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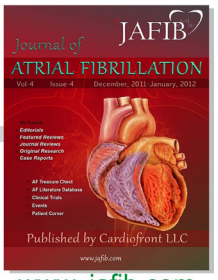

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Renin–Angiotensin System and AtrialFibrillation :Understanding the Connection

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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 keyrole 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 studieswith angiotensin II-receptor blockers returned negative results. Unfortunately, the approach of using RAASinhibitors as antiarrhythmic drugs to prevent both new-onset and recurrent AF is in decline because negativetrial 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 fibri lation arises as a result of a complex interaction of triggers, perpetuators and the substrate. The recu rence 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 morefavorable 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 1–2weeks),suggesting that

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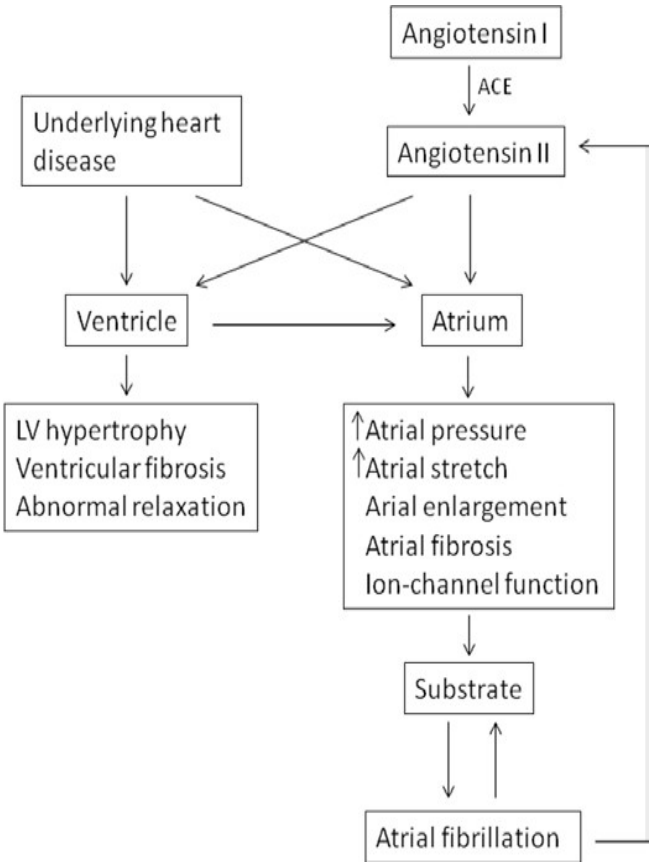
additional or "second factors" operate in the self-perpetuating AF process .[3,4] This leads to the conclusion that other, more slowly developing-factors, like atrial dilatation, enlargement of atrial myocytes, loss of myofilaments, changes in the expression of connections and gap junctions,and altered composition of the extracellular matrix, must be important for the development of the substrate of AF (atrial structural remodeling) .[4] Additionally, patients with paroxysmal lone AF demonstrate bi-atrial abnormalities characterized by structural changes, conduction abnormalities, and sinus node dysfunction. [5]

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 [6,7,8] (Figure 1), and animal models have demonstrated that inhibition of RAAS can prevent AF .[9-13] The idea of modify- ing 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. [14] 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

Figure 1: Direct and indirect actions of angiotensin II on the substrate of atrial fibrillation (AF) and interactions with the underlying heart disease.



The left ventricular impairment leads to increased atrial pressure and atrial stretch. The direct effect of angiotensin II on the atrium leads to increased fibroblast activity and promotes fibrosis. Angiotensin II also has a direct effect on ion channel function. Direct and indirect actions lead to atrial dilatation. The possible underlying heart disease favors the effects of angiotensin II on the AF substrate. AF itself promotes atrial remodeling. From Ehrlich et al. (8), modified.

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

The RAAS plays key roles in the morphological and functional remodeling of the atrium. Angio- tensin II has direct and indirect actions on the AF substrate [8] (Figure 1). Its direct action on the atri- um leads to calcium overload, enhances fibroblast activity, promotes fibrosis and atrial enlargement, and favors apoptosis and gap junction remodel- ing. [12,15] 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 experimen- tal 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. [9] Nakashima et al. [10] observed that in dogs, both candesartan and captopril pre- vented the electrical remodel-

ing during rapid atrial pacing. In a study by Li et al. [11] enala- pril 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. [12] Chen et al. [13] 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 acceler- ated the automatic rhythm, while the ARB losartan inhibited the automatic rhythm and the proarrhyth- mic effect of angiotensin II on cardiomyocytes.

On the contrary, Shinagawa et al. [16] 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. [15] in a goat model of lone AF, cande- sartan had no effect on atrial electrical remodel- ing, on increases in the stability of AF due to sec- ond factors, or on any other electrophysiological parameter. The authors of this last study [15]hy- pothesized that any beneficial effects of RAAS blockade are more likely to be due to positive ef- fects on left ventricular function and improvements in underlying disease processes rather than a di- rect antiremodeling effect. These data do not allow any definite conclusion regarding the efficacy of RAAS inhibitors in the prevention of AF in humans

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND ATRIAL FIBRILLATION: CLINICAL EVIDENCE

AF Primary Prevention

Primary prevention of AF consists of the prevention, by treatment, of the first AF episode (new-onset AF) in patients without history of AF at enrollment

Heart failure

In heart failure patients, some clinical trials have shown a reduction of the first episodes of AF, although they were mostly post hoc analyses of studies designed for an objective other than AF. In a setting of patients with post-infarction ventricular dysfunction, Pedersen et al. [17] demonstrated a reduction in the incidence of AF in association with a treatment with the ACEI trandolapril. The report from the Trandolapril Cardiac Evaluation (TRACE) study [17] was followed by a similar retrospective analysis of the results from the Studies of Left Ventricular Dysfunction (SOLVD) trial ,[18] which also demon strated a lower new-onset AF rate in patients with heart failure with enalapril treatment vs. placebo. Moreover, a recent subanalysis of the Valsartan Heart Failure Trial (Val-HeFT) study [19] showed that valsartan, on top of prescribed therapy for heart failure, significantly reduced the occurrence of AF over a mean follow-up period of 23 months..

One of the limitations of these retrospective analyses was that AF was not a pre-specified endpoint. The Candesartan in Heart failure: As- sessment of Reduction in Mortality and morbid- ity (CHARM) study [20] 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 symp- tomatic 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 dys- function, while the benefit was lower in patients with preserved ventricular function. Similarly, ir- besartan 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. [21]

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, [22] which studied 8851 patients with hy- pertension and left ventricular hypertrophy, showed that losartan treatment was associated with a lower

rate of AF with respect to the ateno- lol treatment. The authors [22] 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 Val- sartan Antihypertensive Long-term Use Evalua- tion (VALUE) trial ,[23] valsartan was compared with amlodipine in hypertensive patients; valsar- tan reduced the development of new-onset AF. In a cohort study of hypertensive patients, L'Allier et al. [24] observed, during 4.5 years of follow- up, that ACEIs were more effective than calci- um channel blockers in reducing new-onset AF.

In contrast, two large trials, the Heart Outcome Prevention Evaluation (HOPE) trial [25] and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial, [26] did not detect any effect of treatment with an ACEI or an ARB on AF. In the HOPE trial ,[25] 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 ,[26] 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 [27-30] 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 fail-

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.

AF primary prevention: meta-analyses	Point estimate (95% confidence interval)	Test for the overall effect: Z
• Congestive Heart Failure		
Healey 2005 (27)	RR 0.56 (0.3 7–0.85)	p=0.007
Anand 2006 (28)	RR 0.57 (0.37–0.89)	-
Jibrini 2008 (29)	RR 0.68 (0.59–0.78)	p<0.001
Schneider 2010 (30)	OR 0.52 (0.31–0.87)	p=0.01
• Hypertension		
Healey 2005 (27)	RR 0.88 (0.66–1.19)	p=0.4
Anand 2006 (28)	RR 0.94 (0.72–1.23)	-
Jibrini 2008 (29)	RR 0.77 (0.67–0.86)	p<0.001
Schneider 2010 (30)	OR 0.89 (0.75–1.05)	p=0.17
• Post-myocardial infarction		
Healey 2005 (27)	RR 0.73 (0.43–1.26)	p=0.3
Anand 2006 (28)	RR 0.73 (0.43–1.26)	-
Jibrini 2008 (29)	RR 0.90 (0.81–0.99)	p<0.05
Schneider 2010 (30)	OR 0.72 (0.41–1.27)	p=0.26

ure. Of the four meta-analyses, only one [29] 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.[31] 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. [32]and Yin et al. [33] 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. [34] randomized 62 patients with lone AF to ramipril vs. placebo. During the 3-year fol- low-up, there were 3/31 recurrences in the ramipril group vs. 10/31 recurrences in the placebo group, with a statistically significant difference. The ro- bustness of monitoring for AF recurrence was based only on the scheduled visits and Holter monitor- ing (every 3–6 months) in all of these ACEI trials

The largest retrospective analysis of AF secondary prevention was the post hoc Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, [35] which included 732 patients. Angiotensin-converting enzyme inhibitors and ARBs showed no effect in the secondary prevention of AF, except in the subgroup of patients with congestive heart failure or impaired left ventricular function. Additionally, the retrospective Canadian Trial of Atrial Fibrillation (CTAF) study [36]demonstrated the absence of protective ef- fects of RAAS inhibitors against AF recurrence

ARBs

In the field of ARBs, large, prospective, randomized trials are available (Table 2). In the earlier trials, ARBs positively affected AF recurrences, [33,37] and subsequent meta-analyses confirmed these results .[27,29,30] However, recent largeclinical trials (38-40) 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. [37] and Yin et al. , [33] 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 amioda- rone 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 2 Prospective randomized studies of angiotensin II-receptor blockers (ARBs) for the secondary prevention of atrial fibrillation (AF) vs. placebo or no drug.

Study	No. Patients	Drugs	Results
Madrid (37)	154	Irbesartan plus Am vs. Am	Reduction of AF recurrences
Yin (33)	118	Losartan plus Am vs. Am	Reduction of AF recurrences
CAPRAF (41)	171	Candesartan vs. placebo	No effect
GISSI-AF (38)	1442	Valsartan vs. placebo	No effect
ANTIPAF (39)	425	Olmesartan vs. placebo	No effect
ACTIVE I (40)	1730	Irbesartan vs. placebo	No effect
Total	4040	ARBs	No Effect

results of the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study [41]with candesartan vs. placebo, the Gruppo Italia- no per lo Studio della Sopravvivenza nell'Infarto miocardio–Atrial Fibrillation (GISSI-AF) study [38] 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 re- lapses (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- currences of AF. The Angiotensin II-antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) trial [39] analyzed the burden of AF in patients with parox- ysmal 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 [40] assessed the efficacy of irbesartan on the recur rence 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 stud- ies. In the earlier trials, [33,37,41] 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 signifi- cant 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 inhibi- tors may facilitate post-ablation atrial remodeling and reduce AF recurrences. Retrospective trials have explored this hypothesis, but with contro- versial 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 co- hort, the RAAS inhibitors, mostly ACEIs, did not appear to affect the maintenance of sinus rhythm (median follow-up 1.7 years from the last abla- tion, 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. [49]observed that RAAS inhibitor treatment was the only independent predictor of late (>3 months) AF recurrence. Berkowitsch et al. [50] in a retrospective analysis of 284 patients, stratified the patients according to atrial fibrillation bur- den. After PVI, RAAS inhibitors appeared to pro- tect 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. Un- fortunately, although the first clinical studies showed positive results, subsequent trials re- ported 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 .[27-30] 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 sec- ondary 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,[39]persistent AF in the CAPRAF study, [41] and paroxysmal-persistent AF in patients with struc- tural heart disease in the GISSI-AF [38]and AC- TIVE I trials. [40] In none of these subgroups did ARBs show positive results in preventing AF re- currences. In contrast, the effect of ACEIs in the secondary prevention of AF is still controversial. We suggest two possible interpretations of the dif- ferent effects of these two drug classes. First, the biology of the RAAS may account for the differ- ent abilities of ACEIs and ARBs to prevent AF .[5 1]Second, the difference between the effects of ACEIs and ARBs may be related to the character- istics of the respective trials because the prospec- tive, randomized trials with ACEIs are too lim- ited 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. [52] 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 pos- sible 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 .[53]Any sin- gle animal model reproduces a limited component of the pathophysiologic spectrum of clinical AF. [53] There is a lack of adequate models of sponta- neously occurring paroxysmal AF.[14] 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 be- gins after an index event has occurred, whereas in an experimental setting the antiremodeling agent is typically administered before the remodeling stimulus.[14]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 hu- mans; 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 consid- erations, RAAS inhibitors seem to be effective in AF therapy only in the clinical setting of congestive heart failure and left ventricular dysfunction ,[27-30] that is, in patients with supposed extended re- modeling. There is a lack of experimental data ad- dressing 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 .[54] It **re**mains unclear whether the antiarrhythmic potential of ACEIs and ARBs goes beyond any effect related to the treat- ment of the underlying heart disease. In conclu- sion, the attractive approach of using RAAS inhibi- tors to prevent and to treat AF is in decline as more and more negative trial results are accumulating.

References

1. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for man- agement of atrial fibrillation. The Task Force for the Manage- ment of Atrial Fibrillation of the European Society of Cardiol- ogy (ESC). Eur Heart J 2010;31:2369-429.
2. Wijffels M, Kirchhof C, Dorland R, Allessie M. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–68.
3. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodelling during atrial fibrillation. Cardiovasc Res 2002;54:230-46.
4. Allessie M. The "Second Factor": a first step toward diagnosing the substrate of atrial fibrillation? J Am Coll Cardiol 2009;53:1192-3.
5. Stiles MK, John B, Wong CX et al. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate. Characterizing the "Second Factor". J Am Coll Cardiol 2009;53:1182-91.
6. Cardin S, Li D, Thorin-Trescases N, Leung TK, Thorin E, Nattel S. Evolution of atrial fibrillation substrate in experimental congestive heart failure: angiotensin-dependent and independent pathways. Cardiovasc Res 2003;60:315-25.
7. Goette A, Staack T, Rocken C, et al. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. J Am Coll Cardiol 2000;35:1669-77.
8. Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: Clinical and experimental evidence. Eur Heart J 2006;27:512-18.
9. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodelling in atrial fibrillation. J Am Coll Cardiol 2003;41:2197-204.
10. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodelling in atrial fibrillation. Circulation 2000; 101:2612-7.
11. Li D, Shinagawa K, Pang L, et al S. Effects of angiotensinconverting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation 2001;104:2608-14.
12. Zhao J, Li J, Li W, et al. Effects of spironolactone on atrial structural remodellling in a canine model of atrial fibrillation produced by prolonged atrial pacing. Br J Pharmacol 2010;159:1584-94.
13. Chen YJ, Chen YC, Tai CT, Yeh HI, Lin CI, Chen SH. Angiotensin II and angiotensin II receptor blocker modulate the arrhythmogenic activity of pulmonary veins. Br J Pharmacol 2006;147:12-22.
14. Nattel S. From guidelines to bench: implications of unresolved clinical issues for basic investigations of atrial fibrillation mechanisms. Can J Cardiol 2011;27:19-26.
15. Hall MGS, Kirubakaran S, Choudhury R, Abidin N, Peters NS, Garrat CJ. Effect of angiotensin receptor blockade on atrial electrical remodelling and the "second factor" in a goat burst-paced model of atrial fibrillation. J Renin Angiotensin Aldosterone Syst 2010;11:222-33.
16. Shinagawa K, Mitamura H, Ogawa, Nattel S. Effects of inhibiting NA+/H+-exchange or angiotensin converting enzyme on atrial tachycardia-induced remodelling. Cardiovasc Res 2002:54:438-46.
17. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. Tran- dolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dys- function. Circulation 1999;100:376–80.
18. Vermes E, Tardif JC, Bourassa MG, et al. Enalapril decreas- es the incidence of atrial fibrillation in patients with left ven- tricular dysfunction: insight from the Studies of Left Ventricu- lar Dysfunction (SOLVD) trials. Circulation 2003;107:2926-31.
19. Maggioni AP, Latini R, Carson PE, et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: Results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2005;149:548-57.
20. Ducharme A, Swedberg K, Pfeffer MA, et al. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: As- sessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J 2006;152:86-92.
21. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-67
22. Wachtell K, Lehto M, Gerdts E, et al. Aangiotensin II re- ceptor blokade reduces new-onset atrial fibillation and subse- quent

stroke compared to atenolol: the Losartan Intervention For End Point reducion in hypertension (LIFE) study. J Am Coll Cardiol 2005;45:712-9.
23. Schmieder RE, Kjeldsen E, Julius S, et al. Reduce incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertens 2008;26:403-11.
24. L'Allier PL, Ducharme A, Keller P-F, Yu H, Guertin M-C, Tardif J-C. Angiotensin-converting enzyme inhibition in hy- pertensive patients is associated with a reduction in the occur- rence of atrial fibrillation. J Am Coll Cardiol 2004;44:159-64.
25. Salehian O, Healey J, Stambler B, et al. Impact of ramipril on the incidence of atrial fibrillation: results of the Heart Out- comes Prevention Evaluation study. Am Heart J 2007;154:448-53.
26. The TRANSCEND Investigators. Effect of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174-83.
27. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a metanalysis. J Am Coll Cardiol 2005;45:1832-9.
28. Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: inhibition of renin-angiotensin system prevents new-onset atrial fibrillation. Am Heart J 2006;152:217-22.
29. Jibrini MB, Molnar J, Arora RR. Prevention of atrial fibrillation by way of abrogation of the renin-angiotensin system: a systematic review and meta-analysis. Am J Ther 2008;15:36-43.
30. Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by renin-angiotensin system inhibition. J Am Coll Cardiol 2010;55:2299-309.
31. Van Den Berg MP, Crijns HJ, Van Veldhuisen DJ, Griep N, De Kam PJ, Lie HI. Effects of lisinopril in patients with heart failure and chronic atrial fibrillation. J Card Fail 1995;1:355-63.
32. Ueng KC, Tsai TP, Yu WC, et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation: results of a prospective and controlled study. Eur Heart J 2003;24:2090-8.
33. Yin Y, Dalal D, Liu Z, et al. Prospective randomized study comparing amiodarone vs. amiodarone plus losartan vs. amiodarone plus perindopril for the prevention of atrial fibrillation recurrence in patients with lone paroxysmal atrial fibrillation. Eur Heart J 2006;27:1841-6
34. Belluzzi F, Sernesi L, Preti P, Salinaro F, Fonte ML, Perlini S. Prevention of recurrent lone atrial fibrillation by angiotensin-II converting enzyme inhibitor ramipril in normotensive patients. J Am Coll Cardiol 2009;53:24-9.
35. Murray KT, Rottman JN, Arbogast PG, et al. Inhibition of angiotensin II signaling and recurrence of atrial fibrillation in AFFIRM. Heart Rhythm 2004;1:669-75.
36. Palardy M, Ducharme A, Nattel S, et al. Absecnce of protective effect of renin-angiotensin system inhibitors on atrial fibrillation development: Insights from the Canadian Trial of Atrial Fibrillation (CTAF). Can J Cardiol 2008;24:709-13.
37. Madrid AH, Bueno MG, Rebollo JM, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. Circulation 2002;106:331-6.
38. The GISSI-AF Investigators. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med 2009;360:1606-17.
39. Goette A, Schon N, Kirchhof P, et, al. Angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) - trial. (Abstr). Hotline III ESC 2010; p3772.
40. The ACTIVE I Investigators. Irbesartan in patients with atrial fibrillation. N Engl J Med 2011; 364:928-38.
41. Tveit A, Grundvold I, Olufsen M, et al. Candesartan in the prevention of relapsing atrial fibrillation. Int J Cardiol 2007;120:85-91.
42. Fogari R, Mugellini A, Destro M, et al. Losartan and prevention of atrial fibrillation recurrence in hypertensive patients. J Cardiovasc Pharmacol 2006;47:46-50.
43. Yamashita T, Inoue H, Okumara K, et al. 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). Europace 2011;13:473-79.
44. Dobrev D, Nattel S. New antiarrhythnic drugs for treatment of atrial fibrillation. Lancet 2010;375:1212-23.
45. Dabrowski R, Borowiec A, Smolis-Bak E, et al. Effect of combined spironolactone-β-blockers ± enalapril treatment on occurence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial fibrillation (SPIR-AF Study). Am J Cardiol 2010;106:1609-14.
46. Richter B, Derntl M, Marx M, Lercher P, Gossinger HD. Therapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins: no effect on ablation outcome after ablation of atrial fibrillation. Am Heart J 2007,153:113-9.
47. Al Chekakie MO, Akar JG, Wang F, et al. The effects of statins and renin-angiotensin system blockers on atrial fibrillation recurrence following antral pulmonary vein isolation. J Cardiovasc Electrophysiol 2007;18:942-6.
48. Tayebjee MH, Creta A, Moder S, et al. Impact of angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers on long-term outcome of catheter ablation for atrial fibrillation. Europace 2010;12:1537-42.
49. Ishikawa K, Yamada T, Yoshida Y, et al. Renin-angiotensin system blocker use may be associated with suppression of atrial fibrillation recurrence after pulmonary vein isolation. PACE 2011;34:296-303.
50. Berkowitsch A, Neumann T, Kuniss M, et al. Therapy with renin-angiotensin system blockers after pulmonary vein iso PACE 2010;33:1101-11.
51. Levy BI. Can angiotensin II type 2 receptors have deleterious effects in cardiovascular disease?: Implication for therapeutic blockade of renin-angiotensin system. Circulation 2004;109:8-13.
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

Rhythm Association. Europace 2007;9:1006-23.
53. Nishida K, Michael G, Dobrev D, Nattel S. Animal models for atrial fibrillation: clinical insights and scientific opportunities. Europace 2010;12.160-72.
54. Shinagawa K, Shi YF, Tardif JC, Leung TK, Nattel S. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. Circulation 2002;105:2672-78