Using Natriuretic Peptides, Troponin, and ST2 to Detect, Risk Stratify, and Guide Therapy of HF

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Outline
1. HF Guidelines
2. hsTn
3. NT-proBNP
4. ST2

Yancy et al. 2017
• Natriuretic peptides
• Markers of injury or fibrosis

1. Prevention of HF
2. Diagnosis
3. Prognosis

Fibrosis/injury markers for risk assessment

2017 ACC/AHA/HFSA HF guidelines

2017 Heart failure clinical practice guidelines

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Prevention of Heart Failure

• STOP-HF
• PONTIAC
STOP-HF trial
St Vincent’s Screening to Prevent HF Study – Randomized, Controlled Trial

- Routine care (n=677)
- Routine PCP care
- Cardiology care PRN
- BNP-directed care (n=697)
  - Annual BNP check
  - If BNP >50 pg/ml at any time: cardiology consult, echo, nurse-coaching

Ledwidge et al. JAMA 2013

1° Endpoint: LV systolic or diastolic dysfunction, or heart failure
2° Endpoints: Emergency hospitalization for arrhythmia, TIA, stroke, MI, PE/DVT, HF

STOP-HF trial: results

Reduction in primary endpoint (p=0.003)

Huelsmann et al. JACC 2013

PONTIAC

- Single center RCT
- N=300 subjects with type 2 diabetes and NT-proBNP >125 pg/mL
- “Control” group – care at diabetes unit
  - “Intensified” group – additional treatment at cardiology clinic for up titration of RAS and BB
- Outcome – hospitalization/cardiac death at 2 years

(Aside: based on post-hoc analysis of HOPE study, showing the benefit was primarily in pts with NT-proBNP > median)


PONTIAC: how was 1° endpoint achieved?

Similar BP, but...
Higher use and doses of RAS and BB

Huelsmann et al. JACC 2013
Why did STOP-HF and PONTIAC work?

- What early signal are the biomarkers picking up on?

Biomarkers as a surrogate for early fibrosis

Frequency of LV scar on LGE cardiac MRI by hs-cTnT category in clinically CVD-free adults

Seliger, Hong, Christensen, Kronmal, Daniels et al. Circulation 2017.

Minor elevations in hsTnT associated with fibrosis and progressive changes in LV structure → precedes HF sx’s by years

Cumulative risk of HFrEF and HFpEF by LVH-biomarker group

*Malignant* LVH defined by LVH + biomarkers → ↑ risk of progression to LV dysfn, HF (HFrEF)

*Elevated hs-cTnT or NT-proBNP defined as upper tertile per decade of age

- No LVH, no biomarker elevated N=2206
- No LVH, ≥1 biomarker elevated N=2275
- LVH, no biomarker elevated N=153
- LVH, ≥1 biomarker elevated N=351

Future Studies

- PONTIAC II – Europe
- ADOPT – Asia; SGLT2i
- Prevention of CVD in patients with type 2 diabetes without known CVD
- Testing strategy of therapy intensification in higher risk pts with NTproBNP > 125 pg/mL to prevent CV events

(But how do we know that those with Ntpro <125 pg/mL wouldn’t benefit too…?)
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Why Switch to hsTroponin?
• Avoids missing small MI’s
• Earlier diagnosis of NSTEMI
• Earlier and safer rule-out of CP without NSTEMI
• Faster turnaround time in ED
• Patient satisfaction

Prognostic Value of Troponin
↑ troponin = ↑ death!

Question:
If you present to the ED with chest pain and a normal, stable hsTn of 10-14 ng/L:
• What is your likelihood of dying in the next 3 years?

Notes:
• 99th percentile: 19 ng/L (or 14 ng/L women, 21 ng/L men)
• Limit of detection in US: <6 ng/L
Question:
If you present to the ED with chest pain and a normal, stable hsTn of 10-14 ng/L:
• What is your likelihood of dying in the next 3 years?
Answer: >1 in 7!
• 15% (Compared to 1 in 56 if hsTn <5 ng/L)
Don’t ignore hsTn in your (HF) patients, even if not an MI!

Relationship of hsTnT and Mortality by Dx in SWEDEHEART Registry
n=46,594 with suspected ACS
Higher hsTn = DEATH, regardless of etiology!

Prognostic Value of hsTnT in Chronic HF

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GUIDE-IT
• ~900 high-risk HFrEF patients randomized to NT-proBNP guided treatment vs usual care
  • EF ≤ 40%
  • Elevated NT-proBNP within 30 days, and
  • Recent HF hospitalization
• Goal of titrating medications to NT-proBNP <1,000 pg/mL
• Endpoint: time to 1st HF admission, or CV mortality

Stopped early for futility.

Primary Outcome: 1st HF hospitalization or CV Death
Similar Improvement in NT-proBNP in BOTH arms

Felker et al. JAMA 2017

GUIDE-IT Explained

- Excellent, highly specialized HF treatment in both arms
- Patients in usual care arm seen monthly, on average
- No difference in GDMT achieved

→ Similar natriuretic peptide lowering in both arms
  • (~50% reduction exceeds that in most other similar studies)

With monthly visits, and a highly specialized HF team, NP-guided treatment may not be "usual" care.

A closer look at NP’s in GUIDE-IT

- GDMT intensity was associated with lower NT-proBNP
- Regardless of dose of GDMT, lower NT-proBNP had better outcomes
  • Those who achieved NT-proBNP < 1000 pg/mL by 90d had:
    - 74% ↓ risk of HF
    - 66% ↓ risk of all-cause mortality
    - Better QOL

Analogous Findings in PARADIGM-HF

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 ≤ 40% (amended to ≤ 35%).
- BNP ≥150 pg/ml (NTpro-BNP ≥600 pg/ml) or if HF hosp. within 12 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 / no decrease >25% (amended to 35%)
- Potassium ≤5.2 run-in/ ≤5.2 at randomization

McMurray et al. NEJM 2014

NP Levels in PARADIGM-HF and Outcomes

Zile et al. JACC 2016.
Monitoring with NP’s: Lessons from PARADIGM

- Among pts with NT-proBNP >1000:
  - A drop to <1000 → better outcomes, in both study arms
  - 2x as likely with sacubitril/valsartan than with enalapril

Dropping NP – better prognosis

Zile et al. JACC 2016

Association of NP levels with CV Events Before and During Treatment with Sacubitril/Valsartan

PARAMOUNT Study: HFpEF

- PARAMOUNT – an NT-proBNP endpoint study (Phase II)
  - LCZ696 200mg bid vs valsartan 160mg bid
  - Primary Endpoint: change in NT-proBNP at 12 weeks
  - N=149, EF ≥45% (mean 58%), class II-IV HF, NT-proBNP>400
  - Results:
    - LCZ696 reduced NT-proBNP levels @ 12 wks (1ˢᵗ outcome)
    - Not powered for events – numerically less in LCZ696 group
    - Similar safety profile

What can NP’s tell us about sacubitril/valsartan in HFpEF?

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PARAMOUNT

ABC

PARAGON Results

ARNI’s in HFpEF: PARAGON

- Phase III study of sacubitril/valsartan in HFpEF –
  - N=4822
  - NYHA Class II-IV
  - EF ≥ 45%
  - Elevated NT-proBNP
  - Structural heart disease
  - Sacubitril/valsartan vs valsartan

RR 0.87
P<0.06

Solomon et al. NEJM 2019.

Await details on NP data

Solomon et al. Lancet 2012

A new class of agents for HFpEF?
Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696

From the 2017 ACC/AHA/HFSA HF Guidelines:

“Note that the type of natriuretic peptide assay that has been performed must be considered during interpretation of natriuretic peptide biomarker levels in patients on ARNI.”

Recommendations for using NP’s in patients on sacubitril/valsartan

- For BNP
  - May need to establish a new baseline/“dry” BNP
  - Or account for ~20% rise within ~1 month of initiation
- For NT-proBNP
  - No adjustment needed

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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.

ST2 in Acute Heart Failure

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

ST2 in Acute Decompensated HF Cohorts

2017 Guidelines Summary: Indications for use of Biomarkers in HF
ST2 in Chronic, Ambulatory HF Cohorts

HR for risk of death at 1 year, with ST2 >35 ng/ml

Univariable
Adjusted for age, sex, NYHA class, EF, GFR, diabetes, HTN, and smoking

Daniels LB, Future Cardiol 2014

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


High and low ST2 separated at median.

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

ST2 Levels: Monitoring and Response to Treatment

Short-Term Changes in ST2 are Associated With Long-Term Events in HF

Bayes-Genis A, et al., Rev Esp Cardiol . 2010

ST2 Ratio: Week 2/Baseline
1-year CV death, hospital admission for HF, or urgent cardiac transplant


Baseline ST2 and Outcomes in PARADIGM-HF

Higher baseline ST2 ⇒ Higher risk

Sacubitril/valsartan lowered ST2 levels in PARADIGM-HF
Baseline vs 8 months

Summary

- GDMT can lower NP, Tn, and ST2 levels
- Lower NP, Tn and ST2 levels are associated with better outcomes
  - Regardless of how you get there
- Biomarkers will make bad doctors worse...
  - And good doctors better.
- Always use them in context!

Thank You