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REVIEW ARTICLE

Angiotensin II-Receptor Blockers: Current Role in Clinical Practice

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ABSTRACT

The implication of the renin angiotensin system (RAS) and specifically angiotensin II in the pathogenesis of essential hypertension, cardiac, cerebrovascular and renal disease is well established. Among the different categories of drugs that manage hypertension, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are notably effective in the downregulation of RAS. Whereas ACEIs achieve RAS inhibition by preventing the conversion of angiotensin I to angiotensin II, they can display adverse effects, such as cough and angioedema that result from the increased production of bradykinin and prostaglandin. The direct antagonistic action of ARBs on angiotensin II receptors has proved to be very well tolerated. Achieving rapid blood pressure reduction and twenty-four hour hypertension control, they may be superior to other antihypertensive agents in the regression of left ventricular hypertrophy, new onset diabetes and stroke and in the delay of renal dysfunction. The combination of ARBs with other drug categories, such as diuretics or calcium channel blockers, can provide additive effects, favoring their recommendation and use for the clinical management of hypertension and cardiovascular diseases. Meta-analyses of clinical trials have provided evidence that ARBs are comparable with other drugs against cardiovascular and all-cause mortality.

KEY WORDS: *Arterial hypertension, cardiovascular disease, renin-angiotensin system, angiotensin II, angiotensin receptor blockers*

Abbreviations
ACEI = angiotensin converting enzyme inhibitor;
ARB angiotensin receptor blocker;
CVD = cardiovascular disease;
LVH = left ventricular hypertrophy;
RAS = renin angiotensin system

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INTRODUCTION

Cardiovascular disease (CVD) is the principal cause of death and disability in industrialized Western countries. It is expected that by 2020 it will have become the leading cause of death worldwide. Among the different risk factors for CVD, arterial hypertension is the most frequent.[1] The European Society of Hypertension-European Society of Cardiology (ESH-ESC) guidelines recognize the importance of global CVD risk and stratify hypertensive subjects as being at low, moderate, high, and very high added risk, according to their family and clinical history, presence of risk factors, subclinical organ damage or established CVD.[2]

Hypertension, which can be defined as elevated blood pressure (≥140/90 mmHg) in its early stages, can provoke subtle target-organ damage, i.e. left ventricular hypertrophy, microalbuminuria and cognitive dysfunction. Catastrophic cardiovascular events, such as stroke, heart attack, renal failure and dementia, are commonly observed after a long period of uncontrolled hypertension.[3] Consequently, 24-hour blood pressure control is necessary to reduce CVD risk, particularly given that surges in blood pressure are more prevalent during the early morning hours.[2]

TABLE 1. General characteristics of clinical trials considered for the present analysis.

Clinical trial	Publication (year)	Follow-up (years)	ARB	Group (n)	Comparator	Group (n)	SBP/DBP difference (mmHg)	Reference
ELITE I	1997	1.0	Losartan	352	Captopril	370	NA	[10]
ELITE II	2000	1.5	Losartan	1.578	Captopril	1.574	NA	[11]
IDNT	2001	2.6	Irbesartan	579	Amlodipine	567	-2.0/0.0	[33]
RENAAL	2001	3.4	Losartan	751	Placebo	762	-1.0/0.0	[32]
OPTIMAAL	2002	2.7	Losartan	2.744	Captopril	2.733	NA	[28]
LIFE	2002	4.8	Losartan	4.605	Atenolol	4.588	-1.0/0.0	[17]
VALUE	2002	4.2	Valsartan	7.699	Amlodipine	7.596	2.0/2.0	[30]
SCOPE	2003	3.7	Candesartan	2.477	Placebo[a]	2.460	-3.0/-1.0	[46]
CHARM-Alternative	2003	2.9	Candesartan	1.013	Placebo	1.015	-4.4/-3.9	[48]
CHARM-Preserved	2003	3.2	Candesartan	1.514	Placebo	1.509	-6.9/-2.9	[37]
CHARM-Added	2003	3.5	Candesartan	1.276	Placebo	1.272	-4.6/-3.0	[47]
VALIANT	2003	2.7	Valsartan	4.909	Captopril	4.909	0.1/-0.9	[8]
DETAIL	2004	5.0	Telmisartan	120	Enalapril	130	NA	[19]
MOSES	2005	2.5	Eprosartan	681	Nitrendipine	671	2.8/3.8	[49]
E-COST	2005	3.1	Candesartan	1.053	CT	995	5.2/2.6	[50]
JIKEI	2007	3.1	Valsartan	1.541	CT	1.540	-0.4/-18.4	[51]
ONTARGET	2008	4.8	Telmisartan	8.163	Ramipril	8.102	-0.9/-0.6	[18]
PROFESS	2008	3.7	Telmisartan	10.146	Placebo	10.186	-3.8/-1.9	[29]
TRANSCEND	2008	4.8	Telmisartan	2.954	Placebo	2.972	-4.0/-2.2	[52]

CHARM, Candesartan cilexitil in Heart failure: assessment of Reduction in morbidity and Mortality; CT = conventional therapy (other than ACEI or ARB); DETAIL, Diabetics Exposed to Telmisartan and Enalapril; ELITE, Evaluation of Losartan In The Elderly; IDNT, Irbesartan Diabetic Nephropathy Trial; JIKEI Heart Study, Valsartan in a Japanese population with hypertension and other cardiovascular disease; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; MOSES, Morbidity and Mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention; ONTARGET; Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint; OPTIMAAL; Optimal Treatment in Myocardial Infarction with the Angiotensin II Antagonist Losartan; PRoFESS, Prevention Regimen For Effectively avoiding Second Strokes; RENAAL, Reduction in Endpoints in patients with Noninsulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan; SCOPE, Study on Cognition and Prognosis in the Elderly; VALIANT, Valsartan in Acute Myocardial Infarction Trial; TRANSCEND; Telmisartan Randomized Assessment Study in ACE intolerant patients with cardiovascular Disease.

[a]Patients of the placebo arm in this study were permitted to receive antihypertensive therapy, including ARBs.

Clinical trials have shown that with the appropriate lifestyle modification and antihypertensive medication, blood pressure control is achievable in the majority of hypertensive individuals, including those at high CVD risk.[4] Given that angiotensin II, the only effector hormone of the RAS, is implicated in the development of hypertensive disease precipitating unfavorable cardiac, vascular and metabolic effects, the pharmacological blockade of the RAS, and especially angiotensin II, is considered an integral component of the treatment for patients at high CVD risk. The RAS can be inactivated by two recognized main mechanisms: the inhibition of angiotensin I conversion to angiotensin II, or the blockade of angiotensin AT1 receptor. Over the past fifty years, mounting evidence has shown that blood pressure lowering prevents damage to the heart, brain, and kidneys. Among the different categories of drugs that manage hypertension, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are notably effective in the downregulation of RAS. In addition to the aforementioned category of drugs, aliskiren, a direct renin inhibitor and the first of a new class of antihypertensive

drugs, has been shown to block the RAS further upstream[5] (Figure). However, longer term outcome studies are necessary to evaluate the tolerability and efficacy of this agent.

It should be noted, however, that these drug categories are contraindicated during pregnancy as several cases of fetal and neonatal morbidity and death have been reported in the second or third trimester of pregnancy.[6] Caution is recommended in specific patient populations, such as those displaying volume or salt depletion, impaired hepatic or renal function, hyperkalemia or bilateral renal artery stenosis. These patients should be treated with antihypertensive drugs that do not influence the RAS.[7]

ANGIOTENSIN-RECEPTOR BLOCKERS IN CLINICAL PRACTICE

Angiotensin-receptor blockers differ from each other in their oral bioavailability, rate of absorption, tissue distribution, metabolism and rate of elimination. Several of these agents act as prodrugs converting to more biologically active metabolites. ARBs are generally administered once daily and show an excellent tolerability profile. Specifically, individuals treated with valsartan have shown greater compliance than those receiving lisinopril or amlodipine. Dry cough was reported by 7.2% of hypertensives taking lisinopril, resulting in a 1.5% withdrawal from the study. In contrast, dry cough occurred in only 1.0% of valsartan-treated patients, none of whom needed to stop treatment.[8,9] It should also be mentioned that fewer losartan-treated individuals with heart failure discontinued therapy owing to adverse events compared with those receiving captopril in the ELITE I, and ELITE II trials.[10,11]

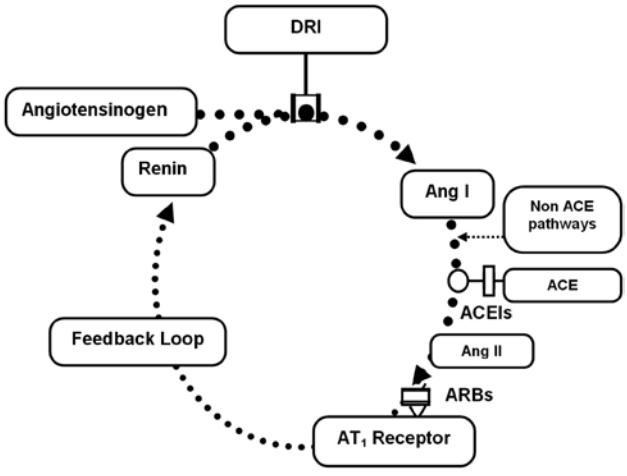

FIGURE 1. Mechanisms of action and inactivation of the RAS. ACE: angiotensin converting enzyme; ACEI: angiotensin converting enzyme inhibitor; Ang: angiotensin; ARB: angiotensin receptor blocker; AT_1: angiotensin II type1; DRI: direct renin inhibitor.

ARBs have been shown to lower blood pressure in approximately 30% to 50% of the general hypertensive population. This is on a par with other monotherapy antihypertensive drugs, such as diuretics, β-blockers and ACEI.[12,13] ARBs as monotherapy achieve optimum blood pressure normalization rates, 30.1% over a 24-hour period, as reported by a large-scale primary-care study conducted in Germany.[14] Similarly, Sharplin et al showed that ARBs surpassed other antihypertensive classes in the reduction of blood pressure.[15] Notably, blood pressure reduction has been observed after just two weeks of treatment with ARBs.[9] A meta-analysis of Blood Pressure Lowering Treatment Trialists Collaboration revealed that ARB-based regimens were superior to other comparative treatments in reducing the incidence of stroke, heart failure and other cardiovascular events.[12]

The Heart Outcomes Prevention Evaluation (HOPE)[16] and Losartan Intervention For Endpoint reduction in hypertension study (LIFE)[17] demonstrate that agents targeting the RAS confer additional benefits beyond their antihypertensive activity in the reduction of target-organ damage. The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET)[18] study reported no additional benefits of combination treatment of ACEI and ARB in the reduction of target-organ damage.

Although the mechanism of action determines a drug's class, this does not imply equality. More specifically, the different structure of the ARB telmisartan provides the longest dissociation half-life, high lipophilicity, high distribution volume and the capacity to cross the blood-brain barrier, explaining its 24-hour blood pressure effect and superiority over other ARBs, not only in reducing the early morning blood pressure surge, but also in protecting subjects at higher CVD risk.[19,20] As this drug acts as a selective activator of peroxisome proliferator-activated receptor-γ (PPARγ), there is evidence that it also has a beneficial effect on high-risk hypertensive subjects with insulin resistance or metabolic syndrome.[21] On the other hand, according to the LIFE study, the unique uricosuric properties of losartan provide an added benefit beyond the lowering of blood pressure.[17]

ARB COMBINATION THERAPY

A combination of an ARB and the *diuretic* hydrochlorothiazide achieves superior blood pressure reduction to that observed with either agent alone.[13] Combined treatment with a long-acting ARB and a long-acting *calcium channel blocker* could be effective in achieving blood pressure goals, as these agents target two different key mechanisms for blood pressure reduction, namely the angiotensin-receptor and calcium-channel blockade. Given their demonstrated efficacy in controlling early morning blood pressure, this combination appears to be

a reasonable choice of treatment for those patients who have failed morning blood pressure control with monotherapy.[22] A Greek hypertensive population that did not achieve blood pressure control with low dose ARB or calcium channel blocker monotherapy was randomly given low dose combination therapy or high dose monotherapy. Interestingly, low dose combination therapy proved to be more efficacious than high-dose monotherapy in 24-hour blood pressure variability.[23] The ultimate therapeutic significance of the combination of a long-acting ARB with a calcium antagonist should be further evaluated to establish the long-term prognosis of hypertensive subjects in terms of cardiovascular morbidity and mortality. Another combination that seems to be effective in the reduction of blood pressure is that of ARB with aliskiren[24,25] but longer term studies are necessary.

ARBS IN CARDIOVASCULAR AND CEREBROVASCULAR DISEASE

Left ventricular hypertrophy (LVH) increases the risk of major cardiovascular events two- to five-fold and is greatly modulated by the activity of the RAS. Thus, the reduction of LVH through the blockade of RAS is of clinical relevance because it translates into a reduced rate of cardiovascular complications. The justification for the choice of ARBs over ACEIs in LVH and heart failure is predicated by several factors. Given that ARBs reduce peripheral resistance, it has been postulated that concomitant reduction in cardiac impedance would promote cardiac emptying with less left ventricular wall stress. An additional benefit provided by the treatment of ARBs is the blockade of the direct hypertrophic action of angiotensin II on the myocardium. It is also known that some intracardiac angiotensin II is formed via a non-ACE-dependent mechanism, and this may explain the superiority of ARBs in the treatment of heart failure.

The ELITE (Evaluation of Losartan in the Elderly) study was designed to determine whether the ARB losartan offered advantages over the ACEI captopril in older patients with heart failure.[10] With regards to the secondary endpoints, losartan showed a 46% lower risk of death, 64% reduction in sudden death, and a 26% lower hospitalization rate compared with captopril. Notably, fewer losartan patients discontinued therapy due to adverse effects than those on captopril (12.2% vs. 20.8%). The lower mortality rate observed with losartan may be attributed to the better suppression of angiotensin II, the absence of bradykinin effects during therapy or the better compliance of patients.

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study demonstrated that losartan was superior to the β-blocker atenolol among hypertensives with LVH in the regression of LVH, cardiovascular morbidity and overall mortality. The diabetic population and subjects without clinically evident vascular disease also proved to benefit from losartan.[17]

Candesartan in Heart failure Assessment of Reduction in Mortality and Mobility (CHARM) and Valsartan Heart Failure (VAL-HEFT) studies demonstrated the beneficial effect of these twenty-four-hour blood pressure control agents, both of which have been indicated for congestive heart failure.[26,27] The OPTIMAAL (Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan) and the VALIANT (Valsartan in Acute Myocardial Infarction Trial) studies show that ARBs confer benefits similar to ACEIs in patients with coronary heart disease, left ventricular hypertrophy, and heart failure.[28,8]

ARBs prove valuable in the primary and secondary prevention of cerebrovascular events. Specifically, the Prevention Regimen For Effectively avoiding Second Stroke (PROFESS) study evaluated the benefit of telmisartan over placebo in preventing secondary stroke. The results showed a non-significant trend in favor of telmisartan, although the treatment period of 2.4 years might have been too short to establish a significant difference.[29] The ONTARGET and the VALIANT studies reported that the cardiovascular benefits of telmisartan and valsartan, respectively, are comparable with those of the ACEI.[8,18] Specifically, the former study indicated non-inferiority of telmisartan versus ramipril. It is reported that the combination of an ARB and ACEI in the ONTARGET study provided no additional benefit in terms of target organ damage in patients with arterial disease; on the contrary, the rate of cardiovascular complications and the number of adverse events increased.[18] Nevertheless, this combination appeared to have a favorable effect on patients with heart failure, although more trials examining the effects of combined ARB with a full dose of an ACEI are needed. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial compared the efficacy of valsartan and amlodipine in the reduction of first cardiac event. No difference in overall cardiac morbidity and mortality or total mortality was documented. Although fewer myocardial infarctions were recorded with amlodipine (4.1%) compared with valsartan (4.8%, p=0.02), it should be noted that heart failure was 19% less among valsartan-treated patients.[30]

Hypertension is the most important risk factor for atrial fibrillation, which increases the risk of cardiovascular mortality two-fold and can be recognized as the underlying cause for 15% of all strokes. In hypertensive subjects without atrial fibrillation at baseline, the LIFE study[17] suggested that treatment with ARBs reduced the frequency of atrial fibrillation by 21% compared to β-blockers. Furthermore, the VALUE study[30] showed that new atrial fibrillation onset was less frequent in those treated with ARBs as opposed to those receiving calcium antagonists. However, newer data from the GISSI-AF trial indicated that treatment with valsartan was not associated with a reduction in the incidence of recurrent atrial

fibrillation in a cohort of 1442 patients, with approximately 85% of them having a history of hypertension.[31]

ARBS IN RENAL DISEASE

RAS blockade reduces the frequency of certain diabetic complications, including diabetic nephropathy. Microalbuminuria predicts cardiovascular events in the general population, including those with diabetes mellitus or arterial hypertension. Consequently, the reduction of microalbuminuria constitutes a significant part of antihypertensive treatment. Both the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and the IDNT (Irbesartan Diabetic Nephropathy) trials showed that ARB-treated groups displayed reduced levels of serum creatinine ranging from 16% to 20%. The relative risk reductions observed in the ARB groups in both studies were also significant for end-stage renal disease (28% in IDNT and 25% in RENAAL).[32,33] Furthermore, subjects with type 2 diabetes treated with ARBs showed a decline in microalbuminuria and a slower progression to macroalbuminuria.[34]

The DETAIL study (Diabetics Exposed to Telmisartan and Enalapril) indicates that telmisartan is clinically equivalent to enalapril in the renal protection of subjects with type 2 diabetes and early nephropathy.[35] Recently, the AVOID trial (Aliskiren in the Evaluation of Proteinuria in Diabetes), whose primary outcome was a reduction in albuminuria in patients with hypertension and type 2 diabetes, reported that the dual blockade of RAS with an ARB and the renin inhibitor aliskiren had a more beneficial renoprotective effect regardless of their blood pressure lowering action.[36]

RATIONALE FOR THE USE OF ARBS

ARBs block the RAS more peripherally than ACEI, lower blood pressure and appear to effectively reduce morbidity and mortality not only in hypertensive persons without significant target organ damage but also in hypertensive individuals with CVD.[37] The possible advantage of ARBs over ACEIs lies in that they allow sufficient quantities of angiotensin II in the circulation to activate the AT2 receptor that causes vasodilation and anti-proliferative action on blood vessels.[38] Additionally, the excellent tolerance of ARBs and limited adverse effects compared to ACEIs favors their use particularly by subjects susceptible to the effects of bradykinin.[11]

The possible superiority of ARBs over other antihypertensive drugs, including ACEIs is further supported by a number of metanalyses that demonstrate regression of left ventricular hypertrophy, stroke, new onset diabetes, diabetic nephropathy and also a delay in renal dysfunction.[39-43]

The ACCOMPLISH study (The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) examined the effects of combination treatment on cardiovascular outcomes, using an ACEI with either amlodipine or hydrochlorothiazide.[44] The former combination proved superior to the latter. The combination of amlodipine with telmisartan achieved greater blood pressure reduction with less adverse effects than respective monotherapy.[45]

In **conclusion**, ARBs can prove equally or more effective than other agents in decreasing cardiovascular morbidity and mortality in hypertensive individuals, benefiting high risk patients, such as those with diabetes mellitus, cardiovascular or renal disease.[17-19,26,28,32-35,38,39,46-52] Furthermore, their combination with other types of antihypertensive drugs, i.e. a thiazide diuretic or a calcium channel blocker, renders them a powerful option in the treatment of subjects with cardiovascular disease.[23,24,44,45]

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