EXPERT OPINION

Azilsartan medoxomil in the treatment of hypertension: the definitive angiotensin receptor blocker?

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Introduction: Azilsartan medoxomil is the newest angiotensin receptor blocker marketed for the treatment of arterial hypertension. The aim of this article was to review the available evidence about this drug alone or combined with other antihypertensive agents in the treatment of hypertensive population.

Areas covered: For this purpose, a search on MEDLINE and EMBASE databases was performed. The MEDLINE and EMBASE search included both medical subject headings (MeSHs) and keywords including azilsartan or azilsartan medoxomil or angiotensin receptor blockers or renin angiotensin system or chlorthalidone and hypertension. References of the retrieved articles were also screened for additional studies. There were no language restrictions.

Expert opinion: Azilsartan medoxomil has a potent and persistent ability to inhibit binding of angiotensin II to AT1 receptors, which may play a role in its superior blood pressure (BP) -lowering efficacy compared with other drugs, including ramipril, candesartan, valsartan or olmesartan, without an increase of side effects. Chlortalidone is a diuretic which significantly differs from other classic thiazides and has largely demonstrated clinical benefits in outcome trials. The fixed-dose combination of azilsartan and chlorthalidone has been shown to be more effective than other potent combinations of angiotensin receptor blockers plus hydrochlorothiazide, with a good tolerability profile.

Keywords: angiotensin receptor blockers, antihypertensive treatment, azilsartan medoxomil, blood pressure control, chlorthalidone, hypertension, renin angiotensin system.

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1. Introduction

Hypertension is one of the most important risk factors for the development of cardiovascular disease [1]. In fact, it has been reported that in middle- and advanced-age subjects, high blood pressure (BP) is markedly and directly related to vascular and overall mortality. Thus, at ages 40 – 69 years, each increase of 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP is associated with more than a two-fold difference in the risk of death for stroke or ischemic heart disease [2]. Moreover, hypertension is a very common condition. Although more than one-third of adults have hypertension, and this percentage strongly increases with age, in the past years the number of young subjects with hypertension has markedly raised [3]. Even more, it has been estimated that in United States the current prevalence of hypertension in children is about 3 – 5% [4].

Notably, reducing BP values to recommended targets has been associated with a reduction in cardiovascular events. For example, in patients with hypertension and ischemic heart disease, those patients with a higher proportion of visits with an

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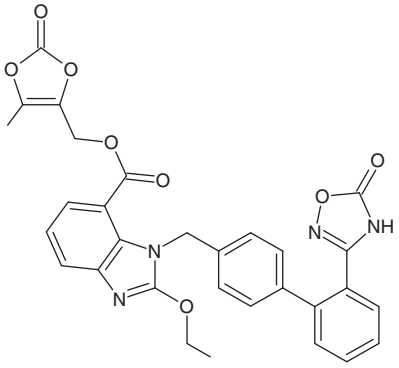
Box 1. Drug summary.

Drug name	Azilsartan medoxomil
Phase	Already marketed
Indication	Treatment of essential hypertension
Pharmacology description	Azilsartan medoxomil is a prodrug that after oral absorption is rapidly hydrolyzed to the active moiety, azilsartan. Azilsartan has a potent and persistent ability to inhibit binding of angiotensin II to AT1 receptors, mainly due to its 5-oxo-1,2,4-oxadiazole moiety.
Route of administration	Orally
Chemical structure	Azilsartan medoxomil: (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2′-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-4-biphenylyl]methyl}-1H-benzimidazole-7-carboxylate.
	
Pivotal trials	[27-31]

adequate BP control had a 32% reduction in the risk of myocardial infarction (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.48 – 0.70) and a 50% reduction in the risk of stroke (HR 0.50; 95% CI 0.37 – 0.67) [5]. It is not sufficient to use antihypertensive drugs, but to achieve BP goals [6].

Unfortunately, although in the past years BP control rates have improved all around the world, there is still a high proportion of patients over recommended targets. Thus, data provided from the National Health and Nutrition Examination Surveys have shown that in the past decade, BP control rates have raised among hypertensive adults from about 29 to 47% in the United States (from about 45 to 60% among treated hypertensive people) [7]. In Canada, these numbers have increased from 13% in 1992 to 64% in 2009 [8]. Similar trends have been observed in Europe [9-11]. Although one of the main reasons for these improvements have been related with the higher use of combined therapy, it is of note that excepting those patients at lower risk, in the great majority of patients the basis of antihypertensive treatment should rely on a renin angiotensin system inhibitor [12-14].

This is not strange, as the renin angiotensin aldosterone system plays a key role in the regulation of BP [15]. Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) are the most common renin angiotensin system inhibitors prescribed for the treatment of hypertension in daily clinical practice [15]. However, some studies have shown that although the prescription of ACEi for the treatment of hypertension have remained constant, the prescription of ARB has markedly increased in the past years [9,16].

Although in the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) trial, an ARB, telmisartan, was equivalent to an ACEi, ramipril, in the reduction of cardiovascular events in a high-risk population, telmisartan was better tolerated than ramipril [17]. This is very relevant, taking into account that those patients intolerant to ACEi before the inclusion were excluded from this trial [17]. Avoiding the discontinuation of medication is essential to assure the benefits of a therapy during the follow-up. This is particularly important in chronic conditions such as hypertension. In fact, when discontinuation of study medication due to side effects was included in the combined primary end-point of ONTARGET, there was a trend toward lesser events with telmisartan [18].

On the other hand, despite the use of ARB or ACEi in ONTARGET, outcomes still remained [17]. This means that the current armamentarium is not enough to provide a complete protection in patients with hypertension. In this context, azilsartan, a new ARB, has been marketed for the treatment of hypertensive patients.

In this article, we update the most relevant available evidences of this drug, from a clinical point of view. For this purpose, a search on MEDLINE and EMBASE databases was performed. The MEDLINE and EMBASE search included both medical subject headings (MeSHs) and keywords including azilsartan or azilsartan medoxomil or angiotensin receptor blockers or renin angiotensin system or chlorthalidone and hypertension. References of the retrieved articles were also

Table 1. Pharmacokinetic properties of azilsartan medoxomil and chlorthalidone.

	Azilsartan medoxomil	Chlorthalidone
Peak plasma concentration	1.5 – 3 h	2 – 6 h
Metabolism	CYP2C9	The major portion of the drug is excreted unchanged by the kidneys.
Elimination half-life	≈ 11 h	42 h (range 29 – 55)

Data taken from [24,56,58].

screened for additional studies (**Box 1**). There were no language restrictions.

2. Pharmacological properties of azilsartan

Azilsartan medoxomil is a prodrug that after oral absorption is rapidly hydrolyzed to the active moiety, azilsartan. Different studies have shown that azilsartan has a potent and persistent ability to inhibit binding of angiotensin II to AT1 receptors, mainly due to its 5-oxo-1,2,4-oxadiazole moiety what may explain at least in part the superior BP-lowering efficacy found with azilsartan compared with other ARB [19-24].

The estimated oral bioavailability is ~ 60% and the peak plasma concentration is reached after 1.5 – 3 h of oral ingestion. Of note, food does not affect the bioavailability of azilsartan. More than 99% of azilsartan is bound to plasma proteins, mainly serum albumin (**Table 1**) [24].

Azilsartan, that is mainly metabolized by CYP2C9, is transformed into two primary metabolites: the major metabolite, known as M-II, and the minor metabolite, known as M-I. None of them contribute to the pharmacologic activity of azilsartan. The elimination half-life of azilsartan is ~ 11 h and renal clearance is ~ 2.3 ml/min (**Table 1**) [24].

Pharmacokinetic properties of azilsartan do not differ significantly according to age. No dose adjustment is required in patients with mild or moderate renal impairment, although caution should be paid in hypertensive patients with severe renal impairment and end-stage renal disease. Remarkably, hemodialysis does not remove azilsartan from the systemic circulation [24]. However, in a recent study performed with the aim to assess the effect of renal impairment on the pharmacokinetics of azilsartan and its major metabolite M-II, no dose adjustment of azilsartan was required for subjects with any degree of renal impairment, including end-stage renal disease [25].

The administration of azilsartan was associated with a slight increase in the exposure of patients with mild-to-moderate hepatic impairment. However, azilsartan has not been studied in patients with severe hepatic impairment, and it is not recommended in this population [24,26].

Azilsartan, similarly to the other ARBs, may increase serum potassium levels. As a result, special caution should be taken when azilsartan is coadministered with other agents than can induce hyperkalemia, such as potassium-sparing diuretics, or potassium supplements, particularly in high-risk patients (i.e., elderly patients, or subjects with renal insufficiency or diabetes) [24].

As with other renin angiotensin system blockers such as ACEi or ARB, the coadministration of azilsartan with lithium raises serum lithium concentrations, increasing the risk of toxicity by lithium. Therefore, the concomitant use of both drugs is not recommended [24]. The addition of nonsteroidal anti-inflammatory drugs to patients taking renin angiotensin system inhibitors, including azilsartan, may attenuate their antihypertensive effect, and increase the risk of renal function worsening and hyperkalemia. Thus, the concomitant use of both should be avoided [24]. By contrast, no relevant interactions have been described with amlodipine, antacids, chlortalidone, digoxin, fluconazole, ketoconazole, metformin or warfarin [24].

3. Azilsartan in the treatment of hypertension as monotherapy

Different clinical trials have investigated the antihypertensive efficacy of azilsartan medoxomil compared with other antihypertensive drugs, including other ARBs [27-32].

In a double-blind, controlled and randomized clinical trial, the efficacy and safety of azilsartan medoxomil versus ramipril were compared in patients with baseline clinic systolic BP 150 – 180 mm Hg. A total of 884 patients were randomly allocated to receive azilsartan medoxomil 20 mg or ramipril 2.5 mg once daily for 2 weeks, then force-titrated to 40 – 80 mg or 10 mg, respectively, for 22 weeks. At baseline, mean BP was 161.1 ± 7.9/94.9 ± 9.0 mm Hg. At study end, clinic systolic BP decreased by 20.6 ± 0.95 mm Hg (azilsartan medoxomil 40 mg), 21.2 ± 0.95 mm Hg (azilsartan medoxomil 80 mg) and 12.2 ± 0.95 mm Hg (ramipril 10 mg) ($p < 0.001$ for both azilsartan doses) (**Table 2**, **Figure 1**). Systolic and diastolic BP responders were defined as subjects who achieved both clinic systolic BP < 140 mm Hg and/or a reduction of ≥ 20 mm Hg and clinic diastolic BP < 90 mm Hg and/or a reduction of ≥ 10 mm Hg at week 24. Response rates at week 24 were higher with azilsartan medoxomil 40 mg (54.0%) and 80 mg (53.6%) compared with ramipril 10 mg (33.8%) ($p < 0.001$ for both azilsartan doses). Despite the higher antihypertensive efficacy of azilsartan medoxomil, adverse events leading to discontinuation were less frequent with azilsartan (2.4% with 40 mg and 3.1% with 80 mg) than with ramipril (4.8%) (**Table 2**). Serious adverse events were reported in 2.7, 4.1 and 2.0%, respectively. Higher rates of cough were reported with ramipril and higher rates of dizziness and hypotension with azilsartan medoxomil [27].

Table 2. Summary of efficacy and safety of azilsartan medoxomil alone and combined with chlorthalidone in patients with hypertension.

Study	Design	Results
Azilsartan medoxomil in monotherapy		
Bönner *et al*. [27].	A total of 884 patients were randomized to azilsartan medoxomil 20 mg or ramipril 2.5 mg once daily for 2 weeks, then force-titrated to 40 – 80 mg or 10 mg, respectively, for 22 weeks	At baseline, mean BP was 161.1 ± 7.9/94.9 ± 9.0 mm Hg At study end, clinic systolic BP decreased by 20.6 ± 0.95 mm Hg with azilsartan medoxomil 40 mg, 21.2 ± 0.95 mm Hg with azilsartan medoxomil 80 mg and 12.2 ± 0.95 mm Hg with ramipril 10 mg ($p < 0.001$ for both azilsartan doses vs ramipril) Adverse events leading to discontinuation were less frequent with azilsartan (2.4% with 40 mg and 3.1% with 80 mg) than with ramipril (4.8%).
Rakugi *et al*. [28].	A total of 622 Japanese patients with grade I-II essential hypertension were randomized to azilsartan medoxomil (20 – 40 mg once daily by forced titration) or candesartan (8 – 12 mg once daily by forced titration) during a 16-week follow-up period	At baseline, mean BP was 159.8/100.4 mm Hg At study end, reductions in diastolic BP were higher with azilsartan medoxomil, compared with candesartan (-12.4 vs -9.8 mm Hg, respectively; mean difference -2.6 mm Hg, $p = 0.0003$). Similar results were found in sitting systolic BP (-21.8 vs -17.5 mm Hg, respectively, mean difference -4.4 mm Hg, $p < 0.0001$) The study drugs were equally well tolerated, and the great majority of adverse events were mild or moderate in intensity in both groups.
Sica *et al*. [29].	A total of 984 patients with hypertension (baseline 24-h mean systolic BP about 145.6 mm Hg) were randomized to azilsartan medoxomil 40, azilsartan medoxomil 80 mg and valsartan 320 mg during 24 weeks of treatment	At study end, 24-h mean systolic BP was reduced by -14.9, -15.3 and -11.3 mm Hg, respectively; $p < 0.001$ for both doses of azilsartan vs valsartan Clinic systolic BP was also reduced in the three groups (-14.9, -16.9 and -11.6 mm Hg; $p = 0.015$ and $p < 0.001$, respectively) Similar results were found in 24-h and clinic diastolic BP Rates of treatment-emergent adverse events were similar in the three groups, and mostly mild to moderate in severity.
Bakris *et al*. [30].	A total of 1,275 hypertensive patients with baseline 24-h mean ambulatory systolic BP of 146 mm Hg, were randomized to placebo, azilsartan medoxomil 20 mg, azilsartan medoxomil 40 mg, azilsartan medoxomil 80 mg and olmesartan 40 mg	After 6 weeks of treatment there was a dose-dependent reduction in 24-h mean systolic BP in all azilsartan groups While azilsartan medoxomil 40 mg was noninferior to olmesartan 40 mg, azilsartan medoxomil 80 mg provided higher reductions in 24-h mean systolic BP than olmesartan 40 mg (treatment difference -2.1 mm Hg; $p = 0.038$) Reductions in ambulatory systolic BP were sustained throughout the 24-h monitoring interval Discontinuations due to adverse events and serious adverse events were reported more frequently in the placebo and azilsartan medoxomil 20 mg groups, whilst serious adverse events were reported in < 1% of patients in the other groups
White *et al*. [31].	In a placebo-controlled study, a total of 1,291 patients, with baseline 24-h mean systolic BP 145 mm Hg, were included. Patients were treated with azilsartan medoxomil 40 and 80 mg, olmesartan 40 mg and valsartan 320 mg for 6 weeks	At study end, whilst azilsartan medoxomil 40 mg was noninferior to olmesartan 40 mg, azilsartan 80 mg (placebo-adjusted 24-h systolic BP -14.3 mm Hg) was more effective than valsartan 320 mg (-10.0 mm Hg; $p < 0.001$) and olmesartan 40 mg (-11.7 mm Hg; $p = 0.009$) Both doses of azilsartan were superior to valsartan and olmesartan in the reduction of clinic systolic BP The incidence of side effects was equal in all treatment groups, and similar to placebo.
Fixed-dose combination of azilsartan medoxomil and chlorthalidone		
Sica *et al*. [59].	In a study that compared the efficacy and safety of the fixed-dose combinations of azilsartan medoxomil and chlorthalidone with the individual monotherapies in a double-blind factorial study, a total of	At baseline, mean trough BP (h 22 – 24) was 149 – 154/89 – 92 mm Hg measured by ambulatory BP monitoring, and 163 – 166/94 – 96 mm Hg by clinic BP At study end, systolic BP measured either by ambulatory BP measurement or clinic, was greater reduced by the highest

Data taken from [27-31] and [59-61].
BP: Blood pressure.

Table 2. Summary of efficacy and safety of azilsartan medoxomil alone and combined with chlorthalidone in patients with hypertension (continued).

Study	Design	Results
	1,714 hypertensive patients with clinic systolic BP between 160 and 190 mm Hg were included. Patients were randomized to azilsartan medoxomil 0 mg, 20 mg, 40 mg, or 80 mg and/or chlorthalidone 0 mg, 12.5 mg, or 25 mg during 8 weeks of treatment	doses of azilsartan medoxomil/chlorthalidone (40/25 mg and 80/25 mg) compared with the highest doses of both drugs in monotherapy These reductions were higher with the combination therapies throughout the 24-h recording interval With regard to side effects, these were dose-dependent and more frequently reported with combined therapy. However, hypotension episodes were infrequent with combined therapy (0.6 – 3.1%)
Bakris *et al*. [60].	A total of 609 patients with stage 2 hypertension (mean baseline clinic BP 164.6/95.4 mm Hg) were randomized to the fixed combination of azilsartan medoxomil and chlorthalidone and the combination of azilsartan medoxomil and hydrochlorothiazide for 10 weeks After being treated with azilsartan medoxomil 40 mg in monotherapy during 2 weeks, all patients received 12.5 mg of chlorthalidone or hydrochlorothiazide for other 4 weeks, and whether BP remained uncontrolled, diuretics were titrated to 25 mg for another 4 weeks	At week 6, those patients treated with the combination of azilsartan medoxomil and chlorthalidone achieved greater clinic systolic BP reduction compared with the combination of azilsartan medoxomil and hydrochlorothiazide (-35.1 vs -29.5 mm Hg, respectively; $p < 0.001$) Similar results were found regarding 24-h ambulatory systolic BP at week 6 (mean difference -5.8 mm Hg; $p < 0.001$) Only 30.8% of patients treated with the combination azilsartan medoxomil/chlorthalidone were titrated to 25 mg of chlorthalidone, compared with 45.9% of those treated with hydrochlorothiazide combination ($p < 0.001$) At study end, greater BP reductions were achieved with azilsartan medoxomil/chlorthalidone combination (mean difference -5.0 mm Hg; $p < 0.001$) With regard to side effects, these were similar in both groups, including serious adverse events (2.0 vs 1.7%, respectively) and discontinuations due to side effects (9.3 vs 7.3%, respectively, $p = 0.38$)
Cushman *et al*. [61].	A total of 1,071 patients with baseline clinic BP 165/96 mm Hg and baseline 24-h mean BP 150/88 mm Hg) were randomized to receive the fixed-dose combinations of azilsartan medoxomil/chlorthalidone (force titrated to either 40/25 mg or 80/25 mg) or a fixed-dose combination of olmesartan plus hydrochlorothiazide (force titrated to 40/25 mg) during 12 weeks of treatment	At study end, both combinations of azilsartan medoxomil/chlorthalidone achieved greater BP reductions than the combination of olmesartan/hydrochlorothiazide in clinic (-42.5 ± 0.8, -44.0 ± 0.8 and -37.1 ± 0.8 mm Hg, respectively; $p < 0.001$) and ambulatory systolic BP (-33.9 ± 0.8, -36.3 ± 0.8 and -27.5 ± 0.8 mm Hg, respectively; $p < 0.001$) The proportion of patients that discontinued from treatment due to adverse events was 7.9, 14.5 and 7.1%, respectively

Data taken from [27-31] and [59-61].
BP: Blood pressure.

Azilsartan medoxomil has been compared with other ARB, including candesartan, valsartan or olmesartan. In a study that compared the efficacy and safety of azilsartan medoxomil versus candesartan, 622 Japanese patients with grade I – II essential hypertension were included. Patients were randomized to azilsartan medoxomil (20 – 40 mg once daily by forced titration) or candesartan (8 – 12 mg once daily by forced titration) during a 16-week follow-up period. Mean BP was 159.8/100.4 mm Hg at baseline. At study end, although both treatments decreased sitting diastolic BP levels, reductions in BP were higher with azilsartan medoxomil, compared with candesartan (-12.4 vs -9.8 mm Hg, respectively; mean difference -2.6 mm Hg, 95% CI -4.08 to -1.22 mm Hg; $p = 0.0003$) (**Table 2**). Similar results were found in sitting systolic BP (-21.8 vs -17.5 mm Hg, respectively, mean difference -4.4 mm Hg, 95% CI -6.53 to -2.20 mm Hg, $p < 0.0001$) (**Figure 1**). Similarly, azilsartan medoxomil was more effective than candesartan on ambulatory BP monitoring at week 14, particularly, in diastolic and systolic BP over a 24-h period, and during the daytime, night-time and early morning. The study drugs were equally well tolerated, as no significant differences were found in the incidence of treatment-emergent adverse events between both the groups. The great majority of adverse events were mild or moderate in intensity in both groups (**Table 2**). The most common adverse events reported were nasopharyngitis, upper respiratory tract inflammation and pharyngitis. Similarly, the overall incidence of hypotension-related events was similar in both groups (3.5 vs 3.2%, respectively) [28].

In a study performed in 984 patients with hypertension (baseline 24-h mean systolic BP about 145.6 mm Hg), azilsartan medoxomil 40 – 80 mg were compared with valsartan

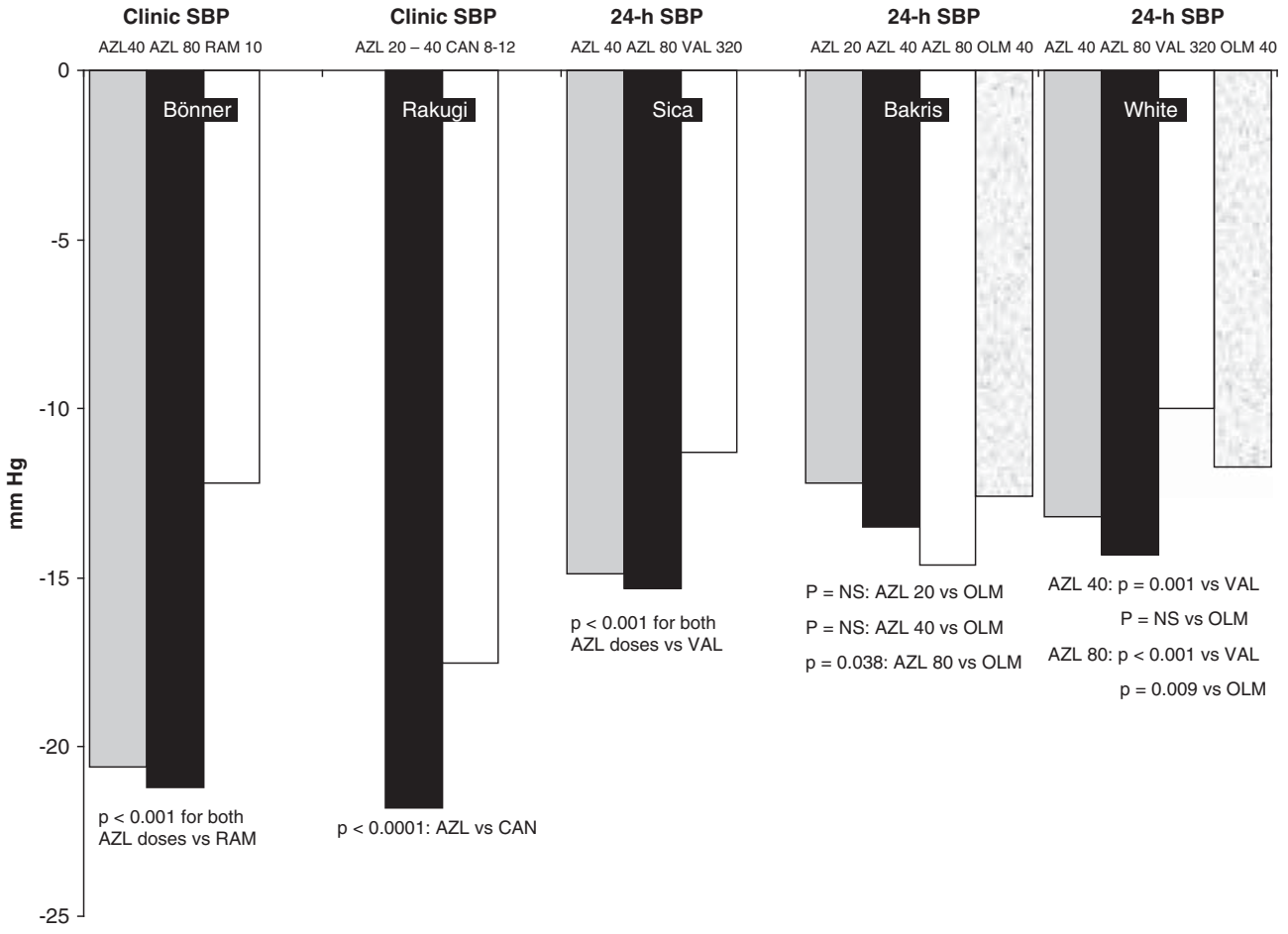


Figure 1. Efficacy of azilsartan medoxomil on systolic blood pressure compared with other angiotensin receptor blockers.
Data taken from [27-31].
24-h: 24 hours; AZL: Azilsartan; CAN, Candesartan; OLM: Olmesartan; RAM: Ramipril; SBP: Systolic blood pressure; VAL: Valsartan.

320 mg during 24 weeks of treatment. At study end, 24-h mean systolic BP was reduced by -14.9, -15.3 and -11.3 mm Hg, respectively; $p < 0.001$ for both doses of azilsartan vs valsartan (**Figure 1**). Clinic systolic BP was also reduced in the 3 groups (-14.9, -16.9 and -11.6 mm Hg; $p = 0.015$ and $p < 0.001$, respectively). Similar results were found in 24-h and clinic diastolic BP. Response to treatment was defined as a reduction in clinic systolic BP to < 140 mm Hg and/or a reduction of ≥ 20 mm Hg. Response rates were significantly greater with azilsartan medoxomil 40 and 80 mg (56 and 59%, respectively) than with valsartan 320 mg (47%; $p = 0.016$ and $p = 0.002$, respectively). Rates of treatment-emergent adverse events were similar in the 3 groups, and mostly mild to moderate in severity (**Table 2**). The most common adverse events during the trial were headache, dizziness and urinary tract infection. Small mean changes in serum creatinine, potassium and liver enzymes were observed in the 3 groups. Mean serum creatinine concentrations increased slightly more with azilsartan. Similarly, hyperkalemia (serum potassium > 6 mmol/L) was more common in those patients assigned to azilsartan medoxomil 40 mg (1.8%), compared with azilsartan medoxomil 80 mg (0.3%) and valsartan 320 mg (0.6%) [29].

Azilsartan medoxomil has also been compared with olmesartan, probably the most potent ARB until the launch of azilsartan. Thus, in a study that included 1,275 hypertensive patients with baseline 24-h mean ambulatory systolic BP ≥ 130 and ≤ 170 mm Hg (mean 146 mm Hg), patients were randomized to placebo (n = 142), azilsartan medoxomil 20 mg (n = 283), azilsartan medoxomil 40 mg (n = 283), azilsartan medoxomil 80 mg (n = 285) and olmesartan 40 mg (n = 282). After 6 weeks of treatment, as expected, there was a dose-dependent reduction in 24-h mean systolic BP in all azilsartan groups. While azilsartan medoxomil 40 mg was noninferior to olmesartan 40 mg (treatment difference -0.92 mm Hg; 95% CI -2.87 to + 1.02 mm Hg; $p = 0.352$), azilsartan medoxomil 80 mg provided higher reductions in 24-h mean systolic BP than olmesartan 40 mg (treatment difference

-2.1 mm Hg; 95% CI -4.0 to -0.1 mm Hg; p = 0.038) (**Figure 1**). Importantly, reductions in ambulatory systolic BP were sustained throughout the 24-h monitoring interval. The proportion of patients who had a reduction in clinic systolic BP to < 140 mm Hg and/or a reduction of ≥ 20 mm Hg were 48% with azilsartan medoxomil 20 mg, 50% with azilsartan medoxomil 40 mg, 57% with azilsartan medoxomil 80 mg and 53% with olmesartan 40 mg. Changes in 24-h mean diastolic BP and clinic diastolic BP were consistent with the results for systolic BP. No significant interaction was observed by age, sex, baseline median 24-h mean systolic BP and baseline estimated glomerular filtration rate. With regard to safety, discontinuations due to adverse events and serious adverse events were reported more frequently in the placebo and azilsartan medoxomil 20 mg groups. However, serious adverse events were reported in < 1% of patients in the other groups (**Table 2**). The most commonly adverse events reported in all groups were headache, dyslipidemia and dizziness [30].

In a placebo-controlled study that compared 3 different ARBs (azilsartan medoxomil 40 and 80 mg, olmesartan 40 mg and valsartan 320 mg), a total of 1,291 patients, with baseline 24-h mean systolic BP 145 mm Hg, were included. The primary efficacy end point was the change from baseline in 24-h mean systolic BP after 6 weeks of treatment. At study end, whilst azilsartan medoxomil 40 mg was noninferior to olmesartan 40 mg (treatment difference -1.4 mm Hg; 95% CI -3.3 to + 0.5 mm Hg), azilsartan 80 mg (placebo-adjusted 24-h systolic BP -14.3 mm Hg) was more effective than valsartan 320 mg (-10.0 mm Hg; p < 0.001) and olmesartan 40 mg (-11.7 mm Hg; p = 0.009) (**Figure 1**). Of note, both doses of azilsartan were superior to valsartan and olmesartan in the reduction of clinic systolic BP. The proportion of patients who achieved a reduction of clinic systolic BP to < 140 mm Hg and/or a reduction of ≥ 20 mm Hg was significantly greater with azilsartan 80 mg (58%) compared with placebo (22%), 320 mg of valsartan 320 mg (49%) and olmesartan 40 mg (49%). With regard to side effects, these were equal in all treatment groups, and similar to placebo. In all groups, about 1% of patients had serious adverse events. The most common adverse events during the trial were headache, dizziness and urinary tract infection (**Table 2**) [31].

In a systematic review performed through August 2011, azilsartan medoxomil 40 mg and 80 mg once daily significantly reduced both systolic and diastolic BP from baseline compared with placebo, and azilsartan medoxomil 80 mg was superior to other ARBs, including olmesartan 40 mg and valsartan 320 mg, measured by both 24-h BP ambulatory monitoring and clinic monitoring. Tolerability and safety of azilsartan medoxomil were similar to other ARBs [32].

4. Pleiotropic effects of azilsartan

The effects of azilsartan medoxomil are not limited to its effects on BP, as different experimental studies have shown [33-41]. Thus, in mice with either surgically induced left ventricular pressure overload (aortic banding) or acute myocardial infarction, the treatment with azilsartan was associated with less left ventricular wall thickness, hypertrophy and dilation compared with that exhibited by controls in drug-treated aortic-banded mice. Moreover, there was a trend to a lesser mortality in drug-treated myocardial infarction mice. Moreover, azilsartan-treated mice with acute myocardial infarction had less cardiomyocyte injury [33]. In a study performed in obese and insulin-resistant mice fed with a high fat diet, with left ventricular pressure overload after aortic banding, the addition of azilsartan was associated with a decrease of left ventricular wall thickness, left ventricular hypertrophy and cardiac plasminogen activator inhibitor-1 (PAI-1), as well as with an increase of cardiac output [34].

In other study, azilsartan, administered during 16 weeks to ApoE knockout mice on a high fat diet, suppressed vascular wall expression of PAI-1 protein. Moreover, cellularity and collagen were increased in lesions, consistent with the development of more stable plaques. This, combined with the suppression of PAI-1 expression, may facilitate the stabilization of atherosclerotic plaques [35]. In male mice with myocardial infarction after left anterior descending coronary artery ligation, cardiac remodeling was significantly attenuated by azilsartan, regardless BP lowering effect [36].

Other study analyzed the potential pleiotropic effects of azilsartan in cell-based assay systems independent of its effects on BP. In cultured 3T3-L1 preadipocytes, azilsartan enhanced adipogenesis and exerted greater effects than valsartan on expression of genes encoding adiponectin, adipsin, leptin and PPARα, PPARδ. Similarly, azilsartan inhibited vascular cell proliferation and in aortic endothelial cells, inhibited cell proliferation, whereas valsartan showed little or no antiproliferative effects [37].

In other study, azilsartan reduced BP more potently and persistently than olmesartan in renal hypertensive dogs. Moreover, after 2 weeks of treatment, azilsartan showed more stable antihypertensive effects than olmesartan and improved the glucose infusion rate more potently (≥ 10 times) than olmesartan. Similarly, azilsartan had a more potent antiproteinuric effect than olmesartan in Wistar fatty rats [38]. Other studies have confirmed the beneficial effect of azilsartan on insulin sensitivity in skeletal muscle of male Sprague–Dawley rats, in obese Koletsky rats and in male KK-A(y) mice, even greater than other ARBs such as candesartan [39-41].

5. Rationale for the use of combined therapy

Although some patients may achieve BP goals with only one antihypertensive agent, in clinical practice most patients will require the combination of at least two drugs to attain BP targets [12,13]. In fact, one of the main reasons that may explain the improvement in BP control rates observed in the past years in many countries is the progressively higher use of combined therapy [7-11]. This is not strange as it has been shown that combining antihypertensive drugs with different

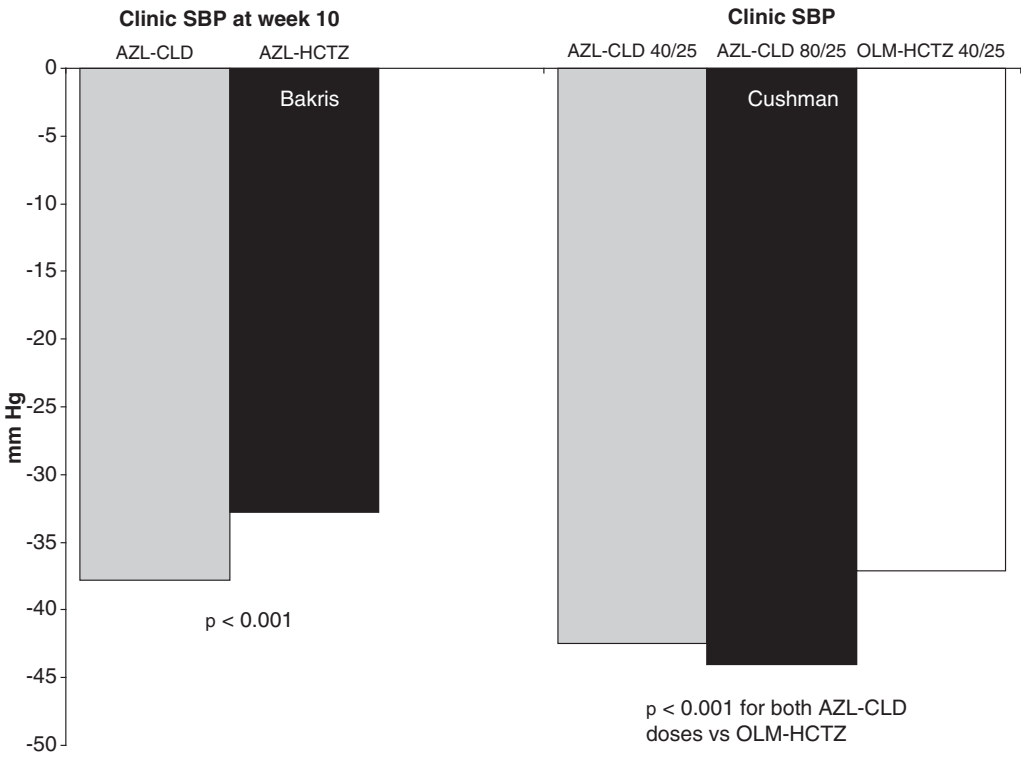


Figure 2. Efficacy of the combination azilsartan medoxomil plus chlorthalidone compared with the combinations azilsartan medoxomil plus hydrochlorothiazide and olmesartan plus hydrochlorothiazide.

Data taken from [60] and [61].

AZL: Azilsartan; CLD: Chlorthalidone; HCTZ: Hydrochlorothiazide; OLM: Olmesartan; SBP: Systolic blood pressure.

mechanisms of action is ~ 5 times more effective in reducing BP values than doubling the dose of 1 drug [42]. Moreover, combined therapy may achieve an earlier response in a larger number of patients. A further advantage is that combining 2 drugs with different mechanisms of action is associated with lesser side-effects and may provide greater benefits than those offered by a single agent [13]. A recent study retrospectively evaluated the effects of initial versus delayed treatment with combined therapy in hypertensive patients. In this study, 1,762 hypertensive patients started with combined therapy and were matched 1:1 with similar patients beginning with monotherapy and later switched to combined therapy. In those patients that started with combined therapy, the risk of cardiovascular events or death was reduced by 44% (HR 0.66; 95% CI 0.52 – 0.84; p = 0.0008). This risk reduction was mainly attributed to a more rapid achievement of target BP [43].

The most recent 2013 ESH/ESC guidelines for the management of arterial hypertension consider that combined therapy can be used in those patients with mild BP elevation or low/moderate cardiovascular risk that remain uncontrolled despite monotherapy, and as first-line therapy in those patients with marked BP elevation or in those at high or very high cardiovascular risk [13].

On the other hand, combined therapy can be taken in a single pill (fixed combinations) or in separate pills (free combinations). Different studies have shown that fixed combinations improve medication adherence [44,45]. Moreover, it has been reported that, compared with initial antihypertensive monotherapy and free combinations, the greater use of single-pill combinations as initial therapy may improve hypertension control and cardiovascular outcomes in untreated and uncontrolled hypertensive patients during their first treatment year [46]. All these benefits translate into lower healthcare costs. In fact, in a 12-month follow-up study performed in South Carolina Medicaid beneficiaries aged ≥ 65 years, the use of fixed-dose combination, compared with free combination, was associated with a reduction of 12.5% in total costs ($p < 0.003$) [45].

All first-line antihypertensive treatments reduce BP effectively. However, not all combinations have been shown to be equally beneficial. Due to their complementary mechanisms of action, the combination of a diuretic and an ARB are particularly recommended [12,13]. The majority of fixed combinations used in clinical practice of an ARB and a diuretic included hydrochlorothiazide as the diuretic [12,13,47-49]. However, it has been suggested that not all diuretics are equal.

6. Differences between hydrochlorothiazide and chlorthalidone in the treatment of hypertension

The SHEP (Systolic Hypertension in the Elderly Program) study showed that in patients ≥ 60 years and isolated systolic hypertension, antihypertensive stepped-care drug treatment with low-dose chlorthalidone as step 1 medication reduced the risk of total stroke by 36%, the risk of major cardiovascular events by 32% and the risk of deaths from all causes by 13% [50]. However, no benefits on cardiovascular events have been shown with low doses of hydrochlorothiazide. Thus, in a systematic review of randomized trials in which 1 arm was based on either hydrochlorothiazide or chlorthalidone, 9 trials were identified (3 based on hydrochlorothiazide and 6 based on chlorthalidone; n = 50,946 in the drug-adjusted analysis and n = 78,350 in the office systolic BP-adjusted analysis). In this study, chlorthalidone was superior to hydrochlorothiazide in preventing cardiovascular events, and this could not be attributed entirely to a lesser effect of hydrochlorothiazide on office systolic BP [51]. In a retrospective observational cohort study from the multiple risk factor intervention, a cardiovascular primary prevention trial, when compared both drugs, chlorthalidone, compared with hydrochlorothiazide, had lesser cardiovascular events ($p = 0.0016$), and was more effective in reducing systolic BP ($p < 0.0001$) [52]. In a small randomized, single-blinded, and crossover study that compared chlorthalidone 12.5 mg/day (force-titrated to 25 mg/day) and hydrochlorothiazide 25 mg/day (force-titrated to 50 mg/day) during 8 weeks of treatment, chlorthalidone 25 mg achieved greater reductions in ambulatory systolic BP than hydrochlorothiazide 50 mg (24-h mean -12.4 ± 1.8 mm Hg vs -7.4 ± 1.7 mm Hg, respectively; $p = 0.054$; nighttime mean = -13.5 ± 1.9 mm Hg vs -6.4 ± 1.8 mm Hg, respectively; $p = 0.009$). However, these differences were not significant when analyzing office BP measurements [53]. Although some guidelines do not provide conclusive recommendations in favor of a particular diuretic agent due to the lack of definitive established evidence [13], others, such as the NICE guidelines, recommend that when a diuretic is prescribed, a thiazide-like diuretic, such as chlorthalidone or indapamide should be preferred over a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide [14].

After oral administration, peak serum concentrations of chlorthalidone are reached at ~ 2 – 6 h. The half-life of chlorthalidone is about 42 h (range 29 – 55 h) with a large interindividual variability. This long half-life is explained by the fact that chlorthalidone rapidly enters and concentrates in erythrocytes and the slow release of chlorthalidone from these erythrocytes. In fact, concentrations of chlorthalidone are 7 – 10 times greater in erythrocytes than in plasma. By contrast, the half-life of hydrochlorothiazide ranges from 5.6 to 14.8 h. Of note, the natriuretic effect of chlorthalidone has been shown to be maximal at 18 h and lasts at least 48 h. With regard to elimination, chlorthalidone is essentially excreted unchanged by the kidney (**Table 1**) [54-58].

7. Clinical data with the combination of azilsartan plus chlorthalidone in the treatment of arterial hypertension

All these data explain why the combination of azilsartan and chlorthalidone is a logical and rational approach for the treatment of patients with arterial hypertension. Several clinical trials have analyzed the efficacy and safety of the fixed combination of azilsartan and chlorthalidone in this population [59-62].

In a study that compared the efficacy and safety of the fixed-dose combinations of azilsartan medoxomil and chlorthalidone with the individual monotherapies in a double-blind factorial study, a total of 1,714 hypertensive patients with clinic systolic BP between 160 and 190 mm Hg were included. Patients were randomized to azilsartan medoxomil 0 mg, 20 mg, 40 mg or 80 mg and/or chlorthalidone 0 mg, 12.5 mg or 25 mg during 8 weeks of treatment. At baseline, mean trough BP (h 22 – 24) was 149 – 154/89 – 92 mm Hg measured by ambulatory BP monitoring, and 163 – 166/94 – 96 mm Hg by clinic BP (**Table 2**) [59].

At study end, systolic BP measured either by ambulatory BP measurement or clinic, was greater reduced by the highest doses of azilsartan medoxomil/chlorthalidone (40/25 mg and 80/25 mg) compared with the highest doses of both drugs in monotherapy. In fact, each of the six individual azilsartan medoxomil/chlorthalidone doses produced significantly greater reductions of trough systolic BP compared with their respective components. Similar findings were reported with regard to trough diastolic BP. The BP reductions were higher with the combinations throughout the 24-h recording interval. These higher reductions found with combined therapy translated into a better achievement of BP goals compared with their respective monotherapies. In fact, 70 – 85% of patients treated with the combination attained BP goals (< 140/90 mm Hg), compared with azilsartan medoxomil (30 – 52%) and chlorthalidone monotherapies (34 – 51%) (**Table 2**) [59].

With regard to side effects, these were dose-dependent and more frequently reported with combined therapy. However, hypotension episodes were infrequent with combined therapy (0.6 – 3.1%). Serious adverse events were reported in 0.7% of patients treated with azilsartan medoxomil/chlorthalidone 40/12.5 mg, 1.3% of patients treated with azilsartan medoxomil/chlorthalidone 80/12.5 mg, 1.3% of patients treated with azilsartan medoxomil/chlorthalidone 40/25 mg and in 1.2% of patients treated with azilsartan medoxomil/chlorthalidone 80/25 mg combinations (**Table 2**) [59].

In a 10-week randomized and double-blind study, the fixed combination of azilsartan medoxomil and chlorthalidone was

compared with the combination of azilsartan medoxomil and hydrochlorothiazide in 609 patients with stage 2 hypertension (mean baseline clinic BP 164.6/95.4 mm Hg). After being treated with azilsartan medoxomil 40 mg in monotherapy during 2 weeks, all patients received 12.5 mg of chlorthalidone or hydrochlorothiazide for other 4 weeks, and whether BP remained uncontrolled, diuretics were titrated to 25 mg for another 4 weeks. At week 6, those patients treated with the combination of azilsartan medoxomil and chlorthalidone achieved greater clinic systolic BP reduction compared with the combination of azilsartan medoxomil and hydrochlorothiazide (-35.1 vs -29.5 mm Hg, respectively; mean difference -5.6 mm Hg; 95% CI -8.3 to -2.9; $p < 0.001$) (**Table 2**) [60].

Similar results were found regarding 24-h ambulatory systolic BP at week 6 (mean difference -5.8 mm Hg; 95% CI -8.4 to -3.2; $p < 0.001$). As a result, more patients treated with chlorthalidone combination achieved BP goals, defined as clinic BP < 140/90 mm Hg, < 130/80 mm Hg for patients with diabetes or chronic kidney disease (64.1 vs 45.9%, respectively, $p < 0.001$). Only 30.8% of patients treated with the combination azilsartan medoxomil/chlorthalidone were titrated to 25 mg of chlorthalidone, compared with 45.9% of those treated with hydrochlorothiazide combination ($p < 0.001$). At study end, greater BP reductions were achieved with azilsartan medoxomil/chlorthalidone combination (mean difference -5.0 mm Hg; 95% CI -7.5 to -2.5; $p < 0.001$) (**Table 2**, **Figure 2**) [60].

With regard to side effects, these were similar in both groups, including serious adverse events (2.0 vs 1.7%, respectively) and discontinuations due to side effects (9.3 vs 7.3%, respectively, $p = 0.38$) (**Table 2**) [60].

In other study performed in 1,071 patients with baseline clinic systolic BP 160 – 190 mm Hg and diastolic BP ≤ 119 mm Hg (baseline clinic BP 165/96 mm Hg and baseline 24-h mean BP 150/88 mm Hg), the fixed-dose combinations of azilsartan medoxomil/chlorthalidone (force titrated to either 40/25 mg or 80/25 mg) were compared with a fixed-dose combination of olmesartan plus hydrochlorothiazide (force titrated to 40/25 mg) during 12 weeks of treatment (**Table 2**) [61]. At study end, both combinations of azilsartan medoxomil/chlorthalidone achieved greater BP reductions than the combination of olmesartan/hydrochlorothiazide in clinic (-42.5 ± 0.8, -44.0 ± 0.8 and -37.1 ± 0.8 mm Hg, respectively; $p < 0.001$) and ambulatory systolic BP (-33.9 ± 0.8, -36.3 ± 0.8 and -27.5 ± 0.8 mm Hg, respectively; $p < 0.001$). With regard to side effects, the proportion of patients that discontinued from treatment due to adverse events was 7.9, 14.5 and 7.1%, respectively (**Table 2**, **Figure 2**) [61].

More recently, in a review that included clinical trials and reviews involving the combination of azilsartan medoxomil and chlorthalidone or each component individually for the treatment of hypertension through December 2012, in four randomized controlled trials the combination of azilsartan medoxomil and chlorthalidone 40/12.5 mg and 40/25 mg achieved larger BP reductions than comparators, including the combinations of olmesartan/hydrochlorothiazide 40/25 mg and azilsartan medoxomil/hydrochlorothiazide. With regard to safety, the combination of azilsartan medoxomil and chlorthalidone was globally well tolerated [62].

The different clinical trials that have analyzed the efficacy and safety of azilsartan medoxomil alone or combined with chlorthalidone in patients with hypertension are summarized in **Table 2**.

8. Expert opinion

To reduce cardiovascular events in hypertensive population, it is necessary to reduce BP levels to recommended targets [12-14]. Moreover, it has been shown that the early control of BP provides additional benefits [43,63]. On the other hand, the inhibition of renin angiotensin system should be the basis of treatment in many hypertensive patients, particularly in those at higher risk, such as those with organ damage (i.e., left ventricular hypertrophy, microalbuminuria) or cardiovascular disease (i.e., myocardial infarction, heart failure, renal disease, among others), as well as the basis when combined therapy is required in the great majority of cases [12-14].

Unfortunately, despite the inhibition of renin angiotensin system with current ACEi and ARB, cardiovascular outcomes (i.e., end-stage renal disease, myocardial infarction) still occur [17,64-66]. Even more, a more complete inhibition of renin angiotensin system inhibition with the combination of two renin angiotensin system inhibitors (ACEi plus ARB or ACEi or ARB with aliskiren) has been shown to be not only no beneficial, but in certain situations might be even harmful [17,67].

Azilsartan medoxomil is the most recent ARB marketed. Its unique pharmacological properties count azilsartan among the most potent ARBs. Different clinical trials have demonstrated that azilsartan medoxomil achieves BP control rates earlier and greater than other inhibitors of renin angiotensin system, such as ramipril, candesartan, valsartan or olmesartan, with low and comparable rates of adverse events [27-32]. However, whether this higher efficacy of azilsartan medoxomil may translate into a marked reduction of cardiovascular outcomes, it has not been demonstrated yet, in contrast with other ARB. Moreover, to date the benefits on organ damage or beneficial effects beyond BP control reported with this drug have only been proved in experimental studies [33-41]. Therefore, new studies specifically performed in humans are warranted to confirm the suggestive potential benefits of azilsartan medoxomil over other ACEis or ARBs. As a result, in contrast to other ARBs, the current indication of azilsartan is only limited to the treatment of essential hypertension. Thus, when an ARB is required in patients with heart failure or left ventricular dysfunction, candesartan, losartan or valsartan could be prescribed; on the other hand, if atherothrombotic cardiovascular disease is present, telmisartan should be preferred [19,68].

It is well recognized that the majority of hypertensive population will actually require the combination of at least two drugs to attain BP targets [12,13]. The combination of an ARB and a diuretic is rational, effective and safe [12,13]. Although in the majority of cases, when ACEi or ARB is combined with a diuretic, the diuretic used is hydrochlorothiazide; the fact is that not all diuretics are equal. Thus, some studies have suggested that chlorthalidone could be superior to hydrochlorothiazide in the reduction of BP and cardiovascular events [51-53]. Since azilsartan medoxomil seems to be more potent than other renin angiotensin system inhibitors and chlorthalidone seems more beneficial than hydrochlorothiazide, the combination of azilsartan medoxomil and chlorthalidone appears an excellent and unique alternative in the treatment of hypertensive patients, particularly those at higher risk. In fact, the fixed-dose combination of azilsartan medoxomil and chlorthalidone has been shown to be more effective than other potent combinations, such as olmesartan plus hydrochlorothiazide, with a good tolerability profile [61]. Moreover, this combination has the same advantages of other fixed combinations that assure a better adherence compared with free combinations [44-46]. However, although this combination has been shown to be more effective than others in the reduction of BP and these data are promising, to date, no clinical trials specifically designed to demonstrate whether this higher efficacy translates into a reduction of cardiovascular events or at least in an improvement of subclinical organ damage have been performed.

Declaration of interest

V Barrios has received honoraria for lectures from Takeda Pharmaceutical Company Limited. C Escobar has no conflicts of interest.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Barrios V, Escobar C. Is a new crash coming? J Hypertens Open Access 2012;1:e105
2. Lewington Clarke R, Qizilbash N, et al. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13
3. Crim MT, Yoon SS, Ortiz E, et al. National surveillance definitions for hypertension prevalence and control among adults. Circ Cardiovasc Qual Outcomes 2012;5:343-51
4. Stephens MM, Fox BA, Maxwell L. Therapeutic options for the treatment of hypertension in children and adolescents. Clin Med Insights Circ Respir Pulm Med 2012;6:13-25
5. Mancia G, Messerli F, Bakris G, et al. Blood pressure control and improved cardiovascular outcomes in the International Verapamil SR-Trandolapril Study. Hypertension 2007;50:299-305
6. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827-38
7. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the national health and nutrition examination survey, 2001 to 2010. Circulation 2012;126:2105-14
8. McAlister FA, Wilkins K, Joffres M, et al. Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. CMAJ 2011;183:1007-13
9. Llisterri JL, Rodriguez-Roca GC, Escobar C, et al. on behalf of the Working Group of Arterial Hypertension of the Spanish Society of Primary Care Physicians (Group HTASEMERGEN); and the PRESCAP 2010 investigators. Treatment and blood pressure control in Spain during 2002 – 2010. J Hypertens 2012;30:2425-31
10. Cífková R, Skodová Z, Bruthans J, et al. Longitudinal trends in cardiovascular mortality and blood pressure levels, prevalence, awareness, treatment, and control of hypertension in the Czech population from 1985 to 2007/2008. J Hypertens 2010;28:2196-203
11. Kastarinen M, Antikainen R, Peltonen M, et al. Prevalence, awareness and treatment of hypertension in Finland during 1982 – 2007. J Hypertens 2009;2788:1552-9
12. Mancia G, De Backer G, Dominiczack A, et al. 2007 guidelines for the management of arterial hypertension: the. Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105-87
13. Mancia G, Fagard R, Narkiewicz K, et al. ESH/ESC Guidelines for the management of arterial hypertension: theTask Force for the management ofarterial hypertension of the European Society ofHypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281-357
14. National Institute for Health and Clinical Excellence (NICE). Hypertension. The clinical management of primary hypertension in adults. August 2011. Available from: www.nice.org.uk/guidance/CG127
15. Escobar C, Barrios V. An evaluation of the latest evidence relating to renin-angiotensin system inhibitors. Expert Opin Drug Metab Toxicol 2013;9:847-58
16. Barrios V, Coca A, Escobar C, et al. Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in clinical practice. Expert Rev Cardiovasc Ther 2012;10:159-66
17. Yusuf S, Teo KK, Pogue J, et al. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59

•• **In this study, telmisartan was equivalent to ramipril in patients with**

vascular disease or high-risk diabetes, but better tolerated.

18. Barrios V, Escobar C, Prieto L, Herranz I. Adverse events in clinical trials: is a new approach needed? Lancet 2008;372:535-6
19. Kurtz TW, Kajiya T. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. Vasc Health Risk Manag 2012;8:133-43
20. Miura SI, Okabe A, Matsuo Y, et al. Unique binding behavior of the recently approved angiotensin II receptor blocker azilsartan compared with that of candesartan. Hypertens Res 2013;36:134-9

• **This study demonstrates that azilsartan has a unique binding behaviour to the AT1 receptor due to its 5-oxo-1,2,4-oxadiazole moiety and this may explain the higher efficacy of azilsartan compared with other ARBs.**

21. Tamura K, Ohsawa M, Kanaoka T, et al. What can we expect from the binding characteristics of azilsartan, a newly available angiotensin II blocker, in hypertension? Hypertens Res 2013;36:107-8
22. Ojima M, Igata H, Tanaka M, et al. In vitro antagonistic properties of a new angiotensin type 1 receptor blocker, azilsartan, in receptor binding and function studies. J Pharmacol Exp Ther 2011;336:801-8
23. Miura SI, Matsuo Y, Nakayama A, et al. Ability of the new AT1 receptor blocker azilsartan to block angiotensin II-induced AT1 receptor activation after wash-out. J Renin Angiotensin Aldosterone Syst 2013;[Epub ahead of print]
24. Edarbi®. Summary of product characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002293/WC500119204.pdf
25. Preston RA, Karim A, Dudkowski C, et al. Single-center evaluation of the single-dose pharmacokinetics of the angiotensin II receptor antagonist azilsartan medoxomil in renal impairment. Clin Pharmacokinet 2013;52:347-58
26. De Caterina AR, Harper AR, Cuculi F. Critical evaluation of the efficacy and tolerability of azilsartan. Vasc Healt Risk Manag 2012;8:299-305
27. Bönner G, Bakris GL, Sica D, et al. Antihypertensive efficacy of the angiotensin receptor blocker azilsartan medoxomil compared with the angiotensin-converting enzyme inhibitor ramipril. J Hum Hypertens 2013;27:479-86
28. Rakugi H, Enya K, Sugiura K, Ikeda Y. Comparison of the efficacy and safety of azilsartan with that of candesartan cilexetil in Japanese patients with grade I-II essential hypertension: a randomized, double-blind clinical study. Hypertens Res 2012;35:552-8
29. Sica D, White WB, Weber MA, et al. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. J Clin Hypertens (Greenwich) 2011;13:467-72
30. Bakris GL, Sica D, Weber M, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. J Clin Hypertens (Greenwich) 2011;13:81-8

•• **In this study performed in 1,275 hypertensive patients, the reduction in 24-h mean systolic BP was significantly greater with azilsartan medoxomil 80 mg than olmesartan 40 mg, and azilsartan medoxomil 40 mg similar to olmesartan 40 mg, with a similar incidence of side effects.**

31. White WB, Weber MA, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension 2011;57:413-20
32. Baker WL, White WB. Azilsartan medoxomil: a new angiotensin II receptor antagonist for treatment of hypertension. Ann Pharmacother 2011;45:1506-15
33. Quinn Baumann P, Zaman AK, McElroy-Yaggy K, Sobel BE. The efficacy and tolerability of azilsartan in mice with left ventricular pressure overload or acute myocardial infarction. J Cardiovasc Pharmacol 2013;61:437-43
34. Zaman AK, McLean DL, Sobel BE. The Efficacy and Tolerability of Azilsartan in Obese Insulin Resistant Mice with Left Ventricular Pressure Overload. J Cardiovasc Pharmacol 2013;Epub ahead of print
35. French CJ, Zaman AK, Sobel BE. The angiotensin receptor blocker, azilsartan medoxomil (TAK-491), suppresses vascular wall expression of plasminogen activator inhibitor type-I protein potentially facilitating the stabilization of atherosclerotic plaques. J Cardiovasc Pharmacol 2011;58:143-8
36. Nakamura Y, Suzuki S, Saitoh S, Takeishi Y. New angiotensin II type 1 receptor blocker, azilsartan, attenuates cardiac remodeling after myocardial infarction. Biol Pharm Bull 2013;36:1326-31
37. Kajiya T, Ho C, Wang J, et al. Molecular and cellular effects of azilsartan: a new generation angiotensin II receptor blocker. J Hypertens 2011;29:2476-83
38. Kusumoto K, Igata H, Ojima M, et al. Antihypertensive, insulin sensitising and renoprotective effects of a novel, potent and long-acting angiotensin II type 1 receptor blocker, azilsartan medoxomil, in rat and dog models. Eur J Pharmacol 2011;669:84-93
39. Lastra G, Santos FR, Hooshmand P, et al. The novel angiotensin II receptor blocker azilsartan medoxomil ameliorates insulin resistance induced by chronic angiotensin II treatment in rat skeletal muscle. Cardiorenal Med 2013;3:154-64
40. Zhao M, Li Y, Wang J, et al. Azilsartan treatment improves insulin sensitivity in obese spontaneously hypertensive Koletsky rats. Diabetes Obes Metab 2011;13:1123-9
41. Iwai M, Chen R, Imura Y, Horiuchi M. TAK-536, a new AT1 receptor blocker, improves glucose intolerance and adipocyte differentiation. Am J Hypertens 2007;20:579-86
42. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009;122:290-300

•• **In this meta-analysis performed in nearly 11,000 patients, combining drugs from 2 different classes was approximately 5 times more effective in reducing BP values than doubling the dose of 1 drug.**

43. Gradman AH, Parisé H, Lefebvre P, et al. Initial combination therapy reduces the risk of cardiovascular events in

hypertensive patients: a matched cohort study. Hypertension 2013;61:309-18

44. Dezii CM. A retrospective study of persistence with single-pill combination therapy vs. concurrent two-pill therapy in patients with hypertension. Manag Care 2000;9(9 Suppl):2-6

45. Dickson M, Plauschinat CA. Compliance with antihypertensive therapy in the elderly: a comparison of fixed-dose combination amlodipine/benazepril versus component-based free-combination therapy. Am J Cardiovasc Drugs 2008;8:45-50

46. Egan BM, Bandyopadhyay D, Shaftman SR, et al. Initial monotherapy and combination therapy and hypertension control the first year. Hypertension 2012;59:1124-31

47. Barrios V, Escobar C. Olmesartan medoxomil plus hydrochlorothiazide for treating hypertension. Expert Opin Pharmacother 2008;9:129-36

48. Barrios V, Escobar C. Candesartan in the treatment of hypertension: what have we learnt in the last decade? Expert Opin Drug Saf 2011;10:957-68

49. Escobar C, Barrios V. Combined therapy in the treatment of hypertension. Fundam Clin Pharmacol 2010;24:3-8

50. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64

51. Roush GC, Halford TR, Guddati AK. Chlortalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. Hypertension 2012;59:1110-17

• **In this systematic review of randomized trials in which 1 arm was based on either hydrochlorothiazide or chlortalidone, chlortalidone was superior to hydrochlorothiazide in preventing cardiovascular events.**

52. Dorsch MP, Gillespie BW, Erickson SR, et al. Chlortalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. Hypertension 2011;57:689-94

53. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension 2006;47:352-8

54. Riess W, Dubach UC, Burckhardt D, et al. Pharmacokinetic studies with chlorthalidone (Hygroton) in man. Eur J Clin Pharmacol 1977;12:375-82

55. McAinsh J, Bastain W, Young J, Harry JD. Bioavailability in man of atenolol and chlorthalidone from a combination formulation. Biopharm Drug Dispos 1981;2:147-56

56. Cheng JWM. Azilsartan/chlorthalidone combination therapy for blood pressure control. Integr Blood Press Control 2013;6:39-48

57. Shuster JE, Bleske BE, Dorsch MP. Clinical utility of azilsartan-chlorthalidone fixed combination in the management of hypertension. Vasc Health Risk Manag 2012;8:381-7

58. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension 2004;43:4-9

59. Sica D, Bakris GL, White WB, et al. Blood pressure lowering efficacy of the fixed dose combination of azilsartan and chlorthalidone: a factorial study. J Clin Hypertens (Greenwich) 2012;14:284-92

60. Bakris GL, Sica D, White WB, et al. Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan medoxomil. Am J Med 2012;125:1229

61. Cushman WC, Bakris GL, White WB, et al. Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorthiazide in stage 2 systolic hypertension. Hypertension 2012;60:310-18

•• **In this study performed in more than 1,000 hypertensive patients, changes in clinic and ambulatory systolic BP were significantly greater with azilsartan medoxomil/chlorthalidone arms (40/25 mg and 80/25 mg) than in the olmesartan/hydrochlorothiazide arm (40/25 mg).**

62. Pierini D, Anderson KV. Azilsartan medoxomil/chlorthalidone: a new fixed-dose combination antihypertensive. Ann Pharmacother 2013;47:694-703

63. Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. Lancet 2004;363:2049-51

• **This study showed that the early BP control was associated with a better prognosis, regardless the type of antihypertensive agent.**

64. Brenner BM, Cooper ME, de Zeeuw D, et al. RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9

65. Parving HH, Lehnert H, Bröchner-Mortensen J, et al. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8

66. Haller H, Ito S, Izzo JL, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907-17

67. Parving HH, Brenner BM, McMurray JJV, et al. Cardiorenal endpoints in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012;367:2204-13

• **This study, that was stopped prematurely, showed that the addition of aliskiren to standard therapy with renin-angiotensin system blockade in patients with type 2 diabetes who are at high risk for cardiovascular and renal events was not beneficial, even harmful.**

68. Farsang C. Indications for and utilization of angiotensin receptor II blockers in patients at high cardiovascular risk. Vasc Health Risk Manag 2011;7:605-22

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