Chapter 1

Atrial Fibrillation and the Renin-Angiotensin-Aldosterone System

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 1% of the general population and up to 8% of subjects over the age of 80 years.[1] AF is a major contributor to cardiovascular mortality and morbidity, being associated with decreased quality of life, increased incidence of congestive heart failure,[2] embolic phenomena, including stroke,[2,3] and a 30 % higher risk of death.[3,4] AF-associated morbidity includes a four- to five-fold increased risk for stroke, [2,5] a two-fold increased risk for dementia,[6,7] and a tripling of risk for heart failure.[5] According to the Framingham Study, the percentage of strokes attributable to AF increases steeply from 1.5% at 50–59 years of age to 23.5% at 80–89 years of age, [2] and the presence of AF accounts for a 50–90% increased risk for overall mortality.[3] From the viewpoint of the AF-related socio-economic burden, it has been estimated that it is consuming between 0.9% and 2.4% of total National Health Service expenditure in the UK,[8] while in the USA, total costs are 8.6–22.6% higher for AF patients in all age- and sex- population strata.[9] Therefore significant clinical, human, social and economical benefits are therefore expected from any improvement in AF prevention and treatment.

It has to be noted that although multiple treatment options are currently available, no single modality is effective for all patients.[10] AF can occasionally affect a structurally normal heart of otherwise healthy individuals (so-called "lone AF")[11], but most typically it occurs in subjects with previous cardiovascular damage due to hypertension, coronary artery disease and diabetes. Moreover, it can be associated with clinical conditions such as hyperthyroidism, acute infections, recent cardiothoracic or abdominal surgery, and systemic inflammatory diseases. Whatever the cause, AF is characterized by very rapid, chaotic electrical activity of the atria, resulting in accelerated and irregular ventricular activity, loss of atrial mechanical function and increased risk of atrial clot formation.

Many studies have shown that the recurrence of AF may be partially related to a phenomenon known as "atrial remodeling", in which the electrical, mechanical, and structural properties of the atrial tissue and cardiac cells are progressively altered, creating a more favorable substrate for AF development and maintenance.[12,13] Atrial remodeling is both a cause and a consequence of the arrhythmia, and in recent years it has become more and more evident that treatment should also be based on an "upstream" therapy[14,10] aimed at modifying the arrhythmia substrate and at reducing the extent of atrial remodelling.

2. Atrial remodeling: electrical and structural factors

According to Coumel´s triangle of arrhythmogenesis, three cornerstones are required in the onset of clinical arrhythmia[15] – the arrhythmogenic substrate, the trigger factor and the modulation factors such as autonomic nervous system or inflammation. Once established, AF itself alters electrical and subsequently structural properties of the atrial tissue and these changes cause or "beget" further AF self-perpetuation.[12] The mechanisms responsible for the onset and persistence of the arrhythmia involve electrical as well as structural determinants, that are very complex and yet poorly understood. From the electrical standpoint, there is still debate on the three models that were proposed in 1924[16] by Garrey for describing the mechanisms of spatiotemporal organization of electrical activity in the atria during AF. According to the *focal mechanism theory,* AF is provoked and perhaps also driven further by the rapid firing of a single or multiple ectopic foci, whereas the *single circuit re-entry theory* assumes the presence of a single dominant re-entry circuit, and the *multiple wavelet theory* postulates the existence of multiple reentry circuits with randomly propagating wave-fronts that must find receptive tissue in order to persist.[17] It has to be recognized that all three models are non-exclusive and each may be applicable to certain subgroups of AF patients, or that they may even coexist in the same subject during different stages of AF development. Moreover, AF persistence is associated with modifications in the atrial myocyte electrical properties (the so-called *electrical remodeling*), that may stabilize the arrhythmia by decreasing the circuit size. The electrophysiological properties of the atrial myocardium may be further modified by changes in autonomic nervous system activity as well as by the interference of drugs and hormones, that may therefore participate in arrhythmogenesis.

Beyond these electrical determinants, AF onset and persistence may be affected by the structural factors, such as the dimensions and geometry of the atrial chambers, the atrial tissue structure and the amount and the composition of the extracellular matrix surrounding the atrial myocytes (i.e. *structural remodeling).* Together, these alterations create an arrhythmogenic substrate essential for the persistence of AF. Atrial structure is modified by volume and pressure overload, due to either mitral valve disease or left ventricular diastolic dysfunction in the setting of arterial hypertension, coronary artery disease or aortic valve disease. Also diabetes is associated with changes in atrial structure and function. It is not therefore surprising that all these clinical conditions are associated with an increased AF incidence and prevalence. Beyond being a possible substrate for AF onset, atrial structure is profoundly altered by the effects of rapid atrial rate. Prolonged rapid atrial pacing induces changes in atrial myocytes such as an increase in cell-size, myocyte lysis, perinuclear accumulation of glycogen, alterations in connexin expression, fragmentation of sarcoplasmic reticulum and changes in mitochondrial shape.[18] Moreover, structural remodeling is characterized by changes in extracellular matrix composition, with both diffuse interstitial and patchy fibrosis.[19] All these alterations results in electrical tissue non-homogeneity, slowed conduction and electrical uncoupling, that facilitate AF continuation. In contrast to electrical remodeling, structural changes are far less reversible and they tend to persist even after sinus rhythm restoration. Among the several mechanisms and signaling pathways involved in structural remodeling and atrial fibrosis, a key role is played by the renin-angiotensin system, and by the transforming growth-factor β_1 (TGF-β_1) pathway, associated with tissue inflammation[19] and reactive oxygen species production.[20,21]

Profibrotic signals act on the balance between matrix metalloproteinases (MMPs) – the main enzymes responsible for extracellular matrix degradation – and their local tissue inhibitors (TIMPs), that can be differentially altered in compensated as opposed to decompensated pressure-overload hypertrophy.[22-25] Furthermore, profibrotic signals stimulate the proliferation of fibroblasts and extracellular deposition of fibronectin, collagens I and III, proteglycans and other matrix components. In a canine model of congestive heart failure, Li *et al.* showed that the development of atrial fibrosis is angiotensin-II dependent,[26] via mechanisms that are partly mediated by the local production of cytokine TGF-β_1.[27] In transgenic mice, overexpression of the latter cytokine has been shown to lead to selective atrial fibrosis, increased conduction heterogeneity and enhanced AF susceptibility, despite normal atrial action potential duration and normal ventricular structure and function.[28]

3. The renin-angiotensin-aldosterone system (RAAS) as a "novel" risk factor for AF

Among many others, two factors contribute to the search of different therapeutic approaches to AF specifically targeting substrate development and maintenance:[29] the recognition of novel risk factors for the development of this arrhythmia and the well-known limitations of the current antiarrhythmic drug therapy to maintain sinus rhythm, still having inadequate efficacy and potentially serious adverse effects.[30] In this setting, the inhibition of the renin-angiotensin-aldosterone system (RAAS) has been considered useful in both primary and secondary prevention of AF, particularly in patients presenting left ventricular hypertrophy (LVH) or heart failure. The RAAS is a major endocrine/paracrine system involved in the regulation of the cardiovascular system.[31] Its key mediator is angiotensin II, an octapeptide that is cleaved from the liver-derived 485-aminoacid precursor angiotensinogen through a process involving the enzymatic activities of renin and angiotensin converting enzyme (ACE). Two main angiotensin II receptors exist, i.e angiotensin II type 1 (AT_1) and type 2 (AT_2). AT_1-receptor mediated pathways lead to vasoconstriction, water retention, increased renal tubular sodium reabsorption, stimulation of cell growth and connective tissue deposition, and impaired endothelial function. AT_2-receptor has opposing effects, inasmuch as it mediates vasodilation, decreases renal tubular sodium reabsorption, inhibits cell growth and connective tissue deposition, and improves endothelial function. These two angiotensin receptors have different expression patterns, AT_1 being constitutively expressed in a wide range of tissues of the cardiovascular, renal, endocrine, and nervous system, and AT_2 expression being activated during stress conditions.[32] It is becoming increasingly evident that all these mechanisms are involved in atrial remodeling and hence in AF development and maintenance. Moreover, among the other biologically active RAAS components that are involved in these processes, angiotensin-(1-7) [Ang-(1-7)] seems to be particularly important. In an experimental canine model of chronic atrial pacing, Ang-(1-7) has been shown to reduce AF vulnerability and atrial fibrosis,[33] influencing atrial tachycardia-induced atrial ionic remodeling. [34]

Among the compounds that may interfere RAAS four classes of drugs are particularly relevant in cardiovascular therapy: angiotensin receptor blockers (ARBs), ACE inhibitors (ACEIs), aldosterone antagonists and direct renin inhibitors. ARBs directly block AT_1 receptor activation, ACEIs inhibit ACE-mediated production of angiotensin II, and the recently developed direct renin inhibitor aliskiren blocks RAAS further upstream.[32,35,36] Over the last decade, these drugs have been tested in the setting of AF treatment and prevention.

4. The role of RAAS in the pathogenesis of AF

4.1. Atrial stretch and AF

Atrial arrhythmias frequently occur under conditions associated with atrial dilatation and increased atrial pressure, causing atrial tissue stretch and modifying atrial refractoriness, and it has been shown in several animal as well as clinical models.[37-40] These factors increase susceptibility to AF, that is associated with shortening of the atrial effective refractory period (AERP), possibly by opening of stretch-activated ion channels. In the setting of arterial hypertension and congestive heart failure (CHF), angiotensin II has been associated with increased left atrial and left ventricular end-diastolic pressure,[41] and both ACEIs and ARBs have been shown to reduce left atrial pressure.[42-45] Therefore, one potential mechanism by which ACEIs and ARBs may reduce atrial susceptibility to AF is by reducing atrial stretch. Many other mechanisms appear to be involved in the antiarrhythmic properties of RAAS inhibition, and in an animal model of ventricular tachycardia-induced CHF it has been shown that ACE inhibition is more successful than hydralazine/isosorbide mononitrate association in reducing burst pacing-induced AF promotion, despite a similar reduction in left atrial pressure.[26] As described below, angiotensin II-mediated mechanisms contribute to both *structural* and *electrical remodeling* of the atrial tissue.

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4.2. The role of RAAS in structural remodeling

Atrial fibrosis causes conduction heterogeneity, hence playing a key role in the development of a vulnerable *structural* substrate for AF, and the proinflammatory and profibrotic effects of angiotensin II have been extensively described.[46-48] Excessive fibrillar collagen deposition, resulting from deregulated extracellular matrix metabolism, leads to atrial fibrosis, and it has been shown that angiotensin II has a direct effect in stimulating cardiac fibroblast proliferation and collagen synthesis, via AT_1 receptor – mediated mechanisms involving a mitogen-activated protein kinases (MAPKs) phosphorylation pathway. [49-51] The latter cascade is inhibited by AT_2 receptor activation, that has an antiproliferative effects.[52] Moreover, cardiac fibroblast function is modulated by angiotensin II through mechanisms involving TGF- ▪ $_1$, osteopontin (OPN), and endothelin-1 (ET-1). [49,53-55] Interestingly, Nakajima and coworkers showed that selective atrial fibrosis, conduction heterogeneity, and AF propensity are enhanced in a $TGF\beta_1$ cardiac overexpression transgenic mice model,[56] as also confirmed by others.[27,28]

Beyond having both direct and indirect effects on collagen synthesis, angiotensin II interferes with collagen degradation by modulating interstitial matrix metalloproteinase (MMP) activity and tissue inhibitor of metalloproteinase (TIMP) concentrations,[52] and an atrial tissue imbalance between MMPs and TIMPs has been reported in both clinical and animal studies on AF. [52,57] Goette and coworkers showed increased atrial expression of ACE and increased activation of the angiotensin II-related intracellular signal transduction pathway in human atrial tissue derived from AF patients,[58] and atrial overexpression of angiotensin II has also been shown in a canine model of ventricular tachycardia-induced CHF[26,59] In transgenic mice experiments with cardiac-restricted ACE overexpression, Xiao et al. have demonstrated that elevated atrial tissue angiotensin II concentrations stimulates atrial fibrosis and hence an AF-promoting substrate.[60] In contrast, RAAS inhibition reduces tissue angiotensin II concentration, and attenuates atrial structural remodeling and fibrosis, thereby contrasting AF maintenance.[26,59,61-64]

4.3. The role of RAAS in electrical remodeling

Electrical remodeling has been hypothesized as a main mechanism by which, once established, “AF begets further AF” self-perpetuation.[12] In the clinical practice, this phenomenon is evident when considering that over time it becomes more and more difficult to keep in sinus rhythm a patient with AF. The concept of electrical remodeling has been originally proposed by Wijffels et al.[12] to explain the experimental observation that when AF is maintained artificially, the duration of burst pacing-induced paroxysms progressively increases until AF becomes sustained. This indicates that AF itself alters the atrial tissue electrical properties, thereby developing a functional substrate that promotes AF perpetuation and may involve alterations in ionic currents and in excitability cellular properties.[65] In their study, Wijffels et al. demonstrated that the increased propensity to AF is associated with shortening of the atrial effective refractory period (AERP) in accordance with the multiple wavelet theory,[12] a mechanism that was subsequently attributed to a reduction of action potential duration (APD) secondary to the progressive downregulation of the transient outward current (Ito) and of the L-typeCa^{2+} current (ICa,L).[66] As to the modulation of the ICa,L current, the role of angiotensin II is controversial, with studies reporting increase, decrease, or even no effect.[29,67] In contrast, angiotensin II has been demonstrated to downregulate Ito current,[68,67] inasmuch as AT_1 receptor stimulation leads to internalization of the Kv4.3 (i.e., the pore-forming α-subunit underlying Ito), regulating its cell-surface expression.[68] As shown by Liu and coworkers, chronic Ang-(1-7) infusion prevented the decrease of Ito, ICa,L, and of Kv4.3 mRNA expression induced by chronic atrial pacing, [34] thereby contributing to reduce AF vulnerability.[33] Subsequently, Nakashima et al. showed that ACEI or ARB treatment results in complete inhibition of the shortening of AERP, that is normally induced by rapid atrial pacing.[69] A further mechanism by which the RAAS may exert a proarrhythmic effect is the modulation of gap junctions, that are low-resistance pathways for the propagation of impulses between cardiomyocytes formed by connexins (Cx).[70] Cx40 gene polymorphisms have been associated with the development of non familial AF,[71] and angiotensin II has been implicated in Cx43 downward remodeling. [72-74] Moreover, angiotensin II directly induces delayed after-depolarizations and accelerates the automatic rhythm of isolated pulmonary vein cardiomyocytes.[75] These cells are considered an important source of ectopic beats and of atrial fibrillation bursts, representing the target of AF treatment with radio-frequency ablation.[76] Therefore these experimental results demonstrate that angiotensin II may play a role in the pathophysiology of atrial fibrillation also by modulating the pulmonary vein electrical activity via an electrophysiological effect that was shown to be AT_1 receptor – mediated, being inhibited by losartan, [75] and that is attenuated by heat-stress responses.[77] Recently, also the direct renin inhibitor aliskiren was shown to reduce the arrhythmogenic activity of pulmonary vein cardiomyocytes.[36] It has also been demonstrated that aldosterone promotes atrial fibrillation, causing a substrate for atrial arrhythmias characterized by atrial fibrosis, myocyte hypertrophy, and conduction disturbances,[78] and the specific antagonist spironolactone has been shown to prevent aldosterone-induced increased duration of atrial fibrillation in a rat model.[79]

4.4. RAAS gene polymorphisms and AF

The ACE DD (deletion/deletion) genotype of the ACE gene has been shown to be a predisposing factor for persistent AF,[80] and it was recently reported that the same genotype is associated with lowest rates of symptomatic response in patients with lone AF.[81] Moreover, polymorphisms of the angiotensinogen gene have also been associated with nonfamilial AF,[82] and it has been shown that significant interactions exist between angiotensinogen gene haplotypes and ACE I/D (insertion/deletion) polymorphism resulting in increased susceptibility to AF.[83,84] Also aldosterone synthase (CYP11B2) T-344C polymorphism, which is associated with increased aldosterone activity, was shown to be an independent predictor of AF in patients with HF.[85] According to Sun and coworkers, this

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aldosterone synthase gene polymorphism might also be associated with atrial remodelling in hypertensive patients.[86]

5. Atrial fibrillation and the renin-angiotensin-aldosterone system (RAAS): Clinical observations

A possible relationship between the RAAS and the risk of developing AF was brought about by several clinical data, derived from patient series in different settings, that are here summarized.

5.1. Heart failure

In heart failure, several observations indicate a possible effect of RAAS inhibition in reducing the incidence of new onset AF. In a retrospective analysis of the SOLVD trial, Vermes et al. showed that enalapril reduces the risk of AF development in patients with various degrees of heart failure.[87] Similarly, Maggioni et al. demonstrated that use of the ARB valsartan is associated with a reduction in the risk of AF in the Val-HeFT trial population.[88] Since the vast majority of these patients (92.5%) were already receiving an ACEI, a combination effect was hypothesized, and the benefit of combined treatment with both an ARB and an ACEI was also supported by the results of the CHARM trial with candesartan.[89] The latter study was composed by three component trials based on left ventricular ejection fraction (LVEF) and ACEI treatment. CHARM-Alternative trial enrolled patients with LVEF ≤40% not treated with ACEIs because of prior intolerance, CHARM-Added recruited patients with LVEF ≤40% already treated with an ACEI, and CHARM-Preserved included patients with LVEF >40%, independent of ACEI treatment. The incidence of new-onset AF was reduced in candesartan-treated patients, especially (but not exclusively) in the CHARM-Alternative trial.[89] These data indicate additional benefits in AF prevention, on the top of the already known effects of ACEI/ARB treatment in patients with heart failure.

5.2. Post-MI

After an acute myocardial infarction, treatment with the ACEI trandolapril reduced the incidence AF in patients with impaired left ventricular function, irrespective of the effects on ejection fraction per se.[90] Similar results were reported by Pizzetti et al. with lisinopril in their analysis of the GISSI-3 trial.[91]

5.3. Hypertension

The issue of the possible role of ACEI/ARB drug treatment in the primary prevention of AF in hypertensive patients derives from several conflicting observations. According to the CAPPP and the STOP-H2 trials, ACEIs were comparable to other antihypertensive regiments in preventing AF.[92,93] In contrast, a retrospective, longitudinal, cohort study by L'Allier et al. reported a benefit of ACEIs over calcium channel blockers in terms of new onset AF and AF-related hospitalizations.[94] Similar results were derived from the LIFE trial, showing that when compared with the β-blocker atenolol, patients receiving the ARB losartan had significantly lower incidence of new-onset AF and associated stroke.[95] A recent nested case-control observational study showed that compared with treatment with calcium channel blockers, long-term antihypertensive treatment with ACEIs, ARBs, or β-blockers may decrease the risk of new-onset AF.[96]

5.4. Increased cardiovascular risk

In patients with increased cardiovascular risk, the rate of new onset AF was not reduced by ramipril in a subanalysis of the HOPE clinical trial by Salehian and coworkers,[97] although in a population with a rather low incidence of AF (2.1%). Also in the ACTIVE I trial, there was no benefit of irbesartan treatment in preventing hospitalization for atrial fibrillation or atrial fibrillation recorded by 12-lead electrocardiography, nor was there a benefit in a subgroup of patients who underwent transtelephonic monitoring.[98] In contrast, according to Schmieder et al. the VALUE trial showed that valsartan-based antihypertensive treatment reduced the development of new-onset AF compared to amlodipine,[99] in subjects at higher risk of this arrhythmia due to an almost 25% prevalence of electrocardiographically-defined left ventricular hypertrophy. These conflicting data may indicate that a possible benefit of ACEI or ARB treatment can at best be observed in patients with the highest probability of increased RAAS activation.

5.5. Postoperative AF

A reduced incidence of new-onset AF was observed in patients undergoing coronary artery bypass graft surgery who were treated with ACEIs,[100] in a large multicenter prospective trial recruiting 4,657 subjects. These results were confirmed with the use of ACEIs alone or associated with candesartan,[101] whereas the reduced risk of developing postoperative AF did not reach the statistical significance in the *post hoc* evaluation of patients enrolled in the AFIST II and III trials.[102]

5.6. Secondary prevention after cardioversion and after catheter ablation

In the setting of secondary prevention, patients undergoing AF cardioversion represent a group in which the potential role of RAAS inhibition has been first investigated by van den Berg et al.[103], iwho studied 30 CHF patients treated with lisinopril or placebo before and after the procedure. Although the reduced incidence of recurrent AF in ACE-I treated patients did not reach the statistical significance, this study was followed by many others. Dagres et al. [104] demonstrated that treatment with the ARB irbesartan is associated with attenuated left atrial stunning after cardioversion. Subsequent studies showed that the association of an ACEI or an ARB with amiodarone prevents AF recurrences after cardioversion when compared with amiodarone alone.[105-107] Interestingly, irbesartan showed a dose-dependent preventive effect.[106] In contrast, Tveit and coworkers did not find any benefit by treating with the ARB candesartan for 3-6 weeks before and 6 months after electrical cardioversion.[108] We contributed to this debate by showing that also in the setting of lone AF,[11] long-term treatment with the ACE-I ramipril is effective in preventing relapses of AF after successful cardioversion.[109] Moreover, at the end of a 3-year follow-up, ramipril treatment also prevented left atrium enlargement,[109] which has been demonstrated to occur in the natural history of lone AF.[110]

In patients undergoing catheter ablation for drug refractory AF, ACEIs or ARBs did not show the same promising results,[111-115] raising the question whether these interventions are indeed able to revert atrial remodeling in this clinical setting.[116]

5.7. Paroxysmal AF prevention

Both ACEIs and ARBs have shown some promise in the setting of the prevention of paroxysmal AF recurrences. In two long-term clinical trials on amiodarone-treated patients, losartan or perindopril were more effective than amlodipine in the maintenance of sinus rhythm. [117,118] The same held true for telmisartan, that Fogari et al. showed as more effective than ramipril in reducing AF recurrence and severity as well as in improving P-wave dispersion, suggesting a possible specific effect of telmisartan on atrial electric remodeling.[119] In a retrospective analysis of patients with predominantly paroxysmal AF, Komatsu and coworkers showed that the enalapril added to amiodarone reduced the rate of AF recurrence and prevented the development of atrial structural remodeling.[120] In a post hoc subgroup analysis of the AFFIRM trial, Murray et al. showed that ACEIs and ARBs reduced the risk of AF recurrence in patients with a history of CHF or impaired left ventricular function. [121] The GISSI-AF trial did not show any significant effect of valsartan treatment on the rate of AF recurrences in a cohort of 1,442 patients with a history of recent AF.[122] Although it has to be noted that valsartan-treated patients had a significantly higher prevalence of coronary artery disease and peripheral artery disease, and that more than half of the patients were already taking concomitant ACEI treatment, the GISSI-AF shed some doubt on the whole issue of the preventive role of RAAS inhibition in AF prevention.[122] In the same line, the very recent ANTIPAF trial concluded that 12-month treatment with the ARB olmesartan did not reduce the number of AF episodes in patients with documented paroxysmal AF without structural heart disease.[123] Similar results were shown by the J-RHYTHM II study comparing the ARB candesartan with the calcium antagonist amlodipine in the treatment of paroxysmal AF associated with hypertension.[124] Both studies used daily transtelephonic monitoring to examine asymptomatic and symptomatic paroxysmal AF episodes. [123,124]

5.8. Emerging role for aldosterone antagonists

In the recent years, it has been suggested that upstream therapy using aldosterone antagonists, such as spironolactone or eplerenone, may reduce the deleterious effect of excessive aldosterone secretion on atrial tissue, thereby contributing to modify the risk of developing and of maintaining AF.[125] Dabrowski et al. showed that combined spironolactone plus beta-blocker treatment might be a simple and valuable option in preventing AF episodes in patients with normal left ventricular function and history of refractory paroxysmal AF.[126] In patients with AF, spironolactone treatment was associated with a reduction in the AF burden, as reflected by a combination of hospitalizations for AF and electrical cardioversion.[127] In a recent trial in patients with systolic heart failure and mild symptoms (EMPHASIS-HF), the aldosterone antagonist eplerenone reduced the incidence of new-onset AF or atrial flutter.[128]

5.9. Meta-analyses

The promise of a protective role of RAAS inhibition is largely based on the analysis of retrospective data, although on several thousands of patients. Another limitation is the fact that in most cases, the detection of AF recurrences is based on annual electrocardiograms, periodical 24-hour Holter analysis, or patient self-reported symptoms symptoms. In recent years, with the analysis of data from patients with an implanted pacemaker, it is becoming increasingly clear that continuous monitoring is much more reliable in identifying the presence of asymptomatic recurrences, with a mean sensitivity in detecting an AF episode lasting >5 minutes that was 44.4%, 50.4%, and 65.1% for 24-hour Holter, 1-week Holter, and 1-month Holter monitoring, respectively.[129] To partially overcome some of these limitations, several meta-analyses of the available trials have been conducted.[130-141] In synthesis, despite the promising preliminary experimental and clinical data, the efficacy of RAAS inhibition in the prevention of atrial fibrillation recurrences is still under debate, leading Disertori et al. in a very recent review article to the definition of "an unfulfilled hope".[136] In meta-analysis including 92,817 randomized patients, Khatib and coworkers concluded that although RAAS inhibition appears to reduce the risk of developing new onset atrial fibrillation in different patient groups, further research with stronger quality trials is required to draw definitive conclusions.[141]

Indeed, ACE-I or ARBs cannot be considered as an alternative to the established antiarrhythmic agents and transcatheter ablation. However, since they are recommended for most concomitant cardiovascular diseases that are associated with an increased risk of AF (i.e., hypertension, heart failure, ischemic heart disease) and since there are several lines of evidence that increased angiotensin II tissue levels are involved in both structural and electrical remodeling of the atrial tissue, it appears reasonable to use these drugs. In general, no substantial difference was found in the comparison between ACE-I and ARB treatment, a finding that was confirmed also by the results of the the ONTARGET and TRANSCEND trials.[142]

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5.10. Atrial remodeling as a therapeutic target: modulation of the renin-angiotensin-aldosterone system

Since angiotensin II plays a central role in the development of atrial fibrosis, inhibition of atrial angiotensin converting enzyme (ACE) and AT_1 angiotensin receptors might be beneficial in AF. In experimental models, AF susceptibility and atrial fibrosis were decreased by candesartan or enalapril, but not by hydralazine or isosorbide mononitrate despite similar hemodynamic effects,[26,63] thus suggesting a key role of targeting renin-angiotensin system, rather than of improving the hemodynamics. This concept was further underscored after demonstrating a preventive role of ramipril treatment in patients with lone AF.[109] Also spironolactone was able to prevent AF episodes in patients with normal left ventricular function and a history of refractory paroxysmal AF.[126] With the notable exception of the GISSI-AF,[122] ANTIPAF,[123] and J-RHYTHM II[124] trials, the majority of the available studies showed that modulation of the renin-angiotensin-aldosterone system is able to reduce the incidence of AF, as well as its recurrence after electrical cardioversion.[134] These data are summarized in several meta-analyses,[131,132,140,143] also including the GISSI-AF data.[135] In a broader view, although ACE inhibitors and angiotensin-II receptor blockers (ARBs) are not to be considered antiarrhythmic drugs, several studies have shown that they are associated with a lower incidence of ventricular arrhythmias in patients with ischemic heart disease and left ventricular (LV) dysfunction,[90,144,145] possibly because of the adverse effects of angiotensin II on the cardiac remodeling process. Indeed, it must be recognized that in the presence of a cardiac disease causing atrial overload and/or dysfunction, the effectiveness of ACE inhibitors and/or ARBs might be attributable either to a direct antiarrhythmic effect or to an effect on atrial structure and/or function likely able to favorably modify the arrhythmic substrate, such as the increase in left atrial (LA) dimensions that is frequently observed in patients with arterial hypertension and/or LV dysfunction.

In the setting of AF, it has to be remembered that angiotensin II not only has several effects on the *structure* of the atrial myocardium, but also on its *electrical* properties, as it has been elegantly shown in isolated pulmonary vein cardiomyocytes,[75] and in instrumented animal studies.[69] Therefore, the protective effect of ACE inhibition or angiotensin II antagonists on the electrical and structural remodeling of the atria is very likely, due to a combination of their actions on atrial distension/stretch, sympathetic tone, local renin-angiotensin system, electrolyte concentrations, and cardiac loading conditions.

6. Conclusions

The onset of atrial fibrillation results from a complex interaction between triggers, arrhythmogenic substrate, and modulator factors. Once established, AF itself alters the electrical and structural properties of the atrial myocardium, thereby perpetuating the arrhythmia. Among many other factors, angiotensin II and aldosterone play an important role not only in determining atrial fibrosis, but also in modulating the electrical properties of the atrial myocardium. These aspects may be relevant in explaining the many clinical observations indicating the role of drugs modulating the renin-angiotensin-aldosterone system in preventing atrial fibrillation in different settings.

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