Biomarcadores en la práctica clínica

(PEPTIDEOS NATRIURETICOS)

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Biomarker: Definition

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

NIH Biomarkers Definition Working Group.
Atkinson, et al. *Clin Pharmacol Ther* 2001

Ideal biomarker

Cost/Eficacy

Acuity in diagnosis and prognosis

Biological variability
References values/cut-off's

Standardized
"low cost"

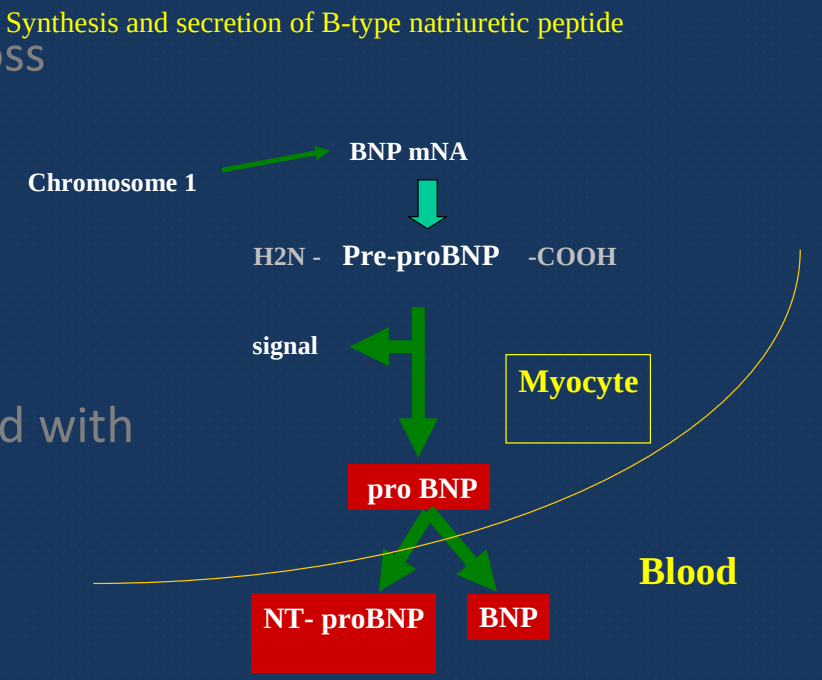
Analytic sensitivity
Reproducibility
Acuity
Easy to perform

Stability in vitro and in vivo

Natriuretic peptides in the management of Heart Failure

- Sensitive / specific for HF
- Reproduced and standartized across clinical lab.
- Easy to perform

- Variations in biomarkers associated with
  - Variations in clinical status
  - Related to interventions
  - Variations in prognosis



European Heart Journal (2012) **33**, 1787–1847
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

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

Journal of Cardiac Failure Vol. 16 No. 6 2010

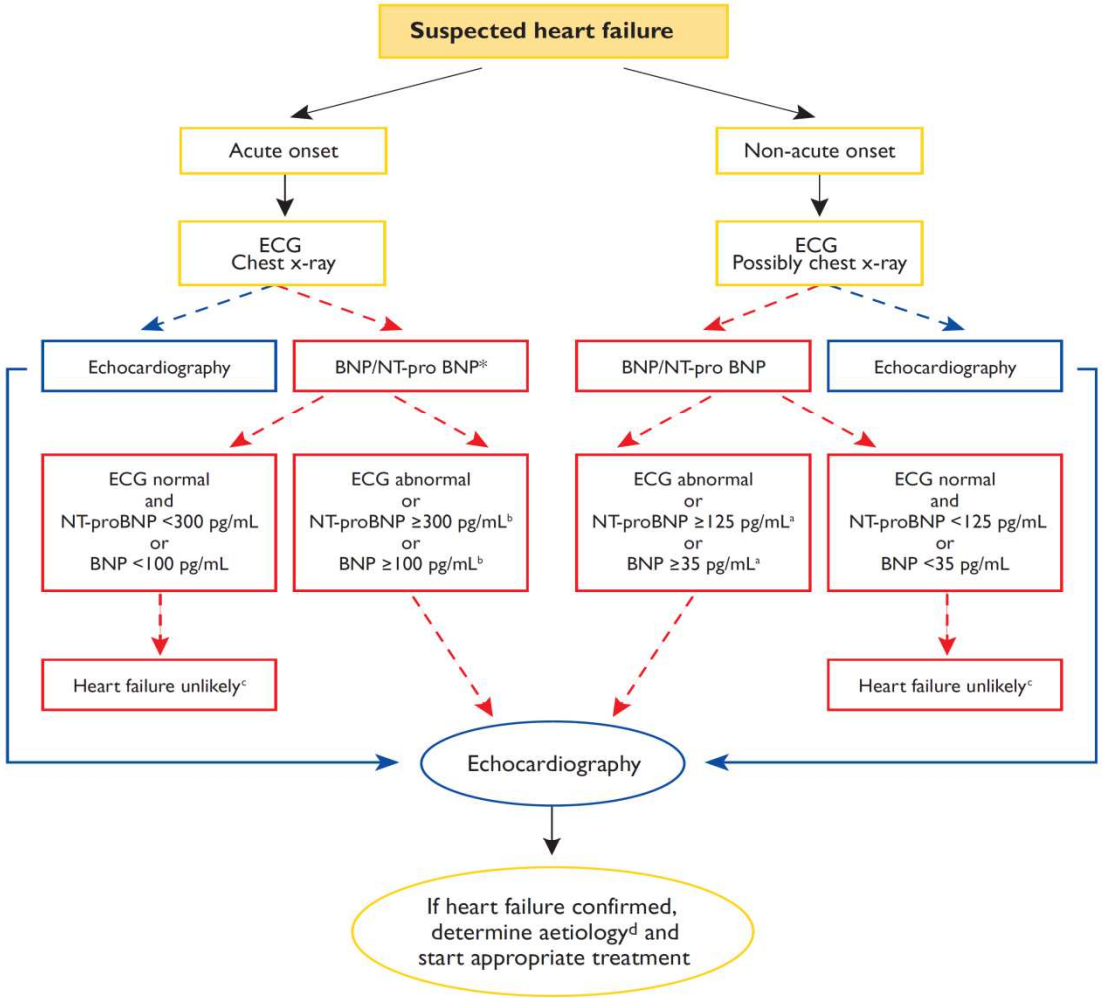
HFSA 2010 Guideline Executive Summary

Executive Summary: HFSA 2010 Comprehensive Heart Failure Practice Guideline

HEART FAILURE SOCIETY OF AMERICA

St. Paul, Minnesota

Diagnosis



*In the acute setting, MR-proANP may also be used (cut-off point 120 pmol/L, i.e. <120 pmol/L = heart failure unlikely).
BNP = B-type natriuretic peptide; ECG = electrocardiogram; HF = heart failure; MR-proANP = mid-regional pro atrial natriuretic peptide; NT-proBNP = N-terminal pro B-type natriuretic peptide.
[a] Exclusion cut-off points for natriuretic peptides are chosen to minimize the false-negative rate while reducing unnecessary referrals for echocardiography.
[b] Other causes of elevated natriuretic peptide levels in the acute setting are an acute coronary syndrome, atrial or ventricular arrhythmias, pulmonary embolism, and severe chronic obstructive pulmonary disease with elevated right heart pressures, renal failure, and sepsis. Other causes of an elevated natriuretic level in the non-acute setting are: old age (>75 years), atrial arrhythmias, left ventricular hypertrophy, chronic obstructive pulmonary disease, and chronic kidney disease.
[c] Treatment may reduce natriuretic peptide concentration, and natriuretic peptide concentrations may not be markedly elevated in patients with HF-PEF.
[d] See Section 3.5 and Web Table 3.

Figure 1 Diagnostic flowchart for patients with suspected heart failure—showing alternative 'echocardiography first' (blue) or 'natriuretic peptide first' (red) approaches.

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

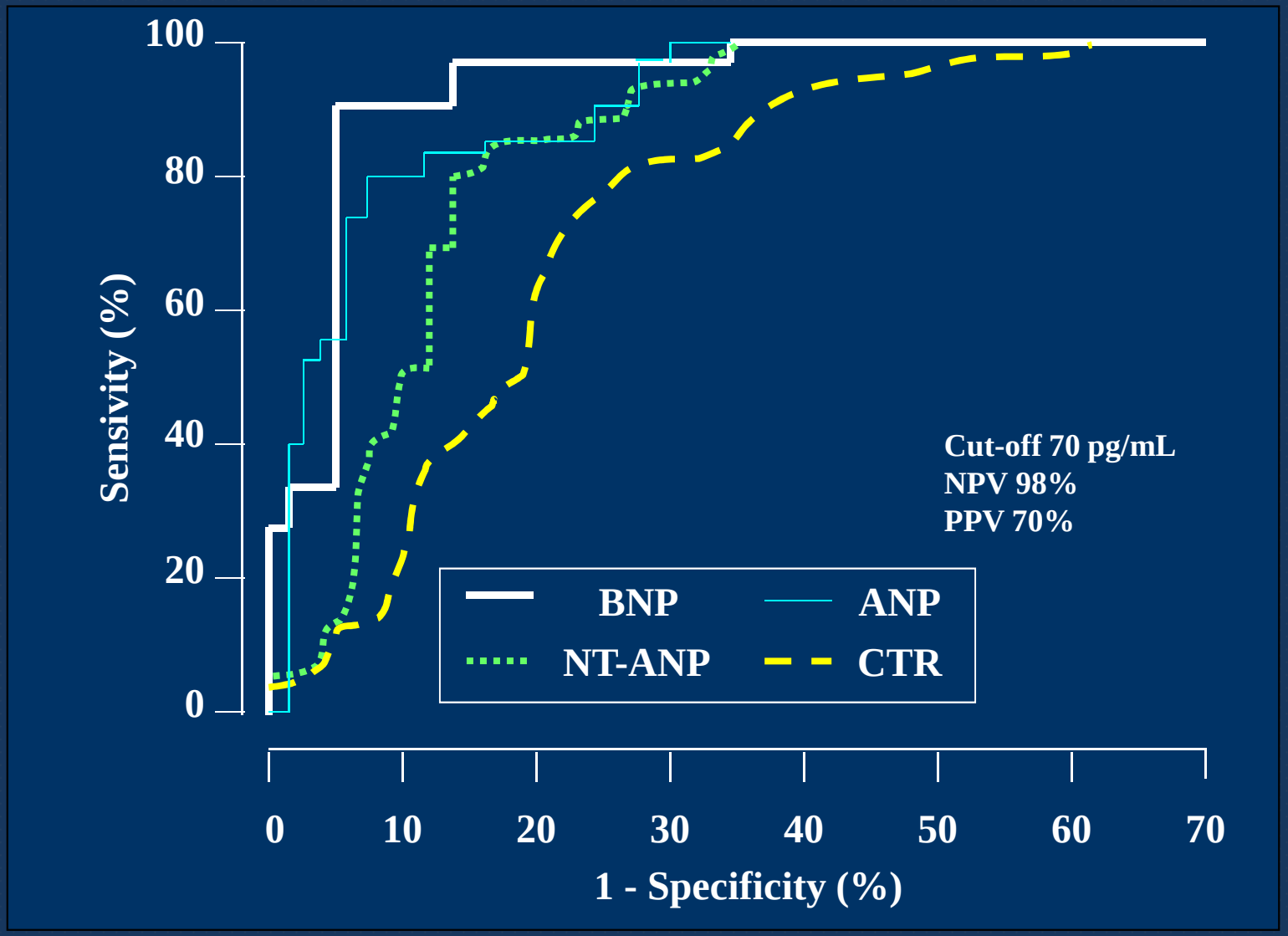
BNP IN THE DIAGNOSIS OF HF

AMBULATORY
ACUTE SETTING

BNP AND PROGNOSIS HF

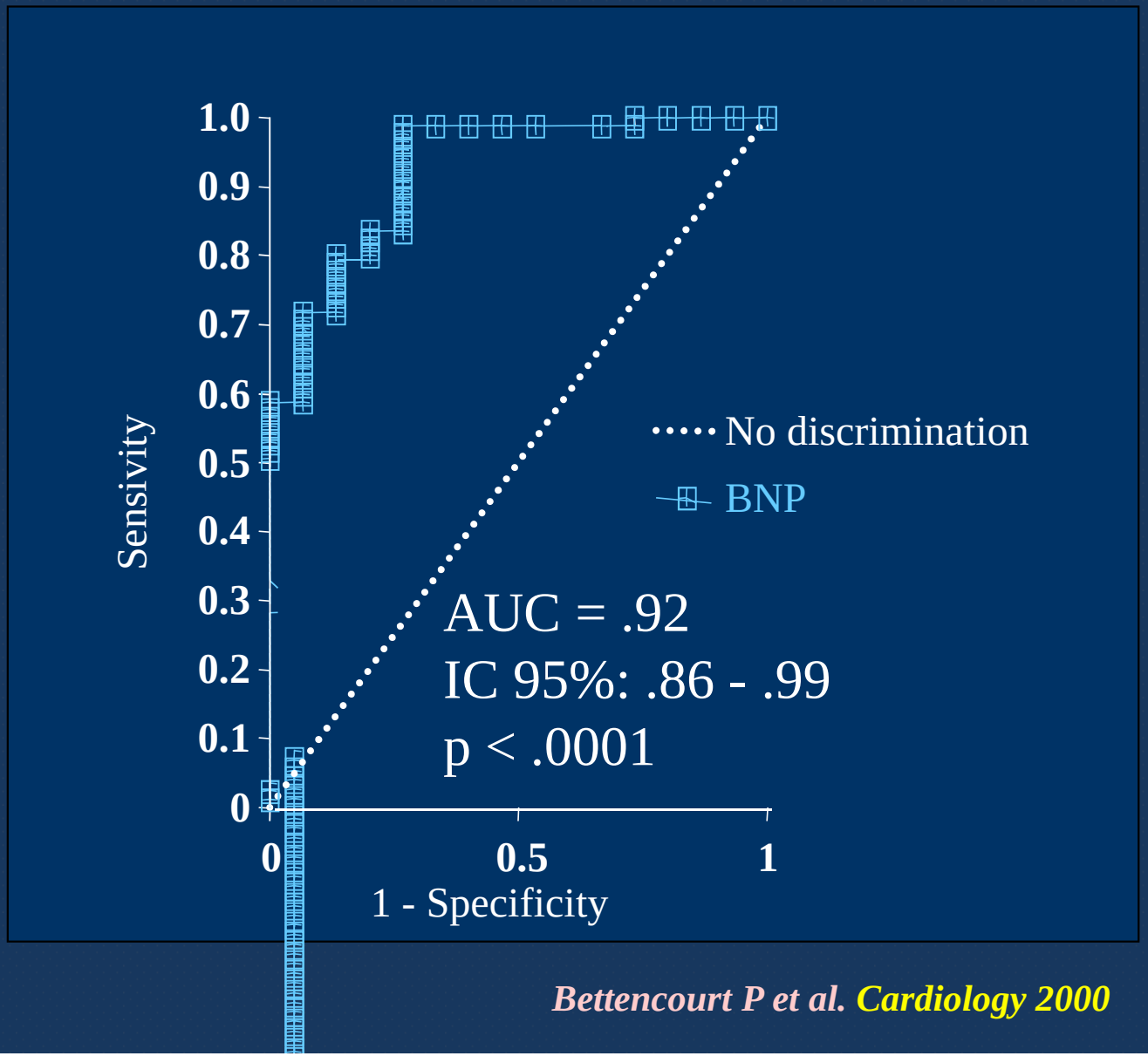
ACUTE HF
CHRONIC HF

BNP in the diagnosis of HF in primary care setting



Cowie MR. Lancet 1997

BNP in the diagnosis of HF



Bettencourt P et al. Cardiology 2000

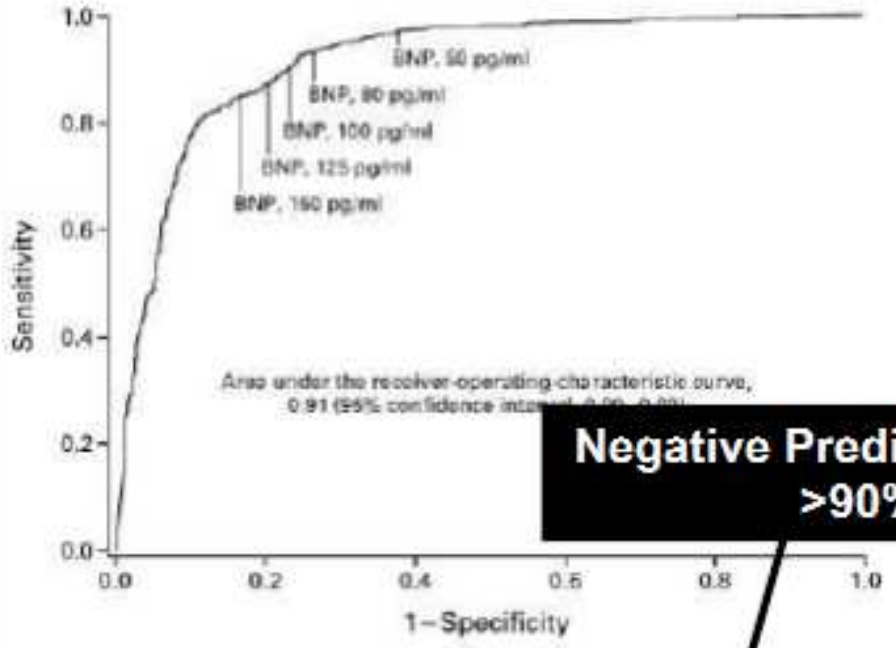
BNP IN THE DIAGNOSIS OF HF

AMBULATORY
ACUTE SETTING

BNP AND PROGNOSIS HF

ACUTE HF
CHRONIC HF

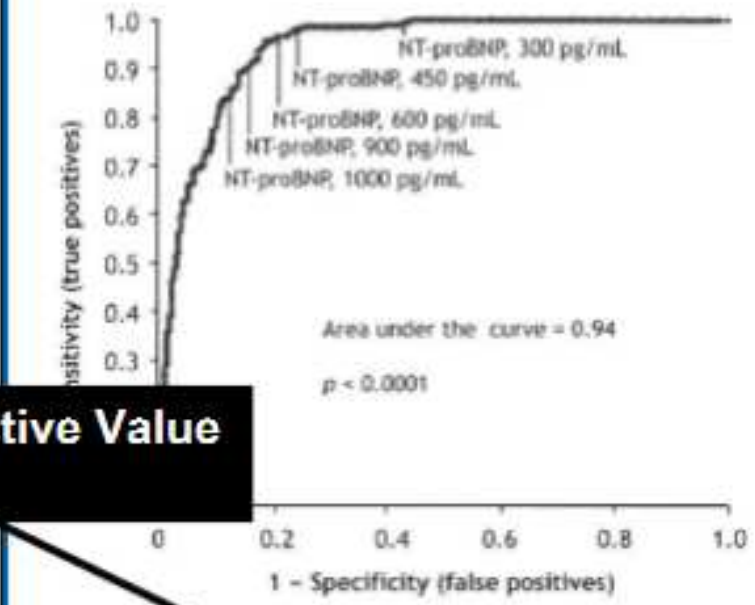
Natriuretic Peptide Testing in Acute Heart Failure



Area under the receiver-operating-characteristic curve, 0.91 (95% confidence interval

BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	95 percent confidence interval				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	82 (80–85)	83 (80–85)	85 (83–88)	84

Negative Predictive Value >90%

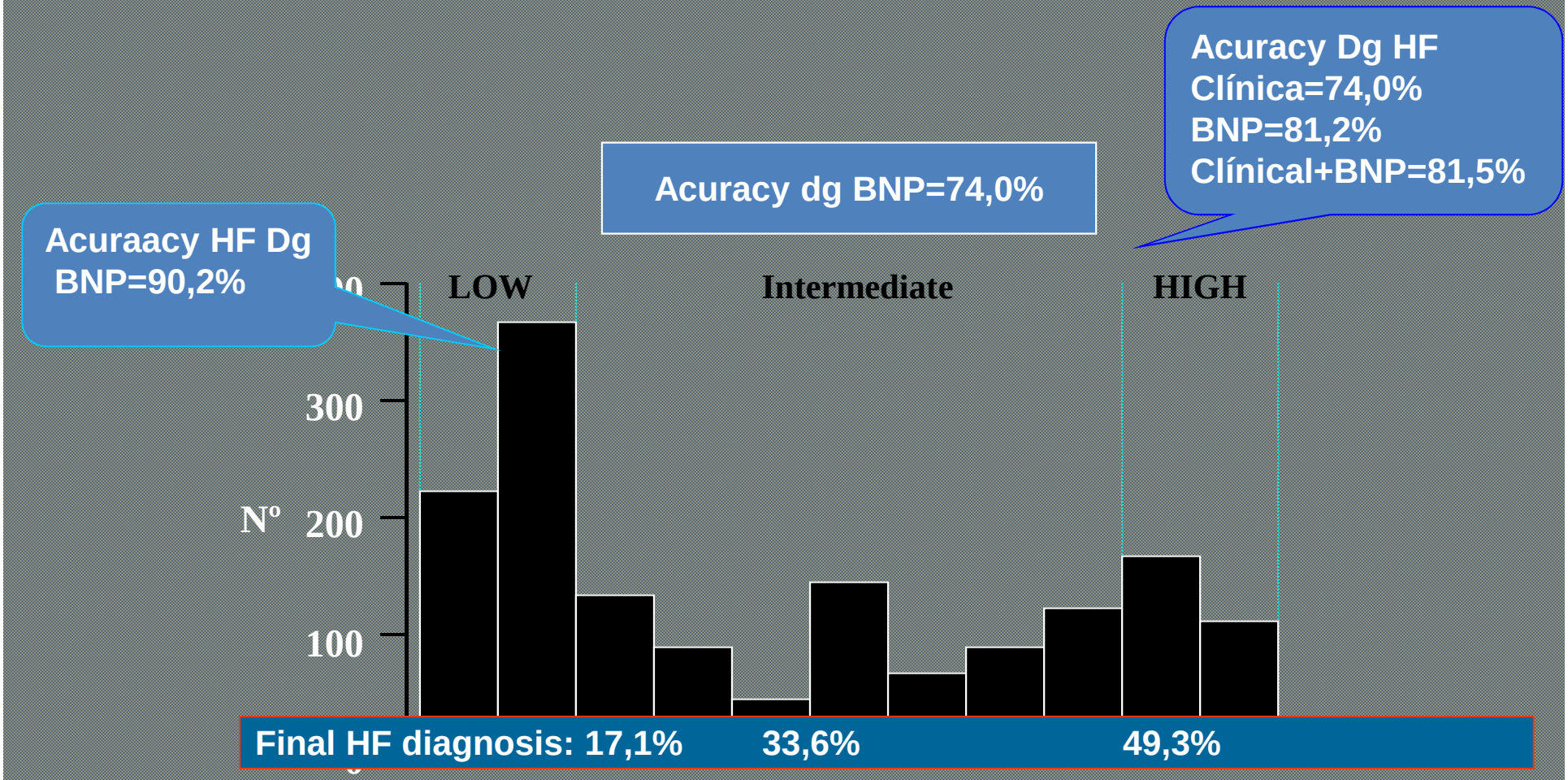


Cutoff, pg/mL	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
300	99	68	62	99	79
450	98	76	68	99	83
600	96	81	73	97	86
900	90	85	76	94	87
1000	87	86	78	91	87

Note: PPV = positive predictive value, NPV = negative predictive value.

Biosite BNP (pg/ml) Maisel et al *N Engl J Med* 2002 Roche NT-proBNP Januzzi et al, *AJC* 2006

BNP and clinical probability of HF diagnosis

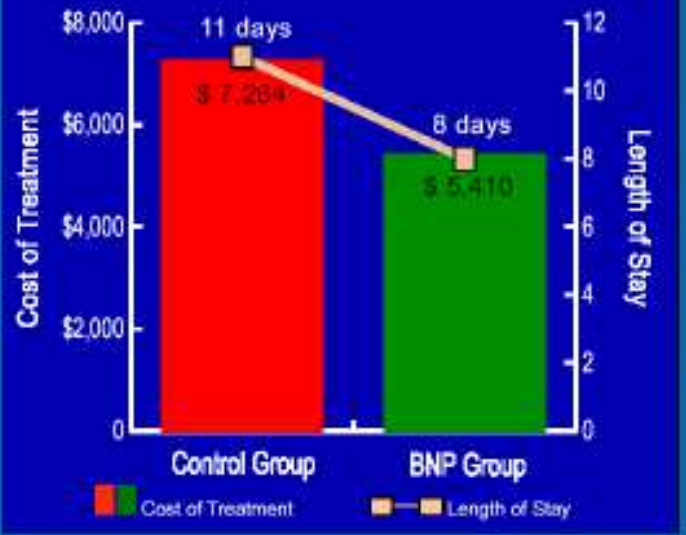


McCullough P. Circulation 2002

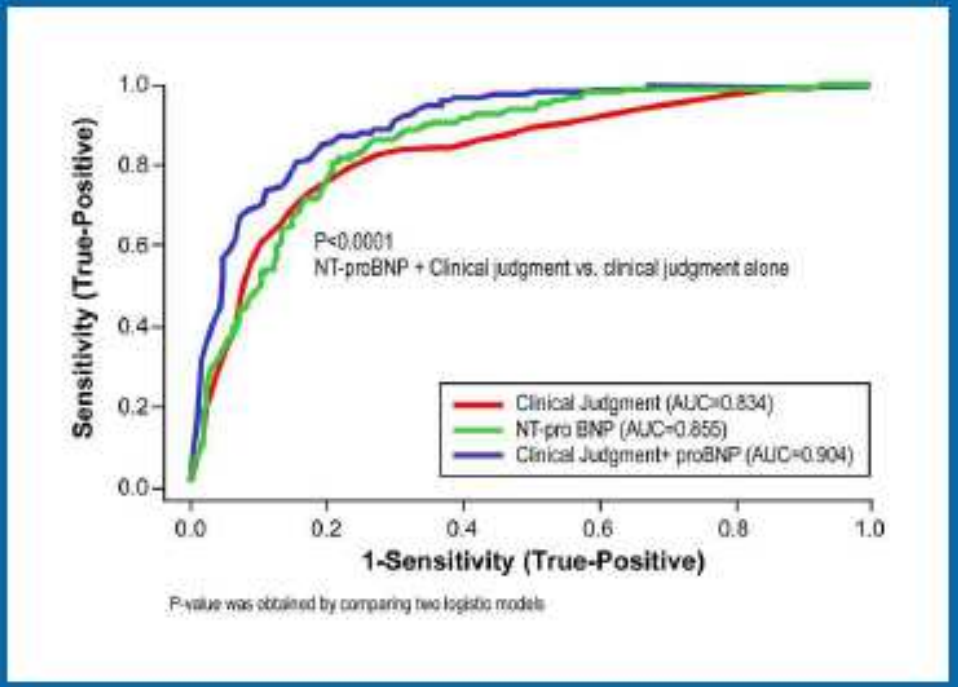
Basel

CLINICAL AND ECONOMIC IMPACT USING RAPID BNP TESTING

	Control Group (n=227)	BNP Group (n=225)
% patients admitted to hospital	85%	75%
% patients in ICU	24%	15%



Improve



Moe, G. W. et al. Circulation 2007;115:3103-3110

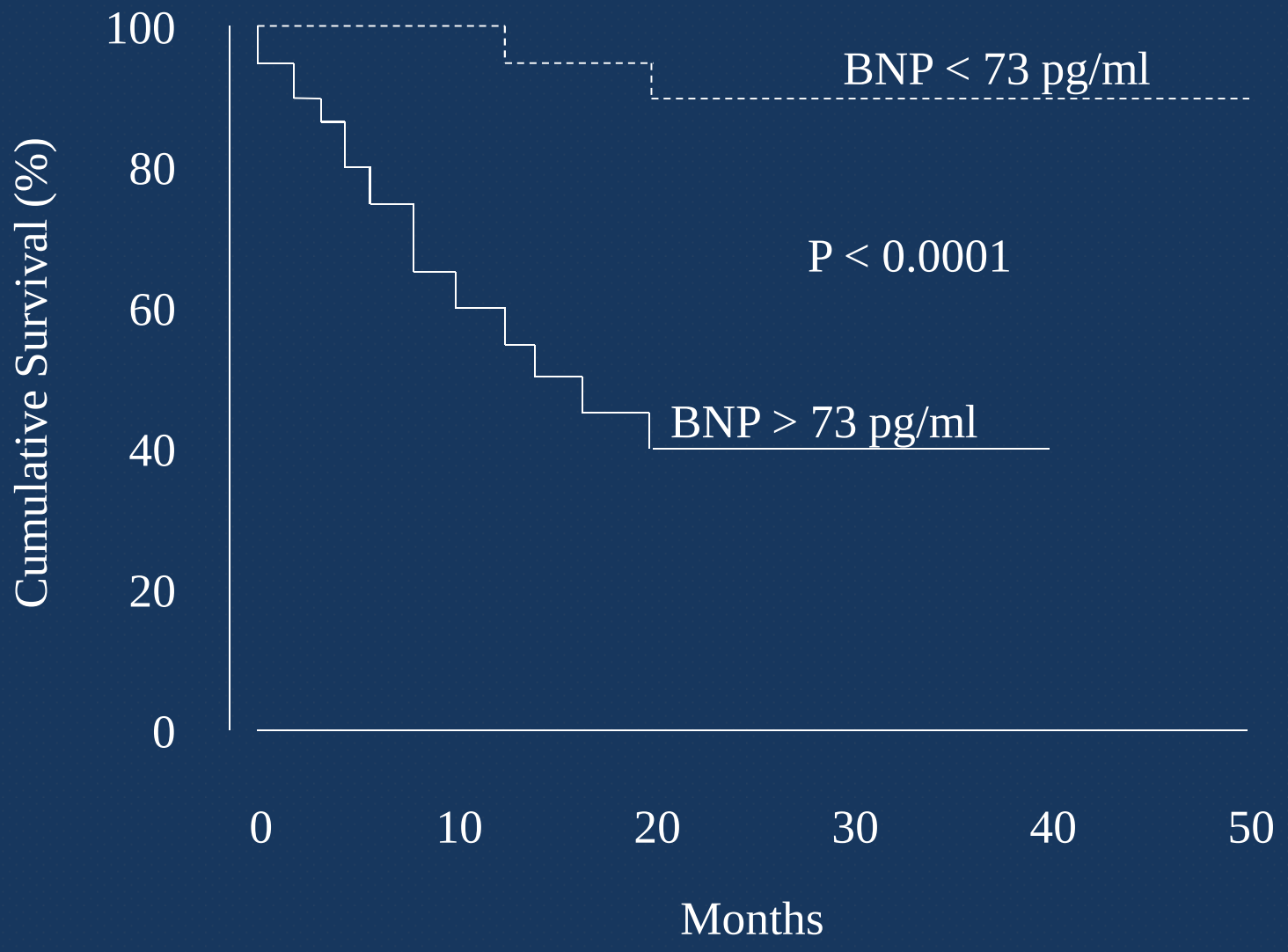
Natriuretic peptides in the management of Heart Failure

BNP IN THE DIAGNOSIS OF HF

AMBULATORY
ACUTE SETTING

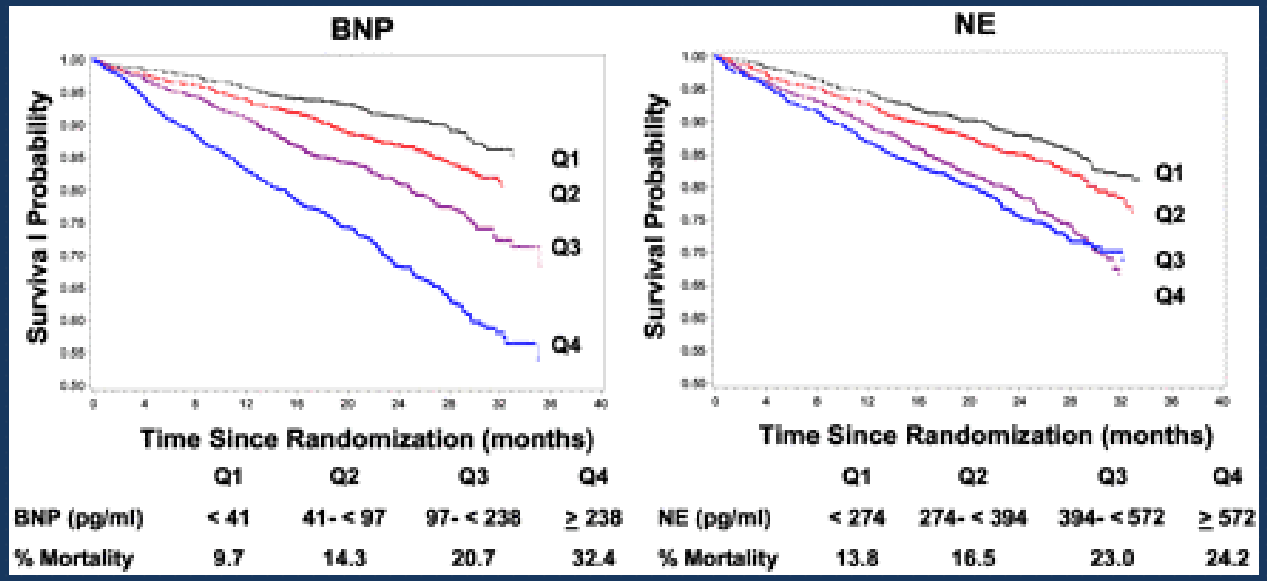
BNP AND PROGNOSIS HF

CHRONIC HF
ACUTE HF



Tsutamoto. Circulation 1997

BNP and prognosis in the ValHeFT trial



	Q1	Q2	Q3	Q4
BNP (pg/ml)	< 41	41- < 97	97- < 238	≥ 238
% Mortality	9.7	14.3	20.7	32.4

	Q1	Q2	Q3	Q4
NE (pg/ml)	< 274	274- < 394	394- < 572	≥ 572
% Mortality	13.8	16.5	23.0	24.2

Kaplan-Meier curves for all-cause mortality and first morbid event in subgroups by quartiles for BNP and NE.

Anand SI. Circulation 2003

Natriuretic peptides in the management of Heart Failure

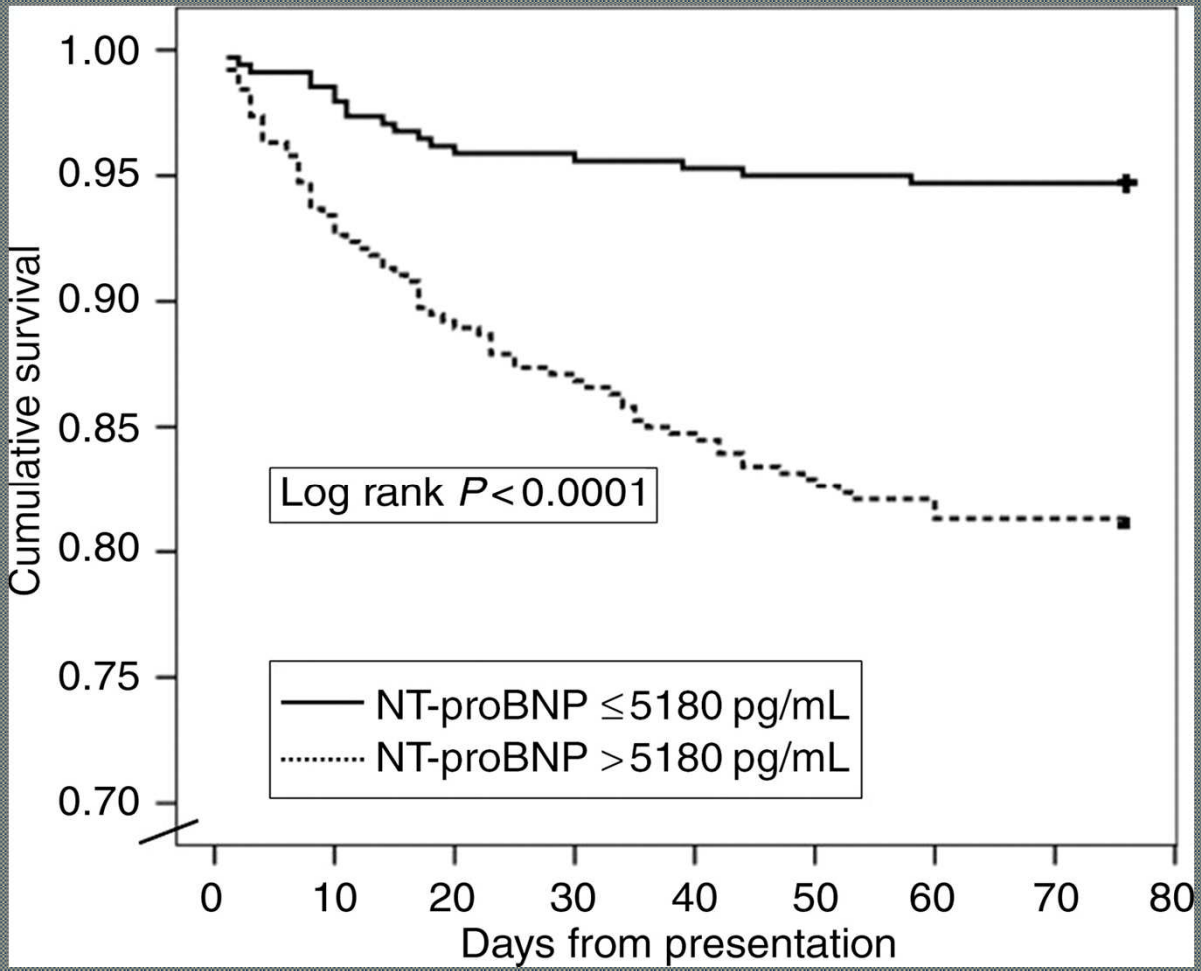
BNP IN THE DIAGNOSIS OF HF

AMBULATORY
ACUTE SETTING

BNP AND PROGNOSIS HF

CHRONIC HF
ACUTE HF

Survival rates of patients with acute HF (n=720) during the first 76 days following presentation

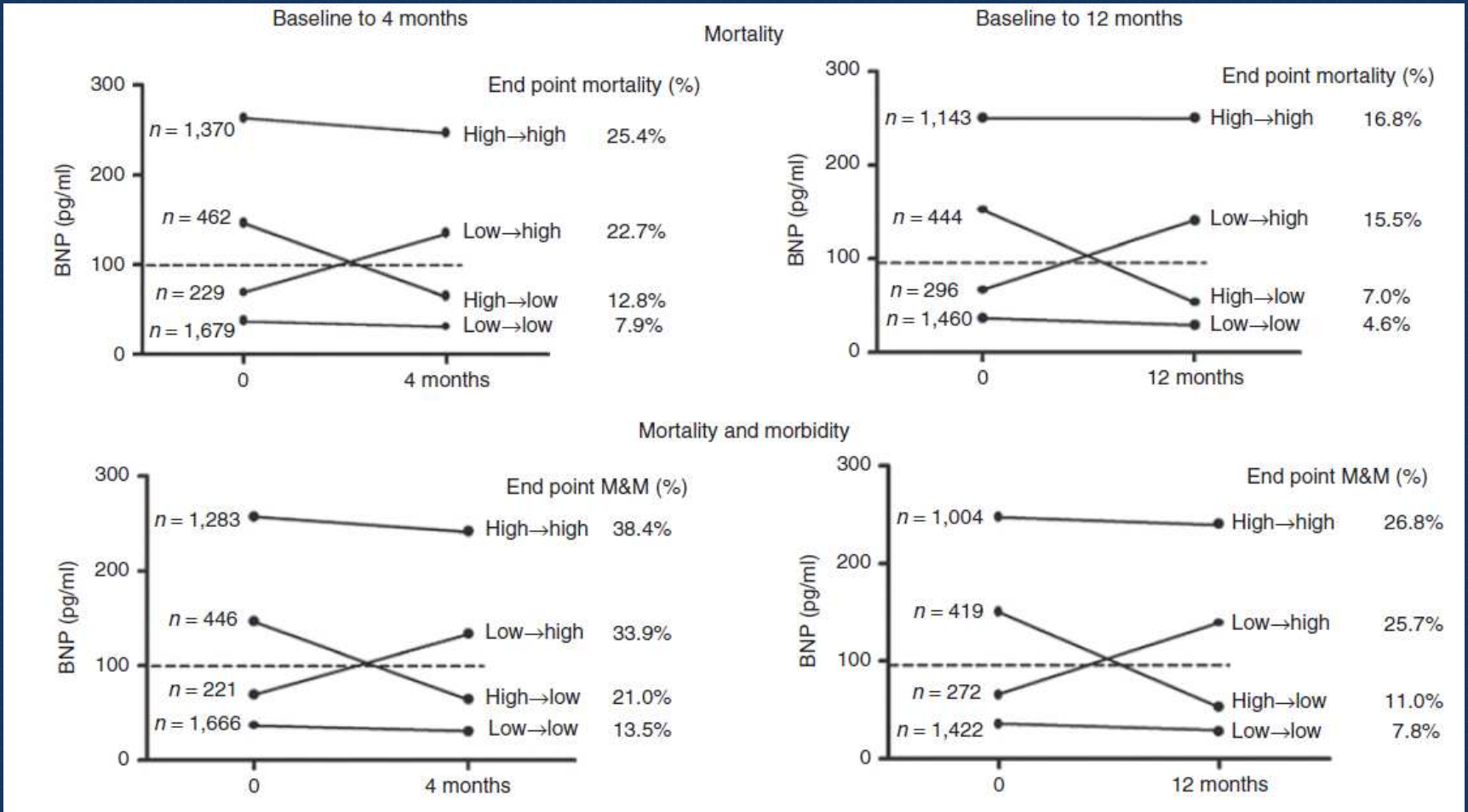


Januzzi J.. Eur Heart J 2005

Biomarkers in the management of Heart Failure

- Sensitive / specific for HF
- Reproduced and standartized across clinical lab.
- Easy to perform

- Variations in biomarkers associated with
  - Variations in clinical status
  - Related to interventions
  - Variations in prognosis – chronic HF



Latini R. Circulation 2004

Biomarkers in the management of Heart Failure

- Sensitive / specific for HF
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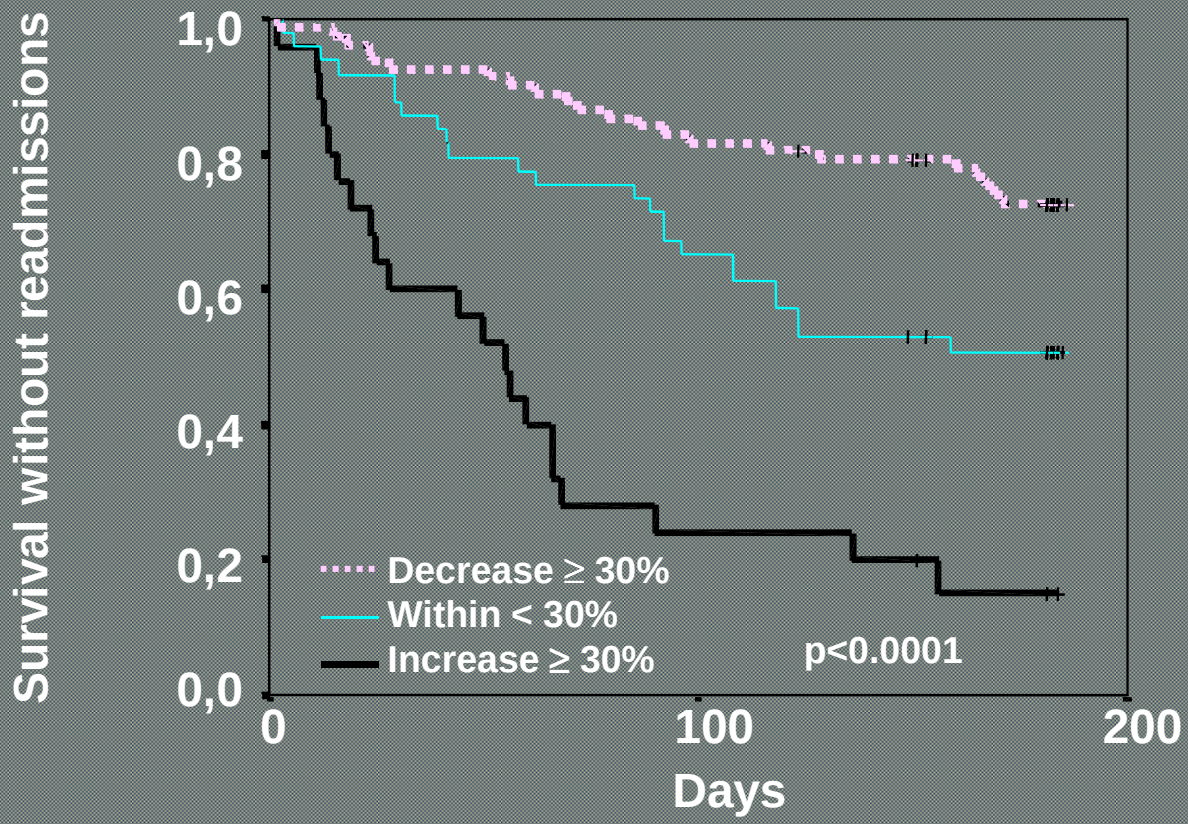
  - Variations in clinical status
  - Related to interventions
  - Variations in prognosis – acute HF

NT-proBNP in acute HF



Bettencourt P. Circulation 2004

ELAN-HF score

Predictors	Score for 180-day mortality*	Regression coefficient
NT-proBNP reduction, ≤30 %	1	0.511
NT-proBNP discharge value, pg/mL		
1500–5000	1	0.713
5001–15 000	3	1.426
>15 000	4	1.776
Age at admission, years≥75	1	0.345
Peripheral oedema at admission		
Yes	1	0.517
SBP at admission, mm Hg≤115	1	0.431
Hyponatremia at admission <135 mEq/L	1	0.374
Serum urea at discharge, mmol/L≥15	1	0.486
NYHA Class at discharge III/IV		
Yes	1	0.403

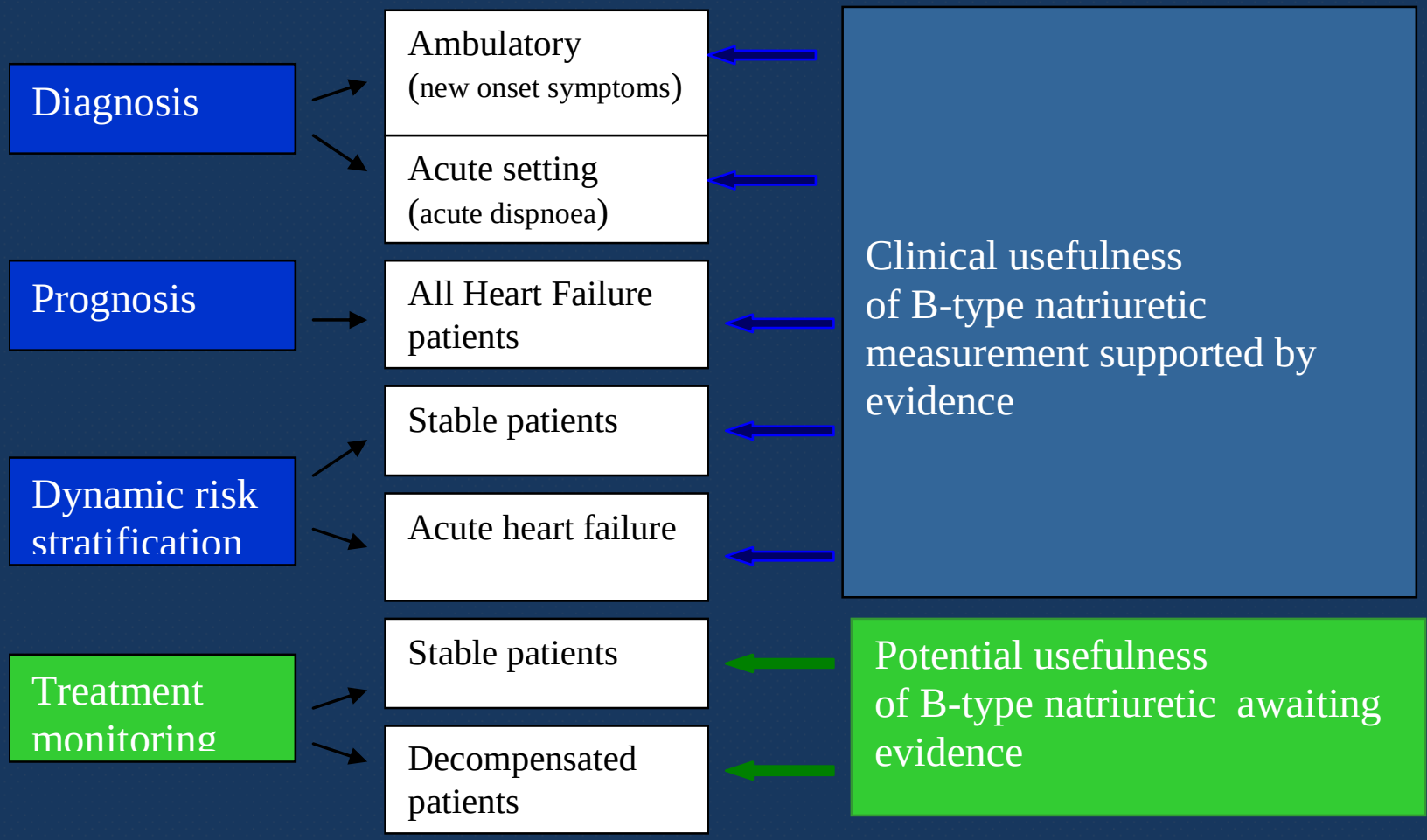
Salah K, KokWE,Eurlings LW, Bettencourt P,Pimenta JM, Metra M, Bayes-Genis, A Verdiani V, Bettari L, Lazzarini V, Damman P, Tijssen JG, Pinto Y. Heart 2013

Mortality rates for the ELAN-HF score

	Study cohort (%)	Validation cohort (%)
Low ≤2	3.6	7.0
Intermediate 3–4	9.2	12.9
High 5–7	23.5	23.4
Very high ≥8	51.1	51.7

Salah K, KokWE,Eurlings LW, Bettencourt P,Pimenta JM, Metra M, Bayes-Genis, A Verdiani V, Bettari L, Lazzarini V, Damman P, Tijssen JG, Pinto Y. Heart 2013

Use of b-type natriuretic peptide in clinical practice



Bettencourt P. Heart 2005

Therapies for HF that may lower natriuretic peptide levels

Therapy	Effect on BNP/NT-proBNP
Diuresis (loop or thiazide)	↓
Angiotensin-converting enzyme inhibitors	↓
Angiotensin II receptor blockers	↓
β-Blockers	Some transiently ↑, most ↓
Aldosterone antagonists	↓
Cardiac resynchronization therapy	↓
Exercise	↓
Rate control of atrial fibrillation	↓

BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, amino-terminal pro-B-type natriuretic peptide.

Biomarker-guided therapy studies

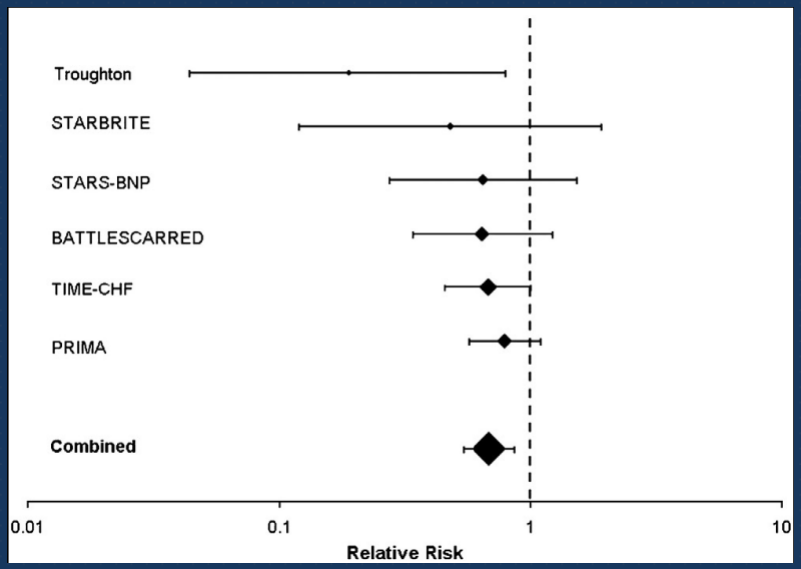
Study (ref.)	Age	HFpEF?	Natriuretic peptide target	Lower NP level achieved in active arm?	Active arm treatment different from that of control arm?	Excess of adverse events in active arm?
Neutral/negative studies						
STARBRITE (64)	60	No	BNP at hospital discharge (~450 pg/ml)	No	Yes	No
PRIMA (62)	72	Yes	NT-proBNP at hospital discharge	No	No	No
SIGNAL-HF (63)	78	No	NT-proBNP 50% below entry to the trial	No	No	No
UPSTEP (65)	71	No	BNP <150 pg/ml for age <75 and <300 pg/ml for age ≥75	Not reported	No	Not reported
Neutral/negative studies with positive trends						
TIME-CHF (61)	77	No	NT-proBNP <400 pg/ml for age <75 and <800 pg/ml for age ≥75	No	Yes	No
BATTLESCARRED (60)	76	Yes	NT-proBNP <1,270 pg/ml	No	Yes	No
Positive studies						
Troughton *et al.* (56)	70	No	NT-proBNP <1,692 pg/ml	Yes	Yes	No
STARS-BNP (58)	65	No	BNP <100 pg/ml	Not reported	Yes	No
Berger *et al.* (57)	71	No	NT-proBNP ≤2,200 pg/ml	Yes	Yes	Not reported
PROTECT (59, 69)	63	No	NT-proBNP ≤1,000 pg/ml	Yes	Yes	No

BNP, B-type natriuretic peptide; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; NP, natriuretic peptide; NT-proBNP, amino-terminal pro-B-type natriuretic peptide.

- **Natriuretic peptides guided therapy**

- Benefits of this treatment approach have been uncertain
- Both positive and neutral results
- Multiple heterogenous studies
  - Small and underpowered
  - Investigating different population
  - Different natriuretic peptide targets established
  - Different clinical endpoints
  - Different control groups and different therapeutic strategies in the study and control groups

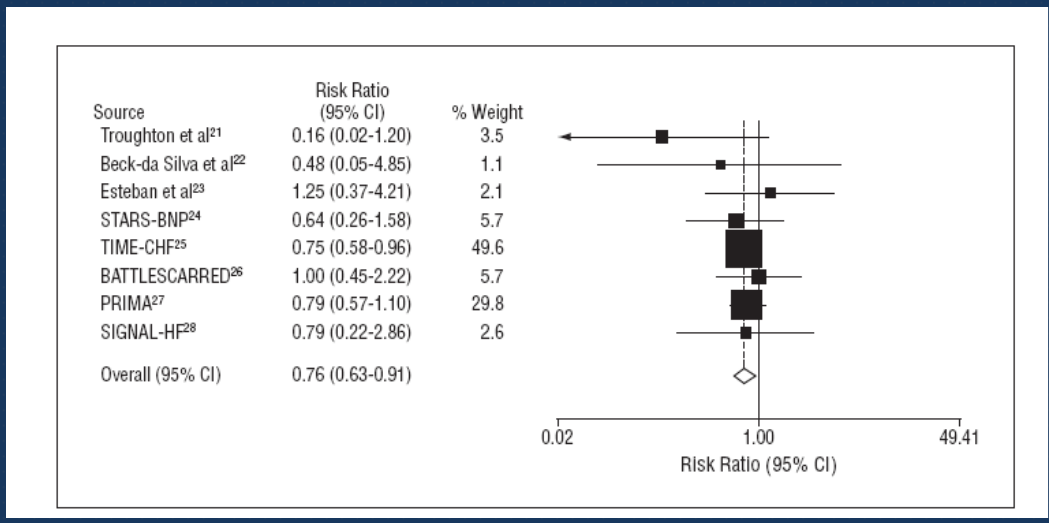
Biomarker-guided therapy meta-analysis



All-cause mortality meta-analysis
Felker, *et al*, Heart j 2009

6 Prospective randomized controlled trials
All-cause mortality
1627 patients

HR for mortality: 0.69 (95% CI: 0.55-0.86)



All-cause mortality meta-analysis
Porapakkham, *et al*, Arch Intern Med, 2010

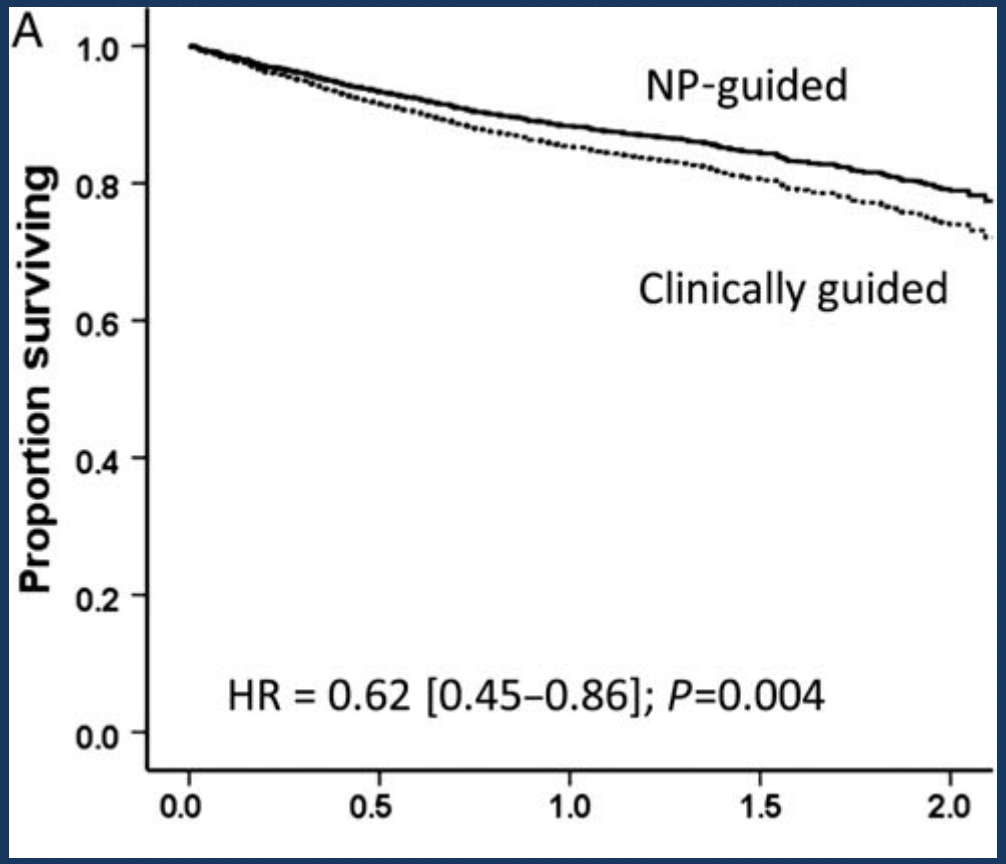
8 Prospective randomized controlled trials
All-cause mortality
1726 Patients

HR for mortality 0.76 (95% CI: 0.63-0.91)

Biomarker-guided therapy meta-analysis

- Pooled analysis of both positive and negative studies: 25-30% adjusted reduction in mortality when biomarker guided therapy is given in adition to standard treatment
    - Treatment effect comparable to that observed with individual components of HF therapy (BB, ACEi, ARBs, aldosterone antagonists and CRT)
- Universally well tolerated, did not lead to higher rates of treatment related side effects

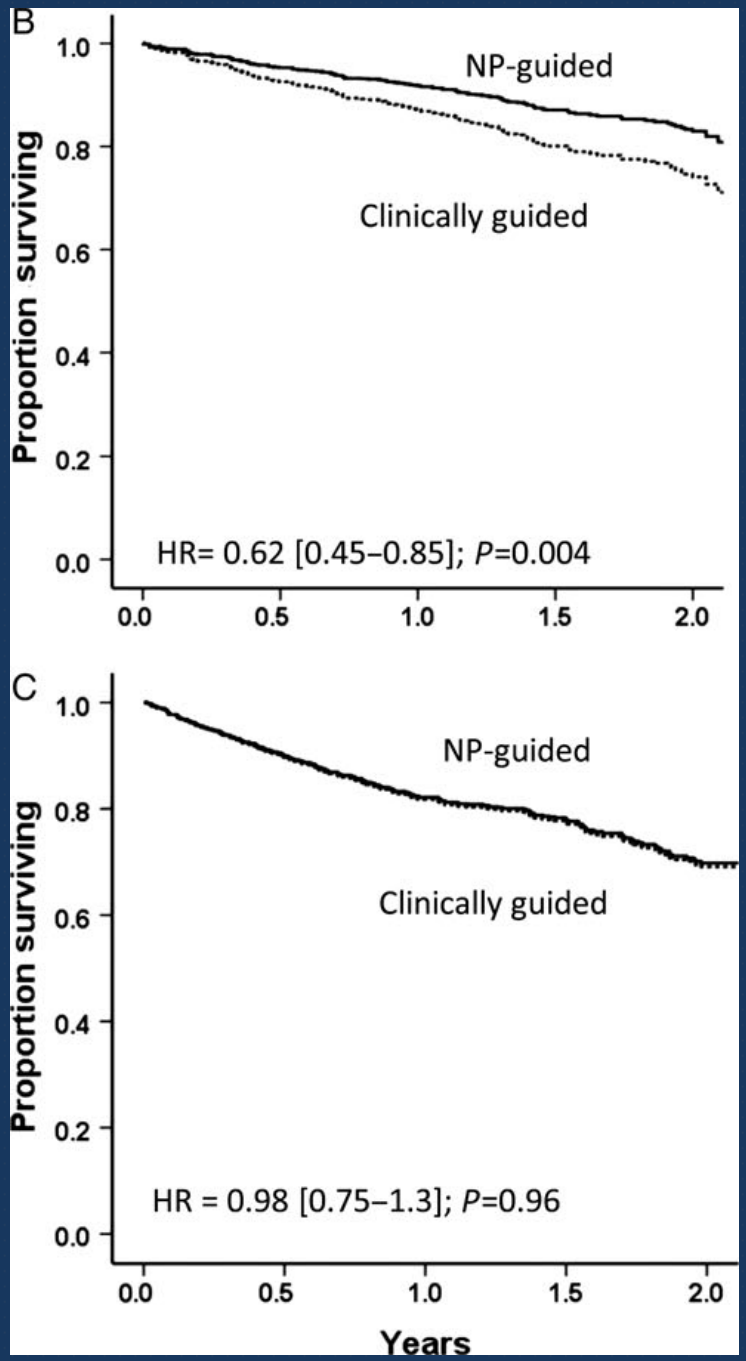
Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis



Kaplan–Meier survival curves for the primary endpoint, overall mortality

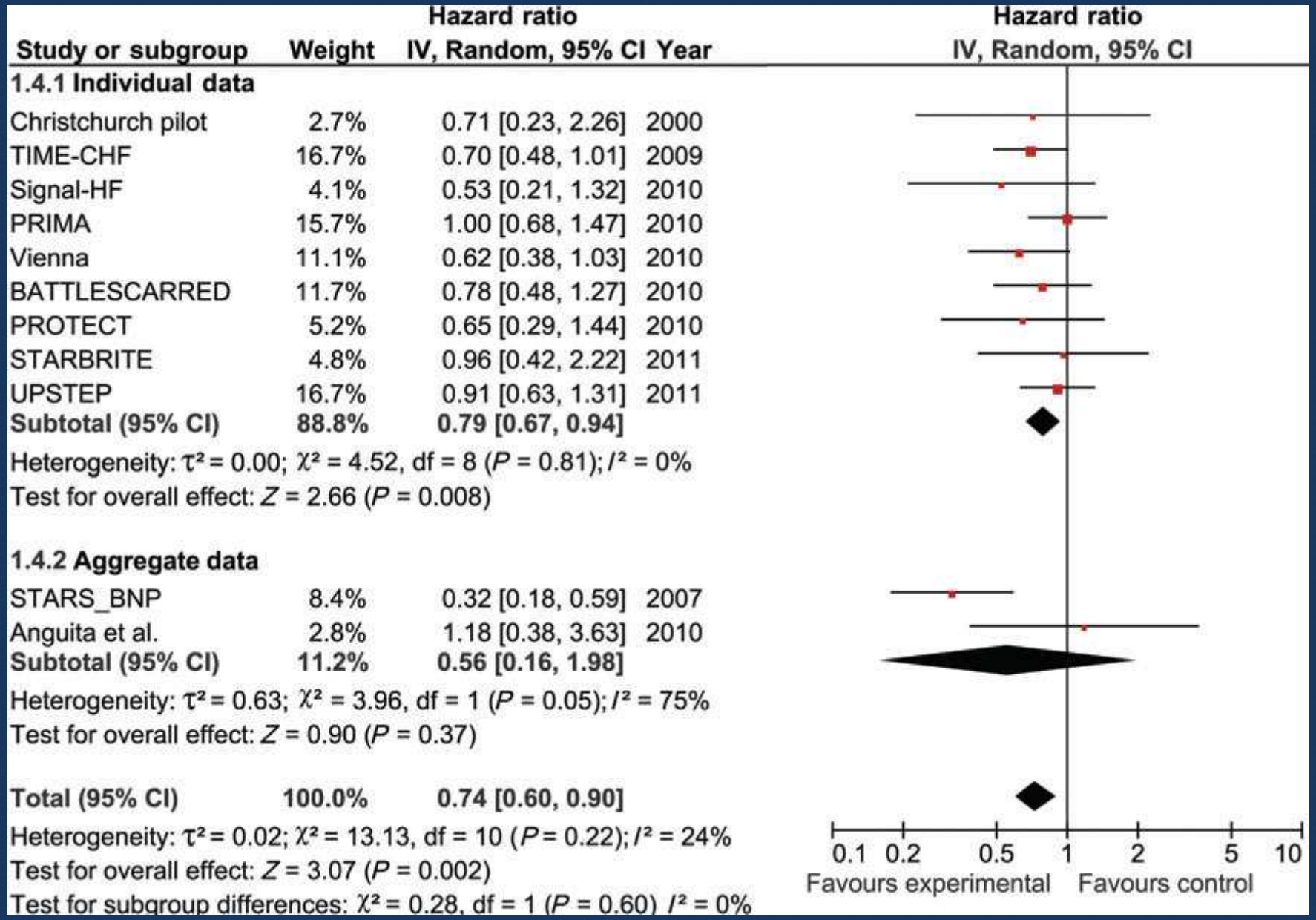
European Heart Journal Advance Access published March 6, 2014

Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis



Kaplan–Meier survival curves for the primary endpoint,
overall mortality: (B) below age 75 years (n ¼ 982), (C) 75 years and above (n ¼ 1018).

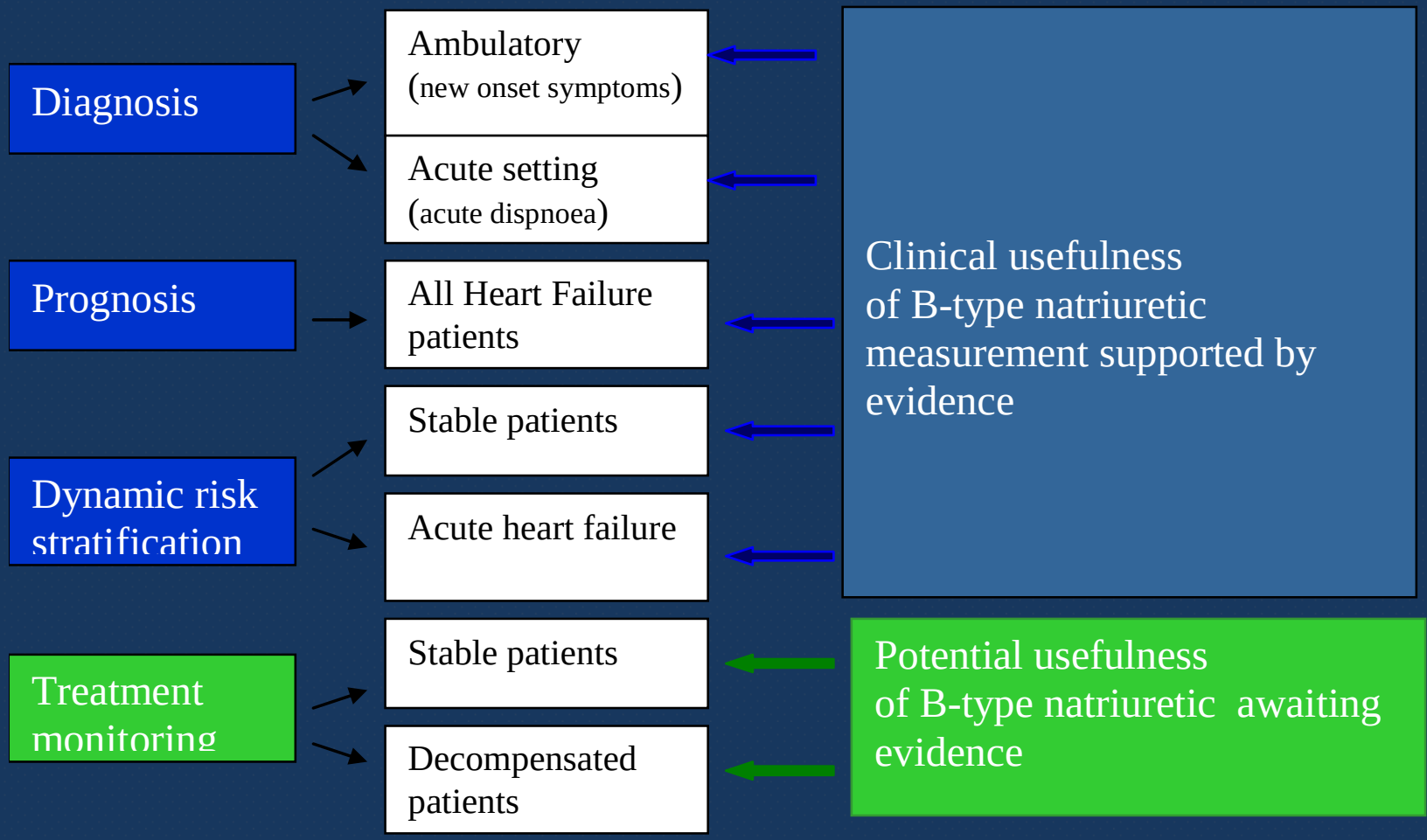
European Heart Journal Advance Access published March 6, 2014



Secondary endpoint, heart failure hospitalization, showing unadjusted individual and mean hazards ratios with 95% ci for nine studies providing individual patient data and two studies providing aggregate data.

European Heart Journal Advance Access published March 6, 2014

Use of b-type natriuretic peptide in clinical practice



Bettencourt P. Heart 2005

BNP guided therapy

- BNP target
- How to
- Age
- Co-morbilities

Biomarker guided therapy key messeges

- 1st A low natriuretic peptide level is needed

Neutral studies (high natriuretic peptide targets, no separation in natriuretic peptide levels between strategies, similar titration of prognostic modifying therapy in both groups)

Positive studies: low target values sought and achieved

- 2nd Biomarker guided care requires effort

Studies with positive outcomes, intervention arms had more visits

- 3rd Adition and uptitration of therapy should be individualized (titrating therapies other than loop diuretics)

In positive studies drugs with proven prognostic efficacy were uptitrated to a greater extent in the biomarker guided groups

- 4th Not all patients respond to biomarker guided care

Older patients appear to benefit less from biomarker guided care (TIME-CHF, BATLLESCARRED); more comorbidities, more frequent and severe intolerances to therapy

Concept of non-response/resistence to natriuretic peptide lowering (UPSTEP)

BNP guided therapy in Heart Failure

Pilot study - ***Troughton RW – NZ***

STARS BNP – Jourdain – France

STARBRITE – Shah – USA

Battlescarred – Ricahards AM – NZ

TIME-CHF – Brunner-la-Rocca – Sw

Protec – Januzzi J- USA

Upstep - Sewden

Biomarkers in Acute HF

Natriuretic peptides

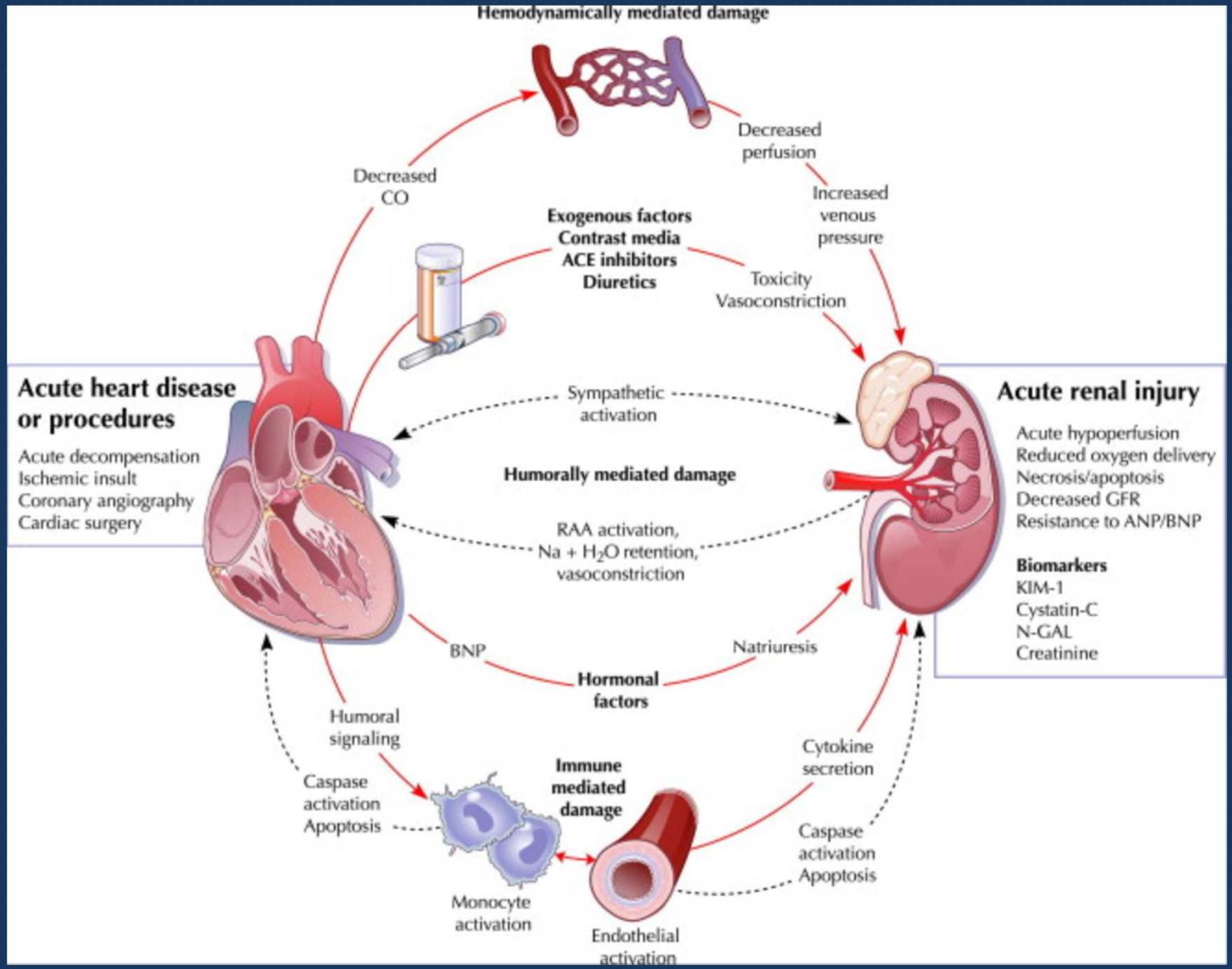
Diagnosis – co-morbilities

- Procalcitonin
- NGAL

Prognosis

- Troponin T and I
- Galectin 3
- ST2
- OPG
- NGAL
- Cystatin C
- …..

Cardiorenal Syndrome



Neutrophil Gelatinase-Associated Lipocalin in the Diagnosis of Type 1 Cardio-Renal Syndrome in the General Ward

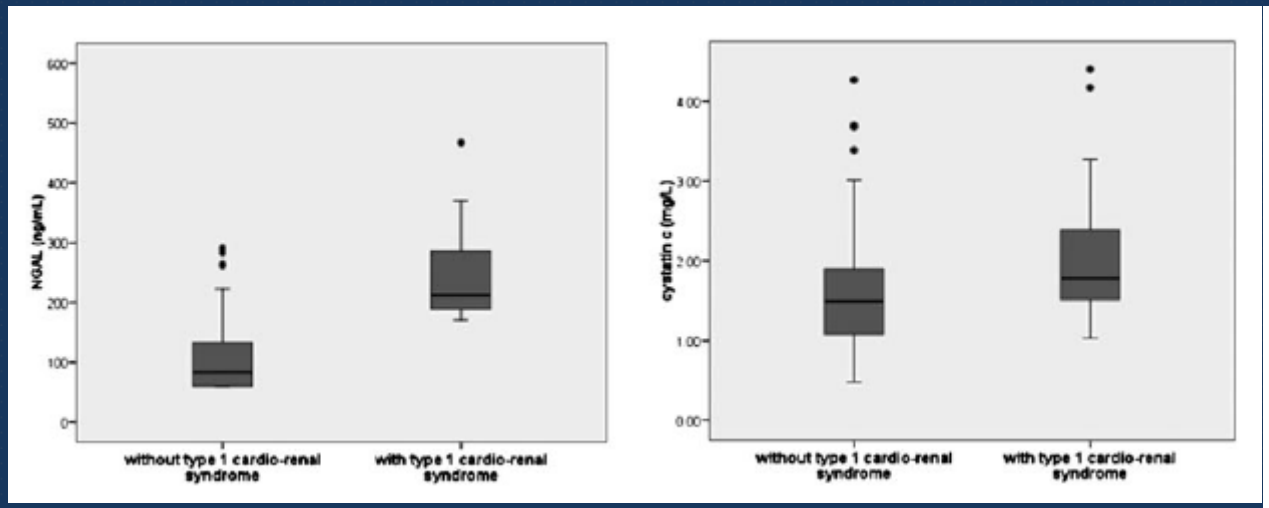


Figure 1. | Depicted are two boxplots. On the left are NGAL value distributions in patients with and without type 1 cardio-renal syndrome within 48 to 72 hours. On the right, the same distribution in shown for cystatin C.

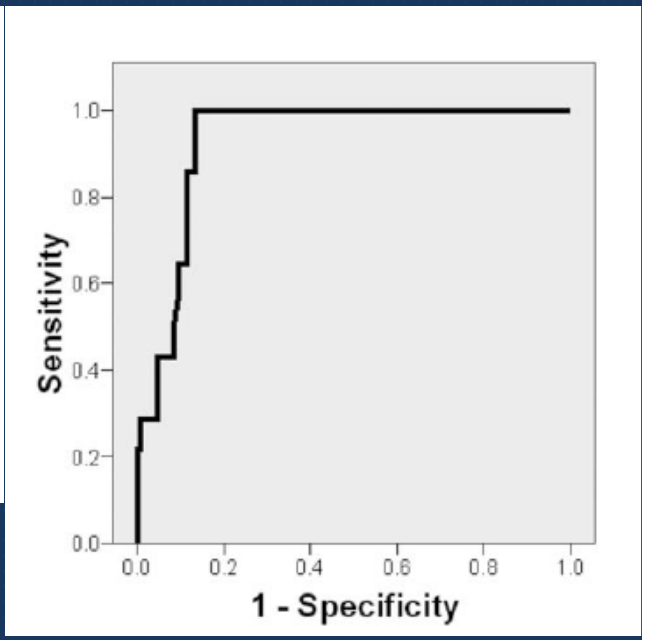


Figure 2. | ROC curve of NGAL for type 1 cardio-renal syndrome prediction. AUC = 0.93 (88 to 98), $P < 0.001$.

Margarida Alvelos,†† Rodrigo Pimentel,*† Elika Pinho,*† André Gomes,*† Patrícia Lourenço,*† Maria José Teles,‡ Pedro Almeida,§ João Tiago Guimarães,‡‖ and Paulo Bettencourt*†*

Clin J Am Soc Nephrol 6: 476–481, 2011.

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Prognostic value of neutrophil gelatinase-associated lipocalin in acute heart failure ☆

Margarida Alvelos [a,b,*], Patrícia Lourenço [a,b], Carla Dias [a,b], Marta Amorim [a,b], Joana Rema [a,b], Ana Bento Leite [a,b], João Tiago Guimarães [c,d], Pedro Almeida [e], Paulo Bettencourt [a,b]

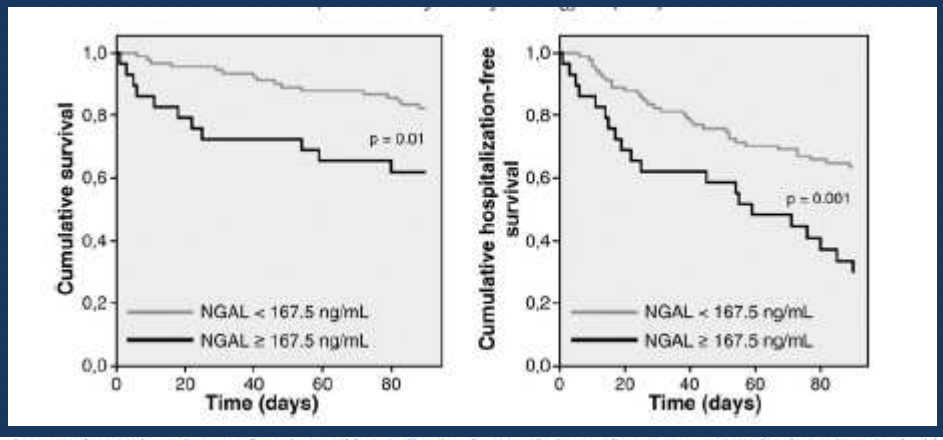


Fig. 1. Kaplan–Meier estimates of survival and hospitalization-free survival according to serum NGAL levels. Patients in the highest NGAL quartile have a significantly worse short term prognosis than the ones in the other quartiles.

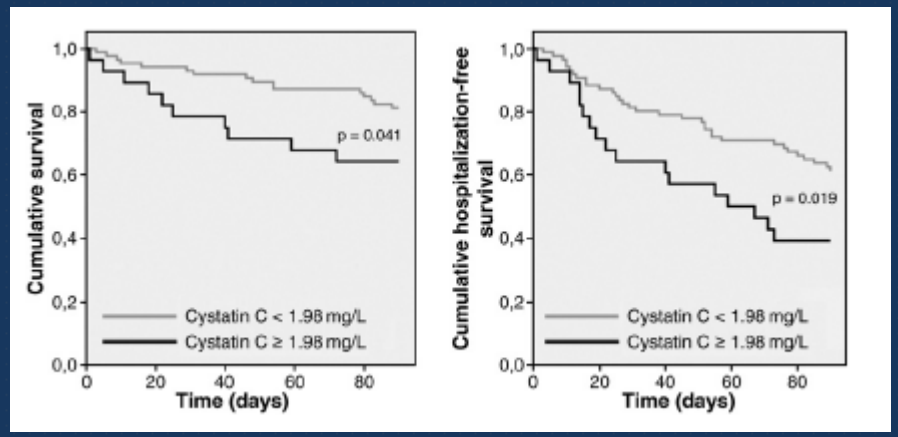


Fig. 2. Kaplan–Meier estimates of survival and hospitalization-free survival according to serum cystatin C levels. Patients in the highest cystatin C quartile have a significantly worse short term prognosis than the ones in the other quartiles.

Multivariate model for prediction of death or hospitalization.

	Death or hospitalization	
	HR (95% CI)	p value
BNP, per 100 pg/mL	1.014 (1.005–1.022)	0.002
NGAL, 75th percentile vs. others	2.860 (1.593–5.136)	<0.001
Age, per year		0.153
Diabetes mellitus		0.061
GFR, per mL/min		0.360
CRS1		0.257
Cystatin C, 75th percentile vs. others		0.621

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European Journal of Internal Medicine

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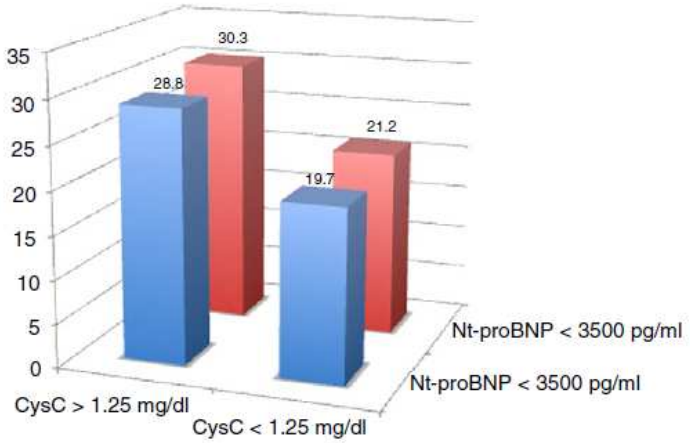
Original article

Prognostic value of serum cystatin C and N-terminal pro b-type natriuretic peptide in patients with acute heart failure

Juan Ignacio Pérez-Calvo [a,b,*], Francisco José Ruiz-Ruiz [a], Francisco Javier Carrasco-Sánchez [c], José Luis Morales-Rull [d], Sergio Manzano-Fernández [e], Luis Galisteo-Almeda [f], Domingo Pascual-Figal [e]



	CysC < 1.25 mg/dl	CysC > 1.25 mg/dl	p
NT-proBNP < 3500 pg/ml	19.7	28.8	0.0002
NT-proBNP > 3500 pg/ml	21.2	30.3	0.2

Mortality rates are expressed as percentages

Fig. 2. All-cause mortality rates according to baseline CysC and NT-proBNP concentrations. Mortality rates are expressed as percentages.

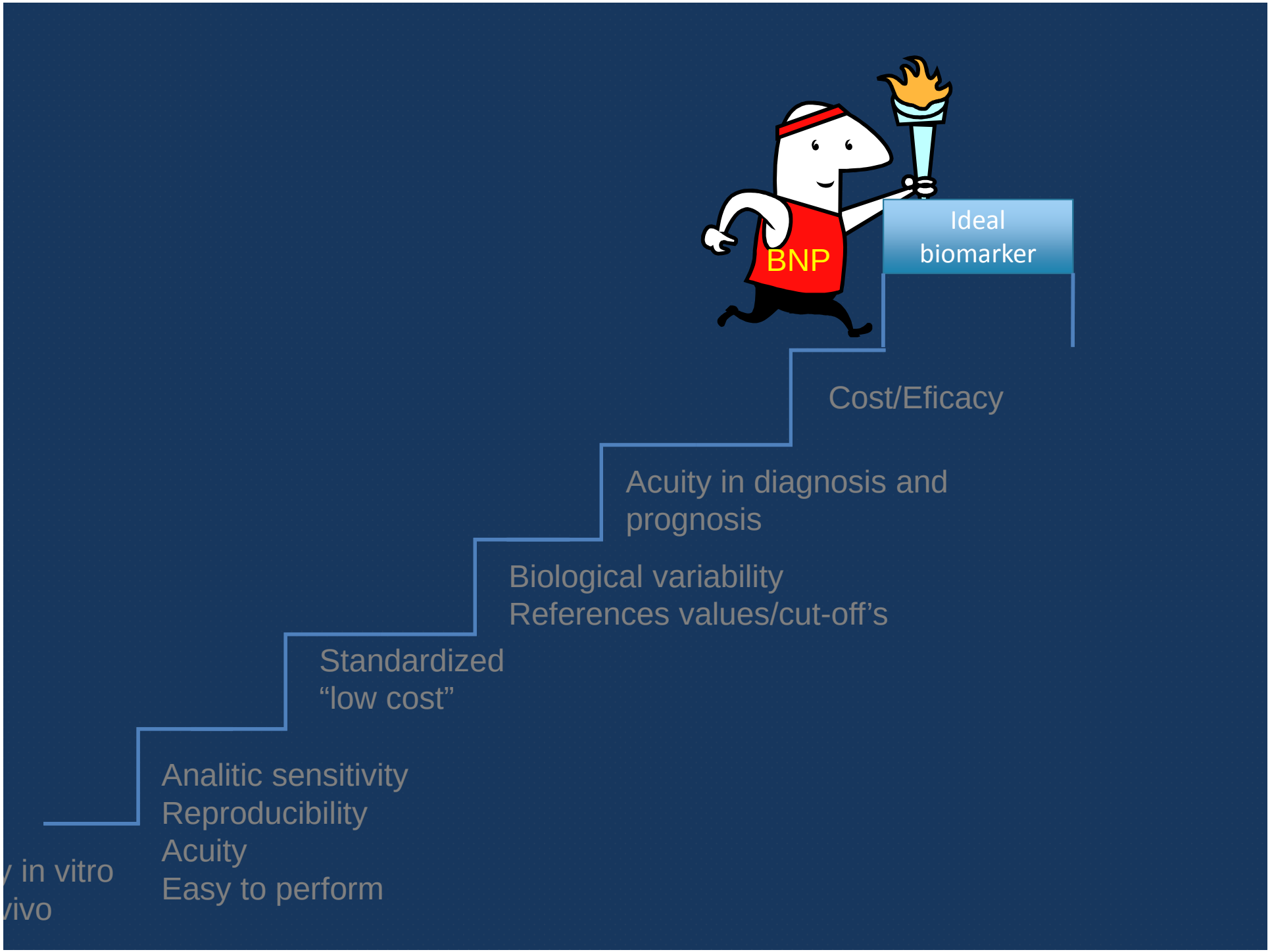
Hazard ratio for all-cause mortality, after multivariable's Cox regression analysis. Data were adjusted for the following variables.

Variable	Hazard ratio (95% CI)	*p*
Gender (male)	1.05 (0.61–1.84)	ns
NT-proBNP (pg/ml)	1.34 (0.72–2.41)	ns
Urea (mg/dl)	0.92 (0.90–1.03)	ns
Cystatin (mg(dl)	2.86 (1.72–4.77)	<0.001
MDRD (ml/min)	1.14 (0.97–1.19)	ns
Hemoglobin (g/dl)	0.91 (0.85–1.11)	ns
Cholesterol (mg/dl)	0.90 (0.83–0.95)	0.01
HFpEF (%)	1.92 (1.12–3.73)	0.04
NYHA (III–IV) (%)	1.25 (0.69–2.42)	ns
Atrial fibrillation (%)	1.13 (0.61–1.97)	ns
Diabetes (%)	1.21 (0.54–1.64)	ns

Biomarkers in Heart Failure

- Sensitive / specific for HF
- Reproduced and standartized across clinical lab.
- Easy to perform

- Variations in biomarkers associated with
    - Variations in clinical status
    - Related to interventions
    - Variations in prognosis


BNP
Ideal biomarker
Cost/Eficacy
Acuity in diagnosis and prognosis
Biological variability
References values/cut-off's
Standardized
"low cost"
Analitic sensitivity
Reproducibility
Acuity
Easy to perform
y in vitro
vivo

Biomarkers evaluated in the Acute HF setting

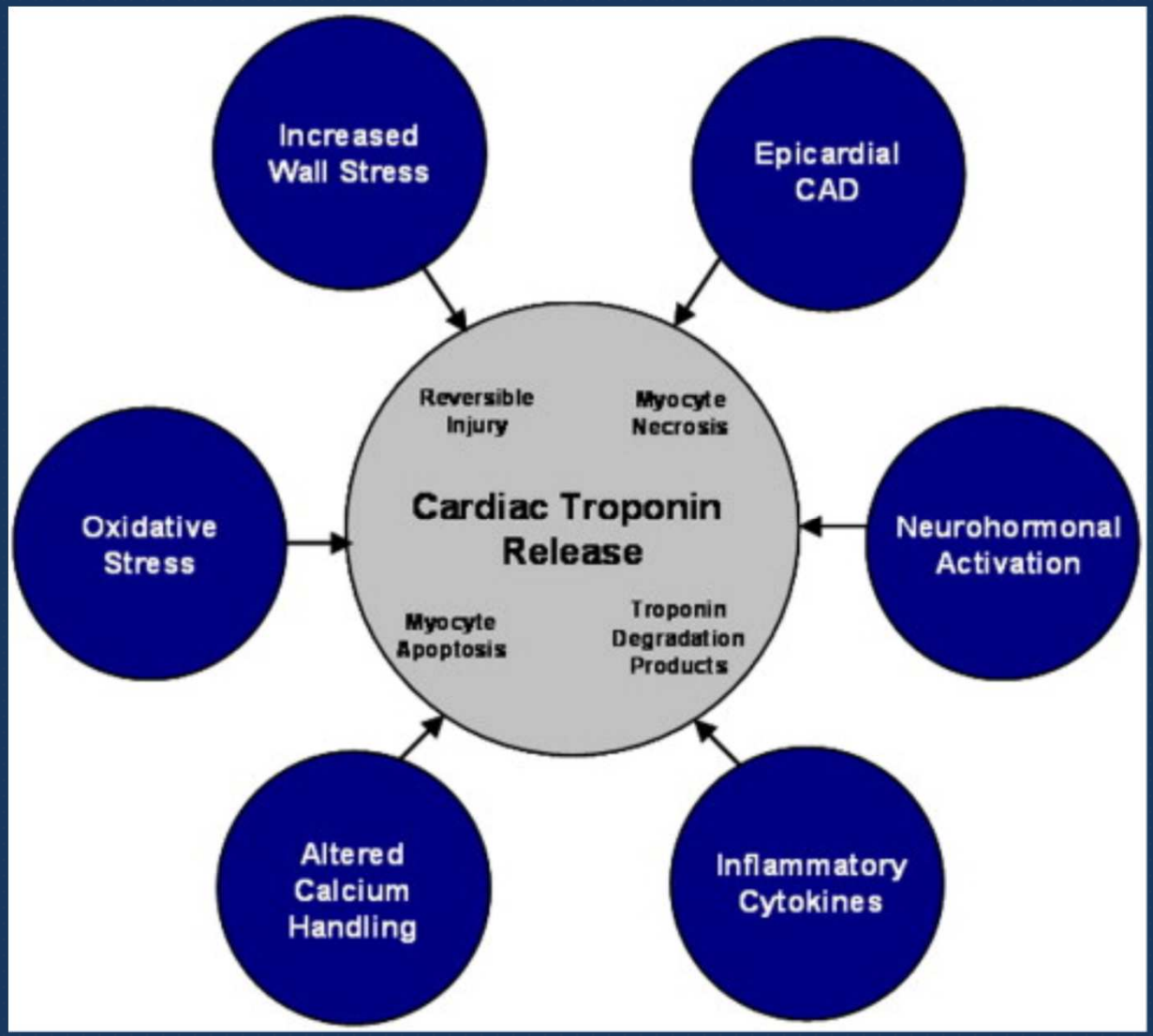
Natriuretic peptides

Diagnosis

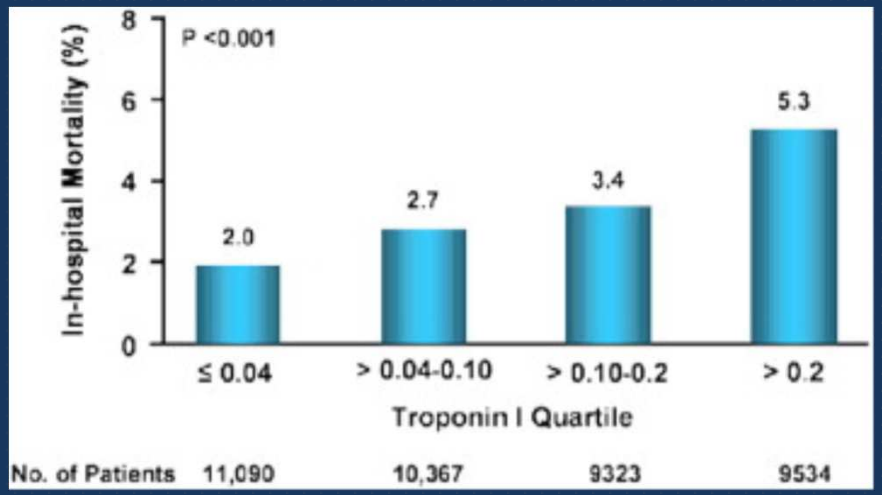
- Procalcitonin
- NGAL

Prognosis

- Troponin T and I
- ST2
- Galectin 3
- Osteoprogesterin
- NGAL
- Cystatin C
- ….


Increased Wall Stress
Epicardial CAD
Reversible Injury
Myocyte Necrosis
Cardiac Troponin Release
Oxidative Stress
Neurohormonal Activation
Myocyte Apoptosis
Troponin Degradation Products
Altered Calcium Handling
Inflammatory Cytokines

Troponin Elevation in Heart Failure: Title and subTitle BreakPrevalence, Mechanisms, and Clinical Implications



Inpatient mortality in patients with acute heart failure by troponin I quartile in the ADHERE (Acute Decompensated Heart Failure National Registry) study.

J Am Coll Cardiol. 2010;56(14):1071-1078. doi:10.1016/j.jacc.2010.06.016

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doi:10.1016/j.jacc.2008.07.042

Biomarkers

Characteristics of the Novel Interleukin Family Biomarker ST2 in Patients With Acute Heart Failure

Shafiq U. Rehman, MD,* Thomas Mueller, MD,† James L. Januzzi, Jr, MD, FACC*

Boston, Massachusetts; and Linz, Austria

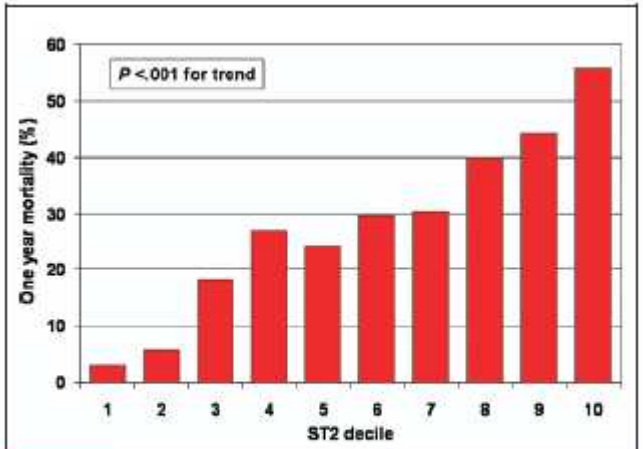

Figure 2 ST2 Concentrations and Mortality Rates

Frequency of mortality at 1 year as a function of ST2 decile.

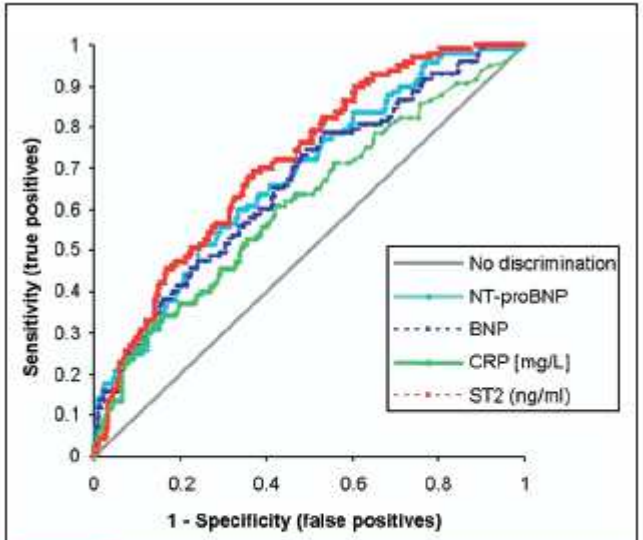

Figure 3 ST2 Compared With Conventional Cardiac Biomarkers for Predicting Death

Receiver-operator characteristic curve analyses comparing ST2 to B-type natriuretic peptide (BNP), amino terminal B-type natriuretic peptide (NT-proBNP), and C-reactive protein (CRP) for predicting death at 1 year after acute heart failure.

The TNF alpha superfamily

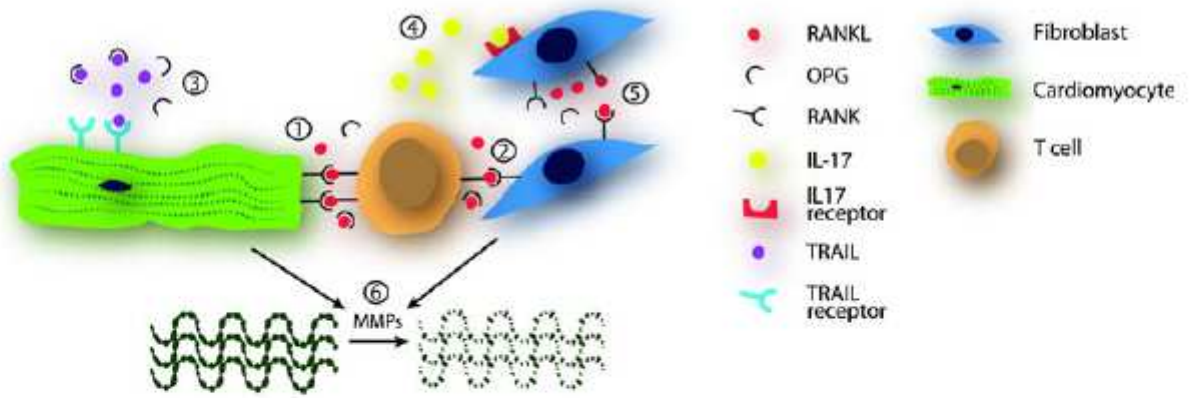

Fig. 1 Proposed model for the effects of the OPG/RANKL/RANK axis in HF. Activated infiltrating T cells with increased surface or soluble RANKL may stimulate the receptor RANK on the surface of (1) cardiomyocytes or (2) fibroblasts present in myocardial tissue. Cardiomyocytes and fibroblasts produce OPG, which may block these effects by binding membrane-bound or soluble RANKL and thereby binding to RANK. (3) OPG also may interact with TRAIL and potentially protect cardiomyocytes from TRAIL-induced cell death. (4) Activated T-cells also may produce the inflammatory cytokine IL-17 that can stimulate the production of OPG/RANKL/RANK in fibroblasts and in turn stimulate neighboring fibroblast comprising (5) an autocrine/paracrine loop. (6) Upon stimulation with RANKL, both cardiomyocytes and fibroblasts may produce MMPs that may regulate collagen degradation. Disruption of this collagen network may lead to myocyte slippage, ventricular dilation, and progressive contractile dysfunction. *OPG* osteoprotegerin; *RANK(L)* receptor activator of nuclear factor-κB (ligand); *HF* heart failure; *TRAIL* TNF-related apoptosis-inducing ligand; *IL* interleukin; *MMPs* matrix metalloproteinases

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Biomarkers

Prognostic Value of Osteoprotegerin in Heart Failure After Acute Myocardial Infarction

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Oslo, Baeum, Nordbyhagen, and Stavanger, Norway; and Leicester, United Kingdom

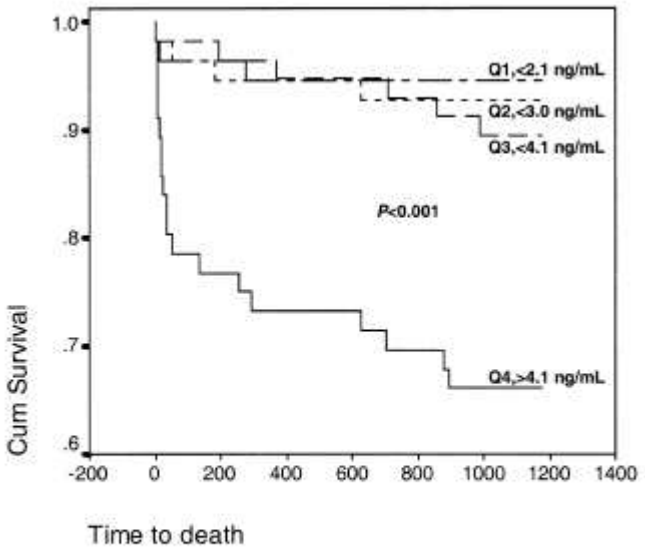


Figure 2. Kaplan-Meier curves showing the cumulative incidence of death during the entire study (median follow-up 27 months), according to the quartiles (Q) of plasma osteoprotegerin at enrollment.

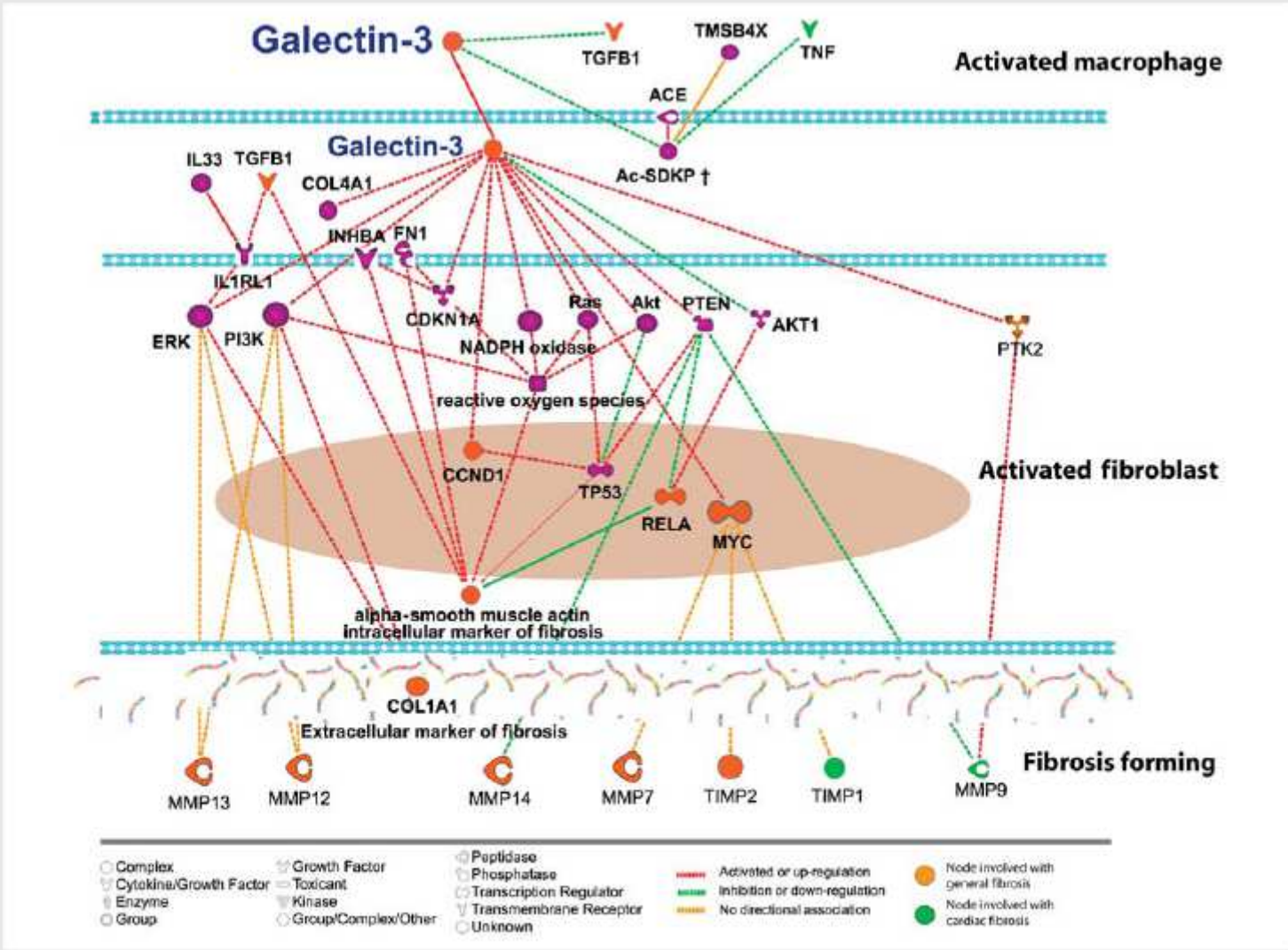


Figure 4 Galectin-3 pathways. The network represents molecular relationships between different gene products. Node shapes indicate the functional class of the gene product, whereas node colours indicate a role in general fibrosis (orange) or cardiac fibrosis (green). Edge colours indicate up-regulation or activation (red), down-regulation or inhibition (green) or involvement without clear directionality (yellow). All relationships are supported by references from the Ingenuity Pathway Knowledge Base or key reference included in this review.[8,12,13,38]

European Journal of Heart Failure (2010) **12**, 826–832
doi:10.1093/eurjhf/hfq091

Galectin-3, cardiac structure and function, and long-term mortality in patients with acutely decompensated heart failure

Ravi V. Shah[1], Annabel A. Chen-Tournoux[1], Michael H. Picard[1], Roland R. J. van Kimmenade[2], and James L. Januzzi[1]*

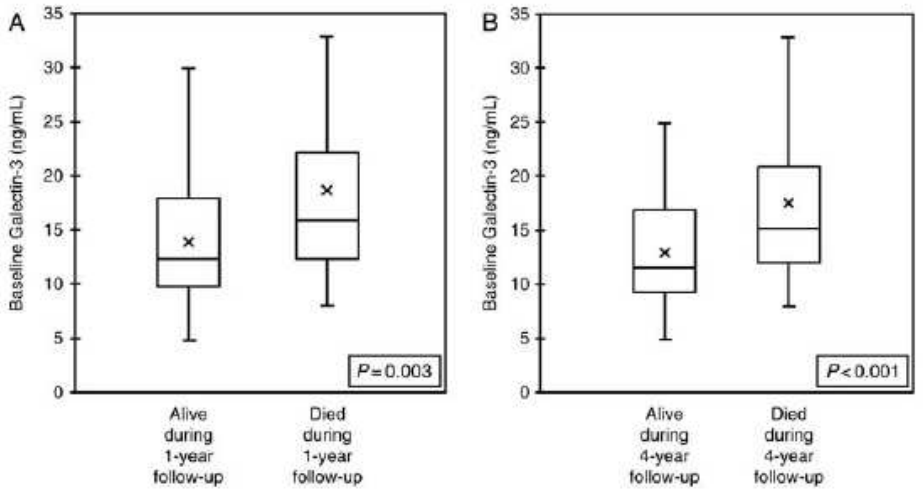


Figure 1 Galectin-3 in patients who died at 1 year (*A*) and 4 years (*B*) in all dyspnoeic patients ($n = 115$).

Table 5 Result of Cox multivariable regression for 4-year mortality in patients ultimately diagnosed with ADHF, including echocardiographic markers of cardiac structure and function[a]

Variable	Hazard ratio (95% CI)	*P*-value
LV end-diastolic dimension	0.81 (0.69–0.95)	0.01
LV end-systolic dimension	1.24 (1.08–1.41)	0.002
LV ejection fraction	1.17 (1.03–1.21)	0.01
RV systolic pressure	1.05 (1.00–1.09)	0.03
Galectin-3	14.5 (3.12–67.6)	0.001

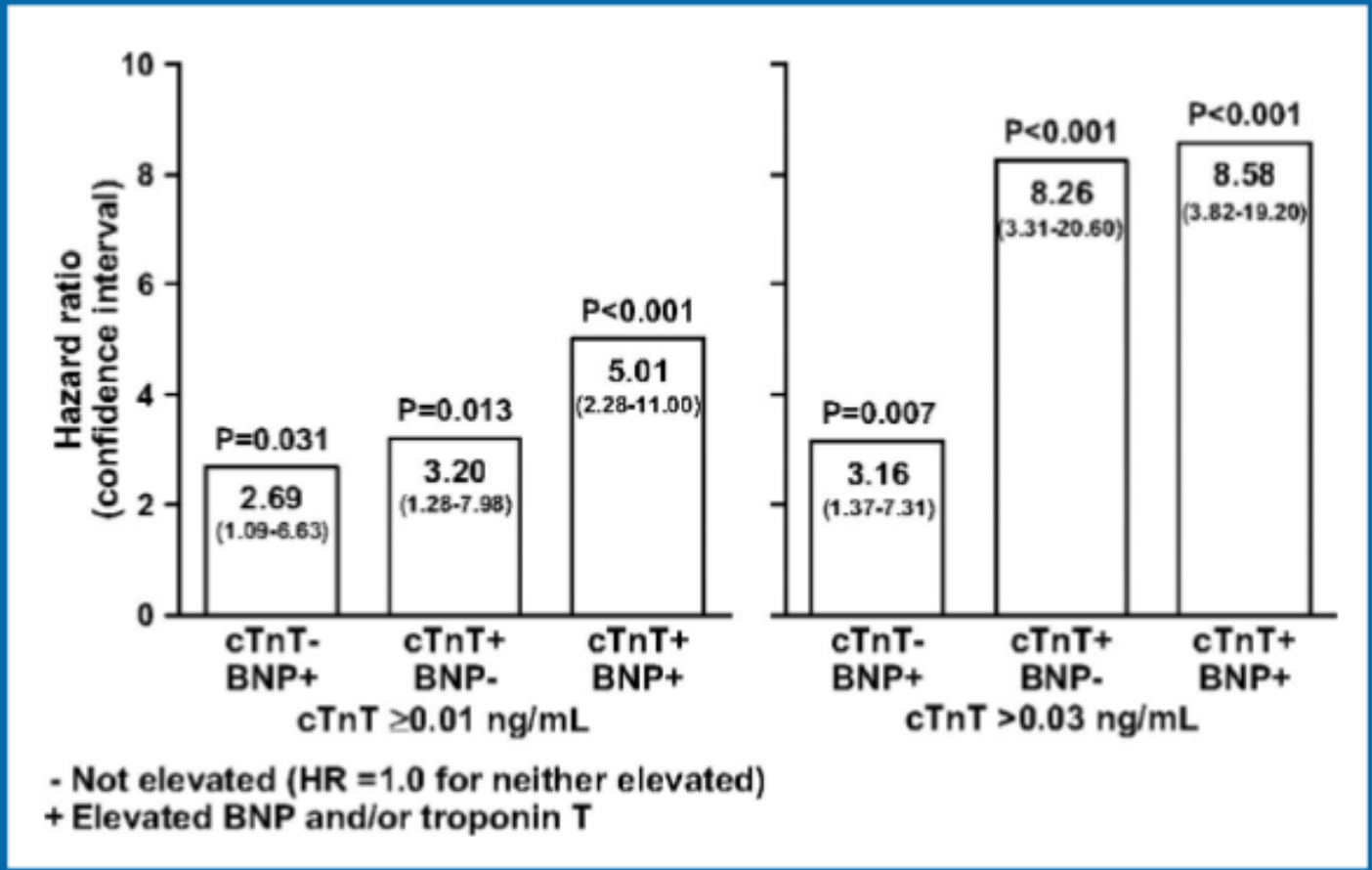
[a]$n = 53$ patients were included in this analysis, all of whom had all covariates listed in text measured. Galectin-3 was treated as a log-transformed continuous variable.

Biomarkers in Acute HF

The future

- Multimarker aproach
- Scores
- Therapy according to risk

Risk Stratification: Multimarker Strategy (Serial)



Shionogi BNP (pg/ml)

Miller et al, *Circulation* 2007

European Journal of Heart Failure (2011) **13**, 718–725
doi:10.1093/eurjhf/hfr047

Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure

Domingo A. Pascual-Figal[1]*, Sergio Manzano-Fernández[1], Miguel Boronat[2], Teresa Casas[2], Iris P. Garrido[1], Juan C. Bonaque[1], Francisco Pastor-Perez[1], Mariano Valdés[1], and James L. Januzzi[3]

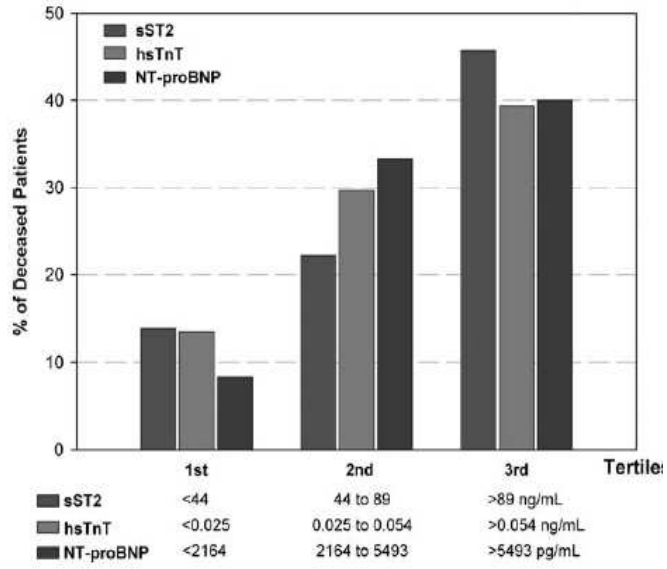


Figure 1 Rates of mortality at 1 year as a function of tertiles of soluble ST2 ($P = 0.003$ for trend), high sensitivity trend), and amino-terminal pro-B type natriuretic peptide ($P = 0.003$ for trend).

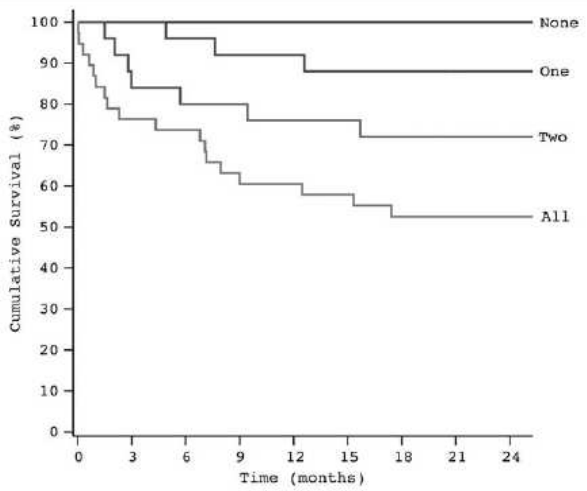


Figure 2 Kaplan–Meier survival curves according to the presence of none ($n = 18$), one ($n = 26$), two ($n = 25$), or three biomarkers ($n = 38$) above optimal cut-off points, as defined in the text.

Biomarkers reflecting remodelling (sST2), myonecrosis (hsTnT), and myocardial stretch (NT-proBNP) provide complementary prognostic information in patients with ADHF. When used together, these novel markers provide superior risk stratification.

Biomarkers in Acute HF

The future

Multimarker aproach

Scores

Therapy according to risk

Protect score

Table 3 PROTECT risk score for 7-day death, worsening HF, or HF rehospitalization

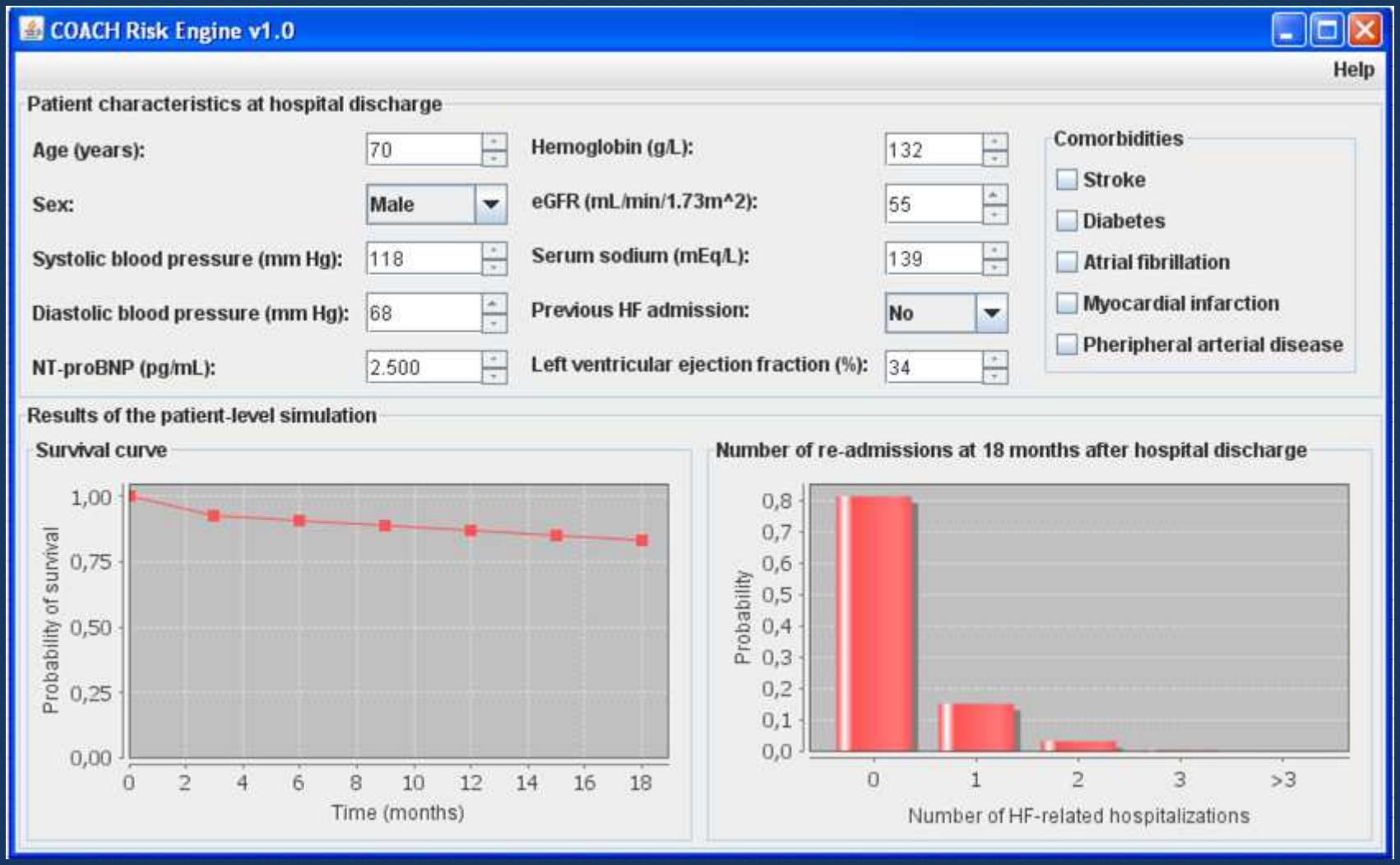
BUN	Points	Albumin	Points
≤8	0	≤2.0	15
>8 and ≤16	8	>2.0 and ≤2.5	13
>16 and ≤32	16	>2.5 and ≤3.0	10
>32 and ≤64	24	>3.0 and ≤3.5	8
>64 and ≤128	32	>3.5 and ≤4.0	5
>128	40	>4.0 and ≤4.5	3
		>4.5	0
Systolic BP		Heart rate	
≤90	12	≤50	0
>90 and ≤100	11	>50 and ≤60	1
>100 and ≤110	9	>60 and ≤70	3
>110 and ≤120	8	>70 and ≤80	4
>120 and ≤130	6	>80 and ≤90	5
>130 and ≤140	5	>90 and ≤100	7
>140 and ≤150	3	>100 and ≤110	8
>150 and ≤160	2	>110 and ≤120	10
>160	0	>120	11
Respiratory rate		Cholesterol	
≤15	0	≤120	7
>15 and ≤20	2	>120 and ≤160	5
>20 and ≤25	4	>160 and ≤200	4
>25 and ≤30	7	>200 and ≤240	2
>30	9	>240	0
Hospitalization for HF in the past year		Diabetes	
No	0	No	0
Yes	3	Yes	3

BP, blood pressure; BUN, blood urea nitrogen; HF, heart failure.

Table 4 Estimated probability of death, worsening heart failure, or heart failure rehospitalization at 7 days on the basis of the PROTECT risk score

Score	Patients	No. (%) of patients with event at 7 days	Estimated probability of event at 7 days (%)
≤ 35	164	6 (3.8)	4.8
36–40	257	16 (6.4)	7.3
41–45	416	41 (10.2)	9.8
46–50	385	50 (13.2)	13.3
51–55	330	63 (19.4)	18.2
>55	314	92 (30.0)	28.7

O'Connor MC *et al.* The PROTECT in-hospital risk model: 7-day outcome in patients hospitalized with acute heart failure and renal dysfunction. *Eur J Heart Fail.* 2012 Apr 25. [Epub ahead of print]



Postmus D *et al*. The COACH risk engine: a multistate model for predicting survival and hospitalization in patients with heart failure. Eur J Heart Fail 2012; 14: 168-75.

A novel discharge risk model for patients admitted for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels

Calculation of our risk score

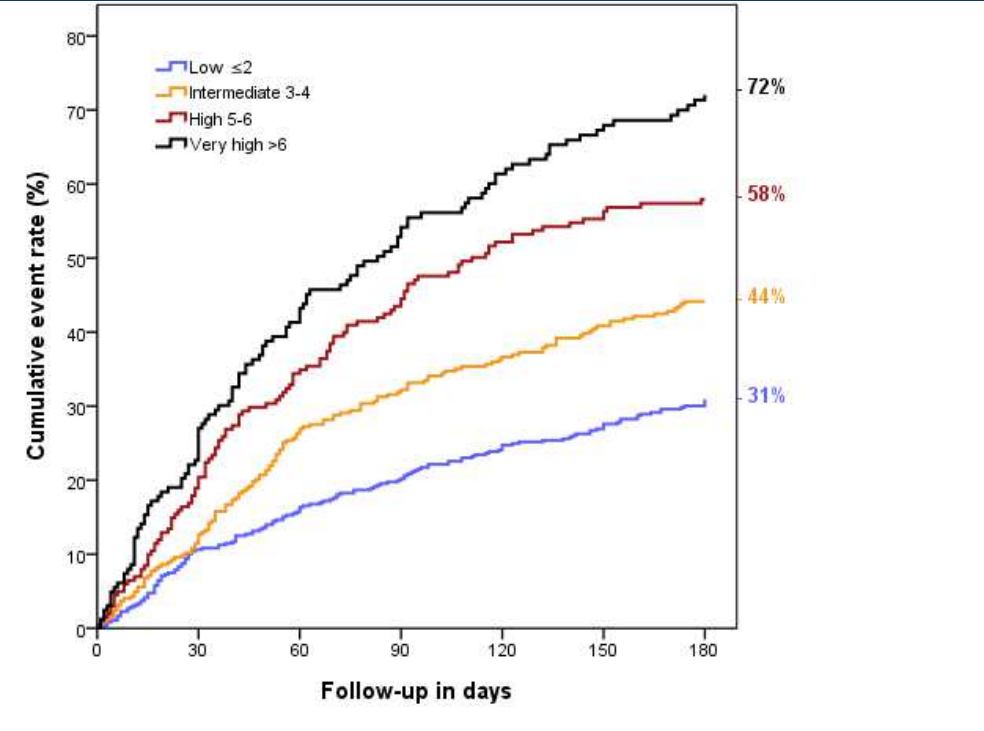
Predictors	Score for 180-day mortality[a]
NT-proBNP reduction, % ≤30	1
NT-proBNP discharge value, pg/ml	
1500-5000	1
5001-15000	3
>15000	6
History of CHF	
Yes	1
Peripheral edema at admission	
Yes	1
SBP at admission, mmHg	
≤115	1
Hyponatremia at admission, mmol/L[b]	
<135	1

Abbreviations: NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; CHF, Congestive Heart Failure; SBP, Systolic Blood Pressure.
[a]Maximum penalty point in our newly developed risk score is equal to 11. [b]Defined as Sodium <135 mmol/l.

Ellan - score

K. Salah, WEM. Kok, LWM. Eurlings, P. Bettencourt, JM. Pimenta, M. Metra,; A. Bayes-Genis, V. Verdiani, L. Bettari, V. Lazzarini, P. Damman, JGP. Tijssen, YM. Pinto.

A novel discharge risk model for patients admitted for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels



Our newly developed Risk Score used to predict 180-day mortality and composite event rate in a cohort of 1301 pts admitted for acute decompensated HF. Event rates increased significantly as the risk core increased (Log Rank p-value <.001).

Effect - score

K. Salah, WEM. Kok, LWM. Eurlings, P. Bettencourt, JM. Pimenta, M. Metra,; A. Bayes-Genis, V. Verdiani, L. Bettari, V. Lazzarini, P. Damman, JGP. Tijssen, YM. Pinto.

Biomarkers in Acute HF

The future

Multimarker aproach

scores

Therapy according to risk

Challenges for the Basis of Practice

Natriuretic Peptide Measurements in Managing Heart Failure

In Theory and in Practice

W.H. Wilson Tang, MD

"Clinicians caring for patients with heart failure are no strangers to ambiguity of clinical presentation and imprecision of diagnostic and monitoring tools…. Anyone who demands the ultimate proof or "evidence" for the clinical utility of natriuretic peptide testing should reflect on what evidence should be demanded for a diagnostic test and whether such standards have been imposed on other clinical tests."

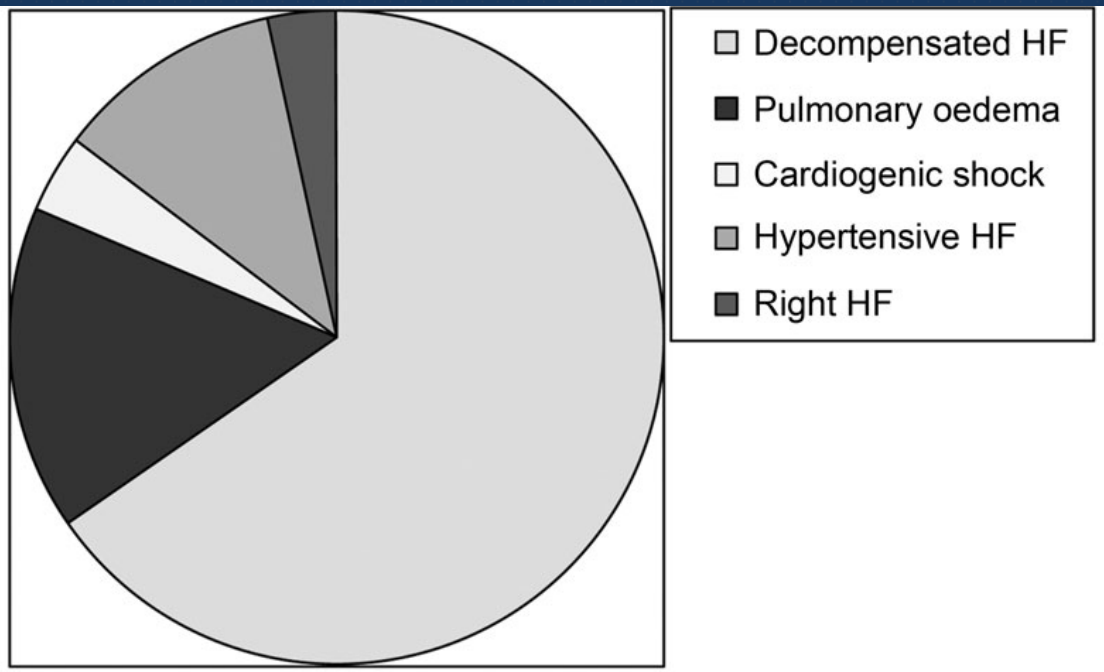
Tang WH, *Circulation Heart Failure* 2009

SÃO JOÃO

HOSPITAL

The potential of natriuretic peptides in the management of HF patients is now obvious

Biomarker guided strategies still have to be validated extensively before coming to daily clinical practice



Classification of AHF %	All	*De novo* AHF	ADCHF
Decompensated HF	65.4	52.4	73.0***
Pulmonary oedema	16.2	26.0	10.4***
Cardiogenic shock	3.9	6.8	2.2***
Hypertensive HF	11.4	11.4	11.3
Right HF	3.2	3.4	3.0

Nieminen M *et al*. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006; 27: 2725–36.

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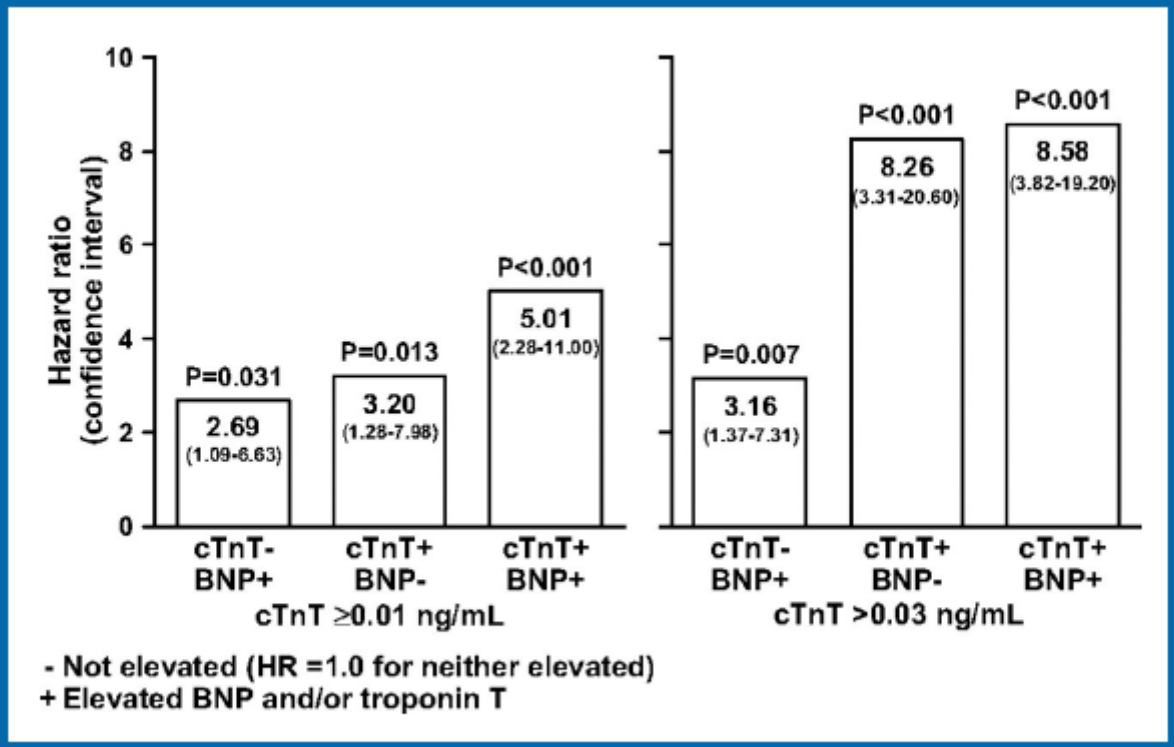


Cleveland Clinic

Miller et al. Circulation 2007

SÃO JOÃO HOSPITAL

Standard laboratory markers:

Sodium, Blood urea nitrogen, Serum creatinine, Hemoglobin, Leukocyte count, Total lymphocyte count, Serum albumin, Total bilirubin, Uric acid, Red blood cell distribution width.

Neurohormones:

Catecholamines (norepinephrine, epinephrine), Renin, ACE activity, angiotensin II, and aldosterone, Natriuretic peptides (ANP, BNP, C-type, N-terminal proANP, N-terminal proBNP, mid-regional pro-ANP), Endothelin-1, Vasopressin/copeptin, Cardiotrophin-1, Novel vasodilators (adrenomedullin and mid-regional pro-adrenomedullin, urotensin-II, urocortin)

Inflammatory biomarkers:

High-sensitivity C-reactive protein, Myeloperoxidase, Galectin-3, Fatty acid binding protein, Soluble ST2 receptor, Tumor necrosis factor-alpha and receptors, Interleukin-6 (IL-6), Growth differentiation factor 15 (GDF-15), Osteopontin

Metabolic biomarkers:

Leptin, Adiponectin, Ghrelin, Apelin, Insulin-like growth factor-1 (IGF-1)

Other miscellaneous biomarkers

G-protein coupled receptor kinase-2 (GRK-2), Cardiac troponin I or troponin T, Myotrophin

Biomarcadores na IC: futuro?

- Evidência publicada ---------- prática clínica
- Pressupostos teóricos ≠ evidência clínica
- Estratégia: Abordagem MULTIMARCADORES

Natriuretic peptides in acute HF

B-type natriuretic peptide give significant prognostic information in acute HF episodes

We should aim for a 30% reduction in NT-proBNP levels together with clinical improvement before discharge of acute HF patients.

Para além do BNP – que BM?

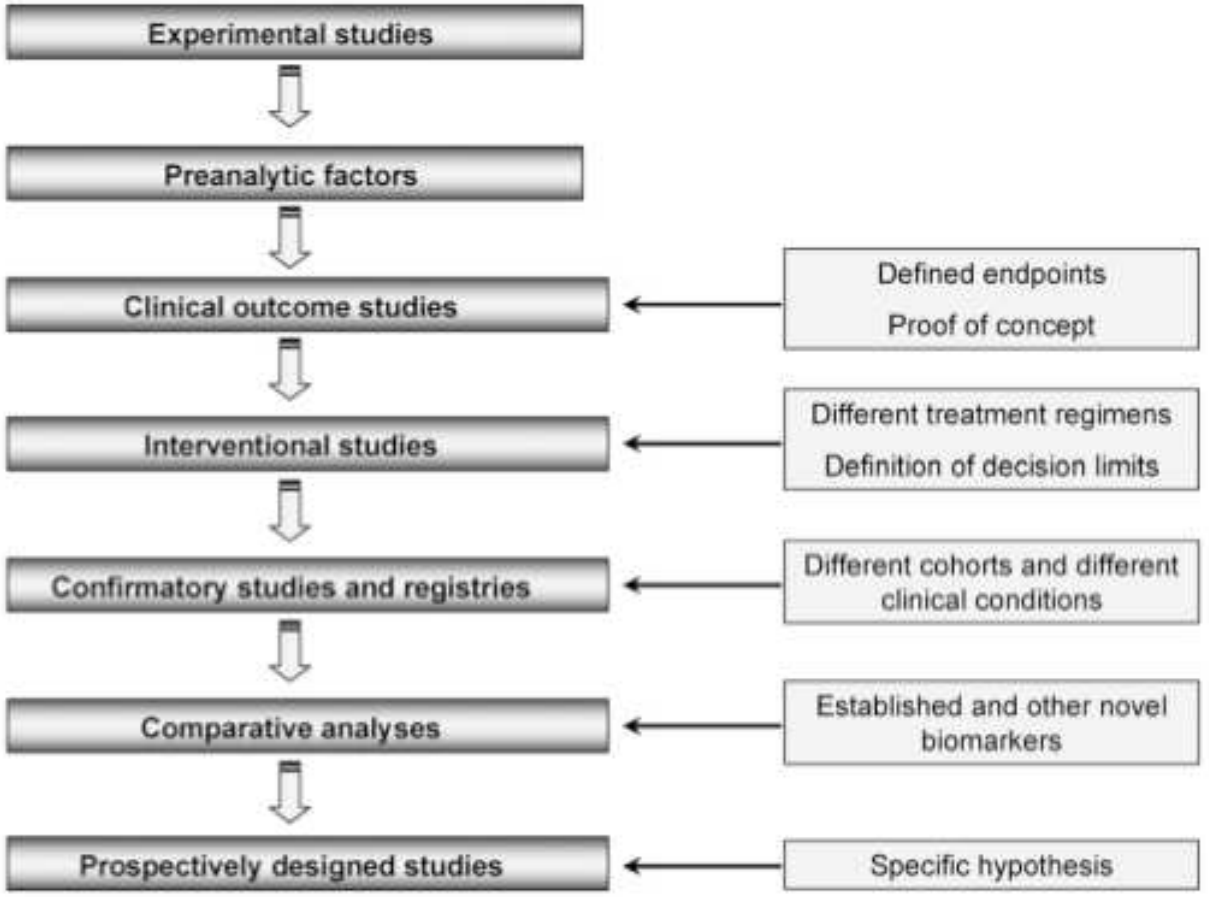


Figure 1 Roadmap for the evaluation of novel biomarkers.

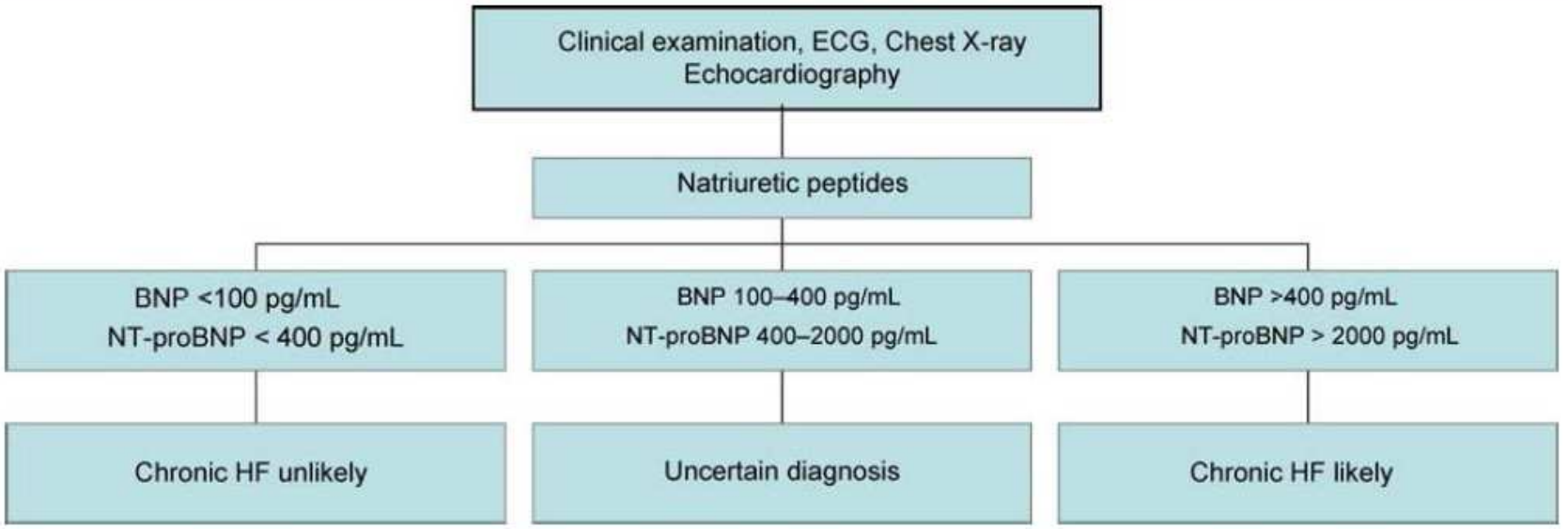


Figure 1 Flow chart for the diagnosis of HF with natriuretic peptides in untreated patients with symptoms suggestive of HF.

Giannessi D. Multimarker…

- Catecholamines
- Renin-angiotensin-aldosterone
- Endothelin
- Natriuretic peptides
- Inflammation markers
- Cardiac injury markers
- Associated disease markers
- Novel markers
- Transcriptomic markers

- Prediction HF incidence
- Diagnosis
- HF risk stratification
- Prognosis
- HF patient management
- Response to therapy

The choice of the biomarker combination is the clue for the performance of the multimarker strategy.

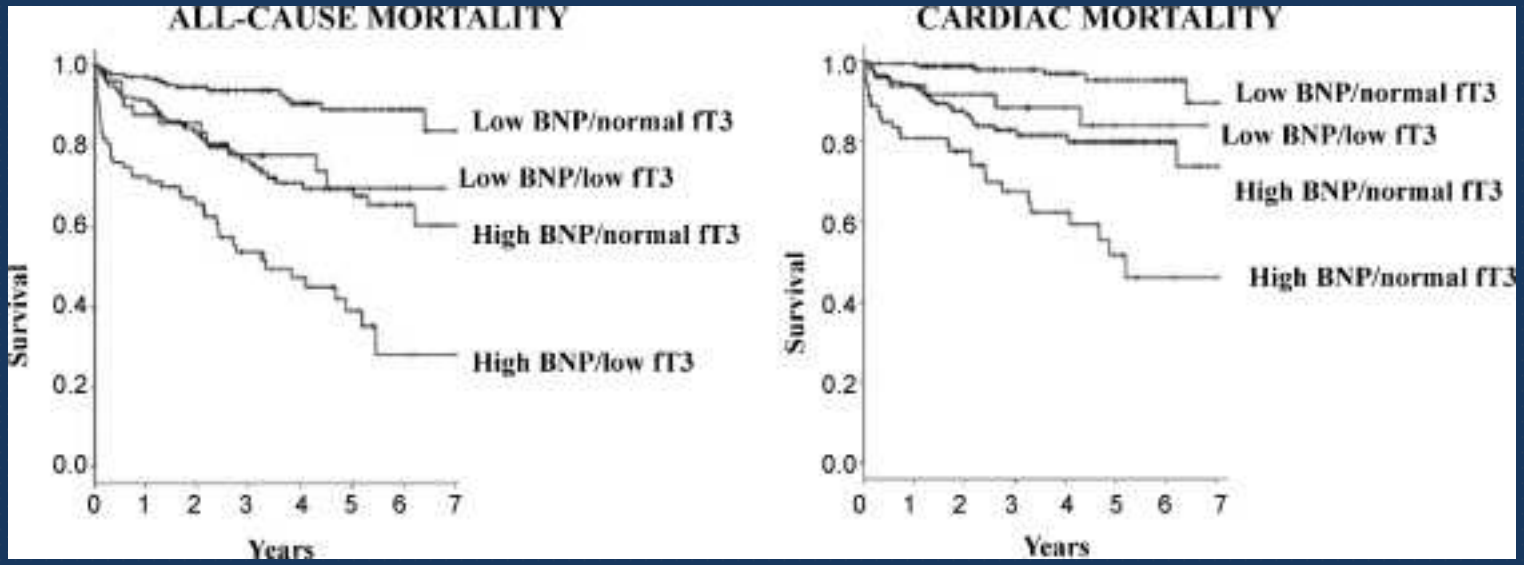


Fig. 5 Kaplan?Meier survival curves for all-cause (left) and cardiac (right) mortality in 4 sub-groups identified according to cut-off values: 2.1<ce:hsp sp="0.25"/> ng/L for fT3, and 165<ce:hsp sp="0.25"/> ng/L for BNP (168<ce:hsp sp="0.25"/> ng...

Daniela Giannessi

Multimarker approach for heart failure management: Perspectives and limitations

Pharmacological Research Volume 64, Issue 1 2011 11 - 24

http://dx.doi.org/10.1016/j.phrs.2011.03.006

Novel biomarkers of heart failure, which are all systemically derived

Table 2 | Novel biomarkers of heart failure, which are all systemically derived

Biomarker	Function
Midregional fragment of proANP	Midregional sequence of the inactive ANP precursor; active ANP stimulates vasodilation, natriuresis, and attenuates of renin–angiotensin–aldosterone system
Midregional fragment of proadrenomedullin	Midregional sequence of the inactive adrenomedullin precursor; active adrenomedullin stimulates vasodilation, inotropy and natriuresis
Copeptin	Inactive cleaved product of the precursor to Arg-vasopressin, vasopressin-neurophysin 2-copeptin; active Arg-vasopressin stimulates renal absorption of water, osmoregulation and cardiovascular homeostasis
Protein ST2	Attenuation of proinflammatory cytokines (IL-6 and IL-12)
Galectin-3	Cell migration and cell–cell interaction
Growth differentiation factor-15	Cardiomyocyte protection via attenuation of apoptosis, hypertrophy and remodeling

Abbreviations: ANP, atrial natriuretic peptide (also known as atrial natriuretic factor); IL, interleukin.

de Couto, G. *et al.* (2010) Early detection of myocardial dysfunction and heart failure
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2010.51

nature REVIEWS CARDIOLOGY

Table IV. Inhospital outcomes over 12 quarters, 2002 to 2004

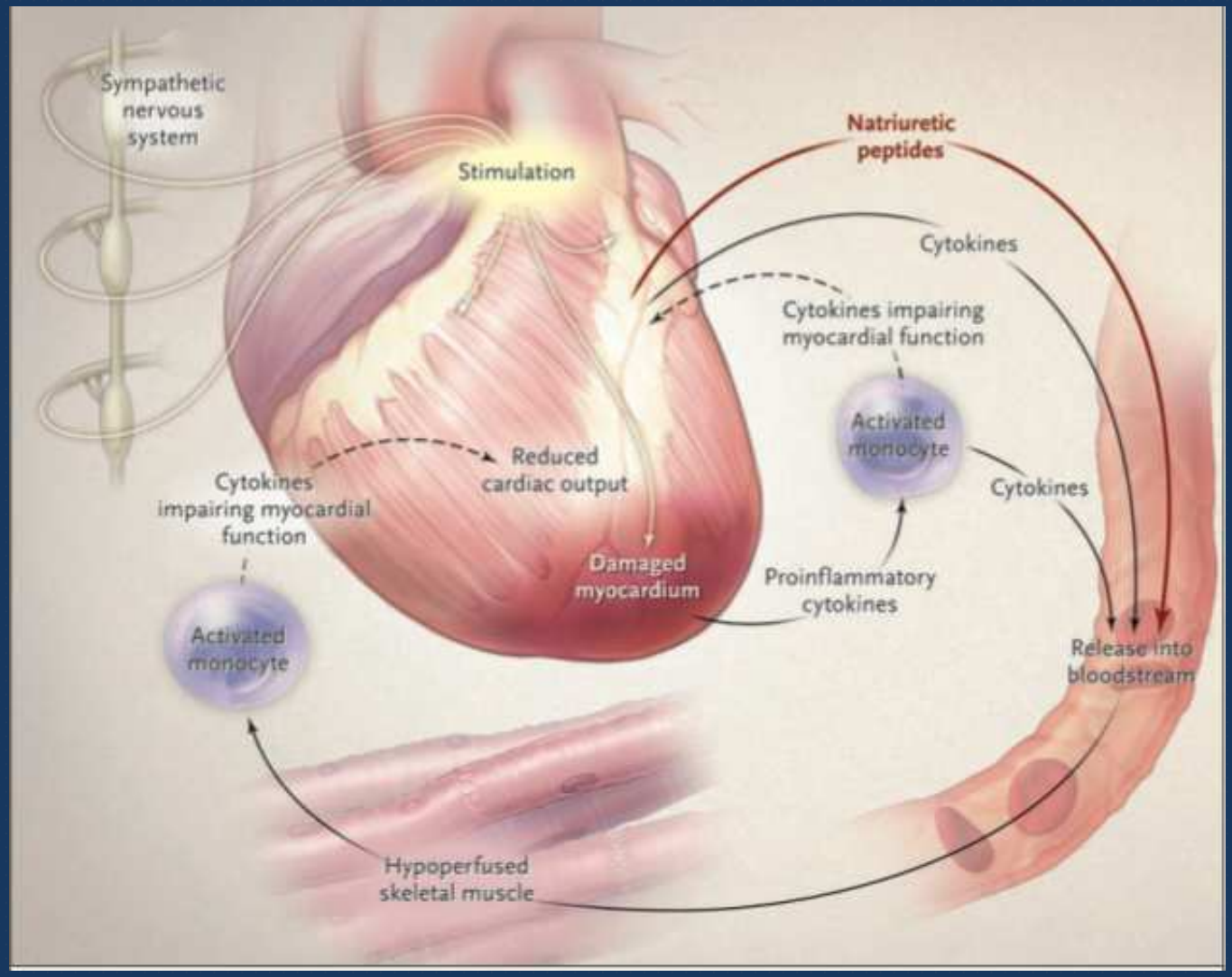
	Q1	Q12	*P*
Outcomes			
Inhospital mortality, n (%)	372 (4.5)	303 (3.2)	<.0001
Mechanical ventilation, n (%)	439 (5.3)	325 (3.4)	<.0001
ICU admissions, n (%)	1555 (18.9)	1460 (15.2)	<.0001
ICU/CCU, Q1 (median) Q3	1.4 (2.8) 5.0	1.3 (2.3) 4.1	.0002
Total LOS, Q1 (median) Q3	2.9 (4.7) 7.7	2.8 (4.1) 6.7	<.0001

CCU, Cardiac care unit.

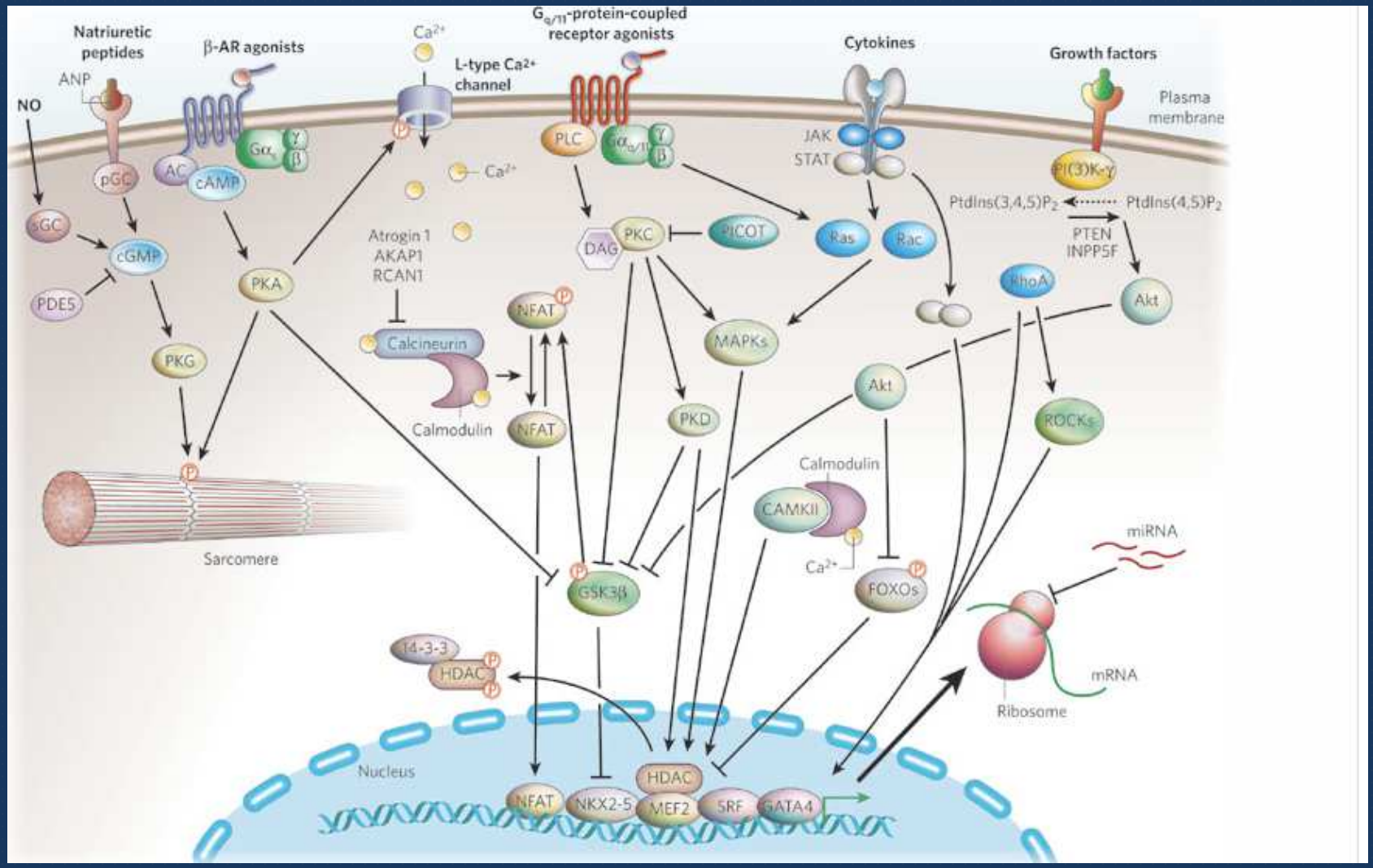
Fonarow G *et al*. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations,2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2007;153:1021-8-

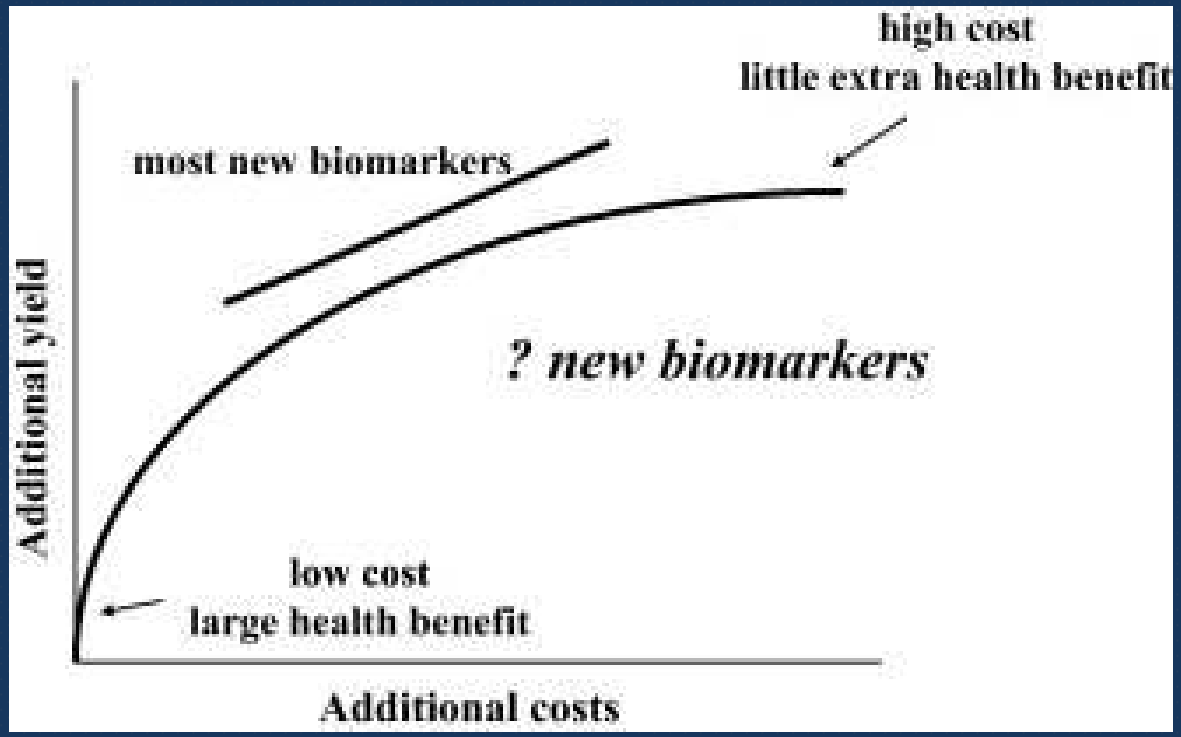
SÃO JOÃO
HOSPITAL

The Cytokine Hypothesis of Heart Failure



Braunwald, NEJM 2008


Natriuretic peptides
ANP
NO
β-AR agonists
Ca2+
L-type Ca2+ channel
Gq/11-protein-coupled receptor agonists
Cytokines
Growth factors
Plasma membrane
pGC
sGC
cGMP
PDE5
PKG
AC
cAMP
Gαs
γ
β
PKA
Ca2+
Atrogin 1
AKAP1
RCAN1
Calcineurin
Calmodulin
NFAT
NFAT
PLC
Gαq/11
DAG
PKC
PICOT
MAPKs
PKD
JAK
STAT
Ras
Rac
PI(3)K-γ
PtdIns(3,4,5)P2
PtdIns(4,5)P2
PTEN
INPP5F
RhoA
Akt
Akt
ROCKs
Calmodulin
CAMKII
Ca2+
FOXOs
Sarcomere
GSK3β
14-3-3
HDAC
HDAC
NFAT
NKX2-5
MEF2
SRF
GATA4
Nucleus
miRNA
mRNA
Ribosome



Health outcome (yield) as a function of the cost. For any new intervention it will need to evaluate where it falls on the curve of additional yield in terms of health benefit versus additional cost. <ce:source> Modified from Cowie <ce:cro...

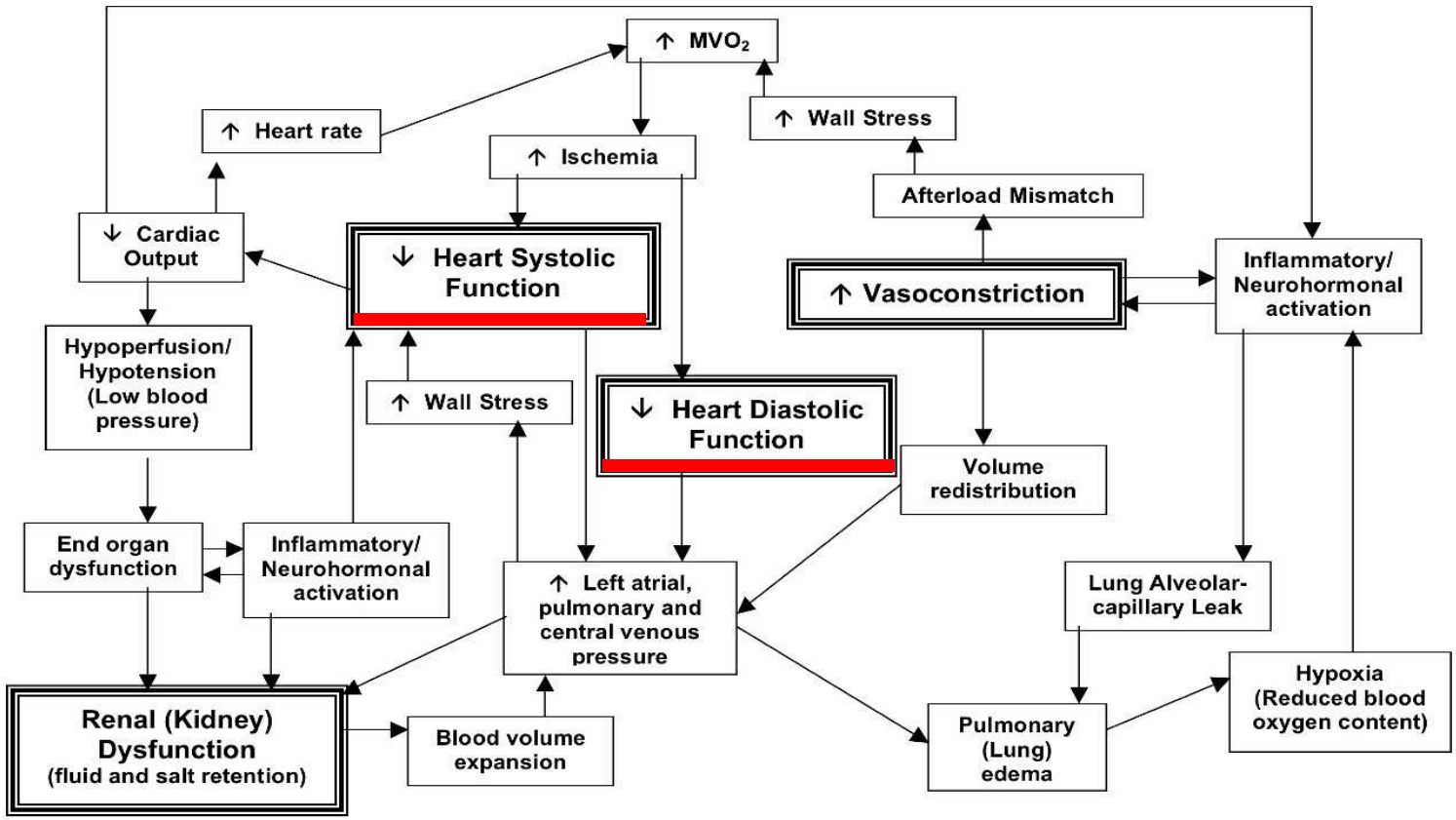
Table II. Comparison of patients in acute heart failure trials and the ADHERE

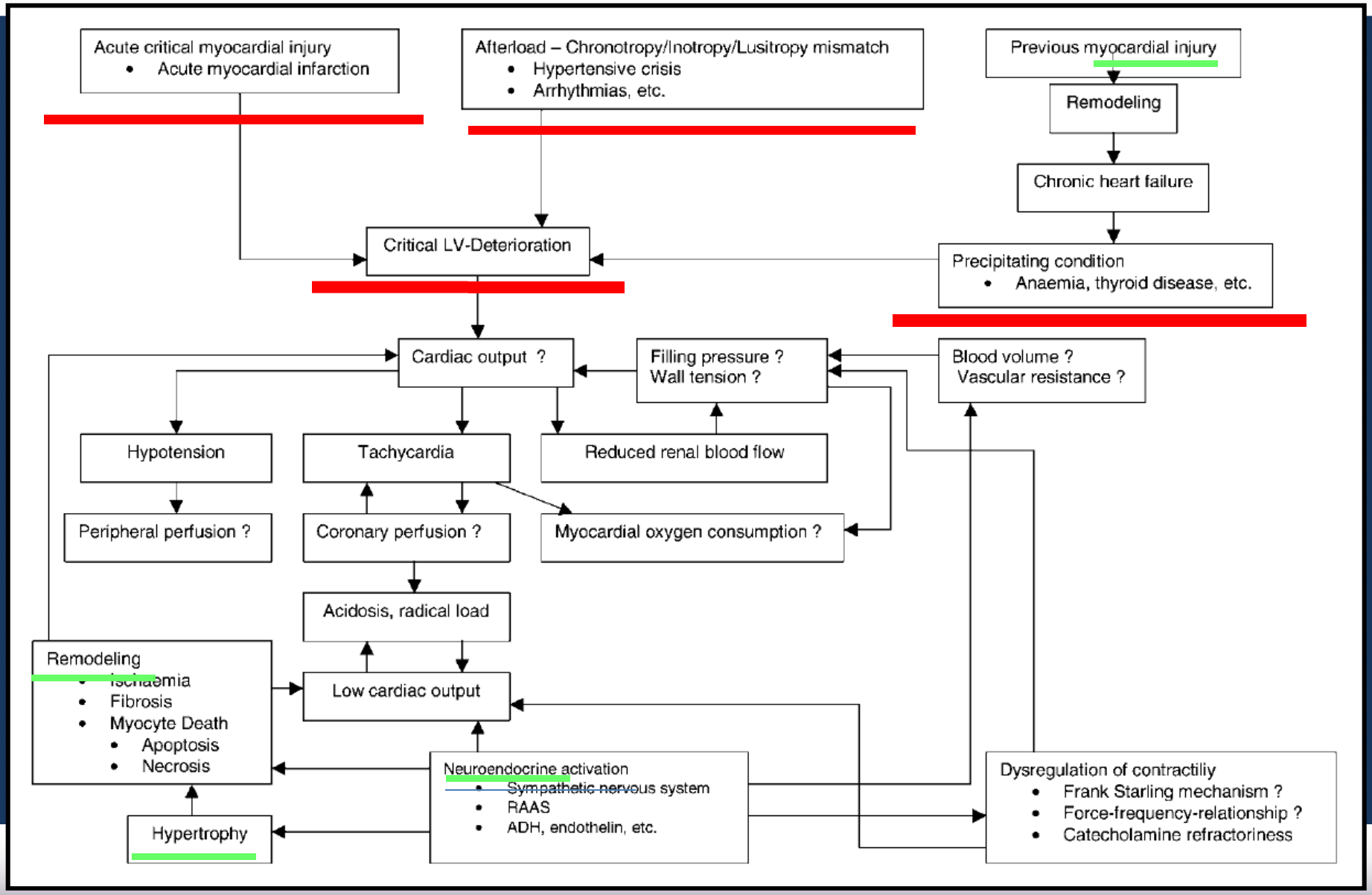
	VMAC* (N = 489)	OPTIME† (N = 949)	ADHERE‡ (N = 105388)
Demographics			
Age	60-62 (13-15)*	66 (14)/65(15)†	72.4 (14.0)
White (%)	58	65	72
Black (%)	24	33	20
Female (%)	31	29	52
Heart failure history			
NYHA II (%)	8	7	20§
NYHA III (%)	42	46	44§
NYHA IV (%)	42	47	32§
Prior hospitalizations	NA	1.9(2.0)/2.1 (2.2)† (last year)	1.0 (1.1) (last 6 mo)
LVEF			
Ejection fraction (prehospital)	27 (14)	24 (8)	34.4 (16.1) ‖
Ejection fraction >40% (prehospital) (%)	13.3 (>40)	NA	37 ‖
Ejection fraction >40%, or normal or mild impairment of systolic function (either before or during index hospitalization) (%)	NA	NA	46#
Medical history			
Coronary artery disease (%)	65	NA	57
Hypertension (%)	70	68	73
Myocardial infarction (%)	46	48	31
Diabetes mellitus (%)	47	44	44
Renal insufficiency (%)	NA	NA	30
Ventricular tachycardia (%)	13 (sustained)	NA	8
Ventricular fibrillation (%)	6	NA	1
Atrial fibrillation (%)	35	32	31
Baseline medications			
ACE inhibitors (%)	60	70	41
Diuretics (%)	86	90	70
β-Blockers (%)	33	22	48
Angiotensin receptor blockers (%)	10	13	12
Nitrates (%)	35	NA	26
Antiarrhythmics (%)	21	NA	11
Digoxin (%)	61	73	28
Physical and laboratory findings			
Systolic blood pressure (mm Hg)	121 (22)	120 (18)/120(19)†	144 (32.6)
Serum creatinine (mg/dL)	NA	1.5 (0.5)/1.4(0.5)†	1.8 (1.6)
Serum creatinine >2 mg/dL	21	NA	20

Data are expressed as mean (±SD), unless otherwise indicated. *NA*, not applicable, not assessed, or not reported; *NYHA*, New York Heart Association Heart Failure Classification.
*Based on data from the 3 treatment groups in the VMAC trial.[10]
†Data presented as placebo (n = 472)/milrinone (n = 477) for the OPTIME trial,[4] which excluded patients with serum creatinine >3.0 mg/dL.
‡n = 98034 to 105388 depending on available data for each specific measure, unless otherwise indicated.
§n for the denominator = 8391; 89% of patients had unknown or no mention of NYHA classification; 4% were classified as NYHA class I.
‖ n for the denominator = 40713.
#n for the denominator = 85270.

Adams KF *et al*. Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;149:209-16.

Figure 1


↑ MVO_2
↑ Heart rate
↑ Ischemia
↑ Wall Stress
Afterload Mismatch
↓ Cardiac Output
↓ Heart Systolic Function
↑ Vasoconstriction
Inflammatory/ Neurohormonal activation
Hypoperfusion/ Hypotension (Low blood pressure)
↑ Wall Stress
↓ Heart Diastolic Function
Volume redistribution
End organ dysfunction
Inflammatory/ Neurohormonal activation
↑ Left atrial, pulmonary and central venous pressure
Lung Alveolar-capillary Leak
Renal (Kidney) Dysfunction (fluid and salt retention)
Blood volume expansion
Pulmonary (Lung) edema
Hypoxia (Reduced blood oxygen content)


Acute critical myocardial injury
• Acute myocardial infarction
Afterload – Chronotropy/Inotropy/Lusitropy mismatch
• Hypertensive crisis
• Arrhythmias, etc.
Previous myocardial injury
Remodeling
Chronic heart failure
Critical LV-Deterioration
Precipitating condition
• Anaemia, thyroid disease, etc.
Cardiac output ?
Filling pressure ?
Wall tension ?
Blood volume ?
Vascular resistance ?
Hypotension
Tachycardia
Reduced renal blood flow
Peripheral perfusion ?
Coronary perfusion ?
Myocardial oxygen consumption ?
Acidosis, radical load
Remodeling
• Ischaemia
• Fibrosis
• Myocyte Death
• Apoptosis
• Necrosis
Low cardiac output
Neuroendocrine activation
• Sympathetic nervous system
• RAAS
• ADH, endothelin, etc.
Dysregulation of contractiliy
• Frank Starling mechanism ?
• Force-frequency-relationship ?
• Catecholamine refractoriness
Hypertrophy

Standard laboratory markers:

Sodium, Blood urea nitrogen, Serum creatinine, Hemoglobin, Leukocyte count, Total lymphocyte count, Serum albumin, Total bilirubin, Uric acid, Red blood cell distribution width.

Neurohormones:

Catecholamines (norepinephrine, epinephrine), Renin, ACE activity, angiotensin II, and aldosterone, Natriuretic peptides (ANP, BNP, C-type, N-terminal proANP, N-terminal proBNP, mid-regional pro-ANP), Endothelin-1, Vasopressin/copeptin, Cardiotrophin-1, Novel vasodilators (adrenomedullin and mid-regional pro-adrenomedullin, urotensin-II, urocortin)

Inflammatory biomarkers:

High-sensitivity C-reactive protein, Myeloperoxidase, Galectin-3, Fatty acid binding protein, Soluble ST2 receptor, Tumor necrosis factor-alpha and receptors, Interleukin-6 (IL-6), Growth differentiation factor 15 (GDF-15), Osteopontin

Metabolic biomarkers:

Leptin, Adiponectin, Ghrelin, Apelin, Insulin-like growth factor-1 (IGF-1)

Other miscellaneous biomarkers

G-protein coupled receptor kinase-2 (GRK-2), Cardiac troponin I or troponin T, Myotrophin

Cardio-renal Syndrom

Creatinin, NGAL, Cystatin

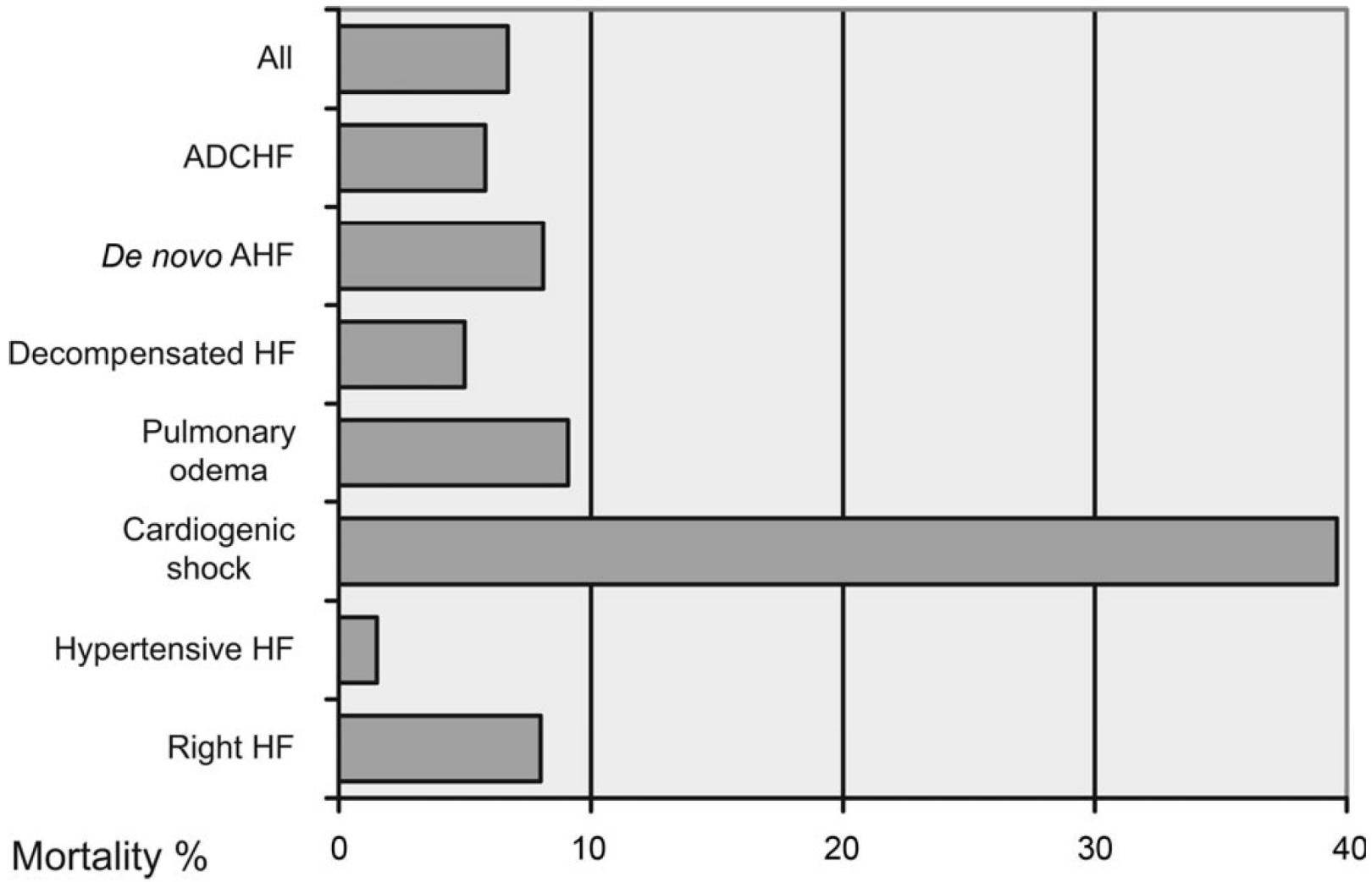
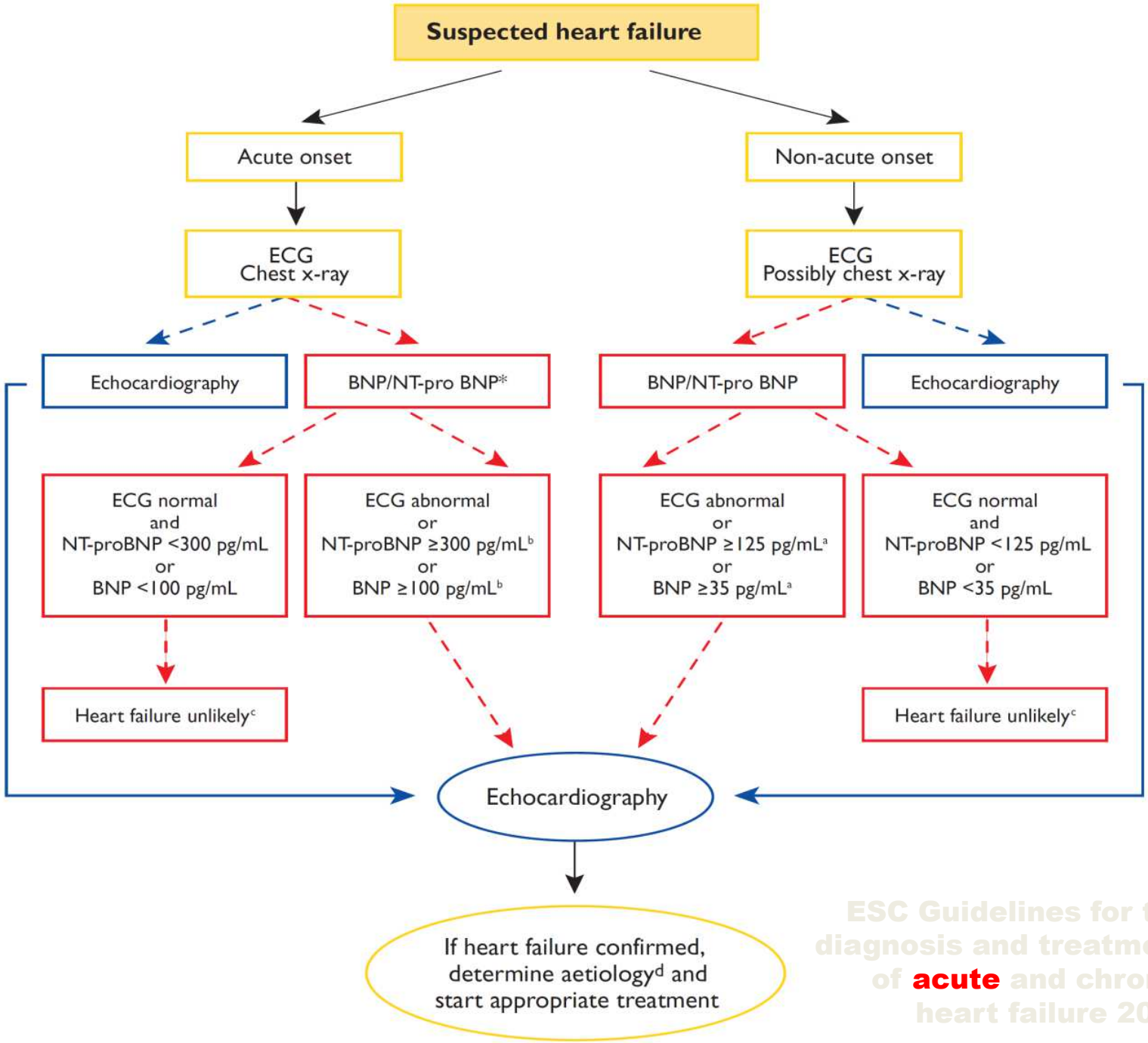
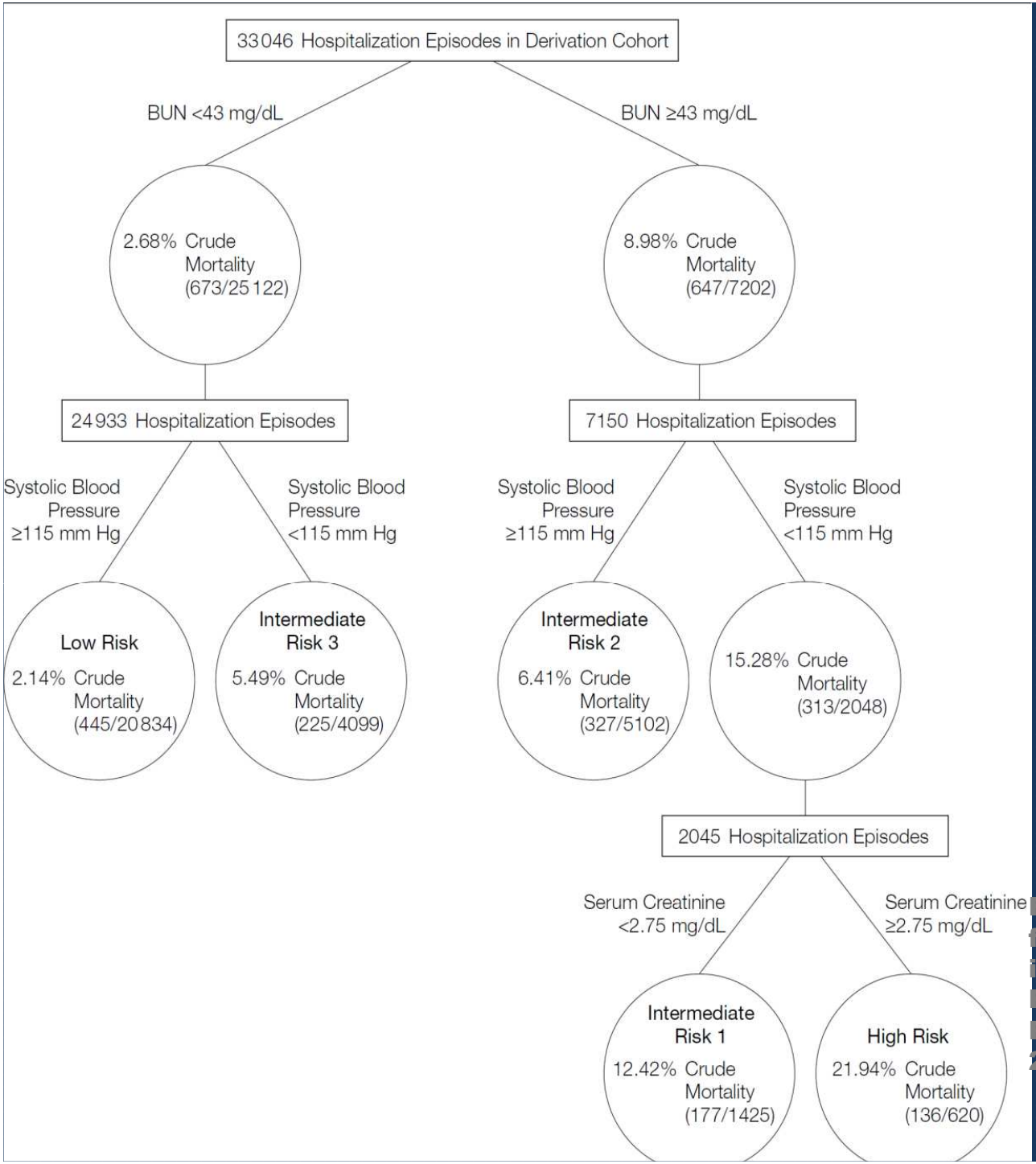


Figure 4 In-hospital mortality in EHFS II by history of HF and clinical class.

Nieminen M *et al.* EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006; 27: 2725–36.

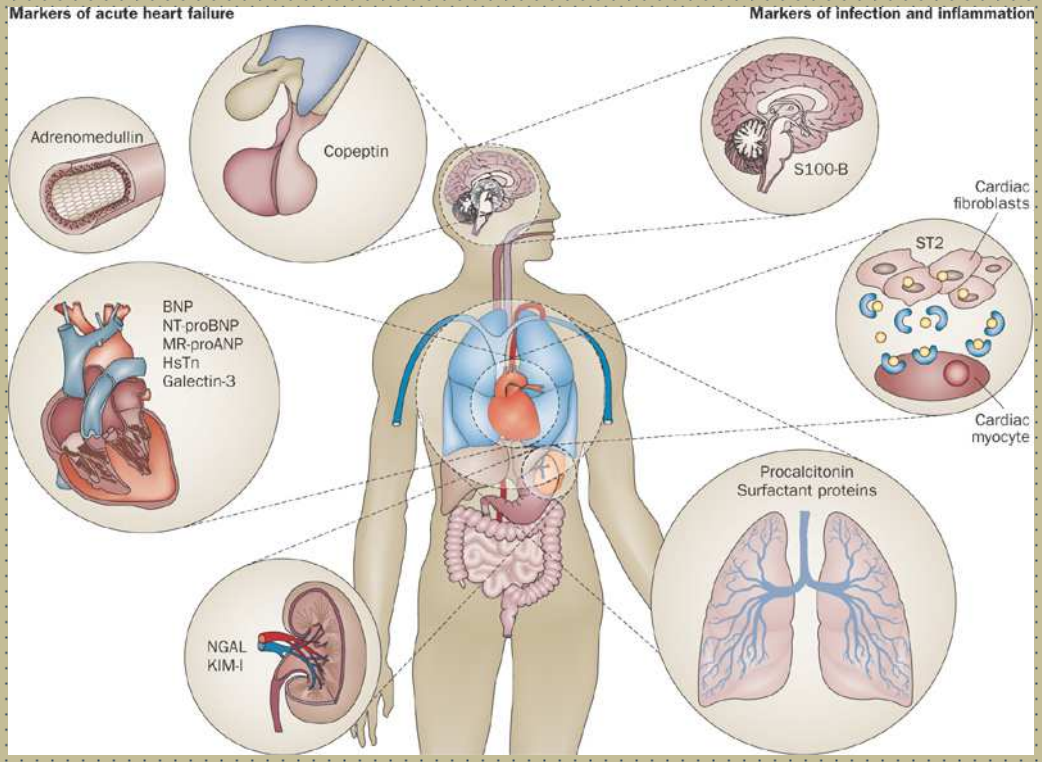


ESC Guidelines for the diagnosis and treatment of **acute** and chronic heart failure 2012



Fonarow G *et al*. Risk Stratification for In-Hospital Mortality in Acutely Decompensated Heart Failure - Classification and Regression Tree Analysis. *JAMA* 2005; 293: 572-580

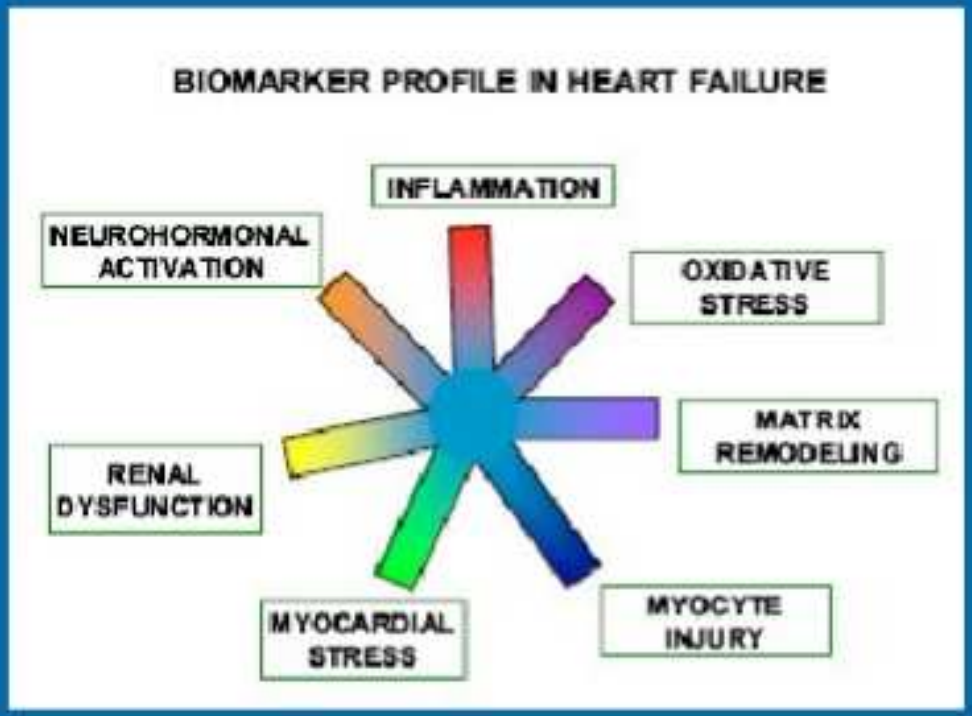
Biomarkers and their organ-specific release sites



Maisel, A. S. & Choudhary, R. (2012) Biomarkers in acute heart failure—state of the art
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2012.60

Non-Specific Blood Biomarkers in Heart Failure

- BUN, creatinine, microalbuminuria
- Bilirubin, INR, albumin, AST/ALT
- Fasting cholesterol panel
- Sodium, potassium
- Hemoglobin
- Iron deficiency panel
- Thyroid panel
- Uric acid
- Leukocyte count
- **C-reactive protein**



Tang W, *Biomarkers Med* 2009; Braunwald, HF Clin NA 2009

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Prognostic value of neutrophil gelatinase-associated lipocalin in acute heart failure ☆

Margarida Alvelos [a,b,*], Patrícia Lourenço [a,b], Carla Dias [a,b], Marta Amorim [a,b], Joana Rema [a,b], Ana Bento Leite [a,b], João Tiago Guimarães [c,d], Pedro Almeida [e], Paulo Bettencourt [a,b]

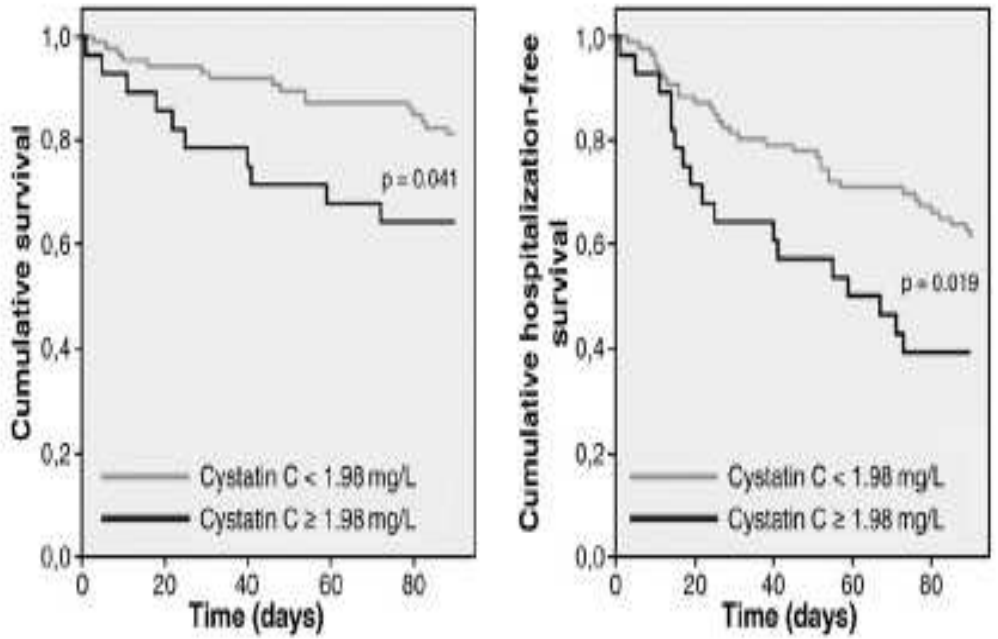


Fig. 2. Kaplan–Meier estimates of survival and hospitalization-free survival according to serum cystatin C levels. Patients in the highest cystatin C quartile have a significantly worse short term prognosis than the ones in the other quartiles.

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doi:10.1016/j.jacc.2010.02.025

Mid-Region Pro-Hormone Markers for Diagnosis and Prognosis in Acute Dyspnea

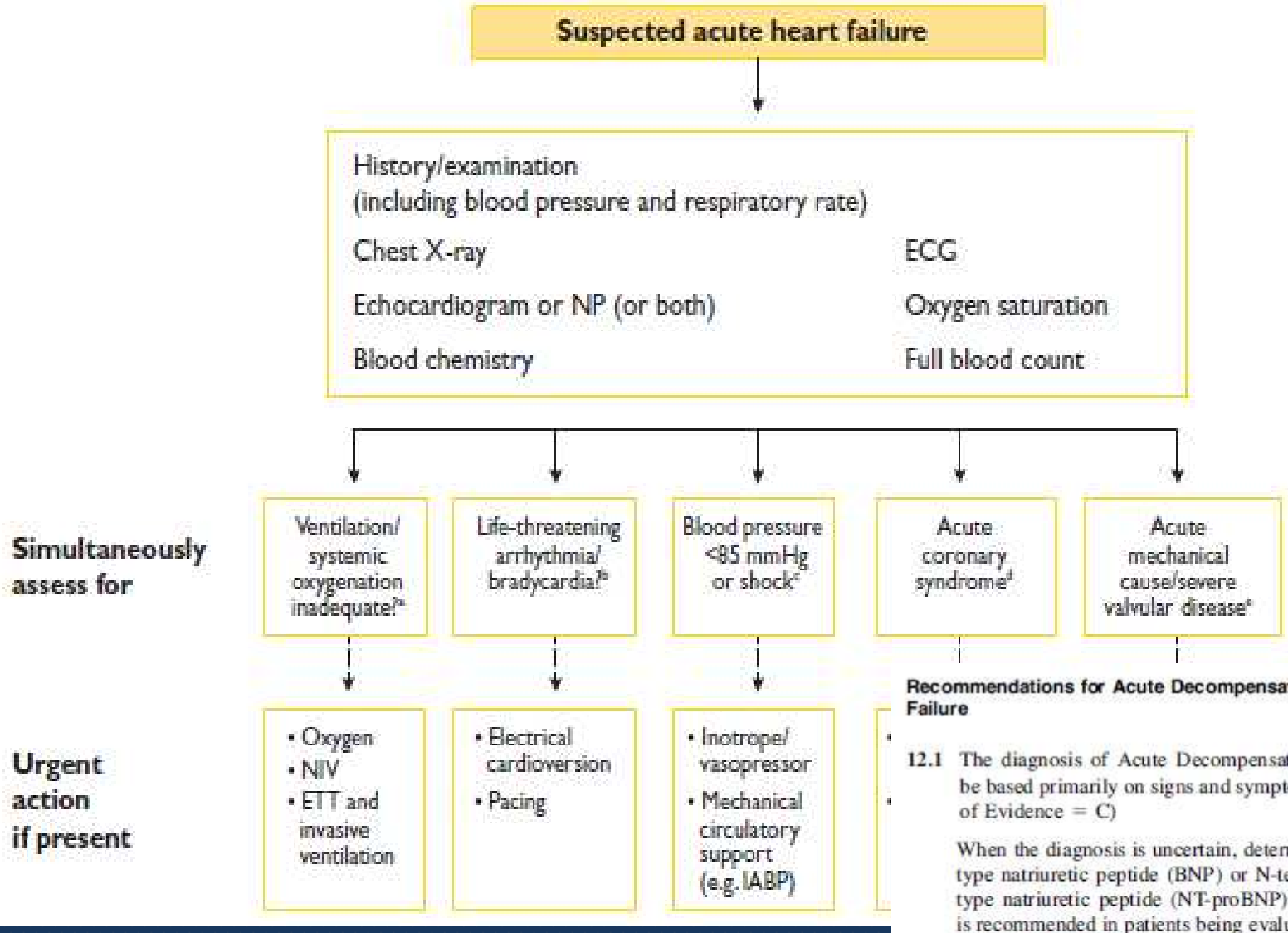
Results From the BACH (Biomarkers in Acute Heart Failure) Trial

Alan Maisel, MD,**** Christian Mueller, MD,† Richard Nowak, MD,‡ W. Frank Peacock, MD,§ Judd W. Landsberg, MD,‖ Piotr Ponikowski, MD, PHD,¶ Martin Mockel, MD,#

Table 2 Acute Heart Failure Diagnostic Performance of MR-proANP Cut at 120 pmol/l and BNP Cut at 100 pg/ml

Measure	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	NPV	PPV
BNP 100 pg/ml	95.6% (93.6–97.0)	61.9% (59.0–64.8)	73.6% (71.4–75.6)	96.4%	57.0%
MR-proANP 120 pmol/l	97.0% (95.2–98.2)	59.9% (56.4–62.8)	72.7% (70.5–74.8)	97.4%	56.0%
Difference	−1.4%	2.1%	0.9%	−1.0%	1.0%
Upper 95% limit	−0.2%	3.8%	2.1%		
Noninferiority p value	<0.001	<0.001	<0.001		

BNP = B-type natriuretic peptide; CI = confidence interval; MR-proANP = mid-regional pro-atrial natriuretic peptide; NPV = negative predictive value; PPV = positive predictive value.



Recommendations for Acute Decompensated Heart Failure

12.1 The diagnosis of Acute Decompensated HF should be based primarily on signs and symptoms. (Strength of Evidence = C)

When the diagnosis is uncertain, determination of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration is recommended in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A)

The natriuretic peptide concentration should not be interpreted in isolation, but in the context of all available clinical data bearing on the diagnosis of HF, and with the knowledge of cardiac and non-cardiac factors that can raise or lower natriuretic peptide levels.

INFECTION

European Journal of Heart Failure (2012) **14**, 278–286
doi:10.1093/eurjhf/hfr177

Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial

Alan Maisel[1,2]*, Se … ian Mueller[3],

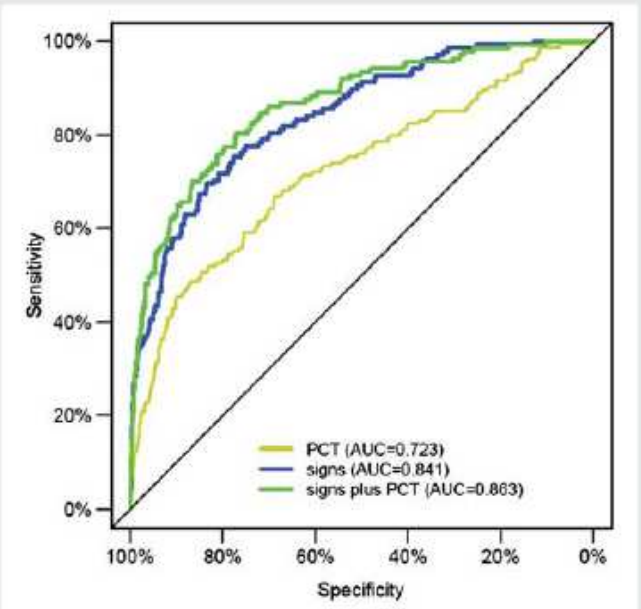
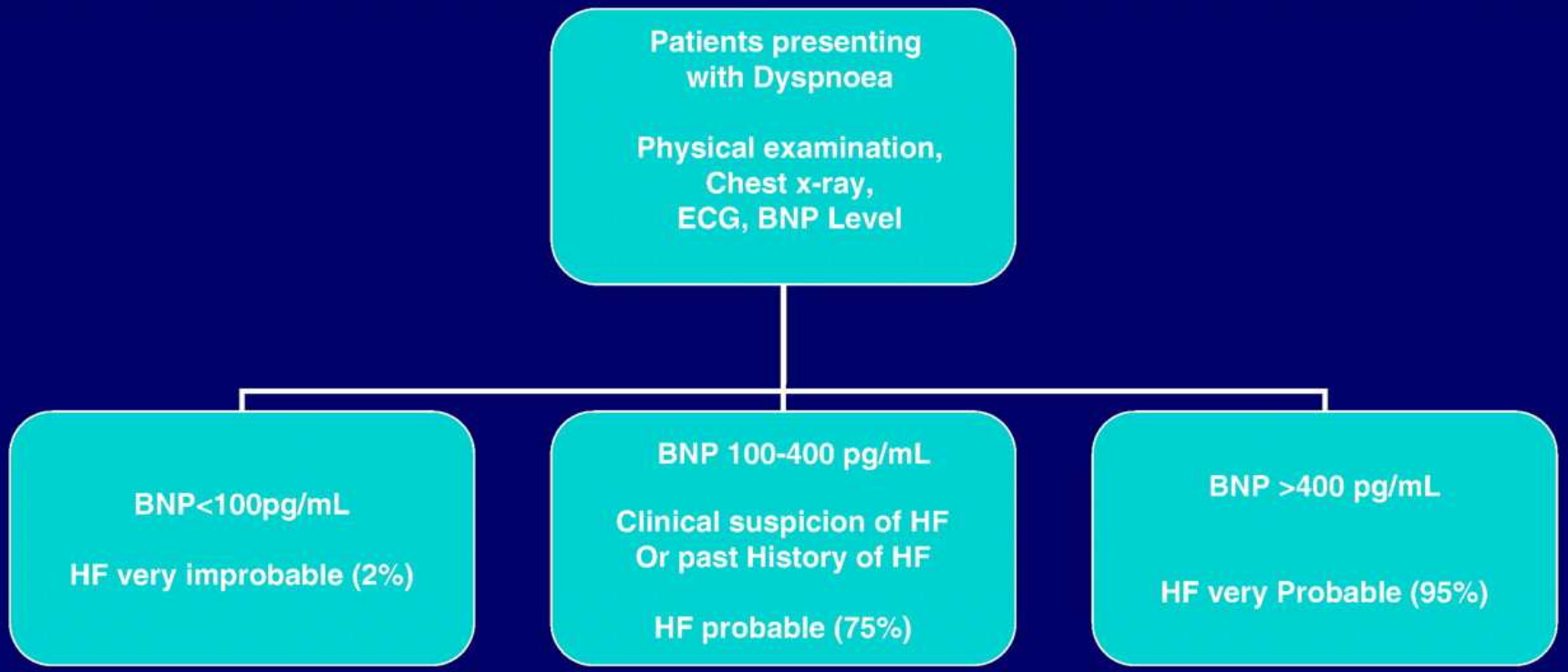


Figure 1 Receiver operating characteristic (ROC) curves for the diagnosis of pneumonia ($n = 155$ events), comparing procalcitonin (PCT), the multivariable model including clinical signs, as

For Heart Failure Diagnosis



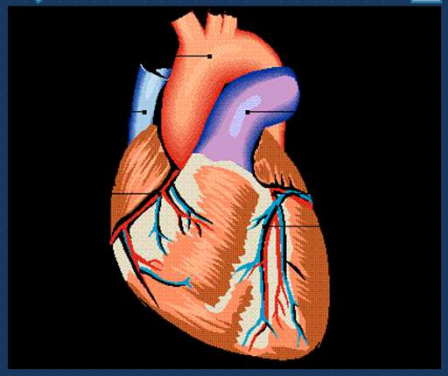
Maisel A et al. Eur J Heart Fail 2008;10:824-839

EUROPEAN JOURNAL OF HEART FAILURE

Cardiac Injury

Neuro-hormones

Caquexia



Oxidative Stress

Inflamation,
Endotelial dysfunction,
remodelling

Genetic

Co-morbilities

Table 3. BNP as a predictor of six-month mortality

Admission BNP	Risk of death
<500 pg/mL	5.0%
500-1500 pg/mL	12.5%
>1500 pg/mL	35.5%
Discharge BNP	**Risk of death**
<500 pg/mL	2.30%
500-1500 pg/mL	29.20%
>1500 pg/mL	26.70%

Source: Adapted from Shah MR, Hasselblad V, Tasissa G, et al. Rapid assay brain natriuretic peptide and troponin I in patients hospitalized with decompensated heart failure (from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness Trial). Am J Cardiol. *2007:100(9);1427-1433.*

Ideal biomarker

Cost/Eficacy

Acuity in diagnosis and prognosis

Biological variability
References values/cut-off's

Standardized
"low cost"

Analitic sensitivity
Reproducibility
Acuity
Easy to perform

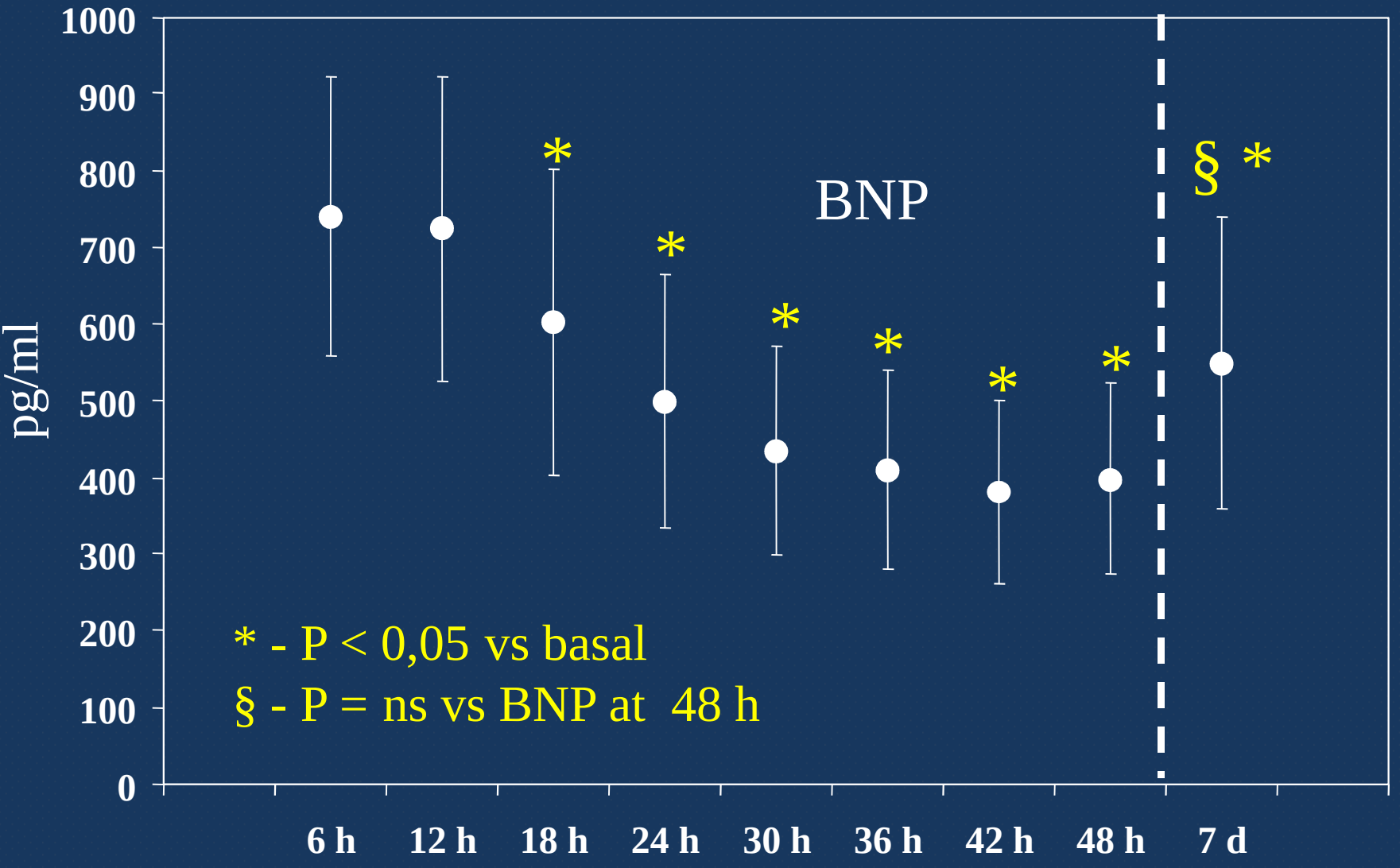
Stability in vitro and in vivo

Natriuretic peptides in the management of Heart Failure

- Sensitive / specific for HF
- Reproduced and standartized across clinical lab.
- Easy to perform

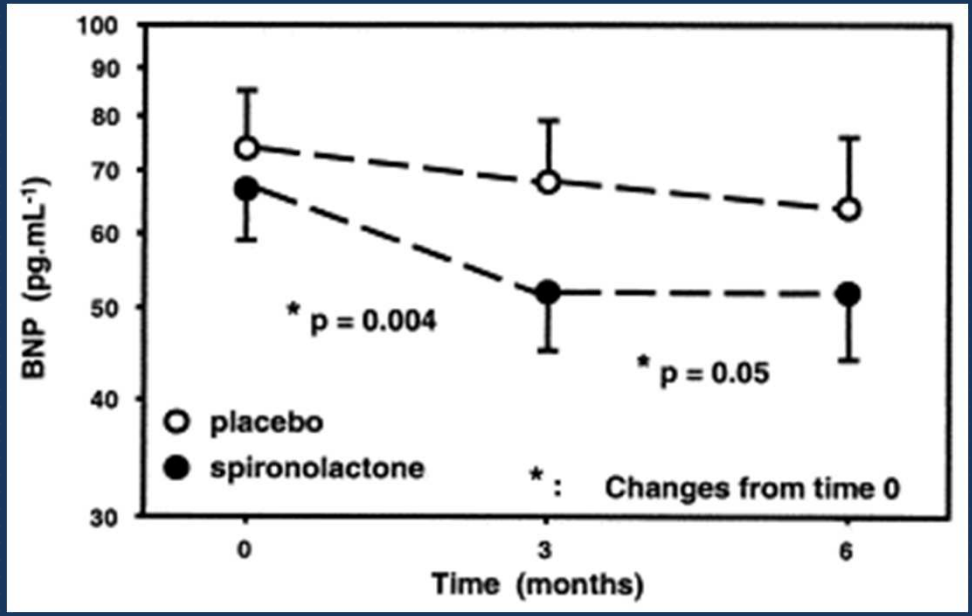
- Variations in biomarkers associated with
  - Variations in clinical status
  - Related to interventions
  - Variations in prognosis

ACE - inhibitors and BNP



Ferreira A. Clinical Science 2001

Beneficial neurohumoral profile of spironolactone in severe HF



Changes in plasma levels of brain natriuretic peptide (BNP) (expressed on a log scale) from baseline to three and six months in the placebo and spironolactone groups.

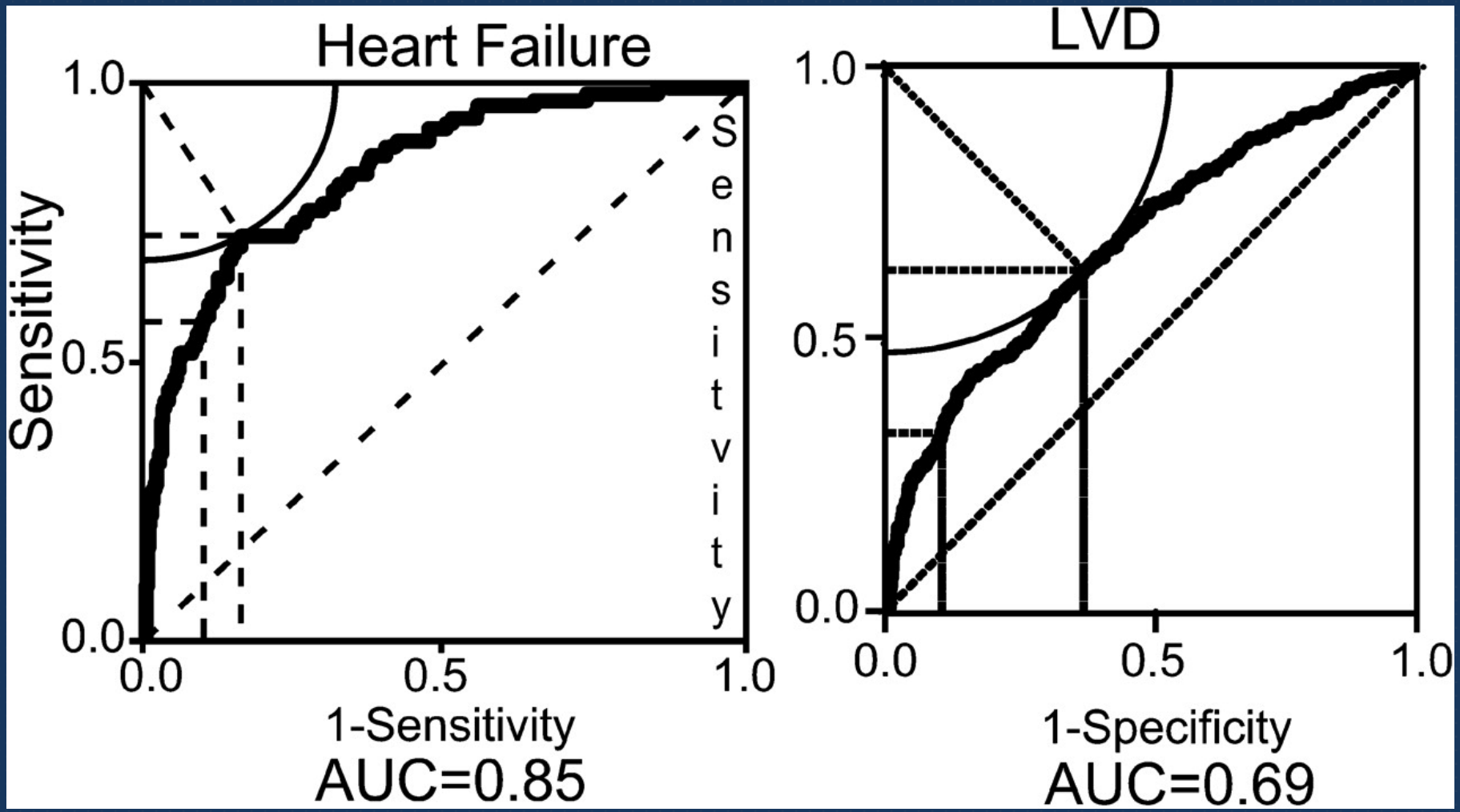
Rousseau MF. JACC 2002

Direct Medical Costs to 60 Days of Follow-Up in the NT-proBNP and Usual Care Groups

	NT-proBNP guided n=246	Usual evaluation n=254	p
Median duration of ED visit (h)	5.6	6.3	0.03
60-day rehospitalization rate (%)	33	51	<0.05
Median duration of ED visit among patients with 20% to 80% likelihood of an HF diagnosis based on physician assessment (h)	5.4	7.5	0.003
All ED visits, hospitalizations and outpatient services ($)	5180	6126	0.023
All ED visits and hospitalizations ($)	4958	5853	0.016

Moe GW et al. *Circulation* 2007; 115:3103-3110.

ROC analysis for the detection of heart failure and LVD.



McDonagh T et al. Eur J Heart Fail 2004;6:269-273

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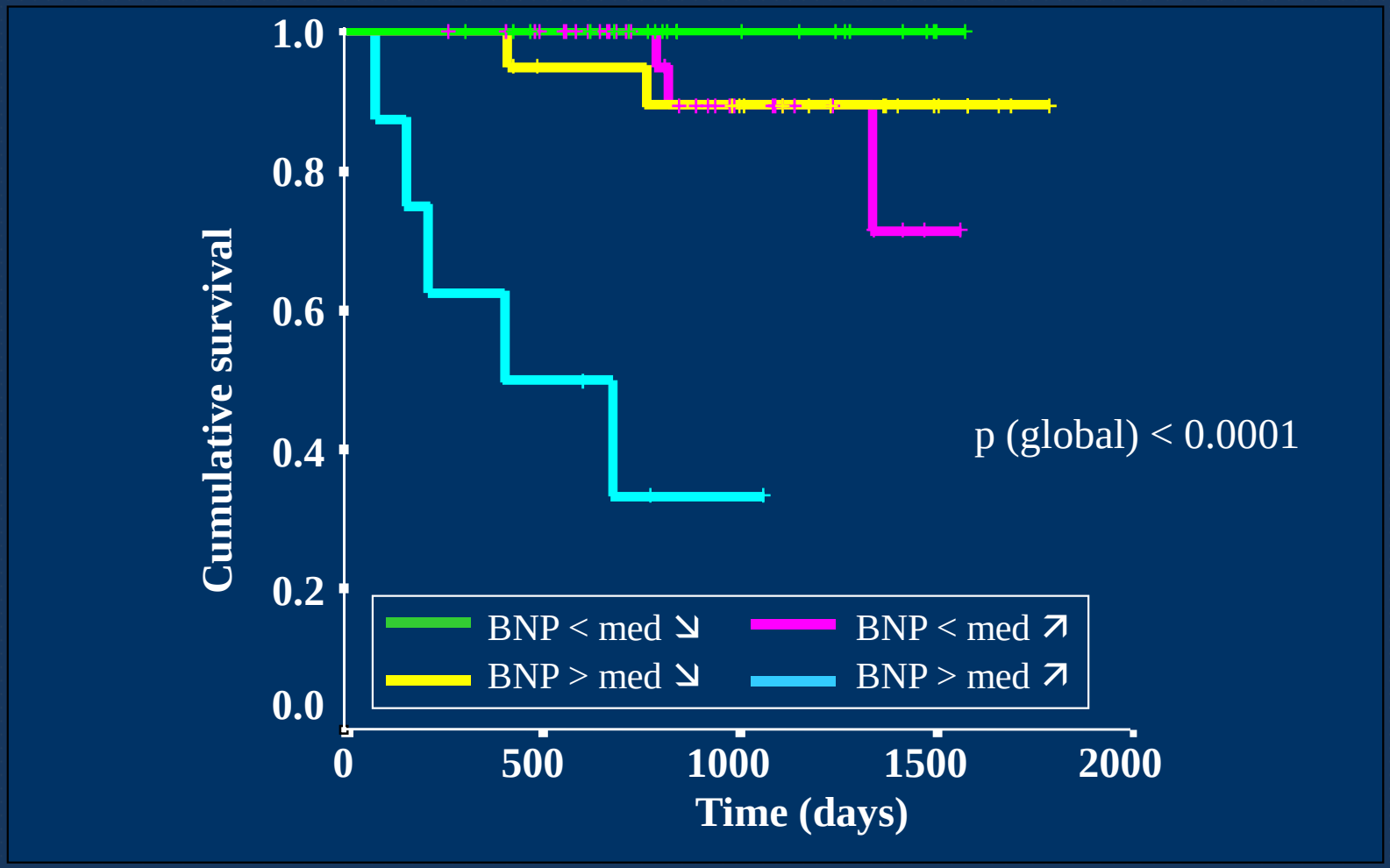
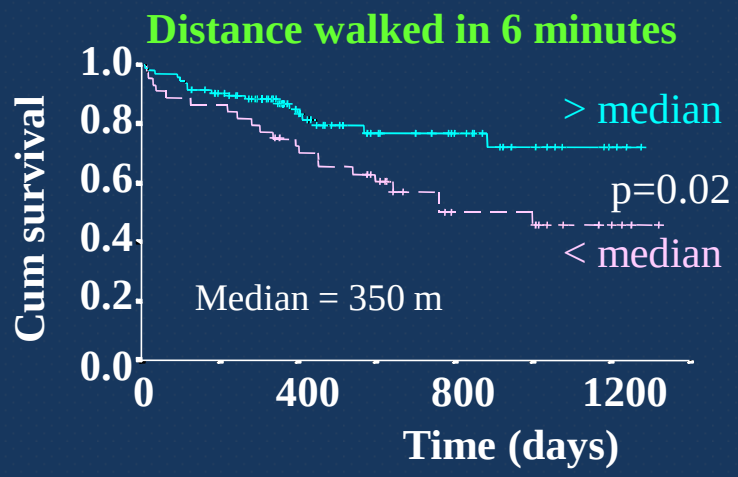
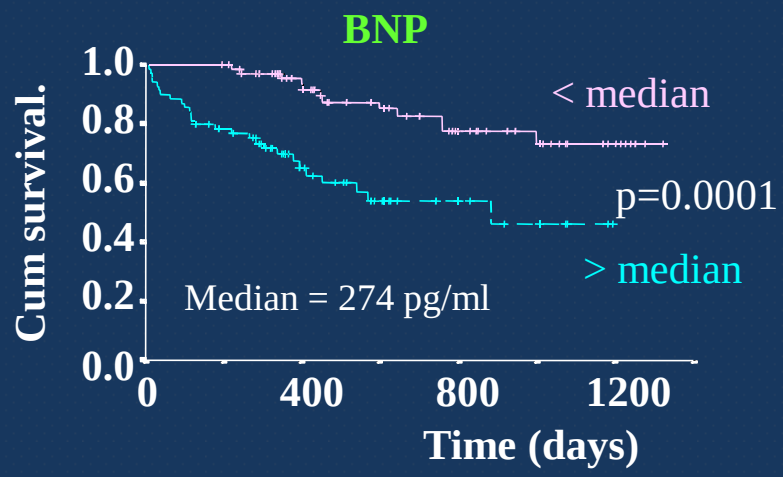
Changes in BNP and prognosis

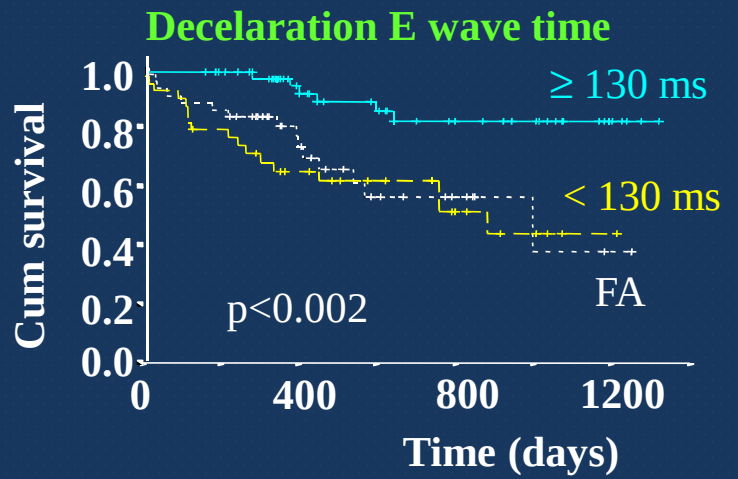


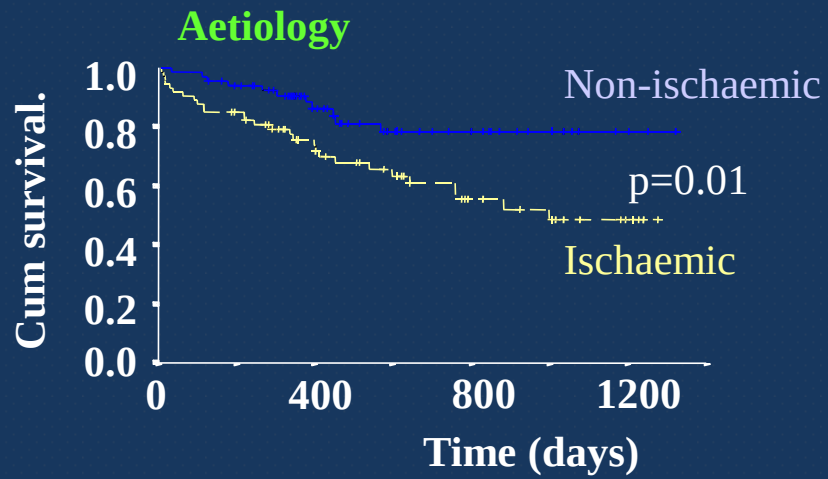
Bettencourt P . Int J Cardiol 2004

Prognosis – Heart Failure









Bettencourt P. J Card Fail 2000