BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2008.03234.x

The role of the renin–angiotensin system in atrial fibrillation and the therapeutic effects of ACE-Is and ARBS

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Keywords
ACE inhibitors, angiotensin receptors blockers, atrial fibrillation, recurrence, renin angiotensin system

Received
19 May 2008
Accepted
21 May 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Atrial fibrillation (AF) is the most common rhythm disturbance in medical practice.
- AF can be managed with the prevention of thromboembolism and either a rate control or rhythm control strategy; however, as both treatment strategies have important limitations, a preventative strategy could be a more attractive option.
- Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin-II receptor blockers (ARBs) may play a role in preventing AF recurrence.

WHAT THIS STUDY ADDS

- The aim of the present review was to analyse evidence supporting the usefulness of renin–angiotensin system (RAS) inhibition in patients with AF and to focus on which specific subset of patients it most favours.
- Although many studies and meta-analysis have supported the advantage of RAS block in preventing AF recurrence, it is not possible to recommend the use of ACE-Is and ARBs in routine clinical practice specifically to prevent AF.
- As these drugs are safe and manageable, they should be considered the drugs of choice in patients with AF and coexisting clinical conditions such as hypertension, coronary disease, heart failure and diabetes mellitus.

Atrial fibrillation (AF) is the most common rhythm disturbance in medical practice and represents a very expensive health problem. AF can be managed with the prevention of thromboembolism and either a rate control or rhythm control strategy. As both strategies have important limitations, probably a preventative strategy in patients at risk of developing arrhythmia can be a more attractive option.

The renin–angiotensin system (RAS) seems to be involved in the genesis of arrhythmia by the following two mechanisms:

1 the induction of atrial fibrosis and structural remodelling by mitogen-activated protein kinase (MAPK) expression and reduction of collagenase activity;
2 the induction of electrical remodelling by shortening of the atrial effective refractory period (AERP) and of the action potential duration.

For these reasons it has been hypothesized that angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin-II receptor blockers (ARBs) may play a role in preventing AF recurrence. The aim of the present review was to analyse evidence supporting the usefulness of RAS inhibition in patients with AF in order to focus on which specific subset of patients it would most favour. After reviewing the literature, we conclude that, although many studies and meta-analyses have supported the advantage of RAS block in preventing AF recurrence, it is premature to recommend the use of ACE-Is and ARBs specifically for the prevention of AF.

However we believe that as these drugs are safe and manageable, they should be considered the drugs of choice in patients with AF and coexisting clinical conditions such as hypertension, coronary disease, heart failure and diabetes mellitus.

Epidemiology, associated conditions and prognosis

AF is the most common rhythm disturbance in medical practice. Almost 7 million people in North America and the EU are affected by paroxysmal or permanent AF [1]. Both the prevalence and incidence increase with age [1].

The median age of people affected by AF is 75 years, equally female and male, whereas in older patients 60% are female [2]. In prospective studies, the incidence is <0.1% per year in patients <40 years old and reaches 1.5–2% per year in those >80 years old [3].

AF can often be linked to reversible causes such as alcohol intake, hyperthyroidism, myocarditis and pericarditis, myocardial infarction, pulmonary embolism, metabolic disorders and cardiac surgery, and very often the treatment of such conditions eliminates the arrhythmia.

Almost one-third of cases of paroxysmal AF and one-quarter of cases of permanent AF occur in young people without demonstrable underlying pathological conditions – 'lone AF' [4]. Among the spectrum of heart diseases, AF is often associated with heart failure, hypertension, left ventricular hypertrophy, coronary artery disease and valvular heart disease (especially mitral valve disease), but potentially each cardiac congenital or acquired pathology can be associated with this rhythm disturbance.

If associated with other arrhythmias, such as Wolff–Parkinson–White syndrome, atrial flutter and atrioventricular re-entrant nodal tachycardia, the treatment of the primary rhythm disturbance reduces the recurrence of AF [5].

Obesity, leading to increased left atrium size, is a very important risk factor for the development of AF [6].

Except those with 'lone AF', patients affected by AF have a worse prognosis compared with those in sinus rhythm. It increases the long-term risk of stroke and heart failure [7, 8], and the mortality rate in the former, linked to the severity of underlying disease, is double that in the latter [9]. AF represents a very expensive health problem – almost €3.000 per patient is spent every year in the EU [10].

As AF is an epidemic problem in terms of morbidity and helathcare cost, it is very important to delineate effective therapeutic and prevention strategies.

AF can be managed with the prevention of thromboembolism and either a rate control or a rhythm control strategy. Recent data suggest that both management strategies are associated with similar outcomes. Although some authors suggest that rate control should be preferred because of pro-arrhythmic effects of the drugs used for maintenance of sinus rhythm [11, 12], we should also consider that the negative dromotropic effect of agents used for rate control may not be tolerated by all patients.

As both treatment strategies for AF have important limitations, a preventative strategy in patients at risk of developing arrhythmia could be a more attractive option.

Researchers are studying the possible role of the RAS in the genesis of this arrhythmia and the potential therapeutic effect of agents able to suppress its actions.

Role of the renin–angiotensin system in atrial fibrosis and electrical remodelling

Several hypotheses have been postulated regarding the possible involvement of the RAS in the occurrence of AF.

The involvement of the RAS in myocardial fibrosis is evident in several pathological conditions such as hypertensive heart disease [13], congestive heart failure [14] and myocardial infarction [15]. Interstitial fibrosis is common in patients with AF [16]. Moreover, the histological substrate of atrial biopsies in patients with lone AF suggests that the likelihood of AF increases with increasing degree of fibrosis [17].

Goette *et al*. showed that atrial expression of the extracellular signal-regulated kinase Erk1/Erk2 and of the ACE is increased in patients with AF compared with those in sinus rhythm. This may represent a possible molecular mechanism for the development of atrial fibrosis [18].

Using a canine model, Danshi Li *et al*. have found that dogs with ventricular tachypacing-induced congestive heart failure had a substrate for AF maintenance, with interstitial fibrosis, local atrial conduction slowing and prolonged atrial burst pacing-induced AF. In these animals, atrial angiotensin II (Ang II) concentration and MAPK expression were increased. Treatment with enalapril significantly reduced these tachypacing-induced changes and attenuated the effects of congestive heart failure on atrial conduction, atrial fibrosis and mean AF duration [19].

It has been showed that Ang II stimulates collagen synthesis and reduces collagenase activity in rat cardiac fibroblasts [20, 21]. On the other hand, a recent study has demonstrated that candesartan, but not hydralazine, prevents the progression of atrial fibrosis as well as left ventricle hypertrophy and dysfunction in a hypertensive rat model induced by chronic inhibition of nitric oxide synthesis [22]. The action of Ang II is mediated by Ang II receptor subtypes 1 and 2 (AT1 and AT2). AF, as found by Boldt *et al*., is associated with upregulation of AT1 in the left atrium, but not in the right atrium. Moreover, it does not influence AT2 expression [23].

In another study, in eight dogs with chronic AF induced by creating moderate mitral regurgitation and rapidly pacing the right atrium, a combination of electrical and structural remodelling increased vulnerability to AF induction [24].

Nakashima *et al*. examined the inhibitory effects of an AT1 receptor antagonist, candesartan, and an ACE-I, captopril, on the atrial electrical remodelling induced by rapid pacing in 24 dogs. The atrial effective refractory period (AERP) was measured before, during and after rapid atrial

pacing. The infusion of saline, candesartan, captopril or Ang II was initiated 30 min before rapid pacing and continued throughout the study. In the saline and Ang II groups, AERP was significantly shortened during rapid atrial pacing and the rate adaptation of the AERP was lost; in contrast, in the candesartan and captopril groups, shortening of the AERP after rapid pacing was completely inhibited and the rate adaptation of the AERP was preserved [25].

These studies indicate that endogenous Ang II may be involved in the mechanism of atrial electrical remodelling and that drugs able to block its action may lead to better therapeutic management of human AF.

Zukav *et al*. recently investigated the effects of Ang II on the slow component of delayed rectifier K+ current (IKs) and action potentials in guinea pig atrial myocyte and found that both application of Ang II, or of the stable analogue Sar1-Ang, increased the amplitude of IKs concentration dependently. The enhancement of IKs was blocked by the AT1 receptor antagonist valsartan. Moreover, Sar1-Ang II markedly shortened the action potential duration, which could be reversed by valsartan [26].

This enhancement of IKs via AT1 stimulation in atrial myocyte and the consequent shortening of the action potential duration represent a potential mechanism by which elevated levels of Ang II may promote AF.

RAS gene polymorphism and atrial fibrillation

On 2002 Ogimoto *et al*. investigated the relation between AF and the RAS in hypertrophic cardiomyopathy (HCM). They genotyped the insertion/deletion (I/D) polymorphism of the ACE gene in 138 patients (26 with AF, 112 with sinus rhythm). The distribution of the ACE genotypes (DD, ID and II) was 15, 46 and 38%, respectively. AF was documented in three patients with the DD genotype, seven with the ID genotype and 16 with the II genotype ($P < 0.03$ *vs.* sinus rhythm group). The odds of AF were 3.2-fold greater in patients with the II genotype than in those with the other genotypes [$P = 0.009$, 95% confidence interval (CI) 1.3, 7.8]. These findings suggested that the II genotype of the ACE gene was a significant risk factor for AF in patients with HCM; the DD genotype seemed less important [27].

Instead, 1 year later, Gensini *et al*. compared 148 patients with persistent AF with 210 control subjects and showed that ACE DD genotype was significantly associated with the risk of AF [28]. The difference between these two studies was probably due to the different examined populations. In 2004, Tsai *et al*. conducted a genetic case–control study (250 patients, 250 controls) to demonstrate that RAS genes are susceptibility genes of nonfamilial structural AF. The ACE gene I/D polymorphism, the T174M, M235T, G-6A, A-20C, G-152A and G-217A polymorphisms of the angiotensinogen gene and the A1166C polymorphism of the angiotensin II type I receptor gene were genotyped. In multilocus haplotype analysis, the angiotensinogen gene haplotype profile was significantly different between cases and controls (262.5, $P < 0.0002$). In single-locus analysis, M235T, G-6A and G-217A were significantly associated with AF. Frequencies of the M235, G-6 and G-217 alleles were significantly higher in cases than in controls ($P < 0.000$, 0.005 and 0.002, respectively) [29].

To investigate whether the response to antiarrhythmic drug (AAD) therapy in patients with AF is modulated by the ACE I/D polymorphism, Darbar *et al*. recently studied 213 patients prospectively enrolled in the Vanderbilt AF Registry. AAD therapy outcome was defined prospectively as response if ≥75% reduction in symptomatic AF burden or nonresponse if AF burden was unchanged, necessitating a change in drugs or therapy. Lone AF was present in 72 patients, whereas hypertension was the commonest underlying disease in the remaining 141. The frequencies of the DD, ID and II genotypes were in equilibrium. Lone AF and DD/ID genotypes were highly significant predictors of failure of drug therapy ($P < 0.005$). In fact, in patients with lone AF, failure of drug response was 5, 41 and 47% in patients with II, ID and DD genotypes, respectively ($P < 0.005$, II *vs*. ID/DD) [30].

These studies demonstrate the association of RAS gene polymorphisms with AF and may provide the rationale to investigate the use of ACE-I or angiotensin II antagonist in the treatment of structural AF.

ACE-Is and ARBs: clinical evidences in atrial fibrillation

Thanks to the growing experimental evidence demonstrating the impact of Ang II on atrial myocardium, several studies have been published on the possible therapeutic effect of ACE-Is and ARBs in patients with AF.

Retrospective subanalysis of the SOLVD trials has shown the association of AF with all-cause mortality and progressive pump failure in patients with symptomatic and asymptomatic left ventricle dysfunction [31] and that treatment with the ACE-I enalapril significantly reduces (as much as 78%) the risk of development of AF in this population [32].

Pedersen *et al*. investigated the effect of ACE inhibition on the incidence of AF in patients with reduced left ventricular function secondary to acute myocardial infarction and in sinus rhythm (TRACE study). Patients were randomized to treatment with the ACE-I trandolapril or placebo and were followed up for 2–4 years: new-onset AF was reduced by 45% in the trandolapril group [33].

In the CAPP and the STOP-2 trials, ACE-Is were administered to hypertensive patients. They did not provide any significant benefit over conventional antihypertensive treatment in the prevention of AF [34, 35]. However, in the

STOP-2 trial patients were receiving more than one antihypertensive drug, with possible pooling effects, and >70% of patients were on β-blockers, which have also been shown to prevent AF.

Wachtell *et al*. analysed data from the LIFE study and showed that, in hypertensive patients with left ventricle hypertrophy, new-onset AF and associated stroke were markedly reduced by losartan treatment compared with atenolol, even if both caused similar blood pressure reduction. Furthermore, patients receiving losartan tended to stay in sinus rhythm longer [36]. These results were consistent with their previous finding that LIFE patients with a history of AF benefited from losartan treatment, with 42% reduction of both composite end-points (cardiovascular mortality, stroke, and myocardial infarction) and cardiovascular mortality and 45% risk reduction for stroke [37]. However, both SOLVD and TRACE were placebo-controlled studies, and probably superior antihypertensive effects of the study drug may have contributed to the lower rate of AF. Wachtell *et al*. with their study not only support this inference, as higher systolic blood pressure was an independent predictor of new-onset AF, but suggest that one antihypertensive treatment with equal blood pressure reduction is more effective than another in reducing new-onset AF [36].

Data from the subanalyses of Val-HeFT demonstrate that AF occurrence worsened the outcome in patients with heart failure and that valsartan on top of prescribed therapy for chronic heart failure (CHF) significantly reduced the incidence of AF by 37% [38].

The CHARM study evaluated the effects of the angiotensin receptor blocker candesartan in a broad spectrum of patients with symptomatic CHF: cardiovascular death or CHF hospitalization and all-cause mortality were the major outcomes, whereas the incidence of new AF was a prespecified secondary outcome. During the median follow-up of 37.7 months, new AF developed in 5.55% of the candesartan group and in 6.74% of the placebo group ($P = 0.039$) [39].

It is important to underline that whereas in the LIFE study heart failure was present in only 16% of hypertensive patients, in the SOLVD, TRACE and Val-HeFT studies all populations were made up of people with left ventricle dysfunction.

In the CHARM study the effectiveness of the ARB candesartan was demonstrated in patients with symptomatic CHF, regardless of the left ventricular ejection fraction.

Madrid *et al*. tested the efficiency of treatment with the ARB irbesartan in maintaining sinus rhythm after cardioversion from persistent AF. Patients were divided into two groups. Group I was treated with amiodarone, group II with amiodarone plus irbesartan. Both groups underwent electrical cardioversion after 3 weeks of amiodarone administration. All patients started amiodarone after at least 3 weeks of anticoagulation with acenocumarol to achieve an International Normalized Ratio of >2. The primary endpoint was the length of time to a first recurrence of AF. On Kaplan–Meier analysis, after 2 months of follow-up, the group treated with irbesartan had fewer recurrences of AF (84.79% *vs.* 63.16%, $P = 0.008$) and had a greater probability of maintaining the sinus rhythm (79.52% *vs.* 55.91%, $P = 0.007$) [40].

Furthermore, in a subsequent study, the combination of irbesartan plus amiodarone decreased the rate of AF recurrence, with a dose-dependent effect, in lone AF patients [41].

Also, 'left atrial stunning', lasting a few weeks after the cardioversion of AF and probably responsible for the increased embolic events after cardioversion, is significantly reduced by pretreatment with irbesartan [42].

Yin *et al*. found that both losartan (ARB) and perindopril (ACE-I) added to a low dose of amiodarone are more effective than amiodarone alone for the prevention of AF recurrence in patients with lone paroxysmal AF [43].

Positive effects have also been shown for enalapril when added to amiodarone for 4 weeks before external cardioversion in patients with persistent AF. It allowed a lower rate of immediate recurrence of AF compared with amiodarone alone and facilitated subsequent long-term maintenance of sinus rhythm after cardioversion [44].

The first meta-analysis, made by Healey *et al*. on a total of 11 studies and published in the *Journal of the American College of Cardiology* in 2004, showed that ACE-Is and ARBs reduced the relative risk of AF by 28% (95% CI 15, 40; $P = 0.0002$) and that the reduction in AF was similar between the two classes of drugs (ACE-Is 28%, ARBs 29%). Moreover, the reduction was greatest in patients with heart failure [45]. The meta-analysis published by Kalus *et al*. to evaluate the effect of suppressing the RAS has showed that the use of an ACE-I or an ARB was associated with a reduction in new-onset AF [odds ratio (OR) 0.51, 95% CI 0.36, 0.72], a lower failure rate of electrical cardioversion of AF (OR 0.47, 95% CI 0.24, 0.92) and a lower rate of recurrence of AF after electrical cardioversion (OR 0.39, 95% CI 0.20, 0.75) [46].

The meta-analysis of Anand *et al*. has also shown similar positive effects: the use of ACE-Is and ARBs had an overall effect of 18% risk reduction in new-onset AF across the trials and 43% risk reduction in patients with CHF [47].

All these data suggest that inhibitors of the RAS may provide benefit across the spectrum of AF, principally in patients with CHF. It is still unclear if these drugs are effective in patients with a healthy heart. In a retrospective study performed by our group, treatment with ACE-Is showed no statistically significant advantage in preventing AF relapses in patients with a normal heart [48]. Moreover, from the reported data it is not clear if ACE-Is and ARBs are equally effective in preventing AF relapse or whether they may act differently in specific settings. In the meta-analysis by Anand, ACE-Is had a greater protective effect than ARBs,

and this finding differed from other meta-analyses, in which the two drugs were equally effective.

A possible answer to this question was expected from the ONTARGET/TRASCEND study, which aimed to demonstrate the non-inferiority of the ARB telmisartan compared with the ACE-I ramipril in preventing cardiovascular morbidity/mortality. The study compared the effectiveness of the two drugs in reducing cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure in patients at risk, as primary composite outcome. The new diagnosis of AF was one of the secondary outcomes [49]. The conclusion of this study, recently published in the *New England Journal of Medicine*, is that telmisartan is not inferior to ramipril in patients with vascular disease or high-risk diabetes. At a median follow-up of 56 months, the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), compared with 1423 patients in the telmisartan group (16.7%; relative risk 1.01; 95% CI 0.94, 1.09). Telmisartan compared with ramipril was associated with lower risk of angio-oedema and cough and higher risk of symptomatic hypotension. The combination of the two drugs is associated with more adverse effects without an increase in benefit. Among secondary outcomes, new AF onset was similar in the telmisartan (6.7%) and in the ramipril groups (6.9%). It shows also for this outcome the non-inferiority of the ARB [50].

If we consider that ARBs are more expensive than ACE-Is, this result of non-inferiority should perhaps lead us to use the former as an alternative to the latter when these are not well tolerated because of cough.

Other clinical trials that will further investigate the relationship between RAS inhibition and AF are the ACTIVE and the GISSI AF [46, 47]. In ACTIVE study, testing new antithrombotic strategies in patients with AF, a nested substudy on 500 patients has been planned to compare irbesartan *vs*. placebo in terms of prevention of AF recurrence [51]. GISSI AF aims to demonstrate that valsartan 320 mg is superior to placebo in reducing AF recurrence when administered to patients with a history of recent AF and already treated with the best recommended therapies [52].

Conclusion

According to all these experimental data, we can postulate that the possible mechanisms by which the RAS is involved in AF are the following:

1 Induction of atrial fibrosis and structural remodelling by MAPK expression and reduction of collagenase activity;
2 Induction of electrical remodelling by shortening of the AERP and of the action potential duration.

We cannot exclude a haemodynamic benefit and a direct antiarrhythmic effect of ACE-Is and ARBs. Probably, as they block the Ang II, they interfere with structural and electrical remodelling and consequently provide benefits across the prevention of AF relapse. Preliminary results are encouraging; however, meta-analysis should be interpreted with caution and large prospective clinical trials are still needed. It is not possible to recommend the use of ACE-Is and ARBs in routine clinical practice specifically for prevention of AF. However, we believe that as these drugs are safe and manageable, they should be considered the drugs of choice in patients with AF and coexisting clinical conditions such as hypertension, coronary disease, heart failure and diabetes mellitus.

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