To BNP or Not to BNP!

Michael Clark, MD FACC DBIM  
Metropolitan Underwriting Discussion Group  
Annual Meeting 2014
Agenda

- Case 1: BNP by any other name?
- Case 2: What's normal?
- Case 3: What are the factors that can influence the BNP level?
- Case 4: BNP as rating credit?
- Case 5: BNP vs ECG: one from column A.....
- And some other brain teasers....
Case 1: BNP by any other name?

LABORATORY DATA: Cardiac enzymes are negative x3 sets. Creatinine 1.8, BUN 33, potassium 4. Liver enzymes are elevated, but improving. BNP was 998 when he went into atrial fibrillation. INR 2.0. White count 13.4, hemoglobin 11.6 and hematocrit 34.7 and platelet count 167.

Impression: Atrial fibrillation with rapid ventricular response. The patient is fully anticoagulated. Therefore, we will start the patient on amiodarone and see if he will convert to normal sinus rhythm. Otherwise, continue his current conservative care as you are doing with rate control. Will wean Diltiazem drip off as his amiodarone bolus goes in. Obviously, the patient is a good long-term Coumadin candidate given his new atrial fibrillation and his history of DVT.

Thank you for this consultation.

65 y.o. male applying for $500,000

Medical history: Episodes of atrial fibrillation since 2006. Normal echo and stress test. Calcium score ZERO!

2 episodes of atrial fibrillation since then (above from 2010 episode).

- Current lab NT-proBNP 300 pg/ml. Blood count and serum creatinine normal. ECG normal.
Synthesis and secretion of BNP and NT-proBNP

Heart (Bettencourt) 2005

- originally "BNP" meant "Brain Natriuretic Peptide"
- "brain" became "B-type"
- actually secreted by the ventricles!

- N
  - "natriuretic" – promotes salt excretion ("diuretic")
  - lowers vascular resistance (reduces cardiac work)

- P
  - "peptide"
  - NT-proBNP has a longer half-life and is easier to collect samples than "brain-type" BNP
  - intra-individual variability 5% – 15%

Current clinical term: BNP = B-type Natriuretic Peptide
Current insurance term: BNP = NT-proBNP
Clinical reference ranges: BNP vs. NT-proBNP

**BNP**

- <100 pg/mL - HF unlikely
- >400 pg/mL - HF likely
- 100-400 pg/mL - Use clinical judgment

**NT-proBNP**

- <300 pg/mL - HF unlikely
- Age <50 years, NT-proBNP >450 pg/mL - HF likely
- Age 50-75 years, NT-proBNP >900 pg/mL – HF likely
- Age >75 years, NT-proBNP >1800 – HF likely

Source: Medscape.com
NT-proBNP
< 300 pg/mL - HF unlikely
Age < 50 years, NT-proBNP >450 pg/mL - HF likely
Age 50-75 years, NT-proBNP >900 pg/mL - HF likely
Age >75 years, NT-proBNP >1800 - HF likely

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Mortality assessment?
Take homes: BNP

- Case 1: BNP by any other name
  - Clinical use of the term "BNP" may be different than what we call "BNP"
  - Thresholds for rating assessment need to be "grey" due to variability in NT-proBNP laboratory measurement
- Case 2: What's normal??
- Case 3: What are the factors that can influence the BNP level?
- Case 4: BNP as rating credit?
- Case 5: BNP vs ECG: one from column A.....
- And some other brain teasers....
### Case 2: What's normal??

71 y.o. female smoker

Normal ECG

Normal TM to early Stage III

Normal echo: EF 60%

NT-proBNP 228
Clinical use of BNP

- **Diagnosis**
  - Ambulatory (new onset symptoms)
  - Acute setting (acute dyspnoea)

- **Prognosis**
  - All heart failure patients
  - Stable patients
  - Acute heart failure

- **Dynamic risk stratification**
  - Stable patients
  - Decompensated patients

- **Treatment monitoring**

- **Clinical usefulness of B-type natriuretic measurement** supported by evidence

- **Potential usefulness of B-type natriuretic** awaiting evidence
Diagnostic clinical use of BNP: acute respiratory failure

- BNP levels were associated with a "continuous" CHF risk
- Risk of heart failure > 50% = BNP level of 175 pg/ml
- Is this the level to use for risk assessment? (Hint: all these patients presented with severe respiratory problems)

"Breathing Not Properly" study AHJ (Maisel) 2004

Multicenter trial of 1500 patients presenting to the ER with respiratory failure
Screening clinical use of BNP

- Risk of cardiovascular events and all-cause mortality appear to rise after NT-proBNP levels of 40 pg/ml.

- Is this the level to use for risk assessment? (Hint: 50% of the cohort had levels higher than this!)

EHJ (Linssen PREVEND cohort) 2009

Community-based study of 8000 individuals
**Prognostic clinical use of NT-proBNP**

JACC (Omland PEACE Trial) 2007
- 3700 patients with stable CAD
- Quartile 4:
  - Males: >98 pg/ml
  - Females: >115 pg/ml

- NT-proBNP thresholds for adverse prognosis were 98 - 115 pg/ml
- How about these cutoffs for risk assessment? (Hint: they all had CAD)
71 y.o. female smoker
Normal ECG
Normal TM to early Stage III
Normal echo: EF 60%
NT-proBNP 228

**Epidemiologic clinical use of BNP**

<table>
<thead>
<tr>
<th></th>
<th>Males (45–59 years)</th>
<th>Females (45–59 years)</th>
<th>Males (≥60 years)</th>
<th>Females (≥60 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NTpBNP</td>
<td>20</td>
<td>49</td>
<td>40</td>
<td>78</td>
</tr>
<tr>
<td>serum concentration</td>
<td>(pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean NTpBNP serum</td>
<td>28</td>
<td>61</td>
<td>53</td>
<td>86</td>
</tr>
<tr>
<td>concentration (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean+2SD NTpBNP</td>
<td>82</td>
<td>145</td>
<td>143</td>
<td>195</td>
</tr>
<tr>
<td>serum concentration</td>
<td>(pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>97.5th percentile for</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTpBNP serum</td>
<td>100 (78–173)</td>
<td>164 (150–181)</td>
<td>172 (144–173)</td>
<td>225 (180–254)</td>
</tr>
<tr>
<td>concentration (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>134</td>
<td>144</td>
<td>51</td>
<td>60</td>
</tr>
</tbody>
</table>

- Laboratory cutoffs for "abnormal" seem to have been established between the “mean” and the “2 SD” concentration
Distribution of NT-proBNP in an insurance applicant population

Clark, Kaufman, Fulks, Dolan, Stout: in press
- 144,000 applicants for life insurance; mostly routine requirements

<table>
<thead>
<tr>
<th>NT-proBNP level</th>
<th>% of general population</th>
<th>% of insurance cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 pg/ml</td>
<td>&gt;90%</td>
<td>&gt;80% to age 69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40% - 60% 70 – 79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25% - 40% &gt;80</td>
</tr>
<tr>
<td>&gt;150 pg/ml (males)</td>
<td>&lt;5%</td>
<td>&lt;5% to age 69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15% 70 – 79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34% &gt;80</td>
</tr>
<tr>
<td>&gt;200 pg/ml (females)</td>
<td>&lt;5%</td>
<td>&lt;5% to age 69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25% 70 – 79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45% &gt;80</td>
</tr>
</tbody>
</table>

- Clinical thresholds for "normal" are different in an insurance applicant population

- If we use clinical "cutoffs", we will be rating a significant number of applicants!
NT-proBNP in an insurance applicant population: mortality

<table>
<thead>
<tr>
<th>NTproBNP (pg/mL)</th>
<th>Number deaths</th>
<th>Total Tested</th>
<th>Age and smoking covariates</th>
<th>Age and CVD tertile covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-300 (ref)</td>
<td>329</td>
<td>75,965</td>
<td>1.0 (Cox) 95% CI Lower: 1.0</td>
<td>1.0 (Cox) 95% CI Lower: 1.0</td>
</tr>
<tr>
<td>301 to 700</td>
<td>41</td>
<td>1,846</td>
<td>3.0 (Cox) 95% CI Lower: 2.1</td>
<td>3.1 (Cox) 95% CI Lower: 2.2</td>
</tr>
<tr>
<td>701+</td>
<td>37</td>
<td>665</td>
<td>7.1 (Cox) 95% CI Lower: 4.9</td>
<td>7.0 (Cox) 95% CI Lower: 4.8</td>
</tr>
</tbody>
</table>

Table 5. Mortality ratios (Cox regression) for age 50 to 89, with no missing physical measurements, no missing eGFR, and no history of heart disease

Clark, Kaufman, Fulks, Dolan, Stout: in press
NT-proBNP in an insurance applicant population

Figure 1. Mortality ratios for NT-proBNP values by age group and sex, cases denying history of heart disease.

Clark, Kaufman, Fulks, Dolan, Stout: in press
### NT-proBNP in an insurance applicant population: sub-groups

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>NT-proBNP (pg/mL)</th>
<th>Number</th>
<th>Total</th>
<th>Mortality Ratio (Cox)</th>
<th>95% CI</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F 50 to 69</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-100 (ref)</td>
<td></td>
<td>54</td>
<td>13,920</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>101-300</td>
<td></td>
<td>18</td>
<td>3,768</td>
<td>1.1</td>
<td>0.6</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>301-1,000</td>
<td></td>
<td>12</td>
<td>431</td>
<td>5.6</td>
<td>2.9</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>1,001+</td>
<td></td>
<td>2</td>
<td>35</td>
<td>9.6</td>
<td>2.3</td>
<td>39.9</td>
<td></td>
</tr>
<tr>
<td><strong>M 50 to 69</strong></td>
<td></td>
<td>256</td>
<td>62,256</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>101-300</td>
<td></td>
<td>71</td>
<td>5,697</td>
<td>2.7</td>
<td>2.0</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>301-1,000</td>
<td></td>
<td>19</td>
<td>742</td>
<td>5.3</td>
<td>3.3</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>1,001+</td>
<td></td>
<td>12</td>
<td>145</td>
<td>16.2</td>
<td>9.0</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td><strong>F 70 to 89</strong></td>
<td></td>
<td>34</td>
<td>3,502</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>101-300</td>
<td></td>
<td>50</td>
<td>3,425</td>
<td>1.3</td>
<td>0.9</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>301-1,000</td>
<td></td>
<td>31</td>
<td>1,051</td>
<td>2.6</td>
<td>1.6</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>1,001+</td>
<td></td>
<td>16</td>
<td>144</td>
<td>10.1</td>
<td>5.5</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td><strong>M 70 to 89</strong></td>
<td></td>
<td>65</td>
<td>8,083</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>101-300</td>
<td></td>
<td>69</td>
<td>3,898</td>
<td>2.0</td>
<td>1.4</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>301-1,000</td>
<td></td>
<td>29</td>
<td>978</td>
<td>3.2</td>
<td>2.0</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>1,001+</td>
<td></td>
<td>24</td>
<td>222</td>
<td>10.5</td>
<td>6.4</td>
<td>17.2</td>
<td></td>
</tr>
</tbody>
</table>

Mortality ratios (Cox regression) by age and sex for NT-proBNP bands, cases denying history of heart disease.

Clark, Kaufman, Fulks, Dolan, Stout in press
Case 2: What's normal??

<table>
<thead>
<tr>
<th>TEST NAME</th>
<th>UNITS</th>
<th>RESULTS</th>
<th>NOTE</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMUNOLOGY</td>
<td></td>
<td></td>
<td></td>
<td>NEG</td>
</tr>
<tr>
<td>HN-1 ANTIBODY (BLOOD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEST NAME</td>
<td>UNITS</td>
<td>RESULTS</td>
<td>NOTE</td>
<td>REFERENCE RANGE</td>
</tr>
<tr>
<td>SERUM APPEARANCE</td>
<td>mg/dL</td>
<td>71.0</td>
<td></td>
<td>0 - 150</td>
</tr>
<tr>
<td>TRIGLYCERIDES</td>
<td>mg/dL</td>
<td>23.0</td>
<td></td>
<td>9 - 26</td>
</tr>
<tr>
<td>BUN (BLOOD UREA NITROGEN)</td>
<td>mg/dL</td>
<td>63.0</td>
<td></td>
<td>60 - 109</td>
</tr>
<tr>
<td>GLUCOSE</td>
<td>mg/dL</td>
<td>1.8</td>
<td></td>
<td>1.2 - 2.0</td>
</tr>
<tr>
<td>FRUCTOSAMINE</td>
<td>%</td>
<td>0.6</td>
<td></td>
<td>0.6 - 1.3</td>
</tr>
<tr>
<td>HEMOGLOBIN A1C</td>
<td>mg/dL</td>
<td>117.0</td>
<td></td>
<td>30 - 125</td>
</tr>
<tr>
<td>CREATININE</td>
<td>U/L</td>
<td>4.0</td>
<td></td>
<td>0.2 - 1.2</td>
</tr>
<tr>
<td>ALKALINE PHOSPHATASE</td>
<td>mg/dL</td>
<td>40.0</td>
<td>H</td>
<td>0 - 33</td>
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<tr>
<td>TOTAL BILIRUBIN</td>
<td>U/L</td>
<td>27.0</td>
<td></td>
<td>0 - 45</td>
</tr>
<tr>
<td>AST (SCOT)</td>
<td>U/L</td>
<td>38.0</td>
<td></td>
<td>0 - 45</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>U/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>U/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDT</td>
<td>g/dL</td>
<td>6.8</td>
<td></td>
<td>6.1 - 7.9</td>
</tr>
<tr>
<td>TOTAL PROTEIN</td>
<td>g/dL</td>
<td>4.3</td>
<td></td>
<td>3.8 - 5.2</td>
</tr>
<tr>
<td>ALBUMIN</td>
<td>g/dL</td>
<td>2.5</td>
<td></td>
<td>2.1 - 3.9</td>
</tr>
<tr>
<td>GLOBULIN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEPATITIS B SURFACE ANTIGEN</td>
<td>ng/mL</td>
<td></td>
<td>NEG</td>
<td></td>
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<tr>
<td>HEPATITIS C ANTIBODY</td>
<td></td>
<td></td>
<td>NEG</td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>mg/dL</td>
<td>167.0</td>
<td></td>
<td>140 - 199</td>
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<tr>
<td>CHOLESTEROL</td>
<td>mg/dL</td>
<td>58.0</td>
<td></td>
<td>35 - 100</td>
</tr>
<tr>
<td>HDL CHOLESTEROL</td>
<td>mg/dL</td>
<td>94.0</td>
<td></td>
<td>0 - 129</td>
</tr>
<tr>
<td>LDL (CALCULATED)</td>
<td>ng/mL</td>
<td>2.9</td>
<td></td>
<td>0.0 - 4.999</td>
</tr>
<tr>
<td>GFR/EPCR</td>
<td>ml/min/1.73m2</td>
<td>1.63</td>
<td></td>
<td>.6 - 4.3</td>
</tr>
<tr>
<td>PRO-BNP</td>
<td>pg/mL</td>
<td>228.0</td>
<td>H</td>
<td>0 - 124</td>
</tr>
</tbody>
</table>

71 y.o. female smoker
Normal ECG
Normal TM to early Stage III
Normal echo: EF 60%
NT-proBNP 228

Mortality assessment?
Take homes: BNP

- Case 1: BNP by any other name??
- Case 2: What's normal
  - Clinicians may use different BNP cutoffs depending on the clinical situation
  - Even "normal ranges" focus only on general population distribution
  - Insurance guidelines need to consider distribution and mortality concerns in insureds or those seeking insurance
- Case 3: What are the factors that can influence the BNP level?
- Case 4: BNP as rating credit?
- Case 5: BNP vs ECG: one from column A.....
- And some other brain teasers....
Case 3: more atrial fibrillation

- 69 y.o. male applying for $250,000
- Medical history:
  - Sick-sinus syndrome: Pacemaker implanted
  - ECG: atrial fibrillation, controlled ventricular response
  - Echo: EF 45%, mild LV and LA dilatation
- Insurance lab NT-proBNP: 1100 pg/ml

Question: How much of the BNP elevation can be attributed to the atrial fibrillation and the pacemaker?
As a cause for BNP elevation, we usually think about fluid overload (heart failure)

- NT-proBNP elevation is seen in both systolic failure (ejection fraction is <40%) and diastolic failure (ejection fraction is normal or near-normal)
Other cardiac factors that impact BNP levels (besides heart failure)

- Acute coronary syndromes (unstable angina, myocardial infarction)
- Atrial fibrillation
- Valvular heart disease
- Left ventricular hypertrophy/hypertension
- Pacemaker implantation

BNP study 2002

Europace (Naegeli) 2007
Non-cardiac factors that impact BNP levels

<table>
<thead>
<tr>
<th>Increases BNP</th>
<th>Decreases BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Obesity</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Cardioactive drugs:</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Systemic HBP</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>? Diabetes</td>
</tr>
<tr>
<td>Conn’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic syndrome</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

- Do these lists look familiar?

- BNP levels are influenced by the same factors as ECGs

Bettencourt 2005
Case 3: more atrial fibrillation

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- Medical history:
  - Sick-sinus syndrome: Pacemaker implanted
  - ECG: atrial fibrillation, controlled ventricular response
  - Echo: EF 45%, mild LV and LA dilatation
- Insurance lab NT-proBNP: 1100 pg/ml

Question: How much of the BNP elevation can be attributed to the atrial fibrillation and the pacemaker?
Agenda

- Case 1: What's normal??
- Case 2: BNP by any other name??
- Case 3: What do our impairment ratings cover
  - BNP levels are influenced by many of the same factors as ECGs
  - BNP levels are influenced by many of the impairments we already rate
- Case 4: BNP as rating credit?
- And other brain teasers...
Case 4: BNP as rating credit?

IMPRESSION:

1. Diffuse coronary artery disease in all coronary territories.
2. Moderate luminal stenosis in the mid RCA.
3. Mild stenosis in the circumflex and LAD distributions.
4. Moderate stenosis in the proximal second diagonal branch. This is a relatively small vessel diameter.
5. Coronary calcium score of 546. This represents the 89th percentile for age, sex, ethnicity. This score places the patient at increased risk of future cardiovascular events.
6. As compared to study of 2008 and a there appears to be some progression of the RCA plaques.

62 y.o. male $1 million WL

Medical history:

- CTA done for family history of CAD
- Normal stress test to Stage 4
- Normal echocardiogram
- Carotid ultrasound with mild bilateral plaque
- BNP 108 pg/ml
Low BNP levels as credit?

Groups identified as having better mortality with low BNP

- Chronic heart failure
- Heart transplantation
- Congenital heart disease
- Implantable defibrillators

**Unknown:**

- BNP that improves on serial testing

**Source:** AJC (Mehra) 2004

**Figure 2:** Cardiac deaths are significantly more prevalent in patients with a high level of BNP and predict a 13.6-fold increase in risk.

Heart transplantation cohort
BNP levels in chronic mitral regurgitation

- Low BNP levels predict low risk for valve disease progression

EJHF (Klaar) 2011
- 87 patients with chronic mitral regurgitation

- BNP levels in chronic mitral regurgitation

- Operation not required
- Required operation

pg/ml

0 50 100 150 200 250

BNP  NT-proBNP  EF(%)
Case 4: BNP as rating credit?

IMPRESSSION:

1. Diffuse coronary artery disease in all coronary territories.
2. Moderate luminal stenosis in the mid RCA.
3. Mild stenosis in the circumflex and LAD distributions.
4. Moderate stenosis in the proximal second diagonal branch. This is a relatively small vessel diameter.
5. Coronary calcium score of 546. This represents the 89th percentile for age, sex, ethnicity. This score places the patient at increased risk of future cardiovascular events.
6. As compared to study of 2008 and a there appears to be some progression of the RCA plaques.

Mortality assessment?

62 y.o. male $1 million WL

Medical history:

- CTA done for family history of CAD
- Normal stress test to Stage 4
- Normal echocardiogram
- Carotid ultrasound with mild bilateral plaque

- BNP 108
Agenda

- Case 1: BNP by any other name??
- Case 2: What's normal??
- Case 3: What are the factors that can influence the BNP level?
- Case 4: BNP as rating credit
  - There is some evidence that low BNP may serve as a rating credit
  - This is more likely applicable to cases of valvular disease and cardiomyopathy than to those with CAD
- Case 5: BNP vs ECG: one from column A.....
- And some other brain teasers....
Case 5: BNP and other cardiac tests

Medical history:
- S/P Inferior MI 5 years ago
- Stress echo: Inferior akinesia but no other changes to Stage 3 exercise

NT-proBNP 2220
ECGs and protective value

I'll give you a moment to look in the mirror!!!
## ECGs and protective value

<table>
<thead>
<tr>
<th>ECG finding</th>
<th>Life Re Guide 1993</th>
<th>Life Guide 2013</th>
<th>Change in rating (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree block</td>
<td>+50</td>
<td>STD</td>
<td>- 33%</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>+50</td>
<td>STD</td>
<td>- 33%</td>
</tr>
<tr>
<td>Major ST, T changes</td>
<td>+200</td>
<td>+75/+100</td>
<td>- 50%</td>
</tr>
<tr>
<td>Positive treadmill</td>
<td>+250</td>
<td>+100</td>
<td>- 45%</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>+100</td>
<td>STD</td>
<td>- 50%</td>
</tr>
</tbody>
</table>

Factors impacting ECG protective value:
- Age/amount guidelines
- Interpretation "flexibility"
- Rating "evolution"
**BNP/NT-proBNP plus: other biomarkers**

- 3600 patients undergoing elective cardiac catheterization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Model</th>
<th>Multivariate Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>BNP &gt;100 pg/ml</td>
<td>2.76 (2.25–3.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsCRP &gt;2 ng/L</td>
<td>2.10 (1.71–2.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPO &gt;322 pmol/L</td>
<td>1.43 (1.12–1.82)</td>
<td>&lt;0.004</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, low-density and high-density lipoprotein cholesterol, systolic blood pressure, former or current cigarette smoking, diabetes mellitus, history of myocardial infarction, and creatinine clearance.

- BNP had the best predictive value as a single biomarker
- Combining biomarkers gave additional prognostic value

AJC (Tang) 2013
BNP/NT-proBNP plus: calcium scanning

- BNP and CAC provide complementary prognostic information

- A negative result on either test implies improved survival over situations where both tests are positive

- EISNER cohort: 2400 asymptomatic adults (mean age 58 – 69 years)

AJC (Shaw) 2009
BNP as credit: exercise test results in patients with low NT-proBNP levels

- 355 patients (aged 63 – 75 years) with stable CAD undergoing stress echocardiography

- Patients with low BNP levels were less likely to have inducible ischemia

- Still, many (up to 30%) CAD patients will have normal BNP levels but positive exercise tests

Proportion of participants with inducible ischemia by quartile of BNP (probability value from $\chi^2 = 0.002$).
BNP plus: model to assess value of NTpro-BNP as a screening test

- Mayo/Olmstead county community cohort (McKie PM, J Am Coll Cardiol 2010;55:2140)
  - 703 "healthy normal" & 1288 stage A/B heart failure patients, diagnosis based on echo and clinical assessment
  - All patients underwent labs, ECGs, and treadmills
- Results:
  - In "healthy normal" subgroup (=no cardiovascular risk factors or echo abnormalities) there was no increased risk of death, heart failure, CVA or MI with increased BNP (above 80th %ile)
  - In stage A/B heart failure subgroup, elevated NT pro-BNP was independently associated with these events, even after adjusting for traditional risk factors

Analysis: Kenneth Krause, MD
Sequential testing, 1% prevalence (BNP then TMT favored)

Analysis: Kenneth Krause, MD
Decision analysis: model to assess value of NT-proBNP

- Conclusions of the analysis:
  - Separate testing model:
    - NT-proBNP gave the "most bang for the buck" in low or medium risk patients. (pretest probability of 1%, 5%, 10%)
    - Treadmills become more protective/cost-effective in higher risk patients (pre-test probability >20%)
    - Despite low cost, ECGs always 3rd place in the analysis of protective value
  - Sequential model:
    - Perform NT-proBNP first then do a treadmill if NT-proBNP abnormal

- Important: the value of the treadmill suffered in this analysis because of cost as compared to NT-proBNP
Agenda

- Case 1: BNP by any other name?
- Case 2: What's normal?
- Case 3: What are the factors that can influence the BNP level?
- Case 4: BNP as rating credit?
- Case 5: BNP vs ECG: one from column A.....
  - ECGs have been very important mortality risk assessment tools, but we as a community have lessened their value
  - BNP is giving us different information, but should also become a valuable tool for underwriting risk
  - And some other brain teasers....
Case 6: Any chance?

- 76 y.o. female applying for $1 million WL
- Medical history:
  - Known "cardiomyopathy" for years
  - "Walks 2/4 miles almost every day"
- ECG: LBBB

<table>
<thead>
<tr>
<th>DATE OF LAST MEAL</th>
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<tr>
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<td>DATE COLLECTED</td>
<td>02-Oct-2011</td>
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<td>TIME COLLECTED</td>
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<td>SERUM APPEARANCE</td>
<td>NORMAL</td>
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<td>GLUCOSE (BLOOD)</td>
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<td>BUN</td>
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<td>CREATININE (BLOOD)</td>
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<td>ALT (SGPT)</td>
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<td>HIV (BLOOD)</td>
<td>NEG</td>
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<td>GLOBULIN (BLOOD)</td>
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<td>HEMOGLOBIN A1C</td>
<td>5.6</td>
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<tr>
<td>TOTAL PROTEIN (BLD)</td>
<td>6.7</td>
</tr>
<tr>
<td>NT-ProBNP</td>
<td>5135**</td>
</tr>
</tbody>
</table>

NORMAL RANGES

- 60-125 MG/DL
- 1.8-2.5 MMOL/L
- 5-25 mg/dL
- 0.5-1.5 mg/dL
- 20-115 U/L
- 0.1-1.5 MG/DL
- 0-41 U/L
- 0-45 U/L
- 2-65 U/L
- 140-240 mg/dL
- 35-55 MG/DL
- 0-7.49
- 0-150 MG/DL
- 3.8-5.2 g/dL
- 2.1-3.9 G/DL
- 4.3-6  %
- 6.1-8.2 G/DL

0-125 pg/ml
Case 7: Any chance?

63 y.o. male $2 million WL

Medical history:

- Anterior MI 2004
- 2 stents placed at the time of MI:
  - proximal LAD (90% stenosis) and mid-LCx (99%)
  - LV function: "mildly impaired consistent with MI"
- ECG: LBBB
- Follow-up 2012 (after 4-year absence)
  - Treadmill: 9 minutes (10 METs). ECG LBBB.
  - SPECT: "No ischemia". EF 36% "mildly impaired"
- Insurance labs:
  - NT-proBNP: 81pg/ml (normal <124 pg/ml)
BNP case studies

- Final thoughts
  - Laboratory reference ranges for NT-proBNP reflect clinical use and are not relevant for underwriting. Our ranges need to be related to insurance distribution and scaled for age, gender, and possibly build
  - Reference to "BNP" in medical records may or may not be the same as what we measure for insurance. Make sure what is being measured before you compare serial BNP measurements
  - NT-proBNP measures cardiac stress, so will be elevated in a number of cardiac conditions, including CAD, valvular heart disease, atrial fibrillation, and left ventricular hypertrophy. Unless the NT-proBNP level is extremely high (>1000 ng/ml), our impairment rating should cover the risk of a small/moderate increase with no or only a small additive rating
  - NT-proBNP is giving us risk information that is different than ECGs, calcium scanning or exercise testing. They can be added together or used as offsets to get to the best risk assessment
  - Very low BNP levels may be useful as rating "credits", particularly in cases of valvular heart disease or left ventricular hypertrophy of questionable severity
  - In the final analysis, BNP underwriting requires guidelines...and good judgment!
Thank you

Questions?
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