Update on Biomarkers in Heart Failure: Risk Stratification and Monitoring

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Biomarkers in HF:

- 1. Diagnosis
- 2. Risk stratification
- 3. Guiding Therapy

- Natriuretic peptides, Troponin, ST2, procalcitonin (PCT)
- HFP EF vs HFREF

2013 ACCF/AHA Guidelines for the Management of HF

NP's: Class I indication for diagnosis and prognosis

BNP predicts survival in HF: Results from ValHeFT

NT-proBNP levels in patients with prior CHF

![NT-proBNP Levels Diagram]

BNP level = baseline BNP (dry) plus change due to increased volume (wet)

![BNP Level Diagram]

Interpreting NP levels in those with prior heart failure

- Know the “dry” (NT-pro)BNP values (i.e. level when patient is stable)
- A change >25% from the “dry” (NT-pro)BNP generally suggests a clinical change
- Irrespective of clinical stability, the “dry” NP value is prognostic

When to Measure NP’s in ADHF?

- ED:
  - Help with diagnosis
  - Help with prognosis
- Inpatient:
  1. After 24-48h to assess adequacy of Rx
  2. Change in status
  3. Pre-discharge
     - Establish “dry (NT-pro)BNP” level
     - Prognosis (30% drop)
What about Monitoring Therapy?

Neprilysin Inhibitors
- Sacubitril/valsartan
- ARNI (Angiotensin Receptor/Neprilysin Inhibitor)

PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

- Age ≥18 years. NYHA class II-IV. LVEF ≤0.40 (amended to ≤0.35).
- BNP ≥150 pg/ml (NTpro-BNP ≥600 pg/ml) or if HF hosp. within12 mo. BNP ≥100 pg/ml (NTpro-BNP ≥400 pg/ml)
- Background RAS blocker therapy equivalent to enalapril ≥10 mg/d
- Beta-blocker and MRA as recommended by guidelines
- SBP ≥100 mmHg run-in/ ≥95 mmHg at randomization
- eGFR ≥30 ml/min/1.73m²/ no decrease >25% (amended to 35%)
- Potassium ≤5.2 mmol/l run-in/ ≤5.2 mmol/l at randomization

PARADIGM-HF: Pre-specified endpoints
- Primary: Cardiovascular death or heart failure hospitalization
  - Cardiovascular death
  - Heart failure hospitalization
- Secondary:
  - Death from any cause
  - KCCQ (CSS - symptoms and physical limitations)
  - New onset atrial fibrillation
  - Decline in renal function
PARADIGM-HF: Primary outcome
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Cumulative Proportion of Patients with Primary End Point (%)
Days after Randomization
0 10 20 30 40

HR: 0.80 (0.73, 0.87) p = 0.0000004

At risk
Enalapril: 4212 3883 3579 2922 2123 1488 853 236
LCZ696: 4187 3922 3663 3018 2257 1544 896 249

CVD Death or HF Hospitalization

NT-proBNP with Treatment:

NT-proBNP vs BNP
PARADIGM

Data from Packer et al. Circulation 2015.
Monitoring with NP’s: Lessons from PARADIGM

- Among pts with NT-proBNP >1000:
  - A drop to <1000 \(\rightarrow\) better outcomes
  - 2x as likely with sacubitril/valsartan than with enalapril

Zile et al. JACC 2016.

What can biomarkers tell us about Diastolic HF?

- PARAMOUNT – phase 2 study
  - 200mg bid vs valsartan 160mg bid
  - N=149, EF ≥45% (mean 58%), class II-IV HF, NTproBNP>400
  - reduced NT-proBNP levels @ 12 wks
  - Similar safety profile


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PARAMOUNT

\[\text{NT-proBNP (pg/mL)}\]

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in HFpEF?

- PARAMOUNT – phase 2 study
  - 200mg bid vs valsartan 160mg bid
  - N=149, EF ≥45% (mean 58%), class II-IV HF, NTproBNP>400
  - reduced NT-proBNP levels @ 12 wks
  - Similar safety profile

- Phase 3 study: PARAGON – not yet out

Heart Failure + infection

- Heart failure + pneumonia is present ~10-15% of the time.
- Heart failure + any infection may occur in up to 20% of hospitalized HF patients.
- Hospital mortality may be up to 20% (vs 5%) in HF patients with untreated infections.

Procalcitonin:
PCT increases with increased likelihood and severity of bacterial infection.

FDA approved for assessing risk of progression to severe sepsis.

Cardiac Troponins

- Troponin T
- Troponin I
- Highly sensitive Troponin T or I
2013 ACCF/AHA Guidelines for the Management of HF

Class I indication for “additive risk stratification”

Causes of Troponin Release in Heart Failure

Januzzi et al. EHJ 2012

Recommendations for using troponin in Acute Heart Failure

- Exclude type I MI (ACS)
  - Rising/falling pattern
  - Signs/symptoms of ischemia
  - Imaging evidence
- May rise and fall even without MI
  - ADHF → rise; treatment of HF → fall
- Tn >99th percentile → worse outcome
  - Regardless of type I MI/ACS

Troponin and Prognosis in ADHF:
Data from the ADHERE Registry

PARADIGM-HF: median hs-TnT (µg/l) concentration by visit

![Graph showing median hs-TnT concentration](image)

Randomization

2-4 wk enalapril

LSZ 1/2 wk

**p=0.0001**

V2/2a Prior to Run-in

V5 Randomization

V7 4 weeks

V10 8 months

Data from Packer et al. Circulation 2015

ST2: Overview

ST2 and IL-33: Cardioprotective

- ST2: member of the Interleukin-1 receptor family
- Exists in two main isoforms
  - ST2L
  - Circulating sST2
- IL-33 binding to ST2L triggers cardioprotective effects.

Kakkar et al. Nat Rev Drug Discov 2008

Competitive Model of ST2/IL-33 Signaling

- sST2 acts as decoy receptor
- IL-33 can bind to sST2, reducing [IL-33] available to ST2L

Kakkar et al. Nat Rev Drug Discov 2008
ST2 Predicts 30-Day Mortality after Acute Decompensation in HF (PRIDE Study)

After acute event:
- ST2 identifies patients at highest risk during first 30-days
- Prognostic value persists to 1 year and beyond.

Kaplan-Meier Curve based on supplemental data provided by investigators from PRIDE study. Original study results published: Januzzi J et al. JACC 2007

ST2 Concentrations and 1-Yr Mortality in Acute HF:
As ST2 levels increase, so does risk...

2013 ACCF/AHA Guidelines for the Management of HF

"Biomarkers of myocardial fibrosis, ST2 and galectin-3, are not only predictive of hospitalization and death in patients with HF, but also additive to NP levels."

TIME-CHF Study
ST2 and 18m survival in HFP EF vs HFR EF

622 symptomatic HF patients

ST2 equally predictive
Changes one might consider on the basis of biomarkers prior to discharge

- Extra hospital time
- One week follow-up
- Home nursing
- Telemonitoring
- More aggressive titration of meds

When to order ST2 in ADHF?

- Admission?
- Discharge?
- Post-discharge?

Admission vs Discharge ST2 in Acute HF

- N=182 pts admitted with AHF; “real life population”
- Admission and d/c ST2 and NT-proBNP

Admission ST2 Level

Discharge ST2 Level

→ Discharge ST2 more predictive of outcomes
**ST2 Levels Predict Response to Treatment: Beta-blockers**

- Cumulative survival
- Days
- BB treated ST2 responder
- untreated ST2 responder
- untreated ST2 non-responder
- p=0.02
- p=0.1

- Risk can be attenuated!
- Patients identified by ST2 are at increased risk and should receive therapy!

**ST2 Predicts Response to Treatment: Aldosterone Blockade in STEMI**

- Eplerenone prevents adverse ventricular remodeling
- ST2 predicts which pts are most at risk...
- AND which pts will benefit most from aldosterone blockade

- Eplerenone attenuates remodeling more in pts with higher baseline ST2.

**Key Take-Home Points**

- NP’s are still the gold standard for diagnosis, prognosis, and guiding therapy
- Troponin – not for HF diagnosis, but often elevated and prognostic in HF
- New-comers:
  - PCT and ST2 have promise for diagnosis and prognosis/guiding therapy, respectively
- For any/all: in clinical context!