Curr Atheroscler Rep (2014) 16:403
DOI 10.1007/s11883-014-0403-7

CORONARY HEART DISEASE (JA FARMER, SECTION EDITOR)

Modulation of the Renin-Angiotensin-Aldosterone System in Heart Failure

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Published online: 9 February 2014

Abstract The renin-angiotensin-aldosterone system (RAAS) is well-established and continues to be pursued as a therapeutic target in the treatment of heart failure, predominantly due to the success of agents that block RAAS in clinical trials of systolic heart failure. The optimal treatment of heart failure patients with preserved ejection fraction (HFpEF), however, remains unclear. Early trials of direct renin inhibitors have suggested that these agents may play a role in HFpEF, but recent clinical trial results have not been encouraging. Preliminary trials of angiotensin-receptor/neprilysin inhibitors look promising. Whether results with these or other drugs will alter current recommendations remains to be seen. In this review, we assess the current understanding of the role of RAAS modulation in heart failure.

Keywords Novel therapy · Treatment · Drugs · Renin-angiotensin-aldosterone blockers · Chronic heart failure · Reduced/preserved ejection fraction

Introduction

Heart failure (HF) is a major cause of morbidity and mortality worldwide, with an increasing prevalence in Western societies [1••, 2••]. The recognition of the role of neurohormonal dysregulation, particularly of the renin-angiotensin-aldosterone system (RAAS), in the pathophysiology of HF with reduced ejection fraction (HFrEF) has led to significant advances [3]. Despite the widespread use of agents that inhibit key functions of RAAS, such as angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), the outlook for patients with HF remains poor, especially among patients who develop acute decompensated HF [4]. Furthermore, many patients remain symptomatic, with poor quality of life. An increasingly recognised subset of HF is in patients with HF and preserved ejection fraction (HFpEF), which may be equally widespread and have similar mortality to HFrEF [5]. There is currently no proven treatment strategy in HFpEF, with trials of RAAS blockade thus far failing to demonstrate improved outcomes [6•].

It is critical that research is focused on understanding the genetic, molecular, biochemical, and structural mechanisms that underpin the pathophysiology of HF, as this would enable opportunities to develop new therapeutic strategies that target the underlying processes that lead to progressive myocardial dysfunction and unfavourable remodelling.

This article is part of the Topical Collection on *Coronary Heart Disease*

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Current Perspectives in the Management of Heart Failure

The American College of Cardiology and the American Heart Association (ACC/AHA) clinical practice guidelines for the management of patients with HF identify optimal pharmacological treatment for HFrEF as the combination of an ACE inhibitor or angiotensin receptor blocker (ARB), a beta blocker, and, in select patients, a mineralocorticoid receptor antagonist (MRA), hydralazine-nitrates, and/or diuretics [1••]. While the cardiac glycoside digoxin has long been used in HF, evidence from the Digitalis Investigation Group (DIG) trial [7] concluded that it did not reduce mortality but rather reduced the rate of hospitalization both overall and for worsening heart failure. Vasopressin antagonists or ultrafiltration could be considered in the short term for patients hospitalised with

volume overload who have persistent severe hyponatraemia despite water restriction and maximisation of GDMT.

ACE Inhibitors

These agents have been shown to reduce mortality in all grades of HFrEF (CONSENSUS and SOLVD-treatment) and left ventricular (LV) dysfunction after myocardial infarction (MI) (SAVE) [8–10]. Cardiac remodelling, particularly fibrosis, seen in both the infarcted and non-infarcted myocardium, is recognised as a major determinant of the development of impaired LV function [11•]. ACE inhibition has been repeatedly shown to attenuate LV remodelling and to improve LV function in patients with HF and after MI [12]. Various mechanisms of action have been proposed. One theory suggests that by inhibiting conversion of angiotensin I (AngI) to angiotensin I (AngII) and by inhibiting the breakdown of bradykinin, ACE inhibitors have a profound effect on the neurohormonal state in HF patients. In addition, multiple effects at the cellular level on apoptosis, fibrosis, and hypertrophy have been proposed as potential mechanisms by which ACE inhibitors may inhibit the remodelling process [13, 14].

Angiotensin Receptor Blockers (ARBs)

Despite the beneficial vasodilatory effects of bradykinin, its accumulation often results in airway irritation and cough. Angioedema, a further serious side effect, is seen more often in certain patient groups such as African or African-American patients. Theoretically, as ARBs do not inhibit bradykinin breakdown, they should not cause cough or angioedema, and therefore it was anticipated that they would be better tolerated than ACE inhibitors. It was also surmised that ARBs may produce more superior RAAS blockade because non-ACE pathways, such as the chymase and cathepsin pathways, exist to generate AngII (Fig. 1). Furthermore, as ARBs are selective antagonists of the AT1 receptor (producing vasodilatation, reduced secretion of vasopressin, and reduced production and secretion of aldosterone), they may proffer the theoretical benefit of unopposed AT2 receptor agonism – increased mucosal nitric oxide production [14].

In head-to-head comparison studies, ARBs have been shown to be non-inferior (e.g., VALIANT) but not superior to (e.g. ELITE II) ACE inhibitors [15, 16], and are clinically often used as an alternative for patients who are intolerant of ACE inhibitors [17]. Studies have explored dual RAAS blockade in HF; the CHARM-Added trial found that candesartan at a target dose of 32 mg once daily reduced both HF hospitalisation (by 17 %) and cardiovascular mortality (by 16 %) [18]. However, the study was not powered to examine all-cause mortality. In the Val-HeFT trial, the addition to an ACE inhibitor of valsartan at a target dose of 160 mg twice daily did not lower mortality compared to placebo, but it did reduce HF hospitalisation [19]. Subsequent ARB "add-on" trials did not find any benefit in patients with acute myocardial infarction (VALIANT) and in patients with stable arterial disease (ONTARGET) [15, 20]. There have been several meta-analyses comparing ACE inhibitors alone or in combination with ARBs in patients with LV dysfunction or HF. The latest of these showed fewer hospital admissions for HF with combination therapy (with significant heterogeneity between included trials), but crucially, no difference for overall mortality, hospitalisation, and fatal or non-fatal MI. However, patients on combination therapy had increased rates of hypotension, renal dysfunction, and hyperkalaemia, and a higher rate of permanent discontinuation of trial medications [21]. Indeed, there is increasing concern regarding acute kidney injury and hyperkalaemia with this combination in light of the recent termination, for the same reasons, of the VA NEPHRON-D study, a multicentre trial to assess the effect of the combination of losartan and lisinopril compared with losartan alone on the progression of kidney disease in patients with diabetes and overt proteinuria [22].

Mineralocorticoid Receptor Antagonists (MRAs)

Although there are doubts regarding dual RAAS blockade with an ACE inhibitor and ARB, this is not the case with dual blockade using an ACE inhibitor and MRA [1••]. Attention was turned towards aldosterone blockade as a result of the recognition of the "aldosterone escape" phenomenon in patients on chronic ACE inhibitor therapy [23, 24]. Furthermore, experimental evidence has shown that aldosterone promotes myocardial fibrosis in animal models, particularly in a perivascular cuffing pattern [25]. The RALES trial was instigated following a proof-of-concept study in man showing that aldosterone blockade had beneficial cardiac effects when given in addition to ACE inhibitors in HF [26]. Patients with severe HFrEF (LVEF <0.35 and NYHA class IV symptoms) were randomised to 25 mg spironolactone or placebo; the primary endpoint was all-cause mortality. The study was terminated early (mean follow-up 24 months), as spironolactone produced a 30 % reduction in total mortality ($p<0.001$) [27]. Notably, spironolactone reduced both sudden deaths (by 29 %) and deaths due to progressive HF (by 36 %) [27]. This concept was then tested in the EPHESUS trial in post-MI LV dysfunction using the agent eplerenone, a much more specific inhibitor of the mineralocorticoid receptor than spironolactone, avoiding anti-androgen side effects such as gynaecomastia. EPHESUS showed a 15 % reduction in overall mortality ($p=0.008$) and 13 % reduction in cardiovascular deaths/hospitalisations ($p=0.002$) in patients with post-MI LV systolic dysfunction [28]. Serious hyperkalaemia (>6 mmol/L) was more common in the eplerenone group (5.5 % vs. 3.9 %, $p=0.002$), though this was balanced by less hypokalaemia (<3.5 mmol/L) (8.4 % vs. 13.1 %, $p<0.001$)

[28]. In the subsequent EMPHASIS–HF trial using the same agent, patients with milder (NYHA class II) symptoms and LVEF <0.35 were randomised to eplerenone (up to 50 mg/day) or placebo [29]. Eplerenone reduced cardiovascular death or HF hospitalisation (the primary endpoint) by 47 % ($p<0.001$) and reduced all-cause mortality (the secondary endpoint) by 24 % ($p=0.008$). The incidence of hyperkalaemia (K>6 mmol/L) was not significantly different (2.5 % vs. 1.9 % $p=0.29$). Of note, concomitant therapy was optimal in EMPHASIS, with 94 % receiving an ACE inhibitor (or ARB) and 87 % receiving a beta-blocker. One of the weaknesses of the RALES trial had been that beta-blockers were used in only 11 % of study participants.

Multicentre studies are underway of MRAs in patients after a MI but without HF [30, 31]. The recently reported REMINDER trial (unpublished as yet) randomised 1,012 patients with acute ST-segment-elevation MI (STEMI) without a history or current signs of HF or LVEF <40 %, to receive eplerenone 25–50 mg/day or placebo. The primary endpoint was a composite of cardiovascular mortality, ventricular arrhythmia, clinical or subclinical heart failure as determined by LVEF <40 % or elevated BNP/NT-proBNP more than one month after enrolment. As a composite, the primary endpoint fell from 29.6 % with placebo to 18.4 % with eplerenone ($p<0.0001$) over a mean 10.5-month follow-up. This improvement in outcome was largely driven by a significant reduction of the BNP/NT-proBNP biomarker component of the endpoint; an elevation of BNP/NT-proBNP after one month was observed in 25.9 % of controls and 16 % of those on eplerenone ($p<0.0002$).

In the light of the EMPHASIS study, guidelines have been modified to recommend the use of MRAs in addition to ACE inhibitors in patients with milder grades of HF due to LVSD [1••]. With the addition of an MRA, close monitoring is essential. A report from Canada showed a concerning increase in hyperkalaemia-related hospitalisations and deaths [30], although this may be due to a lack of recommended monitoring. Indeed, when recommended monitoring was carried out, severe hyperkalaemia was actually reduced despite much greater use of spironolactone [31]. An analysis of EPHESUS showed that independent predictors of a serum potassium >6 mEq/L after aldosterone blockade are a baseline eGFR <60 mL/min/1.73 m^2, a baseline serum K >4.3 mEq/L, diabetes mellitus, or prior anti-arrhythmic use [32].

Heart Failure with Preserved Ejection Fraction

The question regarding optimal treatment of patients with HFpEF remains unresolved, with observational study findings differing from results seen in randomised clinical trials. None of the agents shown to benefit HFrEF have convincingly improved outcomes in HFpEF. For example, the prematurely terminated PEP-CHF trial did not show an improved outcome with ACE inhibitors [33]. Likewise, CHARM-Preserved did not demonstrate survival benefit for ARBs, although a reduction in HF hospitalisations was achieved at a disputed LVEF cut-off of 0.40 [34]. In the I-PRESERVE study, the LVEF cut-off was raised to 0.45 but no outcome benefit was observed [35]. There remains the possibility that these trials were underpowered and suffered from selection bias and high cross-over rates. Data from the Swedish Heart Failure Registry, including 16,216 patients whose ejection fraction remained ≥0.40, found that 77 % of patients received one of these agents. In a matched cohort, 1-year survival was 77 % for patients receiving the treatment and 72 % for those not treated, while 5-year survival rates were 36 % and 34 %, respectively [36].

In a small mechanistic study (Aldo-DHF), spironolactone was also reported to improve diastolic function (decreasing filling pressure) and regress LV hypertrophy in these patients [37]. It did not significantly change exercise capacity as measured by a 6-minute walk test, but this was not designed or powered as an outcome trial. A larger ongoing NIH-funded study (TOPCAT) is currently investigating whether spironolactone will be of benefit to these patients.

Novel Modulators of the RAAS

Direct Renin Inhibitors (DRIs)

The effect of RAAS blockade by ACE inhibitors and ARBs may be limited by the loss of negative feedback. The compensatory increase in renin and the recently discovered prorenin may activate several downstream components, which may in part overcome the effects of ACE inhibitors and ARBs. These downstream components include Ang II escape via chymase and cathepsin and the formation of various angiotensin sub-forms upstream from the blockade, including angiotensin 1–7, angiotensin III, and angiotensin IV. Furthermore, the recently discovered (pro-)renin receptor not only increases local production of Ang I from angiotensinogen, but also induces several complex AngII-independent intracellular signalling pathways [38] that lead to pro-hypertrophic and apoptotic activity, which can trigger extracellular matrix remodelling and deterioration of cardiac function [39].

The concept of renin inhibition, therefore, is not new. The original DRIs such as enalkiren, remikiren, and zankiren all had poor bioavailability (<2 %), short half-life, lack of specificity, and low potency. Aliskiren was the first of a new class of non-peptide orally active DRIs that was successfully brought to market. Although it also has low bioavailability (2.7 %), aliskiren has a half-life of about 45 hours and is therefore suitable as a once-daily medication [40]. Aliskiren blocks the active site of renin and non-proteolytically activated prorenin. It has been shown to reduce plasma renin activity (PRA) [41] and has the potential to block both circulating and

tissue RAAS. In a study of spontaneously hypertensive rats, aliskiren blocked tissue RAAS more effectively than ACE inhibitors and ARBs [42]. In clinical trials involving patients with mild-to-moderate hypertension, aliskiren provided antihypertensive efficacy that was comparable to that of an ARB [43].

There have been only a few studies of aliskiren in patients with HF. The first proof-of-concept study of aliskiren in HF reported on the neurohormonal effects in 27 patients with NYHA class II or III HF and an EF ≤0.35 [41]. Compared to ramipril (target dose 10 mg once daily), aliskiren (target dose 300 mg once daily) resulted in a reduction in PRA and plasma AngII and plasma aldosterone. The ALOFT study followed, in which 322 patients with HF and a plasma BNP >100 pg/mL on ACE inhibitor and beta-blocker therapy were randomised to 3 months of treatment with either aliskiren (150 mg once daily) or placebo. Importantly, 33 % were also taking an MRA – i.e., potentially taking three agents acting on the RAAS. There was a significant reduction in the primary endpoint, a change in plasma NT-proBNP levels (p=0.0106), by aliskiren compared to placebo [44]. PRA and urinary aldosterone levels were also significantly reduced, as were echocardiographic parameters of left ventricular remodelling. There were, however, no differences between treatments for change in symptoms and signs. Echocardiographic parameters of left ventricular remodelling was also examined in the ASPIRE study, though this did not show any improvement in patients with LV function post-MI when treated with aliskiren in addition to a beta blocker and an ACE inhibitor or ARB [45].

Aliskiren treatment was associated with adverse effects in both the ALOFT and ASPIRE studies. In ALOFT, there were slightly higher (but not statistically significant) rates of hypotension and hyperkalaemia. In ASPIRE, there were more investigator-reported adverse events in the aliskiren group, including hypotension, hyperkalaemia, and increases in serum creatinine. These adverse effects are a continuing source of concern. In December 2011, the Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE), was terminated prematurely after the second interim efficacy analysis on the recommendation of its data monitoring committee (DMC) after it had found an increased occurrence of adverse effects, and continuation of the study was deemed "futile" [46]. ALTITUDE was designed to determine whether aliskiren (300 mg once daily or placebo) added to background ACE inhibitor or ARB therapy would improve prognosis by reducing fatal and non-fatal cardiovascular and renal events in type 2 diabetics at high risk of these complications. The primary outcome in ALTITUDE was a composite of cardiovascular death, resuscitated sudden death, non-fatal MI, non-fatal stroke, unplanned hospitalisation for HF, end-stage renal disease, renal death, or doubling of baseline serum creatinine sustained for at least a month. At a median follow-up of 32 months, the primary composite endpoint had occurred in 783 patients (18.3 %) assigned to aliskiren and 732 (17.1 %) assigned to placebo (HR, 1.08; 95 % CI, 0.98–1.20, p=0.12) [47]. At the interim analysis, there was an apparently higher risk of stroke in the aliskiren group than in the placebo group (HR, 1.34; 95 % CI, 1.01–1.77; nominal p=0.044). However, following closeout of the study and the identification of an additional 392 patients with a primary event, including 72 patients with an adjudicated stroke, the effect size for stroke was reduced and the nominal p value was no longer significant. Nonetheless, more patients in the aliskiren group experienced serious hyperkalaemia ≥6 mmol/L (11.2 % vs. 7.2 %) and reported greater hypotension (12.1 % vs. 8.3 %) (p<0.001 for both comparisons). The overall primary endpoint showed a non-significant trend toward a worse outcome in the aliskiren group (HR, 1.08; 95 % CI, 0.98–1.20; p= 0.12). Similar adverse effects (hyperkalaemia and hypotension) were reported in the recent ASTRONAUT study [48], which evaluated whether addition of aliskiren therapy could delay cardiovascular death or HF rehospitalisation within 6 months for an episode of acute decompensated HF. A total of 1,639 patients were randomised, with 1,615 patients included in the final efficacy analysis cohort (808 aliskiren, 807 placebo). Addition of aliskiren to standard therapy did not reduce cardiovascular death or HF rehospitalisation at 6 months (24.9 % of patients receiving aliskiren vs. 26.5 % receiving placebo) or 12 months (35.0 % for the aliskiren group vs. 37.3 % for placebo) after discharge. The rates of hyperkalemia, hypotension, and renal impairment/renal failure were higher in the aliskiren group compared with placebo.

Together, the findings of ALOFT, ASPIRE, ALTITUDE, and ASTRONAUT are cause for concern regarding renal dysfunction and hyperkalaemia with aliskiren when used in combination with an ACE inhibitor or ARB. Indeed, the safety issue of dual RAAS blockade (any two of ACE inhibitors, ARBs, or aliskiren) has recently been examined in a systematic review and meta-analysis of all RCTs reported between January 1990 and August 2012 [49]. Such combination therapy did not reduce mortality and was associated with an increased risk of adverse events (hyperkalaemia, hypotension, and renal failure) compared to monotherapy. The European Medicines Agency has recently initiated a review of the risks of such combination therapy in treatment of HF and hypertension [50].

The ATMOSPHERE study will examine the potential clinical benefit of aliskiren (300 mg once daily) in a head-to-head comparison with enalapril (10 mg twice daily) as well as in addition to enalapril in patients with HFrEF and an elevated BNP or NT-proBNP [51]. It is an event-driven trial, with a primary composite outcome of cardiovascular death or HF hospitalisation. After ALTITUDE, recruitment for ATMOSPHERE was temporarily suspended to allow safety interim analysis by the DMC. Having reviewed the findings, their

recommendation was that the trial should continue as planned. The committee felt that the trials differed considerably in patient characteristics and that the active run-in period should protect against some of the adverse effects, notably hypotension and clinically important changes in renal function and serum potassium. Additionally, the treatment arm with aliskiren alone would not be at risk of excessive RAAS blockade [52•]. This study should define the efficacy and safety of aliskiren in HF.

Angiotensin Receptor-Neprilysin Inhibitors (ARNis)

Neprilysin, or neutral endopeptidase, is a fairly ubiquitous zinc-dependent metalloprotease enzyme (like ACE) that degrades a number of endogenous vasoactive peptides, including the natriuretic peptides (ANP, BNP, and CNP), angiotensin I, bradykinin, and endothelin-1. A neprilysin inhibitor that increases plasma concentrations of atrial natriuretic factors, and thereby produces natriuresis, diuresis, and vasorelaxation, may offer theoretical advantages over standard diuretic therapy in the treatment of patients with HF.

Neprilysin inhibitors have been previously investigated as a therapeutic strategy in HF. Candoxatril, one of the first neprilysin inhibitors developed for clinical use, had a modest effect on blood pressure [53]. However, in HF, although candoxatril treatment increases ANP and BNP levels, it may increase systemic vascular resistance and decrease cardiac index [54–56].

Because neprilysin degrades multiple substrates, neprilysin inhibitors can cause an increase in circulating levels of both vasodilators and vasoconstrictors. Therefore, drugs that inhibit both neprilysin and ACE were developed, which are referred to as vasopeptidase inhibitors [57]. These drugs decrease peripheral vascular resistance and improve local blood flow and sodium/water balance. Omapatrilat was the first vasopeptidase inhibitor to be developed. In the IMPRESS study, 573 patients with NYHA II-IV HF were randomised to omapatrilat 40 mg/day or lisinopril 20 mg/day for 24 weeks [58]. Although exercise tolerance (the primary endpoint) was not different between groups, there was a significant reduction in the predefined composite endpoint of death, admission for HF, or discontinuation of HF treatment due to worsening symptoms. This was followed by the OVERTURE study, which randomised 5,770 HF patients to receive enalapril 10 mg twice daily or omapatrilat 40 mg once daily over a mean duration of 14.5 months [59]. Omapatrilat did not achieve superiority over enalapril in the composite primary endpoint of death or hospitalisation for HF requiring intravenous treatment, although a significant reduction in cardiovascular death or hospitalisation was observed. Use of omapatrilat, however, was associated with increased angioedema. In the OCTAVE trial in hypertension, the frequency of angioedema was three to four times greater with omapatrilat than with enalapril (274 [2 %] of 10,609 patients vs. 86 [<1 %] of 12,557 patients), an effect which was more pronounced in African-Americans [60]. Omapatrilat also inhibits aminopeptidase P, and it is possible that the observed higher incidence of angioedema was due to the inhibition of the breakdown of bradykinin and substance P by aminopeptidase P and ACE [61].

Because of the angioedema experienced with vasopeptidase inhibitors, other approaches have been explored, including the concept of combining neprilysin inhibition with ARBs – a dual-acting angiotensin receptor-neprilysin inhibitor (ARNi), which would not directly affect ACE or aminopeptidase. LCZ696 is a single molecule in which the molecular moieties of valsartan and AHU377 (the neprilysin inhibitor prodrug) are present in a 1:1 molar ratio [62]. LCZ696 has been shown to be a potent antihypertensive agent. In a dose-finding proof-of-concept study involving 1,328 patients with mild–moderate hypertension, LCZ696 provided complementary and fully additive reduction of blood pressure [63]. No cases of angioedema were reported, although the study only had a small proportion (8 %) of Afro-Caribbean patients, so tolerance needs to be confirmed in this group.

LCZ696 is being studied in HF patients. In an open-label study involving 30 patients with stable HFrEF (NYHA II–IV, LVEF <0.40), treatment with LCZ696 (100 mg twice daily for 7 days, then 200 mg twice daily for 14 days) was reported to decrease plasma NT-proBNP from 1,050.0±1,162.3 pg/mL to 664.7±765.9 pg/mL ($p<0.01$) [64].

PARADIGM-HF is an ongoing outcome study of LCZ696 in chronic HF comparing enalapril 10 mg twice daily to LCZ696 200 mg twice daily in patients with HFrEF. The trial has a single-blind run-in phase in which patient tolerability will be assessed for enalapril 5–10 mg twice daily and LCZ696 100–200 mg twice daily. The primary endpoint of this study is cardiovascular death or HF hospitalisation.

LCZ696 has also been studied in patients with HFpEF. The PARAMOUNT study assessed 301 patients with a clinical diagnosis of HF, LVEF ≥0.45, and an increased plasma concentration of NT-proBNP (>400 pg/mL) [65, 66]. The primary endpoint was the effect on plasma NT-proBNP, which dropped 23 % ($p=0.005$) over 12 weeks, but only by 15 % ($p=0.20$) over 36 weeks, among those receiving LCZ696 compared with valsartan. NYHA class also improved significantly with LCZ696 ($p<0.05$) at 36 weeks, as did left atrial width ($p=0.03$), left atrial volume ($p=0.003$), and left atrial volume index ($p=0.007$). Other echocardiographic measures including LVEF, ventricular volumes, and Doppler-derived measures of diastolic function did not change. While LCZ696 reduced blood pressure more than valsartan alone, regression models accounting for the blood pressure changes suggested that the reduction in NT-proBNP and left atrial size were independent of the blood pressure lowering effect.

Table 1 Summary of evidence for pharmacological treatment of symptomatic HFrEF

	All-cause mortality	CV death	CHF hospitalization	Symptoms	Size of treatment effect	Level of evidence
ACE inhibitors	↓	↓	↓		Class I	A
ARBs *	↓	↓	↓		Class I	A
Beta blockers	↓	↓	↓		Class I	A
MRAs	↓	↓	↓		Class I	A
Loop duiretics				↓	Class I	C
Hydralazine / Nitrates **		↓	↓		Class I	A
Digoxin			↓		Class IIa	B
Vaptans ***				↓	Class IIb	B
DRI						
ARNi				↓ (HFpEF)		

* as an alternative to ACE inhibitors

** in African-American patients

*** volume overloaded with persistent severe hyponatraemia

Size of treatment effect:

Class I benefit >>>risk

Class IIa benefit >>risk

Class IIb benefit≥risk

Class III no benefit / harm

Level of evidence:

A multiple populations evaluated

B limited populations evaluated

C very limited populations evaluated

Aldosterone Synthase Inhibitors (ASIs)

A possible new approach to aldosterone blockade is to inhibit aldosterone synthase (CYP11B2). A potential advantage of this approach over traditional MRAs is linked to the effect of ASIs on glucocorticoid synthesis. Through inhibition of negative feedback, MRAs can increase ACTH, which in turn can increase cortisol. Chronic excessive activation of glucocorticoid receptors induces obesity, insulin resistance, glucose intolerance, and dyslipidaemia [67]. Aldosterone synthase inhibitors (ASIs) may not produce this effect on glucocorticoids and the resultant increase in cardiovascular risk. LCI699 was the first orally active ASI to be developed for human use. In patients with primary aldosteronism (PA), LCI699 induced a dose-dependent and reversible decrease in plasma and urinary aldosterone concentration [68]. It did, however, induce biochemical signs of partial inhibition of the glucocorticoid axis, with dose-dependent increases in both plasma ACTH and 11-deoxycortisol (the precursor of cortisol) concentrations, consistent with the inhibition of the CYP11B1 (as well as the intended CYP11B2) gene product. An 8-week placebo-controlled dose-response study on patients with stage 1 and 2 essential hypertension confirmed a blunted cortisol response to ACTH in 20 % of patients, although the clinical and biological safety and tolerability of LCI699 were similar to those of placebo and eplerenone. Second-generation ASIs that may have a role in HF are in development.

Conclusion

The strategy of inhibiting the RAAS has delivered remarkable success in HFrEF and other cardiovascular diseases. The most successful interventions have been ACE inhibitors and MRAs, both of which have produced consistently positive trial results (Table 1). ARBs are an excellent substitute in cases of ACE inhibitor cough but may have no additional benefit in HF. Early trials of DRIs had suggested that they may have a role, but recent results have not been encouraging. An exciting development is in the area of ARNis, where preliminary data look positive. At present, the RAAS modulating strategy recommended for HF is a combination of an ACE inhibitor and MRA. Whether results with DRIs and/or ARNis will alter this recommendation remains to be seen.

Compliance with Ethics Guidelines

Conflict of Interest J. George has had grant/research support from Sanofi Pharmaceuticals and Pfizer Pharmaceuticals.

Chim C. Lang is a consultant to and has had grant/research support from Novartis Pharmaceuticals, and has had grant/research support Pfizer Pharmaceuticals.

A.D. Struthers is a consultant to Merck Pharmaceuticals, is on the speakers bureau for Menarini, is a consultant to and is on the speakers bureau for Pfizer Pharmaceuticals, and is a consultant to Roche Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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