The Latest in Biomarkers: BNP, ST2 and hsTn – What Must You Know?

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Professor of Medicine, University of California, Emeritus
The Epidemic of Heart Failure

- Heart failure is common, costly, and deadly
- Prevention, diagnosis, risk stratification, monitoring, and managing heart failure is challenging
- There has been great interest in the clinical role of biomarkers in heart failure

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Hospital Discharges</th>
<th>Outpatient Visits</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,100,000</td>
<td>670,000</td>
<td>50% at five years</td>
<td>1,023,000</td>
<td>12-15 million</td>
<td>$39.8 billion</td>
</tr>
</tbody>
</table>

Clinical Role of Biomarkers in Heart Disease

**Diagnosis:** Biomarkers may provide additional information beyond standard history, physical examination, and other diagnostic testing to diagnose HF and in MI are often sufficient if a good history is present.

**Screening:** Biomarkers may identify patients at risk for developing CV disease.

**Risk Stratification:** Biomarkers may provide prognostic information that is incremental to other prognostic variables.

**Treatment Guide:** Biomarkers may more effectively guide initiation and titration of certain therapies, improving outcomes.
Objectives of Biomarker Testing in Heart Failure

Condition X

Biomarker

Outcome A

Intervention

Outcome B
Is There Really a Need for Biomarker Guided Titration of GDMT in HF?

The CHAMP Registry

- 3158 patients with HFrEF from 150 practices.
- Prospective, observational, nonrandomized study of adult outpatients with HFrEF (LVEF <40%) receiving at least one oral medication for HF at study enrollment.
- Mean age was 66 years, 29% were female, and mean EF was 29%.
Despite <2% with contraindications, **use** of GDMT was <75% for each therapy.

Use of both MRA and ARNI was particularly low, at 33% and 13%, respectively.

Can This be Fixed? Results from IMPROVE HF

Quality improvement is possible!

Wouldn’t it be nice to target those patients at highest risk for adverse outcome?

167 practices, 34,810 heart failure patients enrolled
Wetterson, Maisel AJM in press
How Good Is the History and Physical in AHF?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx of HF</td>
<td>62</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>56</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>47</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
<td>Rales</td>
<td>56</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>S3</td>
<td>20</td>
<td>99</td>
<td>66</td>
</tr>
<tr>
<td>JVD</td>
<td>39</td>
<td>94</td>
<td>72</td>
</tr>
<tr>
<td>Edema</td>
<td>67</td>
<td>68</td>
<td>68</td>
</tr>
</tbody>
</table>

Raising the bar

Natriuretic peptides are and will remain the standard diagnostic biomarker for acute heart failure.
How Sure Are Physicians in the ED About the Diagnosis of HF?

Significant Indecision Exists 43%
What happens if we misdiagnose the acute breathless patient?

Dyspnea of respiratory origin

- Bronchodilators: 4%
- No therapy: 8%
- CHF Therapy: 14%

P < 0.05

Breathing Not Properly STUDY
Biomarkers Indications for Use

ACC/AHA Stage A/B HF
- At risk for HF
  - Prevention: BNP or NT-proBNP (COR IIa)
  - Diagnosis: BNP or NT-proBNP (COR I)
  - Prognosis or added risk stratification: Other biomarkers of myocardial injury or fibrosis* (COR IIb)

ACC/AHA Stage C/D HF
- Ambulatory pts with new-onset dyspnea
  - BNP or NT-proBNP (COR I)
  - Prognosis or added risk stratification: Other biomarkers of myocardial injury or fibrosis* (COR IIb)

ACC/AHA Acute/Hospitalized HF
- Acute dyspnea to ED
  - BNP or NT-proBNP (COR I)
- Hospitalized for ADHF
  - BNP or NT-proBNP, and cardiac troponin (COR I)
  - Predischarge BNP or NT-proBNP (COR IIa)
  - Other biomarkers of myocardial injury or fibrosis* (COR IIb)
Accuracy is 90%

Optimal cut-off point determined @ 100 pg/mL

Positive predictive value = 75%

Negative predictive value = 90%


<table>
<thead>
<tr>
<th>BNP</th>
<th>Final Diagnosis Heart Failure</th>
<th>Final Diagnosis NOT Heart Failure</th>
</tr>
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<tbody>
<tr>
<td>100 pg/mL</td>
<td>673</td>
<td>227</td>
</tr>
<tr>
<td>&lt;100 pg/mL</td>
<td>71 Sensitivity = 90%</td>
<td>615 Specificity = 73%</td>
</tr>
</tbody>
</table>
Clarification of Diagnosis & BNP

BNP reduces clinical indecision by 74%

- Clinical: 43%
- Clinical Evaluation: 11%
NtproBNP cut-offs

• 1. 125 < 75 y.o. and 450 > 75 yo
• 2. 450, 900, 1800 based on age
• 3. 300 to rule out.
### Confounders of NP interpretation

<table>
<thead>
<tr>
<th>Higher NP levels than expected</th>
<th>Lower NP levels than expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age*</td>
<td>Obesity</td>
</tr>
<tr>
<td>ACS*</td>
<td>Flash pulmonary edema</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Pericarditis/Tamponade</td>
</tr>
<tr>
<td>RV dysfunction*</td>
<td>Genetic polymorphisms</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>“Burned-out” Cardiomyopathy</td>
</tr>
<tr>
<td>Pulmonary hypertension*</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism*</td>
<td></td>
</tr>
<tr>
<td>Anemia/high output states*</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
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<tr>
<td>Mitral Regurgiation*</td>
<td></td>
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* Delineates likely elevation from Ventricular stretch
PATIENT WITH SUSPECTED HF
(non-acute onset)

ASSESSMENT OF HF PROBABILITY

1. Clinical history:
   - History of CAD (MI, revascularization)
   - History of arterial hypertension
   - Exposition to cardiotoxic drug/radiation
   - Use of diuretics
   - Orthopnoea / paroxysmal nocturnal dyspnoea

2. Physical examination:
   - Rales
   - Bilateral ankle oedema
   - Heart murmur
   - Jugular venous dilatation
   - Laterally displaced/broadened apical beat

3. ECG:
   - Any abnormality

≥1 present

Assessment of natriuretic peptides not routinely done in clinical practice

NATRIURETIC PEPTIDES
- NT-proBNP ≥125 pg/mL
- BNP ≥35 pg/mL

All absent

Yes

ECHOCARDIOGRAPHY

Normal

If HF confirmed (based on all available data):
determine aetiology and start appropriate treatment

HF unlikely: consider other diagnosis
NATRIURETIC PEPTIDES

- NT-proBNP $\geq 125$ pg/mL
- BNP $\geq 35$ pg/mL
NT-proBNP in GUIDE IT

Time to First Event After 90 Days

**All-cause mortality**

<table>
<thead>
<tr>
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<th>Non-responder</th>
<th>Responder</th>
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<tbody>
<tr>
<td><strong>HR</strong></td>
<td>0.34</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>0.15 - 0.77</td>
<td>0.15 - 0.46</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.009</td>
<td>&lt;0.001</td>
</tr>
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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.

**CV death/HF hospitalization**

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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.
Change in LV Structure and Function at 1 Year by NT-proBNP Reduction

Daubert et al. JACC Heart Failure, In Press
Reverse remodeling was not obvious until NT-proBNP concentrations were reduced below 1000 pg/mL.
Cardiac Troponins
Overview and Mechanism of Troponin Release

- Increased Wall Stress
- Epicardial CAD
- Oxidative Stress
- Neurohormonal Activation
- Altered Calcium Handling

Cardiac Troponin Release
- Reversible Injury
- Myocyte Necrosis
- Myocyte Apoptosis
- Troponin Degradation Products
- Inflammatory Cytokines

Reversible Injury
Myocyte Necrosis
Myocyte Apoptosis
Troponin Degradation Products
Inflammatory Cytokines
Troponin & Heart Failure

• ANY troponin is worse than NO troponin

Peacock et al. NEJM. 2008:358:2117
Regardless of the Cause, Elevated Troponins Portend Poor Prognosis

**CHF**
- Cardiac Events (%)
  - cTnT ≥ 0.05 μg/L
  - Follow-up (months)
  - P = 0.0004

**Sepsis During ICU Stay**
- Median cTnT (μg/L)
- Non-survivors (n=12)
- Survivors (n=8)

**Acute Stroke**
- Survival (%)
  - Normal troponin (deaths, n=19)
  - Increased troponin (deaths, n=12)
  - Days After Admission
  - P = 0.0012

**Pulmonary Edema**
- Cumulative Survival
  - cTnT ≥ 0.1 μg/L
  - Follow-up (months)
  - P = 0.001

**Non-Cardiac, Critically ill ED Patients**
- Cumulative Survival
  - cTnT ≥ 0.4 μg/L
  - Follow-up (Days)
  - P = 0.91

**Postoperative Vascular Surgery**
- cTnT ≥ 0.8 μg/L (n = 198)
- Weeks after Surgery
sST2- has evolved to be a useful marker
Soluble ST – 2

ST-2: Suppressor of tumorigenicity 2 (IL-1 receptor-like-1)
Member of Interleukin-1 receptor family
membrane bound receptor: ST-2L (Profibrotic signaling)
soluble truncated form: sST-2 (Decoy receptor)

IL-33: Interleukin 33, Binds to ST-2L & Inhibits Profibrotic signaling

Interleukin-33 (IL-33)

ST2L

Fibroblast

Pro-fibrotic Signaling
Pro-fibrotic Signaling

↑ sST-2 binds IL-33 &
↓ inhibition of ST-2L profibrotic signaling
↑ Fibrosis

Interleukin-33 (IL-33)

Decoy Receptor

Pro-fibrotic Signaling
ST2 plays a role in reducing cardiomyocyte hypertrophy and fibrosis

Abnormalities in ST2 experimentally result in severe cardiac remodeling and heart failure

Intact sST2

sST2 knock out
SOLID CUTPOINTS

35 ng/ml > HIGH RISK outpatient

= RISK NG/ML

70 HIGH RISK ED
ST2 not affected by

- Age
- Sex
- BMI
- Etiology of HF
- Atrial Fibrillation
- Anemia
In a cohort of 879 heart failure patients ST2 did not show any correlation with renal function whereas NT-proBNP concentrations increased significantly with decreasing renal function.
sST2 elevated in other conditions

• Severe sepsis
• Inflammatory disease
• Disseminated cancer
• Liver or other organ fibrosis
Mortality Risk Increases With ST2 Levels

One-year mortality exceeded 50% in the highest decile.

One Year Mortality (%)

ST2 Decile

P < 0.001

Additive Value of ST2 to NT-proBNP in Long Term Prognosis

- Both sST2 and NT-proBNP elevated (n=276)
- Only sST2 elevated (n=95)
- Only NT-proBNP elevated (n=54)
- Neither elevated (n=168)

P < .001

Days from enrollment
Cumulative hazard
Ramification of Change in ST2 in PROTECT:

HR\text{adj} for events for rise >35 pg/mL during study was 3.64 (p = .009)

Model adjusted for clinical variables, ejection fraction, renal function, NT-proBNP and GDF-15

sST2 predicted change in LV size/function

Gaggin, et al; JACC Heart Failure, 2013
Prognostic Value of Serial ST2 Measurements in Patients With Acute Heart Failure

Laura C. van Vark, MD, a,b Ivonne Lesman-Leegte, PhD, c Sara J. Baart, MSc, a,b Douwe Postmus, PhD, c Yigal M. Pinto, MD, PhD, d Joke G. Orsel, PhD, e B. Daan Westenbrink, MD, PhD, c Hans P. Brunner-la Rocca, MD, PhD, f Addy J.M. van Miltenburg, MD, PhD, g Eric Boersma, PhD, a,b Hans L. Hillegä, MD, PhD, c K. Martijn Akkerhuis, MD, PhD, a,b for the TRIUMPH Investigators

ABSTRACT

BACKGROUND

Several clinical studies have evaluated the association between ST2 and outcome in patients with heart failure (HF). However, little is known about the predictive value of frequently measured ST2 levels in patients with acute HF.

OBJECTIVES

This study sought to describe the prognostic value of baseline and repeated ST2 measurements in patients with acute HF.

METHODS

In the TRIUMPH (Translational Initiative on Unique and novel strategies for Management of Patients with Heart failure) clinical cohort study, 496 patients with acute HF were enrolled in 14 hospitals in the Netherlands between 2009 and 2014. Repeated blood samples (7) were drawn during 1-year follow-up. ST2 and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured in a central laboratory. The primary endpoint was the composite of all-cause mortality and HF rehospitalization. Associations between repeated biomarker measurements and the primary endpoint were assessed using a joint model.

RESULTS

Median age was 74 years, and 37% of patients were women. The primary endpoint was reached in 188 patients (40%) during a median follow-up of 325 days (interquartile range: 85 to 401). The median baseline ST2 level was 71 ng/ml (interquartile range: 46 to 102). After adjustment for clinical factors and NT-proBNP, baseline ST2 was associated with an increased risk of the primary endpoint, and the hazard ratio per 1 SD increase of the baseline ST2 level (on the log scale) was 1.30 (95% confidence interval: 1.08 to 1.56; \( p = 0.005 \)). When repeated measurements were taken into account, the adjusted hazard ratio per 1 SD increase of the ST2 level (on the log scale) during follow-up increased to 1.85 (95% confidence interval: 1.02 to 3.33; \( p = 0.044 \)), adjusted for clinical factors and repeated measurements of NT-proBNP. Furthermore, ST2 levels appeared to elevate several weeks before the time of the primary endpoint.

CONCLUSIONS

Repeated ST2 measurements appeared to be a strong predictor of outcome in patients with acute HF, independent of repeatedly measured NT-proBNP. Hence ST2 may be helpful in clinical practice for prognostication and treatment monitoring. (TRanslational Initiative on Unique and novel strategies for Management of Patients with Heart failure [TRIUMPH]; NTR1893) (J Am Coll Cardiol 2017;70:2378–88) © 2017 by the American College of Cardiology Foundation.
Patient: H.V.

No readmissions over **One Year**

75 y.o; HFrEF; meds increased:
- Toprol: 100mg
- Hydralazine 100+ mg
- Digoxin: 25 mg

![Line graph showing ST2 concentration levels over time with specific dates and readings: 12-14 (Adm) 3-15 (Clin) 8-15 (Clin) 4-16 (Clin). Normal ST2 level is 35 ng/mL.](image-url)
Patient: B.H.

<table>
<thead>
<tr>
<th>Date</th>
<th>ST2 Level</th>
<th>BNP Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-15 (Adm)</td>
<td>762</td>
<td>61</td>
</tr>
<tr>
<td>8-15 (Adm)</td>
<td>661</td>
<td>61</td>
</tr>
<tr>
<td>11-15 (Adm)</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>12-15 (Died)</td>
<td>511</td>
<td>0</td>
</tr>
</tbody>
</table>

ST2 Concentration Level (ng/mL)

Normal ST2 level (35 ng/mL)

BNP Concentration Level (pg/mL)

Lisinopril: 5mg
Bumex: 1mg po

BNP dropped, but not ST-2
Combined Measurement of Soluble ST2 and Amino-Terminal Pro-B-Type Natriuretic Peptide Provides Early Assessment of Severity in Cardiogenic Shock Complicating Acute Coronary Syndrome

Heli Tolppanen, MD1-3; Mercedes Rivas-Lasarte, MD1,4; Johan Lassus, MD, PhD3; Malha Sadoune, MSc1; Etienne Gayat, MD, PhD1,5; Kari Pulkki, PhD6; Mattia Arrigo, MD1,5,7,8; Evguenia Krastinova, MD, PhD1,9; Alessandro Sionis, MD4; John Parissis, MD, PhD10; Jindrich Spinar, MD, PhD11,12; James Januzzi, MD, PhD13; Veli-Pekka Harjola, MD, PhD14; Alexandre Mebazaa, MD, PhD1,5,15; for the CardShock Study Investigators and the GREAT Network
Figure 1. Kinetics of soluble ST2 (sST2) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP). Levels of sST2 (A) and NT-proBNP (B) in 30-d survivors (white boxes) and nonsurvivors (gray boxes) in time course. Central line represents median, box represents interquartile range, and whiskers represent fifth and 95th percentile.
ST2 in Chronic, Ambulatory HF Cohorts

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

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

Daniels LB, Future Cardiol 2014
Patient: K.E.

- BNP still high but ST2 low
- No readmissions in one year

Graph showing ST2 Concentration Level (ng/mL) and BNP Concentration Level (pg/mL) over time:

- ST2: 320 at 1-15 (Hosp. D/C), 343 at 3-15 (Clin), 260 at 1-16 (Clin)
- BNP: 31 at 1-15 (Hosp. D/C), 19 at 3-15 (Clin), 18 at 1-16 (Clin)

Normal ST2 level (35 ng/mL)

Medications:
- Carvedilol: 12.5mg BLD
- Eplerenone: 25mg
- Lasix: 60 mg
Patient: S.V.

92 y.o HFrEF
Carvedilol: 25mg
Lasix: 20mg

Rising EF over one year
Figure 1. Median sST2 levels before and during LVAD support with IQR (25-75%). The dotted line represents the cut-off value for normal sST2 levels (< 35 ng/ml).
ST2 and Ventricular Tachycardia: Results from MADIT-CRT

- Multivariate analysis demonstrated that ΔST2 from baseline to 12 months was independently predictive for VT (HR 3.71 [95% CI 1.4-9.8]; p=0.008).

- In the 42% of the patients with an ST2 increase of more than 7.1% risk of VT increased by 2.25 fold (95% CI 1.2-4.1; p=0.008).

- ΔST2 remained predictive even after controlling for changes in BNP, LVEF, LVESV, and LVEDV (P=0.0048).

Snider, et al, HFA 2012