Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy – Heart Failure Trial: ATHENA-HF

Discussant
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What went wrong?

1. Wrong Pathophysiology / target ? - NO

- **Neurohormonal target**: succes in chronic HF – but unknown in AHF:
  - “time is muscle” as in ACS?
  - raise ”set-point” in chronic HF? (TRUE-HF did not confirm this)

- In AHF, diuretic resistance is common and aldosterone elevated and associated with poor outcomes (EVEREST, EJHF 2013)
  - But risk factor or risk marker?
2. Wrong Treatment? – NO; Wrong dose? – YES

• Are MRAs natriuretic? In doses ≥50, but up to 400 mg/d may be needed (Bansal Circ HF 2009)

• Previous study: Mean 94.5 mg/d → NT-proBNP 2701 to 1555 (Ferreira Eu J Intern Med 2014)

• ATHENA: 100 mg/d → NT-proBNP 4601 to 2672: Effectiveness confirmed, but no difference vs. placebo

• Minimal changes K and eGFR, No dose finding
  – Need higher dose MRA?
  – ATHENA: 100 mg no safety issues
3. Wrong patient / inclusion criteria? – YES

- **Fluid retention modest:** 1 symptom + 1 sign: less strict than Framingham; NT-pro 1000 ng/L modest and not stratified by AF (50%, rapid AF?); pre-admission weight gain not required or reported

- **No evidence for diuretic resistance:** eGFR ≥30 but median 55-58; lack of diuretic response not required

- **24h from diuretic dose too long?:** Concept of early treatment: e.g. RELAX-2, but not confirmed in TRUE-HF
4. Wrong endpoints? – YES

- Phase 2 with \( n=380 \) patients. Too low. Baseline differences, risk false negatives and false positives

- Surrogate endpoints such as NT-proBNP repeatedly proven unreliable

- In ”real-world” AHF: Half lose \( \leq 5 \) lbs and 20% gain weight (Gheorghiade EHJ Suppl. 2005). In ATHENA: both groups improved dyspnea, congestion, NT-proBNP and negative 6-7 lbs by 96h
  
  –Standard of care in AHF trial setting appears effective for surrogate endpoints
High dose MRA should be further explored in AHF:

- Confirmed diuretic resistance
- Higher dose
- Larger sample size
- Morbidity and mortality

PROPOSAL:

- AHF and in-hospital treatment
- With approved and generic spironolactone:
- Suitable for phase III pragmatic registry-based trial
- With M&M primary end-point collected automatically from registries