The Impact of Statins and Renin–Angiotensin–Aldosterone System Inhibitors on Preventing Atrial Fibrillation Recurrence after Pulmonary Vein Isolation

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ABSTRACT. Pulmonary vein isolation is an effective treatment for atrial fibrillation. However, some patients have recurrences. Upstream therapies such as statins and renin–angiotensin–aldosterone system inhibitors have been suggested to improve procedural success rates. All studies have shown that statins are not effective in preventing recurrences. Some studies report that renin–angiotensin–aldosterone inhibitors may positively impact recurrence rates.

KEYWORDS. angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, pulmonary vein isolation, renin–angiotensin–aldosterone system inhibitors, statins.

Introduction
Pulmonary vein isolation (PVI) is considered to be safe and effective treatment for atrial fibrillation (AF); however, some patients still have recurrences of AF, atrial flutter, and left atrial tachycardia. Atrial arrhythmias within the first 3 months (blanking period) after ablation are not considered relapses. These recurrences are prevalent and transient; nevertheless, some patients may be symptomatic. Early recurrences of AF most likely occur secondary to inflammation and oxidative stress caused by radiofrequency delivery.\(^1,2\)

Many patients are kept on antiarrhythmics post ablation. Antiarrhythmic agents have little effect on underlying causes of early recurrences. Therefore, statins and inhibitors of the renin–angiotensin–aldosterone system (RAAS) are of particular interest. They have anti-inflammatory and antioxidant effects, so theoretically should target the substrate. In this article, we review the potential mechanisms of statins and RAAS inhibitors for the prevention of AF and the clinical evidence for the use of these agents in patients after PVI.

Potential mechanisms of statins in the prevention of AF
AF can occur due to a decreased nitric oxide synthase (NOS) and atrial nitric oxide (NO) bioavailability. Treatment with statins increase endothelial NO production by stimulating and upregulating endothelial NOS. Increased endothelial NOS is associated with better cardiac perfusion, which may prevent AF.\(^3\)\(^-\)\(^5\) Inflammation is often the culprit in the initiation and perpetuation of AF. C-reactive protein (CRP) levels, a marker for inflammation, are often elevated in patients with AF.\(^6\)\(^,\)\(^7\) Treatment with atorvastatin in a canine sterile pericarditis model reduced AF duration and CRP levels.\(^8\) Statins are anti-inflammatory agents because they reduce the number of inflammatory cells and inhibit adhesion molecules. Statins also reduce the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-1 and IL-6.\(^9\)\(^,\)\(^10\)

The authors report no conflicts of interest for the published content. Manuscript received June 28, 2012, Final version accepted October 30, 2012.

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Oxidative stress has been shown to be involved in the initiation and perpetuation of AF. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase induces the production of superoxides in the right atrium and can result in AF. Statins inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase, thus preventing the isoprenylation of Rac1 and reducing reactive oxidative species produced by NADPH oxidases. The risk of AF increases with neurohormonal activation. Atrial fibrosis and hypertrophy can be prevented by blocking angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Statins can decrease angiotensin type I receptors and improve the efficacy of angiotensin receptor blockers (Figure 1).

Potential mechanism of RAAS in the prevention of AF

RAAS is involved in cardiac structural remodeling and fibrosis in patients with congestive heart failure, myocardial infarction, and cardiomyopathy. Angiotensin II stimulates mitogen-activated protein kinases and reduction in collagenase activity, which result in cardiac fibrosis formation. Additionally, angiotensin II binds to angiotensin II type I receptors, which stimulate transforming growth factor (TGF)-β1 production, promoting atrial fibrosis. A dilated left atrium promotes AF by slowing atrial conduction velocity and providing a greater area for re-entry. ACEIs can cause systemic arteriolar dilation and increased large artery compliance that results in a decrease in systolic blood pressure. ACEIs also decrease left atrial pressure and wall stress, which can prevent AF.

Angiotensin II induces the production of reactive oxygen species, inflammatory cytokines, and adhesion molecules. ACEIs reduce CRP TNF-α, and IL-6 in hypertensive patients (Figure 2).

The current literature on the use of statins and RAAS inhibitors for patients undergoing pulmonary vein isolation

Prior treatment with RAAS inhibitors and statins in patients undergoing catheter ablation may impact pre-existing inflammation caused by AF and ablation-related inflammation. Moreover, the treatment with RAAS inhibitors may prevent atrial fibrosis. Subsequently, several studies have been conducted to assess the possibility that statins and RAAS inhibitors can prevent recurrences after catheter ablation by these mechanisms. Treatment with statins and RAAS inhibitors have shown promising results on AF primary prevention. For example, data obtained from the AdvancentSM registry, which included 25,268 patients who had an ejection fraction (EF) of ≤40% and mainly treated with statins, showed there was a 31% reduction in the relative risk of developing AF compared with no therapy (95% CI 0.64–0.74; p<0.001). The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) investigators reported a 28% reduction in relative risk of AF. The TRACE (Trandolapril Cardiac Evaluation) study included patients with recent myocardial infarction and EF ≤35%. Patients who received trandolapril were less

Figure 1: The benefits of statin use on the prevention of atrial fibrillation. AF-atrial fibrillation; enos- endothelial nitric oxide synthases; TNF (alpha)- tumor necrosis factor alpha; NO-nitric oxide, NADPH oxidase- Nicotinamide adenine dinucleotide phosphate oxidase.
likely to develop new-onset AF during the follow-up period than the placebo group (2.8 versus 5.3%; OR, 0.45; 95% CI, 0.26–0.76; p=0.01). Similarly, the SOLVD (Studies of Left Ventricular Dysfunction) trial reported a reduction in AF occurrence in patients with CHF and EF ≤35% with enalapril compared with placebo after 2.9 years of follow-up (5.4% versus 24%; hazard ratio (HR)=0.22; 95% CI 0.11–0.44; p<0.0001). Nonetheless, these promising results have not been consistently duplicated in the prevention of recurrence of AF after catheter ablation.

There have been several retrospective studies that have looked at the impact of RAAS inhibitors on patients post catheter ablation. Ishikawa et al retrospectively studied 264 consecutive patients who underwent PVI for paroxysmal or persistent AF. They found that treatment with RAAS inhibitors significantly lowered AF recurrences after ablation (HR=0.41; 95% CI 0.23–0.71; p=0.002) (follow-up of 195 days). However, the effect of RAAS inhibitors was not significant during the first 3 months. Klemm et al also reported in a matched pair study which included 102 patients that ACEIs and ARBs were effective in maintaining sinus rhythm in those who underwent PVI for paroxysmal AF (HR=0.49; 95% CI 0.32–0.75; p=0.001) (follow-up of median of 2.1 years). Berkowitsch et al reported that in 284 patients RAAS inhibitors appear to prevent AF recurrences after PVI in all populations (112 out of 195 (57%) versus 36 out of 89 (40%); p=0.025), but particularly in those with low burden paroxysmal AF (79 out of 112 (71%) receiving RAAS inhibitors versus 27 out of 55 (49%) being on other drugs; p=0.013). However, RAAS inhibitors failed to prevent recurrences in patients with high-burden AF (33 out of 83 on RAAS inhibitors (40%) versus 9 out of 34 on other drugs (27%); p=0.328). Park et al also studied 152 patients who underwent PVI and were treated with RAAS inhibitors. They reported that ACEIs and ARBs were shown to be effective in preventing AF recurrences after catheter ablation in patients with persistent AF (12.1% versus 61.1%, p<0.01). Patients with paroxysmal AF did not benefit from treatment with RAAS inhibitors (24.2% versus 22.9%; p=0.87) (follow-up of 18±14 months). All other studies that assessed the impact of RAAS inhibitors on recurrence rates after catheter ablation demonstrated no benefit (Table 1).

Al Chekaki et al conducted a retrospective study of 177 consecutive patients who underwent PVI and were followed for 13.8±8.6 months. Treatment with statins did not decrease the recurrence rate (HR=1.10; 95% CI 0.55–2.27; p=0.79); neither did treatment with RAAS inhibitors (HR=0.94; 95% CI 0.46–1.93; p=0.87). A subgroup analysis showed that treatment with ARB was associated with a trend towards lower AF recurrence (HR 0.17; 95% CI 0.02–1.34; p=0.09). Interestingly, Taybje et al also found fewer recurrences of AF in patients treated with ARBs than those with no treatment (61.9% versus 77.6%; p=0.021) (follow-up of median 1.7 years) but this effect was lost after multivariate adjustments.

Richter et al studied 234 patients who underwent PVI. Treatment with statins (HR=1.06; p=0.79; ACEI or ARB HR=1.12; p=0.59), and their combined use (statin+ACEI/ARB; HR=1.17; p=0.54) (follow-up of median 12.7 months) did not significantly influence ablation outcome. Patel et al demonstrated in 372 postmenopausal women with paroxysmal or persistent AF undergoing PVI, that therapy with statins and ARBs/ACEIs failed to prevent both early and late AF recurrences.
recurrence during a median follow-up of 2.1 years. Statin or RAAS inhibitor use did not predict lower recurrence rates (HR = 1.26, p = 0.282; and HR = 1.14, p = 0.728, respectively).

More recently, a double blind, placebo-controlled, randomized trial evaluated the efficacy of statins in preventing AF recurrence following left atrial ablation in patients with no standard indication for statin therapy. One hundred and twenty-five patients undergoing catheter ablation for AF were randomized to receive atorvastatin or placebo for 3 months. The primary endpoint was freedom from symptomatic AF and secondary endpoints included freedom from any atrial arrhythmia recurrence irrespective of symptoms, quality of life, and reduction in CRP. Despite significant reductions in low-density lipoprotein cholesterol and CRP levels, atorvastatin failed to demonstrate reduction in AF recurrence (95% of patients in the atorvastatin group were free of symptomatic AF compared with 93.5%).

**Conclusions**

All the studies that have assessed the benefit of statins and RAAS inhibitors on AF recurrence after catheter ablation have had limitations. The most obvious limitation is that all but one of them were retrospective in nature and thus are subject to selection bias. Patients that were enrolled in these studies had no major cardiac structural disease; however, the group of patients on the statins/RAAS inhibitors were sicker and thereby, were more likely to have recurrences of AF. The differences in baseline characteristics in non-randomized studies are often too significant to assess the true effect of the treatment even with multivariate adjustments. Additionally, in most of these studies different types of statins and RAAS inhibitors were used and there was little homogeneity in terms of dosage.

All studies demonstrated that the anti-inflammatory benefits of statins are not substantial enough to counteract the inflammation secondary to radiofrequency
delivery, therefore, should not be prescribed clinically unless indicated for other use. Whether to use RAAS inhibitors for AF recurrence prevention is still up for debate because the data is conflicting. Larger randomized prospective studies are needed to conclusively answer that question. Therefore, at this juncture it is better not to use RAAS inhibitors solely for the prevention of recurrence of AF in light of the possible side effects of these medications.

References

