Rationale for the use of multiple blockers of the renin–angiotensin–aldosterone system in specific patient populations

Blockers of the renin–angiotensin–aldosterone system (RAAS) have an established role in the management of hypertension, cardiovascular and renal disorders. Since the RAAS can escape blockade from a drug with a single mechanism of action, it has been proposed that combining RAAS blockers with complementary mechanisms of action may provide incremental benefit. Studies utilizing various combinations of RAAS blockers have demonstrated an advantage over monotherapy in patients with resistant hypertension, heart failure and nephropathy, while failing to show benefit in patients at high risk of cardiovascular events (e.g., the ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial) and in those after a myocardial infarction. In this article, we discuss the rationale for the use of multiple blockers of the renin–angiotensin system and the evidence for and against such an approach in particular patient populations by reviewing relevant clinical trials that have addressed this hypothesis.

KEYWORDS: cardiovascular disease ▪ heart failure ▪ hypertension ▪ nephropathy ▪ renin–angiotensin system

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The renin–angiotensin–aldosterone system (RAAS) has a central role in the regulation of blood pressure (BP) and in fluid and electrolyte balance. Malfunctioning of the system has been implicated in the pathogenesis of hypertension, atherosclerosis, cardiovascular and renal diseases [1,2]. The majority of actions that are mediated by the RAAS are a result of the interaction of angiotensin II (AngII) and aldosterone with their specific receptors, the AngII type 1 (AT1) receptor and mineralocorticoid receptor, respectively. The more recent description of a receptor that is activated by binding renin and prorenin may provide yet another pathogenically important pathway, although the implications of this pathway for human disease have not been firmly established [3,4].

Multiple agents have been developed that block the signaling of the RAAS at various steps along the cascade (Figure 1). β-blockers (BBs) inhibit renin release. Unlike other RAAS blockers, BBs have diverse mechanisms of action, some of which are independent of the RAAS. Thus, BBs will not be addressed further in this review. However, it is important to note that in many of the trials discussed in this review, RAAS blockers were used in addition to a background of BBs. The newly developed direct renin inhibitors (DRIs) block the enzymatic activity of renin by competing with angiotensinogen for the active site of the enzyme [4]. Angiotensin-converting enzyme inhibitors (ACE-Is) suppress the generation of AngII by inhibiting angiotensin-converting enzyme (ACE), the major enzyme responsible for converting the physiologically inert AngI into AngII. ACE-Is also inhibit the breakdown of the vasodilator bradykinin. AT1 receptor blockers (ARBs) act by selectively binding and inhibiting activation of the receptor that mediates the pathogenic actions of AngII but does not hinder activation of the other AngII receptors, which may exert vasculoprotective actions [5]. Furthermore, ARBs are better tolerated than ACE-I and block the actions of AngII irrespective of whether it was generated by ACE or other enzymes, such as chymase [6,7]. Mineralocorticoid receptor antagonists (MRAs) block the actions of aldosterone, thus providing incremental benefit to other RAAS blockers [8].

Individual RAAS blockers, when used as monotherapy, are incapable of completely blocking RAAS signaling, often resulting in uncontrolled hypertension and development of target organ damage [9,10]. This is partly due to the ability of the system to escape blockade from an agent with a single mechanism of action, providing a rationale for the hypothesis that combining RAAS blockers with complementary mechanisms of action results in better BP reduction and target organ protection than monotherapy with a RAAS blocker in certain high-risk subsets of patients with hypertension and/or various forms of cardiovascular and renal diseases. In this article, we will review the studies that tested this important clinical hypothesis, highlighting

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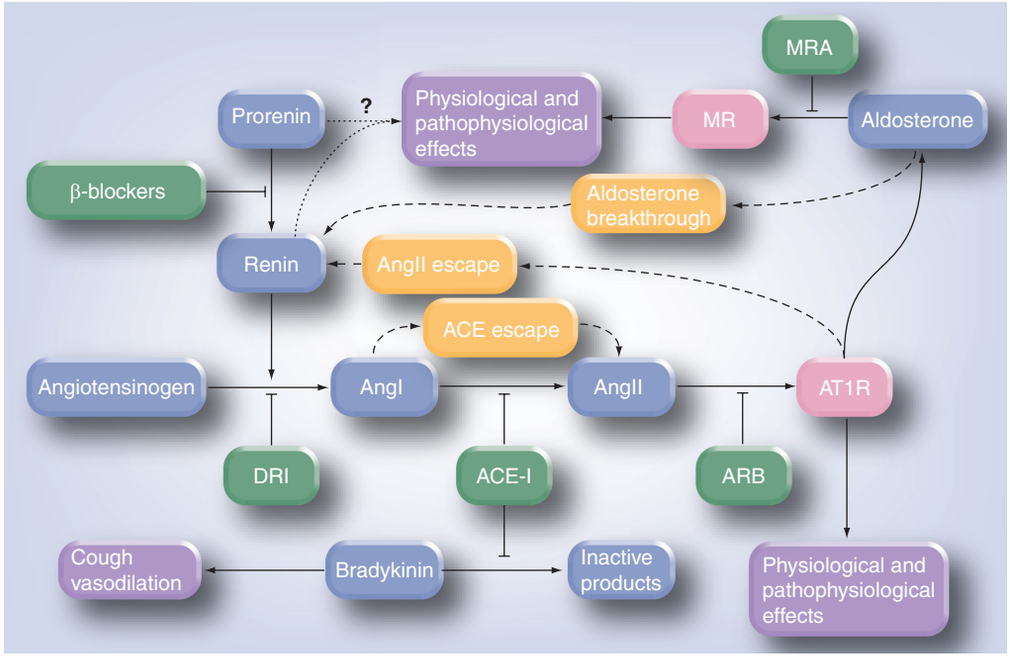

Figure 1. Renin–angiotensin–aldosterone system, showing clinically available classes of agents that can block the system and escape mechanisms inherent within the system. The dashed lines represent mechanisms by which the system escapes blockade with ACE-I, ARB or MRA monotherapy, since these drugs are not capable of fully blocking the system over time. ACE escape occurs when, during chronic ACE-I use, circulating AngII levels return towards normal due to the generation of AngII by pathways that are independent of ACE. AngII escape occurs when the negative feedback loop by which AngII normally inhibits renin release is interrupted during chronic therapy with ARBs or ACE-Is. Aldosterone escape or aldosterone breakthrough occurs when plasma aldosterone levels return towards pretreatment levels in patients on chronic renin–angiotensin–aldosterone system blocker therapy. Prorenin and renin have been proposed to cause physiological and pathophysiological effects independent from AngII by binding to and activating prerenin receptors. This pathway is represented by a dotted line with a question mark since its clinical significance has not yet been validated.
ACE-I: Angiotensin-converting enzyme inhibitor; Ang: Angiotensin; ARB: Angiotensin receptor blocker; AT1R: Angiotensin II receptor type 1; DRI: Direct renin inhibitor; MR: Mineralocorticoid receptor; MRA: MR antagonist; RAAS: Renin–angiotensin–aldosterone system.
Modified with permission from [10].

the potential benefit of dual RAAS blockade in specific patient populations, as well as concerns over its safety.

ARBs in combination with ACE-Is

The RAAS can escape blockade with either ACE-I or ARB when used as monotherapy since these drugs are not capable of fully blocking the system over time (Figure 1) [11]. Thus, after chronic ACE-I use, circulating AngII levels return towards normal due to the generation of AngII by pathways that are not dependent on ACE – a phenomenon commonly referred to as ACE escape. A second compensatory mechanism that contributes to increasing AngII levels after chronic therapy with ACE-I and ARBs, termed AngII escape, is dependent on interruption of the negative feedback loop by which AngII normally inhibits renin release. In patients treated with ACE-I or ARBs, decreased AngII levels (when treated with ACE-I) or decreased action of AngII on the AT1 receptors (when treated with ARB), results in a reactive rise in plasma renin activity (PRA) [12]. It should also be mentioned that the decrease in BP seen with these agents can also contribute to the rise in PRA.

A large proportion of patients with hypertension require multiple medications to achieve BP control [13]. This is usually achieved by combining antihypertensive agents from different drug classes that have complementary mechanisms of action, such as RAAS blockers with thiazide diuretics or calcium channel blockers [14]. Combined use of older RAAS blockers (ACE-Is and ARBs) in patients with uncomplicated hypertension is not usually advocated, due to a lack of evidence of benefit. In a meta-analysis of 14 trials that compared ACE-I/ARB combination therapy to monotherapy with either an ACE-I or an ARB, the combination decreased the clinic and 24-h

ambulatory BP by 3.8/2.7 and 4.7/3.0 mmHg compared with the ACE-I monotherapy and by 3.7/2.3 and 3.8/2.9 mmHg when compared with ARB monotherapy, respectively [15]. It should be noted that in many of these studies suboptimal doses of the drugs were used. The Candesartan and Lisinopril Microalbuminuria (CALM) II study compared the effect of uptitrating the dose of lisinopril from 20 to 40 mg daily to adding candesartan 16 mg daily to lisinopril 20 mg and thus compared full doses of medications in both arms, in patients with diabetes mellitus and hypertension. The CALM study failed to show a difference in either seated or 24-h ambulatory systolic BP between the two groups, although both strategies lowered BP when compared with the initial lisinopril dose [16]. Thus, the combination of an ACE-I with an ARB is not recommended for treatment of uncomplicated hypertension [17,18].

Major benefits have been associated with use of RAAS blockers in patients with heart failure (HF), opening the door for studies that tested whether a combination of an ACE-I with an ARB provides incremental benefit in this population [19]. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study, symptomatic HF patients with depressed left ventricular ejection fraction (LVEF) were randomized to receive the ARB candesartan, the ACE-I enalapril or both [20]. Although there was no difference in the 6 min walk distance, New York Heart Association (NYHA) functional class or quality of life between the groups, there was a smaller increase in ventricular volumes (end systolic and end diastolic) and a trend towards an increase in LVEF in the combination arm compared with either monotherapy. Brain naturetic peptide (BNP) levels, aldosterone levels and BP were lower in the combination group and renin levels were higher. This study suggested that dual blockade of the RAAS may be more beneficial than monotherapy in preventing ventricular dilation and stimulated the design of larger trials that were powered to detect the differential effects of combination versus monotherapy on major clinical outcomes.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial randomized 2548 patients with symptomatic HF and left ventricular (LV) dysfunction who were already on a stable ACE-I dose to receive the ARB candesartan or matching placebo [21]. After a median follow-up of 41 months, the primary outcome (i.e., cardiovascular death or unplanned admission to the hospital for HF) occurred less often in the ACE-I + ARB group than the ACE-I alone group (38 vs 42%, 15% relative risk reduction, $p = 0.01$). Candesartan also reduced the individual components of the primary outcome (each by 17%), as well as each of a host of secondary outcomes, including a composite of cardiovascular death, HF admission, myocardial infarction (MI), stroke or coronary revascularization. The combination treatment was as effective in all predefined subgroups, including those receiving the recommended dose of an ACE-I. Drug discontinuation was higher in patients assigned to the dual therapy than to monotherapy due to any adverse event (24.2 vs 18.3%), including hyperkalemia (3.4 vs 0.7%) and an increase in creatinine (7.8 vs 4.1%).

In the Valsartan Heart Failure Trial (Val-HeFT), addition of an ARB, valsartan, versus placebo to standard therapy for HF (which included an ACE-I in 93% of patients and a BB in 35% of patients in each arm of the study) in patients with symptomatic HF with LV dysfunction and dilation resulted in a lower rate of the composite outcome of death from any cause, hospitalization for HF, cardiac arrest with resuscitation or intravenous inotropic or vasodilator therapy (28.8 vs 32.1%, relative risk reduction 13.2%, $p = 0.009$) [22]. Overall mortality was similar between the groups and the difference in the composite outcome was predominantly due to a lower HF hospitalization rate in the group receiving dual RAAS blockers (13.8 vs 18.2%, 24% relative risk reduction, $p < 0.001$).

Data from CHARM and Val-HeFT led to the class IIb recommendation (level of evidence B) that use of an ARB/ACE-I combination may be considered in current practice guidelines in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy for HF [19]. Importantly, safety data regarding the use of this combination in patients taking a BB, MRA or DRI are limited. In Val-HeFT, the addition of an ARB was associated with an increased risk of mortality and an increased risk of the combined end point of mortality and morbidity in the subgroup of patients who were receiving a BB in addition to an ACE-I at baseline [22]. By contrast, in the CHARM-Added trial, patients who were receiving a BB at baseline experienced similar benefit with the addition of an ARB to an ACE-I as those not on a BB at baseline [21]. Thus, the risk:benefit ratio of adding an ARB to an ACE-I in patients receiving other RAAS blockers is still unclear.

The decision should be individualized for each patient based on the persistence of symptoms of HF in patients on either monotherapy in addition to the risk of hyperkalemia associated with the combination therapy.

Although multiple studies have demonstrated benefit of ACE-I in patients after an acute MI, especially in the presence of LV systolic dysfunction, the Valsartan in Acute Myocardial Infarction (VALIANT) study, did not show a survival benefit from using a combination of an ACE-I (captopril) and an ARB (valsartan) in MI patients with HF or LV dysfunction, as compared with each drug alone [23]. Similarly, the composite outcome of cardiovascular death, MI or hospitalization for HF was not reduced in the group assigned the dual therapy. More patients had adverse events and more patients discontinued study medications in this group compared with the group receiving captopril alone.

The Heart Outcomes Prevention Evaluation (HOPE) trial established a role for the ACE-I ramipril in the prevention of death, MI, stroke, coronary revascularization, cardiac arrest, HF and diabetes mellitus in patients at high risk of cardiovascular events but who have preserved LV function [24]. The Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET) tested whether the combination of the ARB telmisartan and the ACE-I ramipril is more beneficial than the ACE-I alone in preventing cardiovascular disease outcomes in a high-risk HOPE-like population [25]. The study randomized 25,620 patients to receive talmisartan 80 mg, ramipril 10 mg or the combination of both drugs, and followed them for a median of 56 months. Although the BP was lower in the combination group compared with the ramipril group by 2.4/1.4 mmHg, the primary composite outcome of death from cardiovascular causes, MI, stroke or hospitalization for HF, as well as its individual components, was similar in both groups. There was a slightly higher number of deaths in the combination therapy arm (relative risk of 1.07), but this did not reach statistical significance. Significantly more patients in the telmisartan plus ramipril group had hyperkalemia and there was a 33% increased risk of renal impairment (1.33, $p < 0.001$) when compared with the ramipril alone group. Furthermore, discontinuation of the drugs was more frequent in the combination arm.

Patients with chronic kidney disease (CKD) are at increased risk of cardiovascular events as well as progression towards end-stage renal disease, and there is a need for tailoring better therapies in this population [26]. BP control is the single most important treatment goal in patients with CKD, and RAAS blockers are preferred over other antihypertensive medications in CKD patients with diabetes mellitus and/or proteinuria since they can decrease proteinuria and slow the progression of CKD [27]. In the CALM study, use of the ARB candesartan and the ACE-I lisinopril combination resulted in a greater reduction in BP accompanied by a greater reduction in urinary albumin:creatinine ratio than either monotherapy [28]. Several other small studies have also suggested that dual blockade of the RAAS with ACE-Is and ARBs can be more effective than either monotherapy in reducing proteinuria and in slowing the progression of renal dysfunction [29].

A well-performed meta-analysis addressed the effect of RAAS blockers on proteinuria in patients with CKD [30]. Although the main aim of the study was to evaluate the effect of ARBs on urinary protein excretion in patients with nephropathy, it included 16 studies that compared ACE-I/ARB with ARB and 23 studies that compared ACE-I/ARB with ACE-I monotherapy. ACE-I and ARB monotherapy resulted in similar antiproteinuric effects and combination therapy reduced proteinuria beyond the level achieved with ARBs alone (24% at 1–4 months and 25% at 5–12 months) or with ACE-I alone (22% at 1–4 months and 18% at 5–12 months). Sensitivity analysis revealed consistent effects on proteinuria in patients with diabetic and nondiabetic nephropathy. Despite these encouraging results, the authors cautioned against the adoption of this strategy owing to the lack of safety data for the combination therapy. Another reason for caution is that the effect of dual RAAS blockade on proteinuria may not be parallel to its effect on hard renal outcomes. For example, in the ONTARGET trial, the combination of an ARB with an ACE-I resulted in a reduction in the progression of albuminuria compared with ACE-I treatment alone, but was associated with an increase in the primary renal outcome, a composite of dialysis, doubling of serum creatinine or death (HR: 1.09; $p = 0.037$) and an increase of the secondary outcome of dialysis or doubling of serum creatinine (HR: 1.24; $p = 0.038$) [31].

DRIs in combination with ACE-Is & ARBs

Direct renin inhibitors, the newest class of RAAS inhibiting antihypertensive agents, block the RAAS by inhibiting the catalytic action of renin on angiotensinogen and preventing the

generation of AngI [32]. By acting upstream in the RAAS cascade, DRIs may offer advantages over other RAAS blockers, which act downstream of renin (FIGURE 1). Specifically, since DRIs lower circulating AngII by reducing PRA they can partially overcome the ACE escape, caused by the generation of AngII by ACE-independent mechanisms in patients on chronic ACE-I therapy and AngII escape in patients on chronic ARB therapy by blocking AngII-induced feedback inhibition of renin release [33]. Indeed, in healthy volunteers, adding a DRI to an ACE-I or an ARB prevents the rise in PRA seen with either monotherapy [34,35]. Although the prorenin receptor has been suggested to mediate AngII-independent effects, DRIs have not been shown to interfere with this signaling [32,36,37].

In patients with hypertension, combining a DRI with an ACE-I or an ARB provides further BP lowering with minimal adverse effects [33,38–40]. In these trials, combination therapy resulted in a greater rise in plasma renin concentration, assessed by direct measurement of renin protein, while blunting the rise in enzymatically active renin, assessed by generation of AngI in an *in vitro* assay system (i.e., PRA), seen with ACE-I or ARB monotherapy. A large study was designed to assess the efficacy of combining the maximally approved therapeutic doses of a DRI, aliskiren (300 mg), and an ARB, valsartan (320 mg) [38]. It randomized 1797 patients with hypertension to receive either monotherapy, the combination of aliskiren and valsartan or matching placebo for 8 weeks in a double-blind controlled fashion. While both monotherapies provided greater reductions in BP compared with placebo, the combination provided an incremental reduction in mean sitting systolic and diastolic BP from baseline over that of the DRI (4.2/3.2 mmHg, $p < 0.0001$) or the ARB (4.4/2.5 mmHg, $p < 0.0001$) alone. BP control was achieved in a significantly higher proportion of patients receiving the combination than in the DRI or ARB groups (49 vs 37 and 34%, respectively). In a subset of 354 patients, the combination group experienced a greater reduction in mean systolic and diastolic BPs on 24-h ambulatory monitoring than in either monotherapy arm. The combination of a DRI and an ARB resulted in a greater rise in plasma renin concentration compared with either monotherapy, while suppressing the increase in PRA seen in the ARB alone group. Adverse events occurred at a similar frequency in all groups. Serious adverse events (including hyperkalemia) were rare and also comparable between groups.

The benefit of dual blockade of the RAAS with a DRI in addition to an ACE-I or an ARB in patients with symptomatic HF was evaluated in the Aliskiren Observation of Heart Failure Treatment (ALOFT) trial [41]. The study included 302 symptomatic HF patients with hypertension who were already on stable doses of an ACE-I or an ARB and a BB and had a BNP of more than 100 pg/ml. Patients were subsequently randomized in a double-blind fashion to aliskiren or matching placebo for 12 weeks. The main aim of the study was to assess the safety and tolerability of adding a DRI in this population and also to assess the effect of treatment on naturetic peptides, LV remodeling and HF symptoms. The treatment phase was completed in 92% of patients and all treatments were well tolerated, with similar rates of adverse events, including renal dysfunction and hyperkalemia, to placebo. The primary efficacy outcome, plasma N-terminal pro-BNP, increased from baseline by 762 ± 6123 pg/ml (from 2123 ± 3858 to 2885 ± 6393 pg/ml) in the placebo group and decreased by 244 ± 2025 pg/ml (from 2158 ± 2269 to 1915 ± 2373) in the aliskiren group ($p = 0.01$). BNP (from 273 ± 246 to 261 ± 272 pg/ml in placebo group and from 301 ± 269 to 240 ± 307 in aliskiren group, $p = 0.02$), urinary aldosterone (from 37 ± 41 to 31 ± 33 nmol/d in placebo group and from 38 ± 43 to 29 ± 33 nmol/d in aliskiren group, $p = 0.01$) and PRA (from 8.38 ± 12.98 to 7.42 ± 11.54 ng/ml/h in placebo group and from 7.32 ± 11.70 to 1.61 ± 3.47 ng/ml/h in aliskiren group, $p < 0.0001$) decreased more in the DRI group than in the placebo group. No differences were seen between groups in serum aldosterone, signs and symptoms of HF or echocardiographic measurements of LV volume or systolic function. It is notable that the addition of a DRI to an ACE-I or ARB in patients with HF who were receiving a BB (94%) and/or a MRA (33%) was safe and well tolerated. The efficacy data are also encouraging and support the performance of further trials that are powered to detect clinical benefit. The ongoing Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE) will determine whether the addition of a DRI to an ACE-I in symptomatic HF patients with low LVEF will decrease the occurrence of cardiovascular death or HF hospitalization [42].

Other trials have evaluated the effect of combination therapy with a DRI and an ACE-I or an ARB on LV remodeling. The Aliskiren Study in Post-MI Patients to Reduce Remodeling

(ASPIRE) study, failed to show a benefit on LV remodeling, as assessed by echocardiography, of adding a DRI to standard treatment with an ACE-I or an ARB in high-risk post-MI patients with LV dysfunction [43]. The Aliskiren in Left Ventricular Hypertrophy (ALLAY) trial did not show a difference in regression of LV mass by magnetic resonance imaging in overweight or obese hypertensive patients with LV hypertrophy treated with the combination of the DRI aliskiren and the ARB losartan compared with the individual therapies [44].

In patients with diabetic nephropathy, the addition of a DRI to an ARB in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study reduced urinary albumin excretion to a significantly greater extent than maximal recommended doses of the ARB alone [45]. Treatment with aliskiren 300 mg resulted in a 20% lower urinary albumin:creatinine ratio compared with placebo ($p < 0.001$) with all patients receiving losartan 100 mg and additional antihypertensive therapy aimed at achieving an optimal target BP lower than 130/80 mmHg. This effect persisted after adjustment for the change from baseline in systolic BP. A greater than 50% reduction in albuminuria was seen in 25% of patients assigned to the DRI group versus 13% of those in the placebo group ($p < 0.001$). There was no difference in the incidence of total adverse events or serious adverse events between groups. The ongoing Aliskiren Trial in Type 2 Diabetes using Cardiovascular and Renal Disease Endpoints (ALTITUDE) study is testing the hypothesis that addition of a DRI to an ACE-I or ARB will prevent hard cardiovascular and renal outcomes in a large high-risk diabetes mellitus population [46].

MRAs in combination with ACE-Is & ARBs

Aldosterone, a key effector of the RAAS, is a major regulator of sodium and potassium balance and extracellular volume and has also been shown to have potent profibrotic effects [47]. The actions of aldosterone are mediated via MRs that are expressed in the vasculature, heart and kidneys [48]. Although aldosterone is downstream of the AT1 receptor in the RAAS and aldosterone levels decrease after starting an ACE-I or ARB, they generally return towards pretreatment levels in patients who are chronically maintained on RAAS blocker therapy due to aldosterone escape or, more correctly, aldosterone breakthrough. The term aldosterone escape is usually reserved for the physiological phenomenon that occurs in hyperaldosteronism by which urinary sodium returns to normal during prolonged exposure to elevated aldosterone levels [49]. The mechanism by which aldosterone breakthrough occurs remains unclear, but it could be directly related to the rise of AngII levels seen after treatment with ACE-I and ARBs (AngII escape). MRAs can directly block the renal actions of aldosterone to prevent sodium retention and potassium excretion, as well as the profibrotic actions of aldosterone in cardiac and vascular beds. Based on these proof-of-concept studies in animal models, MRAs have been administered, in addition to other RAAS blockers (generally ACE-Is or ARBs) in patients with hypertension, HF, MI and CKD [8].

Hyperaldosteronism is the most common cause of secondary hypertension. It accounts for 5–10% of all hypertension cases and is even more common in those with resistant hypertension [8]. In a study of patients with resistant hypertension (uncontrolled BP on 4 ± 1 antihypertensive medications that included a diuretic, an ACE-I and/or an ARB), addition of low dose (12.5–50 mg) spironolactone resulted in an additional mean decrease of 25/12 mmHg in BP at 6 months of follow-up [50]. In a different study, addition of spironolactone in patients with uncontrolled BP on three to five antihypertensive medications (including a RAAS blocker in most patients), resulted in a mean decrease of 16/9 mmHg in 24-h ambulatory BP and BP control in half of the patients [51]. Interestingly, in both of these studies, the reduction in BP was similar in patients with and without hyperaldosteronism, indicating that MRAs are equally effective in reducing blood pressure in resistant hypertension patients with and without aldosterone excess [50,51]. In the multicenter international Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial, which randomized 19,257 patients with hypertension to a calcium channel blocker ± ACE-I versus a BB ± thiazide diuretic, spironolactone was recommended as a fourth-line agent for patients with uncontrolled BP on maximal doses of the two study medications and an α-blocker [52]. Spironolactone (median dose 25 mg per day) resulted in a mean BP reduction of 22/10 mmHg in the 1411 patients who received it for BP control. The effect of spironolactone was not attenuated by concomitant use of an ACE-I. In this study, adverse events attributed to spironolactone occurred in 13% of patients and resulted in temporary or permanent discontinuation of the drug in 6% of participants. The

most frequent adverse events reported were gynecomastia or breast discomfort and hyperkalemia. These studies provide convincing evidence that MRAs are effective for the control of hypertension, even when added to other RAAS blockers.

Since aldosterone has an important pathophysiological role in HF and, as stated previously, ACE-I/ARBs are unable to chronically suppress aldosterone levels, the Randomized Aldactone Evaluation Study (RALES) was designed to test the hypothesis that spironolactone (25–50 mg) would significantly reduce the risk of death among patients with severe HF as a result of systolic LV dysfunction and who were receiving standard therapy, including an ACE-I [53]. RALES randomized 1663 patients with LVEF of less than 35% who had NYHA class III or IV HF (and NYHA class IV symptoms in the last 6 months) who were being treated with an ACE-I (if tolerated) and a diuretic to receive spironolactone versus placebo. The study was stopped early after a mean follow-up of 24 months due to a 30% reduction in the risk of death in the group receiving spironolactone. There was a similar reduction in the risk of cardiac death (31%), hospitalization for cardiac causes (30%) and hospitalization for worsening HF (35%). Serious hyperkalemia occurred at similar rates in both groups, but gynecomastia occurred more often in the spironolactone group (9 vs 1%, $p < 0.001$). RALES led to the adoption of spironolactone for use in patients with severe HF in clinical guidelines [19]. The recently published Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) extended these benefits to patients with milder HF [54]. EMPHASIS-HF randomized 2737 patients with NYHA class II symptoms and an LVEF less than 30–35% to receive eplerenone (12.5–50 mg, mean dose 40 mg) versus matching placebo. After a median follow-up of 21 months, eplerenone reduced the primary composite outcome (death from cardiovascular causes or a first hospitalization for HF) by 37%, 18% in the eplerenone group versus 26% in the placebo group. Death from any cause was reduced by 24% and HF hospitalization by 42%.

Eplerenone has also been shown to decrease cardiovascular deaths in patients with LV dysfunction who sustained an MI. The Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) randomized 6642 patients with acute MI complicated by LVEF ≤40% and HF or diabetes mellitus to eplerenone (25–50 mg) versus placebo. All participants were treated with standard therapy, which included an ACE-I or ARB in 87% and a BB in 75% of cases. After a mean follow-up of 16 months, eplerenone reduced the risk of overall death by 15% and cardiovascular death by 17% [55].

Mineralocorticoid receptor antagonists may also have a renoprotective role. In a double-blind placebo-controlled study of 81 patients with diabetic nephropathy (urine albumin:creatinine ratio ≥300 mg/g) who were maintained on 80 mg lisinopril, addition of spironolactone (25 mg) resulted in a significant decrease in the urine albumin:creatinine ratio (34%, $p = 0.007$), while addition of losartan (80 mg) did not (17% reduction, $p = 0.2$). Clinic and ambulatory BP were not different between treatment groups and placebo, while both treatments resulted in similar increases in serum potassium [56]. In a small study of obese patients with hypertension and target organ damage, addition of fixed low-dose spironolactone (12.5 mg) to chronic ACE-I therapy resulted in further reductions in BP and urinary albumin excretion [57]. In a meta-analysis of 11 studies, addition of a MRA to an ACE-I and/or an ARB resulted in significant reductions in proteinuria but increased the risk of hyperkalemia [58]. To date, there are no data on the long-term effects of MRAs on hard renal outcomes.

Conclusion & future perspective

The use of multiple blockers of the RAAS has potential for the treatment of hypertension and some comorbidities. In the treatment of uncomplicated hypertension, use of an ACE-I/ARB combination provides incremental BP reduction at the expense of increased adverse events and is therefore generally not recommended. The ARB/DRI combination provides greater BP reduction than the maximum recommended dose of either component and is well tolerated. Use of a MRA with other RAAS blockers provides substantial BP reduction and is a particularly useful treatment strategy for the management of resistant hypertension. Although MRAs are not considered first-line drugs for the treatment of uncomplicated hypertension, multiple studies, some outlined in this review, demonstrate that the addition of a MRA to other RAAS blockers provides substantial benefit in patients with resistant hypertension [13,59].

In patients with HF, the ACE-I/ARB combination can provide additional benefit over each monotherapy as demonstrated in

Table 1. Appropriateness of use of multiple renin–angiotensin–aldosterone system blockers in different clinical scenarios.

Clinical scenario/treatment strategy	ACE-I + ARB	ACE-I or ARB + DRI	ACE-I or ARB + MRA
Hypertension	-	++	+++
Heart failure	++	+	+++
Nephropathy	++	++	++
High risk of CV events	-	NA	NA
Postmyocardial infarction	-	NA	NA

-: Evidence of no benefit and/or of harm; +: Weak evidence of benefit; ++: Moderate evidence of benefit; +++: Strong evidence of benefit;
ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CV: Cardiovascular; DRI: Direct renin inhibitor; MRA: Mineralocorticoid receptor antagonist; NA: Not applicable.

the CHARM-Added and Val-HeFT trials; however, it should be noted that the relative risk reduction in these trials was marginal. Evidence for use of an ACE-I or an ARB in combination with other blockers of the RAAS, such as a BB or a MRA, in HF patients is more compelling. However, data for the quadruple combination of an ACE-I, ARB, BB and MRA are currently not available and use of this combination raises safety concerns. Emerging data for the combination of a DRI with an ACE-I or an ARB and a BB in HF are encouraging, but more definitive studies with hard outcomes are needed and are underway. In patients after a MI (VALIANT) and in those at increased risk of cardiovascular events (ONTARGET) the use of an ACE-I/ARB combination provides no additional benefit to RAAS monotherapy and may cause harm.

Multiple studies have demonstrated the potential benefit of combining RAAS blockers (ACE-I with an ARB, ACE-I or ARB with a MRA or a DRI) in patients with nephropathy, specifically in those with proteinuria. Thus, a strategy of using dual RAAS blockade to decrease proteinuria and slow the progression of CKD seems

Executive summary

Introduction

- Multiple agents have been developed that block the signaling of the renin–angiotensin–aldosterone system (RAAS) at various steps along the cascade.
- Individual RAAS blockers, when used as monotherapy, are incapable of completely blocking RAAS signaling, often resulting in uncontrolled hypertension and development of target organ damage.

AT1 receptor blockers in combination with angiotensin-converting enzyme inhibitors

- The combination of an angiotensin-converting enzyme inhibitor (ACE-I) with an AT1 receptor blocker (ARB) is not recommended for treatment of uncomplicated hypertension.
- Use of an ARB/ACE-I combination may be considered in persistently symptomatic patients with reduced left ventricular ejection fraction who are already being treated with conventional therapy for heart failure (HF).
- ARB/ACE-I combination does not provide benefit over monotherapy in patients after a myocardial infarction and in those at high risk of cardiovascular events, and is associated with increased adverse events.
- ARB/ACE-I combination can be more effective than either monotherapy in reducing proteinuria and in slowing the progression of renal dysfunction.

Direct renin inhibitors in combination with ACE-Is & ARBs

- Direct renin inhibitors (DRIs) can partially overcome the ACE escape and angiotensin II escape in patients on chronic ACE-I/ARB therapy by blocking angiotensin II-induced feedback inhibition of renin release.
- In patients with hypertension, combining a DRI with an ACE-I or an ARB provides further blood pressure lowering with minimal adverse effects.
- Preliminary data suggest that DRIs may be beneficial in patients with HF on top of ACE-I or ARBs.
- In patients with diabetic nephropathy, the addition of a DRI to an ARB reduces urinary albumin excretion to a significantly greater extent than maximal recommended doses of the ARB alone.

Mineralocorticoid receptor antagonists in combination with ACE-Is & ARBs

- Hyperaldosteronism is the most common cause of secondary hypertension.
- Mineralocorticoid receptor antagonists are effective for the control of resistant hypertension, even when added to other RAAS blockers.
- Mineralocorticoid receptor antagonists provide significant benefit for the treatment of moderate and severe HF in patients receiving other RAAS blockers.

Conclusion & future perspective

- The use of multiple blockers of the RAAS has potential for the treatment of hypertension and some comorbidities.
- Multiple RAAS blockers should be used in clinical scenarios in which this strategy has been shown to be safe and provide benefit over RAAS monotherapy.

appropriate. Nevertheless, definitive studies that use hard end points, such as progression to end-stage renal disease and/or cardiovascular events, are needed and some, such as ALTITUDE, are underway [46].

It should also be emphasized that the risk of hyperkalemia increases with the use of multiple RAAS blockers and close monitoring of serum potassium may be needed, especially in patients with renal dysfunction [60]. We recommend judicious use of multiple RAAS blockers only in clinical scenarios in which this strategy has been shown to be safe and provide benefit over RAAS monotherapy (Table 1).

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