination of perindopril/indapamide demonstrated to have efficacy up to 72 h [35].

Finally, even though it not was the objective of the study, it is worth commenting on the speed of reducing BP after starting treatment. Faster reduction in oSBP was observed in the patients receiving olmesartan/amlodipine compared with perindopril/amlodipine (see Table 2). Early BP control was related to a reduction in adverse cardiovascular events in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial [36].

The present study has to be considered within its strengths and limitations. Patients with a broad spectrum of age and BP levels from four European countries were included, reflecting a representative sample of the daily clinical practice. All the included study participants were diabetics with a long history of hypertension, thus the results cannot be extrapolated to the general population. Twenty-four-hour BP monitoring could have given more insight into the efficacy profile of the drug combinations; however, treatment guidelines and cardiovascular risk stratification are mainly based on office BP.

In summary, the olmesartan/amlodipine combination is not inferior to the one with perindopril/amlodipine, and the trend of efficacy is in favour of the olmesartan-based treatment in essential hypertensive patients with diabetes mellitus. Moreover, both treatments were safe and well tolerated. The antihypertensive effect of olmesartan/amlodipine was more rapid than perindopril/amlodipine in initial treatment phases. Apart from this, a lower rate of patients in the olmesartan/amlodipine arm needed uptitration to gain BP control. Furthermore, missing a dose does not leave the patients unprotected with both treatments, even if the olmesartan/amlodipine effect is more permanent and longer lasting compared with perindopril/amlodipine.

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Conflicts of interest

J.R. has been a speaker for Menarini International, Daiichi-Sankyo, Boehringer Ingelheim, Sanofi, MSD. G.P. declares no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

Low adherence to treatment is a notoriously common problem in hypertension, the high number of treated patients in whom adherence to the prescribed treated regimen is low accounting to a major degree for the low rate of blood pressure control worldwide. It is well known that low adherence to treatment exhibits several different patterns, one of which being delayed assumption or even failure to take antihypertensive drugs for one or more days. This paper by Redon and colleagues shows that after many weeks of successful treatment missing a dose of the once-a-day administration of the combination of olmesartan or perindopril with amlodipine allows a clearcut blood pressure reduction to be maintained over the following 24 hours. Albeit not encouraging an irregular drug assumption, this reassures that effective combinations such as those between a blocker of the renin–angiotensin system and a calcium antagonist may not leave patients unprotected when treatment assumption happens to be occasionally missed, as it may often occur.

Reviewer 2

There are several potential strengths of the study. First, the protocol mimics real life behaviour of many patients who for various reasons skip a dose of antihypertensive drugs. Second, the project is focused on fixed drug combinations, which become a cornerstone of hypertension management. Finally, the study includes high-risk patients with diabetes, in whom the benefits of hypertension control might be especially relevant. The study might have been empowered by inclusion of ambulatory blood pressure monitoring.