Spironolactone not reduce primary outcome, did reduce hospitalizations for heart failure

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Findings from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, have revealed that adding the medication known as spironolactone (Aldactone) to existing therapy did not significantly reduce the composite time to either death from cardiovascular causes, surviving a cardiac arrest, or hospitaliization to manage heart failure in patients with heart failure and a preserved ejection fraction in a study funded by the National Heart, Lung and Blood Institute, National Institutes of Health.

The study will be published April 10, 2014 in the *New England Journal of Medicine*.

"There currently are no existing therapies to address the prognoses of the approximately 40 percent of patients with heart failure and a preserved ejection fraction," said Eldrin Lewis, MD, advanced heart failure specialist, Brigham and Women's Hospital (BWH) Division of Cardiovascular Medicine, Department of Medicine, study co-author. "TOPCAT is the first randomized, double-blind trial to assess the effect of a treatment—spironolactone—on clinical outcomes in this patient demographic."

"TOPCAT was robust in its design and was well-conducted, with a strong collaboration between the New England Research Institutes and clinical colleagues at Brigham and Women's Hospital and the University of Michigan, thus ensuring that the results would be reliable," said Sonja McKinlay PhD, president of New England Research Institutes, study co-senior author.

The TOPCAT trial enrolled 3,445 patients from 233 medical sites in six countries. Participants with symptomatic heart failure and a left ventricular ejection fraction of 45 percent or more (normal or near normal contractions) were randomized to receive either spironolactone (15 to 45 milligrams daily) or matching placebo, and were followed for an average of nearly 3.3 years.

The primary outcome consisted of death from cardiovascular causes, surviving a cardiac arrest, or hospitalization for the management of heart failure—whichever happened first—and occurred in 320 of 1,722 patients in the spironolactone group (18.6 percent) and 351 of 1,723 patients in the placebo group (20.4 percent).

Spironolactone belongs to a class of medications known as aldosterone receptor antagonists. Spironolactone is used to treat fluid retention in patients with congestive heart failure, liver cirrhosis or nephrotic syndrome. It is also used to treat high blood pressure, heart failure and low blood potassium (hypokalemia).

Looking at the components of the primary outcome separately, only hospitalizations, specifically for heart failure, had a significantly lower incidence for those taking spironolactone compared to placebo, with 206 patients (12.0 percent) in the spironolactone group undergoing hospitalization versus 245 patients (14.2 percent) in the placebo group.

"While the overall results failed to demonstrate a significant effect of spironolactone on the primary endpoint in TOPCAT, the study provides important insights into the potential efficacy of spironolactone in reducing the need for hospitalizations for heart failure in this population, as well as providing clues for more effectively designing future studies to reduce mortality," said Bertram Pitt, MD, University of Michigan School of Medicine, study co-senior author.

Neither total deaths nor hospitalizations for any reason were significantly reduced by spironolactone. There were no significant differences in the incidence of serious adverse events. However, spironolactone was associated with increased serum creatinine levels and a doubling of the rate of hyperkalemia (high potassium concentration in the blood), but conversely led to reduced hypokalemia (low potassium concentration in the blood). According to the researchers, such findings underscore the importance of monitoring patients prescribed spironolactone.

"When treating patients, clinicians must balance risks and benefits," said Marc A. Pfeffer, MD, PhD, BWH Division of Cardiovascular Medicine, Department of Medicine, study co-senior author. "If clinicians decide to prescribe spironolactone to their patients to reduce their risk of being hospitalized for heart failure, there is an associated responsibility to monitor for serum markers of kidney and electrolyte disorders which can be exacerbated by spironolactone."

Provided by Brigham and Women's Hospital