Natriuretic Peptides
The Cardiologists View

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Disclosures

Research support: Alere, BG Medicine, Critical Diagnostics, Roche Diagnostics, and Singulex

Consulting and Honorarium: Alere, Critical Diagnostics, Roche Diagnostics, Radiometer, Siemens Healthcare Diagnostics and Singulex
Poll Question
Learning Objectives

• Review the recently published recommendations from the 2013 American College of Cardiology/ American Heart Association Guidelines for Heart Failure for natriuretic peptide testing.

• Evaluate the diagnostic accuracy and optimal patient selection for natriuretic peptide testing to diagnose acute heart failure and differentiate from other etiologies of dyspnea.

• Identify a role for serial natriuretic peptide testing in-hospital and how to best utilize these levels for prognosis and predict readmission.

• Consider the state of the evidence for serial natriuretic peptide outpatient testing to optimize the prognosis of ambulatory heart failure patients.
Why Should Cardiologists Pay More Attention to the Natriuretic Peptide Values in Patients with Heart Failure?

The Cardiologist and Emergency Department
Same game, but different perspective

The Cardiologist: the long view
The Emergency Department: short-term diagnostic accuracy
Trends in Heart Failure Hospitalization Rates for Medicare Beneficiaries

1998-2008

Chen J et al. JAMA. 2011;306:1669-1678
Diagnoses of 30-Day Readmissions After Hospitalization for Acute HF

30-day readmission rate 24.8%

Integrating Natriuretic Peptides into Cardiology Practice

• Hospital based practice
  – Diagnosis and prognostication at presentation
  – Inpatient management and discharge planning

• Outpatient clinic based practice
  – Utilizing natriuretic peptide levels to optimize chronic heart failure management
  – Identifying at-risk patients prior to heart failure symptom onset
Biomarkers – diagnosis of Acute HF in ED

ROC curves for the biochemical diagnosis of acute destabilized HF by established and novel biomarkers in short-of-breath patients presenting to the emergency department.

n=251 in total, HF=137, non-HF=114

areas under the curve:
BNP, 0.92 (95% CI, 0.87-0.95)
sST2, 0.62 (95% CI, 0.55-0.69)
Limitation of natriuretic peptides at presentation for early prognosis

Results of the BACH study
Integrating Natriuretic Peptides into Cardiology Practice

• Hospital based practice
  ✔ Diagnosis and prognostication at presentation
    – Inpatient management and discharge planning

• Outpatient clinic based practice
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  – Identifying at-risk patients prior to heart failure symptom onset
Changes in BNP and Pulmonary Capillary Wedge Pressure (PCWP) During 24 Hours of Treatment

NT-proBNP change during acute HF hospitalization

Insights from RELAX-AHF

Cardiac biomarker levels represent a summation of the influence of acute and chronic comorbidities.

Natriuretic Peptides

Cardiac troponins
NT-proBNP/BNP Levels *Without* Acute Decompensated HF

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Effect on (NT-pro)BNP Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome/CAD</td>
<td>↑</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>↑</td>
</tr>
<tr>
<td>Right ventricular overload</td>
<td>↑</td>
</tr>
<tr>
<td>Obesity</td>
<td>↓</td>
</tr>
<tr>
<td>Age</td>
<td>↑</td>
</tr>
<tr>
<td>Renal failure</td>
<td>↑</td>
</tr>
<tr>
<td>Critical illness</td>
<td>↑</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>↑ or ↓</td>
</tr>
</tbody>
</table>
Correlation between PCWP and natriuretic peptide levels in the ICU

Yellow boxes indicate patients with a GFR < 60 ml/min
Closed boxes indicate patients with a GFR >60 ml/min

Forfia et al. J Am Coll Cardiol 2005;45:1667
NT-proBNP Response to Nesiritide Therapy in Patients with Acute Heart Failure

Percent change in NT-proBNP concentration from baseline to 6 hours post nesiritide infusion

Change in NT-proBNP level is unrelated to other clinical findings

## Prognosis summary for natriuretic peptides based on timing of measurement during index hospitalization for acute HF

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Subjects</th>
<th>Outcome</th>
<th>NP</th>
<th>Admit</th>
<th>Pre D/C</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bettoncourt</td>
<td>2004</td>
<td>182</td>
<td>6 mo M/R</td>
<td>NT-pro</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Logeart</td>
<td>2004</td>
<td>202</td>
<td>6 mo M/R</td>
<td>BNP</td>
<td>0.69</td>
<td>0.80</td>
<td>0.76</td>
</tr>
<tr>
<td>Verdiani</td>
<td>2006</td>
<td>100</td>
<td>30-day R</td>
<td>BNP</td>
<td>X</td>
<td>X</td>
<td>NA</td>
</tr>
<tr>
<td>Waldo</td>
<td>2008</td>
<td>164</td>
<td>90-day M</td>
<td>NT-pro</td>
<td>0.788</td>
<td>0.834</td>
<td>NA</td>
</tr>
<tr>
<td>SURVIVE</td>
<td>2009</td>
<td>1038</td>
<td>6 mo M</td>
<td>BNP</td>
<td>NA</td>
<td>0.70</td>
<td>0.71</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>2010</td>
<td>255</td>
<td>6 mo M</td>
<td>BNP</td>
<td>X</td>
<td>0.76</td>
<td>NA</td>
</tr>
<tr>
<td>Novean</td>
<td>2011</td>
<td>171</td>
<td>12 mo M</td>
<td>NT-pro /BNP</td>
<td>0.67</td>
<td>0.77</td>
<td>NA</td>
</tr>
<tr>
<td>OPTIMIZE-HF</td>
<td>2011</td>
<td>7039</td>
<td>12 mo M</td>
<td>BNP</td>
<td>0.684</td>
<td>0.694</td>
<td>0.680</td>
</tr>
<tr>
<td>RELAX-AHF</td>
<td>2013</td>
<td>1161</td>
<td>6 mo M</td>
<td>NT-pro</td>
<td>NA</td>
<td>NA</td>
<td>X</td>
</tr>
</tbody>
</table>

Legend: M, mortality; R, readmission; red= not significant, yellow=significant, green=significant and most prognostic. Numbers are area under the curve. X is any alternative prognostic statistic other than c-statistic. NA=Not assessed in publication.
OPTIMIZE-HF discharge BNP level

Adjusted hazard ratios for one-year outcomes
Integrating Natriuretic Peptides into Cardiology Practice

✓ Hospital based practice
  ✓ Diagnosis and prognostication at presentation
  ✓ Inpatient management and discharge planning

• Outpatient clinic based practice
  – Utilizing natriuretic peptide levels to optimize chronic heart failure management
  – Identifying at-risk patients prior to heart failure symptom onset
Proportion of HF patients achieving therapy targets
IMPROVE HF care metrics at baseline

Potential efficacy of a biomarker adjunctive approach to clinical judgment for management of outpatient HF therapy

- Better achievement of guideline recommended medications and doses
  - Improve patient compliance with prescribed therapy by providing quantitative feedback
  - Overcome provider limitations of reliance on signs and symptoms in “stable” patients
B-Type Natriuretic Peptide-Guided Heart Failure Therapy: A Meta-analysis

All-Cause Mortality

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BNP-guided therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anguita</td>
<td>1.00 (0.23, 4.43)</td>
<td>2.05</td>
</tr>
<tr>
<td>Beck da Silva</td>
<td>0.45 (0.04, 5.39)</td>
<td>0.74</td>
</tr>
<tr>
<td>STARBRITE</td>
<td>0.32 (0.03, 3.19)</td>
<td>0.87</td>
</tr>
<tr>
<td>STARS-BNP</td>
<td>0.61 (0.23, 1.64)</td>
<td>4.68</td>
</tr>
<tr>
<td>UPSTEP</td>
<td>0.95 (0.54, 1.68)</td>
<td>13.94</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.823)</td>
<td>0.81 (0.52, 1.28)</td>
<td>22.27</td>
</tr>
<tr>
<td><strong>NT-proBNP-guided therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BATTLESCARRED</td>
<td>0.95 (0.53, 1.70)</td>
<td>13.37</td>
</tr>
<tr>
<td>Berger</td>
<td>0.64 (0.36, 1.16)</td>
<td>13.25</td>
</tr>
<tr>
<td>PRIMA</td>
<td>0.72 (0.45, 1.14)</td>
<td>21.22</td>
</tr>
<tr>
<td>PROTECT</td>
<td>0.86 (0.18, 2.43)</td>
<td>2.66</td>
</tr>
<tr>
<td>SIGNAL-HF</td>
<td>0.98 (0.33, 2.89)</td>
<td>3.92</td>
</tr>
<tr>
<td>TIME-CHF</td>
<td>0.67 (0.42, 1.05)</td>
<td>22.32</td>
</tr>
<tr>
<td>Troughton</td>
<td>0.13 (0.02, 1.12)</td>
<td>0.98</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.692)</td>
<td>0.72 (0.56, 0.91)</td>
<td>77.73</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.896)</td>
<td>0.74 (0.60, 0.91)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
## B-Type Natriuretic Peptide-Guided Heart Failure Therapy: A Meta-analysis

### Heart Failure related Hospitalization

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anguita</td>
<td>1.00 (0.34, 2.93)</td>
<td>6.70</td>
</tr>
<tr>
<td>STARS-BNP</td>
<td>0.32 (0.18, 0.59)</td>
<td>13.17</td>
</tr>
<tr>
<td>UPSTEP</td>
<td>0.79 (0.49, 1.27)</td>
<td>15.66</td>
</tr>
<tr>
<td>Subtotal (I-squared = 67.7%, p = 0.045)</td>
<td>0.60 (0.30, 1.19)</td>
<td>35.53</td>
</tr>
<tr>
<td>NT-proBNP-guided therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BATTLESCARRED</td>
<td>0.97 (0.62, 1.53)</td>
<td>16.25</td>
</tr>
<tr>
<td>Berger</td>
<td>0.39 (0.23, 0.67)</td>
<td>14.44</td>
</tr>
<tr>
<td>PROTECT</td>
<td>0.31 (0.14, 0.69)</td>
<td>9.91</td>
</tr>
<tr>
<td>TIME-CHF</td>
<td>0.63 (0.43, 0.92)</td>
<td>17.96</td>
</tr>
<tr>
<td>Troughton</td>
<td>0.32 (0.10, 1.02)</td>
<td>5.91</td>
</tr>
<tr>
<td>Subtotal (I-squared = 62.1%, p = 0.032)</td>
<td>0.53 (0.35, 0.81)</td>
<td>64.47</td>
</tr>
<tr>
<td>Overall (I-squared = 58.2%, p = 0.019)</td>
<td>0.55 (0.40, 0.77)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis

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Saverese G. PLoS One 2013;8:e58287
Selected echo results

- Echo results include measures such as LVEF (Left Ventricular Ejection Fraction) and LV end-systolic and end-diastolic volume indices.

- The graph shows absolute and relative changes in LVEF and volume indices for two groups: SOC (N=56) and NT-proBNP (N=60).

- Statistical significance levels are indicated, with P-values of 0.06, 0.01, 0.008, and 0.001 for different comparisons.

Primary Hypothesis of NIH GUIDE-IT trial

- In high risk heart failure patients with LV systolic dysfunction, a strategy of titrating medical therapy based on minimizing natriuretic peptide levels will be superior to usual care with regard to the composite endpoint of heart failure hospitalizations or CV mortality
GUIDE-IT Study Design Overview

**Screening**
- Hospitalization for heart failure
  - LVEF < 40 within 12 months
  - NTproBNP > 2000 pg/mL or BNP > 400 pg/mL during index hospitalization

**Randomization**
- Randomized within 2 weeks of hospital discharge
- Usual Care
  - N= 550
- Biomarker Guided
  - NTproBNP < 1000 pg/mL
  - N=550

**Follow-up**
- Follow up: 2 wks, 6 wks, 3 months, then Q3 month for 12-24 mos
- Additional 2 week follow up after changes in therapy

**Endpoints**
- Primary endpoint: Time to CV death or first HF hospitalization
- Secondary Endpoints:
  - All-cause mortality
  - Total days alive and out of hospital during follow-up
  - CV mortality or CV hospitalization
  - Safety
  - Health related quality of life
  - Resource utilization, costs, cost-effectiveness
The Poll Results
# 2013 ACCF/AHA Guideline for the Management of Heart Failure

## Table 9. Recommendations for Biomarkers in HF

<table>
<thead>
<tr>
<th>Biomarker, Application</th>
<th>Setting</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natriuretic peptides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis or exclusion of HF</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
<td>(212, 217-223, 245-250)</td>
</tr>
<tr>
<td>Prognosis of HF</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
<td>(222, 224-229, 248, 251-258)</td>
</tr>
<tr>
<td>Achieve GDMT</td>
<td>Ambulatory</td>
<td>IIa</td>
<td>B</td>
<td>(230-237)</td>
</tr>
<tr>
<td>Guidance for acutely decompensated HF therapy</td>
<td>Acute</td>
<td>IIb</td>
<td>C</td>
<td>(259, 260)</td>
</tr>
</tbody>
</table>

**Biomarkers of myocardial injury**

| Additive risk stratification | Acute, Ambulatory | I   | A   | (238-244, 248, 253, 256-267) |

**Biomarkers of myocardial fibrosis**

| Additive risk stratification | Ambulatory       | IIb | B   | (238, 240-244, 280)         |
|                             | Acute            | IIb | A   | (248, 253, 256, 257, 261-267) |

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.
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  – Utilizing natriuretic peptide levels to optimize chronic heart failure management
  – Identifying at-risk patients prior to heart failure symptom onset
NT-proBNP predicts cardiovascular outcomes in asymptomatic community dwelling older adults

The Cardiovascular Health study (n=4312)

Time to new-onset heart failure

Time to Cardiovascular Death

deFilippi et al. J Am Coll Cardiol 2010;55:441-50
NT-proBNP and Echocardiography together to predict new-onset heart failure

The Cardiovascular Health study

Time to new-onset heart failure

deFilippi et al. J Am Coll Cardiol 2011;58:1497-1506
Using natriuretic peptide levels to guide primary prevention of cardiovascular events

The next big thing?

• The STOP-HF randomized trial
• The PONTIAC randomized controlled trial
Natriuretic Peptide-Based screening and collaborative care for heart failure
The STOP-HF randomized trial study design

3123 Patients assessed for eligibility

1749 Excluded
1203 Did not meet inclusion criteria
546 Declined to participate

1374 Randomized

697 Randomized to receive BNP screening and protocol referral for BNP ≥50 pg/mL to specialist cardiovascular center (collaborative care)
697 Received BNP screening as randomized
263 With BNP ≥50 pg/mL received Doppler echocardiography and collaborative care follow-up

677 Randomized to receive usual primary care physician management
677 Received usual care as randomized

Ledwidge M JAMA 2013;310:66-74
The STOP-HF randomized trial

Outcomes

Admission for major adverse cardiovascular event

Ledwidge M JAMA 2013;310:66-74
PONTIAC (NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of diabetic patients without A history of Cardiac disease) 
A Prospective Randomized Controlled Trial

The PONTIAC Study
Two-Year Outcomes

<table>
<thead>
<tr>
<th>Hospitalization Due to</th>
<th>All</th>
<th>Control</th>
<th>Intensified</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any reason</td>
<td>136 (45%)</td>
<td>77 (51%)</td>
<td>58 (39%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>25 (8%)</td>
<td>18 (12%)</td>
<td>7 (5%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>19 (6%)</td>
<td>14 (9%)</td>
<td>5 (3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8 (3%)</td>
<td>7 (5%)</td>
<td>1 (1%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Integrating Natriuretic Peptides into Cardiology Practice

Conclusions

• NP’s have excellent accuracy to differentiate acute HF from other causes of dyspnea

• Discharge, more than admission, NP levels are powerful prognosticators for cardiovascular outcomes

• BNP and NT-proBNP are promising tests to optimize outpatient chronic HF management to reduce readmissions and death

• NP’s can identify “at-risk” asymptomatic individuals in the community and may be useful to direct more intensive interventions to reduce cardiovascular hospitalizations