REVIEW

Renin Angiotensin Aldosterone System in the Cardiovascular Continuum: An Overview of the Trial Evidence and Clinical Practice

Beyla Zuberi, Ishma Aijazi, Alaaeldin Bashier, Elamin Abdelgadir, Hina Zia Mirza, Manoj Pazhampattel Mathew, Sona Mahmoud Abuelkeir

Departments of Internal Medicine and Endocrinology, Dubai Hospital, Dubai Health Authority, Dubai, United Arab Emirates

Corresponding author: Dr. Beyla Zuberi Email: beylazuberi@gmail.com
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Abstract

The renin angiotensin aldosterone system (RAAS) inhibitors represent an invaluable class of drugs in the management of various stages of the cardiovascular disease continuum. Both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have unique pharmacodynamics properties. These enable them to block the RAAS system at multiple levels. The ARBs inhibit RAAS in a mechanistically distinct fashion when compared to the ACEIs. Whereas ACEIs decrease the synthesis of angiotensin II, ARBs selectively and competitively bind to the AT1 receptors hence preventing there activation by angiotensin II. The differential effects of these two groups of drugs, resulted in them playing different roles in primary and secondary cardiovascular protection. It is suggested that ACEIs tend to be more "cardioprotective" whereas ARBs may be more "cerebral-protective".

In this review article, we will attempt to enhance understanding of the role of RAAS blockers in cardiovascular disease continuum and help make the most appropriate selection of ACEIs and ARBs according to their attributes and the needs of the clinical situation. We will initially described the role of RAAS activation in the pathophysiology of common cardiovascular disease processes. This will be followed by a review of the major clinical trials of different ACEIs and ARBs in the primary prevention and secondary prevention of cardiovascular diseases.

In conclusion, the effects of ACEIs across a wide spectrum of cardiovascular diseases remain indisputable. However, ARBs showed a superior effect to ACEIs with regard to stroke, but their efficacy in certain major clinical end points seems limited.

Key words: RAAS blockade, ACE inhibitors; stroke; Cardiovascular continuum, ARB's, Endothelial dysfunction, Heart failure, Atrial fibrillation. Myocardial infarction.

Introduction

The renin angiotensin aldosterone system (RAAS) blockers represent an invaluable class of drugs that influence the cardiovascular disease continuum. Both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have unique pharmacodynamics properties, which enables them to block the RAAS system at multiple levels. It is seen that the ARBs inhibit RAAS in a mechanistically distinct fashion from ACEIs. Whereas ACEIs decrease the synthesis of angiotensin II, ARBs selectively and competitively bind to the AT1 receptors hence preventing their activation by angiotensin II. Due to the differential effects of these two groups of drugs, they tend to play different roles in primary and secondary cardiovascular protection. ACEIs tend to be more cardio protective whilst ARBs are more cerebro-protective. The RAAS pathophysiology and the role of their inhibition at various stages of the renal continuum has recently been reviewed in this *Journal* (1). In the present review, we will firstly explore the role of RAAS activation in the pathophysiology of various cardiovascular disease processes. We will follow a comprehensive descriptive review of the major clinical trials on various ACEIs and ARBs in the primary and secondary prevention of cardiovascular disease. We hope that this review will enhance the understanding of the role of RAAS blockers in cardiovascular diseases continuum and help Practicing clinicians make the most appropriate selection of ACE Is and ARBs according to the clinical situation at hand and the characteristics of the individual drugs.

RAAS and the Endothelial Function in Health and Disease

Endothelial dysfunction

Over the last few years the relationship of atherosclerosis with diabetes, dyslipidemia, hypertension, and smoking has become more clearly established. This relation is basically due to loss of nitric oxide, which is not only a potent vasodilator, but also possesses anti-atherogenic properties. These include inhibition of platelet aggregation, prevention of smooth muscle cell proliferation, reduction of lipid peroxidation, and inhibition of adhesion molecule expression (2). Suwaidi et al. enrolled 157 patients with mild coronary artery disease. Patients underwent one graded administration of acetylcholine, adenosine and nitroglycerin with intracoronary ultrasound to assess the reactivity of coronaries. Patients were divided according to the response into those with normal response, mild endothelial dysfunction, and those with severe endothelial dysfunction. After 28 months of follow up, all events occurred in those with severe endothelial dysfunction (3) and the majority of adverse events occurred in the group with only a mild vasodilation in the microcirculation in response to acetylcholine (3). RAAS blockade was proved effective in preventing endothelial dysfunction. Perhaps TRENDY trial was the best "proof of concept" trial in this regard comparing Ramipril to Telmisartan in 66 patients with hypertension and type 2 diabetes. The endothelial function was evaluated by measuring renal plasma flow after infusion of N-monmethyl-L-arginine (L-NMMA). Both drugs led to significant Nitric oxide activity in response to the infusion of L-NMMA (4).

Regression of the intima-media thickness

ACE inhibition can result in anti-atherosclerotic effects, reduce neo-intimal formation; improve endothelial function and lead to plaque stabilization. The multicentre Olmesartan atherosclerosis regression evaluation (MORE) study (5), a randomized, double blind, multicenter study, recruited 165 patients with hypertension and CCA-IMT (common carotid artery intima media thickness) ≥ 0.8 mm and ≤ 1.5 mm, in addition to one or more predefined cardiovascular risk factor(s). The primary end point was comparing the effects of treatment with Olmesartan or Atenolol on changes in IMT. IMT was measured by 2-D ultrasound, and the volume of atherosclerotic plaque was measured using 3-D ultrasound. Mean change from baseline in IMT of the leading side of the CCA after 104 weeks of treatment, was -0.090 mm with Olmesartan and -0.082 mm with Atenolol ($P < 0.0001$ for both). In patients with baseline plaque volume greater or equal to the median (≥ 33.7 mcL), plaque had regressed on Olmesartan (-11.5 mcL, P=0.014) but not on Atenolol (+0.6 mcL). Changes in plaque volume were limited because the study was not powered for its secondary endpoint. Additionally, the population was small, and the sub-analyses based on plaque volume were not pre-specified (5).

RAAS and Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is associated with increased cardiovascular mortality in both genders (6). The trial LIFE evaluated the benefits of Losartan in high-risk patients with hypertension (7). It was a double-blind study that included 9193 patients. Blood pressure here was higher than that in the HOPE and EUROPA trials (8,9). The primary end point was cardiovascular death, myocardial infarction (MI), or stroke, while the composite end point was any one

Table 1. Summary of trials on RAAS blockers in post myocardial patients.

Trial Acronym (ref)	Design	Results/Conclusions
EUROPA (9)	Double blind randomized placebo controlled multicenter trial on effect of Perindopril in post MI patients	Perindopril reduced the primary end point of cardiovascular morbidity and mortality [RRR: 20%; P=0.0003]
JIKEI Heart Study (12)	Randomized, open label, blinded endpoint morbidity and mortality in Japanese patients with high BP and CHF of Valsartan versus a non-ARB regimen. Target: Aggressive BP control	Valsartan reduced cardiovascular mortality and morbidity by 39% (HR 0.61, 95% CI: (0.47-0.79); p=0.00021
PREAM (13)	A randomized trial of Perindopril vs. placebo in post MI patients with an ejection fraction of at least 40%	Perindopril produced 0.22 absolute risk reduction in death, hospitalization due to heart failure, or remodeling (HR 0.22, 95% CI: 0.16-0.28; P <0.010).

EUROPA: Efficacy of Perindopril in Reduction Of cardiovascular events among Patients with stable coronary Artery disease; JIKEI = JIKEI Heart Study. PREAM = trial Perindopril and Remodeling in Elderly with Acute Myocardial infarction. BP blood pressure, CHF= Congestive heart failure; MI: myocardial infarction.

of these primary events. Compared with Atenolol, Losartan was associated with a significantly decreased incidence of the primary composite end point [11% versus 13%; adjusted hazard ratio (AHR) 0.87]. This was primarily due to a reduction in fatal or nonfatal stroke (5 v 7%; AHR: 0.75) (7). Antihypertensive therapy was associated with regression of LVH in 77% of patients. The degree of regression, using ECG criteria, was approximately twice at one year with Losartan compared to Atenolol. The relative benefit was particularly greater in patients with diabetes. A meta-analysis published, evaluated the relative efficacy of different antihypertensive drugs for their ability to reverse LVH in patients with hypertension (10). RAAS blockers were clearly the most effective class of drugs resulting in significant regression of LVH (10).

RAAS and the Post MI Patient

ACEIs and ARBs can both reduce the cardiovascular morbidity and mortality post myocardial infarction. Use of RAAS blockers post myocardial infarction has been shown to improve survival and delay the progression to heart failure and reduce ventricular remodeling (11). ACEIs also cause a stabilization of heart size, and since they cause a delay in ventricular remodeling they decrease the progression of systolic and diastolic dysfunction post myocardial infarction (8). The beneficial effects of ACE inhibition in reducing cardiovascular events in patients aged 55 years and above at high risk for cardiovascular events, was clearly demonstrated in the HOPE study (8). For instance, EUROPA trial compared Perindopril to placebo in secondary prevention, it showed 20% relative risk reduction with Perindopril (P=0.0003) (9). The JIKEI trial compared the effects of Valsartan to non-ARB regimens in Japanese population on the reduction of the primary cardiovascular endpoints. A 39% reduction in morbidity and mortality was reported (12). The PREAM trial evaluated the elderly patients with acute MI comparing Perindopril versus placebo (13) (Table 1). Safety and efficacy of ARBs in comparison to ACEIs post myocardial infarction has been evaluated in many trials. Of these, OPTIMAAL compared Losartan (50mg daily) to Captopril (50 mg 3 times daily) for morbidity and mortality after acute myocardial infarction. The results showed a non-significant difference in total mortality in favor of captopril (14). The VALIANT; a double blinded, multicenter international trial that was conducted in patients post myocardial infarction who developed systolic dysfunction or heart failure within 12 hours to 10 days (15). Treatment with valsartan alone

Table 2. Meta-analysis of 6 trials of ARBs versus ACEIs.

Trial Aronym*(ref)	Analysis Design	Results	Conclusions
ONTARGET (14)	49,924 patients were included in the meta-analysis from all studies.	Similar effects on reducing the risk of MI [OR 1.01, P=0.75], CV mortality [OR: 1.03, p=0.23 and total mortality [OR: 1.03, p=0.20].	There is an 8% difference in primary risk favoring ARBs over ACEIs
ELITE (32)			
ELITE II (33)			
OPTIMAAL (12)	31,632 received ARBs, and 18292 received ACEIs.	Risk of stroke: 8% lower with ARBs vs. ACEIs; OR: 0.92, p=0.037].	
DETAIL (70)			
VALLIANT (13)			

ONTARGET: ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial, ELITE: Evaluation of Losartan in The Elderly, ELITE II: Losartan heart failure Survival Study, OPTIMAAL: Optimal Trial in Myocardial Infarction With Losartan, DETAIL: Diabetics Exposed to Telmisartan and Enalapril, VALLIANT: Valsartan in Acute MI.; MI Myocardial infarcrtion; CV: Cardiovascular,

was compared with combination with Captopril. Valsartan was neither superior nor inferior to Captopril for the primary endpoint [Mortality was not significantly different between groups being around 19%; p=0.98] (15,16). The ONTARGET trial compared Telmisartan and Ramipril in reducing the risk of myocardial infarction, cardiovascular death, stroke and hospitalization for heart failure in high-risk patients. The relative risk of these cardiovascular events was 1.01 for Telmisartan versus Ramipril (16).

RAAS in Heart Failure

RAAS activation in Heart Failure

In fibrotic hypertrophied cardiac cells, RAAS activation results in fluid retention and peripheral vasoconstriction with consequent cardiac overload and heart failure (17). Furthermore, it stimulates heart rate and contractility resulting in reduction of coronary flow and arrhythmias (18,19). Recent studies in conscious animals have shown that plasma rennin activity and aldosterone levels are elevated in the acute phase of heart failure and were normal in the chronic compensated phase of heart failure (20-22). Exposure of the myocardial cells to high levels of angiotensin II and aldosterone resulted in fibrosis. This suggests a critical role for RAAS blockers in myocardial remodeling. Angiotensin II exerts its effects through AT-1 receptor that mediates the systemic and cardiac effects, and AT-2 receptors, which affects natriuresis and inhibition of cell proliferation. AT-1 receptors in cardiac tissue were down-regulated in decompensated heart failure, whereas AT-2 receptors remain unchanged (23,24).

Role of ACEIs in heart failure

The benefits of ACEIs have been demonstrated in MI survivors and in patients with left ventricular dysfunction (NYHA I-IV). In these populations, they have been shown to improve cardiac performance, relieve symptoms, decrease hospitalizations and prolong survival, all these data were collected from different RCTs. For instance CONSENSUS trial, the first RCT to evaluate the effect of Enalapril on mortality in severe CHF (Class IV). Reduction in mortality by 40% and 31% were evident in patients treated with Enalpril at 6 and 12 months respectively. This decrease in mortality was due to preventing the progression of CHF as no effect was seen on sudden cardiac death (25). The SOLVD trial evaluated the addition of ACEI (Enalapril) to conventional therapy, on mortality and hospitalization in patients with chronic heart failure and ejection fractions. Reduction in mortality was 16% P = 0.0036 (26,27). Moreover, ATLAS study (Assessment of Treatment with Lisinopril and Survival), an international, multicenter, randomised, double-blind study compared two dosages (2.5 to 5 mg/day vs 32.5 to 35 mg/day) of Lisinopril on the morbidity and mortality of patients with CF. The higher dose resulted in 24% less hospitalization (28).

Role of ARBs in heart failure

The Valsartan Heart Failure Trial (Val-HeFT), a randomized, double blind, controlled trial, investigated the effect of valsartan versus placebo in heart failure patients who were treated with ACEI (29). A total of 5010 patients with NYHA class II-IV symptoms, with evidence of left

ventricular dilatation, and ejection fraction of 40% or less were randomized. The combined end point of mortality and morbidity was significantly reduced in patients receiving valsartan as compared to placebo (p=0.009). In the valsartan group, 28.8% patients reached the combined end point, as compared with 32.1% in placebo group (29). The CHARM Program trial was one of the largest trials using candesartan in heart failure patients (30-33). It consisted of 3 arms, CHARM ALTERNATIVE, CHARM PRESERVED and CHARM ADDED. The incidence of cardio vascular death in candesartan group was 18% vs 20% in placebo group (primary end point). In CHARM alternative, incidence of hospitalization or cardio vascular deaths in Candesartan versus placebo (33% vs. 40%; p=0·0004) (31). On the other hand, ELITE I, ELITE II evaluated the Losartan versus Captopril in different doses, while the HEAAL trial assessed different doses of Losartan and the effects on the cardio-vascular outcomes. The ELITE I trial (Evaluation of Losartan In the elderly) have tested Losartan versus Captopril, the primary endpoint was the effects on the Creatinine, while the secondary endpoint was the mortality and hospitalization where Losartan was superior to Captopril (34). ELITE II (Losartan heart failure survival study) again compared Losartan to Captopril, there were no differences in the effectiveness of the drug, although there were more deaths in the Losartan group (35). The HEAAL trial was conducted in 3846 patients, they concluded that the higher dose of Losartan (150mg) led to fewer cardiovascular deaths and hospitalization in comparison to Losartan 50mg (36).

RAAS and Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia and affects 6% of people above 65 years of age (37). Recurrence of AF in patients treated with beta- blockers and/ or antiarrhythmic agents is between 45 -55% when followed over a period of 6 months (38-42). In experimental models RAAS blockade has shown a favorable impact on the electrical and structural remodeling of atrium in experimentally induced atrial fibrillation (43-45). Development of atrial fibrillation in patients with heart failure is an important event as it worsens the prognosis and favors occurrence of serious events such as stroke and embolism (46-48). Many studies have shown the benefit of RAAS blockade in preventing new onset AF. In Val-HeFT trial, 4395 patients with heart failure were randomized to valsartan or placebo in addition to their prescribed treatment for heart failure (29). During the mean follow up of 23 months, AF was reported in 287 patients who were in sinus rhythm at baseline. Out of these 117 patients were prescribed valsartan and 174 were given placebo .The results of this study demonstrate that adding valsartan to prescribed therapy for heart failure significantly reduces the incidence of AF by 37% (49). In the left ventricular dysfunction trial (SOLVD), 391 patients treated with Enalapril showed significant reduction in the development of AF in patients with left ventricular dysfunction (50). Similar results were obtained by TRACE investigators in patients with left ventricular dysfunction after myocardial infarction. Pedersen et al demonstrated a reduction of 55% in the incidence of AF in association with the treatment with an ACEI Trandolapril (51). In a recent study, the combination of Irbesartan plus Amiodarone was more useful in preventing recurrence of AF than Amiodarone alone in a heterogeneous population of patients recently cardioverted to sinus rhythm with and without HF. (52). Another study of patients with hypertension and LVH, Losartan reduced incidence of new onset atrial fibrillation by 29%. All these data suggest that the blockade of the RAAS can play a role in the prevention of AF. Possible mechanism by which RAAS blockade helps in decreasing new onset AF could be the reduction of collagen deposition in the atria, limiting the delay in atrial activation (53).

RAAS Blockade and Stroke

Although good blood pressure control is critical for stroke prevention and RAAS blockers contribute to blood pressure lowering but trials suggest that ARBs may be superior to ACEIs for the same degree of blood pressure control. ARBs prevent stroke incidence by blocking the AT1 receptors and allowing stimulation of the AT2 receptors, which improve brain ischemia (54)**.** Angiotensin II binds to either the angiotensin II type 1 receptor (AT1R), which is responsible for most of the physiological and pathological actions of angiotensin II, or the angiotensin II type2 receptor (AT2R), which opposes the actions of the AT1R. Data from animal studies have shown that blockers of AT1R (i.e. ARBs) improve cerebral perfusion during an ischemic event, thus reducing neuronal damage possibly by increasing cerebral vascular compliance during stroke (55-56). In addition, they are known to have anti-apoptotic, anti-inflammatory, and anti-oxidant properties. (57-60) Stimulation of AT2R has regenerative capabilities associated with restored behavioral function, and increased neurite extension in cell culture. (61-64). Oxidative stress is a major contributing factor to the pathology of stroke. AT1R stimulation causes an increase in superoxide production, whereas AT2R opposes this effect (65-66).

ACE Inhibitors and stroke prevention

Clinical studies of ACE inhibitors have produced mixed results on cerebral protection. ACE inhibitors tend to result in indiscriminate reduction in both AT1 and AT2 stimulation in the brain. However, their systemic anti atherosclerotic effects may reduce cardiac complications and secondarily lead to reduction in strokes. The PROGRESS study was a randomized trial comparing perindopril to placebo. It showed that perindopril alone had no benefits in primary stroke reduction since it did not effect cereberal blood vessels directly (67). However, the HOPE trial which compared Ramipril to a placebo (8), showed that Ramipril caused a 32% relative risk reduction in stroke (P<0.01).This is because Ramipril reduced cardiac complications and had a plaque stabilizing effect which caused a secondarily reduction in cereberovascular complications. This may account for the conflicting results of the effect of ACEIs on the incidence of strokes (67-69).

ARB's in prevention of Stroke

Primary Prevention: Maximum stimulation of AT2 receptor by ARB is needed for primary and secondary stroke prevention. A meta-analysis of head-to-head studies clearly confirmed that treatment with ARBs provides better protection against the risk of stroke compared with ACE inhibitors. Six randomized comparative trials with an average follow-up of at least 1 year were included in the meta-analysis (70). The ONTARGET study showed that the ARB Telmisartan reduced the risk of primary stroke by 9% compared with the ACE inhibitor Ramipril (16). Compared to other ARBs, Telmisartan seems to be superior owing to its lipophilic properties, which allows it to cross the blood–brain barrier to inhibit centrally mediated angiotensin II effects.

Primary Prevention: Maximum stimulation of AT2 receptor by ARB is needed for primary and secondary stroke prevention. A meta-analysis of head-to-head studies clearly confirmed that treatment with ARBs provides better protection against the risk of stroke compared with ACE inhibitors (68). Six randomized comparative trials with an average follow-up of at least 1 year were included in the meta-analysis; these included ONTARGET (14), ELITE study (34), ELITE II (35), OPTIMAAL study (14), DETAIL (69), and VALIANT study (12) (Table 2). The 2 classes had similar effect in reducing the risk of myocardial infarction, CV mortality, and total mortality, however ARBs reduced the risk of stroke by 8% Odd ratios 0.92, P=0.037. The ONTARGET study showed that Telmisartan reduced the risk of primary stroke by 9% compared with Ramipril (16). Compared to other ARBs, Telmisartan seems to be superior owing to its lipophilic properties, which allows it to cross the blood–brain barrier to inhibit centrally mediated angiotensin II effects. On the contrary, Captopril Prevention Project (CAPP) has randomized patient to receive either Captopril or conventional antihypertensive agents, looking at the fatal and non-fatal stroke, the Captopril group showed more incidences of fatal and non-fatal strokes (70). Similar results were obtained from ALLHAT (Antihypertensive and Lipid-Lowering Treatment to prevent Heart attack Trial). Patients who had at least one cardiovascular risk were randomized to receive Chlorthalidone, Amlodipine or Lisinopril. Lisinopril was less effective in preventing stroke than diuretic therapy (71).

Secondary prevention: In addition to reducing the incidence of first stroke, clinical trials have also demonstrated the benefits of ARBs in secondary prevention of stroke. In the relatively small ACCESS trial (Acute Candesartan Cilexetil Therapy in Stroke Survivors), 342 patients with ischemic stroke and hypertension were randomized to double-blind treatment with the ARB candesartan or placebo for 7 days post-stroke (72). After which all patients received the ARB plus other antihypertensive treatments as required for 1 year. (54) ARB treatment was associated with significant reductions in both cumulative 12-month mortality (2.9 vs. 7.2%, P = 0.07) and the number of vascular events (9.8 vs.18.7%, P = 0.026) as compared with placebo. MOSES (Eprosartan compared with Nitrendipine for Secondary Prevention) is another trial that studied a total of 1405 high-risk hypertensive patients who already had a cerebral event in the preceding 24 months (73). They were randomized to either Eprosartan or Nitrendipine and were followed for a mean of 2.5 years. Similar levels of blood pressure reduction were achieved in both these groups. The primary end point was the composite of total mortality, all cerebrovascular and cardiovascular events. Eprosartan produced a significantly greater reduction in recurrence of stroke as compared with the calcium channel blocker (102 vs. 134, relative risk: 0.75 , P = 0.03; absolute risk reduction was 2.2% (73).

Summary and conclusions

The effects of ACEIs across a wide spectrum of cardiovascular diseases remain indisputable. It seems that the efficacy of ARBs is limited to certain surrogate clinical end points namely control of hypertension, renal function, and signs and symptoms of heart failure. The Efficacy of ARBs with regard to certain major clinical end points

(other than stroke) seems to be limited. They do not reduce the rate of MI or CV death. Selection of these agents in clinical practice should be individual based on evidence on efficacy and safety attributes and the clinical case at hand.

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