Do non-antiarrhythmic drugs have enough pleiotropic power to reduce atrial fibrillation?

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This editorial refers to ‘The impact of statins and renin–angiotensin–aldosterone system blockers on pulmonary vein antrum isolation outcomes in post-menopausal females’ by D. Patel et al., on page 322.

Epidemiological studies have identified several differences in atrial fibrillation (AF) between men and women. Men are more prone to AF at a younger age, probably due to larger left atria. On the other hand, women are more commonly symptomatic, have a higher risk of stroke, and much more frequently suffer from diastolic heart failure than men. Despite being more frequently symptomatic with AF, women are less likely to undergo rhythm control.1,2 Gender differences concerning the response to drug treatment between men and women with AF are not frequently reported. The study by Patel et al.3 describes the effects of therapy with statins and renin–angiotensin–aldosterone system (RAAS) antagonists for secondary AF prevention after pulmonary vein isolation (PVI) in postmenopausal women. This observational multicentre study included 372 women: 111 (30%) on statins, 59 (16%) on a RAAS blocker, and 202 (54%) not using these drugs. Patients who received both agents were excluded. Persistent AF was present in 28% of patients and another 28% had long-lasting persistent AF. C-reactive protein levels were measured before and 48 h after the procedure. There was no protective effect of therapy with statins or RAAS blockers after a follow-up of 24 ± 8 months. Of note, C-reactive protein levels did not predict recurrences after PVI.

The RAAS plays an important role in structural and electrical atrial remodelling. Angiotensin II (AT-II) increases the afterload leading to atrial dilation. In addition, AT-II stimulates collagen synthesis via direct cardiac intracellular pathways, thereby increasing heterogeneity of conduction.4 Angiotensin-receptor blockers reduce cardiac fibrosis and make the atria less vulnerable to AF. Apart from promoting the arrhythogenic substrate, AT-II also increases electrical remodelling by shortening of the atrial refractory period. Thus, RAAS inhibition may prevent shortening of the refractory period, suggesting that these drugs may protect against electrical remodelling and AF.5 Theoretically, statins may prevent AF by their anti-inflammatory effects, since inflammation promotes atrial collagen deposition and reduces overall cardiac function. Other effects include a reduction in endothelial dysfunction (prevention of ischaemia), oxidative stress (prevention of left ventricular hypertrophy and fibrosis), and modulation of neurohumoral activation.6,7

Renin–angiotensin–aldosterone system inhibitors and statins may protect from AF if the atrial substrate is in transition due to transient metabolic or inflammatory damage like early after cardioversion to sinus rhythm from persistent AF or early after coronary artery bypass surgery.7,8 In this respect, it is tempting to speculate that these non-antiarrhythmic drugs effectively prevent AF recurrences during the so-called blanking period after ablation. Unfortunately, these data remained ‘blanked’ in the present report. Also, the literature suggests that RAAS inhibitors may prevent AF when the substrate for AF still has to be formed, e.g., early after myocardial infarction or in the setting of heart failure or recently detected hypertension. The present study did not, however, find any relationship between the stage of atrial remodelling, e.g., represented by duration of AF history or right and left atrial sizes, and the efficacy of upstream therapy. It is uncertain whether these potential relationships were investigated, but if true it would lend support to the above notions.

It seems unlikely that statins and RAAS inhibitors may have any beneficial effect after PVI—also not in postmenopausal women—for several reasons. First, AF is frequently driven by atrial trigger beats from within the pulmonary veins which may be eliminated by PVI.9 However, it is doubtful whether intervention with statins and RAAS blockers may reduce atrial ectopy, e.g., residual ectopy after successful ablation. It is also uncertain whether these agents would improve scar formation after ablation, thereby preventing re-connection. Although RAAS inhibitors and statins may reduce fibrosis, it remains unproven whether they reduce the critical substrate responsible for maintaining AF. Therefore, it would be interesting to study whether these drugs may prevent progression from paroxysmal to persistent AF, as the
latter may be more substrate-driven. Only if this were the case, these drugs would become ‘pre-procedural augmenting agents’. Similarly, it would be interesting to know whether these drugs could prevent iatrogenic post-ablation macro-reentrant left atrial flutter.9

Secondly, the population included in the present study was a mixture of patients with variable stages of structural and electrical remodelling. Showing the benefit of an intervention aimed at ameliorating atrial remodelling obviously becomes difficult for significant dilution of the effect of the intervention since there is lack of the intended effect in some (e.g. patients with advanced remodelling) and the absence of the need for the intervention in others (e.g. patients with lone AF).

Thirdly, the observational nature of the study led to the inclusion of patients who suffered from AF despite treatment with a statin or a RAAS blocker. It seems reasonable to assume that since this drug did not prevent AF before ablation (making ablation necessary), it will not be able to prevent AF after ablation. This negative selection bias may, theoretically, have filtered out the patients in whom these drugs would have prevented or reduced AF.

Fourthly, one might speculate that statins and RAAS inhibitors may actually increase the recurrence rate after PVI since they reduce active scar formation by ameliorating inflammation. This may enhance re-conduction from the pulmonary veins to the left atrium or over ablation lines.

C-reactive protein is never helpful in predicting short-term clinical results in small cohort studies. The notion that catheter ablation would be associated with ‘massive’ inflammation is not mirrored by vast increases in C-reactive protein levels which then could be prevented by ‘higher’ dosages of statins, as the authors suggest. In our opinion, it seems as if ablationists mix up the clinical use of C-reactive protein level measurement as a monitor for acute inflammatory disease with the epidemiological tool to identify cohorts with increased risk of inflammation related to vascular disease. Hence, it was not very surprising that baseline C-reactive protein levels neither correlated with outcome of ablation, nor that the change in C-reactive protein levels after ablation would predict this outcome. In addition, using post-ablation C-reactive protein levels to predict long-term outcome is not clinically appealing. If anything, there is a need to select ablation non-responders before ablation rather than after. However, C-reactive protein levels were at least lower in the statin users, and in non-users they increased after the ablation which did not happen in statin users.

The absence of pleiotropic effects on AF-related outcomes in this—and many previous—studies relates to the fact that the atrial damage leading to AF has already occurred long before treatment with statins or RAAS blockers has been started. This is also recognized by the authors of the present report. Unfortunately, statins and RAAS blockers do not have enough ‘pleiotropic power’ to reverse atrial remodelling. Upstream therapy to prevent development of AF substrate cannot be started early enough. The big difficulty is finding the patients prone to developing the AF substrate on time. Screening of high AF risk populations may be the way to go, but has not been tested, especially not since the parameters indicating susceptibility to AF have not been identified.

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References


