Biomarkers to Detect, Risk Stratify and Help Manage Heart Failure

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Disclosures

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• Clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, CVRx, Janssen, MyoKardia, and Takeda

• Trustee, American College of Cardiology
# HF Clinical Practice Guidelines

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**Indications Class LOE**

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LOE, level of evidence.

NT-proBNP Levels Were Elevated in Patients With Acute HF in the PRIDE Study*

CHF, congestive heart failure; PRIDE, N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department.
*Patients (N = 599) were consenting adults ≥21 years of age presenting to the emergency department of the Massachusetts General Hospital with complaint of dyspnea. †P value represents the comparison of acute CHF with patients with not-acute CHF.

## Changes in HF demographics since early 2000’s

<table>
<thead>
<tr>
<th>Changes</th>
<th>Possible effects on NT-proBNP cut offs</th>
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<tbody>
<tr>
<td>Patients are older</td>
<td>Higher optimal threshold?</td>
</tr>
<tr>
<td>More AF</td>
<td>Higher optimal threshold?</td>
</tr>
<tr>
<td>More CKD</td>
<td>Higher optimal threshold?</td>
</tr>
<tr>
<td>More HFpEF</td>
<td>Lower optimal threshold?</td>
</tr>
<tr>
<td>Patients are heavier</td>
<td>Lower optimal threshold?</td>
</tr>
<tr>
<td>Clinicians are treating to lower NT-proBNP</td>
<td>Lower optimal threshold?</td>
</tr>
<tr>
<td>Changes in HF therapies (neprilysin inhibition)</td>
<td>Lower optimal threshold?</td>
</tr>
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</table>
A new trial was needed to validate NT-proBNP cut-offs in the ED setting.

- A multi-center, international trial, sponsored by Roche Diagnostics and performed by the Baim Institute for Clinical Research (Boston, MA).


International Collaborative of NT-proBNP: Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department.
ICON-RELOADED Results: NT-proBNP

ICON-RELOADED Results: Cost-effectiveness

- 14% fewer initial hospitalizations
- 15% fewer admissions to cardiology or ICU
- 30% reduction in echocardiograms
- 26% fewer ED or hospital readmissions

Siebert, et al, Submitted, 2020
• Use of NT-proBNP decreased the average inpatient management costs by a relative 10.4% ($20,247 vs. $22,584) and reduced the total length of stay in ED and hospital, yielding cost savings of $2,337/pt

• NT-proBNP reduced SAEs by 5.9% compared to clinical assessment alone

Siebert, et al, Submitted, 2020
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LOE, level of evidence.

Discharge NT-proBNP Values and Change in NT-proBNP Levels During Hospitalization Predict CV Event Rates

Meta-analysis of patients (N = 1301) hospitalized for acute decompensated heart failure from 7 prospective cohort studies. Permission requested from Heart for figure use. Salah K et al. Heart. 2014;100:115-125.
Operationalizing NT-proBNP Monitoring to Enhance Clinical Decision Making in ADHF

• Two measurements:
  • At presentation for diagnosis, triage, and prognostication
  • At the end of hospitalization to evaluate for treatment response and provide hospital to home link
    ✓ 30% drop is desirable, and lower is always better
    ✓ If baseline levels are not available, discharge NT-proBNP <4000 pg/mL is desirable
    ✓ Non-falling or rising values identify a patient at imminent risk for rehospitalization and/or death

ADHF, acute decompensated heart failure.
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LOE, level of evidence.
Judging longitudinal risk in chronic HF

- Physical findings
- Signs/symptoms
- Quality of life scores (e.g. KCCQ)
- Filling pressures (e.g. CardioMems)
- Biometric data (e.g. activity, HR patterns)
- Imaging
- Biomarkers
Outcomes and achieved NT-proBNP

Number of events per 100 patient-years of follow-up

- All-course death
- CV death or HF hosp

Log2 of NT-proBNP at 90 days and clinical outcomes

<table>
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<tr>
<th>Outcome</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
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<td>All Cause Death(^A)</td>
<td>0.58 (0.50–0.68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HF Hosp/CV Death(^B)</td>
<td>0.65 (0.57–0.73)</td>
<td>&lt;.001</td>
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HR is with respect to halving of NT-proBNP

\(^A\)Adjusted for history of ischemic heart disease, depression treated with medication, third heart sound, age, diastolic BP, congestion score, HF duration, heart rate, SpO2, sodium, and 6-minute walk distance.

\(^B\)Adjusted for sleep apnea, depression treated with medication, Hispanic ethnicity, ICD or pacemaker, atrial fibrillation at baseline, Black race, history of ischemic heart disease, NYHA class, diastolic BP, creatinine, heart rate, potassium, and sodium.
Time to first event after 90 days

All-cause mortality

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<th>Responder</th>
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<tr>
<td>HR^A</td>
<td>0.34</td>
<td>0.15–0.77</td>
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CV death/HF hospitalization

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<th>Responder</th>
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<td>HR^B</td>
<td>0.26</td>
<td>0.15–0.46</td>
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^AAdjusted for history of ischemic heart disease, depression treated with medication, third heart sound, age, diastolic BP, congestion score, HF duration, heart rate, SpO2, sodium, and 6-minute walk distance.

^BAdjusted for sleep apnea, depression treated with medication, Hispanic ethnicity, ICD or pacemaker, atrial fibrillation at baseline, Black race, history of ischemic heart disease, NYHA class, diastolic BP, creatinine, heart rate, potassium, and sodium.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NTproBNP, N-terminal pro-B type natriuretic peptide.
Lower NT-proBNP is associated with better KCCQ scores

Pina, et al, AHA 2019
Change in LV structure and function at 1 year by NT-proBNP reduction

ΔNT-proBNP (pg/mL): -1000 -2000 -3000 -4000 -5000

EF, ejection fraction; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; LV, left ventricular; NTproBNP, N-terminal-pro-B type natriuretic peptide.
Importance of biomarker testing for HF monitoring

**Studies to Consider Initially:**
(see full guidelines for details)

- BNP/NT-proBNP
- CBC, basic metabolic panel, liver function, iron studies, thyroid studies, HbA1c
- EKG
- Chest X-ray
- Echocardiogram
- Coronary angiogram, cardiac MRI, biopsy, other imaging as appropriate

**Serial Evaluation and Titration of Medications**

- Clinic visit with history symptoms, vitals, exam labs
- If volume status requires treatment, adjust diuretics, follow up 1–2 weeks
- If euvoledmic and stable, start/increase/switch GDMT, follow-up 1–2 weeks via phone or repeat clinic visit with basic metabolic panel as may be indicated
- Repeat cycle until no further changes are possible or tolerated

**End-intensification/maintenance**

- Ongoing assessment
- Additional adjustments as indicated
- Repeat objective data as needed to reestablish prognosis

**Assess response to therapy and cardiac remodeling**

- Repeat laboratory tests, for example, BNP/NT-proBNP and basic metabolic panel
- Repeat echocardiagram (or similar imaging modality for cardiac structure and function)
- Repeat EKG
- Consider EP referral for those eligible for CRT or ICD

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**Remember acronym to assist in decision making for referral to advanced heart failure specialist: I-NEED-HELP**

<table>
<thead>
<tr>
<th>I</th>
<th>N</th>
<th>E</th>
<th>E</th>
<th>D</th>
<th>H</th>
<th>E</th>
<th>L</th>
<th>P</th>
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<tr>
<td>IV inotropes</td>
<td>NYHA IIIB/IV or persistently elevated natriuretic peptides</td>
<td>End-organ dysfunction</td>
<td>Ejection fraction ≤ 35%</td>
<td>Defibrillator shocks</td>
<td>Hospitalisations &gt;1</td>
<td>Edema despite escalating diuretics</td>
<td>Low blood pressure, high heart rate</td>
<td>Prognostic medication – progressive intolerance or down titration of GDMT</td>
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**BNP, B type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal-pro-B type natriuretic peptide.**

Operationalizing NT-proBNP monitoring to enhance clinical decision-making in chronic HF

- In recently decompensated patients, measure 1–2 weeks after discharge (office or home).
- In stable ambulatory patients, measure every 3 months
  - Stable concentrations <1000 pg/mL: imaging and other testing may be deferred
  - Elevated/rising concentrations: repeat imaging, further evaluations, review medication/lifestyle program and adjust as appropriate
- Markedly elevated concentrations: Consider transplant referral, consider diagnoses associated with “unexpectedly elevated” NT-proBNP (amyloidosis).

HF, heart failure; NT-pro-BNP, N-terminal pro-B type natriuretic peptide.
Other risk biomarkers predictive of remodeling

- Soluble ST2: a biomarker of myocardial fibrosis and remodeling
- High sensitivity cardiac troponin
- Collagen markers, mimecan, IGFBP7
Excessive fibrosis in dysregulated ST2 signaling

Aimo, et al, JACC Heart Failure 2017
Serial measurement of sST2

The ST2-R2 score consists of:

- sST2 < 48 ng/mL = 3 pts
- Non-ischemic etiology = 5 pts
- No LBBB = 4 pts
- HF < 1 year = 2 points
- LVEF <24% = 1 point
- Beta blocker therapy = 2 points
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LOE, level of evidence.

STOP-HF Trial to Investigate the Efficacy of a Screening Program Using BNP and Collaborative Care

**Routine PCP Care**
- Annual BNP not available to clinicians
- At least annual review by PCP
- Cardiology review only if requested by PCP

**BNP-Directed Care**
- In addition to routine care, annual BNP in all patients
- If BNP >50 pg/mL at any time
  - Shared care
    - Cardiology review
    - Echo-Doppler
    - Other CV investigations
    - CV nurse coaching
    - Cardiology follow-up

A parallel-group randomized trial involving 1374 participants with cardiovascular risk factors recruited from 39 primary care practices in Ireland between January 2005 and December 2009 and followed up until December 2011.

PCP, primary care physician; STOP-HF, St. Vincent’s Screening to Prevent Heart Failure.

Prevalence of Asymptomatic LVSD Was Lower Following BNP-Directed Care

LV Dysfunction and HF at 8 Years

Control Group (n = 677)  BNP Group (n = 697)

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<th>Condition</th>
<th>Control</th>
<th>BNP</th>
<th>P-value</th>
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<tr>
<td>LVDD</td>
<td>3.8</td>
<td>2.0</td>
<td>.08</td>
</tr>
<tr>
<td>LVSD</td>
<td>2.8</td>
<td>2.3</td>
<td>.26</td>
</tr>
<tr>
<td>HF</td>
<td>2.1</td>
<td>1.0</td>
<td>.17</td>
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LVDD, left ventricular diastolic dysfunction.
Neurohormonal Therapy for Primary Prevention of CV Events in Patients With Diabetes With Elevated NT-proBNP

The PONTIAC Trial investigated the preventive effect of neurohormonal therapy in high-risk patients with diabetes with elevated NT-proBNP.

Cox Regression Models

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<th>Endpoint</th>
<th>HR</th>
<th>95% CI</th>
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<td>Hospitalization or death due to cardiac disease</td>
<td>0.351</td>
<td>0.127-0.975</td>
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<td>All-cause hospitalizations</td>
<td>0.657</td>
<td>0.465-0.927</td>
<td>.02</td>
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<td>0.376</td>
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<td>.03</td>
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<td>0.140</td>
<td>0.017-1.137</td>
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Endpoints

- Hospitalization or death due to cardiac disease: HR = 0.351 (95% CI: 0.127-0.975), P = .04
- All-cause hospitalizations: HR = 0.657 (95% CI: 0.465-0.927), P = .02
- Unplanned CV hospitalization or death: HR = 0.376 (95% CI: 0.157-0.899), P = .03
- HF hospitalizations: HR = 0.140 (95% CI: 0.017-1.137), P = .07

Patients (N = 300) with type 2 diabetes and elevated NT-proBNP (>125 pg/mL), but free of cardiac disease. Control group patients (n=150) were treated at 4 diabetes care units. Treatment group patients (n=150) were additionally treated at a cardiac outpatient clinic for the up-titration of RAAS antagonists and beta-blockers.

Conclusions

• Biomarkers play a clinical role for diagnosis, prognosis, management and possibly prevention of HF

• The natriuretic peptides play the largest role but this says more about our lack of imagination than anything else

• Other biomarkers with links to remodeling may add information for diagnosis and prognostication