Regional Analysis of Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)

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Perspective

• Marked differences in numerous important patient characteristics in Russia/Georgia vs the Americas (age, race, diabetes, CKD, CVD, atrial fibrillation)
• Placebo event rates were markedly lower in Russia/Georgia
• Potentially different entities &/or pathophysiology of HFpEF in the 2 regions
  • Different response to spironolactone (K, cre, BP); likely due to different patient profiles/pathophysiology
• Interpreting subgroups-- hypothesis generating
  • Negative trial- TOPCAT primary endpoint failed to confirm superiority
  • Region x treatment interaction p=NS
  • Multiple (15) subgroups examined- increases risk of chance findings
  • Is there a mechanism to explain differential subgroup treatment effect
    • Physiologic response to spironolactone paralleled apparent outcome response

Geographic differences and renin-angiotensin-aldosterone system (RAAS) inhibitors for HFpEF in a broader context ...
Pathophysiology of heart failure with a preserved ejection fraction (HFpEF)

Co-morbidities have a major impact on the syndrome and mortality

Furthermore…confirming the diagnosis of HFpEF may be difficult

Dyspnea, orthopnea, fatigue, lower extremity edema may be caused by other conditions

Geographic differences in event rates (placebo and active groups combined)  
**CHARM-Preserved, I-PRESERVE, TOPCAT**

Heart Failure Hosp or Cardiovascular Death

![Graph showing event rates for CHARM-Preserved, I-PRESERVE, TOPCAT. **includes small # of aborted arrest.](image)

HFrEF showed much less regional variation

- **TOPCAT** - BNP was infrequently used as entry criteria
- **I-Preserve** - NT pro-BNP levels were significantly lower in Eastern Europe/Russia vs US/Canada
  
  Median 277 vs 633

What proportion did not truly have HFpEF?

Incidence per 100 pt years

Pfeffer, Circ Epub ahead of print; McMurray, Circ Epub ahead of print
Large Trials of ARBs or Aldosterone Antagonist in Heart Failure with Preserved EF

CHARM-Preserved: n=3023, placebo vs candesartan; primary outcome cardiovascular death or admission to hospital for CHF

I-PRESERVE: n=4128, Irbesartan vs placebo. Primary outcome: death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke)

TOPCAT: n=3445; primary outcome death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure


CHARM-Preserved: 0.86 (0.74 - 1.0, 95% CI, p=0.051)*

I-PRESERVE: 0.95 (0.86 – 1.05, 95% CI, p=0.35)

TOPCAT: 0.87 (0.74 – 1.01, 86% CI, p=0.061)*

* covariate adjusted
Conclusion

• Pathophysiology of HFpEF differs from HFrEF
  • Marked heterogeneity in HFpEF
• Trials of inhibitors of renin – angiotensin – aldosterone system show consistent benefit for HF reduced EF, including across geographic regions in contrast to
• Overall negative trial results for HFpEF, with marked differences in patient characteristics and event rates between Americas and Russia/Eastern Europe
• Subgroup findings are hypothesis generating
• Entry criteria for HFpEF trial need refinement
• It is reasonable to try a mineralocorticoid receptor antagonist antagonist for symptomatic HFpEF pts with ‘anticipated risks similar to those enrolled from the Americas’ … requires careful monitoring of K+ and creatinine