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Abstract: Since the launch of the first orally available angiotensin II (AngII) type 1 receptor (AT₁R) blocker (ARB) losartan (Cozaar) in the late 1990s, the class of ARBs (or ‘sartans’, short for Angiotensin-Receptor-AntagonistS) quickly expanded to include candesartan, eprosartan, irbesartan, valsartan, telmisartan, and olmesartan. All ARBs have high affinity for the AT₁ receptor, expressed in various tissues, including smooth muscle cells, heart, kidney, and brain. Since activation of AT₁R, the target of these drugs, leads, among other effects, to vascular smooth muscle cell growth, proliferation and contraction, activation of fibroblasts, cardiac hypertrophy, aldosterone secretion from the adrenal cortex, thirst-fluid intake (hypervolemia), etc., the ARBs are nowadays one of the most useful cardiovascular drug classes used in clinical practice. However, significant differences in their pharmacological and clinical properties exist that may favor use of particular agents over others within the class, and, in fact, two of these drugs, candesartan and valsartan, continuously appear to distinguish themselves from the rest of the ‘pack’ in recent clinical trials. The reason(s) for the potential superiority of these two agents within the ARB class are currently unclear but under intense investigation. The present short review gives an overview of the clinical properties of the ARBs currently approved by the United States Food and Drug Administration, with a particular focus on candesartan and valsartan and the areas where these two drugs seem to have a therapeutic edge. In the second part of our review, we outline recent data from our laboratory (mainly) on the molecular effects of the ARB drugs on aldosterone production and on circulating aldosterone levels, which may underlie (at least in part) the apparent clinical superiority of candesartan (and valsartan) over most other ARBs currently in clinical use.

Keywords: adrenal gland, aldosterone, angiotensin receptor blocker, clinical comparison, heart disease, heart failure, pharmacotherapy

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Introduction

The first angiotensin II (AngII) type 1 receptor (AT₁R) blocker (ARB) or sartan (short for Angiotensin-Receptor-Antagonist) approved by the United States Food and Drug Administration (FDA) for hypertension was losartan in the 1990s, rapidly followed by candesartan, eprosartan, irbesartan, valsartan, telmisartan, and olmesartan. The ARBs bind the AT₁R with high affinity.¹ ARBs were developed to complement the efficacy of angiotensin converting enzyme inhibitors (ACEIs) and to also do away with the major adverse effects of the latter drug class, that is, dry cough, thought to result from elevation of proneuro-inflammatory

bradykinin levels in the lungs (ACE activates bradykinin from precursor kinins and the vast lung endothelium is particularly rich in this enzyme), and angioedema (also kinin-dependent).² ACEIs do not completely abrogate AngII production in the body, as synthesis of this peptide hormone can occur *via* alternative enzymatic pathways, such as chymase and other tissue-based proteases.³ These alternative pathways can become upregulated upon long-term ACEI use, resulting in reduced antihypertensive efficacy. The hemodynamic effects of ARBs are similar to those of ACEIs. Because AngII is a very potent vasoconstrictor peptide (second most potent endogenous

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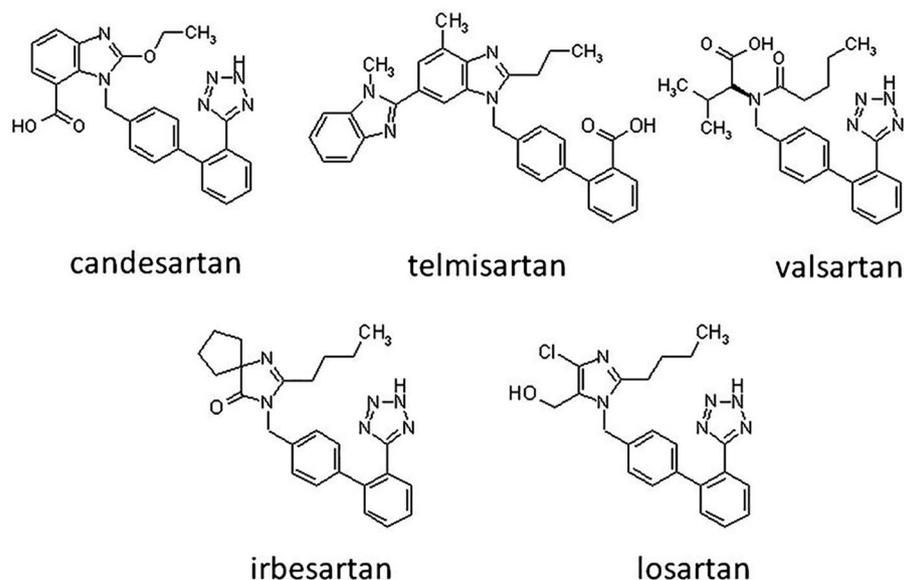


Figure 1. Chemical structures of the individual angiotensin II [AngII] type 1 receptor (AT₁R) blockers (ARBs) discussed extensively in the present review.

vasoconstrictor hormone behind endothelin), AT₁R blockade leads to vasodilation and reduction in total peripheral resistance (i.e. cardiac afterload) and blood pressure lowering.⁴ Cardiac output remains unchanged. Despite BP lowering, heart rate remains unchanged, and there is no postural hypotension, likely because ARBs reset baroreceptor function.⁴

Like ACEIs, ARBs are able to protect target organs in hypertensive patients. Indeed, long-term administration of ARBs reduces left ventricular hypertrophy, improves endothelial function, induces destiffening of large arteries and reverse remodeling of large and small arteries.^{5–7} Relaxation of large arteries leads to lowering of central systolic and pulse pressures.⁸ Renal protection is observed in early diabetic nephropathy, and proteinuria is reduced independently of the hypotensive effect.^{9,10} ARBs are contraindicated in pregnancy, in the presence of hyperkalemia, and in bilateral renal artery stenosis.¹¹ ARBs differ in their AT₁R binding kinetics. Candesartan is known to confer insurmountable (noncompetitive) antagonism at the receptor thanks to the carboxyl group attached to its benzimidazole side-chain (Figure 1).¹² However, telmisartan, which lacks this carboxyl moiety, and valsartan, which has it but lacks the benzimidazole ring, also exhibit noncompetitive antagonism of the AT₁R

(Figure 1).¹² In addition, candesartan and valsartan are known to stabilize the AT₁R in its inactive conformation, that is, they are, in essence, inverse agonists.^{10–13} All ARBs in clinical use are >10,000-fold selective for the AT₁R *versus* AT₂R, with candesartan being among the most AT₁R-selective agents.^{13–16}

Clinical comparison of ARB agents

In a meta-analysis of 14 studies, comprising 8 on hypertensive patients and 6 on heart failure (HF) patients, candesartan was found to induce a (albeit slightly) greater extent of blood pressure reduction compared with losartan.¹⁷ Nevertheless, this difference was deemed unlikely to be cost effective. In HF patients, both ARBs were found more or less equieffective at symptomatic improvement.¹⁸ In one study, however, candesartan was found superior to losartan in terms of mortality and hospitalization rate reductions, although the fact that the losartan might have been underdosed in the patients of this study casts doubt on its conclusions.¹⁹ Unfortunately, clinical head-to-head comparisons between other ARB agents, or between candesartan or losartan *versus* any other ARB agent, are still lacking.

An interesting new angle on the therapeutic efficacy of ARBs for HF was provided recently with

the approval and market entry of Novartis's Entresto® (sacubitril/valsartan), the first first-in-class drug to be approved by the FDA for HF treatment in more than two decades.^{20–23} In this drug, the potent ARB valsartan is combined with sacubitril, which is a neprilysin (NEP) inhibitor. NEP is a neutral endopeptidase that degrades natriuretic peptides and other vasodilating peptides, for example, substance P and bradykinin, as well as vasoconstricting peptides, for example, endothelin and AngII.²⁴ In fact, exactly because NEP inhibition can increase AngII levels, sacubitril and all NEP inhibitors have to be combined with an ARB for HF treatment.²⁴ The 1:1 stoichiometric combination of sacubitril and valsartan was shown to confer additional clinical benefit in HF with reduced ejection fraction (HFrEF) patients on top of their standard treatment. Importantly, NEP inhibition with sacubitril seems to provide clinical benefits that valsartan (Diovan) alone cannot, including reduction in the left atrial size, reverse left atrial remodeling, and New York Heart Association (NYHA) class improvement.^{21,23} In the PARADIGM trial, which pivoted Entresto® into regulatory approval in the US and in Europe, sacubitril/valsartan conferred benefits for HFrEF patients, significantly reducing morbidity and mortality compared with enalapril.²¹ The molecular mechanisms underlying the additional clinical benefits of NEP inhibition when added to the ARB valsartan are presently unknown. Interestingly, however, modulation of aldosterone levels (see below) might be a major part of this mechanism, since natriuretic peptides inhibit aldosterone secretion from the adrenal cortex, which means that NEP promotes it while degrading AngII, the major physiological stimulus for adrenal aldosterone secretion (again, see below), at the same time.^{25–28} It is thus plausible that an ARB (e.g. valsartan) alone is insufficient to fully suppress aldosterone in HFrEF, due to elevated overall (and obesity-specific) NEP activity, and the addition of a NEP inhibitor (such as sacubitril in Entresto®) helps produce the additional aldosterone suppression necessary to confer substantial clinical benefits in human HFrEF. In other words, the degree of adrenal-derived aldosterone suppression may hold the mechanistic key to Entresto®'s clearly demonstrated clinical benefits in HF. This, of course, remains to be validated in clinical trials of HF patients

treated with Entresto® and assessing/comparing their circulating aldosterone levels *versus* patients treated with valsartan (or some other ARB) without a NEP inhibitor.

Effects of ARBs on aldosterone production

AngII, alongside hyperkalemia, is the most powerful physiological stimulus for adrenocortical aldosterone synthesis and secretion. This effect is mediated by the adrenocortical AT₁R, which is a G protein-coupled receptor (GPCR) that can signal to aldosterone production *via* two independent pathways: a well-established G protein-dependent pathway, *via* generation of the second messengers diacylglycerol and inositol trisphosphate, which ultimately upregulate StAR (steroidogenic acute regulatory) protein, and β -arrestin-1 (also known as Arrestin-2), which also can upregulate StAR in the adrenal cortex *via* ERK activation (Figure 2).^{29,30} Full blockade of both pathways is required to suppress adrenal aldosterone production completely.^{31,32} Interestingly, several ARBs have been reported to be ineffective at lowering aldosterone in HF, despite completely blocking the AT₁R-G protein interaction.^{33–38} This has prompted recent screenings of ARB efficacies at inhibiting the β -arrestin-1-dependent aldosterone production. Losartan was found largely ineffective at blocking β -arrestin-1-dependent aldosterone production and at combatting hyperaldosteronism in animal models of HF due to very weak adrenal β -arrestin-1 inhibition.^{30,39} In contrast, losartan's active metabolite (EXP1374) was an effective suppressor of β -arrestin-1-dependent aldosterone.³⁹ Regarding the rest of the currently FDA-approved ARBs, candesartan and valsartan were found the most potent blockers of adrenal β -arrestin-1-dependent aldosterone both *in vitro* and *in vivo* (Figure 2).^{39,40} Conversely, irbesartan, similarly to losartan, was a very weak β -arrestin-1 inhibitor, and, thus, ineffective at suppressing aldosterone, despite its excellent G protein-inhibitory activity (Figure 2).^{39,40} Importantly, the effects of these ARBs on cardiac function of HF animals *in vivo* followed closely their effects on circulating aldosterone levels, that is, candesartan and valsartan induced significant improvements in cardiac function and adverse remodeling, whereas irbesartan and losartan were unable to halt progression of myocardial infarction to full-blown HF in rats.⁴⁰

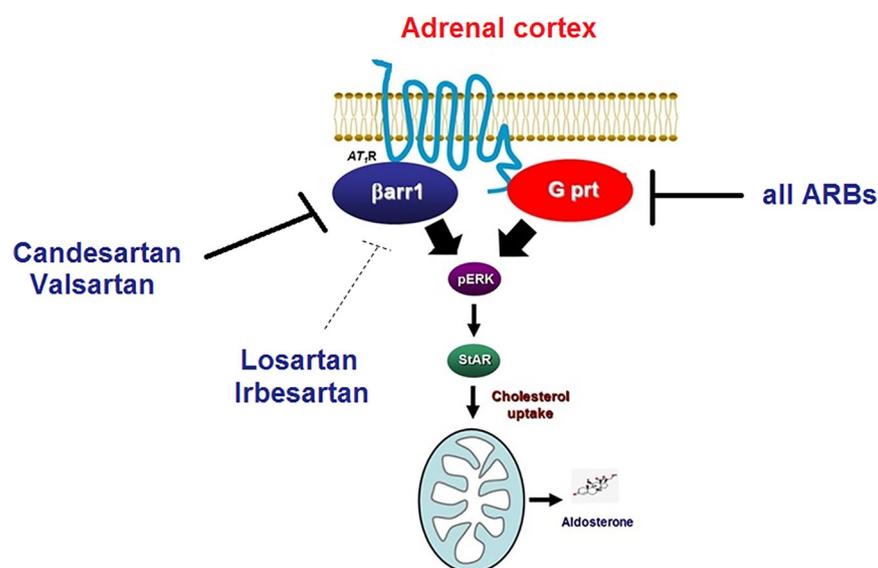


Figure 2. The two components of adrenocortical aldosterone production and the degree of their inhibition by ARBs.

AT₁R, Angiotensin II type 1 receptor; βarr1, β-arrestin-1; G prt, G protein; pERK, phospho-extracellular signal-regulated kinase; StAR, Steroidogenic Acute Regulatory protein. The solid black inhibition sign denotes potent inhibition. The dashed black inhibition sign denotes weak inhibition.

Although virtually next to nothing is known about the structural requirements for β-arrestin agonism or inverse agonism, it is interesting to point out that both of the weak β-arrestin-1-dependent aldosterone inhibitors irbesartan and losartan lack the side-carboxyl group present in the potent β-arrestin-1-dependent aldosterone inhibitors candesartan and valsartan (Figure 1). Moreover, EXP1374, losartan's active metabolite that potently inhibits β-arrestin-1-dependent aldosterone,³⁹ also has this carboxyl moiety. It is thus tempting to speculate that carrying a second negative charge (in addition to the indispensable tetrazole ring that mimics the Phe8 C-terminus of AngII) is essential not only for binding the orthosteric site of AT₁R, thereby sterically blocking receptor interaction with AngII,⁴¹ but also potentially for β-arrestin inverse agonism. The stereochemical space ('bulkiness') occupied by the side moieties has to be taken into account as well; for instance, a recent study demonstrated the effect of the bulkiness of the Ile5 side-chain in AngII on β-arrestin agonism at the AT₁R.⁴²

In conclusion, based on the above, the ARBs that suppress aldosterone (including adrenal β-arrestin-1-dependent aldosterone) most effectively (e.g. candesartan, valsartan) might work better for HF therapy. In contrast, irbesartan and losartan, both

weak adrenal β-arrestin-1-dependent aldosterone inhibitors, might be therapeutically inferior for clinical HFrEF in terms of morbidity/mortality reduction.^{43–45} Of course, data on serum aldosterone levels of ARB-treated HF patients are required to confirm or refute this mechanistically derived pharmacological rationale. Moreover, the degree of adrenal β-arrestin-1-dependent aldosterone inhibition conferred by each individual ARB drug might have a bearing on the 'aldosterone breakthrough' or 'aldosterone escape' phenomenon, which basically describes the long-term failure to suppress circulating aldosterone.^{36–38} In other words, the more potent adrenal β-arrestin-1-dependent aldosterone suppression an ARB induces, the less its propensity for 'aldosterone breakthrough' manifestation. Indeed, there is already some experimental evidence pointing to adrenal β-arrestin-1 as a possible culprit for the 'aldosterone breakthrough' or 'aldosterone escape' phenomenon observed with ARBs: a decade-old study on candesartan-dependent suppression of AngII-induced aldosterone secretion in human adrenocortical cells *in vitro* suggested that bone morphogenetic protein (BMP)-6 mediates the resistance of these cells to candesartan's hypoaldosteronic actions.⁴⁶ Since β-arrestins are known to enhance BMP signaling in various cell types,⁴⁷ it is

quite plausible that adrenal β -arrestin-1 activation by the AT₁R promotes AngII's pro-aldosterone effects and the adrenocortical cell's refractoriness to AT₁R blockade (with an ARB) over time, that is, the ARB-associated 'aldosterone breakthrough.' The potential role of adrenal β arrestin1 in the development of the ARB-associated 'aldosterone breakthrough' phenomenon definitely warrants further investigation in the future.

Conclusion/future perspectives

It is now clear that not all ARBs are clinically or pharmacologically equivalent. Thus, neither are they therapeutically equal, especially when the treatment of a very complex syndrome such as HF is considered. Unfortunately, studies comparing them head-to-head are very scarce and inconclusive. Based on the very limited data available as of now, certain agents (candesartan, valsartan) seem to stand out from their class both clinically and pharmacologically. In the present review, we have presented some molecular evidence for why these two ARBs in particular might be superior over others in the same class: the reason may lie in the degree of adrenal aldosterone suppression, and, more specifically, in the extent of inhibition of the adrenal β -arrestin-1 component of aldosterone production. The level of aldosterone suppression afforded may even hold the key to the apparent therapeutic success of the sacubitril/valsartan combination recently introduced into clinical practice. This hypothesis is definitely worth investigating in the future. Of course, there is currently no clinical evidence that ARBs are superior to ACE inhibitors for patients with HFrEF, and more comprehensive prospective comparative head-to-head trials of the ARBs to evaluate their relative efficacy at preventing aldosterone escape or breakthrough are definitely warranted. However, given the complex hormonal interplay underlying HF pathophysiology, in which AngII and aldosterone play prominent roles, the fields of ARB pharmacology, and, more broadly, of the renin-angiotensin-aldosterone system, are bound to keep HF specialists and cardiovascular scientists alike on edge for new discoveries and therapeutic advances for many years to come.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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