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Sex Differences in Outcomes and Responses to Spironolactone in Heart Failure With Preserved Ejection Fraction: A Secondary Analysis of TOPCAT Trial

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Abstract

Objectives

This study sought to investigate sex differences in outcomes and responses to [spironolactone](#) in patients with [heart failure with preserved ejection fraction](#) (HFpEF).

Background

HFpEF affects women more frequently than men. Sex differences in responses to effects of [mineralocorticoid antagonists](#) have not been reported.

Methods

This was an exploratory, post hoc, non-pre-specified analysis of the TOPCAT (Aldosterone Antagonist Therapy for Adults With [Heart Failure](#) and Preserved Systolic Function) trial. Subjects with symptomatic HF and a [left ventricular ejection fraction](#) $\geq 45\%$ were randomized to spironolactone or placebo therapy. Subjects

enrolled from the Americas were analyzed. The primary outcome was a composite of cardiovascular (CV) death, cardiac arrest, or HF hospitalization. Secondary outcomes included all-cause mortality, CV, and non-CV mortality and CV, HF, and non-CV hospitalization. Sex differences in outcomes and treatment effects were determined using time-to-event analysis.

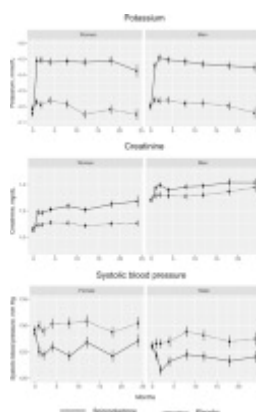
Results

In total, 882 of 1,767 subjects (49.9%) were women. Women were older with fewer comorbidities but worse patient-reported outcomes. There were no sex differences in outcomes in the placebo arm or in response to spironolactone for the primary outcome or its components. Spironolactone therapy was associated with reduced all-cause mortality in women (hazard ratio: 0.66; $p = 0.01$) but not in men ($p_{\text{interaction}} = 0.02$).

Conclusions

In TOPCAT, women and men presented with different clinical profiles and similar clinical outcomes. The interaction between spironolactone and sex in TOPCAT overall and in the present analysis was nonsignificant for the primary outcome, but there was a reduction in all-cause mortality associated with spironolactone therapy in women, with a significant interaction between sex and treatment arm. Prospective evaluation is needed to determine whether spironolactone therapy may be effective for treatment of HFpEF in women. (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved [Systolic Function](#) [TOPCAT]; [NCT00094302](#))

Graphical abstract



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Key Words

heart failure with preserved ejection fraction; sex differences; spironolactone; women

Abbreviations and Acronyms

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid antagonist; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure

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