HOW TO USE BIOMARKERS IN HEART FAILURE

Gordon Moe, MD, FACC, FAHA
Disclosure

My institution has received research support from Roche Diagnostics and Alere Inc.
Workshop Objectives

1. Leverage heart failure biomarkers to improve patient care and management.
2. Relate emerging uses of biomarkers for the prevention of heart failure hospitalization.
3. Identify novel heart failure-related biomarkers currently under investigation.
Definition of a Biomarker

- Biological marker that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to therapeutic interventions.

- Focuses on circulating biomarkers other than those routinely measured as part of clinical care such as electrolytes and hemoglobin.

Biomarker Definitions Working Group Clin Pharmacol Ther 2001;69:89-95
Questions for you

- Measure BNP/NT-proBNP?
- Use BNP/NT-proBNP to manage your patients with heart failure?
Pathophysiologica\(\text{al} \) Role
1. Leverage heart failure biomarkers to improve patient care and management.
   • **Diagnosis of heart failure**
Case study for diagnosis of heart failure

- 65 year old male, smoker, history of CAD and COPD but **not** HF
- Had previous percutaneous coronary intervention
- One week history of increasing dyspnea and cough and orthopnea, no chest pain
- History of diabetes and hypertension
- On examination, mildly ↑JVP. Bilateral crackles and wheeze. Mild ankle edema
- Meds: bronchodilator puffers, ramipril, hydrochlorothiazide and metformin
Case study for diagnosis of heart failure

- Hb 125; WBC 12.5; platelet count 130,000
- Na 135; K 4.8; creatinine 89, random BS 7
Case study for diagnosis of heart failure

What is the diagnosis here?

1. Exacerbation of COPD?
2. Acute heart failure?
3. Both
4. Neither
Case study for diagnosis of heart failure

**NT-proBNP = 345 pg/ml**

Table 2. Natriuretic peptides cut points for the diagnosis of heart failure

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>HF is unlikely</th>
<th>HF is possible but other diagnoses need to be considered</th>
<th>HF is very likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>All</td>
<td>&lt; 100 pg/ml</td>
<td>100-500 pg/ml</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>&lt; 50</td>
<td>&lt; 300 pg/ml</td>
<td>300-450 pg/ml</td>
</tr>
<tr>
<td></td>
<td>50 - 75</td>
<td>&lt; 300 pg/ml</td>
<td>450-900 pg/ml</td>
</tr>
<tr>
<td></td>
<td>&gt; 75</td>
<td>&lt; 300 pg/ml</td>
<td>900 - 1800 pg/ml</td>
</tr>
</tbody>
</table>

HF, heart failure
Heart Failure

N-Terminal Pro-B-Type Natriuretic Peptide Testing Improves the Management of Patients With Suspected Acute Heart Failure

Primary Results of the Canadian Prospective Randomized Multicenter IMPROVE-CHF Study

Gordon W. Moe, MD; Jonathan Howlett, MD; James L. Januzzi, MD; Hanna Zowall, MA; for the Canadian Multicenter Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) Study Investigators

Circulation 2007;115:3103-3110
ROC curves for ED physician judgment, NP, and combined clinical judgment and NP

P < 0.00001
NT-proBNP + clinical judgment vs. clinical judgment alone

P-value was obtained by comparing two logistic models.

Moe GW et al. Circulation. 2007;115:3103-3110
Improving the Diagnosis of Acute Heart Failure Using a Validated Prediction Model

Erian Steinhardt, MD,§ Keven E. Thorpe, MMSc,## Ahmed M. Bayomi, MD,*††
Gordon Moe, MD,*†† James L. Januzzi, Jr, MD,## C. David Mazer, MD,##

Toronto, Ontario, Canada; and Boston, Massachusetts

Pr(aHF) = 1/1 + exp (8 + 0.011 age – 5.9 ptprob – 2.3lnbnp + 0.82 pt prob x ln bnp)

Pr(aHF)= Posttest probability for aHF; ptprob= patient’s pretest probability; Intbnp= log (to base 10) of NT-proBNP value

Clinical Trials

A Randomized Control Trial Using a Validated Prediction Model for Diagnosing Acute Heart Failure in Undifferentiated Dyspneic Emergency Department Patients—Results of the GASP4Ar Study

BRIAN D. STEINHART, MD, PHILLIP LEVY, MD, MPH, HILDE VANDENBERGHE, PHD, GORDON MOE, MD, MS, ANDREW T. YAN, MD, ASHLEY COHEN, MS, KEVIN E. THORPE, MMath, MELISSA MCGOWAN, MHK, AND C. DAVID MAZER, MD

Toronto, Ontario, Canada, and Detroit, Michigan

Model Performance

Accuracy 76% (sensitivity 68.2%, specificity 83.9%), no significant difference between exposed versus blinded arms (accuracy 77% vs 74%; P = .77).

Using the model treatment thresholds would have redirected 48% of patients with 95% accuracy.

## Secondary Outcomes: Health Benefits

<table>
<thead>
<tr>
<th></th>
<th>Blinded</th>
<th>Exposed</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>*<em>Time EP Care</em> (hours)**</td>
<td>2.59 (3.3± 2.8) (n=96)</td>
<td>2.70 (3.2±1.9) (n=101)</td>
<td>0.884</td>
</tr>
<tr>
<td><strong>Time to readiness for discharge (hours)</strong></td>
<td>3.79 (4.77-3.93) (n=78)</td>
<td>3.87 (4.70-2.88) (n=98)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>ED LOS (hrs)</strong></td>
<td>6.35 (8.99-12.16) (n=78)</td>
<td>5.38 (7.67- 7.94) (n=98)</td>
<td>0.366</td>
</tr>
<tr>
<td><strong>ICU admission</strong></td>
<td>17%</td>
<td>13%</td>
<td>0.499</td>
</tr>
<tr>
<td><strong>60 day mortality</strong></td>
<td>97% survival</td>
<td>92% survival</td>
<td>0.495</td>
</tr>
</tbody>
</table>

*Time from initial EP assessment to end of EP care (i.e. consultation or ED discharge)*

## Confounders of interpretation

<table>
<thead>
<tr>
<th>Higher values</th>
<th>Lower values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased age</td>
<td>Obesity</td>
</tr>
<tr>
<td><strong>Acute coronary syndrome</strong></td>
<td>Flash pulmonary edema</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td></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>
</tbody>
</table>
Natriuretic peptides and Heart Failure with Preserved Ejection Fraction (HFpEF)
Heart Failure with Preserved Ejection Fraction (HFpEF)

- NP levels are elevated but lower than in HFrEF, possibly related to smaller cavity, thicker wall and therefore less wall stress.
- Direct relationship to LV end-diastolic wall stress.

Iwanaga Y, et al. J am Coll Cardiol 2006;47:742-8
NP Cut Points for Diagnosis in HFpEF

- BNP ≥ 100 pg/mL
- NT-proBNP ≥ 800 pg/mL

Significant overlap, and non-hemodynamic factors apply

McMurray JJ, et al. Fur Heart J 2012;33:1787-847
DIAGNOSIS

Recommendation: We recommend that BNP/NT-proBNP levels be measured to help confirm or rule out a diagnosis of HF in the acute or ambulatory care setting in patients in whom the cause of dyspnea is in doubt (Strong Recommendation, High Quality Evidence).

Values and preferences: High quality RCT evidence in the Canadian setting also demonstrates favorable cost-effectiveness. Elevated NP levels are recommended as an additional diagnostic criterion for HFPpEF and are associated with increased risk, although the levels may be lower than in HFrEF. Older age and comorbidities may also influence variations in NP levels.
Workshop Objectives

1. Leverage heart failure biomarkers to improve patient care and management.
   - Diagnosis of heart failure
   - Prognostic stratification
BNP and Primary Endpoint (Death and HF Hospitalization) in Patients with LVEF <40% and >40%

The Importance of Serial NP Measurements for Prognostication in Chronic HF

↑ BNP and cGMP levels reflect neprilysin inhibition with sacubitril/valsartan

**BNP**

- BNP levels are reflective of the action of LCZ696, whereas NT-proBNP levels reflect the effects of LCZ696 on the heart.

**Urinary cGMP**

- cGMP is a secondary messenger of the natriuretic peptide system that is generated when natriuretic peptides bind to the natriuretic peptide receptors A (NPR-A) and B (NPR-B).

*p*-values denote significant difference between the two treatment groups.

Sacubitril/valsartan reduced levels of NT-proBNP and troponin T

Levels of NT-proBNP reflect drug effects on cardiac wall stress

Troponin T is a biomarker of myocardial wall-injury associated higher risk of disease progression in heart failure

*p-values denote significant difference between the two treatment groups
†Troponin T was not measured at the end of the enalapril phase of the run-in period. All patients received enalapril, followed by LCZ696, during the single-blind run-in period to ensure an acceptable side effect profile. Groups represented here show division by final randomization group

1. Packer et al. Circulation 2014; epub ahead of print
2017 CCS Heart Failure Guideline Recommendation

**PROGNOSTIC STRATIFICATION**

**Recommendation:** We recommend that measurement of BNP/NTproBNP levels be considered in patients with an established diagnosis of HFrEF for prognostic stratification, in view of optimizing medical therapy (Strong Recommendation, High Quality Evidence).

**Practical tip:**

For patients receiving an angiotensin-receptor-neprilysin-inhibitor (ARNI), the use of NT-proBNP should be preferred to evaluate prognosis during the first year of treatment. BNP levels will be increased as a consequence of the ARNI’s mechanisms of action over at least the first 8 months of treatment.
Workshop Objectives

1. Leverage heart failure biomarkers to improve patient care and management.
   • Diagnosis of heart failure
   • Prognostic stratification
   • Outpatient management
Case study for the use of NP in outpatient management of HF

- 82 year old female followed in the HF clinic for HFPeF
- Had previous percutaneous coronary intervention and COPD
- Lives 5 hours by driving from the clinic, last HF admission 2 years ago
- Complained of worsening dyspnea post 2 weeks
- Meds: bronchodilator puffers, candesartan 16 mg daily and furosemide 20 mg daily
Case study for the use of NP in outpatient management of HF

- Examination: well perfused, HR 60, BP 135/55mmHg (usual), JVP not elevated. **Clear lungs**, very mild peripheral edema.
- Laboratory evaluation 4 weeks ago: Hb 125, creatinine 120, Na 130, and K 4.0
- Echocardiogram: small pericardial effusion, LVH, normal systolic function
Case study for the outpatient management of heart failure

NT-proBNP = 2380 pg/ml (4 weeks ago and other times)

NT-proBNP = 4560 pg/ml (now)

<table>
<thead>
<tr>
<th>Acute setting</th>
<th>Age, years</th>
<th>HF is unlikely</th>
<th>HF is possible</th>
<th>HF is likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>All</td>
<td>&lt; 100 pg/mL</td>
<td>100-400 pg/mL</td>
<td>&gt; 400 pg/mL</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>&lt;50</td>
<td>&lt; 300 pg/mL</td>
<td>300-450 pg/mL</td>
<td>&gt; 450 pg/mL</td>
</tr>
<tr>
<td></td>
<td>50-75</td>
<td>&lt; 300 pg/mL</td>
<td>450-900 pg/mL</td>
<td>&gt; 900 pg/mL</td>
</tr>
<tr>
<td></td>
<td>&gt;75</td>
<td>&lt; 300 pg/mL</td>
<td>900-1800 pg/mL</td>
<td>&gt; 1800 pg/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ambulatory-care setting</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>&lt; 50 pg/mL</td>
<td>&lt;125 pg/mL</td>
</tr>
</tbody>
</table>
Case study for diagnosis of heart failure

What is the diagnosis here in the clinic?

1. Exacerbation of COPD?
2. Exacerbation of chronic heart failure?
3. Both
4. Neither
# RCTs of NP-Guided Therapy in Chronic Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>HFpEF?</th>
<th>Low Target Natriuretic Peptide?</th>
<th>Natriuretic Peptide Reduced Significantly?</th>
<th>Did Natriuretic Peptide Guidance Change Therapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARBRITE</td>
<td>60</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>TIME-CHF</td>
<td>77</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>B'SCAR</td>
<td>76</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PRIMA</td>
<td>72</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SIGNAL</td>
<td>78</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Troughton</td>
<td>70</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>STARS-BNP</td>
<td>65</td>
<td>No</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
</tr>
<tr>
<td>Berger</td>
<td>71</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PROTECT</td>
<td>63</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

B'SCAR indicates BATTLESCARRED (NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death); HFpEF, heart failure with preserved ejection fraction; PRIMA, Primary Rituximab and Maintenance; PROTECT, ProBNP Outpatient Tailored Chronic Heart Failure; SIGNAL-HF, Swedish Intervention study–Guidelines and NT-proBNP Analysis in Heart Failure; STARBRITE, Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score; STARS-BNP, Systolic HF Treatment Supported by BNP; and TIME-CHF, Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure. Reprinted from Januzzi et al. with permission from Elsevier. Copyright © 2011, Elsevier Inc.
Effect of NP-guided Management on HF hospitalizations: Meta-analysis

1.4.1 Individual data

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Year</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christchurch pilot</td>
<td>2.7%</td>
<td>0.71 [0.23, 2.26]</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>TIME-CHF</td>
<td>16.7%</td>
<td>0.70 [0.48, 1.01]</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Signal-HF</td>
<td>4.1%</td>
<td>0.53 [0.21, 1.32]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>PRIMA</td>
<td>15.7%</td>
<td>1.00 [0.68, 1.47]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Vienna</td>
<td>11.1%</td>
<td>0.62 [0.38, 1.03]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>BATTLESCARRED</td>
<td>11.7%</td>
<td>0.78 [0.48, 1.27]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>PROTECT</td>
<td>5.2%</td>
<td>0.65 [0.29, 1.44]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>STARBRITE</td>
<td>4.8%</td>
<td>0.96 [0.42, 2.22]</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>UPSTEP</td>
<td>16.7%</td>
<td>0.91 [0.63, 1.31]</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>88.8%</strong></td>
<td><strong>0.79 [0.67, 0.94]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.00; X^2 = 4.52, df = 8 (P = 0.81); I^2 = 0$

Test for overall effect: $Z = 2.66 (P = 0.008)$

1.4.2 Aggregate data

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Year</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARS_BNP</td>
<td>8.4%</td>
<td>0.32 [0.18, 0.59]</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Anguita et al.</td>
<td>2.8%</td>
<td>1.18 [0.38, 3.63]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>11.2%</strong></td>
<td><strong>0.56 [0.16, 1.98]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.63; X^2 = 3.96, df = 1 (P = 0.05); I^2 = 75$

Test for overall effect: $Z = 0.90 (P = 0.37)$

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Year</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100.0%</strong></td>
<td><strong>0.74 [0.60, 0.90]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.02; X^2 = 13.13, df = 10 (P = 0.22); I^2 = 24$

Test for overall effect: $Z = 3.07 (P = 0.002)$

Test for subgroup differences: $X^2 = 0.28, df = 1 (P = 0.60); I^2 = 0$
Evidence supporting NP-Guided Therapy

• In the 3 systematic reviews and meta-analyses synthesizing the RCT results, NP-guided therapy has been shown to improve survival and reduce HF hospitalizations.

• In these studies, however, NP-guided therapy had no benefits in 2 subgroups: 1) age >75 years and 2) with HFpEF.

• A multicenter trial the, Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT, NCT01685840), of a single-target NP level (NT-proBNP 1000 pg/ml) and the use of guideline-approved therapies in both treatment arms is terminated.

• The ongoing single-centre EX-IMPROVE-CHF, NCT00601679) will also help clarify the role of NP-guided therapy in HF management.
2017 CCS HF guideline recommendations

NPs for the Outpatient Management of Chronic HFrEF:

- **Recommendation:** We suggest, in ambulatory patients with HFrEF, measurement of BNP or NTproBNP to guide management should be considered to decrease HF-related hospitalizations and potentially reduce mortality. The benefit is uncertain in individuals older than 75 years of age (Weak Recommendation, Moderate Quality Evidence).

- **Values and preferences:**
  - These recommendations are based on multiple small randomized controlled trials (RCTs), most of which demonstrated benefit, and 3 meta-analyses, which universally demonstrated benefit. Any ongoing RCT is likely to affect this recommendation.
2017 CCS HF guideline recommendations

NPs for the Outpatient Management of Chronic HFrEF (continued):

Practical tips:

• A change in NP levels by > 30% probably reflects more than daily variation in patients with compensated HF.

• The timing of NP measurements in outpatient settings should be dictated by clinical status and should be used when they may aid in clinical decision making.
# Algorithm of use of NP in prevention and management of ambulatory and hospitalized patients with HP

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Natriuretic Peptide Level</th>
<th>Actions</th>
</tr>
</thead>
</table>
| Risk factors for HF in ambulatory care setting | • NT-proBNP > 125 pg/mL  
• BNP > 50 pg/mL | More frequent follow up, consideration of intensification of existing therapy |
| Stable ambulatory HF                    | • > 30% ↑ from clinic baseline value                           | More frequent follow up ± intensification of HF therapy |
| Hospitalized for HF and before discharge | • > 30% ↓ from admission value                                 | Discharge if relatively free from congestion |

*Figure 3. Algorithm of the use of natriuretic peptide in the prevention and management of ambulatory and hospitalized patients with heart failure.*
Workshop Objectives

1. Leverage heart failure biomarkers to improve patient care and management.
2. Relate emerging uses of biomarkers for the prevention of heart failure hospitalization.
   • In patient pre-discharge management
3. Identify novel heart failure-related biomarkers currently under investigation.
Case study for pre-discharge assessment following HF admission

- 72 year old male, followed in clinic with stable HFrEF.
- Previous smoker, history of CAD, has CRT-D in place.
- HF medications in clinic: Eplerenone 50 mg/d; Sacubitril/Valsartan 48/52 mg one tablet twice daily; Carvedilol 25 mg twice daily; and furosemide 40 mg twice daily
- Admitted with acute exacerbation of HF.
Case study for pre-discharge assessment following HF admission

- In hospital, received furosemide infusion 10 mg/hr and metolazone 2.5 mg every other day
- 3 days later, diuresed and lost 3.5 kg, less edematous

- Laboratory: Creatinine 102 (admission) to 123
  Na 135 to 130
  K 4.5 to 3.4
  NT-proBNP 9054 to 8500
Case study for pre-discharge assessment following HF admission

What would you do now?

1. Discharge home?
2. Keep in hospital for further more diuretics?
3. Observe in hospital further without change in therapy?
A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European collaboration on Acute decompensated Heart Failure: ÉLAN-HF Score

Khibar Salah, Wouter E Kok, Luc W Eurlings, Paulo Bettencourt, Joana M Pimenta, Marco Metra, Antoni Bayes-Genis, Valerio Verdi, Luca Bettarì, Valentina Lazzarini, Peter Damman, Jan G Tijssen, Yigal M Pinto.
Natriuretic Peptide Treatment Response

Absolute Target and Percent Change

- NT-proBNP at discharge < 1500 pg/mL
- NT-proBNP at discharge 1500-5000 pg/mL
- NT-proBNP at discharge 5001-15,000 pg/mL
- NT-proBNP at discharge > 15,000 pg/mL

Data courtesy of Yigal Pinto, MD.
2017 CCS HF Guideline Recommendations

NPs for the Management of Hospitalized Decompensated HFrEF:

- **Recommendation:** We suggest that measurement of BNP or NT-proBNP in patients hospitalized for HF should be considered before discharge in order to optimize medical therapy, given the prognostic value of these biomarkers in predicting rehospitalization and mortality (Strong Recommendation, Moderate Quality Evidence).

- **Values and preferences:**
  - This recommendation is based on multiple small RCTs, all of which demonstrated an association with clinical outcomes. For patients who are about to be discharged from the hospital after a HF hospitalization, physicians should ensure that they are relatively free from congestion and with a NP level that is lower than that on admission (preferably >30%). Although the risk of readmission is decreased with lower NP levels, clinicians should also consider the limitations of delaying discharge from the hospital for this purpose.
NPs for the Management of Hospitalized Decompensated HFrEF:

- **Practical tip:**

- A patient with persistently elevated NP levels may need closer follow-up in order to reduce the risk of rehospitalisation.
Workshop Objectives

1. Leverage heart failure biomarkers to improve patient care and management.
2. Relate emerging uses of biomarkers for the prevention of heart failure hospitalization.
3. Identify novel heart failure-related biomarkers currently under investigation.
# Selected other biomarkers with potential for clinical use

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Pathophysiological pathways</th>
<th>Populations targeted</th>
<th>Advantages</th>
<th>Potential Benefits</th>
<th>Challenges for implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac hs-troponins</td>
<td>Myocyte death</td>
<td>Acute and chronic HF</td>
<td>Very sensitive marker predicting risk of CV events regardless of etiology</td>
<td>Optimization of therapy in patients with elevated hs-cTn</td>
<td>Use to modify therapy has not been tested</td>
</tr>
<tr>
<td>sST2</td>
<td>Fibrosis/inflammation</td>
<td>Acute and chronic HFrEF, HFpEF</td>
<td>Additional prognostic value beyond NPs, low week-to-week variations</td>
<td>Additional value for short and long term prognostication, regardless of LVEF</td>
<td>Unclear if using sST2 in HF to modify therapies improves clinical outcomes</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>Bacterial infection</td>
<td>Acute HF</td>
<td>Early detection of bacterial infection</td>
<td>Guiding antibiotic therapy in acute HF and suspected respiratory infection</td>
<td>Level ↑ in HF without ongoing bacterial infection. No clear cutoff identified in HF</td>
</tr>
</tbody>
</table>
Other biomarkers with potential for clinical use (continued)

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Pathophysiological pathways</th>
<th>Populations targeted</th>
<th>Advantages</th>
<th>Potential Benefits</th>
<th>Challenges for implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galectin-3</td>
<td>Cardiac fibrosis</td>
<td>HFrEF and HFPF</td>
<td>Early detection and long term prognostication</td>
<td>Preventive measures improve outcome</td>
<td>ST2 may be superior in a multivariate model</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Renal function</td>
<td>Acute and chronic HF</td>
<td>Sensitive</td>
<td>Preventive measures improve outcome</td>
<td>Incremental benefit unclear</td>
</tr>
<tr>
<td>NGAL</td>
<td>Renal function</td>
<td>Acute HF</td>
<td>Early detection of renal failure</td>
<td>Adjust therapy by avoiding renal failure progression</td>
<td>Benefit in improving outcome is unclear</td>
</tr>
</tbody>
</table>
Myocardial Injury, Myocyte Death and Troponins

- 92% of subjects with HFrEF have detectable cardiac troponin T (cTnT) using high-sensitivity assay (hs-cTnT, detection limit 0.001 ng/mL)\(^1\)
- Possible mechanisms of increase\(^2\):
  - Subendocardial ischemia and myocyte necrosis
  - Myocyte damage from inflammation and oxidative stress
  - Apoptosis
  - ↑ membrane permeability

Patients chronic HF with cTNT > median have worse outcomes

Patients acute HF with $\uparrow cTn$ have worse outcomes

2017 CCS HF guideline recommendations

Troponins in heart failure

**Recommendation:** We recommend that high-sensitivity troponins be measured on admission for acute HF, to rule out acute coronary syndromes and for prognostic stratification (Strong Recommendation, High Quality Evidence).

**Values and preferences:** The degree of hs-troponin elevation is a powerful predictor of mortality and CV events in both ambulatory and acutely decompensated patients with chronic HFrEF, even after adjustment for traditional risk predictors including NPs. However, it is unclear how the use of serial measurements in addition to NPs would provide additional and cost-effective benefits in terms of improving outcomes. Also, limited data are available regarding the prognostic significance of hs-troponin elevations in ambulatory patients with HFpEF.
Soluble ST2

• Soluble ST2 (sST2) is an interleukin-1 receptor family member.
• Integrates inflammation, fibrosis, and cardiac stress.
• Lacks disease specificity and, therefore, is not a valuable marker for the diagnosis of HF.
• Adopted by current ACCF/AHA guideline for additive risk stratification of patients with HF.

Dieplinger B et al. Clinic Chimica Acta 2015;443:57-70
Pathophysiologica actions of sST2 in HF

Prognostication by sST2 in Acute HF

Prognostic Value of Baseline and Changes in Circulating Soluble ST2 Levels and the Effects of Nesiritide in Acute Decompensated Heart Failure

W.H. Wilson Tang, MD,* Yuping Wu, PhD,† Justin L. Grodin, MD, MPH,* Amy P. Hsu, MS,* Adrian F. Hernandez, MD, MHS,† Javed Butler, MD,§ Marco Metra, MD,|| Adriaan A. Voors, MD,¶ G. Michael Felker, MD,† Richard W. Troughton, PhD, MBBS,# Roger M. Mills, MD,** John J. McMurray, MD,|| Paul W. Armstrong, MD,;;;; Christopher M. O’Connor, MD,† Randall C. Starling, MD, MPH*
Kaplan-Meier Analysis for 180-Day Survival

Baseline sST2 prognostic value not independent of BNP

Tang WHW et al. JACC: Heart Failure 2016;4:68-77
Measurement of the Interleukin Family Member ST2 in Patients With Acute Dyspnea

Results From the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) Study

James L. Januzzi, Jr., MD, FACC,* W. Frank Peacock, MD,† Alan S. Maisel, MD, FACC,‡ Claudia U. Chae, MD, MPH, FACC,§ Robert L. Jesse, MD, FACC,§ Aaron L. Baggish, MD,* Michelle O’Donoghue, MD,* Rahul Sakhija, MD,* Annabel A. Chen, MD,* Roland R. J. van Kimmenade, MD,‖ Kent B. Lewandrowski, MD,* Donald M. Lloyd-Jones, MD, MSc, FACC,¶ Alan H. B. Wu, PHD#

Boston, Massachusetts; Cleveland, Ohio; San Diego and San Francisco, California; Richmond, Virginia; Maastricht, the Netherlands; and Chicago, Illinois
Mortality at one year and sST2

[Box plot showing mortality and sST2 levels]

Prognostication by sST2 + BNP in Acute HF

Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: The Multinational Observational Cohort on Acute Heart Failure (MOCA) study

Johan Lassus a, b, 1, Etienne Gayat c, d, 1, Christian Mueller e, W.Frank Peacock f, Jindrich Spinar g, h, Veli-Pekka Harjola a, Roland van Kimmenade i, Atul Pathak j, Thomas Mueller k, Salvatore di Somma l, Marco Metra m, Domingo Pascual-Figal n, o, Said Laribi b, p, Damien Logeart b, q, Semir Nouira r, Naoki Sato s, Michael Potocki e, Jiri Parenica g, h, Corinne Collet b, Alain Cohen-Solal b, q, James L. Januzzi Jr. t, Alexandre Mebazaa b, c, *

and for the GREAT-network 2

1Division of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands, 2Leiden University Medical Center, Leiden, the Netherlands.
The relative importance of sST2 in predicting outcomes over clinical evaluation as compared with other biomarkers in acute HF

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>NRI [95% CI]</th>
<th>IDI [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>sST2</td>
<td>10.3 [1.9; 18.7]</td>
<td>0.048 [0.028; 0.067]</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>9.1 [4.0; 14.1]</td>
<td>0.025 [0.016; 0.034]</td>
</tr>
<tr>
<td>MR-proADM</td>
<td>9.1 [2.4; 15.8]</td>
<td>0.042 [0.028; 0.057]</td>
</tr>
<tr>
<td>MR-proANP</td>
<td>7.4 [1.5; 13.2]</td>
<td>0.028 [0.014; 0.041]</td>
</tr>
<tr>
<td>BNP</td>
<td>6.5 [1.5; 9.4]</td>
<td>0.020 [0.012; 0.027]</td>
</tr>
<tr>
<td>CRP</td>
<td>6.3 [1.9; 8.8]</td>
<td>0.011 [0.006; 0.016]</td>
</tr>
<tr>
<td>Troponin T</td>
<td>0.0 [-0.9; 1.0]</td>
<td>0.000 [-0.001; 0.002]</td>
</tr>
<tr>
<td>Troponin I</td>
<td>-0.2 [-1.8; 1.5]</td>
<td>0.000 [-0.001; 0.002]</td>
</tr>
</tbody>
</table>

NRI
Net reclass index
IDI
Integrated discrimin improvement

Galactin-3 (Gal-3)

- Gal-3 is a protein encoded by the LGALS3 gene.¹
- A member of the lectin family; 14 mammalian galectins have been identified.
- Also a member of the beta-galactoside-binding protein family that plays an important role in cell-cell adhesion, cell-matrix interactions, macrophage activation, angiogenesis, metastasis and apoptosis.

Pathophysiological actions of Galactin-3 in HF

Galactin-3 (Gal-3)

- Correlates with various types of fibrosis
- ↑ circulating level associated with ↑ risk of death in acute\(^1\) and chronic HF.\(^2\)
- Predicts favourable response to treatment e.g. statins in patients with ischemic HFrEF.\(^3\)
- Promotes repair in patients following mitral valve repair.\(^4\)

Implications of increasing Gal-3

1329 patients in CORONA and COACH

Prognostication by Gal-3 + NT-proBNP in Acute HF

sST2 versus Gal-3, which one is more predictive?

Research Article

Prognostic value of sST2 and galectin-3 for death relative to renal function in patients hospitalized for heart failure
sST2 vs. Gal-3 for death in HF according to renal function

1161 patients AHF followed for 1 year

Procalcitonin (PCT) is the precursor of calcitonin (CT) and is expressed by the CALC-1 gene on chromosome 11.
Procalcitonin (PCT) in heart failure

- Help to exclude pneumonia and bacterial infections and determine whether antibiotic therapy is appropriate, with or without concomitant HF\textsuperscript{1}

- Improves prognosis in acute dyspnea, by avoiding unnecessary use of antibiotics, or by promoting earlier appropriate use of antibiotics\textsuperscript{2}

Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: Results from the randomized ProHOSP trial

Philipp Schuetz a, Alexander Kutz a,*, Eva Grolimund a, Sebastian Haubitz a, Désirée Demann a, Alaadin Vögeli a, Fabienne Hitz a, Mirjam Christ-Crain b, Robert Thomann c, Claudine Falconnier d, Claus Hoess e, Christoph Henzen f, Robert J. Marlowe g, Werner Zimmerli d, Beat Mueller a, for the ProHOSP Study Group
ProHOSP trial: Primary Endpoint

![Graph showing adverse outcome percentages for PCT < 0.25μg/L and PCT ≥ 0.25μg/L, with P=0.01 and ns significance levels.](image)

Antibiotics use

Procalcitokin values as a function of infection in patients with acute dyspnea

Algorithm of the use of Procalcitonin in Suspected Acute HF

ER with dyspnea → Suspect AHF

- BNP <350 pg/ml
- NT-proBNP <1800 pg/ml

- BNP >350 pg/ml
- NT-proBNP >1800 pg/ml

- PCT <0.2 ug/ml

- PCT >0.2 ug/ml → Antibiotic
Case study for the use of PCT in suspected infection +HF

- 72 year old male to ER with chest pain and dyspnea
- CAD with previous stenting
- $\text{SaO}_2$ 95%; RR 25/min HR 90 bpm; Chest auscultation scattered crackles; minimal ankle edema
- Chest X-ray: ?early infiltrate
- EKG: LVH

Adapted from Maisel As and Jaffe AS. Cardiac Biomarkers: Case studies and clinical correlations. Oct 2016, Springer
**Case study for the use of PCT in suspected infection + HF**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC: 11.5</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Creatinine 110</td>
<td>No antibiotics given</td>
</tr>
<tr>
<td>TNT: negative</td>
<td>Clinically well 4 weeks later</td>
</tr>
<tr>
<td>NT-proBNP: 2578 pg/ml</td>
<td></td>
</tr>
<tr>
<td>PCT: 0.1 ug/ml</td>
<td></td>
</tr>
</tbody>
</table>
Ongoing study of procalcitonin in heart failure

- **IMPACT-EU;** ClinicalTrial.gov identifier NCT02392689
  - A prospective trial evaluating whether PCT helps in guiding antibiotic therapy in heart failure
## Multiple Biomarkers in Heart Failure: Numerous Studies!

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Patients</th>
<th>Biomarkers</th>
<th>Outcome(s)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Kimmenade/PRIDE</td>
<td>ADHF</td>
<td>209</td>
<td>Apelin, galectin-3, NT-proBNP</td>
<td>60-day mortality</td>
<td>Galectin-3 and NT-proBNP predicted mortality; apelin did not. Galectin-3 superior to NT-proBNP. Elevated galectin-3 and NT-proBNP associated to 20% mortality</td>
</tr>
<tr>
<td>Shah/PRIDE</td>
<td>ADHF in SOB</td>
<td>180</td>
<td>NT-proBNP, MR-proANP, MR-proADM, galectin-3</td>
<td>1- and 4-year mortality</td>
<td>MR-proANP and MR-proADM added prognostic value to NT-proBNP and clinical variables. The predictive model including both MR-peptides showed a NRI of 86%</td>
</tr>
<tr>
<td>Pascual-Figal Zairis</td>
<td>ADHF (severe)</td>
<td>107</td>
<td>sST2, hs-TnT, NT-proBNP</td>
<td>Mortality after 739-day follow-up</td>
<td>Each biomarker predicted mortality. Mortality 0% when all biomarkers were not elevated and 53% when all were elevated. Only BNP and cTnI predicted mortality. Mortality of 4.9% if all biomarkers were not elevated and 53.5% when all were elevated. Inclusion of biomarker improved c-statistics of clinical variables from 0.70 to 0.82. sST2, MR-proANP, NT-proBNP best markers with NRI 25% for 1-month mortality and around 10% for 1-year mortality. Combination of CRP with MR-proANP or sST2 have a NRI of 36.8% and 20.3% for 1-month and 1-year mortality, respectively.</td>
</tr>
<tr>
<td>Lassus/MOCA</td>
<td>ADHF</td>
<td>5306</td>
<td>BNP, NT-proBNP, MR-proANP, cTnI, cTnT, sST2, MR-proADM, CRP</td>
<td>1-month and 1-year mortality</td>
<td>Patients in the highest multimarker tertile of biomarkers risk 14-fold higher than in the lowest tertile. A multimarker score reclassified 24% at higher risk mortality.</td>
</tr>
<tr>
<td>Ky/PHFS</td>
<td>CHF</td>
<td>1513</td>
<td>Hs-CRP, BNP, sFlt-1, cTnI, sST2, plasma creatinine</td>
<td>Need of cardiac transplantation or death</td>
<td>Combined addition of hs-TnT and sST2 to a clinical model improved c-statistics from 0.76 to 0.789; NRI was of 14%. The risk predicted by combined sST2 and hs-TnT not improved by adding NT-proBNP to the model, except when both were below cut-off points. Only sST2 improved the risk estimation of a model with clinical variables and NT-proBNP.</td>
</tr>
<tr>
<td>Lupon/Barcelona</td>
<td>CHF</td>
<td>876</td>
<td>NT-proBNP, sST2, hs-TnT</td>
<td>3.5-year mortality</td>
<td></td>
</tr>
<tr>
<td>Gaggin/PROTECT</td>
<td>CHF</td>
<td>151</td>
<td>sST2, GDF-15, hs-TnT, NT-proBNP</td>
<td>Cardiovascular events in 10-months</td>
<td></td>
</tr>
</tbody>
</table>
Survival based on Biomarkers Levels > Cut Points in Acute HF

107 patients hospitalized

hsTnT, NT-proBNP, sST2

Barcelona Bio-HF calculator (www.bcnbiohfcalculator.cat)

Clinical Variables
- Age, years
- Sex
- Heart Failure
- NYHA Functional class:
  - I
  - II
  - III
- BNP
- eGFR, creatinine x 1.73²
- LA size
- TV size
- Mitral regurgitation
- A2 on Ech

Treatment
- Loop diuretics, mg/d
- Furosamide
- ST elevation
- Transamides
- NT-proBNP, mg/dL

Biomarkers
- hsCTnT
- sST2
- NT-proBNP

Mortality
- Risk at 1 year
- Risk at 2 years
- Risk at 3 years

Life expectancy
- years

- Model without biomarkers
- Model without biomarkers + Combined Biomarkers

No biomarkers

With biomarkers: hsCTnT, sST2, NT-proBNP
HOW TO USE BIOMARKERS IN HEART FAILURE

KEY MESSAGES

Gordon Moe, MD, FACC, FAHA
Natriuretic peptides are the only established biomarkers in the management of HF.

- Diagnosis, prognosis, guidance for treatment of acute and chronic HF as well as HFrEF and HFP EF
- Promising biomarkers include sST2, procalcitonin and many others.
  - Their role in HF remain to be defined.
- Risk stratification may be refined by the use of multiple biomarkers, for different pathobiological processes that established risk factors do not directly reflect.
  - An optimal panel of markers, the change in these markers over time, and how these changes might help guide therapeutic interventions remain to be defined.
• Quam ob rem cave Catoni anteponas ne istum quidem
  • Cum saepe multa, tum memini domi in hemicyclo sedentem, ut solebat, cum et ego essem una et pauci admodum familiares, in eum sermonem.
• Sed fruatur sane hoc solacio atque hanc insignem

<table>
<thead>
<tr>
<th>Ut navem declinantes</th>
<th>Superiore Caesarem</th>
<th>Maxime nihil quidquid</th>
<th>Mos et penitus et qua</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catoni anteponas</td>
<td>46</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Paulus eminebat</td>
<td>45</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Sed fruatur</td>
<td>40</td>
<td>35</td>
<td>10</td>
</tr>
</tbody>
</table>
### Other Biomarkers in HFrEF and HFpEF

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Potential Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Markers of diastolic function</strong></td>
<td></td>
</tr>
<tr>
<td>Insulin growth factor binding protein 7</td>
<td>• Correlates with diastolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Predicts mortality and functional capacity</td>
</tr>
<tr>
<td><strong>Markers of inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>sST$_2$</td>
<td>• Correlates with ↑LVEDP</td>
</tr>
<tr>
<td></td>
<td>• Supports diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Predicts prognosis</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>• Supports diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Predicts prognosis</td>
</tr>
<tr>
<td><strong>Markers of matrix turnover</strong></td>
<td></td>
</tr>
<tr>
<td>Collagen propeptides</td>
<td>• Support diagnosis</td>
</tr>
<tr>
<td>PICP, PINP, PIINP</td>
<td>• Predict prognosis</td>
</tr>
<tr>
<td>MMPs, TIMPs</td>
<td>• Supports diagnosis</td>
</tr>
</tbody>
</table>