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EDITORIAL

Aldosterone Antagonism in Atrial Fibrillation: Implications for AF-Predominant HFpEF

Jennifer E. Ho, MD

The complex interplay between atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) is well recognized.[1] More than a third of individuals with AF develop HF, and AF precedes incident HFpEF more frequently than heart failure with reduced ejection fraction.[2] Notably, the 5-year incidence of HF is double that of incident stroke after diagnosis of AF,[3] yet clinically, much of the focus is on stroke prevention after AF onset rather than prevention of HF. While shared mechanisms underlying AF and HF remain incompletely understood, cardiac fibrosis is thought to contribute to both. It is within this context that Shantsila et al designed the IMPRESS-AF trial (Improved Exercise Tolerance in Patients With Preserved Ejection Fraction by Spironolactone on Myocardial Fibrosis in Atrial Fibrillation), to evaluate the role of mineralocorticoid receptor antagonism in individuals with AF.[4]

See Article by Shantsila et al.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Shantsila et al highlight the primary results of this single-center double-blind randomized placebo-controlled trial, which randomized a total of 250 individuals with permanent AF and preserved ejection fraction to spironolactone versus placebo for 2 years.[5] There was no treatment effect on the primary end point (exercise capacity as ascertained by peak Vo_2) or secondary end points (6-minute walk test distance, quality of life metrics, and diastolic function as ascertained echocardiographically with mitral E/e′ ratio). First, the authors are to be congratulated for completing an ambitious and well-done trial. A few questions emerge as we consider the potential clinical implications of this neutral finding.

First, while study end points were carefully designed around what is expected in a HFpEF rather than an AF trial with evaluation of exercise intolerance as the cardinal clinical manifestation, were these actually individuals with HFpEF? The authors do not include information on prior clinical HFpEF, which would be helpful to gauge generalizability. However, the median peak Vo_2 of 14 mL/kg per minute across study groups is in line with prior HFpEF trials, with a mean peak Vo_2 of ≈14.9 mL/kg per minute calculated across 13 representative trials[6] and similar comparisons of 6-minute walk distance. Interestingly, while participants enrolled in IMPRESS-AF appear similarly limited in functional capacity compared with individuals enrolled in previous HFpEF trials, natriuretic peptides and diastolic function measures appear less abnormal than individuals enrolled in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist),[7] raising the possibility that this sample is earlier along the HFpEF disease spectrum with high prevalence of risk factors including obesity, diabetes mellitus, and treatment with hypertension medications. Indeed, prior studies have shown significant exercise limitations among individuals with American College of Cardiology/American Heart Association "stage B" HFpEF,[8] and targeted preventive therapies in this population would be of high interest. Again, clarification around this issue would lend further insights into how we think about the sample at hand.

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Correspondence to: Jennifer E. Ho, MD, Massachusetts General Hospital, 185 Cambridge St, CPZN #3192, Boston, MA 02114. E-mail: jho1@mgh.harvard.edu

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Second, recognizing that HFpEF is phenotypically heterogeneous, is AF-predominant HFpEF a distinct entity worth studying and targeting? The concept of left atrial myopathy as an important contributor to HFpEF has recently been recognized, with disproportionate left atrial myopathy portending adverse hemodynamic consequences including congestion and exercise intolerance.[9] Further, a cluster-based analysis of individuals enrolled in the TOPCAT trial identified 3 clinical phenogroups, including a subset of older individuals with high prevalence of AF, characterized by greater arterial stiffness, concentric left ventricular hypertrophy, and markers of innate immunity/inflammation among other biomarkers.[10] It is thus reasonable to hypothesize that targeting AF-predominant HFpEF may be fruitful, though much remains to be learned with respect to mechanisms linking AF and HFpEF development that would allow therapeutic targeting.[1]

Lastly, how convinced are we that this trial is definitively "negative"? IMPRESS-AF was powered to detect a 2 mL/min per kg difference in peak Vo_2 between groups and met the target sample size (100 in each arm) despite attrition in follow-up of ≈17% at 2 years. The trial however, was not powered for detecting a difference in clinical outcomes, although a notable finding was that at least 1 hospitalization occurred in 15% of patients in the spironolactone group versus 23% in the placebo group (hazard ratio 0.65; 95% CI, 0.36–1.17). In this context, one wonders whether a larger trial might show different results with respect to clinical end points. Having said that, we know from post-hoc analyses of the TOPCAT trial that the spironolactone treatment effect was not modified by the presence of AF at enrollment among 446 of 1754 individuals enrolled in the Americas.[11] Similarly, in the AF-predominant phenogroup identified using cluster analysis, spironolactone had no treatment benefit.[10]

In sum, IMPRESS-AF was a well-performed trial with a clinically relevant hypothesis. It demonstrated no effect of spironolactone on exercise capacity among individuals with permanent AF with limited exercise tolerance and unclear prevalence of clinical HFpEF. In weighing the totality of the evidence, IMPRESS-AF adds further to existing data among patients with AF and HFpEF that show no benefit to aldosterone antagonism. We remain on the search for effective HFpEF therapies, with or without AF.

ARTICLE INFORMATION

Affiliations

From the Division of Cardiology, Cardiovascular Research Center, Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, MA.

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