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REVIEW ARTICLE

RAAS Inhibitors and Cardiovascular Protection in Large Scale Trials

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Abstract Hypertension, coronary artery disease and heart failure affect over half of the adult population in most Western societies, and are prime causes of CV morbidity and mortality. With the ever-increasing worldwide prevalence of CV disease due to ageing and the "diabetes" pandemic, guideline groups have recognized the importance of achieving cardioprotection in affected individuals as well as in those at risk for future CV events. The renin-angiotensin-aldosterone system (RAAS) is the most important system controlling blood pressure (BP), cardiovascular and renal function in man. As our understanding of the crucial role of RAAS in the pathogenesis of most, if not all, CV disease has expanded over the past decades, so has the development of drugs targeting its individual components. Angiotensin-converting enzyme inhibitors (ACEi), Ang-II receptor blockers (ARB), and mineralcorticoid receptor antagonists (MRA) have been evaluated in large clinical trials for their potential to mediate cardioprotection, singly or in combination. Direct renin inhibitors are currently under scrutiny, as well as novel dual-acting RAAS-blocking agents. Herein, we review the evidence generated from large-scale clinical trials of cardioprotection achieved through RAAS-blockade.

Keywords RAAS · ACE-inhibitor · ARB · Cardioprotection · Hypertension · Heart failure

Introduction

Activation of the RAAS occurs throughout the entire continuum of CV disease. Two key neurohormones within the RAAS, Ang-II and aldosterone, are crucially involved in mediating adverse effects on the CV system both systemically and within tissues. Among these effects are pathological fibrosis and hypertrophy of heart, kidney, and vasculature. Activation of the RAAS also facilitates stimulation of the adrenergic system, another system of major importance in CV pathogenesis [1]. Abrogation of excessive Ang-II and aldosterone activation is widely believed to reduce CV morbidity and mortality. Numerous experimental and clinical studies have demonstrated RAAS blockade being able to regress or reverse Ang-II mediated left ventricular hypertrophy (LVH), a strong predictor of CV morbidity and mortality. Therefore, RAAS blockade has evolved into a cornerstone of CV pharmacotherapy. Currently, ACE-inhibitors (ACEi), Ang-II receptor blockers (ARB) and aldosterone or, more accurately, mineralcorticoid receptor antagonists (MRA) are the most commonly prescribed RAAS-blocking agents. While these drug classes were traditionally employed for the treatment of hypertension and to halt progression of cardiac dysfunction/heart failure (HF) following myocardial infarction (MI), their use has steadily expanded to target asymptomatic CV disease and to provide cardioprotection in individuals only at risk for developing CV disease [2]. However, as drug classes differ substantially in their mode of actions, recent data also suggest beneficial BP-independent effects.

This review summarizes our current understanding of cardioprotection achieved by RAAS-blocking drugs, based

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on evidence from key, large-scale randomized controlled trials (RCT).

Clinical Outcome Trial-Based Evidence for Cardioprotection by RAAS-Blockade

Angiotensin-Converting Enzyme Inhibitors (ACEi)

Reduction of Ang-II biosynthesis through inhibition of ACE was the initial RAAS-blockade strategy which underwent large-scale clinical evaluation. Over two decades ago, the pioneering Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) demonstrated a 40% reduction in the primary endpoint (EP) of mortality by enalapril relative to placebo in 253 patients with advanced HF [3]. As this marked survival benefit was driven by amelioration of HF progression, but not that of sudden cardiac death, CONSENSUS firmly established proof-of-concept that ACEi favourably influenced the course of HF, and paved the way for a series of large scale trials that evaluated ACEi throughout the CV disease continuum.

Early seminal trials in post-MI myocardial dysfunction and HF such as SOLVD, SAVE, AIRE, TRACE and SMILE all showed that ACEi favourable mediated outcome, but are beyond the scope of this review on cardioprotection in lower-risk cohorts [4–9]. The Assessment of Treatment with Lisinopril and Survival (ATLAS) study compared the efficacy and safety of low and high doses of ACEi on the risk of death and hospitalization in HF, and provided first evidence of the importance of up-titrating ACEi in HF to the highest tolerated (and preferably) target dose [10].

In the landmark Heart Outcomes Prevention Evaluation (HOPE) trial, 9,297 patients with CV risk factors, but no HF were randomized to the ACEi ramipiril or placebo [11]. After a mean follow-up (FU) of 5 years, ramipiril-treated patients had a 22% lower relative risk (RR) compared to placebo of the primary composite of CV death, MI, or stroke. A similar benefit for ACEi was observed in the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA). EUROPA enrolled a similar low-risk cohort (n=13,655) as HOPE, with coronary artery disease (CAD) but no LV dysfunction or HF. After a mean FU of 4.2 years, perindopril reduced the RR for the composite of CV death, cardiac arrest or MI by 20% compared to placebo [12]. The Second Australian National Blood Pressure (ANBP2) trial examined the efficacy of antihypertensive treatment with ACEi compared to diuretics in 6,083 older subjects in an outpatient setting [13]. The choice and dose of the specific agents used in both arms were at the discretion of the treating family practitioner although enalapril and hydrochlorthiazide were the recommended ACEi and diuretic, respectively. ANBP2 showed that even in that relatively healthy cohort ACEi reduced the primary EP of CV events or all-cause mortality, particularly in men. Of note, this benefit was seen despite similar reductions of blood pressure with ACEi compared to diuretics. The ACEi trandolapril was scrutinized in 8,290 patients with stable coronary heart disease and preserved left ventricular function in the Prevention of Events with ACE inhibition (PEACE) [14]. The reported rate of CV events was substantially lower than in previous trials of ACEi in patients with vascular disease. After a median FU of 4.8 years, no differences between ACEi and placebo treated patients were discerned for the composite of death from cardiovascular causes, MI, or coronary revascularization, or pre-specified secondary EP.

Together, there is an overwhelming body of evidence for cardioprotection afforded by ACEi treatment throughout most CV disease severities.

Angiotensin-II (Ang-II) Receptor Blockers (ARB)

Acknowledging a certain pathway redundancy for the generation of Ang-II in the human body and the fact that ACEi may lose effect over time, specific antagonists of the pathogenetically most important Ang-II type 1 receptor subtype were developed, referred to as Ang-II receptor blockers (ARBs). The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study provided first evidence of cardioprotection afforded by an ARB [15]: In LIFE, 9,193 patients with hypertension and evidence of LVH received either losartan or atenolol over a period of at least 4 years. At similar and marked reduction in BP for both arms, losartan significantly reduced the composite of CV death, stroke or myocardial infarction. This benefit was almost exclusively due to the reduced risk for fatal or non-fatal stroke, while the incidence of CV death or MI was not different between the treatment arms.

Important outcome studies evaluated ARBs in the setting of LV dysfunction and HF, using ACEi as comparator. Following encouraging signals in a phase-2 Evaluation of Losartan in the Elderly (ELITE) trial, ELITE-II set out to assess whether losartan (50 mg once daily) was superior to captopril (50 mg 3 x daily) to lower all-cause death or the composite of sudden death or cardiac arrest in 3,152 subjects with NYHA II-IV HF and reduced LVEF [16, 17]. After a mean follow-up of 19 months, all-cause death was similar in both arms, with a trend towards more sudden death or cardiac arrests in losartan-treated patients (P=0.08). The Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study randomized 5,477 patients with acute MI and HF or reduced LV function to losartan (50 mg once daily) or captopril (50 mg 3 x daily). After a mean follow-up of 2.7 years, investigators reported significantly higher CV mortality and a strong trend for increased all-cause mortality

in losartan-treated patients [18]. In the Valsartan in Acute Myocardial Infarction VALIANT trial, a total of 14,723 patients with acute MI and HF and/or LV dysfunction randomly received valsartan, valsartan+captopril, or captopril [19]. No difference between treatment arms were found for the incidence of death or CV events after a mean follow-up of 25 months, and dual valsartan+captopril treatment led to significantly more adverse events without further improvement in outcomes. The important issue of what was an appropriate dose of ARB, at least in the context of HF was not addressed until several years later. The High-Dose Versus Low-Dose Losartan on Clinical Outcomes in Patients with Heart Failure (HEAAL study) randomized 3,846 patients with NYHA II-IV HF, reduced LVEF and intolerance to ACEi to receive losartan 150 or 50 mg once daily [20]. Significantly fewer patients on high-dose ARB died or were admitted for HF after a median follow-up of 4.7 years. One of the most comprehensive analyses of the putative cardioprotective effects of ARB in HF was provided by the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) programme [21–24]. A total of 7,601 patients with NYHA II-IV HF were randomized to candesartan or placebo and in three prespecified distinct trials: those with reduced EF and either intolerant to ACEi (CHARM-alternative) [24] or symptomatic despite being on an ACEi (CHARM-added) [22], and those with preserved EF (CHARM-preserved) [23]. After a median follow-up of 38 months, significantly fewer CV deaths and HF hospitalizations were found, as well as a strong trend towards reduced all-cause death in each individual analysis. In CHARM-added in 2,548 HF-patients that were already on ACEi, but still symptomatic (NYHA class II-IV), add-on ARB reduced the primary composite of CV death and HF hospitalizations and each of its components after 41 months of follow-up. Of note, over half of those patients were on betablockers (BB), and one in six on MRA, reflecting contemporary background medication [22].

The Valsartan Heart failure Trial (ValHeFT) evaluated add-on ARB (Valsartan) to standard therapy in 5,010 HF-patients (NYHA class II-IV) [25]. Add-on ARB did not lower mortality, but reduced the primary composite (of all-cause mortality, cardiac arrest with resuscitation, HF hospitalization, or therapy with IV inotropes or vasodilators), obviously mainly driven by reduced HF hospitalizations. About 93% of patients in ValHeFT were on ACEi. Of these, two thirds did not take betablockers (BB), but only those had reduced incidence of the primary composite. In contrast, there were indications of actual harm for the remaining third of patients which were on ACEi, ARB and BB. With regard to all-cause mortality, no benefit of add-on ARB to ACEi was seen in ValHeFT. With BB now being a class 1A indication for CV diseases such as MI, CAD and HF, the relevance to daily practice is questionable.

The largest trial in CV medicine to date, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) Trial assessed the effects of Telmisartan, Ramipiril or both on morbidity and mortality in 25,620 patients with vascular disease or high-risk diabetes [26]. After a median follow-up of 56 months (representing a remarkable 120,000 patient-years), the three treatment regimen exhibited virtually identical occurrence of the primary composite outcome (CV death, MI, stroke, or hospitalization for HF), inspite of significantly greater BP reduction by telmisartan or combination therapy.

In daily clinical practice, as many as 10–20% of patients may not tolerate ACEi with cough and angioedema as the most frequently reported side effects. The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) evaluated whether telmisartan would be effective in patients with established CV disease or diabetes with end-organ damage that are intolerant to ACEi [27]. 5,926 patients were randomized to either telmisartan or placebo, and after a median follow-up of 56 months, despite a significant reduction in BP, no effect on the primary composite outcome (CV death, MI, stroke, or hospitalization for HF) by telmisartan compared to placebo was found.

Similarly, in the recent Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Valsartan, along with lifestyle intervention, led to a modest (i.e. 14%) reduction of new-onset diabetes in impaired glucose-tolerance compared to placebo but did not alter any CV EPs in that cohort [28]. Another rather concerning signal was seen in the recent ROADMAP trial which investigated whether the ARB olmesartan would delay or prevent the occurrence of microalbuminuria in patients with type 2 diabetes and normoalbuminuria (total n=4,447). Despite greater BP reduction and lower incidence and delayed onset of microalbuminuria, a significant five-fold increase of fatal CV events in Olmesartan-treated patients compared to placebo-treated patients was found, with most CV death occurring in patients with pre-existing CAD [29].

Thus, for all practical matters, current data do not support the routine use of ARB other than in patients either intolerant to ACEi, or those with HF symptoms despite target-dose ACEi or as dual therapy but only following MRAs. Current guidelines reflect this change in view with ARBs considered inferior to ACEi as the best cardioprotective drugs [30, 31].

Mineralcorticoid Receptor Antagonists (MRAs)

Aldosterone and its detrimental effects on the CV system upon overactivation may rightfully be called “the forgotten child of the RAAS” in terms of clinical evaluation. Plasma levels of aldosterone are increased in CV diseases such as hypertension and HF, and often in concert with elevated Ang-II. For instance in HF, pharmacotherapy using ACEi, ARBs, or even

both, only transiently reduces plasma aldosterone levels as reported by the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study investigators [32]. Recent data from patients with acute MI suggest that plasma aldosterone levels predict mortality independent of whether patients are in HF or not [33]. Based on considerations of potent pro-fibrotic effects on heart, kidneys and vasculature, the concept of blocking the adverse effects of aldosterone with MRAs was tested in patients where most were already receiving RAAS-blockade with ACEi or ARB [34].

The first large-scale RCT with MRAs was the Randomized Aldactone Evaluation Study (RALES) in patients in severe HF (NYHA II-IV) with reduced systolic LV function [35]. 1,663 patients who were already receiving treatment with ACEi and diuretic were randomized to spironolactone 25 mg or placebo. RALES was stopped prematurely after 24 months of follow-up because of a substantial reduced risk of death and HF hospitalization alongside significant symptomatic improvements. Importantly, the survival benefit was consistent across prespecified subgroups and the risk reduction was similar for sudden cardiac death or death from progressive HF. Of note, 10% of spironolactone-treated male patients reported gynecomastia or breast pain, but serious hyperkalemia was rare.

The 4E-left ventricular hypertrophy study, performed in 202 patients with primary hypertension and evidence of LVH, demonstrated similar BP-lowering and LVH-regressing effects of eplerenone as enalapril [17]. The subsequent Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) evaluated the much more specific MRA eplerenone in 6,642 patients with reduced systolic LV function early after MI and HF or diabetes [36]. After a mean follow-up of only 16 months, eplerenone-treated subjects had a significant 15% reduction in all-cause death and of 13% in the composite of CV death and CV hospitalizations. 86% of the 3,319 patients receiving eplerenone were on ACEi/ARB, and 75% on BB. Changes in BP were, however, not different from placebo, and one might therefore speculate whether avoidance of hypotension (and thus, low perfusion pressures of vital organs post-MI) maybe important to the benefits in a HF setting [36].

Extending the evidence from EPHESUS, the EMPHASIS-HF study randomized 2,737 patients with only mildly symptomatic HF (NYHA class II) and reduced LVEF to eplerenone or placebo [37, 38]. As with RALES, EMPHASIS-HF was stopped prematurely after a median FU of 21 months due to a 37% reduction in the primary composite of CV death or HF hospitalization (driven by a 24% reduction in CV death, and a 42% reduction in HF hospitalization). In EMPHASIS, almost all of the 1,364 mildly symptomatic HF patients receiving eplerenone were on ACEi and/or ARB (94%), and 87% were on BB.

The jury is still out on how much of cardioprotection afforded by MRA is due to BP-lowering, versus direct myocardial, renal and vascular anti-aldosterone actions. In resistant hypertension, aldosterone has been postulated to contribute importantly to the hypertensive state which is often maintained despite treatment including target-dose RAAS-blockade with ACEi and ARBs.

Recent *posthoc* data from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) reported that add-on spironolactone as fourth drug, on top of either ACEi or ARB, significantly reduced BP in 1,411 patients with treatment-resistant hypertension [39]. The efficacy of MRA in this context was confirmed by similar findings with eplerenone in a smaller study [40].

Little is known about the potential cardioprotectice effects of MRA in early stages of CV disease, in HF without LV dysfunction, or in asymptomatic individuals at risk. Two currently ongoing trials are investigating the potential benefit of MRA in patients with HF and preserved EF: the Aldosterone Receptor Blockade in Diastolic HF (ALDO-HF) is evaluating the effect of spironolactone on exercise capacity and diastolic functional indices (by echocardiography) in 420 patients with HF (NYHA II-III) and preserved systolic LV function [41]. The larger Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist Trial (TOPCAT) is designed to test the effect of spironolactone on mortality, morbidity and quality of life in 3,515 patients with HF (NYHA II-III) and preserved systolic LV function [42]. The ongoing SCREEN-HFI (SCReening Evaluation of the Evolution of New Heart Failure Intervention Study) is evaluating the potential of spironolactone relative to placebo to prevent HF in 600 asymptomatic individuals at risk (identified by elevated BNP levels) [43].

The consistent beneficial effects of MRA in LV dysfunction, HF and hypertension have been acknowledged in recent international guidelines updates [30]. Importantly, increase of potassium levels is inherent to MRA therapy. In general, the incidence of clinically relevant hyperkalemia in most trials was low and similar for adding an ARB to ACEI compared to adding MRA to ACEI. The latter strategy seems to be safe provided that BP, renal function and electrolyte levels are carefully monitored throughout, and of much greater efficacy.

Direct Renin-Inhibition

The latest RAAS-blocking strategy undergoing scrutiny in clinical trials is the concept of renin-inhibition. Renin is the most upstream component of the RAAS cascade, thus conceptually, its inhibition should profoundly reduce the generation of Ang-II and (unlike ACEi) its precursor Ang-I. The renin inhibitor aliskiren is currently being evaluated in two clinical HF trials, the Aliskiren Trial on Acute Heart

Failure Outcomes (ASTRONAUT) and the Aliskiren Trial of Minimizing Outcomes for Patients with Heart Failure (ATMOSPHERE) [44, 45]. In ASTRONAUT, 1,782 patients hospitalized with worsening chronic HF and reduced systolic LV function will be randomized to aliskiren or placebo, and evaluated for the composite of time to either cardiovascular death or first occurrence of HF re-hospitalization. The larger ATMOSPHERE study will assess the effect of both aliskiren and enalapril monotherapy and dual aliskiren/enalapril therapy on CV mortality and HF hospitalization in approximately 7,000 patients with HF (NYHA II-IV), reduced systolic LV function and elevated plasma levels of BNP. A third ongoing study, the Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE) is comparing aliskiren versus placebo, added to either ACEi or ARB, in diabetic patients with known CV disease and evidence of impaired renal function [46, 47]. ALTITUDE was recently stopped for futility on the recommendation of its Data Monitoring Committee (DMC) [48].

Novel RAAS-Blocking Approaches

Dual modulation of RAAS and other systems operative in CV disease may overcome current limitations of cardioprotective pharmacotherapy. The natriuretic peptide (NP) system is the body´s own BP-lowering system that also promotes natriuresis and counteracts pathological fibrosis. Increased cardiac wall stress (such as occurring in hypertension or HF) is a well-established stimulus of NP secretion within the heart [49, 50]. NPs are degraded by the ectoenzyme neutral endopeptidase (NEP), and NEP-inhibition (NEPi) augments beneficial NP activity. Of note, NEP also degrades a number of other vasoactive factors such as bradykinin, endothelin, Ang-II and adrenomedullin. This may explain why early NEPi such as candoxatril produced neutral net effects with regards to BP lowering and cardioprotection [51, 52]. The effectiveness of NEPi to augment levels of endogenous NPs and to mediate cardioprotection was only finally realized when combined with RAAS blockers.

Dual RAAS/NEP Inhibition

The RAAS and NP system serve as a counter-regulatory constraint on the activity of the other [53]. Conceptually, the beneficial effects of inhibition of RAAS may potentially be augmented by enhancement of NP activity, and thus, perhaps overcome the disappointing clinical effects of NEP inhibitors (NEPi) as monotherapy [54, 55].

ACEi/NEPi (Vasopeptidase Inhibition)

The most extensively studied dual-acting ACEi/NEPi thus far has been omapatrilat. OCTAVE was the definitive clinical outcome trial to evaluate the beneficial effects of omapatrilat in 25,302 untreated or uncontrolled hypertensives [55]. OCTAVE demonstrated that omapatrilat improved BP control compared to ACEi (enalapril), but also increased the prevalence of angioedema, presumably due to excessive increase of bradykinin levels.

In HF, a 573 patient Phase IIB study (IMPRESS) compared omapatrilat to ACEi (lisinopril) [56]. Omapatrilat reduced the composite endpoint of death, HF admission or discontinuation of study treatment for worsening HF, and without increase of angioedema occurrence. A major outcome study, OVERTURE randomized 5,770 NYHA Class II-IV systolic HF patients to enalapril or omapatrilat [57]. After a mean FU of 14.5 months, the occurrence of the primary composite (death or hospitalisation for HF requiring IV therapy) was not significantly different compared to enalapril.

Angiotensin Receptor Neprilysin Inhibitors (ARNi)

With further clinical development of ACEi/NEPi programs essentially abandoned, novel agents have emerged combining not an ACEi but ARB with NEPi with (so-called ARNi). As demonstrated experimentally, ARNi are less likely to interfere with bradykinin metabolism and thus, avoid augmentation of cough and angioedema [58]. The first and most clinically advanced compound in this new class LCZ-696, a fixed dose 1:1 combination of valsartan and NEPi pro-drug AHU377. Pre-clinically, LCZ-696 was able to lower BP in several hypertension models with associated increases in plasma cGMP, renin and Ang-II levels indicating that appropriate receptors were targeted as per expected pharmacological actions [59]. Moreover, we demonstrated robust anti-fibrotic and anti-hypertrophic effects of LCZ-696 in cardiac cells that were superior compared to Valsartan monotherapy [60].

Recently, a large phase-II study of LCZ-696 (compared to ARB, Valsartan) has been undertaken in 1,328 patients with mild to moderate hypertension [61]. After 8 weeks of FU modest, LCZ-696 produced modest, but significantly greater reductions in office BP compared to the equivalent dose of valsartan alone. These office BP data were supported by greater overall 24-hr BP control with LCZ-696, and no cases of angioedema were reported. Based on the above efficacy and safety findings, further development is being undertaken of LCZ-696 in hypertension.

LCZ-696 may also have considerable potential in the setting of HF. The PARADIGM-HF study [62] is an ongoing efficacy and safety assessment of LCZ-696 in patients with stable chronic HF (left ventricular ejection fraction <40%), with ACEi (enalapril) as comparator. Patients post-randomisation will be followed until 2,410 primary outcome events (CV death or HF hospitalisation) have been achieved.

One obvious area worthy of exploration is that of HF with preserved ejection fraction (HFPEF), a heterogenous

disorder that is often driven by hypertension and chronic ischemia. HFPEF is a disease characterized by pathological myocardial fibrosis and thus the augmented anti-fibrotic activity of a combined ARB/NEP inhibitor may be of particular benefit in this setting.

The recently published PARAMOUNT-study was a phase-II parallel-group, double-blinded RCT comparing LCZ-969 with valsartan in 301 patients with HFPEF and elevated plasma levels of NT-proBNP [63]. Patients assigned to LCZ-969 showed a greater reduction in NT-proBNP at 12 weeks of follow-up, the primary endpoint. More patients on LCZ-969 exhibited improved NYHA functional class and of note, reduced LA size compared to valsartan, consistent with reverse LA remodelling. Another encouraging signal was that two important risk groups, namely diabetics and those with the highest BP exhibited greater reductions of plasma NT-proBNP by LCZ-969 than valsartan, although the study was underpowered to detect subgroup differences [64]. At the same time, no enhanced risk of angioedema or other adverse events were reported in PARAMOUNT. Together, there seems to be considerable further therapeutic potential for the concept of ARNi with accumulating evidence of superior cardioprotection.

Discussion

There is now a wealth of data underpinning RAAS-blockade as single most important cardioprotective strategy across the entire CV disease continuum.

Among the individual drug classes, data from several RCTs prompted concerns that ARBs may augment the risk of cardiac events, in particular of MI [29, 65]. Recently, a large and comprehensive study analyzing 37 RCTs with a total of 147,020 patients and a total follow-up amounting to almost half a million patient-years refuted these concerns [66]. Rather, the authors failed to detect a reduction in all-cause or CV mortality by ARB in that broad patient cohort. In addition, a very recent metaanalysis including almost 160,000 hypertensive patients from 20 major RCT reported significant reduction in all-cause (5%) and CV mortality (7%) for the combined class of RAAS-inhibiting drugs [67]. That general survival benefit in the overall RAAS-inhibitor cohort was confined to those treated with an ACEi which exhibited a 10% reduced all-cause death. Conversely, no such survival benefits were discerned for ARBs (significantly different from ACEi); a fact that corroborates the data by Bangalore et al. [66]. Effects of ACEi vs ARB on MI risk are yet to be reported. Increasing utilization of risk-reducing drugs (statins, BB, platelet-inhibitors) as background medication in RCTs over time, and relative paucity of head-to-head comparisons between ACEI and ARB, however, warrant caution when interpreting any aggregate data.

Given the complexities of the RAAS and the shortcomings with each of the drug classes discussed above, RAAS blockade at multiple levels appears as an intuitively attractive approach. Only few large-scale RCTs have exhaustively assessed dual or triple RAAS blockade, and even less is known about optimal dosing of the individual components of such combination therapies. *Post-hoc* subgroup analyses of large RCTs have provided valuable insight into multiple RAAS-antagonism. Current knowledge suggests ACEi plus MRA as the preferred dual RAAS-blocking strategy although the total number of patients evaluated is still considerably less than those in ACEi/ARB trials.

Conclusions

The question arising hereafter is whether any RAAS blocker still could be considered a first-line cardioprotective drug [68]. Given the evidence above, reflected by current treatment guidelines, ACEi remain the first line drug as cardioprotection in all patients. In the case of true intolerance to an ACEi, an ARB should be prescribed if tolerated. Dual ACEi and ARB treatment is not generally recommended, and restricted to those systolic HF patients who remain symptomatic on ACEi.

Despite strong evidence, MRA seem still underutilized in clinical practice, but are evolving into a cornerstone of cardioprotection, and will likely expand their indications ultimately far beyond those outlined in current guidelines [69]. In this rapidly evolving field, concomitant ACEi and MRA therapy is now the preferred dual RAAS-blocking strategy for most HF and reduced LV systolic function, in particular post-MI. Novel promising drug classes such as direct renin-inhibitors and ARNi (dual-acting ARBs) are in different stages of clinical development, and data on their putative cardioprotective actions are eagerly awaited.

Disclosures

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