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The past, present and future of renin–angiotensin aldosterone system inhibition☆

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Abstract

The renin–angiotensin aldosterone system (RAAS) is central to the pathogenesis of cardiovascular disease. RAAS inhibition can reduce blood pressure, prevent target organ damage in hypertension and diabetes, and improve outcomes in patients with heart failure and/or myocardial infarction. This review presents the history of RAAS inhibition including a summary of key heart failure, myocardial infarction, hypertension and atrial fibrillation trials. Recent developments in RAAS inhibition are discussed including implementation and optimization of current drug therapies. Finally, ongoing clinical trials, opportunities for future trials and issues related to the barriers and approvability of novel RAAS inhibitors are highlighted.

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

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Keywords

Renin–angiotensin aldosterone system; Hypertension; Heart failure; Myocardial infarction; Clinical trials

1. Introduction

The renin–angiotensin aldosterone system (RAAS) is central to the pathogenesis of cardiovascular disease through vascular inflammation, an increase in reactive oxygen species, endothelial dysfunction, and atherosclerosis with subsequent complications such as myocardial infarction (MI), chronic heart failure (HF) and renal disease [1]. Medications inhibiting the RAAS such as angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) are several of the most significant advances in cardiovascular medicine [2,3]. Since the CONSENSUS trial over 20 years ago [2], the field has seen multiple strategies of RAAS inhibition with varying success from single drug optimization to combination therapies. We provide an overview of the history of RAAS inhibition, discuss recent RAAS developments and present practical ways to overcome the challenges of drug optimization. Finally, ongoing clinical trials, opportunities for future trials and issues related to the barriers and approvability of novel RAAS inhibitors are highlighted.

2. RAAS background

RAAS is the hormone system that regulates intravascular volume, blood pressure and tissue repair via inflammatory and proliferative mechanisms (Fig. 1). While protective during an acute stress response, chronic stimulation has detrimental effects including vasoconstriction, vascular smooth muscle proliferation, endothelial dysfunction, inflammation, fibrosis, and thrombosis [4]. The RAAS cascade begins when renal juxtaglomerular cells secrete renin in response to renal hypoperfusion, decreased sodium delivery, and sympathetic activation [5]. Plasma renin converts hepatically produced angiotensinogen to inactive angiotensin I. ACE cleaves angiotensin I to generate angiotensin II (AII). Only approximately 10% of ACE circulates in the plasma and controls acute hemodynamic modulation, whereas tissue-specific RAAS uses local angiotensin I to form AII. Independent of ACE activity, serine proteases are also capable of converting angiotensin I to AII. Although the peripheral or circulating RAAS may be involved in cardiovascular remodeling and restructuring, it is the autocrine or paracrine production of AII that may be most important in promoting these changes [6,7]. AII is responsible for vasoconstrictive, proliferative and pro-inflammatory effects while the actions of angiotensin-(1–7) mainly oppose those of angiotensin II [8]. ACE hydrolyzes angiotensin-(1–7) into its inactive form, such that ACE-Is result in greater availability of angiotensin-(1–7) with its vasodilatory and antiproliferative actions. AII stimulates adrenal cortex secretion of aldosterone and posterior pituitary secretion of arginine vasopressin with resultant volume expansion. Aldosterone is also regulated through non-AII pathways and is involved in sodium and potassium homeostasis. Above and beyond their renal actions, AII and aldosterone exert synergistic and independent systemic and autocrine/paracrine pleiotropic effects that result in myocardial and vascular remodeling

[5,9]. AII promotes atherogenesis through effects on smooth muscle cell growth and migration, macrophage activation and vascular invasion, inhibition of apoptosis, increased oxidative stress and stimulation of thrombosis [10]. RAAS inhibition has been shown to positively impact disease progression via these mechanisms [10]. Given the impact of the RAAS on metabolic signaling, oxidative stress, and endothelial dysfunction, a role for RAAS inhibitors has been supported to prevent or delay the development of type 2 diabetes via effects on insulin sensitivity and signal transduction [11]. Pleiotropic effects of aldosterone include an increase in reactive oxygen species, endothelial dysfunction, apoptosis, inflammatory cytokine activation, and collagen formation [12,13]. The association between genetic variants of the RAAS and blood pressure response to RAAS inhibitors and clinical outcomes has been inconsistent [14]. Recent data suggesting that polymorphisms of the RAAS may be associated with hypertension and reduced systolic function require further evaluation and confirmation [15].

3. Contemporary RAAS inhibitors

The three main classes of RAAS inhibitors currently used in clinical practice are ACE-Is, ARBs and MRAs with a fourth class of agents – the direct renin inhibitors (DRIs) – under active investigation (Fig. 2). ACE-Is decrease the formation of angiotensin II and inhibit the breakdown of bradykinin with the formation of nitric oxide and other vasodilators [16]. For patients intolerant of ACE-Is, ARBs may represent an alternative. ARBs bind competitively to and dissociate slowly from AT_1 receptors [17]. The observed differences in lipid solubility, plasma protein binding, bioavailability, plasma half-life, and systemic elimination for these agents influence their onset, duration of action, and efficacy in blocking tissue RAAS which impacts their cardiovascular protection profiles [18]. The difference between the dose requirement to reduce blood pressure and that needed to achieve cardiovascular protection varies based on the pharmacokinetic profiles of RAAS inhibitors even within the same general therapeutic class [19]. MRAs reduce the number of available epithelial sodium channels in the distal renal tubule through competitive inhibition of the mineralocorticoid receptor. Eplerenone is a more selective mineralocorticoid receptor blocker with lower affinity for progesterone and androgen receptors than spironolactone [20]. Conventional agents that block RAAS induce a reflex increase in renin which may lead to RAAS ‘escape’. DRIs inhibit the RAAS at the most proximal, specific, and rate-limiting step [21]. Aliskiren is the only currently available DRI with approval for use in hypertension.

4. Heart failure

Since the CONSENSUS and SOLVD trials first demonstrated the effectiveness of ACE-Is in chronic HF with left ventricular systolic dysfunction (LVSD) over 20 years ago (Table 1) [2,22], multiple trials have demonstrated the beneficial effects of ACE-Is on clinical status, neurohormonal activation, quality of life, HF hospitalization and survival [23]. ACE-Is reduce the risk of death due to HF, sudden cardiac death, and MI in a broad range of patients with LVSD [23]. Conversely, the PEP-CHF trial investigating the use of ACE-Is in patients with HF and a preserved left ventricular ejection fraction (HFpEF) did not show improved outcomes [24].

With regard to ARBs, the CHARM-Alternative study demonstrated that candesartan use in symptomatic HF patients with LVSD reduced cardiovascular mortality and HF hospitalization [25]. The HEAAL study (n=3846) evaluated the effects of high-dose versus low-dose losartan on clinical outcomes in patients with HF with ejection fraction (EF) ≤40% [26]. High-dose ARB significantly reduced the rate of death or admission for HF, supporting the value of dose up-titration to maximize benefit. Adverse events such as renal impairment, hypotension and hyperkalemia occurred more commonly in the high-dose ARB arm, but did not lead to excess treatment discontinuation. In head-to-head comparison of ACE-Is and ARBs, ELITE II failed to demonstrate ARB superiority [27]. Similar to the data on ACE-Is, two randomized trials investigating the use of ARBs in HFpEF were neutral with respect to mortality [28,29].

For HF patients who remain symptomatic on an ACE-I, the addition of an ARB has the potential to more completely inhibit RAAS. The Valsartan in Heart Failure Trial of >5000 HF patients showed that valsartan, when added to an ACE-I, had no effect on mortality but reduced HF hospitalizations [30]. CHARM-Added supported this finding where dual RAAS blockade with candesartan+ACE-I was associated with a reduction in cardiovascular death or HF hospitalization [31]. However, these combinations have been associated with more adverse events. Therefore, in clinical practice, dual blockade with an ACE-I and an ARB is not commonly employed.

Despite treatment with ACE-Is/ARBs, patients with HF may demonstrate elevated aldosterone levels [32]. The RALES trial in patients with systolic HF and severe symptoms (NYHA classes III–IV) demonstrated a reduction in all-cause mortality with spironolactone [3]. Spironolactone use was also associated with reduced HF hospitalization. The EMPHASIS-HF trial supported the benefits of eplerenone in chronic systolic HF and mild symptoms (NYHA class II), where there was a reduction in the primary endpoint of cardiovascular death or HF hospitalization as well as a significant reduction in mortality and hospitalizations [33]. Future studies will determine whether these benefits extend to HF patients who are asymptomatic or have HFpEF [34].

The American College of Cardiology (ACC)/American Heart Association (AHA) as well as European Society of Cardiology (ESC) guidelines recommend that ACE-Is (or an ARB, if ACE-Is are not tolerated) should be started and continued indefinitely in HF patients with LVSD unless contraindicated [35,36]. LVSD patients with symptomatic HF receiving an ACE-I and a beta-blocker should also receive an MRA, except when moderate to severe renal failure or hyperkalemia is present.

5. Myocardial infarction

Long-term trials of ACE-Is in high-risk patients with LVSD or HF after an MI demonstrated a 20% risk reduction in mortality (~5–8% absolute risk reduction) as well as reduced stroke, cardiovascular death, sudden cardiac death, recurrent MI, progression to severe HF and HF hospitalization[37–39]. In acute MI complicated by LVSD, HF or both, the VALIANT trial demonstrated similar benefits for captopril and valsartan on mortality and cardiovascular events [40]. Combination therapy with an ACE-I+ARB increased the adverse event rate

without improved survival. However, in the OPTIMAAL trial of captopril versus lostartan in acute MI patients with HF, there was a non-significant difference in mortality in favor of captopril [41]. In both trials, ACE-I and ARB use had similar effects on recurrent MI and re-hospitalization [40,41]. ARBs were better tolerated with fewer patients discontinuing therapy compared to ACE-Is in OPTIMAAL. In contrast, short-term post-MI trials of ACE-Is (i.e. 6 weeks) that enrolled a broader population demonstrated a more modest mortality reduction, with the greatest benefit seen in high-risk subgroups [42–44].

Supporting the role of MRAs post-MI, the EPHESUS trial in acute MI complicated by LVSD and HF (or diabetes) found that eplerenone was associated with a reduction in mortality, cardiovascular death/hospitalization and sudden death [45]. Two ongoing trials, ALBATROSS [46] and REMINDER (Clinicaltrials.gov: NCT01176968), are investigating whether early use of a MRA will improve outcomes in patients with an acute MI but without HF.

The most recent ACC/AHA guidelines recommend that ACE-Is (or, if not tolerated, an ARB) should be started and continued indefinitely in all ST-elevation MI (STEMI) patients except those at lower risk (normal EF in whom cardiovascular risk factors are well controlled and revascularization has been performed) and in those with non-STEMI with clinical HF, LVSD, hypertension or diabetes, unless contraindicated [47,48]. The ESC guidelines recommend ACE-I use in all post-STEMI patients (regardless of baseline risk) to reduce the risk of recurrent MI (and other vascular events) [49]. MRAs have a class I indication for STEMI and non-STEMI patients who are receiving therapeutic doses of ACE-Is and beta-blockers, have an EF≤40%, and have either symptomatic HF or diabetes without renal failure or hyperkalemia.

6. Hypertensive patients and others at increased cardiovascular risk

The benefits of blood pressure control on the risk of stroke, coronary heart disease and HF have been established [50]. However, it has not been firmly established whether RAAS inhibitors have a greater impact on events than alternative agents that produce similar reductions in blood pressure.

6.1. Hypertension and stroke: ACE-Is and ARBs

The ALLHAT study showed no differences in coronary heart disease or mortality when chlorthalidone, amlodipine, and lisinopril were compared [51]. However, the decrease in blood pressure was not the same with the three agents, and many of the patients did not have clinical disease. Similar findings were observed in the VALUE trial comparing valsartan and amlodipine in 15,245 patients with hypertension [52]. In contrast, the ANBP-2 study found that in older patients with hypertension, ACE-Is were superior to diuretics at reducing cardiovascular events or deaths [53]. The SCOPE and PROGRESS trials in those with hypertension and a history of stroke or transient ischemic attack, respectively, found that ARB/ACE-I use was associated with a reduction in stroke compared to placebo [54,55]. The LIFE study of losartan versus beta-blockers in hypertension patients found a risk reduction in death, MI, or stroke in the losartan group [56]. The most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) indicate that for patients

<55 years, an ACE-inhibitor or a low cost ARB should be prescribed as first line based on randomized controlled trial and cost-effectiveness evidence [57].

6.2. Arterial disease and others at increased cardiovascular risk: ACE-Is and ARBs

In the PEACE trial, there was no significant difference in the risk of cardiovascular death, MI, or coronary revascularization among low-risk patients with stable CAD randomized to ACE-Is [58]. In contrast, the HOPE study in a large population of patients with vascular disease or diabetes in addition to 1 other cardiovascular risk factor found that ACE-I treatment was associated with a reduction in cardiovascular death, nonfatal MI or stroke [59]. Similar but smaller benefits were reported in the EUROPA study [60]. However, the recently published TRANSCEND trial failed to show a benefit of telmisartan in patients intolerant to ACE-Is who had similar entry criteria to the HOPE trial [61]. The interpretation of this negative finding, inconsistent with those of previous RAAS trials in at risk patients, is unclear. This negative trial should not divert from the robust evidence collected so far.

6.3. Diabetic nephropathy: ACE-Is and ARBs

In patients with diabetic nephropathy, data from randomized trials have demonstrated the benefits of ACE-Is/ARBs on renal disease progression [62,63] and cardiovascular events [64–66]. However, not all studies have supported this reduction in cardiovascular events [66,67]. For instance, olmesartan use in the ROADMAP trial prevented new onset microalbuminuria, but was associated with an unexpected higher cardiovascular mortality compared to placebo [68]. However, ROADMAP was underpowered for a mortality evaluation. These findings question the value of proteinuria as a surrogate for nephroprotection and demonstrate the need for additional outcome trials. The ongoing VA NEPHRON-D trial will help determine whether RAAS combinations may slow nephropathy progression in advanced diabetic nephropathy [69].

6.4. Hypertension and renal disease: aldosterone antagonists

Aldosterone levels correlate with incident and resistant hypertension [70]. Several studies have demonstrated the effectiveness of MRAs in lowering blood pressure as monotherapy as well as add-on therapy [71–73]. In essential hypertension, eplerenone as monotherapy has been shown to reduce blood pressure and left ventricular hypertrophy at least as well as an ACE-I/ARB, with the combination superior to either agent alone [74–76]. Aldosterone has also been implicated in the development and progression of renal disease in hypertensive and diabetic patients [77,78]. MRAs have been shown to reduce albuminuria in these patient populations [79,80]. The addition of spironolactone is an evidence-based strategy for the management of resistant hypertension related to obesity, sleep apnea, and secondary hyperaldosteronism [57,81]. However, randomized studies are needed to further investigate MRAs in patients with hypertension and renal disease to establish whether these medications impact outcomes and not just surrogate endpoints.

6.5. Hypertension and renal disease: direct renin inhibitors

Aliskiren has been shown to reduce BP and proteinuria in diabetics when added to losartan [82–84]. Several clinical trials based on these pilot studies were designed to investigate the

impact of aliskiren on cardiovascular outcomes. The ALTITUDE study (estimated n=8600) investigating whether aliskiren added to an ACE-I/ARB reduces cardiovascular and renal morbidity and mortality in high-risk diabetics [85] was stopped early by the Data Monitoring Board given increased stroke, renal complications, hyperkalemia, and hypotension with aliskiren. After the European Medicines Agency reviewed the data, they recommended that in those with an indication for aliskiren (i.e. hypertension), it should not be used in combination with an ARB or ACE-I if the patient also has diabetes or an estimated glomerular filtration rate of <60 mL/min [86]. The Food and Drug Administration indicated that aliskiren is contraindicated in combination with ACE-Is/ARBs for patients with diabetes [88]. The APOLLO trial (estimated n=11,000) investigating the role of aliskiren in preventing cardiovascular death, MI, stroke and HF in patients with hypertension was also stopped early (ClinicalTrials.gov: NCT01259297).

7. Atrial fibrillation

There is evidence that RAAS inhibition may have an antiarrhythmic effect on AF. For primary prevention of AF, post-hoc analyses of trials in patients with LVSD have shown an association between ACE-I use and a reduced risk for incident AF [89,90]. Several small, prospective studies of ACE-I/ARB use for secondary AF prevention demonstrated a significant reduction in the risk of further AF and hospitalizations [91,92]. In 2005, a meta-analysis of 11 randomized trials evaluating ACE-Is/ARBs for the prevention of AF (primary and secondary) found that these agents reduced the risk of AF with greatest benefit in patients with HF or left ventricular hypertrophy [93]. A more recent meta-analysis found similar results [94]. While the mechanisms for such benefit are unclear, hypotheses include an effect on atrial electrical remodeling [95]. However, the prospective GISSI-AF trial of 1442 patients in normal rhythm with a history of AF randomized to valsartan or placebo did not demonstrate a reduction in AF recurrence with ARBs [96]. In terms of AF treatment, the ACTIVE-I trial (n=9016) of irbesartan in patients with a history of AF was neutral with respect to stroke/MI/death from vascular causes and this composite+HF hospitalization [97]. Regarding MRA use and AF, eplerenone was associated with a significant reduction in the incidence of new onset AF in the EMPHASIS-HF trial [98]. Thus, these data support the role for RAAS inhibition in primary prevention and potentially secondary prevention of AF, but given continued controversy [99–101], widespread application will depend on definitive, adequately powered randomized trials.

8. Adverse RAAS inhibitor effects

Dry cough, related to increased bradykinin levels, occurs in 5% to 15% of patients taking ACE-Is, but not those taking ARBs [5]. Angioedema, a potentially life-threatening complication occurs in a small percentage of patients receiving ACE-Is (estimated at 0.1% to 0.5%). Given the potential for cross reactivity of angioedema with ARBs [102], patients with history of ACE-I related angioedema should be prescribed ARBs only for clear indications and under close monitoring [103].

Serious hyperkalemia, defined as a serum potassium ≥6.0 mmol/L, can occur with all RAAS inhibitors especially in patients with renal insufficiency, diabetes or those taking potassium-

sparing diuretics or potassium supplements. With patient education and close monitoring, hyperkalemia from RAAS inhibitors can be predicted and averted in many cases [104]. Novel approaches such as the use of potassium binding resins are currently under investigation. The PEARL-HF trial (n=105) evaluated the efficacy and safety of a potassium binder (RLY 5016) in patients with chronic HF and prior hyperkalemia or chronic kidney disease receiving spironolactone [105]. Potassium binder use was associated with significantly lower potassium levels, a lower incidence of hyperkalemia and a higher proportion of patients on higher spironolactone doses compared with placebo. The long term efficacy and safety of this binder remains to be determined.

Progressive renal dysfunction can occur with ACE-Is/ARBs in the setting of hypovolemia or renovascular hypertension. Although this complication is more common in HF patients, and probably inherent to the pharmacological effect on renal hemodynamics, worsening renal function is usually mild and reversible. It is unfortunately one of the main reasons for the use of suboptimal doses. ACE-Is/ARBs and aliskiren are contraindicated during pregnancy. Regarding spironolactone use, other adverse effects, particularly in men, include gynecomastia and breast pain. Newer, more selective aldosterone receptor antagonists such as eplerenone as well as others in development have improved sexual side effect profiles.

9. Monitoring and dose adjustment

In clinical practice, renal function and potassium levels should be monitored similar to the manner used in clinical trials. In general, a metabolic panel should be obtained within 72 h of initiation, after 4 weeks of therapy and every 3–4 months routinely. After dose adjustments or pertinent changes in clinical status, laboratories should be obtained. Medication doses should be decreased for a serum potassium >5.5 mmol/L and held for a serum potassium >6.0 mmol/L. Since the initiation of ACE-inhibitors and ARBs can be associated with an increase in serum creatinine, dose adjustment for renal function should be individualized with intensification of monitoring in the setting of dynamic renal function changes. Recommendations are to avoid aldosterone antagonists with a potassium ≥5.0 mEq/L or a creatinine >2.5 mg/dL in men or >2.0 mg/dL in women and to use them cautiously in patients with more modest renal insufficiency [35,36].

10. Optimization of RAAS inhibition

RAAS inhibitors proven to improve outcomes are frequently underutilized or prescribed at inadequate doses [106]. For example, in chronic HF, physicians are often reluctant to aggressively titrate therapies in apparently stable patients. Data support that higher doses of RAAS inhibition result in improved outcomes compared to lower doses [26,107]. Evidence-based RAAS inhibitors should be titrated to doses attained in clinical trials or to the maximally tolerated dose [35,36].

Those patients most likely to benefit from combined RAAS blockade, and specifically which combination, are currently unknown. In trials of HF patients, an ARB+ACE-I did not further reduce mortality, but combination therapy reduces HF hospitalizations and composite endpoints including cardiovascular death [30,31,40]. However, the combination is associated with more symptomatic hypotension and renal dysfunction [108]. Similarly, the

combination of aliskiren with an ACE-I/ARB in high-risk patients increased adverse events such that regulatory agencies have recommended against such combinations [86]. In the EMPHASIS-HF trial of MRAs in patients with HF and LVSD, 94% of patients receiving eplerenone were taking an ACE-I/ARB and there was a reduction in cardiovascular death or HF hospitalization [45]. Similarly, in essential hypertension, combination therapy with an MRA and an ACE-I/ARB appears superior to either agent alone [75]. Therefore, future studies will need to explore the optimal balance of RAAS blockade in different patient groups.

11. New RAAS inhibitors

While DRIs are not currently approved in HF, pilot studies have demonstrated the benefits of aliskiren on surrogate endpoints (e.g. natriuretic peptides) [109] and trials with aliskiren in both acute [110] and chronic [111] HF are ongoing. Despite concerns about aliskiren therapy in combination with ACE-Is/ARBS, particularly in diabetics and those with renal dysfunction, the importance of completion of these ongoing aliskiren trials in HF with heightened safety monitoring has been reviewed [112]. The ASPIRE trial in 820 patients with LVSD after MI found that a DRI added to standard therapy did not result in further attenuation of LV end-systolic volume, and was associated with more adverse effects [113].

Novel ARBs such as azilsartan medoxomil have been compared with traditional ARBs and appear to exhibit superior blood pressure reduction, yet data on cardiovascular morbidity or mortality are lacking [114]. High-dose azilsartan was superior to high-dose valsartan or olmesartan in lowering blood pressure in short-term studies [115–117]. Azilsartan reduces blood pressure by 12–15 mm Hg/7–8 mm Hg, with additional reduction expected in combination with a diuretic such as chlorthalidone [114].

Given the undesirable effects of spironolactone (e.g. gynecomastia, mastodynia, menstrual disturbance) due to its poor selectivity for the mineralocorticoid receptor and the renal tubular effects (i.e. hyperkalemia) with both spironolactone and eplerenone, third- and fourth-generation MRAs are currently in development [118]. These non-steroidal agents will aim for the potency of spironolactone and selectivity of eplerenone along with tubule-sparing properties. The aims of the ongoing ARTS trial (ClinicalTrials.gov: NCT01345656) are to evaluate a novel, non-steroidal, MRA with greater selectivity than spironolactone and stronger mineralocorticoid receptor binding affinity than eplerenone in patients with HF. Given eplerenone's effect on lowering the burden of atherosclerosis [119], MRAs may also have pleiotropic effects on cardiovascular and inflammatory diseases.

Another mechanism to antagonize aldosterone is to inhibit its formation by aldosterone synthase. The novel aldosterone synthase inhibitor, LCI-699, was shown to suppress serum aldosterone levels in a small proof-of-concept study in primary aldosteronism [120]. In a randomized trial in primary hypertension, this agent was shown to significantly lower blood pressure, but 20% of subjects developed blunted release of cortisol [121]. Therefore, the development of LCI-699 was stopped in favor of developing more specific inhibitors.

In addition to ACE, there are other metallopeptidases such as neutral endopeptidase/neprilysin (NEP) that convert vasoactive substances and could be a therapeutic target.

Research on the dual NEP/ACE-I omapatrilat provides the basis for these novel agents. Trials supported the benefits of omapatrilat in hypertension and HF [87,122]. However, given that these peptidases are the major pathways responsible for bradykinin degradation, dual blockade resulted in a higher incidence of angioedema. Therefore, substitution of an ARB for the ACE-I in this combination, a so-called AT_1R/NEP antagonist (ARNI) could prove more favorable. The first in class ARNI, LCZ696, reduced blood pressure without an increase in angioedema in one study of 1328 hypertensive patients [123]. Since ARNIs also increase natriuretic peptide levels, these agents may prove beneficial in HF patients [124]. The PARAMOUNT phase 2 trial demonstrated that LCZ696 significantly reduced NT-proBNP levels compared with valsartan at 12 weeks in HFpEF patients [125]. The PARADIGM-HF trial is evaluating the efficacy and safety of LCZ696 on morbidity and mortality in patients with HF and LVSD (ClinicalTrials.gov: NCT01035255).

Angiotensin-converting enzyme 2 is a recently recognized ACE homolog that appears protective in HF [126]. Recent studies have shown that the increased levels of the soluble form of the peptide-correlate with worsening HF symptoms, lower EF, higher natriuretic peptide levels and adverse clinical events [127,128]. These results suggest that a cardioprotective arm of the RAAS is active in HF and could be a target of future HF therapies.

12. Developmental challenges and the approvability of new RAAS inhibitors

Multiple recent reviews have summarized issues related to the development and approvability of novel RAAS inhibitors [124,129]. In brief, the key issues include the complexities of trial design and background therapies, side effects and costs. The investigation of novel agents in an existing field like RAAS inhibition means that drugs are commonly evaluated as add-on therapy with current agents or as alternative therapy in those intolerant to current therapies. Given that these compounds target the same axis, there are questions about the magnitude of blood pressure or HF efficacy that remains for new agents. Logistically, it is important that the background therapies in these trials occur at the maximum tolerated doses or defined optimal doses. These considerations are particularly relevant since even in the setting of controlled trials, dosing is frequently not optimized due to clinical inertia and intolerance (real or perceived). Furthermore, as has been seen in multiple trials of add-on RAAS therapy, the side effect profile may become less favorable with the combination of multiple agents [108]. The potential side effects of these agents are also ill-defined. How is hypotension defined and does it need to be symptomatic? What is the clinical relevance of a small decrease in estimated glomerular filtration rate with combination RAAS inhibition? As the therapeutic window narrows with combination RAAS inhibition, it will likely become increasingly difficult to demonstrate efficacy in a broad population. Trials may need to increasingly focus on patient subgroups with specific cardiovascular phenotypes most likely to benefit from novel therapies without adverse events.

13. Conclusions

The RAAS is central to the pathogenesis of cardiovascular disease. Contemporary RAAS inhibition includes monotherapy and various combination regimens with ACE-Is, ARBs and MRAs. We highlighted key trials of RAAS inhibition in various at-risk populations including those with HF, MI and hypertension. Optimization of RAAS inhibition can be obtained through medication uptitration and combination with close monitoring for side effects. Pilot studies of novel RAAS inhibitors as well as ongoing morbidity and mortality trials with DRIs, novel MRAs and ARBs, aldosterone synthase inhibitors and ARNIs demonstrate the ever-changing landscape of this field. The development of these agents is challenged by complex trial designs and background therapies, side effect profiles and high costs. The history of RAAS inhibition demonstrates how the field has evolved from the early days where ACE-Is resulted in striking mortality benefits to one where complex polypharmacy and individualized regimens are increasingly the norm.

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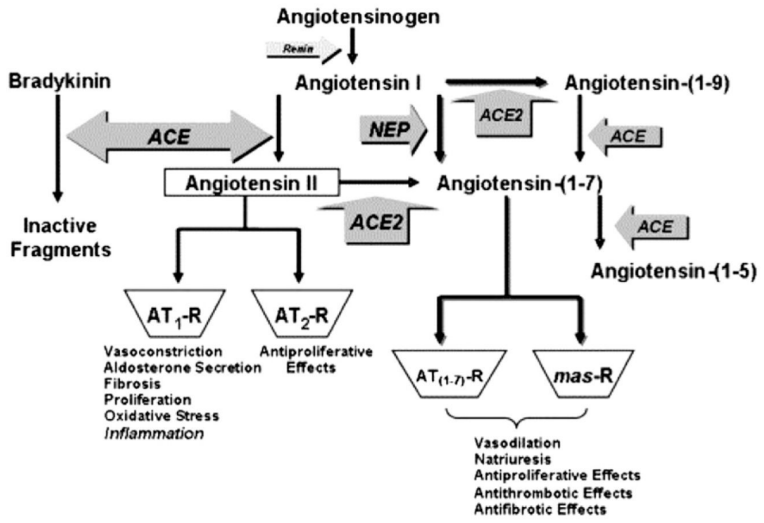

Fig. 1.

Biochemical mechanisms for the production of angiotensin peptides. Illustrated are the recognized enzymatic pathways leading to the formation and metabolism of products derived from angiotensinogen. ACE cleaves angiotensin I to generate angiotensin II (angiotensin-[1–8]), while neutral endopeptidases (NEP) cleave angiotensin I to produce angiotensin-(1–7). ACE hydrolyzes the heptapeptide into biologically inactive angiotensin-(1–5). ACE-2 catalyzes the conversion of angiotensin I to angiotensin-(1–9) and converts angiotensin II into angiotensin-(1–7). The proinflammatory actions of angiotensin II are mediated primarily through the AT_1 receptor, whereas the anti-inflammatory actions of angiotensin-(1–7) are exerted through receptors that include a mas oncogene-encoded G protein-coupled receptor. AT-R = angiotensin type receptor and mas-R = mas receptor. Reprinted from Am J Cardiol, Vol 98, Ferrario CM et al., Role of the renin–angiotensin–aldosterone system and proinflammatory mediators in cardiovascular disease, pages 121-8, Copyright (2006) [1] with permission from Elsevier.

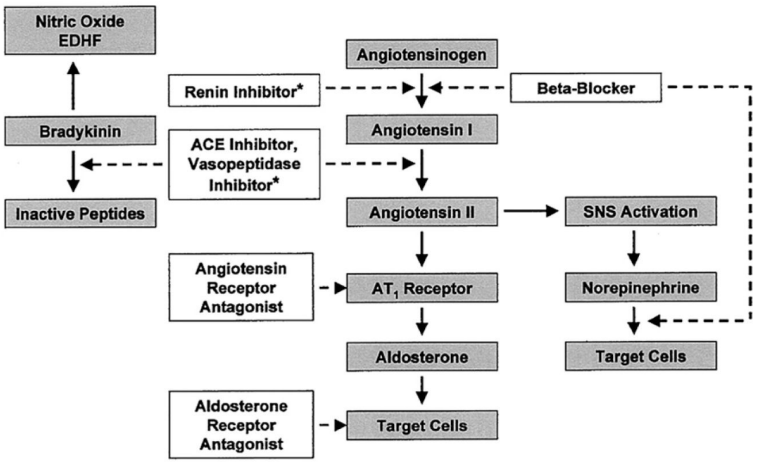

Fig. 2.

Pharmacological agents (open boxes) used to manipulate the RAAS (shaded boxes). Dashed lines signify inhibitory pathways. EDHF indicates endothelium-derived hyper-polarizing factor and SNS, sympathetic nervous system.

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Table 1

Pivotal trials of renin angiotensin aldosterone inhibitors.

Trial name	Drug studied	Patient population	Primary conclusion(s)
Heart failure trials			
CONSENSUS [2]	Enalapril (2.5–40 mg daily; mean 18.4 mg daily) vs. placebo.	N=253. Severe congestive heart failure (NYHA IV). Mean follow-up 188 days.	The primary endpoint of mortality at 6 months occurred in 26% of the patients receiving enalapril vs. 44% of the placebo group (RRR=40%; P=0.002). The RRR over the entire duration of follow-up was 27% with an ARR of 15%.
SOLVD [22]	Enalapril (2.5–20 mg daily; mean 11.2 mg daily) vs. placebo.	N=2569. Chronic HF and EF≤35%. Mean follow-up 41.4 months.	4.5% ARR in mortality with enalapril (35.2% vs. 39.7% mortality; RRR=16%; P<0.0036).
PEP-CHF [24]	Perindopril (4 mg daily) vs. placebo. At 1 year, almost 90% of patients were treated with perindopril 4 mg.	N=850. Patients ≥70 years with a diagnosis of HF with diastolic dysfunction. Median follow-up 2.1 years.	For the entire duration of follow-up, 25.1% patients assigned to placebo and 23.6% to perindopril experienced the composite of all-cause mortality or unplanned HF-related hospitalization (HR 0.92; 95% CI, 0.70–1.21; P=0.545).
Val-HeFT [30]	Valsartan 160 mg BID vs. placebo. Target valsartan dose was achieved in 84% of patients.	N=5010. HF patients with NYHA class II–IV symptoms and LVEF<40%. Patients had to have been receiving a fixed-dose drug regimen that could include ACE inhibitors, diuretics, digoxin, and beta-blockers for at least two weeks. Mean follow-up 23 months.	19.7% of patients assigned to valsartan and 19.4% of patients assigned to placebo died (RR 1.02; 98% CI, 0.88–1.18; P=0.80). For a combined endpoint of mortality and morbidity, 28.8% of patients assigned to valsartan and 32.1% of patients assigned to placebo experienced the composite (ARR=3.3%; RR 0.87; 97.5% CI, 0.77–0.97, P= 0.009).
HEAAL [26]	Losartan 150 mg vs. 50 mg daily (target doses). The mean doses in these two groups were 129 mg and 46 mg, respectively.	N=3846. HF patients with NYHA classes II–IV symptoms, EF≤40%, and intolerance to ACE-inhibitors. Median follow-up 4.7 years.	For the primary endpoint, 43% patients in the 150 mg group vs. 46% in the 50 mg group died or were admitted for heart failure (ARR=3%; HR 0.90, 95% CI 0.82–0.99; P=0.027).
ELITE II [27]	Losartan 50 mg daily vs. captopril 50 mg TID.	N=3152. HF patients aged ≥60 years with NYHA classes II–IV symptoms, and EF≤40%. Median follow-up 555 days.	For the primary endpoint of all-cause mortality, 17.1% of losartan and 15.9% of captopril patients experienced the endpoint (HR 1.13; 95% CI, 0.95–1.35; P=0.16).
CHARM-Alternative [25]	Candesartan 32 mg daily vs. placebo. At 6 months, the mean candesartan daily dose was 23 mg.	N=2028. Symptomatic HF patients with EF≤40% who were not receiving ACE-inhibitors because of previous intolerance. Median follow-up 33.7 months	For the primary composite endpoint of CV death or hospital admission for HF, 33.0% of candesartan patients and 40.0% of placebo patients experienced the composite (ARR=7%; unadjusted HR 0.77; 95% CI, 0.67–0.89; P=0.0004).
CHARM-Added [31]	Candesartan 32 mg daily vs. placebo. At 6 months, the mean candesartan daily dose was 24 mg.	N=2548. HF patients with NYHA classes II–IV symptoms, EF≤40%, and who were being treated with ACE-inhibitors. Median follow-up 41 months.	For the primary composite endpoint of CV death or hospital admission for HF, 37.9% of candesartan patients and 42.3% of placebo patients experienced the

Trial name	Drug studied	Patient population	Primary conclusion(s)
			composite (ARR=4.4%; unadjusted HR 0.85; 95% CI, 0.75–0.96; P=0.011).
CHARM-Preserved [28]	Candesartan 32 mg daily vs. placebo. At 6 months, the mean candesartan daily dose was 25 mg.	N=3023. HF patients with NYHA classes II–IV symptoms, and EF>40%. Median follow-up 36.6 months.	For the primary composite endpoint of CV death or hospital admission for HF, 22.0% of candesartan patients and 24.3% of placebo patients experienced the composite (unadjusted HR 0.89; 95% CI, 0.77–1.03; P=0.118).
I-PRESERVE [29]	Irbesartan 300 mg daily vs. placebo.	N=4128. HF patients ≥60 years, NYHA classes II–IV symptoms, and EF≥45%. Mean follow-up 49.5 months.	For the primary composite outcome of death from any cause or hospitalization for a CV cause occurred in 36% of the irbesartan patients and 37% of the placebo patients (HR 0.95; 95% CI, 0.86–1.05; P=0.35).
RALES [3]	Spironolactone 25–50 mg daily (mean dose 26 mg) vs. placebo.	N=1663. Severe HF patients (NYHA classes III–IV) with EF≤35% who were being treated with an ACE-inhibitor. Trial was discontinued early, after a mean follow-up period of 24 months.	The primary end point of death from all causes occurred in 35% of the spironolactone group and 46% of the placebo group (ARR=11%; RR 0.70; 95% CI, 0.60–0.82; P<0.001).
EMPHASIS [33]	Eplerenone (up to 50 mg daily) vs. placebo.	N=2737. HF patients with NYHA class II symptoms and EF≤35%. Trial was discontinued early, after a median follow-up period of 21 months.	The primary composite outcome of death from CV causes or hospitalization for HF occurred in 18.3% of patients in the eplerenone group and 25.9% in the placebo group (ARR=7.6%; HR 0.63; 95% CI, 0.54–0.74; P<0.001).
Myocardial infarction			
SAVE [37]	Captopril vs. placebo. Target dose of captopril 150 mg daily reached in 79% of patients.	N=2231. Patients with EF≤40% within 3 to 16 days after MI, but without overt HF or symptoms of myocardial ischemia. Average follow-up 42 months.	5% ARR in mortality with captopril (20% vs. 25% mortality; risk reduction=19%; P=0.019).
AIRE [38]	Ramipril vs. placebo. Initial dose of 2.5 mg BID up to 5 mg BID.	N=2006. Patients within 3–10 days of an acute MI with clinical evidence of HF. Average follow-up 15 months.	6% ARR in mortality with ramipril (17% vs. 23% mortality; risk reduction=27%; P=0.002).
TRACE [39]	Trandolapril vs. placebo. Initial dose of trandolapril 1 mg daily up to 4 mg daily.	N=1749. Patients with acute MI and EF≤35% randomized on days 3–7 after MI. The duration of follow-up was 24 to 50 months.	7.6% ARR in mortality with trandolapril (34.7% vs. 42.3% mortality; RR 0.78; 95% CI, 0.67–0.91; P=0.001).
VALIANT [40]	Valsartan vs. valsartan plus captopril vs. captopril. 3-month target doses of valsartan 160 mg BID, valsartan 80 mg BID and captopril 50 mg TID, or captopril 50 mg TID.	N=14,703. Patients with MI complicated by LVSD, HF, or both randomized at 0.5 to 10 days after acute MI. Median follow-up 24.7 months.	For the primary end point of death from any cause, the mortality rates in the valsartan, captopril, and combination therapy groups were 19.9%, 19.5% and 19.3%, respectively. HR for valsartan group vs. captopril group, 1.00; 97.5% CI, 0.90–1.11; P=0.98; HR for combination group vs. captopril group, 0.98; 97.5% CI, 0.89–1.09; P=0.73.
OPTIMAAL [41]	Losartan (target 50 mg daily) vs. captopril (target 50 mg TID).	N=5477. Patients ≥50 years with acute MI and HF.	For the primary end point of death from any cause, the

Trial name	Drug studied	Patient population	Primary conclusion(s)
		Mean follow-up 2.7 years.	mortality rate was 18% in the losartan group and 16% in the captopril group (RR 1.13; 95% CI, 0.99–1.28; P=0.07).
EPHESUS [45]	Eplerenone (25 mg daily, titrated to 50 mg daily). vs. placebo	N=6632. Patients with acute MI complicated by LVSD and HF. Mean follow-up 16 months.	The primary end points of death from any cause and death from CV causes or hospitalization for CV causes occurred in 14.4% of the eplerenone group vs. 16.7% of the placebo group (ARR=2.3%; RR 0.85; 95% CI, 0.75–0.96; P=0.008) and 26.7% of the eplerenone group vs. 30.0% of the placebo group (ARR=3.3%; RR 0.87; 95% CI, 0.79–0.95; P=0.002), respectively.
Hypertension and stroke			
ALLHAT [51]	Chlorthalidone (12.5–25 mg daily) vs. amlodipine (2.5–10 mg daily) vs. lisinopril (10–40 mg daily).	N=33,357. Patients ≥55 years with hypertension and at least 1 other coronary heart disease risk factor. Mean follow-up 4.9 years.	There was no difference in the primary outcome of fatal coronary heart disease or nonfatal MI between treatments. Compared with chlorthalidone (6-year rate, 11.5%), the RR was 0.99; 95% CI, 0.91–1.08 for lisinopril.
VALUE [52]	Valsartan vs. amlodipine.	N=15,245. Patients ≥50 years with hypertension and a high risk of cardiac events. Mean follow-up 4.2 years	The primary composite endpoint of cardiac mortality and morbidity occurred in 10.6% of the valsartan group and 10.4% of the amlodipine group (HR 1.04; 95% CI, 0.94–1.15; P=0.49).
ANBP-2 [53]	ACE-inhibitor vs. diuretic. Enalapril and hydrochlorothiazide were recommended as initial therapy.	N=6083. Patients with hypertension who were 65 to 84 years of age. Median follow-up 4.1 years.	The primary end point of all CV events or death from any cause occurred in 56.1 per 1000 patient-years in the ACE-inhibitor group and 59.8 per 1000 patient-years in the diuretic group (HR 0.89; 95% CI, 0.79–1.00; P= 0.05).
SCOPE [54]	Candesartan (8–16 mg daily) vs. placebo.	N=4964. Patients aged 70–89 years, with systolic blood pressure 160–179 mm Hg, and/or diastolic blood pressure 90–99 mm Hg, and a Mini Mental State Examination test score ≥24. Mean follow-up 3.7 years.	The primary outcome of CV death, non-fatal stroke and non-fatal MI occurred at a rate of 26.7 events per 1000 patient-years in the candesartan group and 30.0 events per 1000 patient-years in the placebo group. Risk reduction= 10.9%; 95% CI, −6.0 to 25.1, P=0.19.
PROGRESS [55]	Perindopril (4 mg daily), +/− indapamide vs. placebo.	N=6105. Hypertensive and non-hypertensive patients with a history of stroke or transient ischemic attack. Mean follow-up 3.9 years	The primary outcome of stroke (fatal or non-fatal) occurred in 10% of the treatment group and 14% of the placebo group (ARR=4%; RRR=28%; 95% CI, 17–38; P<0.0001).
LIFE [56]	Losartan-based (50 mg daily) vs. atenolol-based (50 mg daily) antihypertensive treatment.	N=9193. Patients aged 55–80 years with essential hypertension and left ventricular hypertrophy on electrocardiography. Mean follow-up 4.8 years.	The primary outcome of CV event (death, myocardial infarction, or stroke) occurred in 11% of the losartan group and 13% of the atenolol group (ARR=2%; unadjusted RR 0.87; 95% CI, 0.77–0.98; P=0.021).
Arterial disease and others at increased cardiovascular risk			

Trial name	Drug studied	Patient population	Primary conclusion(s)
PEACE [58]	Trandolapril (4 mg daily) vs. placebo.	N=8290. Patients ≥50 years with stable coronary artery disease and EF>40%. Median follow-up 4.8 years.	The primary end point of death from CV causes, MI, or coronary revascularization occurred in 21.9% of the trandolapril group and 22.5% of the placebo group (HR 0.96; 95% CI, 0.88–1.06; P=0.43).
HOPE [59]	Ramipril (10 mg daily) vs. placebo. The percentage of patients who were receiving 10 mg of ramipril per day was 82.9% at one year.	N=9297. Patients ≥55 years who had evidence of vascular disease or diabetes plus one other CV risk factor and who were not known to have a low ejection fraction (EF>40%) or HF. Follow-up period 5 years.	The primary outcome of MI, stroke, or death from CV causes occurred in 14.0% of those in the ramipril group and 17.8% in the placebo group (ARR=3.8%; RR 0.78; 95% CI, 0.70–0.86; P<0.001).
EUROPA [60]	Perindopril (8 mg daily) vs. placebo.	N=12,218. Patients with stable coronary artery disease, but no clinical HF. Mean follow-up 4.2 years.	The primary endpoint of CV death, MI, or cardiac arrest occurred in 8% of the perindopril group and 10% of the placebo group (ARR=2%; RRR=20%; 95% CI, 9–29; P=0.0003).
TRANSCEND [61]	Telmisartan (80 mg daily) vs. placebo.	N=5926. High-risk patients with cardiovascular disease or diabetes with end-organ damage and intolerance to ACE-inhibitors. Median follow-up 56 months.	The primary outcome of the composite of CV death, MI, stroke, or hospitalization for HF occurred in 15.7% in the telmisartan groups and 17.0% in the placebo group (HR 0.92; 95% CI, 0.81–1.05; P=0.216).
Diabetic nephropathy			
RENAAL [62]	Losartan (50–100 mg daily) vs. placebo.	N=1513. Patients with type 2 diabetes and nephropathy. Mean follow-up 3.4 years.	The primary outcome of the composite of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death occurred in 43.5% of the losartan group and 47.1% of the placebo group (ARR=3.6%; risk reduction 16%; 95% CI 2–28; P=0.02).
Irbesartan Diabetic Nephropathy Trial [63]	Irbesartan (300 mg daily) vs. amlodipine (10 mg daily) vs. placebo.	N=1715. Hypertensive patients with nephropathy due to type 2 diabetes. Mean follow-up 2.6 years.	The primary composite end point of a doubling of the base-line serum creatinine concentration, the development of end-stage renal disease, or death from any cause occurred in 32.6% of the irbesartan group, 41.1% of the amlodipine group, and 39.0% of the placebo group. The irbesartan group had an ARR of 6.4% and a RR of 0.80; 95% CI, 0.66–0.97; P=0.02 vs. placebo and an ARR of 8.5% with a RR 0.77; 95% CI, 0.63–0.93; P=0.006 vs. amlodipine.
ABCD Substudy [64]	Nisoldipine vs. enalapril.	N=470. Patients with non-insulin-dependent diabetes and hypertension. Five year follow-up.	The endpoint of this analysis was fatal or non-fatal MI, a secondary endpoint of the ABCD trial. 10.6% of patients in the nisoldipine group (25 events) experienced the outcome compared with 2.1% in the enalapril group (5 events). ARR=8.5% with unadjusted risk ratio of 5.5; 95% CI, 2.1–14.6.
FACET [65]	Fosinopril (20 mg daily) vs. amlodipine (10 mg daily).	N=380. Patients with hypertension and	The secondary endpoint of CV events (acute MI, stroke,

Trial name	Drug studied	Patient population	Primary conclusion(s)
		non-insulin-dependent diabetes followed for up to 3.5 years.	or hospitalized angina) occurred in 7.4% of the fosinopril group and 14.1% of the amlodipine group (HR 0.49; 95% CI, 0.26–0.95).
UKPDS 39 [67]	Atenolol vs. captopril.	N=1148. Hypertensive patients with type 2 diabetes.	One of the primary outcomes was all-cause mortality which occurred in 18.8% of the captopril group and 16.5% of the atenolol group (RR for captopril 1.14, 95% CI 0.81–1.61; P=0.44).
ROADMAP [68]	Olmesartan (40 mg daily) vs. placebo.	N=4447. Patients with type 2 diabetes and normoalbuminuria. Median follow-up 3.2 years	The primary outcome was the time to the first onset of microalbuminuria. Microalbuminuria developed in 8.2% of the olmesartan group and 9.8% of the placebo group (HR for onset of microalbuminuria, 0.77; 95% CI, 0.63–0.94; P=0.01). The secondary composite endpoint of death from CV causes occurred in 0.7% of the olmesartan group (15 events) and 0.1% of the placebo group (3 events). HR 4.94; 95% CI, 1.43–17.06; P=0.01.
Atrial fibrillation			
GISSI-AF [96]	Valsartan (target 320 mg daily) vs. placebo.	N=1442. Patients who were in sinus rhythm but had had either ≥2 documented episodes of AF in the previous 6 months or successful cardioversion for AF in the previous 2 weeks. Patients also had to have underlying CV disease, diabetes, or left atrial enlargement. One year follow-up.	The co-primary endpoint of AF recurrence occurred in 51.4% of the valsartan group and 52.1% of the placebo group (HR 0.98; 96% CI, 0.85–1.14; P=0.83).
ACTIVE-I [97]	Irbesartan (target dose 300 mg daily) vs. placebo.	N=9016. Patients with a history of risk factors for stroke and a systolic blood pressure of at least 110 mm Hg. Mean follow-up 4.1 years.	The coprimary outcome of stroke, myocardial infarction, or death from vascular causes occurred at a rate of 5.4% per 100 person-years in both groups (RR with irbesartan, 0.99; 95% CI, 0.91–1.08; P=0.85).

Abbreviations: NYHA = New York Heart Association, HF = heart failure, EF = ejection fraction, HR = hazard ratio, ARR = absolute risk reduction, RR = relative risk, CI = confidence interval, CV = cardiovascular, MI = myocardial infarction, AF = atrial fibrillation, LVSD = left ventricular systolic dysfunction, BID = twice daily, and TID = three times daily.