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Lessons from the Trials

TOPCAT misses its primary endpoint: Should spironolactone be abandoned in HFpEF?

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) continues to be a challenging form of heart failure – one in which no therapy has yet been proven to improve outcome. Aldosterone antagonists have previously been shown to improve survival in a wide spectrum of patients with heart failure with reduced ejection fraction (HFrEF), and more recently, small trials suggested that they might have role in HFpEF patients. The effect of spironolactone on clinical outcomes in HFpEF was tested in the TOPCAT study.

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INTRODUCTION

With no therapy shown to improve clinical outcomes to date, the management of patients suffering from heart failure with preserved ejection fraction (HFpEF) represents an ongoing challenge. Therapies of proven benefit in heart failure with reduced ejection fraction (HFrEF) have repeatedly been shown to add little if any benefit in HFpEF,[1–5] and the treatment of the latter group remains largely directed towards underlying risk factors and/or comorbidities. The **T**reatment **O**f **P**reserved **C**ardiac function heart failure with an **A**ldosterone an**T**agonist (TOPCAT) trial was designed to test the clinical benefit of spironolactone in patients with HFpEF.[6]

THE STUDY

TOPCAT was a multicenter, double-blind, randomized, placebo-controlled study designed to evaluate the efficacy of spironolactone relative to placebo on the cumulative incidence of a composite endpoint of cardiovascular death, heart failure hospitalization, or aborted cardiac arrest in patients with HFpEF. Secondary endpoints included all-cause mortality, new onset of diabetes mellitus or atrial fibrillation, and quality of life. HFpEF was determined by the presence of LVEF $>45\%$, signs and symptoms of heart failure in conjunction with prior hospital admission for HF within the prior year or elevated natriuretic peptides (BNP >100 pg/ml or NT-proBNP >360 pg/ml) within the 60 days preceding randomization. Importantly, objective evidence of diastolic dysfunction was not required for enrolment in the study. Patients with uncontrolled hypertension, those with infiltrative or hypertrophic cardiomyopathy and patients with elevated baseline serum potassium levels (>5.0 mmol/L) were excluded. A total of 3445 subjects were recruited over a period of 4 years from 270 clinical centers in the United States (1151), Russia (1066), Georgia (612), Canada (326), Brazil (167) and Argentina (123), and were randomized on 1:1 basis to either spironolactone (target dose of 30 mg daily) or placebo. The study was funded by the National Heart, Lung, and Blood Institute (NHLBI).

RESULTS

The results were recently presented at the American Heart Association Meeting in Dallas and will be published in the next issue of Circulation Heart Failure. After a mean follow-up period of 3.3 years, the primary endpoint occurred in 320 (18.4%) and 351 (20.4%) of patients in the spironolactone and placebo groups respectively [HR $=0.89$ ($0.77-1.04$), $p=0.138$]. Patients receiving spironolactone had significantly fewer hospitalizations for heart failure compared to placebo (245 (14.2%) vs. 206 (12%), HR $=0.83$ ($0.69-0.99$), $p=0.042$) but all-cause hospitalization did not differ between both groups [HR $=0.94$; ($0.85-1.04$)]. The two other components of the primary endpoint – cardiovascular mortality and aborted cardiac arrest – did not differ between both groups. Hyperkalemia was more common in patients receiving spironolactone [322 (18.7%) vs. 157 (9.1%) for placebo, $p<0.001$], but there were no deaths related to hyperkalemia. Patients in the spironolactone group were also almost 50% more likely to experience doubling of creatinine above the upper limit of normal [HR 1.49 ($1.18-1.87$), $p<0.001$]. However, the number of patients with creatinine levels ≥ 3 mg/dL and the number of patients who required dialysis did not differ between both groups. Amongst 22 pre-specified subgroups, only patients with elevated natriuretic peptides showed a significant interaction with treatment. An interesting post-hoc analysis showed a striking regional difference in the placebo event rates: 280/881 (31.8%) in the Americas vs. 71 (8.4%) in East Europe.

DISCUSSION

Aldosterone has several deleterious effects in patients with heart failure including salt and water retention, endothelial dysfunction, ventricular hypertrophy, and myocardial fibrosis.[7] Aldosterone receptor blockers have previously been shown to significantly reduce mortality in a wide spectrum of patients with HFrEF.[8–10] In HFpEF, a number of small studies have previously suggested a beneficial effect with spironolactone,[11,12] and more recently, the ALDO-DHF study showed that spironolactone improved left ventricular diastolic function and remodeling compared to placebo.[13] TOPCAT is the largest study conducted to date to test the effect of spironolactone on clinical outcomes in HFpEF, and is one of the largest studies performed in this patient population in general. The investigators are commended for successfully conducting such a large study – with patients recruited from 270 centers across 6 countries – in a disease entity where patient recruitment is notoriously known to be difficult. The study's rigorous monitoring system contributed to a low dropout rate of only 3.9% by the end of the

study, and more importantly, prevented hyperkalemia-related deaths and/or increased dialysis in the active treatment group.

A number of features in TOPCAT however raise some concern as to whether the study subjects truly represent the "real-life" HFpEF population. First, the overall event rate was low, with 3-year mortality being 10.2 %. This is in sharp contrast with the previously reported annual mortality rates of 22–29% in large community-based studies.[14,15] This concern is further intensified by a primary event rate (in the placebo group) of 8.4% in Russia and the Republic of Georgia: a rate which not only is unheard of in heart failure studies, but also one that is remarkably less than that observed in the "American" arm of the same study (31.8%). Second, the investigators recently published the findings from the echocardiographic substudy of TOPCAT where the echocardiograms of 935 patients – approximately 27% of the TOPCAT population – were analyzed centrally in a blinded core laboratory.[16] The echo substudy revealed that 46% of this group had normal left atrial size (indexed left atrial volume <29 mL/m2) and 17% of patients had normal tissue-Doppler derived diastolic velocities. Third, compared to patients qualifying for TOPCAT on the basis of prior hospitalization, those enrolled via the elevated natriuretic peptide route were more likely to be recruited in the Americas, had significantly larger indexed left atrial volumes (median 26.6 vs. 30.3 mL/m2, $p < 0.0001$), and were more likely to benefit from spironolactone with the primary endpoint occurring in 15.9% in the spironolactone arm vs. 23.6% with placebo, $p = 0.003$ (compared to 19.6% vs 19.1% respectively, $p = 0.92$ in the heart failure hospitalizations group). Fourth, the primary end point hazard ratio for the "American" group (almost half of TOPCAT's population) was 0.82 (95% CI 0.69–0.98) compared to 1.1 (95% CI 0.79–1.51) in the Eastern European group. Collectively, these points raise the possibility that a considerable number of patients qualifying for TOPCAT because of prior hospitalization for heart failure, might not have suffered from HFpEF in the first place; a limitation previously encountered with other major HFpEF trials owing to the non-specific signs and symptoms of HFpEF. In fact, recruiting markedly heterogonous patient populations (including non-cardiac patients) and non-adherence to the recommended diagnostic criteria (which require objective evidence of LV diastolic dysfunction) have previously been suggested as possible explanations for the neutral/negative outcomes of HFpEF trials.[17,18] Whether these limitations might have masked a beneficial effect in the spironolactone group remains subject to further detailed analysis. One might be tempted to choose focusing on the positive effect seen with spironolactone in the "American" arm or in those with elevated natriuretic peptides, however, this can be very misleading from a statistical standpoint.

WHAT HAVE WE LEARNED?

TOPCAT was a negative study; spironolactone failed to reduce the primary outcome compared to placebo in patients with HFpEF. However, it did reduce the rate of heart failure hospitalizations. A signal of benefit was also seen in patients with elevated natriuretic peptides and in a geographical subset of patients. Based upon these findings, a mixed response from the medical community is expected: some clinicians will not prescribe spironolactone for HFpEF patients, while others will continue using it especially in patients with elevated natriuretic peptides and/or in those with objective evidence of diastolic dysfunction. Careful monitoring of renal function and serum potassium levels is mandatory in the latter situation. Given the lack of interest from the pharmaceutical industry in a cheap generic drug and the finite resources of the NHLBI, it is doubtful that there will be any large spironolactone trials in the near future. It is therefore unlikely that this "therapeutic dilemma" will be definitively resolved soon.

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