Efficacy and tolerability of olmesartan/amlodipine combination therapy in patients with mild-to-severe hypertension: focus on 24-h blood pressure control

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Abstract: European guidelines recommend that treating patients with hypertension to blood pressure (BP) goal is an important target for cardiovascular (CV) risk reduction. However, office BP may be a suboptimal target, given its limitations. Indeed, there is evidence that 24-h ambulatory BP monitoring (ABPM) parameters may score better in this regard, representing more accurate predictors of CV risk. In particular, mean 24-h BP and BP variability both correlate closely with hypertension end-organ damage and rate of CV events, which suggests that antihypertensive therapy should provide smooth BP control over the full 24-h dosing interval. The use of ABPM has demonstrated that fixed-dose combination therapy, comprising agents with complementary mechanisms of action, may overcome the challenge of suboptimal BP control by providing improvements in antihypertensive efficacy and tolerability throughout the 24-h period. Olmesartan/amlodipine is one of the latest combination therapies to be approved, and a number of large clinical trials have demonstrated the efficacy and tolerability of this combination in patients with mild-to-severe hypertension. Furthermore, recent ABPM studies of olmesartan/amlodipine-based treatment algorithms have shown the satisfactory 24-h antihypertensive efficacy of this fixed-dose combination. This review provides an overview of recent clinical data on the efficacy and tolerability of fixed-dose olmesartan/amlodipine combination therapy for the treatment of mild-to-severe hypertension, with a focus on sustained 24-h BP control.

Keywords: ambulatory blood pressure monitoring, amlodipine, angiotensin II type 1 receptor blockers, calcium channel blockers, hypertension, olmesartan

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Introduction

The global burden of hypertension is substantial and continues to grow. In 2001, an estimated 7.6 million premature deaths worldwide were attributed to high blood pressure (BP) [Lawes *et al.* 2008], contributing to a relevant proportion of the global disease burden [Ezzati *et al.* 2002].

Despite the well-documented relationship between hypertension and increased cardiovascular (CV) risk, BP goal achievement rates remain suboptimal. In Europe, the proportion of hypertensive patients with BP $\geq$ 140/90 mmHg is still greater than 50% [Pereira *et al.* 2009; Wang *et al.* 2007]. It is important for patients to reach BP goal in order to optimize their protection against increased CV risk [Benetos *et al.* 2003], and the use of goal BP as a treatment target to reduce CV risk is supported by European guidelines for the treatment of hypertension [Mancia *et al.* 2009, 2007b].

However, office BP may be a suboptimal target in this regard, given its limitations [Parati and

Valentini, 2007]. Indeed, there is evidence that 24-h ambulatory BP monitoring (ABPM) parameters may represent more accurate predictors of CV risk [Mancia *et al.* 1993]. In particular, mean 24-h BP and BP variability have both been shown to correlate closely with hypertension end-organ damage and rate of CV events [Schillaci and Parati, 2010; Eguchi *et al.* 2009; Pierdomenico *et al.* 2009; Delgado-Mederos *et al.* 2008; Bilo *et al.* 2007; Mancia *et al.* 2007a; Tatasciore *et al.* 2007; Verdecchia *et al.* 2007; Parati and Valentini, 2006; Eto *et al.* 2005; Mena *et al.* 2005; Parati, 2005; Bjorklund *et al.* 2004; Pringle *et al.* 2003; Kikuya *et al.* 2000; Sander *et al.* 2000; Staessen *et al.* 1999; Tozawa *et al.* 1999; Frattola *et al.* 1993; Parati *et al.* 1987]. This suggests that, in order to improve the CV risk profile of patients with hypertension, optimal antihypertensive therapy should provide sustained BP reduction and smooth BP control over the full 24-h period. This concept is exemplified in Figure 1 [Parati *et al.* 1998], which illustrates the correlation between the reduction in left ventricular mass index and the smoothness index in treated hypertensive patients, the latter computed as the ratio between the average reduction in 24 h BP values and its standard deviation. This index represents a quantification of how homogeneous the BP reduction is over 24 h, and it appears to be more closely associated with the treatment-induced regression in cardiac damage than the trough : peak ratio.

Data from clinical trials clearly indicate that the majority of hypertensive patients will require two or more antihypertensive agents to achieve BP control [Palatini, 2005]. Furthermore, the importance of combination therapy is acknowledged by European treatment guidelines [Mancia *et al.* 2009, 2007b]. Indeed, the use of fixed-dose combinations of agents with complementary mechanisms of action has the potential

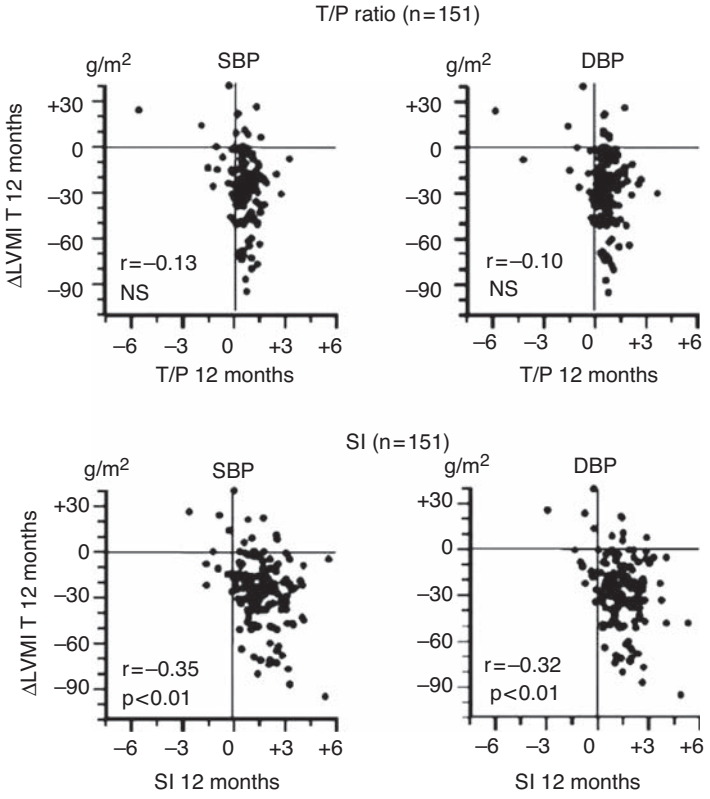


Figure 1. The relationship between the regression of LVMI in hypertensive patients with left ventricular hypertrophy following 1 year of combination treatment with lisinopril 20 mg and hydrochlorothiazide (12.5 or 25 mg as required for blood pressure control) and T/P ratio (upper panels) and SI values (lower panels). The SI is the ratio between the treatment-induced reduction of the mean of 24 h blood pressure values and the standard deviation of such a mean value. Data for SBP and DBP are shown separately [Parati *et al.* 1998]. DBP, diastolic blood pressure; LVMI, left ventricular mass index; SBP, systolic blood pressure; SI, smoothness index; T/P, trough-to-peak. [Adapted with permission from Parati *et al.* 1998].

to increase antihypertensive efficacy throughout the whole 24-h dosing period, reduce unwanted side effects and improve patient compliance [Rosenthal and Gavras, 2006].

This article will review recent clinical data on the efficacy and tolerability of fixed-dose olmesartan/amlodipine therapy for the treatment of mild-to-severe hypertension, with its focus on the importance of providing sustained 24-h BP control.

Efficacy of fixed-dose combination therapy

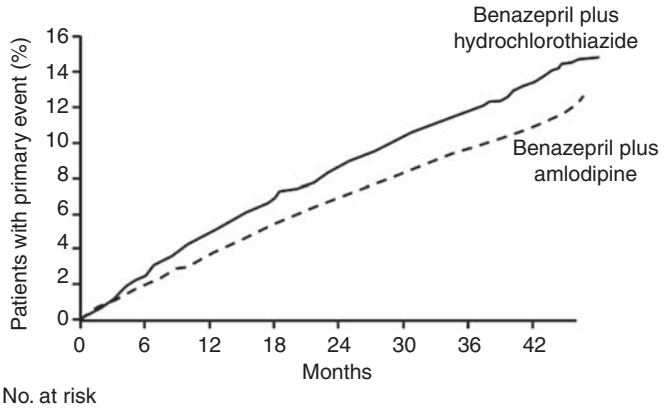
One way to overcome the challenge of suboptimal BP control in patients with hypertension is to increase antihypertensive efficacy by the use of fixed-dose combination therapy. The use of fixed-dose combinations comprising two or more drugs can provide a number of advantages including simplification of treatment, improvements in patient compliance, better tolerability and reductions in costs. Furthermore, guidelines recommend that combination therapy should comprise agents with complementary mechanisms of action, which may provide greater improvements in efficacy than the component monotherapies alone [Mancia *et al.* 2007b].

Titrating the dose of a single agent is limited by the dose-response profile and the proximity of the plateau phase, and also by the likelihood of an increased incidence of side effects. In contrast, additive BP reductions can be achieved by combining different agents if these affect different mechanisms involved in BP regulation. Agents like angiotensin II type 1 receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) block the activity of the renin angiotensin system (RAS) and promote vasodilation and sodium and water excretion. Dihydropyridine calcium channel blockers (CCBs) block vascular smooth muscle cell calcium channels and reduce peripheral vascular resistance. This reduces BP and also leads to a compensatory increase in RAS activity, which helps to reinforce the effect of ARB treatment [Bakris, 2008; Jamerson *et al.* 2004; Jinno *et al.* 2004].

The avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) trial was a large randomized, double-blind study that compared the effects of two fixed-dose combination therapies, the ACEI/CCB combination benazepril/amlodipine and the ACEI/diuretic combination benazepril/hydrochlorothiazide (HCTZ), on CV morbidity and mortality in patients with hypertension who were at a high risk of CV events [Jamerson *et al.* 2008]. At study end, BP control was achieved by 72% and 75% of patients in the benazepril/HCTZ and benazepril/amlodipine treatment groups, respectively. Moreover, after 36 months of follow up, the composite primary CV endpoint (CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina pectoris, resuscitation after sudden cardiac arrest and coronary revascularization) was reported in significantly fewer benazepril/amlodipine recipients compared with benazepril/HCTZ recipients (Figure 2). Therefore, the findings of ACCOMPLISH not only demonstrate the clinical benefits of fixed-dose combination therapy, but also provide further evidence supporting the use of RAS blocker/CCB combination therapy for effective BP control and CV risk reduction.

Olmesartan/amlodipine is one of the latest fixed-dose ARB/CCB combination therapies to be approved for the treatment of hypertension. This combination is well established, with demonstrated efficacy and tolerability as shown in the multicentre, randomized, double-blind, 8-week combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure (COACH) trial. In the COACH trial, significantly greater BP reductions (up to −30.1/−19.0 mmHg) and improvements in BP goal achievement rates (up to 53.2% of patients) were obtained with olmesartan/amlodipine combination therapy, compared with olmesartan and amlodipine monotherapies in patients with mild-to-severe hypertension [Chrysant *et al.* 2008]. Prespecified subgroup analyses of COACH confirmed that the antihypertensive efficacy of olmesartan/amlodipine was maintained irrespective of age, sex, ethnicity, diabetic status, hypertension stage or previous antihypertensive treatment experience [Oparil *et al.* 2009]. Furthermore, a 44-week, open-label extension of the COACH trial showed that initial therapy with olmesartan/amlodipine 40/5 mg, followed by uptitration to 40/10 mg and the addition of HCTZ in patients who did not achieve BP control, enabled the majority of patients to reach BP goal [Chrysant *et al.* 2009].

In two similar double-blind, randomized controlled trials, olmesartan/amlodipine was shown to provide additional improvements in antihypertensive efficacy in patients with



No. at risk

Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390

Figure 2. This figure shows the Kaplan-Meier curves for the composite primary cardiovascular endpoint in the avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) trial [Jamerson *et al.* 2008], in which a 20% reduction in the relative risk of cardiovascular morbidity and mortality was seen in the benazepril plus amlodipine group compared with the benazepril plus hydrochlorothiazide group. [Reproduced with permission from Jamerson *et al.* 2008]. Copyright© *[2008] Massachusetts Medical Society. All rights reserved.*

moderate-to-severe hypertension who were inadequately controlled by olmesartan [Barrios *et al.* 2009] or amlodipine [Volpe *et al.* 2009a] monotherapy, respectively. In the study by Volpe and colleagues all patients received open-label amlodipine 5 mg monotherapy for 8 weeks (period I), followed by randomization to 8 weeks of double-blind treatment with amlodipine 5 mg or olmesartan/amlodipine 10/5, 20/5 or 40/5 mg if their BP was not adequately controlled (period II). Patients who still failed to achieve adequate BP control had their treatment further uptitrated for an additional period of 8 weeks (period III) (Figure 3). Combination therapy with olmesartan/amlodipine provided significantly greater BP reductions and significantly higher BP goal rates compared with amlodipine monotherapy in period II [Volpe *et al.* 2009a]. Furthermore, uptitration of olmesartan/amlodipine resulted in additional BP reductions and enabled more patients to achieve BP goal in period III.

A 28-week, open-label extension of the study by Volpe and colleagues was conducted to evaluate further the long-term effect of a step-wise treatment algorithm based on olmesartan/amlodipine [Volpe *et al.* 2009b]. All patients who entered the 28-week, open-label phase were initially treated with olmesartan/amlodipine 40/5 mg/day. Patients whose BP remained uncontrolled were uptitrated in a stepwise manner to olmesartan/amlodipine 40/10 mg, then to olmesartan/amlodipine/HCTZ 40/10/12.5 mg, and finally to olmesartan/amlodipine/HCTZ 40/10/25 mg as required. Effective BP control was achieved with this stepped-care regimen in the majority of patients (approximately 67%), which further underlines the antihypertensive efficacy of combining a dihydropyridine CCB, an ARB and, if necessary, a thiazide diuretic, and emphasizes the importance of combination therapy in the management of hypertension. It should also be noted that less than 20% of patients required the addition of HCTZ, demonstrating that adequate BP control is maintained in the majority of patients following long-term treatment with the combination of olmesartan/amlodipine alone.

Based on the available clinical evidence, combination therapy with olmesartan/amlodipine has been established as an effective antihypertensive regimen in a controlled clinic setting. However, it is also important not to overlook the assessment of BP over 24 h outside of a clinic environment, to ensure the maintenance of BP control in daily life. For agents that are dosed once daily, duration of action is an important factor to take into account when selecting the components of fixed-dose combinations. Amlodipine has a long half-life and has been shown to provide effective BP reductions over 24 h [Coca *et al.* 1993]. A systematic review of clinical studies involving ARBs found that ambulatory BP reductions were affected by the drug used, and indicated that olmesartan effectively reduced BP over

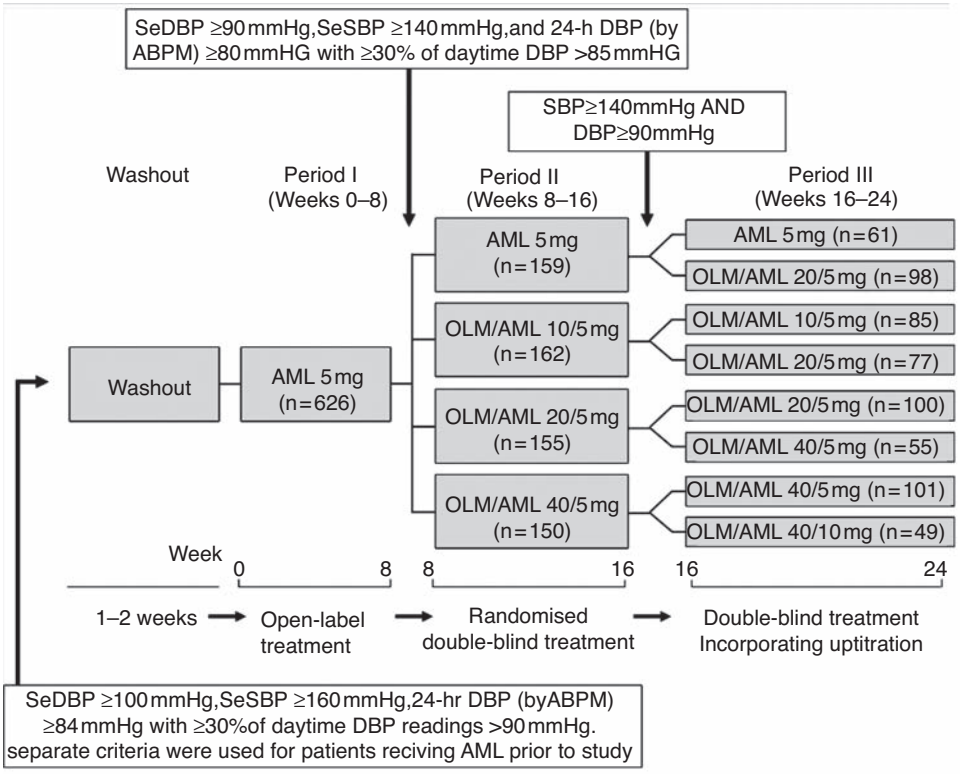


Figure 3. Study design of the randomized, double-blind, parallel-group, multicentre study determining the efficacy and safety of OLM/AML combination therapy in patients with moderate-to-severe hypertension whose blood pressure was inadequately controlled following 8 weeks of open-label AML monotherapy [Volpe *et al.* 2009a]. ABPM, ambulatory blood pressure monitoring; AML, amlodipine; DBP, diastolic blood pressure; OLM, olmesartan; SBP, systolic blood pressure; SeDBP, seated DBP; SeSBP, seated SBP. [Adapted with permission from Volpe *et al.* 2009a].

24 h, including the night-time and final hours of the dosing interval [Fabia *et al.* 2007].

Measurement of BP outside the office setting

In addition to reducing BP and achieving BP goals, accurate measurement of BP is also critical for the evaluation of CV risk associated with hypertension. However, BP measurements made in the office or clinic setting are associated with several limitations:

1. inaccuracies associated with single readings taken on the spot [Pickering, 2008; Parati and Valentini, 2007];
2. technical issues associated with auscultatory measurements of diastolic BP (DBP) in specific patient populations [Pickering, 2008; Parati and Valentini, 2007];
3. the inability to account for the considerable physiological variability that characterizes BP in daily life [Parati and Bilo, 2008; Tatasciore *et al.* 2007; Parati *et al.* 1987];
4. the 'white-coat' phenomenon, which results in an overestimation of initial BP and in a possible underestimation of the effectiveness of antihypertensive therapy [Pickering, 2008; Parati and Valentini, 2007; Mancia *et al.* 1983].

To overcome these limitations, out-of-office BP monitoring can be undertaken to supplement BP readings obtained in an office or clinic setting. At present, the two methods of out-of-office BP monitoring used in clinical practice are home (or self) BP monitoring (HBPM) and ABPM, both of which have been shown to be better predictors of CV risk than office BP [Pickering, 2008; Parati and Valentini, 2007; Giles, 2006]. These two methods allow multiple BP measurements to be collected on a regular basis, which can be used to provide a more accurate assessment of average BP and a better reflection of subjects' prevailing BP levels than isolated clinic BP readings [Giles, 2006]. Table 1 shows

Table 1. A comparison of the main features of office blood pressure, ambulatory blood pressure monitoring and home blood pressure monitoring [Parati *et al.* 2009b]. [Reproduced with permission from Parati *et al.* 2009b].

Feature	Office blood pressure	Ambulatory blood pressure monitoring	Home blood pressure monitoring
Number of readings	Low	High	Medium
White-coat effect	Yes	No	No
Operator dependency	Yes	No	No
Need of device validation	No(yes, if oscillometric device used)	Yes	Yes
Daytime blood pressure	+	+++	++
Night-time blood pressure and dipping	–	+++	–
Morning blood pressure	±	++	+
24-h blood pressure variability	–	++	±
Long-term blood pressure variability	–	±	++
White coat hypertension and masked hypertension diagnosis	–	++	++
Placebo effect	++	–	–
Reproducibility	Low	High (24-h average values)	High (average of several values)
Prognostic value	+	+++	++
Patient involvement	–	–	++
Need of patient training	–	±	++
Physician involvement	+++	++	+
Patient acceptance	++	±	++
Monitoring of treatment effects	Limited information	Extensive information on diurnal blood pressure profile, cannot be repeated frequently	Appropriate for long-term monitoring, limited information on blood pressure profile
Hypertension control improvement	+	++	+++
Cost	Low	High	Low
Availability	High	Low	High

a comparison of the main features of office (or clinic) BP assessment, ABPM and HBPM.

Home BP monitoring

HBPM involves the patient measuring his or her own BP outside an office or clinic environment. This method is associated with a number of advantages including the absence of the 'white-coat' effect and the ability to take several measurements over time, which may lead to an improvement in both patient compliance and BP control [Parati *et al.* 2008], especially when used together with teletransmission facilities [Parati *et al.* 2009b; Parati and Pickering, 2009]. However, an important limitation of HBPM is its inability to provide information on 24-h BP profiles, especially on nocturnal BP and short-term BP variability [Parati *et al.* 2008]. However, it may allow assessment of day-by-day BP variability [Kikuya *et al.* 2008; Parati and Bilo, 2008], therefore offering a means to quantify long-term BP variations which, as recently suggested, may have prognostic significance [Rothwell *et al.* 2010].

ABPM

ABPM allows BP to be monitored continuously over a 24-h period and provides a comprehensive assessment of the BP load under daily, real-life conditions, together with estimates of BP variability. Perhaps most importantly, nocturnal BP can be recorded in patients undergoing ABPM, which is considered to be the strongest predictor of CV risk [Pickering *et al.* 2006; Dolan *et al.* 2005; Sega *et al.* 2005; Staessen *et al.* 1999]. Additional advantages of ABPM include the absence of observer bias and digit preference (these advantages are also shared by HBPM), and the higher reproducibility of 24-h average BP.

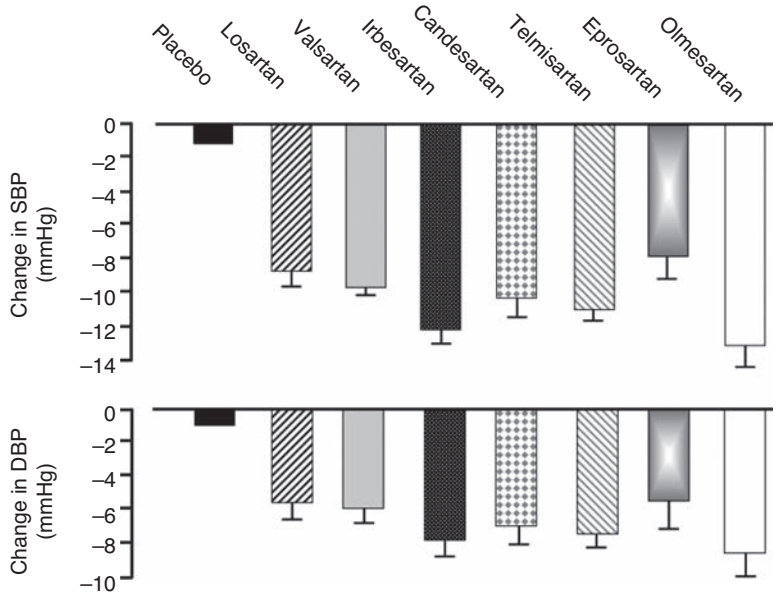


Figure 4. Change in 24-h SBP and DBP, as assessed by ambulatory blood pressure monitoring, following treatment with different angiotensin II type 1 receptor blockers or placebo [Fabia *et al.* 2007]. DBP, diastolic blood pressure; SBP, systolic blood pressure. [Adapted with permission from Fabia *et al.* 2007].

The extent of end-organ damage and the rate of CV morbidity and mortality have been shown to be closely related to 24-h mean BP and BP variability in patients with hypertension [Tatasciore *et al.* 2007; Dolan *et al.* 2005; Sega *et al.* 2005; Staessen *et al.* 1999; Palatini *et al.* 1992; Parati *et al.* 1987]. This emphasizes the diagnostic and prognostic importance of monitoring BP over a 24-h period. Indeed, ABPM has come to play an important role in clinical studies of antihypertensive agents since it can be used alongside clinic BP measurements to identify patients with white-coat hypertension and thus confirm the diagnosis of hypertension and so reduce inappropriate diagnosis and treatment [Palatini *et al.* 2004]. ABPM is also useful in clinical trials as it provides information about a drug's duration of action and ability to provide control BP over the entire 24-h dosing interval [Parati *et al.* 1998]. Of particular importance for antihypertensive agents that are administered once-daily is the maintenance of BP control at both peak and trough times, including the early morning hours when a natural increase in BP, known as the early morning 'surge', occurs, which can trigger CV events in patients with hypertension [Gosse *et al.* 2004; Kario *et al.* 2003].

Previously, olmesartan has demonstrated effective 24-h angiotensin II type 1 (AT_1) receptor blockade [Hasler *et al.* 2005], which appears to translate into highly effective 24-h ABPM lowering compared with recommended doses of other ARBs [Fabia *et al.* 2007; Stumpe, 2004] (Figure 4). Therefore, it is anticipated that combination therapy with olmesartan plus amlodipine, both of which are characterized by a prolonged duration of action, may also provide a high level of 24-h ambulatory BP control.

Olmesartan/amlodipine and 24-h BP control

As mentioned earlier, the once-daily, fixed-dose combination of olmesartan/amlodipine has demonstrated excellent clinic BP-lowering efficacy and tolerability in patients with mild-to-severe hypertension. More recently, two trials have assessed the 24-h BP-lowering activity of olmesartan/amlodipine using ABPM [Heagerty *et al.* 2009; Neutel *et al.* 2009a].

An ABPM substudy of the double-blind, randomized controlled trial conducted by Volpe and colleagues was undertaken in order to assess the 24-h BP-lowering efficacy of olmesartan/amlodipine [Volpe *et al.* 2009a]; some initial findings from this substudy were presented at the 2009 European Society of Hypertension Annual Scientific Meeting [Heagerty *et al.* 2009]. Eight weeks of double-blind treatment with olmesartan/amlodipine (10/5, 20/5 and 40/5 mg) (period II) was associated with significantly greater 24-h, daytime and night-time ambulatory

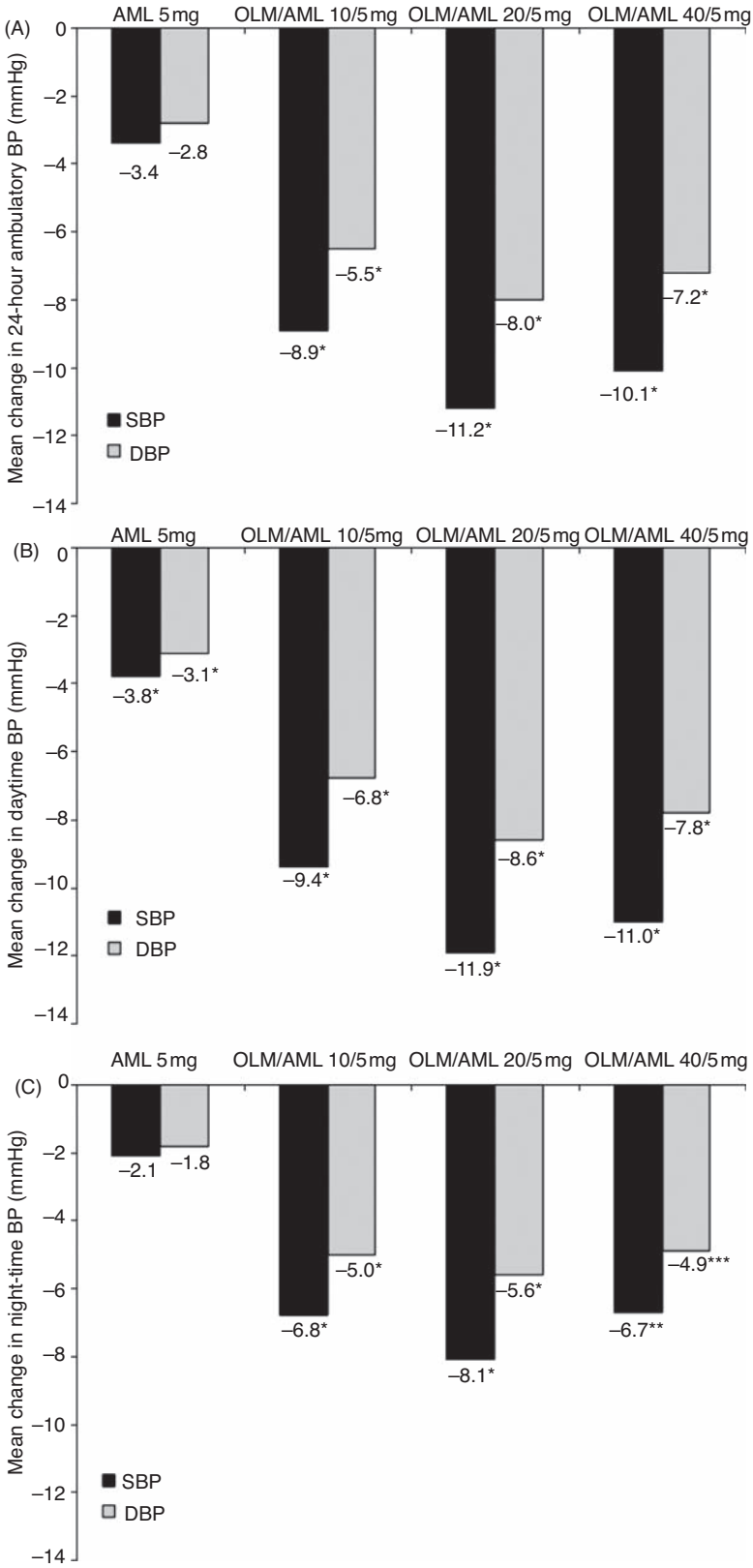


Figure 5. Mean changes in ambulatory BP over (A) 24-h, (B) daytime BP and (C) night-time after 8 weeks of double-blind treatment with OLM/AML 10/5 mg, OLM/AML 20/5 mg, OLM/AML 40/5 mg and AML 5 mg [Heagerty *et al.* 2009] (from week 8 to week 16 of the study described in Figure 3 [Volpe *et al.* 2009a]). *$p \leq 0.0001$ *versus* AML 5 mg; **$p < 0.0002$ *versus* AML 5 mg; ***$p < 0.0005$ *versus* AML 5 mg. AML, amlodipine; BP, blood pressure; DBP, diastolic blood pressure; OLM, olmesartan; SBP, systolic blood pressure.

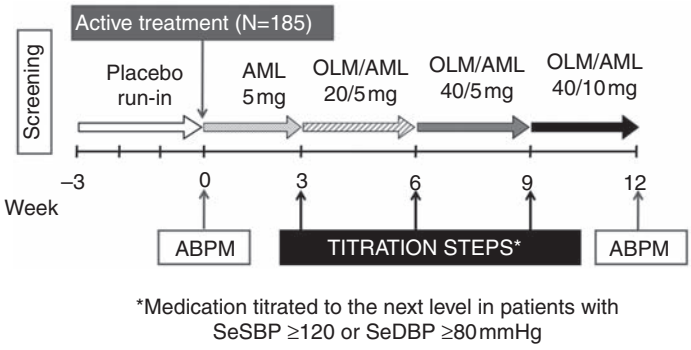


Figure 6. Study design of the AZTEC trial [Neutel *et al.* 2009b]. ABPM, ambulatory blood pressure monitoring; AML, amlodipine; OLM, olmesartan; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure. [Reproduced with permission of Blackwell Publishing Ltd.]

BP reductions compared with amlodipine 5 mg monotherapy [Heagerty *et al.* 2009] in patients whose BP was inadequately controlled by amlodipine 5 mg (Figure 5). Furthermore, uptitration in patients who did not achieve BP control on their initial dose of olmesartan/amlodipine during period III resulted in additional dose-dependent reductions in 24-h, daytime and night-time ambulatory BP [Heagerty *et al.* 2009]. Additional 24-h ambulatory BP profile data also showed that combination therapy with olmesartan/amlodipine provided superior BP lowering compared with amlodipine monotherapy over the entire 24-h period [Parati and Bilo, 2009]. The 24-h systolic BP (SBP) profiles for amlodipine 5 mg monotherapy and olmesartan/amlodipine 20/5 and 40/5 mg combination therapy were similar prior to randomized treatment in period II. At the end of period II, 24-h SBP profiles showed significantly greater reductions with olmesartan/amlodipine 20/5 and 40/5 mg combination therapy than with amlodipine 5 mg monotherapy (both −10.4 *versus* −3.3 mmHg, respectively); these reductions remained consistent throughout the entire 24-h dosing interval. Likewise, the uptitration of olmesartan/amlodipine during period III in patients whose BP was uncontrolled on their original dose of combination therapy resulted in additional reductions in 24-h SBP that remained consistent throughout the entire 24-h dosing period [Parati and Bilo, 2009] (manuscript in preparation), while in those who did not require uptitration during period III 24-h SBP profiles were maintained. Similar trends in 24-h ambulatory DBP profiles were also seen during periods II and III (data not shown). Consistency in 24-h BP control is of particular importance because the antihypertensive effect of BP-lowering agents that are administered once daily is often lost during the last few hours of dosing in patients treated with monotherapy. These data show that the combination of olmesartan/amlodipine provides consistent and smooth BP control throughout the entire 24-h dosing interval in patients with moderate-to-severe hypertension who are inadequately controlled by monotherapy.

The AZOR trial evaluating blood pressure reductions and control (AZTEC) was a recent 12-week, open-label, treat-to-target study that assessed the 24-h antihypertensive efficacy of an olmesartan/amlodipine-based treatment algorithm in 185 patients with stage 1 or 2 hypertension [Neutel *et al.* 2009b]. Study participants were initially treated with amlodipine 5 mg monotherapy for 3 weeks, followed by stepwise uptitration of olmesartan/amlodipine (20/5 to 40/5 and, finally, to 40/10 mg) at 3-week intervals if seated BP was ≥120/80 mmHg (Figure 6). According to data presented at the 2009 American Society of Hypertension Annual Scientific Meeting, significant reductions from baseline in mean 24-h ambulatory SBP (−21.4 mmHg) and DBP (−12.7 mmHg) were observed at week 12 [Neutel *et al.* 2009b]. Furthermore, significant reductions from baseline in ambulatory BP were maintained throughout the night-time period (−18.5/−10.9 mmHg) and during the last 6 h (−18.8/−11.1 mmHg), 4 h (−19.5/−11.8 mmHg) and 2 h (−20.6/−12.4 mmHg) of dosing [Neutel *et al.* 2009b]. In addition, the mean hourly ambulatory SBP and DBP profiles at study end were also consistently lower than baseline values throughout the entire 24-h dosing period [Neutel *et al.* 2009a].

These findings from AZTEC confirm the excellent 24-h antihypertensive efficacy of an olmesartan/amlodipine-based treatment algorithm, which, importantly, is sustained during the final hours of dosing.

In conclusion, the data provided by recent ABPM studies indicate that olmesartan/amlodipine is associated with effective and smooth 24-h BP control, particularly during the final hours of dosing, in patients with moderate-to-severe hypertension. Further clinical data will also be provided by the ongoing blood pressure control in all subgroups with hypertension (BP CRUSH) study [Weir *et al.* 2009], which is a prospective, open-label titration study evaluating BP control after switching to an olmesartan/amlodipine-based treatment algorithm in patients with hypertension who are uncontrolled by monotherapy. Patients from a range of demographic subgroups based on age, race, ethnicity, obesity status, diabetic status and the presence or absence of metabolic syndrome will be recruited to mimic a 'real-world' clinical setting. In addition, a prespecified subset of patients will undergo ABPM to determine if 24-h BP control can be maintained with this treatment regimen.

Tolerability of olmesartan/amlodipine

Large controlled clinical trials have demonstrated that combination therapy with olmesartan/amlodipine at doses of 10–40/5–10 mg was generally well tolerated in patients with mild-to-moderate [Chrysant *et al.* 2008] and moderate-to-severe hypertension [Barrios *et al.* 2009; Volpe *et al.* 2009]. In general, the majority of adverse events observed with olmesartan/amlodipine combination therapy were consistent with the tolerability profiles of ARB and CCB monotherapies. Overall, similar incidence rates were observed for olmesartan/amlodipine combination therapy, amlodipine monotherapy, olmesartan monotherapy and placebo, with the exception of peripheral oedema. Peripheral oedema is an adverse event that is commonly associated with amlodipine therapy. In two recent studies comparing olmesartan/amlodipine combination therapy with amlodipine monotherapy, the incidence of peripheral oedema was shown to be lower with combination therapy *versus* amlodipine monotherapy at a dose of 5 mg [Volpe *et al.* 2009a] or 10 mg [Chrysant *et al.* 2008]. During the COACH trial, the rate of oedema incidence in patients receiving amlodipine 10 mg was 36.8%, but this was considerably lower in patients who received olmesartan 20 mg (25.6%) or 40 mg (23.5%) in combination with amlodipine 10 mg [Chrysant *et al.* 2008]. Similarly, in the study by Volpe and colleagues the incidence of peripheral oedema was two- to four-fold higher with amlodipine 5 mg monotherapy than with olmesartan/amlodipine 10–40/5 mg (2.1% *versus* 0.5%–1.1%, respectively) [Volpe *et al.* 2009a]. These findings may be explained by the reduction in peripheral capillary pressure obtained by the combined arteriolar and venular dilation induced by the addition of olmesartan, compared with the selective arteriolar dilation following the administration of amlodipine monotherapy.

Conclusion

Achieving BP goal is crucial for the optimization of CV protection in patients with hypertension. Furthermore, the established association of increased BP variability over the 24-h period with a worsening of hypertensive end-organ damage and the development of CV events indicates the importance of achieving smooth control of 24-h BP, which may confer additional CV protection.

Fixed-dose combination therapy can be used to overcome the challenges involved in improving BP goal attainment and 24-h BP control. Olmesartan/amlodipine is one such treatment option, and ABPM studies have shown that this combination therapy provides well-tolerated and effective 24-h BP control across the entire 24-h dosing period in patients with mild-to-severe hypertension. Furthermore, the results obtained with uptitration of olmesartan/amlodipine following an insufficient BP response demonstrate that it is possible to achieve further additional ambulatory BP reductions and improvements in BP control rates without a worsening of side effects in patients who are more challenging to treat. Taken together, the findings of these recent clinical studies indicate that olmesartan/amlodipine combination therapy provides a high level of protection from elevated BP over the full 24-h dosing period in patients with mild-to-severe hypertension, which may translate into improvements in their overall CV risk profile. The good tolerability of olmesartan/amlodipine may also lead to improvements in patient compliance over prolonged follow-up periods.

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Conflicts of interest statement

Gianfranco Parati and Grzegorz Bilo have received lecture fees and honoraria for consultancy from Daiichi Sankyo Europe. Juan Eugenio Ochoa, Carlos Ramos, Satoshi Hoshide and Laura Lonati have no disclosures to make.

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