

Editorial

Regional Differences in Heart Failure with Preserved Ejection Fraction Trials

Wilbert S. Aronow*

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

***Corresponding author:** Wilbert S. Aronow,

Department of Medicine, Cardiology Division, New York Medical College Macy Pavilion, Room 138, Valhalla, NY 10595, Tel: (914) 493-5311; Fax: (914) 235-6274; Email: wsaronow@aol.com

Received: February 24, 2015; **Accepted:** February 26, 2015; **Published:** February 27, 2015**Editorial**

Approximately half of patients with heart failure have a preserved left ventricular ejection fraction [1-5]. Despite the high mortality and rehospitalization for heart failure in patients with heart failure and a preserved left ventricular ejection fraction [5-7], evidence-based drug therapies for treatment of heart failure with preserved left ventricular ejection fraction are still lacking [8]. 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 show a reduction in primary endpoints [9-14].

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 higher to either spironolactone 15 mg to 45 mg daily or placebo [11-14]. Of these patients, 1,767 patients (51%) were enrolled from the United States, Canada, Brazil, and Argentina, and 1,678 patients (49%) 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.

At 3.3-years follow-up, the primary outcome occurred in 320 of 1,722 patients (18.6%) randomized to treatment with spironolactone and in 351 of 1,723 patients (20.4%) randomized to treatment with placebo (an 11% insignificant reduction in patients treated with spironolactone) [11]. Only hospitalization for heart failure was significantly lower in patients treated with spironolactone compared to patients treated with placebo (17% reduction, $p = 0.04$) [11]. Treatment with spironolactone was associated with increased serum creatinine levels, increased hyperkalemia (18.7% for spironolactone versus 9.1% for placebo), and decreased hypokalemia [11].

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 [12]. 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 [12].

In the Americas group, compared with placebo, spironolactone decreased the primary outcome 18% from 12.6% to 10.4% ($p = 0.026$), decreased cardiovascular mortality 26% from 14.4% to 10.8% ($p = 0.027$), decreased hospitalization for heart failure 18% from 24.5% to 20.8% ($p = 0.042$), decreased recurrent heart failure 25% from 438 events to 361 events ($p = 0.024$), decreased all-cause mortality 17% from 23.5% to 20.1% ($p = 0.08$), had a 60% increased incidence of doubling of serum creatinine from 11.6% to 17.8% ($p < 0.001$), increased hyperkalemia (≥ 5.5 mmol/L) 3.46 times from 8.9% to 25.2% ($p < 0.001$), and reduced hypokalemia (serum potassium < 3.5 mmol/L) 49% from 26.2% to 15.2% ($p < 0.001$) [12].

In the Russia and Georgia group, all of these outcomes were similar for patients treated with spironolactone or placebo [12]. These marked regional differences suggest that clinical diagnostic criteria were not uniformly interpreted or applied [12]. The event rates of the patients enrolled from the Americas are reflective of other clinical trial populations with symptomatic heart failure and preserved left ventricular ejection fraction [9-14].

In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved study [9], 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 whereas 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 [11-14]. In the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) study [10], 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, whereas 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 [11-14].

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 [13]. The differences in event rates observed [9-14] 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 [14]. It is very alarming that the patients enrolled in Russia/Georgia in the TOPCAT trial did not show either the expected morbidity and mortality associated with symptomatic heart failure or most pharmacological responses to spironolactone [12]. On the basis of these data, I would use spironolactone for treatment of patients with heart failure and a preserved left ventricular ejection fraction and

not enroll patients with heart failure from Eastern Europe in future clinical trials.

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