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CLINICA DEL LAVORO E DELLA RIABILITAZIONE
I.R.C.C.S.

XXIV Giornate Cardiologiche Torinesi

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Modern Approach to Treatment of Heart Failure

Role of Biomarkers in Management of HF Patients

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Congestive Heart Failure: Fifty Years of Progress

Eugene Braunwald, MD; Michael R. Bristow, MD, PhD

..” Thus the view of chronic myocardial failure as an irreversible, end-stage process, is being supplanted by the idea that it is possible to effect true biologically based improvement in the intrinsic defects of function and structure that afflict the chronically failing heart.”

Circulation 2000; 102 (suppl 4): IV 14-IV 23

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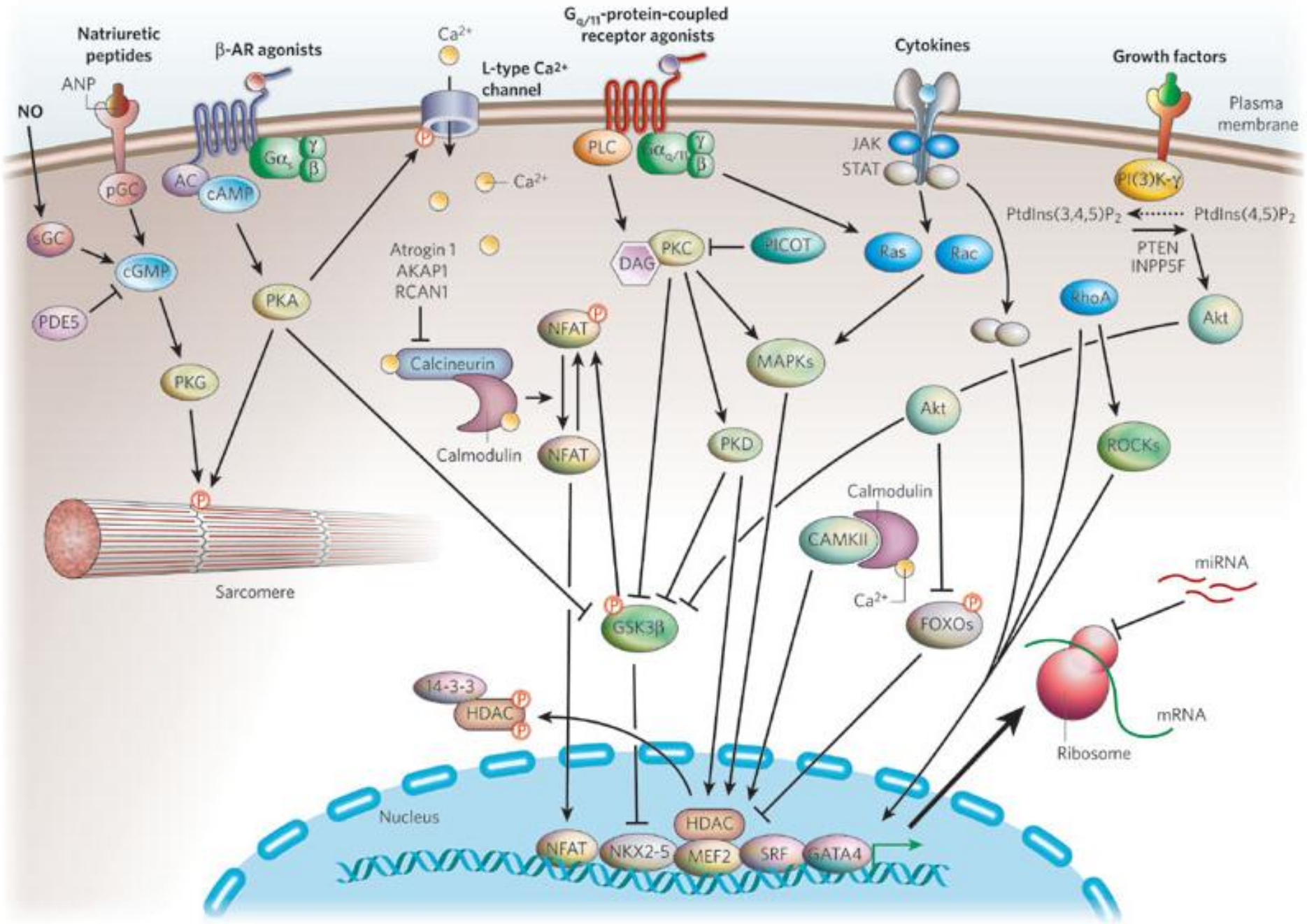
Biomarkers in Heart Failure

Biomarker	Suggested clinical applications
Neurohormones	
Catecholamines	Prognosis
Renin–angiotensin–aldosterone system (RAAS)	Prognosis
Natriuretic peptides (*ANP, BNP, NT-proBNP, MR-proANP* and *other related peptides*)	Diagnosis, prognosis, risk stratification, therapy monitoring
Arginine vasopressin and copeptin	Prognosis
Endothelin	Prognosis, therapeutic target
Chromogranin A and B	Diagnosis
Adrenomedullin	Prognosis
Myocyte injury	
Cardiac troponins (*cTnI* and *cTnT*)	Diagnosis, prognosis, risk stratification
Heart-type fatty acid binding protein (H-FABP)	Diagnosis, prognosis, risk stratification
Myosin light-chain kinase I	Prognosis
Fas (APO-1)	Prognosis
Pentraxin (PTX)3	Prognosis, risk stratification
Inflammation	
C-reactive protein	Prognosis, risk stratification
Cytokines and related receptors (*IL-1, IL-2, IL-6, IL-8, IL-18, TNFα, growth differentiation factor 15, ST2*)	Prognosis, risk stratification
PTX3	Prognosis, risk stratification
Adipokines (*adiponectin, leptin, resistin, ghrelin*)	Prediction of HF incidence, prognosis, risk stratification
Procalcitonin	Prognosis
Neopterin	Prognosis
Osteoprotegerin	Prognosis, risk stratification

Biomarker	Suggested clinical applications
Oxidative stress	
Oxidized low-density lipoproteins	Prognosis
Myeloperoxidase (MPO)	Prognosis
Urinary piopyrrins	Prognosis
Urinary and plasma isoprostanes	Prognosis
Plasma malondialdehyde	Diagnosis
Gamma-glutamyl transferases (GGT)	Prognosis
Uric acid	Prognosis
Matrix and cellular remodelling	
Matrix metalloproteinases (MMPs) and MPP tissue inhibitors (TIMPs)	Prognosis, risk stratification, aid in elucidating the HF pathogenesis
Collagen propeptides	Prognosis
Propeptide procollagen type I and III	Prognosis
Osteopontin (OPN) (*and other matricellular proteins*)	Prognosis, aid in elucidating the HF pathogenesis
Galectin-3	Prognosis, risk stratification
Endothelial dysfunction	
Adhesion molecules (ICAM, selectin-P)	Prognosis
Endothelin	Prognosis, therapeutic target
Adiponectin	Prediction of HF incidence, prognosis, risk stratification
Homocysteine	Prediction of HF incidence
C-type natriuretic peptide (CNP)	Diagnosis, prognosis, aid in elucidating the HF pathogenesis
Other markers (organ failure, cachexia, comorbidity)	
Triiodothyronine	Prognosis, risk stratification
Cystatin C	Prognosis, risk stratification
Plasminogen activator inhibitor (PAI)-1	Prognosis, risk stratification
Cholesterol	Prognosis, risk stratification
Urinary albumin-to-creatinine ratio	Prognosis, risk stratification
Haemoglobin	Prognosis
Creatinine, glomerular filtration rate	Prognosis


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

Treatment of Heart Failure

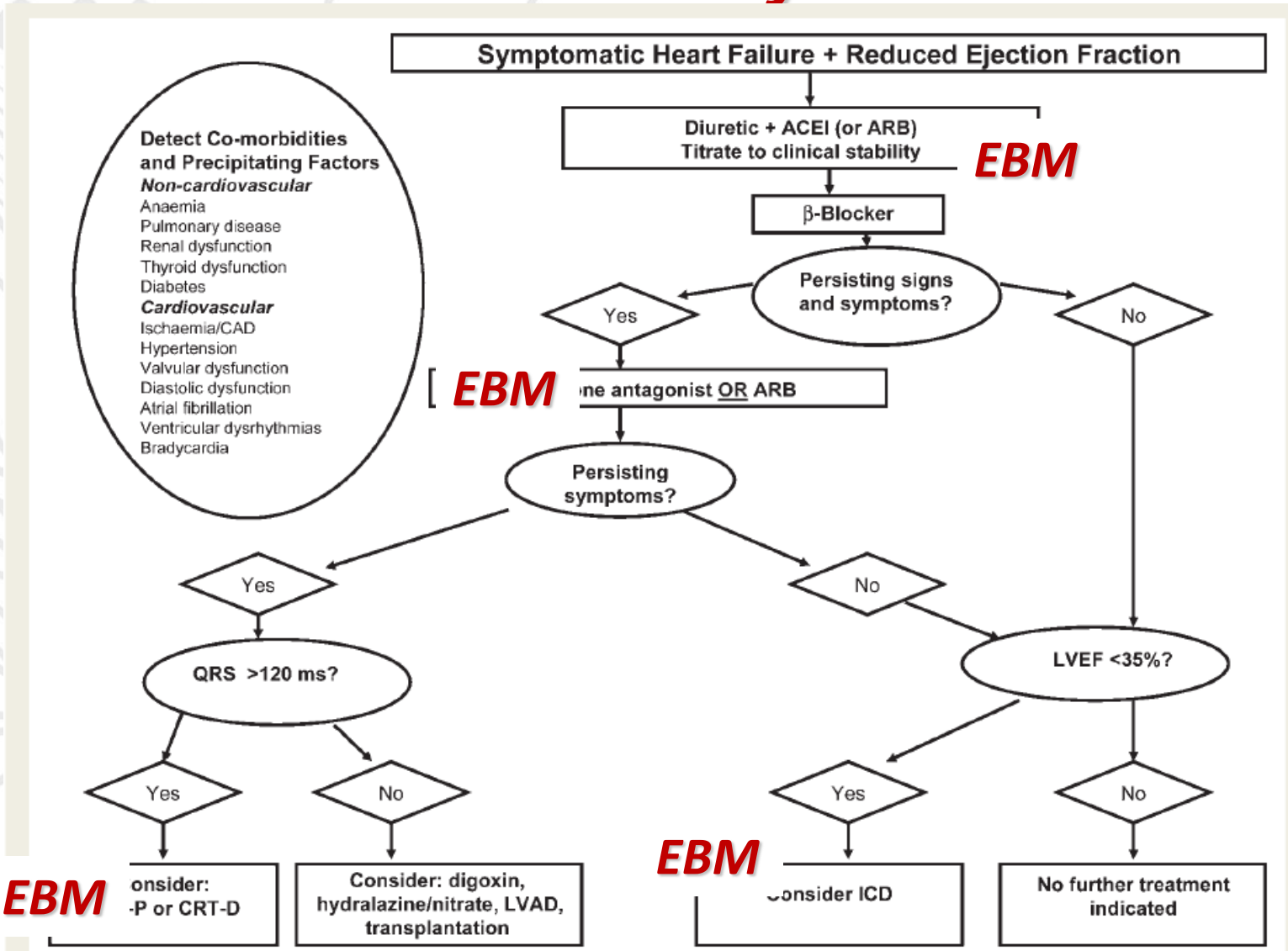


Figure 2 A treatment algorithm for patients with symptomatic heart failure and reduced ejection fraction.

ESC Guidelines, Eur Heart J 2008

Potential Shortcomings of the EBM Approach

- Is the premise the same for all patients?
- Are the effects of treatment the same for all patients?
- Is the chance of a beneficial effect of therapy similar in all patients?
- Are there better options than to give everything to everybody?
- Is an individual approach better than standard therapy?

Management of Heart Failure: a Major Challenge

- Frequent office visits along with constant evaluation most often needed to optimize care

- Great skill is required to recognise opportunities to titrate therapies (adherence to HF clinical practical guidelines inadequate)

- Few standard tools to add to standard management to assist in monitoring and manage HF patients

Biomarkers and Unmet Needs in HF Management

- Markers that tell us what to we should do (ie what is likely to work) or what we should not do (ie, what is unlikely to work) for an individual patients

- Markers that may lead to new therapeutic targets

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Haemoglobin	Prognosis
Creatinine, glomerular filtration rate	Prognosis

Main Criteria for a Biomarker to be Useful in Clinical Practice (EBLM)

1. Can the clinician easily measure the biomarker?

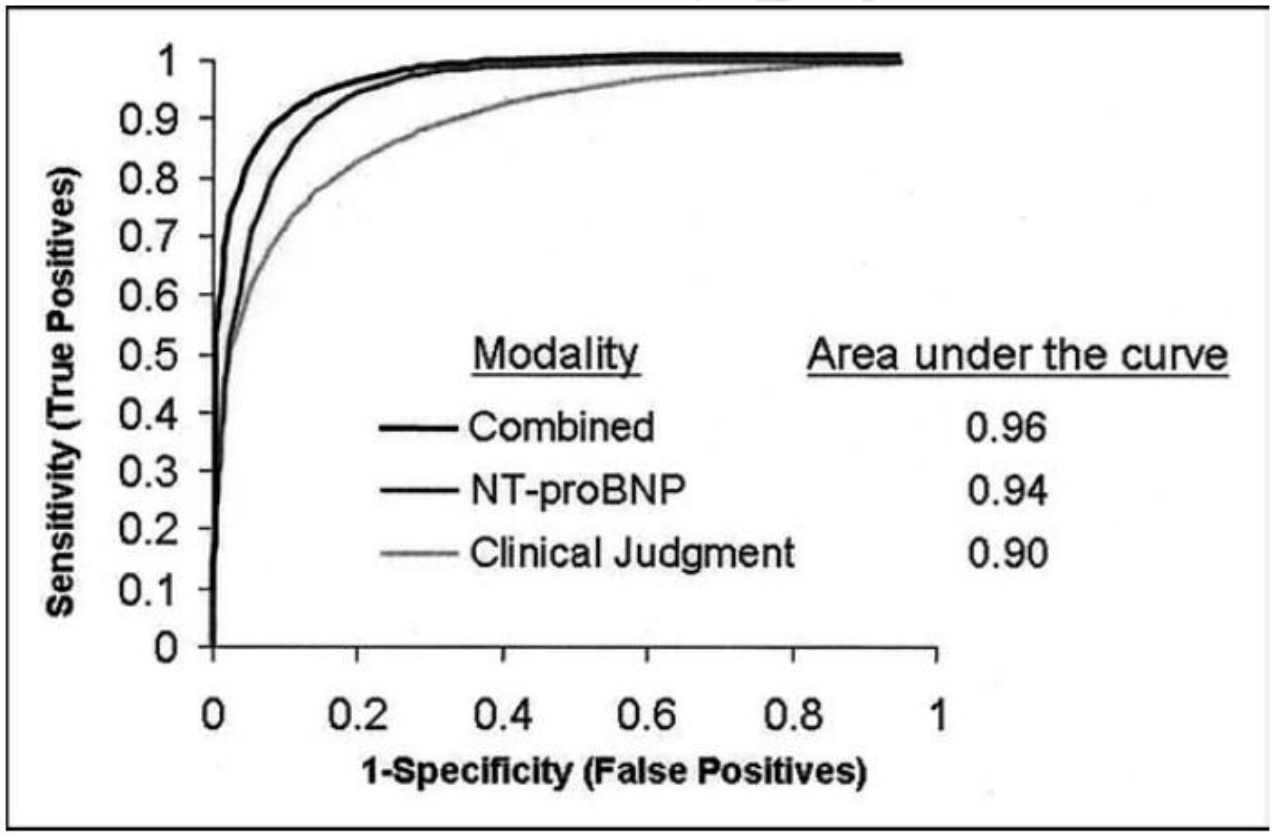
2. Does the biomarker add new information?

3. Will it help the clinician manage patients?

CP Price et al , Clin Chem 2000; 46: 1041-50

Role of Natriuretic Peptides Assay

- Diagnosis: NPs levels accurately reflect the cause of dyspnea in patients presenting to the ED and add additional information beyond standard Hx, PE, and diagnostic testing



Role of Natriuretic Peptides Assay

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2008) **29**, 2388–2442
doi:10.1093/eurheartj/ehn309

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008‡

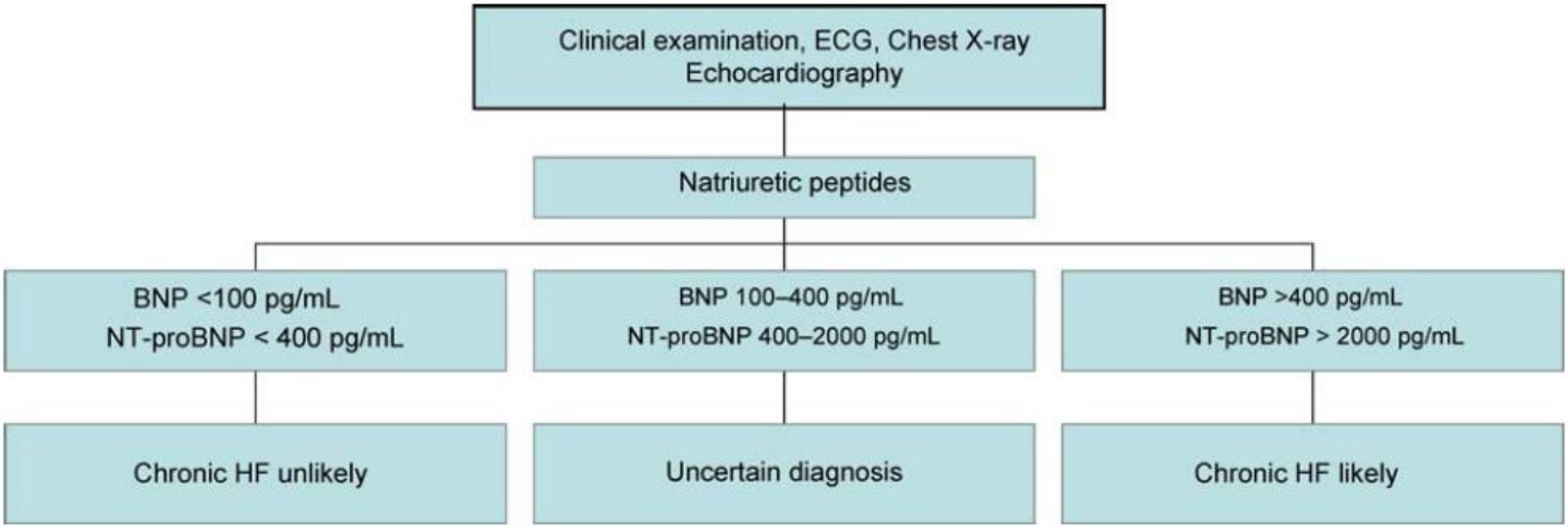
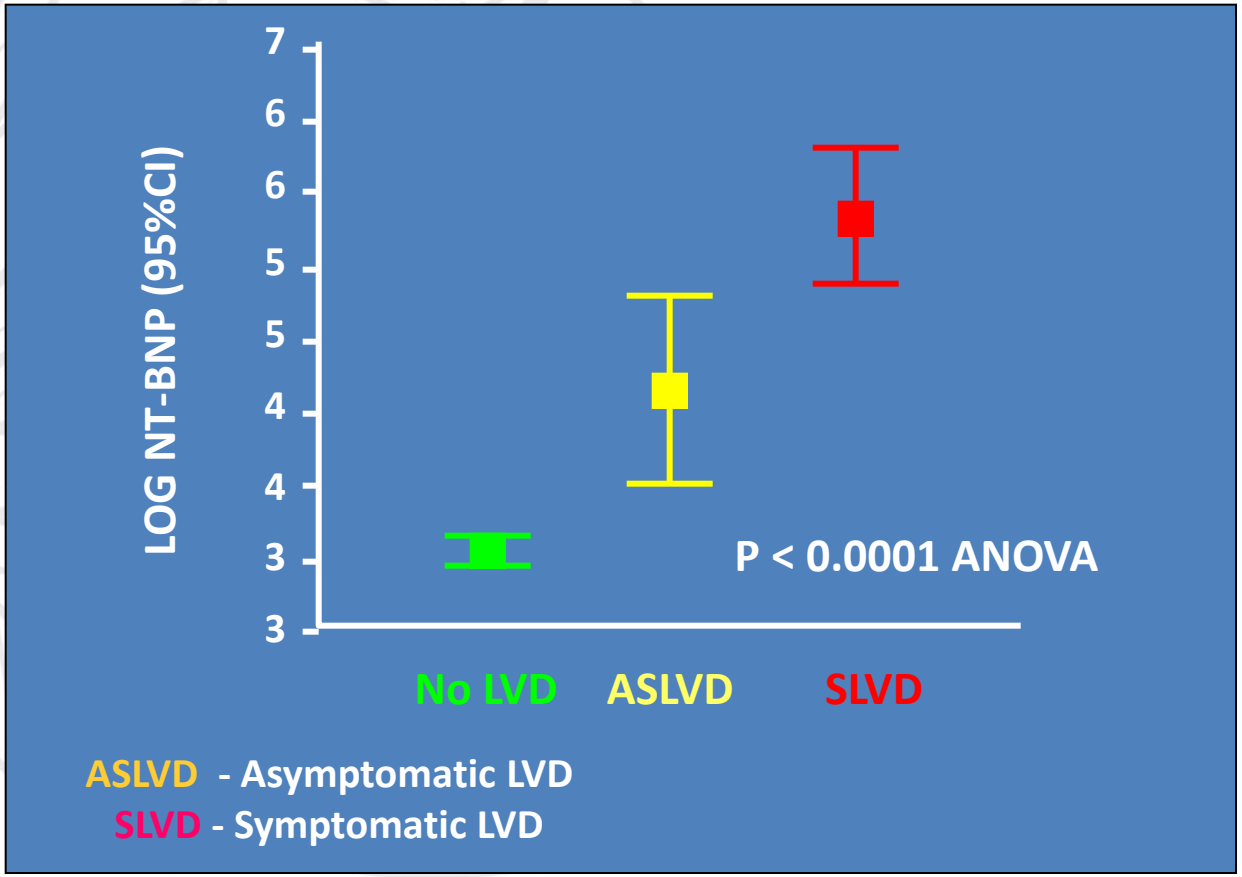


Figure 1 Flow chart for the diagnosis of HF with natriuretic peptides in untreated patients with symptoms suggestive of HF.

Role of Natriuretic Peptides Assay

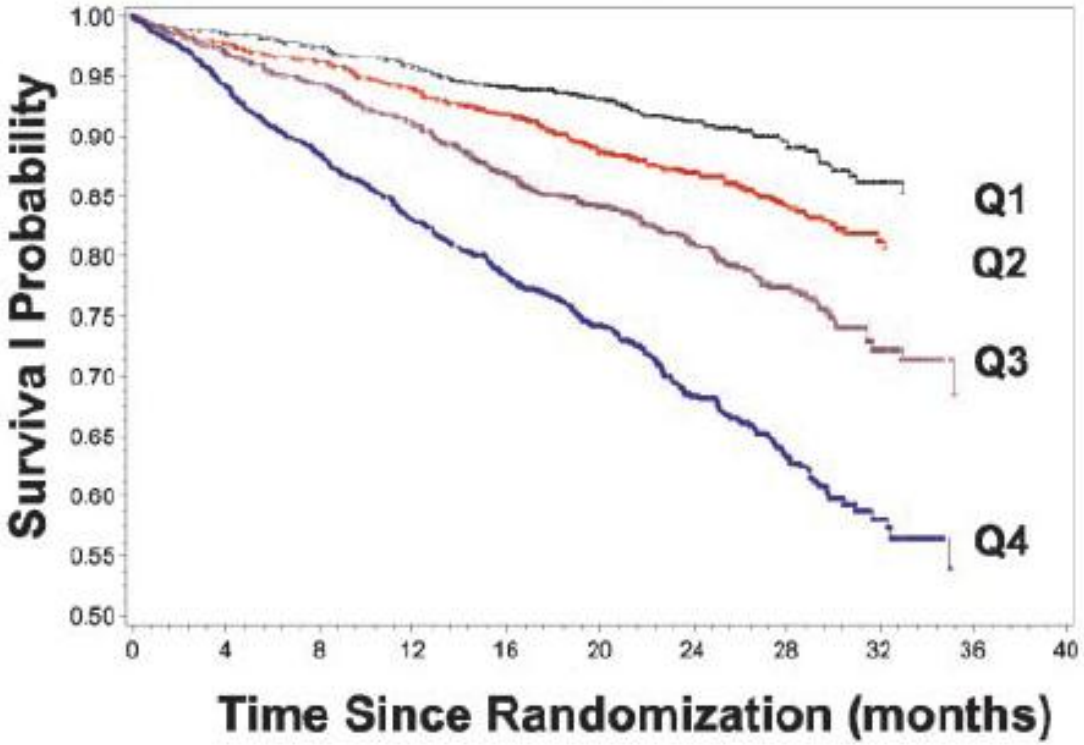
- Screening: NPs accurately detect abnormal left ventricular function in patients with or without Sx of CHF or a previous history of CHF



Role of Natriuretic Peptides Assay

Risk Stratification: BNP levels are associated with risk of hospitalization and death in patients with CHF

4305 patients with stable, symptomatic HF
LVEF < 40%
Baseline BNP: 181±230pg/mL
BNP re tested at 4 months



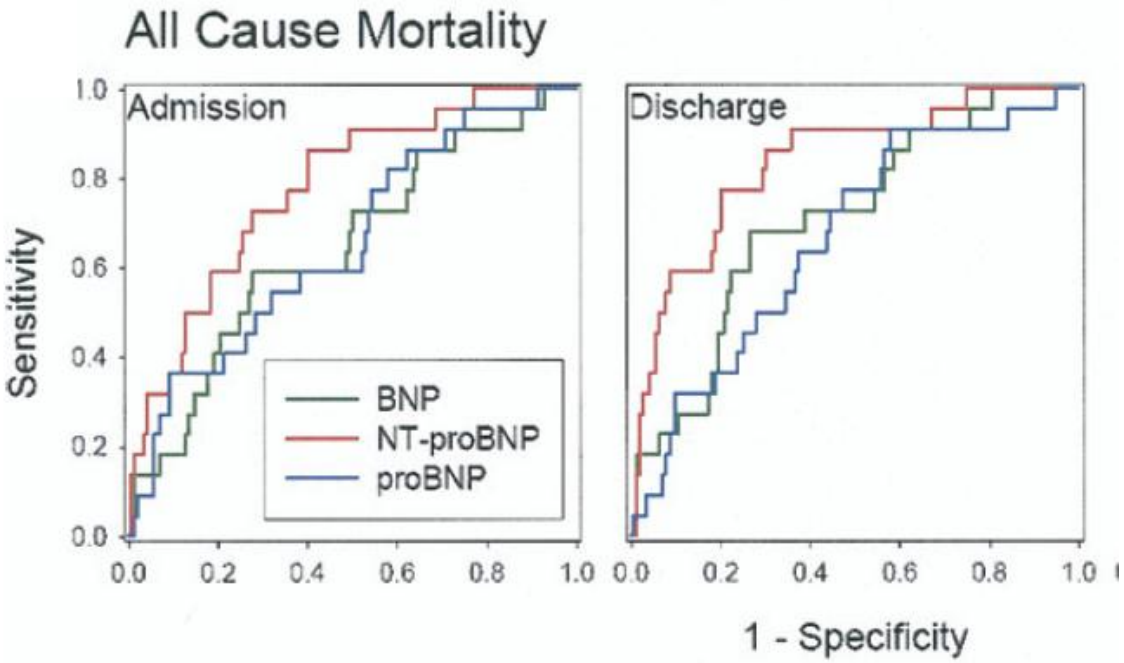
	Q1	Q2	Q3	Q4
BNP (pg/ml)	< 41	41- < 97	97- < 238	≥ 238
% Mortality	9.7	14.3	20.7	32.4

IS Anand et al ,
Circulation 2003; 107: 1278

Role of Natriuretic Peptides Assay

Risk Stratification: NPs levels are associated with risk of hospitalization and death in patients with ADHF

164 patients admitted because of acute decompensated HF

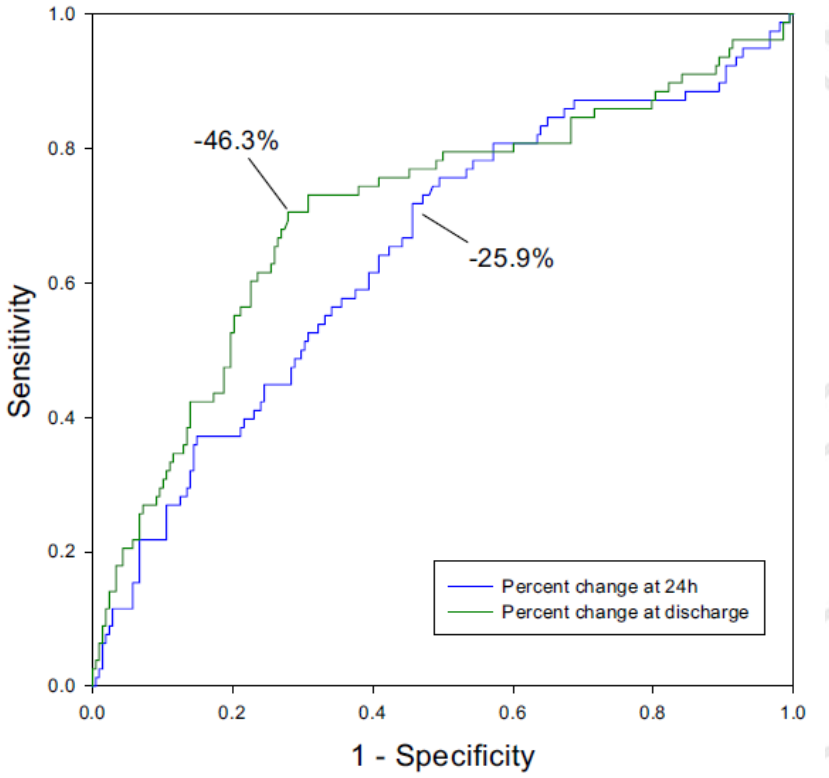


	AUC	95 % CI	P	AUC	95 % CI	P
B	0.644	0.519-0.769	0.030	0.709	0.598-0.820	0.002
N	0.778	0.679-0.876	0.000	0.834	0.743-0.924	0.000
P	0.653	0.532-0.774	0.021	0.666	0.550-0.782	0.012

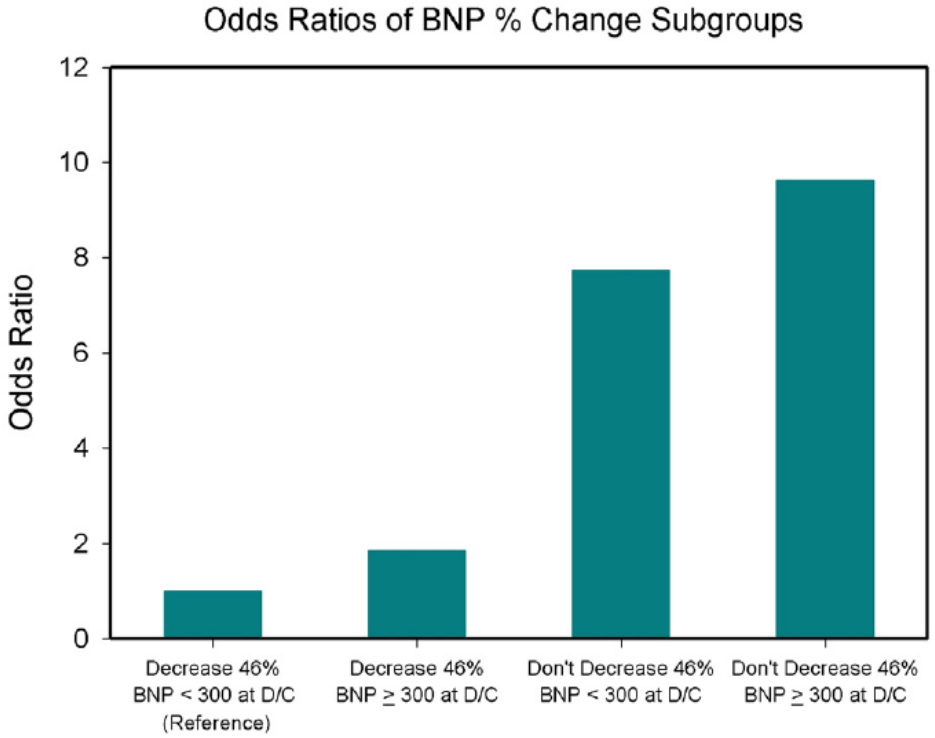
SW Waldo et al , JACC 2008; 51: 1874

Prognostic Value of Serial Measurements of NPs

282 patients wuth ADHF
BNP at admission, at 24 h, at discharge



Probability of new cardiovascular events or rehospitalization

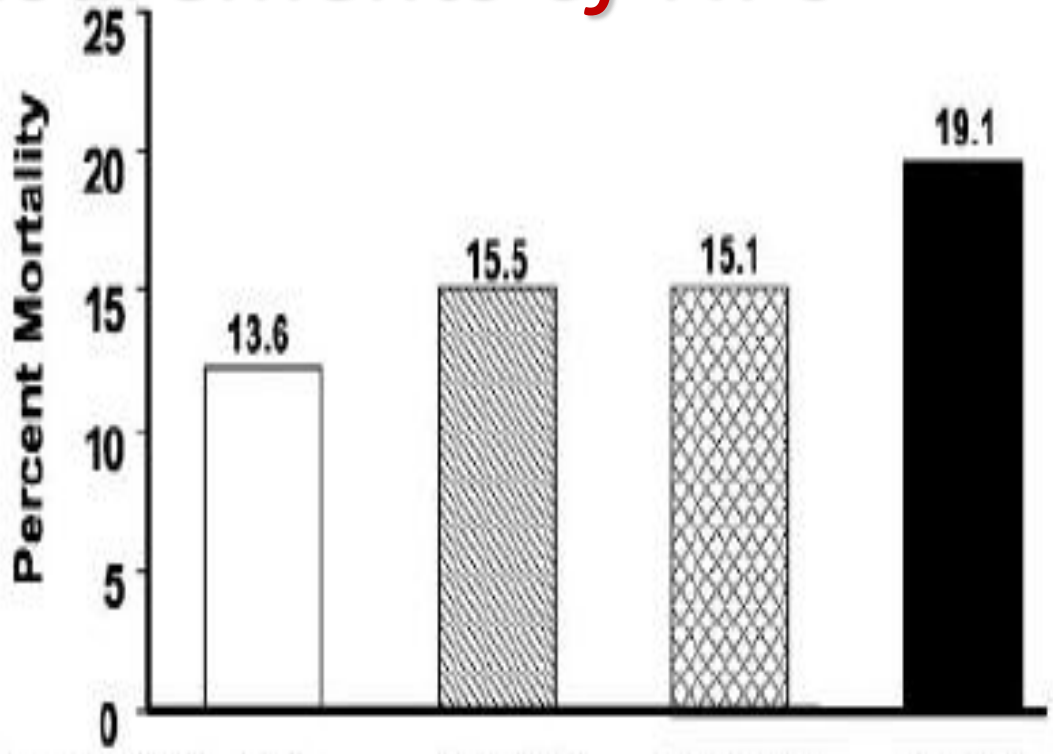


THE ITALIAN RED STUDY

S Di Somma et al , Critical Care 2010; 14: R116

Prognostic Value of Serial Measurements of NPs

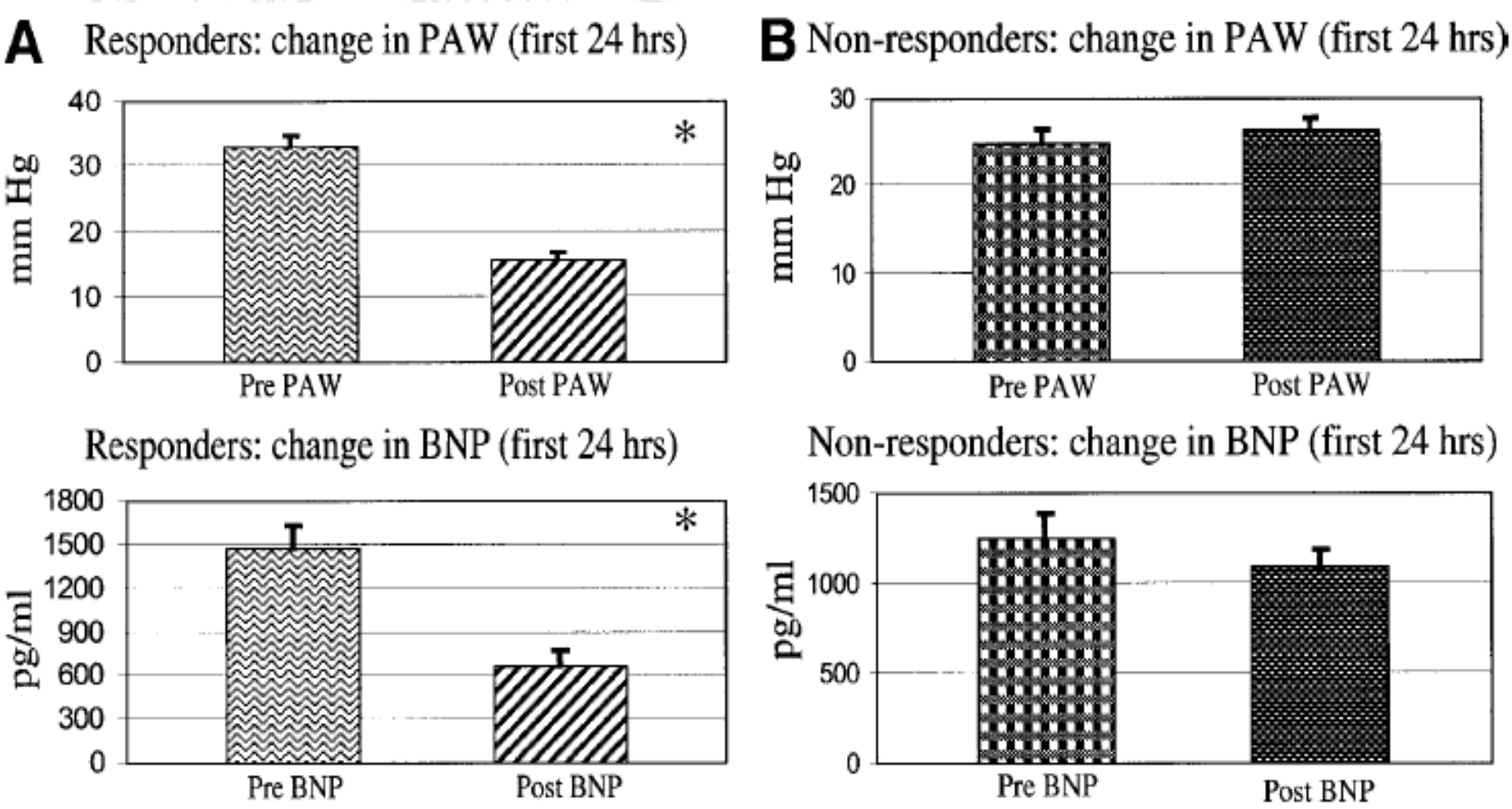
Val-HeFT Study Changes from Baseline to 4 Months



Quartile % change in BNP	> - 45 %	- 45 to -13 %	- 13 to + 30 %	> + 30 %
Mean change in BNP	-143	-57	+ 8	+ 118
Mean BL BNP	214	193	157	122
Mean % change in BNP	- 66 %	-30 %	+6 %	+380 %
Number of Patients	933	939	939	938

IS Anand et al , Circulation 2003; 107: 1278

Treatments Associated with a Reduction in BNP Levels



R Kazanegra et al , J Card Fail 2001; 7: 21

Role of Natriuretic Peptides Assay

Treatment Guide: Natriuretic Peptides may guide initiation and titration of HF therapy

The concept of an intensified NPs guided therapy may be particularly attractive in: older pts who are less physically active, pts in whom symptoms are less reliable, pts who are more susceptible to drug-induced side effects

B-Type Natriuretic Peptide- Guided Heart Failure Therapy

Table 2. Treatment Group Targets in Included Trials

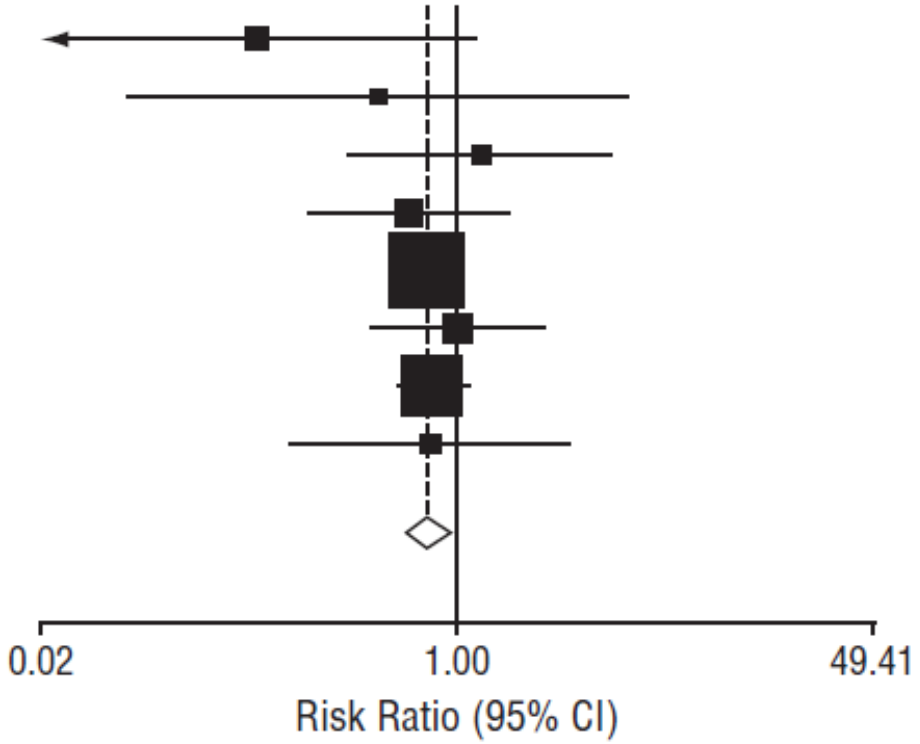
Source	Target BNP/NT-Pro-BNP–Guided Therapy	Target Control Group	Medical Adjustment Involved
Troughton et al[21]	NT-pro-BNP <1700 pg/mL	HF score[a] <2 (based on Framingham criteria)	ACEI, diuretic, digoxin, aldactone, metolazone then additional vasodilator (isosorbide dinitrate and felodipine)
Beck-da-Silva et al[22]	Based first on BNP level and then clinical status evaluation; BB up-titrated when: 1. BNP level is lower + unchanged or better clinical status 2. There are mild signs of congestion but BNP level >10% lower than previous value 3. BNP is within ±10% previous level, clinical signs were primarily considered	Up-titrate medication when no sign of deterioration (worsening FC, HR <55, BP <80, increase congestion)	Only BB (ACEI or ARB and digoxin were unchanged)
Esteban et al[23]	NA	Framingham score	NA
STARS-BNP[24]	BNP <100 pg/mL	Based on PE + usual paraclinical + biological parameter	BB, ACEI, aldactone, diuretic
TIME-CHF[25]	NT-pro-BNP + FC ≤II <400 pg/mL (<75 y), <800 pg/mL (≥75 y)	FC ≤ II	BB, ACEI, or ARB, aldactone, diuretic, nitrate
BATTLESCARRED[26]	NT-pro-BNP <1300 pg/mL	HF score[a] <2	BB, ACEI, aldactone, diuretic, digoxin, metolazone
PRIMA[27]	Individual NT-pro-BNP target (lowest level during the first 2 wk after treatment of HF) together with clinical assessment	Clinical assessment	BB, ACEI, or ARB, aldactone, diuretic, digoxin
SIGNAL-HF[28]	NT-pro-BNP plus clinical symptoms and signs	Clinical symptoms and signs	BB, ACEI, or ARB, aldactone

P Porapakkam et al; Arch Int Med 2010; 170: 507

B-Type Natriuretic Peptide- Guided Heart Failure Therapy

All Cause Mortality

Source	Risk Ratio (95% CI)	% Weight
Troughton et al[21]	0.16 (0.02-1.20)	3.5
Beck-da Silva et al[22]	0.48 (0.05-4.85)	1.1
Esteban et al[23]	1.25 (0.37-4.21)	2.1
STARS-BNP[24]	0.64 (0.26-1.58)	5.7
TIME-CHF[25]	0.75 (0.58-0.96)	49.6
BATTLESCARRED[26]	1.00 (0.45-2.22)	5.7
PRIMA[27]	0.79 (0.57-1.10)	29.8
SIGNAL-HF[28]	0.79 (0.22-2.86)	2.6
Overall (95% CI)	0.76 (0.63-0.91)	

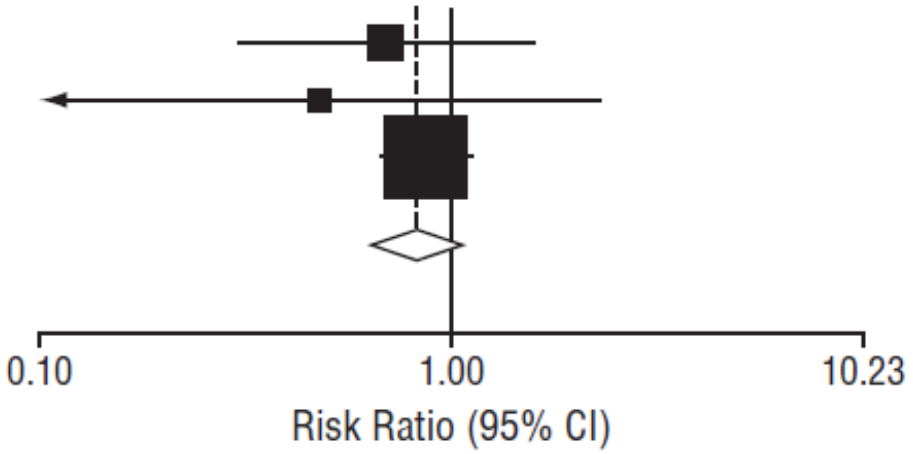


P Porapakkam et al; Arch Int Med 2010; 170: 507

B-Type Natriuretic Peptide- Guided Heart Failure Therapy

All Cause Hospitalization

Source	Risk Ratio (95% CI)	% Weight
Troughton et al[21]	0.69 (0.31-1.58)	14.1
Beck-da Silva et al[22]	0.48 (0.10-2.32)	5.5
STARS-BNP[24]	0.87 (0.67-1.12)	80.4
Overall (95% CI)	0.82 (0.64-1.05)	

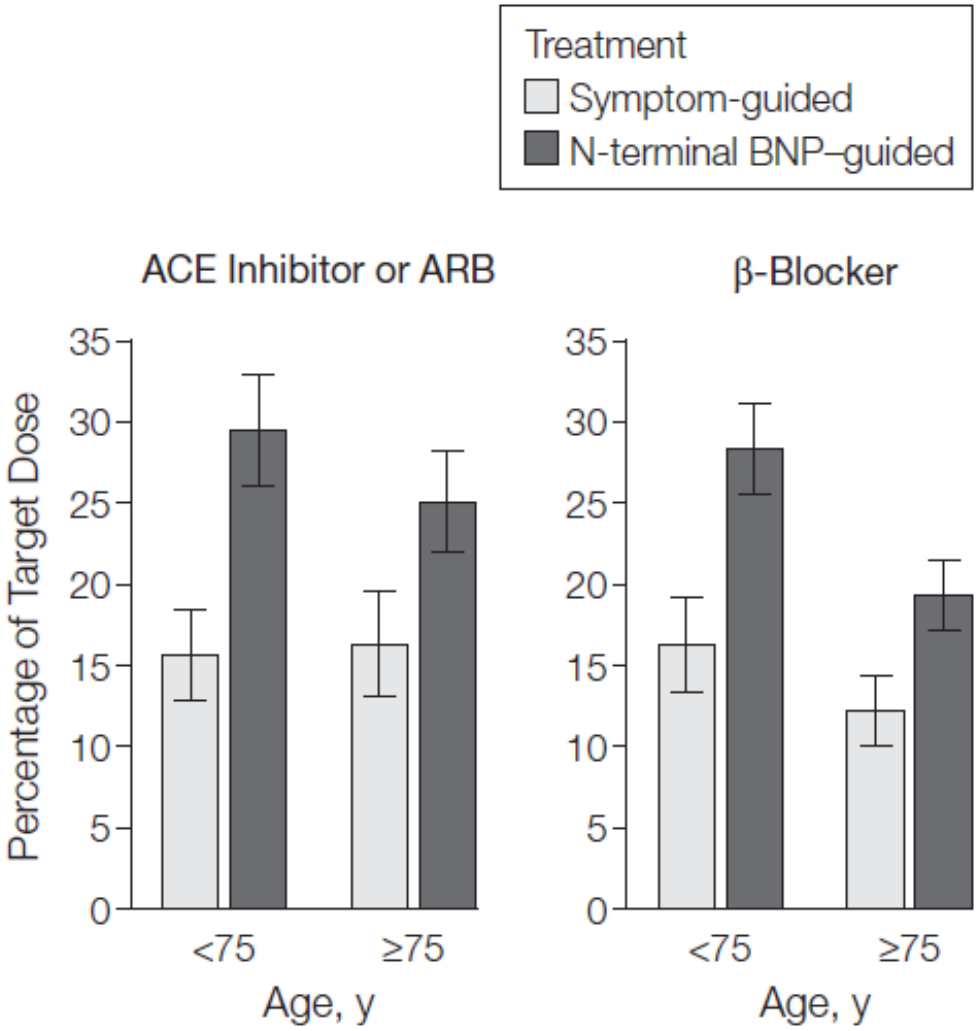


P Porapakkam et al; Arch Int Med 2010; 170: 507

BNP-Guided vs Symptoms-Guided Heart Failure Therapy (TIME-CHF)

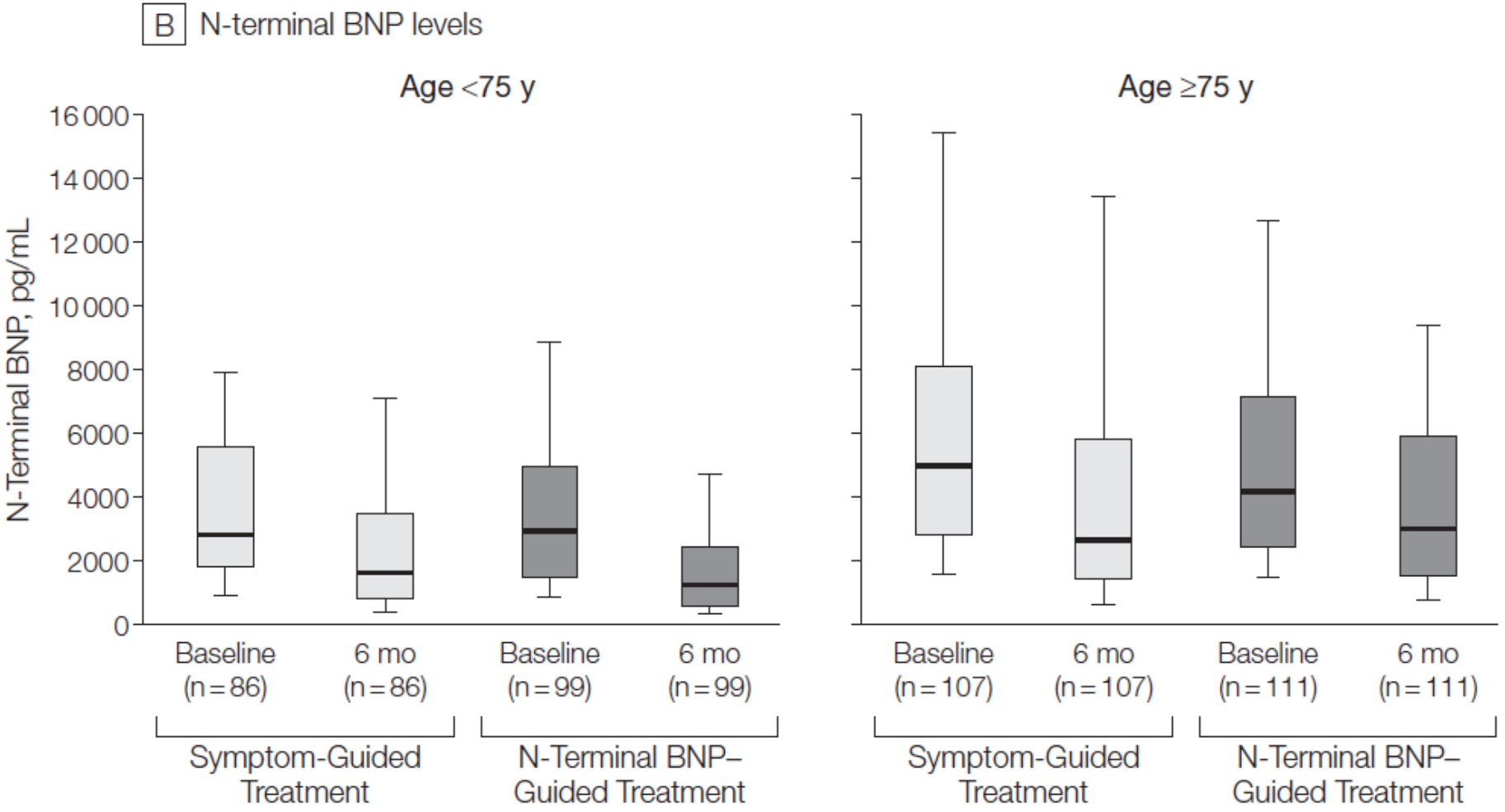
499 outpatients
- Age: 60 or older
- LVEF ≤ 45%
- NYHA II or greater
- prior hospitalization for HF within 1 year
-NT-proBNP 2 or more times the upper limit of normal

PRIMARY OUTCOME:
18-month survival free of all-cause hospitalization



M Pfisterer et al , JAMA 2009; 301: 383

BNP-Guided vs Symptoms-Guided Heart Failure Therapy (TIME-CHF)



M Pfisterer et al , JAMA 2009; 301: 383

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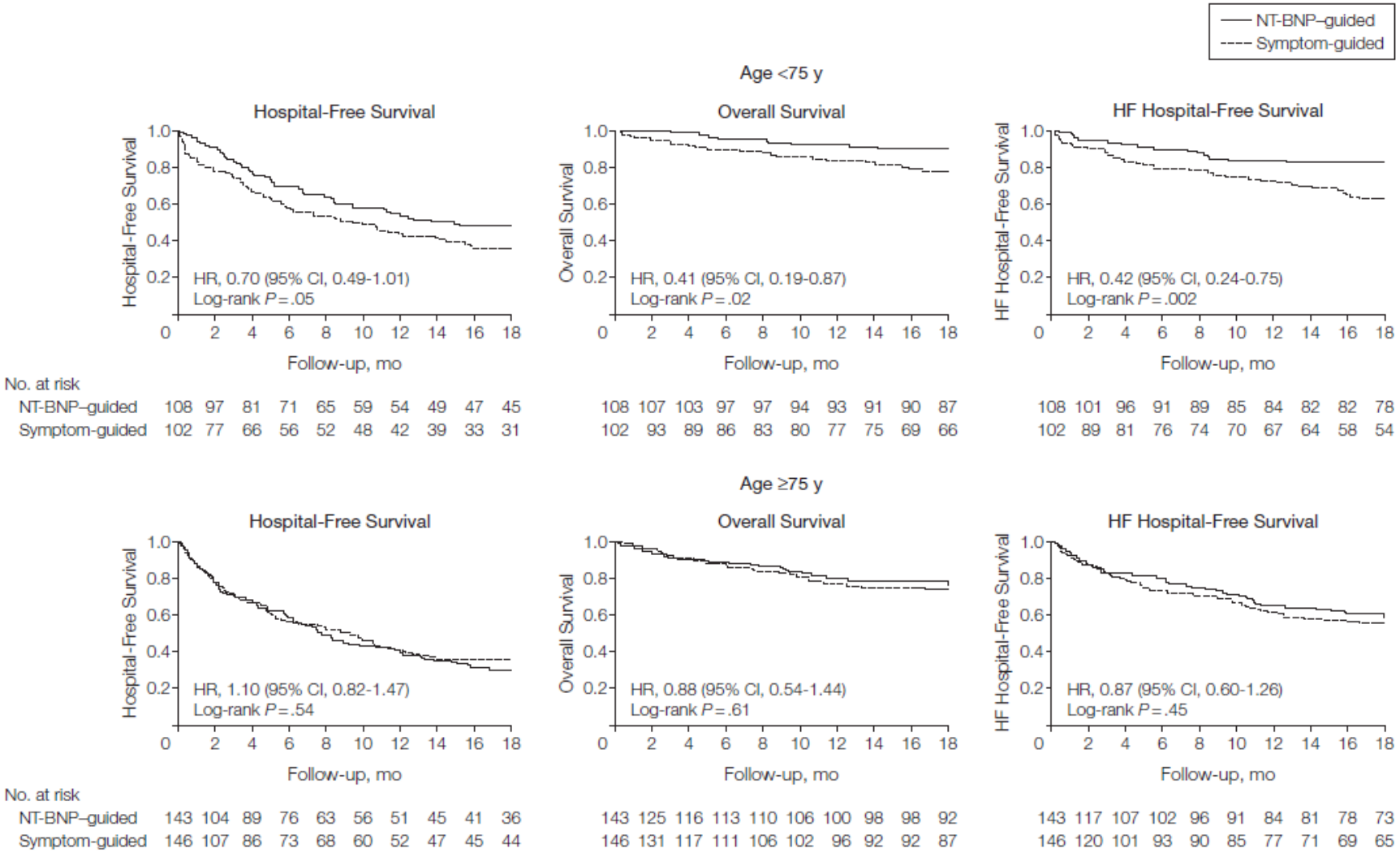

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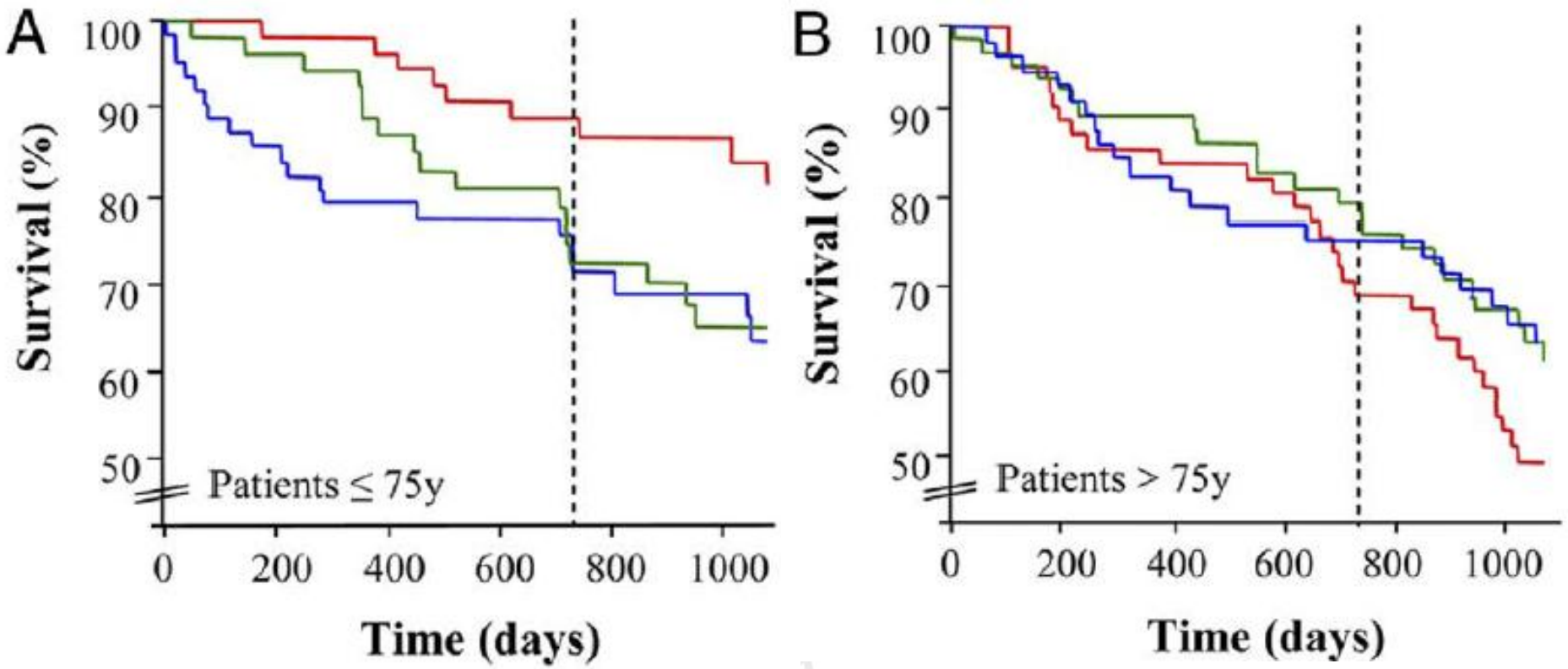
NT-proBNP-Guided Treatment for CHF (BATTLESCARRED Trial)



JG Lainchbury et al, JACC 2010; 55: 53

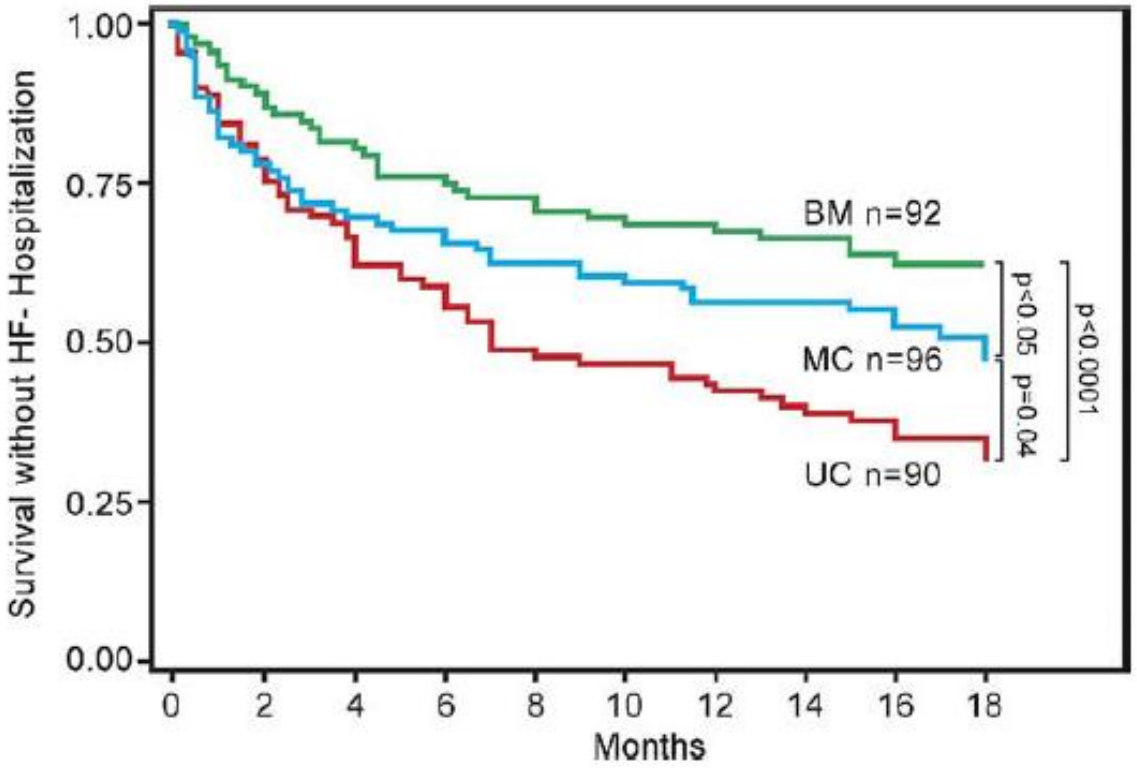
NT-proBNP-Guided Intensive Patient Management in Addition to Multidisciplinary Care in CHF

278 patients
- hospitalized for HF
- NYHA III/IV at admission
-LVEF < 40%

Randomly allocated to:
- Usual Care
- Multidisciplinary Care
- BNP guided management

Follow-up: 1 year

PRIMARY OUTCOMES:
HF hospitalization
Death + HF hospitalization



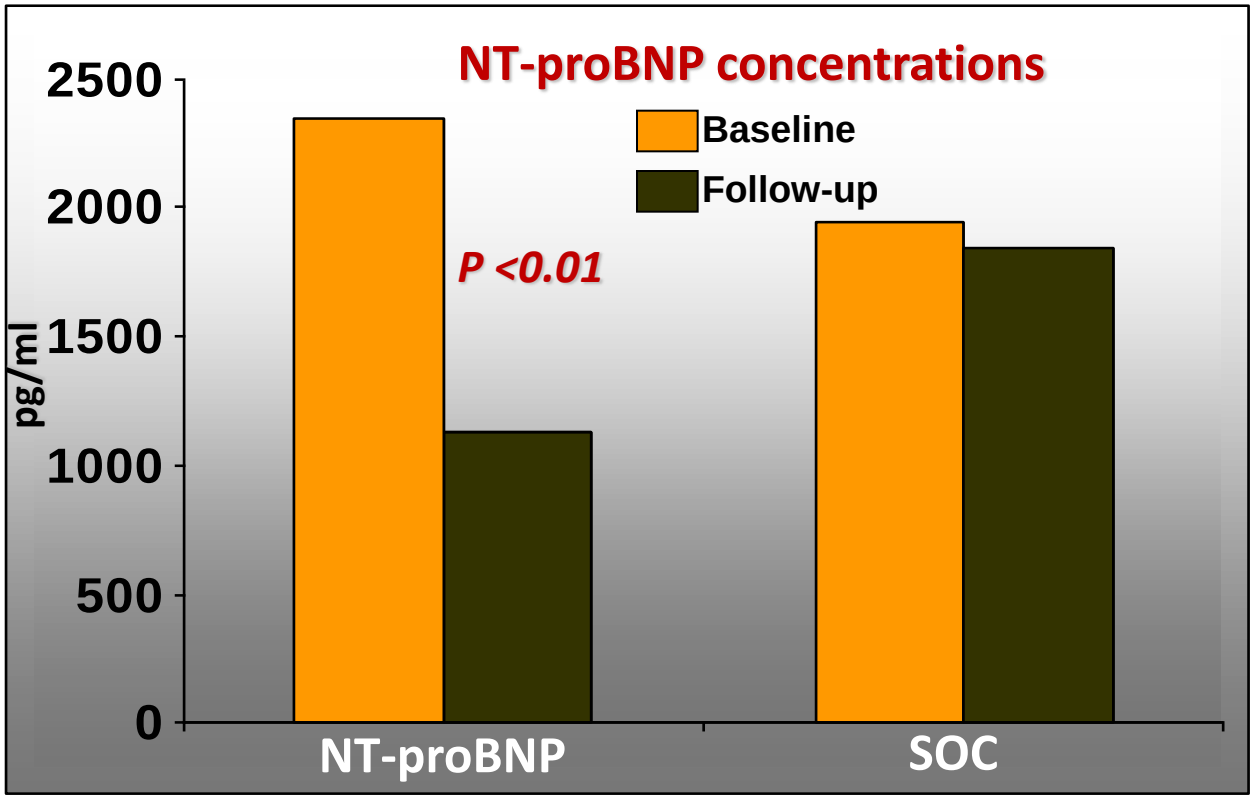
R Berger et al, JACC 2010; 55: 645

Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting PROTECT

151 patients
- HF due to LV systolic dysfunction
- 63±14 yrs (22% ≥ 75yrs)

Randomly allocated to:
- Standard Care
- Standard Care + a goal to reduce NT-proBNP to < 1000 pg/ml

PRIMARY OUTCOME:
Total cardiovascular events



JL Jannuzzi et al, JACC 2011; 58: 1881

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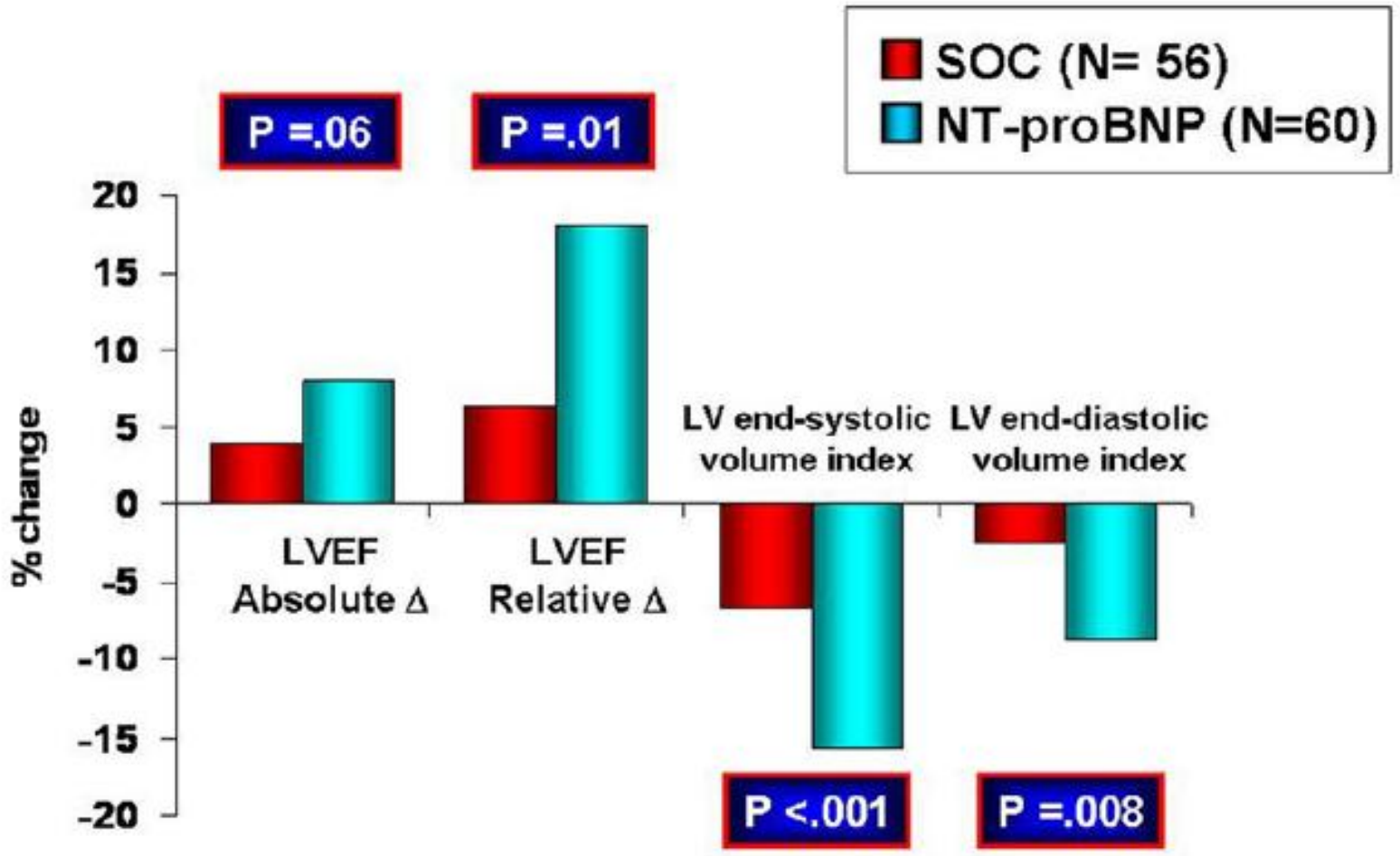


JL Jannuzzi et al, JACC 2011; 58: 1881

BNP – NTproBNP Caveats

False Positive

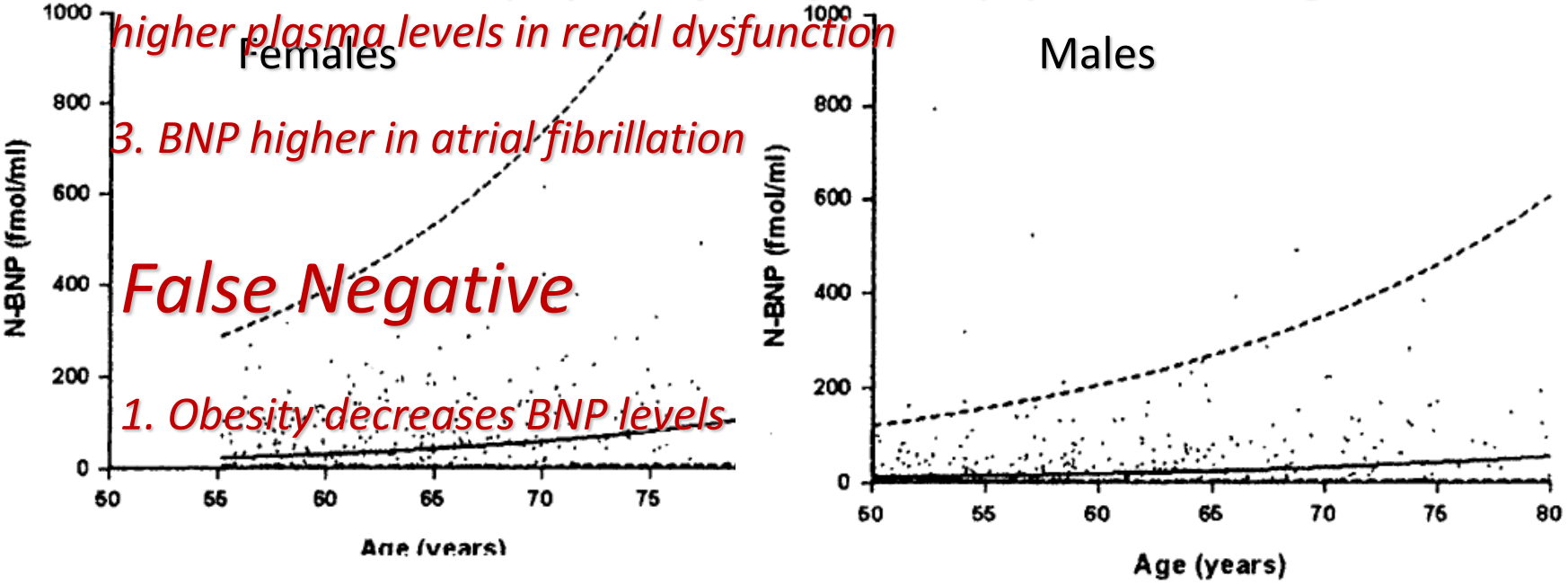
1. Age and gender relationship

2. Renal elimination plays a key role for both peptides resulting in higher plasma levels in renal dysfunction

3. BNP higher in atrial fibrillation

False Negative

1. Obesity decreases BNP levels



Median and 95% CI in relation to age and gender

I Loke et al, Eur J Heart Fail 2003; 5: 599

Conclusions

- Natriuretic peptides are an effective clinical tool in the management of heart failure
- Besides their well –established diagnostic and prognostic utility, NPs guided therapy is possible, safe, and beneficial
- However, they should always be used as a tool together with clinical experience