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Angiotensin Type 1 Receptor Blockers in Heart Failure

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Abstract

Homeostasis in the cardiovascular system is maintained by physiological functions of the Renin Angiotensin Aldosterone System (RAAS). In pathophysiological conditions, over activation of RAAS leads to an increase in the concentration of Angiotensin II (AngII) and over activation of Angiotensin Type 1 Receptor (AT_1R), resulting in vasoconstriction, sodium retention and change in myocyte growth. It causes cardiac remodeling in the heart which results in left ventricular hypertrophy, dilation and dysfunction, eventually leading to Heart Failure (HF). Inhibition of RAAS using angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has shown to significantly reduce morbidity and mortality due to HF. ACEi have been shown to have higher drug withdrawal rates due to discomfort when compared to ARBs; therefore, ARBs are the preferred choice of physicians for the treatment of HF in combination with other anti-hypertensive agents. Currently, eight ARBs have been approved by FDA and are clinically used. Even though they bind to the same site of AT_1R displacing AngII binding but clinical outcomes are significantly different. In this review, we described the clinical significance of each ARB in the treatment of HF and their clinical outcome.

Keywords

AT_1R; AngII; angiotensin receptor blockers; heart failure; cardiovascular diseases; hypertension; GPCRs

1. INTRODUCTION

Renin angiotensin aldosterone system (RAAS) is a major hormonal system in the body which regulates blood pressure and sodium homeostasis [1, 2]. Its major components are – angiotensinogen (Agt), renin, angiotensin converting enzyme (ACE) and angiotensin type 1 and 2 receptors (AT_1R and AT_2R) [3]. Agt is a globular protein (α2-globulin) from the serpin family, primarily produced in the liver and released into the circulation [4, 5]. The juxtaglomerular cells in the kidneys convert a proenzyme called pro-renin into a fully active

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enzyme renin which is released into the circulation when renal blood flow is reduced. Renin converts angiotensinogen to angiotensin I (AngI), a deca-peptide (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu) inactive hormone precursor by cleaving on the N-terminal side of the protein. AngI is then further converted into the active octa-peptide (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu) hormone angiotensin II (AngII). AngII is produced when ACE, primarily found in lung vascular endothelial cells, cleaves two residues on the C-terminal side of AngI [6, 7]. The active peptide hormone AngII binds to AT_1R and induces a conformational change to recruit hetero-trimeric G-proteins ($G_{\alpha\text{-}\beta\text{-}\Upsilon}$). After G-proteins fall from the receptor, G-protein couple receptor kinases called GRKs phosphorylate the receptor and recruit β-arrestin. After recruitment of β-arrestin by the receptor, it initiates receptor desensitization [8]. Simultaneously, the hetero-trimeric G-protein subunits are split into two parts, G_α and $G_{\beta\Upsilon}$. $G_{\beta\Upsilon}$ remains in the plasma membrane and G_α activates an enzyme called phospholipase C (PLC) in the cytosol. PLC cleaves a phospholipid Phosphatidylinositol 4, 5-bisphosphate (PIP_2), which is a minor component of cell membrane into diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). DAG remains bound to the membrane but IP_3 binds to the IP_3 receptor (a component of Ca^{2+} channel) in the smooth endoplasmic reticulum and releases Ca^{2+} which is required for vasoconstriction, hence blood pressure (BP) is elevated [6–8].

In pathophysiological conditions, there is chronic activation of AT_1R by AngII. This leads to over activation of the receptor and subsequently results in high BP, sodium and water retention, neurohumoral activation, and increased vascular ROS production [9–12]. Chronic activation of the receptor also leads to cardiac hypertrophy which causes thickening of the cardiac wall. This phenomenon leads to the development of diastolic and systolic dysfunction which are associated with cardiac morbidity and mortality. Enhanced over-activation of the receptor also leads to increase in ROS production and decrease in NO generation leading to endothelial dysfunction [13, 14]. The combination of these two abnormalities leads to decrease in cardiac output [13, 14]. It causes activation of neurohormonal stimulation, resulting in an increase of circulating catecholamines and AngII, inducing a cascade of events leading to impairment of downstream signaling outcomes including loss of tissue contraction in heart [15]. This increases pre- and post-load in the heart leading to heart failure. Therefore, inhibiting RAAS or blocking AT_1R is proposed to control these abnormalities. Angiotensin-converting enzyme inhibitors (ACEi) have limitations when compared with ARBs, this includes – ACEi causing side effects in some patients like dry cough and leading to prejunctional nor-epinephrine release, ARBs are highly specific to AT_1R and the beneficial physiological functions of AT_2R are unopposed [16, 17].

In this review, we will discuss the importance of ARBs in heart failure. Until now, eight ARBs have been approved by the FDA. They are azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. These ARBs are all highly specific to AT_1R and show poor binding to AT_2R.

2. STRUCTURE OF AT_1R

AT_1R is a seven transmembrane G-protein couple receptor. The structure of AT_1R was first solved with an antagonist ZD7511 (Pdb id: 4yay) [18] and the clinically used ARB olmesartan (Pdb id: 4zud) [19]. Singh *et al.,* 2017, extensively studied the binding pattern of clinically used ARBs using molecular docking and dynamic simulations and found that all ARBs bind to the same site and reported that two acid moieties are required for binding to AT_1R [18, 20]. The major residues involved in ARBs binding are Tyr35, Trp84, Tyr87, Tyr92, Arg167 and Tyr282 (Fig. 1). The mutation of these residues completely abolished the binding of ARBs and AngII. Radiolabelled binding experiments testing ARBs binding to membranes were isolated from HEK-293 AT_1R expressing cells and demonstrated that telmisartan has the highest binding affinity [20]. Recently, an active state structure of AT_1R bound with SI-AngII (Pdb id: 6do1) was also solved [21]. This study reports that the orthosteric site becomes smaller when bound with SI-AngII and the position of helix-8 embedded in the membrane is different from the ZD7511 structure and it projects into cytosol [21]. The molecular mechanism of how AngII activates the receptor has also been studied recently using molecular dynamic simulations [22].

3. ANGIOTENSIN RECEPTOR BLOCKERS (ABRs)

ARBs are broadly classified into two types based on their chemical structures (Fig. 2). They are either bi-phenyl tetrazole analogues or non-biphenyl tetrazole analogues. The bi-phenyl tetrazole analogues are azilsartan, candesartan, irbesartan, losartan, olmesartan and valsartan and non-biphenyl tetrazole analogues are eprosartan and telmisartan [20]. Even though all ARBs bind to the same receptor, each has different clinical outcomes. The binding affinity of ARBs with AT_1R is in ascending order as follows: telmisartan, candesartan, olmesartan, irbesartan, azilsartan, eprosartan, losartan and valsartan [20].

3.1. Losartan

Losartan was the first discovered ARB and it is a prodrug [23]. Losartan is quickly metabolized into Exp3174 by the liver enzyme CYP2C9. E3174 is responsible for the long-lasting effect of losartan and selective blockage of AT_1R [24]. ACEi were frequently used but not considered the first choice of physicians for heart failure treatment due to their severe side effects. Therefore, ELITE (Evaluation of Losartan in Elderly) study was performed to study the effect of losartan in heart failure patients due to its similar mechanism of action. The result shows an unexpected survival benefit in elderly heart-failure patients, compared with ACEi (captopril). This led to the ELITE II study with a bigger sample size and found that losartan was not superior to captopril in elderly heart-failure patients but was better tolerated, suggesting that losartan is a good option [25]. However, Svanstrom *et al.,* (2012) reported that a low dose of losartan is associated with higher mortality rate in heart failure patients [26]. Losartan in low or high doses has additional beneficial hemodynamic effects which are observed after 12 weeks of therapy [27].

3.2. Azilsartan

Azilsartan was approved by the FDA in 2011 and used for oral administration as Azilsartan Medoxomil to control high BP [28]. It has an inverse agonistic property and therefore it is clinically significant. It has been shown to better control ambulatory or clinical BP when compared with olmesartan or valsartan [29]. Heart failure patients with high BP show improved diastolic function with azilsartan treatment [30]. Nakamura *et al.*, (2013) observed that azilsartan suppressed cardiac remodeling in post-myocardial infarction (MI) patients without lowering BP [31]. Azilsartan is shown to be better in controlling BP in pre-diabetic and type 2 diabetes mellitus patients suggesting that azilsartan could be an important drug that could reduce morbidity and mortality related to cardiovascular diseases associated with diabetes [32–34].

3.3. Candesartan

Candesartan Cilexetil is orally administered and quickly metabolized as candesartan and absorbed in the gastrointestinal tract [24]. It is shown to significantly reduce mortality due to chronic heart failure in low left ventricular ejection fraction (LVEF) trail with candesartan therapy in combination with other antihypertensive drugs [35–39]. A systematic review on Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) studies reveals that candesartan is a safe and effective option for patients with systolic heart failure [40]. Candesartan therapy has improved heart failure (HF) with mid-range ejection fraction [40].

3.4. Eprosartan

Eprosartan is a well-tolerated AT_1R blocker which is very effective in controlling BP as well as providing secondary prevention of cerebrovascular events [24]. It can be used to correct hypercoagulatory syndrome in chronic kidney disease. It has an inhibitory effect on sympathetic nervous activity compared to other ARBs [41] suggesting that it may have beneficial effects in post-MI patients where RAAS is upregulated. Eprosartan better blocked the development of cardiac hypertrophy in rats with aortocaval fistula than the ACEi (enalapril) [42]. Studies have also shown that administration of eprosartan reduces catecholamine release in animal models [43]. It also reduces cardiac hypertrophy which is an index of heart failure, protects renal structural integrity and prevents end-organ failure due to high BP and ultimately reduces mortality [44, 45]. Suzuki *et al.*, (2003) reported that the administration of eprosartan prevents left ventricular dystrophy in dogs with heart failure [46].

3.5. Irbesartan

Irbesartan is taken orally and it is very effective in controlling BP. In addition to its BP-lowering effect, it can also activate $PPAR_\Upsilon$ which has been shown to improve insulin intolerance and aid patients who suffer from metabolic abnormalities such as atherosclerosis [24]. Therefore, it may have indirect effects on heart failure associated with other metabolic disorders. Several studies including I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Study) have been performed to study the effect of irbesartan in ejection fraction (EF) in heart failure patients and found that there was no significant

improvement [47, 48]. Furthermore, no significant effect was seen in the improvement of morbidity and mortality in HF patients [47]. However, irbesartan treatment significantly reduced aldosterone hormone compared to a benazepril treatment group of older patients [49]. It has also been reported that irbesartan has a cardio-protective effect in post-MI patients who have renal dysfunction [50]. Irbesartan in combination with metoprolol and hydrochlorothiazide with non-invasive ventilator in the emergency treatment of severe HF patients improved cardiac function and restored respiratory function [51].

3.6. Olmesartan

Olmesartan is an orally administered drug which is very effective in controlling BP. It has shown to improve insulin sensitivity and produce anti-atherogenic and anti-inflammatory effects in patients with diabetic nephropathy [52]. It has also shown to have beneficial effects in HF patients with preserved left ventricular ejection fraction in combination therapy with beta blockers [53] but no benefits were observed in olmesartan monotherapy in a SUPPORT TRIAL [54]. Animal experiments have shown that olmesartan therapy could be beneficial in combating inflammation, oxidative stress, apoptosis in signaling pathways associated with HF [55, 56]. Long term therapy of olmesartan led to improved clinical outcomes, and it may also produce cerebro- and cardio-vascular events by changing the atheroma volume [57]. SUPPORT TRIAL also observed that triple combination therapy with ACEi and beta-blockers is significantly associated with increased cardiac events [54]. Padwal *et al.*, (2014) observed that olmesartan therapy may contribute to worsened diabetes in patients with a history of cardio-vascular diseases and chronic kidney diseases and suggest caution in olmesartan use [58].

3.7. Telmisartan

Telmisartan is among the widely used anti-hypertensive agents which can effectively control BP [24]. It has the longest plasma half-life, highest lipophilicity and strongest binding to the receptor [20, 24]. A recent meta-analysis and systematic review have shown that telmisartan therapy can improve insulin resistance when compared to other ARBs [59, 60]. This property of telmisartan is known to activate $PPAR_{\Upsilon}$ and mediate insulin sensitization and it also has renal anti-inflammatory and anti-oxidant effects [61]. It can also reduce the CVD risks in patients with atherothrombotic disease or diabetes with end-organ damage. It was also reported that telmisartan monotherapy was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema but the combination of two drugs was associated with adverse events without any benefits [62] however it significantly reduced all-cause mortality, cardiovascular death, and hospital admission for decompensated heart failure in hemodialysis patients with chronic HF and left ventricular ejection fraction [63]. Therefore, telmisartan is better tolerated and could be regarded as a potential treatment for patients with vascular disease or high-risk diabetes, if ACEi is not tolerated [64]. The Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND) found that MI may be further reduced by telmisartan in hypertensive patients [65]. In rats, treatment with telmisartan is associated with significantly improved left ventricular function and it ameliorated the progression of cardiac remodeling with chronic HF after experimental autoimmune myocarditis [66]. In other studies, telmisartan has shown to decrease the serum

copeptin level and alleviated inflammatory reactions, leading to improved heart function in chronic HF patients [67]. On the other hand, it can also increase the serum Adiponectin (APN) levels and significantly reverse the left ventricular remodeling while reducing the blood pressure [68]. It is more effective in reducing Left Ventricular Remodeling and kidney disorders than enalapril treatment for patients with coronary artery disease with diabetic nephropathy [69].

3.8. Valsartan

Valsartan has been shown to be very effective in controlling high BP and it is well-tolerated [24]. In rats, valsartan has been shown to inhibit Hypoxia Inducible Factor (HIF)-1α mediated gene activation and decreases the pathogenic factors in diabetic nephropathy, preventing renal damage [70]. Val-HeFT result has shown significant reduction in morbidity and mortality in the total patient population, reduced the risk of hospitalization [71], and reduced HF-related hospitalization in addition to valsartan-prescribed HF therapy [72]. A significant reduction in aldosterone concentrations in pigs was also observed when using valsartan and benazepril combination therapy [73]. Valsartan therapy was effective in decreasing the frequency of atherosclerotic events such as fetal and non-fatal myocardial infarction, angina, revascularization and stroke, similar to ACEi [74]. However, in elderly patients, hypotension, renal dysfunction and hyperkalemia were more common [74, 75]. Combination therapy results in severe adverse event and no improvement in survival or morbidity were observed in VALIANT trail [74]. Therefore, valsartan could be an alternative to ACEi intolerant patients but shows no improvement in combined therapy with ACEi in post-MI patients. However, extensive studies are currently undergoing testing for combination therapy of valsartan with sacubitril for the treatment of heart failure and have shown some promise [76, 77].

CONCLUSION

Inhibition of RAAS in HF patients significantly decreased morbidity and mortality. ACEi remains the first choice of therapy [78]. ACEi are favored over ARBs due to a study which showed that ACEi can prevent coronary artery diseases in addition to controlling BP [79–81]. ACEi have higher withdrawal due to intolerance. ARBs have significantly lower withdrawal rates than ACEi and most of the ARBs are nearly as effective as ACEi in the treatment of HF. Hence, choosing ARBs as the first line of therapy for the pathophysiology underlying HF significantly reduces morbidity and mortality. All ARBs are very effective at blocking AT_1R and reducing blood pressure; however there are notable differences in their efficacy against tissue pathogenesis and related clinical outcomes. Even though all ARBs are as effective as ACEi in the treatment of HF. Out of eight FDA approved ARBs, irbesartan and telmisartan have shown $PPAR_\Upsilon$ agonistic properties resulting in improved insulin intolerance. Olmesartan treatment also improves insulin sensitivity and produces anti-atherogenic and anti-inflammatory effects in patients with diabetic nephropathy. All the ARBs demonstrate beneficial effects similar to ACEi in the treatment of HF except lower doses of losartan which leads to increased mortality in HF patients. Valsartan in combination with sacubitril therapy proved to be a promising therapy for HF. Eprosartan has an effect on the sympathetic nervous system when compared to other ARBs and it is also able to reduce

catecholamine release in animal models. Therefore, eprosartan therapy may have an additional beneficial effect in the treatment of heart failure. However, eprosartan has the shortest bioavailability (< 6 hours) when compared to other ARBs. Large number of studies that show beneficial effects on animals have been reported but there are limited studies on humans. Hence, more human studies are warranted. Recently, crystal structures of AT_1R in inactive and active state structures have been solved. Using these crystal structures and cheminformatics tools, exploring structures similar to eprosartan with an increase in bioavailability and affinity may enhance the treatment of HF.

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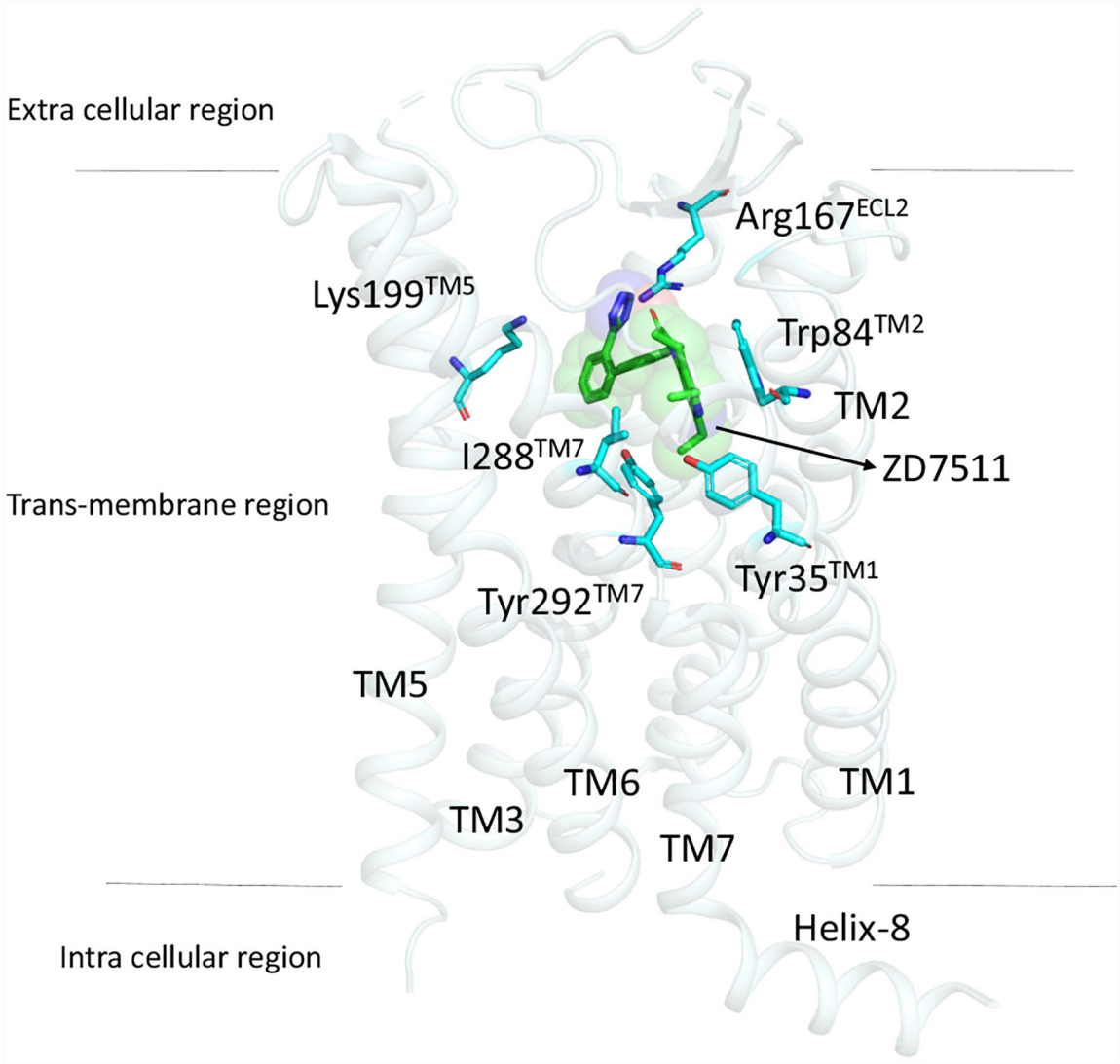

Fig. (1).

Binding mode of ZD7511 in the orthosteric site of AT_1R with residues critical for all ARBs binding. All the ARBs share similar binding residues (detail see reference 20).

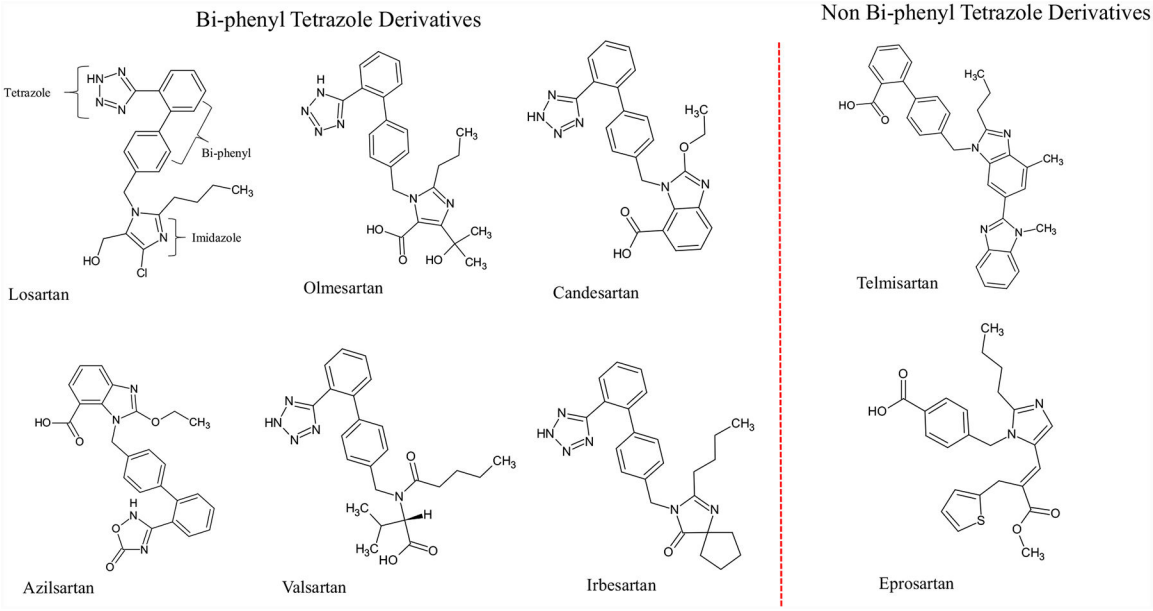

Fig. (2).
Chemical structures of eight FDA approved clinically used ARBs.