The Clinical Value of Cardiac Biomarkers in the Management of Acute Coronary Syndrome And Heart Failure
Incidence Rates for STEMI and NSTEMI by Study Year

Acute Coronary Syndromes

No ST Elevation

ST Elevation

~70%

Unstable Angina

NQW-MI

QW-MI

~30%

Platelet rich clot

Fibrin rich clot

In Hospital Mortality

<table>
<thead>
<tr>
<th>Year</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>12%</td>
</tr>
<tr>
<td>1997</td>
<td>12%</td>
</tr>
</tbody>
</table>

In Hospital Mortality

<table>
<thead>
<tr>
<th>Year</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>24%</td>
</tr>
<tr>
<td>1997</td>
<td>14%</td>
</tr>
</tbody>
</table>

In-Hospital, Thirty Days, and One-Year Case-Fatality Rates for STEMI and NSTEMI by Study Year

Chest Pain...Is It From the Heart or Not?

Myocardial Pain

- Musculoskeletal Pain
- IVDA Pulm Infarction
- Blunt Chest Trauma
- Anxiety
- Pulmonary Embolus
- Empyema
- Mediastinitis
- Panic Attack
- Pneumonia
- Breast Implant
- Panic Attack
- Pneumonia
- Breast Implant
- Mondor’s Syndrome
- GERD
- Asthma
- Contact
- Dermatitis
- Mallory-Weiss
- Weiss
- Sickle cell
- Anemia
- Boerhaave Syndrome

Other Conditions:
- Musculoskeletal Pain
- IVDA Pulm Infarction
- Breast Abcess
- Aortic Dissection
- Tietze’s disease
- Thoracic Pneumothorax
- Spine Ds
- Herpes
- Zoster
- Breast Cancer
- Cancer
- Subdiaphrag Abcess
- Empyema
- Amniotic Fluid Embolus
- Lung
- Cancer
- Cancer
- Amniotic Fluid Embolus
- Lung
- Cancer
Cardiac Damage Is Often Not ACS-related

The ED Physician’s Dilemma . . .

A typical situation:
- acute chest pain
- electrocardiogram is non-diagnostic
- low risk for myocardial infarction
- moderate risk for unstable angina

The most critical questions:
- Should the patient be sent home?
- Should the patient be admitted for observation?
- Should the patient be admitted to the cath lab?
# Troponin Cutpoints have Decreased Over Time

<table>
<thead>
<tr>
<th>Year</th>
<th>Cutpoint</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>3.1 ng/mL</td>
<td>First non-commercial troponin assay</td>
</tr>
<tr>
<td>1995</td>
<td>1.5 ng/mL</td>
<td>First commercial troponin assay</td>
</tr>
<tr>
<td>2000</td>
<td>0.40 ng/mL</td>
<td>Any increase of troponin is significant</td>
</tr>
<tr>
<td>2007</td>
<td>0.04 ng/mL</td>
<td>New definition: 99th percentile, 10% CV</td>
</tr>
</tbody>
</table>

Troponin assays are not standardized, values for each method are different.
Standardization has not yet been achieved

• A working group of the IFCC is cooperating with manufacturers to address the question of whether cTnI standardization or harmonization can be achieved ?!
• The most common reason for the discrepancy in cTn measurements is the difference in epitope specificity of the antibodies used in different assays
• cTn measurements are influenced by multiple factors, among which are the posttranslational modifications such as proteolytic degradation, phosphorylation and complexing with other molecules such as TnC, heparin, heterophile or human antimouse antibodies and cTn specific autoantibodies circulating in patients' blood
• Different mono- and polyclonal antibodies used in assays are sensitive to these factors to varying degrees
• It becomes increasingly important that hs-cTn assays use antibodies specific to epitopes in the central part of the troponin molecule that are not affected by the numerous modifications found in human blood
Troponin I Molecule

Antibody pair binds to stable region of troponin molecule

N-terminal

1
30
110

Proteases

C-terminal

209

Proteases
Milestones in Myocardial Infarction Guideline Developments

1979

- Chest discomfort for > 20 minutes
- ECG changes with ST-segment elevation
- Elevated cardiac biomarkers
Milestones in Myocardial Infarction Guideline Developments

2000

- Relies on the use of cTn for diagnosis
- Focus shifted to early detection
- Redefined cTn cutoff for MI as 99th percentile based on presumed-healthy reference control group

Milestones in Myocardial Infarction Guideline Developments

2000

- Supports ESC/ACC 2000 guidelines
- Rise/fall of TnI pattern is essential to diagnosis
- Optimal precision at the 99th percentile should be total CV ≤10%

2007

Third universal definition of MI (2012): Biochemical criteria for acute MI (AMI)

Evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia.

- Detection of a rise or fall of cardiac biomarker values, preferably cTn, with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following symptoms:
  
  * Symptoms of Ischemia
  * New or presumed new significant ST-segment-T wave changes or new left bundle branch block (LBBB)
  * Development of pathological Q waves on the ECG
  * Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  * Identification of an intracoronary thrombus by angiography or autopsy.

ESC pocket guidelines 2012 3rd Universal AMI
Clinical Classification of MI According to the Third Universal Definition of MI (2012)

Type 1: Associated with atherosclerotic plaque

Type 2: Associated with Imbalance between myocardial oxygen supply and/or demand

Type 3: Associated with cardiac death due to MI without available biomarker values

Type 4a: Associated with PCI

Type 4b: Associated with Stent Thrombosis

Type 5: Associated with CABG
2014 AHA/ACC Guidelines for Management of NSTEMI

- To establish the diagnosis of ACS, serial cTn testing should be obtained at presentation and at 3-6 hours.

- Assess change value in cTn rising or falling pattern using the 99th percentile from the baseline to distinguish acute-from chronic elevations of cTn concentrations that are associated with structural heart disease.

- Additional cTn testing beyond 6 hours if time of symptom onset is unclear or if clinical suspicion for MI remains.
2014: IFCC Task force on clinical applications of cardiac biomarkers

ACC/ESC current guidelines:

99th percentile cut-off universally endorsed
• Determined in a healthy population
• Derived from peer-reviewed literature, or manufacturer
• Analytical precision should be \( \leq 10\% \) CV
• Results are generally reported in ng/mL in the US

Under discussion in the US:

• High-sensitivity assays should have total imprecision (CV) of \( \leq 10\% \) at the 99th percentile.

• Measurable concentrations below the 99th percentile (LoD) should be attainable with an assay at a concentration value above the assay's limit of detection for at least 50% (and ideally >95%) of healthy individuals to attain the highest level of scorecard designation.

• Analysis of the diagnostic accuracy of absolute and relative Troponin changes.

• Results reported in ng/L instead of ng/mL (gives whole number values instead of decimals for easier interpretation.)
Current Landscape of Troponin Assays

<table>
<thead>
<tr>
<th>Not Acceptable</th>
<th>Clinically Usable</th>
<th>Guideline Acceptable</th>
<th>High Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV &gt; 20% @ 99th Percentile</td>
<td>CV between 10% and 20% @ 99th Percentile</td>
<td>CV ≤ 10% @ 99th Percentile</td>
<td>CV ≤ 10% @ 99th Percentile ≥ 50% of Patients between LOD and 99th</td>
</tr>
</tbody>
</table>

Classical
Conventional
Sensitive
Comment Regarding the 99th Percentile Cutoff

- The guidelines do not suggest that all increases of these biomarkers should elicit a diagnosis of MI or high-risk profile, only those associated with the appropriate clinical, EKG, imaging, or pathological findings.

- When Troponin increases are not due to acute ischemia, the clinician is obligated to search for another etiology for the elevation.
Causes of Elevated Troponin Values

Injury related to primary myocardial ischemia
- Plaque rupture
- Intraluminal coronary artery thrombus formation

Injury related to supply/demand imbalance of myocardial ischemia
- Tachy-/brady arrhythmias
- Aortic dissection or severe aortic valve disease
- Hypertrophic cardiomyopathy
- Cardiogenic, hypovolemic or septic shock
- Severe respiratory failure
- Severe anemia
- Hypertension with or without LVH
- Coronary spasm
- Coronary embolism or vasculitis
- Coronary endothelial dysfunction w/o significant CAD

Injury not related to ischemia
- Cardiac contusion, surgery, ablation, pacing or defibrillation
- Rhabdomyolysis with cardiac involvement
- Myocarditis
- Cardiotoxic agents, e.g. anthracyclines, Herceptin

Multifactorial or indeterminate myocardial injury
- Heart failure
- Stress (Takotsubo) cardiomyopathy
- Severe pulmonary embolism or pulmonary hypertension
- Sepsis and critically ill patients
- Renal failure
- Severe acute neurological diseases, e.g. stroke, subarachnoid hemorrhage
- Infiltrative diseases, e.g. amyloidosis, sarcoidosis
- Strenuous exercise, e.g. marathon runners
Most contemporary and high-sensitivity assays have comparable diagnostic accuracy

Reichlin et al. 2009 NEJM. 361:858-67
What constitutes a significant change?

Based on Reichlin et al. Circulation 2011;124;136-45

Guidelines are absent. More research is needed.
Why earlier cTn detection?

Clinically Usable cTn assays

Guideline Compliant cTn assays

cTn serum concentration

99th percentile

Diagnostic cut point (10% CV)

Diagnostic cut point (99th percentile)

Improved time to diagnosis

Hours after symptoms onset

Multiples of the URL

99th percentile
Troponin: Key Points to Remember for AMI Earlier Diagnosis

- The diagnosis of AMI requires both clinical (e.g., ECG, history, imaging) and biochemical data.
- A patient with an elevated troponin (>99\textsuperscript{th} percentile) is experiencing cardiac damage, but not necessarily AMI.
- The guideline for assay acceptability is ≤ 10% at the 99\textsuperscript{th} percentile cut-off.
- Guideline-acceptable assays can reduce length of stay and improve MI diagnosis.
- Blood samples for the measurement of cTn should be drawn on first assessment and repeated 3–6 h later.
- Troponin assays are not standardized, therefore values are not equivalent.
- Serial measurements are required for diagnosing NSTEMI and must use the same assay.
Summary of High Sensitive cTn

- High sensitive Troponin assays may allow for earlier and faster recognition of ACS.
- High sensitive troponin may play an important role in assessing change value in cTn rising or falling pattern using the 99th percentile from the baseline to distinguish acute-from chronic elevations of cTn concentrations that are associated with structural heart disease.
- With higher sensitivity comes the responsibility of understating and interpreting very low levels of hsTn elevation.
- Despite the high specificity of these assays, no Tn assay alone allows a clinician to determine the etiology of myocyte necrosis.
- While high precisions quite valuable in these tests, especially at the low levels, biological variability again makes interpretation of hsTn elevations difficult, and new thresholds will have to be defined for clinical use.
- Absolute rather than percent change seems to be a better predicator of AMI.
Why Testing for Natriuretic Peptides?

McCullough et al. Circulation 2002;106: 416-422
Natriuretic Peptides

Pre-proBNP

Physiologically Inactive

Physiologically Active

NT-proBNP

Half-Life: 120 min
Renal Clearance

Half-Life: 20 min
Receptor Mediated
Enzymatic Degradation
Renal Clearance

Physiologically Inactive

Physiologically Active


BNP

Renal Clearance
Similarities

BNP
NT-proBNP
Cardiovascular and Renal Actions of BNP/NT-pro BNP

- Powerful diuretic/natriuretic
- Antimitotic
- Vascular smooth muscle relaxing action
- Antagonists for the RAAS/SNS
- ↓ Arterial and Venous Pressure
Effect of Body Mass Index on natriuretic peptide levels.

NP Concentrations in Healthy Individuals

Differences in half-life and clearance explain the differences in value amplitude

Median Concentration (pg/ml)

- BNP
- NT-proBNP

Age Group (years)
- <45
- 45-54
- 55-64
- 65-74
- >75

Package Inserts from (BNP) and (NT-proBNP)
NPs Correlation with NYHA Classification

Median Concentration (pg/ml)

BNP  NT-proBNP

NYHA Class

I  II  III  IV

Impact of NPs in Patients with Renal Dysfunction and HF

Am J Kidney Dis 2003;41:571-579

J Am Coll Cardiol 2006;47:91–7

NT-proBNP

GFR (mL/min/1.73m2)

No HF

With HF

< 30

30-59

60-90

> 90

BNP

GFR (mL/min/1.73m2)

No HF

With HF

< 30

30-59

60-90

> 90

NT-proBNP (pg/mL)

BNP (pg/mL)
Association Between Natriuretic Peptides and 1-Year Mortality: Higher Value, Worse Prognosis

<table>
<thead>
<tr>
<th>Quartile</th>
<th>BNP pg/mL</th>
<th>NT-proBNP pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>&lt; 88</td>
<td>&lt; 472</td>
</tr>
<tr>
<td>Q2</td>
<td>88 – 333</td>
<td>472 – 1728</td>
</tr>
<tr>
<td>Q3</td>
<td>334 – 800</td>
<td>1729 – 6000</td>
</tr>
<tr>
<td>Q4</td>
<td>&gt; 800</td>
<td>&gt; 6000</td>
</tr>
</tbody>
</table>

The best approach remains the combination of clinical judgment and natriuretic peptide measurement!

PRIDE and BNP Studies on Acute Dyspnea

AUC
0.86: E.D. Probability
0.90: BNP
0.93: Combined

McCullough et al. Circulation 2002; 106:416-422

Answers for life.
Differences

BNP
NT-proBNP
**BNP/NT-proBNP: Differences in Clearance Mechanisms**

1. Diuresis
2. Vasodilation
3. Inhibition of angiotensin-aldosterone production
4. Inhibition of cardiac and vascular myocyte growth

**Acting on distance tissues causing**

- Passive diffusion across the renal basement membrane

**Proteolysis by Neutral Endopeptidase**

- Results in accumulation of GTP and cGMP

**Renal Excretion**

**Vascular Smooth Muscle Cell**
Differences in Sample Stability

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Room Temp. Stability</th>
<th>Stability @ 2-8 °C</th>
<th>Stability @ -20 °C</th>
<th>Sample Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDTA</td>
<td>20 min.</td>
<td>4h</td>
<td>24h</td>
<td>Heparinized</td>
</tr>
<tr>
<td>Heparinized</td>
<td>90 min.</td>
<td>72h</td>
<td>72h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 month</td>
<td>12 months</td>
<td></td>
</tr>
</tbody>
</table>

**Half-life**

- BNP: 20 min.
- NT-proBNP: 90 min.
Differences in median concentrations between Systolic-Diastolic HF on the basis of their Ejection Fraction (PRIDE)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Systolic Heart Failure</th>
<th>Non-systolic HF</th>
<th>False Negative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>592pg/ml</td>
<td>259pg/ml</td>
<td>20%*</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>6,196pg/ml</td>
<td>2,849pg/ml</td>
<td>9%*</td>
</tr>
</tbody>
</table>

Among those with non-systolic HF, the false negative rate of BNP was significantly higher than NT-proBNP.

Data from O'Donoghue et al.10 *p<0.001 for lower sensitivity of BNP versus NT-proBNP.

Use of age stratification does not change either sensitivity or specificity, but improves positive predictive value significantly.

Monitoring BNP or NT-proBNP enabled identification of asymptomatic patients at risk for the development of HF. NT-proBNP showed better accuracy than BNP for identifying mild HF.

## Differences in Optimal Cut-offs

<table>
<thead>
<tr>
<th>Situation</th>
<th>Optimal Cut-off</th>
<th>NT-proBNP Optimal Cut-offs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of heart failure (out-patient/office evaluation)</td>
<td>100pg/ml</td>
<td>125pg/ml for age &lt;75 years</td>
</tr>
<tr>
<td>Evaluation of acute dyspnea (emergency department)</td>
<td>100pg/ml</td>
<td>450pg/ml for age ≥75 years</td>
</tr>
<tr>
<td>Diagnosis of heart failure</td>
<td>100pg/ml</td>
<td>Exclusion of heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300pg/ml, age independently</td>
</tr>
<tr>
<td></td>
<td></td>
<td>450pg/ml for age &lt;50 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>900pg/ml for age 50–75 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,800pg/ml for age &gt;75 years</td>
</tr>
</tbody>
</table>


Use of age stratification does not change either sensitivity or specificity, but improves positive predictive value significantly. Notably, such a comprehensive understanding of optimal cut-offs is lacking for BNP use.
Primary Care Setting

- NT-proBNP testing has been recommended as part of the screening process of outpatients with signs and symptoms suggestive of HF.

- In primary care patients, NT-proBNP is a ‘rule out’ test to exclude significant cardiac disease and a normal result (i.e. below the age-stratified cut-off level) obviates the need for further cardiovascular investigations such as echocardiography.

- On the other hand, a positive NT-proBNP test result does not absolutely indicate the presence of HF and a more directed cardiovascular workup is indicated.

- Compared with NT-proBNP values in ED patients with acute dyspnea, lower values are expected in HF patients in the community. The following NT-proBNP cut-off values are recommended for HF exclusion in primary care:

  - < 75 years 125 pg/mL
  - = or >75 years 450 pg/mL

Eur Heart J. 2005; 26: 1115-40
Am J Cardiol. 2008; 101 (Suppl.): 25A-28A
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 Jr, Roland van Kimmenade, John Lainchbury, Antoni Bayes-Genis, Jordi Ordonez-Llanos, Miguel Santalo-Bel, Yigal M. Pinto, and Mark Richards

1 Cardiology Division, Massachusetts General Hospital, Yawkey 5984, 55 Fruit Street, Boston, MA 02114, USA; 2 Cardiology Department, University Hospital, Maastricht, The Netherlands; 3 Christchurch Cardioendocrine Research Group, Department of Medicine, Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand; 4 Cardiology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 5 Biochemistry Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; and 6 Emergency Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

Received 5 July 2005; revised 14 September 2005; accepted 13 October 2005; online publication 21 December 2005.
Age-Independent “rule out” Cut Point in the Acute Setting (The ICON Study)

Age-Independent “rule out” Cut Point-300pg/mL is 99% sensitive, 60% specific and 98% NPV

The ICON Study NT-proBNP Decision Levels

### NT-proBNP “Rule-In” Cutpoints

<table>
<thead>
<tr>
<th>Age Strata</th>
<th>Optimal Cutpoint</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50 (n=183)</td>
<td>450 pg/mL</td>
<td>97%</td>
<td>93%</td>
<td>76%</td>
<td>99%</td>
<td>95%</td>
</tr>
<tr>
<td>50-75 (554)</td>
<td>900 pg/mL</td>
<td>90%</td>
<td>82%</td>
<td>82%</td>
<td>88%</td>
<td>85%</td>
</tr>
<tr>
<td>≥ 75 (n=513)</td>
<td>1800 pg/mL</td>
<td>85%</td>
<td>73%</td>
<td>92%</td>
<td>55%</td>
<td>83%</td>
</tr>
<tr>
<td>Overall Average</td>
<td></td>
<td>92%</td>
<td>84%</td>
<td><strong>88%</strong></td>
<td>66%</td>
<td>93%</td>
</tr>
</tbody>
</table>

### NT-proBNP “Rule-Out” Cutpoints

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Optimal Cutpoint</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule-Out</td>
<td>300 pg/mL</td>
<td>99%</td>
<td>62%</td>
<td>55%</td>
<td>99%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Differential Diagnosis Associated with Elevations of BNP or NT-proBNP

**Myocardial Processes**
- Systolic dysfunction
- Diastolic dysfunction
- Fibrosis or scaring
- Hypertrophy
- Infiltrative diseases

**Valvular Abnormalities**
- Mitral stenosis or regurgitation
- Aortic stenosis or regurgitation
- Tricuspid regurgitation
- Pulmonary stenosis

**Cardiac Chamber Size**
- Ventricular enlargement
- Atrial enlargement

**Filling Pressures**
- Atrial or ventricular
- Pulmonary

**Ischemic Heart Disease**
- Coronary artery ischemia

**Heart Rhythm Abnormalities**
- Atrial fibrillation or flutter

**Pericardial Diseases**
- Constriction, tamponade

**Congenital Abnormalities**
- Shunts or stenotic lesions
We included 182 patients consecutively admitted to hospital because of decompensated HF. Patients were followed up for 6 months.

The primary end point was death or readmission. Twenty-six patients died in hospital.

The median admission NT-proBNP level was 6778 pg/mL, and the median level at discharge was 4137 pg/mL (P<0.001).

Patients were classified into 3 groups:

1. decreasing NT-proBNP levels by at least 30% (n=82)
2. no significant modifications on NT-proBNP levels (n=49)
3. increasing NT-proBNP levels by at least 30% (n=25)

Cumulative hospitalization-free survival according to patterns of response of NT-proBNP


NT-proBNP levels are potentially useful in the evaluation of treatment efficacy and might help clinicians in planning discharge of HF patients.
**Treatment Guidance:** When treatment is adjusted based on NP results, patients do better than when it is adjusted based on clinical judgment only.

**Graph:**
- Cardiovascular events over time after randomization (days)
- Event-free (%) vs. Time after randomization (days)
- Patients in the NT-proBNP group have a lower event-free rate compared to the Clinical group.
- N = 69
- P = 0.034

**References:**

**Text:**
Dose selection for many HF therapies is based on maximum tolerability rather than on physical function or volume status.
Risk reduction in rates of death or hospitalization free survival between therapy guided NP vs clinical judgment

- Of the seven published clinical trials of therapy guided by natriuretic peptide levels:
  - Three were positive (The Christchurch, New Zealand NT-pro trial, The STARS-BNP trial, The PROTECT NT-pro trial)
  - Three were negative (The STARBRITE BNP trial, The BATTLESCARRED NT-pro trial, and The PRIMA NT-pro trial)
  - One had mixed results (The TIME-CHF NT-pro trial - The largest trial-499 - no survival benefit but lower rate of hospitalization)
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*
Conclusions from the PARADIGM-HF Trial

PARADIGM-HF Trial

- Entresto was more effective than Enalapril for patients with HFrEF in reducing the risk of CV death and HF hospitalization, reducing the risk of CV death, reducing all-cause mortality, and incrementally improving symptoms and physical limitations.

- Entresto was better tolerated than Enalapril
  - Less likely to cause cough, hyperkalemia, or renal impairment.
  - Less likely to be discontinued due to an adverse event.
  - More hypotension, but no increase in discontinuations.
  - Not more likely to cause serious angioedema.

- However, because BNP (but not NT-proBNP) is a substrate for neprilysin, levels of BNP will reflect the action of the drug, whereas levels of NT-proBNP will reflect the effects of the drug on the heart.
Entresto™ (sacubitril/valsartan) Tablets

- The FDA approved Entresto™ on July 7, 2016 for the treatment of heart failure (NYHA II-IV) with reduced ejection fraction (HFrEF).
- Entresto consists of Valsartan which is an angiotensin receptor blocker and Sacubitril which is a neprilysin inhibitor.
- Neprilysin is an enzyme that degrades BNP.
- It is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other angiotensin receptor blocker.

ENTRESTO inhibits neprilysin, one of the enzymes that degrades BNP. The Lancet authors hypothesized that NT-proBNP would be less “confounding” than BNP and reflect more truly the de novo synthesis.

Entresto Mechanism of Action

Heart Failure

Pre-ProBNP

NT-proBNP

No Effect

Entresto Valsartan & Sacubitril

Sacubitril

Sacubitril Metabolite

Inhibits

BNP

Nephrilysin

BNP Fragments

Valsartan
Angiotensin Receptor Blocker
Lowers blood pressure
Prevents blood vessel constriction

Neprilysin

Vasodilation
Renal Effects

<table>
<thead>
<tr>
<th>Veins</th>
<th>Diuresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteries</td>
<td>Natiureisis</td>
</tr>
<tr>
<td>Coronary Arteries</td>
<td>GFR</td>
</tr>
</tbody>
</table>

Entresto

BNP Fragments

Valsartan & Sacubitril
The Effect of Entresto on NT-proBNP and BNP

- Panel A shows the effects on NT-proBNP in patients being treated with either Enalapril or Entresto.

- NT-proBNP shows a modest decrease in patients being treated with Enalapril paralleling some clinical improvement.

- On the other hand, NT-proBNP shows a marked decrease in patients receiving Entresto again paralleling enhanced clinical improvement.
The Effect of Entresto on NT-proBNP and BNP

Panel A shows the effects on NT-proBNP in patients being treated with either Enalapril or Entresto.

NT-proBNP shows a modest decrease in patients being treated with Enalapril paralleling some clinical improvement.

On the other hand, NT-proBNP shows a marked decrease in patients receiving Entresto again paralleling enhanced clinical improvement.

Panel B shows the effects on BNP in patients being treated with either Enalapril or Entresto.

Again the Enalapril treated patients show a modest decrease in BNP while the BNP actually increases in the Entresto treated patients despite clinical improvement.
## BNP / NT-proBNP Comparison

<table>
<thead>
<tr>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derived from Pre-proBNP due to LV stretch</td>
<td>Derived from Pre-proBNP due to LV stretch</td>
</tr>
<tr>
<td>Shorter half life (~20 min)</td>
<td>Longer half life (~120 min)</td>
</tr>
<tr>
<td>Renal clearance, Receptor, Enz. degradation</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>Less stable in the tube after collection</td>
<td>More stable in the tube after collection</td>
</tr>
<tr>
<td>Normal values increase with age</td>
<td>Normal values increase with age</td>
</tr>
<tr>
<td>Single reference range cutpoint</td>
<td>Age dependent reference ranges</td>
</tr>
<tr>
<td>Values increase with severity of disease</td>
<td>Values increase with severity of disease</td>
</tr>
<tr>
<td>Can be used to monitor therapy</td>
<td>Can be used to monitor therapy</td>
</tr>
<tr>
<td>Values increase as GFR decreases</td>
<td>Values increase as GFR decreases</td>
</tr>
<tr>
<td>Values decrease as BMI increases</td>
<td>Values decrease as BMI increases</td>
</tr>
<tr>
<td>Better as a rule-out test</td>
<td>Better as a rule-out/in test?</td>
</tr>
</tbody>
</table>
Conclusions

NP’s testing are useful adjunct to history and physical examination for the evaluation of dyspneic patient in the ED.

When evaluating dyspneic patient, results of NP’s should be used in the context with history and physical examination.

Logical use of NP’s testing is cost-effective for the evaluation and triage of the patient with suspected acute HF.

To exclude acute destabilized HF an NT-proBNP <300ng/L is recommended.

To identify acute destabilized HF, an age-independent NT-proBNP cut-point of 900ng/L has similar sensitivity, specificity, PPV as BNP=100ng/L.
Conclusions

The ICON “triple cut point” of 450/900/1800 is recommended for its superior performance.

Age stratification of NT-proBNP reduces false negative and false positive and improves PPV without a change in the overall sensitivity or specificity.

Optimal application of elevated NP’s are in the context of the knowledge of the correct differential diagnosis.

NT-proBNP measurements may be most useful for detecting early LV dysfunction without overt CHF.

Future applications of NT-proBNP will no doubt include its use for the monitoring and titrating of therapy for HF.

BNP (but not NT-proBNP) is a substrate for neprilysin, levels of BNP will reflect the action of the drug, whereas levels of NT-proBNP will reflect the effects of the drug on the heart.