Ortho Clinical Diagnostics

Heart Failure and Natriuretic Peptides

Maria-Magdalena Patru, MD, PhD
Director, Medical and Scientific Affairs

Learning objectives

• Heart failure: definition, prevalence and economic burden
• Natriuretic peptides: BNP and NTproBNP:
  ➢ Biology, characteristics and clinical uses
  ➢ Medical decision cut-offs
  ➢ Assays comparison
• Novel heart failure therapy affects BNP biomarker
• Future directions for heart failure laboratory testing
Heart Disease Facts

- Heart disease is the leading cause of death for both men and women
- About 610,000 Americans die from heart disease each year—that's 1 in every 4 deaths
- Each minute, someone in the US dies from a heart disease-related event


Heart Failure (HF) Facts

- ~5.1 million people in the US have heart failure
- African Americans are more likely to:
  - have HF than other races;
  - suffer symptoms at a younger age;
  - have more hospital visits and die from HF
- 1 in 9 deaths include HF as contributing cause
- About 50% of HF patients die within 5 years of diagnosis
- HF costs the nation an estimated $32 billion each year


Heart Failure Distribution
B-type Natriuretic Peptides

Biology of B-type Natriuretic Peptides

Both BNP and NT-proBNP are released from myocytes in response to stretch – BNP is active hormone, NT-proBNP is inactive.

Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>32 amino acids</td>
<td>76 amino acids</td>
</tr>
<tr>
<td>Half life</td>
<td>20 minutes</td>
<td>60-120 minutes</td>
</tr>
<tr>
<td>Stability at RT</td>
<td>4 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>Clinical Range</td>
<td>0-5,000 pg/mL</td>
<td>0-35,000 pg/mL</td>
</tr>
</tbody>
</table>

The in vivo longer half-life results in higher levels of NT-proBNP than BNP. The in vitro stability is particularly valuable for outpatient testing.
Clinical Uses of B-type Natriuretic Peptides
BNP and NT-proBNP

Both NT-proBNP and BNP are the recommended biomarkers in the 2013 ACCF/AHA Guidelines for:

- Diagnosis or exclusion of heart failure
- Prognosis of heart failure
- Achieve GDMT (Guideline Directed Medical Therapy)
- Guidance for acutely decompensated heart failure therapy

Potential Causes of BNP and NT-proBNP Elevation

Potential causes of an abnormal cardiac troponin in B-type natriuretic peptide (BNP and NT-proBNP) concentration: possible diagnoses:

- Heart muscle disease
- Hypertrophic heart muscle disease
- Inflammatory myocardial diseases such as myocarditis
- Acute coronary syndromes, such as acute heart failure syndrome
- Inflammatory, including myocarditis and chemotherapy
- Valvular heart disease
- Acute pericarditis and pericardial disease
- Septic diseases
- - Acute peritonitis and sepsis
- - Bacterial peritonitis
- - Renal failure
- - Acute tubular necrosis
- - Renal disease
- - Pulmonary heart disease
- - Sleep apnea
- - Pulmonary embolism
- - Pulmonary hypertension
- - Congestive heart failure
- - Myocardial infarction
- - Cardiomegaly
- - Valvular diseases

“Breathing Not Properly” Multinational Study

Area under the curve representing operating characteristics curve (% true positive - 1% false positive): 0.80-0.82


© Ortho Clinical Diagnostics 2016
Use of BNP biomarker

- "...useful in establishing or excluding the diagnosis of CHF in patients with acute dyspnea."
- 100 pg/ml cutoff (for ruling out)
  - 90% sensitivity
  - 76% specificity
  - 89% NPV
- BNP > 500 pg/ml PPV=90%
- Grey zone 100pg/ml-500pg/ml where there are a number of conditions that could cause increased levels


Val-HeFT Study: 2006

An NT-proBNP cut-point of 900 pg/mL Performs Similarly to a BNP cut-point of 100 pg/mL

**NT-proBNP in the chronic stable and asymptomatic population**

- Non-acute symptomatic/asymptomatic population are mostly encountered in primary care and outpatient clinics
- Dual cut-point for ruling out HF: 125 pg/mL for patients < 75 years of age and 450 pg/mL for those ≥ 75 years of age
- European guidelines recommend 125 pg/mL as the ruling-out cut-point in the non-acute setting

*Mueller et al, Heart 2005; 91: 606-612
**Ponikowski et al, Eur Heart J 2016; 37: 2129-2299

---

**NT-proBNP in the acute symptomatic population**

- Patients with acute heart failure are mostly encountered in the emergency department setting
- Main symptom of HF: dyspnea or shortness of breath
- European guidelines recommended NT-proBNP ≤ 300 pg/mL for ruling out HF in the acute setting, with a NPV of 98%

*Ponikowski et al, Eur Heart J 2016; 37: 2129-2299
**Januzzi et al, Eur Heart J 2006; 27: 839-845

---

*European Heart Journal Advance Access published November 17, 2016
National Heart, Lung, and Blood Institute
**Clinical research

**NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients**

The International Collaborative of NT-proBNP Study

James L. Januzzi, MD, FACP, FACC, FRCP; Antoni Bayes-Genis, MD, PhD; Roland RJ van Kimmenade, MD; Yigal Pinto, MD; A. Mark Richards, MD, FRCP

ICON Study Group: James Januzzi, Aaron Baggish (Boston), Antoni Bayes-Genis (Barcelona), Roland P.J. van Kimmenade, Yigal Pinto (Maastricht), A. Mark Richards, John Lainchbury (Christchurch)

---
NT-proBNP Levels by Diagnosis in Patients with Acute Dyspnea

NT-proBNP Levels in Acute Heart Failure as a Function of Heart Failure Severity

NT-proBNP Levels Predict Survival in Patients with Acute Heart Failure

Age-independent Rule-out Cut-point

International Collaborative of NT-proBNP (ICON) Study data (acute setting):

- 300 pg/ml, age independent
- 99% sensitive
- 60% specific
- 98% NPV


Age-stratified Rule-in Cut-points

International Collaborative of NT-proBNP (ICON) Study data (acute setting):

<table>
<thead>
<tr>
<th>Age strata</th>
<th>Optimal cut-point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All &lt;50 years</td>
<td>450 pg/ml</td>
<td>57%</td>
<td>93%</td>
<td>76%</td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td>All 50-75 years</td>
<td>900 pg/ml</td>
<td>95%</td>
<td>82%</td>
<td>82%</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td>All &gt;75 years</td>
<td>1800 pg/ml</td>
<td>85%</td>
<td>73%</td>
<td>92%</td>
<td>85%</td>
<td>83%</td>
</tr>
</tbody>
</table>

*Very superior to single cut-point strategy in multivariable bootstrapping models


Age stratified NT-proBNP cut-points reduce the grey zone in HF diagnosis

- Both BNP and NT-proBNP have "grey zones", in which the NP levels are between the rule out and rule in cut-points*

- Some of the clinical conditions moderately elevating NP levels into the grey zones are: COPD, renal dysfunction, arrhythmia, ACS, pulmonary hypertension, and pulmonary embolism*

- Using a single cut-point, the grey zone incidence for BNP is 27%**, while NT-proBNP age stratified cut-points reduce the likelihood of a grey zone to 16%***

*Van and Januzzi, Am J Cardiol (2008);101:39-42
***Januzzi et al., Eur Heart J (2005) 631;: 330-337
NT-proBNP and BNP in patients with renal dysfunction

- The levels of both NT-proBNP and BNP are elevated in patients with chronic kidney disease (CKD).
- Different cut-offs should be used in patients with renal dysfunction**
- However, NT-proBNP age stratified cut-points maintained their value in diagnosing HF even in the presence of impaired renal function*

<table>
<thead>
<tr>
<th>Cut Point (pg/mL)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>1000</td>
<td>88</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>1200</td>
<td>89</td>
</tr>
<tr>
<td>Age-stratified approach</td>
<td>97</td>
<td>68</td>
</tr>
</tbody>
</table>

*McCullough et al., Am J Kidney Dis (2003);41:571-9
**Januzzi et al., JACC (2006) 45::91-97

NT-proBNP and BNP in patients with COPD

The median NT-proBNP levels are significantly higher in patients with new-onset HF compared with those with COPD or asthma exacerbation *

The diagnostic accuracy of BNP in patients with concurrent of HF and COPD is less certain than NT-proBNP**

![Image](https://example.com/image.jpg)

**Hawkins et al., Eur J Heart Fail. 2009 Feb;11(2):130-9

### B-type Natriuretic Peptide Assays

<table>
<thead>
<tr>
<th>Company</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Architect®</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Alere Triage®</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Beckman Access®/UniCel®/DxI®</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Biomerieux Vidas®</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mitsubishi PATHFAST®</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ortho Clinical Diagnostics VITROS®</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Roche Cobas®</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Siemens Centaur®</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Siemens VISTAR®</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Siemens Immulite®</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>


Trademarks not owned by Ortho Clinical Diagnostics are the property of their respective owners.

---

### VITROS® NT-proBNP Assay

**Intended Use:**

For the quantitative measurement of NT-proBNP in human serum and plasma (EDTA or heparin) using the VITROS ECi/ECiQ, the VITROS 3600, and the VITROS 5600 Integrated Systems:

- To aid in the diagnosis of congestive heart failure
- For the risk stratification of acute coronary syndrome and congestive heart failure.
- To aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease.
- In the assessment of heart failure severity in patients diagnosed with congestive heart failure.

Source: Ortho Clinical Diagnostics Pub. Instructions For Use No. GEM1315_US_EN

---

### BNP and NT-proBNP Assays

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Assay 1</th>
<th>Assay 2</th>
<th>Pearson correlation coefficient</th>
<th>Agreement <em>k</em></th>
<th>Agreement <em>r</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>0.992</td>
<td>0.975</td>
<td>0.953</td>
<td>0.995</td>
<td>0.975</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.992</td>
<td>0.975</td>
<td>0.953</td>
<td>0.995</td>
<td>0.975</td>
</tr>
</tbody>
</table>

**BNP results between vendors demonstrate variability with only “poor to substantial” agreement.**

**NT-proBNP results between vendors demonstrate “substantial to almost perfect” agreement.**

Novel HF Therapy: ENTRESTO™

ENTRESTO™ Mechanism of Action

ENTRESTO™ PI

Indications and Usage

ENTRESTO is a combination of sacubitril, an angiotensin receptor and neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (LVEF ≤ 40%).

ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

Source: ENTRESTO™ Package Insert T2015-131 August 2015.
"We extrapolated from the available short-term follow-up data to estimate that treatment with sacubitril–valsartan would result in a projected benefit of 1 to 2 years of increased life expectancy and survival free from heart failure."

Source: NEJM 2015; 373 (23): 2289-2290.

Key difference between NT-proBNP and BNP:
BNP levels increase with ENTRESTO™ therapy initially, while NT-proBNP levels decrease.

Source: DOI: 10.1161/CIRCULATIONAHA.114.013748.

Note: LCZ696 is the name used for ENTRESTO™ in this study.

Source: http://dx.doi.org/10.1016/j.ddstr.2013.11.002.
Support for using NT-proBNP vs. BNP

BNP is not a suitable biomarker of heart failure in patients treated with LCZ696 (ENTRESTO™) because BNP is a neprilysin substrate. NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.


Support for using NT-proBNP vs. BNP

"If physicians use serial measurements of BNP to assess risk and make therapy decisions based on those levels in a patient receiving ENTRESTO™, it’s going to make interpretation of BNP extremely challenging."

Source: James Januzzi, MD from CAP Today, November 2015

Note: Dr. James Januzzi is a paid consultant for Ortho Clinical Diagnostics
Conclusions

Based on the information available from published research and clinical studies, clinical practice is expected to shift towards using an NT-proBNP assay in heart failure patients treated with ENTRESTO™.

BNP to NT-proBNP Biomarker Crossover

Lead might be the operative word whenever laboratories weigh in on using NT-proBNP or BNP, according to Lori Daniels, MD from UCSF.

Impose is unlikely to work.

Therefore:
- Work closely with the cardiologists and develop a transition plan
- Offer educational speakers/review evidence for change with medical staff
- Offer both biomarkers for a short transition period
- Make NT-proBNP the default biomarker


NT-proBNP and BNP for Acute Heart Failure—Summary

- Individuals with heart failure typically have approximately 8-10X higher levels of NT-proBNP versus BNP.
- The ICON triple "rule-in" NT-proBNP cut points for acute heart failure (age-specific cutpoints of 470, 900, and 1800 pg/mL) are designed to account for the impacts of age and renal function
  - Both BNP and NT-proBNP increase with increasing age and decreasing renal function.
  - The ICON triple NT-proBNP cutpoints are designed to provide similar information, but with better performance, relative to the BNP cut-point of 100 pg/mL.
- Relative to BNP, NT-proBNP also offers the benefits of enhanced analyte stability, both in vitro and in vivo
- Better agreement between the NT-proBNP assays than between the BNP assays.
- In patients taking Entresto™, only NT-proBNP can be used.