Ο ρόλος του NT-proBNP στη διαχείριση της καρδιακής ανεπάρκειας

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Conflicts of interest

• Honoraria for lectures and/or Advisory boards Novartis, Servier, Pfizer, ELPEN, Servier, Roche
Presentation Format

- Basics
- Diagnosis of HF
- Risk stratification of HF
- Guided-therapy in HF
- Screening for prevention of HF
Basics

Diagnosis of HF

Risk stratification of HF

Guided-therapy in HF

Screening for prevention of HF
Synthesis of BNP and NT-proBNP

H₂N 1

Pro-BNP

Cardiomyocyte

COOH

H₂N

NT-proBNP

Peripheral Circulation

COOH

BNP

H₂N

Corin

COOH

108

77

76

120 minutes

COOH

108

77

20 minutes

Circulation 1994;90:195–203
Cardiac Secretion of Natriuretic Peptides Maintain Intravascular Volume Homeostasis

Ventricular Loading Conditions (end-diastolic pressure, wall stress)
Natriuretic Peptide System

ET inhibition
Vasodilation

CNP

Antiproliferation effect

Sympathoinhibitory

ANP
BNP

Antifibrotic
Lusitropic

Aldosterone
inhibition

Diuresis
Natriuresis
Renin inhibition

Basics

Diagnosis of HF

Risk stratification of HF

Guided-therapy in HF

Screening for prevention of HF
Natriuretic peptides in HF

- HF first postulated to be a NP-deficient state

- Development of plasma BNP assays subsequently indicated increased circulating BNP in HF

- Despite increased natriuretic effect expected with increased levels of BNP, overt HF patients display fluid and salt retention

- End-organ resistance or abnormal proBNP processing, with reduced levels of biologically active BNP, may contribute to this paradox

Lam et al. JACC 2007
Diagnosis in ED
Clinical Indecision in the Emergency Room

Physician Report on Clinical Probability of Congestive Heart Failure

![Bar Chart]

Pretest Probability of CHF

Number of Cases

Significant Indecision Exists

"43%"

Clinical Indecision in the Emergency Room

0 10 20 30 40 50 60 70 80 90 100

0 50 100 150 200 250 300 350
Limited value of physical signs and symptoms in the diagnosis of heart failure

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath at rest</td>
<td>50%</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>70%</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>26%</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>26%</td>
</tr>
<tr>
<td>Edema</td>
<td>46%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical exam</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rales</td>
<td>34%</td>
</tr>
<tr>
<td>Wheeze</td>
<td>27%</td>
</tr>
<tr>
<td>JVP elevation</td>
<td>19%</td>
</tr>
<tr>
<td>Murmurs</td>
<td>20%</td>
</tr>
<tr>
<td>Systolic blood pressure $&gt;149$</td>
<td>28%</td>
</tr>
<tr>
<td>S3</td>
<td>8%</td>
</tr>
<tr>
<td>S4</td>
<td>5%</td>
</tr>
</tbody>
</table>
## NT-proBNP cut-offs in the ED

**ICON trial**

- 1,259 patients presenting to the emergency department with dyspnea
- 4 prospective studies, retrospective pooled analysis
- 720 patients (57.3%) had a final diagnosis of acute HF

### Optimal cut-off values

<table>
<thead>
<tr>
<th>Category: “rule out” (Exclusionary cut-off)</th>
<th>Optimal cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 1,256)</td>
<td>300 pg/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category: ‘rule in’ (Confirmatory cut off)</th>
<th>Optimal cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years (n = 184)</td>
<td>450 pg/mL</td>
</tr>
<tr>
<td>50 – 75 years (n = 537)</td>
<td>900 pg/mL</td>
</tr>
<tr>
<td>&gt; 75 years (n = 535)</td>
<td>1,800 pg/mL</td>
</tr>
</tbody>
</table>

ED, emergency department; HF, heart failure

**ICON:**

*Incidence of "Gray Zone" Diagnosis*

Patients with and without acute HF
N = 1256

- **Rule-Out Cut-point:** 300 pg/mL 43%
- **Gray Zone:** 300 pg/mL to age-adjusted rule-in cut-point 16%
- **Rule-In Cut-Point:**
  - <50 yr: 450 pg/mL
  - 50 to 75 yr: 900 pg/mL
  - >75 yr: 1800 pg/mL 41%

Diagnosed with HF 50%

## Regarding applied diagnostic measurements

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upon presentation a measurement of plasma natriuretic peptide level (BNP, NT-proBNP or MR-proANP) is recommended in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>At admission in all patients presenting with suspected AHF, the following diagnostic tests are recommended:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. 12-lead ECG;</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>b. chest X-ray to assess signs of pulmonary congestion and detect other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms;</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>c. the following laboratory assessments in the blood: cardiac troponins, BUN (or urea), creatinine, electrolytes (sodium, potassium), glucose, complete blood count, liver function tests and TSH.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Echocardiography is recommended immediately in haemodynamically unstable AHF patients and within 48 hours when cardiac structure and function are either not known or may have changed since previous studies.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
NT-proBNP expressed as a function of NYHA classes

*In subjects with acute HF*

Increasing values of NT-proBNP noted as severity of HF progresses

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>Median (pg/mL)</th>
<th>IQR (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>3,512</td>
<td>1,395 - 8,588</td>
</tr>
<tr>
<td>III</td>
<td>5,610</td>
<td>2,260 - 11,001</td>
</tr>
<tr>
<td>IV</td>
<td>6,196</td>
<td>2,757 - 13,295</td>
</tr>
</tbody>
</table>

Boxes represent IQRs; Whiskers represent the 5th and 95th percentiles

HF, heart failure; IQR, interquartile range

NT-proBNP interpretation in the ED

**Causes of false negative values**

- Defined as confirmed acute HF in the context of a NT-proBNP <300 pg/mL

- Generally related to **decompensated end-stage HF, right sided HF, flash pulmonary edema, or very high body-mass index**

- NPs have reduced sensitivity for HF in severe obesity (BMI >35 kg/m²)\(^1\)

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BMI, body mass index; ED, emergency department; HF, heart failure; NPs, natriuretic peptides

## Causes of elevated concentrations of natriuretic peptides

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Non-cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>Ischaemic stroke</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Subarachnoid haemorrhage</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Liver dysfunction (mainly liver cirrhosis with ascites)</td>
</tr>
<tr>
<td>Hypertrophic or restrictive</td>
<td>Paraneoplastic syndrome</td>
</tr>
<tr>
<td>cardiomyopathy</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Severe infections (including pneumonia and sepsis)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Severe burns</td>
</tr>
<tr>
<td>Atrial and ventricular</td>
<td>Anaemia</td>
</tr>
<tr>
<td>tachyarrhythmias</td>
<td>Severe metabolic and hormone abnormalities (e.g. thyro-toxicosis, diabetic</td>
</tr>
<tr>
<td></td>
<td>ketosis)</td>
</tr>
<tr>
<td>Heart contusion</td>
<td></td>
</tr>
<tr>
<td>Cardioversion, ICD shock</td>
<td></td>
</tr>
<tr>
<td>Surgical procedures involving</td>
<td></td>
</tr>
<tr>
<td>the heart</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
</tr>
</tbody>
</table>
Interpreting values with renal disease

- NP levels are higher in patients with significant renal failure and lower in obese patients; therefore, different decision limits are required to rule-out HF.

**Rule out cut offs in the presence of renal failure (eGFR < 60 mL/min/1.73 m²)**

- BNP: 200–225 pg/mL²
- NT-proBNP: 1,200 pg/mL³
- Exclusion of HF less accurate in patients with eGFR <30 mL/min/1.73 m²²,⁴,⁵

---

eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HF, heart failure; NPs, natriuretic peptides

• NT-proBNP and BNP are both elevated in kidney dysfunction
  • Both assays remained sensitive and specific among patients with eGFR <60 mL/min
• When using appropriate cut-offs stratified according to kidney dysfunction, NT-proBNP predicts systolic HF better than BNP
• In another study, NT-proBNP was superior to BNP as a predictor of HF mortality across the spectrum of renal function

Improved performance in a variety of care settings
Predicts HF better than BNP in patients with renal dysfunction

ROC curve of NT-proBNP and BNP for HF in entire study group

AUC, area under curve; eGFR, estimated glomerular filtration rate; HF, heart failure; SHF, systolic heart failure; ROC, receiver operating characteristic

AUC: NT-proBNP=0.86; AUC: BNP=0.70

Diagnosis in CHF
## Definition of heart failure

**With preserved (HFrEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)**

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>PFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs</td>
<td>Symptoms ± Signs</td>
<td>Symptoms ± Signs</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>1. Elevated levels of natriuretic peptides.</td>
<td>1. Elevated levels of natriuretic peptides.</td>
</tr>
<tr>
<td></td>
<td>2. At least one additional criterion: a. relevant structural heart disease (LVF and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2.)</td>
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<td></td>
</tr>
</tbody>
</table>
Diagnostic algorithm for a diagnosis of heart failure of non-acute onset

**PATIENT WITH SUSPECTED HF**

*non-acute onset*

**ASSESSMENT OF HF PROBABILITY**

1. **Clinical history:**
   - History of CAD (MI, revascularization)
   - History of arterial hypertension
   - Exposure to cardiotoxic drug/radiation
   - Use of diuretics
   - Orthopnoea / paroxysmal nocturnal dyspnœa

2. **Physical examination:**
   - Rales
   - Bilateral ankle oedema
   - Heart murmur
   - Jugular venous dilatation
   - Laterally displaced/broadened apical beat

3. **ECG:**
   - Any abnormality

---

**≥1 present**

**NATRIURETIC PEPTIDES**

- NT-proBNP ≥125 pg/mL
- BNP ≥35 pg/mL

---

**ECHOCARDIOGRAPHY**

**All absent**

- HF unlikely: consider other diagnosis

**√**

**Yes**

- Normal

**No**

- If HF confirmed (based on all available data): determine aetiology and start appropriate treatment

---

Assessment of natriuretic peptides not routinely done in clinical practice
NT-proBNP: Medical value in diagnosis of heart failure

The PRIDE study has shown that NT-proBNP based diagnosis of HF in patients with dyspnea was superior to clinical judgment alone and NT-proBNP + clinical judgment was superior to NT-proBNP or clinical judgment alone.

Januzzi. Am J Cardiol 2005;95:948-954
NT-proBNP Higher in HFrEF vs HFpEF

- Measured at discharge after hospitalization for acute HF
AF and HFPpEF

AF is independently associated with natriuretic peptide elevation in HFPpEF

Reprinted from JACC Heart Fail, 5, Lam CS, et al., Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction Association With Exercise Capacity, Left Ventricular Filling Pressures, Natriuretic Peptides, and Left Atrial, 5, 92-98., Copyright 2017, with permission from Elsevier.
BACH: AF Impairs Diagnostic Performance of Cardiac Natriuretic Peptides in Dyspneic Patients

Reprinted from JACC Heart Fail, 1, Richards M, et al., Atrial Fibrillation Impairs the Diagnostic Performance of Cardiac Natriuretic Peptides in Dyspneic Patients Results From the BACH Study (Biomarkers in Acute Heart Failure), 192-199., Copyright 2013, with permission from Elsevier.
Incidence of HF in Patients with AF Presenting to the ED with Acute Dyspnea

Breathing Not Properly 2002\textsuperscript{a}
• 75%

PRIDE 2007\textsuperscript{b}
• 79%

BACH 2013\textsuperscript{c}
• 66%

In patients presenting with acute dyspnea and AF, HF should be presumed present until proven absent\textsuperscript{c}

Thinking outside the box

• Use concentrations of NT-proBNP to identify when a patient’s symptoms are not from worsening HF

• They may be from cardiac output restriction or other things might cause symptoms in our patients that often are quite polymorbid

• Multiple comorbidities to consider
Basics

Diagnosis

Risk stratification

Guided-therapy

Screening for prevention of HF
Risk stratification in the Emergency Department and hospital discharge
Risk stratification of admission NT-proBNP in patients with acute decompensated HF in the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study

**With history of HF**

**Without history of HF**

NT-proBNP in mortality prediction: PROMPT trial

Emergency department admission value predicts outcomes

Discharge NT-proBNP correlates with death and CV events

*Mortality was 41% in patients with NT-proBNP >15,000 pg/mL*

Composite event rate also highest in patients with discharge NT-proBNP levels ≥15,000 pg/mL; risk increased noted with each quartile.
NT-proBNP delta correlates with death and CV events

Mortality twice as high in patients with reduction ≤30% vs. 30%

Composite event rate was higher in patients with a percentage reduction in NT-proBNP ≤30% compared with >30%

Risk stratification in chronic HF
The Importance of Serial NP Measurements for Prognostication in Chronic HF

Mortality (%)  | Hospitalization for HF (%)  
---|---
High→High  | 25.6  | 26.8  
Low→High  | 17.2  | 21.1  
High→Low  | 13.6  | 10.1  
Low→Low  | 8.6  | 6.7  

Risk stratification in chronic HF
The power of combining cTnT-hs and NT-proBNP

- All-cause mortality risk in chronic HF

- Highest when both biomarkers elevated
  - HR=7.42* (p<0.001)

- Hazard ratio (HR) with only one elevated biomarker
  - cTnT-hs: HR=3.68* (p<0.001)
  - NT-proBNP: HR=1.73* (p=0.136)

* Compared with patients with both biomarkers below the optimal cutoffs
  HR, hazard ratio

Survival according to elevated cTnT-hs and NT-proBNP

<table>
<thead>
<tr>
<th>cTnT-hs</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16 ng/L</td>
<td>&lt;1720 ng/L</td>
</tr>
<tr>
<td>≥16 ng/L</td>
<td>≥1720 ng/L</td>
</tr>
<tr>
<td>≥16 ng/L</td>
<td>&lt;1720 ng/L</td>
</tr>
<tr>
<td>≥16 ng/L</td>
<td>≥1720 ng/L</td>
</tr>
</tbody>
</table>

Log rank p<0.001

PARADIGM-HF: Reduction of NT-proBNP to ≤ 1000 pg/mL Leads to Better Outcomes

Reprinted from *J Am Coll Cardiol*, 68, Zile MR, et al., Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure, 2425-2436., Copyright 2016, with permission from Elsevier.
BNP (but not NTproBNP) is a substrate for neprilysin, thus, levels of BNP will reflect the action of the drug, whereas levels of NTproBNP will reflect the effects of the drug on the heart.

NT-proBNP As a Motivator for Patients

- Involve patients in their numbers
- Educate patients on rationale regarding their medication
- Empower patients toward their own improvement
- NT-proBNP is their scorecard
  - Seeing that number come down gives them a goal
Basics

Diagnosis of HF

Risk stratification of HF

Guided-therapy in HF

Screening for prevention of HF
Guided therapy from other areas of medicine

• Diabetes mellitus  HbA1c ✓
• Hypertension        Blood pressure ✓
• Hyperlipidemia      LDL ✓
• Anticoagulation     INR ✓
• Heart failure       NT-proBNP ?
RCT meta-analyses in chronic HF guided therapy

*Lower risk associated with biomarker guided therapy*

- Meta-analyses\(^1,2,3\) show decreased risk of mortality in data pooled across the positive, neutral and negative clinical trials of guided HF therapy

- Biomarker-guided therapy resulted in a reduction in all-cause mortality of approximately 30\(^1\)

- Beyond considerations of all-cause mortality, meta-analysis have shown reduced readmission rates for HF and CV events\(^3\)

---

**All-cause mortality among chronic HF patients randomised to biomarker-guided therapy versus standard of care\(^1\)**

![Graph adapted from Felker et al, 2009.](image-url)

Outcome primary endpoint:

<table>
<thead>
<tr>
<th></th>
<th>positive</th>
<th>positive (&lt;75 y)</th>
<th>neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troughton</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STARBRITE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STARS-BNP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BATTLESCARRED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIME-CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRIMA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The size of the marker for the point estimate (diamond) is proportional to the sample size for each study. Horizontal lines show 95% CIs.

---

CV, cardiovascular; HF, heart failure; RCT, randomised controlled trial

Therapy guidance: PROTECT Study

*Improvement in time to first event and total CV events*

**Time to first event**

- NT-proBNP (n=75)
- Standard-of-care (n=76)

**Total CV events** (p=0.009)

CV, cardiovascular; SOC, standard of care

GUIDE-IT

Study Design

- Primary end point: time to CV death or first HF hospitalization
- Secondary end points: time to all-cause mortality; days alive and not hospitalized for CV reasons; recurrent hospitalization; time to CV death; time to first HF hospitalization; HRQoL; resource use, costs, and cost-effectiveness

Patient with high-risk systolic HF
LVEF ≤ 40%
HF event within 12 mo (HF hospitalization, ED visit, or outpatient IV diuretic)
NT-proBNP > 2000 pg/mL or BNP > 400 pg/mL within last 30 d

Usual care (n = 550)

Follow-up:
2 wk, 6 wk, 3 mo, then q3mo for 12 to 24 mo

Biomarker-guided NT-proBNP < 1000 pg/mL (n = 550)

Additional 2-wk follow-up after changes in therapy

## GUIDE-IT
### Outcomes

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>NT-proBNP-Guided Strategy vs Usual Care</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint*</td>
<td>0.98 (0.79, 1.22)</td>
<td>.88</td>
</tr>
<tr>
<td>CV death</td>
<td>0.94 (0.65, 1.37)</td>
<td>.75</td>
</tr>
<tr>
<td>Death by any cause</td>
<td>0.86 (0.62, 1.20)</td>
<td>.37</td>
</tr>
</tbody>
</table>

*First HF hospitalization or CV death.

Basics

Diagnosis of HF

Risk stratification of HF

Guided-therapy in HF

Screening for prevention of HF
## Natriuretic Peptide Screening for Prevention of HF

### 2017 ACC/AHA/HFSA Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>&quot;For patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.&quot;</td>
<td>&quot;NEW: New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF.&quot;</td>
</tr>
</tbody>
</table>

PONTIAC
Study Design

Inclusion
- T2D
- ≥ 18 y
- NT-proBNP > 125 pg/ml
- Cardiac disease-based criteria

Exclusion

Control group
cared for at
4 diabetes care
units

Primary endpoint:
Hospitalization/
death because of
cardiac disease after 2 y

Intensified group
additional
treatment at a
cardiac outpatient
clinic for up titration
of RAS inhibitors
and β-blockers

N = 300

*≥ 1 of the following: history of cardiac disease; signs of cardiac disease on electrocardiogram; ST-T-wave
abnormalities or BBB; abnormal echocardiography (except diastolic dysfunction); wall motion abnormalities,
significant valve dysfunction, or other significant alteration.

Accelerated uptitration of RAS antagonists and β-blockers is an effective intervention for primary prevention of cardiac events in Patients with diabetes preselected using NT-proBNP.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPs for diagnosis</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>NPs for prognosis</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>NPs for predischARGE risk assessment</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>NPs to prevent HF onset</td>
<td>IIa</td>
<td>B-R</td>
</tr>
<tr>
<td>NPs to guide HF therapy</td>
<td>IIb</td>
<td>B-NR</td>
</tr>
<tr>
<td>Fibrosis/injury markers for risk assessment</td>
<td>IIb</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

Thank you
STOP-HF
Outcomes

Patients randomly assigned to the intervention group had a significant reduction in the primary outcome as well as in the secondary outcome of emergency hospitalization for major cardiovascular events.

BNP-based screening and collaborative care reduced combined rates of LV systolic dysfunction, diastolic dysfunction, and HF

*95% CI.
PONTIAC
Study Design

Inclusion
- T2D
- ≥ 18 y
- NT-proBNP > 125 pg/ml
- Cardiac disease-based criteria*

Exclusion
- Cardiac disease-based criteria*

Control group cared for at 4 diabetes care units

Intensified group additional treatment at a cardiac outpatient clinic for up titration of RAS inhibitors and β-blockers

Primary endpoint:
Hospitalization/death because of cardiac disease after 2 y

N = 300

*≥ 1 of the following: history of cardiac disease; signs of cardiac disease on electrocardiogram; ST-T-wave abnormalities or BBB; abnormal echocardiography (except diastolic dysfunction); wall motion abnormalities, significant valve dysfunction, or other significant alteration.