New Biomarkers for the management of heart failure

J. Parissis
Attikon University Hospital
Athens, Greece

Disclosures related to this presentation: Horonaria from Roche Diagnostics

Editorial

Benchmarks for the Assessment of Novel Cardiovascular Biomarkers

David A. Morrow, MD, MPH; James A. de Lemos, MD

A

1) Can the clinician measure the biomarker?

- **a) Accurate and reproducible analytical method(s)**
- **b) Pre-analytical issues (including stability) evaluated and manageable**
- **c) Assay is accessible**
- d) Available assays provide high through-put and rapid turn-around
- e) Reasonable cost

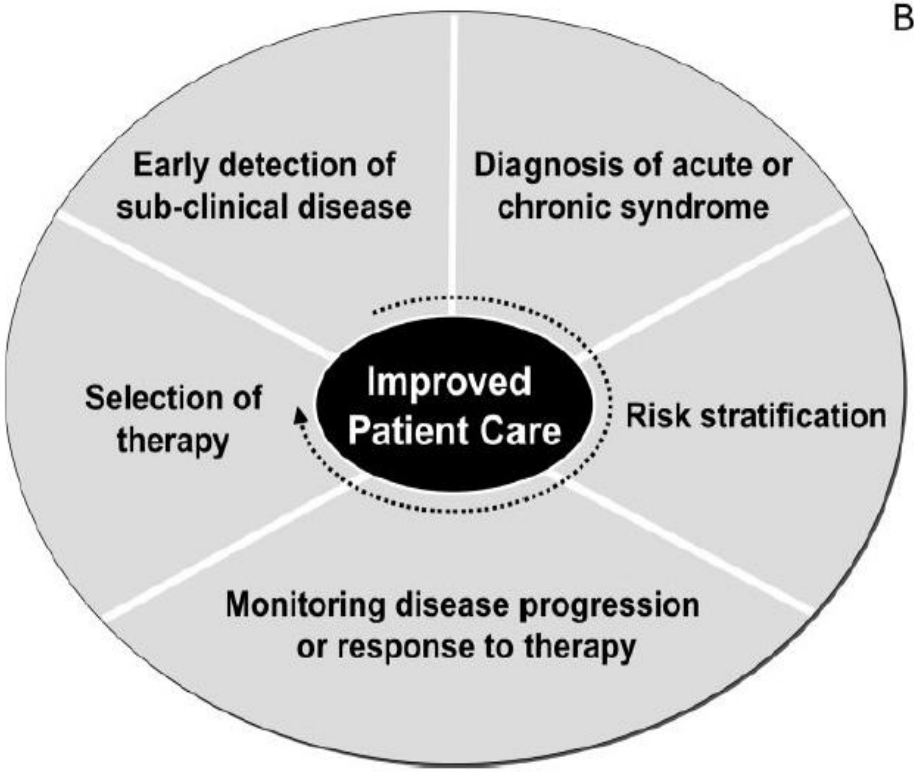
2) Does the biomarker add new information?

- **a) Strong and consistent association between the biomarker and the outcome or disease of interest in multiple studies**
- **b) Information adds to or improves upon existing tests**
- c) Decision-limits are validated in more than one study
- d) Evaluation includes data from community-based populations

3) Will the biomarker help the clinician to manage patients ?

- **a) Superior performance to existing diagnostic tests, or**
- **b) Evidence that associated risk is modifiable with specific therapy, *or***
- **c) Evidence that biomarker-guided triage or monitoring enhances care**
- d) Consider each of multiple potential uses (SEE PANEL B)

B



Morrow D. Circulation 2007; 115: 949

Multimarkers in chronic HF

BNP ,NTproBNP, MR-proANP, adrenomedullin, ST2, GDF15 ...

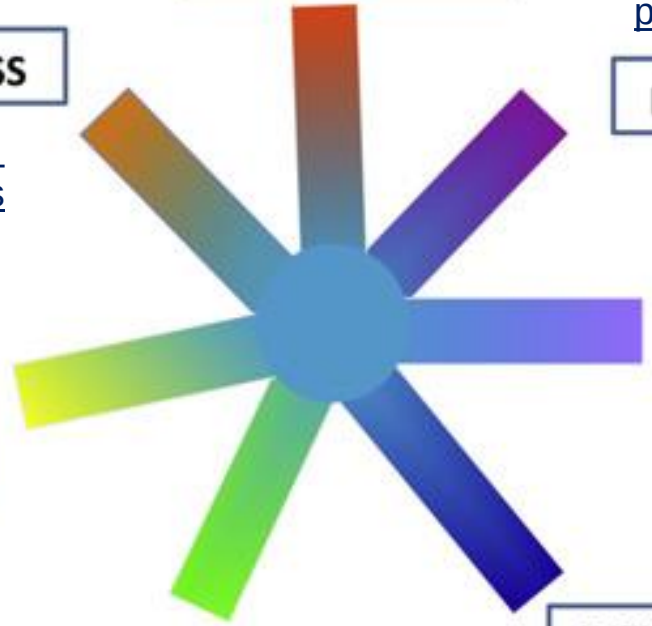
MYOCARDIAL STRETCH

hs-cTnT, hs-cTnI, H-FABP, pentraxin-3, Fas (Apo1) ...

OXIDATIVE STRESS

MPO, GGT, urate, oxLDL, isoprostanes

MYOCYTE INJURY



MATRIX REMODELING

ST2, Gal-3, PICP, PIIP, MMPs, TIMPs, osteopontin, osteoprotegerin ...

NEUROHUMORAL ACTIVATION

BNP, NTproBNP MR-proANP, ET-1 Adrenomedullin, copeptin ...

INFLAMMATION

Hs-CRP, GDF-15, ST2, TNF-α, IL1,2,6,8,18, adipokynes, Procalcitonin, neopterin, pentraxin-3, CD40-CD154 ...

RENAL DYSFUNCTION

eGFR, BUN, cystatin C, NGAL...

Value of clinical exam for diagnosis of HF

Table 2. Sensitivity, Specificity, and Positive and Negative Predictive Values of Clinical Findings for Normal Systolic Function (Ejection Fraction ≥45%)

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
			Percentage	
Historical factors				
Age ≥60 years	52	61	53	60
Female sex	56	65	58	63
Hypertension	78	26	48	57
Diabetes mellitus	40	66	51	56
Hyperlipidemia	6	94	46	53
Smoking	39	55	43	51
History of coronary disease	22	70	39	51
Chronic renal failure	15	91	59	55
Alcohol use	20	63	32	48
Symptoms				
Dyspnea at rest	39	56	42	52
Dyspnea on exertion	98	2	46	50
Orthopnea	86	14	47	55
Paroxysmal nocturnal dyspnea	74	23	45	50
Angina	4	89	24	52
Nonanginal chest pain	37	74	54	57
Physical examination				
Body mass index ≥30 kg/m^2	62	52	54	60
Heart rate ≥100 beats per minute	31	50	34	45
Systolic blood pressure ≥160 mm Hg	50	73	62	63
Diastolic blood pressure ≥110 mm Hg	25	87	63	57
Pulse pressure ≥60 mm Hg	61	55	54	62
Jugular venous distention	72	26	46	53
Pedal edema	83	25	48	63
Rales	80	11	43	38
S_3 gallop	28	59	37	49
S_4 gallop	11	93	56	55
Electrocardiogram				
Atrial fibrillation	19	90	61	57
Abnormal Q waves	18	79	42	53
Left ventricular hypertrophy	22	58	31	47
Left atrial abnormality	22	48	25	45
Chest radiograph				
Cardiomegaly	86	7	45	36
Cephalization	79	9	43	34
Pleural effusion	26	81	55	56
Pulmonary edema	14	85	45	53

Am J Med.2002;112:437– 445

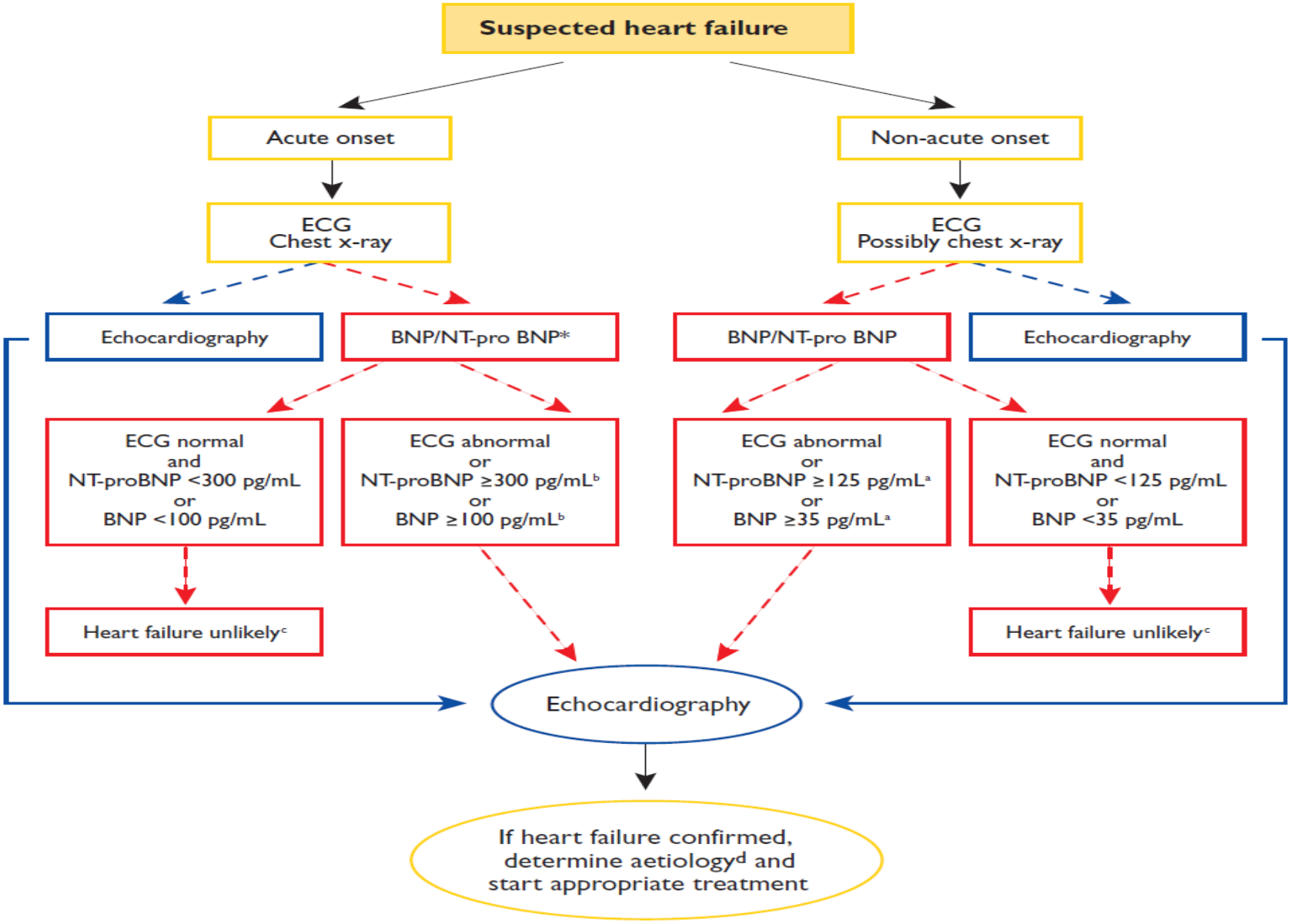
Diagnostic pitfalls: radiology

- Chest hyperinflation reduces cardiothoracic ratio
- Pulmonary vascular remodelling and radiolucent lung fields mask typical alveolar shadowing in pulmonary oedema
- Asymetric, regional and reticular patterns of pulmonary oedema
- Vascular bed loss with upper lobe venous diversion mimics HF
- 20-30 % of pts with AHF had negative chest X ray for pulmonary congestion (ADHERE, ALARM)

Diagnostic pitfalls: echocardiography, CMR

- Inadequate visualisation related to air trapping (10-50%)
- Inadequate collaboration with dyspneic patient
- High cost of comprehnsive echo-Doppler cardiac examination
  (need for new sophisticated echo TDI markers)
- Limited efficacy of LV filling pressure estimation in patients with high HR.

Diagnostic flowchart for patients with suspected HF



ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012

Established biomarkers for diagnosis: Greater value as a rule – out approach

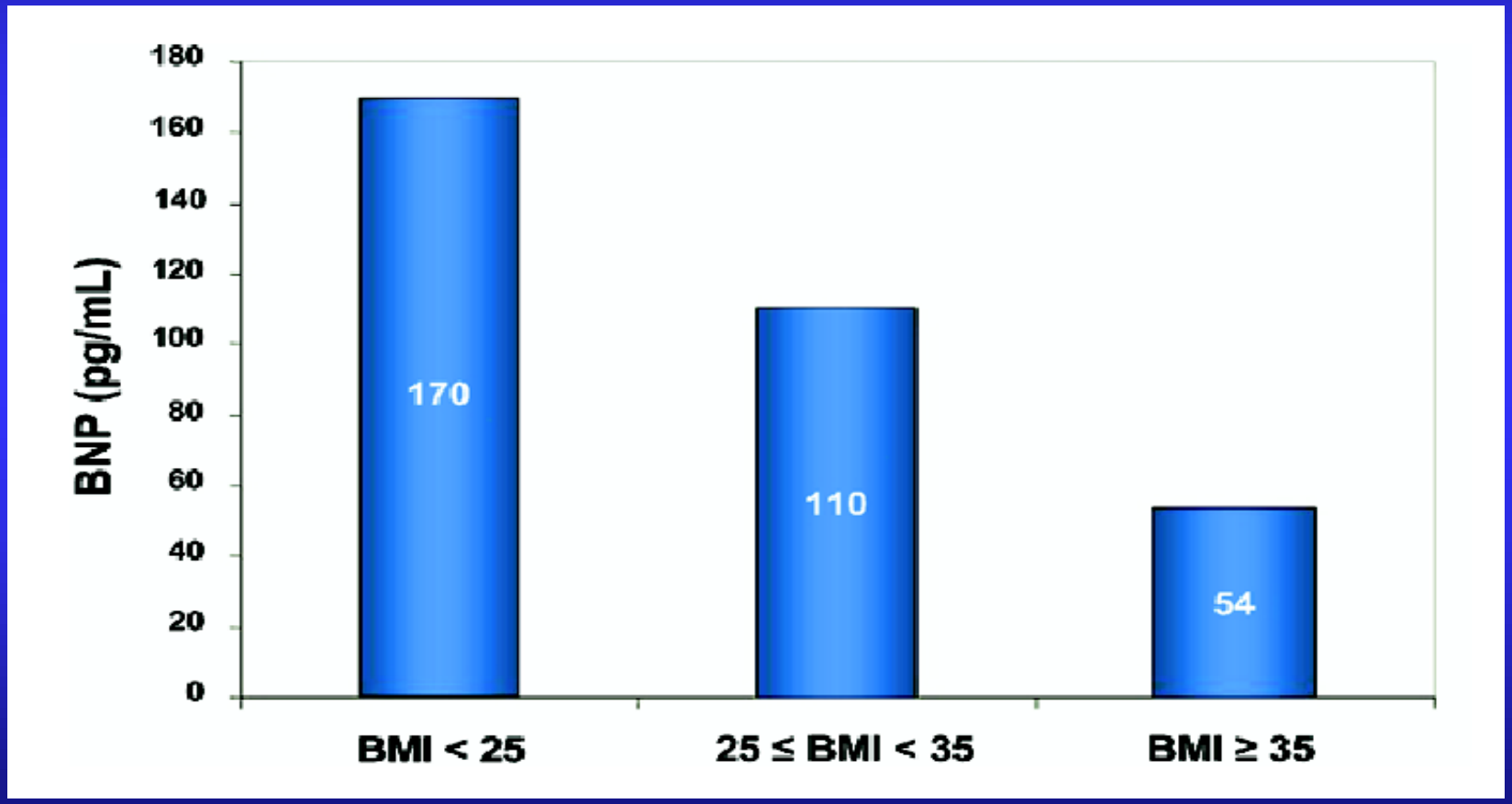
- BNP/NT-proBNP for diagnosis of CHF and ADHF
- Hs troponin for diagnosis of new ACS complicating HF
- Procalcitonin for diagnosis of infection
- MR-proANP for diagnosis of HF in grey zones of NPs
- N-gaL/ Cystatin-C for early diagnosis of acute kidney injury

Limitations of biomarkers for diagnosis of HF

- Their levels are affected by:

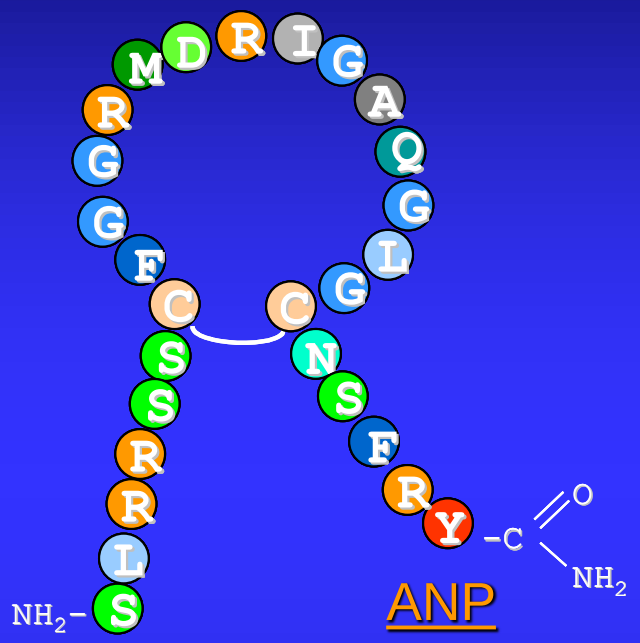
  - Age, gender, BMI,
  - Renal function, Hb levels
  - Timing of evaluation,
  - Type of HF (systolic vs diastolic, backward vs forward)
  - Severity of disease and background treatment (e.g beta blockers)

BNP Cut Off-Points According to Body Mass Index

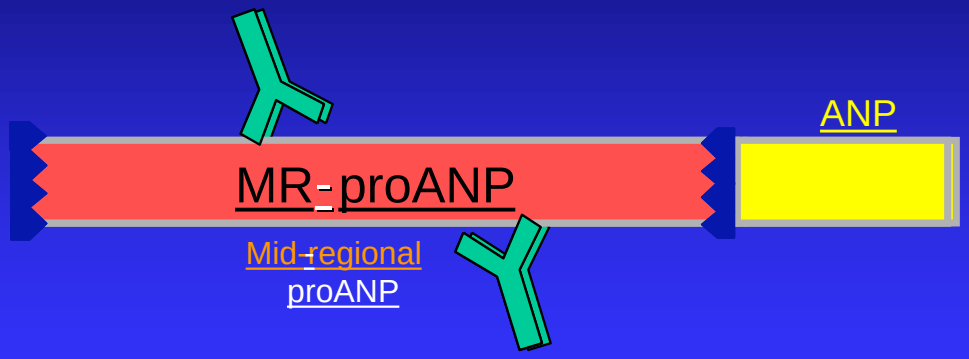


Daniels et al. Am Heart J 2006;151:999 –1005.

MR-proANP is a stable and reliable surrogate marker of the mature hormone



ANP
(diuretic, vasodilator)

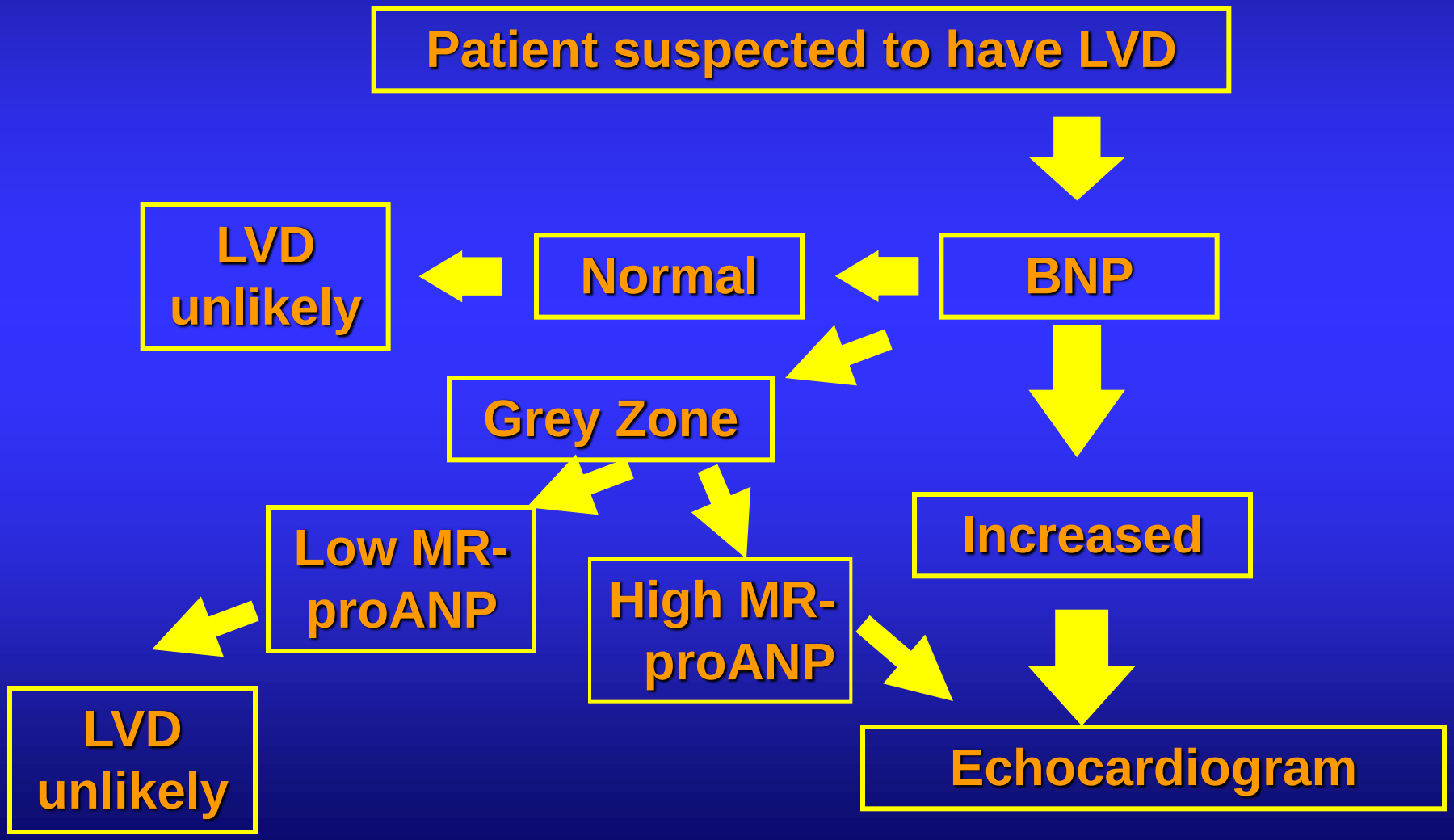


- prohormone (fragment)
- can be easily measured by standard sandwich immunoassay technology
- stable & reliable surrogate marker of the mature hormone

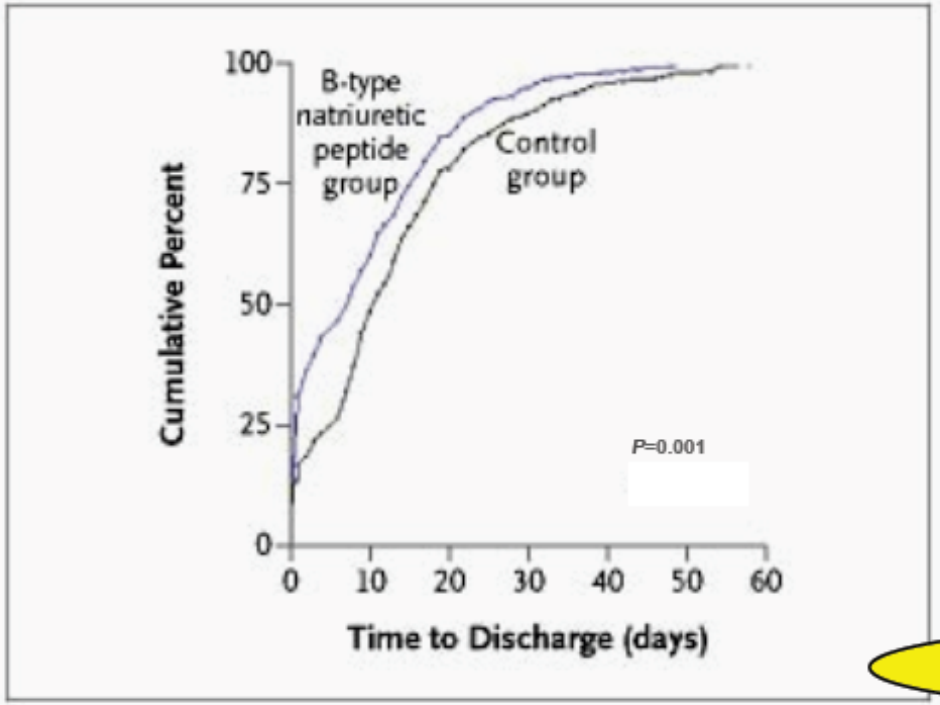
Peptides are instable *in vivo* and *ex vivo*, therefore not suitable for clinical diagnosis.

Morgenthaler NG et al., Clin Chem. 2004;50:234-6.
Morgenthaler NG et al., Clin Chem. 2005;51:1823-9.

Future diagnostic algorithm



Cost-Effectiveness of BNP at ED: The BASEL Study

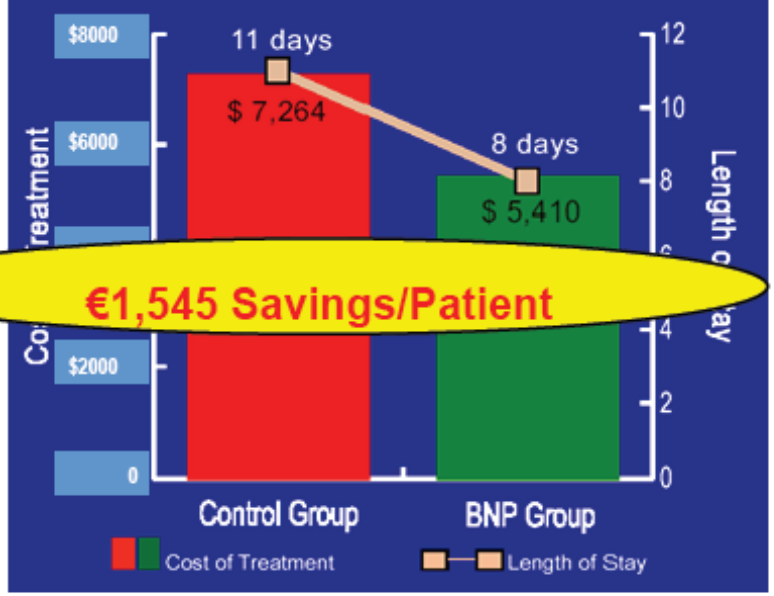


Biosite Triage BNP (in pg/mL)

Muller C, et al. *N Engl J Med.* 2004;350:647-654.

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%



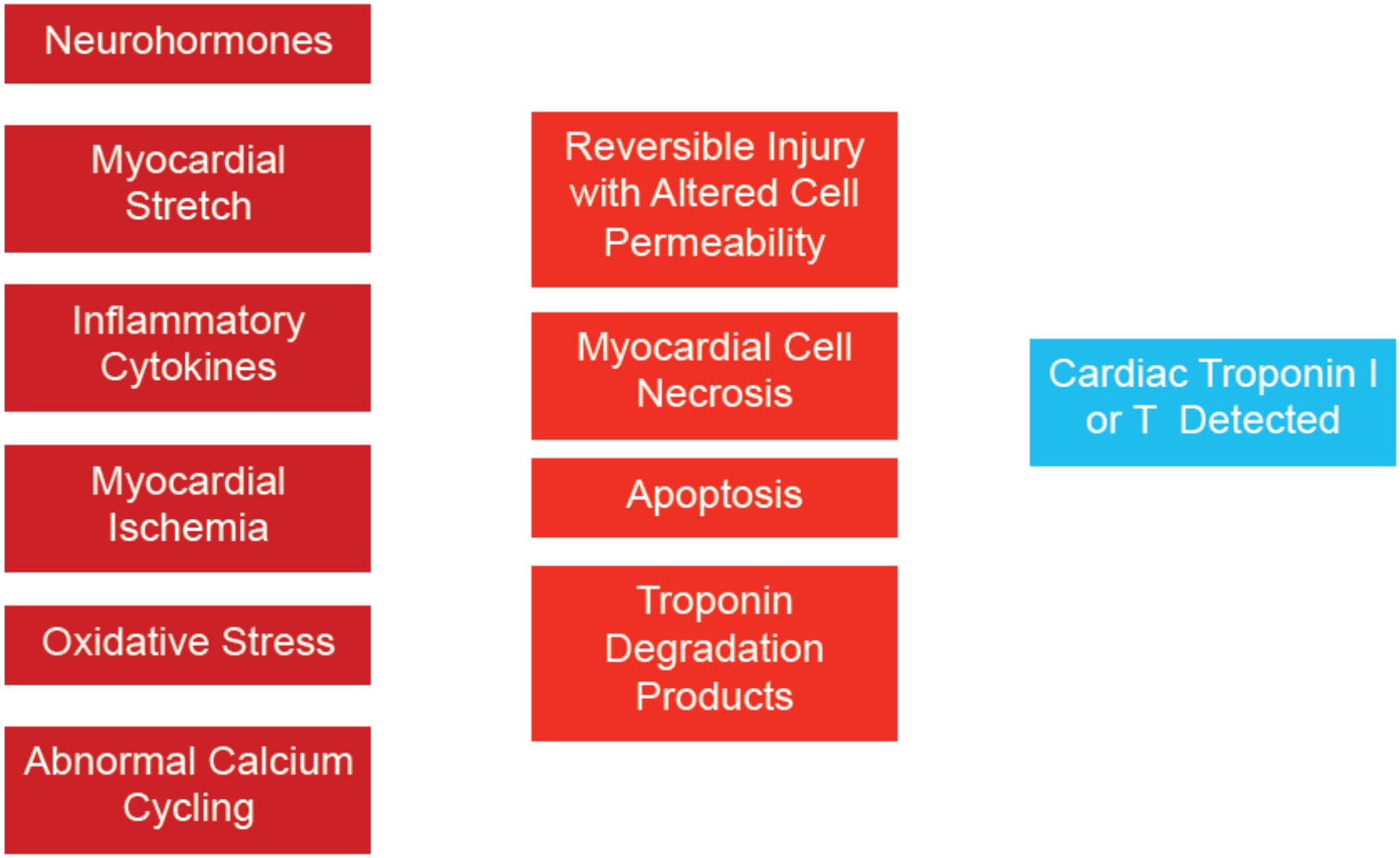
€1,545 Savings/Patient

Strength of evidence for individual biomarkers for diagnosis and prognosis of HF

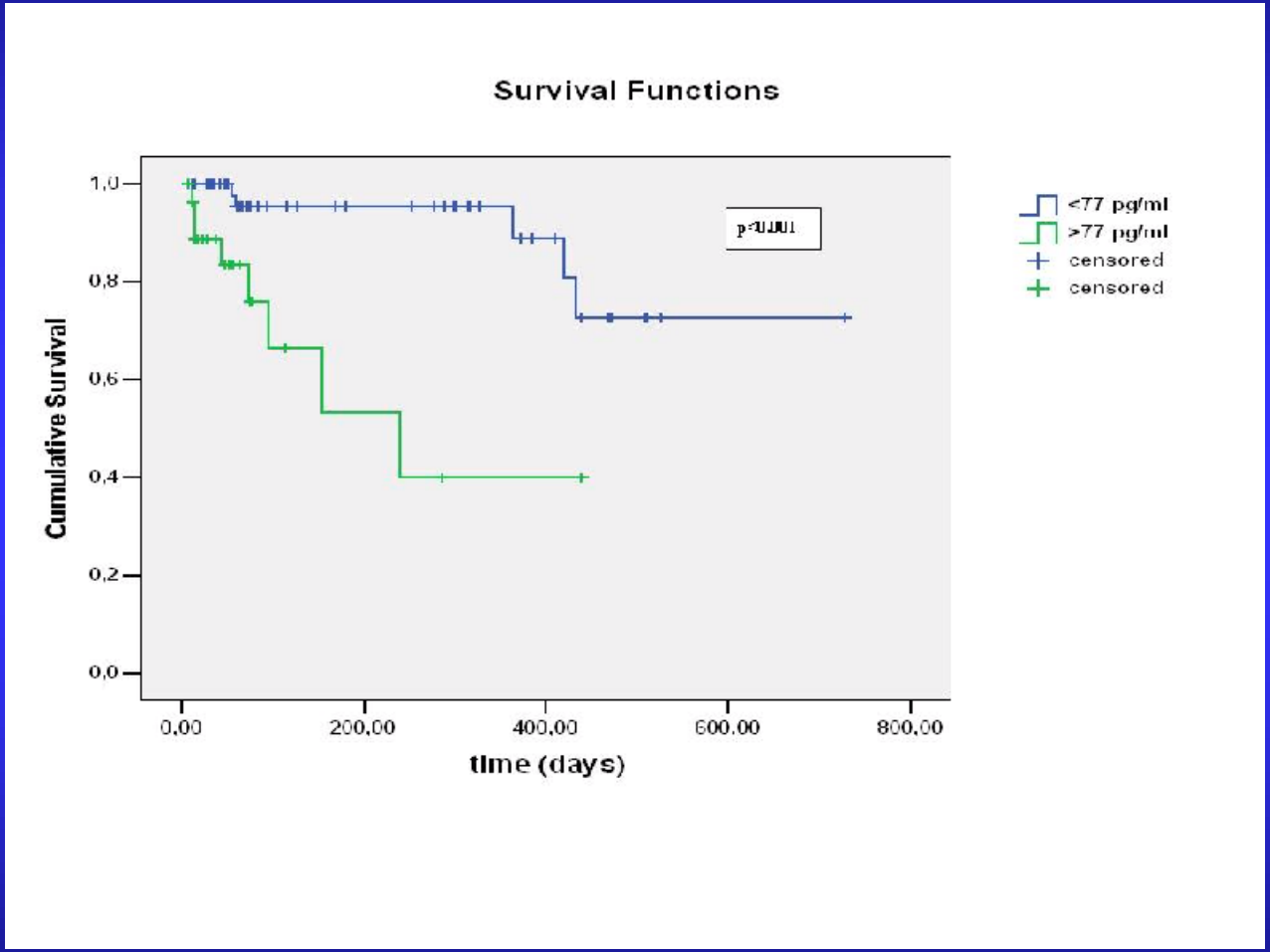
Biomarker	Diagnostic Capability	Prognostic Capability
BNP	+++	+++
NT-proBNP	+++	+++
ST2	-	++
GDF-15	-	+
Galectin	-	+
MR-proANP	++	++
NGAL	+++	+++
Hs-Tn	+++	+++
MR-proADM	-	+++
Procalcitonin	+++	+++

Maisel. Cardiovasc Diagn Ther 2012;2(2):147-164

Potential Mechanisms for Cardiac Troponin Elevations in HF

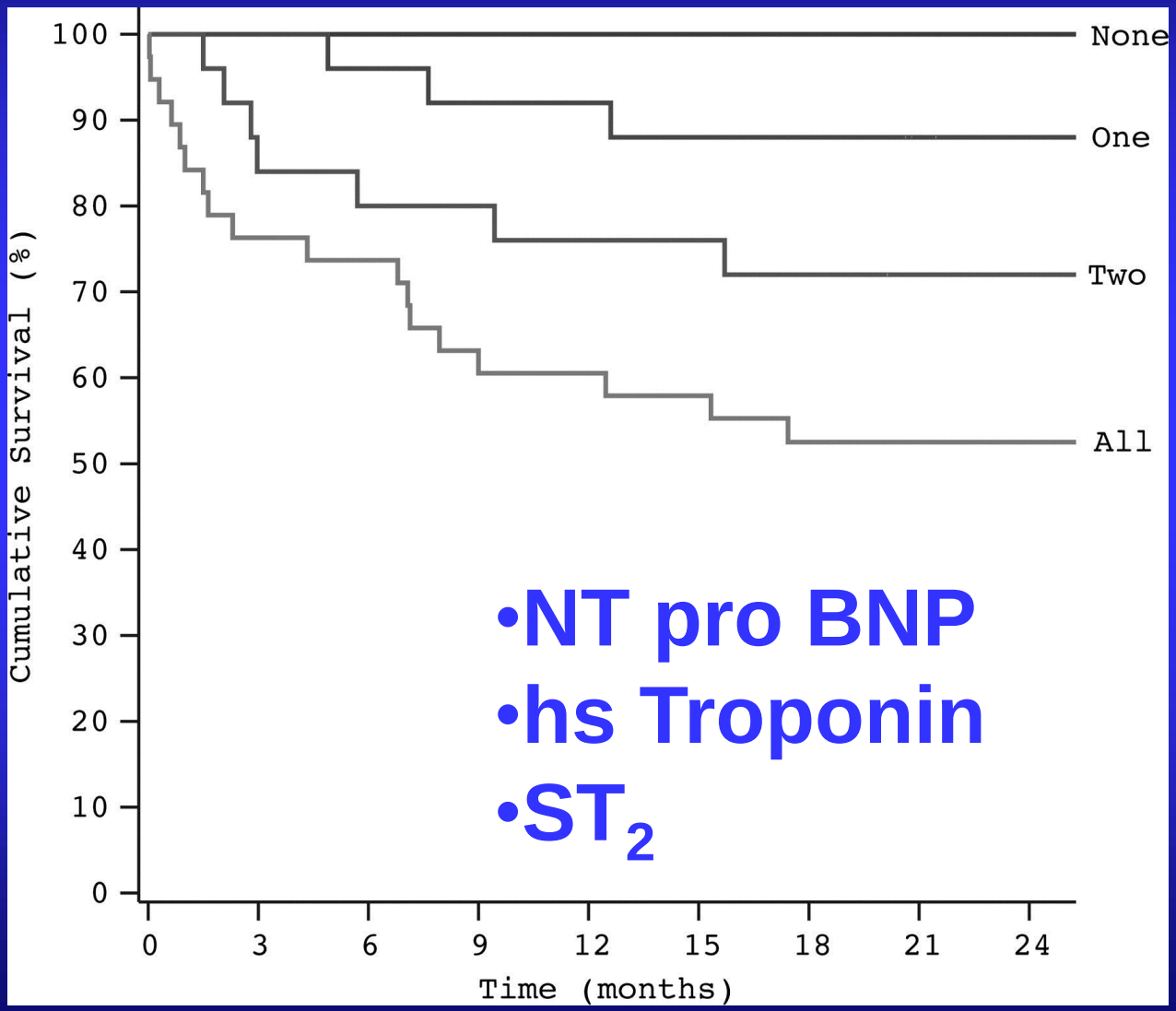


Prognostic value of hs- troponin T in patients with ADHF and non-detectable conventional troponin T levels



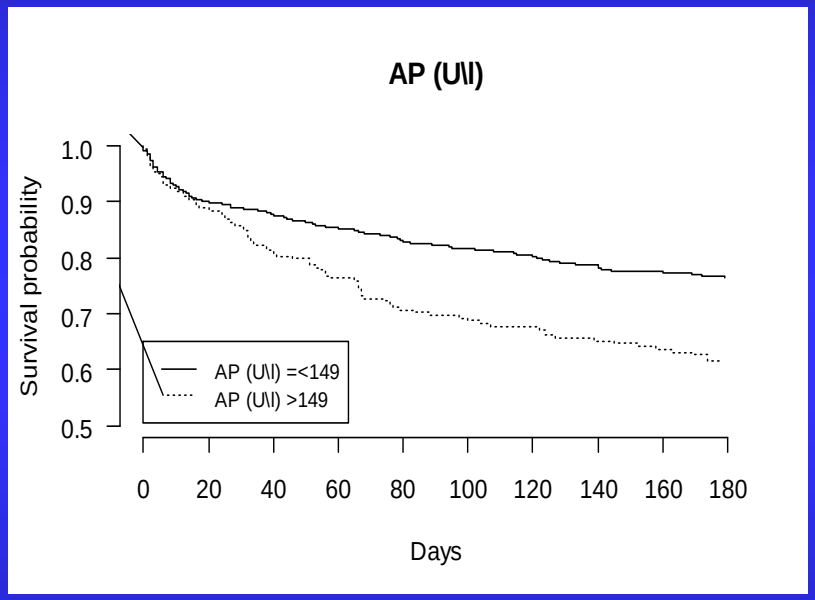
Parissis et al. IJC 2012

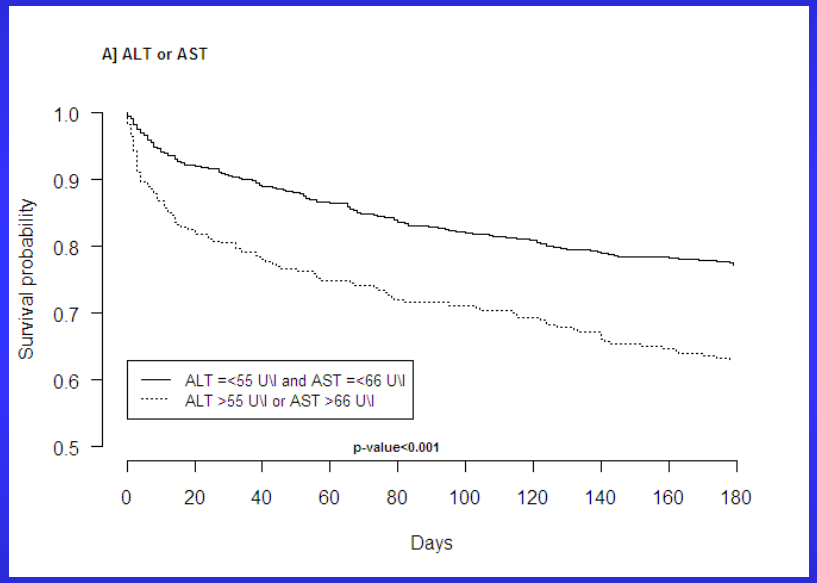
Kaplan–Meier survival curves according to the presence of none (n= 18), one (n= 26), two (n= 25), or three biomarkers (n= 38) above optimal cut-off points



Pascual-Figal D A et al. Eur J Heart Fail 2011;13:718-725

Prognostic role of liver congestion in ADHF: A SURVIVE subanalysis





Evidence for cardio-hepatic syndrome

Nikolaou M, Parissis J, …, Mebazaa A. EHJ 2013;34:742-749

Additive values of abnormal transaminases and abnormal alkaline phosphatase on a short- andlong-term outcome

	AST and ALT normal	AST and/or ALT abnormal
30-day mortality		
AP (%)		
Normal	46/587 (7.8)	53/307 (17.3)
Abnormal	13/129(10.0)	21/111 (18.9)
180-day mortality		
AP (%)		
Normal	118/587 (20.1)	92/307 (30.0)
Abnormal	40/129 (31.0)	41/111 (36.9)

Nikolaou M, Parissis J, …, Mebazaa A. EHJ 2013;34:742-749

Clinical Assessment of Acute Heart Failure Syndromes

CONGESTION?

ADEQUATE PERFUSION?

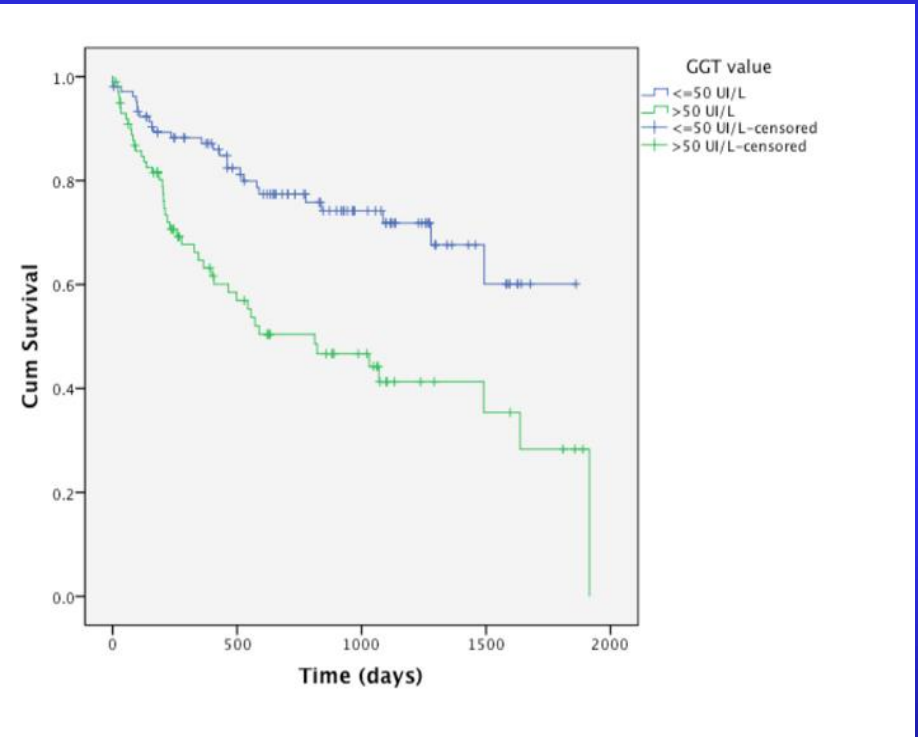
↓Proportional pulse pressure
Cool extremities
Altered mentation
ACE-I intolerance
Worsening renal function

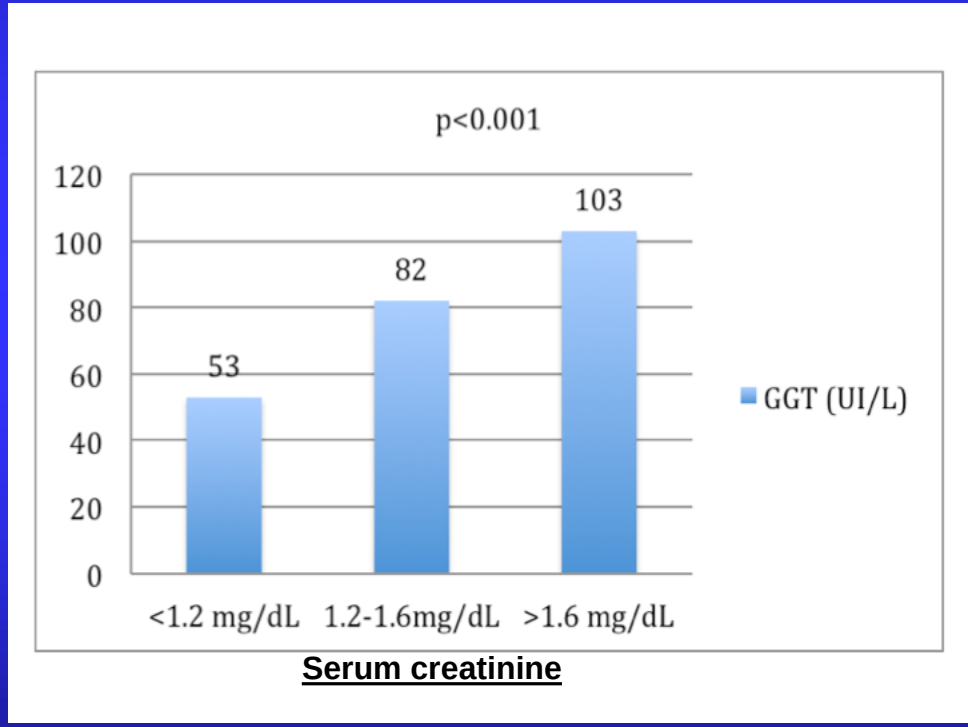
	−	+
+	Normal *Dry and Warm*	High ALP *Wet and Warm*
−	High Transaminases *Dry and Cold*	High Transaminases plus ALP *Wet and Cold*

Orthopnea
Rales
Abnormal BP response to Valsalva maneuver
↑Jugular venous pressure
Abdominojugular reflux
Hepatomegaly
Ascites
Edema

Nohria et al. Am J Cardiol 2005;96[suppl]:32G–40G

GGT levels in ADHF: prognostic value and relationship with renal function





Parissis et al. Int J Cardiol 2014

Biomarker-guided therapy: which molecules?

Cardiac stress

- **BNP/ NT-pro-BNP**
- MR-proANP
- Copeptin
- ST2

Cardiac injury

- **Hs troponins**

Cardiac fibrosis/remodeling

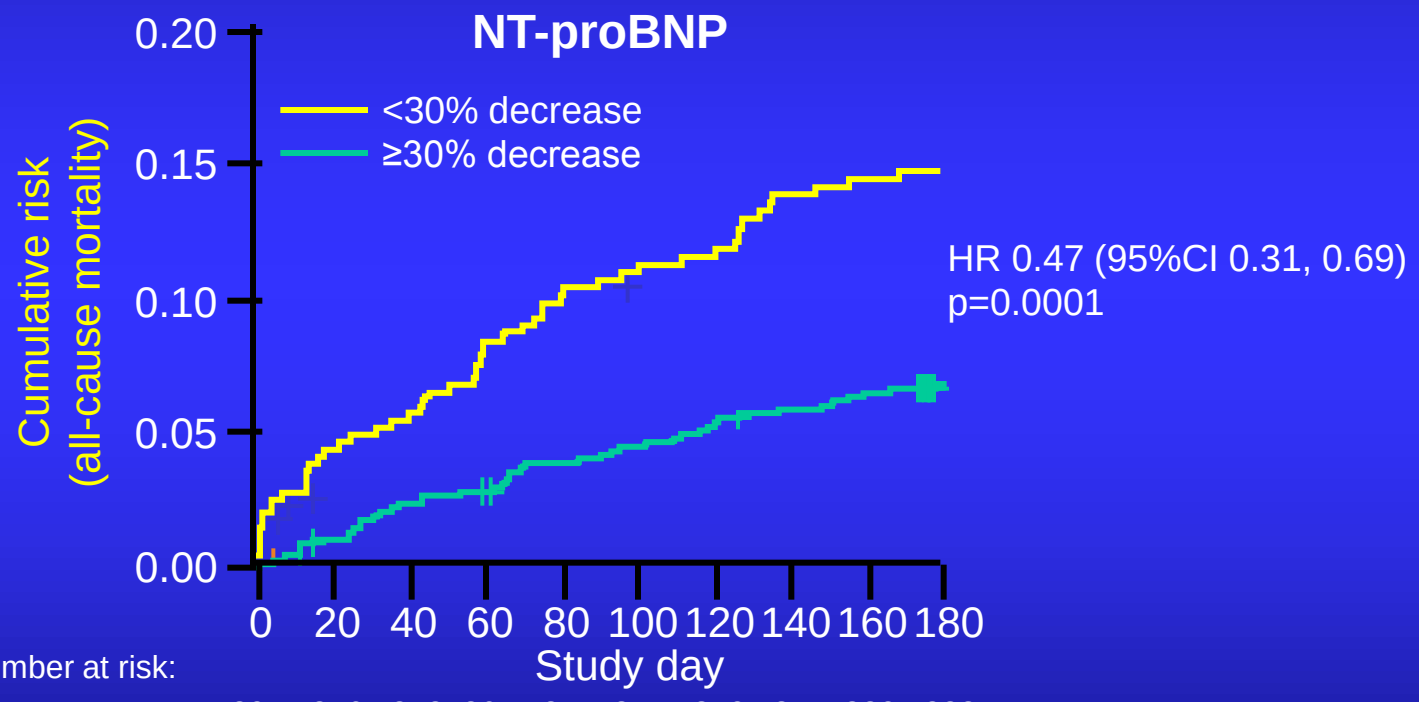
- **Galectin-3**
- PNIII/CT1

Co-morbidities

- **NGAL (renal)**
- cystatin-c
- Pro-calcitonin (respiratory)

RELAX-AHF: decreases from baseline in NT-proBNP levels are associated with decreased mortality in patients with AHF

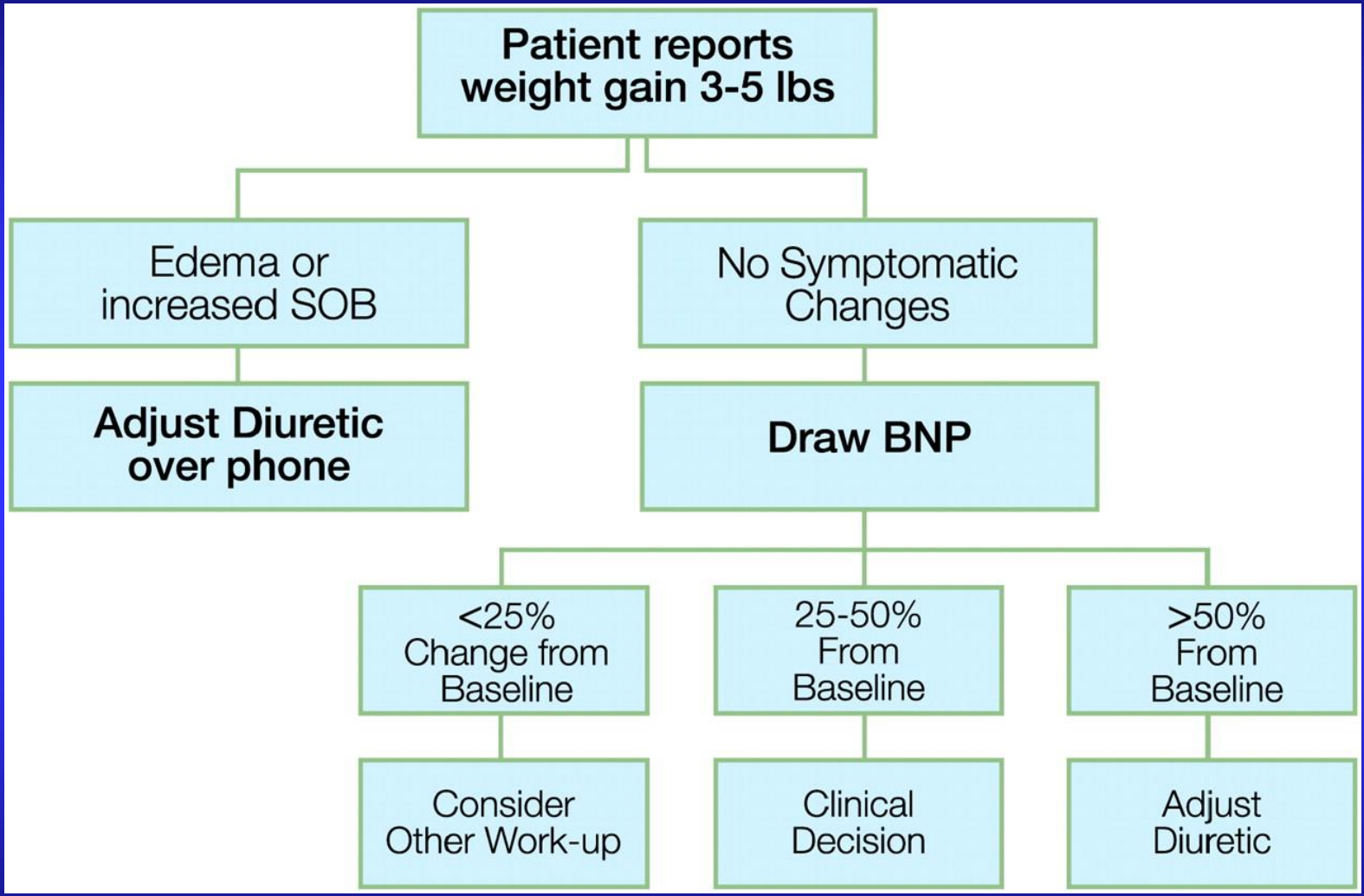
- At Day 2, a decrease in NT-proBNP ≥30% below baseline, indicative of decongestion, more than halved the risk of mortality through Day 180



Number at risk:										
<30% decrease	395	376	372	365	357	351	349	341	339	288
≥30% decrease	686	677	668	663	656	652	647	642	638	559

AHF=acute heart failure; CI=confidence interval; HR=hazard ratio;
NT-proBNP=N-terminal pro B-type natriuretic peptide; RELAX-AHF=RELAXin in Acute Heart Failure
Metra et al. J Am Coll Cardiol 2013;61:196–206

Algorithms for determining decompensation.



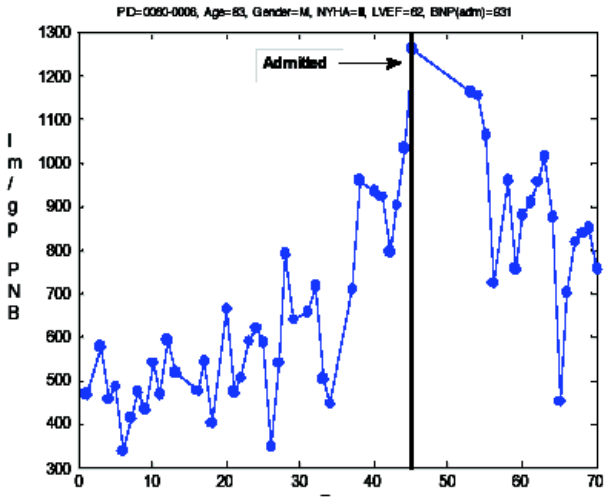
Maisel A S et al. Nephrol. Dial. Transplant. 2010;ndt.gfq647

HABIT-protocol

- Discharged from hospital for HF with BNP > 400 pg/ml
- Outpatient decompensaton
- Daily fingersticks of BNP at home (patient and MD blinded) x 60 days
- > 150 patients have completed trial
- Results to be presented at HFSA

HABIT

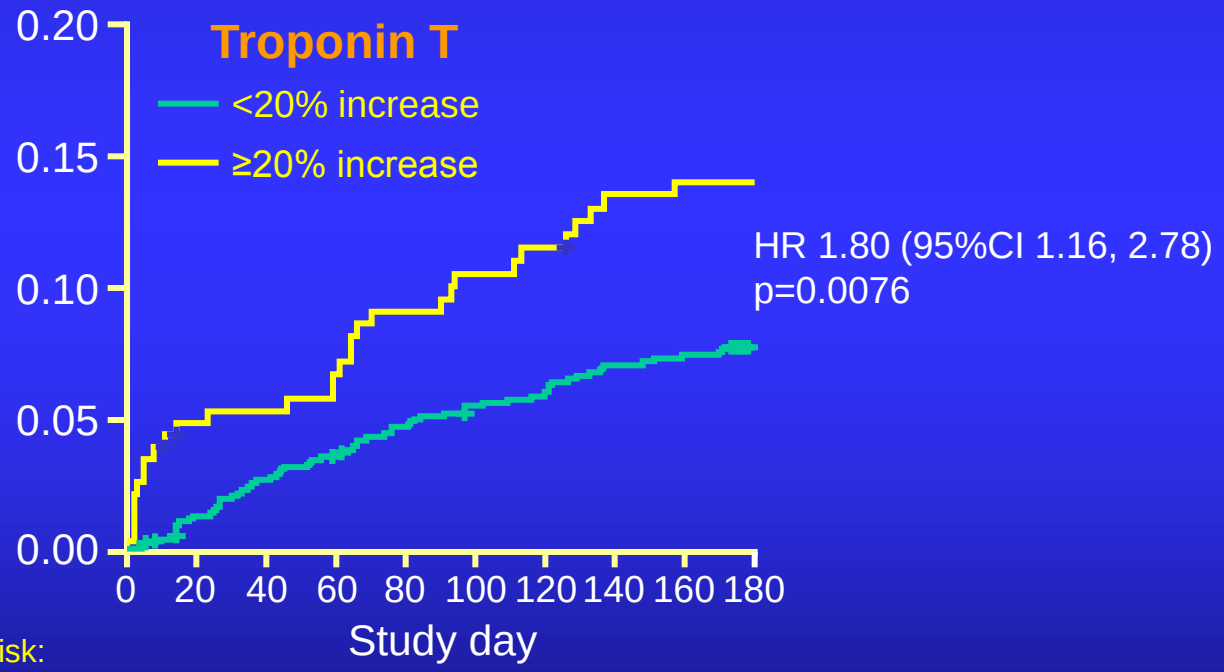
HF **A**ssessment with **B**NP **I**n **T**he Home



A Maisel JACC 2013

RELAX AHF: increases from baseline in hs-cTnT levels are associated with increased mortality in patients with AHF

- Increased hs-cTnT levels from baseline were associated with increased 180-day mortality
- At Day 2, an increase in hs-cTnT ≥20% over baseline, indicative of substantial additional myocardial necrosis, nearly doubled the risk of mortality through Day 180



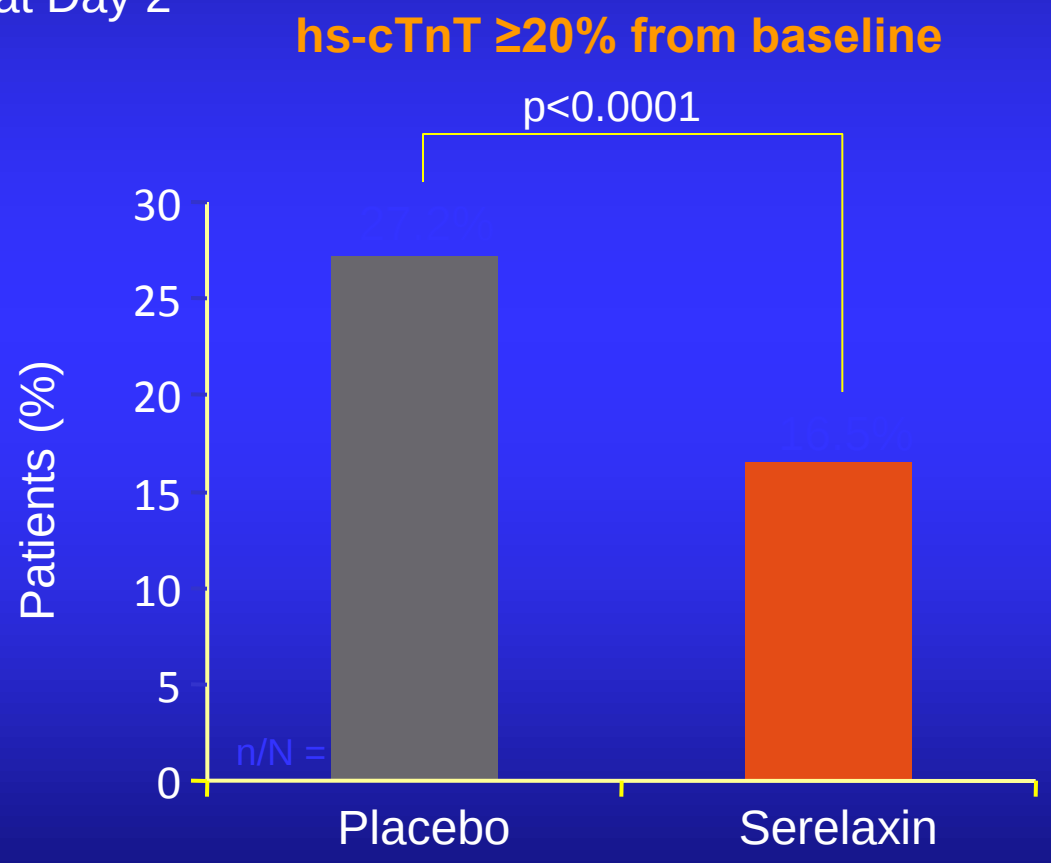
Number at risk:										
<20% increase	825	810	799	790	782	775	771	762	759	654
≥20% increase	231	219	218	216	210	207	204	200	199	174

AHF=acute heart failure; CI=confidence interval; HR=hazard ratio; hs-cTnT=high sensitivity cardiac troponin T; KM=Kaplan-Meier; RELAX-AHF=RELAXin in Acute Heart Failure

Metra et al. J Am Coll Cardiol 2013;61:196–206

RELAX-AHF: Vasoactive treatment lowered the incidence of increased hs-cTnT levels in patients with AHF

- Fewer patients had increased hs-cTnT ≥20% with serelaxin compared with placebo at Day 2



AHF=acute heart failure; hs-cTnT=high sensitivity cardiac troponin T;
RELAX-AHF=RELAXin in Acute Heart Failure
Metra et al. J Am Coll Cardiol 2013;61:196–206

NPs vs Clinical Judgment guided therapy in Heart Failure

Current evidence

Benefit in subjects younger than 75 years

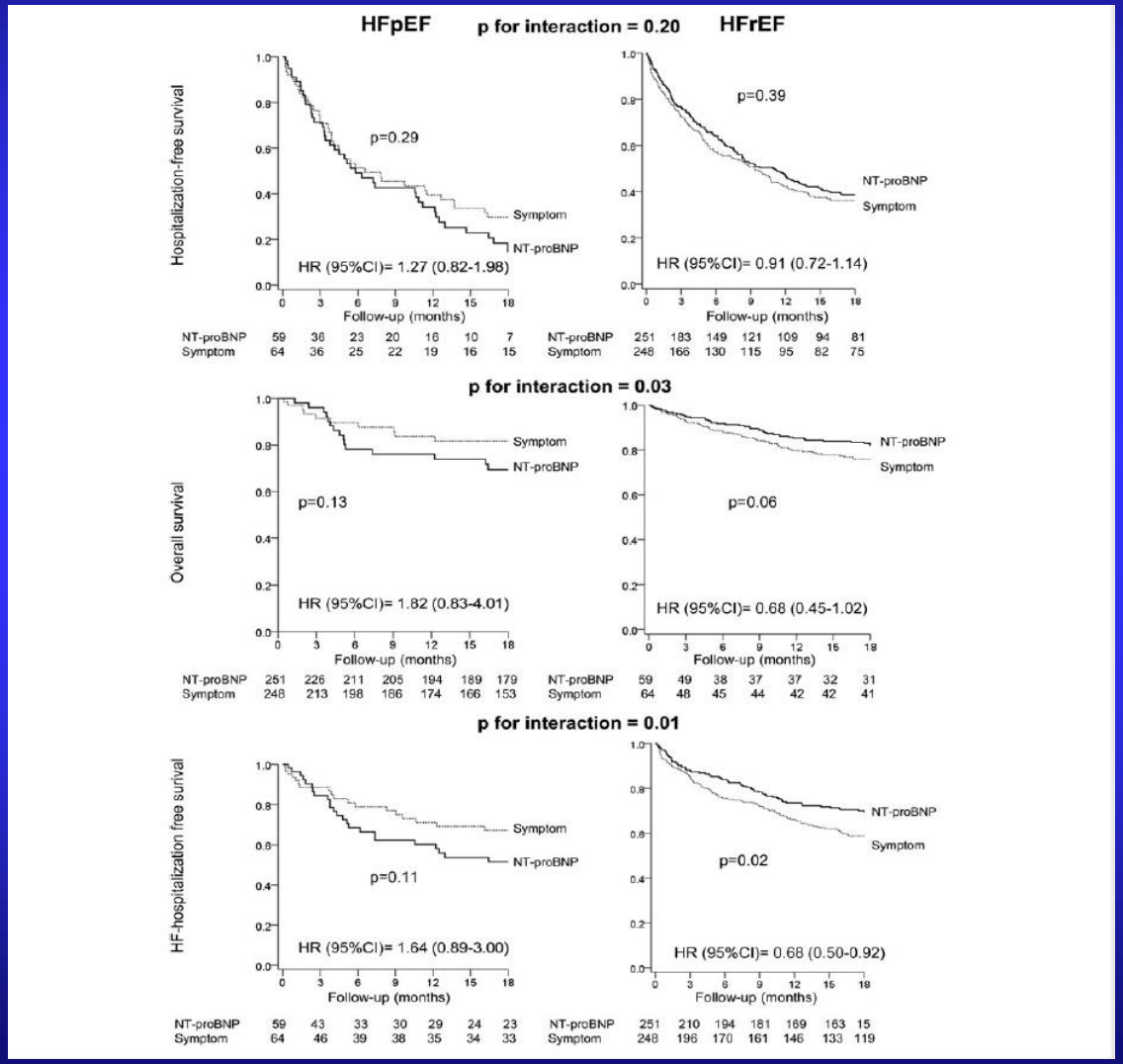
Study		STARS-BNP	TIME-CHF	BATTLESCARRED
N		220	499	364
Fixed target		100 pg/ml	400 / 800 pg/ml	1300 pg/ml
Reduction:	primary endpoint	yes	no	no
	overall mortality	no	no	no
	Mortality < 75 years	----------	yes	yes, 10.9% vs 21.7%
Target reached		33%	minority	minority

Jourdain P et al. JACC 2007; 49:1733

TIME-CHF Pfisterer M et al. JAMA 2009;301:383

BATTLESCARRED Richards M et al. JACC 2009

TIME-CHF sub-analysis: NT-proBNP guided therapy in patients with HFpEF



Maeder et al. Eur J Heart Fail 2013;15:1148–1156

NP-guided treatment in CHF: unsolved issues

- Cut-off limits of therapeutic target ?
- BNP or NT-proBNP or something else ?
- One biomarker or multi-marker strategy ?
- Biomarker alone or combined with “hard” clinical end –points ?

PROTECT TRIAL: Study Design

Patient with Class II-IV symptoms, EF ≤ 40%, recent HF event

Randomization echocardiogram

Standard of Care

Minnesota Living With HF Questionnaire quarterly

Therapy adjusted to achieve optimal drug targets

Visits q3 months

Extra visits as needed for treatment goals

Standard of Care + NT-proBNP

Minnesota Living With HF Questionnaire quarterly

Therapy adjusted to achieve optimal drug targets *PLUS* NT-proBNP ≤ 1000 pg/mL

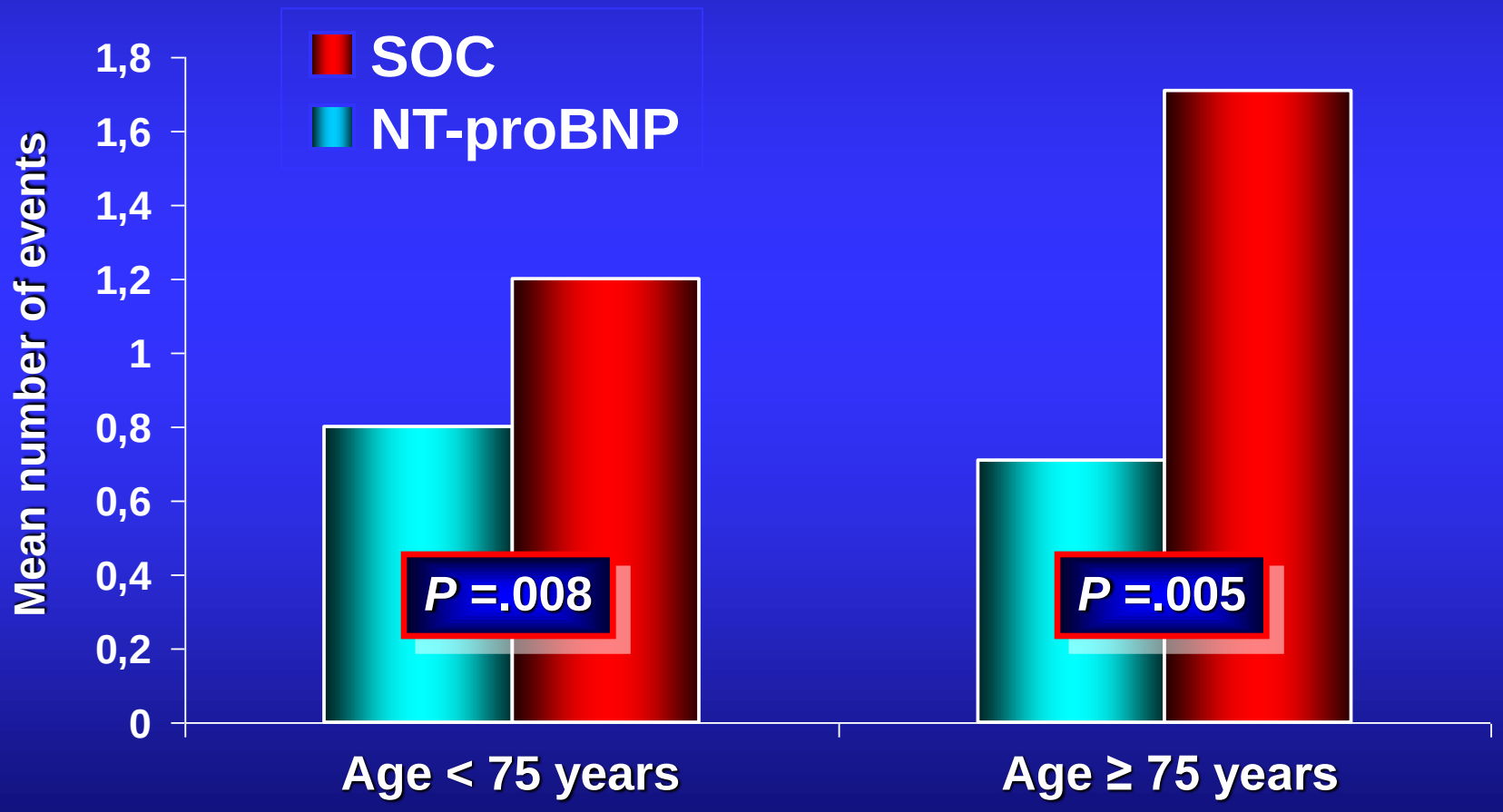
Visits q3 months

Extra visits as needed for treatment goals

Close-out echocardiogram

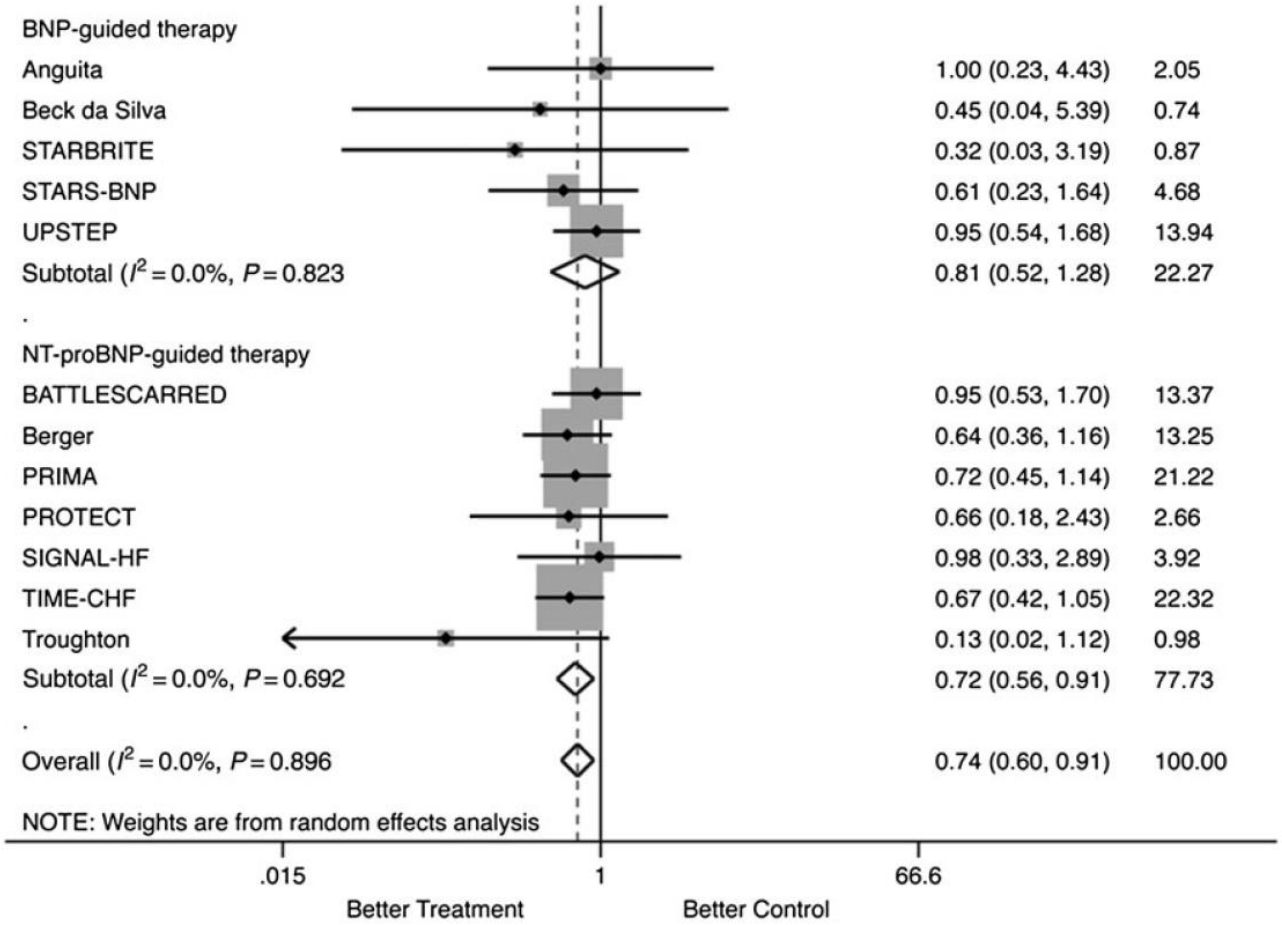
Total cardiovascular events assessed

Age and outcomes



*No interaction between age and NT-proBNP guided care was found (P =.11)

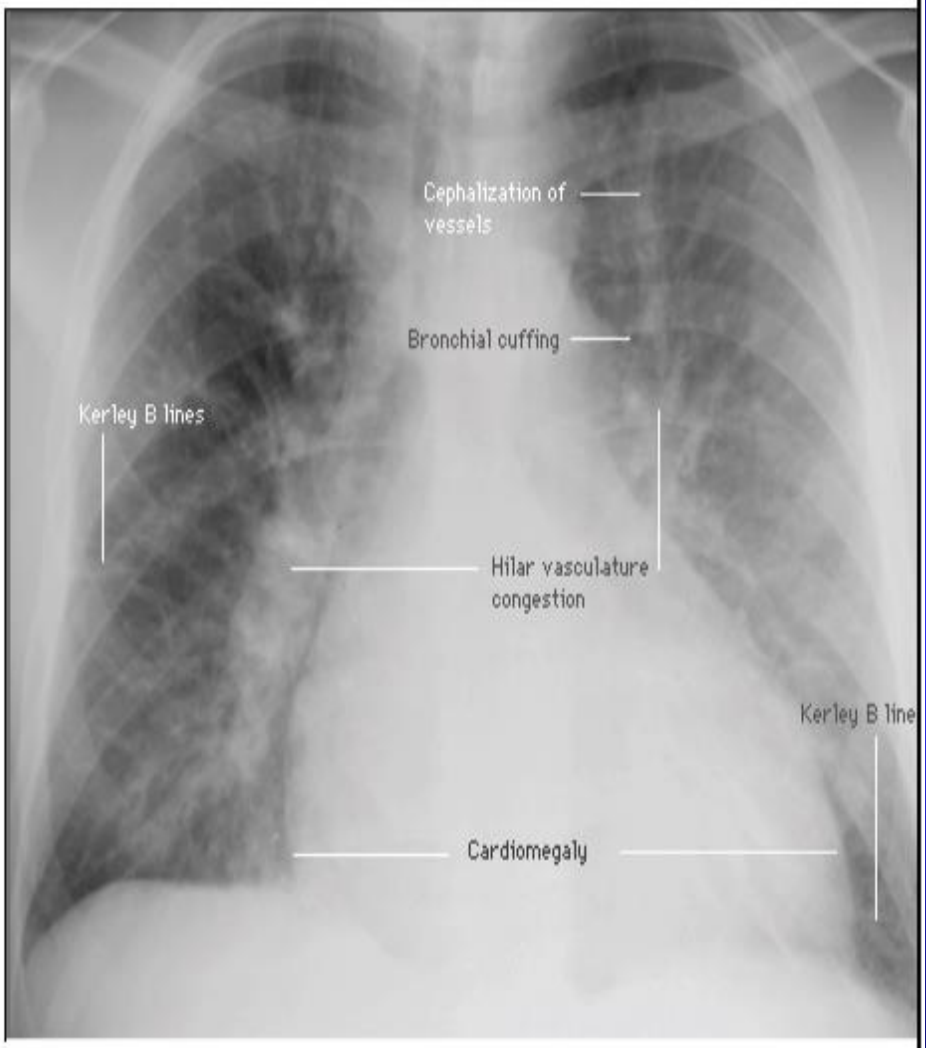
Meta-analysis of NP guided therapy



Troughton et al. Eur Heart J 2013 November

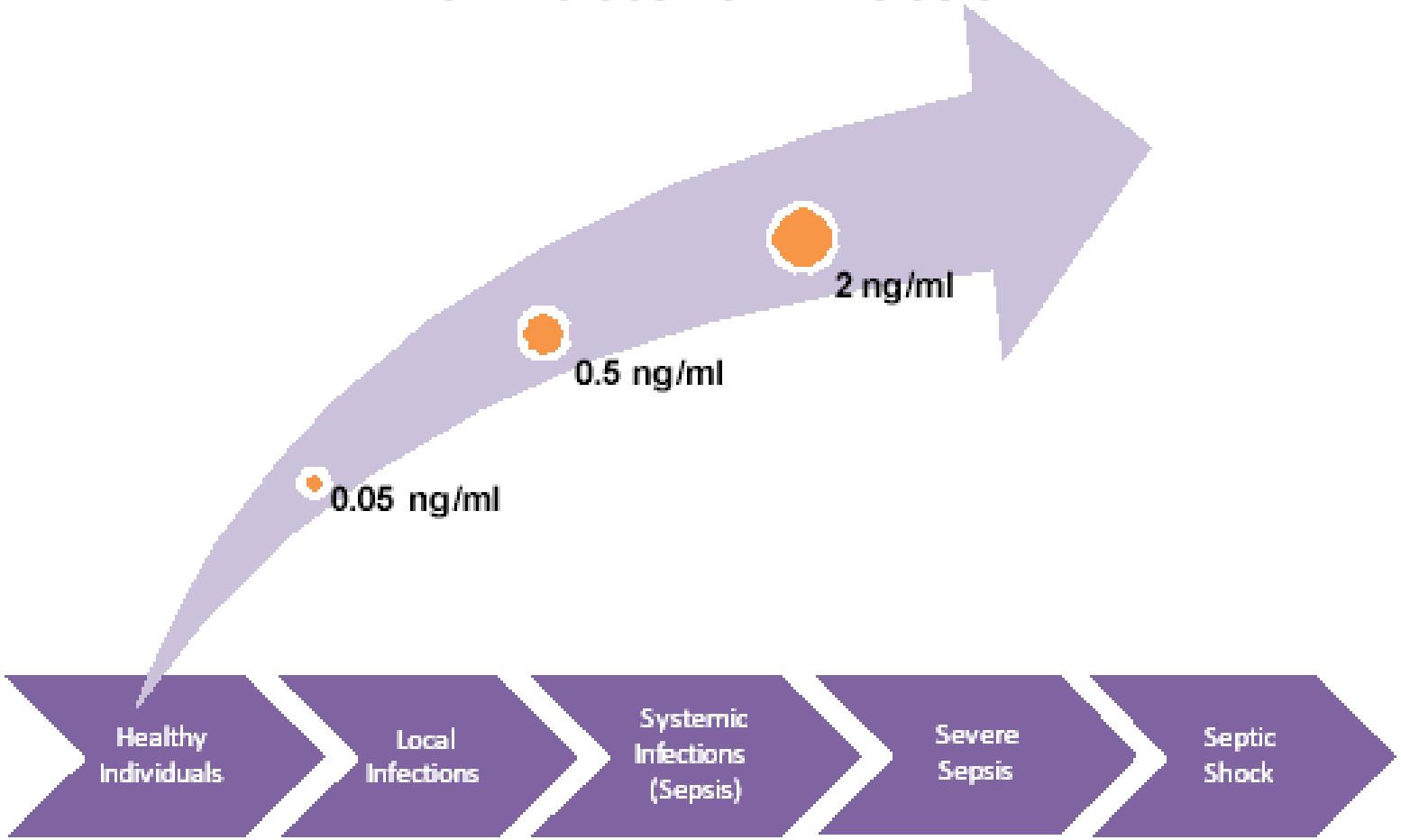
Heart Failure + infection

- Heart failure plus pneumonia is present about 10-15% of time
- Heart failure plus any infection may occur in up to 20% of hospitalized heart failure patients.
- Hospital Mortality may be up to 20% (versus 5%) in heart failure patients with untreated infections



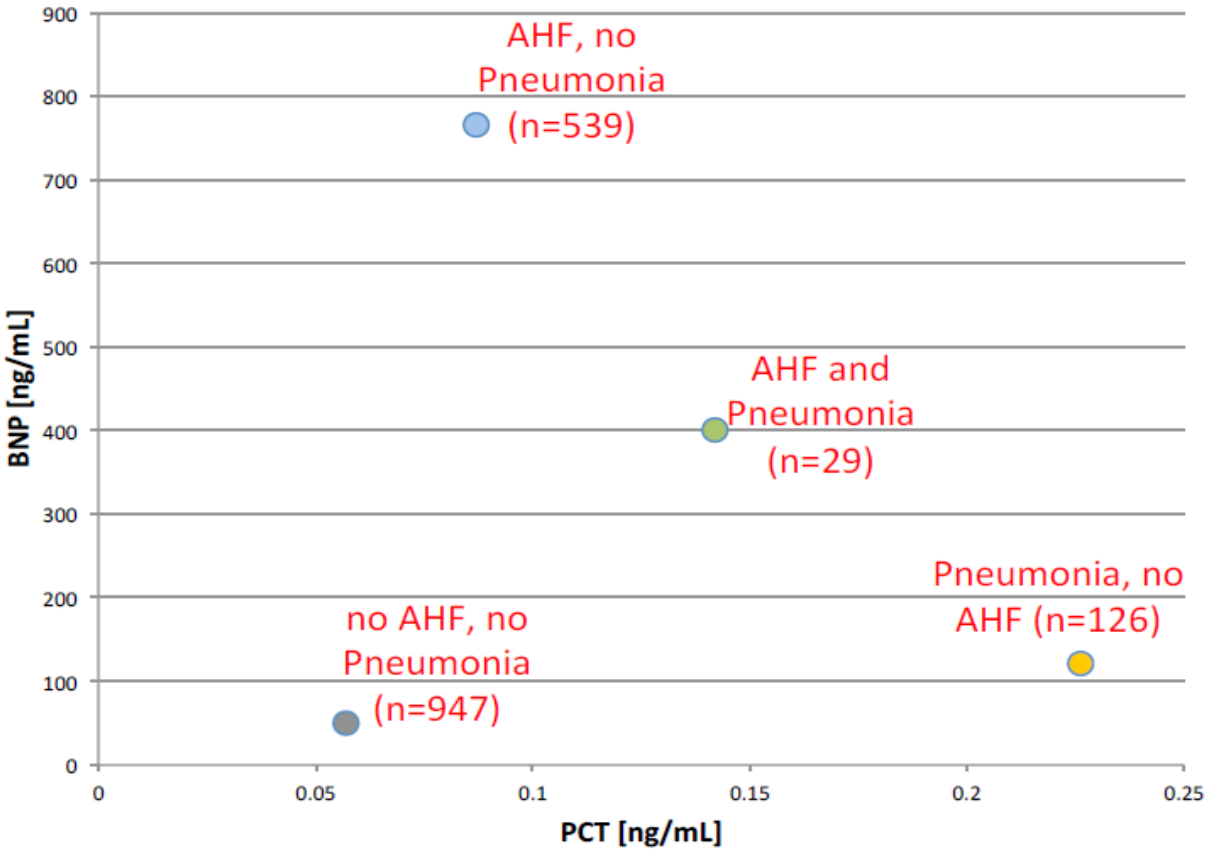
Follath et al. Int Care Med 2011

PCT Level Increase = Increased Significance of Bacterial Infection



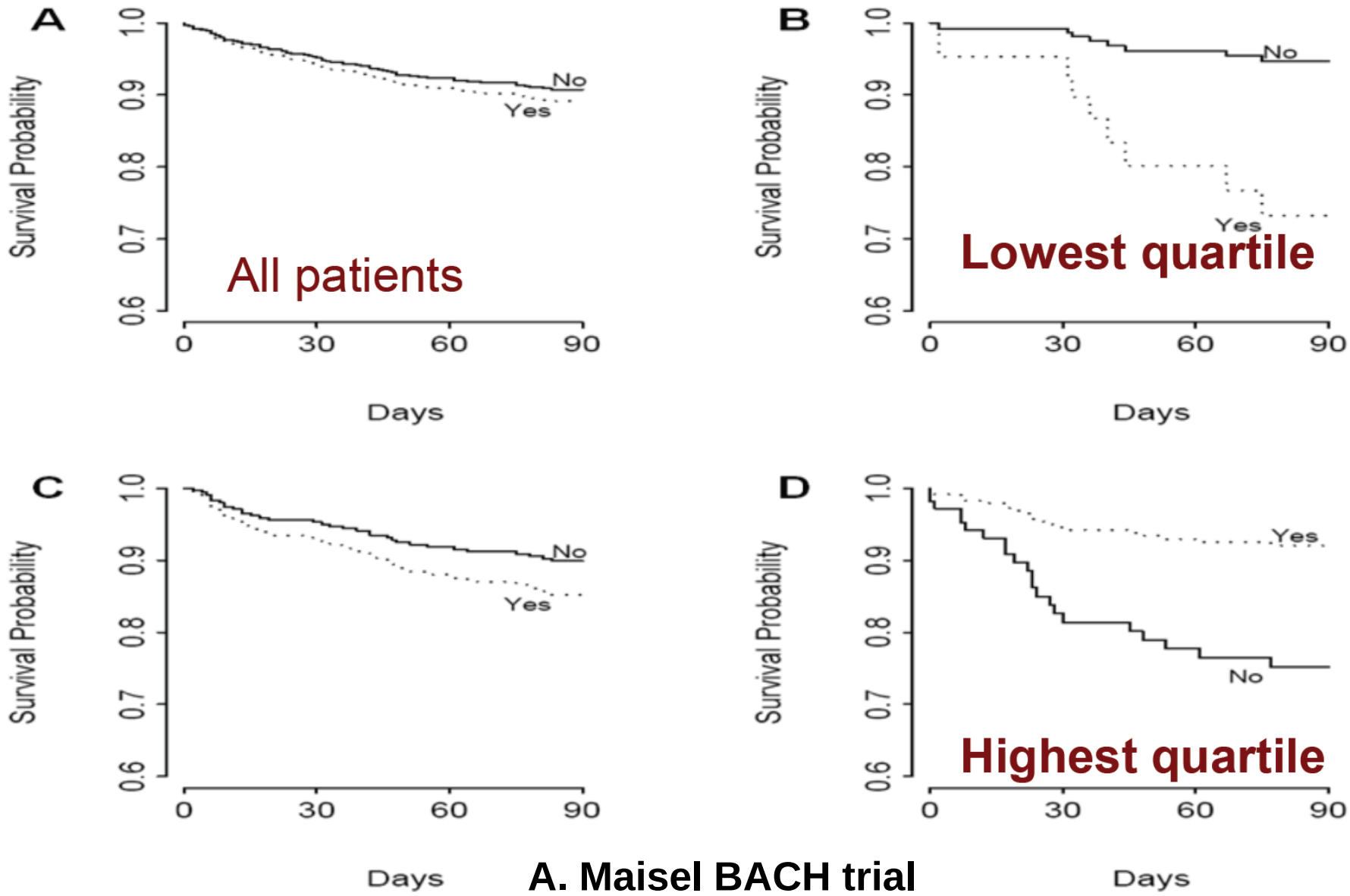
- In critically ill patients, **PCT levels** elevate in correlation to the severity of bacterial infection
- **In healthy people**, PCT concentration are found below 0.05ng/ml
- **Concentrations exceeding** 0.5ng/ml can be interpreted as abnormal

BACH TRIAL: Combining BNP and PCT in differential diagnosis of dyspnea



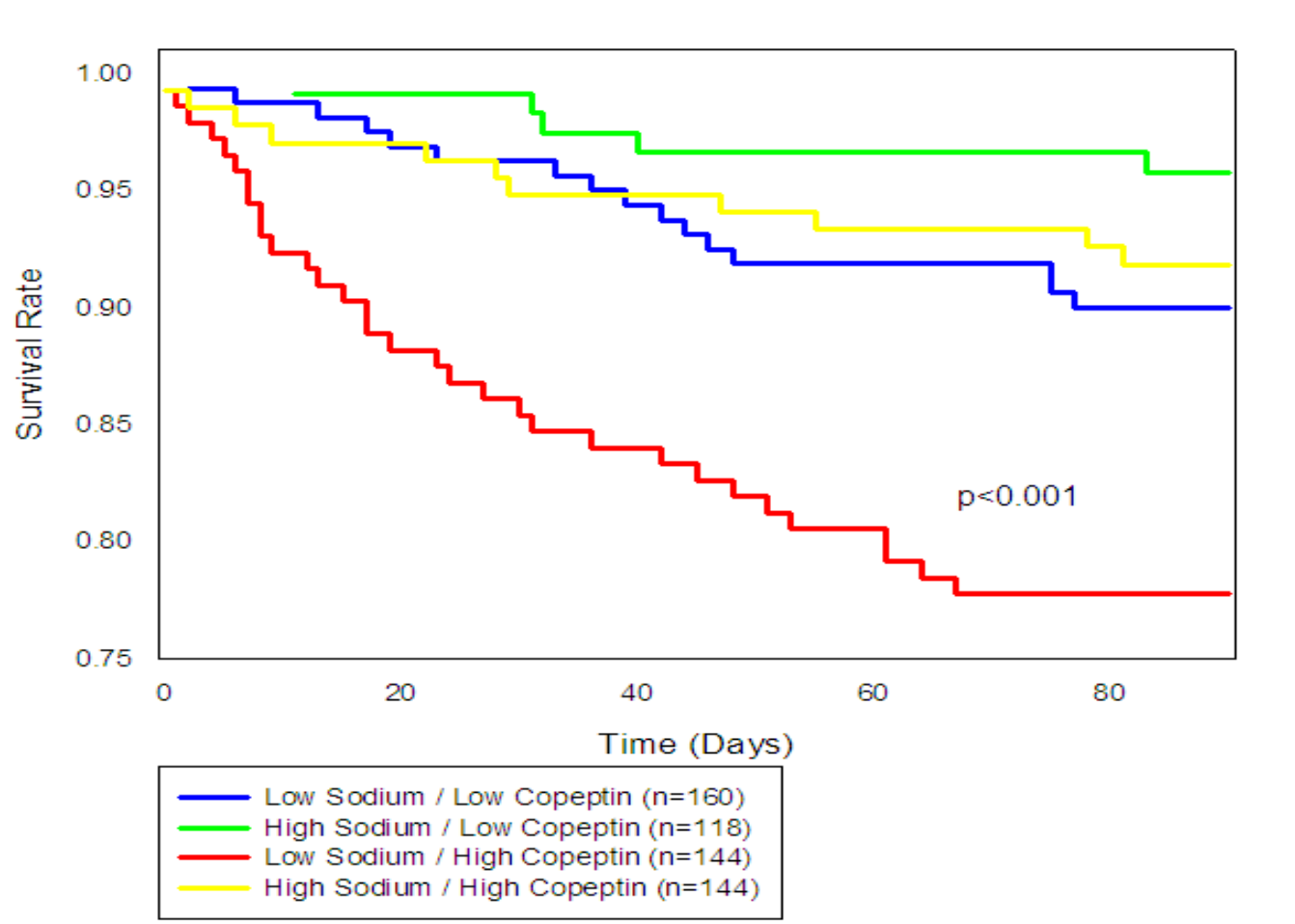
Maisel et al EJHF in press

Antibiotic treatment (yes or no) and all cause mortality within 90 days



A. Maisel BACH trial

Copeptin in Heart Failure

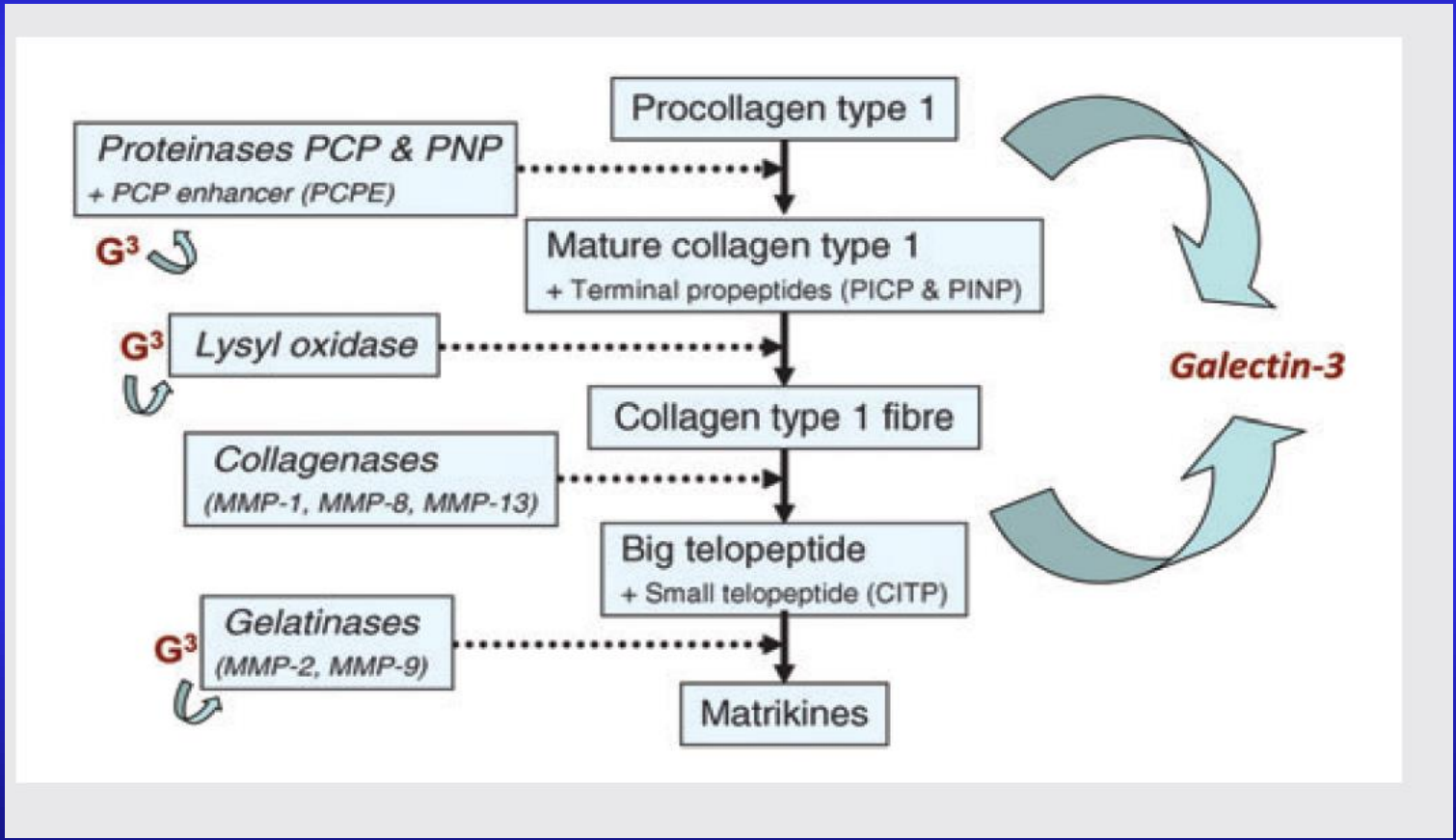


Xue et al. from the BACH Trial

ACTIVATE

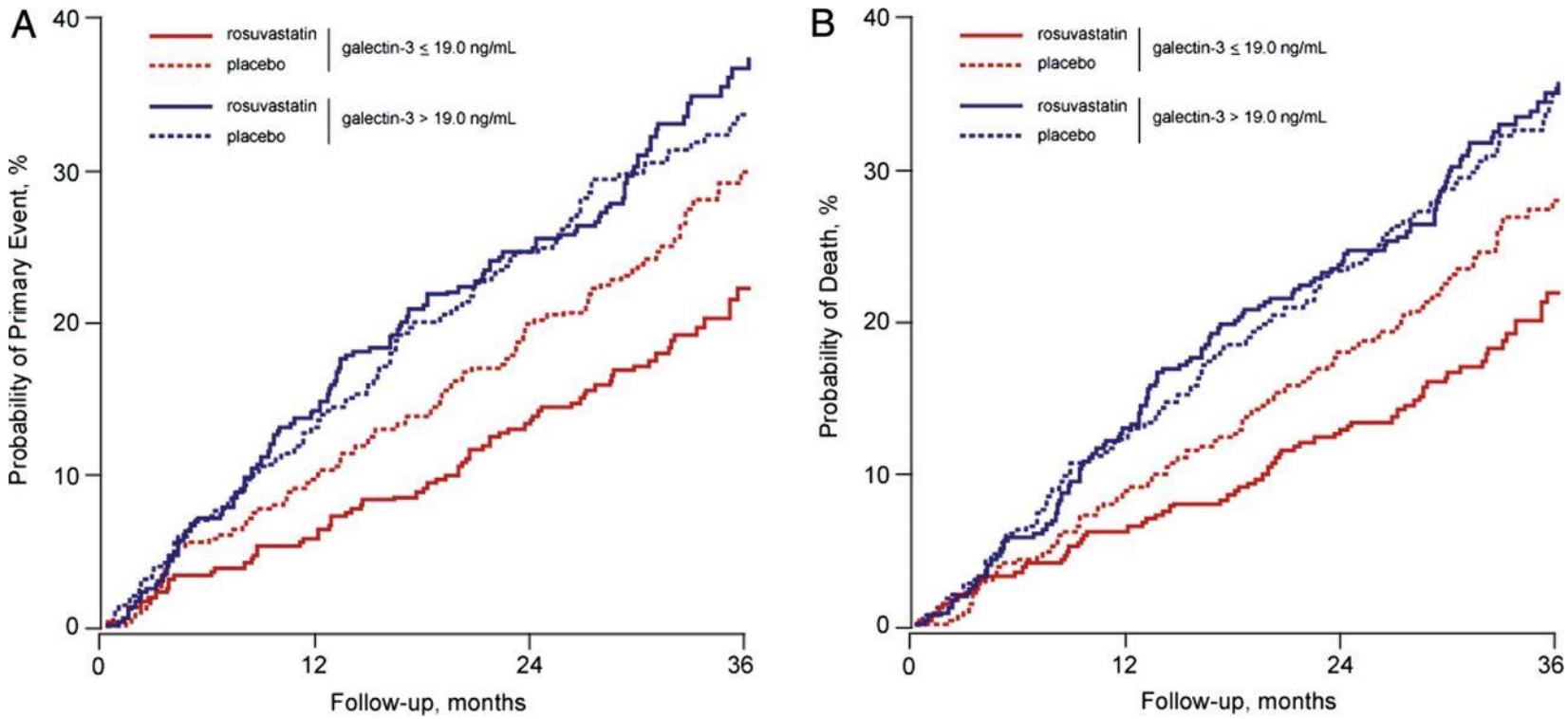
Acute heart failure patients with high Copeptin levels treated with Tolvaptan targets Increased aVp Activation for Treatment Efficacy

Galectin-3 a biomarker of cardiac fibrosis



De Boer et al. Eur J Heart Fail 2013;15: 1095–1101

Galectin-3 predicts response to statin therapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

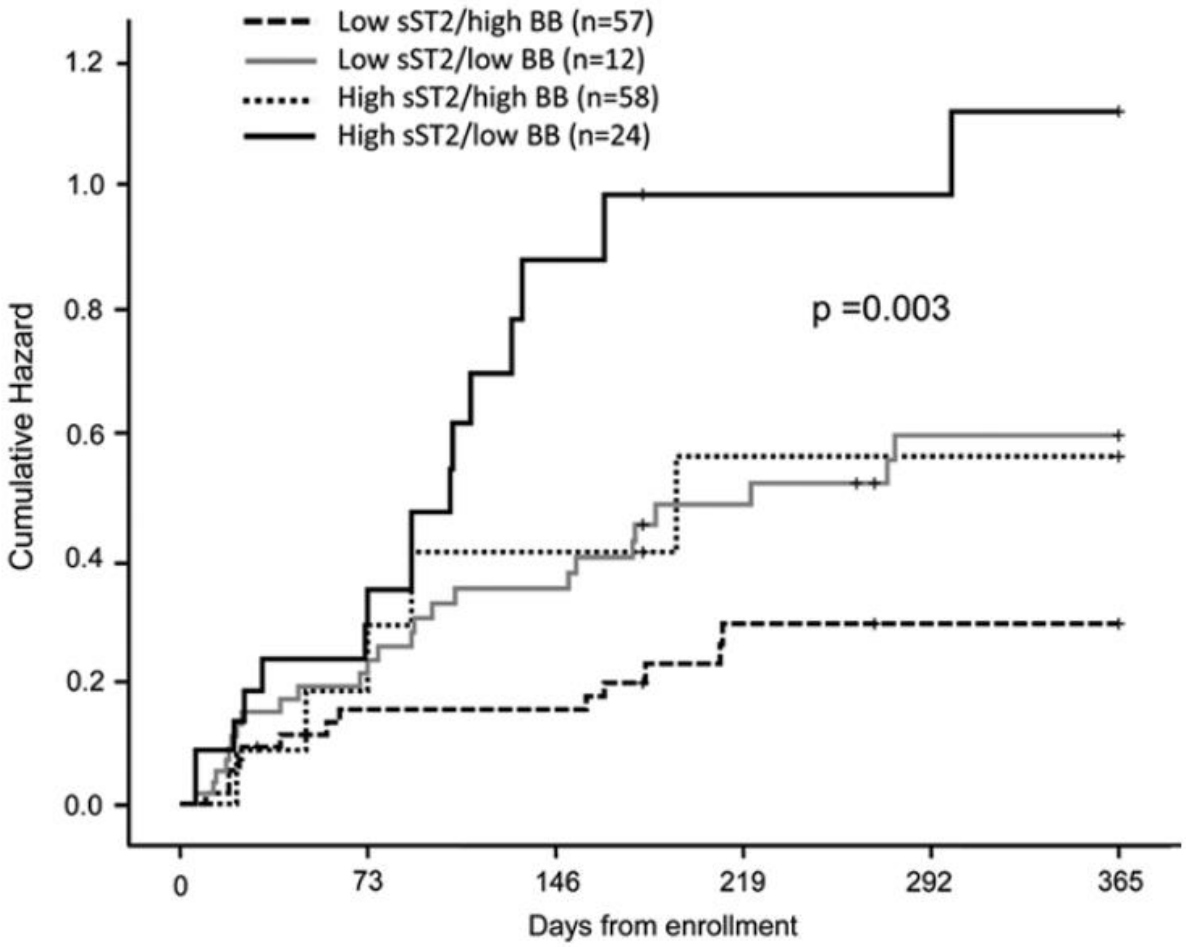


The Kaplan–Meier estimates for the primary endpoint (cardiovascular death and non-fatal myocardial infarction and stroke) (A) and for total mortality (B) by galectin-3 category (above and at or below the median level, 19.0 ng/mL).

Gullestad L et al. Eur Heart J 2012;33:2290-2296

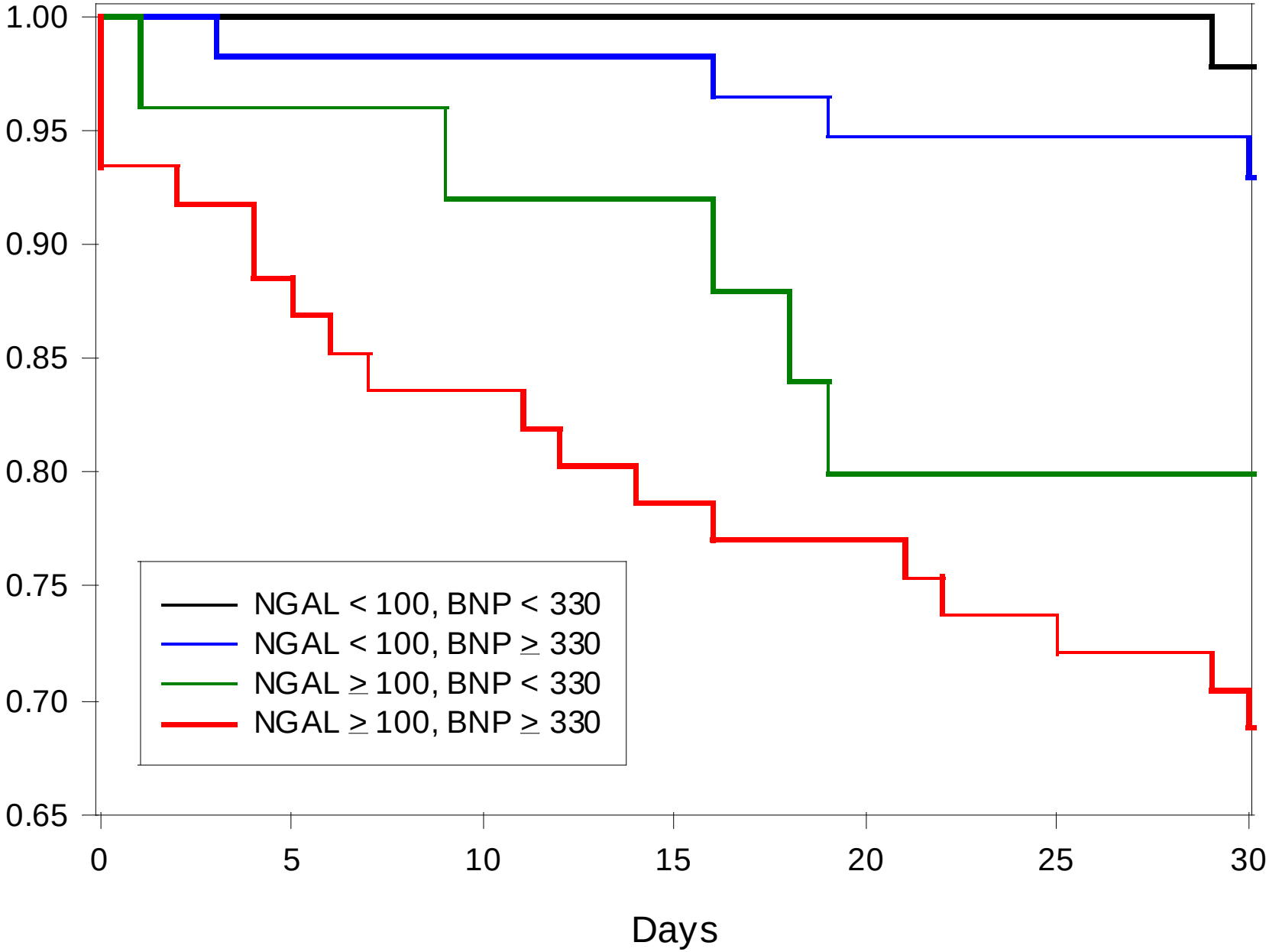
European Heart Journal

ST2 levels and beta-blocker up-titration in CHF

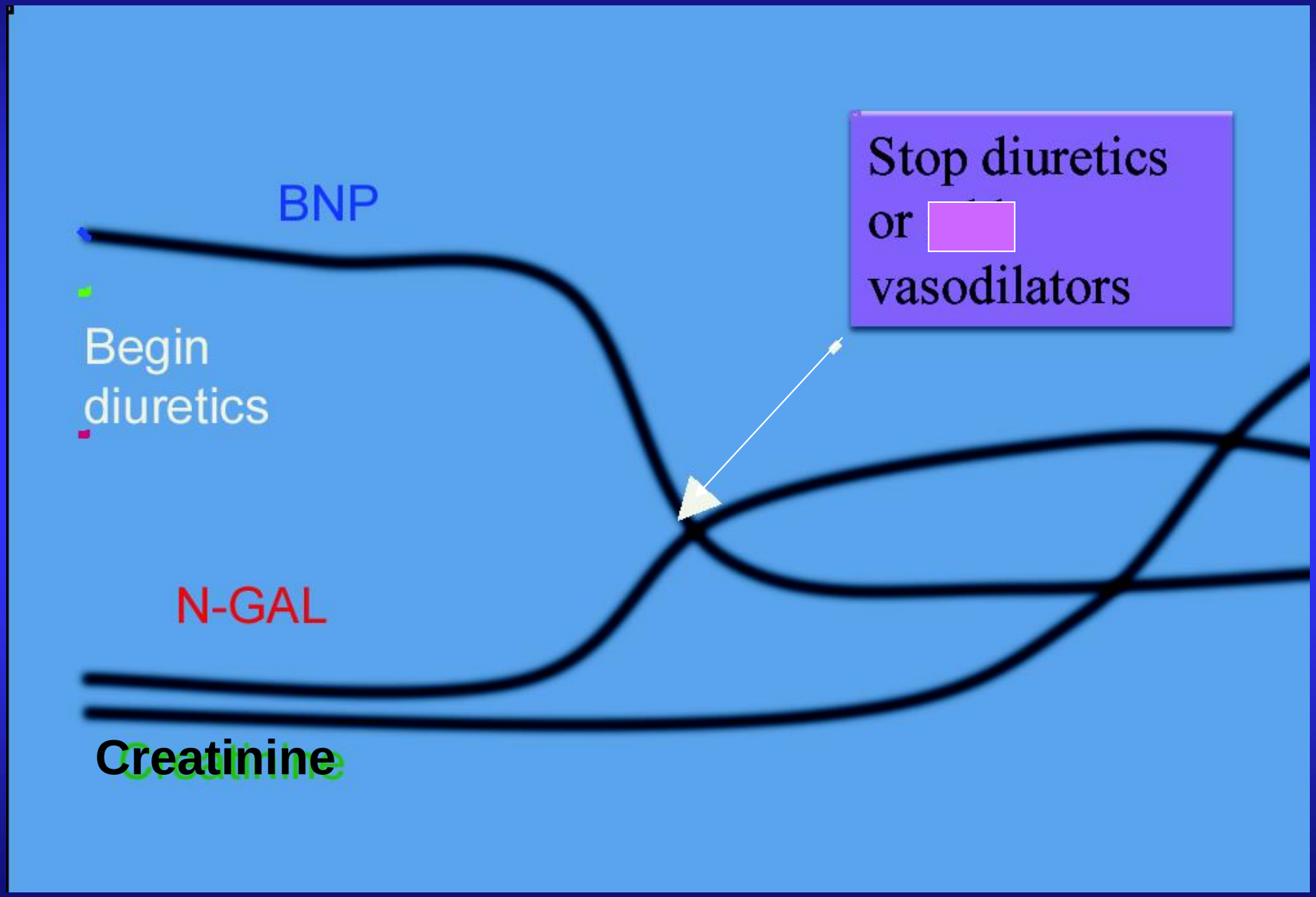


/high BB:	57	49	48	30	29	28
/low BB:	12	9	8	6	6	5
2/high BB:	58	47	41	30	25	24
2/low BB:	24	18	10	8	8	7

Gaggin et al. Circ Heart Fail. 2013;6:1206-1213


1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0
5
10
15
20
25
30
Days
NGAL < 100, BNP < 330
NGAL < 100, BNP ≥ 330
NGAL ≥ 100, BNP < 330
NGAL ≥ 100, BNP ≥ 330

NGAL may provide the “sweet spot”



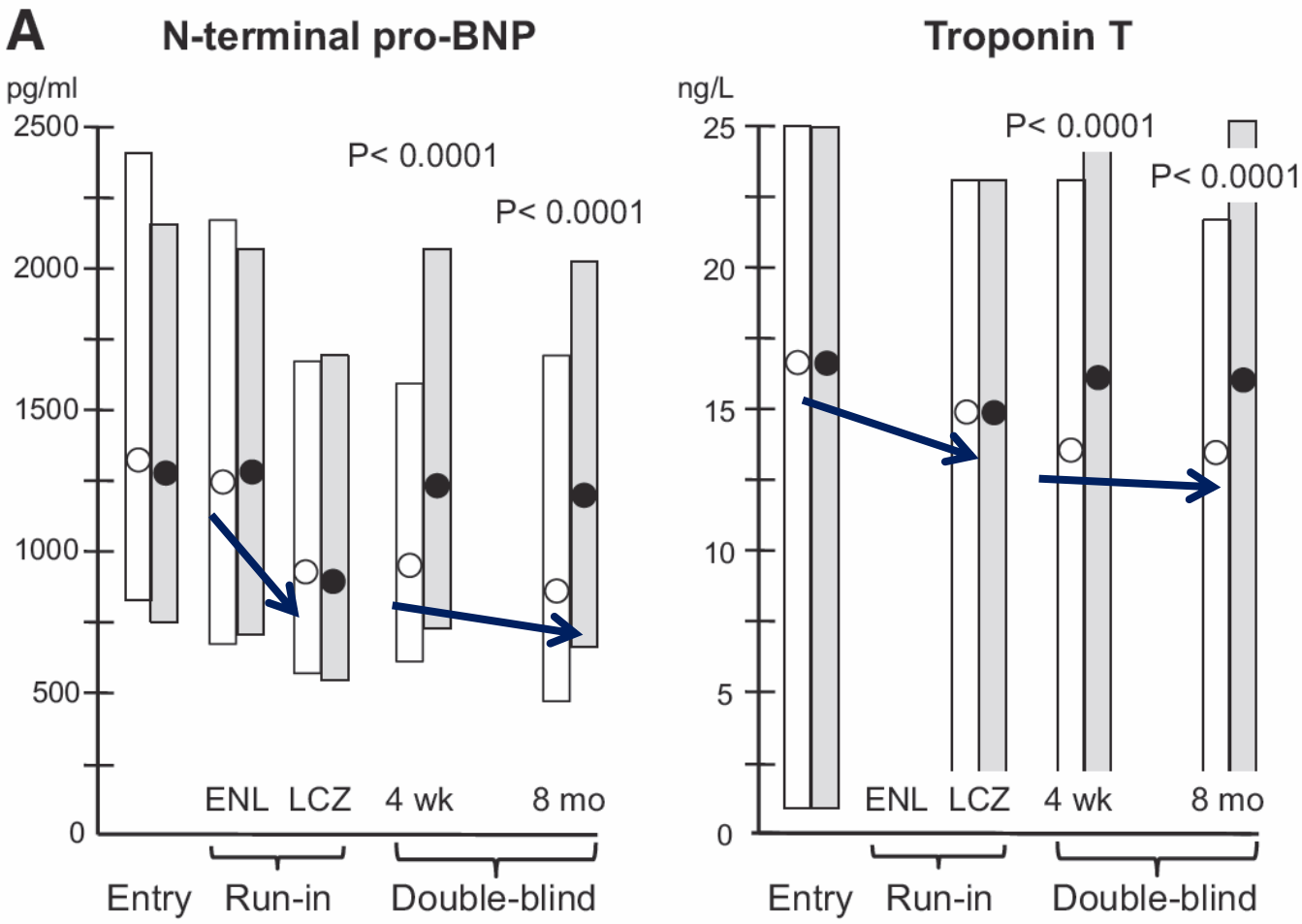
A. Maisel Courtesy

Recommendations for Biomarkers in HF

Biomarker, Application	Setting	COR	LOE
Natriuretic peptides			
Diagnosis or exclusion of HF	**Ambulatory, Acute**	**I**	**A**
Prognosis of HF	**Ambulatory, Acute**	**I**	**A**
Achieve GDMT	**Ambulatory**	**IIa**	**B**
Guidance of acutely decompensated HF therapy	**Acute**	**IIb**	**C**
Biomarkers of myocardial injury			
Additive risk stratification	**Acute, Ambulatory**	**I**	**A**
Biomarkers of myocardial fibrosis			
Additive risk stratification	**Ambulatory**	**IIb**	**B**
	Acute	**IIb**	**A**

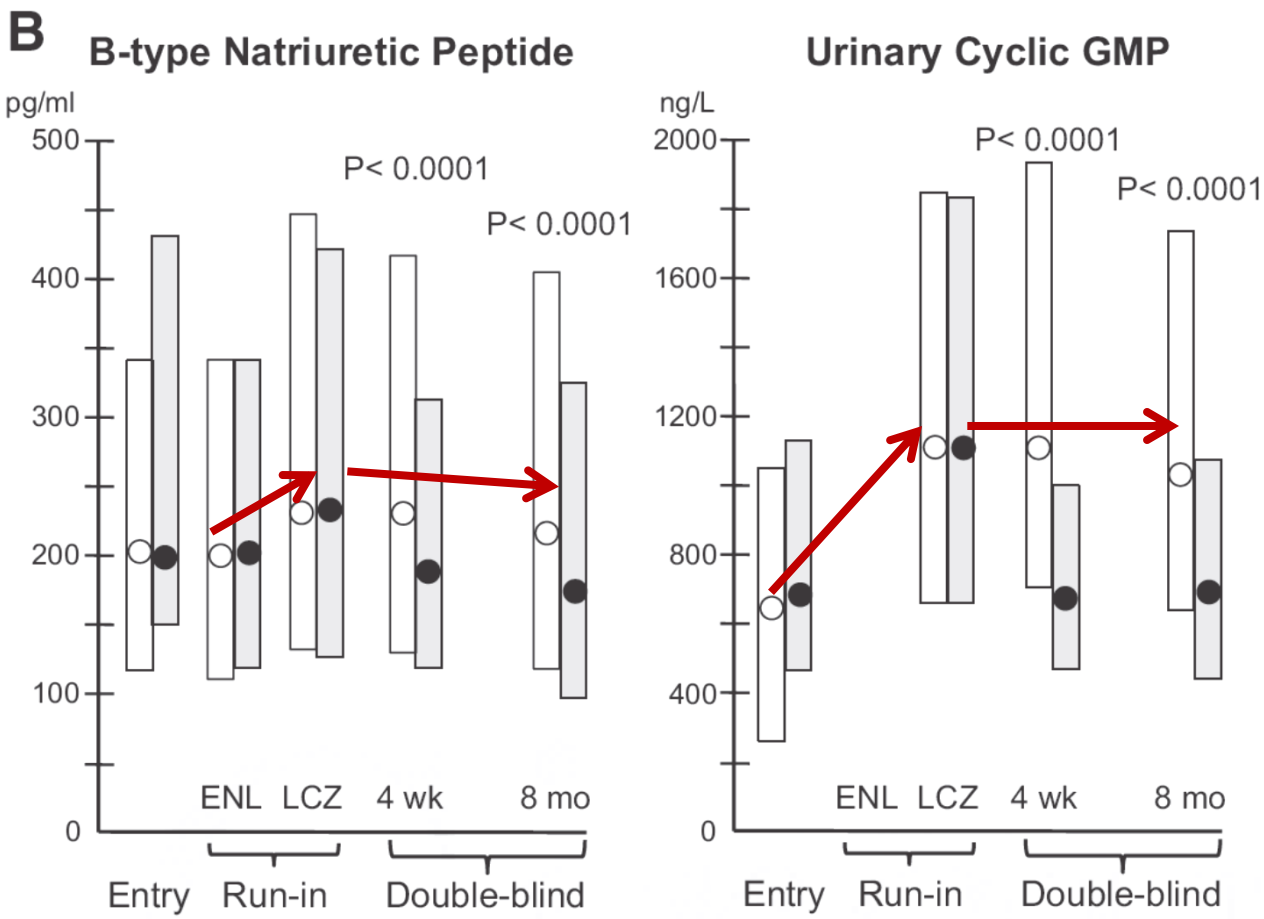
AHA/ ACC guidelines on HF 2013

PARADIGM-HF biomarker profile



Packer M et al. Circulation. Online Nov 2014

PARADIGM-HF biomarker profile



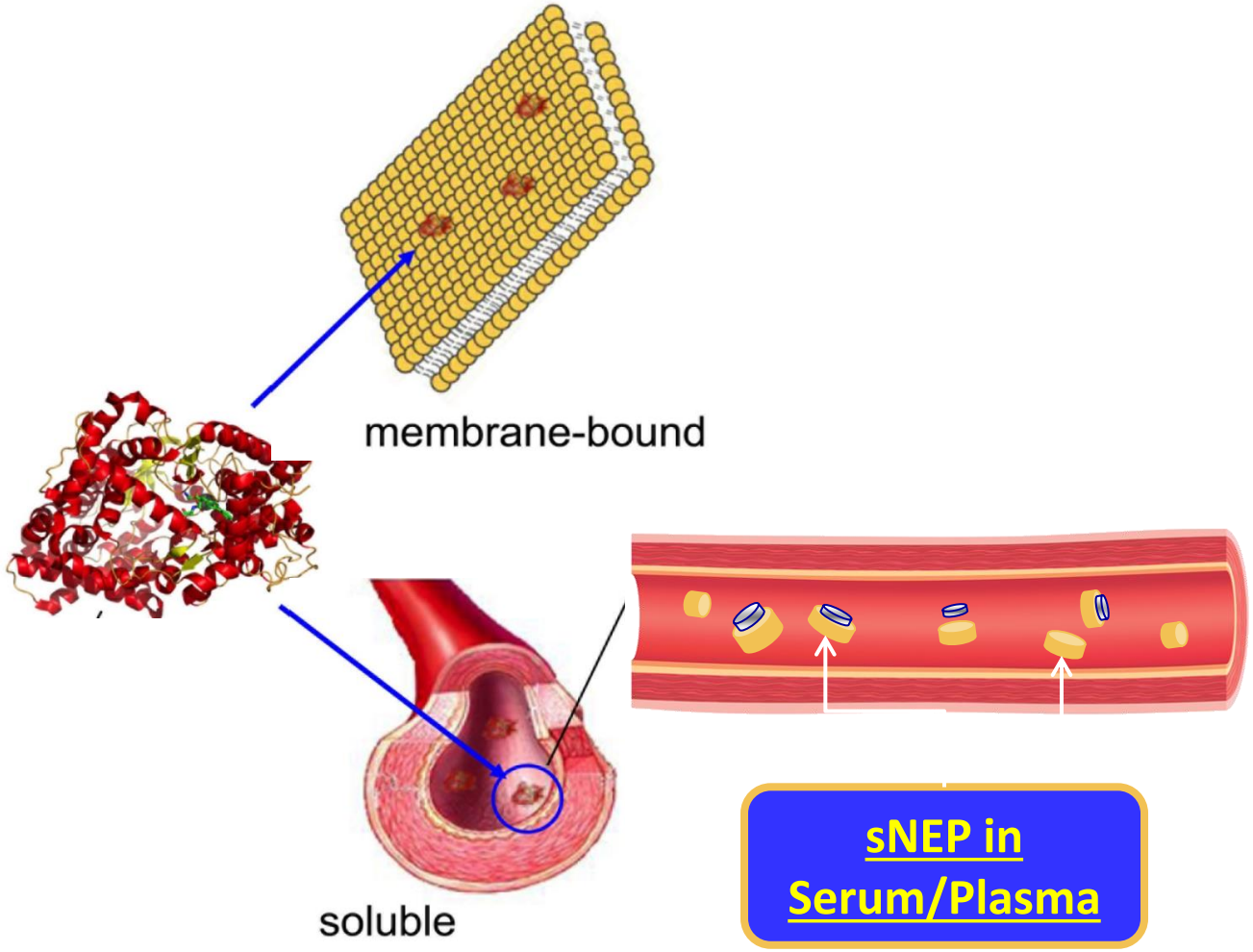
Packer M et al. Circulation. Online Nov 2014

Post Paradigm NP Biomarkers

BNP ≠ NTproBNP

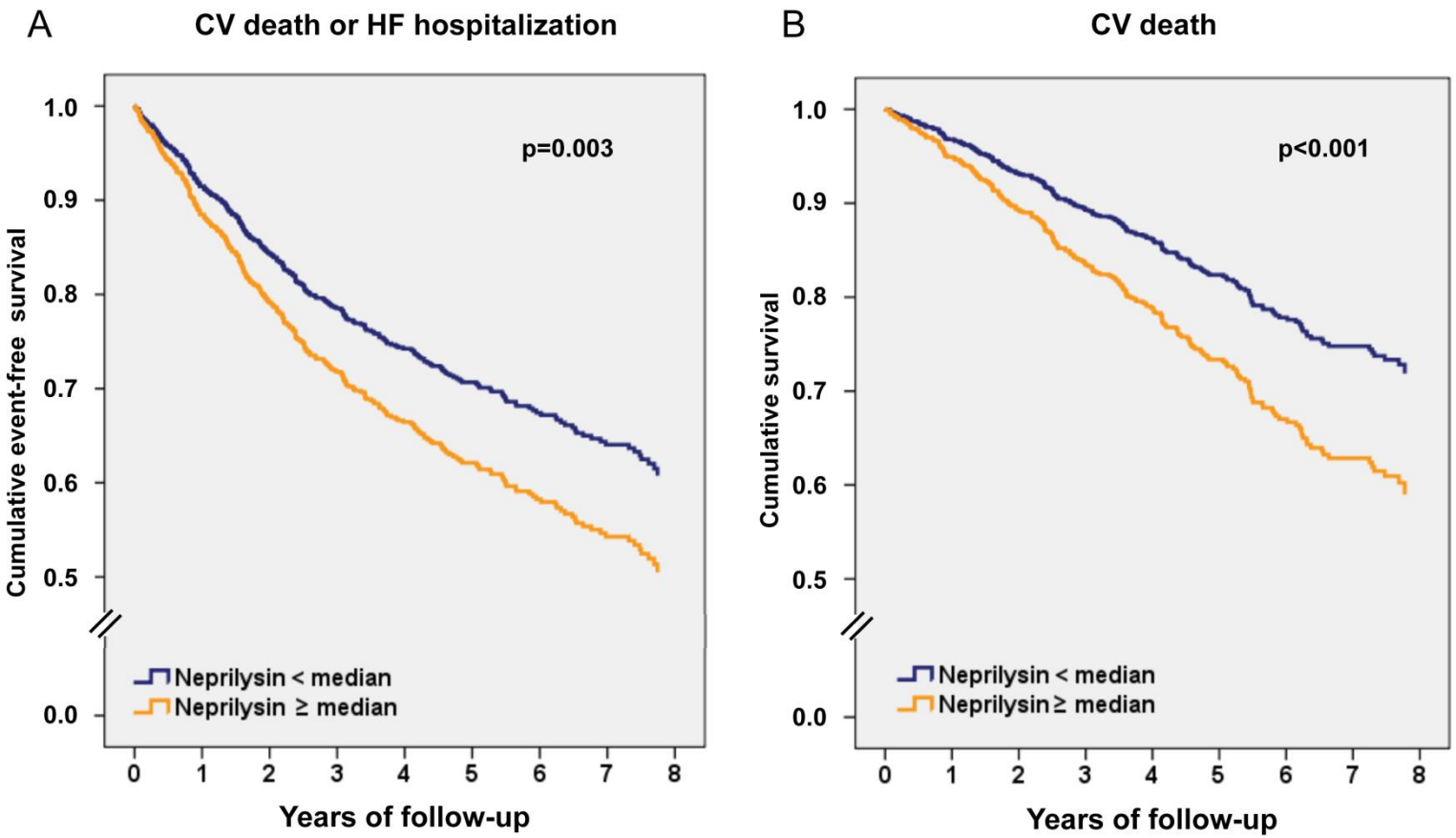
- Diagnosis
- Prognosis and risk stratification
- Monitoring
- Guided-therapy

sNEP: soluble circulating NEP



sNEP as a target for LCZ696 treatment monitoring ?

sNEP events curves



Bayes-Genis A et al. JACC 2014 In Press

The Ideal Biomarker

2001	2014
Sensitive and specific	Either highly sensitive (diagnosis) or highly specific (treatment effect)
Reflects disease severity	Reflects abnormal physiology or biochemistry
Correlates with prognosis	Prognosis is most meaningful if level is clinically actionable
Should aid in clinical decision making	Should be used as a basis for specific "biomarker-guided therapy"
Level should decrease after effective therapy	"Biomonitoring" during treatment is an effective surrogate of improvement

A. Maisel . JACC 2014