RESEARCH ARTICLE

Experience with Azilsartan and Azilsartan Combined with Chlorthalidone in a Preventive Cardiology Center. Fighting the Therapeutic Inertia with a Program Based on Evidence, Personalization, and Empowerment

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Abstract

In patients with hypertension (HT), cardiovascular risk reduction is directly proportional to the reduction in blood pressure sustained over time. However, in "real life," blood pressure control is often insufficient or not sustained over time to achieve optimal cardiovascular risk reduction. In this article, we comment on the multiple reasons which explain this common therapeutic failure.

Also, in this article, we summarize the amazing basic and clinical phase III evidence of azilsartan (AZL) and azilsartan combined with chlortalidone (CLD), two excellent therapeutic options for HT control. With such evidence as scientific background, we communicate our results with almost 300 HT patients treated with azilsartan and azilsartan/chlortalidone in "real life." In brief, our findings were the following:

a) In HT patients with blood pressure (BP) <150/90 mmHg, AZL 40 mg as monotherapy provides practically 100% success to achieve a target BP <140/90 and <130/80 mmHg, in a subpopulation that we have called "hyper-responders"

b) In HT patients with BP <150/90 mmHg (naive or with another treatment failure), AZL/CLD 40/12.5 mg provides practically 100% success to achieve a target BP <140/90 mmHg and 90% to achieve a target BP <130/80 mmHg;

c) In HT patients with BP >150/90 mmHg (generally with another treatment failure), AZL/CLD 80/12.5 mg gives women a success rate greater than 60% to achieve a target BP <140/90 mmHg and greater than 50% to achieve a target BP <130/80 mmHg. The success rates were higher in men, greater than 75% to achieve a target BP <140/90 mmHg and greater than 60% to achieve a target BP <130/80 mmHg. In both cases, the use of amlodipine (2.5, 5, or 10 mg) made it possible to achieve a target BP <140/90 mmHg in 100% of the cases and <130/80 mmHg in 80% of the cases.

Finally, according to our results, we propose a simple three-step strategy based on evidence, personalization, and empowerment which allows reaching a target BP <140/90 mmHg in more than 90% of cases and a target BP <130/80 mmHg in more than 75% of cases in 4 to 12 weeks.

Introduction

There are two indisputable principles in preventive cardiology; the first reads, "in patients with hypertension, cardiovascular risk reduction is directly proportional to the reduction in blood pressure sustained over time."[1,2] However, in clinical practice, blood pressure control is often insufficient or not sustained over time to achieve the optimal cardiovascular risk reduction. In other words, in real life, achieving and maintaining recommended optimal therapeutic targets is not the rule, rather, it is the exception.[1,2]

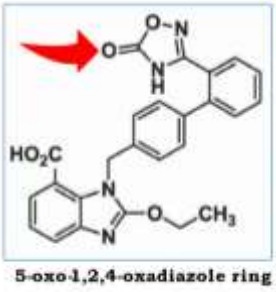
There are multiple reasons to explain this common therapeutic failure. From the authors' perspective, there are physician-related, individual, and social reasons. Among the most important are the following. *Physician-related*: Physician´s unconscious unawareness of the therapeutic targets, pharmacological options, interaction between the clinical profile of the HT patient with the pharmacological profile of the various therapeutic options; and the most frequent and serious, the so-called therapeutic inertia, that implies the conscious unawareness and therefore the lack of observance of the concepts above. *Individual:* The lack of an empowerment process in which the HT patient receives from the physician the tools to adopt a permanent healthy lifestyle, including adherence to pharmacological treatment. According to their clinical profile, the physician must provide information about the therapeutic targets, optimal pharmacological options, and the net benefit. *Social:* The availability and accessibility to different pharmacological options are multi-determined, and it is undeniable that the price of efficient drugs can be a limitation. However, this limitation is attenuated when the physician knows the therapeutic targets and the efficient pharmacological options and matches said knowledge with the patient's clinical profile. An informed decision to accept or reject the recommended treatment plan can be taken when the patient is empowered on the concept of value or net benefit rather than price.

This article aims to summarize the basic and clinical evidence of an excellent therapeutic option for HT control. With this information, we can explain the outstanding clinical results of AZL and AZL combined with chlorthalidone (AZL/CLD), both in phase III trials and in our center's "real life" experience reported here.

AZILSARTAN

1. Unique structure

Azilsartan or TAK-536 [2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid], is a selective angiotensin II type 1 (AT1) receptor blocker (AT1RB). Unlike other AT1RB, it is the only one designed with a "5-oxo-4,5-dihydro-1,2-4-oxadiazole" molecule instead of a tetrazole ring. It shares with candesartan a "7-carboxylic acid" group on the 1H-benzimidazole ring.[3] In in-vitro studies, the "7-carboxylic acid" molecule shows high-affinity binding to the Lys199 residue of AT1 receptor and the 5-oxo-4,5-dihydro-1,2-4-oxadiazole molecule, also with high-affinity (greater than the tetrazole ring) to the Gln257, Lys199, or Asn295 residues of the AT1 receptor.[3] This way, both distinctive characteristics of AZL are related to the insurmountable behavior (superior to other AT1RB) in AT1 receptor inhibition and explain most of the experimental and clinical effects summarized here (Figure 1).[3]



Affinity to and AT1 receptor dissociation

Drug	Baseline IC50 nM	Post-washout IC50 nM	Ratio
Azilsartan	**2.6 (01.7-04.1)**	**7.4 (03.9-0014.2)**	**3**
Olmesartan	6.7 (03.8-10.8)	242.5 (91.0-1056.8)	36
Telmisartan	5.1 (03.0-08.1)	191.6 (124.1-303.2)	37
Valsartan	44.9 (30.5-64.7)	>10,000	>223
Irbesartan	15.8 (08.5-29.7)	>10,000	>635
	AT1-R affinity	**AT1-R dissociation**	**A/P**

Figure 1. This image shows AZL molecular structure, the 5-oxo 1,2,4 oxadiazole ring responsible for the high-affinity, and the low dissociation to the AT1 receptor (indicated with the red arrow). Baseline and post-washout IC50s for angiotensin II binding to the AT1 receptor for azilsartan, olmesartan, telmisartan, valsartan, and irbesartan are shown in the table. According to these results, among AT1RBs, azilsartan has the highest affinity to and the lowest dissociation from the AT1 receptor.[3]

2. Experimental effects on affinity, dissociation to the AT1 receptor, and hemodynamics

Experimental data shows that among the AT1RB studied, AZL compared face-to-face with olmesartan (OLM), telmisartan (TEL), valsartan (VAL), and irbesartan (IRB) has higher affinity ratios for the AT1 receptor of 2.57, 1.96, 17.26, and 6.07, and higher persistence ratios of the post-wash AT1 receptor affinity of 32.77, 25.89, >1351, and >1351, respectively.[3,4] These pharmacodynamic properties are explained by the unique characteristics of the structure of the AZL molecule that, unlike other AT1RB, provide it with two sites of high and persistent affinity to the AT1 receptor.[3] The preceding translates into five experimental models; superiority to inhibit the "cascade" generation of inositol 1-phosphate,[3] muscle contractility in isolated aortic strips,[3] hypertensive response induced by angiotensin II (AII) in normotensive rats,[4] hypertension in salt-hypersensitive rats,[4] and induced renovascular hypertension in dogs.[5] Finally, AZL stabilizes the progression of proteinuria in hypertensive-diabetic rats and has shown very high selectivity to the AT1 receptor and inverse agonism capacity.[3,4]

3. Experimental effects on cell metabolism and proliferation

Beyond the hemodynamic effects associated with the high-affinity agonism and persistence of AZL at the AT1 receptor, in cellular models lacking AII or AT1 receptors and various animal models, AZL has demonstrated the following pleiotropic effects: increased sensitivity to insulin,[4,5,6] stimulation of adipogenesis,[7] and expression of genes that code for different adipokines, especially adiponectin.[7] Likewise, an antiproliferative effect of endothelial and smooth muscle cells has been reported, both independent and dependent on AII via mitogen-activated protein kinase.[7] However, to date, reproducing these pleiotropic experimental findings in human clinical models has been a challenge.[8]

4. Clinical studies with Azilsartan as monotherapy

In HT and other therapeutic areas, the comparison between two or more drugs should be double-blind, with the most effective drug in its maximum therapeutic dose as a comparator and in the case of HT with the measurement of blood pressure including the use of 24-hour ambulatory blood

pressure monitoring (ABPM). The AZL phase III research program adopted this requirement for the first time and, using the 24-hour ABPM selected two AT1RB; valsartan, the most widely used by then, and olmesartan, the most effective or "potent," both at their maximum therapeutic doses. Below are the prototype double-blind studies of AZL as monotherapy.

a) Azilsartan versus Olmesartan and Valsartan[9]

Using 24-hour BP measurement, AZL 80 mg was significantly superior to VAL 320 mg and OLM 40 mg. Likewise, AZL 40 mg was superior to VAL 320 mg and non-inferior to OLM 40 mg. In clinic BP measurement, AZL 40 and 80 mg were superior to VAL 320 mg and OLM 40 mg. The superiority of AZL was not associated with an increase of adverse events incidence compared to placebo, VAL 320 mg, and OLM 40 mg (Figure 2).

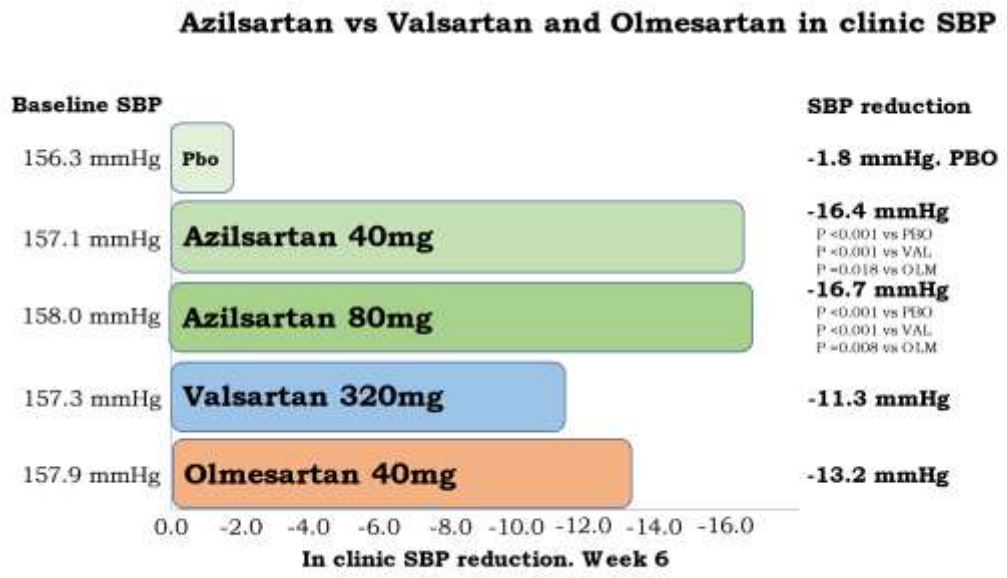


Figure 2. This graph shows clinic systolic blood pressure reduction at week 6 of treatment with azilsartan 40 and 80 mg compared with valsartan 320 mg and olmesartan 40 mg. Both doses of azilsartan were statistically superior to the maximum therapeutic doses of valsartan and olmesartan.[9]

b) Azilsartan versus Valsartan[10]

Using 24-hour BP measurement, AZL 40 and 80 mg were significantly superior to VAL 320 mg. Likewise, in clinic BP measurements AZL 40 and 80 mg were also superior to VAL 320 mg. The superiority of AZL was not associated with an increase of adverse events incidence compared to VAL 320 mg.

c) Azilsartan versus Olmesartan[11]

Using 24-hour BP measurement, AZL 80 mg was significantly superior to OLM 40 mg. Likewise, in clinic BP measurement AZL 80 mg was also superior to OLM 40 mg. The superiority of AZL was not associated with an increase of adverse events incidence compared to OLM 40 mg.

d) Azilsartan versus Candesartan[12]

Using a clinic-measured BP, AZL 40 mg (maximum dose approved in Japan) was significantly superior to candesartan (CAN) 12 mg (maximum dose approved in Japan). Likewise, in 24-hour systolic and diastolic BP, AZL 40 mg was also superior to CAN 12 mg. Furthermore, as in other studies, the superiority of AZL 40 mg was not associated with an increase of adverse events incidence compared to CAN 12 mg.

The four summarized studies confirm that: a) in the Japanese population, AZL 40mg is significantly superior to CAN 12mg; b) in the American and Hispanic population, AZL 80 mg is significantly superior to VAL 320 mg and OLM 40 mg (maximum therapeutic doses approved outside of Japan), both in reducing mean 24-hour systolic blood pressure (SBP) and in clinic SBP, with proportional and significant reductions in diastolic blood pressure (DBP).

Consequently, therapeutic target achievement (SBP <140 mmHg or ≥20 mmHg reduction) was superior with AZL 80 mg versus VAL 320 mg and OLM 40 mg. The superior efficacy of AZL 80 mg was not associated with an increase in adverse events or treatment discontinuation compared to VAL 320 mg and OLM 40 mg. The degree of AZL superiority versus VAL and OLM is concordant among the different studies analyzed. The difference in mean 24-hour SBP between AZL and VAL 320 mg was from -2.0 to -4.3 mmHg and from -5.3 to -5.4 mmHg in clinic SBP. The same parameters with AZL versus OLM 40 mg were from -2.0 to -2.5 and from -2.9 to -3.5, respectively. Although the magnitude of these differences could appear minor, since the beginning of the century, differences in SBP ≥2 mmHg have been associated with significant differences in cardiovascular outcomes.[1,2,13]

5. Clinical studies with Azilsartan combined with Chlorthalidone

There are vast (although ignored by many physicians) references that sustain that CLD is a thiazide-like antihypertensive that milligram by milligram is more effective than the thiazide hydrochlorothiazide (HCT) in reducing clinic and 24-hour ambulatory BP.[14,15,16,17,18,19,20,21] Such efficacy has been associated, unlike HCT, with a favorable impact on HT surrogates such as left ventricular hypertrophy,[22] and a significant reduction in cardiovascular events.[23,24,25,26,27] Hence, the second phase of AZL research focused on demonstrating the additive effect of AZL/CLD and the superiority of the AZL/CLD combination over AZL/HCT and on OLM/HCT. The latter was previously classified as the most effective or powerful fixed combination. Below are the prototype double-blind studies with AZL/CLD.

a) Azilsartan plus Chlorthalidone[28]

Using an excellent factorial design, this study confirmed the superiority of the fixed combination of AZL/CLD over both of its components in reducing clinic SBP and mean 24-hour BP. In stage 2 HT patients (SBP ≥160 mmHg), 75% reached the therapeutic target with AZL 40-80/CLD 12.5 mg, while around 50% achieved it with AZL or CLD as monotherapies. These results guide the type of therapy (monotherapy or combination therapy) based on the therapeutic BP gap (20/10 rule) (Figure 3).[1,2]

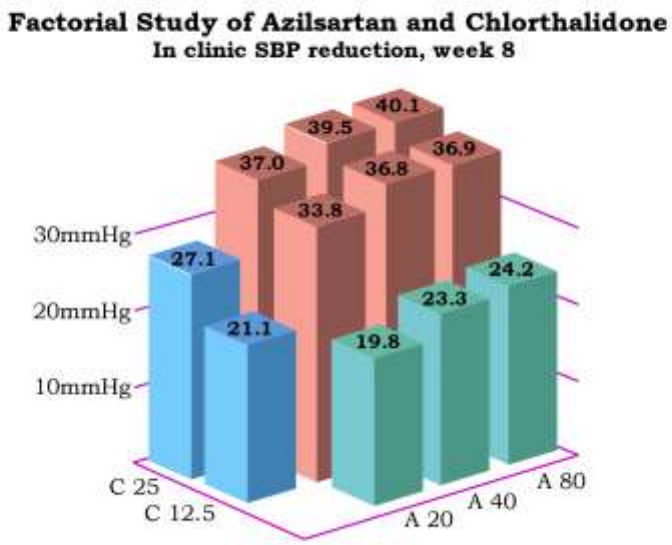


Figure 3. This graph clearly shows the clinic SBP reduction effect at week 8 of treatment with the monotherapies of azilsartan (green bars) and chlorthalidone (blue bars). Likewise, the synergistic effect of the combination of azilsartan 20, 40, and 80 mg with chlorthalidone 12.5 and 25 mg is observed. The combinations of azilsartan/chlorthalidone 40/12.5 and 80/12.5 mg reduce SBP between 35 and 40 mmHg, while monotherapy with azilsartan 40 and 80 mg reduces it between 20 and 25 mmHg.[28] This range of therapeutic efficacy with monotherapy or the fixed-dose combination has great clinical relevance and as corroborated in other studies, it is constant.[29,30]

b) Azilsartan combined with Chlorthalidone versus Azilsartan plus Hydrochlorothiazide[29]

In an interesting and well-designed clinical trial with AZL 40 mg combined with CLD and HCT, the superiority of CLD over HCT in reducing clinic SBP and mean 24-hour BP was confirmed in a double-blind, double-dummy trial. Likewise, in stage 2 HT patients (SBP ≥160 mmHg), two-thirds reached the therapeutic target with AZL 40/CLD 12.5 mg, while <50% achieved it with AZL 40 plus HCT 12.5 mg; this was a clinically and statistically very significant difference.

c) Azilsartan combined with Chlorthalidone versus Olmesartan combined with Hydrochlorothiazide[30]

In a daring and well-designed clinical trial with AZL 40 and 80 mg titrated to 25 mg of CLD compared to the maximum dose of OLM (40 mg), also titrated to 25 mg of HCT, the superiority of CLD over HCT in reducing clinic SBP and mean 24-hour BP was confirmed in a double-blind trial. We can infer (since it is impossible to dissect the effects of both components) the superiority of AZL over OLM with deltas in clinic SBP at week 8 of -5.6 and -5.9 mmHg and in week 12 of -5.4 and -6.9 mmHg for AZL 40/CLD 12.5 and AZL 80/CLD 12.5 mg versus OLM 40/HCT 12.5 and OLM 40/HCT 25 mg, respectively. In this force-titrated to a high dose study, a higher incidence (directly proportional to the doses) of dizziness, hypotension, and "functional" creatinine increase was observed, especially in the group with forced titration (regardless of BP) to AZL 80/CLD 25 mg; however, it did not determine a significant increase in serious adverse events or treatment discontinuation.

Characterized by high quality in design and management, the seven previous studies confirm the following clinical concepts related to the pharmacological characteristics of azilsartan and chlorthalidone. First, AZL is a more efficient AT1RB than VAL, CAN, and OLM; we can infer it is most likely the most efficient.[31,32] The association of AZL with chlorthalidone has a

substantial additive effect, as is the combination of a fixed-dose AT1RB with a more effective diuretic, with a reduction of clinic SBP close to 40 mmHg (AZL/CLD 80/12.5 mg) and target achievement of <140/90 mmHg close to 80% (AZL 80/CLD 12.5 mg) in patients with HT >160/90 mmHg; higher achievements are observed with the AZL/CLD 80/25mg dose. The above mentioned, without an increase in significant adverse events, mainly when an appropriate therapeutic plan is used for the blood pressure gap of every HT patient based on the approved marketed presentations in each region.

6. Experience at the Aguascalientes Cardiometabolic Research Center

Considering the previous summarized evidence and approval in Mexico of azilsartan and azilsartan/chlortalidone in 2015, as of 2015, our clinical experience has increased. This section presents the retrospective, systematic and consecutive analysis of the clinical efficacy results using AZL and AZL/CLD in our center.

Methods: We conducted a retrospective, systematic, and consecutive review of our database between March and May 2020, selecting the records of all HT patients treated "de novo/switch" with AZL or AZL/CLD as of 2015. This analysis included all HT patients treated with AZL or AZL/CLD who had a baseline BP measurement and at least one control BP measurement with stable treatment for at least four weeks.

Analysis and results: We carried out a descriptive analysis to evaluate the antihypertensive efficacy of AZL and AZL/CLD; 297 HT patients treated "de novo/switch" with AZL, or AZL/CLD were detected. Among them, 86, 84, 7, and 120 patients were treated with AZL 40, AZL/CLD 40/12.5, AZL 80, and AZL/CLD 80/12.5 mg per day, respectively. All had a baseline and a control BP measurement with treatment; measurements in the office were performed according to the AHA guidelines,[1] with a mercury sphygmomanometer (Tycos CE 0050) by a cardiologist (ECMV). However, the time between baseline BP measurement and control measurement was variable since clinical practice in our center is based on the 2017 AHA/ACC Guidelines, considering <130/80 mmHg as the desired target. In general, the prescription of AZL as monotherapy or AZL/CLD was fundamentally based on the clinical profile of the HT patient (absolute risk), on the therapeutic BP gap (real pressure - target pressure), in their current state of antihypertensive treatment (naive or insufficient previous treatment), and the pressure response with the initial treatment. In other words, these results reflect our titrate-to-target practice, which in most cases requires only one step, although less frequently, it may require two or three steps.

a) Azilsartan 40 mg group

In total, 86 patients were included; female/male sex 50/36; average age women/men 63.0/57.4 years; **average baseline SBP/DBP, women 146.8/84.0 and men 144.5/88.8 mmHg**; control SBP/DBP with treatment women 116.5/70.3 and men 116.6/73.4 mmHg; average reduction SBP/DBP, women -30.2 /-13.7 and men -27.8/-15.3 mmHg. *Efficacy in women:* 50/50 (100%) achieved a target BP <140/90 mmHg with AZL 40 mg, and 49/50 (98%) achieved a target BP <130/80 mmHg with AZL 40 mg; in 1 case of 50 (2%) amlodipine 2.5 mg was added, achieving a pressure <130/80 mmHg. *Efficacy in men:* 36/36 (100%) achieved a target BP <140/90 and <130/80 mmHg with AZL 40 mg (Figure 4).

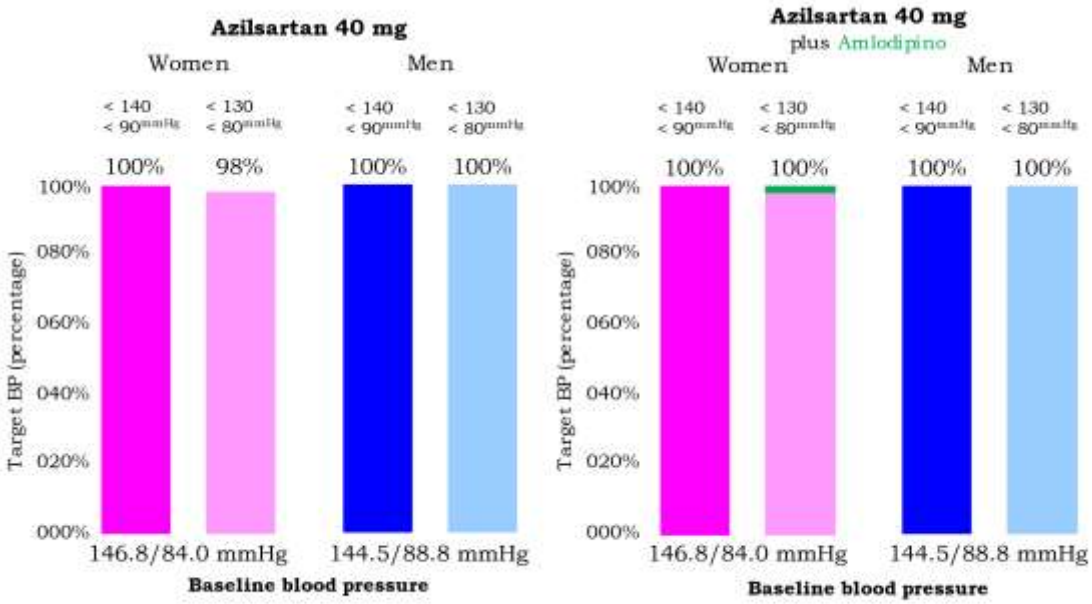


Figure 4. This graph shows that in HT patients with BP <150/90 mmHg, AZL 40 mg as monotherapy effectively achieved the target BP <140/90 and <130/80 mmHg. Thus, this group of "hyper-responding" patients reflects a higher therapeutic response (measured in reduction of SBP) than the reported in the white population and similar to the reported in the Japanese population with a reduction in SBP >20 mmHg with a proportional reduction in DBP.

b) Azilsartan combined with Chlorthalidone 40/12.5 mg group

In total, 84 patients were included; female/male sex 57/27; average age women/men 60.5/60.1 years; **average baseline SBP/DBP, women 144.4/86.1 and men 144.2/86.5 mmHg**; control SBP/DBP with treatment women 116.5/71.2 and men 117.4/73.2 mmHg; average reduction SBP/DBP, women -28.9/-14.8 and men -26.8/-13.3 mmHg. *Efficacy in women:* 57/57 (100%) achieved a target BP <140/90 mmHg with AZL/CLD 40/12.5 mg, and 50/57 (89%) achieved a target BP <130/80 mmHg with AZL/CLD 40/12.5 mg; titration was not considered in 7 patients who did not achieve the <130/80 mmHg target. *Efficacy in men:* 26/27 (96.2%) achieved a target BP <140/90 and 24/27 (88.8%) achieved a target BP <130/80 mmHg with AZL/CLD 40/12.5 mg; in 1 case of 27 (3.7%) amlodipine 2.5 mg was added, achieving a BP <130/80 mmHg; titration was not considered in 2 patients who did not achieve the <130/80 mmHg target (Figure 5).

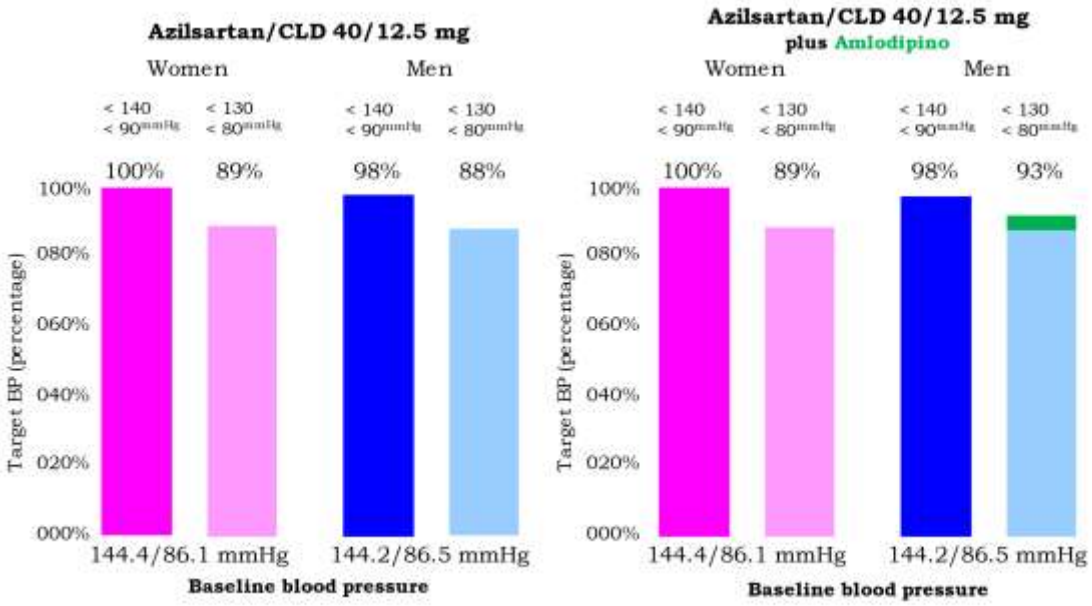


Figure 5. This graph shows that in HT patients with BP <150/90 mmHg, AZL/CLD 40/12.5 mg was very effective in achieving the target BP <140/90 and <130/80 mmHg. This group of "normo-responding" patients reflects the expected therapeutic response (measured as reducing SBP) reported in the white population, with an SBP reduction between 30 and 35 mmHg, with a proportional reduction in DBP. This explains the high therapeutic success in patients whose baseline therapeutic gap is <20/10 mmHg.

c) Azilsartan 80 mg group

Only 7 patients were included; female/male sex 3/4; average age women/men 77.0/54.7 years; **average baseline SBP/DBP, women 172.6/88.3 and men 139.0/84.5 mmHg;** control SBP/DBP with treatment women 116.6/64.6 and men 118.7/73.0 mmHg; average reduction SBP/DBP, women -56.0/-23.6 and men -20.2/-11.5 mmHg. *Efficacy in women:* 1/3 (33.3%) achieved a target BP <140/90 mmHg with AZL 80 mg; in one case, amlodipine 5 mg was added, in other case amlodipine 10 mg was added, achieving a pressure <140/90 mmHg; with this treatment plan all patients achieved a target BP <130/80 mmHg. *Efficacy in men:* 3/4 (75%) achieved a target BP <140/90; in one case (25%), amlodipine 5 mg was added, achieving a target BP <130/80 mmHg (not graphed due to the low number of cases); 3/4 men (75%) achieved a target BP <130/80 mmHg with AZL 80 mg.

d) Azilsartan combined with Chlorthalidone 80/12.5 mg group

In total, 120 patients were included; female/male sex 83/27; average age women/men 65.3/60.4 years; **average baseline SBP/DBP, women 161.4/88.9 and men 157.5/92.2 mmHg;** control SBP/DBP with treatment (includes treatment with amlodipine) women 122.9/73.5 and men 121.5/74.2 mmHg; average reduction SBP/DBP (includes treatment with amlodipine) women -38.4/-15.6 and men -36.0/-18.0 mmHg. *Efficacy in women:* 53/83 (63.8%) achieved a target BP <140/90 mmHg with AZL/CLD 80/12.5 mg; in 3/83 (3.6%), 23/83 (27.7%), and 4/83 (4.8%) amlodipine 2.5, 5, and 10 mg, was added respectively, achieving BP <140/90 mmHg; 44/83 (53%) achieved a target BP <130/80 mmHg with AZL/CLD 80/12.5 mg, and in 3/83 (3.6%), 17/83 (20.4%), and 2/83 (2.4%) amlodipine 2.5, 5, and 10 mg was added respectively, achieving BP <130/80 mmHg. *Efficacy in men:* 29/37 men (78.3%) achieved a target BP <140/90; in 2/37 (5.4%) and 6/37 (16.2%) amlodipine 2.5 and 5 mg, was added respectively, achieving BP <140/90 mmHg; 23/37 (62.1%) achieved a target BP <130/80 mmHg with AZL/CLD 80/12.5 mg, and in 1/37 (2.7%), and 5/37 (13.5%) amlodipine 2.5 and 5 mg was added respectively, achieving BP <130/80 mmHg (Figure 6).

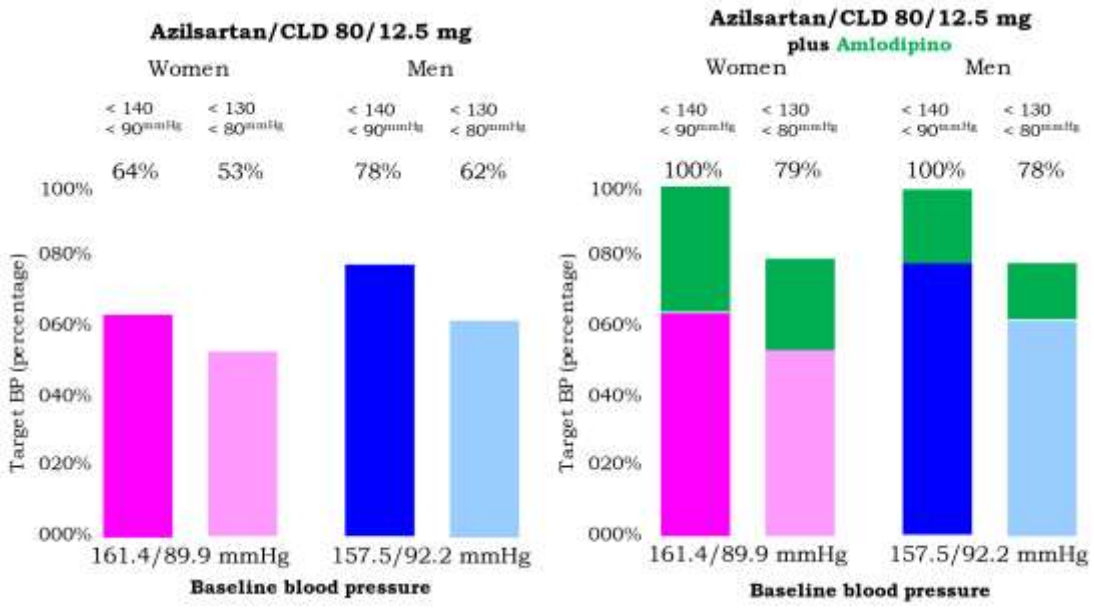


Figure 6. This graph shows that in HT patients with BP >160/90 mmHg, AZL/CLD 80/12.5 mg effectively achieved the target BP <140/90 and <130/80 mmHg. This group of "normo-responding" patients reflects the expected therapeutic response (measured as reducing SBP) reported in the white population, with an SBP reduction between 35 and 39 mmHg, with a proportional reduction in DBP. Unlike the AZL/CLD 40/12.5 mg group, in this group with a higher BP and therefore a greater therapeutic gap (> 30/10 mmHg), therapeutic success is consistent with that reported in the white population (60-75 %), making it necessary to supplement treatment with amlodipine in 40 to 25% of cases, thus reaching the target of <140/90 mmHg in practically 100% and <130/80 mmHg in almost 80% of cases.

Analysis and resulting recommendations

Our experience with almost 300 HT patients treated "de novo or switch" with AZL, or AZL/CLD is consistent with the reported efficacy in phase III studies. We understand that our results have the implicit limitations of a retrospective review of a specialist´s database, with a solely descriptive analysis on efficacy. However, these results allow us to do real-life observations not feasible in clinical studies. The practical conclusions of our review are as follows:

a) In HT patients with BP <150/90 mmHg (especially naive to pharmacological treatment), AZL 40 mg as monotherapy provides practically 100% success to achieve a target BP <140/90 and <130/80 mmHg, in a subpopulation that we have called "hyper-responders."
b) In HT patients with BP <150/90 mmHg (naive or with another treatment failure), AZL/CLD 40/12.5 mg provides practically 100% success to achieve a target BP <140/90 mmHg and 90% to achieve a target BP <130/80 mmHg which, if indicated, can be optimized by titrating to AZL/CLD 80/12.5 mg or with the use of amlodipine.
c) AZL 80mg as monotherapy is of little use, and we cannot make clinically important conclusions.
d) In HT patients with BP >150/90 mmHg (generally with another treatment failure), AZL/CLD 80/12.5 mg gives women a success rate greater than 60% to achieve a target BP <140/90 mmHg and greater than 50% to achieve a target BP <130/80 mmHg. The success rates are higher in men, greater than 75% to achieve a target BP <140/90 mmHg and greater than 60% to achieve a target BP <130/80 mmHg. In both cases, the use of amlodipine (2.5, 5, or 10 mg) makes it possible to achieve a target BP <140/90 mmHg in 100% of the cases and <130/80 mmHg in 80% of the cases.

Based on these results, our clinical recommendations are as follows:

1. In HT patients with BP <150/90 mmHg, naive to treatment, especially with low or intermediate

cardiovascular risk with no damage to "target" organs, we suggest (as a partial variation to the current guidelines), to start AZL 40 or 80 mg as monotherapy and to evaluate the therapeutic response in 4 to 8 weeks.

2. In HT patients with BP <150/90 mmHg with another treatment failure, switch to AZL/CLD 40/12.5 mg and, if necessary, titrate to 80/12.5 mg in 4 to 8 weeks and reassess the therapeutic response in a similar period.
3. In HT patients with BP >150/90 mmHg naive or with treatment failure, start AZL/CLD 80/12.5 mg and, if necessary, add amlodipine (2.5, 5, or 10 mg) in 4 to 8 weeks according to the desired target.

With this treatment plan, a target BP <140/90 mmHg is ensured in more than 90% of cases and a target BP <130/80 mmHg in more than 75% in 4 to 12 weeks (Figure 7).

An analysis of the incidence of adverse events was not formally performed in our review. However, given our practice of selecting the initial dose according to the clinical characteristics discussed previously and titrating the treatment according to the therapeutic response, a satisfactory clinical balance between efficacy and safety is achieved with a very low incidence of adverse events.

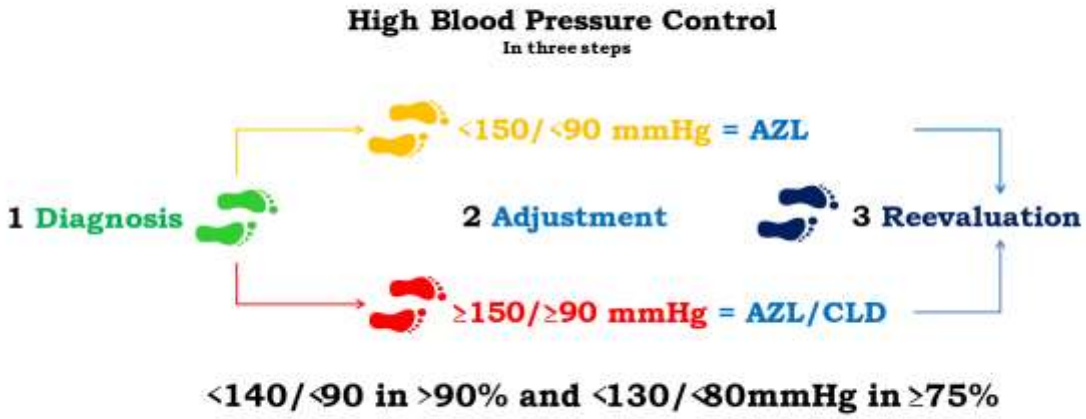


Figure 7. Therapeutic scheme based on azilsartan and azilsartan/chlortalidone (see text).

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