Renin–Angiotensin System and Atrial Fibrillation: Understanding the Connection

Marcello Disertori, Silvia Quintarelli

Department of Cardiology, S Chiara Hospital, Trento, Italy

Abstract

Atrial fibrillation (AF) arises as a result of a complex interaction of triggers, perpetuators and the substrate. The recurrence of AF may be partially related to a biologic phenomenon known as remodeling, in which the electrical, mechanical, and structural properties of the atrial tissue and cardiac cells are progressively altered, creating a more favorable substrate. Atrial remodeling is in part a consequence of arrhythmia itself. Therefore, to prevent and to treat AF, much attention has been directed to upstream therapies to alter the arrhythmia substrate and to reduce atrial remodeling. The renin-angiotensin-aldosterone system (RAAS) plays a key role in these strategies. In this review we analyze the experimental and clinical evidence regarding the efficacy of RAAS inhibitors in AF treatment. In the primary prevention of AF, meta-analyses have shown that risk of new-onset AF in patients with congestive heart failure and left ventricular dysfunction is reduced by RAAS inhibitors, whereas in hypertensive and post–myocardial infarction patients, the results are less evident. In the secondary prevention of AF, some large, prospective, randomized, placebo-controlled studies with angiotensin II-receptor blockers returned negative results. Unfortunately, the approach of using RAAS inhibitors as antiarrhythmic drugs to prevent both new-onset and recurrent AF is in decline because negative trial results are accumulating, with the exception of the results in patients with congestive heart failure.

Introduction

Although atrial fibrillation (AF) is the most common cardiac arrhythmia, no current therapy is ideal for the control of this condition. 1 Multiple treatment options exist, but there is no single modality effective for all patients. Atrial fibrillation is such a complex and composite arrhythmia that it would be better regarded as “atrial fibrillations”. Atrial fibrillation arises as a result of a complex interaction of triggers, perpetuators and the substrate. The recurrence of AF may be partially related to a biologic phenomenon known as 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. 2,3 Atrial remodeling is in part a consequence of arrhythmia itself. The extension of the underlying structural cardiac disease can also influence the manifestations of AF. Atrial electrical remodeling (“first factor”) refers to the shortening and reversal of rate adaptation of the atrial effective refractory period, which occurs as a result of AF. In animal models of AF, the time course of electrical remodeling (2–3 days) differs from the time course of progression to persistent AF (approximately 1–2 weeks), suggesting that

Corresponding Address: Dr. Marcello Disertori, Department of Cardiology, S. Chiara Hospital, Largo Medaglie d’Oro, 38122 Trento, Italy.

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additional or “second factors” operate in the self-perpetuating AF process. This leads to the conclusion that other, more slowly developing factors, like atrial dilatation, enlargement of atrial myocytes, loss of myofilaments, changes in the expression of connections and gap junctions, and altered composition of the extracellular matrix, must be important for the development of the substrate of AF (atrial structural remodeling). Additionally, patients with paroxysmal lone AF demonstrate bi-atrial abnormalities characterized by structural changes, conduction abnormalities, and sinus node dysfunction.

The progression of atrial alteration is a fundamental component of AF pathophysiology. The renin-angiotensin-aldosterone system (RAAS) plays direct and indirect roles in the development of the AF substrate (Figure 1), and animal models have demonstrated that inhibition of RAAS can prevent AF. The idea of modifying the evolution of the AF substrate is intriguing and has been called “upstream therapy” because it affects the cascade leading to AF upstream to the final manifestation of the arrhythmia. To date, many clinical studies have tested the effect of RAAS inhibitors as upstream therapies, both in the prevention of new-onset AF and in the treatment of recurrent AF. The aim of the present review is to analyze and discuss the possible roles of RAAS inhibitors in atrial remodeling and in AF treatment.

**RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND ATRIAL FIBRILLATION: EXPERIMENTAL EVIDENCE**

The RAAS plays key roles in the morphological and functional remodeling of the atrium. Angiotensin II has direct and indirect actions on the AF substrate (Figure 1). Its direct action on the atrium leads to calcium overload, enhances fibroblast activity, promotes fibrosis and atrial enlargement, and favors apoptosis and gap junction remodeling. Its indirect effects on the ventricle (left ventricular hypertrophy, ventricular fibrosis and abnormal relaxation) increase atrial pressure and atrial stretch. Atrial fibrillation itself is a potent promoter of the atrial actions of the RAAS, with the potential to lead to a positive feedback loop of further RAAS activation and AF promotion.

It has been hypothesized that antagonists of the RAAS might retard or reverse atrial electrical and structural remodeling. The results in animal models are controversial. In some experimental models, the blockade of the activation of the RAAS through the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) positively impacts the electrical and structural remodeling in animal atria with AF. Nakashima et al. observed that in dogs, both candesartan and captopril prevented the electrical remodeling of the atrial wall.
ing during rapid atrial pacing. In a study by Li et al. enalapril significantly reduced tachypacing-induced changes in atrial angiotensin II concentration and attenuated the effects of congestive heart failure on atrial conduction, atrial fibrosis and mean AF duration. Additionally, spironolactone prevented the increased inducibility and duration of AF that are induced by tachypacing in a canine model. Chen et al. evaluated whether angiotensin II and angiotensin II receptor blockers could modulate the pulmonary vein electrical activity, which plays a role in the pathophysiology of AF. Angiotensin II induced delayed afterdepolarizations and accelerated the automatic rhythm, while the ARB losartan inhibited the automatic rhythm and the proarrhythmic effect of angiotensin II on cardiomyocytes.

On the contrary, Shinagawa et al. observed that, in contrast with short-term (several hours) atrial tachycardia-induced remodeling, remodeling induced by 7-day tachycardia is not affected by ACE inhibition. Moreover, in a recent study by Hall et al. in a goat model of lone AF, candesartan had no effect on atrial electrical remodeling, on increases in the stability of AF due to secondary factors, or on any other electrophysiological parameter. The authors of this last study hypothesized that any beneficial effects of RAAS blockade are more likely to be due to positive effects on left ventricular function and improvements in underlying disease processes rather than a direct antiremodeling effect. These data do not allow any definite conclusion regarding the efficacy of RAAS inhibitors in the prevention of AF in humans.

One of the limitations of these retrospective analyses was that AF was not a pre-specified endpoint. The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) study selected AF as one of the secondary endpoints. The AF substudy from the CHARM trial showed that adding candesartan to conventional therapy in 6379 patients with symptomatic heart failure and without history of AF at enrollment led to a lower incidence of new-onset AF vs. placebo, though this reduction was not as significant as in previous studies. The magnitude of candesartan’s positive effect varied according to the extent of left ventricular impairment, with a greater result in patients with left ventricular dysfunction, while the benefit was lower in patients with preserved ventricular function. Similarly, irbesartan did not influence the incidence of AF in patients with heart failure but preserved ejection fraction in the Irbesartan in Heart Failure and Preserve Ejection Fraction (I-PRESERVE) study.

HYPERTENSION

Whereas the data are clear in the congestive heart failure setting, the results in hypertensive patients are controversial.

A specific analysis of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, which studied 8851 patients with hypertension and left ventricular hypertrophy, showed that losartan treatment was associated with a lower
rate of AF with respect to the atenolol treatment. The authors hypothesized that the superior regression of electrocardiographic and echocardiographic signs of left ventricular hypertrophy with losartan compared to atenolol might correspond to a greater reduction of left atrial overload and dilatation, thereby reducing the stimuli of new-onset AF. Likewise, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, valsartan was compared with amlodipine in hypertensive patients; valsartan reduced the development of new-onset AF. In a cohort study of hypertensive patients, L’Allier et al. observed, during 4.5 years of follow-up, that ACEIs were more effective than calcium channel blockers in reducing new-onset AF.

In contrast, two large trials, the Heart Outcome Prevention Evaluation (HOPE) trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial, did not detect any effect of treatment with an ACEI or an ARB on AF. In the HOPE trial, over the 4.5 years of follow-up in 8335 patients without known heart failure or left ventricular systolic dysfunction, ramipril did not significantly reduce the rate of new-onset AF compared with placebo. In the TRANSCEND trial, the secondary outcome included AF. In a follow-up of 56 months, in high-cardiovascular-risk patients, there was no reduction of new-onset AF in the telmisartan group compared to placebo.

Meta-analyses

Four meta-analyses have shown that risk of new-onset AF in patients with congestive heart failure and left ventricular dysfunction was reduced by 30–48% by ACEIs and ARBs, suggesting that these drugs may be effective in the primary prevention of AF in this clinical setting (Table 1). The effect of RAAS inhibition on the primary prevention of AF in other clinical scenarios was significantly less evident than in heart failure.

<p>| Table 1: Efficacy of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in the primary prevention of atrial fibrillation (AF) in patients with congestive heart failure, with hypertension or after myocardial infarction: results of 4 meta-analyses. |</p>
<table>
<thead>
<tr>
<th>AF primary prevention: meta-analyses</th>
<th>Point estimate (95% confidence interval)</th>
<th>Test for the overall effect: Z</th>
</tr>
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<tbody>
<tr>
<td>• Congestive Heart Failure</td>
<td></td>
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<tr>
<td>Healey 2005 (27)</td>
<td>RR 0.56 (0.37–0.85)</td>
<td>p=0.007</td>
</tr>
<tr>
<td>Anand 2006 (28)</td>
<td>RR 0.57 (0.37–0.89)</td>
<td>-</td>
</tr>
<tr>
<td>Jibrini 2008 (29)</td>
<td>RR 0.68 (0.59–0.78)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Schneider 2010 (30)</td>
<td>OR 0.52 (0.31–0.87)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>• Hypertension</td>
<td></td>
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<td>Healey 2005 (27)</td>
<td>RR 0.88 (0.66–1.19)</td>
<td>p=0.4</td>
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<tr>
<td>Anand 2006 (28)</td>
<td>RR 0.94 (0.72–1.23)</td>
<td>-</td>
</tr>
<tr>
<td>Jibrini 2008 (29)</td>
<td>RR 0.77 (0.67–0.86)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Schneider 2010 (30)</td>
<td>OR 0.89 (0.75–1.05)</td>
<td>p=0.17</td>
</tr>
<tr>
<td>• Post-myocardial infarction</td>
<td></td>
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<tr>
<td>Healey 2005 (27)</td>
<td>RR 0.73 (0.43–1.26)</td>
<td>p=0.3</td>
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<tr>
<td>Anand 2006 (28)</td>
<td>RR 0.73 (0.43–1.26)</td>
<td>-</td>
</tr>
<tr>
<td>Jibrini 2008 (29)</td>
<td>RR 0.90 (0.81–0.99)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Schneider 2010 (30)</td>
<td>OR 0.72 (0.41–1.27)</td>
<td>p=0.26</td>
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</table>
ure. Of the four meta-analyses, only one showed that risk of new-onset AF in hypertensive and post-myocardial infarction patients was reduced.

### AF Secondary Prevention

Secondary prevention of AF consists of the reduction or abolition, by treatment, of AF recurrences in patients with a known history of AF.

### ACEIs

In the field of ACEIs, only small, prospective, randomized versus placebo or no-treatment trials on AF secondary prevention are available. In the first published study, Van Den Berg et al. randomized to lisinopril vs. placebo a small group of patients with heart failure. In a follow-up of 6 weeks, the lisinopril group showed a non–statistically significant trend in favor of a reduction of AF recurrences. In two open-label trials, Ueng et al. and Yin et al. compared amiodarone alone to amiodarone plus enalapril, amiodarone plus perindopril and amiodarone plus losartan. All of the various associations were more effective in preventing AF recurrences than amiodarone alone. Recently, Belluzzi et al. randomized 62 patients with lone AF to ramipril vs. placebo. During the 3-year follow-up, there were 3/31 recurrences in the ramipril group vs. 10/31 recurrences in the placebo group, with a statistically significant difference. The robustness of monitoring for AF recurrence was based only on the scheduled visits and Holter monitoring (every 3–6 months) in all of these ACEI trials.

### ARBs

In the field of ARBs, large, prospective, randomized trials are available (Table 2). In the earlier trials, ARBs positively affected AF recurrences, and subsequent meta-analyses confirmed these results. However, recent large clinical trials failed to show a reduction in AF relapses, thus questioning the role of RAAS inhibitors in the secondary prevention of AF. Two early ARB trials, by Madrid et al. and Yin et al., were open-label and relatively small. They compared amiodarone plus ARB (irbesartan or losartan) to amiodarone alone, with a positive result in favor of a reduction of AF recurrences in the groups with amiodarone plus ARB compared to amiodarone alone.

In contrast, the results of the four most recent prospective, randomized, double-blind, placebo-controlled studies were neutral. After the neutral

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Drugs</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Madrid (37)</td>
<td>154</td>
<td>Irbesartan plus Am vs. Am</td>
<td>Reduction of AF recurrences</td>
</tr>
<tr>
<td>Yin (33)</td>
<td>118</td>
<td>Losartan plus Am vs. Am</td>
<td>Reduction of AF recurrences</td>
</tr>
<tr>
<td>CAPRAF (41)</td>
<td>171</td>
<td>Candesartan vs. placebo</td>
<td>No effect</td>
</tr>
<tr>
<td>GISSI-AF (38)</td>
<td>1442</td>
<td>Valsartan vs. placebo</td>
<td>No effect</td>
</tr>
<tr>
<td>ANTIPAF (39)</td>
<td>425</td>
<td>Olmesartan vs. placebo</td>
<td>No effect</td>
</tr>
<tr>
<td>ACTIVE I (40)</td>
<td>1730</td>
<td>Irbesartan vs. placebo</td>
<td>No effect</td>
</tr>
<tr>
<td>Total</td>
<td>4040</td>
<td>ARBs</td>
<td>No Effect</td>
</tr>
</tbody>
</table>
results of the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study \(^4\) with candesartan vs. placebo, the Gruppo Italia-n per lo Studio della Sopravvivenza nell’Infarto miocardio-Atrial Fibrillation (GISSI-AF) study \(^3\) was the first large prospective, randomized, double-blind, placebo-controlled trial on the role of the ARB valsartan in AF secondary prevention. It enrolled 1442 patients who were similar to those encountered in clinical practice in terms of both the underlying cardiac disease and the treatment. After 12 months, it failed to show a reduction in first AF recurrences in the valsartan arm (51.4% vs.52.1% in the placebo group) or in multiple AF recurrences (26.9% in valsartan group vs. 27.9% in the placebo group). Neither amiodarone nor ACEIs at baseline influenced the effect of valsartan on re-occurrences of AF. The Angiotensin II-antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) trial \(^9\) analyzed the burden of AF in patients with paroxysmal AF and without structural heart disease. The 12-month follow-up did not show any difference in recurrences or the burden of AF in patients treated with olmesartan vs. placebo. Finally, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE I) study \(^10\) assessed the efficacy of irbesartan on the recurrence of AF. In the 1730 patients in sinus rhythm at baseline, AF recurred in 36.8% of patients who re- ceived irbesartan, compared with 38% of patients who received placebo, over a mean follow-up of 4.1 years. Additionally, in the 185 patients who participated in the transtelephonic monitoring substudy, the results of irbesartan were neutral, with 68% AF recurrence in the irbesartan group vs. 62% in the placebo group. The robustness of monitoring for AF recurrence varies among studies. In the earlier trials, \(^3,37,41\) AF recurrences were diagnosed at scheduled visits or ECG Holter recording, while in the later and larger trials (GIS-SI-AF, \(^38\) ANTIPAF, \(^39\) ACTIVE I subgroup, \(^40\)) transtelephonic monitoring was added.

**Aldosterone antagonists**

There are limited clinical data regarding aldosterone in the development and maintenance of AF. Patients with primary hyperaldosteronism have a 12-fold greater risk of AF than do controls matched for blood pressure. \(^44\) Recently, Dabrowski et al. \(^45\) in a cohort of 164 patients with a history of recurrent AF, observed a significant reduction in the incidence of AF episodes in patients treated with spironolactone plus beta-blockers versus a group of patients treated with enalapril plus beta-blockers or beta-blockers alone.

The possible effectiveness of aldosterone receptor blockers in the secondary prevention of AF is still pending more conclusive data, and ongoing trials are set to investigate the antiarrhythmic effect of spironolactone and eplerenone in AF in patients undergoing heart surgery, in patients with recent heart failure, and after electrical cardioversion.

**AF recurrences after AF ablation**

The presence of recurrent AF during the first 3 months after pulmonary vein isolation (PVI) is common. These early AF recurrences often recede spontaneously after several months upon maturation of lesions and resolution of inflammation, without the need for re-ablation. The RAAS inhibitors may facilitate post-ablation atrial remodeling and reduce AF recurrences. Retrospective trials have explored this hypothesis, but with controversial results. In the study of Richter et al. \(^46\) in 234 patients who underwent PVI, RAAS inhibitors did not improve the outcome of AF ablation. Similar results were observed by Al Chekakie et al. \(^47\) in patients with paroxysmal and persistent AF. A large prospective registry was published by Tayebjee et al. \(^48\): 419 patients, 142 of whom were treated with RAAS inhibitors, underwent a long-term follow-up after catheter ablation for AF, in some cases with repeated procedures. In this cohort, the RAAS inhibitors, mostly ACEIs, did not appear to affect the maintenance of sinus rhythm (median follow-up 1.7 years from the last ablation, up to 5 years in some patients). The authors highlighted that the impact of an intervention targeting the structural remodeling of the atrial substrate needs to be evaluated on the basis of a long-term outcome. Moreover, catheter ablation causes dense transmural scar; therefore, even if RAAS inhibitors could determine atrial structural effects, these might be overshadowed by the gross macroscopic changes induced by catheter ablation.

However, two recent studies provided evidence of a positive effect of RAAS inhibitors on AF recurrences after PVI. In a retrospective study of 264 patients who underwent successful PVI, Ishikawa
et al. observed that RAAS inhibitor treatment was the only independent predictor of late (>3 months) AF recurrence. Berkowitsch et al. in a retrospective analysis of 284 patients, stratified the patients according to atrial fibrillation burden. After PVI, RAAS inhibitors appeared to protect against AF recurrences only in patients with low-burden paroxysmal AF. However, all these factors should be tested in a prospective study.

**DISCUSSION**

Given the fundamental role of the RAAS in atrial remodeling, the approach of using RAAS inhibitors in AF therapy is intriguing. Theoretically, these drugs may provide primary prevention of new-onset AF and secondary prevention of recurrent AF. Experimental data in animals have only partially confirmed this hypothesis. Unfortunately, although the first clinical studies showed positive results, subsequent trials reported a low efficacy of RAAS inhibitors in AF.

In primary prevention, different effects according to the underlying cardiac disease have been observed. Clinical trials have shown a reduction of new-onset AF in patients with congestive heart failure and left ventricular dysfunction, whereas RAAS inhibitors are less effective in hypertensive and post-myocardial infarction patients. It should be highlighted that comparisons of different trials are sometimes difficult because the posology of the chosen drugs is not always equivalent.

In the secondary prevention of AF, there seems to be a difference between ACEIs and ARBs. The ARBs failed to show a positive effect on AF secondary prevention. Therefore, the available data do not suggest the use of ARBs as an alternative to antiarrhythmic agents or catheter ablation. The neutral ARB trials included all clinical types of AF: lone paroxysmal AF in the ANTIPAF trial, persistent AF in the CAPRAF study, and paroxysmal-persistent AF in patients with structural heart disease in the GISSI-AF and AC-TIVE I trials. In none of these subgroups did ARBs show positive results in preventing AF recurrences. In contrast, the effect of ACEIs in the secondary prevention of AF is still controversial. We suggest two possible interpretations of the different effects of these two drug classes. First, the biology of the RAAS may account for the different abilities of ACEIs and ARBs to prevent AF. Second, the difference between the effects of ACEIs and ARBs may be related to the characteristics of the respective trials because the prospective, randomized trials with ACEIs are too limited to permit a definitive conclusion. Moreover, ACEI studies have not had a robust follow-up algorithm to recognize all the episodes of AF, as recently suggested for clinical trials in AF. If the mechanism of the prevention of AF recurrences is the same with ACEIs and ARBs, the efficacy is expected to be the same at comparable dosages

Why are RAAS inhibitors minimally effective in the treatment of AF in clinical practice? It is possible that their clinical effect could not be exactly reproduced in experimental models. All available animal models mimic clinical diseases leading to AF, but they have major limitations. Any single animal model reproduces a limited component of the pathophysiologic spectrum of clinical AF. There is a lack of adequate models of spontaneously occurring paroxysmal AF. Moreover, animal models are essentially disease-free. Perhaps ACEIs and ARBs work in experimental settings because they are used before the disease has even appeared. The reversibility of remodeling remains a key issue because clinical application usually begins after an index event has occurred, whereas in an experimental setting the antiremodeling agent is typically administered before the remodeling stimulus. Consequently, the negative clinical results of RAAS inhibitors might be attributable to intervention after remodeling was established. The RAAS inhibitors target structural rather than electrical remodeling and therefore they may be less effective in the clinical setting of AF and may need a long-term results evaluation. In contrast to the
animal models, AF mechanisms and the atrial remodeling processes are more complex in humans; they depend on the individual subject, the underlying cardiac disease, and the time in their clinical history at which the therapy is introduced.

Unexpectedly, on the basis of the previous considerations, RAAS inhibitors seem to be effective in AF therapy only in the clinical setting of congestive heart failure and left ventricular dysfunction, that is, in patients with supposed extended remodeling. There is a lack of experimental data addressing the effect of RAAS inhibitors applied after the development of such a substrate. Research in dogs suggested no reversal of atrial fibrosis induced by congestive heart failure, despite a complete hemodynamic recovery. It remains unclear whether the antiarrhythmic potential of ACEIs and ARBs goes beyond any effect related to the treatment of the underlying heart disease. In conclusion, the attractive approach of using RAAS inhibitors to prevent and to treat AF is in decline as more and more negative trial results are accumulating.

References


52. Kirchhof P, Auricchio A, Bax J, et al. Outcome parameters for trials in atrial fibrillation: Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and European Heart