The clinical value of natriuretic peptide testing in heart failure

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Harvard Medical School
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Massachusetts General Hospital
Disclaimer

• During this lecture will you not hear me suggest that we should stop thinking critically about our patients, put our stethoscopes away, or apply natriuretic peptide testing without thinking about every possibility.
pro-BNP (aa1 - aa108)

Cleavage

NT-proBNP (aa1 - aa76)

BNP (aa77 - aa108)
Biology of the NP System

Synthesis and Release

pre-proBNP<sub>1-134</sub> → Signal peptide (26 amino acids)

proBNP<sub>1-108</sub>

NT-proBNP<sub>1-76</sub>

BNP<sub>1-32</sub>
Biology of the NP System

**Synthesis and Release**

- **pre-proBNP$_{1-134}$**
- **Signal peptide (26 amino acids)**
- **proBNP$_{1-108}$**
- **NT-proBNP$_{1-76}$**
- **BNP$_{1-32}$**
- **proBNP$_{1-108}$**
- **BNP$_{3-32}$**
- **DPP-IV**
- **Meprin A**
- **BNP$_{7-32}$**

DPP-IV = dipeptidyl peptidase–IV
Natriuretic Peptide Clearance

- **BNP**
  - NPR
  - Neutral endopeptidases
  - Renal excretion

- **NT-proBNP**
  - Less well understood
  - Renal excretion partially responsible
Equal Renal Clearance of BNP and NT-proBNP

In simultaneously sampled renal artery and vein:
NO DIFFERENCE BETWEEN CLEARANCE OF BNP AND NT-proBNP

van Kimmenade et al, JACC, 2009
Correlations of Natriuretic Peptides with Cardiac Structure and Function

• Left ventricle
  – Size
  – Systolic function
  – Diastolic function

• Right ventricle
  – Size
  – Systolic function

• Atrial size and pressure

• Valve disease
  – Aortic
  – Mitral
  – Tricuspid

• Heart rhythm

• Ischemic heart disease

• Pericardial disease
Correlations of Natriuretic Peptides with Cardiac Structure and Function

<table>
<thead>
<tr>
<th>Left ventricle</th>
<th>Right ventricle</th>
<th>Valve disease</th>
<th>Heart rhythm</th>
<th>Ischemic heart disease</th>
<th>Pericardial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Size</td>
<td>Aortic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic function</td>
<td>Systolic function</td>
<td>Mitral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td>Tricuspid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial size and pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
How not to get burned by NP’s:
Know the Differential Diagnosis of an Elevated Natriuretic Peptide

- Unrecognized HF
- Prior HF
- LVH
- Valvular heart disease
- Atrial fibrillation
- Advancing age
- Myocarditis
- ACS
- Pulmonary hypertension
- Congenital heart disease

- Anemia
- Pulmonary embolism
- Cardiac surgery
- Sleep apnea
- Critical illness
- Sepsis
- Burns
- Renal failure
- Toxic-metabolic insults
Natriuretic Peptides: Major Clinical Utilities

- Acute patient evaluation
- Estimation of prognosis
- Monitoring HF therapy
Diagnostic Uncertainty is Common in Dyspnea Evaluation

Following full evaluation, managing physician asked to provide an estimate from 0% to 100% for the likelihood for heart failure as the cause of dyspnea.

“Uncertainty zone” 31% of subjects

Green et al, Arch Int Medicine, 2008;168:741
Diagnostic Uncertainty is Associated with Poor Prognosis in Acute Dyspnea

31% of subjects in PRIDE were judged uncertainly by the managing physician. Their prognosis was significantly worse, with higher rates of death and re-hospitalization and longer lengths of stay!

Log rank P < .001

Green et al, Arch Int Medicine, 2008;168:741
Results: NT-proBNP Levels

\[ P<0.001 \]

Januzzi et al, AJC 2005
NT-proBNP Levels and Symptoms

Januzzi et al, AJC 2005

NT-proBNP Levels and Symptoms

Class II (n=17) Class III (n=80) Class IV (n=112)

P=0.001

NYHA
### Results: Predictors of HF

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Intervals</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated NT-proBNP</td>
<td>44</td>
<td>21.0-91.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Interstitial edema on chest X-ray</td>
<td>11</td>
<td>4.5-26.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>9.6</td>
<td>4.0-23.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Loop diuretic use at presentation</td>
<td>3.4</td>
<td>1.8-6.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Rales on pulmonary examination</td>
<td>2.4</td>
<td>1.2-5.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.03</td>
<td>1.01-1.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Cough</td>
<td>0.43</td>
<td>0.23-0.83</td>
<td>0.05</td>
</tr>
<tr>
<td>Fever</td>
<td>0.17</td>
<td>0.05-0.50</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Januzzi et al, AJC 2005
REDHOT Study: BNP Values & Patient Disposition

- BNP values blinded to physicians judging severity of HF
- BNP median values ~22% higher in patients discharged home from E.D.

Maisel, et. al, JACC, 2004
REDHOT Study: Baseline BNP Values and Mortality

Maisel, et. al, JACC, 2004
Delayed BNP Equals Delayed Treatment

Maisel et al JACC, 2008
Mortality vs. Quartiles of Diuretic Time & BNP Level

Maisel et al JACC, 2008
Results: Primary Endpoint

- Clinical Judgment, AUC=0.90
- NT-proBNP, AUC=0.94
- Combined, AUC=0.96

- Combined versus NT-proBNP, p=0.04
- Combined versus Clinical Judgment, p<0.001
## Where does NT-proBNP help most?

### Data from the Canadian IMPROVE-CHF Study

*Although NT-proBNP added incremental information at both ends of the spectrum of heart failure likelihood…*

<table>
<thead>
<tr>
<th>Clinician impression</th>
<th>Model impression</th>
<th>Not HF</th>
<th>HF</th>
<th>% Appropriately Reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low prob (n=343)</td>
<td>LP (n=282)</td>
<td>276</td>
<td>6</td>
<td>(2.1)*</td>
</tr>
<tr>
<td>(Accuracy =89%)</td>
<td>IP (n=58)</td>
<td>30</td>
<td>28</td>
<td>48.3</td>
</tr>
<tr>
<td></td>
<td>HP (n=3)</td>
<td>0</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Avg prob (n=139)</td>
<td>LP (n=33)</td>
<td>37</td>
<td>1</td>
<td>97.3</td>
</tr>
<tr>
<td></td>
<td>IP (n=77)</td>
<td>25</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HP (n=24)</td>
<td>0</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>High prob (n=91)</td>
<td>LP (n=0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(Accuracy =95%)</td>
<td>IP (n=18)</td>
<td>4</td>
<td>14</td>
<td>22.2</td>
</tr>
<tr>
<td></td>
<td>HP (n=73)</td>
<td>1</td>
<td>72</td>
<td>(1.4)*</td>
</tr>
</tbody>
</table>

Where does NT-proBNP help most?

*Data from the Canadian IMPROVE-CHF Study*

Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses suggested the biggest “bang” was in the indecision zone…

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<td></td>
<td>HP (n=3)</td>
<td>0</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Int prob (n=139)</td>
<td>LP (n=38)</td>
<td>37</td>
<td>1</td>
<td>97.3</td>
</tr>
<tr>
<td></td>
<td>IP (n=77)</td>
<td>25</td>
<td>52</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>HP (n=24)</td>
<td>0</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>High prob (n=91)</td>
<td>LP (n=0)</td>
<td>0</td>
<td>0</td>
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<td></td>
<td>HP (n=73)</td>
<td>1</td>
<td>72</td>
<td>(1.4)*</td>
</tr>
</tbody>
</table>

What is the best **single** cut point?

<table>
<thead>
<tr>
<th>Cut Point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 pg/ml</td>
<td>99%</td>
<td>68%</td>
<td>62%</td>
<td>99%</td>
<td>79%</td>
</tr>
<tr>
<td>450 pg/ml</td>
<td>98%</td>
<td>76%</td>
<td>68%</td>
<td>99%</td>
<td>83%</td>
</tr>
<tr>
<td>600 pg/ml</td>
<td>96%</td>
<td>81%</td>
<td>73%</td>
<td>97%</td>
<td>86%</td>
</tr>
<tr>
<td>900 pg/ml</td>
<td>90%</td>
<td>85%</td>
<td>76%</td>
<td>94%</td>
<td>87%</td>
</tr>
<tr>
<td>1000 pg/ml</td>
<td>87%</td>
<td>86%</td>
<td>78%</td>
<td>91%</td>
<td>87%</td>
</tr>
</tbody>
</table>

- NT-proBNP, 300 pg/ml
- NT-proBNP, 450 pg/ml
- NT-proBNP, 600 pg/ml
- NT-proBNP, 900 pg/ml
- NT-proBNP, 1000 pg/ml
Looks an awful lot like BNP…

An NT-proBNP of 900 pg/mL provides identical performance to a BNP of 100 pg/mL.
Is there anything to do to improve the comparatively low PPV of NP’s?

PRIDE

Breathing Not Properly
Causes of lower positive predictive value of natriuretic peptides

Predictors of Elevated B-Type Natriuretic Peptide Concentrations in Dyspneic Patients Without Heart Failure: An Analysis From the Breathing Not Properly Multinational Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate CI 95%</th>
<th>Multivariate CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age/10-y increase</td>
<td>1.0–1.6</td>
<td>1.4–6.7</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic congestive heart f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6</td>
<td>1.1–2.3</td>
</tr>
<tr>
<td><strong>Clinical findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ saturation (per 5% decrease)</td>
<td>1.2</td>
<td>1.1–1.4</td>
</tr>
<tr>
<td>JVD</td>
<td>1.8</td>
<td>1.1–3.1</td>
</tr>
<tr>
<td>Absence of wheezing</td>
<td>1.9</td>
<td>1.2–2.8</td>
</tr>
<tr>
<td>Murmurs</td>
<td>2.4</td>
<td>1.5–3.9</td>
</tr>
<tr>
<td>Rales</td>
<td>1.8</td>
<td>1.3–2.7</td>
</tr>
<tr>
<td>Body mass index (per 5 kg/m² decrease)</td>
<td>1.4</td>
<td>1.2–1.6</td>
</tr>
<tr>
<td><strong>Chest radiograph findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>3.2</td>
<td>1.9–5.3</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2.0</td>
<td>1.0–3.7</td>
</tr>
<tr>
<td>Interstitial edema</td>
<td>2.5</td>
<td>1.1–5.8</td>
</tr>
<tr>
<td><strong>Blood value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (increase per mg/dL)</td>
<td>2.4</td>
<td>1.6–3.6</td>
</tr>
<tr>
<td>Hemoglobin (decrease per g/dL)</td>
<td>1.3</td>
<td>1.2–1.4</td>
</tr>
<tr>
<td>ECG abnormal</td>
<td>3.0</td>
<td>2.0–4.4</td>
</tr>
</tbody>
</table>
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. Januzzi1*,†, Roland van Kimmenade2†, John Lainchbury3, Antoni Bayes-Genis4, Jordi Ordonez-Llanos5, Miguel Santalo-Bel6, Yigal M. Pinto2, and Mark Richards3

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

ICON Study Group:
James Januzzi, Aaron Baggish (Boston)
Antoni Bayes-Genis (Barcelona)
Roland RJ van Kimmenade, Yigal Pinto (Maastricht)
A. Mark Richards, John Lainchbury (Christchurch)
Age-independent rule out cut point

- International NT-proBNP Collaboration data (acute setting):
  - 300 pg/ml, age independent
    - 99% sensitive
    - 60% specific
    - 98% NPV

### Age-stratified “rule in” cut point

**International NT-proBNP Collaboration data (acute setting):**

*To diagnose acute HF*

<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 (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>All 50-75 years (n=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>All &gt;75 years (n=519)</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</td>
<td></td>
<td>90%</td>
<td>84%</td>
<td><strong>88%</strong></td>
<td>66%</td>
<td>86%</td>
</tr>
</tbody>
</table>

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

Logical use of natriuretic peptide values: it isn’t black and white!!

Optimizing Natriuretic Peptide Use in Acute Diagnosis:

Not everything with a high natriuretic peptide level is HF!
How Not to Get **Burned** by Elevated B-type Natriuretic Peptide Levels:

*Know the Differential Diagnosis*

- Unrecognized HF
- Prior HF
- LVH
- Valvular heart disease
- Atrial fibrillation
- Advancing age
- Myocarditis
- ACS
- Pulmonary hypertension
- Anemia
- Pulmonary embolism
- Cardiac surgery
- Sleep apnea
- Critical illness
- Sepsis
- Burns
- Renal failure
- Toxic-metabolic insults

Baggish, et al, Crit Path Cardiol, 2004
What Causes “False Negative” B-type Natriuretic Peptides?

- It happens, sometimes without explanation!
- Right heart failure
- Mild HF
- Chronic, more compensated HF (consider cut-points!)
- Non-systolic HF
- Obesity
Natriuretic Peptides: Major Clinical Utilities

- Acute patient evaluation
- Estimation of prognosis
- Monitoring therapy
AHA Stages

Stage A
- At risk for heart failure
- Diabetes
- Coronary disease
- Hypertension

Stage B
- Asymptomatic LV dysfunction
- Prior MI
- Hypertension

Stage C
- Symptomatic heart failure

Stage D
- End-stage heart failure
### Results: Bayesian information criterion

**Predictors of mortality at 4 years among those with acute HF**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>974.66</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>961.90</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>953.35</td>
</tr>
<tr>
<td>hsCRP</td>
<td>947.72</td>
</tr>
<tr>
<td>No loop diuretic at D/C</td>
<td>945.44</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>944.99</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>941.43</td>
</tr>
</tbody>
</table>

Januzzi, et al., Clin Chem 2010
Cumulative Hazard: NT-proBNP

Januzzi, et al., Clin Chem 2010
Natriuretic Peptides: Major Clinical Utilities

- Acute patient evaluation
- Estimation of prognosis
- Monitoring therapy
Why might natriuretic peptide testing assist with heart failure management?

- Earlier diagnosis
- Better triage

- As a target of therapy?
Effect of Selective NT-proBNP Testing On Costs/Outcomes:

Results of the Randomized IMPROVE-CHF Trial

Moe, Howlatt, Januzzi, Zowall on behalf of the IMPROVE-CHF Investigators, 2007, Circulation
Why might natriuretic peptide testing assist with heart failure management?

✓ Earlier diagnosis

• As a target of therapy?
## Therapies with Effects on B-Type Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect on NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis</td>
<td>↓</td>
</tr>
<tr>
<td>ACE-I</td>
<td>↓</td>
</tr>
<tr>
<td>ARB</td>
<td>↓</td>
</tr>
<tr>
<td>β-blockers</td>
<td>↓</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>↓</td>
</tr>
<tr>
<td>BiV pacing</td>
<td>↓</td>
</tr>
<tr>
<td>Exercise</td>
<td>↓</td>
</tr>
<tr>
<td>Rate control of AF</td>
<td>↓</td>
</tr>
<tr>
<td>BNP infusions</td>
<td>↓</td>
</tr>
</tbody>
</table>
Natriuretic peptide treatment response: Absolute target or % change?

Data courtesy of Yigal Pinto, MD
Recommended Protocol for NT-proBNP Testing in Acute HF

• Baseline measurement for diagnosis

• Pre-discharge measurement for both ‘dry’ NT-proBNP estimation and to assess for treatment response:
  – If rise >30%: discharge delayed, ↑Rx
  – If change <30%: possible discharge delay
  – If fall >30%: discharge authorized
The Importance of Serial NT-proBNP Measurements for Prognostication in Chronic HF

![Graph showing changes in NT-proBNP levels over 4 months with mortality and hospitalization rates for different categories.]

- **High→High**: Mortality 25.6%, Hospitalization 26.8%
- **Low→High**: Mortality 17.2%, Hospitalization 21.1%
- **High→Low**: Mortality 13.6%, Hospitalization 10.1%
- **Low→Low**: Mortality 8.6%, Hospitalization 6.7%
Rationale for “guided” therapy

• *Proactively* identify those on an inadequate medical program

• *Reactively* identify those at high risk for impending complication

• Directly address the underlying biology of HF guided by tools that reflect it
Characteristics of ‘guided therapy’ trials

- Well tolerated
- More often up-titration of therapies in biomarker guided arm
- When a low target was selected and natriuretic peptide lowering was achieved, better outcomes were observed

Januzzi, Journal of Cardiac Failure, 2011
Guided therapy combined analyses

Meta analysis of publication data

Pooled patient data from all available trials

Felker et al, Am Heart Journal, 2009

Troughton et al, ESC 2011
### NT-proBNP Concentrations

#### Overall

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2118 [1122-3831]</td>
<td>1321 [554-3197]</td>
<td>.02</td>
</tr>
</tbody>
</table>

#### By treatment allocation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC</td>
<td>1946 [951-3488]</td>
<td>1844 [583-3603]</td>
<td>.61</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2344 [1193-4381]</td>
<td>1125 [369-2537]</td>
<td>.01</td>
</tr>
</tbody>
</table>

\[ P = .40 \text{ for SOC baseline versus NT-proBNP baseline} \]
### NT-proBNP Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>2118 [1122-3831]</td>
<td>1321 [554-3197]</td>
<td>.02</td>
</tr>
</tbody>
</table>

**By treatment allocation**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC</td>
<td>1946 [951-3488]</td>
<td>1844 [583-3603]</td>
<td>.61</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2344 [1193-4381]</td>
<td>1125 [369-2537]</td>
<td>.01</td>
</tr>
</tbody>
</table>

\(P = .03\) for SOC follow-up versus NT-proBNP follow-up

44.3% of NT-proBNP subjects \(\leq 1000\) pg/mL
Events as a function of NT-proBNP

Mean number of events

Achieved NT-proBNP value

≤1000 pg/mL
1001-2000 pg/mL
2001-3000 pg/mL
>3000 pg/mL

P < .001
Primary Endpoint

Number of events

Total CV Events

*Logistic Odds_{NT-proBNP} = 0.44 (95% CI = .22-.84; \( P = .019 \))

*Adjusted for age, LVEF, NYHA Class, and eGFR
TIME-CHF Cost-Effectiveness

Acceptability curves for LY’s without residence costs

Probability cost-effective

Value for a Lifeyear

Sanders-van Wijk, JACC: HF, 2013
GUIDE-IT
The clinical value of natriuretic peptide testing

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