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CARDIOLOGY JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

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DOI: 10.5603/CJ.a2022.0061

Article type: Review Article

Submitted: 2021-10-22

Accepted: 2022-05-25

Published online: 2022-06-23

Atrial fibrillation in heart failure patients: An update on renin–angiotensin–aldosterone system pathway blockade as a therapeutic and prevention target

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Abstract

Heart failure (HF) and atrial fibrillation (AF) are two cardiovascular (CV) entities that affect millions of individuals worldwide and their prevalence is translated into a significant impact on health care systems. The common pathophysiological pathways that these two share have created an important clinical interrelation, as the coexistence of HF and AF is associated with worse prognosis and treatment challenges. Renin–angiotensin–aldosterone system (RAAS), a critical mechanism in blood pressure (BP) control, was proved to be involved in the pathogenesis of both conditions contributing to their further coexistence. Successful control of BP is of great importance to the management of HF, crucial for the prevention of arrhythmiogenic substrates, while RAAS antagonists may possibly affect the development of new-onset AF as well. There are numerous studies that evaluated the effectiveness of RAAS blockade in AF/HF population and despite comparable or modest results, there is a well-established suggestion that RAAS blockers may contribute to a reduction of HF, CV events and recurrence of AF, along with their potential effective role in the new-onset AF prophylaxis. Angiotensin receptor blockers, according to the evidence, are more effective in that direction, followed by angiotensin converting enzyme inhibitors, whereas the data on aldosterone antagonists are not encouraging, yet do have the potential of significant CV disease modificators regardless of their effects on BP.

Key words: renin–angiotensin–aldosterone system (RAAS) blockers, atrial fibrillation, heart

failure, angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEIs), aldosterone antagonists (AAs)

Introduction

In the ever-changing medical field, heart failure (HF) and atrial fibrillation (AF) remain firmly two of the most important health conditions [1]. Their impact on cardiovascular (CV) mortality is undeniable and their consequences in healthcare systems are significant worldwide [2–4]. A number of common risk factors contribute to the increasing incidence of both HF and AF. High blood pressure (BP), obstructive sleep apnea, diabetes, smoking, valvular and coronary heart disease constitute several of the determinant and modifiable factors [5]. The structural, inflammatory and neurohormonal alterations contributing to the development of HF and AF reveal great similarities. While, the interplay of underlying pathophysiological processes seem to be bidirectional, HF, with reduced or preserved ejection fraction (HFrEF, HFpEF), can predispose in the development of AF at some point [6], demonstrating adverse cardiovascular outcomes more often, as AF is considered an independent risk factor [7]. Likewise, AF can conduce to HF in over one third of patients, while the coexistence of these two entities is associated with poorer prognosis [8]. A strong interconnection between HF and AF indicates how each condition aggravates the other [9]. RAAS has a leading role in the regulation of BP and volume homeostasis (Central illustration) [10]. The contribution of this mechanism to functional modifications and its chronic activation has also been associated with structural changes in the whole CV system. Consequently, RAAS represents an important therapeutic target for several chronic CV diseases, including arterial hypertension (AH) management, the elimination of HF symptoms and adverse outcomes as well as effective treatment of concomitant HF and AF [11].

RAAS: Crossing over from arterial pressure regulation to HF and AF

The activation of RAAS leads to secretion of renin from the juxtaglomerular apparatus of the kidney and circulating angiotensinogen (AGT) is urged to form angiotensin I (Ang I). Angiotensin-converting enzyme (ACE) mainly expressed on the surface of endothelial cells, activates Ang I to Ang II [12]. Ang II was initially identified to be responsible for the activation of aldosterone but has also proved to act as a vasoconstrictor on the CV system, regulator of oxidative stress participating in the metabolism of several organs, including the nervous system, digestive organs, skin, reproductive tract, sensory organs, lymphatic tissue, adipose tissue, adrenals and kidneys [13]. Aldosterone contributes to the homeostatic regulation of BP and of sodium (Na+) and potassium (K+) plasma levels, acting primarily on the mineralocorticoid receptors (MRs) in the distal tubules and collecting ducts of the

nephron. Aldosterone influences the reabsorption of Na+ and excretion of K+, affecting water retention as well as BP and blood volume [14]. The chronic upregulated secretion of aldosterone has been associated with a prominent CV risk, CV and renal inflammation, fibrosis and remodeling [15]. The further description of RAAS has recognized different receptors (such as Ang-[1-7] peptide) and signal transduction pathways (such as the serine protease chymase) [16]. There are also data available supporting the existence of numerous RAASs presenting with different physiological activity within various organs, with their effects being expressed independently from the systemic RAAS [10]. Additionally, the interaction between RAAS and the natriuretic peptide system has affected clinical practice after the introduction of a novel drug that is able to enhance its activity and improve the HF outcomes [17]. Natriuretic peptide system acts opposite to the detrimental effects of RAAS upregulation occurring in HF, as it inhibits secretion of arginine vasopressin and modulates the autonomic nervous system. The activation of RAAS and sympathetic nervous system exert their CV effects, leading to increased ventricular preload, afterload, elevated wall stress, as well as to the production of pre-pro B-type natriuretic peptide (BNP) which is further cleaved to BNP and N-terminal proBNP (NT-proBNP) [18]. BNP inhibits RAAS and induces natriuresis and vasodilation, while NT-proBNP has no physiological function. Atrial natriuretic peptide (ANP) also presents with similar biological properties whereas C-type natriuretic peptide (CNP) can indirectly act as a potent vasodilator with inotropic and chronotropic properties [19].

Impact of RAAS on HF

The activation of RAAS is responsible for the CV remodeling and maintenance of BP and extracellular fluid volume [11]. Upregulation of RAAS activity results in many pathologic conditions, including AH, which lead to direct damage on cardiac, vascular and renal tissues [20]. AH has been recognized as a significant risk factor for the development of symptomatic HF. The very first observational studies based on the Framingham cohort have demonstrated the association between the AH and HF. According to the data occurring from the first 16 years of follow-up, Kannel et al. [21] in 1972 observed that the risk for hypertensive patients to develop HF was 6 times higher compared to the control group. Furthermore, 75% of those who developed HF during follow-up had a history of AH. As the typical hypertension diagnosis was set many years before the diagnosis of HF, it has not yet been possible to create safe estimating tools of the impact of AH on the risk of HF [11]. In 2002, Lloyd-Jones et al. [22] calculated the lifetime risk for HF development in patients from the Framingham cohort. The subjects were categorized in groups based on the BP measurements: systolic BP < 140 mmHg and diastolic BP < 90 mmHg; systolic BP from 140 to 159 mmHg and diastolic BP from 90 to 99 mmHg; systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg. A 2-fold increase for HF in remaining lifetime risk was observed from the lowest to highest BP group: 17.4% in a 60-year-old

male with a BP < 140 mmHg compared to 29% in a same age male with BP ≥ 160 mmHg, and similarly, in a 60-year-old female the percentages of remaining lifetime risk were increased from 14.4% to 27% for the same BP parameters [22].

The differentiation of HF patients based on the measurement of left ventricular (LV) ejection fraction (LVEF) has been beneficial in terms of optimal targeted therapy and definition of different CV population characteristics [11]. In a sub-analysis of the Framingham Heart Study cohorts, D.S. Lee et al. [23] examined the patients' onset characteristics of HFpEF versus HFrEF between 1981 and 2004. Pre-onset AH was linked to more than a two time increase in odds of developing HFpEF versus HFrEF and, at the onset of HF, a higher systolic BP was associated with a higher risk of HFpEF versus HFrEF progress by 13% for each 10-mmHg increase [23]. A later meta-analysis by Lam et al. [24] demonstrated that older age, female sex, high prevalence of AF and non-CV comorbidities presented a greater association with HFpEF compared with HFrEF, whereas AH was the most prevalent CV risk factor regarding the development of HFpEF [24]. Additionally, Ho et al. [25] reported a poor association between AH as a risk factor and HFrEF, while the relative risk of the development of HFpEF increased by 14% per 20 mmHg increase of systolic BP and by 42% in case of antihypertensive treatment administration [25]. According to the American College of Cardiology Foundation/American Heart Association stages of HF, AH patients can be classified as having stage A HFpEF [26, 27]. The underlying mechanisms that cause the transition from asymptomatic to overt hypertensive heart disease (stages B, C, D of HFpEF) are still basically unknown and represent a field of extensive research and a potential target for more effective therapeutic or preventive strategies [11]. The earliest evidence of heart disease in AH patients is LV diastolic dysfunction and cardiac remodeling. Cardiac remodeling as a result of a predominant pressure overload is accompanied with a concentric LV hypertrophy as well as a typical diastolic dysfunction [28]. This observation differentiates the cardiac remodeling due to predominant volume overload occurring from obesity, chronic kidney disease, anemia, heart valve regurgitation, that finally results in eccentric hypertrophy [29]. The development of decompensated concentric remodeling predisposes to HFpEF, while in general, eccentric remodeling leads to HFrEF [30]. Eventually, the coexistence of longstanding pressure and volume overload in end-stage hypertensive heart disease leads to dilated cardiomyopathy with diastolic and systolic dysfunction. In this condition systolic BP is usually low (decapitated hypertension), due to the impaired pump function and cardiac output, despite the existence of compensatory mechanisms such as peripheral vasoconstriction [31]. In this population the HF management is quite challenging as the administration of medication that reduces BP (ACEs, angiotensin receptor blockers [ARBs], diuretics and beta-blockers) are usually not tolerated [32]. On the contrary, it has been observed that in patients recovering from decompensated HF, BP measurements are increased [33], it has also been shown in patients undergoing successful cardiac

resynchronization therapy [34]. This finding may explain the protective effect of higher BP in the survival of patients with acute or chronic overt HF [11].

Effect of RAAS on AF

There is evidence that RAAS is associated with the development of AF in subjects with AH and HF [35]. An analysis of human atrial myocytes sampled from patients undergoing cardiac surgery has reported increased tissue levels of ACE and Ang II receptors in AF patients compared to those in sinus rhythm (SR) [36]. The activation of RAAS leads to electrical and structural changes and eventually atrial remodeling, therefore its role in the development of AF should be assessed. Activation of RAAS in hypertensive patients with heart disease results in elevation of left atrial pressure and LV end diastolic pressure [37–39]. Atrial dilatation is a result of ion-channel alterations that precede electrophysiological changes e.g., shortened refractory periods [40]. An extended activation of RAAS leads to high myocardial tissue levels of ACE and Ang II receptors, that provoke inflammation and fibrosis induced by cytokines such as transforming growth factor-beta (TGF-β) and phosphorylation pathways which cause a release of mitogen-activated protein kinases (MAPK). Ang II mediates the production of metalloproteinases that along with an extreme upregulation of extracellular matrix metabolism result in extensive atrial collagen deposition and atrial structural remodeling. In experimental animal models with rapid atrial pacing induced AF, high atrial tissue levels of ACE, chymase and angiotensinogen have been observed, that were associated with the high production levels of atrial tissue Ang II. Fibroblast proliferation and myocyte hypertrophy are also involved in atrial remodeling, induced by the previously mentioned mechanisms, contributing to the further development of AF [35]. The association of RAAS with atrial remodeling in AF and the variations observed among individuals have led to the suggestion that genetic polymorphisms in the ACE gene may play a role in this condition. The human ACE gene is located in chromosome 17q23.3 and there is a polymorphism reported regarding an insertion (I) or deletion (D) in the intron [41]. There are three genotypes in human populations: homozygous D/D and I/I and heterozygous I/D. ACE I/D polymorphism is responsible for 50% of the varied ACE levels observed in humans, and it has been linked with CV diseases such as LV hypertrophy, essential hypertension, dilated cardiomyopathy and myocardial infarction (MI) [42], as well as the development of non-familial AF [43, 44], whereas the association with the higher risk for AF development has been described as more significant in hypertensive patients [45]. The D/D polymorphism is connected with highest levels of ACE [46] and with poor response to anti-arrhythmic medications in subjects with AF [47]. In a prospective study evaluating 238 patients with paroxysmal or persistent AF undergoing catheter ablation, the ACE D/D homozygous polymorphism was associated with an increased risk of post ablation AF recurrence [48]. The upregulation of aldosterone levels due to the aldosterone synthase (CYP11B2) T-344C gene

polymorphism has been linked as an independent factor to an increased risk of AF in subjects with symptomatic HF. A LVEF case control study on 620 individuals in China has shown that the CC homozygous polymorphism of this gene was associated with echocardiographic evidence of atrial remodeling in hypertensive patients. There was no significant difference however, in the distribution of the polymorphisms (TT/TC/CC) among AH and control group [49].

Upstream therapy

The administration of RAAS blockers in individuals with CV disease risk factors is vital in the clinical practice and there are studies that support their therapeutic benefit in high CV disease risk patients [50, 51]. AF is the most commonly prevalent form of arrhythmia in patients with HF, also accompanied with a high risk of adverse clinical outcomes in these patients [9]. Alongside with rate and rhythm control therapy approaches, an upstream therapy — independent of ion channels has been introduced. The upstream therapy is gaining respectability following our understanding in the fundamental role of myocardial remodeling in the pathophysiology of AF. The drugs included in this context, target the structural and electrical remodeling of the atrial myocardium. When fibrosis is reduced, hypertrophy, inflammation and oxidative stress are further attenuated, while the atrial tissue ceases to be fertile ground for arrhythmia induction. Data from a 2009 European survey showed that patients with concomitant AF and HFrEF had a lower prescription rate of recommended drugs, such as beta-blockers and ACE inhibitors (ACEI) or ARBs [52]. Despite the previous observations, a number of randomized control trials (RCTs) report that the administration of HF therapy in patients with both HF and AF is beneficial. Boldt et al. [53] underlined the importance of aggressive HF treatment in AF patients who underwent cardioversion, that was further associated with higher rates of success [53]. The use of RAAS pathway antagonists including ACEIs, ARBs and aldosterone antagonists (AA) has been proved to act positively upon the electrical and ultrastructural changes in AF patients [35]. The positive effect of ACEI and ARBs in the prevention of AF recurrences remains to be clarified and is a subject for research in future clinical trials [54].

RAAS blockers on CV outcomes

The results of RCTs, assessing the effect of RAAS blockers on clinical outcomes in AF patients, are thus far inconclusive. A systematic review and meta-analysis of 6 RCTs aimed to evaluate RAAS blockers' effects in high-risk CV disease individuals with AF in comparison with non-AF patients [55]. The RCTs studied in this meta-analysis included LIFE (Losartan Intervention for End Point Reduction in Hypertension) [56], VALUE (Valsartan Antihypertensive Long-term Use Evaluation) [57], ADVANCE (Action in Diabetes and Vascular disease — preterax and diamicron MR controlled evaluation) [58], ACTIVE-I (Atrial Fibrillation Clopidogrel Trial with Irbesartan for

Prevention of Vascular Events) [59], GISSI-AF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico – Atrial Fibrillation) [60] and PROGRESS (Perindopril protection against recurrent stroke study) [61]. The endpoints of the study were all-cause mortality, CV mortality, HF, stroke, acute MI (AMI) and CV events, along with a composite of stroke, HF, AMI, or CV death. Despite the differences between the individual endpoints of the RCTs, meta-analysis end points were the same for the two groups studied (AF and non-AF patients) [55]. Based on data collected from the analysis of 53,510 patients, it was suggested that RAAS blockers are beneficial in terms of HF (14% incidence reduction) and CV events (17% incidence reduction) protection in high-risk CV disease patients with AF. Meanwhile, in the non-AF cohort RAAS blockers demonstrated no statistical significance in CV events and a 10% reduction in HF incidence that reached borderline statistical significance. The relative effect of RAAS blockers was comparable in the AF group (particularly ACTIVE-I trial [59]) and non-AF group. According to LIFE [56] and VALUE [57] trials, RAAS blockers have been proved effective suppressors of AF development compared to beta-blockers and calcium blockers, respectively. A modest beneficial effect in the protection of the AF subjects against CV events was noted in VALUE trial [57], a fact that can be attributed to the low number of events in that cohort and slightly higher BP measurements in valsartan arm of the study. The administration of losartan in AH patients with LV hypertrophy was estimated to be more beneficial than atenolol, especially in an AF population [55].

In the 4 placebo-controlled trials (PROGRESS [61], ADVANCE [58], ACTIVE-I [59], GISSI-AF [60]) RAAS blockers were associated with greater effect size in the AF than the non-AF group. It is also significant to mention that a large number of patients enrolled with advanced AF (persistent or permanent) and administered in a high rate as a background therapy antiarrhythmic drugs and antihypertensive drugs including ACEI with a modest difference in interarm BP throughout the trial BP measurements. ACTIVE I trial [59] reported a statistically significant 14% reduction in HF related hospital admissions as well as a 11% reduction in the risk of composite endpoint of stroke, systemic embolism, AMI, or CV mortality. GISSI-AF [60] was not associated with a significant difference in the hospitalization rate for CV or non-CV events, whereas there were fewer events observed in a smaller sample in a follow-up of 1 year. ADVANCE [58] and PROGRESS [61] trials used perindopril–indapamide combination revealing no significant inter-arm difference in BP reduction and therefore this combination was comparable to monotherapy with ARB trials. In the PROGRESS trial [61] perindopril monotherapy was associated with only a 14% and 15% reduction respectively in the risk of HF and CV events in comparison with the placebo administration. The difference in effect size between the two arms of the PROGRESS trial [61] underlines the necessity of optimized therapy using a combination of antihypertensive medication in the management of AH (Table 1).

The ACEIs as a cornerstone in the treatment for HFrEF are associated with a reduction in the mortality rates among symptomatic patients. The effect of ARBs on mortality has been so far inconsistent, although their use is indicated in patients where there are observed side effects by the use of ACEIs (primarily cough) [62]. Neprilysin, a neutral endopeptidase, participates in the degradation of vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin [63–65]. Inhibition of neprilysin leads to an increase in the levels of these substances, contributing to a restriction of vasoconstriction, sodium retention, and maladaptive remodeling [66, 67]. Therefore, a combined inhibition of the RAAS and neprilysin was presented with effects superior to those of either drug being used alone [68, 69]. Angiotensin receptor-neprilysin inhibitor (ARNI) LCZ696, the neprilysin inhibitor sacubitril combined with the ARB valsartan is associated with better hemodynamic and neurohormonal effects than those of an ARB alone [70, 71]. PARADIGM-HF trial [62] evaluated the long-term effects of sacubitril/valsartan on morbidity and mortality in comparison to those of ACE inhibition with enalapril in patients with chronic HFrEF. 8442 patients with New York Heart Association (NYHA) class II, III, or IV HF and an ejection fraction of 40% or less were randomized to either sacubitril/valsartan (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to the recommended therapy. The primary outcome was a composite of CV morbidity death or hospitalization in HF adverse events. The use of sacubitril/valsartan was more effective in reducing the risk of primary outcome as well as in reducing symptoms and physical limitations of HF. There was no proof of superiority of either method in the prevention of new-onset AF. However, ARNI via neprilysin inhibition result in an increase in the circulating levels of natriuretic peptides that further induce intracellular cGMP and protein kinase G signaling cascades. This activation further leads to cardiac inflammation and cell death reduction as well as hypertrophy and fibrosis inhibition that potentially reverse/decrease LV remodeling and exert anti-arrhythmic action via ventricular arrhythmia substrate modification [72].

RAAS blockers on the prevention of AF

The impact of AF in clinical outcomes in HF patients is well recognized, therefore, enthusiasm over using the RAAS blockers as an upstream therapy could be incomplete, without a clinical confirmation of their effects in the prevention of AF. Currently this is a theoretically attractive concept, not adequately explored and possibly quite challenging regarding poor data to date. A systematic review and meta-analysis on 26 RCTs assessed the efficacy of RAAS blockers in the prophylaxis of AF in patients with HF [73]. A total of 28 reports from 26 RCTs including 165,387 enrolled patients were further analyzed and the result concluded that RAAS blockers led to a

statistically significant 24% reduction in the risk of AF, particularly in patients with systolic dysfunction where the estimated reduction of AF risk was up to 49%. Additionally, a 37% reduction in the risk of AF was observed in hypertensive patients, with a 54% risk reduction in the prevention of recurrent AF and a 19% risk reduction in the development of new onset AF (Table 2). The use of RAAS blockers was associated with 40% lower risk of AF in comparison with the use of beta-blockers along with 39% discontinuation of previous anti-hypertensive medications, accompanied by the introduction of optimal BP control therapy after a washout period. Systolic BP ≥ 160 mmHg was associated with greater risk of AF, while the risk was progressively reduced when BP levels were controlled [74]. The VALUE [57] was the largest trial to demonstrate 24% risk reduction in the first 3 years and 16% at 6 years in the development of AF in hypertensive patients. Additionally, a pooled estimate from 3 recent large trials including 47,943 patients depicted a statistically significant 20% reduction in new-onset AF [73]. However, the failure of ACTIVE-I [59], GISSI-AF [60], ANTIPAF (Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation) [75], and J RHYTHM II (Japanese Rhythm Management Trial for Atrial Fibrillation II studies) [76] to demonstrate a positive effect of the RAAS blockade use and the modest risk reduction in NTP-AF (Nifedipine Versus Telmisartan on Prevention of Atrial Fibrillation) trial [77] suggests that the results from a pooled estimation in terms of secondary prevention should be cautiously assessed, as the presence of comorbidities (e.g. LV hypertrophy) could have affected the effect size as it has been indicated by the LIFE trial [56]. Moreover, RAAS blockade decreased by 34% the progression to persistent AF according to pooled estimations from VALUE [57], NTP-AF [77], J RHYTHM II trial [76], and the study of Galzerano et al. [78], with a total enrollment of 14,359 patients. Interestingly, ANTIPAF [75] and J RHYTHM II [76] reported a decreased use of antiarrhythmic drugs in RAAS arm of the studies [73]. The benefit of RAAS blockers in AF prophylaxis in high-risk CV disease patients without adverse structural damage is suggested to be a result of mainly BP lowering. Additionally, the arrhythmiogenic background might lead to differences in RAAS blockade efficacy in AF prevention in patients with systolic or diastolic HF.

Another systematic review and meta-analysis of 14 trials aimed at the demonstration of the role of ACEIs, ARBs, or AAs compared with conventional therapy or the administration of placebo on the new-onset AF prophylaxis, as well as the impact of RAAS blockade (ACEIs, ARBs, AAs) among different patient groups (HF, MI, coronary artery disease, CV risk factors) [79]. The results revealed a 21% reduction of new onset AF associated with the RAAS blockade. Reduction in new onset AF was comparable for the ACE (21%) and ARB (22%) arm of the meta-analysis. It was, however, suggested by the evidence the studies provided that ARBs have a more effective role in the prevention of new onset AF. AAs were not associated with effective prevention of new onset AF, according to data presented in EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart

Failure) [80] and EPHESUS (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) [81] trials [79]. Among the different patient groups, RAAS inhibition had a statistically important effect on the reduction of AF in HF patients but not in the post MI group and in the AH/coronary artery disease individuals. The lower prevalence of new onset AF in the HF group is possibly linked to ARBs and ACEIs and not to AAs. Despite the encouraging results of this meta-analysis, the low evidence quality of the results as well as the heterogeneity of the population indicate careful application in clinical practice until further evidence is provided [79].

Atrial fibrillation is either a result of atrial cardiomyopathy or indicates a structural atrial remodeling, therefore the use of non-conventional antiarrhythmic drugs (AADs) may prevent the atrial remodeling and the new onset AF. The activation of RAAS system is upregulated in AF. The use of ACEI/ARBs is presented with superiority in the prevention of the new-onset AF in patients with LV dysfunction, hypertrophy or hypertension although ARBs was not proved to be beneficial in AF patients without structural heart disease [82]. However, larger RCTs are presented with controversial results in the role of ACEI or ARBs in secondary (post-cardioversion) prevention of AF most possibly due to the complicated pathophysiological pathways of AF development [82].

Role of AAs in the background mechanism of AF

Aldosterone, is an adrenal hormone secreted after the activation of RAAS, contributing critically to the control of BP and electrolyte homeostasis [83]. The production of aldosterone in HF is increased and the use of AAs in cardiac disease has been reported to have multiple effects regardless of the role in BP control. Aldosterone is produced by cells in the adrenal cortex and the synthesis is induced by Ang II. Evidence reporting myocardial aldosterone synthesis has been added to the pathophysiological role description of this hormone. Aldosterone interacts with MRs, located in cardiomyocytes and cardiac fibroblasts, amplifies Ang II signaling and the expression of ventricular and vascular angiotensin type-1 receptors (AT1R) and ACE. Additionally, aldosterone controls vascular transcription of pro-atherogenic and oxidant genes, regulates nongenomic changes mediated by uncharacterized plasma membrane receptors and therefore contributes to modulation of cardiac oxidative stress damage, inflammation and fibrosis pathways, structural and electrical remodeling, a composite of which further generates the substrate of AF [84]. The suggested connection between the pathophysiology of aldosterone and AF has also extended interest to the effect of AA or MR antagonists to the management of CV diseases (HF, AF, MI). In human model studies, spironolactone therapy was accompanied with a reduction in AF outcomes and hospitalizations for AF direct current cardioversion [85]. Moreover, according to a recent study, eplerenone was beneficial in the

maintenance of SR after catheter ablation in persistent AF patients [86]. There is also evidence for preventing onset of AF and atrial flutter in systolic HF patients treated with AAs [80]. Data from the RALES (Randomized Aldactone Evaluation Study) [87] showed an improvement in LVEF, reduction in cardiac fibrosis and sudden death in severe HF patients post the use of spironolactone, with more evidence stemming from an observation that the 6 month use of spironolactone led to a significant decrease in the 24-hour mean heart rate, the frequency of atrial and ventricular premature beats, and the risk of AF or atrial flutter in HF patients, via controlling magnesium homeostasis [88]. Other contributing factors may be the reduction of norepinephrine levels, the threshold of ventricular fibrillation and the improvement in atrial conduction and remodeling in HF patients [89]. According to these findings the role of AAs/MR antagonists in the AF incidence in the setting of HF may be favorable [84]. Another potential future strategy may include aldosterone synthase inhibition (FAD286), as the reported evidence demonstrates improvement of LV function and cardiac remodeling similar to spironolactone, and additionally a persistent reduction of LV oxidative stress [90]. The reported antiarrhythmic effects of MR antagonists additionally to Ang II or catecholamines support their inclusion in the ACEI/ARBs or beta-blockers therapeutic strategies in CV disease patients. There is also some proof that in post MI patients MR antagonists combined with ACEI prevented LV remodeling (against the single use of ACEI) [79], along with mortality and morbidity reduction [87, 92], while the use of spironolactone and atenolol in permanent AF patients reduced atrial and ventricular remodeling [93]. Based on studies to date the AAs seem to more possibly contribute to the prevention of AF progression rather than new-onset AF prophylaxis [84]. The TOPCAT (Treatment of preserved cardiac function heart failure with an aldosterone antagonist trial) [94] has proved no significant effect of spironolctone treatment on CV death, cardiac arrest, hospitalization for HF and quality of life in patients with HFpEF. On the other hand, the PAPPHY (Prospective Appraisal of the Prevalence of Primary aldosteronism in Hypertensive patients presenting with atrial flutter or fibrillation study) [95] evaluated the prevalence of primary aldosteronism in hypertensive patients presenting with unexplained atrial flutter or AF. According to the results the prevalence of primary aldosteronism is high in hypertensive patients with unjustified AF, and moreover it is suggested that any unidentified cause of arrhythmia should be screened for primary aldosteronism, concerning the beneficial application of AA treatment on those individuals who would be markedly improved or even cured [95]. The field of AAs in the management of AF and HF patients despite the little clinical evidence remains still a promising target of future studies and trials that will reveal their potential role in an optimal HF-AF therapeutic strategy.

Conclusions

As the interest around the use of RAAS blockers as an upstream therapy is growing, there is a well-established need of evidence regarding their effectiveness in HF patients with AF. Placing emphasis on this need, a satisfactory number of clinical trials have been conducted. ARBs more than ACEI have been identified to fulfill an important cardiac remodeling role [96]. Furthermore, clinical trials have underscored additional positive impacts in high-risk CV disease subjects with AF as a modest, yet significant, reduction in CV events and HF outcomes. Given that the remodeling action has been confirmed, a reduction in the risk of AF was something to wait and hope for. Indeed, a marked decline in AF risk is recorded. The contribution of the RAAS system suppression in the primary as well as the secondary prevention of AF in hypertensive patients has been stated. In regard to the new onset AF, ARBs have been reported to contribute the most to the reduction. However, both ACEs and ARBs are deemed to be beneficial in minimizing the number of recurrent AF, whereas contribution of the MR antagonists is slight.

In conclusion, the main aim of this review was the demonstration of the beneficial contribution of RAAS blockade in AF patients as a therapeutic and prevention strategy in the context of HF. Based on the updated HF guidelines classification [97], HF can be further divided in HFrEF, HF with mildly reduced ejection fraction and HFpEF while these patients can be in normal SR or AF.

Presented herein, is a practical treatment algorithm based on presence/absence of underlying HF and/or no concomitant AF incorporating the European Society of Cardiology guidelines of HF [97], AF [82] and cardiac pacing/cardiac resynchronization therapy [98].

Conflict of interest: None declared

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Table 1. Effect of renin–angiotensin–aldosterone system (RAAS) blockers on cardiovascular outcomes in patients with atrial fibrillation (AF).

RCTs [Supporting references]	Number of patients	Treatment medication	Control medication	Results
LIFE [56]	342 patients with new-onset AF 8851 patients documented with SR and no history of AF	Losartan (n = 120)	Atenolol (n = 221)	Losartan compared with atenolol-based antihypertensive treatment was associated with longer maintenance of SR in patients with history of AF Losartan was more effective in the reduction of new-onset AF and stroke (25%) with similar reduction in BP compared with the administration of atenolol
VALUE [57]	551 patients with new onset of AF (229 patients with persistent AF) 13,209 patients with no history of AF never had AF	Valsartan (n = 252)	Amlodipine (n = 299)	The treatment of high-risk patients with RAAS blockers may lead to reduction of the incidence of new-onset AF and the mortality risk of CV events Greater reduction was observed in valsartan arm of the study
ADVANCE [58]	847 patients with AF 10,293 patients with no history of AF	Perindopril + Indapamide (n = 5569)	Placebo (n = 5571)	Perindopril and indapamide administration as an anti-hypertensive treatment of patients with diabetes is beneficial in preventing CV outcomes, regardless of the initial BP measurements The routine antihypertensive treatment was beneficial in patients with AF The evaluation for the presence of AF in diabetic patients is important in the prevention of CV events in high-risk patients Routine administration of arterial hypertension treatment, as well as antiplatelet agents, statins, and oral anticoagulants may reduce the incidence of adverse CV outcomes
ACTIVE-I [59]	9016 patients (6847 patients with AF)	Irbesartan (n = 4518)	Placebo (n = 4498)	Irbesartan was linked with a modest reduction in BP as well as a reduction in HF and hospitalizations for CV causes No significant reduction was observed in CV events A more aggressive BP control in AF individuals

				has not, to date, been proved to be effective
GISSI-AF [60]	1442 patients (746 patients with recurrent AF)	Valsartan (n = 722)	Placebo (n = 720)	Treatment with valsartan was not significantly associated with reduction in the incidence of recurrent AF in comparison with the administration of placebo
PROGRESS [61]	6105 patients (476 patients with AF)	Perindopril + Indapamide (n = 3051)	Placebo (n = 3054)	BP lowering treatment was associated with a reduction in the risk of major vascular events, prior stroke or TIA in AF patients Routine BP lowering treatment is contributing to the beneficial effects of anticoagulation A lower threshold of initiating anti-hypertensive treatment in AF patients is suggested, despite the need for additional research
Chaugai et al. meta-analysis and systematic review [55]	53,510 patients (6474 patients with AF in the intervention group)	RAAS blockers offer protection against HF (14% incidence reduction) and cardiovascular events (17% incidence reduction) in high-risk for CV diseases patients with AF The absolute risk reduction against HF is higher in the AF group than in the non-AF group of patients		

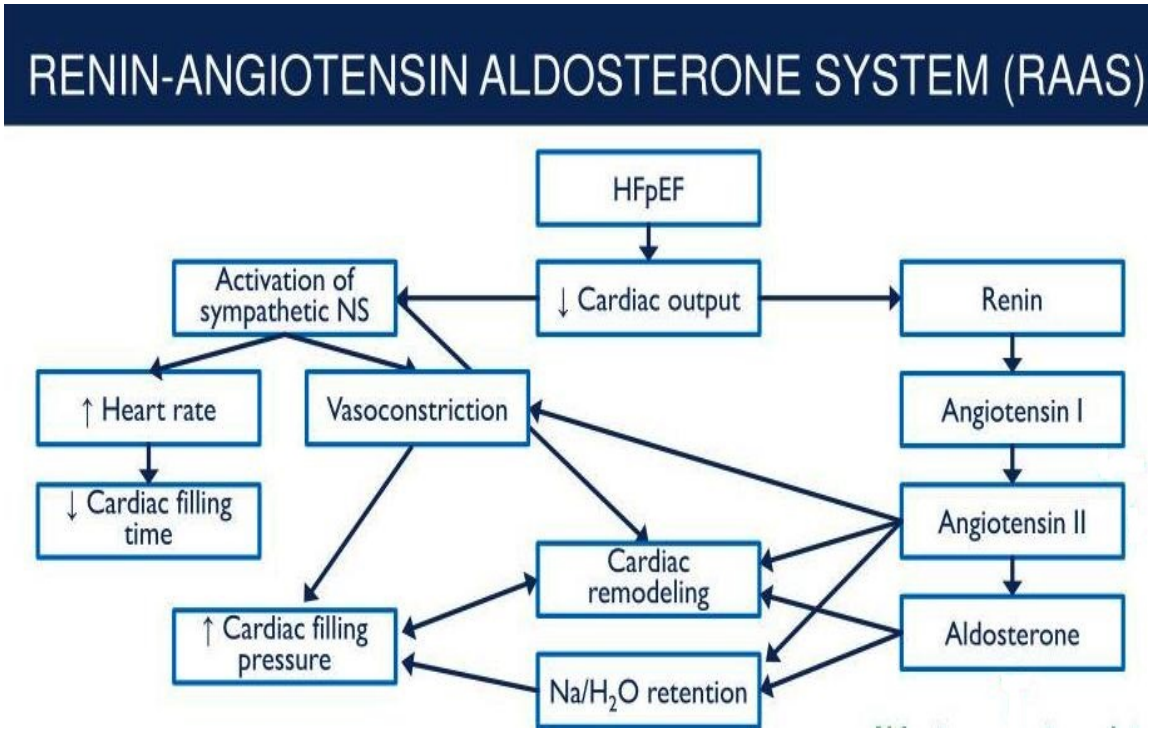
ACTIVE-I — Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; ADVANCE — Action in Diabetes and Vascular disease—preterax and diamicron MR controlled evaluation; BP — blood pressure; CV — cardiovascular; GISSI-AF — Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation; HF — heart failure; LIFE — Losartan Intervention for End Point Reduction in Hypertension; n — number of patients; PROGRESS — Perindopril protection against recurrent stroke study; RCT — randomized control trials; SR — sinus rhythm; TIA — transient ischemic attack; VALUE — Valsartan Antihypertensive Long-term Use Evaluation

Table 2. Effect of renin–angiotensin–aldosterone system (RAAS) blockers on the prevention of atrial fibrillation (AF).

Meta-analysis and systematic review [Supporting references]		
	Chaugai et al. [73]	**Khatib et al. [79]**
Number of patients	165,387	
Number of analyzed RCTs	26	14
RAAS medication	ARBs, ACEIs	ARBs, ACEIs, AAs
Results	RAAS blocker therapy is associated 24% reduction in the risk of new-onset and/or recurrent AF, especially in patients with HF with reduced LVEF (49%) RAAS are preferable to beta-blockers and are associated with a 37% reduction of the risk	21% reduction of new onset AF associated with the RAAS blockade ARBs were presented to have a more effective role in the prevention of new onset AF compared to ACEIs

	for AF in hypertensive patients, recurrent AF (54%) or the prevention of new-onset AF (19%) Reduction in AF recurrence, new-onset AF or progression to persistent AF risk, reversal of cardiac remodeling and discontinuation of AADs and the associated side effects, along with the observed benefits in clinical practice require confirmation in large-scale trials	AAs were not associated with effective prevention of new onset AF (EMPHASIS-HF, EPHESUS trials) RAAS inhibition was with statistical significance associated with the reduction of AF in HF patients but not in the post MI group and in the AH/CAD individuals The low evidence quality of the results and the heterogeneity of the population indicate careful application of the results in the clinical practice, until further results are published

AADs — antiarrhythmic drugs; AAs — aldosterone antagonists; ACEIs — angiotensin converting enzyme inhibitors; AH — arterial hypertension; ARBs — angiotensin receptor blockers; CAD — coronary artery disease; EMPHASIS-HF — Eplenerone in Mild Patients Hospitalisation and Survival Study in Heart Failure; EPHESUS — Eplenerone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Guide; HF — heart failure; LVEF — left ventricular ejection fraction; MI — Myocardial Infarction; RCT — randomized control trials



Central illustration. The renin–angiotensin–aldosterone system (RAAS) system and stages of inhibition (green lines) by angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, aldosterone antagonists; HFpEF — HF with preserved ejection fraction.

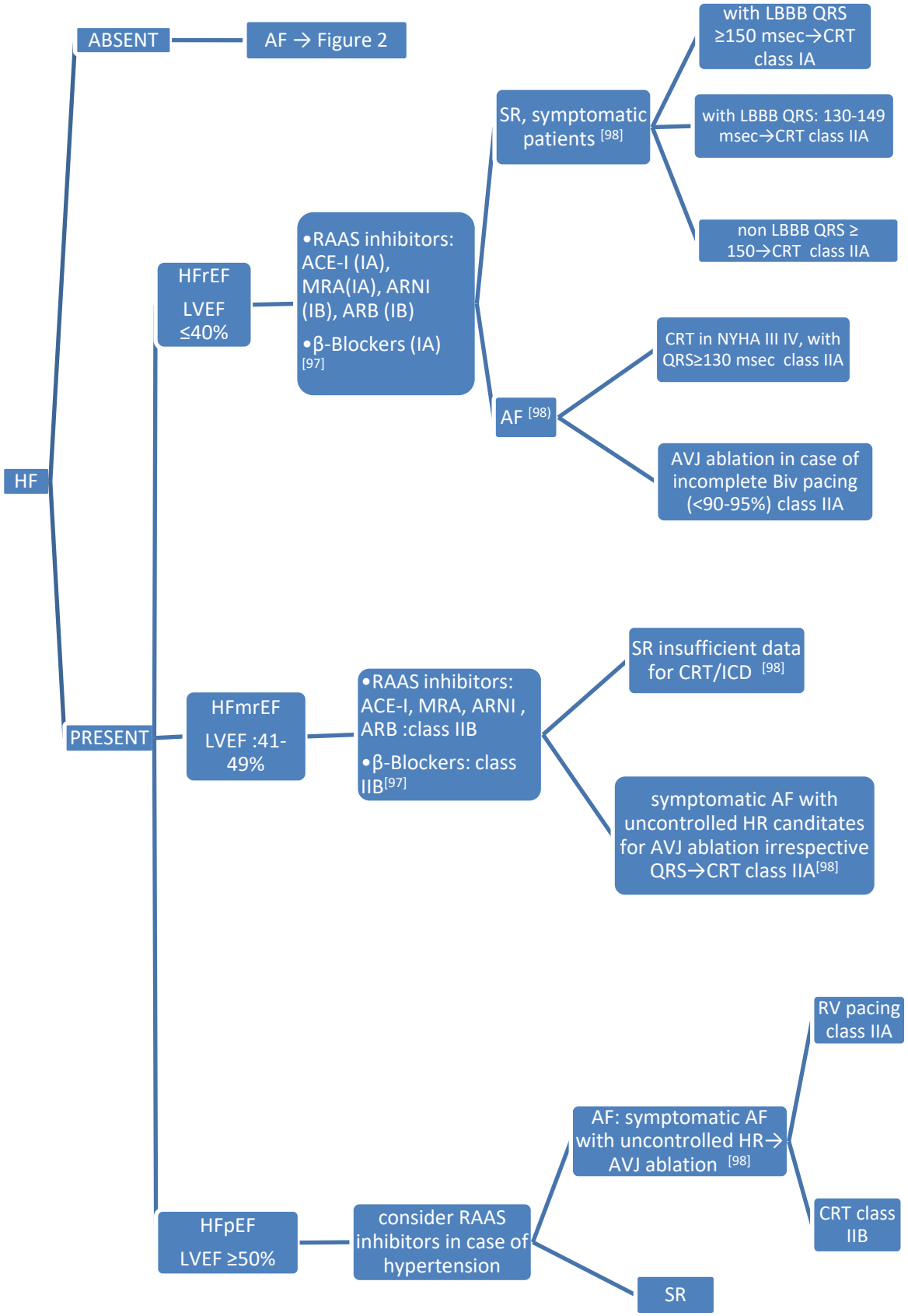


Figure 1. Management algorithm in patients with heart failure (HF) and/or no concomitant atrial

fibrillation (AF) and class of recommendation based on European Society of Cardiology HF, AF and pacing/cardiac resynchronization therapy (CRT) guidelines; ARNI — angiotensin receptor-neprilysin inhibitor AVJ — atrioventricular junction; LBBB — left bundle branch block; HFrEF — HF with reduced ejection fraction; HFmrEF — HF with mildly reduced ejection fraction; HFpEF — HF with preserved ejection fraction; MRAs — mineralocorticoid receptor antagonists; RAAS — renin–angiotensin–aldosterone system; SR — sinus rhythm.

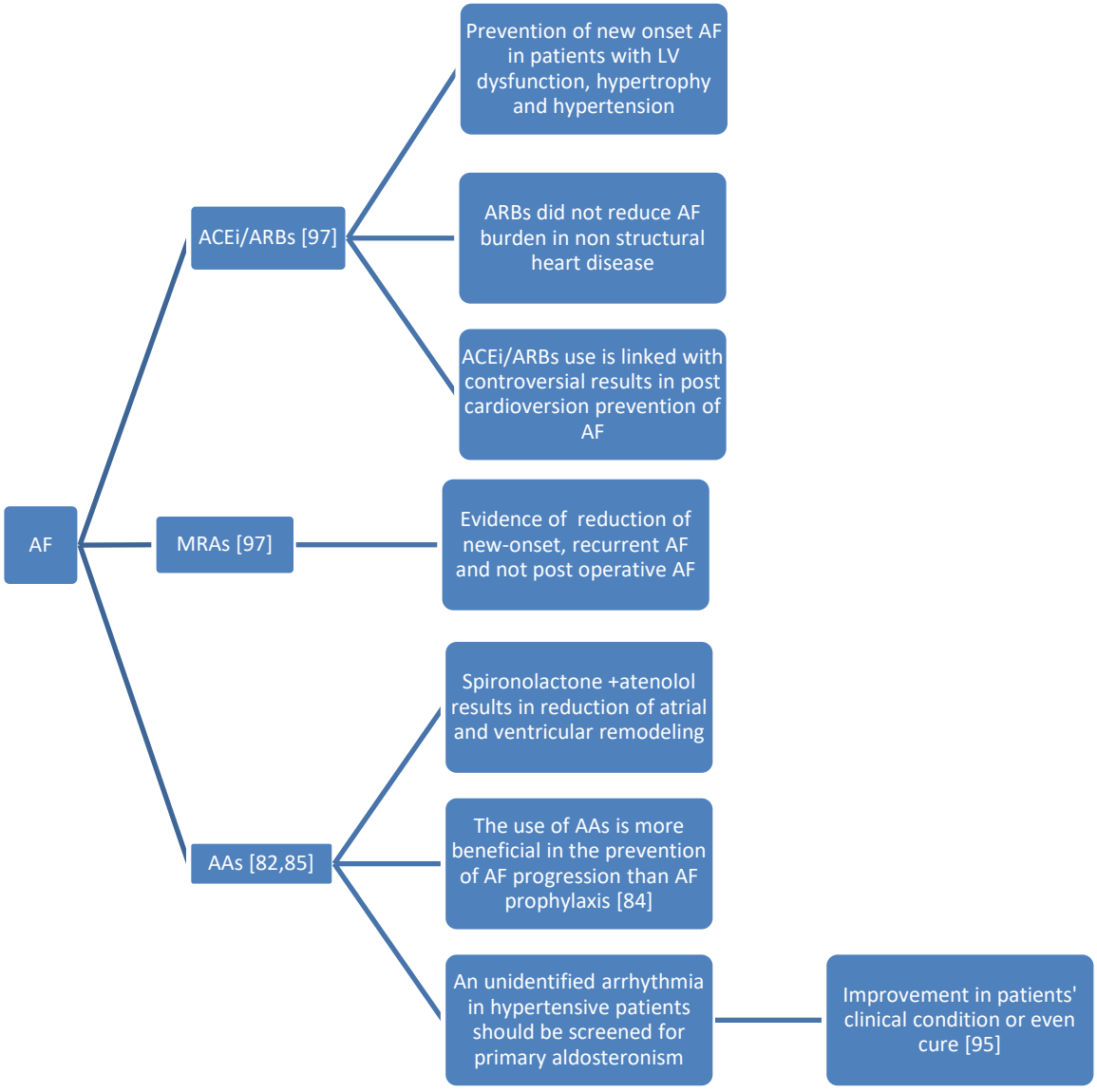


Figure 2. Management of atrial fibrillation (AF) population with renin–angiotensin–aldosterone system upstream therapy; AAs — aldosterone antagonists; ACEI — angiotensin converting enzyme inhibitors; ARBs — angiotensin receptor blockers; MRAs — mineralocorticoid receptor antagonists.