Azilsartan, a promising Angiotensin II Receptor Blocker in the management of hypertension

C. Antza[1], I. Doundoulakis[2], S. Stabouli[3], V. Kotsis[1]

[1]*3rd Department of Internal Medicine, Aristotle University, Hypertension, Hypertension-24h Ambulatory blood pressure monitoring center, Papageorgiou Hospital, Thessaloniki*

[2] *School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece*

[3] *Pediatric Intensive Care Unit, Hippokration Hospital, Thessaloniki*

Abstract

Renin-angiotensin-aldosterone system blockers are important drugs for the treatment of hypertension and its complications such as arterial stiffening, left ventricular hypertrophy and microalbuminuria. New drugs in this category are in request and research is ongoing to find new agents. Azilsartan was discovered in such an effort. This newly approved angiotensin-receptor blocker has similar properties with previous drugs of the same category, but seems to be more effective in the treatment of hypertension. In this review, the pharmacology, the adverse events and the differences to other drugs of the same category in the efficacy on reducing blood pressure will be discussed.

Key words: azilsartan; ARB; RAAS; hypertension

SUBMISSION: 04/04/2016 | ACCEPTANCE: 30/05/2016

Citation

Antza C, Doundoulakis I, Stabouli S, et al. Azilsartan, a promising Angiotensin II Receptor Blocker in the management of arterial hypertension. *Hell J Atheroscler* 2016, 7:53-62

Introduction

Hypertension is a major risk factor for cardiovascular disease (CVD), the leading cause of mortality and morbidity and its prevalence is expected to rise in the future because of the aging population.[1] The European Society of Hypertension and the European Society of Cardiology defined hypertension as blood pressure (BP) values > 140mmHg SBP and/

***Corresponding author: Ass. Prof. V Kotsis**
3rd Department of Internal Medicine, Aristotle University,Hypertension-24h ambulatory blood pressure monitoring center,Papageorgiou Hospital,Thessaloniki
Mobile number: (+30) 6974748860, E-mail: vkotsis@auth.gr

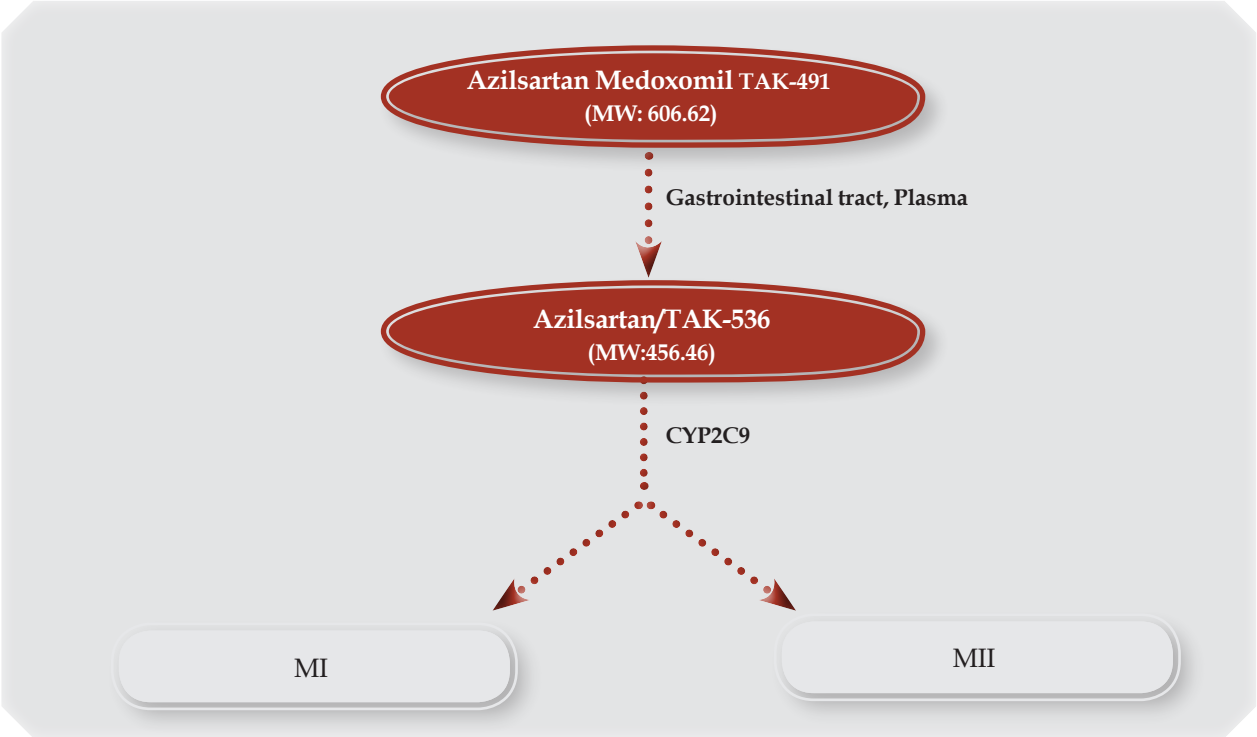

Figure 1. Metabolism of azilsartan
MW= molecular weight, MI= minor metabolites, MII= major metabolites

or > 90mmHg DBP. This definition was based on the evidence from randomized clinical trials reported that patients with BP treatment-induced reductions at these levels were beneficial to cardiovascular hard end points such as morbidity and hospitalization.[2] In clinical trials, antihypertensive therapy is associated with reductions in stroke incidence (35-40%), myocardial infarction (20-25%) and heart failure (more than 50%).[3] Blood pressure control is essential to reduce cardiovascular events and requires patient co-operation with lifestyle modifications, such as reduction in salt consumption, weight loss and exercise, adherence to treatment and effective drug administration either with monotherapy or combination therapy.

In the management of hypertension there are drugs targeting different mechanisms of the disease i.e. volume overload, vasoconstriction and increased cardiac stroke volume. Treatment can inhibit the renin–angiotensin–aldosterone system (RAAS) or calcium channels causing vasodilatation; diuretics reduce volume overload and beta-blockers reduce cardiac index. As regards to the RAAS, there are 3 different pathway inhibitors, those reducing the production of the angiotensin converting enzyme (ACE), the angiotensin receptor blockers (ARBs), and the direct renin inhibitors (DRIs).

ARBs are a purposeful choice for BP control, as effective as ACE inhibitors and better tolerated due to the lack of bradykinine accumulation resulting in reduced side effects such as cough, which is very common in patients treated with ACEI, making them incompliant to treatment. A great number of clinical trials evaluated the role of ARBs in reducing CV mortality and morbidity in patients at risk for CV events.[4] Results showed that ARBs improved CV outcomes in patients with hypertension,[5,6] heart failure,[7,8] and diabetic kidney disease.[9,10]

Azilsartan (AZL) is a new ARB recently approved for the treatment of hypertension. Other available ARB drugs are candesartan (CAN), eprosartan, irbesartan, losartan, olmesartan (OLM), telmisartan and valsartan (VAL). Azilsartan was discovered through the efforts of scientists to find a new class

Table 1. **Pharmacokinetics of Azilsartan**

	Azilsartan/TAK-536
Molecular Weight	456.46
Bioavailability	60%
Affected by food administation	No
Half-life time	11 hours
Metabolized	Liver
Eliminated	Urine (42%), Feces (55%)
Renal Clearance	2.3 ml/min

of AT1 antagonists by modifying the tetrazole ring present in candesartan[11] and was approved by the US Food and Drug Administration in February 2011 for the treatment of hypertension, either alone or in combination with other agents such as diuretics.[12]

Differential Pharmacology, Pharmacokinetics and Pharmacodynamics

The chemical structure of azilsartan is very similar to the structure of candesartan and differs only by the replacement of candesartan's 5 member tetrazole ring with the 5 member oxo-oxadiazole ring of azilsartan.[11,13] Azilsartan medoxomil with molecular weight 606.62 (TAK-491), following oral administration, is hydrolyzed into azilsartan with molecular weight 456.46 (TAK-536) in both the gastrointestinal tract and plasma.[14,15] TAK-536, the bioactive molecule, selectively blocks angiotensin II-induced activation of AT1 receptors in different tissues including the adrenal gland as well as the smooth muscle cells. Azilsartan is metabolized via CYP2C9 to major (M-II) and minor (M-I) metabolites that do not significantly contribute to AT1 receptor blockade.[16-18] Its affinity is greater than 10,000-fold for the angiotensin II subtype-1 receptors than for subtype-2 receptors. Thus, the beneficial effects of subtype-2 receptor stimulation (vasodilation, tissue repair, and inhibition of cell growth) remain unaffected with its use. (**Figure 1**)[12]

Azilsartan's bioavailability is approximately 60%, and it seems not to be affected by food administration, reaching peak plasma concentrations within 1.5 to 3 hours. Azilsartan has an elimination half-life of 11 hours, is metabolized in the liver and is eliminated in both urine (42%) and feces (55%), with a renal clearance about 2.3 mL/min. It is achieving steady-state levels within 5 days after once daily dosing.[12,19] The azilsartan is indicated for the treatment of hypertension and can be used either as monotherapy or as combination therapy. The dosage is 40mg or 80mg once daily. (**Table 1**)[12,15]

In safety studies for the approvement of azilsartan, 4,814 patients took part in trials with duration up to 1 year. Adverse events were not affected by gender, age, or race. Adverse events were diarrhea (up to 2% *vs* 0.5% placebo), weakness with 0.3% incidence, fatigue, muscle spasm, dizziness, postural dizziness and cough. Common side effects (1-10%) were dizziness, diarrhea and increased serum CPK, while uncommon (0.1-1%) were hypotension (increased to common when co administered with chlorthalidone), fatigue and peripheral edema (increased to common

when co administered with amlodipine (AML), but less than with amlodipine alone).[12]

No major drug interaction studies on azilsartan have been reported to date; however, some reports confirm disruptions for numerous drugs combined with either 40 mg or 80 mg doses of azilsartan. When Azilsartan co-admistated with non-steroid anti-inflammatory drugs or cyclooxygenase-2 inhibitors, renal function is deteriorated, including acute renal failure, in patients who are geriatric, volume-depleted or have compromised renal function; these side effects are reversible after drug interruption. Furthermore, the combination of azilsartan with sparing potassium diuretics may increase the risk of hyperkalemia. Finally, lithium and azilsartan should not co-administated due to reversible changes in lithium concentration and toxicity.[12]

Azilsartan must not be co-administrated with aliskiren in diabetes and with lithium as well as it must be avoided during the pregnancy. Also, special caution is indicated in patients with aortic stenosis and mitral stenosis. Severe aortic stenosis patients are more likely to have hemodynamically significant decrease in systolic BP with vasodilator stress, especially after using vasodilator factors such as azilsartan.[20] However, ARBs seems to be associated with an improved survival and a lower risk of CV events in patients with aortic stenosis.[21] Azilsartan may cause hypotension in volume -or salt- depleted patients and worsen renal function in susceptible individuals. Modest increases in peak plasma azilsartan concentration reported in geriatric patients and in patients with mild to severe renal impairment or mild to moderate hepatic impairment; while studies in patients with severe hepatic impairment are lucking. Adverse events (oliguria, progressive azotemia, acute renal failure or severe renal impairment) have occurred due to the inhibition of the RAAS. Patients should be monitored for worsening renal function, with serum creatinine and blood urea nitrogen.[12]

Azilsartan: Combination with other antihypertensive therapies

The combination of azilsartan with chlorthalidone (CHL) is a new combination treatment first to combine an ARB with the diuretic, CHL. This fixed-dose combination is available at 40/12.5 mg and 40/25 mg dosages. The first phase III trial to evaluate this combination was a randomized, double-blind, multicenter, 6-week treatment study comparing two different doses of AZL (40 mg or 80 mg) in combination with 25 mg CHL to 25 mg CHL monotherapy in patients with hypertension.[22] The results showed a statistically significant decrease in 24-hour mean SBP in both the AZL/CHL 40/25 mg and 80/25 mg groups (-31.72 and -31.3 mmHg, respectively; P , 0.001) when compared to CHL alone (-15.85 mmHg). Similar results were seen when comparing mean diastolic pressure, mean daytime systolic pressure, and mean nighttime systolic pressure.

Another multicenter, randomized, double-blind, parallel-group, 8-week study from Rakugi et al.[23] reported the efficacy and tolerability of the AZL and AML compared with those of AZL monotherapy and AML monotherapy in Japanese patients with grade 1 to 2 essential hypertension. The mean reduction in seated blood pressure was 35.3/22.3 mmHg in the AZL/AML 20/5 mg group and 31.4/19.2 mmHg in the AZL/AML 20/2.5 mg group, indicating a reduction significantly greater than that in corresponding monotherapy groups (21.5/ 13.9 mmHg in the AZL 20mg group, 26.4/15.5 mmHg in the AML 5 mg group and 19.3/11.6 mmHg in the AML 2.5 mg group). In the AZL/AML group 20/5mmHg, common adverse events (nasopharyngitis at 8.0% and dizziness at 2.7%) were reported, while in the AZL/AML 20/2.5 mmHg group nasopharyngitis (12.6%), upper respiratory tract inflammation (4.6%), increased blood creatine phosphokinase level (3.3%), and influenza (2.0%) were recorded.

The efficacy of combining azilsartan medoxomil with amlodipine to reduce BP in patients with stage 2 hypertension were reported in a study from Weber et al.,[24] in a randomized, controlled, double-blind study of 6 weeks' duration in 566 patients. After 6 weeks, 24-h BP decreased by 25/15 mmHg in both the AZL/AML 40/5 and 80/5 mg groups. These reductions were greater than the 14/8 mmHg decrease with placebo plus amlodipine 5 mg. All treatments were

Table 2. **Azilsartan in combination with other antihypertensive therapies**

	Outcome in monotherapy	Outcome in combination therapy	P
NCT00591773[22]	CHL 25mg 24hour SBP: -15.85mmHg	AZL/CHL 40/25mg 24hour SBP: -31.75mmHg AZL/CHL 80/25mg 24hour SBP: -31.3mmHg	<0.001
Rakugi et al.[23]	AML 2,5mg seated BP: -19.3/11.6mmHg AML 5mg seated BP: -26.4/15.5mmHg	AZL/AML 20/2.5mg seated BP: -31.4/19.2mmHg AZL/AML 20/5mg seated BP: -35.3/22.3mmHg	<0.001
Weber et al.[24]	AML 5mg 24hour BP: -14/8mmHg	AZL/AML 40/5mg 24hour BP: -25/15mmHg AZL/AML 80/5 24hour BP: -25/15mmHg	<0.001

well tolerated, and adverse events were not increased in the azilsartan group, with a slightly lower rate in the AZL/AML 80/5 mmHg group. Data summary report is shown in **Table 2**.

Azilsartan: Compared to other antihypertensive therapies

Bakris et al.,[25] compared the efficacy and safety of azilsartan medoxomil to olmesartan medoxomil. 1,275 individuals, 58±11 years were included in this randomized, double-blind, placebo controlled, multicenter 6-week study. The baseline 24-hour mean ambulatory systolic pressure was ≥ 130 mmHg and ≤ 170 mmHg; 142 received placebo and the remainder received 20 mg, 40 mg, or 80 mg AZL or 40 mg OLM. Reduction in 24-hour mean SBP was greater with AZL 80 mg than OLM 40 mg by 2.1 mmHg, while AZL 40 mg was non inferior to OLM 40 mg. The side effect profiles of both ARBs were similar to placebo. Headache, dyslipidemia, and dizziness were reported as common adverse events and were similar in all groups.

Sica et al.,[26] investigated the difference between azilsartan and valsartan in a randomized, double-blind, multicenter study using ambulatory and clinic blood pressure (BP) measurements with 984 patients with primary hypertension. The mean age of participants was 58 years, 52% were men, and 15% were black. The baseline 24-hour mean of systolic BP was similar (approximately 145.6 mmHg) in each group. AZL 40 mg and 80 mg lowered 24-hour mean systolic BP (14.9 mmHg and 15.3 mmHg, respectively) more than VAL 320 mg (11.3 mm Hg). Clinic systolic BP reductions were consistent with the ambulatory results (14.9 mmHg for AZL 40 mg and 16.9 mmHg for AZL 80 mg vs 11.6 mmHg for VAL; P= 0.015 and P < 0.001, respectively). Similar were the results in the reductions in 24hour mean and clinic diastolic BPs. Only 1 patient, each in the AZL 40 mg and 80 mg groups, had increased serum creatinine ≥ 50% above the upper limit of normal.

Comparing azilsartan with olmesartan and valsartan at their maximal approved doses White et al.,[27] showed that AZL had superior efficacy to both OLM and VAL without increasing adverse events. 1291 patients, with mean age 56 years, were included in the study. AZL at 80 mg had superior efficacy from both VAL at 320 mg and OLM at 40 mg, while AZL at 40 mg was non-inferior to 40 mg of OLM, whereas 40 mg of AZL also lowered 24-hour and clinic diastolic BPs to a greater extent than 320 mg of VAL. Clinic systolic BP reductions were superior by both doses of azilsartan medoxomil compared to the other two ARBs. Changes in serum creatinine and potassium had similar findings in all treatment groups.

Azilsartan differs from candesartan by replacement

Table 3. **Azilsartan better reduces 24h SBP than other antihypertensive therapies**

	AZL vs other Antihypertensive therapy	Difference in 24h SBP	P
Bakris el al.[25]	AZL80mg vs OLM 40mg	-2.1mmHg	0.38
Sica et al.[26]	AZL 40mg vs VAL 320mg	-3.6mmHg	<0.001
	AZL 80mg vs VAL 320mg	-4mmHg	<0.001
White et al.[27]	AZL 40mg vs VAL 320mg	-3.2mmHg	0.001
	AZL 80mg vs VAL 320mg	-4.3mmHg	<0.001
	AZL 40mg vs OLM 40mg	-1.4mmHg	0.136
	AZL 80mg vs OLM 40mg	-2.5mmHg	0.009
Bonner et al.[29]	AZL 40mg vs RAM 10mg	-8.4mmHg	<0.001
	AZL 80mg vs RAM 10mg	-9mmHg	<0.001

of candesartan's tetrazole ring with the oxo-oxadiazole ring. The study of Rakugi et al.,[28] compared 275 patients treated with CAN (8-12 mg once daily) with 273 patients treated with AZL (20–40 mg once daily). After 14 weeks, the results showed that once-daily azilsartan improved the non-dipping SBP to a greater extent than candesartan in Japanese patients with grade I – II essential hypertension.

Finally, another study compared azilsartan with ramipril (RAM). In this double-blind, controlled, randomized trial, 884 individuals aged 57 ± 11 years were included.[29] The included patients, with SBP 150–180 mmHg, were randomized to 20mg azilsartan or 2.5 mg ramipril once daily for 2 weeks and then force-titrated to 40 or 80 mg azilsartan or 10mg ramipril for 22 weeks. The results clearly demonstrated that azilsartan was more effective in reducing BP than ramipril as well as better tolerated. Increases in serum potassium, sodium and uric acid were observed more often during treatment with the AZL 40 and 80 mg as compared with ramipril, respectively. Data summary report is shown in **Table 3**.

Discussion

The aim of this review was to identify the effectiveness of azilsartan, a newly ARB drug, in lowering blood pressure as well as its side effects, especially against antihypertensive drugs in the same category. ARBs could be a safe and effective choice in hypertensive patients, both for lowering blood pressure and protecting from cardiovascular diseases. Trials for azilsartan should be focused in this direction. Azilsartan has a great efficacy at lowering blood pressure and is poor at adverse events, but research at the field of diabetes, cardiovascular and renal protection is necessary. This could be the key in order to establish azilsartan as a powerful antihypertensive agent not only against the hypertensive population but also against the high cardiovascular risk population.

Randomized clinical trials have proven that therapy with ARBs may be beneficial in primary and secondary prevention in several pathological conditions including hypertension, atherosclerosis, heart failure, and renal disease.[30-33] In the LIFE trial[5] it was clearly observed that losartan prevents cardiovascular morbidity and deaths more than atenolol for a similar reduction in blood pressure in patients with essential hypertension and left ventricular hypertrophy. Treatment with losartan was associated with 25% lower incidence of new-onset of diabetes. Both hypertension and diabetes may induce renal damage in patients at risk for cardiovascular diseases. Vice versa, renal disease may increase the cardiovascular risk even at a preclinical stage. In the ROADMAP study, olmesartan was associated with a delayed

onset of microalbuminuria, although this drug did not reduce the cardiovascular complications associated with diabetes and development of cardiovascular events.[34] Moreover, irbesartan delayed the progression from microalbuminuria to proteinuria and the reset of normoalbuminuria in a significant proportion of patients with hypertension and type 2 diabetes.[35] In over 25,000 patients with coronary, peripheral or cerebrovascular disease and diabetes, ONTARGET trial[36] has shown that telmisartan had similar effect to ramipril either on primary or secondary outcomes including cardiovascular death, stroke, myocardial infarction, hospitalization for heart failure and death from any cause. The question whether azilsartan has the same protecting actions like the other ARBs is still open while studies are scare.

The strength of our review is that all available studies for azilsartan were included. On the other hand, limitation of this review is the little knowledge for azilsartan action in diabetes mellitus, renal protection, atherosclerosis and heart failure, which is an open field for new research.

In conlusions, azilsartan should be considered as an alternative agent for treating hypertension either as monotherapy or as combination therapy with other antihypertensive drugs. Little adverse events and the efficacy of azilsartan make it a good antihypertensive choice. Long term prospective studies for the efficacy of azilsartan in cardiovascular hard end points are needed to establish its effectiveness to cardiovascular protection and disease.

Conflict of interest:
Prof. Kotsis has received honoraria from VIANEX and received support by a grand of Hellenic Society Atherosclerosis.

Περίληψη

Αζιλσαρτάνη, ένας πολλά υποσχόμενος ανταγωνιστής των υποδοχέων της αγγειοτενσίνης ΙΙ στην θεραπεία της υπέρτασης

Χ. Άντζα[1], Ι. Δουνδουλάκης[2], Σ. Σταμπουλή[3], Β. Κώτσης[1]

[1]*Γ' Πανεπιστημιακή Παθολογική Κλινική ΑΠΘ, Ιατρείο Υπέρτασης-24ωρης καταγραφής της αρτηριακής πίεσης, Νοσοκομείο Παπαγεωργίου, Θεσσαλονίκη*

[2]*Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Θεσσαλονίκη, Ελλάδα*

[3]*Α΄ Πανεπιστημιακή Παιδιατρική Κινική ΑΠΘ, Νοσοκομείο Ιπποκράτειο, Θεσσαλονίκη*

Οι αναστολείς του συστήματος ρενίνης-αγγειοτενσίνης-αλδοστερόνης αποτελούν σημαντική θεραπεία για την υπέρταση και τις επιπλοκές αυτής όπως είναι η αρτηριακή σκληρία, η υπερτροφία της αριστεράς κοιλίας και η μικροαλβουμινουρία. Για το σκοπό αυτό, οι ερευνητές αναζητούν νέα φάρμακα αυτής της κατηγορίας και σε μια τέτοια ερευνητική προσπάθεια ανακαλύφθηκε η αζιλσαρτάνη. Αυτός ο προσφάτως εγκεκριμένος ανταγωνιστής των υποδοχέων αγγειοτενσίνης έχει παρόμοιες φαρμακολογικές ιδιότητες με τα υπόλοιπα φάρμακα αυτής της κατηγορίας, φαίνεται όμως να είναι ακόμη πιο αποτελεσματικός στη θεραπεία της υπέρτασης. Σε αυτήν την συστηματική ανασκόπηση θα μελετηθούν η φαρμακολογία, οι ανεπιθύμητες ενέργειες και οι διαφορές με άλλα αντιυπερτασικά της ίδιας κατηγορίας ως προς την αποτελεσματικότητα στη μείωση της αρτηριακής πίεσης.

Λέξεις ευρετηρίου: αζιλσαρτάνη, ανταγωνιστής υποδοχέα αγγειοτενσίνης ΙΙ, σύστημα ρενίνης-αγγειοτενσίνης-αλδοστερόνης, υπέρταση

***Στοιχεία υπεύθυνου συγγραφέα: Αναπληρωτής Καθηγητής Β. Κώτσης**
Γ' Πανεπιστημιακή Παθολογική Κλινική ΑΠΘ, Ιατρείο Υπέρτασης-24ωρης καταγραφής της αρτηριακής πίεσης, Νοσοκομείο Παπαγεωργίου, Θεσσαλονίκη
Τηλ.: 6974748860, E-mail: vkotsis@auth.gr

References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics-2010 update: A report from the American Heart Association. *Circulation* 2010, 121:e46–e215
2. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *Journal of Hypertension* 2013, 31:1281–1357
3. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000, 356: 1955–1964
4. Munger MA. Use of angiotensin receptor blockers in cardiovascular protection: Current evidence and future directions. *P T* 2011, 36:22–40
5. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomized trial against atenolol. *Lancet* 2002, 359:995–1003
6. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomized trial. *Lancet* 2004, 363:2022–2031
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001, 345:1667–1675
8. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function taking angiotensin-converting enzyme inhibitors: The CHARM–Added trial. *Lancet* 2003, 362:767–771
9. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001, 345:861–869
10. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001, 345:851–860
11. Kohara Y, Imamiya E, Kubo K, et al. A new class of angiotensin II receptor antagonists with a novel acidic bioisostere. *Bioorganic Medicinal Chemistry Letters* 1995, 5:1903-1908
12. Product Information: Edarbi oral tablets, azilsartan medoxomil oral tablets. Takeda Pharmaceuticals America, Inc., Deerfield, IL, 2011
13. Kohara Y, Kubo K, Imamiya E, et al. Synthesis and angiotensin II receptor antagonistic activities of benzimidazole derivatives bearing acidic heterocycles as novel tetrazole bioisosteres. *J Med Chem* 1996, 39:5228–5235
14. Center for Drug Evaluation and Research [website on the Internet]. Silver Spring, MD: NDA 200-796: Azilsartan medoxomil, Clinical Pharmacology and Biopharmaceutics Review(s). 2010. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200796Orig1s000ClinPharmR.pdf
15. Edarbi (azilsartan medoxomil) prescribing information, Takeda Pharmaceuticals America, Inc. 2012.
16. Takeda Pharmaceuticals North America. Edarbi prescribing information. 2011
17. 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, 336:801–808
18. 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
19. Kajiya T, Ho C, Wang J, et al. Molecular and cellular effects of azilsartan: A new generation angiotensin II receptor blocker. *J Hypertens* 2011, 29:2476–2483
20. Hussain N, Chaudhry W, Ahlberg AW, et al. An assessment of the safety, hemodynamic response, and diagnostic accuracy of commonly used vasodilator stressors in patients with severe aortic stenosis. *J Nucl Cardiol* 2016
21. Nadir MA, Wei L, Elder DH, et al. Impact of Re-

nin-Angiotensin System Blockade Therapy on Outcome in Aortic Stenosis. *Journal of the American College of Cardiology* 2011, 58:570-576

22. Clinicaltrials.gov. Efficacy and safety of azilsartan medoxomil co-administered with chlorthalidone in participants with essential hypertension. Study NCT00591773. Available from: http://clinicaltrials.gov/ct2/show/NCT00591773?term=NCT00591773&rank=1
23. Rakugi H, Nakata E, Sasaki E, et al. Evaluation of the Efficacy an Tolerability of Fixed-Dose Combination Therapy of Azilsartan and Amlodipine Besylate in Japanese Patients With Grade I to II Essential Hypertension. *Clinical Therapeutics* 2014, 36:711-721
24. Weber M, White W, Sica D, et al. Effects of combining azilsartan medoxomil with amlodipine in patients with stage 2 hypertension. *Blood Pressure Monitoring* 2014, 19:90–97
25. Bakris G, Sica D, Weber M, et al. The Comparative Effects of Azilsartan Medoxomil and Olmesartan on Ambulatory and Clinic Blood Pressure. *J Clin Hypertens* 2011, 13:81–88
26. Sica D, White W, Weber M, et al. Comparison of the Novel Angiotensin II Receptor Blocker Azilsartan Medoxomil *vs* Valsartan by Ambulatory Blood Pressure Monitoring. *J Clin Hypertens* 2011, 13:467–472
27. White W, Weber M, 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, 57:413-420
28. Rakugi H, Kario K, Enya K, et al. Effect of azilsartan versus candesartan on nocturnal blood pressure variation in Japanese patients with essential hypertension. *Blood Pressure* 2013, 22: 22–28
29. Bonner G, Bakris G, Sica D, et al. Antihypertensive efficacy of the angiotensin receptor blocker azilsartan medoxomil compared with the angiotensin-converting enzyme inhibitor ramipril. *Journal of Human Hypertension* 2013, 27:479–486
30. Schiffrin E, Park J, Inteng H. Correction of Arterial Structure and Endothelial Dysfunction in Human Essential Hypertension by the Angiotensin Receptor Antagonist Losartan. *Circulation* 2000, 101:1653-1659
31. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008, 372: 1174-1184
32. Cohn JN, Tognoni G. A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure. *N Engl J Med* 2001, 345:1667-1675
33. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: The candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000, 321:1440-1444
34. Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011, 364: 907–917
35. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001, 345:870–878
36. The ONTARGET Investigators, Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *N Engl J Med* 2008, 358:1547-1559