REVIEW

# Azilsartan medoxomil in the management of hypertension: an evidence-based review of its place in therapy

Emiliano Angeloni

Cardiovascular Pathophysiology and Imaging, Sapienza Università di Roma, Rome, Italy

**Background:** Azilsartan (AZI) is a relatively new angiotensin receptor blocker available for the treatment of any stage of hypertension, which was eventually given in combination with chlorthalidone (CLT).

**Objective:** To review pharmacology and clinical role of AZI monotherapy and AZI/CLT or AZI/amlodipine combination therapies for hypertension management.

**Methods:** PubMed, Embase, and Cochrane Library were searched using search terms "azilsartan", "chlorthalidone," "pharmacology," "pharmacokinetics," "pharmacodynamics," "pharmacoeconomics," and "cost-effectiveness." To obtain other relevant information, US Food and Drug Association as well as manufacturer prescribing information were also reviewed.

**Results:** Randomized controlled trials demonstrated AZI to be superior to other sartans, such as valsartan, olmesartan, and candesartan, in terms of 24-hour ambulatory blood pressure monitoring (ABPM) reduction with respect. That beneficial effect of azilsartan was also associated with similar safety profiles. When compared to other antihypertensive drugs, azilsartan was found to be superior to any angiotensin-converting enzyme inhibitor, including ramipril, in terms of ABPM results, and noninferior to amlodipine in terms of sleep-BP control. The association of AZI and CLT was then found to be superior to other sartans + thiazide combination therapies in terms of both BP lowering and goal achievement. The combination of AZI and amlodipine has also been tested in clinical trials, but compared only with placebo, demonstrating its superiority in terms of efficacy and similarity in terms of safety.

**Conclusion:** Azilsartan is a safe and effective treatment option for every stage of hypertension, both alone or in fixed-dose combination tablets with chlorthalidone or amlodipine. Beneficial effects of AZI were also noted in patients with any degree of renal impairment. In addition, safety profiles of AZI were similar to that of the placebo.

**Keywords:** hypertension, pharmacology, azilsartan, blood pressure, pharmacokinetics, cost-effectiveness

**Core evidence clinical impact summary for azilsartan**

| Outcome measures | Evidence | Implications |
|---|---|---|
| Disease-oriented evidences | Randomized controlled trials demonstrated that azilsartan is an effective option for the treatment of hypertension in several settings, for example in patients with renal impairment. | Azilsartan represent an optimal choice as monotherapy for the treatment of stage I hypertension, and, in association with chlorthalidone, for the treatment of more advanced stages of hypertension. |
| | | *(Continued)* |

Correspondence: Emiliano Angeloni
Department of Cardiac Surgery,
Sapienza Università di Roma, Ospedale
Sant'Andrea, Via di Grottarossa 1035,
00189 Rome, Italy
Tel +39 06 3377 5593
Fax +39 06 3377 6317
Email emiliano.angeloni@uniroma1.it

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| (Continued) | | |
|---|---|---|
| **Outcome measures** | **Evidence** | **Implications** |
| Patient-oriented evidences | Azilsartan is a safe and effective treatment for hypertension. Dose adjustment is not needed, even in patients with most severe renal disease. | Low-incidence rates of side effects make it a suitable option for every patient, especially for those with chronic renal disease wishing to avoid the need for dose adjustment. |
| Economic evidence | To date, no trial assessing cost-effectiveness of azilsartan is available in literature. | Whole price of azilsartan and of its fixed-dose combination tablet is equal to that of other competitors. |

## Introduction

According to the 2015 AHA statistical report,[1] over 75% of the population aged at least 40 years has elevated blood pressure (BP) levels (65.3% among those aged 40–59 years, and 84.3% among those aged >59 years). Furthermore, only 60% of patients achieve good BP control, and despite the decreasing cardiovascular (CV) morbidity, BP is still a leading cause of death in Western countries, affecting nearly 230 of every 100,000 individuals.[1] In addition, the annual direct and indirect cost of CV diseases in the United States is an estimated US$320.1 billion. This includes US$195.6 billion in expenditures (direct costs, which include the cost of physicians and other professionals, hospital services, prescribed medication, and home health care, but not the cost of nursing home care) and US$124.5 billion in lost future productivity attributed to premature cardiovascular disease and stroke mortality (indirect costs).[1]

Hypertension is one of the leading risk factors for ischemic heart disease, stroke, heart failure, and renal dysfunction.[2] Thus, management of hypertension should be targeted not only for BP control but also for the reduction of overall cardiovascular and renal morbidity and mortality.[3] In these settings, the lack of medical success is one of the many reasons triggering the development of new antihypertensive agents.

Due to their beneficial effects in reducing both cardiovascular morbidity and mortality, angiotensin receptor blockers (ARBs) alone or in combination are considered among the best available therapeutic options for the treatment of hypertension even in patients with compelling indications, such as heart failure, diabetes, and previous myocardial infarction.[3] In addition, the use of fixed-dose combination therapies demonstrated the potential to increase patient adherence[4] and overall clinical effect.[5]

Nonpeptide antagonists of the angiotensin II type 1 (AT1) receptor constitute a very useful and widely prescribed class of antihypertensive drugs.[6] After the US Food and Drug Administration approved losartan in 1995,[7] a host of other AT1 receptor antagonists were rapidly introduced in clinical practice.

Beneficial effects of ARBs are supposed to be mediated mainly by mechanisms independent from BP reduction, and include endothelial modulation, renoprotection, and reduction of fibrosis.[6,8,9] However, protection against target organ damage and improvement of clinical outcomes is still considered to be largely mediated by the BP decrease correlated to ARBs administration.[8,10]

Clinically available sartans are known to have several differences in terms of plasma half-life, intensity of AT1 blockade, and slope of the BP-lowering dose–response curve.[9,11] However, clinical studies always failed to identify an ARB more effective than others in terms of BP lowering.[12]

Ultimately, a large body of literature[13–16] prompted the comparison of clinical safety and effectiveness of different ARBs; hence, the aim of this paper was to review latest evidences about the use of azilsartan, alone or in fixed-dose combination (FDC) regimens, in comparison with other antihypertensive drugs.

## Pharmacology of azilsartan
### Mechanism of action

Azilsartan is a selective blocker of AT1 receptors that prevents angiotensin II binding, resulting in vasodilation and decrease in the effects of aldosterone, because of the presence of such receptors in the vascular smooth muscle and in the adrenal gland.[17,18] With respect to other ARBs, azilsartan is highly selective for the AT1 receptor and not the AT2 receptor.[19]

### Pharmacokinetics

Azilsartan medoxomil is a prodrug subject to hydrolyzation of its active moiety, azilsartan, at the level of the gastrointestinal tract. Azilsartan reaches its peak plasma concentration between 1.5 and 3 hours following oral administration.

Coadministration with food does not affect bioavailability, which is approximately 58%.[18] Metabolization of azilsartan occurs in the liver via cytochrome P450 (CYP) 2C9, resulting in the formation of a nonactive metabolite, M-II (formed by O-dealkylation). Metabolization to a lesser extent is then provided by CYP2B6 and CYP2C8, resulting in the formation of another inactive metabolite, M-I (formed by decarboxylation). Azilsartan is primarily excreted by the kidney, as inactive metabolites, with a clearance of 2.3 mL/min. The elimination half-life is approximately 11 hours, with steady-state plasma concentrations reached 5 days after oral administration.[18] In conclusion, the dose range of 20–320 mg does not need any adjustment based on patient's age, sex, race, or degree of renal/hepatic impairment.

## Drug interactions

Drug interactions of azilsartan with caffeine, antacid, warfarin, digoxin, tolbutamide, glyburide, metformin, pioglitazone, chlorthalidone, amlodipine, dextromethorphan, midazolam, and fexofenandine have been studied; any other significant interactions have also been observed. In another drug interaction study, azilsartan clearance was reduced when coadministered with fluconazole (a CYP2C9 inhibitor), but not when coadministered with ketoconazole (a CYP3A4/5 inhibitor).

It is well known that angiotensin II increases the glomerular filtration rate by means of efferent arteriole vasoconstriction, therefore reduced angiotensin II binding caused by azilsartan slightly decreases the glomerular filtration rate because of efferent arteriole vasodilation. Given that, nonsteroidal anti-inflammatory agents and COX-2 inhibitors cause prerenal acute renal failure by blocking prostaglandin production, which also alters local glomerular arteriolar perfusion,[20] the use of these agents concurrently with azilsartan may increase the risk of renal function deterioration.

## Experimental evidences

Several studies investigated pleiotropic effects of azilsartan and their effectiveness in treating pathological conditions underlying hypertension.

For example, an insulin-sensitizing effect of azilsartan has been demonstrated in obese rats, regardless of food intake and body weight increase, introducing a possible role of azilsartan in the treatment of metabolic syndrome.[21,22] Another beneficial effect of azilsartan was also confirmed in animal models, with studies showing that azilsartan medoxomil, independently of BP lowering, offers preventive and therapeutic vasculoprotection in diabetes-induced cerebrovascular remodeling and myogenic dysfunction.[23]

In addition to the vasculoprotective effect, reduced left ventricular wall thickness and hypertrophy were also demonstrated, leading to increased cardiac output after aortic banding compared with controls, thus suggesting a favorable biological effect on the hearts of obese, insulin-resistant mice subjected to LV pressure overload.[24] Beneficial effects on left ventricular remodeling regardless of BP lowering have also been seen in mice after creation of an anterior myocardial infarction.[25]

Azilsartan has also been claimed to have renoprotective effects, in terms of reducing proteinuria,[26] albuminuria, and nephrinuria along with reduced tubular cast formation and glomerular injury.[27]

Besides this, azilsartan has also been advocated for its anti-inflammatory effects, such as reducing plasma monocyte chemoattractant protein-1 levels[28] and increasing the anti-inflammatory cytokine IL-10 levels.[29] Therefore, by reducing vascular inflammation, azilsartan also exerts beneficial effects in terms of endothelial restoration, thus preventing its dysfunction;[30] for example, reducing tumor necrosis factor-$\alpha$ and IL-1$\beta$ levels, and upregulating the vascular endothelial growth factor.[31] In addition, via the suppression of plasminogen activator inhibitor type-I expression, azilsartan also may attenuate the evolution of atherosclerotic plaques vulnerable to rupture.[32]

## Clinical evidences
### Comparison of azilsartan vs other sartans

Trials comparing clinical safety and efficacy of azilsartan with that of other antihypertensive drugs are listed in Table 1.

Bakris et al[14] published the first study investigating the antihypertensive efficacy and safety of azilsartan in 2011. It was a placebo-controlled trial involving a total of 1,275 patients who were randomized to placebo, azilsartan 20, 40, or 80 mg daily, or olmesartan 40 mg daily for 6 weeks. Twenty four-hour mean systolic BP (SBP; measured by 24 hours ambulatory blood pressure monitoring [ABPM]) was found to be significantly reduced in all azilsartan groups (−12.2, −13.5, and −14.6 mmHg) and in the olmesartan 40 mg group (−12.6 mmHg). Reductions were significantly greater with azilsartan 80 mg than olmesartan 40 mg ($P$=0.038), while azilsartan 40 mg was not inferior to olmesartan 40 mg. Safety profiles of both drugs were similar to placebo, although statistical comparison was not performed.

Another double-blind, randomized, placebo-controlled trial[13] compared azilsartan with olmesartan and valsartan. A total of 1,285 patients were randomized to placebo, azilsartan 40–80 mg daily, olmesartan 40 mg daily, or

**Table 1** Outlook of trials comparing azilsartan with other antihypertensive therapies

| Source | Design | Sample size | Duration (weeks) | Competitors | End point | Efficacy results | Safety results |
|---|---|---|---|---|---|---|---|
| White et al[13] | RCT | 1,285 | 6 | AZI 40/80 mg vs OLM 40 mg vs VAL 320 mg vs placebo | S-ABPM | −14.3 mmHg vs −10.0 mmHg (P<0.001) and vs −11.7 mmHg (P=0.009) | Similar to placebo |
| Bakris et al[14] | RCT | 1,275 | 6 | AZI 20/40/80 mg vs OLM 40 mg vs placebo | S-ABPM | −12.2 mmHg, −13.5 mmHg, −14.6 mmHg vs −12.6 mmHg; P=0.05 for all | Similar to placebo |
| Sica et al[15] | RCT | 984 | 24 | AZI 40 mg vs AZI 80 mg vs VAL 320 mg | S/D-ABPM | −14.9 mmHg vs −15.3 mmHg vs −11.3 mmHg (P<0.001) similar results with P<0.0001 favoring AZI 80 for DBP | Similar |
| Rakugi et al[16] | RCT | 622 | 16 | AZI 20–40 mg vs CAN 8–12 mg | BP and ABPM | DBP: −12.4 mmHg vs −9.8 mmHg SBP: −21.8 mmHg vs −17.5 mmHg ABPM also favored AZI | Similar; most common: nasopharyngitis (16–18%) |
| Bonner et al[35] | RCT | 884 | 24 | AZI 20–80 mg vs RAM 2.5–10 mg | SBP | −20.6 mmHg vs −21.2 mmHg vs −12.2 mmHg (P<0.001) | AE leading to discontinuation: AZI 40: 2.4% vs AZI 80: 3.1% vs RAM: 4.8% |
| Kario et al[36] | RCT | 668 | 8 | AZI 20 mg vs AML 5 mg | Sleep-ABPM | Among those >60 years. Similar control rate of sleep BP, despite a trend favoring AML (35% vs 30%) | Similar |
| Schmieder et al[37] | POR | 1,153 | 52 | AZI vs any ACEi | BP Goal | AZI provides superior BP control compared with ACEi | Similar |
| Takagi et al[38] | M-A | 6,152 | n/a | RCT comparing AZI 40 mg vs control | SBP/DBP | SBP red diff: −4.2 mmHg; DBP red diff: −2.58 mmHg; S-ABPM: −3.33 mmHg; D-ABPM: −2.12 mmHg (All P<0.0001) | Not evaluated |

**Abbreviations:** ACEi, angiotensin concerting enzyme inhibitors; ABPM, ambulatory blood pressure monitoring; AE, adverse effect; AML, amlodipine; AZI, azilsartan; BP, blood pressure; CAN, candesartan; D, diastolic; M-A, meta-analysis; OLM, olmesartan; POR, prospective observational registry; RAM, ramipril; RCT, randomized controlled trial; red diff, reduction difference; S, systolic; VAL, valsartan; SBP, systolic blood pressure; DBP, diastolic blood pressure.

valsartan 320 mg daily for 6 weeks. Placebo-adjusted ABPM-SBP was lowered by azilsartan (−14.3 mmHg) significantly more than by valsartan (−10.0 mmHg; P<0.001) and olmesartan (−11.7 mmHg; P=0.009). Safety profiles were not statistically investigated, nonetheless the raw data reported show similar results between study groups.

Comparison of azilsartan and valsartan has been further investigated by Sica et al[15] in another double-blind, randomized trial including 984 patients randomized to placebo, azilsartan 20 mg titrated to 40 mg, 40 mg titrated to 80 mg, or valsartan 80 mg titrated to 320 mg for 24 weeks. Azilsartan 40 and 80 mg lowered 24-hour mean SBP (−14.9 and −15.3 mmHg, respectively) more than valsartan 320 mg (−11.3 mmHg; P<0.001 for both comparisons).

Furthermore, safety and efficacy of azilsartan (20–40 mg) has also been compared to candesartan (8–12 mg) in a 16-week randomized controlled trial involving 622 patients.[16] Results demonstrated a significant BP reduction among patients administered azilsartan (−12.4 mmHg diastolic blood pressure [DBP] and −21.8 mmHg SBP) in comparison with those receiving candesartan (−9.8 mmHg DBP and

−17.5 mmHg SBP). This analysis of sitting BP was further confirmed by ABPM findings. The most common adverse effect was nasopharyngitis (interesting 18% vs 16% patients, P= nonsignificant), and safety profiles were also similar between treatment groups.

## Use of azilsartan in patients with renal impairment

The use of azilsartan in patients with renal impairment has received special focus. First, Preston et al[33] demonstrated that no dose adjustment is needed for patients with mild, moderate, or even severe chronic kidney disease, as well as those with end-stage renal disease requiring hemodialysis, when administering azilsartan 40 mg. Indeed, they found that patients with renal impairment had increased accumulation of the major metabolite of azilsartan (called M-II), which is pharmacologically inactive; thus this increase was not considered important in dose selection in subjects with renal disease.

Then, Kusuyama et al[34] published a retrospective study investigating 17 hemodialysis patients receiving azilsartan

20 or 40 mg. After 6 months of therapy, ABPM revealed significant BP decrease (–19.6 mmHg), along with significant reductions of serum noradrenaline (–198.4 pg/mL) and left ventricular indexed mass (–6 g/m²).

## Comparison of azilsartan vs other antihypertensive drugs

Monotherapy with azilsartan 20 mg (forced titrated to 80 mg) has been compared to ramipril 2.5 mg (forced titrated to 10 mg) in a recent randomized, double-blind, controlled trial investigating changes in SBP after 24 weeks of treatment among 884 hypertensive patients.[35] The main finding was that azilsartan significantly decreased SBP (–21.2 mmHg) much more than ramipril (–12.2 mmHg; $P<0.001$). Adverse effects leading to treatment discontinuation were more likely to occur among patients administered ramipril (4.8%) than those administered azilsartan (3.1%), but this trend did not reach statistical significance.

A recent multicenter, randomized, controlled trial by Kario et al,[36] aimed to compare minimum dosage of azilsartan (20 mg) and amlodipine (5 mg) for the treatment of stage I and II hypertension in 668 patients. The primary end point was control rate of sleep-ABPM after 8 weeks of therapy; no significant difference was found between study groups, despite a nonstatistically significant trend favoring amlodipine (34.7% vs 30%), especially among patients aged over 60 years.

Another study, named EARLY registry, comparing angiotensin-converting enzyme (ACE) inhibitors therapy with ARB therapy (by means of azilsartan as first-line therapy) in patients with newly diagnosed hypertension has been recently published.[37] Data from this prospective, "real-world" registry were used to compare achievement of BP control (<140/90 mmHg) between patients administered azilsartan (n=789) and those administered any other ACE inhibitor (n=364) as monotherapy. The authors concluded that in newly diagnosed hypertensive patients, azilsartan monotherapy provided superior BP control with a similar safety profile compared with ACE inhibitors.

In addition, a recent meta-analysis[38] compared azilsartan 40 mg vs any other control therapy (including placebo). End points estimated were SBP and DBP reductions both in clinical and ambulatory monitoring settings; statistically significant reductions were found always favoring azilsartan.

## Comparison of azilsartan + chlortalidone vs other combination therapies

Trials comparing clinical safety and efficacy of azilsartan/chlorthalidone with that of other combination therapies for the treatment of stage II hypertension are listed in Table 2.

The first investigation dealing with combination therapies involving azilsartan was a double-blind, randomized, placebo-controlled trial by Kipnes et al[39] investigating DBP reduction after 32-week treatment with azilsartan 40 mg (forced titrated to 80 mg) with or without the adjunct of chlorthalidone 25 mg if required, to reach target BP. Among the 418 patients randomized to different treatment strategies, mean changes in SBP/DBP from baseline were –23/–16 mmHg. The most common adverse events, irrespective of treatment, were dizziness (8.9%) and headache (7.2%), while serious adverse events were reported in only eight patients (1.9%). Mean DBP was maintained through the reversal phase in patients receiving azilsartan monotherapy, but increased with placebo (difference: –7.8 mmHg; $P<0.001$).

Efficacy and safety of azilsartan/chlorthalidone FDC therapy has been compared with that of the individual mono-therapies in a double-blind factorial study[40] involving a total of 1,714 patients with grade II hypertension randomized to azilsartan 0, 20, 40, or 80 mg and/or chlorthalidone 0, 12.5, or 25 mg. The primary efficacy end point (change of mean ABPM-SBP from baseline to 8 weeks) was –28.9 mmHg for the pooled azilsartan/chlorthalidone 40/25 and 80/25 mg FDC (similar between 40/25 and 80/25 mg), significantly exceeding that of azilsartan 80 mg and chlorthalidone 25 mg monotherapies ($P<0.001$ for both comparisons). In addition, despite African–American patients having been previously demonstrated to be less responsive to azilsartan alone,[41] treatment with azilsartan/chlorthalidone FDC resulted in a similar magnitude of BP reduction in this subset of patients. Discontinuation rates and elevations in serum creatinine were dose-dependent and occurred more often in the azilsartan/chlorthalidone FDC groups (0.6%–5% compared to 0.1% in monotherapy groups).

Moreover, the efficacy of azilsartan/chlorthalidone FDC therapy force titrated to highest dosage (80/25 mg) has been compared to olmesartan/hydrochlorothiazide FDC therapy force titrated to 40/25 mg in a trial[42] comprising a total of 1,071 patients with stage II hypertension randomly assigned to different treatment strategies. After 12 weeks, mean ABPM-SBP reductions were significantly greater in both the azilsartan/chlorthalidone arms rather than in the olmesartan/hydrochlorothiazide arm (–42.5, –44.5, and –37.1 mmHg, respectively; $P<0.001$ for all comparisons). Adverse events leading to drug discontinuation occurred in 7.9%, 14.5%, and 7.1% of the patients, respectively, and hence the authors concluded that the azilsartan/chlorthalidone combination was more effective in reducing BP than the olmesartan/hydrochlorothiazide combination, even if the approximate equivalent dose of chlorthalidone 25 mg

**Table 2** Outlook of trials comparing azilsartan/chlorthalidone with other combinations therapies for the treatment of stage II hypertension

| Author | Design | Sample size | Duration (weeks) | Competitors | End point | Efficacy results | Safety results |
|---|---|---|---|---|---|---|---|
| Kipnes et al[39] | RCT | 418 | 32 | AZI 40–80 mg± CLT 25 mg vs placebo | DBP | −7.8 mmHg vs −9.8 mmHg | Serious 1.9% Most common dizziness 8.9% |
| Sica et al[40] | RCT | 1,714 | 8 | AZI 0/20/40/80 mg or CLT 0/12.5/25 mg | S-ABPM | −14 and −13 mmHg reduction differences favoring FDC (P<0.0001) | Similar |
| Cushman et al[42] | RCT | 1,071 | 12 | AZI 40 mg+ CLT 25 mg vs AZI 80 mg+ CLT 25 mg vs OLM 40 mg+ HCT 25 mg | S-ABPM | −42.5 and −44.5 mmHg vs −37.1 mmHg; P<0.001 | AEs leading to discontinuation occurred in 7.9%, 14.5%, and 7.1%, respectively |
| FDA[43] | RCT | 609 | 6 | AZI 40 mg+ CLT 12.5/25 mg vs AZI 40 mg+ HCT 12.5/25 mg | BP goal | 64.1% vs 45.9%; P<0.001 | Similar |
| Bakris et al[44] | RCT | 609 | 6/10 | AZI 40 mg+ CLT 12.5/25 mg vs AZI 40 mg+ HCT 12.5/25 mg | BP/ABPM | 6 wk BP: −35 mmHg vs −29 mmHg for CLT (P<0.0001). ABPM: −5.8 mmHg vs −3.2 mmHg for CLT. GOAL: 64.1% vs 45.9% for CLT | Similar AE rates (9.3% vs 7.3%; P=ns) |
| Rakugi et al[45] | MC-RCT | 603 | 8 | AML 5/2.5 mg and AZI 20 mg (alone or FDC) | DBP/SBP | DBP: −22.3 and −19.2 mmHg vs −13.9, −15.5, −11.6 mmHg; P<0.0001. SBP: −35.3, −31.4 mmHg vs −21.5, −26.4, −19.3 mmHg; P<0.0001. Goal: 0.56% vs 0.42% vs 0.2% vs 0.24% (P<0.0001) | Common AEs (interesting >2% of SS) were nasopharyngitis (8.0%) and dizziness (2.7%). Severe AEs were reported in two patients. Incidence similar between groups |
| Weber et al[46] | RCT | 566 | 6 | AML 5 mg+ AZI 40 mg vs AML 5 mg+ AZI 80 mg vs AML 5 mg+ placebo | ABPM | S-ABPM: −25 mmHg vs −14 mmHg (P<0.001 irrespective of age, sex, BMI). D-ABPM: −15 mmHg vs −7 mmHg. P<0.0001. 6wGOAL: 49.2% vs 46.4% vs 25.1% (P<0.0001) | Similar AE rates (40%–48%; serious 0.5%–1%). Edema less common in combinations (3% vs 8%) |

**Abbreviations:** ABPM, ambulatory blood pressure monitoring; AEs, adverse effects; AML, amlodipine; AZI, azilsartan; CLT, chlorthalidone; D, diastolic; DBP, diastolic blood pressure; FDA, US Food and Drug Association; FDC, fixed-dose combination; HCT, hydrochlorothiazide; RCT, randomized controlled trial; OLM, olmesartan; S, systolic; SBP, systolic blood pressure; MC, multi-center; SS, sample size.

is hydrochlorothiazide 50 mg; therefore, it is possible that unequal potency doses were being compared.

One more randomized, placebo-controlled, double-blind trial compared the efficacy of azilsartan/chlorthalidone and azilsartan/hydrochlorothiazide combinations.[43] A total of 609 patients with stage II primary hypertension were randomized to receive 12.5 mg of chlorthalidone or hydrochlorothiazide in addition to azilsartan 40 mg for 4 weeks, and diuretics were titrated up to 25 mg for another 4 weeks if BP was not controlled. Target clinical BP (<140/90 mmHg for participants without diabetes or chronic kidney disease, otherwise <130/80 mmHg) represented the main end point of the study. Results showed that the association of azilsartan/chlorthalidone provided greater reduction in SBP than the combination of azilsartan with hydrochlorothiazide

(−31.5 mmHg vs −29.5 mmHg, P<0.001). The percentage of patients achieving target BP after 6 weeks of treatment was greater for the chlorthalidone vs hydrochlorothiazide combination (64.1% vs 45.9%; P<0.001). Drug discontinuation due to adverse events was not statistically significantly different between groups (9.3% vs 7.3%; P=0.38). It is also important to note that the approximate equivalent dose of chlorthalidone 25 mg is hydrochlorothiazide 50 mg; while the latter study compared unequal dosage of such diuretics.[43]

Furthermore, study 491-CLD-301 compared the efficacy of once-daily FDC of azilsartan/chlorthalidone 20/12.5 or 40/25 mg with a FDC of olmesartan/hydrochlorothiazide 20/12.5 mg among a total of 1,085 patients randomized to different treatment strategies.[44] After the first 4 weeks of treatment, subjects achieving both target SBP and diastolic

BP (<140/90 mmHg for subjects without diabetes or chronic kidney diseases, otherwise <130/80 mmHg) continued to receive their starting dose for the duration of the study. For subjects who did not achieve target BP, the following dose titrations were prescribed: azilsartan/chlorthalidone 40/25 mg, 80/25 mg and olmesartan/hydrochlorothiazide 40/25 mg. After 8 weeks of treatment, SBP reductions in both azilsartan/chlorthalidone treatment groups (–33 to –38 mmHg) were significantly (P<0.05) greater than in the olmesartan/hydrochlorothiazide groups (–27 to –32 mmHg). The most common side effects in the azilsartan/chlorthalidone group included serum creatinine elevation (2.5% in the higher dosage group), fatigue (3.8% in the higher dosage group), and hypotension (1.1% in the higher dosage group). It is again important to point out that the approximate equivalent dose of chlorthalidone 25 mg is hydrochlorothiazide 50 mg, despite only hydrochlorothiazide 25 mg having been tested in this study.

More recent trials compared azilsartan with amlodipine. The first among them was a multicenter, randomized, double-blind trial investigating 603 patients randomized for 8 weeks to receive azilsartan 20 mg and amlodipine 2.5 or 5 mg either alone or in a fixed-dose combination fashion.[45] Both DBP (–22.3 and –19.2 mmHg; P<0.0001 vs other regimens) and SBP (–35.3 and –31.4 mmHg; P<0.0001 vs other regimens) reductions were significantly greater for patients administered the fixed-dose combination therapies. In addition, BP goal achievement rate was higher for patients taking the fixed combinations (56.4% and 41.7% vs 19.9%, 24%, and 11.8%). Common adverse effects were nasopharyngitis (8%) and dizziness (2.7%); overall tolerability was similar between study groups, and serious adverse effects were registered in only two patients (0.3%). Another randomized, placebo-controlled, double-blind trial compared efficacy of amlodipine 5 mg associated with placebo, azilsartan 40 mg or azilsartan 80 mg among 566 patients with stage II hypertension.[46] Reductions of SBP (measured by 24-hour ABPM) were significantly higher for patients receiving the addition of azilsartan (–25 and –14 mmHg; P<0.0001 for both comparisons), as were DPB reductions (–15 and –7 mmHg; P<0.0001 for both comparisons). The latter findings were found to be independent of age, sex, and body mass index. In addition, 6-week BP goal achievement was greater among patients receiving azilsartan (49.2% and 46.4% vs 25.1%; P<0.0001). Incidence of adverse events was similar between groups (40%–48%), and severe adverse events were recorded rarely (0.5%–1%); of note, peripheral edema was less common in patients taking the combination therapies (3% vs 8%).

Furthermore, clinical studies also revealed a 30% reduction in total mortality in chronic heart failure.[47]

Overall, the association of azilsartan and chlorthalidone has been demonstrated to lower BP much more than olmesartan and hydrochlorothiazide; furthermore, little difference was noted between the 40 and 80 mg dosage of azilsartan.

## Side effects

According to the manufacturer, more than 4,000 patients were evaluated in premarketing clinical trials when treated with azilsartan or azilsartan plus chlorthalidone for 6 months to 1-year.[18,48] Both were generally well tolerated, and the adverse events that occurred were frequently mild and transient. Common side effects included dizziness (8.9%) and fatigue (2%).[48] Only 1.7% and 0.3% of patients reported hypotension and syncope episodes, respectively.

Side effects causing therapy cessation were only seen in 8.3% of patients administered the azilsartan/chlorthalidone, in 3.2% of patients receiving azilsartan, and in 3.2% of patients receiving chlorthalidone. Increase of creatinine levels (3.6%) and dizziness (2.3%) were noted as the most frequent events causing treatment discontinuation.

The FDC of azilsartan/chlorthalidone showed a safety profile similar to that of placebo.

Because of the well-known pharmacologic effect of the renin–angiotensin–aldosterone system blockade, both ARBs and ACE inhibitors are known to potentially result in increased creatinine levels, often related to the magnitude of BP decrease. Of note, the incidence of consecutive increases of creatinine >50% from baseline was 2.0% in patients receiving azilsartan/chlorthalidone FDC compared to 0.4% and 0.3% with azilsartan and chlorthalidone alone, respectively. Mean increases in blood urea nitrogen were observed with azilsartan/chlorthalidone (5.3 mg/dL) compared to azilsartan (1.5 mg/dL) and chlorthalidone (2.5 mg/dL) alone.

In addition, based on the manufacturer recommendations, anuria is the only contraindication to the use of azilsartan/chlorthalidone. An additional issue preventing the use of azilsartan/chlorthalidone should be pregnancy (because of fetal and neonatal morbidity and death when renin–angiotensin system blockers are administered during the second and the third trimester[48]). In addition, patients who are volume- or salt-depleted may be more sensitive to the hypotensive effect of azilsartan. Along with the enhanced hypotensive effect in volume- or salt-depleted patients, it needs to be pointed out that hypokalemia is a dose-dependent adverse reaction correlated with chlorthalidone, which may be exacerbated by digitalis coadministration. As a counterpoint, azilsartan may attenuate chlorthalidone-related hypokalemia.

Other adverse events registered during clinical trials along with efficacy evaluations have been explained earlier in this section. These side effects were recorded mainly during the trial, in the absence of any poststudy surveillance.

## Pharmacoeconomics/cost-effectiveness

A literature search found that no formal cost-effectiveness study has been performed to date for azilsartan. The average cost of azilsartan is slightly higher compared to other antihypertensive drugs. On the other hand, the average wholesale price of azilsartan/chlorthalidone for a 30-day supply is similar, and often cheaper, than other ARB/thiazide combinations available on the market.[49]

## Conclusion

Randomized controlled trials demonstrated that azilsartan is superior, in terms of 24-hour ambulatory BP monitoring reduction, with respect to other sartans, such as valsartan, olmesartan, and candesartan. In addition, safety profiles of the latter drugs were similar and not statistically different from placebo.

Moreover, beneficial effects of azilsartan were also noted in patients with any degree of renal impairment, even in case of patients with end-stage renal disease; with anuria being the only absolute contraindication to the association of azilsartan plus chlorthalidone. With respect to other antihypertensive medications, azilsartan was found to be superior to any ACE inhibitor in terms of ABPM results and noninferior to amlodipine in terms of sleep-BP control.

Furthermore, the association of azilsartan and chlorthalidone was then found to be superior to other combination therapies, including a sartan plus thiazide combination, in terms of both BP lowering and BP goal achievement. Of note, it has to be pointed out that those comparisons were carried out between unequal dosages of thiazide and chlorthalidone, favoring the latter; hence, this may be a bias affecting results of such comparisons.

Besides this, the other available combination of azilsartan with amlodipine has also been tested in clinical trials. That comparison was only made vs placebo, demonstrating its superiority in terms of efficacy and similar tolerability.

Conclusions coming from drug interactions studies should result in paying special attention when administering azilsartan with fluconazole, which is a CYP2C9 inhibitor. Moreover, given that nonsteroidal anti-inflammatory agents and COX-2 inhibitors cause prerenal acute renal failure by blocking prostaglandin production, further altering local glomerular arteriolar perfusion, the concomitant use of these agents with azilsartan may increase the risk of renal dysfunction. Many other studies demonstrated no interaction with caffeine, antacid, warfarin, digoxin, tolbutamide, glyburide, metformin, pioglitazone, chlorthalidone, amlodipine, dextromethorphan, midazolam, and fexofenandine.

Many studies investigated the pleiotropic effects of azilsartan and showed that it may be effective in ameliorating several pathological patterns underlying hypertension.

In conclusion, azilsartan is a safe and effective treatment option for every stage of hypertension, both alone or in fixed-dose combination tablets with chlorthalidone or amlodipine. Azilsartan demonstrated a good and stable BP improvement, free from significant complications, even in a titrate-to-target approach. This was found both in case of azilsartan monotherapy or fixed-dose combination therapies with chlorthalidone or amlodipine. In addition, several experimental evidences indicate an interesting series of pleiotropic actions resulting in different beneficial effects in terms of renal, and endothelial function, and metabolic homeostasis.

On the other hand, it has to be disclosed that many other antihypertensive drugs cheaper than azilsartan have been found to show efficient BP control. In addition, older drugs have been tested in more large trials, thus data demonstrating safety and efficacy of azilsartan are expected to be corroborated, in the near future, from further clinical studies.

## Disclosure

The author reports no conflicts of interest in this work.

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