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Lessons Learned from the TOPCAT Trial

Wilbert S Aronow*

Department of Medicine, Cardiology Division, New York Medical College, Valhalla, New York, USA

***Corresponding author**: Wilbert S Aronow, Cardiology Division, Department of Medicine, New York Medical College, Valhalla, New York 10595, USA; Tel-914-493-5311; Fax- +358 3 364 1512; E-mail: wsaronow@aol.com

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Summary

Approximately half of patients with heart failure have a preserved left ventricular ejection fraction [1-5]. In sharp contrast to treatment of heart failure with reduced left ventricular ejection fraction, evidence-based drug therapies for treatment of heart failure with preserved left ventricular ejection fraction are still lacking [6]. The 3 major outcome trials performed in patients with heart failure and preserved left ventricular ejection fraction using inhibitors of the renin-angiotensin-aldosterone system did not meet their primary endpoints [7-12].

The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial was a randomized, double-blind, placebo-controlled trial which randomized 3,445 patients with symptomatic heart failure and a left ventricular ejection fraction of 45% or more to receive either spironolactone 15 mg to 45 mg daily or placebo [9-12]. Of these patients, 1,767 patients were enrolled from the United States, Canada, Brazil, and Argentina, and 1,678 patients were enrolled from Russia and Georgia. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for treatment of heart failure. The mean follow-up was 3.3 years.

The primary outcome occurred in 320 of 1,722 patients (18.6%) randomized to spironolactone and in 351 of 1,723 patients (20.4%) randomized to placebo (hazard ratio=0.89; 95% CI, 0.77-1.04; p=0.14) [9]. Of the primary outcome components, only hospitalization for heart failure was significantly lower in patients treated with spironolactone compared to placebo (hazard ratio=0.83; 95% CI, 0.69-0.99; p=0.04) [9]. Treatment with spironolactone was associated with increased serum creatinine levels, increased hyperkalemia (18.7% for spironolactone versus 9.1% for placebo), and decreased hypokalemia. There were no significant differences between spironolactone and placebo in the incidence of serious adverse events, a serum creatinine level of 3.0 mg/dL or higher, or dialysis [9].

The patients from the Russia and Georgia group were younger, had less atrial fibrillation and diabetes mellitus, and were more likely to have had a prior myocardial infarction or a hospitalization for heart failure, a lower ejection fraction and serum creatinine, and a higher diastolic blood pressure than the patients from the Americas group [10]. Hyperkalemia and doubling of serum creatinine were more likely and hypokalemia less likely in patients treated with spironolactone in the Americas group than in the Russia and Georgia group [10].

In the Americas group, compared with placebo, spironolactone reduced the primary outcome 18% from 12.6% to 10.4% (p=0.026), reduced cardiovascular mortality 26% from 14.4% to 10.8% (p=0.027), reduced hospitalization for heart failure 18% from 24.5% to 20.8% (p=0.042), reduced recurrent heart failure 25% from 438 events to 361 events (p=0.024), reduced all-cause mortality 17% from 23.5% to 20.1% (p=0.08), had similar incidences of all-cause hospitalization, myocardial infarction, and stroke, had a 60% increased incidence of doubling of serum creatinine from 11.6% to 17.8% (p<0.001), had a similar incidence of serum creatinine ≥ 3.0 mg/dL, increased hyperkalemia (≥ 5.5 mmol/L) 3.46 times from 8.9% to 25.2% (p<0.001), and reduced hyokalemia (serum potassium<3.5 mmol/L) 49% from 26.2% to 15.2% (p<0.001) [10].

In the Russia and Georgia group, all of these outcomes were similar for patients treated with spironolactone or placebo [10]. These marked regional differences suggest that clinical diagnostic criteria were not uniformly interpreted or applied [10]. The event rates of those enrolled from the Americas are reflective of other clinical trial populations with symptomatic heart failure and preserved left ventricular ejection fraction [7-10].

In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved study [7], the rates of the composite of cardiovascular death or heart failure hospitalization in the United States/Canada group was 10.9 per 100 patient-years which is similar to the 12.6 per 100 patient–years in the TOPCAT study , whereas the the rates of the composite of cardiovascular death or heart failure hospitalization in the Eastern Europe/Russia group in the CHARM-Preserved study was 4.4 per 100 patient-years [9-12]. In the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) study [8], the rates of the composite of cardiovascular death or heart failure hospitalization in the United States/Canada group was 10.3 per 100 patient-years which is similar to the 12.6 per 100 patient –years in the TOPCAT study , whereas the the rates of the composite of cardiovascular death or heart failure hospitalization in the Eastern Europe/Russia group in the I-PRESERVE study was 6.1 per 100 patient-years [9-12].

The clinical meaning and prognostic value of a history of heart failure hospitalization are not met in Russia/Georgia in TOPCAT and other heart failure trials [11]. The differences in event rates observed [7-12] show international geographic variation in the diagnosis of heart failure with preserved left ventricular ejection fraction, risk profile of enrolled patients, and threshold for heart failure hospitalization, which must be considered in performing future international trials [12]. It is very disturbing that the patients enrolled in Russia/Georgia in the TOPCAT trial did not demonstrate either the expected morbidity or mortality associated with symptomatic heart failure or most pharmacological responses to spironolactone [10].

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