Effect of Obesity on Response to Spironolactone in Patients with Heart Failure with Preserved Ejection Fraction

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Introduction:

- Heart failure (HF) with preserved ejection fraction (HFpEF) is one of the most prevalent cardiovascular conditions, and is associated with significant morbidity and mortality.
- The complex pathophysiology of HFpEF remains incompletely understood and unlike HF with reduced ejection fraction (HFrEF), there is no evidence-based treatment that improves clinical outcomes.
- Obesity is a well-established risk factor for HFpEF, and is associated with a systemic pro-inflammatory state and activation of the renin–angiotensin-aldosterone system with established deleterious cardiovascular effects.
- Drugs that antagonize aldosterone have been shown to decrease the systemic pro-inflammatory state and could be an attractive therapeutic option for patients with obesity-related HFpEF.
- In the TOPCAT (Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function) trial, spironolactone failed to show any beneficial effect compared to placebo.

Purpose:

- In light of the inflammatory phenotype associated with obesity and the anti-inflammatory effects of spironolactone, we aimed to investigate the effect of obesity, defined by body mass index (BMI) and waist circumference (WC), on response to spironolactone in patients with HFpEF enrolled in TOPCAT trial.

Methods:

- For the current analysis we included 1751 patients that were enrolled from the Americas cohort (USA, Canada, Argentina, Brazil). We didn't include those who were enrolled from Europe (Russia, Georgia) due to the previously reported significant regional differences between the Americas and Europe cohorts.
- Obesity was defined according to WHO criteria: BMI≥30Kg/m^2 for obese group and <30Kg/m^2 for non-obese group. Men and women with WC values <102cm and <88cm, respectively, were considered to have a normal WC (NWC), whereas those with WC values ≥102 cm and ≥88 cm, respectively, were considered to have high WC (HWC) according to American Heart Association defined cut-offs.
- Associations between BMI or WC (both as a continuous and categorical variable) and end points were determined using Cox proportional hazards models. The effect of spironolactone vs. placebo on end points was calculated for BMI and WC categories.
- Interactions between BMI or WC and spironolactone effect on end points were assessed by introducing an interaction term BMI or WC variable × spironolactone.

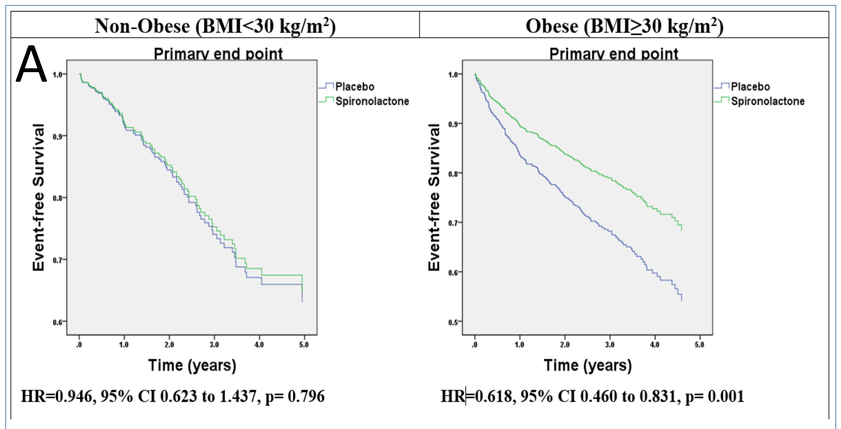


Figure (A). Kaplan-Meier survival curves stratified by BMI group and treatment arm in the Americas only cohort of TOPCAT shows that use of spironolactone in obese was associated with a significant reduction in the primary end point compared to placebo but not in the non-obese group.

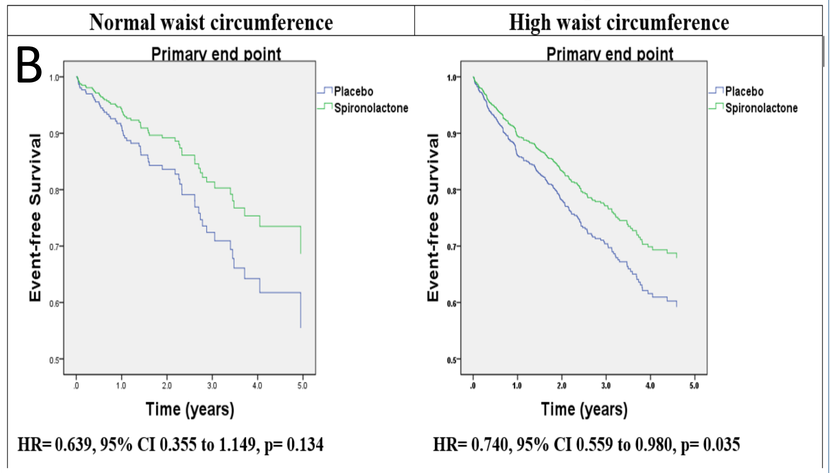
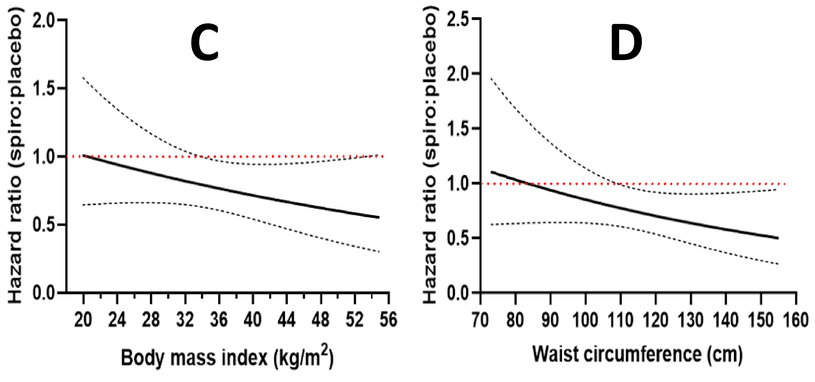


Figure (B). Kaplan-Meier survival curves stratified by WC group and treatment arm in the Americas only cohort of TOPCAT shows that use of spironolactone in HWC was associated with a significant reduction in the primary end point compared to placebo but not in the NWC group.



Figures (C, D) Plot of the spironolactone effect vs. placebo as a function of continuous BMI (C) and WC (D) in the adjusted model for the primary outcome shows linear association between BMI, WC and the effect of spironolactone. The beneficial effect of spironolactone on the primary end point became statistically significant at BMI of 33kg/m^2 and WC of 109 cm.

Results:

- Obese and HWC groups had higher prevalence of comorbidities including diabetes, hypertension, dyslipidemia, atrial fibrillation and asthma.

- **For BMI analysis**:

1- There was no difference in the primary endpoint or any of the secondary endpoints between the obese and non obese groups.
2- In obese group, spironolactone use was associated with 39% significant decrease in the primary endpoint (HR=0.618, 95% CI 0.460-0.831, p=0.001), 52% significant decrease in cardiovascular death (HR=0.483, 95% CI 0.281-0.833, p=0.009) and 36% significant decrease in the rate of HF hospitalization (HR=0.641, 95% CI 0.465-0.883, p=0.007) when compared to placebo.
3- In non-obese group, there was no difference between spirnolactone Vs placebo effect on the primary or any of the secondary endpoints.
4- When BMI was treated as a continuous variable, there was a linear association between BMI and the effect of spironolactone vs. placebo for the primary outcome and cardiovascular death, with the benefit becoming statistically significant at 33kg/m2 and 30kg/m2, respectively.

- **For WC analysis**:

1- There was no difference in the primary endpoint or any of the secondary endpoints between the NWC and HWC groups.
2- In HWC group, spironolactone use was associated with 26% significant decrease in the primary endpoint (HR=0.740, 95% CI 0.559-0.980, p=0.035) and 46% significant decrease in cardiovascular death (HR= 0.541, 95% CI 0.335-0.873, p=0.012) when compared to placebo.
3- In NWC group, there was no difference between spirnolactone Vs placebo effect on the primary or any of the secondary endpoints.
4- When waist circumference was treated as a continuous variable, there was a linear association between WC and the effect of spironolactone vs. placebo for the primary outcome, cardiovascular death and HF hospitalizations, with the benefit becoming statistically significant at 109cm, 103cm and 123cm, respectively.

Conclusions:

- **Use of spironolactone in HFpEF patients with obese-inflammatory phenotype was associated with a decreased risk of the primary end point, cardiovascular death and HF hospitalizations, compared to placebo.**
- **Nonetheless, this analysis represents a post-hoc, secondary analysis and should only be regarded as hypothesis-generating. Further prospective randomized studies in obese subjects are required to confirm the validity of this finding prior to clinical application.**

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