Biomarkers in heart failure: state of the art

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# The Epidemic of 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>

- 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

Objectives of Biomarker Testing in Heart Disease

**Diagnosis**
- To establish or refute a diagnosis
- To understand the underlying pathophysiologic processes

**Risk Stratification/Screening**
- To determine the presence or severity of disease
- To detect adverse consequences

**Monitoring/Therapeutic Guidance**
- To facilitate selection of an appropriate therapeutic intervention
- To guide or monitor responses to treatment

Many biomarkers may be risk factors themselves; therefore, may be potential targets of therapy.

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HF, heart failure.

Heart failure is mainly a clinical diagnosis. Biomarkers will aid in diagnosis and tell you which one of these men is likely to be dead in six months.
Wetterson, Maisel AJM in press
Raising the bar

Natriuretic peptides are and will remain the standard diagnostic biomarker for acute heart failure.
Accuracy is 90%

Optimal cut-off point determined @ 100 pg/mL

Positive predictive value = 75%

Negative predictive value = 90%

<table>
<thead>
<tr>
<th>BNP Value</th>
<th>Final Diagnosis</th>
<th>Final Diagnosis NOT Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100 pg/mL &quot;Test positive&quot;</td>
<td>673</td>
<td>227</td>
</tr>
<tr>
<td>&lt;100 pg/mL &quot;Test negative&quot;</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 Evaluation

Clinical

43%

11%
The likelihood and severity of bacterial infection increase with increasing PCT levels

Müller B. et al., Crit. Care Med. 2000
Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial

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Received 3 September 2011; revised 5 November 2011; accepted 12 December 2011; online publish-ahead-of-print 2 February 2012
A combination of Natriuretic Peptide and PCT can be used to better diagnose dyspneic patients

Maisel Eur J HF 2012
High Sense Troponin in Heart Failure:

Can it guide us?
cTnT/I: quantitative marker of cardiomyocyte injury

cTnT/I: structural proteins unique to the heart

Cardiomyocyte injury: AMI, multiple other causes
Are they really false positives when the elevation gives you greater risk?

- Chronic HF
  - Elevated in 50%
- Acute HF
  - Elevated in >80%
It’s Bad to Have an MI in HF

Peacock, NEJM, 2008,
To Cath or Not to Cath

Troponin Elevation in Heart Failure
Prevalence, Mechanisms, and Clinical Implications

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Durham, North Carolina; Chicago, Illinois; and Los Angeles, California
Cardiac Cath When Appropriate Improves Outcomes

This meta-analysis of the 3 trials that assessed the long-term impact of a RI strategy demonstrated a sustained advantage for the RI strategy in reducing subsequent CV death or nonfatal MI. The 19% relative risk reduction (HR: 0.81, 95% CI: 0.71 to 0.93) reflected a 3.2% absolute reduction in the combined end point. The difference was mainly driven by the 23% relative 2.9% absolute reduction in MI. However, there was also a consistent strong trend to a reduction in cardiovascular and total mortality. The randomized treatment was applied on top of the contemporary standard of secondary prevention therapy and the treatment effect was seen despite the fact that adjunctive therapy and instrumentation evolved over the course of the successive trials (e.g., use of thienopyridines, glycoprotein IIb/IIIa antagonists, stent and catheter technology). Furthermore, the benefit was seen despite a substantial cross-over to invasive treatment event in the noninvasive treatment arm in several of the trials.

The hypothesis has been proposed that the timing of revascularization influences outcome but the most recent and largest of the studies of timing demonstrated overall benefit of an early routine intervention compared with a delayed routine intervention.

Resolving the differences in outcome compared with individual studies. Previous combined analyses have not been conducted using individual patient data, and they lacked outcomes beyond a year. Why are the findings more clear-cut in this meta-analysis compared with individual trials? First, the substantially greater sample size, and second, the greater number of outcome events over 5 years. Individual trials had limited statistical power for cardiovascular death or MI. They either had composite end points (RITA-3, ICTUS), or they were powered for a large anticipated (33%) reduction in death or MI (FRISC-II). What accounts for the trial-to-trial differences in outcomes? First, there were different inclusion criteria in the trials with more unselected populations included in the first performed trials—FRISC-II and RITA-3. In the ICTUS study, patients included were all troponin-positive and had either ischemic chest pain or documented coronary artery disease. This may in part explain the high revascularization rate in the SI arm of ICTUS. In FRISC-II and RITA-3, there was a wide separation in the frequency of early and late revascularization rates between the 2 arms of the respective trials. In FRISC-II, the revascularization rates were 71% within 10 days and 78% within 12 months in the RI group. This compares with 9% and 43%, respectively, in the SI group. In RITA-3, for the RI group, the revascularization rates were 44% within index hospitalization and 57% within 12 months compared with 10% and 28%, respectively, in the SI group. In ICTUS, for the RI group, 76% within index hospitalization and 79% within 12 months compared with 40% and 54%, respectively, in the SI group. Thus, especially the early rate of revascularization in the SI strategy was substantially higher in ICTUS than in FRISC-II or RITA-3, and the rate remained higher thereafter. In RITA-3, the rates of both early and late intervention, in the SI and RI strategies were lower than in FRISC-II and ICTUS. In fact, the rate of intervention in the SI arm of ICTUS resembled the rate in the RI arm of RITA-3.
Dilemma - Type 1 or Type 2 MI in Heart Failure

• Troponin elevations very common in heart failure
• Could be from Type 1 or Type 2
• Missing Type 1 could lead to increased mortality
• Testing (catheterization) for Type 2 exposes to risks of procedure and increased costs
First diagnose the problem

**AHF & cTn↑↑↑ → AMI**

- + typical ischemic chest pain
- + new ST ↑ or ↓
- + delta cTn 3h ↑↑

(DD: rapid AF, RR↑)
Patients with a discharge TnI >23.25 ng/L had significantly higher 90-day mortality and HF-related readmissions than patients with a discharge TnI <23.25 ng/L ($P=0.003$, HR, 3.547)$^2$

ACS, acute coronary syndrome; AHF, acute heart failure; CHF, chronic heart failure; HR, hazard ratio; hs-cTnT, high-sensitive cardiac troponin T; TnI, troponin I.

AHF Contributes to the Progression of HF

**Goal:** prevent myocardial and renal damage and implement “life-saving therapies”

**Hypothesis:** with each hospitalization there is myocardial and/or renal damage

Expression of ST2 in Cardiomyocytes

- In a study to identify novel pathways in cardiac myocyte mechanotransduction, DNA microarray technology was applied to cultured cardiac myocytes subjected to mechanical overload.

- Of the 7000 gene transcripts of known function, ST2 was extremely up-regulated in this model.
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
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
## Biological Variation Summary

*Wu, 2013, accepted Am. Heart J.*

- sST2 has the lowest intra-individual variation and smallest relative change value compared to other biomarkers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Duration</th>
<th>CV₁</th>
<th>RCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>2 mths</td>
<td>30%</td>
<td>82%</td>
</tr>
<tr>
<td>BNP</td>
<td>2 mths</td>
<td>50%</td>
<td>138%</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2 mths</td>
<td>33%</td>
<td>92%</td>
</tr>
<tr>
<td>hs-cTnI</td>
<td>2 mths</td>
<td>14%</td>
<td>63%</td>
</tr>
<tr>
<td>hs-cTnI</td>
<td>9 mths</td>
<td>28%</td>
<td>73%</td>
</tr>
<tr>
<td>hs-cTnT</td>
<td>1 mths</td>
<td>31%</td>
<td>87%</td>
</tr>
<tr>
<td>Gal-3</td>
<td>2 mths</td>
<td>20%</td>
<td>61%</td>
</tr>
<tr>
<td>sST2</td>
<td>1.5 mths</td>
<td>10.5%</td>
<td>30%</td>
</tr>
<tr>
<td>sST2</td>
<td>2 mths</td>
<td>11%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Single ST2 Cut-point:

> 35 ng/ml = RISK
ST2 not effected 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.
ST2 in Acute Heart Failure
sST2 is NOT a diagnostic marker of AHF

- Severe sepsis
- Inflammatory disease
- Disseminated cancer
- Liver or other organ fibrosis

- It is elevated in almost everyone with AHF
- It is very prognostic in AHF
  - Short-term
  - Long-term
- Risk can be mitigated by lowering level
Mortality Risk Increases With ST2 Levels

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

ST2 and BNP for HF Admission

Sensitivity

1 - Specificity

2 - AUC 0.917
P - AUC 0.625
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, c Addy J.M. van Miltenburg, MD, PhD, g Eric Boersma, PhD, a,b Hans L. Hillege, 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.
Following initial hospitalization, the average estimated ST2 levels in patients who reached the primary endpoint were higher than in their counterparts who remained free of the primary endpoint. Furthermore, the average estimated ST2 levels increased several weeks before the time of the primary endpoint (Central Illustration). The shape of the average estimated NT-proBNP pattern following initial FIGURE 1 Examples of the ST2 Pattern During Follow-Up in Different Patients

The ST2 level of 6 patients during follow-up. The vertical dotted line represents the time of occurrence of the primary endpoint or the scheduled end of follow-up. Patients I, II, and III demonstrate a U-shaped ST2 pattern and reach the primary endpoint. Patients IV, V, and VI demonstrate a J-shaped ST2 pattern and remained event free during follow-up.
Patient: H.V.

No readmissions over One Year

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

BNP Concentration Level (pg/mL)

ST2 Concentration Level (ng/mL)

Date

7-15 (Adm) 8-15 (Adm) 11-15 (Adm) 12-15 (Died)

Normal ST2 level (35 ng/mL)

BNP dropped, but not ST-2

Lisinopril: 5mg
Bumex: 1mg po
Additive Value of ST2 to NT-proBNP: Acute HF

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

Reclassification

Patient would have been classified as moderate risk with only NT-proBNP, but is considered high risk with the addition of ST2.

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, MD\(^1\,^3\); Mercedes Rivas-Lasarte, MD\(^1\,^4\); Johan Lassus, MD, PhD\(^3\); Malha Sadoune, MSc\(^1\); Etienne Gayat, MD, PhD\(^1\,^5\); Kari Pulkki, PhD\(^6\); Mattia Arrigo, MD\(^1\,^5\,^7\,^8\); Evguenia Krastinova, MD, PhD\(^1\,^9\); Alessandro Sionis, MD\(^4\); John Parissis, MD, PhD\(^10\); Jindrich Spinar, MD, PhD\(^11\,^12\); James Januzzi, MD, PhD\(^13\); Veli-Pekka Harjola, MD, PhD\(^14\); Alexandre Mebazaa, MD, PhD\(^1\,^5\,^15\); 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 Ambulatory Heart Failure
### ST2 in Chronic, Ambulatory HF Cohorts

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

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>Observed outcome</th>
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</thead>
<tbody>
<tr>
<td>Barcelona</td>
<td>891</td>
<td>78</td>
<td>4.10 (2.22–7.57)</td>
<td>0.50 3.00 9.00</td>
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<tr>
<td>PHFS</td>
<td>1125</td>
<td>72</td>
<td>4.67 (2.83–7.71)</td>
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<tr>
<td>HF-ACTION</td>
<td>910</td>
<td>43</td>
<td>4.95 (2.72–9.01)</td>
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<tr>
<td>SDVA Echo HF</td>
<td>157</td>
<td>13</td>
<td>2.66 (0.89–7.95)</td>
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</table>

**Univariable**

<table>
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<th>Population</th>
<th>n</th>
<th>Events</th>
<th>HR (95% CI)</th>
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<tr>
<td>Barcelona</td>
<td>876</td>
<td>76</td>
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<td>PHFS</td>
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<tr>
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<td>817</td>
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<td>3.20 (1.66–6.17)</td>
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<tr>
<td>SDVA Echo HF</td>
<td>157</td>
<td>13</td>
<td>3.19 (0.99–10.28)</td>
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**Risk-Adjusted**

<table>
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<th>Population</th>
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<th>Events</th>
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<th>Observed outcome</th>
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<tbody>
<tr>
<td>Barcelona</td>
<td></td>
<td></td>
<td>3.11 (2.17–4.44)</td>
<td>0.50 3.00 9.00</td>
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<td>PHFS</td>
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<tr>
<td>HF-ACTION</td>
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<tr>
<td>SDVA Echo HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Daniels LB, Future Cardiol 2014
Patient: F.S.

68 y.o; HFpEF
Spironolactone: 25mg
Carvedilol: 25mg
Lasix: 60 mg

Normal ST2 level (35 ng/mL)

No Admissions-1 year
Patient: K.E.

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

Carvedilol: 12.5mg BLD
Eplerenone: 25mg
Lasix: 60 mg

Normal ST2 level (35 ng/mL)

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

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).
Figure 2. Relationships between baseline sST2 concentrations and clinical outcomes
sST2 as a decoy receptor → when elevated binds IL-33, effectively reducing the concentration of IL-33 that is available to ST2L, thus diminishing the cardioprotective effect of IL-33.

**Figure 1** sST2 the HbA1c of heart failure.
Do we need another heart failure biomarker: focus on soluble suppression of tumorigenicity 2 (sST2)

Alan S. Maisel¹* and Salvatore Di Somma ²
sST2 as a decoy receptor → when elevated binds IL-33, effectively reducing the concentration of IL-33 that is available to ST2L, thus diminishing the cardioprotective effect of IL-33.

Figure 1 sST2 the HbA1c of heart failure.