Atrial fibrillation and renin–angiotensin–aldosterone system: believe it or not

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This editorial refers to ‘Association between angiotensin-converting enzyme insertion/deletion gene polymorphism and atrial fibrillation: a meta-analysis’ T. Liu et al., on page 346.

There is compelling evidence that the renin–angiotensin–aldosterone system (RAAS) is involved in the pathogenesis of atrial fibrillation (AF). Currently, it is recognized that there is a sustained reduction in new-onset AF in patients with significant underlying heart disease (e.g. left ventricular dysfunction and hypertrophy) treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), but evidence is less convincing in patients with moderate structural heart disease and recurrent AF.1–3 Negative results have recently been reported in two large prospective studies with ARBs in patients with mild structural disease and this clearly raises the issue that these therapies may not offer the same benefit in all patients.4,5 Some probably assumed that since an ARB did not reduce the number of AF episodes in patients with paroxysmal AF without structural heart disease in the Angiotensin II Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) study, RAAS blockade was not really effective in treating AF in general.

Let us go back to basics. There is experimental evidence of anti-fibrillatory and anti-fibrotic effects of ACEIs and ARBs in various AF models. Their potential mechanisms of action include haemodynamic, antiproliferative, anti-inflammatory, and antioxidant effects that may prevent the development of left atrial stretch and enlargement, interstitial fibrosis, and adverse atrial electrical remodelling, which is manifested by shortened duration of the action potential, abnormalities of intracellular calcium handling, and alteration in cell-to-cell conduction.6,7 RAAS activation particularly increases the risk of developing AF by aggravating atrial remodelling in the setting of structural heart disease. Consequently, once AF has developed, RAAS activation in the fibrillating atria perpetuates AF. Angiotensin II also contributes to arrhythmogenesis by modulation of ion channels and gap junctions, suggesting that blocking the RAAS may offer an incremental benefit in patients with AF beyond the therapeutic effects on hypertension and heart failure.

The ACE I/D polymorphism accounts for approximately half the observed variance in ACE levels. Mean ACE activity levels in DD carriers are approximately twice those found in II genotype individuals while subjects with the ID genotype have intermediate levels. This directly influences the effect of ACEIs and ARBs, and patients with a D allele often respond differently to these agents compared with those without a D allele.8 Although reports on most of the cardiovascular phenotypes are still controversial, ACE I/D polymorphism represents a target for association studies and/or for pharmacogenomics in AF.9,10 However, previous studies have shown inconsistent results.

Liu et al.11 conducted a comprehensive meta-analysis of all available data regarding the association between ACE I/D gene polymorphism and AF risk. They found that the ACE I/D polymorphism recessive mutation (DD genotype vs. ID and II genotypes) was associated with increased risk of AF. A significant heterogeneity was evident between the individual studies with different models and conditions. In such circumstances, determination of the reasons for heterogeneity rather than a single conclusion is really a key point in a meta-analysis. Subgroup analyses were performed for populations of different ethnicity, comorbidities (i.e. lone AF, AF with hypertension, AF with heart failure), and sources of controls to investigate the possible origin of heterogeneity. The authors have to be congratulated for this work. They found a significant association between ACE I/D polymorphism and AF in association with hypertension (odds ratio 2.3) without significant heterogeneity. Ethnicity did not influence the overall results, and the findings in hypertensive patients were obtained homogeneously in East Asian and Caucasian patients.

Why would ACE I/D polymorphism increase the risk of developing AF in hypertension and apparently not in other condition, while at the same time RAAS blockade appears to be the most efficient in preventing new onset AF in heart failure and not in hypertension?12 Hypertension is a condition in which the incidence of AF is relatively low (4% during follow-up in clinical trials) compared...
with other populations (ranging from 7% in new onset AF for heart failure or post-myocardial infarction patients to 49% in secondary prevention of AF episodes). It is possible that the DD genotype only plays a role in the presence of a condition associated with a low or intermediate risk of AF. It may have a less important role in patients a priori prone to AF, with significant mechanical or electrical remodelling. In circumstances when the ACE I/D polymorphism is a major determinant, one would expect a higher percentage of patients with AF to have a DD genotype, particularly those with lone AF, but this was not the case. This clearly suggests the association rather than the cause of AF. In hypertensive patients, the reason for increased risk of AF may be a modulating effect of the ACE I/D polymorphism on a otherwise moderate left atrial remodelling secondary to hypertension. It is possible that the DD genotype amplifies the degree of remodelling induced by hypertension (including possible conduction disturbances) to a significant level, leading to sustained AF, which in turn creates a vicious circle.12

The fact that ARBs sometimes failed to prevent AF has been explained by a possible role of target and timing.13 Patients with normal heart are unlikely to benefit from RAAS inhibition. It is also likely to be true in patients with long-standing AF and stabilised substrate, particularly if duration of treatment with RAAS inhibitors is short. The work by Liu et al. suggests that individuals with II or ID genotypes (with the lowest or intermediate ACE levels) may be relatively protected against AF compared with DD genotypes, particularly in the presence of hypertension. Whether RAAS blockade may prevent AF and AF-related events more efficiently in patients with low, intermediate, or high levels of ACE has to be determined.

As for any other treatment when one analyses its possible benefit in AF, one should probably not limit the evaluation of RAAS inhibition for the reduction of the occurrence of AF episodes, but also its effect on AF-related events and hard clinical endpoints. In addition, angiotensin II plays an important pathophysiological role in prothrombotic endocardial remodeling in AF and this can be attenuated by ARBs.14 This benefit, if clinically relevant, will certainly not appear in any rhythm analysis or AF burden quantification. Neither the Valsartan Anti-hypertensive Long-term Use Evaluation (VALUE) nor the Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza cardiaca Atriale Fibrillazione (GISSI-AF) study has shown an improved outcome withARB-based therapy in AF patients. However, data from the Losartan Intervention for Endpoint reduction in hypertension (LIFE) trial and first results from Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-I) indicate that RAAS blockade reduces cardiovascular morbidity and mortality in patients with persistent AF.3 RAAS inhibition may therefore be effective across the continuum of AF, from prevention of AF to reducing many of its consequences in patients in whom sinus rhythm can no longer be restored.

There are reasonably convincing data from clinical trials, indicating that RAAS blockade is effective for the primary prevention of AF in some patients, while several other studies failed to show any benefit for ARBs in preventing recurrences of paroxysmal AF or evolution to more sustained forms of AF. ACE I/D polymorphism may significantly favour AF under certain circumstances and may then modulate the response to ACEIs and ARBs. This may explain why some, but not all, patients respond favourably to these agents. The study by Liu et al. indirectly suggests that therapy, guided by genetic variations, may eventually improve both the rhythm control treatment and general outcome in AF.

**Conflict of interest:** none declared.

**References**