Chapter

The Role of the Renin-Angiotensin-Aldosterone System in Cardiovascular Disease: Pathogenetic Insights and Clinical Implications

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Abstract

Increased attention has been placed on the activation of the renin-angiotensin-aldosterone system (RAAS) and pathogenetic mechanisms in cardiovascular disease. Multiple studies have presented data to suggest that cardiac and arterial stiffness leading to adverse remodeling of both the heart and vasculature leads to the various pathological changes seen in coronary artery disease, heart failure (with preserved and reduced ejection fractions), hypertension and renal disease. Over-activation of the RAAS is felt to contribute to these structural and endocrinological changes through its control of the Na+/K+ balance, fluid volume, and hemodynamic stability. Subsequently, along these lines, multiple large investigations have shown that RAAS blockade contributes to prevention of both cardiovascular and renal disease. We aim to highlight the known role of the activated RAAS and provide an updated description of the mechanisms by which activation of RAAS promotes and leads to the pathogenesis of cardiovascular disease.

Keywords: cardiovascular disease, coronary artery disease, heart failure, hypertension

1. Introduction

Cardiovascular disease is the leading cause of death in men and women in the United States and throughout the world [1]. Current efforts are focused on decreasing the burden of death due to atherosclerosis and cardiac disease overall. Increased attention has been placed on the activation of the renin-angiotensin-aldosterone system (RAAS) and pathogenetic mechanisms in cardiovascular disease. The RAAS system effects blood pressure control and electrolyte and fluid balance and therefore plays a significant role in cardiovascular hemodynamics [2–4].

Classically, it is known that angiotensinogen is cleaved by renin to form angiotensin-I (Ang I), which is then converted to angiotensin-II (Ang II) by angiotensin converting enzyme (ACE), however other peptides and products of this axis have

been shown to play a role in the development of cardiovascular disease [3, 4]. It is thought that two of these products (angiotensin 1-7 and angiotensin 1-9) may have counterregulatory effects on the development of atherosclerosis and cardiovascular disease [4]. Although the role of angiotensin II is understood more clearly, these peptides provide other targets by which the RAAS system can be utilized to prevent atherosclerosis.

Overactivation or pathologic activation of the RAAS system, specifically angiotensin II, has been shown to play a specific role in endothelial dysfunction, inflammation, intense vasoconstriction, increased vascular and cardiac hypertrophy, fibrosis and the development of atherosclerosis [2–5]. Multiple large investigations have shown that direct inhibition of the effects of angiotensin II via angiotensin converting enzyme inhibitors (ACE-I) and angiotensin-receptor blockers (ARB) improve mortality, prevent renal disease and decrease cardiovascular events in this subset of patients. Additionally, some studies have shown that utilization of both ARB and ACE-I may have cumulative effects on inhibiting the adverse effects of an overactivated RAAS system [6, 7].

We aim to highlight the known role of the activated RAAS and provide an updated description of the mechanisms by which overactivation of RAAS promotes disease and provide a summary of the clinical implications of RAAS inhibition in cardiovascular disease.

2. Overview of the RAAS system

The RAAS system has several moving parts, with different organ systems stimulating its activation and suppression. Renin, the active form of prorenin, is secreted by the granular cells of the kidney. Although renin's role is that of an enzyme, its means of expression are more hormonal. Renin's production is stimulated by hypotension, hyponatremia, and decreased sympathetic activity. Renin is responsible for cleaving angiotensinogen, a protein produced in the liver. Angiotensinogen is regulated via thyroid hormone, steroids, and levels of circulating angiotensin II. Angiotensinogen is cleaved into angiotensin I, which is further converted into angiotensin II by angiotensin converting enzyme [3, 4].

RAAS key players are composed of renin, angiotensin I & II, and angiotensin converting enzyme located in the heart atria, conduction system, valves, ventricles, coronary vessels, fibroblasts and myocytes [8, 9]. Ang II is the effector hormone playing a pivotal role in the cardiac RAAS and has a widespread effect throughout the body, targeting different mechanisms of action.

Ang II acts via the angiotensin receptors mediating the following actions [9, 10]:

1. Cardiovascular system - vasoconstriction, increased blood pressure, increased cardiac contractility, vascular and cardiac hypertrophy

2. Renal system - tubular sodium reabsorption, inhibition of renin release

3. Sympathetic nervous system stimulation

4. Aldosterone synthesis through adrenal cortex

5. Cell growth and proliferation, inflammatory response, and oxidative stress.

Angiotensin converting enzyme 2 (ACE 2) is involved in the degradation of Ang II to Ang (1-7) and Ang (1-9), which provide a relative vasodilatory effect

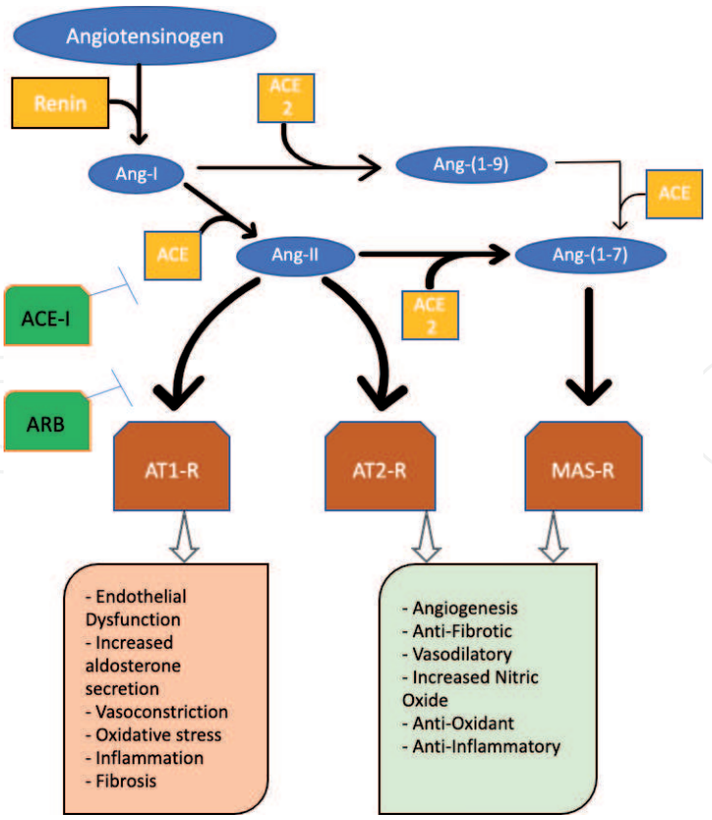

Figure 1.
Schematic of the RAAS as it pertains to angiotensin II and angiotensin (1-7) (Ang-(1-7)) and their counter-regulatory effects via angiotensin receptors 1 and 2 (AT1-R and AT2-R respectively) and MAS receptor (MAS) [5, 6, 11]. Abbreviations: ACE-I (angiotensin converting enzyme inhibitor), ARB (Angiotensin-II receptor blocker), Ang (1-9) (angiotensin 1-9), ACE (angiotensin converting enzyme).

as outlined in **Figure 1**. ACE 2 is restricted to vascular endothelial cells, arterial smooth muscle cells, myofibroblasts, carotid arteries and renal tubular epithelium [8–10]. The effects of Ang II, Ang (1-7) and Ang (1-9) have been uncovered in the past several years, specifically their role in hypertension, endothelial damage, and cardiovascular disease [5, 6, 9, 12]. The role of Ang (1-7) and Ang (1-9) is further outlined in **Figure 1** as they pertain to the pathophysiologic changes in the cardiovascular system.

3. Pathogenic insights

3.1 Atherosclerosis and endothelial dysfunction

Endothelial dysfunction is thought to be a precursor to atherosclerosis, or the thickening and stiffness of vessels. This damage often cultivates in an atherosclerotic plaque, which is a fibrin and cholesterol contained structure that deposits on the inner lumen of blood vessels and can impede oxygen delivery to tissues and organs. Endothelial damage and inflammation allow for the migration of monocytes and macrophages to the site of injury and the formation of foam cells [13–15]. Additionally, stimulation of inflammatory mediators also promotes smooth muscle cell (SMC) thickening, stiffness of vessels and forms a fibrous cap on the atherosclerotic plaque (**Figure 2**) [16]. The pathophysiology of plaque development is very closely tied to RAAS as Ang II plays a key role in these pathophysiologic changes.

Ang II acts on the AT1 and AT2 receptors (AT1-R and AT2-R) causing arteriolar vasoconstriction, and inflammation through generation of reactive oxygen species

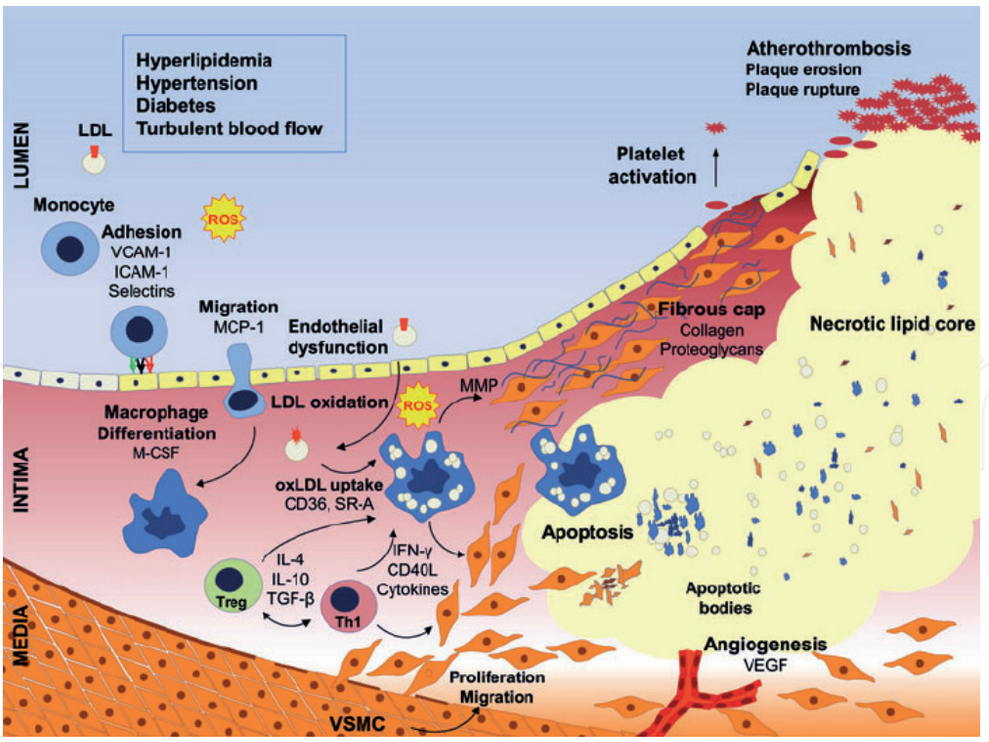

Figure 2.
A schematic depicting the dynamic changes involved in the formation of an atherosclerotic plaque [16]. Abbreviations: ROS, reactive oxygen species; ICAM-1, intracellular adhesion molecule 1; IFN-c, interferon-gamma; IL, interleukin; LDL, low-density lipoprotein; M-CSF, macrophage colony-stimulating factor; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; oxLDL, oxidized LDL; SR-A, scavenger receptor A; TGF-b, transforming growth factor beta; VCAM-1, vascular adhesion molecule 1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cells. Reproduced with permission from Mary Ann Liebert, Inc.

(ROS), proinflammatory transcription factors such as nuclear factor kB (nf-kB), and the proliferation of smooth muscle cells contributing to atherogenesis [17, 18]. Activated nf-kB increases inflammatory mediators including interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and platelet derived growth factor (PDGF), all of which mediate inflammation, endothelial damage and monocyte migration and adhesion leading to fibrosis [6, 18].

Ang II induces NF-kappaB (NF-kB) and inflammation through its binding to AT1-R. This has been demonstrated extensively as AT1-R blockers have shown to significantly decrease inflammation. Induction of NF-kB leads to the expression of pro-inflammatory cytokines such as IL-6 and TNF-alpha [19, 20]. Additionally, IL-6 itself can activate AT1-R resulting in overexpression and production of reactive oxidative species (ROS) when RAAS is overstimulated [19]. The RAAS is also a potent oxidant stimulator, as it activates the NADH/NADPH oxidase signaling pathway, and thereby produces superoxide anions and other ROS. TNF-alpha impairs endothelial nitric oxide (NO) production in coronary arteries thereby causing vasoconstriction. Additionally, ACE plays a role in the degradation of bradykinin, which depletes NO formation as well [6, 18–20]. Overall, we have a RAAS mediated expression of ROS, inflammatory mediators, and depletion of vasodilatory NO.

This inflammation mediated cellular injury and production of ROS, activates the endothelium and increases expression of intercellular adhesion molecules (ICAM-1) and vascular cell adhesion molecules (VCAM-1), which promote endothelial damage and make cells leaky [9, 21, 22]. The endothelial damage promotes further migration of leukocytes, production of inflammatory cytokines and chemokines.

Finally, RAAS promotes thrombosis through Ang II receptors located on human platelets. Through these receptors Ang II promotes the release of thromboxane A2

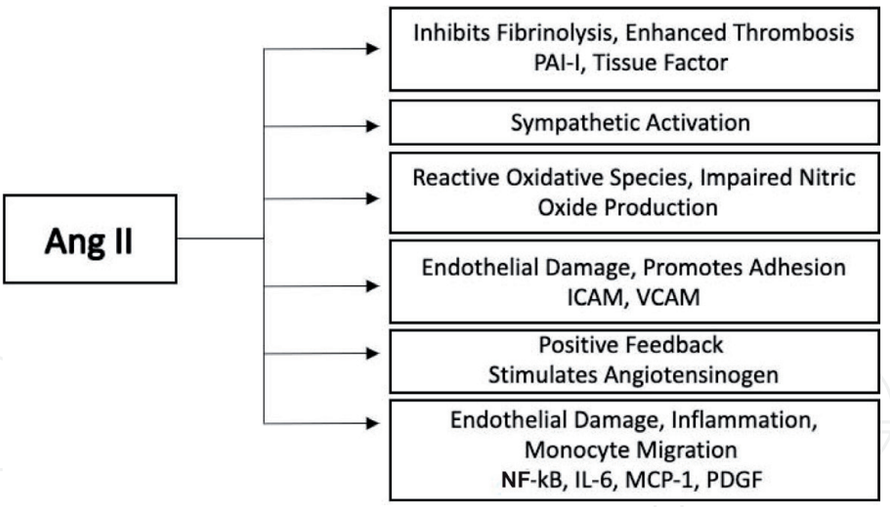

Figure 3.
Summarized effects of Ang II as it is known to cause endothelial damage, inflammation, migration and adhesion of monocytes, proliferation of vasculature and platelets and formation of atherosclerotic plaque and thrombus [6, 18–23].

and platelet derived growth factor, which promote atherosclerotic plaque formation and thrombus formation [22, 23]. Ang II involvement in endothelial dysfunction and atherosclerotic plaque formation is summarized in **Figure 3**.

4. Hypertension

Hypertension, defined as a systolic blood pressure greater than 120 and diastolic pressure greater than 80, affects a quarter of the world's population. When the etiology of hypertension is unknown, it is termed essential hypertension. When the cause of hypertension is known, by way of underlying metabolic, hormonal, neurogenic, or cardiovascular dysfunction, it is deemed as secondary hypertension [24]. As we have reviewed thus far, RAAS is responsible for maintaining sodium concentration in the blood, fluid status, and hemodynamic stability and therefore has a significant effect on blood pressure. Overactivation of RAAS can perpetuate unwanted elevations in blood pressure.

Increased levels of Ang II and subsequently aldosterone cause increases in vascular tone and hypertension. Aldosterone, a mineralocorticoid, takes its effect by binding to mineralocorticoid receptors (MR) and translocating into nucleus. Here, it integrates with cellular DNA and induces transcription of genes that regulate electrolytes and fluid balance. An over expression of aldosterone causes an elevated aldosterone-renin ratio which leads to systemic complications [4].

Patient's with primary aldosteronism (PA) and increased aldosterone levels are at higher risk for cerebrovascular complications. Although PA is not a common diagnosis, fifteen percent of patients with essential hypertension have higher than normal levels of circulating aldosterone. We can conclude that this sub-set of essential hypertension patients will have similar end-organ effects of elevated aldosterone as do patients with PA [4].

Hypertension itself can cause endovascular injury, which leads to increased production of ROS and inflammatory mediators ultimately contributing to atherosclerosis [25, 26]. The result of such endothelial injury is worsening cardiovascular disease, hypertension, and renal dysfunction. We see this manifest in the kidney with proteinuria and collagen deposition. Eventually, healthy kidney parenchyma is replaced with fibrotic tissue, leading to even more dysregulation with blood

pressure homeostasis. In the cardiovascular system, inflammatory damage from overactivation of RAAS and hypertension causes calcifications and fibrosis. As such, inhibition of the RAAS system with ACE-I and ARB has become a cornerstone in therapy for hypertensive patients, particularly those with evidence of diabetes, microalbuminuria and in CAD patients overall [15, 25–28]. The details of some of the landmark clinical trials contributing to the guidelines in treatment with ACE-I and ARB are further discussed in this chapter.

5. Ischemic heart disease

Coronary artery disease (CAD) or Ischemic heart disease (IHD), develops when there is a limitation of blood flow within the coronaries. It occurs due to the gradual buildup of atherosclerotic plaque within the wall of arteries leading to reduced oxygen delivery to cardiac myocytes. It comprises a clinical spectrum based on the degree of luminal narrowing and the activation of the atherosclerotic plaque [13, 14]. The RAAS plays a vital role in the pathogenesis of CAD. Evidence supports that RAAS controls atherosclerosis through intracellular signaling pathways by mediating endothelial function, inflammation, fibrinolytic balance, growth, lipid-glucose metabolism, and its vasoconstrictor function.

Ang II has growth promoting effects by regulating growth of vascular smooth muscle cells and activating the growth associated kinase pathways. In states of ischemia, there is increased vascular endothelial growth factor (VEGF) expression. In vascular smooth muscle cells, transforming growth factor B1, platelet derived growth factor causes fibrosis and cellular hypertrophy. These angiogenic factors lead to the formation of new cells, fibrin, and collagen deposition leading to growth of the plaque and thickening of vessels [20, 21].

RAAS plays a role in altering the fibrinolytic balance as well by inhibiting fibrinolysis and enhancing thrombosis. Within the vessels, Ang II stimulates the release of plasminogen activator inhibitor - I (PAI-I) thereby reducing the fibrinolytic activity. It activates tissue factor which acts as a cofactor for factor VII, potentiating the coagulation cascade [22, 23]. The above mechanism increases the thrombogenic activity.

Ang II overexpression causes endothelial inflammation and activation of cytokine cascade thereby causing progression of atherosclerotic plaque. The silent plaque ruptures when the inflammation overwhelms the stable fibrous cap causing thrombosis and acute ischemia [13, 14].

6. Heart failure

Heart failure is a clinical syndrome categorized based on clinical signs and symptoms and further subclassified by echocardiography findings. As per the American College of Cardiology, left ventricular ejection fraction (LVEF) of ≥50% is defined as heart failure with preserved ejection fraction (HFpEF), LVEF 41-49% as heart failure with mid-range ejection fraction (HFmrEF), LVEF≤40% as heart failure with reduced ejection fraction (HFrEF). HFrEF particularly occurs after an inciting event like myocardial injury, arrhythmias, cardiomyopathies, substance abuse, infections or genetic diseases which put the heart in a state of stress leading to contractile dysfunction and cellular remodeling [29]. The circulatory changes arising from heart failure are sensed by the peripheral baroreceptors and chemoreceptors, thereby activating a sequalae of compensatory neurohormonal mechanisms. The compensatory mechanisms include activation of sympathetic nervous

system (SNS) and RAAS. RAAS plays an integral role in cardiac contractility, homeostatic control of blood pressure and electrolyte-fluid balance [30, 31].

In an adult with normal circulation, the baroreceptors located in the carotid sinus and aortic arch balance the sympathetic and parasympathetic outflow from the central nervous system. Alterations in the cardiac output change the effective arterial blood volume resulting in inhibition of parasympathetic response and a reflux increase in the sympathetic vascular tone. The increased sympathetic activity leads to vasoconstriction of the renal afferent arteriole and decreases blood flow to the kidney [29, 32]. This activates renin secretion and thereby RAAS.

Renin is secreted in response to 4 main stimuli [10, 33]:

1. Decreased renal perfusion pressure sensed by baroreceptor cells in the arterial vessel wall

2. Decreased intracellular chloride levels (altered NaCl delivery)

3. Sympathetic nerve stimulation via beta-1 adrenergic receptors

4. Negative feedback by a direct action of Ang II

The pathophysiology of heart failure allows for decreased renal perfusion and increased sympathetic response, both of which cause an overactivation of the RAAS [34]. The overstimulation of RAAS in heart failure is further depicted in **Figure 4**.

In pathological states like pressure or volume overload, cardiac tissues exhibit elevated levels of renin and Ang II levels leading to cardiac hypertrophy, myocardial fibrosis, hypertensive heart disease and chronic heart failure through mechanics explained earlier. Additionally, post-infarction levels of ACE-2 have been shown to be elevated, which may explain a counter-regulatory mechanism to protect against the Ang-II mediated myocardial damage. When this natural counter-regulatory mechanism is lost in ACE-2 knockout animal models the levels of dilated cardiomyopathy were much more pronounced. Several trials have also looked at specific levels of plasma renin and HFrEF and have found that those with elevated levels had an associated worse outcome than their counterparts. In patients with advanced heart failure, baseline levels of plasma renin and plasma aldosterone are persistently high, which further exemplifies the role of RAAS in cardiac remodeling and heart failure [35–37].

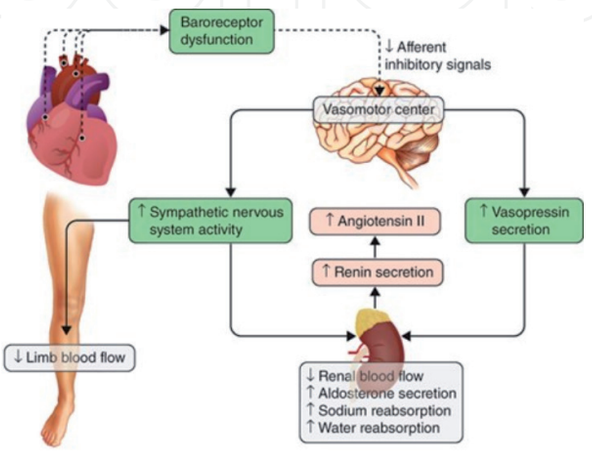

Figure 4.
The regulatory effects of RAAS as it pertains to heart failure mechanics [34]. Reproduced with permission from McGraw Hill LLC.

Innovative studies have discovered that a particular breakdown product of Ang 1-7, also known as Alamandine, has shown to prevent ventricular and vascular remodeling in animal models [11]. Studies of by-products offer areas of potential research as we grow to understand the intricacies of the molecular pathways that play a role in the development of heart failure.

7. Clinical implications

The overactivation of RAAS and its effects on the pathophysiology of hypertension, vascular stiffness, ischemia, thrombosis, and left ventricular (LV) remodeling has been well documented. As such, several medications that impede the harmful effects of the overactivation of RAAS have been shown to prevent the negative clinical outcomes. Here we review some of the landmark clinical trials that have contributed to the current guidelines and recommendations for the treatment of hypertension, ischemic heart disease and heart failure (**Table 1**).

In the treatment of hypertension, the patient's specific co-morbidities must be considered prior to initiating therapy including, race, diabetes, kidney function and other high-risk pre-existing conditions that may predispose to CV outcomes. One landmark trial, the AASK trial (2002), studied African Americans with hypertension and kidney disease and compared intensive blood pressure control versus conservative blood pressure control with ACE-I, metoprolol, and amlodipine. The two groups had no difference in the progression to CKD, however patients on ACE-I had less chronic kidney disease events and death, which solidified the use of ACE-I in patients with CKD [38].

The mainstay of treatment in patients with heart failure and CAD is blockade of the RAAS. Multiple trials highlighted in **Table 1** have been performed showing improvement in cardiovascular (CV) outcomes and reduced CV mortality.

The first trial to demonstrate improved CV outcomes with HFrEF is the CONSENSUS (1987) trial conducted among New York Heart Association (NYHA) Class IV HF and cardiomegaly patients which compared enalapril and placebo. Six-month mortality with enalapril was 26% as opposed to 44% with placebo [39]. The SOLVD (1991) treatment trial chose patients with HF and LVEF ≤35%, NYHA II-IV, with similar randomization, showing mortality reduction by 16% due to reduction of death in patients on enalapril versus placebo. This study also showed a decrease in CV related hospitalizations [40]. Further research with the V-HeFT II (1991) trial showed that ACE-I was superior in improving survival to vasodilators such as isosorbide dinitrate and hydralazine [41]. Additionally, use of ACE-I as a disease modifying drug was established post-MI in the SAVE trial (1992), which is further discussed in **Table 1** [42].

Additional studies looked to compare the effects of ACE-I versus ARB. These trials were the VALIANT (2003) trial and the OPTIMAAL (2002) trial. The VALIANT trial showed that valsartan was as effective as captopril in improving survival among patients with HF and/or LV disfunction in the post-MI period [43]. The OPTIMAAL trial compared losartan and captopril in high-risk patients after acute myocardial infarction with LV-dysfunction and heart failure and found no difference in mortality outcomes [44]. Similar studies in patients with HFpEF were conducted, including the CHARM-Preserved trial (2003) and the I-PRESERVE trial (2008). CHARM- Preserved showed that candesartan modestly reduced HF-related hospitalizations however had no effect on mortality [45]. I-PRESERVE used Irbesartan in HFpEF patients and similarly found no reduction in mortality [46].

The thought that the addition of an ARB to an ACE inhibitor could inhibit RAAS more significantly was established. This was compared in two large significant

Trial Name (Date)	Primary/ Secondary Outcomes	Inclusion Criteria	Intervention	Number of Patients / Follow-up Time	Results
AASK Trial (2002) [38]	Rate of eGFR change, progression of CKD or all-cause mortality	AA, Age 18-70, DBP >95 mmHg, HTN renal Disease, eGFR 20-65	BP control – with ramipril, amlodipine or metoprolol	1,094/4 years	No difference in progression of CKD. Use of ACE-I associated with fewer CKD events or death
CONSENSUS (1987) [39]	6 Month Mortality	NYHA IV HFrEF, optimal treatment with at least diuretic and digitalis or other medications (nitrates, prazosin, hydralazine)	Enalapril VS placebo	253/6-20 months (about 1 and a half years)	Six-month mortality with enalapril was 26% as opposed to 44% with placebo
SOLVD (1991) [40]	All-cause mortality, CV death, Death due to MI, Death due to stroke	HF, LVEF <35%, Receiving conventional therapy without ACE-I	Enalapril VS placebo	2,569/3.5 years	Enalapril reduces 4-year mortality by 16% and reduces HF hospitalizations
V-HeFT II (1991) [41]	2-year mortality, hemodynamic effects, EF, exercise tolerance, adherence	Men ages 18-75, reduced exercise tolerance, cardiac dysfunction, receiving optimal and stable therapy	Enalapril. VS ISDN/ hydralazine	804 men/2.5 years	Enalapril improved survival compared to combination of ISDN and hydralazine
SAVE (1992) [42]	All-cause mortality	Age over 21 years, MI in prior 3 days, new onset LVEF less than 40%, absence of overt signs of CHF	Captopril VS placebo	2,231/42 months (about 3 and a half years)	In patients with acute MI complicated by low EF, captopril led to 19% reduction in all-cause mortality
VALIANT (2003) [43]	All-cause mortality	Age > 18 years, Acute MI within prior 10 days complicated by HF, LVEF <35% on echocardiogram or < 40% on radionucleotide ventriculography	Valsartan VS valsartan + captopril VS captopril	14,703/ 24 months (about 2 years)	Valsartan was as effective as captopril in improving survival
OPTIMAAL (2002) [44]	All-cause mortality	50 years of age or older with confirmed acute MI and HF in acute phase or a new Q-wave anterior infarction or reinfarction	Losartan VS captopril	5,477/2.7 years	No significant change in mortality between the two drugs, however losartan was better tolerated
CHARM-Preserved (2003) [45]	Cardiovascular death or HF admission	LVEF>40%, NYHA class II-IV symptoms for at least 4 weeks, history of at least one cardiac hospitalization	Candesartan VS placebo	3,020/3 years	Candesartan modestly reduced the rate of HF-related hospitalizations. No effect on CV mortality

Trial Name (Date)	Primary/ Secondary Outcomes	Inclusion Criteria	Intervention	Number of Patients / Follow-up Time	Results
I-PRESERVE (2008) [46]	Death from any cause, hospitalization for CV disease	40 years of age or older and had NYHA class II-IV and an EF of at least 45%	Irbesartan VS placebo	4,128/49 months	Irbesartan did not improve mortality in patients with HFpEF
CHARM added (2003) [47]	CV mortality or HF hospitalizations	Age > 18 years, LVEF<40% in prior 6 months, NYHA II-IV, treatment with stable ACE-I dose for >30 days	Candesartan VS placebo	2,548/ 41 months	Addition of candesartan reduced CV mortality of HF hospitalization
VAL-HeFT (2001) [48]	All-cause mortality, cardiac arrest with resuscitation, HF hospitalization	Age > 18 years, NYHA II-IV, receipt of a fixed dose of medical therapy (ACE, digoxin, diuretics, and/or BB) for >2 weeks, EF < 40%	Valsartan VS placebo	5,010/23 months (about 2 years)	In a time where HF management included ACE but not BB, addition of ARB decreased HF hospitalizations
ON TARGET (2008) [49]	CV mortality, MI, stroke, HF hospitalization	Age over 55 years with CAD, PAD, CV disease or high-risk DM	Telmisartan VS Ramipril VS Telmisartan and Ramipril	25,620/56 months (about 4 and a half years)	Patients with CV disease or DM with complications telmisartan was as good as Ramipril in preventing death, MI, and stroke. The combination of both however had no increase in benefit and was associated with more adverse events.
RALES (1991) [50]	All-cause mortality	NYHA IV within 6 months to enrollment, NYHA III or IV at the time of enrolment, treatment with ACE and a loop diuretic, LVEF <35%	Spironolactone VS placebo	1,663/2 years	Spironolactone led to 30% reduction in all-cause mortality without significant side-effects
TOPCAT (2014) [51]	CV mortality, aborted cardiac arrest, or HF hospitalization	Age > 50 years, LVEF >45%, SBP <140 or < 160 if on 3 anti-hypertensives, serum potassium <5, elevated BNP in last 60 days, or HF hospitalization in last 12 months	Spironolactone VS placebo	3,445/3 years	Spironolactone did not reduce CV mortality however did result in a small reduction in HF hospitalizations
EMPHASIS-HF Trial (2011) [52]	CV death or hospitalization, all-cause mortality, fatal or non-fatal MI	Age > 55 years, NYHA II, EF < 30%, treatment with ACE, ARB or both, treatment with BB, CV hospitalization in last 6 months	Eplerenone VS placebo	2,737/21 months (about 2 years)	Eplerenone reduces the risk of death and hospitalization in patients with low EF and NYHA II

Trial Name (Date)	Primary/ Secondary Outcomes	Inclusion Criteria	Intervention	Number of Patients / Follow-up Time	Results
PARADIGM-HF Trial (2014) [53]	CV mortality or HF hospitalization	Age > 18 years, NYHA class II-IV, EF <35%, if no HF hospitalizations in last year BNP >150 pg./mL, ACE, or ARB and BB with stable dose, If HF hospitalization in last year BNP >100 pg./mL	ARNI VS enalapril	8,399/27 months (about 2 and a half years)	ARNI reduces CV mortality or HF hospitalizations when compared to enalapril. Also reduces all-cause mortality
PARAGON-HF Trial (2019) [54]	HF hospitalizations and CV mortality, change in NYHA class at 8 months, all-cause mortality	>50 years of age, LVEF>45%, NYHA II-IV, and at least one of the following: HF hospitalization with NT-proBNP>200 (no AFIB) or > 600 (AFIB) or NT-proBNP>300 (no AFIB) or > 900 (Afib) on screening visit ECG	ARNI VS valsartan alone	4,822/35 months (about 3 years)	ARNI did not lower hospitalizations or death from CV causes, however there was a modest improvement in NYHA class and a slower decline in renal function than what was seen in valsartan alone
PIONEER-HF Trial (2019) [55]	Time-averaged change in NT-proBNP concentration from baseline through weeks 4-8	Age > 18 years, LVEF<40%, NT-proBNP of 1600 pg./mL or more, or BNP of 400 pg./mL or more, receiving diagnosis of acute decompensated HF up to10 days after presentation	ARNI versus enalapril	881/2 years	ARNI decreased NT-proBNP compared to enalapril therapy without significant change in rate of adverse events
ALTITUDE Trial (2012) [56]	Death from CV causes, nonfatal MI, nonfatal stroke, ESRD, death attributable to kidney failure, or the need for RRT	35 years or older with type 2 diabetes and evidence of microalbuminuria, macroalbuminuria, or cardiovascular disease	Aliskiren VS placebo	8,561/32 months (about 2 and a half years)	The addition of aliskiren to standard therapy in patients with type 2 diabetes who are at elevated risk for CV and renal events is potentially harmful

Summarized landmark clinical trials depicting the benefits of RAAS inhibition in cardiac and renal patients. Abbreviations: CKD: Chronic kidney disease, AA: African American, SBP: systolic blood pressure, DBP: diastolic blood pressure, CV: cardiovascular, EF: ejection fraction, LV: left ventricular, MI: Myocardial infarct, ESRD: End stage renal disease, RRT: renal replacement therapy.

Table 1.
Trials documenting improvement in cardiovascular outcomes and reduced cardiovascular mortality with renin-angiotensin-aldosterone system inhibition.

trials. The CHARM-added trial compared symptomatic HF patients with LVEF ≤40% who were already on an ACE inhibitor with either addition of candesartan or placebo. This trial showed a reduction in CV mortality and HF hospitalizations; however, it was accompanied by a significant increase in hyperkalemic events [47]. The Val-HeFT (2001) compared patients with symptomatic HF, LVEF <40% with LV dilatation and on ACE inhibitors by adding either valsartan or placebo. There was no effect on mortality however, there was a 23% reduction in HF hospitalization in the treatment group [48]. Finally, the ONTARGET trial (2008) compared ramipril to telmisartan to a combination of both in patients with CV disease or diabetes with complications and found that the combination of telmisartan plus ramipril had no increase in benefit and was associated with more adverse events [49].

Several trials looking at the effects of aldosterone antagonists and heart failure patients were conducted with overall favorable results. Patients benefit from reduced sympathetic stimulation and alleviate fluid overload from sodium and water retention through aldosterone blockade. The RALES trial (1999) studied the role of spironolactone in patients with LVEF≤35% and NYHA class III-IV, which showed that Spironolactone, along with ACE-I (as most patients were already on ACE-I) showed a 11% reduction in CV mortality compared to placebo [50]. The TOPCAT trial (2014) done in patients with HFpEF and controlled blood pressures to receive spironolactone or placebo. This study conversely showed that spironolactone did not reduce CV mortality however did result in a small reduction in HF hospitalizations [51]. Another trial, the EMPHASIS-HF trial (2011), looked at Eplerenone versus placebo in HF patients, NYHA class II, showed that Eplerenone reduced the risk of death and hospitalizations in patients with HF [52].

A newer group of RAAS inhibition medications combining an ARB and neprilysin inhibitor (ARNI) was studied in 2014 in the PARADIGM-HF trial. Neprilysins are key enzymes in the degradation of natriuretic peptides. They increase endogenous natriuretic peptide levels including bradykinin, thereby promoting vasodilation and natriuresis. Neprilysins were initially attempted with an ACE inhibitor combination however this led to incidences of angioedema given increased levels of bradykinin. PARADIGM - HF trial was conducted in patients with symptomatic HF and LVEF ≤40% assigned to enalapril alone or valsartan-sacubitril combination. This showed significant reduction in CV mortality, all-cause mortality, and HF hospitalizations with no increase in angioedema events [53]. The PARAGON-HF trial (2019) studied ARNI versus valsartan alone in HFpEF patients with EF > 45% and NYHA II to IV and showed that ARNI did not lower hospitalizations or death from CV causes, however there was a modest improvement in NYHA class and a slower decline in renal function than what was seen in valsartan alone [54]. The PIONEER-HF trial (2019) showed that initiated of ARNI versus enalapril in acute diastolic heart failure patients allowed for significant reductions in HF biomarker, NT-proBNP, without significant change in adverse effects [55].

Direct renin inhibitors have been attempted with the goal of reducing renin and thereby the entire RAAS cascade. The ALTITUDE trial (2012) added aliskiren to patients with diabetes type 2 in order to prevent kidney disease and CV outcomes. These patients were on ACE-I however the addition of aliskiren led to an increase in CV mortality, hypotension, and adverse hyperkalemic events. The trial was stopped early due to higher mortality findings [56].

8. Summary and conclusions

RAAS is a complex and evolving pathway that has been implicated in the pathogenesis of endothelial damage, atherosclerosis, and cardiac remodeling. Inhibition

of the negative effects of overactivated RAAS has shown to cause morbidity and mortality benefits in cardiovascular disease outcomes. Significant research has yet to be performed on the possibility of stimulating the counter-regulatory effects of RAAS through AT2-R and MAS-R. Such mechanisms are still being studied in animal models; however, the effects of AT2-R and MAS-R offer potential areas of continued research and potential targets for future therapy.

Conflict of interest

No conflicts of interest exist for this work by any of the authors.

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