natriuretic peptides in the management of patients with heart failure

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before we start ..

- Biomarkers are a support to clinical judgment
- But they do not replace clinical judgment
- In unclear clinical situations, in the patient's bedside can guide the treatment way

it is also important to say that
1. Natriuretic peptides is useful to define worsening heart failure
2. Epidemiology of WHF
3. Prognostic role of BNP in WHF
4. Differential effect of drugs based on baseline BNP levels
the heart as an endocrine organ?

Braunwald, American Journal of Medicine, 1964
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force on the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

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2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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NPs oppose the RAAS

Diagram showing the interaction of ANP/CNP, BNP, NPR-A, NPR-B, NPR-C, and Ang II with receptors and signaling pathways, leading to vasodilation and vasoconstriction.
natriuretic peptide clearance

- BNP$^1$
  - NPR
  - Renal excretion
  - Neprilysin

- NT-proBNP$^{1,2}$
  - Less well understood
  - Renal excretion partially responsible

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**BNP and NT-proBNP Clearance Are Equally Dependent on Renal Function**

*B* in patients with hypertension (N=165) undergoing renal arteriography with invasive renal plasma flow measurements and echocardiography.

cardiac correlates for NP values

- Left ventricle
  - Systolic function
  - Diastolic function
  - Chamber size
  - Wall thickness
- Right ventricle
  - Systolic function
  - Chamber size
- Atria
  - Size
- Valves
  - AS, AI
  - MR, MS
  - TR, TS
- Filling pressures
  - Pulmonary
  - Left ventricle, left atrial
- Coronary ischemia
- Heart rhythm
- Aortic capacitance
# clinical correlates of elevated NPs

## Selected Potential Causes of Elevated Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
<td>HF, including RV syndromes, acute coronary syndromes, heart muscle</td>
</tr>
<tr>
<td></td>
<td>disease, including LVH, valvular heart disease, pericardial disease</td>
</tr>
<tr>
<td></td>
<td>atrial fibrillation, myocarditis, cardiac surgery, cardioversion</td>
</tr>
<tr>
<td></td>
<td>toxic-metabolic myocardial insults, including cancer chemotherapy</td>
</tr>
<tr>
<td><strong>Noncardiac</strong></td>
<td>advancing age, anemia, renal failure, pulmonary: obstructive sleep</td>
</tr>
<tr>
<td></td>
<td>apnea, severe pneumonia, pulmonary hypertension, critical illness</td>
</tr>
<tr>
<td></td>
<td>bacterial sepsis, severe burns</td>
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</tbody>
</table>
NPs in clinical practice guidelines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPs for diagnosis&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>NPs for prognosis&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>NPs for predischarge risk assessment&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>NPs to prevent HF onset&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>IIa</td>
<td>B-R</td>
</tr>
<tr>
<td>NPs to guide HF therapy&lt;sup&gt;4&lt;/sup&gt;</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

NPs in clinical practice guidelines

⭐ Plasma concentrations of NPs are recommended as initial diagnostic tests in patients with symptoms suggestive of HF to rule out the diagnosis.

⭐ Elevated concentrations support a diagnosis of HF, are useful for prognostication and may guide further cardiac investigation.
# Recommended diagnostic tests in all patients with suspected chronic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP/NT-proBNPc</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Transthoracic echocardiography</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Chest radiography (X-ray)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin)</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide; ECG = electrocardiogram; HbA1c = glycated haemoglobin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSAT = transferrin saturation.

aClass of recommendation.
bLevel of evidence.
cReferences are listed in section 4.2 for this item.

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**Diagnosis of Heart Failure in non Acute setting**

<table>
<thead>
<tr>
<th>NT-proBNP cut-offs</th>
<th>HF unlikely</th>
<th>HF likely, consider confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;125 pg/ml</td>
<td></td>
<td></td>
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<tr>
<td>&gt;125 pg/ml</td>
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</table>

### Setting | Nutriuretic peptide value | Interpretation
---|---------------------------|----------------|
| Non-acute setting | BNP < 35 pg/ml or NT-proBNP < 125 pg/ml | HF is unlikely |
| Acute setting | BNP < 100 pg/ml or NT-proBNP < 300 pg/ml | HF is unlikely |
|               | BNP > 250 pg/ml or NT-proBNP > 500 pg/ml (in patients < 50 years) | HF is likely |
|               | NT-proBNP > 900 pg/ml (in patients 50 or 75 years) | HF is likely |
|               | NT-proBNP > 1,800 pg/ml (in patients > 75 years) | HF is likely |

BNP = B-type natriuretic peptide; HF = heart failure; NT-proBNP = N-terminal pro B-type natriuretic peptide.

Cut-off values and interpretation of natriuretic peptide in patients with suspected HF in non-acute and acute setting.
NT-proBNP Levels Were Elevated in Patients With Acute HF in the PRIDE Study*

<table>
<thead>
<tr>
<th>Group</th>
<th>Median NT-proBNP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prior CHF (n = 355)</td>
<td>114</td>
</tr>
<tr>
<td>Prior CHF (n = 35)</td>
<td>1175</td>
</tr>
<tr>
<td>Acute CHF (n = 209)</td>
<td>4054</td>
</tr>
</tbody>
</table>

$P < .001$†

CHF, congestive heart failure; PRIDE, N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department.

*Patients (N = 599) were consenting adults ≥21 years of age presenting to the emergency department of the Massachusetts General Hospital with complaint of dyspnea. †$P$ value represents the comparison of acute CHF with patients with non-acute CHF.

PRIDE study

NT-proBNP versus Clinical Judgment, \( p=0.006 \)

Combined versus NT-proBNP, \( p=0.04 \)
Combined versus Clinical Judgment, \( p<0.001 \)

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

PMID: 15820160. DOI: 10.1016/j.amjcard.2004.12.032
NT pro BNP: utility in outpatient dyspnea

Measure NT-proBNP

NT-proBNP < 125 pg/mL?
- HF unlikely: Seek alternative diagnosis

NT-proBNP ≥ 125 pg/mL?
- HF possible: Cardiac work up

History
Physical examination
NT-proBNP and prognosis after ADHF treatment

Salah, et al, Heart, 2014
Individualized care based on discharge NT-proBNP

Discharge NT-proBNP concentration

- Low: Routine follow up
- Medium: Early follow up, Home nursing
- High: Rehab stay, Early follow up, Home nursing, Telemonitoring
bridge from hospital to home
When does NT-pro BNP rise relative to events?

Serial results of NT-proBNP differed considerably among study participants with and without events (CV death/HF hospitalization)

Event happens here

Fuery M et al in preparation
change in LV structure and function at 1 year by NT-pro BNP reduction
operationalizing NP monitoring to enhance clinical decision-making chronic HF

- **Hospital to home**: In recently decompensated patients, measure 1-2 weeks after discharge (office or home).

- **Outpatients**: measure every 3 months
  - Facilitates GDMT decision making (removal of diuretic after GDMT)
  - Stable concentrations <1000 pg/mL (NT-proBNP) or <100 pg/mL (BNP): imaging and other testing may be reasonably deferred
  - **Elevated/rising concentrations**: repeat imaging, further evaluations, review medication/lifestyle program and adjust as appropriate
  - **Markedly elevated concentrations**: Consider transplant referral, consider diagnoses associated with “unexpectedly elevated” NP (amyloidosis).

*HF: heart failure; NT-pro-BNP, N-terminal pro-B type natriuretic peptide.*
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UDHF stages of heart failure

Stages A and B represent the earliest and best opportunity to detect and prevent HF
Stage B heart failure and biomarkers for early detection

Older Adults, "Malignant" Left Ventricular Hypertrophy, and Associated Cardiac-Specific Biomarker Phenotypes to Identify the Differential Risk of New-Onset Reduced Versus Preserved Ejection Fraction Heart Failure: CHS (Cardiovascular Health Study)

Stephan L. Seliger 1, James de Lemos 2, Ian J. Neeland 2, Robert Chaitman 3, Robert Christenson 3, John Gottlieb 3,
Mark H. Drazner 5, Marcella Barry 2, John Seikkin 3, Christopher deFilippi 3

[Heart diagrams showing diastolic and systolic functions: Stiff and thick chambers versus stretched and thin chambers.]

[Graph showing disease burden, cost, biomarker-based detection, clinical events, interventions, baseline risk, earliest molecular detection, structural changes, and current intervention.]
NT-proBNP and prognosis in stage A HF

Seliger et al, JACC, 2010
NT-proBNP and prognosis in stage A HF

Seliger et al, JACC, 2010
Conclusion & take home message

➤ Over the past 20 years, NT pro BNP has evolved (evrimleşmek) from a curiosity to an essential tool in the daily monitoring of individuals with suspected heart failure.

➤ NPs are the main tool not only in diagnosing heart failure, but in evaluating the effectiveness of our treatment and determining the patient's prognosis.

➤ It is also important in the early diagnosis of heart failure and in the management of patients with unexplained dyspnea.