Ο ρόλος του Ntpro-BNP στην πρόγνωση και θεραπεία της καρδιακής ανεπαρκείας εν μέσω νεοτερων θεραπειών

ΧΡΙΣΤΙΝΑ ΧΡΥΣΟΧΟΟΥ
ΚΑΡΔΙΟΛΟΓΟΣ
ΔΙΕΥΘΥΝΤΡΙΑ ΕΣΥ
Α ΠΑΝΕΠΙΣΤΗΜΙΑΚΗ ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΙΓΝΑ
Despite substantial spending, re-hospitalization and mortality rates remain high.

About 1 in 4 re-admitted within **30 days** of discharge\(^1,2,3\)

About 1 in 2 re-admitted within **6 months**\(^4\)

More than 1 in 2 die in **5 years**, with survival rates worse than major cancers like bowel, breast and prostate cancer\(^2\)

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Currently, there are unmet medical needs in HF

**HF symptoms unspecific** and hard to tell apart in elderly and lung disease patients

Echocardiograms are resource-intensive

Need for **early and accurate HF diagnosis to improve outcomes and save resources**

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**In-hospital management**

Need to aid **discharge planning to avoid early readmission**

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**Disease monitoring**

Need for **objective marker to monitor patient’s condition for improved outcomes**, including those on sacubitril-valsartan

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ΚΑΤΕΥΘΥΝΣΗ ΘΕΡΑΠΕΙΑΣ;
Serial NT-proBNP measurements provide prognostic information on mortality and hospitalization for HF

HF, heart failure; NP, natriuretic peptide
Graph from adaptation by Januzzi, 2012, Figure 1 from a study by Masson, S. et al.

NP secretion

- Myocardial stretch (increased wall stress) directly or through AgII, endothelin, NO
- Intracardial filling pressures
- Myocardial ischemia and tachycardia
- Circulating glucorticoids
- Renal failure
- Clearance affected by renal function

Increased LVFP is not necessarily associated with myocardial stretch

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect on BNP/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>May transiently ↑, then ↓</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>
</tbody>
</table>
NT-proANP levels are specifically and significantly elevated in response to cardiac remodeling

- In blood plasma, only NT-proANP levels were specifically and significantly elevated in response to cardiac remodeling in all mouse models.
- Circulating levels of Gal-3, GDF-15 and TIMP-1 were strongly influenced by extra-cardiac tissues and their elevation also reflects enhanced stress and concomitant productions in these extra-cardiac tissues due to comorbidities or even MS.
## Nt proBNP and filling pressures

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Size</th>
<th>Description</th>
<th>NT-proBNP</th>
<th>PCWP</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tschope [35]</td>
<td>2005</td>
<td>118</td>
<td>Patients with exertional dyspnea with preserved LV function</td>
<td>NT-proBNP</td>
<td>PCWP</td>
<td>NT-proBNP at rest correlated with PCWP at peak exercise</td>
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<tr>
<td>Tschope [66]</td>
<td>2005</td>
<td>30</td>
<td>Patients with exertional dyspnea, preserved LV function with ↑ LVFP at exercise</td>
<td>NT-proBNP</td>
<td>PCWP</td>
<td>NT-proBNP at rest correlated with PCWP at peak exercise</td>
</tr>
<tr>
<td>Fukuta [39]</td>
<td>2007</td>
<td>140</td>
<td>Patients undergoing exercise echocardiography</td>
<td>BNP</td>
<td>E/E’</td>
<td>BNP correlated with postexercise E/E’ only in patients with abnormal LV filling pattern</td>
</tr>
</tbody>
</table>
The severity of PAH or right heart strain (as measured by hemodynamic data) could be estimated by a biochemical assay. In addition, it could also be used as an indicator of treatment efficacy (e.g. Correlation with mPAP, RVEDP) and hence guide-therapy for PAH.

- Potentiation of natriuretic peptide action via NEP inhibitors or recombinant BNP may also have beneficial effects in reducing cardiac fibrosis or hypertrophy in RV dysfunction.
Παράδειγμα: ασθενής A
Παράδειγμα ασθενής Α

Ο καρδιακός καθετηριασμός RA=10, V=15 (32), RV=61/11. PA=62/22/37, PW=18, SAT=95% Lvdiasole=19, Pa SAT=64%, PVR=4woods και επηρεασμένη απόδοση δεξιάς κοιλίας (Κλάσμα εξώθησης αυτής 30%).
Η καρδιοαναπνευστική δοκιμασία κόπωσης είναι σταδίου C κατά Weber με Vo2mas=12,6 ml/kg/min, VE/VCO2=39, Nt-proBNP=9000pg/ml

Ασθενής 52 ετών με μη-ισχαιμική καρδιακή ανεπάρκεια σε NYHA III-IV, σε αγωγή valsartan 40-80mg, Furosemide 540mg, eplerenone 50mg, carvedilol 12,5-25mg, cumadin, thiazide diuretic.
Στην κλινική πράξη

- Τα μοντέλα αδυνατούν να αποτυπώσουν την πραγματικότητα
- BUN και Na έχουν δείξει υψηλή διαγνωστική αξία σε μοντέλα (αντανάκλαση νευροορμονικού άξονα)
- Στο Seattle Heart Failure model σε 7000 ασθενείς η δόση διουρητικού είχε υψηλότερη διαγνωστική αξία (ROC) από BUN και Na.

- Data from patients with HFrEF (Val-HeFT [Valsartan Heart Failure Trial]) and HFpEF (I-PRESERVE [Irbesartan in Heart Failure With Preserved Ejection Fraction Study]) trials show that despite significantly higher baseline levels of NP in HFrEF, the hazard for mortality associated with 1 log unit increase in N-terminal pro–B-type natriuretic peptide (NT-proBNP) is similar in both HFrEF and HFpEF populations (hazard ratio: ~1.70)
Είναι ζήτημα αιμοδυναμικής;

HFpEF haemodynamics result from the tight interplay of both cardiac and non-cardiac factors. HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LVEDP = left ventricular end diastolic pressure.

Table 1: Haemodynamic Parameters at Rest in Healthy Adults and HFpEF Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy adults</th>
<th>Early HFpEF</th>
<th>Advanced HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>0–6</td>
<td>0–8</td>
<td>≥10</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>≥25</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>6–15</td>
<td>6–18</td>
<td>≥20</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>&lt;16</td>
<td>&lt;16</td>
<td>≥16</td>
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NP levels seem to reflect LV wall stress more closely than other ventricular parameters in HF.
**Nt pro BNP in different types of HF**

<table>
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<tr>
<th>Category of Heart Failure</th>
<th>NT-proBNP Median (pg/mL)</th>
<th>N</th>
<th>Study/Trial</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute decompensated heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFrEF</td>
<td>6356</td>
<td>358</td>
<td>ICON</td>
<td>Januzzi et al, 12 2006</td>
</tr>
<tr>
<td>HfPfEF</td>
<td>3070</td>
<td>295</td>
<td>ICON</td>
<td>Januzzi et al, 12 2006</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFrEF</td>
<td>895</td>
<td>3916</td>
<td>ValHeFT</td>
<td>Masson et al, 40 2006</td>
</tr>
<tr>
<td>HFpEF</td>
<td>339</td>
<td>3480</td>
<td>I-PRESERVE</td>
<td>Komajda et al, 23 2011</td>
</tr>
</tbody>
</table>

LV structure and function influence plasma NT-proBNP. Specifically, plasma NT-proBNP plasma concentrations in HFpEF are approximately half those observed in HFrEF (Table 2) in both acute and chronic HF.6,7,22 This reflects the integrated influence of ventricular internal dimensions, wall thickness, and intraventricular pressures (embodied in the law of Laplace) on unit wall stress and cardiomyocyte stretch, the primary driver of NP synthesis and release. In the event, the diagnostic performance of NT-proBNP in HFpEF is only marginally impaired in view of the high signal-to-noise ratio in acute HF, as discussed elsewhere in this article. In contrast, in the setting of incipient or treated HF, NP values often fall into the subdiagnostic range and this is particularly so in HFpEF.23 This phenomenon holds for both plasma NT-proBNP and BNP.
Correlation of NT-proBNP levels and cardiac iron concentration in patients with transfusion-dependent thalassemia major

Polyxeni Delaporta a, Antonios Kattamis a, Filia Apostolakou b, Sorina Boiu a, Anastasia Bartzeiotou b, Evangelos Tsoukas b, Ioannis Papassotiriou b,*

**Discussion**

Our study demonstrated for the first time that plasma levels of NT-proBNP, a proven diagnostic biomarker for heart failure due to left ventricular systolic dysfunction were significantly associated with cardiac iron concentration in patients with β-thalassemia major linking blood chemistry and imaging techniques.

- Nt pro BNP levels can be used as a marker for primary detection of hemosiderosis in order to intense chelation therapy?

![Graph showing correlation between NT-proBNP and [Fe] levels](image)

*Fig. 2. Correlation of NT-proBNP (pg/mL) levels with cardiac iron concentration [Fe] (mg/g dry weight) in thalassemic patients with cardiac siderosis (r = 0.520, p < 0.001).*
From NP-driven treatment to individualization

Pathophysiology of sudden cardiac death as demonstrated by molecular pathology of natriuretic peptides in the myocardium

Jian-Hua Chen a,b, Tomomi Michiue a,b,*, Takaki Ishikawa a,b, Hitoshi Maeda a,b

diseases, representing clinical features: (1) overall high myocardial ANP/BNP expressions in AIHD, indicating acute cardiac overload; (2) lower ANP/BNP mRNA expressions especially in bilateral atrial walls in RMI, suggesting a lower cardiac compensatory capacity; (3) high ANP/BNP mRNA expressions with increased pericardial BNP in CHD, indicating acute-on-chronic aggravation of heart failure; (4) low right ventricular BNP mRNA expression but high ANP/BNP mRNA expressions at other sites in HP, indicating right ventricular hypotension due to the compressive effects of cardiac tamponade mainly on the right atrium and/or vena cava, accompanied by increased strain in other cardiac cavities, involving elevated central venous (right atrial) and left atrial blood pressures; (5) lower ANP/BNP mRNA expressions in the left ventricle but high expressions at other sites in PTE, indicating markedly decreased left ventricular preload due to decreased right ventricular output; (6) higher expressions of ANP/BNP mRNA in bilateral ventricular and atrial walls in RVC, indicating marked cardiac strain due to impaired ventricular contractility. These findings may be helpful for understanding and interpreting different cardiac dysfunction involved in sudden death from various heart diseases in relevance to the pathologies and clinical findings. However, in conclusion, the present study shows characteristic molecular biological responses of myocardial natriuretic peptides in individual heart diseases and suggests the possible application of molecular pathology to demonstrate cardiac dysfunction as a cause of sudden cardiac death, even after death.
Echo, NPs and Heart failure

- E/e’ can not accurately estimate LV filling pressure and neither can identify increased LV filling pressure in patients with dyspnoea.
- LA reservoir, LA size and function; RV function; IVC and TAPSE have prognostic value.
- Several echo markers must be evaluated at the same time.

Circulation: Heart Failure 2015 8 749–756
Ασθενής Β

- Άνδρας 75 ετών με ιστορική ισχαιμικής μυοκαρδιοπαθείας, χρόνια κολτική μαρμαρυγή, ολική καρδιακή ανεπάρκεια με συχνές νοσηλείες με οιδήματα κάτω άκρων, πλευριτική συλλογή, ασκιτική συλλογή, ισχαιμική ηπατίτιδα

- Νοσηλεία 13/9/2016 με απορρύθμιση ΚΑ (ινότροπα, διουρητική αγωγή) Υποτιτλοποιημένη λοιπή αγωγή λόγω υπότασης (eplerenone μονο από θεραπεία άξονα)

- Εμφύτευση CRT-D. Μη καλή ανταπόκριση

- Βελτίωση αμφικοιλιακής βηματοδότησης με πολυεστιακή
Υπερηχοκαρδιογραφικός έλεγχος
28/9/2016
Ο ρόλος της Αμφικοιλιακής πολυεστιακής βηματοδότησης

-CRT (NT-proBNP=4100)  +CRT (NT-proBNP=2850)  +CRT 5-5-15msec (NT-proBNP=980)
Major guidelines recognize the value of NPs testing for the in-hospital management of HF

- **Pre-discharge assessment** of NP levels may be considered for *prognostic evaluation*\(^1\)
- Measuring natriuretic peptides during the hospital admission can help with discharge planning.
- **Patients whose natriuretic peptide concentrations fall during admission have lower cardiovascular mortality and readmission rates at 6 months**\(^1\)

Also recognized by the Canadian Cardiovascular Society (CCS) for similar uses.

### 2013 AHA/ACC heart failure clinical practice guidelines

<table>
<thead>
<tr>
<th>Indication: Guided therapy</th>
<th>Class</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>To improve outcome in chronic heart failure</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>To assist in achievement of GDMT</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

**Class** – size of treatment effect  
**LOE**, level of evidence – estimate of certainty (precision) of treatment effect  
**GDMT**, guideline directed medical therapy

NT-proBNP-based care in ED dyspnoeic patients

Reduction in the number of hospitalisations

- A decision-analytical model using data from the PRIDE study (n=599) predicted a 13% reduction in initial hospitalisations if clinical aided by NT-proBNP interpretation¹

- Associated with:
  - a 1.6% relative reduction of serious adverse event risk
  - savings of $474 per patient, compared with standard clinical assessment
  - 1.0% relative reduction in post-discharge mortality

Ασθενής με γνωστή καρδιακή ανεπάρκεια και αναφερόμενη δύσπνοια

- Ισχαιμική καρδιακή ανεπάρκεια
- PCI στον LAD
- Εχει αρνηθεί ICD και ΗΦΕ
- Πρώην καπνιστής
- Νοσηλεία με απορρύθμιση KA προ έτους
- Δαμβάνει eplerenone 50, sacubitril/valsartan 103/97, furosemide, 40mg, bisoprolol, atorvastatin/ezetimibe, aspirine
- Αναφέρει δύσπνοια
- Nt-proBNP=70pg/ml

E/E’=10, SRV=9cm/sec, PASP=25mmHg
Cost-effectiveness of N-terminal pro-B-type natriuretic-guided therapy in elderly heart failure patients: results from TIME-CHF

- 467 patients (age 76 ± 7 years, 66% male) with left ventricular ejection fraction of ≤45% were randomized to receive intensified NT-proBNP-guided therapy or standard, symptom-guided therapy.

- NT-proBNP-guided therapy was dominant (i.e., more effective and less costly) over symptom-guided therapy, saving $2,979 USD per patient, with incremental effectiveness of +0.07 life-years and +0.05 QALYs.

- Cost-effectiveness of NT-proBNP-guided therapy was most pronounced in patients <75 years old and in those with <2 significant comorbidities, being dominant in all sensitivity analyses.

- In the worst-case scenario (excluding residence costs in those with ≥2 comorbidities), the incremental cost-effectiveness ratio was $11,935 per life-year gained.

JACC Heart Fail. 2013 Feb;1(1):64-71
Meta-analysis of NP Guided Therapy Trials
All cause mortality

Savarese 2013
Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial

The GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study was a randomized multicenter clinical trial conducted between January 16, 2013 and September 20, 2016 at 45 clinical sites in the United States and Canada. This study planned to randomize 1,100 patients with HFrEF (ejection fraction ≤40%), elevated natriuretic peptide levels within the prior 30 days, and a history of a prior HF event (HF hospitalization or equivalent) to either an NT-proBNP-guided strategy or usual care.

—In high-risk patients with HFrEF, a strategy of NTproBNP-guided therapy was not more effective than a usual care strategy in improving outcomes.

...because nearly all of them achieved NtproBNP<1000

*JAMA*. 2017 August 22; 318(8): 713–720
Ασθενής κλινικά βελτιωμένος

- Ασθενής 77 ετών με γνωστή ισχαιμική καρδιακή ανεπάρκεια, με CRT-D
- Sacubitril/valsartan 49/51, furosemide 80mg, bisoprolol 10mg, spironolactone 25mg, atorvastatin
- ΑΠ=130/60mmHg.
- ΧΑΠ
- Μέτρια MR
- Αναφέρει σημαντική βελτίωση συμπτωμάτων
- Ε=102, Α=33, Ε’=7, SRV=13, PASP=30mmHg
- NT-proBNP=2100pg/ml
- Περαιτέρω τίτλοποίηση αγωγής;
Ασθενής υπο sacubitril/valsartan

- Άνδρας 62 ετών με ισχαιμική καρδιακή ανεπάρκεια και ICD.
- Παλαιός καπνιστής. Ηπια ΧΑΙ
- NYHA II
- Αγωγή eplerenone 50mg, sacubitril/valsartan 103/97, bisoprolol 5mg, furosemide 20mg, atorvastatin 20mg, aspirine 100mg.
- Τελευταίο μήνα αναφέρει δύσπνοια ανεξάρτητα δραστηριότητας.
- Όχι S3, οιδήματα, διάταση σφαγιτίδων, E/E′=13, PASP=35mmHg
- Αύξηση διούρησης?
- BNP=206 pg/ml
- NTproBNP=232,5pg/ml
New biomarkers for early detection of cardiotoxicity after treatment with docetaxel, doxorubicin and cyclophosphamide

- Romano et al. (2011) showed that persistently elevated NTproBNP levels during anthracycline treatment are correlated with left ventricular impairment after 12 months.
- All paediatric studies concluded that NT-proBNP may be a useful marker for detection of subclinical cardiotoxicity (Germanakis et al., 2006; MavinkurveGroothuis et al., 2009; Soker & Kervancioglu, 2005).

<table>
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<tr>
<th>Biomarkers</th>
<th>LVEF</th>
<th>NT-proBNP</th>
<th>TNF-α</th>
<th>Galectin-3</th>
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Assessment by Pearson’s correlation. \(^a\)\(p \leq 0.01\).

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Biomarkers, 2015; 20(2): 143–148
NPs in cardio-oncology

- A study of 100 breast cancer patients treated with anthracyclines demonstrated that those with increased risk of cardiotoxicity had elevated Nt proBNP levels at 3-6 and 12 months interval after chemo completion and before LVEF decrease became evident.
- Serial NPs measurements are superior of echo evaluation.
- Persistent and not transient elevations of BNP had prognostic role.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Malignancy</th>
<th>Number</th>
<th>Treatment</th>
<th>NT-pro BNP Cutoff Values</th>
<th>NT-pro BNP Levels</th>
<th>Measurement of LVEF</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandri et al.</td>
<td>Various aggressive malignancies 52</td>
<td>High-dose chemo-based on study institution protocol</td>
<td>NT-pro BNP cutoff values differed based on age and gender: &gt;153 ng/mL for women &lt; 50 y; &gt;88 ng/mL for men &lt;50 y; 334 ng/mL for women &gt;50 y; 227 ng/mL for men &gt;50 y</td>
<td>NT-pro BNP levels were drawn at baseline (before each treatment), at the end of chemo infusion, and 12, 24, 36, and 72 h after the end of each chemo cycle</td>
<td>BNP levels were drawn at baseline and at 4 and 12 mo after treatment</td>
<td>Concentrations of BNP increased after treatment. Persistent elevations in BNP were associated with poor prognosis.</td>
<td></td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>Hematologic malignancies 27</td>
<td>Anthracyclines</td>
<td>BNP &lt; 19 pg/mL</td>
<td>TTE was performed at baseline and at 4 and 12 mo after treatment.</td>
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<tr>
<td>De Iuliis et al.</td>
<td>Breast CA 100</td>
<td>Anthracyclines, Taxanes, trastuzumab</td>
<td>Not defined</td>
<td>NT-pro BNP and LVEF were measured at baseline, 3, 6, and 12 mo</td>
<td>-</td>
<td>Significant increase in NT-proBNP (P &gt; 0.0001) was seen before LVEF decrease became evident. There was a correlation between increased NT-proBNP after chemo and predicted 1 year mortality.</td>
<td></td>
</tr>
</tbody>
</table>
LCZ696 and biomarkers
Conclusions

- The financial impact of HF is expected to increase
- NT-pro BNP testing in conjunction with clinical assessment can:
  - Reduce uncertainty about the diagnosis of HF
  - Facilitate early detection of preclinical HF
  - Improve the overall management of patients presenting to the ED with suspected acute HF
  - Reduce the number of hospitalisations and re-hospitalisations

Shorten lengths of stay
Provide more efficient utilization of healthcare resources such as the echocardiogram
Cost savings can be accomplished without compromising patient care

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ΕΥΧΑΡΙΣΤΩ!