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The renin-angiotensin-aldosterone system: a crossroad from arterial hypertension to heart failure

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Abstract
The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the regulation of blood pressure and volume homeostasis, promoting critical structural changes in every component of the cardiovascular system, including the heart and blood vessels. Consequently, the RAAS is a crucial therapeutic target for several chronic diseases of the cardiovascular system, spanning from arterial hypertension (AH) to heart failure (HF). AH represents a leading risk factor for the development of symptomatic HF, particularly with left ventricle (LV) preserved ejection fraction (HFpEF). LV diastolic dysfunction and cardiac remodelling are the first discernible manifestations of heart disease in patients with AH. Typically, AH develops many years before the diagnosis of overt HF, providing a therapeutic target for preventive strategies. Treatment of AH is based on different classes of antihypertensive drugs, which show differences in their capacity to prevent the evolution towards HF. The blockers of the RAAS are effective drugs to treat AH and prevent HF with reduced ejection fraction (HFrEF), but the evidence of the potential benefits in patients with HFpEF remains limited. In this review, the authors summarise data from several clinical trials of HFpEF and HFrEF, focusing on the mechanisms leading the transition from AH to HF and late complications.

Keywords Renin-angiotensin-aldosterone system · Arterial hypertension · Heart failure · Preserved ejection fraction

Introduction

The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the regulation of blood pressure (BP) and volume homeostasis [1]. While these activities were initially considered limited to transient functional modifications, it became progressively clear that the chronic activation of the RAAS promotes critical structural changes in every component of the cardiovascular system, including the heart, the large and small vessels (Fig. 1). Consequently, the RAAS has emerged as a crucial therapeutic target for several chronic diseases of the cardiovascular system, spanning from the early manifestation of arterial hypertension (AH) to the overt heart failure (HF). When the system undergoes activation, the renin is secreted from the juxtaglomerular apparatus of the kidney and cleaves the circulating angiotensinogen (AGT) to form angiotensin I (Ang I). In turn, Ang I is easily activated to Ang II by angiotensin-converting enzyme (ACE), which is predominantly expressed on the surface of endothelial cells [2]. Although Ang II was initially identified as a potent activator of aldosterone acting at the level of the zona glomerulosa of the adrenal cortex in the adrenal gland, this molecule has now emerged as the most potent active product of the RAAS. Ang II acts as a vasoconstrictor on the cardiovascular system and regulates the production of oxidative stress and the metabolism of several organs, including the nervous system, digestive organs, skin, reproductive tract, sensory organs, lymphatic tissue, adipose tissue, adrenals and kidneys [3].

Aldosterone, the last component of the RAAS, contributes to the homeostatic regulation of BP, plasma sodium (Na+) and potassium (K+) levels. It does so primarily by acting on the mineralocorticoid receptors (MRs) in the distal tubules and collecting ducts of the nephron: it influences the reabsorption of sodium and excretion of potassium (from and into the tubular fluids, respectively), thereby affecting water retention or loss, BP and blood volume [4]. Its chronic upregulated secretion aldosterone has emerged as a prominent cardiovascular risk factor, promoting cardiovascular and renal inflammation, fibrosis and remodelling, showing precisely the opposite function of the atrial natriuretic hormone secreted by the heart [5, 6].

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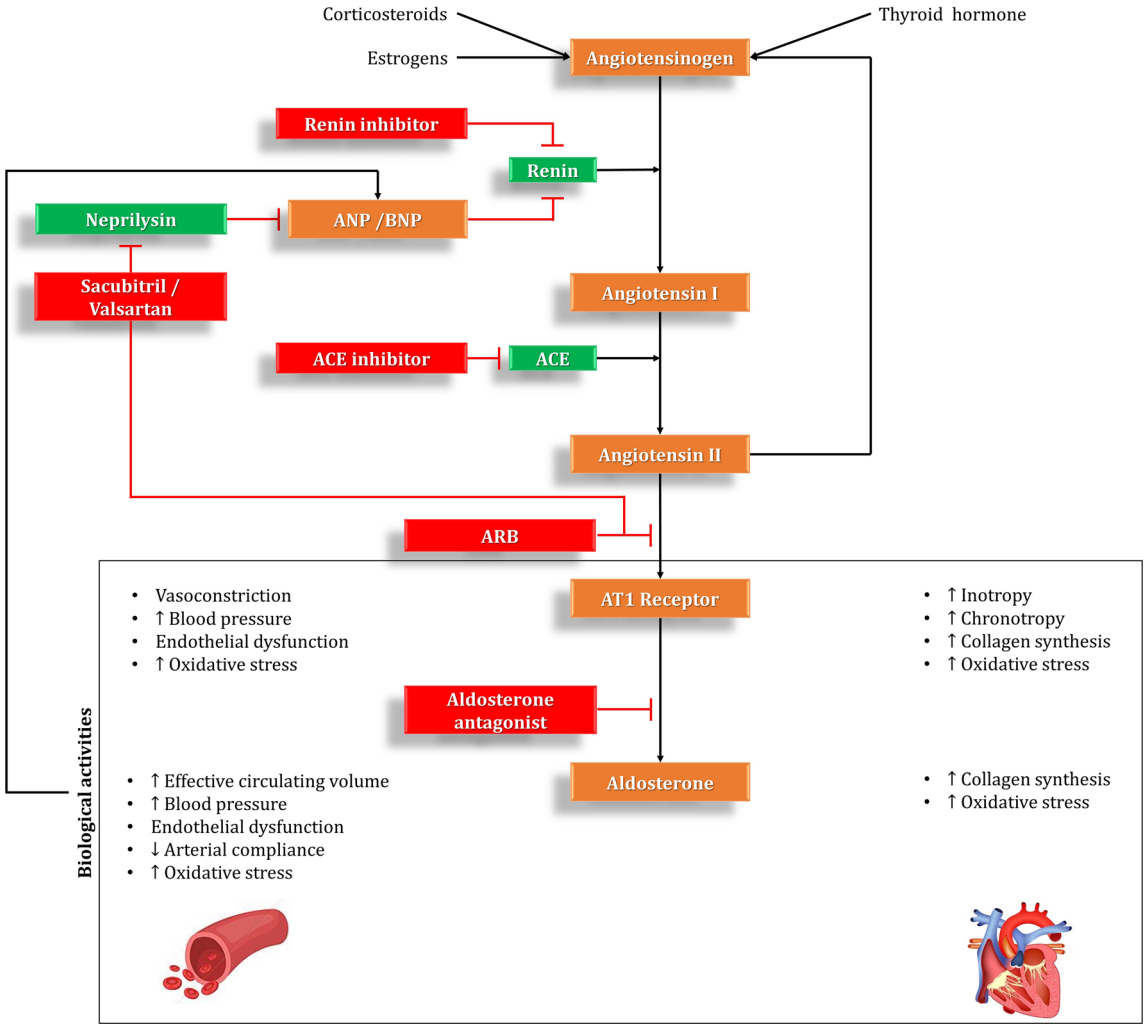

Fig. 1 Simplified flowchart of the renin-angiotensin-aldosterone system (RAAS) showing the site of actions of RAAS blockers and the biological effects of the RAAS active products on the heart and blood vessels. Orange boxes represent endogenous substrates/peptides, green boxes endogenous enzymes and red boxes drugs. ACE: angiotensin-converting enzyme; ANP: atrial natriuretic peptide; ARB: angiotensin II receptor blockers; AT1 receptor: angiotensin II receptor type 1; BNP: brain natriuretic peptide

The complexity of the RAAS has been further increased due to the description of different receptors and signal transduction pathways. Additional peptides, such as Ang 1~7, have been recognised, and alternative pathways of Ang II formation, such as the serine protease chymase, have been proposed [7]. Also, a large body of data is now available to support the existence of numerous RAASs with different physiological effects that can undergo activation within various organs. Importantly, the activity of these organ-based RAASs is independent of the activation of the systemic RAAS [8].

The interaction between RAAS and the natriuretic peptide system (NPS) has prompted renewed interest after the introduction of a novel drug that is able to potentiate its activity and has shown to improve the outcome of patients with HF significantly [9]. Actually, NPS counter-regulates the detrimental effects of RAAS upregulation that occurs in HF; NPS also inhibits secretion of arginine vasopressin and modulates the autonomic nervous system. Indeed, sodium and water retention, together with the vasoconstriction caused by activation of RAAS and the sympathetic nervous system, lead to increased ventricular preload and afterload and elevated wall stress which in turn lead to the production of pre-pro B-type natriuretic peptide (BNP) which is cleaved to BNP and N-terminal proBNP (NT-proBNP) [10]. BNP is a selective agonist for the A-type natriuretic receptor (NPRA). BNP inhibits RAAS and promotes natriuresis and vasodilation, while NT-proBNP is physiologically inactive. The NPS also includes other natriuretic peptides, such as the atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP). ANP results from atrial stretch and has similar biological properties to BNP, acting on NPRA. CNP is released from endothelial cells and acts in a paracrine fashion on the B-type natriuretic receptor (NPRB); it does not have direct natriuretic activity but is a potent vasodilator with inotropic and chronotropic properties [11].

The role of renin-angiotensin-aldosterone system in arterial hypertension and heart failure

The RAAS is responsible for BP stability, extracellular fluid volume homeostasis and cardiovascular remodelling [4, 12, 13]. Uncontrolled RAAS activity can lead to numerous pathologic conditions, mainly AH, which contribute to the development of end-organ damage through direct effects on cardiac, vascular and renal tissues [14]. In particular, the intrarenal RAAS markedly contributes to the development and progression of systemic AH and chronic renal failure [15–18]. Ang II receptor type 1 and type 2 (AT1 and AT2, respectively) regulate sodium excretion, but evidence in cross-transplanted kidney suggests that the AT1 receptor has a dominant role in mediating BP responses to Ang II, notably when AGT and renin are overexpressed in the proximal tubules [19, 20]. Also, Ang II activates epithelial sodium channels (ENaCs) in the distal nephron promoting sodium reuptake, in both an acute and chronic fashion [21]. In contrast, the AT2 receptor promotes sodium excretion directly or indirectly by acting on the kidney, mainly at the level of interlobular arteries, the proximal tubules, collecting ducts, renal interstitial cells, arcuate arteries, afferent arterioles and outer medullary descending vasa recta [22]. The AT1 and AT2 receptors have also been identified in the brain, where the microinjection of Ang II elicits an increase in BP and sympathetic activation via the AT1 receptor [23]. In contrast, AT2 receptor activation suppresses the sympathetic tone and induces a diuretic effect [22]. This implies the ACE-inhibitor block of Ang II reduces the activation of both AT1 and AT2, maintaining the sodium balance at a neutral level. Instead, an AT1 blocker can hinder sodium resorption in both the proximal and distal nephrons directly and through an additional sympatholytic effect, ultimately resulting in a negative sodium balance [24]. Noteworthy, AT1/AT2 receptor signalling may also be stimulated by bradykinin or other receptor-associated proteins, independently of Ang II [25–27].

Traditionally, the mechanism of action of aldosterone-mediated AH was thought to be restricted to renal genomic effects of the mineralocorticoid hormone, causing sodium and water retention [28]. Evidence has accumulated over the years for effects of aldosterone on endothelial cell and vascular smooth muscle cell that may or may not be mediated by the MR [29, 30]. Aldosterone may have a direct role in AH and cardiovascular fibrosis: a study in blood vessel–specific MR-deficient mice revealed that MR could increase the expression of voltage-gated calcium channels, which raises peripheral arterial resistance [31]. Also, under high salt intake or treatment with ACE inhibitors, Ang II receptor antagonists or renin inhibitors, the RAAS axis is suppressed; nevertheless, aldosterone receptor blockade is effective in lowering BP [23]. The effectiveness of MR antagonists (MRA) irrespective of the circulating aldosterone levels can be explained by several mechanisms, such as the increasing number of MRs, as demonstrated in animal models [32, 33]. Other studies showed MR is activated independently of aldosterone: MR can be activated in the kidney by rac1, a small G protein associated with salt-sensitive AH [34], probably activated by the local Ang II [35]. Cyclin-dependent kinase 5 may be another mediator in the increase MR activation, particularly in the brain, where MRs regulate the transcription of other genes closely related to BP control, as AGT, ACE and AT1 [36]. They also increase oxidative stress or sensitise the effect of Ang II, thereby activating the paraventricular nucleus to induce sympathetic overactivity [36, 37].

Arterial hypertension and heart failure

Epidemiology AH represents a leading risk factor for the development of symptomatic HF. The observational studies based on the Framingham cohort provide the most relevant evidence on the natural history of HF and its link with blood-pressure status. In the first report from this study, AH was arbitrarily defined as the finding of two systolic pressures of 160 mmHg (or greater) or two diastolic pressures of 95 mmHg (or greater), while normotension was defined as systolic pressures below 140 and diastolic pressures below 90. The diagnosis of HF was entertained on clinical grounds, chest x-ray and total vital capacity [38, 39]. Analysing the data from the first 16 years of follow-up, Kannel et al. in 1972 observed that the risk for hypertensive patients to develop HF was six times that for normotensive patients. Furthermore, 75% of those who acquired HF during the follow-up had prior AH [39]. As AH typically develops many years before the diagnosis of HF, it has been challenging to identify risk estimator tools that could provide reliable estimates of the impact of AH on the risk of HF. Lifetime risk algorithms represent novel and practical approaches to estimate the cumulative risk of developing a disease during the remaining lifespan. In 2002, Lloyd-Jones et al. calculate the lifetime risk of HF in subjects from the Framingham cohort who underwent an examination between 1971 and 1996 [40]. They stratified subjects according to the BP in three groups: systolic BP < 140 mmHg and diastolic BP < 90 mmHg; systolic BP from 140 to 159 mmHg and diastolic BP from 90 to 99 mmHg; ≥ 160 mmHg of systolic BP or ≥ 100 mmHg of diastolic BP. They found a twofold increase in remaining lifetime risk for HF from the lowest to highest BP group: from the 17.4% of a 60-year-old man with a BP less than

140 mmHg to the 29% of a man of the same age with a BP of 160 mmHg or greater. Similarly, the rise of lifetime HF risk goes from 14.4 to 27% in a 60-year-old woman [40, 41]. Accordingly, AH is now considered the factor which carries the highest attributable risk for HF in the general population [42].

Heart failure with preserved vs reduced ejection fraction Beyond the clinical, instrumental and laboratory diagnostic criteria, the main terminology used to classify HF is based on the measurement of left ventricular ejection fraction (LVEF), describing HF patients with reduced LVEF (< 40%; HFrEF), normal LVEF (≥ 50%; HFpEF) and a LVEF in the range of 40–49%, (defined as HF with mid-range LVEF, HFmrEF) [43]. Differentiation of HF patients based on LVEF is essential due to different population characteristics and response to therapies [43]. The introduction of HFpEF in official nomenclature is recent [44] and, in the last years, intense research activity has been taking place to identify the characteristic of patients with HFpEF. In a sub-analysis of the Framingham Heart Study, D.S. Lee et al. examined the pre-onset and time-of-onset characteristics of HFpEF versus HFrEF between 1981 and 2004. Pre-onset AH carried a more than twofold increased odds of HFpEF versus HFrEF and, at the onset of HF, a higher systolic BP increased the odds of HFpEF versus HFrEF by 13% for each 10-mmHg increase [45]. Later, Lam et al. published a meta-analysis aimed to clarify the epidemiological characteristics of HFpEF patients. They found that older age, female sex, high prevalence of atrial fibrillation and non-cardiovascular comorbidities were more commonly associated with HFpEF compared with HFrEF. AH represented the most prevalent cardiovascular risk factor associated with HFpEF [46]. Ho et al. examined the risk profile of HF patients from four longitudinal community-based cohorts, suggesting a poor association between AH and HFrEF, while the relative risk of HFpEF increased by 14% per 20 mmHg systolic BP and by 42% if taking antihypertensive treatment [47]. Based on these findings, hypertensive patients can be classified as having stage A HFpEF, according to the American College of Cardiology Foundation/American Heart Association stages of HF [42, 48]. The mechanisms underpinning the transition to asymptomatic hypertensive heart disease (stage B HFpEF) and overt clinical failure (stage C–D HFpEF) remain mostly unknown and represent an area of intensive research in cardiovascular medicine, as they could identify novel potential targets for more effective therapeutic or preventive strategies.

Pathophysiology LV diastolic dysfunction and cardiac remodelling are the first discernible manifestations of heart disease in patients with AH. Cardiac remodelling due to a predominant pressure overload consists of concentric LV hypertrophy (increase in cardiac mass at the expense of chamber volume) and is typically associated with diastolic dysfunction [49]. This is in contrast with cardiac remodelling due to predominant volume overload (e.g. obesity, chronic kidney disease, anaemia, heart valve regurgitation), resulting in eccentric hypertrophy (increase in cardiac mass and chamber volume) [50]. The adverse evolution of decompensated concentric remodelling is towards HFpEF, while the eccentric remodelling generally progresses to HFrEF [51]. Isolated diastolic dysfunction in HFpEF can trigger pulmonary congestion and acute oedema, even in the presence of a normal EF [52]. However, the end-stage of hypertensive heart disease is characterised by the coexistence of longstanding pressure and volume overload, causing a dilated cardiomyopathy with both diastolic and systolic dysfunctions. In this advanced stage, systolic BP is usually low, a phenomenon termed as "decapitated hypertension". The cause is to be looked in the severe LV systolic and diastolic dysfunctions, which results in a reduced pump function and fall in cardiac output, despite the presence of compensatory mechanisms such as peripheral vasoconstriction [53]. Patients with decapitated hypertension are challenging to manage because of their inability to tolerate high doses of HF medications, most of which tend to lower BP, such as ACE inhibitors or angiotensin receptor blockers (ARBs), diuretics and beta-blockers [54]. In turn, raise of BP values is a common finding when patients recover from decompensated HF [55], as demonstrated in HF patients who responded to cardiac resynchronisation therapy [56]. This could explain the evidence that higher BP in patients with overt HF seems to have a protective effect on survival in both acute [57] and chronic [58] settings. The magnitude of heart rate reduction triggered by beta-blockers or ivabradine is indirectly proportional to the increase in central BP, and this raise may be an additional reason for the beneficial effect of these drugs in HF [59, 60]. In parallel, the same hemodynamic mechanism accounts for the failure to reduce outcomes in patients with AH and coronary artery disease [61].

Other characteristics of heart disease in HFpEF are coronary microvascular rarefaction and myocardial fibrosis. Both features may be the result of a systemic inflammatory state and oxidative stress, accelerated by the previously described comorbidities of HFpEF [62, 63]. In turn, these alterations affect other target organs, e.g. the kidney, whose function and structure become progressively impaired with longstanding hypertensive cardiovascular disease. The so-called cardiorenal syndrome can occur acutely or chronically and evolve in both directions: from HF to renal failure and vice versa [64, 65]. Independently from the renal or cardiac origin of this syndrome, the coexistence of heart and kidney dysfunction significantly complicates clinical management: renal failure in HF requires incremental therapies, but enhances the risk of hyperkalemia and limits the therapeutic armamentarium available to the clinician [43].

Drugs inhibiting the renin-angiotensin-aldosterone system in the management of arterial hypertension and prevention of heart failure

Treatment of AH is based on different classes of drugs; even if all antihypertensive drugs lower BP, there are significant differences in their capacity to prevent the evolution towards HF as well as the occurrence of HF complications.

Beta-blockers remain a cornerstone in the treatment of HF, but in a large meta-analysis conducted in patients with AH, they did not prove a better preventive effect on HF than do other antihypertensives; this might be related to the limited capacity of beta-blockers to reduce central blood pressure compared with other classes of antihypertensive drugs [66]. Also, beta-blockers were associated with increased stroke risk in the elderly [67]. As regards calcium-channel blockers (CCBs), a meta-analysis demonstrated that CCBs increased the risk of HF events when compared with diuretics, ACE inhibitors and ARBs [68]; therefore, caution should be exercised when using CCBs for prevention of HF in hypertensive patients. A similar approach can be recommended for alpha-blockers, as they are associated with a higher risk of stroke and HF when compare with chlorthalidone [67, 69]. On the contrary, thiazide-like diuretics chlorthalidone and indapamide are useful antihypertensive drugs to prevent HF [70–72]. The efficacy of diuretics as a group in HF prevention was tested in multiple randomised controlled trials, showing a significant superiority to the other antihypertensives [73]. No outcome data are available for hydrochlorothiazide, regarding HF or any other cardiovascular endpoint; that is why hydrochlorothiazide should not be considered the first-line treatment in hypertensive patients at risk for HF [51].

The blockers of the RAAS are effective drugs to treat AH and prevent HF. There are no differences in antihypertensive efficacy between ACE inhibitors and ARBs [74, 75]. However, the assumption that the BP-lowering effect is dose-dependent is not appropriate for all the drugs that block the RAAS. Indeed, most ACE inhibitors and ARBs have a flat dose-response curve for BP decrease, meaning an increase in dose prolongs the duration of action but does not yield higher potency. Perindopril is the only compound of its class to show a real dose-response curve for BP decrease [76]. Irrespective of pharmacokinetics, different studies demonstrated that the effectiveness of RAAS blockers (both ACE inhibitors and ARBs) on target organ damage is dose-dependent and at least partially unrelated to BP control [24, 28, 77].

Finally, there is growing evidence to suggest the use of MRAs in resistant hypertension [78, 79]. Noteworthy, some patients develop antiandrogenic side effects (e.g. breast tenderness or gynecomastia, impotence in men and menstrual irregularities in women) and the use of MRAs should be restricted to patients with an eGFR $\geq$45 mL/min and a plasma potassium concentration of $\leq$4.5 mmol/L, with electrolytes and eGFR monitoring soon after initiation and at least annually thereafter [78].

Drugs inhibiting the renin-angiotensin-aldosterone system in the management of HFrEF

Current recommendations contained in HF guidelines suggest the use of RAAS inhibitors at the maximum tolerated dose in HFrEF [14]. So far, ACE inhibitors have been shown to have a better impact in reducing all-cause mortality than ARBs, thanks to the results of ASCOT-BPLA, ADVANCE and HYVET trials [80–82]. Also, ACE inhibitors showed to reduce LV size and maintain LV function after MI, both in animal [83] and humans [84] studies. The reverse remodelling of LV was confirmed after a 1-year follow-up [85, 86] and in patients with non-ischemic LV dysfunction [87]. ACE inhibitors do not completely suppress the RAAS, because of the generation of Ang II through alternative pathways; therefore, the combination of ARB to an ACE inhibitor can suppress the RAAS more effectively. Three large randomised trials have explored the additive benefits of combination therapy: the VAL-HeFT trial [88], the VALIANT trial [89] and the CHARM-Added trial [90]. No effect on mortality was observed, even if the VAL-HeFT and the CHARM-Added trial showed a significant reduction in HF hospitalisation. However, dual RAAS inhibition caused more side effects than monotherapy, in particular, hypotension, worsening renal function and hyperkalaemia [90, 91]. Therefore, aldosterone antagonism is to be preferred over ARB/ACE inhibitor combination. Aldosterone actively participates in the initiation and progression of HF, enhancing pro-inflammatory and profibrotic signalling [28]. The use of aldosterone antagonists reduces the risk of arrhythmia because of higher serum potassium levels and promotes LV reverse remodelling both in animal [92] and humans [93] studies. The RALES trial investigated the use of spironolactone in HFrEF patients, demonstrating a significant reduction in the risk of mortality, HF deaths, sudden cardiac deaths and HF hospitalisation [94]. Similar findings were confirmed with eplerenone in the EPHESUS [95] and the EMPHASIS-HF trials [96]. Notably, all the trials excluded patients with significant renal dysfunction (serum creatinine $>$2.5 mg/dL in men or $>$2 mg/dL in women or glomerular filtration rate $<$30 mL/min/1.73 m^2) or hyperkalemia ($>$5 mmol/L), and the treatment groups had higher rates of hyperkalemia. The American and European HF Guidelines recommend against the use of all three RAAS inhibiting agents (ACE inhibitors, ARBs and aldosterone antagonists) concomitantly [43, 97].

The first direct renin inhibitor introduced was aliskiren: it blocks the initiation of the RAAS cascade, reducing levels of

renin and angiotensin. The initial enthusiasm for this drug, capable of lowering neurohormone levels in patients already on optimal therapy [98], collided with the results of large randomised trials: in the ALTITUDE, aliskiren increased the rate of CV death compared with placebo in patients with diabetes and either kidney disease or known CV disease [99]; in the ASPIRE, aliskiren did not have additional effects on LV remodelling in patients after MI and increased the incidence of adverse effects (hypotension, renal dysfunction and hyperkalemia) [100]; in the ASTRONAUT, aliskiren addition to the standard therapy in HFrEF did not reduce CV deaths or HF hospitalisation and increased adverse events [101]. Currently, there are no recommendations regarding direct renin inhibitors in international guidelines [43, 97].

Recently, a novel drug has been introduced in HF management: the angiotensin II receptor–neprilysin inhibitor (ARNI) valsartan/sacubitril [43]. The clinical breakthrough of ARNI came after disappointing efforts in modulating NPS, which started with nesiritide, a recombinant human BNP [102], and carperitide, a recombinant ANP [103]. Afterwards, neprilysin inhibitors to prevent the breakdown of natriuretic peptides were developed; they successfully promote natriuresis and increase urinary excretion of ANP but also increase angiotensin II levels (and other substrates for neprilysin such as endothelin, vasopressin and bradykinin) potentially counteracting the actions of the former peptides [104]. The first solution to the problem was the adoption of a dual blockade of RAAS and the natriuretic peptide system: the combined ACE and neprilysin inhibitor omapatrilat did not reduce the primary endpoint (death from any cause or HF hospitalisations) in a large randomised controlled trial against enalapril [105]. Moreover, the rate of angioedema was much higher in the omapatrilat group, due to the inhibition of aminopeptidase P, which catabolises bradykinin. Therefore, the combination of ARB and a neprilysin inhibitor was tested, leading to the design of ARNI sacubitril/valsartan. Prodrug sacubitril, when active as sacubitrilat, does not inhibit aminopeptidase P. Also, sacubitril/valsartan is given twice daily, with a sustained neprilysin and RAAS inhibition over a 24-h period and in the absence of the significant early postdose hypotension seen with omapatrilat [106]. The randomised control trial was conducted in HFrEF outpatients and terminated early due to a sustained and highly significant reduction in the risk of the primary composite endpoint (CV death or HF hospitalisation) and CV mortality in the sacubitril/valsartan group compared with the enalapril group [43]. There was no statistically significant between-group difference in the rate of angioedema; hypotension was significantly more common with sacubitril/valsartan than with enalapril, although this rarely led to study-drug discontinuation ($p = 0.38$ vs enalapril). ARNI represents not only a treatment for HF but has been suggested as a very effective antihypertensive drug [9, 107, 108], above all in HF patients with persisting AH, in which treatment recommendations are purely empirical [51]. Of course, all HF patients should have a baseline triple therapy, consisting of an ACE inhibitor or an ARB, plus a beta-blocker and a loop diuretic. If despite this medical therapy patients still exhibit residual hypertension, the addition of an MR antagonist or switch to ARNI is advisable to reduce cardiac afterload [43, 109].

Drugs inhibiting the renin-angiotensin-aldosterone system in the management of HFpEF

Data available on the use of RAAS inhibitors in patients with HFpEF are fewer and less precise. In the CHARM-Preserved trial, candesartan was compared with placebo in HF patients with an LVEF > 40%, demonstrating no difference in the primary outcome of CV death or HF hospitalisation [110]. Likewise, perindopril and irbesartan did not reduce the same

Table 1 Effects of renin-angiotensin-aldosterone system blockade

	Outcomes			Guideline-directed medical therapies			
	Morbidity	Mortality	Surrogate endpoints	ACEI	ARB	MRA	ARNI
Hypertension	↓ Heart failure [74, 75]	↓ All-cause death [80–82]	↓ LV size [84–87, 93] ↑ LV function [84–87] ↓ Arrhythmias [93]	I	I	I	?
HFpEF	No benefit [110–113]	No benefit [110–113]	↓ NT-proBNP [114] ↓ NYHA class [114] ↓ LA size [114]	X	IIb	IIb	?
HFrEF	↓ Hospitalisation [94–96]	↓ All-cause death [43, 94–96] ↓ HF death [43, 94–96] ↓ Sudden cardiac death [43, 94–96]	↓ NYHA class [42, 43, 48] ↑ Quality of life [42, 43, 48] ↑ Exercise tolerance [42, 43, 48]	I	I	I	I

ACEI, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin II receptor blocker; *ARNI*, angiotensin receptor–neprilysin inhibitor; *HFpEF*, heart failure with preserved ejection fraction; *HFrEF*, heart failure with reduced ejection fraction; *LA*, left atrium; *LV*, left ventricle; *MRA*, mineralocorticoid receptor antagonist; *NT-proBNP*, N-terminal pro-brain natriuretic peptide

primary endpoint in the PEP-CHF [111] and I-PRESERVE trials [112], respectively. In the TOPCAT trial, HFpEF patients were randomised to spironolactone or placebo: there was no reduction in the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest or HF hospitalisation [113]. There is little experience with sacubitril/valsartan in HFpEF: in a phase 2 randomised trial of patients with HFpEF, NT-proBNP fell in the sacubitril/valsartan group in comparison with valsartan, along with reductions in NYHA class and left atrial volumes [114]. A large multicentre randomised outcome trial of sacubitril/valsartan versus valsartan in HFpEF [115] has been terminated early, and results will be available shortly. The effects of RAAS blockade in AH, HFpEF and HFrEF are summarised in Table 1.

The different responses to therapies in HFrEF and HFpEF can be attributed to the distinct demographic characteristics, aetiologies and comorbidities between the two groups. Thus, the American and European recommendations for the management of HFpEF currently suggest focussing on managing comorbidities and risk factors [43, 97]. Diuretic therapy can help alleviate symptoms in patients who exhibit signs of congestion, while there are no specific guideline-directed medical therapies that are class IIa– or class I–recommended to improve outcomes for patients with HFpEF.

Summary

Based on current evidence, AH remains the leading cardiovascular risk factor for HF. It is conceivable that common pathophysiological mechanisms underlie both diseases. Among these, the hyperactivation of the RAAS represents a central alteration, promoting the vascular and cardiac modifications detected in both disorders. Consequently, the use of RAAS blockers remains the cornerstone of both AH and HF treatment. However, evidence of the potential benefits related to the administration of this class of drugs in patients with HFpEF remains limited. This drawback might reflect the lack of knowledge on the mechanisms leading the transition from AH to HF and late complications; more studies are needed to fill this gap.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation