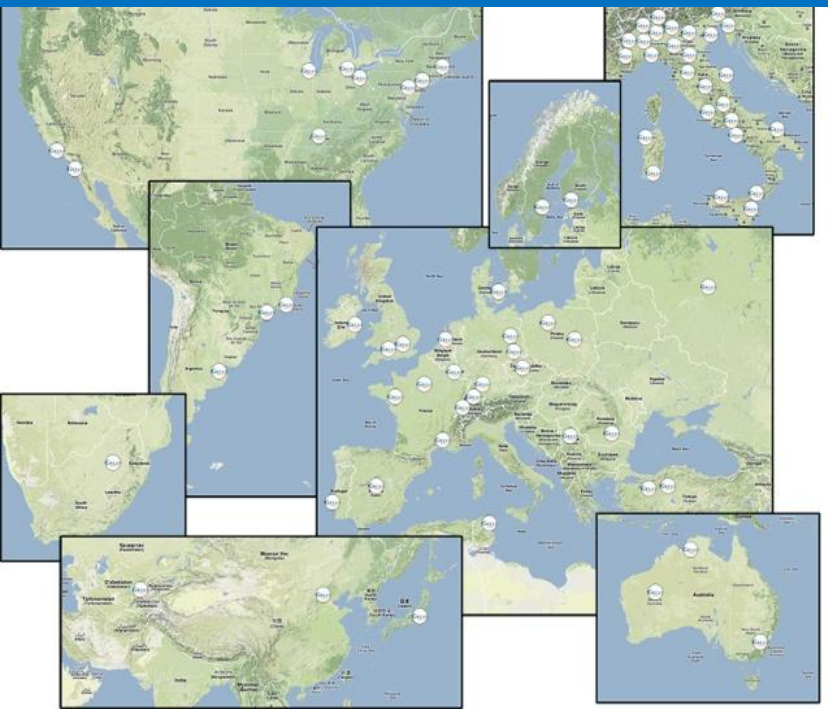
I nuovi biomarkers nello scompenso di cuore: ruolo negli anziani

Global REsearch Acute conditions Team Network



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Postgraduate School of Emergency Medicine
Faculty od Medicine and Psycology

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

Torino 27-29 Novembre 2013

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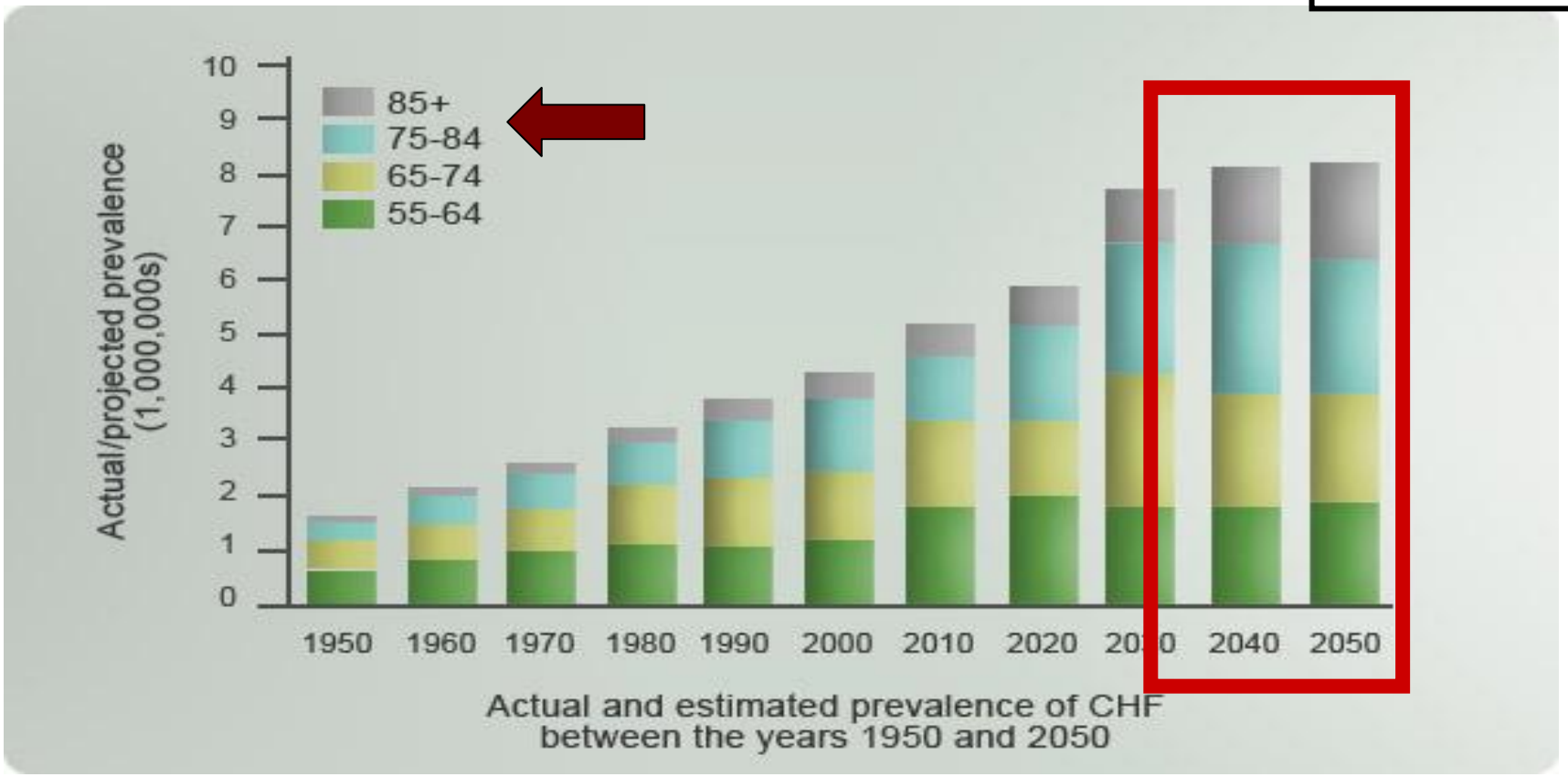
HF Epidemiology



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

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Importance of early therapies for AHF as consequence of prompt diagnosis

- In 46,599 patients with ADHF (ADHERE)
- ***a delay in Treatment*** was associated with:

- ***250% ↑ in acute mortality;***
- ***150% ↑ in Hospital length of stay***

W.F. Peacock,S. Di Somma et al. Congest Heart Fail. 2008

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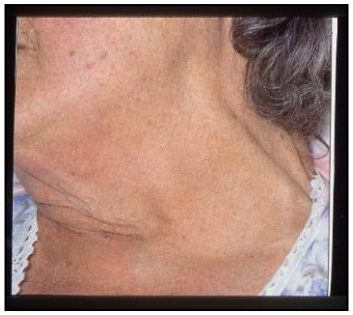
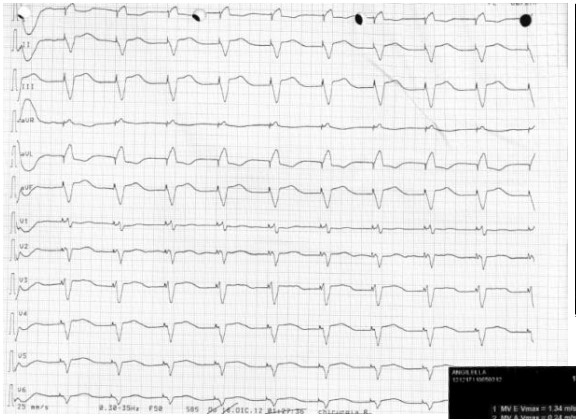
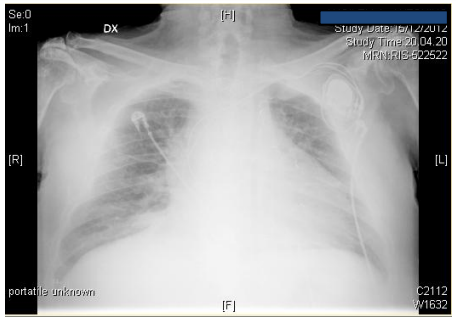
Acute Hearth Failure Diagnosis

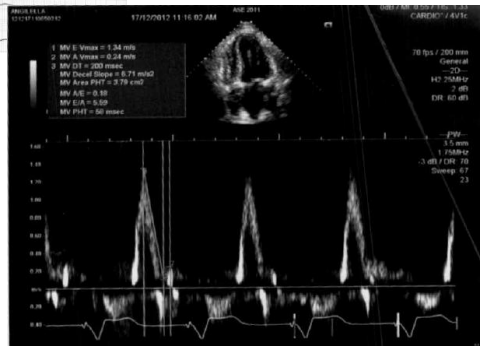


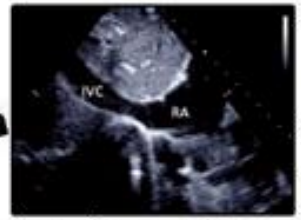
Physical examination





Thoracic ultrasound





Echocardiography (IVC)

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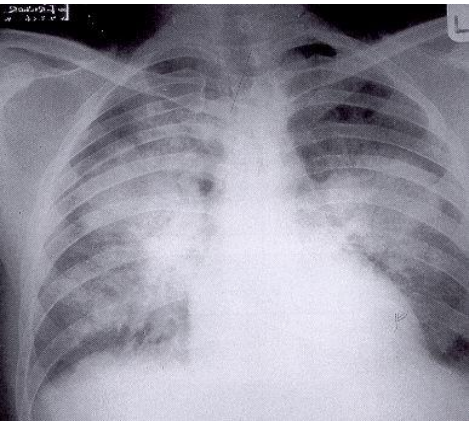
Chest X-Ray

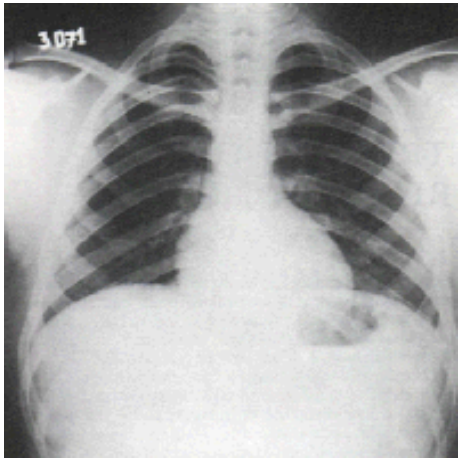


X-ray abnormalities can appear 6 hours....after symptoms onset

A, Cohen HE, Meltzer LE, et al:

The bedside chest evaluation of incipient heart failure.

Radiology 105:563, 1972



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

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

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

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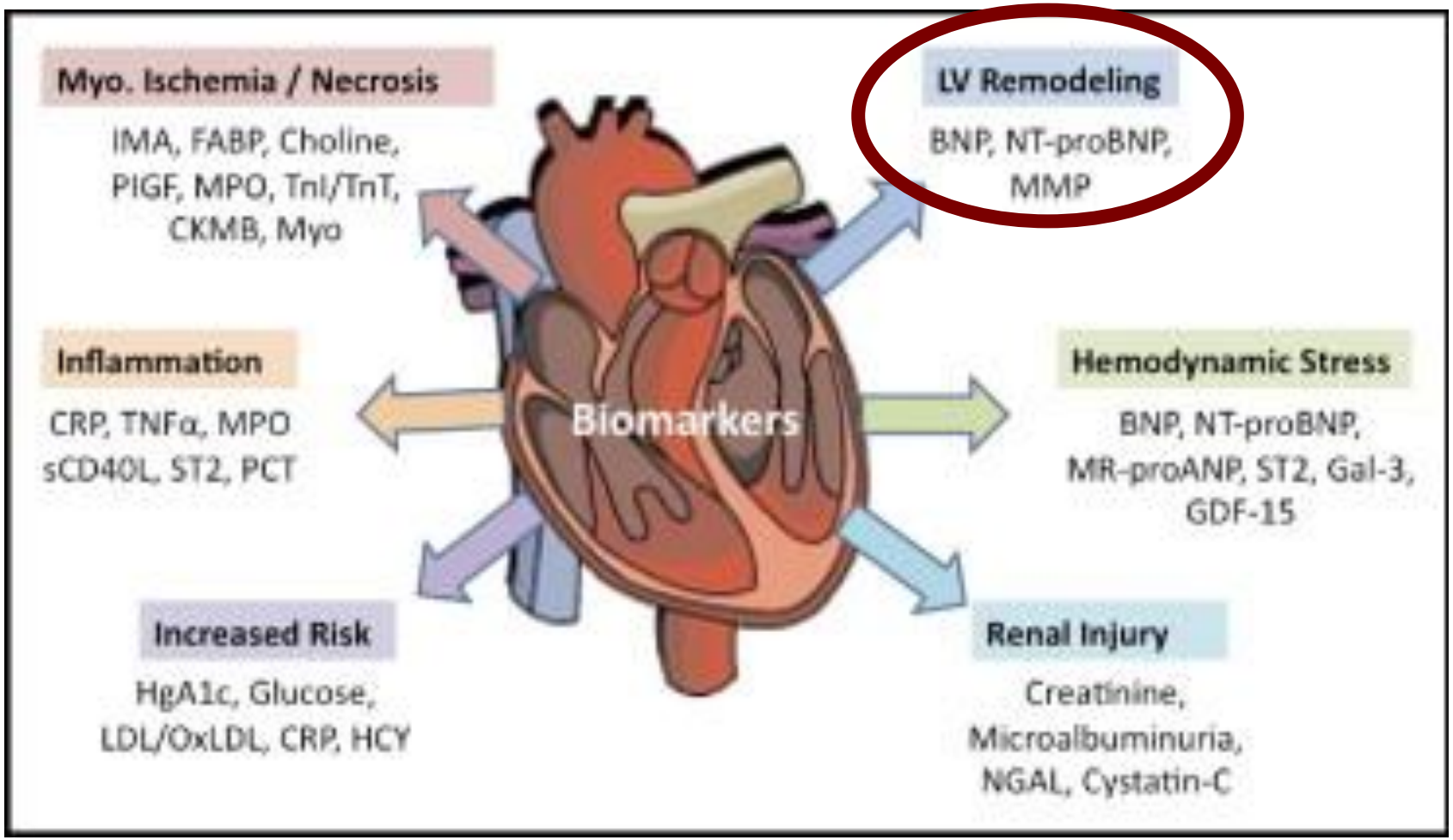
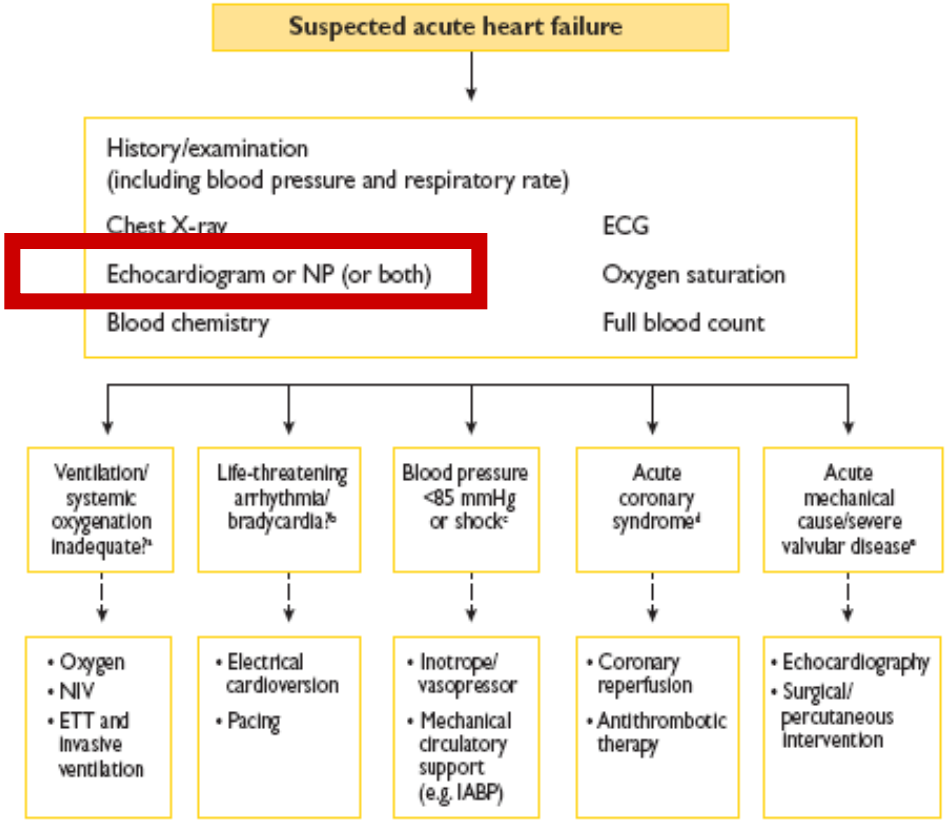
GREAT

Biomarkers in Heart Failure



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

AHF Management in ED:



ECG = electrocardiogram; ETT = endotracheal tube; IABP = intra-aortic balloon pump; NIV = non-invasive ventilation; NP = natriuretic peptide.

[a]For example, respiratory distress, confusion SpO_2 <90%, or PaO_2 <60 mmHg (8.0 kPa).

[b]For example, ventricular tachycardia, third-degree atrioventricular block.

[c]Reduced peripheral and vital organ perfusion—patients often have cold skin and urine output ≤15 ml/h and/or disturbance of consciousness.

[d]Percutaneous coronary revascularization (or thrombolysis) indicated if ST-segment elevation or new left bundle branch block.

[e]Vasodilators should be used with great caution, and surgery should be considered for certain acute mechanical complications (e.g. inter-ventricular septal rupture, mitral valve papillary muscle rupture).

ESC guidelines: European Journal Heart Failure (2012) 33, 1787–1847

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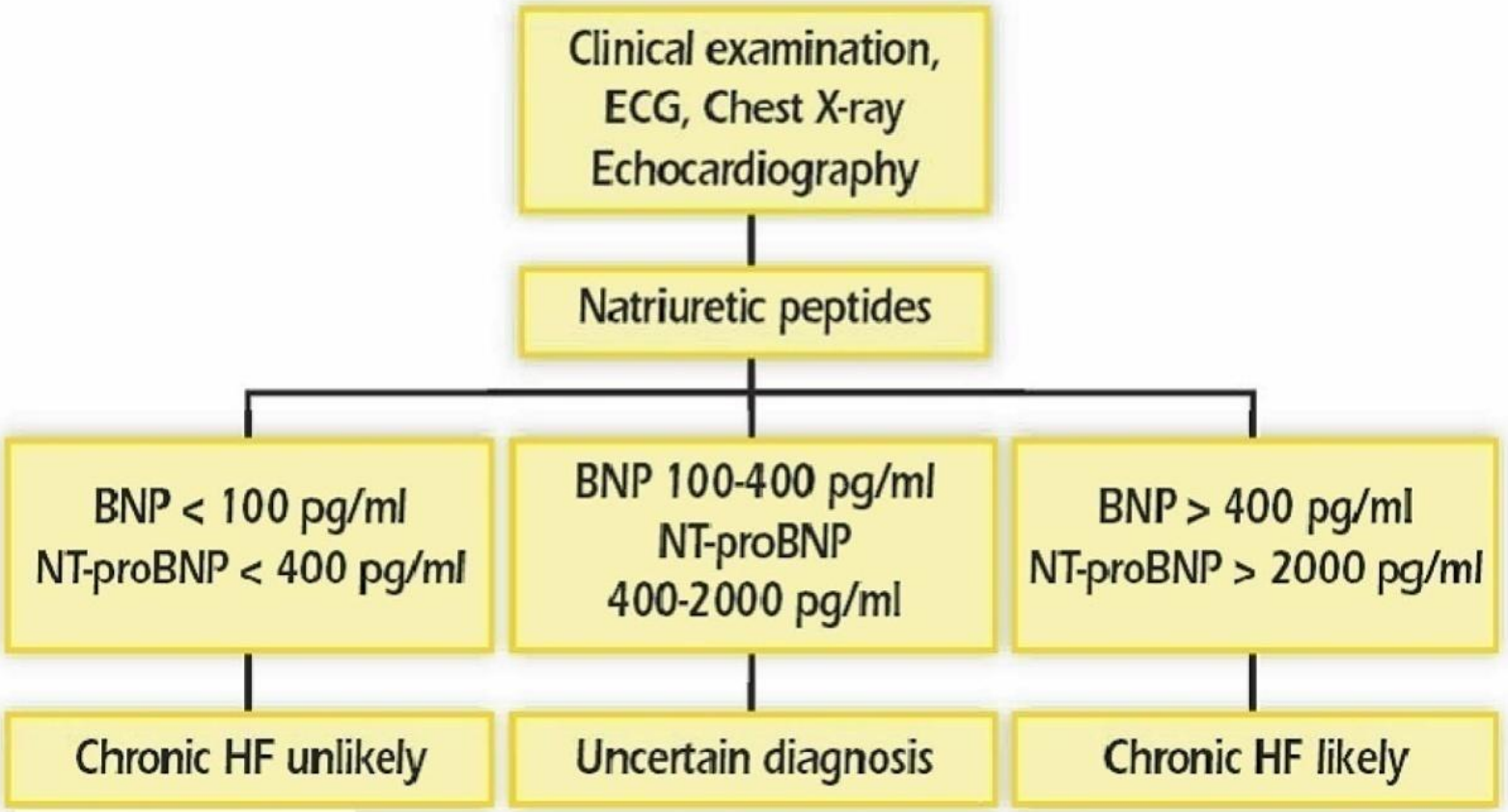
Flow-chart for the diagnosis of HF in untreated patients with symptoms suggestive of HF using natriuretic peptides



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www.escardio.org

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

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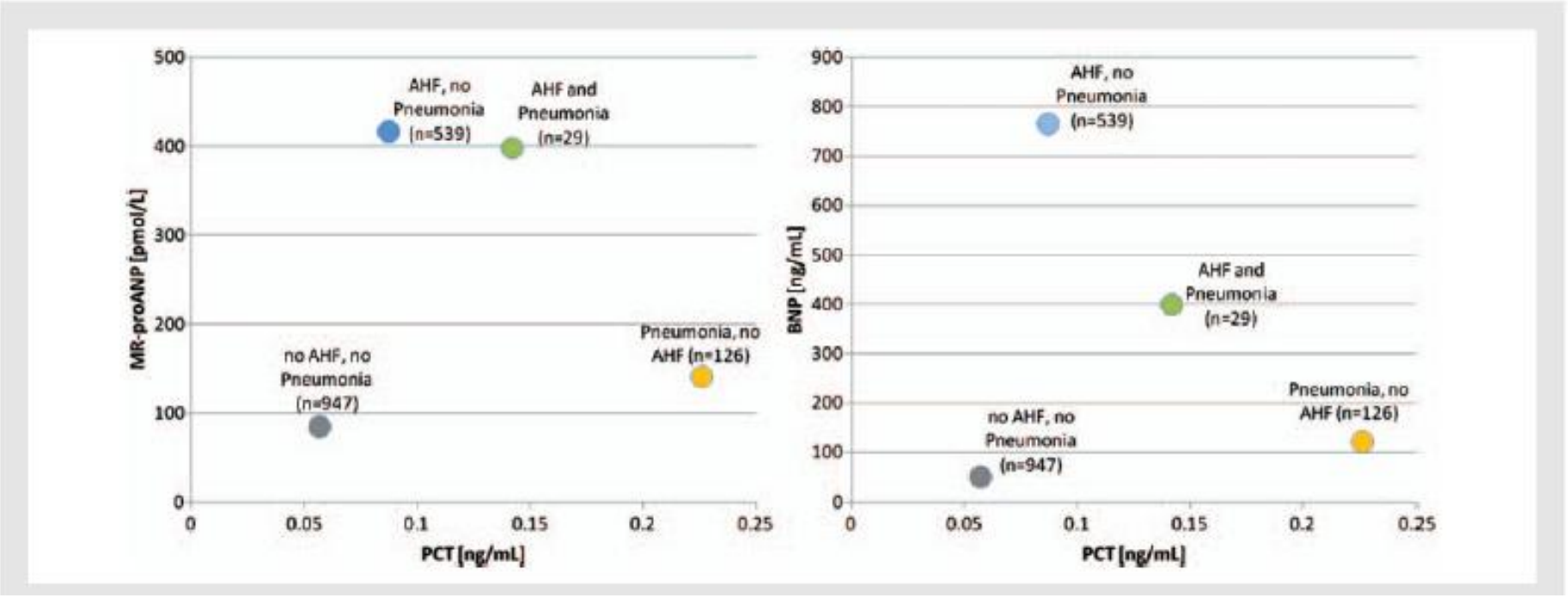
PCT +NPs for distinguishing S.O.B. In ED



A. Maisel ,.Di Somma et al. Eur J Heart F 2012 mar;14(3)278-81

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European Heart Journal
Acute Cardiovascular Care
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Original scientific paper

European Heart Journal: Acute Cardiovascular Care
0(0) 1–12
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DOI: 10.1177/2048872613499282
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SAGE

IL-18 stimulates B-type natriuretic peptide synthesis by cardiomyocytes *in vitro* and its plasma levels correlate with B-type natriuretic peptide in *non-overloaded* acute heart failure patients

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

Number of Patients	**38**
Age (mean ± SE)	**76.2 ± 1.9**
Sex	
Male	19
Female	19

Conclusion
This investigation provided the first evidence of the ability of IL-18 to induce B-type natriuretic peptide synthesis *in vitro* and highlighted the correlation between the two molecules in plasma from non-overloaded HF patients

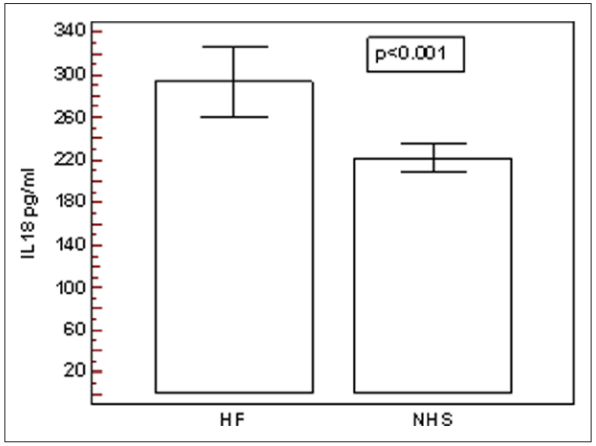

Figure 4. IL-18 concentrations in plasma from acute HF patients and normal human subjects.
Enzyme-linked immunosorbent assay was used to quantify IL-18 concentration in plasma from acute HF patients in comparison with plasma from normal human subjects. Acute HF patients had significantly higher IL-18 plasma levels than normal human subjects ($p<0.001$). NHS, normal human subjects.

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American Journal of Emergency Medicine (2007) **25**, 335–339

ELSEVIER

The American Journal of Emergency Medicine

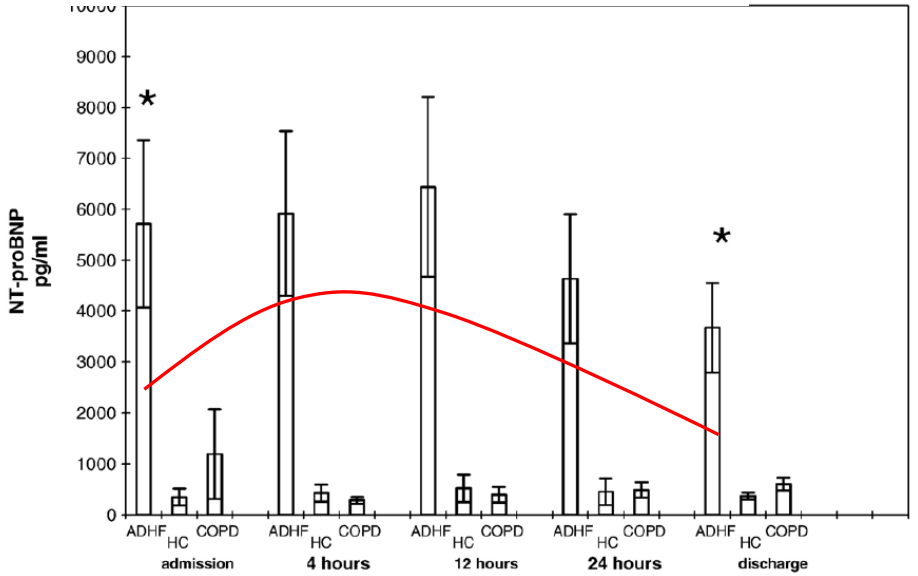
www.elsevier.com/locate/ajem

Brief Report

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

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

Characteristics of patients and controls	ADHF
No.	37
Age (y)*	75.4 ± 9.1
Sex, M/F	16/21



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http://ccforum.com/content/14/3/R116

CRITICAL CARE

RESEARCH Open Access

In-hospital percentage BNP reduction is highly predictive for adverse events in patients admitted for acute heart failure: the Italian RED Study

Salvatore Di Somma*[1], Laura Magrini[1], Valerio Pittoni[1], Rossella Marino[1], Antonella Mastrantuono[1], Enrico Ferri[1], Paola Ballarino[2], Andrea Semplicini[3], Giuliano Bertazzoni[4], Giuseppe Carpinteri[5], Paolo Mulè[6], Maria Pazzaglia[7], Kevin Shah[8], Alan Maisel[8] and Paul Clopton[8]

Number of patients	**247**
Age in years (mean ± SD)	**76 ± 12**
Sex	
Male	**118**
Female	**129**
NYHA functional classification	
III	**33%**
IV	**67%**

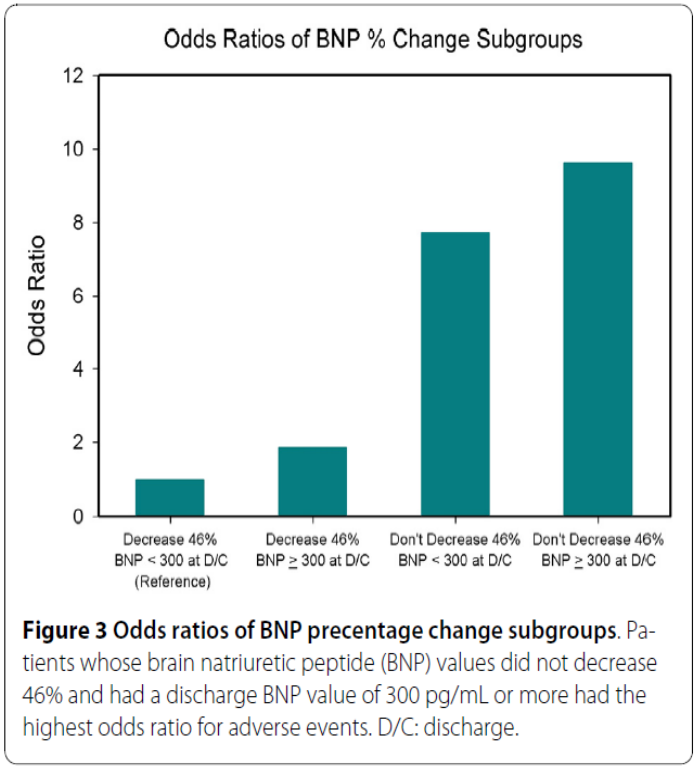

Figure 3 Odds ratios of BNP precentage change subgroups. Patients whose brain natriuretic peptide (BNP) values did not decrease 46% and had a discharge BNP value of 300 pg/mL or more had the highest odds ratio for adverse events. D/C: discharge.

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Curr Emerg Hosp Med Rep
DOI 10.1007/s40138-013-0009-3

Biomarkers for Diagnosis and Prognosis of Acute Heart Failure

Rajiv Choudhary · Salvatore Di Somma · Alan S. Maisel

tients with

	BNP	NT-proBNP
Factors affecting NP levels		
Pulmonary disease[a]	↑	↑
Renal disease[b]	↑	↑
Diastolic dysfunction[c]	↑	↑
Obesity[d]	↓	↓
Flash pulmonary edema[e]	↓	↓
Other causes[f]	↓	↓
Diagnostic cut-off		
HF present (pg/ml)	>400	<50 years: >450 50–75 years: >900 >75 years: >1800
HF absent (pg/ml)	<100	<75 years: 125 >75 years: 450
Grey-zone (pg/ml)	100–400	<50 years: 300–450 50–75 years: 300–900 >75 years: 300–1800

BNP B-type natriuretic peptide, *NT-proBNP* amino-terminal B-type natriuretic peptide

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Comparison of:BNP, NTproBNP and Mr-pro ANP for the Diagnosis of HF

BACH

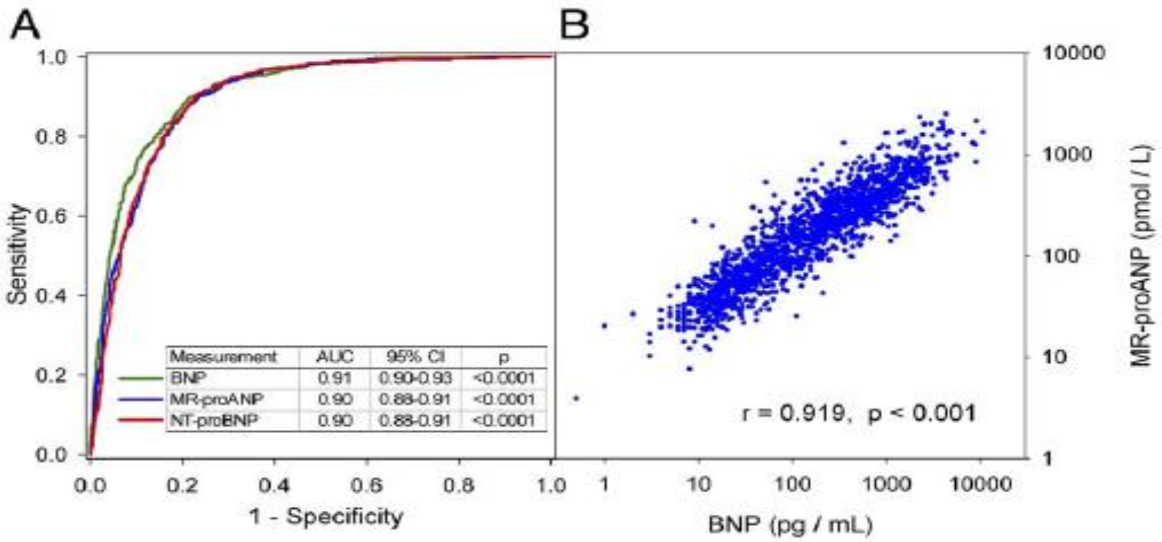

Figure 1 **Comparison of Diagnostic Biomarkers**

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

Maisel A.,Di Somma S. Et al.JACC 2010

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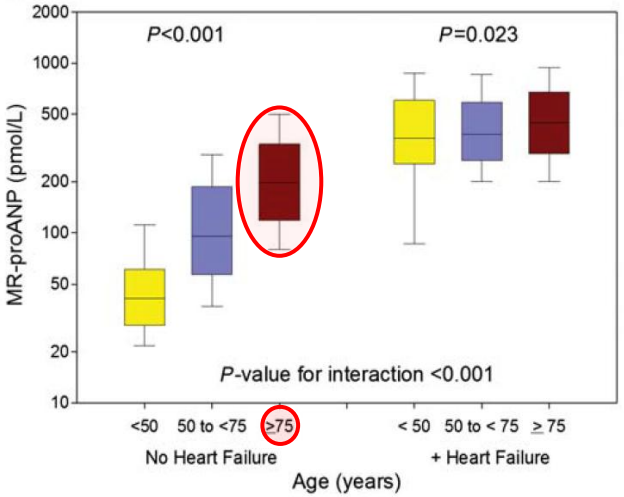
European Journal of Heart Failure (2012) **14**, 22–31
doi:10.1093/eurjhf/hfr157

Influence of age, race, sex, and body mass index on interpretation of midregional pro atrial natriuretic peptide for the diagnosis of acute heart failure: results from the BACH multinational study

Lori B. Daniels[1]*, Paul Clopton[1,2], Mihael Potocki[3], Christian Mueller[3], James McCord[4], Mark Richards[5], Oliver Hartmann[6], Inder S. Anand[7], Alan H.B. Wu[8], Richard Nowak[4], W. Frank Peacock[9], Piotr Ponikowski[10], Martin Mockel[11], Christopher Hogan[12], Gerasimos S. Filippatos[13], Salvatore Di Somma[14], Leong Ng[15], Sean-Xavier Neath[1], Robert Christenson[16], Nils G. Morgenthaler[6], Stefan D. Anker[9,17], and Alan S. Maisel[1,2]

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

Subgroup	No heart failure		Heart failure	
	P[a]	Mean MR-proANP[b]	*P*[a]	Mean MR-proANP[b]
Age group	<0.001		0.55	
< 50 years		55		393
50 to <75 years		104		438
≥ 75 years		177		448



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Diagnostic and Prognostic Biomarkers for AHF

Curr Emerg Hosp Med Rep
DOI 10.1007/s40138-013-0009-3

HEART FAILURE (F PEACOCK, SECTION EDITOR)

Biomarkers for Diagnosis and Prognosis of Acute Heart Failure

Rajiv Choudhary · Salvatore Di Somma · Alan S. Maisel

upcoming biomarkers provide more information on cardiac remodeling and are indicative of AHF progression, monitoring these biomarkers in hospitalized patients with AHF may help identify those at high risk of worsening HF. Biomarkers allow monitoring response to treatment. Moreover, using multiple biomarkers in bio-monitoring and guiding treatment may prove beneficial in improving mortality associated with AHF.

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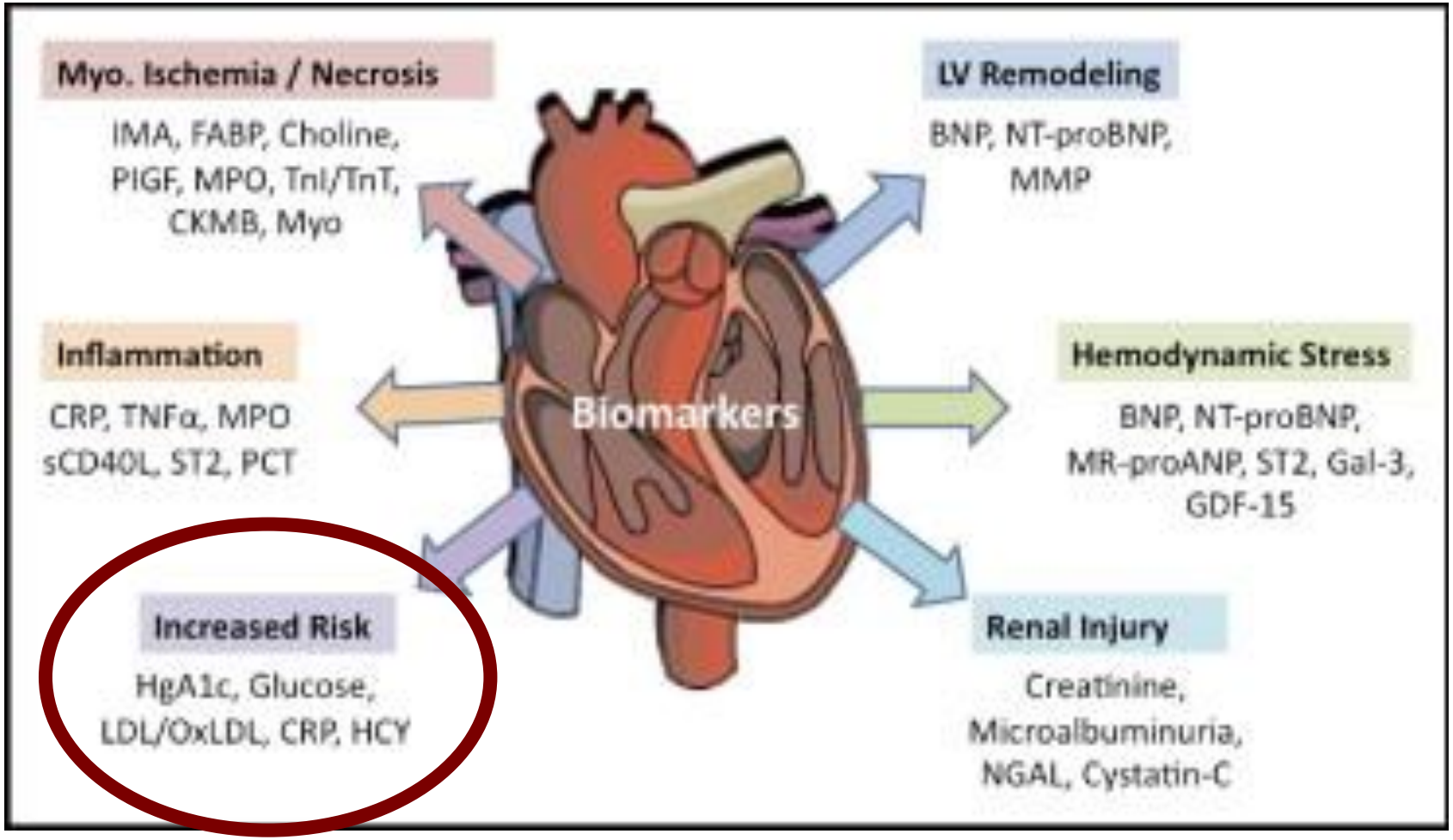
European Heart Journal (2012) **33**, 1787–1847
doi:10.1093/eurheartj/ehs104

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

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

Web Table 10: Prognostic variables in heart failure
A very large number of variables have been shown to relate to outcome in HF (and new prognostic markers are regularly identified). This table lists some of the more commonly described prognostic variables.
Demographics, history, and physical examination Age, sex, ethnicity, NYHA class, body mass index. Signs of congestion, increased jugular venous pressure, third heart sound, low systolic blood pressure, higher heart rate. Diabetes mellitus, renal dysfunction, depression, COPD. Ischaemic aetiology, history of myocardial infarction.

Biomarkers in Heart Failure



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

European Heart Journal (2006) 27, 65–75
doi:10.1093/eurheartj/ehi555

EUROPEAN SOCIETY OF CARDIOLOGY®

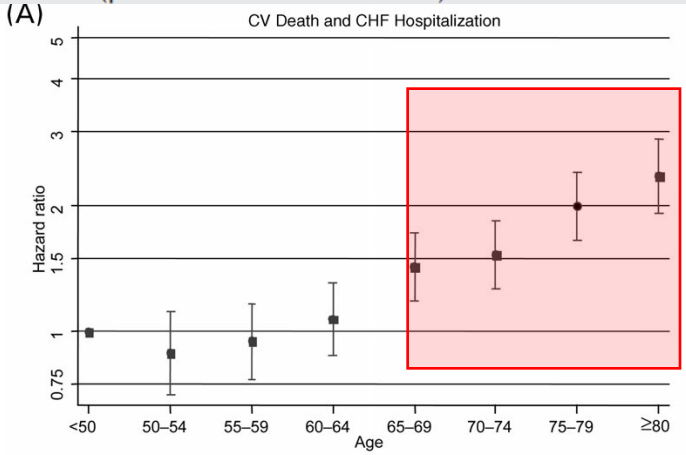
Clinical research

Predictors of mortality and morbidity in patients with chronic heart failure

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

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

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



7599 subjects

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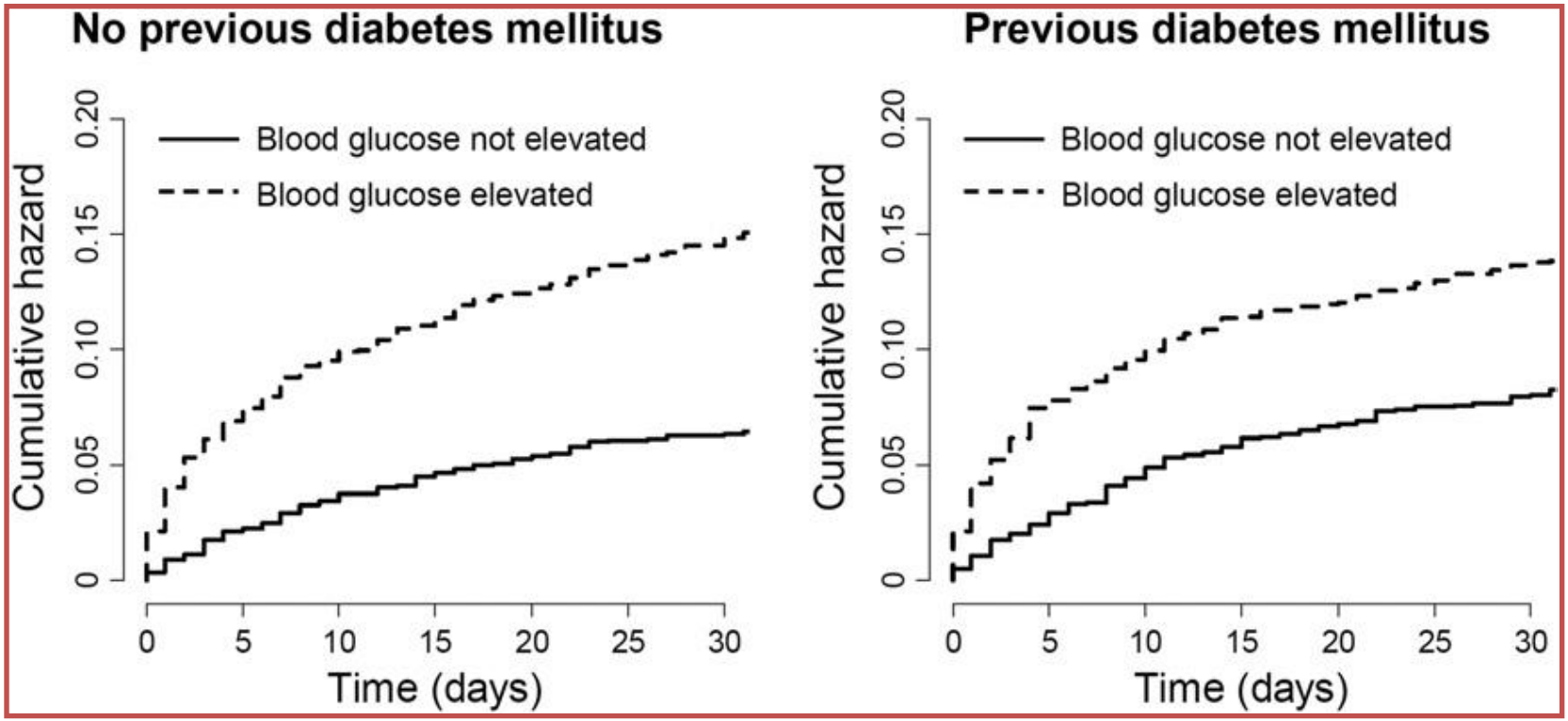
Association Between Elevated Blood Glucose and Outcome in Acute Heart Failure



Mebazaa *et al.*
Hyperglycemia and Outcome in AHF

JACC Vol. xx, No. x, 2013
Month 2013:xxx

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Vol. 58, No. 10, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.006

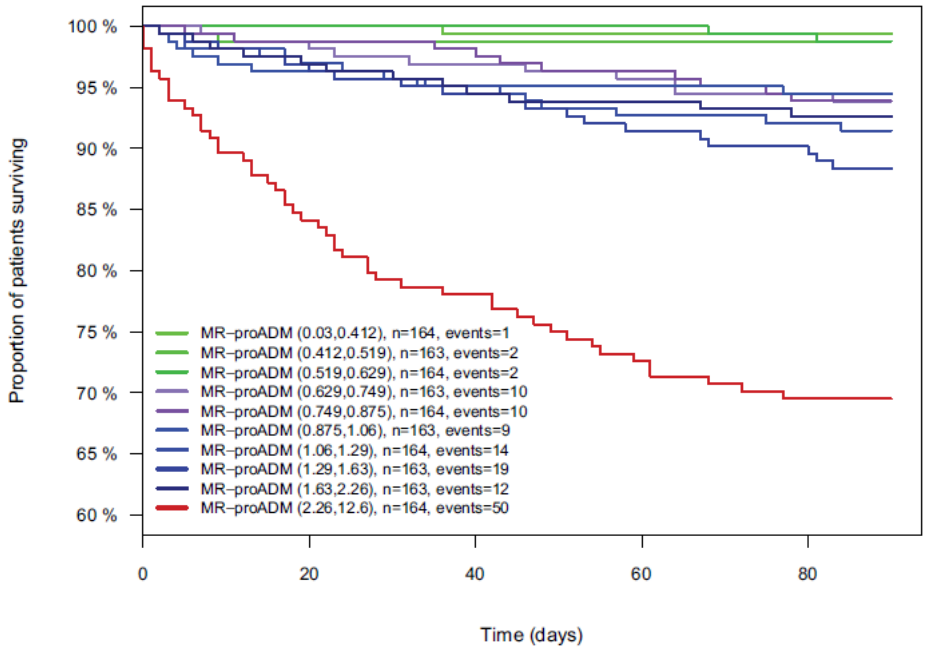
Biomarkers

Midregion Prohormone Adrenomedullin and Prognosis in Patients Presenting With Acute Dyspnea

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

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

Variable	n	Dead (n = 130)	Alive (n = 1,511)	p Value
Demographics				
Age (yrs)	1,641	72.8 ± 13.2	63 ± 17	<0.0001
Male	1,641	79 (60.8%)	780 (51.6%)	0.0543



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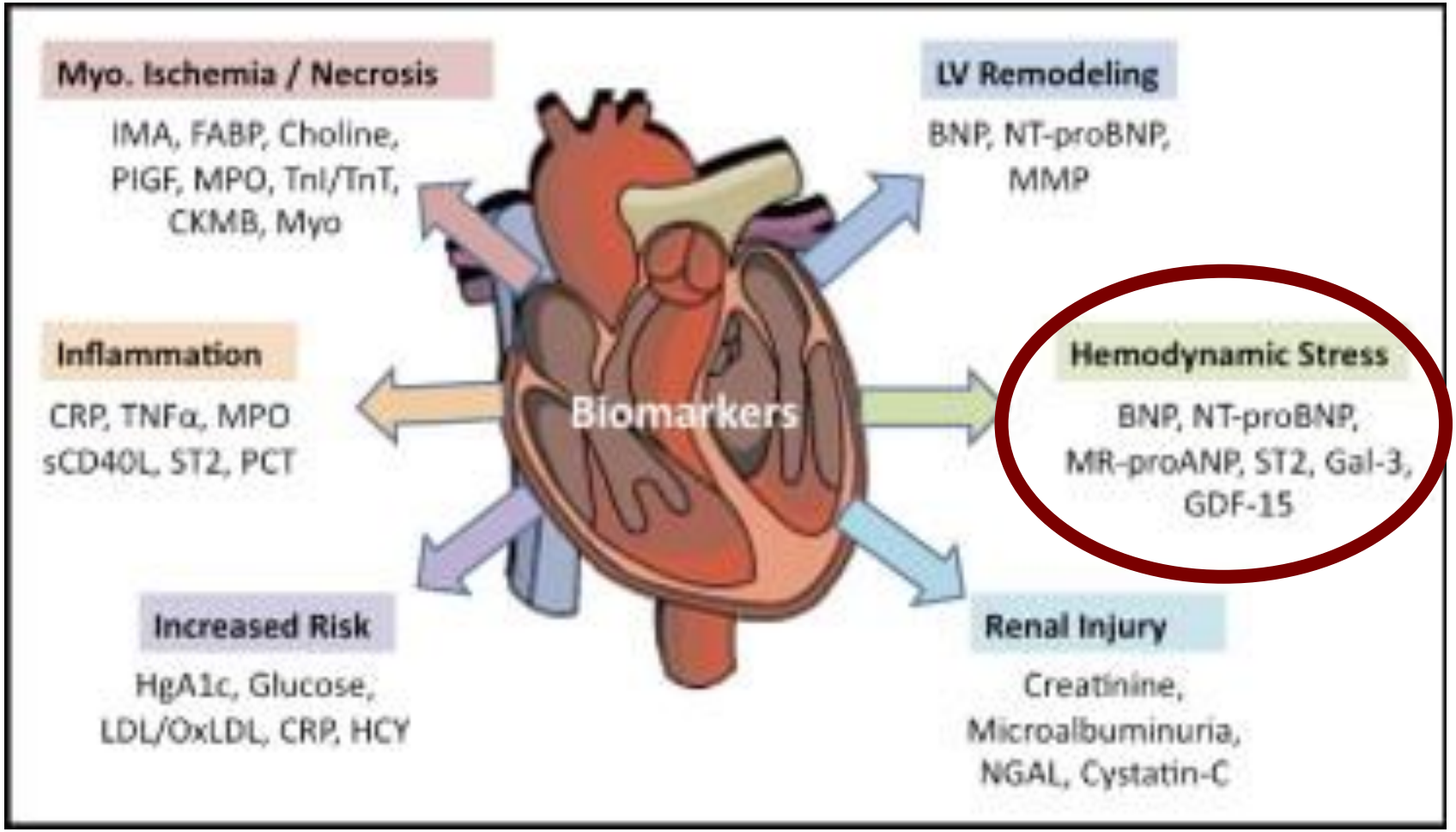
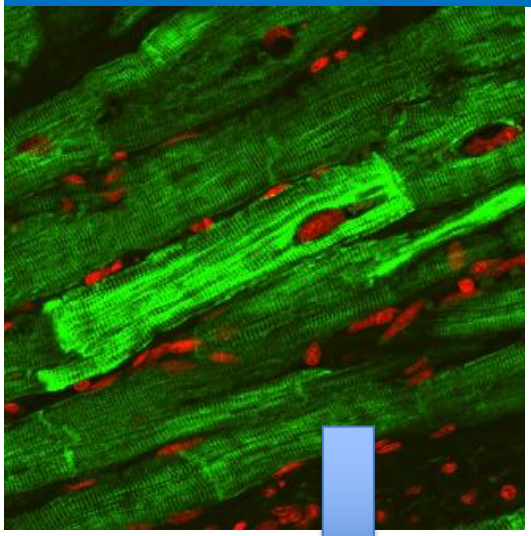
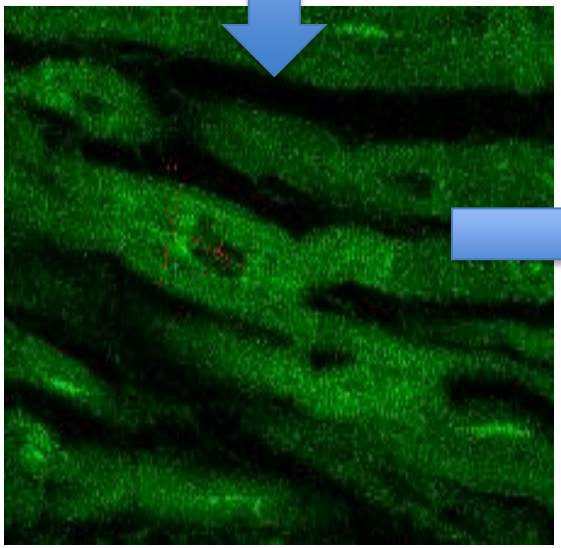
Biomarkers in Heart Failure

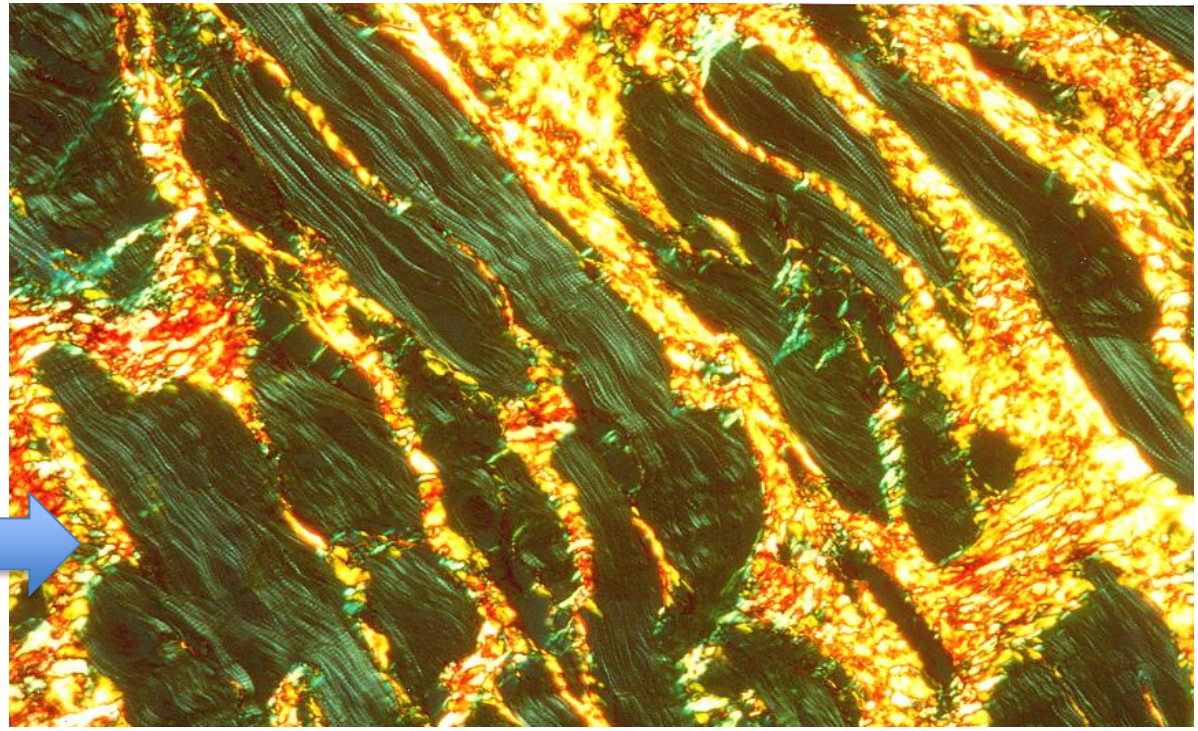


Moriates, Maisel: The Utility of Biomarkers in Sorting Out the Complex Patient. Review JAMA 2013

Replacement Myocardial Fibrosis in HF







Picrosirium in explanted heart (post-ischemic cardiomyopaty

Di Somma S. et al Heart ,2000

S. Di Somma et al. European Journal of Heart Failure 2004; 6:389-398

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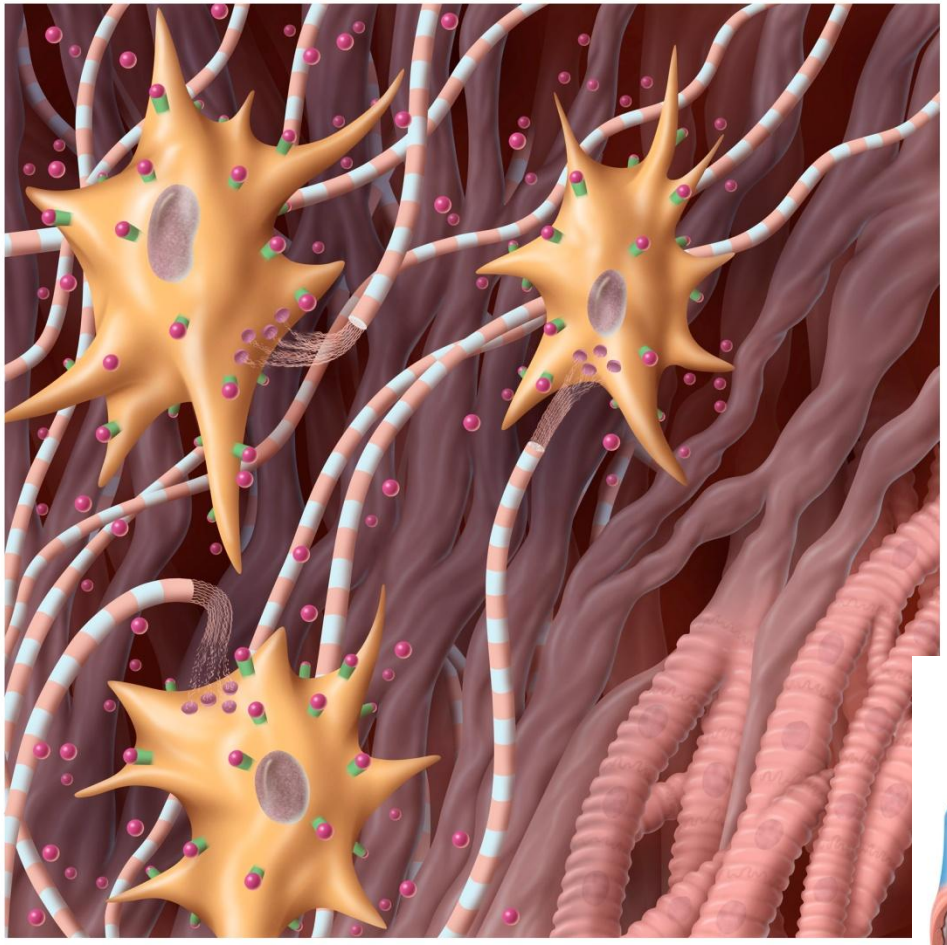
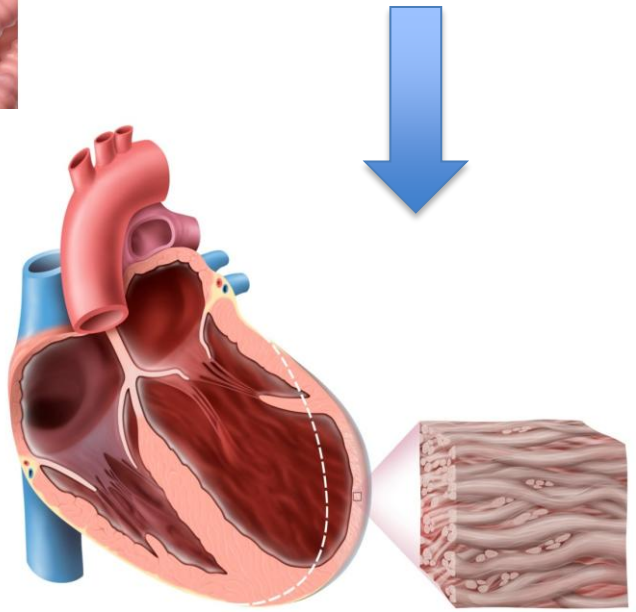
Galectin-3 new biomarker for heart disease



- Increased G-3 induces cardiac fibroblasts to proliferate an deposit type I collagen
- **Collagen deposition leads to scar**



Sharma et al. Circulation, 110; 3121-28, 2004
De Boer et al.curr. Heart Fail. Rep. 7; 1 – 8, 2010

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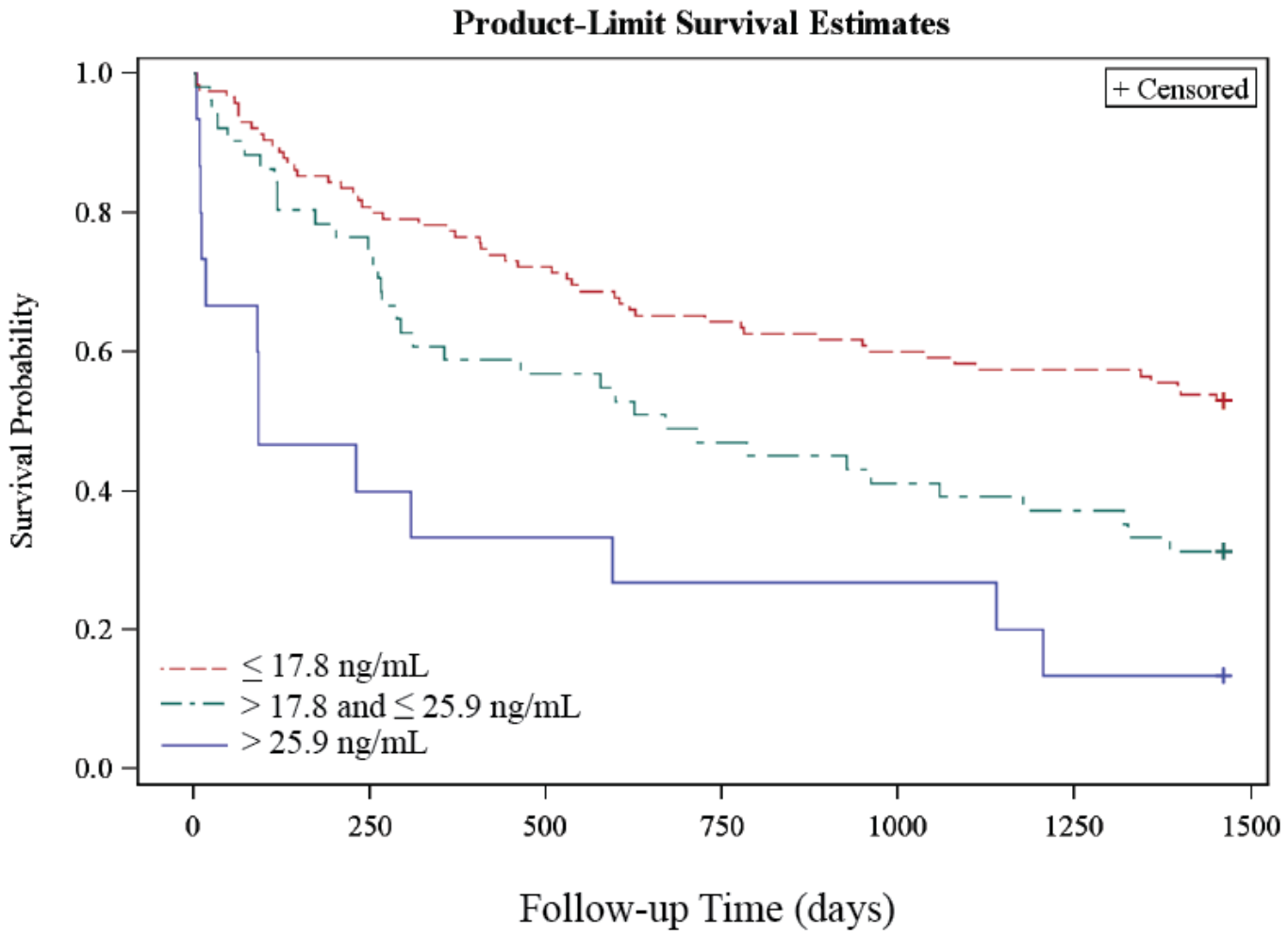
Survival Probability Curves by Baseline Galectin-3 Category in the Acutely Decompensated Heart



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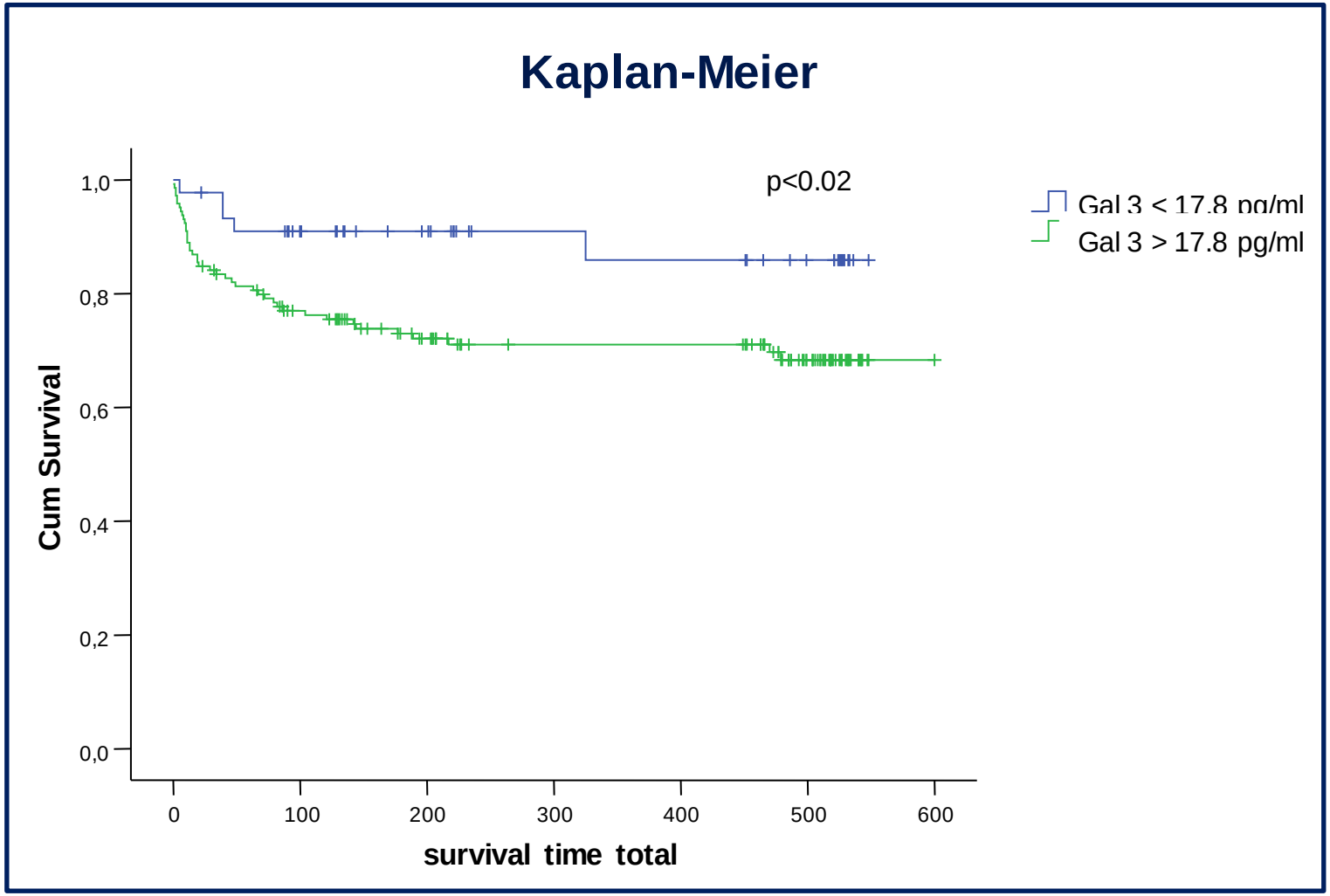
18 months mortality



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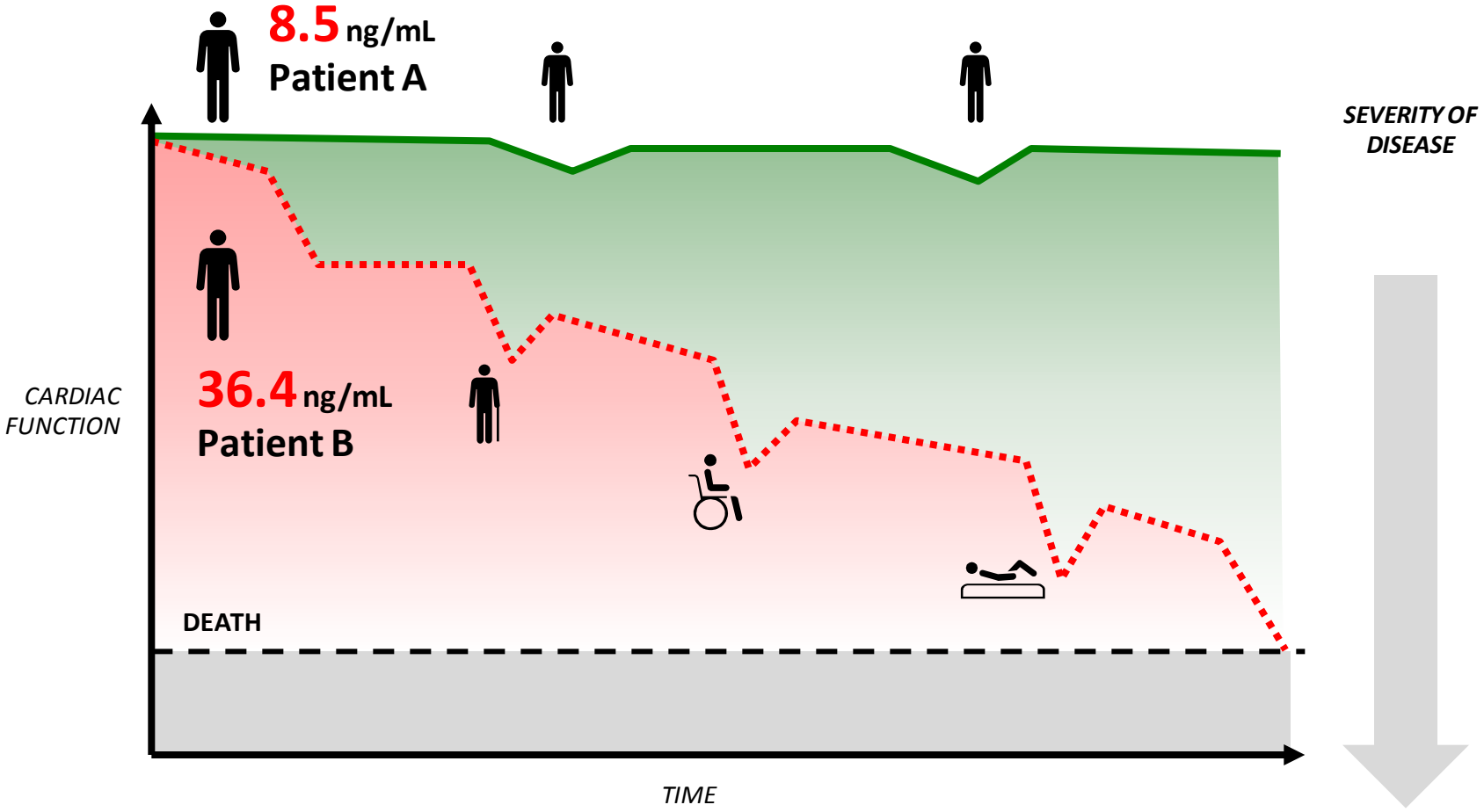
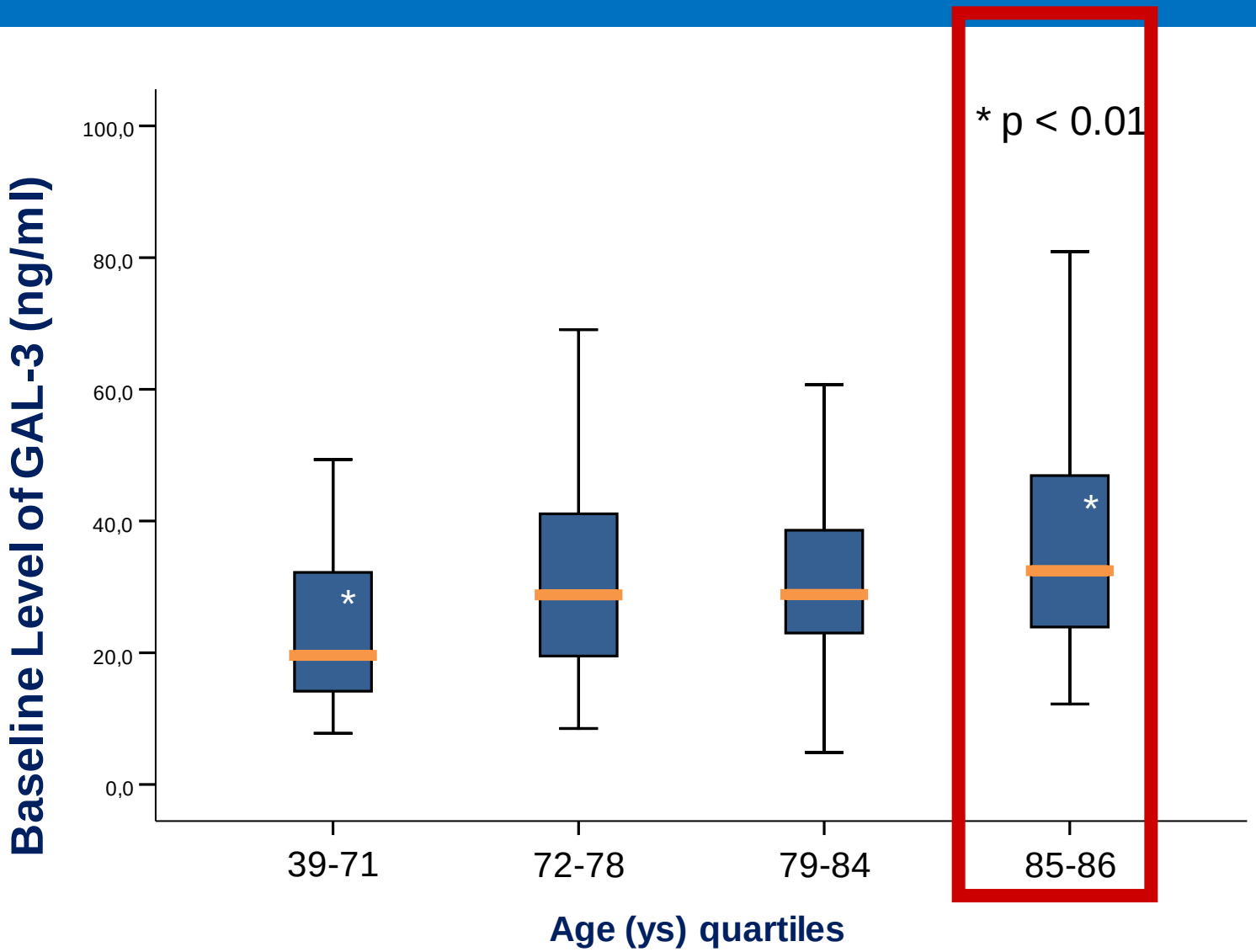
Galectin-3 Mediated HF is Inherently Progressive

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



Galectin-3 levels increase proportionally with age



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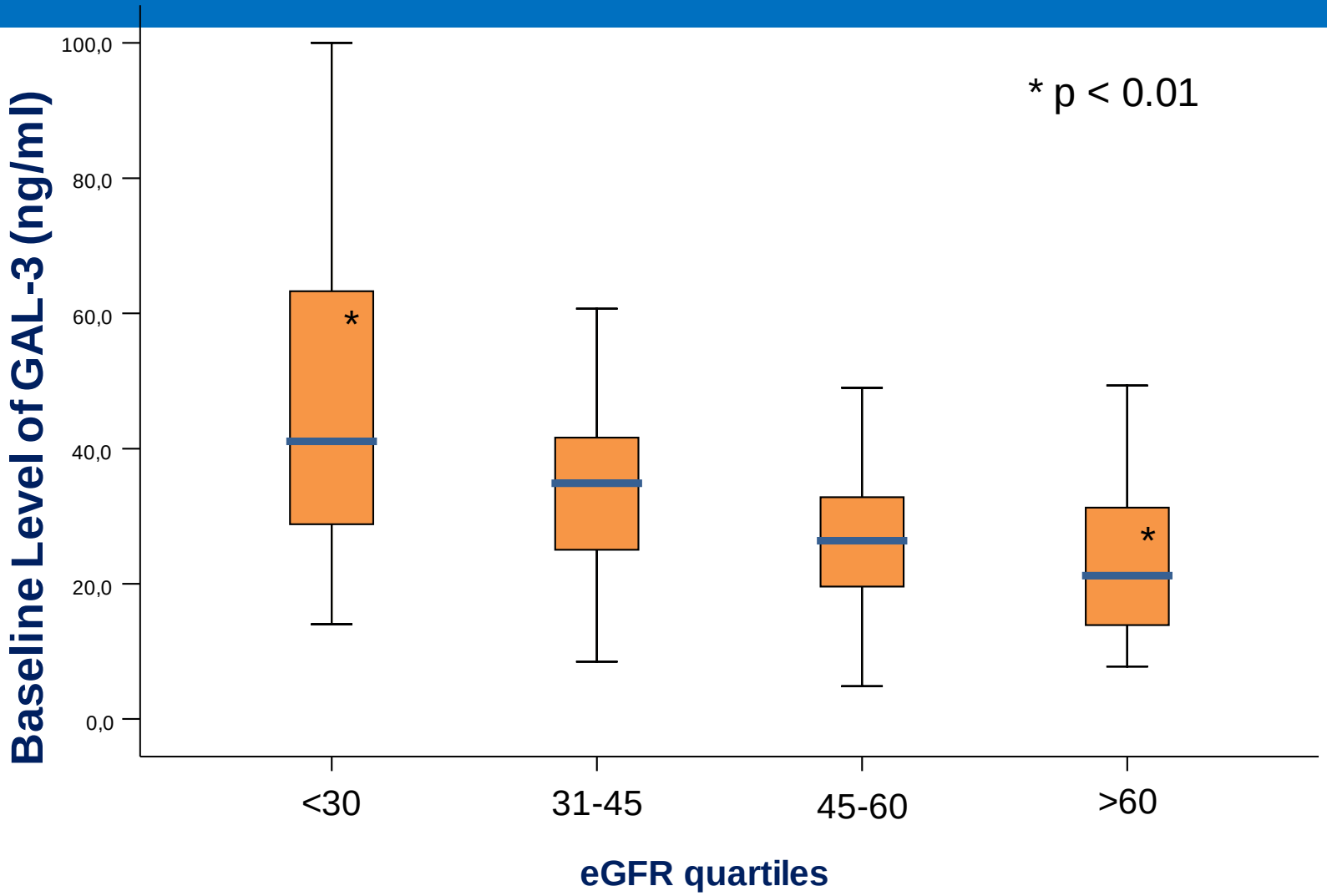
Galectin-3 levels correlate with eGFR



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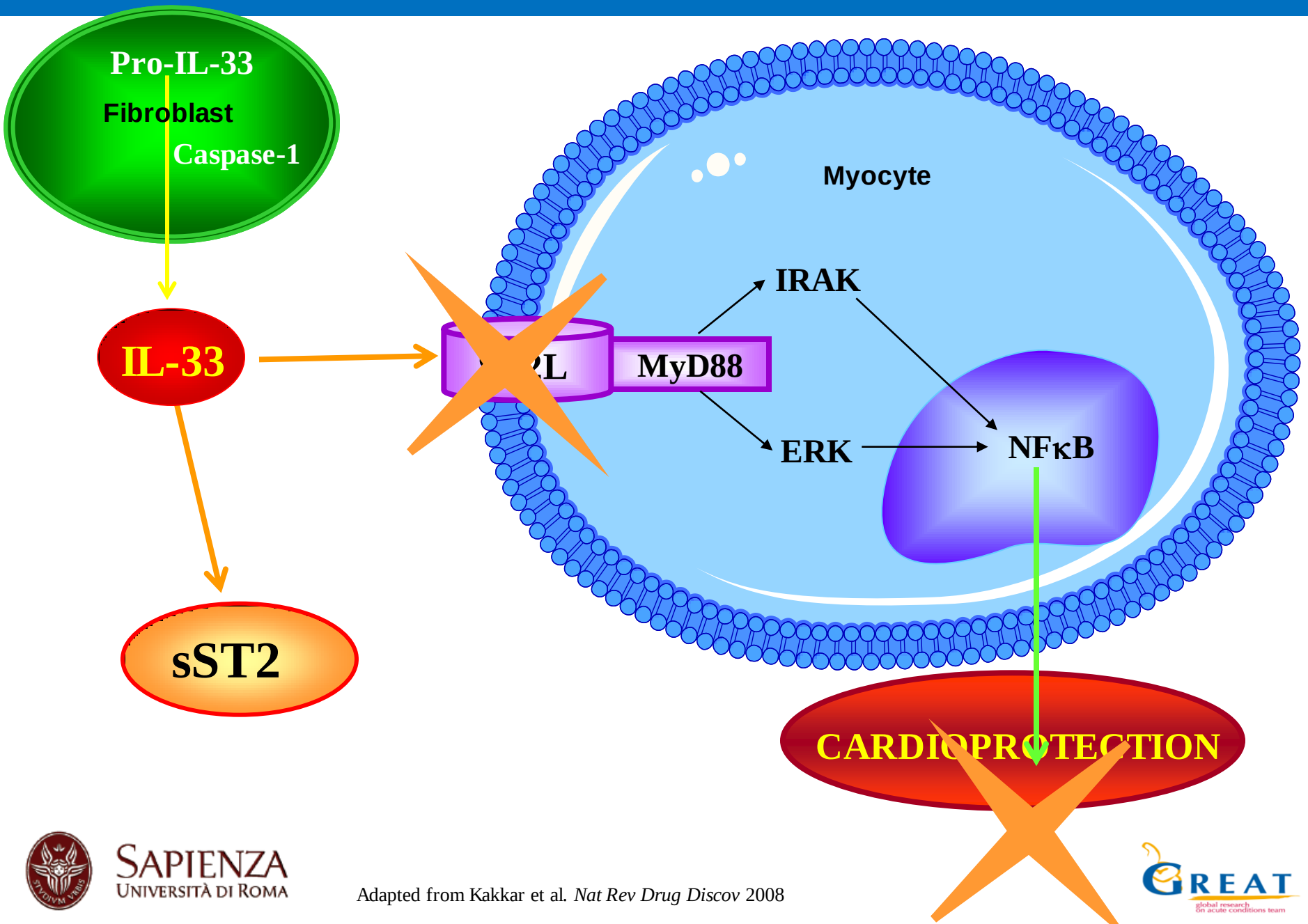
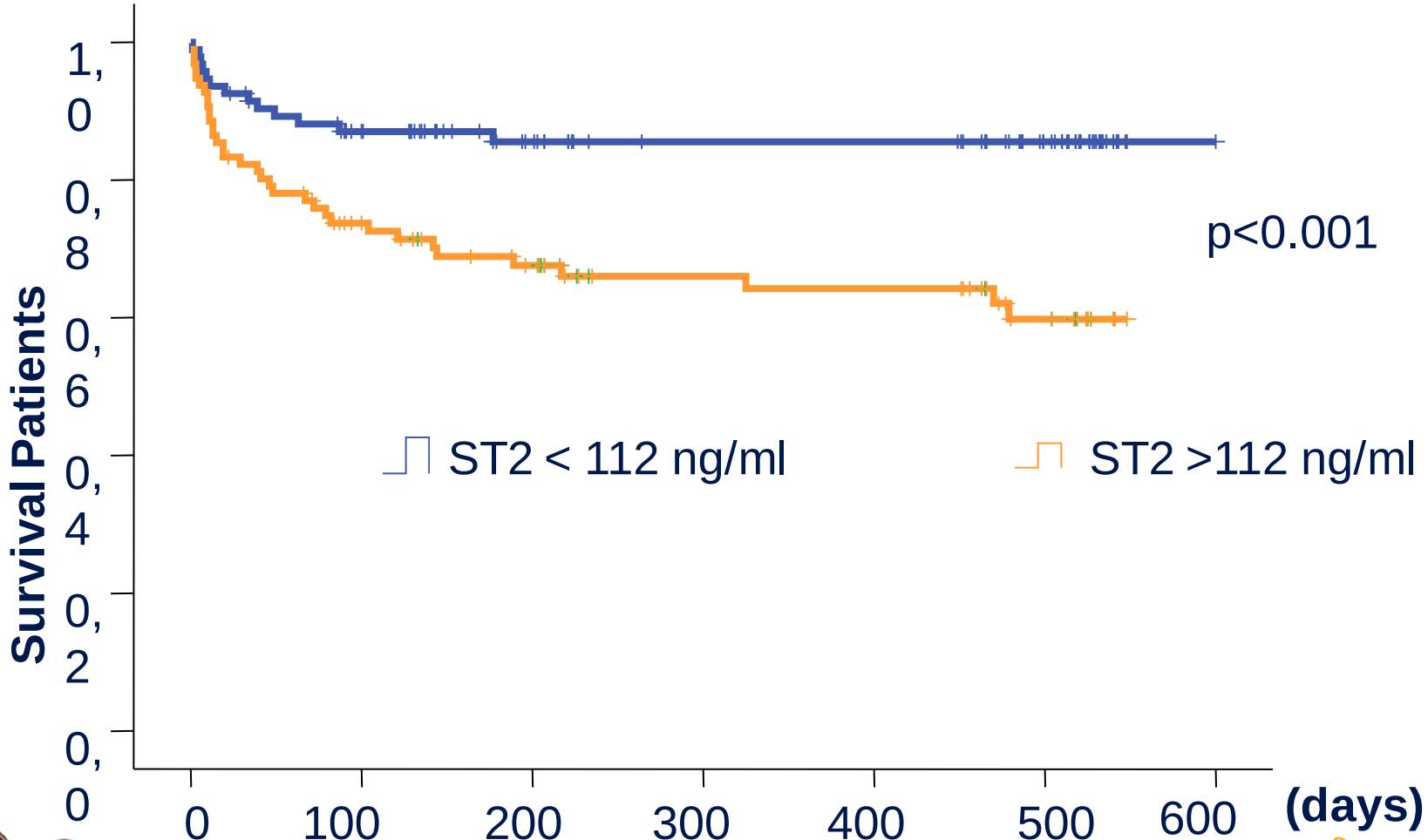
ST2: A DECOY RECEPTOR



Adapted from Kakkar et al. *Nat Rev Drug Discov* 2008

Kaplan-Meier 18 months mortality in AHF



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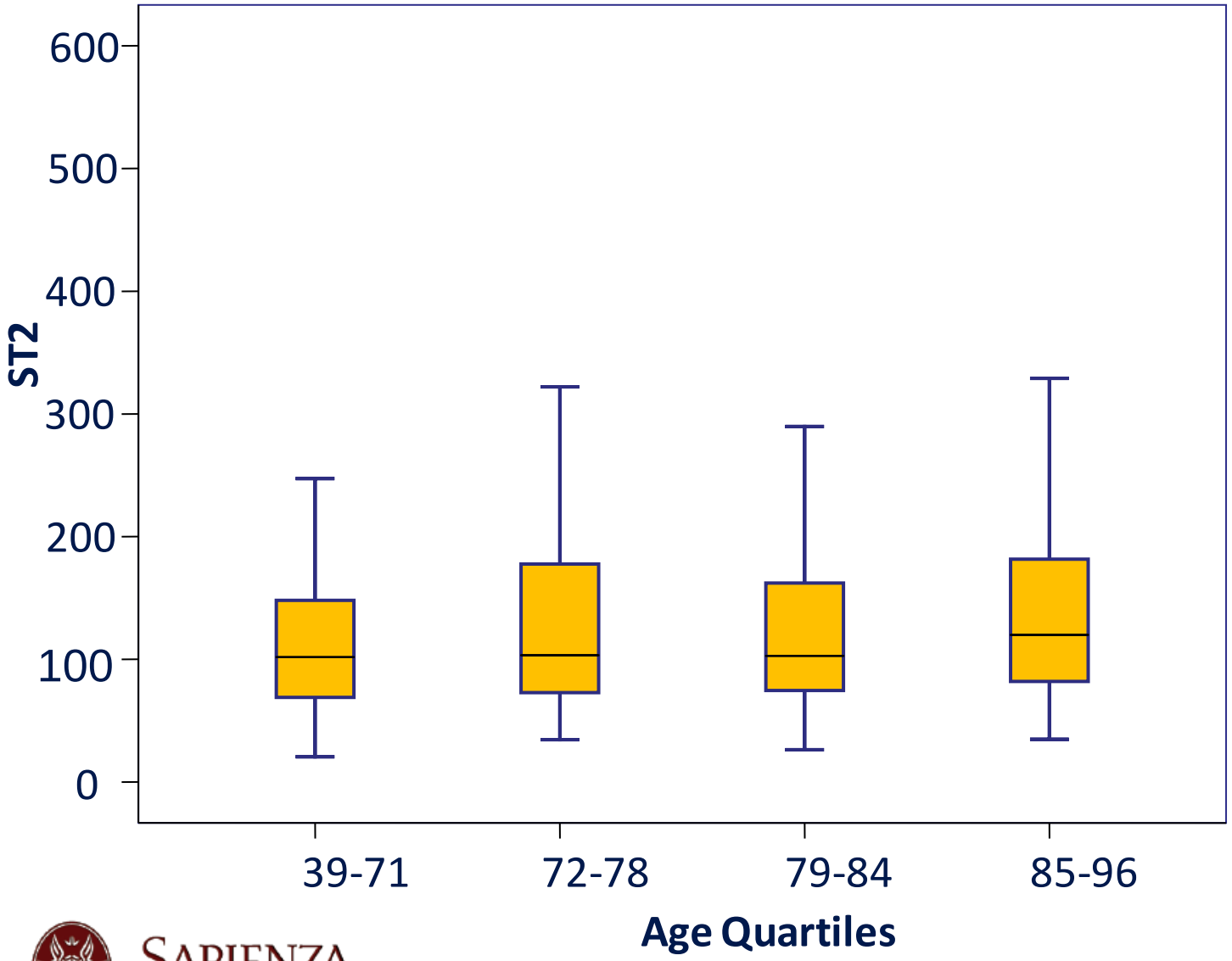
ST2 median values in Age quartiles



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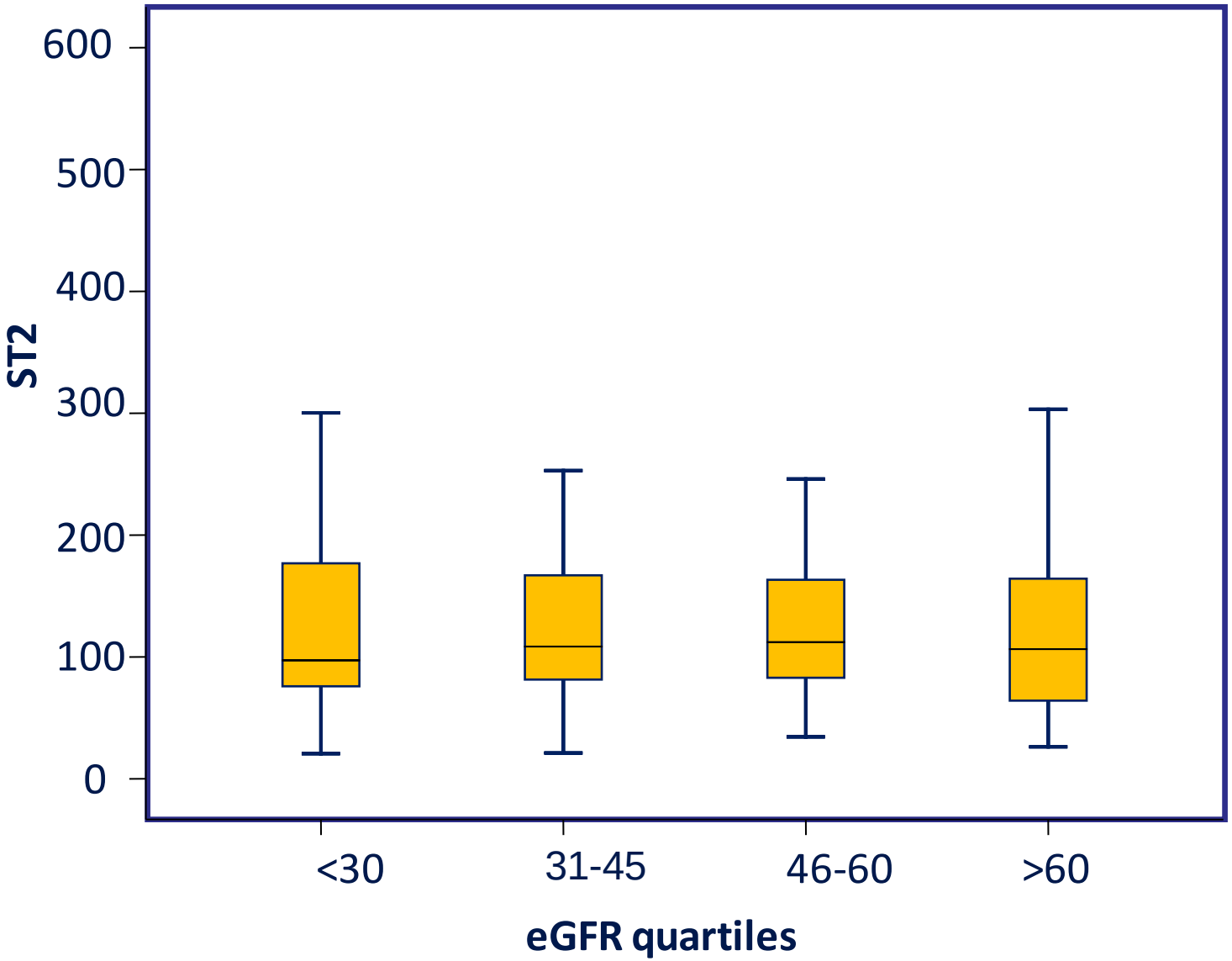
ST2 median values in eGFR quartiles



Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

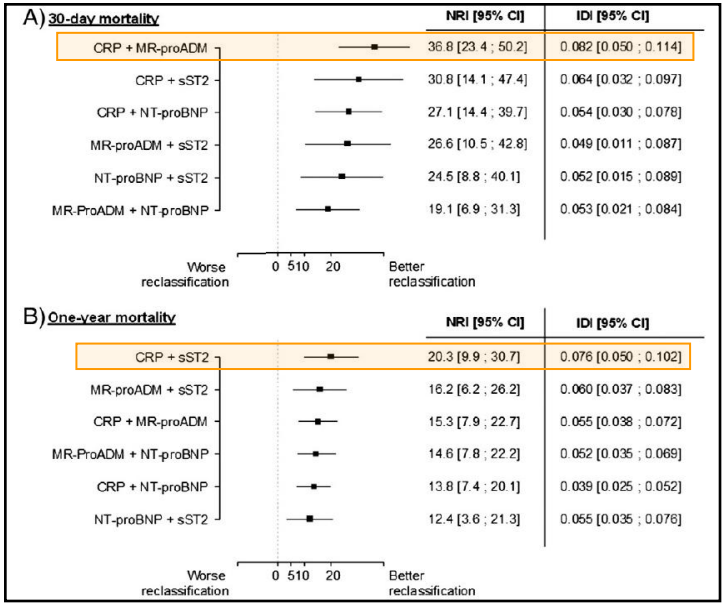
journal homepage: www.elsevier.com/locate/ijcard

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

Johan Lassus [a,b,1], Etienne Gayat [c,d,1], Christian Mueller [e], W.Frank Peacock [f], Jindrich Spinar [g,h], Veli-Pekka Harjola [a], Roland van Kimmenade [i], Atul Pathak [j], Thomas Mueller [k], Salvatore diSomma [l], Marco Metra [m], Domingo Pascual-Figal [n,o], Said Laribi [b,p], Damien Logeart [b,q], Semir Nouira [r], Naoki Sato [s], Michael Potocki [e], Jiri Parenica [g,h], Corinne Collet [b], Alain Cohen-Solal [b,q], James L. Januzzi Jr. [t], Alexandre Mebazaa [b,c,*] and for the GREAT-network [2]

Characteristics of the study population (n=5306).

	Value
Variables	
Age (years)	75 (65–81)
Male gender n=(%)	3002 (56.6)



Conclusion

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

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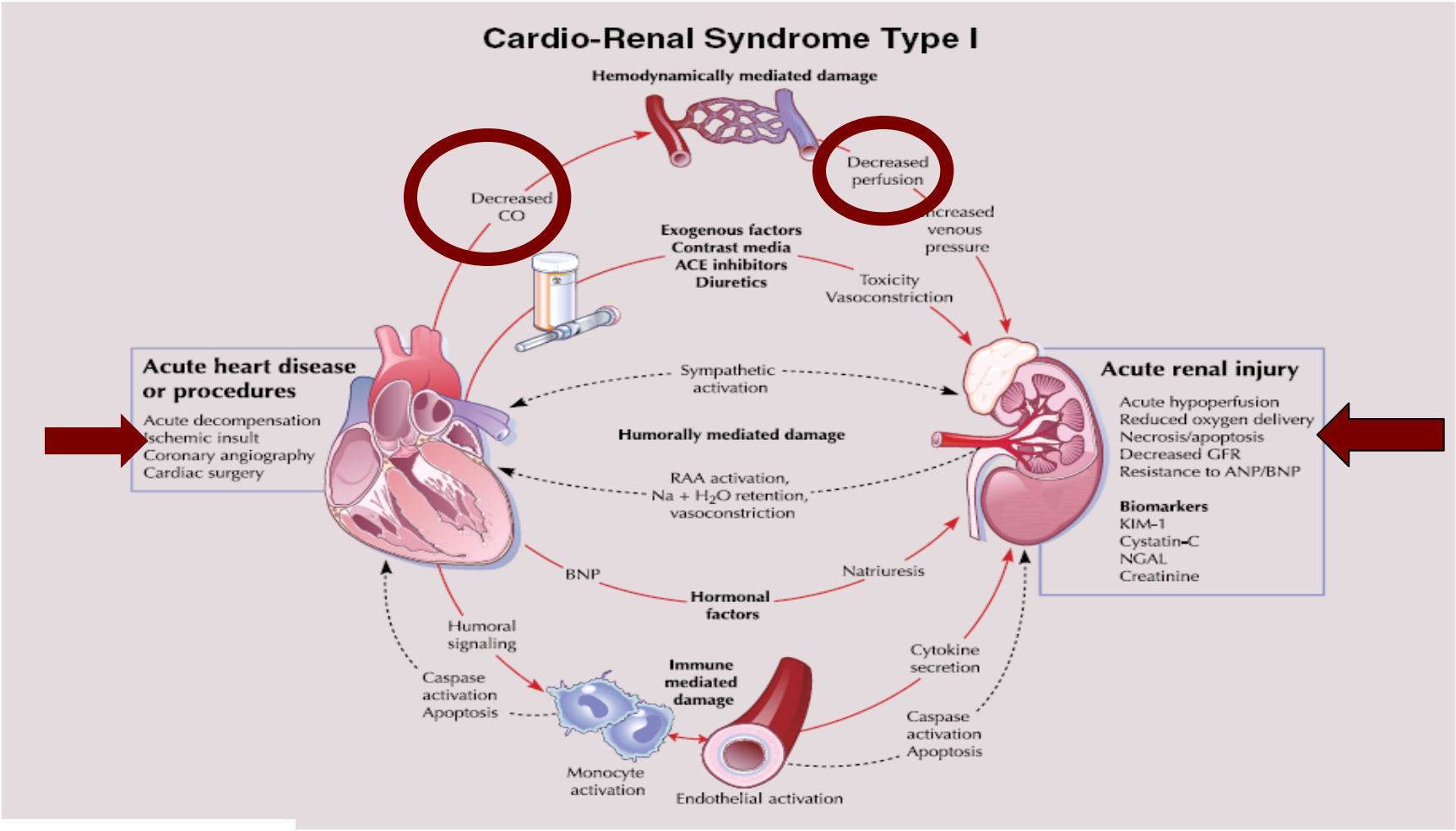
AKI in Heart Failure



Ronco C. et al. JACC 2008,52

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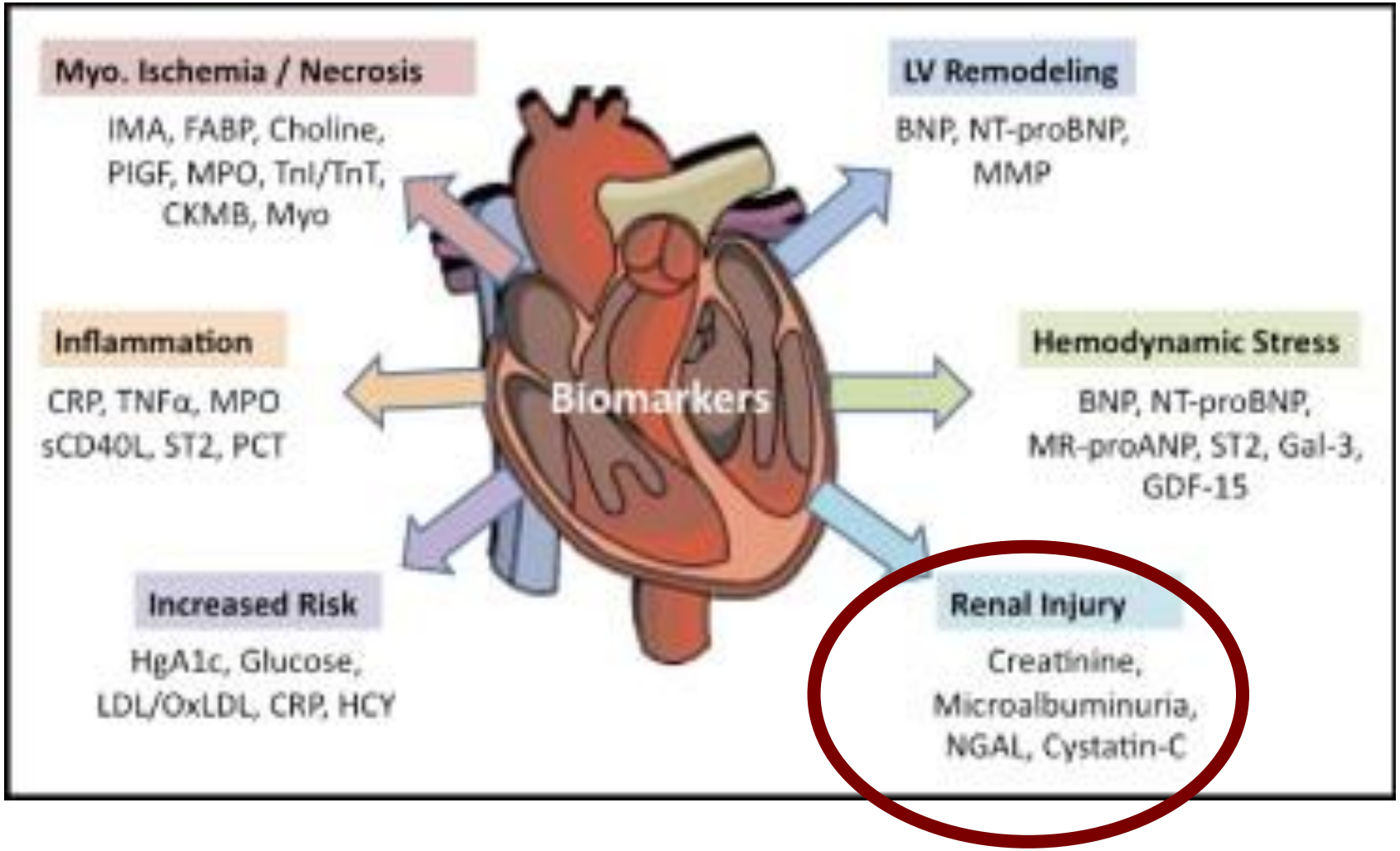
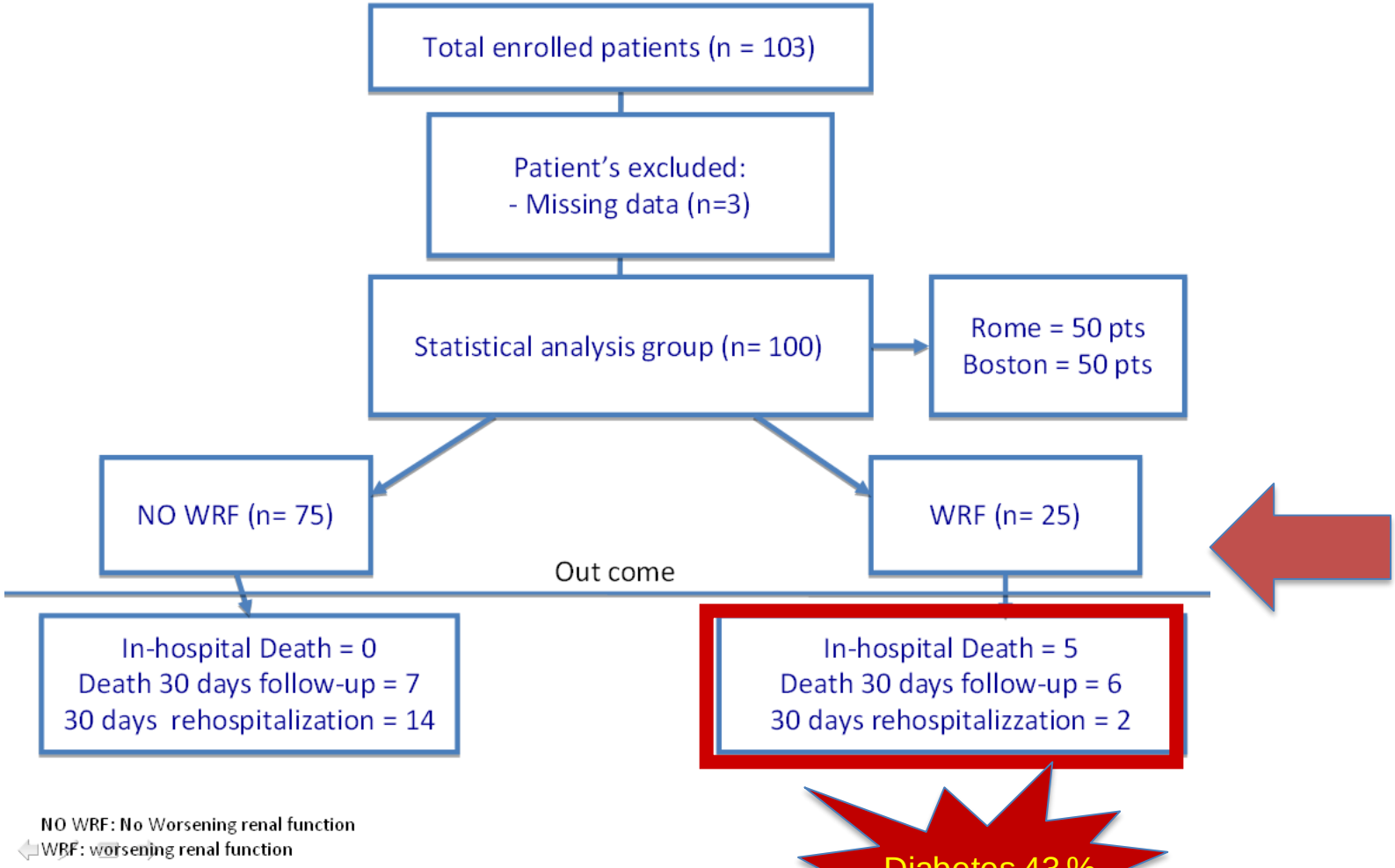
Biomarkers in Heart Failure



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

Cardiorenal Syndrome type I in ED: The BIONICS HF Study



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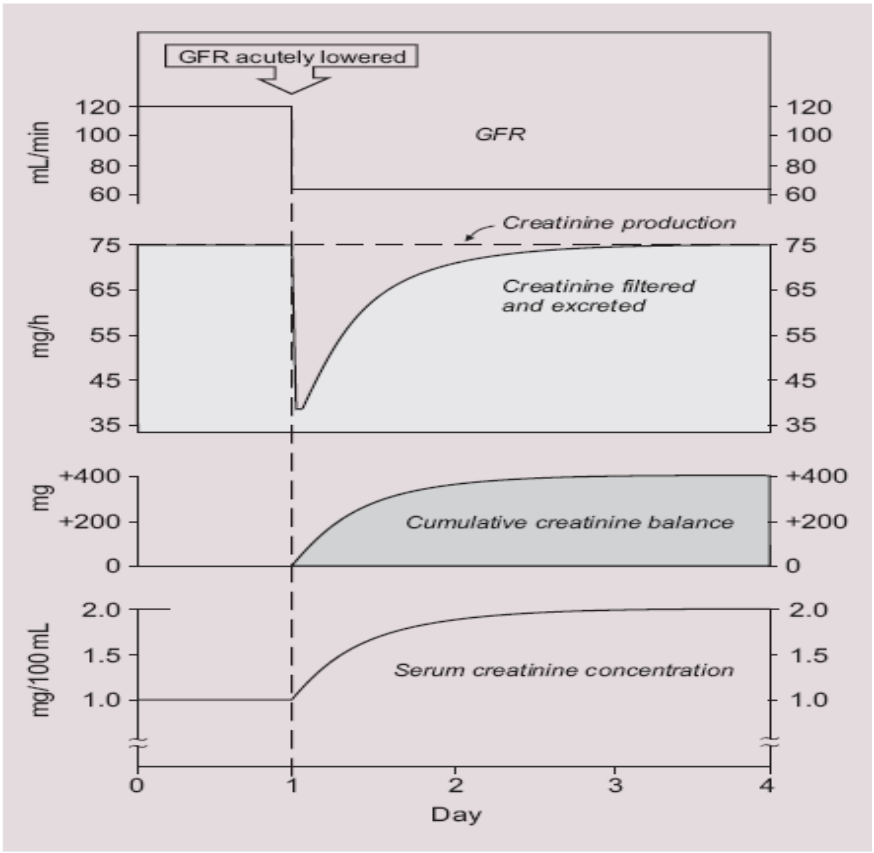
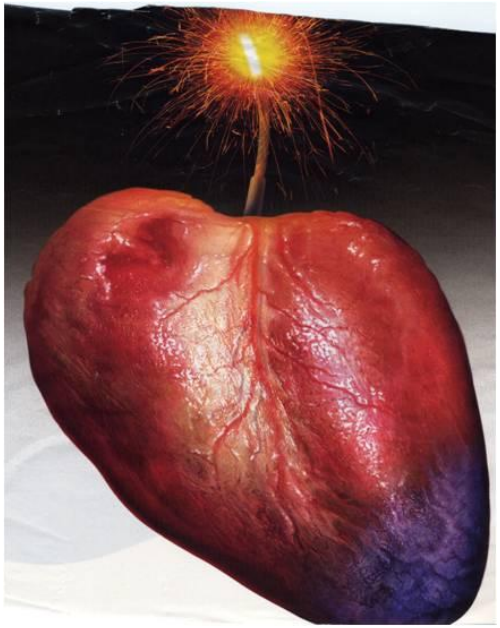
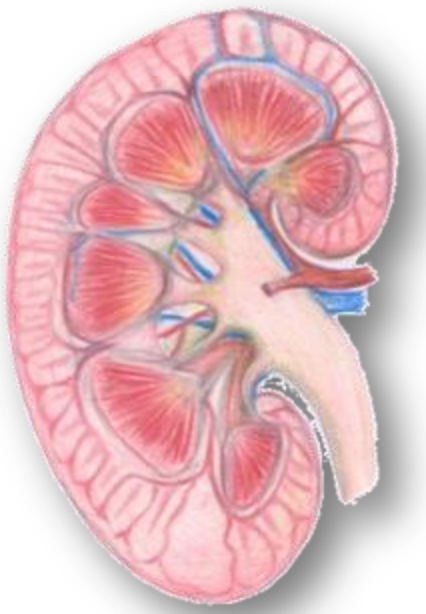
Importance of Time in Acute Kidney Injury: we need AKI biomarker !







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

IN AKI Time is important to stop the progression of nephrons loss ? ? We need AKI biomarker like troponin….

Impossibile trovare nel file la parte immagine con ID relazione rId4.

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Di Somma *et al. Critical Care* 2013, **17**:R29
http://ccforum.com/content/17/1/R29

CRITICAL CARE

RESEARCH Open Access

Additive value of blood neutrophil gelatinase-associated lipocalin to clinical judgement in acute kidney injury diagnosis and mortality prediction in patients hospitalized from the emergency department

Salvatore Di Somma[1*], Laura Magrini[1], Benedetta De Berardinis[1], Rossella Marino[1], Enrico Ferri[1], Paolo Moscatelli[2], Paola Ballarino[2], Giuseppe Carpinteri[3], Paola Noto[3], Biancamaria Gliozzo[3], Lorenzo Paladino[4] and Enrico Di Stasio[5]

	TOTAL COHORT n (%)
Total	665
Men	358 (53.8%)
Women	307 (46.2%)
Mean age ±SD, y	74 ± 14.4
Mean BMI ±SD(m^2/h)	26.3 ± 4.7
Mean systolic blood pressure ± SD *mmHg*	137 ± 58
Mean diastolic blood pressure ±SD *mmHg*	77 ± 15

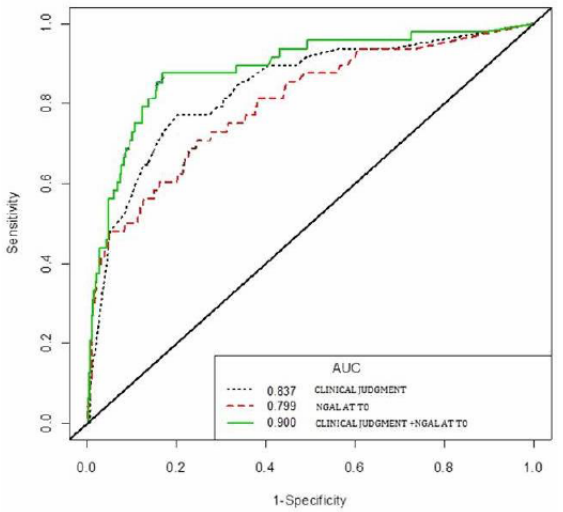

Figure 4 T0 receiver-operating characteristic (ROC) curves by adjudicated acute kidney injury (AKI) based on neutrophil gelatinase-associated lipocalin (NGAL), clinical judgment of developing AKI, and NGAL combined with clinical judgment.

Conclusion

- Admission blood NGAL measurements are useful in the early diagnosis of AKI.
- Baseline NGAL measurement allows detection of AKI earlier than sCr.
- Blood NGAL assessment at the moment of hospital admission from ED predicted the combined outcome of RRT and in-hospital mortality.

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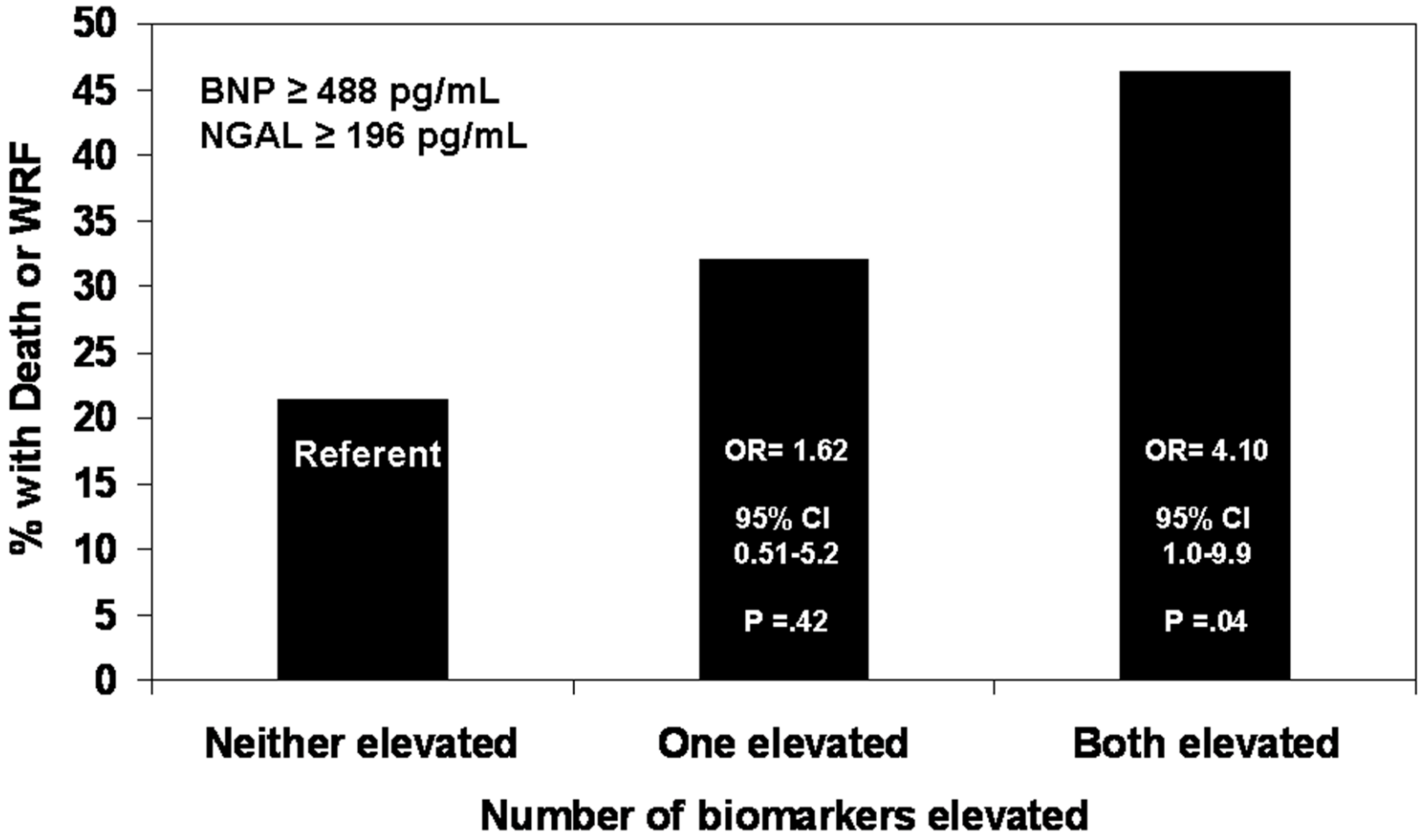

Di Somma S.,Jannuzzi J. et submitted JACC

The Ideal Cardiac Biomarker

2007	2013
Sensitive and specific	Either highly sensitive (diagnosis) OR highly specific (treatment effect)
Reflects disease severity	Reflects abnormal physiology/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 following effective therapy	"Bio-monitoring" during treatment is an effective surrogate of improvement

Conclusion1

- **The utility of heart failure biomarkers** and their clinical applications **continues to grow**

- Ongoing research on multimarker strategies will likely identify **biomarker panels** useful for monitoring **the evolution of heart failure, ranging from their use for screening, diagnosis, determining prognosis, and guiding therapy**

Conclusion2

- The mean age of patients form many trials confirming the utility of Biomarkers in the management of AHF is greater than 75 years;
- Caveats still remain in the evaluating the right cut-offs of biomakers of HF in elderly patients.

Biomarkers should be used wisely

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

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