**Angiotensin II and angiotensin 1-7: which is their role in atrial fibrillation?**

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**Running head:** Angiotensin II and angiotensin 1-7 in atrial fibrillation

**Abstract**Atrial fibrillation (AF) is a significant cause of morbidity and mortality as well as a public health burden considering the high costs of AF-related hospitalizations. Pre-clinical and clinical evidence showed a potential role of the renin angiotensin system (RAS) in the etiopathogenesis of AF. Among RAS mediators, angiotensin II (AII) and angiotensin 1-7 (A1-7) have been mostly investigated in AF. Specifically, the stimulation of the pathway mediated by AII or the inhibition of the pathway mediated by A1-7 may participate in inducing and sustaining AF. In this review, we summarize the evidence showing that both RAS pathways may balance the onset of AF through different biological mechanisms involving inflammation, epicardial adipose tissue (EAT) accumulation and electrical cardiac remodeling. EAT is a predictor for AF as it may induce its onset through direct (infiltration of epicardial adipocytes into the underlying atrial myocardium) and indirect (release of inflammatory adipokines, the stimulation of oxidative stress, macrophage phenotype switching, and AF triggers) mechanisms. Classic RAS blockers such as angiotensin converting enzyme inhibitors (ACE-I), and angiotensin receptor blockers (ARB) may prevent AF by affecting the accumulation of the EAT, representing a useful therapeutic strategy for preventing AF especially in patients with heart failure and known left ventricular dysfunction. Further studies are necessary to prove this benefit in patients with other cardiovascular diseases. Finally, the possibility of using the A1-7 or ACE2 analogues, to enlarge current therapeutic options for AF, may represent an important field of research.  **Keywords**: atrial fibrillation, epicardial adipose tissue, angiotensin, renin angiotensin system inhibitors

**1. Introduction**Atrial fibrillation (AF) is the most prevalent arrhythmia that affects 0.12%–0.16% of people younger than 49 years, 3.7%–4.2% of those aged 60–70 years, and 10%–17% of those older than 80 years [1]. It is a significant cause of morbidity and mortality as well as a public health burden considering the high costs of AF-related hospitalizations [2-8]. Today, the use of pharmacological interventions, such as the use of rate control or rhythm control agents, or non-pharmacological interventions, such as catheter ablation, is very effective in preventing secondary episode of AF but still far away from curing this disease [9, 10]. In fact, new strategies for the primary and secondary prevention of AF are needed to reduce AF-related morbidity, mortality and health care costs [11-14].

Regardless of enormous efforts, a significant resistance to present-day treatment options characterizes AF. The reason for an apparent lack of causal therapy may lie in our incomplete understanding of mechanisms and etiology of AF. The notion is that pharmacological, non-pharmacological, cardioversion and ablation therapies do not completely resolve this clinical problem [15]. Undoubtedly, better understanding of the mechanisms for AF is needed to tailor a more effective treatment. In this regard, pre-clinical and clinical evidence show a possible role of the renin angiotensin system (RAS) in the etiopathogenesis of AF [16]. Moreover, the existence of a classic and non-classic RAS pathway composed of different mediators has led to the possibility of a binary influence of this system on the development of AF [17].

Among classic and non-classic RAS pathways, those mediated by angiotensin II (AII) and angiotensin 1-7 (A1-7) have been mostly investigated in AF. In particular, the stimulation of the classic RAS pathway (angiotensin II, AII/AT1 receptors axis) and the inhibition of the non-classic RAS pathway (angiotensin 1-7, A1-7/MAS1 receptors axis) may both participate in inducing and sustaining AF through three possible mechanisms involving inflammation, epicardial fat accumulation and electrical cardiac remodeling. The modulation of epicardial fat accumulation by RAS is a recent and relevant topic as this factor may induce the onset of AF through direct (infiltration of epicardial adipocytes into the underlying atrial myocardium) and indirect (release of inflammatory adipokines, stimulation of oxidative stress, macrophage phenotype switching, and AF triggers) mechanisms [18].

 This review aims to provide an overview of the evidence of the possible role of these two pathways in the pathophysiology of AF, the proposed cellular and molecular mechanisms and the results from clinical studies with classic RAS antagonists.

**2. Epicardial fat as risk factor for atrial fibrillation**Recently, pericardial and epicardial adipose tissue (EAT) have been included among the novel AF risk factors [19]. Because of its anatomical proximity to the myocardium, EAT can have a predominant role in the cardiovascular biology [17] and in inducing AF through direct and indirect pathophysiological mechanisms [18].

The direct mechanism include the infiltration of epicardial adipocytes into the underlying atrial myocardium [20].

The indirect mechanism, instead, is mediated by the pro-inflammatory effect of the epicardical adipocytes. The epicardial fat may act as a metabolically active tissue that releases inflammatory adipokines that can stimulate atrial remodeling and fibrosis, such as the tumor necrosis factor-α (TNF-α), the interleukin-6 (IL-6), and the monocyte chemoattractant protein-1 (MCP-1), reactive oxygen species (ROS) as well as secrete matrix metalloproteinases 2 and 7 [21-27]. Moreover, it has been demonstrated that the hypertrophy of the adipose tissue and the obesity can stimulate the switch of macrophages in adipose tissue from an anti-inflammatory M2 polarization state to a pro-inflammatory M1 polarization state that facilitates the secretion of pro-inflammatory cytokines and chemokines [28].

Another indirect mechanism by which the EAT may induce AF is through the activation of ganglionated plexi located in the epicardial fat that can stimulate the parasympathetic tone and induce a shortening of action potential duration, or can stimulate the sympathetic tone and increase the calcium transient in the atrial myocardium [18]. Finally, EAT may influence AF triggers [29, 30] typically localized at the pulmonary vein, which are a source of spontaneous, rapid, and repetitive electrical activity that can induce and sustain AF [31]. Epicardial fat may facilitate the activation of these triggers by any of the direct or indirect mechanisms discussed above.

In conclusion, EAT may induce and sustain AF provoking structural and electrical atrial remodeling through the direct infiltration in the atrial myocardium or through indirect effects such as the release of inflammatory mediators, the stimulation of the parasympathetic/sympathetic tone in the ganglionated plexi, and the activation of AF triggers.

**3. Angiotensin II and angiotensin 1-7 in epicardial fat accumulation and atrial fibrillation**A1-7 and AII are two major peptides of the RAS system exerting opposing effects in developing fat accumulation and atrial fibrillation [32-35]. A simplistic illustration is shown in figure 1.

**3.1 Angiotensin II in inflammation, electrical cardiac remodeling and epicardial fat accumulation**

**3.1.1. Biosynthesis of angiotensin II**

The synthesis of AII, main effector peptide of the classic RAS [32], begins with the proteolytic and non-proteolytic activation of the pro-enzyme ‘pro-renin’ into renin in the juxtaglomerular cells of the kidney [36]. As shown in figure 2, when the renin is released, the angiotensinogen is cleaved into angiotensin I (AI), which in turn is converted into AII by the Angiotensin Converting Enzyme (ACE) [37]. Moreover, the AII can be synthetized through other enzymes like chimase, chymostatin-sensitive angiotensin II-generating enzyme (CAGE), and cathepsin G.

**3.1.2. The role of local biosynthesis of angiotensin II in the development of atrial fibrillation**

The locally production of cardiac AII from angiotensin 1-12 by chimase has proven to be important in inducing adverse left ventricular cardiac remodeling post-myocardial infarction [38]. This local production participates importantly in the increased expression of myocardial collagen I and III mRNA, and fibronectin mRNA [39]. Additionally, by binding the AT1 receptors [33] it can stimulate inflammatory processes, atrial fibrosis, reduction of collagenase activity, expression of mitogen-activated protein kinase (MAPK) and changes in the electrophysiological properties of the heart (electrical cardiac remodeling) [40, 41].

Among pro-inflammatory processes, AT1 receptors can down-regulate the NADPH oxidase expression in smooth muscle cells and enhance the production of ROS, and the activity of pro-inflammatory transcription nuclear factors like nuclear factor-kappaB (NF-kB) and E26 transformation-specific sequence (Ets) [42]. Moreover, AT1 receptors can stimulate the release of different type of cytokines such as TNF-α, IL-6, and MCP-1 involved in the cardiac and electrical remodeling [43]. As a proof of the role of AT1 receptors in AF, an up-regulation of these receptors has been found in human left atrial tissue in patients with lone AF or AF with underlying mitral valve disease compared to patients in sinus rhythm whereas no difference was observed in the expression of AT2 receptors [44]. In fact, AT2 receptors are a part of the protective RAS that can induce anti-inflammatory, anti-fibrotic and antioxidative effects [43].

Another potential mechanism by which elevated levels of AII, via AT1 receptors, may promote AF involves the electrical cardiac remodeling. AII could indeed shorten the atrial effective refractory period and the action potential duration potentiating the slow component of delayed rectifier K+ channels in guinea pig atrial myocytes [45].

Finally, there is the more recent hypothesis that the classic RAS may be associated with epicardial fat accumulation and inflammation, which can induce AF through any of the pathophysiological mechanisms described in the aforementioned section [17]. The adipose tissue is considered an endocrine organ that can contributes to the release of circulating angiotensinogen and can produce and secrete AII, which in turn induces autocrine and paracrine effects through the activation of AT1 and AT2 receptors [46]. These receptors can both promote the growth of adipocytes through the inhibition of adipose tissue lipolysis (AT1) and stimulation of adipose tissue lipogenesis (AT2)[47].

Finally, AT1 receptors are also expressed on the macrophage surface and can facilitate the inflammation of adipose tissue shifting the macrophage phenotype toward the M1 polarization state [48].

In conclusion, AII can induce AF through the stimulation of local inflammation, alteration of action potential duration, and epicardial fat accumulation.

**3.2 Angiotensin 1-7 in inflammation, electrical cardiac remodeling and epicardial fat accumulation**

**3.2.1. Biosynthesis of angiotensin 1-7**

The synthesis of the non-classic peptide A1-7 starts with the cleavage of AII by the carboxypeptidase ACE2, or the conversion of AI into angiotensin 1-9 (A1-9) that is then converted to A1-7 by ACE (Figure 2).

**3.2.2. The protective role of angiotensin 1-7 in the development of atrial fibrillation**

The A1-7 activates the G protein-coupled receptor MAS1 that promotes nitric oxide release, Akt phosphorylation and anti-inflammatory effects [49]. As opposed to the classic RAS, the A1-7/MAS1 axis may play a protective role in AF as it may reduce inflammation, fibrosis, and cardiac electrical remodeling along with vasodilation and the reduction of hypertrophy and thrombosis [50].

In particular, in preclinical models, A1–7 can prevent AF ionic remodeling, investigated as changes in the voltage-dependent L-type Ca2+ current (ICaL), the transient outward current (ITO), expression of Kv4.3 potassium channel subunit mRNA, and Ca2+ channel α-subunit protein mRNA [51]. It prevents atrial fibrosis and the increasing Extracellular Signal-regulated Kinase-1 (ERK)1/ERK2 mRNA expression [52] and, through MAS1 receptors expressed on the macrophage surface inhibits the inflammatory macrophage phenotype and the release of pro-inflammatory cytokines [53]. Moreover, the ACE2 overexpression reduces the transient receptor potential melastatin 7 (TRPM7) expression, which is a predominant Ca2+ channel expressed on fibroblast surface that can contribute to the transforming growth factor (TGF) mediated fibrogenesis [54]. Accordingly, ACE2 knockout mice had a worsening of EAT inflammation, an increase of resident adipose tissue macrophages and expression of pro-inflammatory cytokines (TNF-a, IL-1b, IL-6) and iNOS [55].

Another crucial protective mechanism of A1-7 is through the reduction of cardiac remodeling and the consequent prevention of heart failure (HF) occurrence as HF and AF are closely interconnected. In this regards, the structural remodeling of the atria, consisting of inflammatory infiltrates and abundant collagen fibers that brake normal tissue microarchitecture and disturb physiological cell-to-cell interconnections and spatial coherence of ion currents, is a key component of the genesis and maintenance of AF but its importance extends beyond this arrhythmia. Atrial remodeling frequently coincides with ventricular remodeling in HF increasing the complexity of the problem. AF can be both a consequence and cause of HF as their pathophysiology is closely associated. Neurohormonal and structural alterations in HF make the onset and advance of AF more probable while AF is linked with an increased risk of incident HF [6, 56]. The progressive nature of atrial remodeling and fibrosis is characteristic and particularly relevant in patients with HFpEF [57, 58].

While it is recognized that myocardial inflammation favors fibrosis, the involvement of monocytes in AF and HF is increasingly gaining attention [59]. Interestingly, human monocytes express ACE and ACE2 and metabolize AI to multiple angiotensin peptides. In particular, classical monocytes produce both AII and A1–9/A1–7, whereas non-classical subtype predominantly generates A1–7 [60]. That indicates that monocytic ACE and ACE2 are the components of a local RAS at sites infiltrated by monocytes/macrophages. This can be important as the actions of ‘non-classical’ angiotensins could be especially important in the paracrine regulation of tissue physiology. In fact, also the non-classical angiotensin IV showed a protective effect on AII-induced cardiac injury by inhibiting cardiac cell apoptosis, cardiomyocyte hypertrophy and proliferation, and collagen synthesis of cardiac fibroblasts via AT4 receptor [61]. Therefore, it is plausible that the potential interventions on both arms of RAS system at myocardial and EAT levels may extend their effects way beyond AF involving not only the progression of the disease but also the process of reverse remodeling [62].

In conclusion, A1-7 may exert a protective cardiac effect and prevent AF through the inhibition of local inflammation, EAT accumulation, and structural and electrical cardiac remodeling.

**4. Clinical evidence on the role of ACE inhibitors and angiotensin receptor blockers in atrial fibrillation**

Clinical evidence showed that the therapy with classic RAS blockers (ACE-Is and ARBs) can reduce the incidence and the recurrence of AF [40]. These include clinical trials that have investigated the effect of RAS blockers in preventing primary or secondary AF in patients with HF, hypertension, post-myocardial infarction, metabolic syndrome, stroke, post-cardioversion, or after elective cardiac surgery (Table 1).

The available evidence seems to suggest a beneficial effect mostly in the prevention of primary AF rather than secondary AF and mostly in patients with early stage of heart failure and/or not severe hypertension. These results seem indirectly correlated to the biological mechanism leading to the protective effects of ACE-I/ARBs on atrial fibrillation. In fact, these drugs are particularly effective in preventing the pathophysiological changes associated with local inflammation and heart remodeling and, as expected, their effect is maximum in patients in early stages of diseases like heart failure and hypertension. In patients with underlying damage of tissues dedicated to the electrical conductance in the heart or in patients for which the heart remodeling is already ongoing and/or in more advanced stages the protective effects of these drugs, as expected, was reduced. Therefore, it is not surprising to find lower efficacy of these drugs in secondary prevention and/or in populations of patients with more advanced stages of the aforementioned diseases or with unknown left ventricular dysfunction as highlighted in the clinical trials described below.

**4.1 Clinical trials investigating the protective effect of ACE inhibitors and angiotensin receptor blockers in the primary prevention of atrial fibrillation**

**4.1.1Clinical trials in patients with heart failure**

Most of evidence available on the topic are retrospective analyses of randomized clinical trials conducted in patients with HF that have demonstrated a reduction in the incidence of AF during the treatment with an ACE-I or an ARB [63-66] due to their effect on reverse remodeling. As expected, these effects were evident only if compared with placebo and not with drugs with similar mechanism of action and/or with antiarrhythmic properties. In particular, four clinical trials (SOLVD, Val-HeFT, CHARM, and TRACE trials) showed a difference in a comparison with placebo for the abovementioned outcome, while no difference was observed in three clinical trials (including the PARADIGM-HF) that compared drugs with a similar mechanism of action (ACE-I vs. ARB or vasopeptidase inhibitor) [67-69]. Specifically,the retrospective analysis of patients from the Montreal Heart Institute (MHI) included in the *Studies Of Left Ventricular Dysfunction* (SOLVD) has shown that the ACE-I enalapril prevents the development of AF in patients with left ventricular dysfunction [10/186 (5.4%) vs 45/188 (24%), p-value<0.001] [63]. A subanalyses of *Valsartan Heart Failure Trial* (Val-HeFT) has also demonstrated that adding the ARB valsartan to prescribed therapy for HF reduces the incidence of AF compared to placebo [113/2205 (5.12%) vs 174/2190 (7.95%), p-value<0.001] [64]. The *Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity* (CHARM) program has found the same results in reducing the incidence of AF with candesartan treatment compared to the placebo [177/3803 (5.55%) vs 215/3796 (6.74%), p-value=0.047] in a large population of patients with symptomatic chronic HF and preserved or reduced ejection fraction [65]. The *TRAndolapril Cardiac Evaluation* (TRACE) study has also demonstrated that the ACE-I trandolapril compared to placebo reduces the incidence of AF [22/790 (2.8%) vs 42/787 (5.3%), p-value<0.050] in patients with left ventricular dysfunction after acute myocardial infarction [66]. As opposed, the PARADIGM-HF clinical trial has shown no difference in the development of new-onset AF between LCZ696 (valsartan plus sacubitril) and enalapril [84/2670 (2.0%) vs 83/2638 (1.9%), p-value=0.84] in patients with HF with reduced ejection fraction [67] and no difference was also observed in the onset of arrhythmic adverse events between patients treated with lisinopril vs omapatrilat [14/284 (5%) vs 13/289 (4%), p-value=0.811] [68] and elderly patients treated with losartan vs captopril [1/352, (0.3%) vs 4/370 (1.1%), p-value=0.237] [69].

**4.1.2 Clinical trials in patients with hypertension and/or other cardiovascular diseases** (**myocardial infarction, cardiac surgery, vascular disease, diabetes**)

A reduction in new-onset AF and associated stroke has been demonstrated in the *Losartan Intervention For Endpoint reduction in hypertension* (LIFE) study in hypertensive patients treated with losartan compared with atenolol despite the similar effect in reducing blood pressure [70]. Prevention of new-onset AF was also observed in hypertensive patients at high cardiovascular risk treated with valsartan compared to amlodipine, suggesting a more benefit affect with the use of ARBs than calcium channel blockers in this subpopulation [71]. Despite these findings, some conflicting data have been published in the literature. Two clinical trials have found that the treatment with an ACE-I in hypertensive patients did not add any benefit in the prevention of AF [72, 73]. In these studies, most patients were treated with a β-blocker, which can in turn prevent the occurrence of AF.

A benefit effect in preventing new-onset AF was also observed in the *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico* (GISSI)-3 trial in post myocardial infarction patients treated with the ACE-I lisinopril [74].

A randomized double-blind placebo-controlled trial investigating the incidence of AF after cardiac surgery has shown that the ACE-I ramipril did not decrease postoperative AF in patients with normal sinus rhythm [75].

The lack of benefit of ramipril in reducing new-onset AF has also been observed in a randomized clinical trial in patients without known left ventricular dysfunction [76]. Similarly, in the *Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial* (ONTARGET)/*Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease* (TRANSCEND) studies, both evaluating the new-onset AF as a secondary aim and both excluding patients with known HF, the dual RAS blockade with ramipril combined to telmisartan or the use of telmisartan alone did not prevent the development of AF when compared with telmisartan alone or placebo, respectively [77].

Moreover, in patients with hypertrophic cardiomyopathy, lower risk of new AF was detected following treatment with ACEIs or ARBs [78].

 **4.2 Clinical studies evaluating the role ofACE inhibitors and angiotensin receptor blockers in the secondary prevention of atrial fibrillation**

Different studies have evaluated the use of ACE-Is and ARBs in the prevention of secondary AF, considering the hypothesis that RAS blockers can facilitate the direct current cardioversion through the attenuation of the atrial structural remodeling, which is a substrate for the perpetuation of AF. A randomized clinical trial has demonstrated the efficacy of telmisartan compared to carvedilol in preventing AF recurrence in hypertensive patients in sinus rhythm who had experienced one or more AF episodes in the previous six months [79]. A similar effect in reducing AF recurrence in hypertensive patients has been observed with losartan, valsartan, or ramipril [80, 81].

The efficacy in preventing AF with RAS blockers has also been evidenced in patients that underwent electrical cardioversion. In fact, the treatment with the ARB irbesartan for two weeks was effective in reducing the transient impairment of left atrial function (left atrial stunning) after electrical cardioversion of AF [82]. Moreover, fewer recurrences of AF and a better maintenance of sinus rhythm were observed when irbesartan was added to amiodarone treatment after cardioversion for persistent AF [83, 84]. A similar result was observed in patients treated with irbesartan for maintaining sinus rhythm after video-assisted minimally invasive radiofrequency ablation for long-lasting persistent AF [85]. Additionally, adding losartan or perindopril to a low dose of amiodarone was effective in preventing AF recurrence in patients with lone paroxysmal AF [86].

Similarly, the addition of the ACE-I enalapril to the amiodarone therapy for 4 weeks before external cardioversion in patients with persistent AF reduced the rate of AF recurrence and facilitated the long-term maintenance of normal sinus rhythm compared with amiodarone alone [87]. Moreover, a decreased AF recurrence was also found in patients with lone AF treated with ramipril compared to placebo [88].

However, some studies have found contrasting results. The GISSI-AF trial evaluated the addition of the ARB valsartan to established therapies in reducing the rate of AF recurrence in patients with a history of AF associated with cardiovascular disease, diabetes, or left atrial enlargement. This study has not found that valsartan reduced the risk of either a first recurrence or multiple recurrences of AF. One hypothesis potentially explicative of the lower rate of detection of AF is the use of a frequent transtelephonic monitoring instead of a monitoring at scheduled visits or a patient’s report of symptoms. Moreover, this study compared to other clinical trials had a short duration of the follow-up period [89]. Conflicting results were also found in three recent clinical trials evaluating the role of RAS blockers in the prevention of AF [90-92]. Specifically, the *Angiotensin II-antagonist in paroxysmal atrial fibrillation* (ANTIPAF) and *Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension* (J-RHYTHM II study) trials have not shown any benefit of the RAS antagonism for the prevention of secondary AF [90, 92]. Moreover, in a substudy on the recurrence of atrial fibrillation (ACTIVE-I), irbesartan did not show a significant reduction of the risk of hospitalization for AF or cardioversion compared to the placebo [93]. Finally, two post-hoc analyses of data from the *Atrial Fibrillation Follow-up Investigation of Rhythm Management* (AFFIRM) and the *Canadian Trial of Atrial Fibrillation* (CTAF) studies have shown that RAS inhibitors did not add any benefit in reducing AF recurrence in patients with paroxysmal AF [94, 95].

**4.3 Meta-analyses**

Conflicting data were also observed from the results of different meta-analyses. A first meta-analysis, published in 2005, showed a similar reduction of the relative risk of AF for either ACE-Is and ARBs, with the higher reduction in patients with HF [96]. Two subsequent meta-analyses have shown that the use of an ACE-I or an ARB is associated with a reduction in new-onset AF especially in patients with left ventricular dysfunction or HF [97, 98]. Another meta-analysis has also found that RAS inhibition reduced the risk of new-onset AF in different patient groups with coronary artery disease [99]. As opposed, the same benefit has not been observed with ARBs in the secondary prevention of AF [100]. However, another meta-analysis has demonstrated that the use of ACE-Is or ARBs reduced AF recurrence in patients with essential hypertension [101]. Finally, a more recent meta-analysis has shown that RAS blockers are associated with a reduction in both AF onset and recurrence, with the greatest benefit observed in patients with HF with systolic dysfunction [102]. These results undoubtedly highlight the efficacy of RAS blockers in preventing AF in patients with structural heart diseases.

**5. Postulated mechanisms on the role of ACE inhibitors and angiotensin receptor blockers in AF**Among the hypothetical mechanisms mediated by ACE-Is and ARBs for preventing the new-onset or recurrence of AF there is the inhibition of atrial fibrosis and inflammation, the electrical cardiac remodeling, and the modulation of the EAT (Figure 1).

**5.1 Control of inflammation and fibrosis**

Regarding the control of inflammation, many studies have demonstrated that the use of ARBs and ACE-Is is associated with anti-inflammatory and anti-oxidative effects. Specifically, both drug classes have shown the ability of reducing pro-inflammatory mediators such as C-reactive protein, IL-6, MCP-1, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, NF-kB, and ROS, and increasing anti-inflammatory mediators such as inhibitor of kB and IL-10 [43]. Moreover, some ARBs have shown anti-inflammatory effects in view of the agonism for the peroxisome proliferator-activated receptor γ (PPARγ), an intracellular nuclear hormone receptor that regulates pathways involving the metabolism of carbohydrates and lipids and control the expression of pro-inflammatory genes through the inhibition of the AP-1 and NF-kB transcription factors. However, ARBs can display a different selectivity for PPARγ with the higher affinity associated with the ARB telmisartan (existence of biphenyl-tetrazole group) following by candesartan and losartan. Specifically, only telmisartan and less candesartan have shown a significant effect on PPARγ in cells [103].

**5.2.Electrical cardiac remodeling**

In the modulation of the electrical conduction system of the heart, evidence showed that ARBs and ACE-Is may directly modulate ion channels and the excitability of cardiomyocytes. In this regards, RAS blockers may prevent the shortening of the atrial effective refractory period [104], prolong the action potential duration [45] and improve intra-atrial conduction [105]. Furthermore, a study showed that the ACE inhibition with enalapril may reduce atrial fibrosis, conduction abnormalities, and AF promotion through the reduction of atrial AII concentrations and ERK activation in dogs with ventricular tachypacing-induced congestive HF [41].

**5.3. Modulation of the epicardial adipose tissue**

ACE-Is and ARBs may influence the accumulation of epicardial fat and induce a downsize of adipocytes. In fact, treatment with valsartan (10 mg/kg) or telmisartan (5 mg/kg) for 16 weeks in spontaneously type 2 diabetic obese rats downsized adipocytes in visceral fat with the greater effect observed with telmisartan than valsartan [106]. Moreover, the long-term use of RAS blockers may affect the differentiation of adipocytes, reduce adipose tissue mass, and increase glucose tolerance [107]. Finally, in the modulation of EAT, RAS blockers may improve obesity-associated inflammation and lipotoxicity, and potentially prevent all mechanisms related to epicardial fat-induced AF [17].

**6. Conclusion**In conclusion, the RAS may play an important role in the induction of AF influencing inflammatory processes, cardiac electrical remodeling, and the accumulation of epicardial fat. Specifically, the ACE/AII/AT1 axis has a pro-inflammatory effect by the stimulation of oxidative stress, cytokines release, ROS production, and macrophage phenotype switching. Through these mechanisms, this axis can participate to the electrical cardiac remodeling inducing morphological changes in atrial cardiomyocytes. Moreover, it may stimulate epicardial fat accumulation and inflammation that may in turn directly or indirectly influence the onset of AF. Finally, this axis may directly influence the electrical cardiac remodeling through the potentiation of the slow component of delayed rectifier K+ channels that reduces the atrial effective refractory period.

As opposed, the ACE2/A1-7/MAS-1 axis is a negative modulator of inflammation able to inhibit the pro-inflammatory macrophage polarization state, oxidative stress, and cytokines release, reducing atrial fibrosis and cardiac remodeling. Moreover, this axis may reduce EAT accumulation, inflammation, lipotoxicity and adipokines release, and increase levels of myocardial adiponectin. Furthermore, this axis may prevent ionic cardiac remodeling typical of AF. Therefore, the balance between the activities of these two axes of RAS system can be considered important in determining and sustaining AF.

Clinical studies showed that ACE-Is and ARBs may reduce the incidence of new-onset AF in patients with HF with left ventricular dysfunction as a proof of their role in the reverse remodeling. However, most clinical studies have evaluated the risk of developing AF in this subpopulation from subsequent post-hoc analyses. Less clear is the evidence regarding the prevention of primary or secondary AF in patients with hypertension or normal left ventricular function. In fact, RAS blockers seem less effective in patients without structural heart disease or LV dysfunction. Moreover, most studies found that the combination with a RAS inhibitor and amiodarone is more effective than amiodarone alone in preventing AF recurrence.

Despite some advantages found in some groups of patients treated with RAS inhibitors, further studies are needed to better characterized the risk of primary or secondary AF in patients with cardiovascular diseases. Finally, enhancers of the non-classic RAS such as MAS1 agonists or ACE2 analogues may enlarge the current therapeutic option for AF, representing an interesting point of view for future researches. Recently, another possibility to prevent secondary AF has been hypothesized with the use of the monoclonal antibody canakinumab in the phase 2 randomized, double blind, placebo controlled trial (CONVERT-AF) whose results have not been published yet (NCT01805960).

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**8. Figure legendes**

**Fig. 1** Main mechanisms balanced by AII and A1-7 in the pathophysiology of atrial fibrillation. ACE/AII/AT1 axis promotes inflammation through cytokines release (e.g. TNF-α, IL-6, MCP-1) epicardial fat accumulation, end electrical cardiac remodeling by reducing the AERP. On the contrary, ACE2/A1-7/MAS1 axis inhibits the aforementioned processes.
*AII= angiotensin II, A1-7= angiotensin 1-7, ACE= angiotensin converting enzyme, AERP= atrial effective refractory period, IL-6= interleuchin-6, MCP-1= monocyte chemoattractant protein-1, RAS= renin angiotensin system, ROS= reactive oxygen species, TNF-α= tumor necrosis factor- α.*

**Fig. 2** Syntheses of AII and A1-7 and their main effects in AF. AII synthesis starts with conversion of angiotensinogen into AI by renin and the subsequent cleavage of AI into AII. A1-7 synthesis starts with the cleavage of AII by the carboxypeptidase ACE2, or the conversion of AI into A1-9 that is then converted to A1-7 by ACE.
*AI= angiotensin I, AII= angiotensin II, A1-7= angiotensin 1-7, A1-9= angiotensin 1-9, ACE= angiotensin converting enzyme, ACE2= angiotensin converting enzyme 2, CAGE= chymostatin-sensitive angiotensin II-generating enzyme, EAT= epicardial adipose tissue, MAPK= mitogen-activated protein kinase, ROS=* *Reactive oxygen species, ERP= effective refractory period, TRPM7= transient receptor potential melastatin 7, ACE-Is= angiotensin converting enzyme inhibitors, ARBs= angiotensin receptor blockers.*