Karolinska Institutet

KAROLINSKA Universitetssjukhuset

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

ATHENA-HF

Discussant

Lars H. Lund, MD PhD

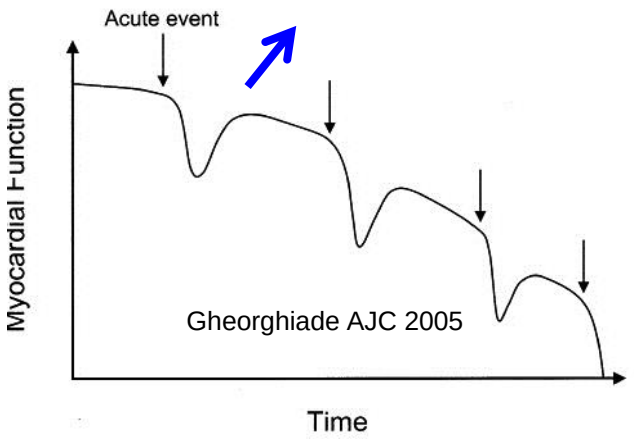
RiksSvikt nationellt hjärtsviktsregister

UCR

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 ≤ 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**