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EDITORIAL COMMENT

Mineralocorticoid Receptor Antagonism for the Treatment of AF and HFpEF

Preserving Hope*

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Atrial fibrillation (AF) and heart failure (HF) are overlapping epidemics. The burden of both conditions is increasing over time. Moreover, patients with both AF and HF have worse outcomes compared with patients with either AF alone or HF alone. Thus, there is an urgent need for a better understanding of therapies that may reduce the risk of developing AF in patients with HF or improve outcomes in patients with both AF and HF. These 2 conditions represent overlapping epidemics, in part, because of shared risk factors including age, hypertension, and obesity. There are pathophysiologic similarities in both conditions as well. Structural remodeling of myocytes is observed in both conditions. For example, collagen content (fibrosis) is increased in atrial myocytes in AF and in ventricular myocytes in HF (including heart failure with preserved ejection fraction [HFpEF]). These changes lead to abnormal atrial conduction and abnormal diastolic function, respectively. Thus, one might hypothesize that therapies that modify risk factors or impede adverse cardiac myocyte remodeling might improve outcomes in both AF and HF.

Aldosterone is known to have several important downstream effects that increase the likelihood of AF and worsening HF. In particular, aldosterone increases afterload, promotes myocyte hypertrophy, atrial and ventricular fibrosis, endothelial dysfunction, and oxidative stress. Aldosterone has also been shown to cause increased sarcoplasmic reticulum calcium loading in atrial myocytes (1) and serum aldosterone levels fall after successful cardioversion in patients with persistent AF (2). Finally, and most importantly, data from randomized clinical trials have shown that therapy with mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, can improve cardiovascular outcomes in patients with HF and a reduced ejection fraction, including a reduction in new-onset atrial arrhythmia, hospitalization, and cardiovascular death (3,4). However, it remains unknown if MRA therapy improves outcomes in patients with AF and HFpEF.

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In this issue of *JACC: Heart Failure*, investigators from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial describe several key findings on the impact of spironolactone on AF in patients with HFpEF (5). This study adds to a growing body of literature on AF, HFpEF, and activation of the renin-angiotensin-aldosterone system. There are several important findings from the TOPCAT analysis. First, 760 of 1,765 (43%) patients in the analysis had a history of AF at enrollment (either by history or baseline electrocardiogram). Second, incident AF (post-randomization) occurred in 85 (9%) patients without prior AF and recurrent AF occurred in 27 (9%) patients with a prior history of AF but no AF on the baseline electrocardiogram. Third, the presence of AF as confirmed

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by baseline electrocardiogram was associated with worse outcomes, including more frequent cardiovascular mortality, aborted cardiac arrest, or HF hospitalization (adjusted hazard ratio [HR]: 1.34; 95% confidence interval [CI]: 1.09 to 1.65). Fourth, the development of AF after enrollment was also associated with worse outcomes. Fifth, from a therapeutic standpoint, the efficacy of spironolactone was similar irrespective of the presence or absence of AF. Finally, and regrettably, spironolactone did not reduce the risk of AF in follow-up according to intention to treat (HR: 0.98; 95% CI: 0.68 to 1.42) or on-treatment analysis (HR: 0.93; 95% CI: 0.59 to 1.46).

Taken together, these data are consistent with prior findings that AF is an important marker of risk in HFpEF. In fact, as highlighted in this TOPCAT analysis, the risk of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization was highest in the first 90 days after incident AF. However, there are important limitations to the data in terms of drawing conclusions about the impact of MRAs on AF in patients with HFpEF. First, the study cohort size was small. That is, because of regional variation in patient characteristics, 1,678 patients enrolled from Russia and Georgia were excluded from this analysis. Second, the prevalence of AF at enrollment was high, limiting the ability to detect a beneficial effect of MRA on new-onset AF as was observed in EMPHASIS HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) (4). Third, not highlighted in the manuscript, the occurrence of permanent treatment discontinuation was high in the Americas component of TOPCAT, 25% at <1 year and 47% by the end of the study in the spironolactone arm. Finally, it is also important to note that information on treatments for AF including catheter ablation procedures and antiarrhythmic medications were not available.

In contrast, prior studies do suggest a role for renin-angiotensin-aldosterone system inhibition, including the use of MRAs, for the prevention of recurrent AF in patients with HF. For example, in the CHARM program that included HF with a broad range of left ventricular ejection fractions, post-randomization AF occurred in 392 (6%) patients and treatment with candesartan reduced this risk (adjusted odds ratio: 0.80; 95% CI: 0.65 to 0.99) with no heterogeneity among the 3 trials with different inclusion and exclusion criteria (6). The SPIR-AF randomized, open-label trial of 164 patients with paroxysmal AF without HF also provides evidence that MRA therapy may be beneficial. All patients in SPIR-AF received a beta-blocker and patients randomized to spironolactone had less AF recurrences compared with patients randomized to enalapril at multiple time points during 1 year of follow-up (7). Finally, in the previously mentioned post hoc analysis of EMPHASIS-HF, patients randomized to eplerenone had a notably lower risk of new-onset AF compared with those randomized to placebo (HR: 0.58; 95% CI: 0.35 to 0.96) (4).

The disparate results from TOPCAT and other studies are complex and lead one to ask “Do the results of TOPCAT signal a dead-end for MRA therapy in the prevention of new-onset or recurrent AF in HF?” We think caution is required before drawing definitive conclusions about the role of MRA therapy in patients at risk for AF or in patients pursuing a rhythm control strategy. MRAs may be a potential tool available to clinicians in the battle against AF and HF. The role of catheter ablation of AF in HF continues to hold promise. Several trials have demonstrated improved cardiovascular outcomes in patients with HF and a reduced ejection fraction (8,9). Of note, there are very little data on catheter ablation in HFpEF despite the overlapping pathophysiology (10). MRA therapy may improve maintenance of sinus rhythm after ablation in patients with advanced AF (11). Thus, the potential role of MRA therapy in patients with HF and AF remains unclear. Data will be available from ongoing clinical trials of MRAs in HFpEF, such as SPIRRIT-HFpEF (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction; NCT02901184). However, more studies are needed on strategies to prevent and treat AF in HF overall and in HFpEF.

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