Statins, Inflammation, Oxidative Stress, and Atrial Fibrillation

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Editorial Comment

In this issue of the Journal, Negi et al.1 reported their study investigating whether or not high-dose atorvastatin could reduce atrial fibrillation (AF) recurrence after electrical cardioversion (EC) by modifying systemic oxidative stress and inflammation. They concluded that while high-dose atorvastatin could reduce selective markers of inflammation, it did not affect systemic oxidative stress and did not prevent the recurrence of AF post-EC. Ironically, the “SToP AF trial” of Negi et al.1 failed to stop AF recurrence! Their results may not be surprising because the AF guideline from the European Society of Cardiology recommends that upstream therapies with statins are not recommended for primary prevention of AF in patients without cardiovascular disease.2 Rather, statin therapy should be considered for prevention of new-onset AF after coronary artery bypass grafting, isolated or in combination with valvular interventions, and patients with underlying heart disease, particularly heart failure.2

AF is the most frequently encountered arrhythmia occurring in 1-2% of the general population; it can increase the risk of stroke, thromboembolic events, heart failure, rates of death, and is an independent predictor of mortality.2 Antiarrhythmic drugs plus anticoagulation treatment is currently the first-line therapy in patients with symptomatic AF. However, current pharmacological treatments have limited therapeutic efficacy. Radiofrequency atrial ablation is often adopted with high success rate in patients with AF to restore their sinus rhythm.3 Recently, attentions have been paid to the upstream therapy including statins, because systemic and cardiac inflammation and related oxidative stress are associated with the initiation and maintenance of some forms of AF.4

Since statins have both antioxidant and antiinflammatory properties, several studies have been conducted to test their efficacy in the treatment and prevention of AF. Unfortunately, the results are conflicting and confusing. In a retrospective study, the use of simvastatin or atorvastatin was shown to be associated with a significant decrease in the risk of arrhythmia recurrence after successful EC in patients with lone AF.5 Atorvastatin has been demonstrated to significantly decrease the recurrence rate of AF after successful EC,6 and statin therapy can have benefits on the recurrence rates of AF after EC in patients with a significant prevalence of coronary artery disease.7 Furthermore, there is some evidence of a beneficial effect of rosuvastatin in terms of the reduction in AF occurrence in patients with chronic heart failure.8 However, negative results have also been reported. For instance, pravastatin or atorvastatin have not been shown to reduce the recurrence rate of AF after EC9 or maintain sinus rhythm 1 month after EC.10 The study of Negi et al.1 demonstrated again that high-dose atorvastatin did not prevent the recurrence of AF post-EC. Thus, whether or not statins can protect against AF and reduce the recurrence rate of AF remains to be settled. A more detailed clinical study with careful design and larger populations is warranted to provide a conclusive answer to this question.

It has been demonstrated that patients with AF have elevated levels of inflammatory markers such as C-reactive protein (CRP),11 interleukin-6 (IL-6),12 and tumor necrosis factor α (TNF-α), and the CRP has been shown to be a marker of AF persistence, AF recurrence after EC, and postoperative occurrence of AF.13 If statins do have potent antiinflammatory properties,14 they should be useful in the prevention and reversal of AF. However, the study of Negi et al. failed to confirm this conjecture, since the levels of IL-6 and high sensitivity CRP were significantly lowered by high-dose atorvastatin, supporting the antiinflammatory properties of statins.14,15 but the effects on AF were not altered. Thus, whether or not inflammation plays a role in the initiation and maintenance of AF remains to be determined.

Carnes et al.16 hypothesized that increased oxidative stress may underlie both postoperative AF and the electrophysiological remodeling associated with rapid atrial pacing. They showed that ascorbate can attenuate atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative AF.17 Subsequent data using cDNA microarray showed that the gene expression profiles of atrial tissue from AF patients are associated with increased oxidative stress, and that the intracellular mechanism of oxidative stress plays a pivotal role in the pathologic progression of AF and offers novel insight into potential treatment with antioxidants.17 Since statins also have antioxidant properties,18,19 they were tried in the treatment and prevention of AF. Unfortunately, the study of Negi et al. demonstrated that high-dose atorvastatin did not affect the systemic oxidative stress in patients with AF recurrence after EC, in contradiction to the results of Delbosc et al.18 and Briones et al.19 Whether or not statins have antioxidant properties in the treatment of AF recurrence after EC remains controversial. Though the “SToP AF trial” of Negi et al.1 failed to stop AF recurrence, their study seemed to suggest that the suppression of systemic oxidative stress might be the key mechanism for the successful prevention of AF recurrence post-EC.

The answers to some questions in science inevitably cause researchers to identify new puzzles that await elucidation from further studies. The study of Negi et al.1 is not an exception to this rule. Thus, the disclosure of the aforementioned conflicting results1 is paving the way to a better
understanding about the interplay among statins, inflammation, and oxidative stress in the pathogenesis of AF.

References