Brain Natriuretic Peptide
Structures of natriuretic peptide family

Stein Am Heart J 1998;135
Secretory granules discovered in the atria - Kisch (1956) - Jamieson and Palade (1964)

Infusion of extracts of atrial tissue increased natriuresis and diuresis - deBold, et al (1981)

BNP was characterized by amino acid sequence and DNA clones - Sudoh, et al. (1988 and Seilhamer, et al. 1989).
Release of C-type natriuretic peptides from vascular endothelium

Release of B-type natriuretic peptides from ventricles

Release of A-type natriuretic peptides from atria

Supression of renin-angiotensin and endothelin

Decreased peripheral vascular resistance (decreased blood pressure)

Increased natriuresis
Figure 1. The cardiac natriuretic peptide family. BNP, B-type natriuretic peptide; NT, N-terminal; aa, amino acid.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components</td>
<td>BNP molecule</td>
<td>NT fragment (1–76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NT-proBNP (1–108)</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>3.5 kd</td>
<td>8.5 kd</td>
</tr>
<tr>
<td>Hormonally active</td>
<td>Yes</td>
<td>No, inactive peptide</td>
</tr>
<tr>
<td>Genesis</td>
<td>Cleavage from NT-proBNP</td>
<td>Release from ventricular myocytes</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 minutes</td>
<td>120 minutes</td>
</tr>
<tr>
<td>Clearance mechanism</td>
<td>Neutral endopeptidase clearance receptors</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>Increases with normal aging</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Correlation with estimated glomerular filtration rate</td>
<td>~0.20</td>
<td>~0.60</td>
</tr>
<tr>
<td>Approved cutoff(s) for CHF diagnosis</td>
<td>100 pg/mL</td>
<td>Age &lt; 75 years: 125 pg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 75 years: 450 pg/mL</td>
</tr>
<tr>
<td>Approved for assessment of CHF severity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Approved for prognosis in ACS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prospective ED studies completed</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Community screening studies completed</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Available at the point of care</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>No. studies completed</td>
<td>1370</td>
<td>39</td>
</tr>
<tr>
<td>Date of entry on U.S. market</td>
<td>November 2000</td>
<td>December 2002</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; NT, N-terminal; CHF, congestive heart failure; ACS, acute coronary syndrome; ED, emergency department.
• Age
• Sex
• Exercise
• Drugs
Fig. 1. NT-pro BNP concentrations before and after exercise.

- BNP1: immediately before the test
- BNP2: at peak exercise
- BNP3: 0 min after exercise
- BNP4: 60 min after exercise
- BNP2 exp: expected value according to changed plasma volume (0 min after exercise)
Figure 2. BNP Levels in Patients with CHF and Symptomatic LV Dysfunction

FIGURE 1. Brain natriuretic peptide (BNP) levels in normal subjects and in patients with heart failure.

DATA FROM BIOSITE PACKAGE INSERT
BNP levels correlate with Left Ventricular Ejection Fraction

Patients with LVEF greater than 55% had lower BNP levels than those with LVEF less than 40%
Συσχετισμός του NT proBNP με τη μέγιστη κατανάλωση οξυγόνου
DIAGNOSTIC TOOL
Difficulty in the ER diagnosis of CHF

- Signs and symptoms of CHF - non-specific
- ECG, CXR often not helpful
- ECHO - gold standard but:
  - Costly
  - Pt is unable to hold still due to dyspnea
  - “Poor window”
Maisel AS et al. NEJM 2002;347:161-167

- Prospective study on 1586 pts in ER with acute dyspnea
- ER Physicians blinded to BNP results assessed the probability of CHF as the cause of dyspnea on a scale of 0-100
- Patients divided in 3 groups:
  - No CHF
  - Dyspnea due to noncardiac cause with hx of CHF
  - Dyspnea due to CHF

- Subsequently 2 cardiologists reviewed medical records during the hospitalization (CXR, ECHO, MUGA etc.)
Median level of BNP measured in the ER
Results

• CHF → BNP 675 ±450 pg/ml

• No CHF but hx of CHF → 346 ±390 pg/ml

• No CHF → BNP 110 ±225 pg/ml
BNP values in relation to NYHA class

New York Heart Association Class

- Class I: N = 18
- Class II: N = 152
- Class III: N = 351
- Class IV: N = 276
• BNP level was the single most accurate predictor of the presence or absence of CHF

• BNP cut-off of 100 pg/ml was more accurate (83%) than the Framingham criteria (73%)
Accuracy of a single BNP level (>100 pg/mL) in diagnosing CHF compared with established criteria of NHANES and Framingham.
BNP levels beat physical examination in diagnosing heart failure

FIGURE 2. Receiver operating characteristic curves for the accuracy of elevated brain natriuretic peptide (BNP) levels and physical examination in the emergency department in 250 patients with suspected heart failure. AUC, area under the curve; the larger the AUC, the better the test.

How accurate is BNP in differentiating between these two important clinical entities?
CHF vs. COPD

Morrison JACC 2002;39:202-209
Types of Lung Disease and BNP

Morrison JACC 2002;39:202-209
CHF vs. COPD

Confounding factors:
- Cor pulmonale
- Pneumonia leading to CHF exacerbation
- Acute RV failure due to PE

PPV of BNP decreases
BNP for therapeutic monitoring of CHF patients

- 69 pts with EF < 40% and NYHA II-IV CHF
- Randomized to Rx guided by BNP or clinical assessment
- 6-month f/u
- End-point: total CV event (CV death or first readmission for CHF)
Cardiovascular event

Patients remaining event-free (%)

Number at risk

<table>
<thead>
<tr>
<th>BNP</th>
<th>39</th>
<th>31</th>
<th>29</th>
<th>28</th>
<th>26</th>
<th>24</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>36</td>
<td>33</td>
<td>29</td>
<td>25</td>
<td>21</td>
<td>17</td>
<td>15</td>
</tr>
</tbody>
</table>

p = 0.034
• Fewer total CV events (death, admission, HF decompensation) in BNP group (19 vs. 54, \(p=0.02\))

• At 6 mo, 27% of BNP pts and 53% of the clinical group had experienced a first CV event (\(p=0.034\))
Plasma Brain Natriuretic Peptide-Guided Therapy to Improve Outcome in Heart Failure

The STARS-BNP Multicenter Study

Objectives: The aim of this multicenter study was to evaluate the prognostic impact of a therapeutic strategy using BNP levels.

Methods: 220 NYHA II to III patients considered optimally treated with ACEIs, BBs, and diuretics were randomized to either current guidelines (clinical group) or a goal of decreasing BNP plasma levels <100 pg/ml (BNP group). Outpatient visits were scheduled every month for 3 months, then every 3 months. The primary combined end point was CHF-related death or hospital stay for CHF.

Results: Both groups were similar for baseline clinical and biological characteristics. LV EF was slightly lower in the BNP group than in the clinical group (29.9 ± 7.7% vs. 31.8 ± 8.4%, p = 0.05). At the end of the first 3 months, all types of drugs were changed more frequently in the BNP group. Mean dosages of ACEIs and beta-blockers were significantly higher in the BNP group (p < 0.05), whereas the mean increase in furosemide dosage was similar in both groups. During follow-up (median 15 months), significantly fewer patients reached the combined end point in the BNP group (24% vs. 52%, p < 0.001).

Conclusions: In optimally treated CHF patients, a BNP-guided strategy reduced the risk of CHF-related death or hospital stay for CHF. The result was mainly obtained through an increase in ACEI and beta-blocker dosages.

J Am Coll Cardiol, 2007; 49:1733-1739
Event-Free (Hospital Stay for HeartFailure or Death Related to Heart Failure) Survival in the 2 Groups

Number of Changes in Medical Therapy During the First 3 Months

p<0.05

Clinical Group

BNP Group

No. of occasions

Occasions due to clinical reasons

Occasions related to BNP value

BNP in Diastolic Heart Failure

- 294 pts referred for ECHO to evaluate. LVEF
- EF < 50% excluded
- Pt classification:
  - Normal
  - Impaired relaxation
  - Pseudonormal
  - Restrictive like filling
BNP and diastolic HF

A. Mean±SEM for normal BNP values vs impaired relaxation, pseudonormal, and restrictive like filling patterns. Each abnormal group was different from normal group by post hoc Tukey tests (P<0.001). B. Comparison of 3 diastolic filling patterns subdivided by whether patients had symptoms. Values are mean±SEM. Subgroups of diastolic dysfunction patients with clinical CHF overall had higher BNP levels than those without symptoms. P<0.05 by post hoc Tukey test.
Doppler measurements and BNP

BNP levels expressed as reflection of E/A ratios and DTs. Values are mean±SEM. BNP levels were highest in patients with E/A ratios >1.5 (227±61 pg/mL) and in those patients with DTs of <160 ms (249±43 pg/mL). In patients with normal E/A ratio (1 to 1.5), BNP levels were 139±65 pg/mL. However, when this group was separated by DTs, those with normal DTs (160 to 240 ms) had mean BNP levels of only 77±34 pg/mL.
Detecting Diastolic Heart Failure by BNP

BNP of 62 pg/ml:

- sensitivity 85%
- specificity 83%
- accuracy 84%
BNP and DRUGS

- Diuretics
- B-blockers
- Ace Inhibitors
- ARBS
- Digitalis
- Calcium Chanel Blockers
BNP a helpful tool for hospital discharge
When should we discharge a pt after CHF exacerbation?

End-point of our hospital treatment:

- Symptomatic improvement
- Cardiac function tests do not correlate well with symptomatic changes

In-hospital mortality and readmission rates are extremely high

Most patients are discharged when they feel better
BNP correlates with falling wedge pressure

Kazanegra et al. J Cardiac Fail 2001;7:21-29

• Pilot study:

- 22 pts with decompensated CHF
- Hemodynamic monitoring with Swan-Ganz catheter
- All pts in NYHA IV
- Starting wedge pressure > 20 mmHg
- Attempt made to decrease wedge pressure (<20 ) in 24 hours
- BNP levels recorded at baseline an q2-4 h x 24-48h
15 responders in 24h:

- wedge pressure ↓ by 51%
- BNP dropped by 55%
- average fall of BNP/hour: 33 ±5pg/ml
- When wedge pressure was kept low, the BNP fell an additional 37% in the next 24h
• Significant correlation between percent change in wedge pressure from baseline in hour and the percent change of BNP per hour

• $R = 0.73 \quad P < 0.05$
Can BNP predict outcome?

- 13 end-points (4 death, 9 readmission)

- BNP increased (mean $\uparrow$233 pg/ml; $P<.001$)

- In pts without end-points BNP decreased (mean $\downarrow$215 pg/ml)
Can BNP predict outcome?

• 13 end-points (4 death, 9 readmission)

• BNP increased (mean ↑233 pg/ml; P < .001)

• In pts without end-points BNP decreased (mean ↓215 pg/ml)
Reverse Kaplan-Meir plot showing cumulative risk of any hospitalization or death from CHF, stratified by BNP levels at the time of initial visit to the emergency department. Higher BNP levels are associated with progressively worse prognosis. Patients with BNP levels >480 pg/mL had a 6-month cumulative probability of CHF admission or death of 42%. Patients with BNP levels <230 pg/mL only had a 2% chance of such an event.