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EDITORIAL

Renin–angiotensin blockade in atrial fibrillation: where are we now?

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Atrial fibrillation (AF) is associated with a fivefold increase in the risk of stroke, with AF-related stroke patients having a higher mortality and greater morbidity than patients with non-AF-related stroke.[1] Between 14–17 million patients will be diagnosed with this most prevalent arrhythmia within the European Union by 2030. The use of oral anticoagulant therapy, whether with the vitamin K antagonists (for example, warfarin) or more recently, the non-VKA oral anticoagulants, results in a marked reduction in stroke and all-cause mortality.[2,3] At present, a focus on preventing AF-related stroke is the mainstay of medical management. However, prevention of AF occurrence and reduction of AF burden at the population level offers major advantages for both reduction of health care cost, longevity and quality of life.

Activation of the renin–angiotensin system (RAS) is closely linked to the development of AF, especially in hypertensive patients.[4] It promotes fibrotic changes in the atria, which subsequently leads to the pro-arrhythmogenic electrophysiological abnormalities. This favours the onset and perpetuation of AF.[5] Multiple mechanisms have been identified to mediate the activation of RAS and initiation of AF.[4] For example, angiotensin II activates the profibrotic pathways by the triggering differentiation of atrial fibroblasts into myofibroblasts that have an adverse effect on atrial remodelling. The subsequent release of proinflammatory cytokines, such as transforming growth factor β-1, modulates the electrical properties of atrial myocytes.[6] Also, by blocking the action of angiotensin II, angiotensin-converting enzyme inhibitors reduce cardiac sympathetic activity, a contributor to AF development.[4] Of note, recent studies have found a lower incidence of AF in hypertensive patients receiving RAS inhibitors compared to controls.[5,7]

A causative role for aldosterone in the pathogenesis of AF is supported by findings from large retrospective cohort studies in patients with primary aldosteronism who were compared to matched patients with essential hypertension.[8] The mechanisms behind the increased risk of AF in subjects with high aldosterone production is multifactorial. The process of left atrial dilatation, along with enhanced deposition of the extracellular matrix all conform to the end results of myocardial fibrosis.[9] This manifests itself clinically as diastolic dysfunction, left ventricular hypertrophy and eventual remodelling of the left ventricle.[10]

In theory, all anti-hypertensive medications may be effective in reducing the incidence of AF by preventing diastolic dysfunction, atrial dilatation and to some extent fibrosis. Nonetheless, there have been conflicting results as to whether RAS blockade provides superior efficacy in this regard, with a meta-analysis showing a 28% relative risk reduction in preventing AF.[11] The Losartan Intervention For End Point Reduction in Hypertension study which compared the efficacy of losartan to atenolol in 8300 hypertensive patients, found a marked reduction of new-onset AF in the losartan group (6.8 vs 10.1 per 1000 person-years, relative risk 0.67, 95% confidence interval 0.55–0.83, $P < 0.001$) despite similar reductions in blood pressure.[5] Benefits of losartan in this cohort may be due to the more favourable effect on atrial remodelling, both due to improved haemodynamics and inhibition of collagen deposition, thereby reducing the stimuli for onset AF. However, similar rates of AF occurrence were observed in the ACEI and conventional therapy arms in the Captopril Prevention Project and the Swedish Trial in Old Patients with Hypertension.[12,13] The differences in study findings may be explained by the fact that the Losartan Intervention For End Point Reduction in Hypertension study enrolled patients with left ventricular hypertrophy, which in itself has a strong association with increased left atrial size and likely more cardiac fibrosis. However, methodology of AF recording could also affect how complete these data were, a particularly important issue given that AF is often 'silent'.

In this issue of the *Journal of Human Hypertension,* Takeshi *et al.*[14] present results of an observational study aiming to provide further insight into the potential benefits of RAS blockade in the prevention of new-onset AF in hypertensive subjects. A total of 964 eligible patients were enrolled in the study and observed for over 4-year medium duration. Only patients taking an angiotensin-converting enzyme inhibitor or angiotensin receptor

Table 1. Summary of randomised control trials in the use of RAS blockade in the primary prevention of AF

Study	*Population*	*Follow-up*	*ACEI/ARB*	*Control group*	*Outcome*
CAPP[12]	10,915	73	Captopril	Dieuretic, β blocker	No significant difference between intervention and control group
STOP-H2[13]	6303	60	Enalapril/Lisinopril	Dieuretic, β blocker	No significant difference between intervention and control group
LIFE[5]	8480	57	Losartan	Atenolol	Significant reduction in incidence of AF (6.8% vs 10.1% in Losartan vs atenolol group, per 1000 perosn-years, RR 0.67, $P < 0.001$)
HOPE[16]	8335	54	Ramipril	Placebo	No significant difference between rampiril vs placebo in the onset of new AF
VALUE[7]	13,760	50	Valsartan	Amplodopine	Reduced incidence of new-onset AF in valsartan group vs amlodopine (3.67% vs 4.34%, respectively; HR 0.843, $P = 0.0046$)
TRASCEND[15]	5701	56	Telmisartan	Placebo	No significant difference between the two trial arms ($P = 0.829$)

Abbreviations: CAPP, Captopril Prevention Project; HOPE, Heart Outcomes Prevention Evaluation study; LIFE, The Losartan Intervention For End Point Reduction in Hypertension; STOP-H2, Swedish Trial in Old Patients with Hypertension; TRASCEND, Telmisartan Randomised Assessment Study in Angiotensin converting Enzyme inhibitor intolerant subjects with Cardiovascular Disease; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

blocker though to the end of the study formed the RAS inhibitor group. Along with echocardiography, anthropometric and physical examinations were carried out.

Diagnosis of AF can be challenging with many cases missed in routine practice. The design of study by Takeshi *et al.*[14] employed measures to improve detection of AF, by clinical pulse assessment every 1–2 months and annual ECG. Although this approach is likely to miss some cases of paroxysmal AF, both branches of the study are likely to be equally affected this preventing any major bias in equality of AF detection in patients with or without RAS inhibition. Detection of new-onset AF was taken as the end point of the study, with no distinction between paroxysmal or persistent AF.

During a mean follow-up of 4.6 years, 49 cases of new-onset AF were detected, with an annual incidence of 1.1%. There was no statistical significance in the incidence of new AF between the RAS inhibit group and control, although rates were lower in the RAS inhibitor group. RAS inhibitors were associated with a lower incidence of AF upon multivariable analysis, with an adjusted hazard ratio of 0.52 (95% confidence interval 0.29–0.93, $P = 0.027$). To account for the marked differences in medical background between the RAS inhibit population and control group, propensity matched analysis was undertaken and showed a lower cumulative incidence of new AF in the RAS inhibitor group. Admittedly, despite almost twice higher occurrence of AF in the non-RAS group, the effect was statistically significant, notwithstanding the small population of the censored analysis and large spread of the confidence interval.

To date, there have only been six randomised control trials comparing the benefits of RAS blockade for the development of new AF (Table 1).[5,7,12,13,15,16] Other evidence in this field has been compiled from observational studies in hypertensive patients. Despite encouraging data to suggest a benefit in the primary prevention of AF in patients with RAS inhibitors, the fact that such studies are non-randomised, and observational with variable risk factor profiles between study groups makes it difficult to draw definitive conclusions.[17,18]

Aldosterone inhibitors, such spironolactone, are also widely used for inhibition of the renin–angiotensin-aldosterone axis, but their use was not considered in the analysis by Takeshi *et al.*[14] To better understand the mechanisms and therapeutic options in patients who already have AF, the IMPRESS-AF (IMproved exercise tolerance in patients with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in AF) trial is currently underway.[19] This prospective randomised trial tests the effectiveness of spironolactone to improve cardiac diastolic function along with exercised tolerance and quality of life. The trial utilises antifibrotic properties of spironolactone with a potential to reduce aldosterone-induced cardiac fibrosis and subsequent adverse cardiac remodelling.[19] Clearly, further adequately designed and powered randomised controlled trials with clinical outcomes are essential to firmly establish the capacity of RAS inhibitors to prevent AF.

CONFLICT OF INTEREST

GYHL is the consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. The remaining authors declare no conflict of interest.

F Shahid[1], GYH Lip[1,2] and E Shantsila[1]
[1]*University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK and*
[2]*Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*
E-mail: shantsila@gmail.com

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