Biomarcadores na IC
Actualização em 2013- o presente e as perspectivas

Brenda Moura

Serviço de Cardiologia

Hospital Militar D.Pedro V - Porto

10 de Fevereiro de 2013

Características de um biomarcador

atinine, which are routinely determined as part of clinical care.

Morrow and de Lemos[1] have set out three criteria a biomarker should fulfill to be useful clinically. First, accurate, repeated measurements must be available to the clinician at a reasonable cost and with short turnaround times; second, the biomarker must provide information that is not already available from a careful clinical assessment; and finally, knowing the measured level should aid in medical decision making.

Morrow DA, de Lemos JA. Circulation 2007;115:949-52

A First Warning

- The use of Biomarkers for diagnosis is always secondary to clinical judgment

A day in the life of an associate editor

Another novel biomarker paper??????

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B.Moura, 2013

Características de um marcador útil

diovascular disease. The National Academy of Clinical Biochemistry has set forth comparable goals in a consensus document that states that a biomarker in HF ideally enables clinicians to (*i*) identify possible underlying (and potentially reversible) causes of HF; (*ii*) confirm the presence or absence of the HF syndrome; and (*iii*) estimate the severity of HF and risk of disease progression *(3)*. Other investigators have further emphasized the importance of patient-based understanding of the biomarker result, and the behaviors that follow *(4)*.

With the explosion of novel biomarkers available, it is reasonable to extend this important foundation. For a biomarker to be useful, the following conditions are necessary:

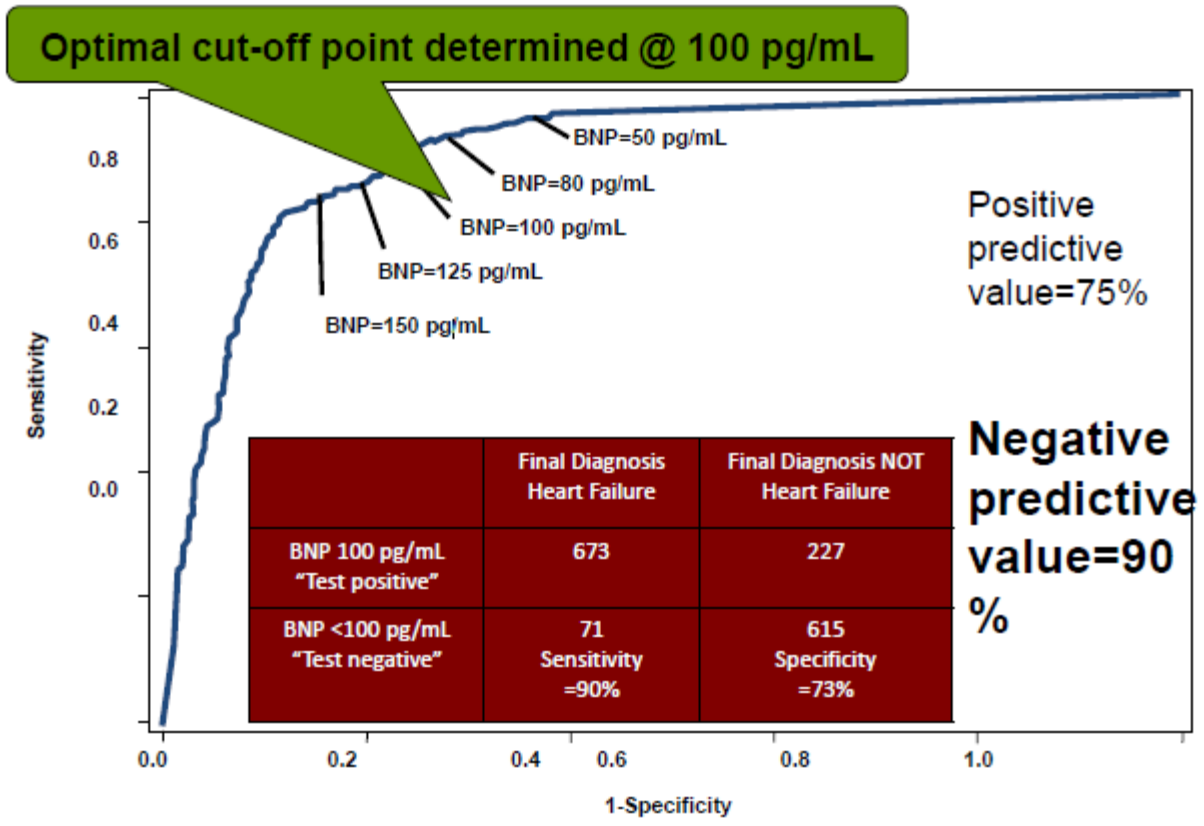
1. The method by which a novel biomarker is judged (including and especially compared to or in combination with other biomarkers) should be thorough: novel tests should be evaluated across a wide range of patients typical of the diagnosis for which the biomarker will be applied, and the statistical methods used to evaluate the biomarker (relative to clinical variables as well as other biomarkers) should be contemporary, rigorous, standardized, and fair.
2. Measurement of a novel HF biomarker (e.g., in blood, urine, or any easily obtainable tissue) should be easily achieved within a short period of time and provide acceptable accuracy, and assays for its measurement should have defined biological variation and low analytical imprecision.
3. The biomarker should primarily reflect important (patho)physiological process(es) involved in HF presence and progression; use of a biomarker that is reflective of heart disease but originates outside the myocardium is acceptable as long as such a biomarker provides independently useful information involved in the diagnosis, prognosis, progression, or therapy of HF syndromes.
4. The biomarker must provide clinically useful information for caregivers (physician, nurses, and others) and patients to facilitate more swift and reliable establishment/rejection of a diagnosis and more accurate estimation of prognosis and to inform more successful therapeutic strategies. The information from such a biomarker should not recapitulate clinical information already available at the bedside, and must be additional to information provided by other biomarkers.

Besides the natriuretic peptides, none of the presently available or studied biomarkers meet these standards, although several may be close to doing so. Evaluating such markers is a complex process, however, because HF is not the result of one single patho-

Kimmenade RRJ, Januzzi JL. Clinical Chemistry 2012; 58:1. 127-138

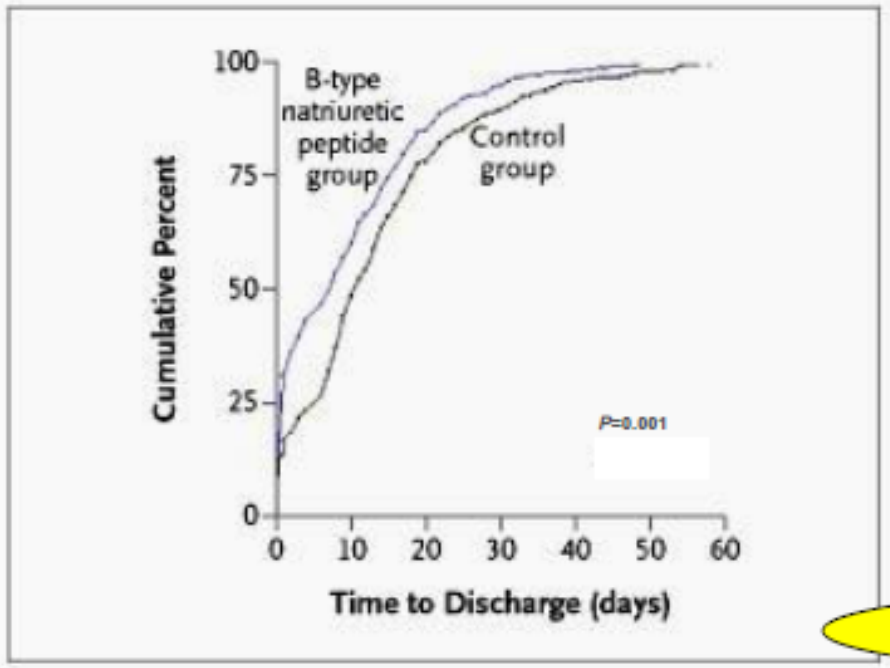
BNP - Diagnóstico

Accuracy is 90%



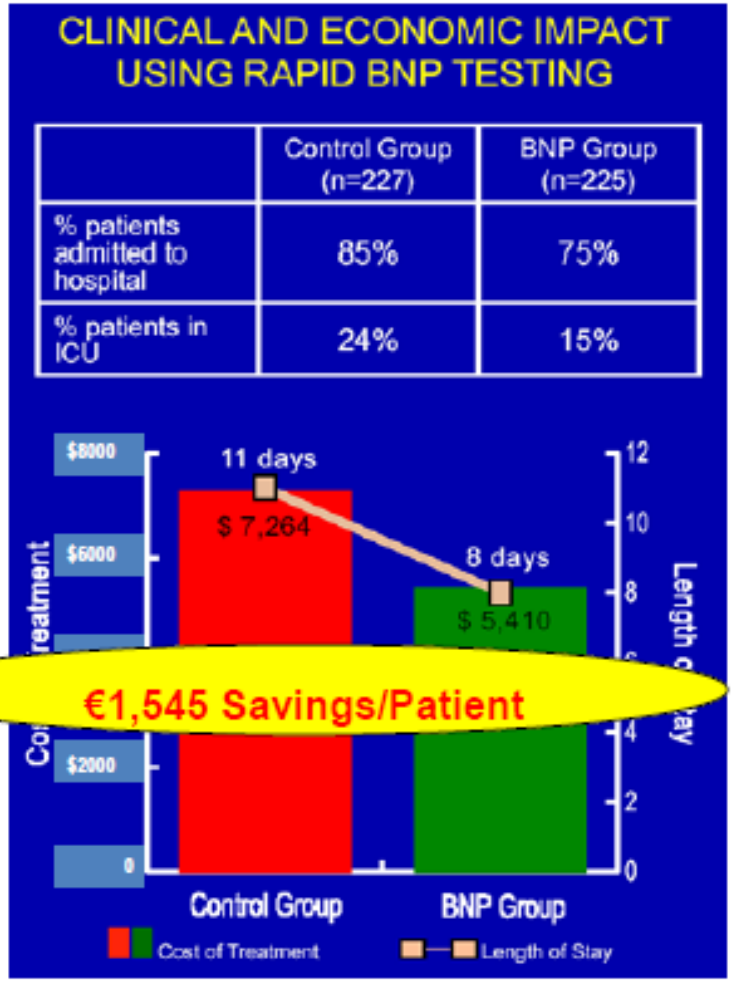
Maisel AS et al. *N Engl J Med.* 2002;347:161-167.

Cost-Effectiveness of BNP at ED: The BASEL Study

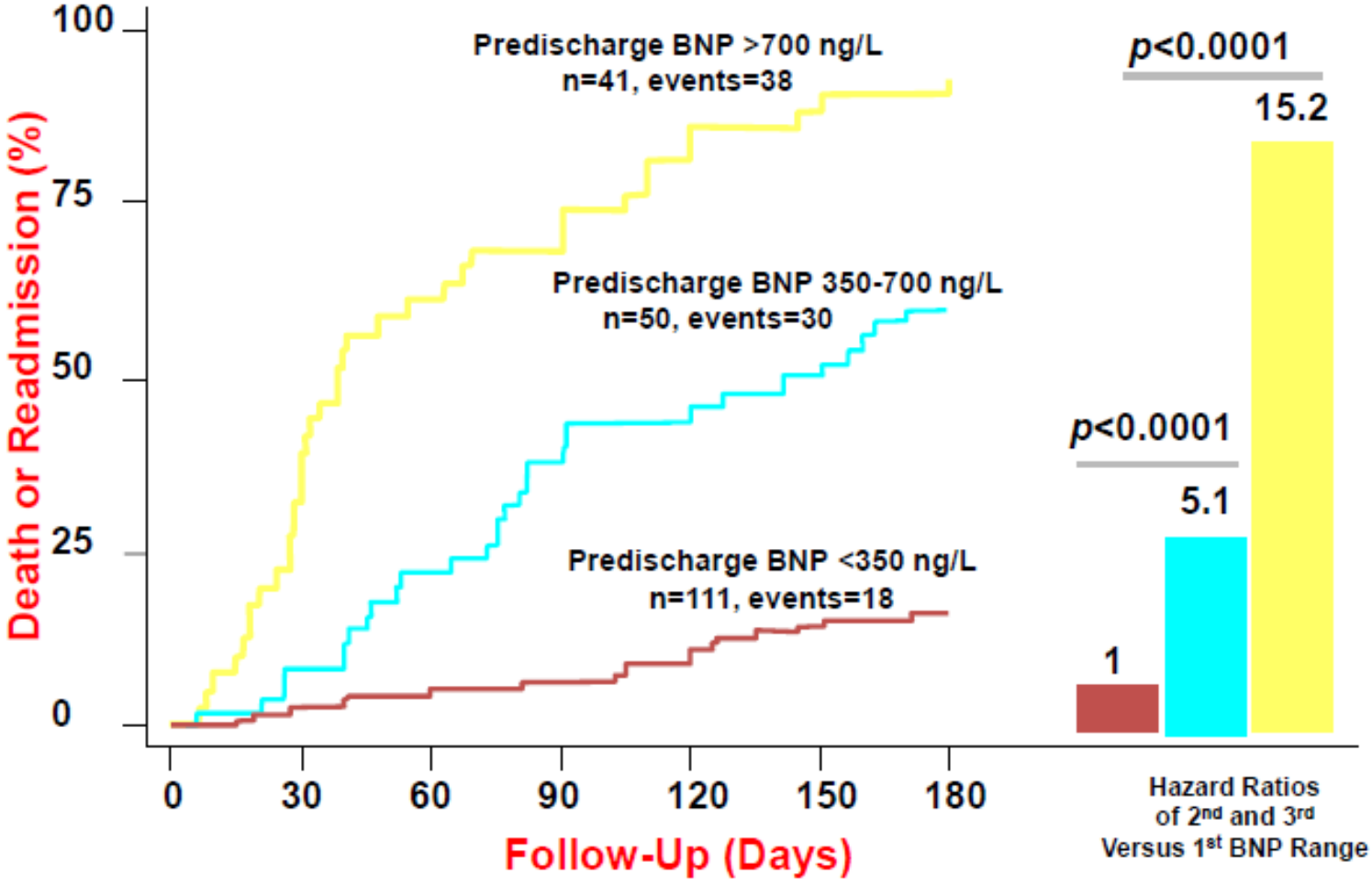


Biosite Triage BNP (in pg/mL)

Muller C, et al. *N Engl J Med.* 2004;350:847-854.



BNP on Discharge Predictive of Events



Logeart D et al. *J Am Coll Cardiol* 2004;43(4):635-41.

O presente – PN e monitorização IC

- “Biomonitoring of the disease is appealing”
- “Studies have yelded equivocal and controversial results”
- “Generally accepted that there is some benefit”
- “Weakness –NP were infrequently measured, and litle was done with the result”
- “Attempt to achieve a lowering to pre-specified low level”

Maisel A. , Daniels L.JACC 2012(24);277-282

O presente - BNP e NT-proBNP

- Zonas “cinzentas”
- Valores mais elevados - sexo feminino, idosos, hipertensão pulmonar, fibrilhação auricular, insuficiencia renal, estados inflamatórios, patologia da tiroide.
- Valores mais baixos – obesos

ESC guidelines on HF -2012
Maisel A. , Daniels L.JACC 2012(24):277-282

O presente - BNP e NT-proBNP

- **Exclusão diagnóstico** - BNP< 100 pg/ml
  - NT-proBNP < 300 pg/ml
- **Prognóstico** – valores na admissão BNP – mortalidade hospitalar
  - valores à alta BNP < 300-400pg/ml – melhor prog.
  - valores seriados
- **Guia para intervenção terapeutica**

ESC guidelines on HF -2012
Kimmenade R, Januzzi J, Clinical Chemistry 58:1(2012)

O Futuro ?

Table 1. Examples of candidate biomarkers in HF, divided into categories.

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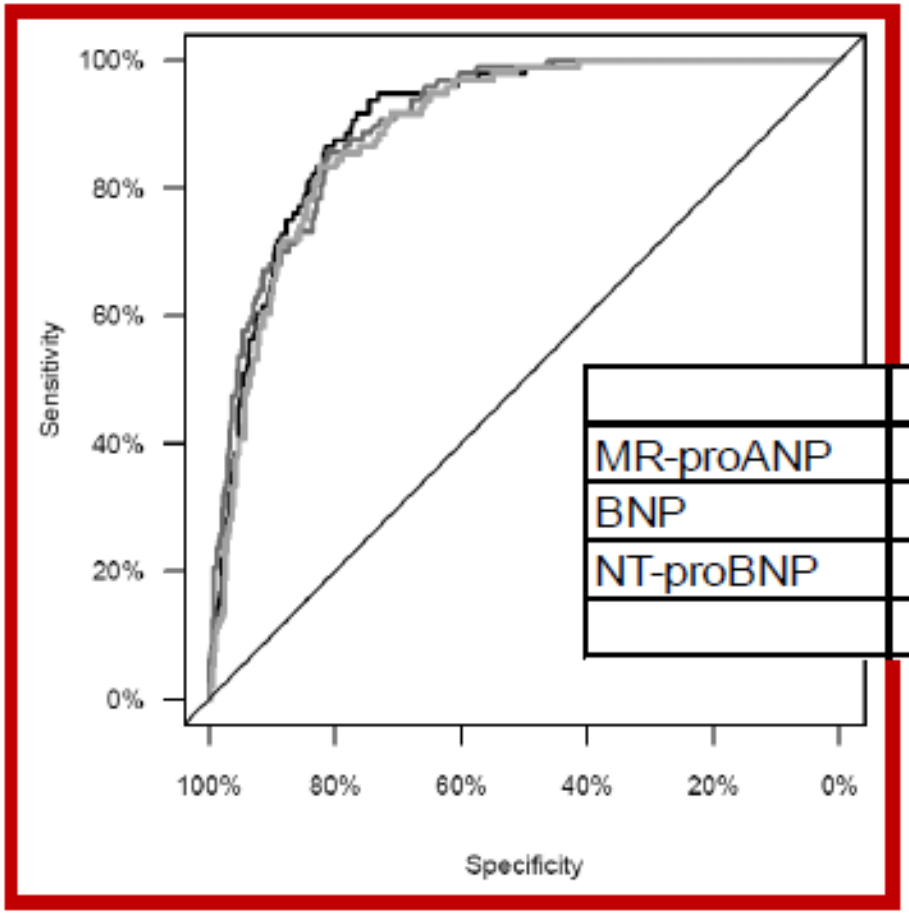
Myostatin	
Syndecan-4	
Galectin-3	

MR-proANP- Diagnóstico

Comparing Diagnostic Prediction on patients without BNP/NT-proBNP lab data



	AUC
MR-proANP	0.904
BNP	0.904
NT-proBNP	0.890
	n=655 (97 HF)

Maisel A et al. Biomarkers in Acute Heart Failure (BACH) Trial.JACC 2010

MR-proANP- Diagnóstico

Gray Area Analysis

Subgroup Measure	Subgroup Criterion	n	MR-proANP adds to BNP		MRproANP adds to NT-proBNP	
			OR per log_{10}	p	OR per log_{10}	p
BNP	≥ 100 and < 500	490	5.7	0.001		
NT-proBNP	≥ 300 and < 900	228			16.1	0.004
NT-proBNP	≥ 300 and <450 if age < 50 ≥ 300 and < 900 if age 50-75 ≥ 300 and < 1800 if age > 75	288			9.5	0.008
Renal	Creatinine ≥ 1.6	563	2.5	0.135	9.5	<0.001
Obese	BMI ≥ 30	518	6.8	0.009	17.4	<0.001
Elderly	Age ≥ 70	658	2.6	0.076	6.7	<0.001
Edema	Present	588	1.7	0.379	7.4	0.001

Maisel A et al. Biomarkers in Acute Heart Failure.JACC 2010

ST2- Mecanismo de acção

ST2/IL-33 Cardioprotective Effects

- IL-33 is a fibroblast product, induced by cellular stretch.
  - Provides protection against myocardial fibrosis and hypertrophy in the context of pressure overload
- The effects of IL-33 may be blunted or blocked by high concentrations of sST2 or by knocking out the ST2 gene
  - This suggests a soluble receptor 'decoy' role for sST2

ST2- Prognóstico

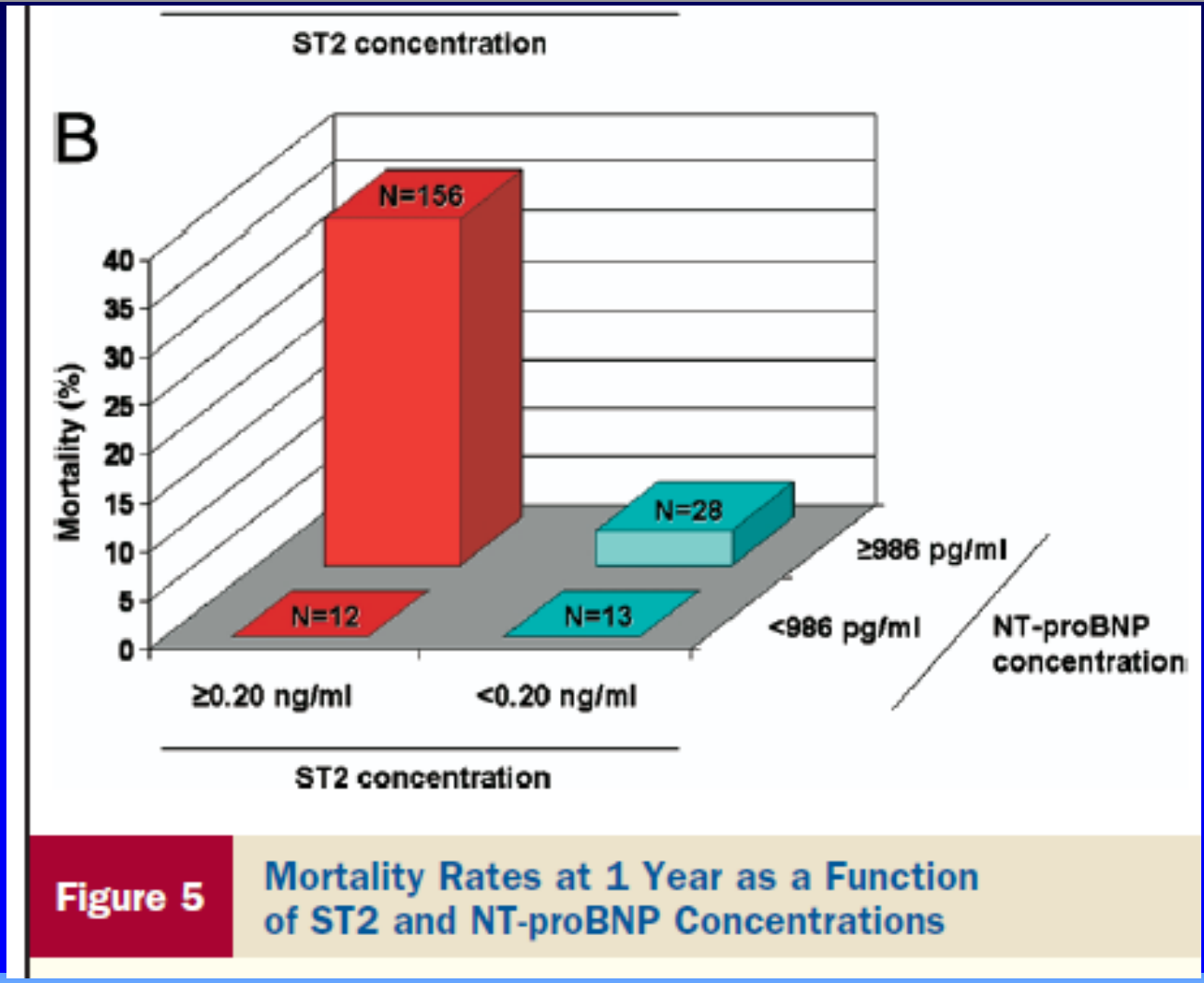


Figure 5 Mortality Rates at 1 Year as a Function of ST2 and NT-proBNP Concentrations

Januzzi et al. PRIDE Study.JACC 2007

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Galectin-3	

Arginina vasopressina

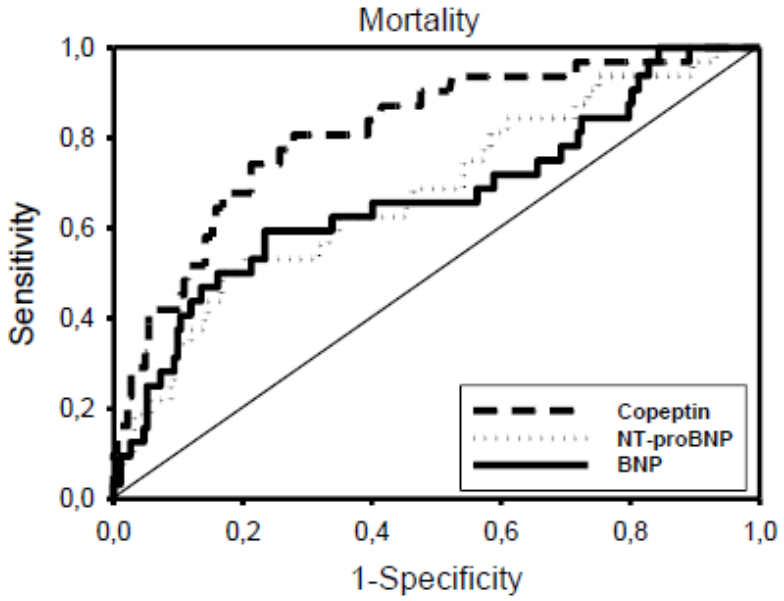
- Hormona anti-diurética e com acção vasoconstritora
- Aumentada na IC
- Doseamento dificil por semi-vida curta e instabilidade in vitro
- C-terminal portion of provasopressin- copeptina
- Interesse na hipovolemia hiponatrémica ?

Kimmenade RJ, Januzzi J. Clinical Chemistry. 2012

Copeptina - Prognóstico

Biomarker Pitfalls

Prognosis: Copeptin better than BNP/NT-proBNP?

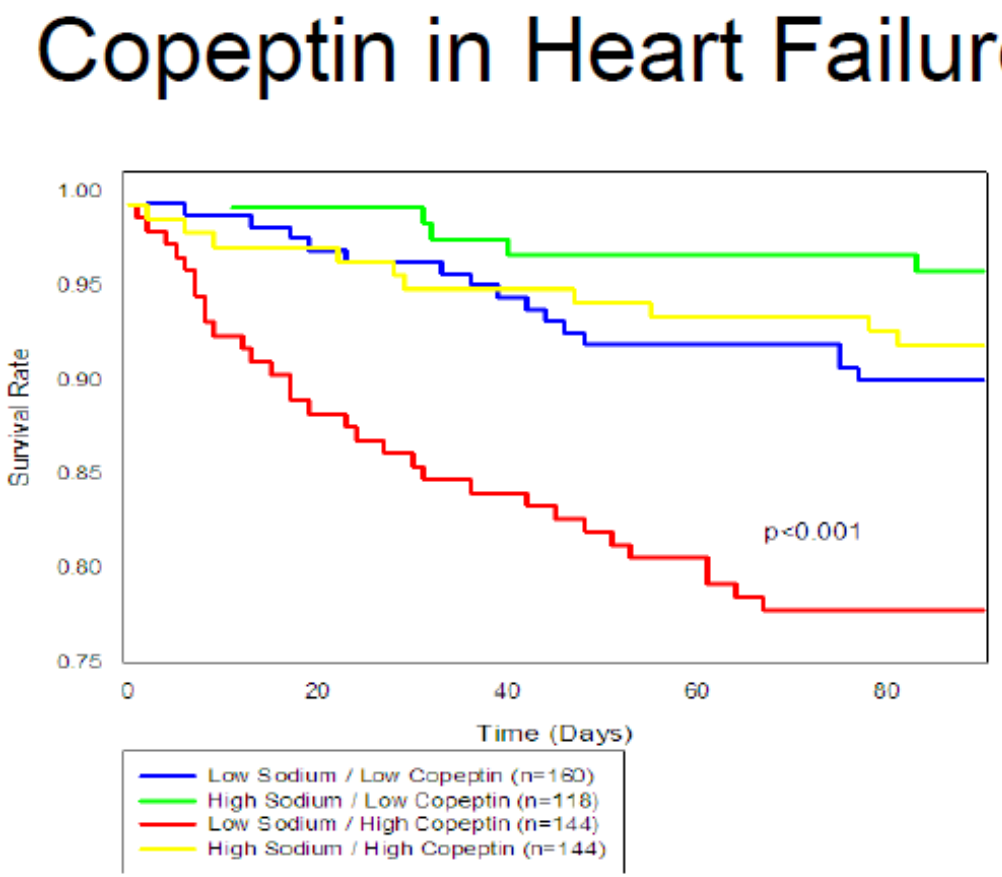


Receiver Operating Characteristics (ROC) curves for copeptin, NT-proBNP and BNP to predict mortality. Areas under the ROC curves were 0.81 for copeptin, 0.67 for NT-proBNP, and 0.66 for BNP (copeptin vs. NT-proBNP: p = 0.0016; copeptin vs BNP: p = 0.0063)

Voors et al. EHJ 2009

University Medical Cente

Copeptina - Prognóstico



Adrenomedulina

- Vasodilatador- via estimulação da produção de NO
- Aumentado na IC como mecanismo compensatório
- MR-proADM- mais facil de dosear

Kimmenade RJ, Januzzi J. Clinical Chemistry. 2012

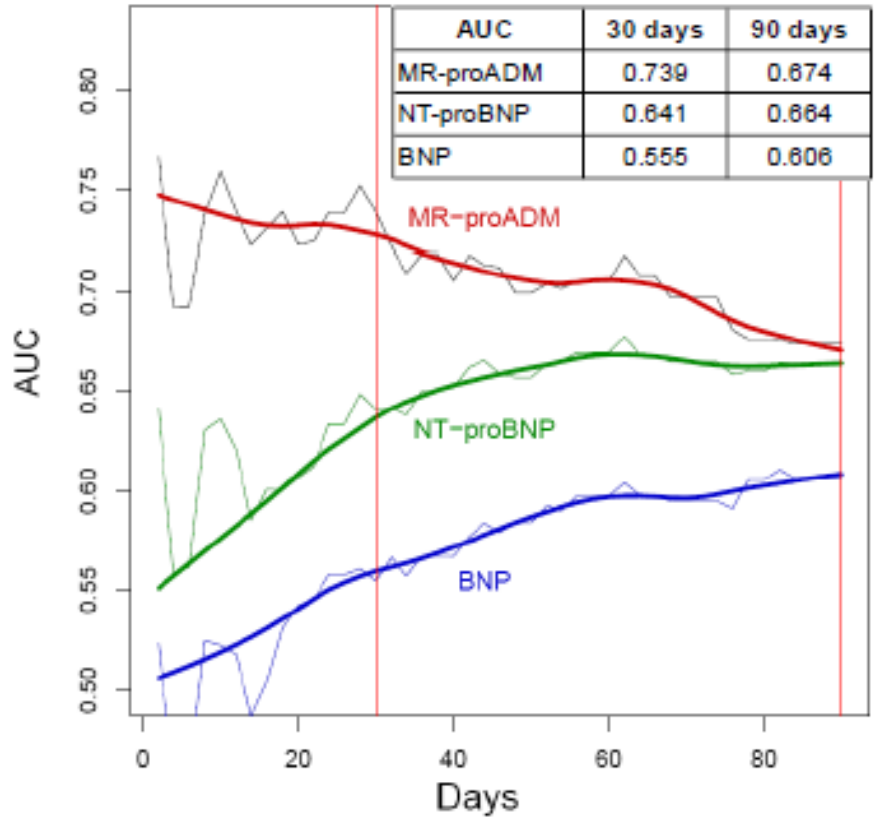
MR-proAdrenomedulina - Prognóstico

BACH

Survival in AHF - Area Under the ROC Curve Comparison

MR-proADM predicts short term (30 day) survival exceptionally well.

AUC	30 days	90 days
MR-proADM	0.739	0.674
NT-proBNP	0.641	0.664
BNP	0.555	0.606



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Matriz Extra-celular

Papel na progressão da IC

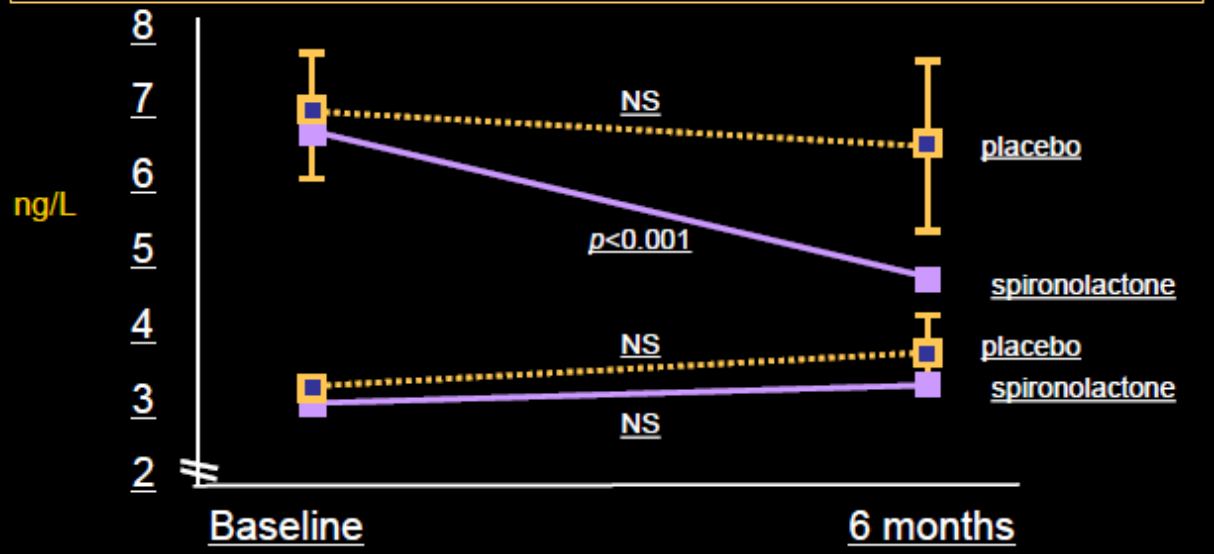
- Remodelagem deletéria com degradação de colegeneo e outras proteinas da MEC
- Acção das colagenases, MMP, TIMP
- Produtos de turnover do colageneo fornecem imagem da degradação da MEC e reflectem a presença de fibrose-CITP, PIIINP

Ho CY, Lopez B, et al. N Engl J Med. 2010;363:552-63

PIIINP - RALES

Aldosterone Receptor Antagonism & Cardiac Remodelling

Baseline PIIINP* > 3.85 g/L was associated with an increased risk of death (RR 2.36, 95% CI 1.34 to 4.18) & death+hospitalisation (RR 1.83, 95% CI 1.18 to 2.83)



Changes of serum levels of PIIINP from baseline to 6 months according to baseline levels above or below median (ng/L)

*Procollagen type III amino-terminal peptide (PIIINP) is a serum marker of cardiac fibrosis

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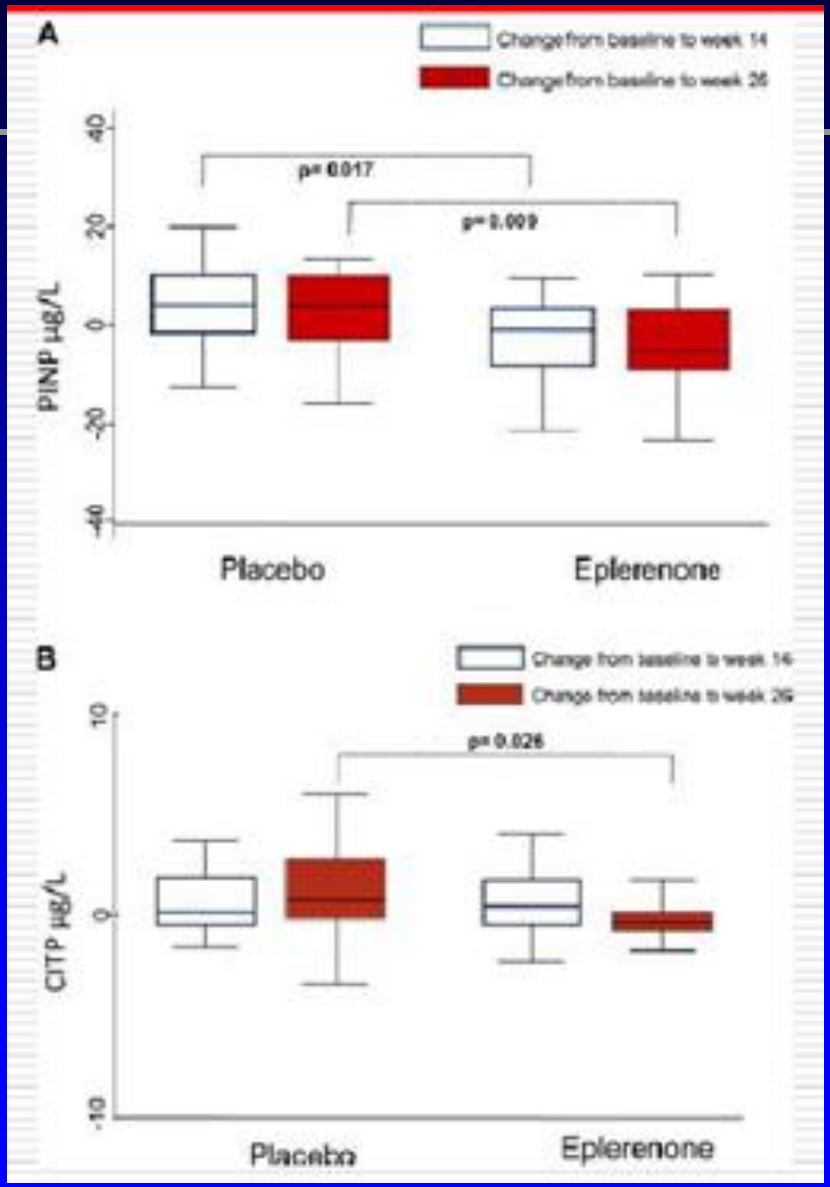
RAAM-PEF study
Eplerenone in HFPEF

6 min walking test : neg
markers colagen turnover :pos
E/E´ :pos

44 pts; 50 mg Eplerenone



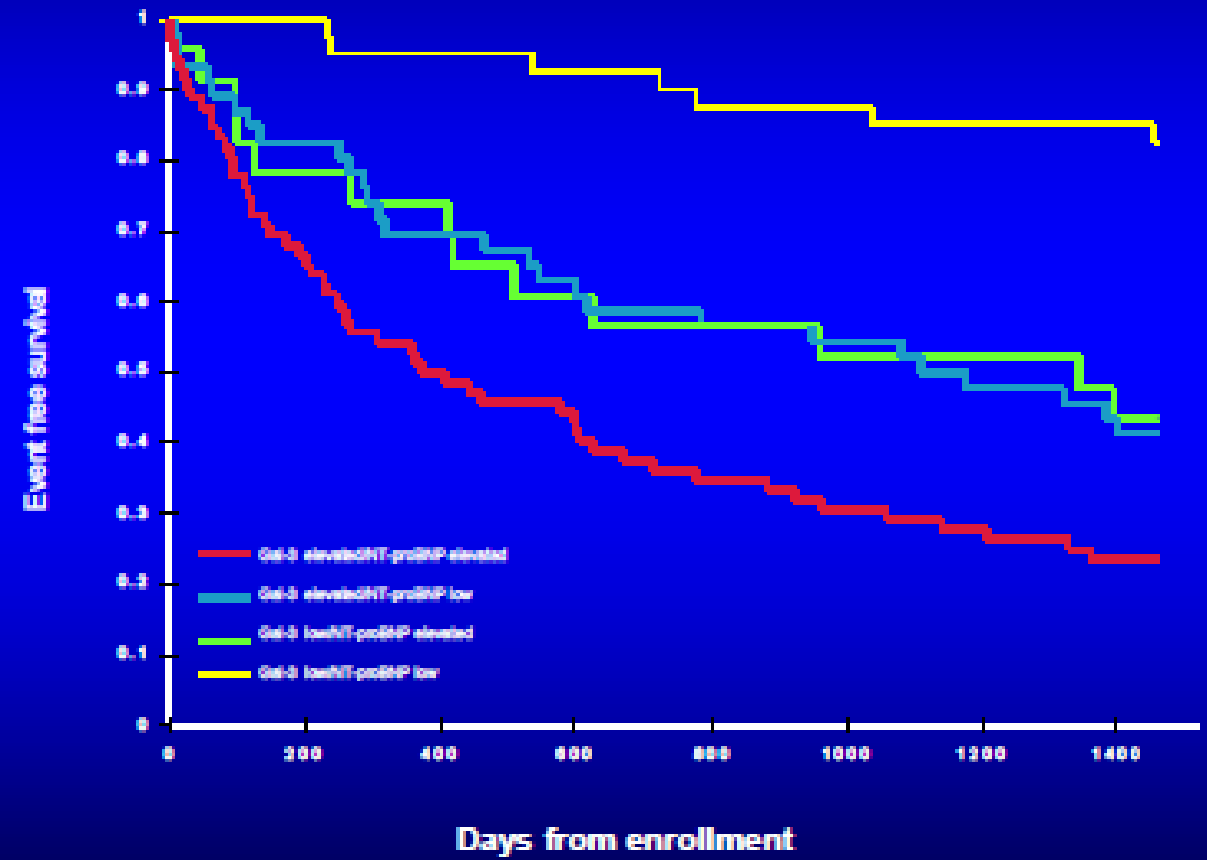
Deswal A, et al. J Card Fail. 2011 Aug;17(8):634-42

Galectina -3

- Proteina da familia das lectinas, expressa em numerosas celulas (neutrófilos, macrófagos, fibroblastos…)
- Ligandos- Proteinas MEC, de membrana, intracelulares, AGE
- Representa elo entre inflamação e fibrose
- Estimula a proliferação de fibroblastos e produção de colageneo
- Niveis de GAL-3 correlacionam-se com MMP2 e TIMP-1

Rudolf A. de Boer. Curr Heart Fail Rep (2010) 7:1–8

Galectin-3 and long term outcomes in ADHF



P < .001

Shah, Eur J Heart Fail, 2011

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Galectina -3

- Sem valor acrescido para diagnóstico em relação aos PN
- Dados relativos a interacções terapeuticas e comportamento após terapeutica inexistentes

Kimmenade RJ, Januzzi J. Clinical Chemistry. 2012

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Stress oxidativo

- Resulta de desiquilibrio entre ROS e os mecanismos de defesa antioxidantes endógenos
- Danifica proteinas celulares e causa apoptose e necrose.
- Associa-se a arritmias e disfunção endotelial
- Redução da actividade da sintase do NO, e inactivação do NO
- Dificuldade na medição das ROS, usando-se marcadores indirectos

Eur Heart J 2003;24:2161-3

Ácido úrico - Prognóstico

- Associado a pior prognóstico
- Aumento da Xantina-oxidase – produção ROS- stress oxidativo
- Inibição da XO – vasodilatação dependente do endotelio, diminuição dos niveis de stress oxidativo, melhora eficiencia miocárdica.
- Alopurinol EV – aumenta disponibilidade de ATP em doentes CMD

JACC 2012;59:802-808

Ácido úrico - Prognóstico

- OPT-CHF- ICFVER – Oxipurinol 600 mg – redução de mortalidade/morbilidade/QoL
- EXACT-HF- Alopurinol
  - FE Reduzida
  - ác. Urico >9,5 mg/dL.

OPT-CHF JACC 2008;51:2301-2309; clinicaltrials.gov/ct2/show/NCT00987415

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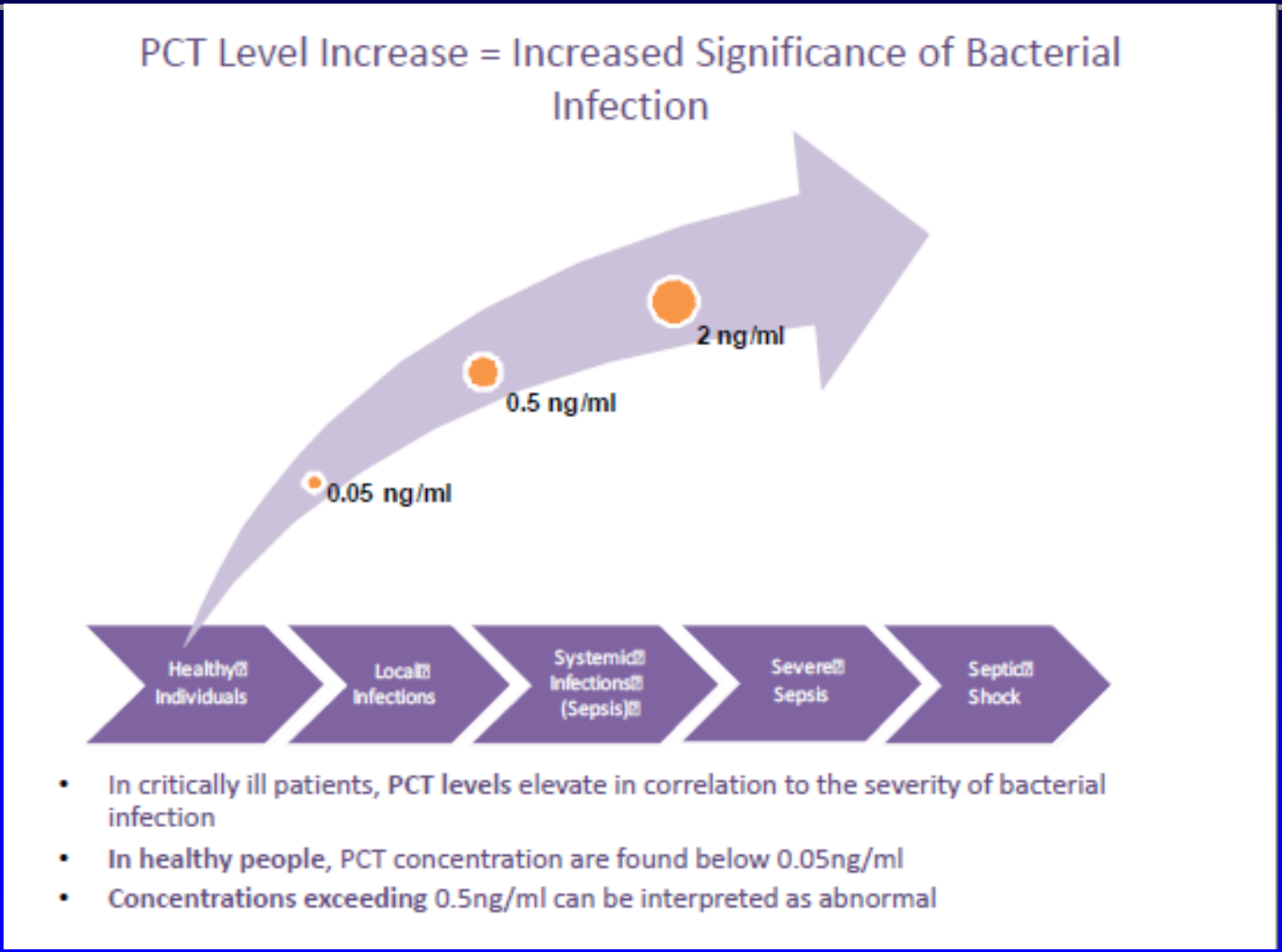
Procalcitonina



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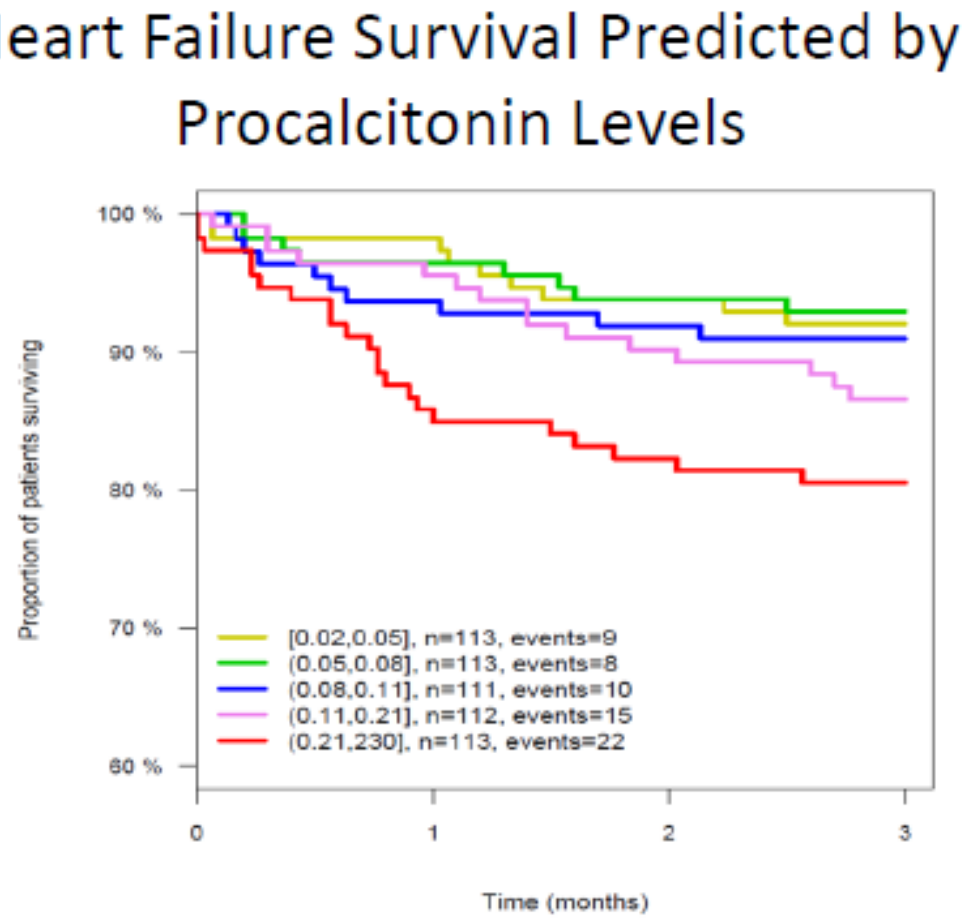
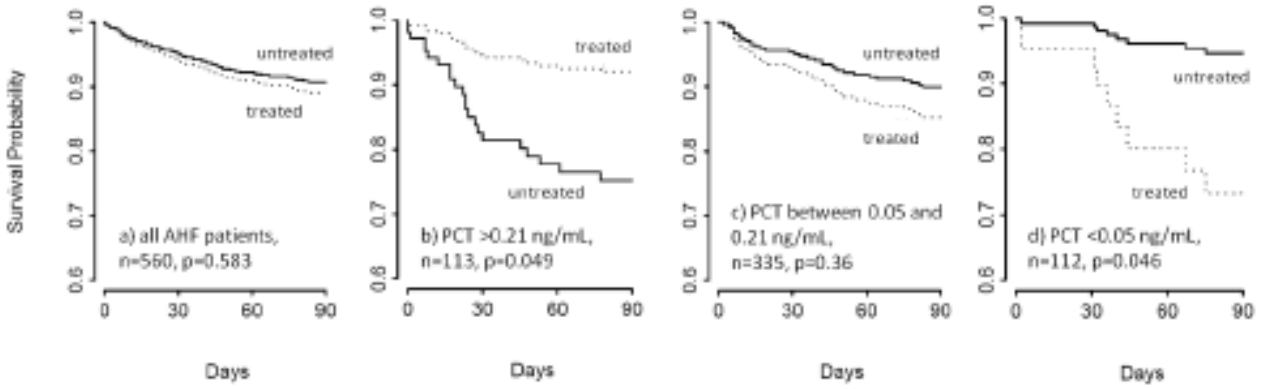
Procalcitonina - Prognóstico



Maisel Eur J HF 2012

Procalcitonina - Prognóstico

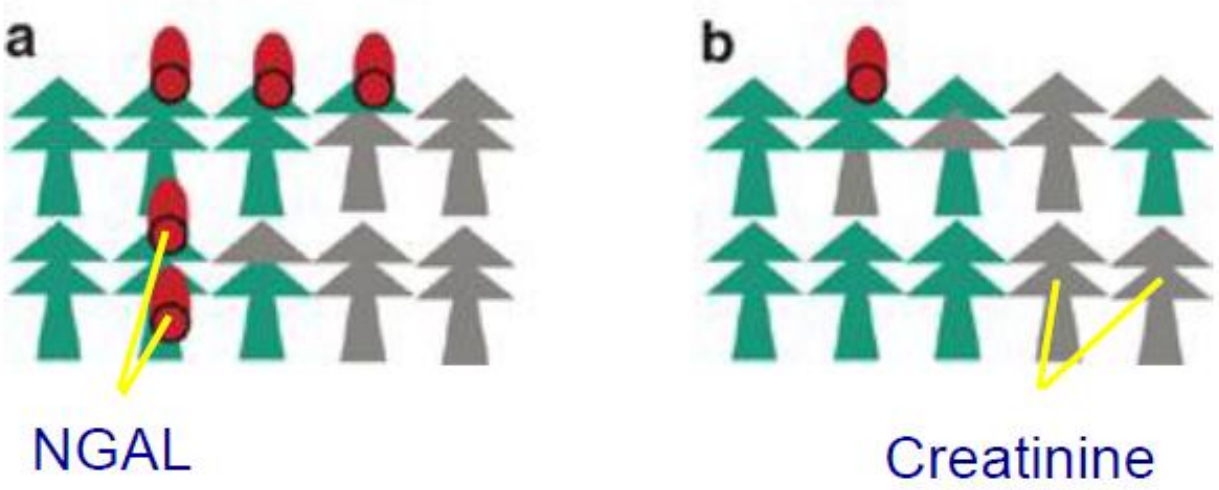
Antibiotic Treatment Discordant with PCT Levels Was Associated with Death



Maisel Eur J HF 2012

NGAL

What can NGAL detect?



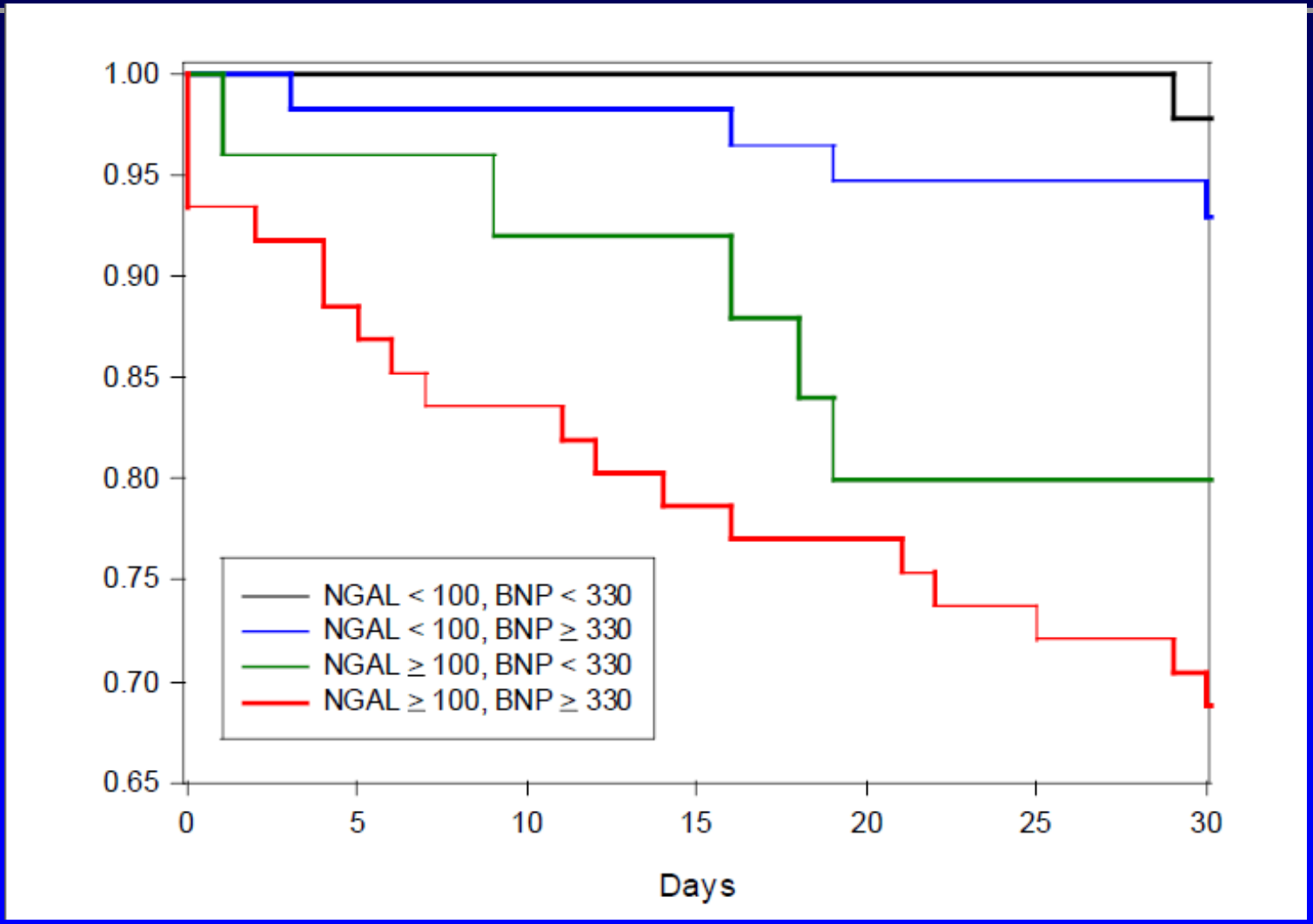
- Marker of Renal Injury
- High Sensitivity for Injury
- Moderate Specificity for underlying nephropathy

NGAL

- Neutrophil gelatinase associated-lipocalin, proteina expressa no tubo colector proximal
- Na lesão aguda dos túbulos renais é induzida rapidamente a expressão do RNAm do NGALm

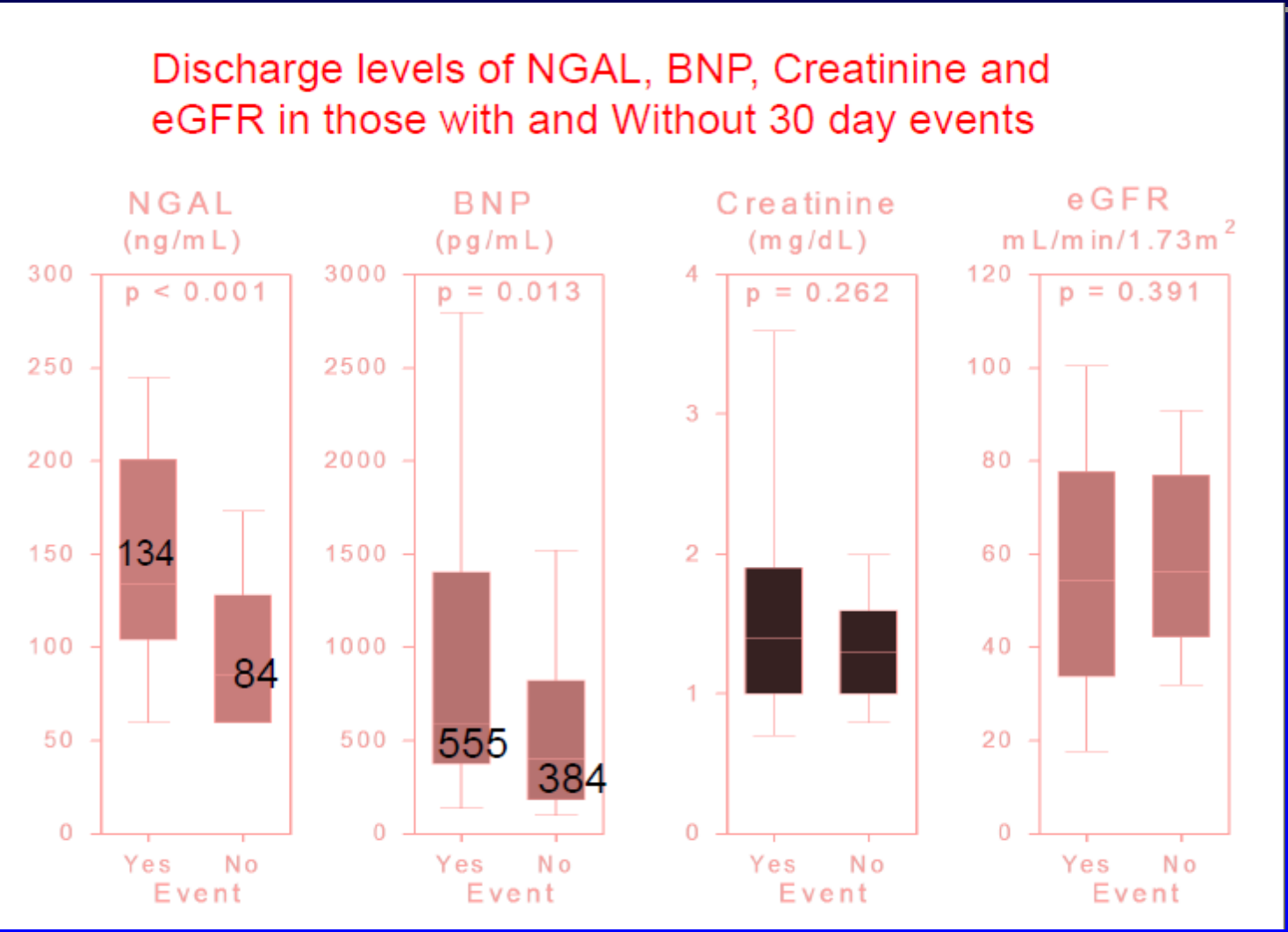
Damman K, Van Veldhuisen DJ, et al. Heart 2010;96:1297-302

NGAL – Prognóstico



Maisel AS, Mueller C, et al. GALLANT trial. Eur J Heart Fail. 2011 Aug;13(8):846-51.

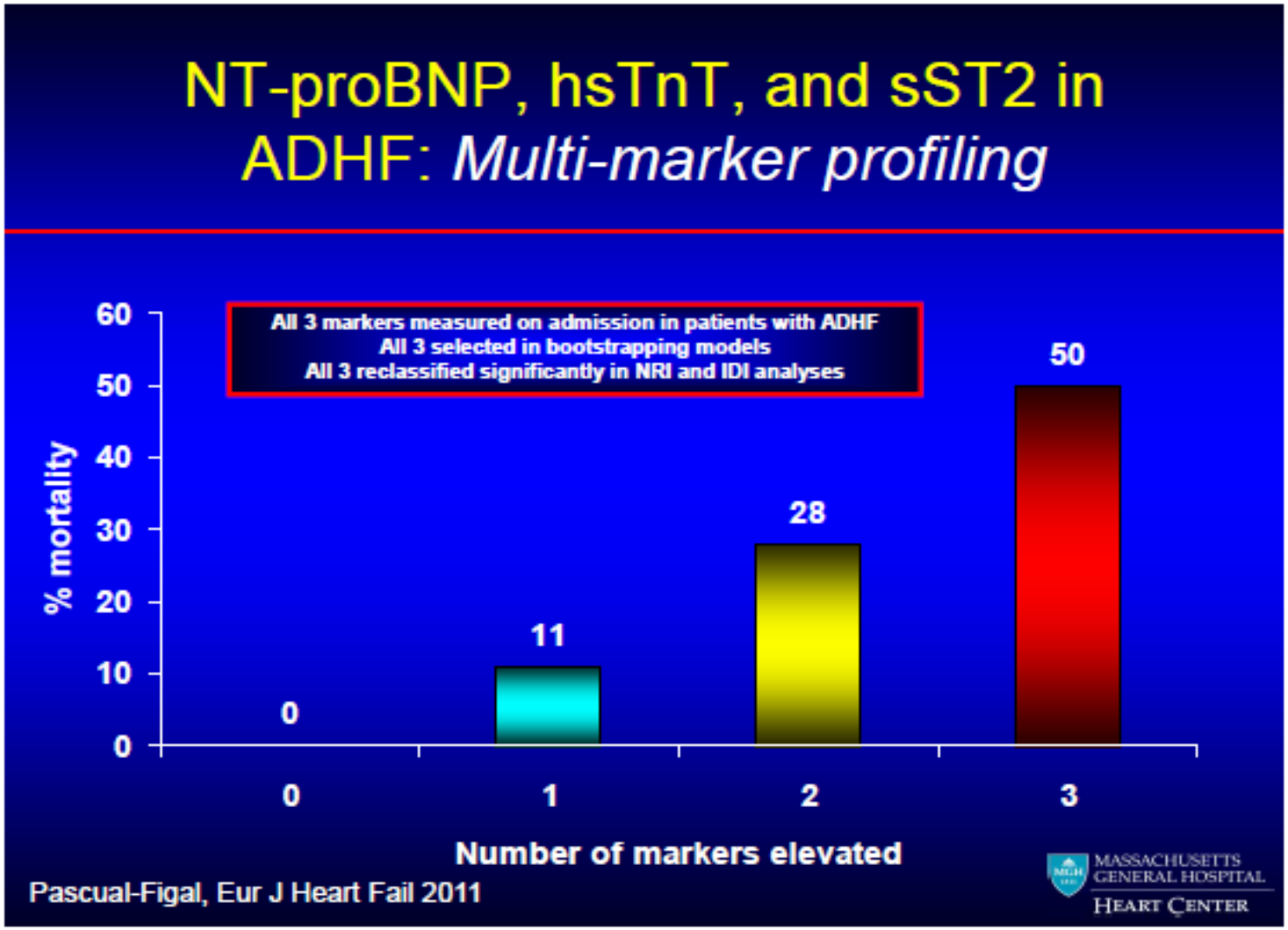
NGAL- Prognóstico



B.Moura, 2013

Maisel AS, Mueller C, et al. GALLANT trial. Eur J Heart Fail. 2011 Aug;13(8):846-51.

Futuro – Paineis de biomarcadores?



Biomarkers in Heart Failure: Future Directions

- More studies on what is cost effective
- Evaluation of the new biomarkers in clinical trials
- Multi-marker Approach by using different biomarker for diagnosis, prognosis, therapy
- Serial (rather than static) testing
- Role of “omic” technologies in biomarker discovery/validation

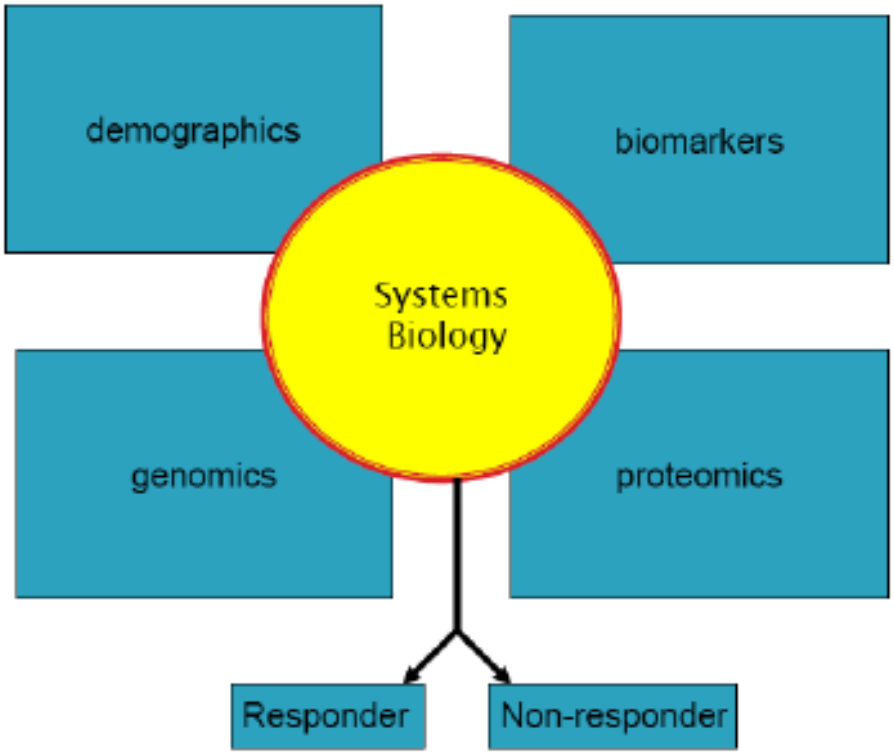
Typical JACC meeting

"You're fired"

"We have another great prognostic Biomarker paper this week"

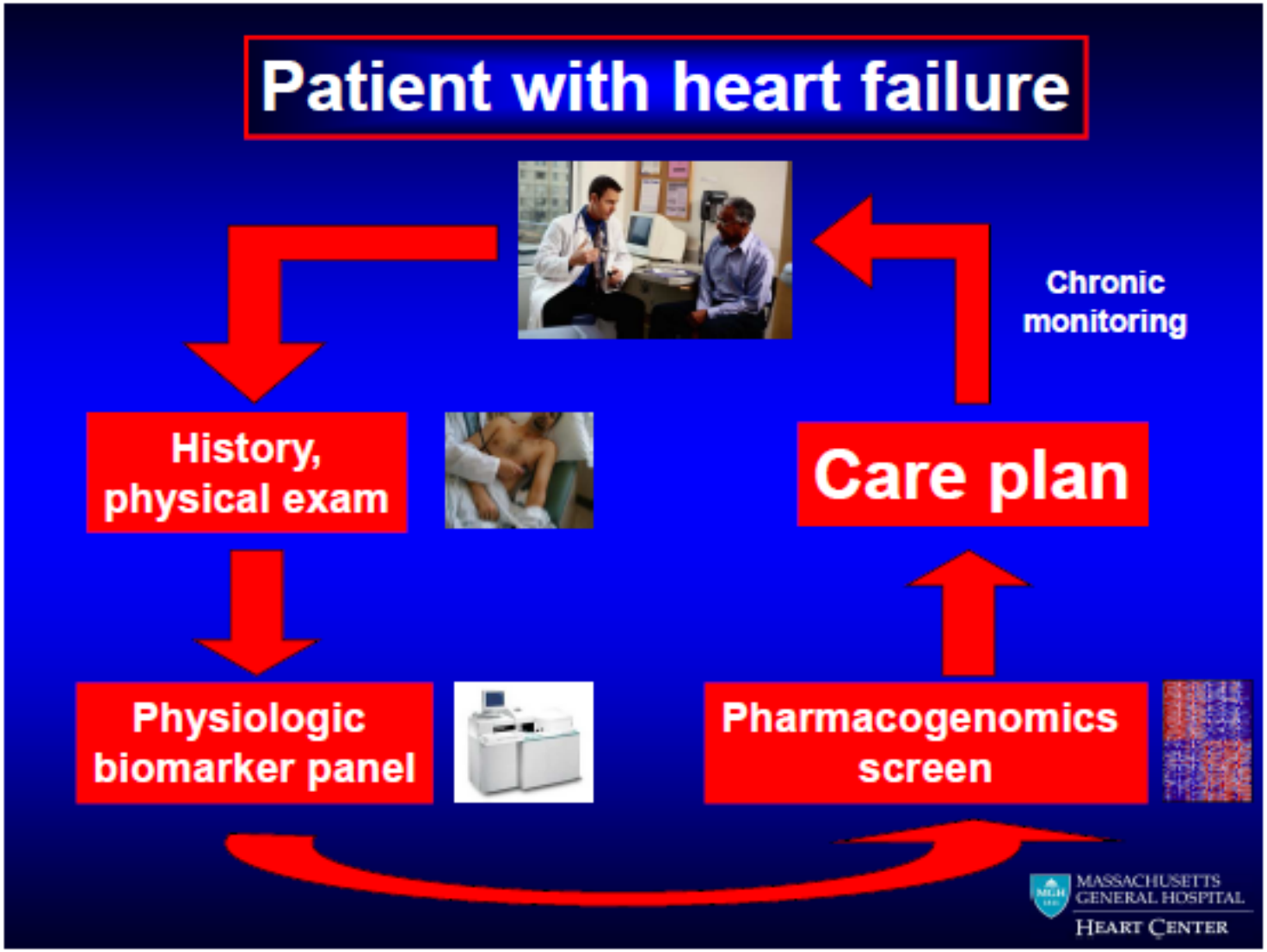
Futuro – terapeutica à medida?

Integrated systems biology approach to determine characteristics of responders and non-responders to evidence based CHF therapy



BIOSTAT-CHF (A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure)
EU Project (Coordinator; A. Voors, NL)

Futuro


Patient with heart failure
Chronic monitoring
History, physical exam
Care plan
Physiologic biomarker panel
Pharmacogenomics screen
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER