I nuovi biomarkers nello scompenso di cuore: ruolo negli anziani

Global REsearch Acute conditions Team Network

Postgraduate School of Emergency Medicine
Faculty od Medicine and Psycology

Prof. Salvatore Di Somma MD, PhD
Professor of Medicine, Director and Chairman

Torino 27-29 Novembre 2013
HF Epidemiology

Actual and estimated prevalence of CHF between the years 1950 and 2050

- 85+
- 75-84
- 65-74
- 55-64

Graph showing the increase in prevalence from 1950 to 2050.
Importance of early therapies for AHF as consequence of prompt diagnosis

- In 46,599 patients with ADHF (ADHERE)
- a delay in Treatment was associated with:
  - 250% ↑ in acute mortality;
  - 150% ↑ in Hospital length of stay

Acute Hearth Failure Diagnosis

Physical examination

Thoracic ultrasound

Echocardiography (IVC)
X-ray abnormalities can appear 6 hours after symptoms onset.


- 1/5 patient in the ED with ADHF had normal chest X-rays.

- We can not exclude ADHF on the basis of negative chest radiography.

Cooper, R. Misleading Negative Chest Radiographs: Should We ADHERE to the Conclusions? Annals of Emergency Medicine, Volume 47, Issue 1, Pages 19-21, 2005
Biomarkers in Heart Failure

Moriates, Maisel: The Utility of Biomarkers in Sorting Out the Complex Patient. Review JAMA 2013
Flow-chart for the diagnosis of HF in untreated patients with symptoms suggestive of HF using natriuretic peptides

Clinical examination, ECG, Chest X-ray, Echocardiography

Natriuretic peptides

- BNP < 100 pg/ml, NT-proBNP < 400 pg/ml: Chronic HF unlikely
- BNP 100-400 pg/ml, NT-proBNP 400-2000 pg/ml: Uncertain diagnosis
- BNP > 400 pg/ml, NT-proBNP > 2000 pg/ml: Chronic HF likely
PCT +NPs for distinguishing S.O.B. In ED

A. Maisel , Di Somma et al. Eur J Heart F 2012 mar;14(3)278-81
IL-18 stimulates B-type natriuretic peptide synthesis by cardiomyocytes \textit{in vitro} and its plasma levels correlate with B-type natriuretic peptide in non-overloaded acute heart failure patients

Salvatore Di Somma$^1$, Valerio Pittoni$^1$, Salvatore Raffa$^2$, Laura Magrini$^1$, Giulia Gagliano$^1$, Rossella Marino$^1$, Valerio Nobili$^2$ and Maria Rosaria Torrisi$^2$

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean ± SE)</strong></td>
<td>76.2 ± 1.9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
</tr>
</tbody>
</table>

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{chart.png}
\caption{IL-18 concentrations in plasma from acute HF patients and normal human subjects. Enzyme-linked immunosorbent assay was used to quantify IL-18 concentration in plasma from acute HF patients in comparison with plasma from normal human subjects. Acute HF patients had significantly higher IL-18 plasma levels than normal human subjects (p<0.001). NHS, normal human subjects.}
\end{figure}

\textbf{Conclusion}
This investigation provided the first evidence of the ability of IL-18 to induce B-type natriuretic peptide synthesis \textit{in vitro} and highlighted the correlation between the two molecules in plasma from non-overloaded HF patients.
Brief Report

Decrease in NTproBNP plasma levels indicates clinical improvement of acute decompensated heart failure

Salvatore Di Somma MD\textsuperscript{a,*}, Laura Magrini MD\textsuperscript{a}, Marinella Mazzone MD\textsuperscript{b}, Raffaella De Leva MD\textsuperscript{a}, Fabio Tabacco MD\textsuperscript{c}, Rossella Marino MD\textsuperscript{a}, Veronica Talucci MD\textsuperscript{a}, Enrico Ferri MD\textsuperscript{a}, Paola Forte MD\textsuperscript{a}, Patrizia Cardelli MD\textsuperscript{c}, Nicola Gentiloni MD\textsuperscript{b}, Valerio Pittoni MD\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristics of patients and controls</th>
<th>ADHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>37</td>
</tr>
<tr>
<td>Age (y)*</td>
<td>75.4 ± 9.1</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>16/21</td>
</tr>
</tbody>
</table>

![Graph showing NTproBNP levels over time for different conditions](image-url)
In-hospital percentage BNP reduction is highly predictive for adverse events in patients admitted for acute heart failure: the Italian RED Study

Salvatore Di Somma*1, Laura Magrini1, Valerio Pittoni1, Rossella Marino1, Antonella Mastrantuono1, Enrico Ferri1, Paola Ballarino2, Andrea Semplicini3, Giuliano Bertazzoni4, Giuseppe Carpenteri5, Paolo Mulè6, Maria Pazzaglia7, Kevin Shah8, Alan Maisel8 and Paul Clopton8

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Number of patients: 247

Age in years (mean ± SD): 76 ± 12

Sex:
- Male: 118
- Female: 129

NYHA functional classification:
- III: 33%
- IV: 67%
Biomarkers for Diagnosis and Prognosis of Acute Heart Failure

Rajiv Choudhary · Salvatore Di Somma · Alan S. Maisel

<table>
<thead>
<tr>
<th>Factors affecting NP levels</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary disease</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Renal disease</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Obesity</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Flash pulmonary edema</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Other causes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic cut-off

- **HF present (pg/ml)**
  - >400

- **HF absent (pg/ml)**
  - <100

- **Grey-zone (pg/ml)**
  - 100–400

- **<50 years**: >450
- **50–75 years**: >900
- **>75 years**: >1800

- **<75 years**: 125
- **>75 years**: 450

- **<50 years**: 300–450
- **50–75 years**: 300–900
- **>75 years**: 300–1800

*BNP B-type natriuretic peptide, NT-proBNP amino-terminal B-type natriuretic peptide*
Comparison of: BNP, NTproBNP and Mr-pro ANP for the Diagnosis of HF

Figure 1: Comparison of Diagnostic Biomarkers

(A) Receiver-operating characteristic curves for B-type natriuretic peptide (BNP) (green line), N-terminal pro-B-type natriuretic peptide (NT-proBNP) (red line), and mid-regional pro-atrial natriuretic peptide (MR-proANP) (blue line) for detecting acute heart failure. (B) Spearman’s correlation between BNP and MR-proANP. AUC = area under the curve; CI = confidence interval.

Maisel A., Di Somma S. Et al. JACC 2010
Influence of age, race, sex, and body mass index on interpretation of midregional pro atrial natriuretic peptide for the diagnosis of acute heart failure: results from the BACH multinational study


Table 2 Adjusted midregional pro atrial natriuretic peptide (MR-proANP) levels among various subgroups, by final diagnosis of heart failure

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No heart failure</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean MR-proANP</td>
<td>Mean MR-proANP</td>
</tr>
<tr>
<td></td>
<td>(P^a)</td>
<td>(P^a)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>55</td>
<td>393</td>
</tr>
<tr>
<td>50 to &lt; 75 years</td>
<td>104</td>
<td>438</td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>177</td>
<td>448</td>
</tr>
</tbody>
</table>

\(P<0.001\)  \(P=0.023\)  \(P\)-value for interaction <0.001
Biomarkers for Diagnosis and Prognosis of Acute Heart Failure

Rajiv Choudhary · Salvatore Di Somma · Alan S. Maisel

Upcoming biomarkers provide more information on cardiac remodeling and are indicative of AHF progression. Monitoring these biomarkers in hospitalized patients with AHF may help identify those at high risk of worsening HF. Biomarkers allow monitoring response to treatment. Moreover, using multiple biomarkers in bio-monitoring and guiding treatment may prove beneficial in improving mortality associated with AHF.
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

Web Table 10: Prognostic variables in heart failure

A very large number of variables have been shown to relate to outcome in HF (and new prognostic markers are regularly identified). This table lists some of the more commonly described prognostic variables.

<table>
<thead>
<tr>
<th>Demographics, history, and physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, sex, ethnicity, NYHA class, body mass index.</td>
</tr>
<tr>
<td>Signs of congestion, increased jugular venous pressure, third heart sound, low systolic blood pressure, higher heart rate.</td>
</tr>
<tr>
<td>Diabetes mellitus, renal dysfunction, depression, COPD.</td>
</tr>
<tr>
<td>Ischaemic aetiology, history of myocardial infarction.</td>
</tr>
</tbody>
</table>
Biomarkers in Heart Failure

Moriates, Maisel: The Utility of Biomarkers in Sorting Out the Complex Patient. Review JAMA 2013
Predictors of mortality and morbidity in patients with chronic heart failure

Stuart J. Pocock\(^1\)*, Duolao Wang\(^1\), Marc A. Pfeffer\(^2\), Salim Yusuf\(^3\), John J.V. McMurray\(^4\), Karl B. Swedberg\(^5\), Jan Östergren\(^6\), Eric L. Michelson\(^7\), Karen S. Pieper\(^8\), and Christopher B. Granger\(^8\) on behalf of the CHARM investigators

Table 2 Final prognostic model for CV death or HF hospitalization based on forward stepwise Cox proportional hazard regression

<table>
<thead>
<tr>
<th>Standard variable</th>
<th>Hazard ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>(\chi^2)-value</th>
<th>Coefficient</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years over age 60)</td>
<td>1.46</td>
<td>1.38</td>
<td>1.54</td>
<td>181.8</td>
<td>0.379</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes: insulin-treated</td>
<td>2.03</td>
<td>1.80</td>
<td>2.29</td>
<td>134.7</td>
<td>0.707</td>
<td>0.061</td>
</tr>
<tr>
<td>Diabetes: other</td>
<td>1.58</td>
<td>1.43</td>
<td>1.74</td>
<td>85.2</td>
<td>0.455</td>
<td>0.049</td>
</tr>
<tr>
<td>Ejection fraction (per 5% decrease below 45)</td>
<td>1.13</td>
<td>1.11</td>
<td>1.16</td>
<td>119.9</td>
<td>-0.123</td>
<td>0.011</td>
</tr>
</tbody>
</table>

(A)

CV Death and CHF Hospitalization

7599 subjects
Association Between Elevated Blood Glucose and Outcome in Acute Heart Failure

No previous diabetes mellitus

- Blood glucose not elevated
- Blood glucose elevated

Cumulative hazard

Time (days)

Previous diabetes mellitus

- Blood glucose not elevated
- Blood glucose elevated

Cumulative hazard

Time (days)
Midregion Prohormone Adrenomedullin and Prognosis in Patients Presenting With Acute Dyspnea

Results From the BACH (Biomarkers in Acute Heart Failure Dyspnea) Trial

Alan Maisel, MD,*### Christian Mueller, MD,† Richard M. Nowak, MD,‡ W. Frank Peacock, MD,§ Piotr Ponikowski, MD, PhD∥ Martin Mockel, MD,¶ Christopher Hogan, MD,# Alan H. B. Wu, PhD,** Mark Richards, MD, PhD,†† Paul Clopton, MS,* Gerasimos S. Filippatos, MD,‡ Salvatore Di Somma, MD,§§ Inder Anand, MD, DPhil (Oxon),|||| Leong L. Ng, MD,¶¶ Lori B. Daniels, MD, MAS,## Sean-Xavier Neath, MD, PhD,## Robert Christenson, PhD,### Mihael Potocki, MD,† James McCord, MD,‡ Oliver Hartmann, MSc,††† Nils G. Morgenthaler, MD, PhD,‡‡ Stefan D. Anker, MD, PhD§§§

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Dead (n = 130)</th>
<th>Alive (n = 1,511)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>1,641</td>
<td>72.8 ± 13.2</td>
<td>63 ± 17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>1,641</td>
<td>79 (60.8%)</td>
<td>780 (51.6%)</td>
<td>0.0543</td>
</tr>
</tbody>
</table>
Biomarkers in Heart Failure

Moriates, Maisel: The Utility of Biomarkers in Sorting Out the Complex Patient. Review JAMA 2013
Replacement Myocardial Fibrosis in HF

Picrosirium in explanted heart (post-ischemic cardiomyopathy)

Galectin-3 new biomarker for heart disease

- Increased G-3 induces cardiac fibroblasts to proliferate and deposit type I collagen

- Collagen deposition leads to scar

Sharma et al. Circulation, 110; 3121-28, 2004
De Boer et al. curr. Heart Fail. Rep. 7; 1 – 8, 2010
Survival Probability Curves by Baseline Galectin-3 Category in the Acutely Decompensated Heart

Product-Limit Survival Estimates

Follow-up Time (days)

Survival Probability

- ≤ 17.8 ng/mL
- > 17.8 and ≤ 25.9 ng/mL
- > 25.9 ng/mL
18 months mortality

Kaplan-Meier

Cum Survival

Gal 3 < 17.8 pg/ml
Gal 3 > 17.8 pg/ml

p<0.02

Survival time total
Galectin-3 Mediated HF is Inherently Progressive

Illustration of two clinically very similar patients with different galectin-3 levels and dramatically different clinical paths

Patient A: 8.5 ng/mL
Patient B: 36.4 ng/mL
Galectin-3 levels increase proportionally with age

Baseline Level of GAL-3 (ng/ml) vs Age (ys) quartiles

* p < 0.01
Galectin-3 levels correlate with eGFR

Baseline Level of GAL-3 (ng/ml)

<30
31-45
45-60
>60
eGFR quartiles

* p < 0.01
ST2: A DECOY RECEPTOR

Pro-IL-33
Fibroblast
Caspase-1

IL-33

sST2

MyD88

ERK

NFκB

IRAK

Myocyte

CARDIOPROTECTION

Adapted from Kakkar et al. Nat Rev Drug Discov 2008
Kaplan-Meier 18 months mortality in AHF

ST2 < 112 ng/ml

ST2 >112 ng/ml

p<0.001

Survival

Patients

(days)
ST2 median values in Age quartiles
ST2 median values in eGFR quartiles
Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: The Multinational Observational Cohort on Acute Heart Failure (MOCA) study

Johan Lassus a,b,1, Etienne Gayat c,d,1, Christian Mueller e, W.Frank Peacock f, Jindrich Spinar g,h, Veli-Pekka Harjola a, Roland van Kimmenade i, Atul Pathak j, Thomas Mueller k, Salvatore diSomma l, Marco Metra m, Domingo Pascual-Figal n,o, Said Laribi b,p, Damien Logeart b,q, Semir Nouira r, Naoki Sato s, Michael Potocki e, Jiri Parenica g,h, Corinne Collet b, Alain Cohen-Solal b,q, James L. Januzzi Jr. t, Alexandre Mebazaa b,c,*

and for the GREAT-network 2

Conclusion

ST2 and MR-proADM detect features of risk not identified by conventional risk markers and improve risk prediction models of both short-term (30-day) and one-year mortality in ADHF.
AKI in Heart Failure

Cardio-Renal Syndrome Type I

Hemodynamically mediated damage

Decreased CO

Decreased perfusion

Increased venous pressure

Exogenous factors
- Contrast media
- ACE inhibitors
- Diuretics

Toxicity
- Vasoconstriction

Humorally mediated damage

Humoral signaling
- BNP

Humoral mediated damage

Immune mediated damage
- Cytokine secretion
- Caspase activation
- Apoptosis

Hormonal factors
- Natriuresis

Acute renal injury

Acute hypoperfusion
- Reduced oxygen delivery
- Necrosis/apoptosis
- Decreased GFR
- Resistance to ANP/BNP

Biomarkers
- KIM-1
- Cystatin-C
- NGAL
- Creatinine

Acute heart disease or procedures

Acute decompensation
- Ischemic insult
- Coronary angiography
- Cardiac surgery

Ronco C. et al. JACC 2008,52
Biomarkers in Heart Failure

Moriates, Maisel: The Utility of Biomarkers in Sorting Out the Complex Patient. Review JAMA 2013
Cardiorenal Syndrome type I in ED: The BIONICS HF Study

Total enrolled patients (n = 103)

Patient’s excluded:
- Missing data (n=3)

Statistical analysis group (n= 100)

WRF (n= 25)

Rome = 50 pts
Boston = 50 pts

NO WRF (n= 75)

Out come

In-hospital Death = 0
Death 30 days follow-up = 7
30 days rehospitalization = 14

In-hospital Death = 5
Death 30 days follow-up = 6
30 days rehospitalization = 2

Diabetes 43%

NO WRF: No Worsening renal function
WRF: Worsening renal function

SAPIENZA
Università di Roma
HARVARD
MEDICAL SCHOOL

GREAT
Importance of Time in Acute Kidney Injury:

we need AKI biomarker!

In ACS Time is Myocardium!!
And we have troponin...

IN AKI Time is important to stop the progression of nephrons loss ??
We need AKI biomarker like troponin....
Additive value of blood neutrophil gelatinase-associated lipocalin to clinical judgement in acute kidney injury diagnosis and mortality prediction in patients hospitalized from the emergency department

Salvatore Di Somma¹, Laura Magrini¹, Benedetta De Berardinis¹, Rossella Marino¹, Enrico Ferri¹, Paolo Moscatelli², Paola Ballarino², Giuseppe Carpinteri³, Paola Noto³, Biancamaaria Gliozzo³, Lorenzo Paladino⁴ and Enrico Di Stasio⁵

<table>
<thead>
<tr>
<th>TOTAL COHORT</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>665</td>
</tr>
<tr>
<td>Men</td>
<td>358 (53.8%)</td>
</tr>
<tr>
<td>Women</td>
<td>307 (46.2%)</td>
</tr>
</tbody>
</table>

Mean age ±SD, y: 74 ± 14.4
Mean BMI ±SD(m²/h): 26.3 ± 4.7
Mean systolic blood pressure ± SD mmHg: 137 ± 58
Mean diastolic blood pressure ±SD mmHg: 77 ± 15

Conclusion
• Admission blood NGAL measurements are useful in the early diagnosis of AKI.
• Baseline NGAL measurement allows detection of AKI earlier than sCr.
• Blood NGAL assessment at the moment of hospital admission from ED predicted the combined outcome of RRT and in-hospital mortality.
Di Somma S., Jannuzzi J. et submitted JACC

BNP ≥ 488 pg/mL
NGAL ≥ 196 pg/mL

% with Death or WRF

Neither elevated
Referent
OR = 1.62
95% CI 0.51-5.2
P = .42

One elevated
Or = 4.10
95% CI 1.0-9.9
P = .04

Both elevated

Number of biomarkers elevated
## The Ideal Cardiac Biomarker

<table>
<thead>
<tr>
<th>2007</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive and specific</td>
<td>Either highly sensitive (diagnosis) OR highly specific (treatment effect)</td>
</tr>
<tr>
<td>Reflects disease severity</td>
<td>Reflects abnormal physiology/biochemistry</td>
</tr>
<tr>
<td>Correlates with prognosis</td>
<td><strong>Prognosis is most meaningful if level is clinically actionable</strong></td>
</tr>
<tr>
<td>Should aid in clinical decision making</td>
<td><strong>Should be used as a basis for specific “biomarker guided-therapy”</strong></td>
</tr>
<tr>
<td>Level should decrease following effective therapy</td>
<td>“Bio-monitoring” <strong>during</strong> treatment is an effective surrogate of improvement</td>
</tr>
</tbody>
</table>
The utility of heart failure biomarkers and their clinical applications continues to grow.

Ongoing research on multimarker strategies will likely identify biomarker panels useful for monitoring the evolution of heart failure, ranging from their use for screening, diagnosis, determining prognosis, and guiding therapy.
• The mean age of patients from many trials confirming the utility of Biomarkers in the management of AHF is greater than 75 years;
• Caveats still remain in the evaluating the right cut-offs of biomarkers of HF in elderly patients.
Biomarkers should be used wisely

- They should be used as a tool **together** with clinical experience;
- You need to know:
  - clinical indications,
  - cut-off ranges and limitations of the biomarker

A fool with a tool is still a fool...