



ΠΑΛΑΙΑ ΚΑΙ ΝΕΑ ΝΑΤΡΙΟΥΡΗΤΙΚΑ ΠΕΠΤΙΔΙΑ

ΝΙΝΙΟΣ ΒΛΑΣΙΟΣ
ΚΛΙΝΙΚΗ ΑΓΙΟΣ ΛΟΥΚΑΣ
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NATRIURETIC PEPTIDES

- ANP
- BNP
- CNP



ANP

- First described by De Bold in 1981
- released from myocardial cells in the atria and in some cases the ventricles

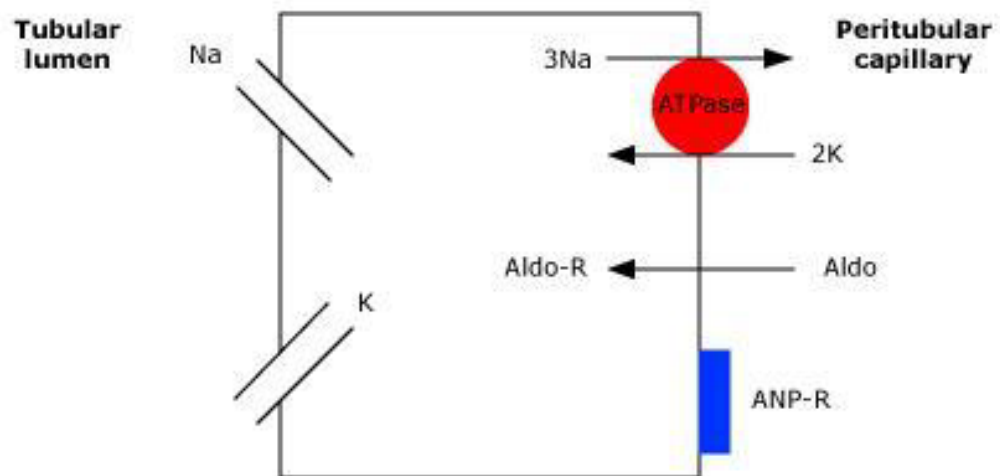


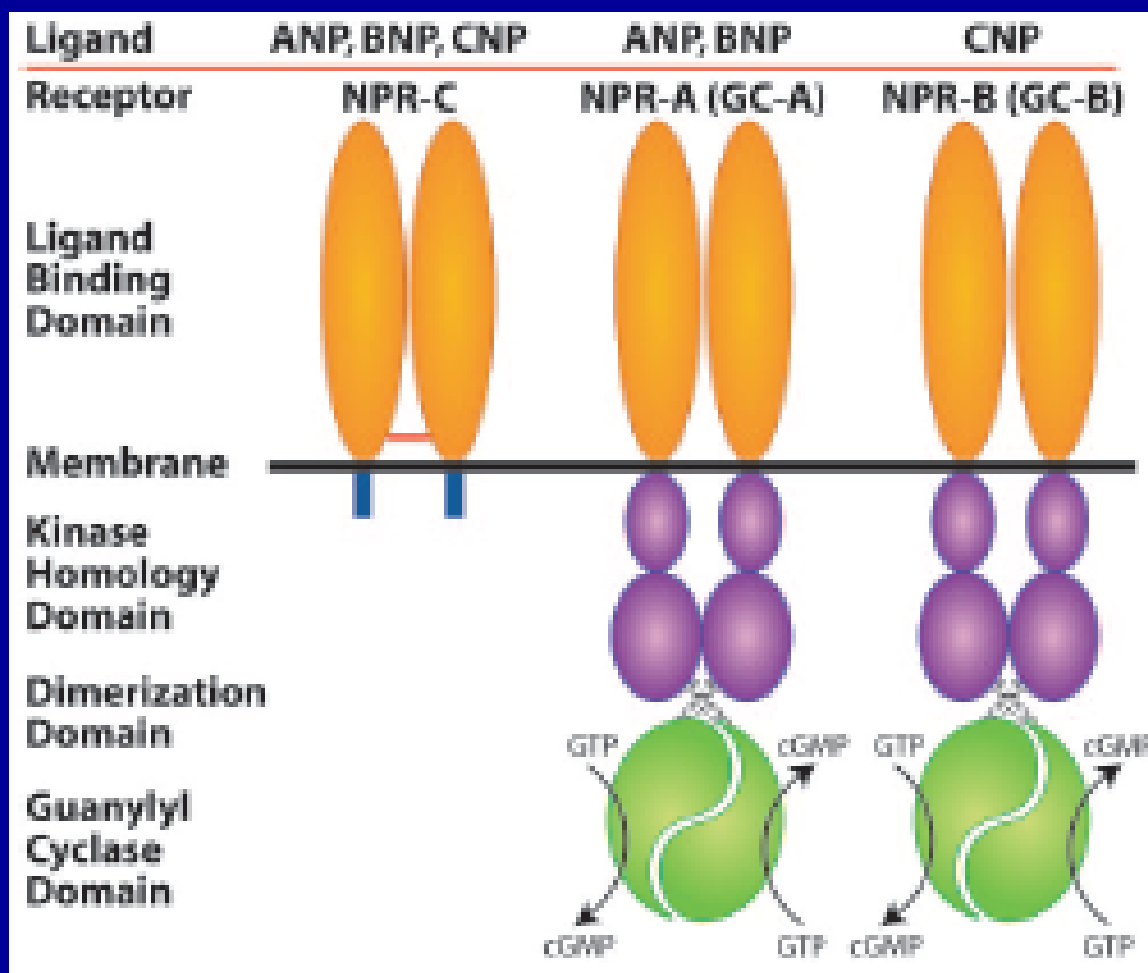
ANP ACTIONS

- direct vasodilator
- increases urinary Na^+ and water excretion
 - directly increases the GFR
 - reduces Na^+ reabsorption
- may diminish Na^+ reabsorption in the proximal tubule
- (extrarenal) produced in the vascular wall where it may diminish endothelial and vascular smooth muscle growth



Ion transport in collecting tubule cell







Control of ANP secretion

- Stored and released from the atria in response to volume expansion as a response to atrial stretch
- In chronic cardiac overload new hormone production by the ventricular myocardium



Physiologic role of ANP

- Uncertain role
- ANP produces modest diuresis, perhaps because the concomitant fall in blood pressure induced by ANP counteracts its natriuretic effects
- ANP acts as the primary circulating natriuretic peptide hormone under normal conditions



ANP-like peptides

- ANP aminoacids 98-126
- pro-ANP fragments 1-30, 31-67
 - Hypotensive and natriuretic effect
- Fragment 79-98 enhance K secretion



Table 1 Biological actions of atrial natriuretic peptide

Haemodynamic	Vasorelaxation of artery and vein (endothelium independent); decrease in excessive blood volume overload
Renal	Increase in glomerular filtration rate; increase in renal blood flow; suppression of Na and water re-absorption at collecting duct; induction of diuresis and natriuresis
Endocrine	Suppression of renin release, aldosterone synthesis, endothelin-1 synthesis, sympathetic nerve activity
Cell growth, survival	Growth inhibition of cardiac fibroblasts, mesangial cells and vascular smooth; inhibition of hypertrophy in cardiac myocytes; inhibition of fibrosis in cardiac fibroblasts, mesangial cells; inhibition of apoptosis in cardiac myocytes and endothelial cells
Inflammation	Inhibition of the activation of NF-kappa B; inhibition of cytokine production



Biological actions of ANP

- ANP has a variety of biological actions that protect cardiac tissue from ischaemia/reperfusion injury
- ANP can inhibit early activation of neurohormonal factors and inflammation after reperfusion therapy in AMI
- ANP can reverse arrhythmias, apoptosis of cardiac myocytes and endothelial cells, and limit infarct size and LV remodelling,
- ANP can reduce subsequent re-hospitalization or death due to heart failure.
- A low dose of ANP is required without a large effect on systemic BP in patients with AMI.



	ANP	BNP	CNP
Plasma half life (min)	~2 (1.7 -3.1) [328, 329]	~20 (19.5 -22.6) [330]	2.6 [331]
Plasma concentration (pmol/liter)			
Normal	6.4 ± 0.9 [42] (1.1 -13.7) [42, 332-334]	0.9 ± 0.007 [42] (0.9 -6) [42, 332-335]	1.4 ± 0.6 [332] (1.4 -1.9) [332, 336, 337]
In congestive heart failure	87 ± 12 [321] (26 -164) [42, 321, 332]	87 ± 11 [321] (3.9 -267) [42, 321, 332, 335]	1.4 ± 0.2 [332] (1.4 -1.85) [332, 338]
In myocardial infarction	33.4 ± 6.1 [321] (33.4 -55.3) [321, 337, 339]	60 ± 9.4 [287] (26.6 -62.2) [321, 337, 339]	N.D.
In pulmonary arterial hypertension	14.0 [260] (8.8 -20.5) [260]	15.3 [260] (9.2 -49.4) [260]	N.D.
In chronic renal failure	43 ± 11 [332] (43 -48) [321, 332]	130 ± 37.4 [332] (28 -130) [321, 332, 335, 340]	3.0 ± 0.4 [332]
In subarachnoid hemorrhage	5.9 ± 1.0 [341] (5.46 -10.5) [341, 342]	15.1 ± 3.8 [341] (0.64 -23.2) [341, 342]	2.0 -2.6 [343] (0.91 -9.1) [342, 343]
In cirrhosis	27.98 ± 3.71 [333]	16.0 ± 1.91 [333] (1.2 -43.1) [333, 335]	1.36 ± 0.18 [336]



Urodilatin

- ANP-like hormone in human urine
- produced within the kidney
- May be more important natriuretic factor than ANP
- The natriuretic effect is not limited by BP changes

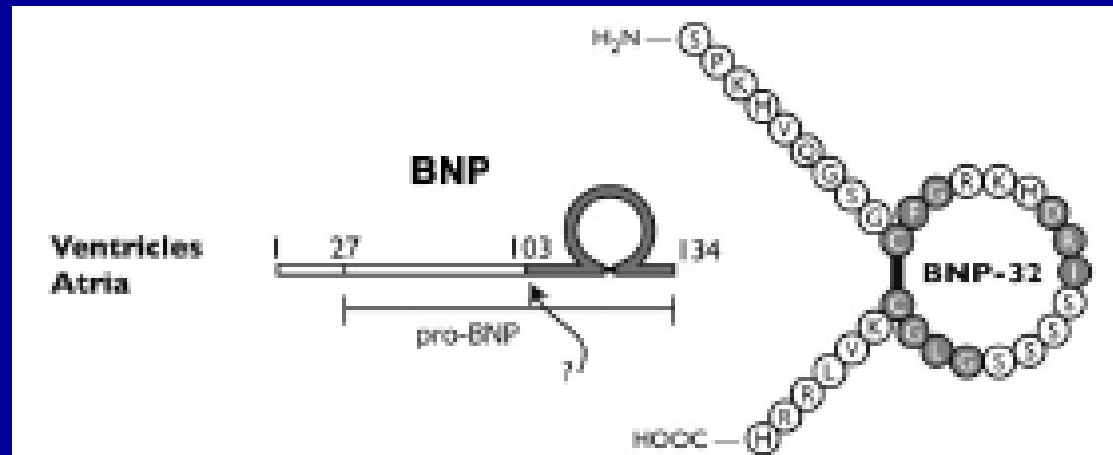


Mid-regional Pro-atrial Natriuretic Peptide (MR-proANP)

- More stable in vivo or ex vivo than ANP
- Levels increase proportionally with NYHA class
- It appears that it is also a powerful predictor of mortality like pro-BNP
- **Biomarkers in Acute Heart Failure (BACH)** trial showed that it may enhance the diagnostic ability of the BNP's for patients in the 'grey' zone



BNP



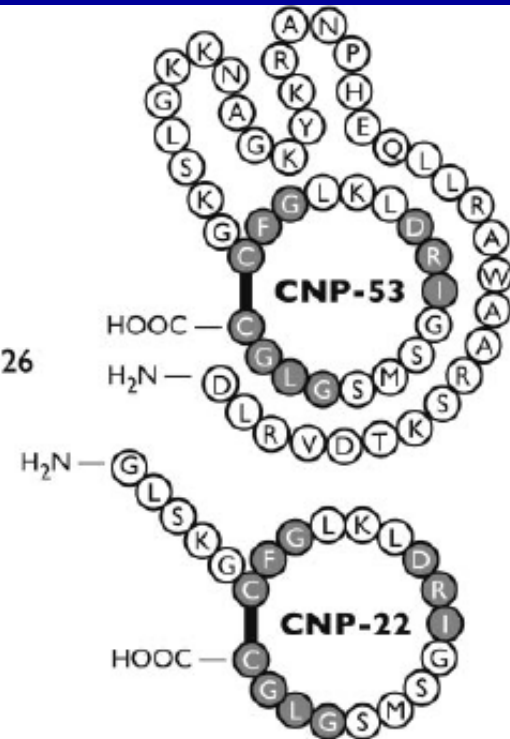
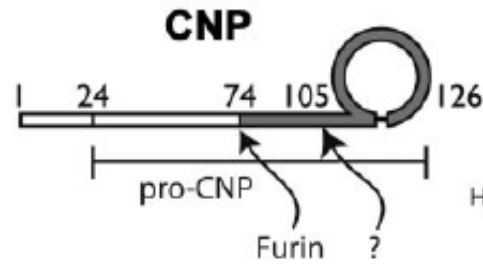


- initially purified from porcine brain extracts
- circulating concentration of BNP is less than 20 % of that of ANP
- much higher concentrations in cardiac ventricles from patients or animals undergoing cardiac stress
- 200-300fold increase during stress
- More prolonged plasma half life than ANP



CNP

Bone
Brain
Endothelium
Heart





CNP

- Found in brain in chondrocytes and cytokine-exposed endothelial cells
- its major function may involve regulation of local blood flow
- has little effect on systemic hemodynamics, renal function or the renin-angiotensin system



BNP assay methods

- RIAs
- IRMAs
- Rapid fluorescence immunoassay



Utility of NP (BNP, pro-BNP)

- Use of natriuretic peptide levels in patients presenting with acute dyspnoea
- NP levels in the inpatient setting
- The use of NP levels in the intensive care unit
- Monitoring NP levels post-hospitalisation NP-guided outpatient treatment



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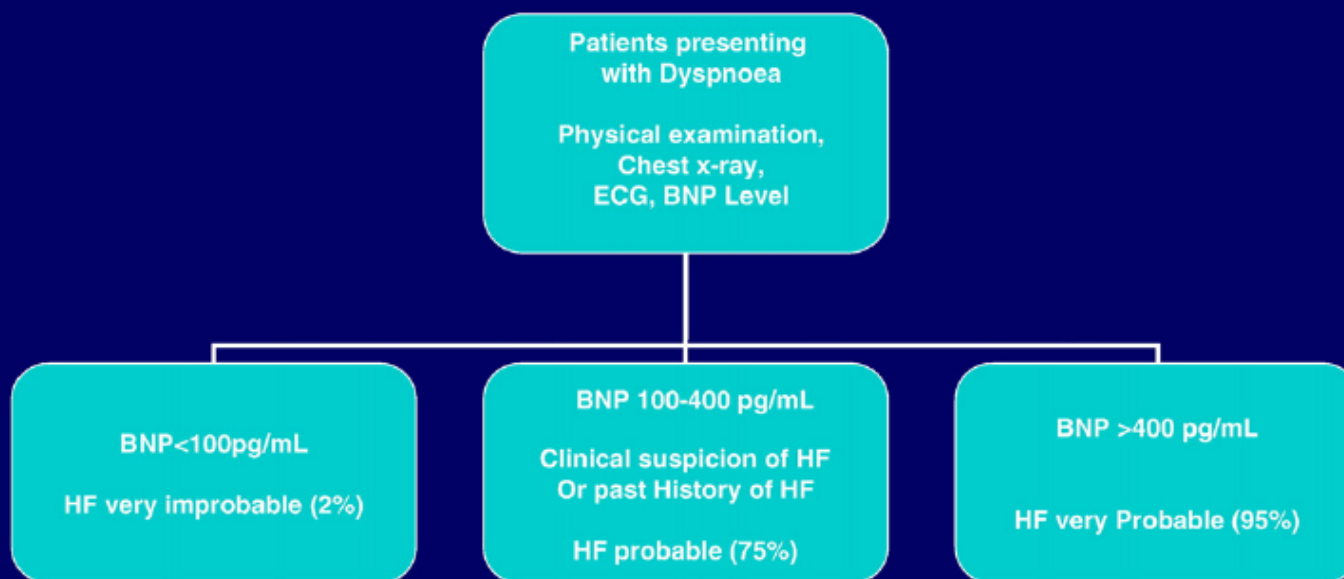
Review

State of the art: Using natriuretic peptide levels in clinical practice

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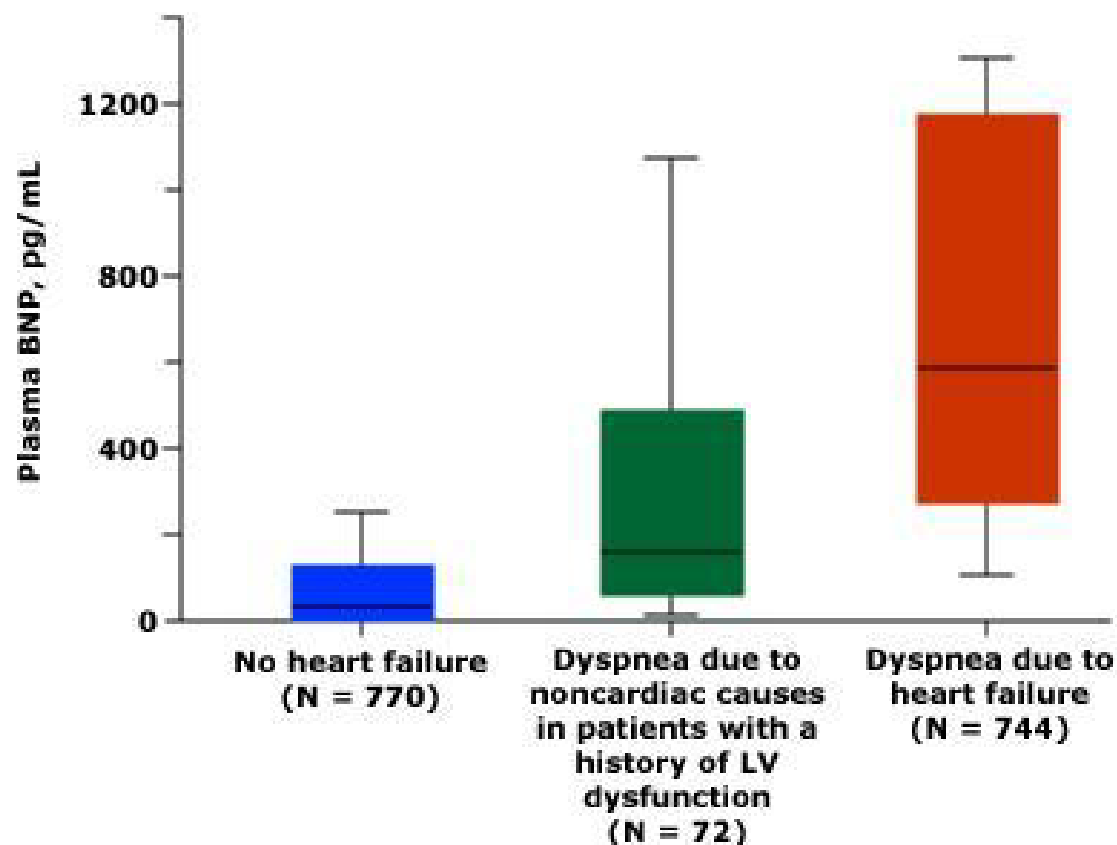


For Heart Failure Diagnosis





Plasma BNP in the diagnosis of dyspnea



Breathing Not Properly (BNP) study

Maisel AS N Engl J Med 2002



Optimal NT-proBNP Cut-points

“Rule in”

Age strata	Optimal cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
All <50 years (n=183)	450 pg/ml	97%	93%	76%	99%	95%
All 50-75 years (n=554)	900 pg/ml	90%	82%	82%	88%	85%
All >75 years (n=519)	1800 pg/ml	85%	73%	92%	55%	83%
Overall average		92%	84%	88%	66%	93%

“Rule out”

	Optimal cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
Rule out	300 pg/ml	99%	62%	55%	99%	83%



BNP in the emergency dept is cost saving

- BASEL study(1); a single measurement of BNP
 - reduced the time to the initiation of the correct treatment,
 - reduced in hospital days
 - reduced overall cost by 26%.
 - Findings persisted in 6 month FU
- IMPROVE-CHF study (2); NT-proBNP levels (measured at presentation and at 72 h)
 - reduced the duration of the ED visit by 21%,
 - the number of patients re-hospitalised over 60 days by 35%
 - Direct medical cost by 15%

1 Mueller C, Archives of Internal Medicine 2006

2 Moe GW, Circulation 2007



BNP [28]

100–400 pg/ml

NT-proBNP [27]

<50 years old 300–450 pg/ml

50–75 years 300–900 pg/ml

>75 years 300–1800 pg/ml

Only 25% of patients are within the 'grey' zone
¾ of those have HF as diagnoses



Caveats in measurements (BNP and pro-BNP)

- Levels lower in obese people (double the levels to correct for the increased BMI)
- Levels higher in renal failure
- HF due to causes upstream from the LV (MS, acute MR, pericardial disease)
- Flash pulmonary oedema



NP levels in the inpatient setting

“Wet” versus “Optivolaemic” NP levels: Definition

Wet NP level

- Any NP level 25-50% over what the patients optivolaemic BNP level is
- If patient comes to ER, often >600 pg/ml for BNP and > 900 pg/ml for NT-proBNP
- Falls rapidly with treatment

Optivolaemic NP level

- NP level once optimum fluid status is reached
- Correlated with functional class and prognosis
- May be 20-2,000 pg/ml- depending on severity of disease
- Falls slowly with treatment



NP levels in the inpatient setting

- A drop in NP level in response to treatment is important
- the final NP level seems to be the most accurate predictor of death or readmission.
- $\text{BNP} < 350\text{--}400 \text{ pg/ml}$ or $\text{NT-proBNP} < 4000 \text{ pg/ml}$ at the time of discharge, especially in the setting of optimal volume, predicts a stable post-hospital course.
- Failure of the NP levels to drop with treatment predict poor prognosis. Consider more aggressive treatment



The use of NP levels in the intensive care unit

- Higher 'rule out' levels i.e. 150 pg/ml in the case of BNP
- BNP <150 pg/ml had a negative predictive value of 97% for the presence of cardiac dysfunction (1).
- patients with cardiac pulmonary oedema have substantially higher NP levels than patients with ARDS (1)
- NPs DO NOT seem to be useful diagnostically when the differential diagnosis includes shock of any type (2)
- Plasma NP is higher in patients who fail a weaning trial as compared to those with successful weaning (3)

1 Karpaliotis D, Chest 2007;

2 Tung RH, Crit Care Med 2004

3 Mekontso-Dessap A, Intensive Care Med 2006



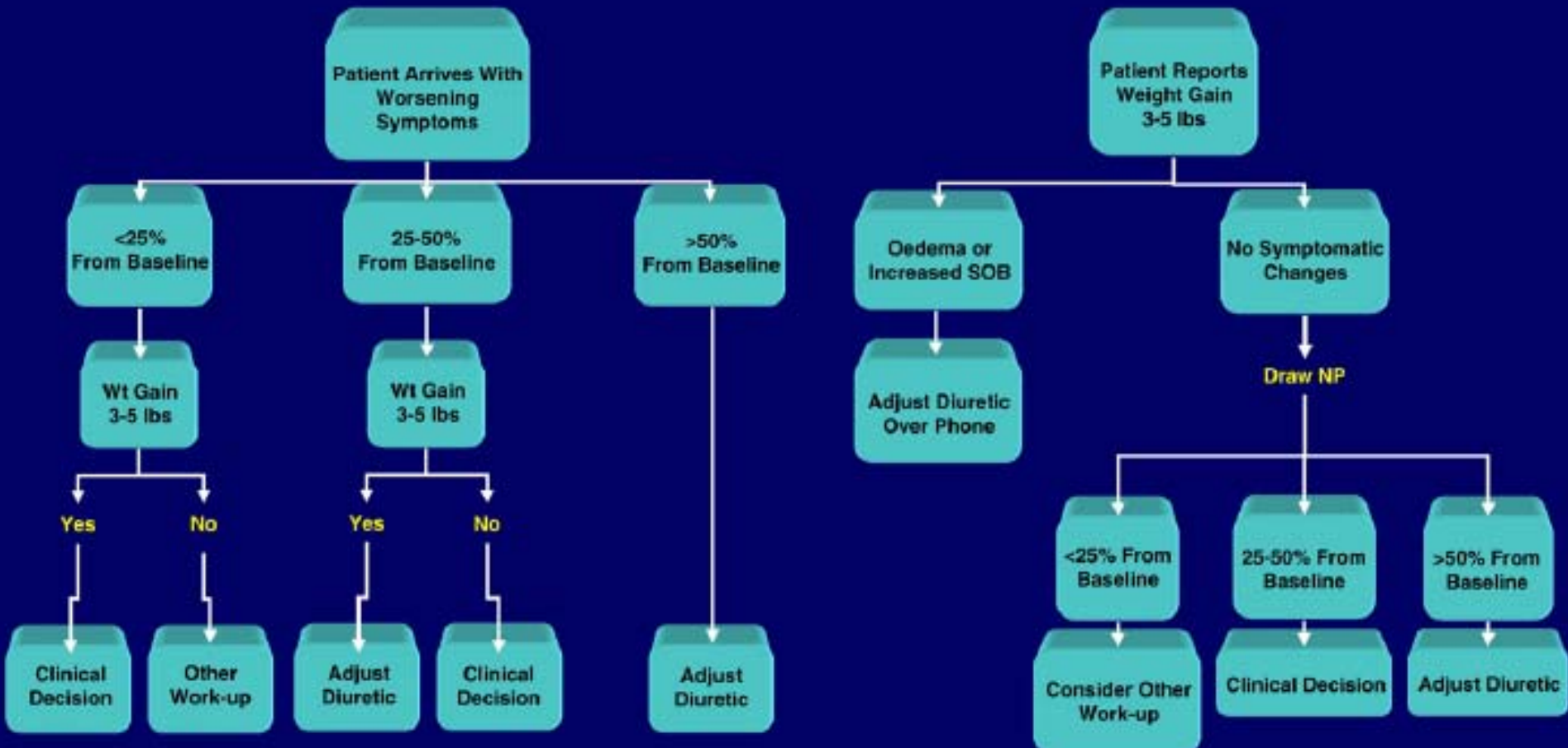
Monitoring NP levels post-hospitalisation: NP-guided outpatient treatment

- Large variability ranging 40-130%
- A change of $>50\%$ is meaningful if associated with clinical changes
- 'dry' NP levels are difficult to define; it is thought that discharge levels may be a good surrogate

Algorithms for NP Outpatient Management

OUTPATIENT CLINIC

TELEMEDICINE





STARS-BNP trial (Jourdain P, J Am Coll Cardiol 2007;

- 220 patients with NYHA class II to III HF and LV systolic dysfunction
- standard care or to BNP-guided therapy (target BNP <100 pg/mL)
- BNP group were more likely to have dose adjustments of diuretics, ACE-I and beta blockers.
- BNP group had a significantly lower incidence of the combined endpoint of HF related hospitalization or HF related death
- In the BNP group, at 3 month follow up, the mean BNP level fell from 352 to 284 pg/mL. Only 16 percent had BNP<100
- It is possible that the fall in BNP levels per se was not the reason for improved outcome. It might have simply worked as a reminder for more intensive evidence based treatment



Prognostic importance of NP levels

- Intensive evidence based pharmacotherapy is associated with a fall in NP levels
- In the Val-HeFT and CARE-HF studies, the changes of BNP over time predicted outcomes
- One analysis of the COMET trial demonstrated the prognostic importance of plasma NT-proBNP in chronic heart failure patients taking beta-blockers

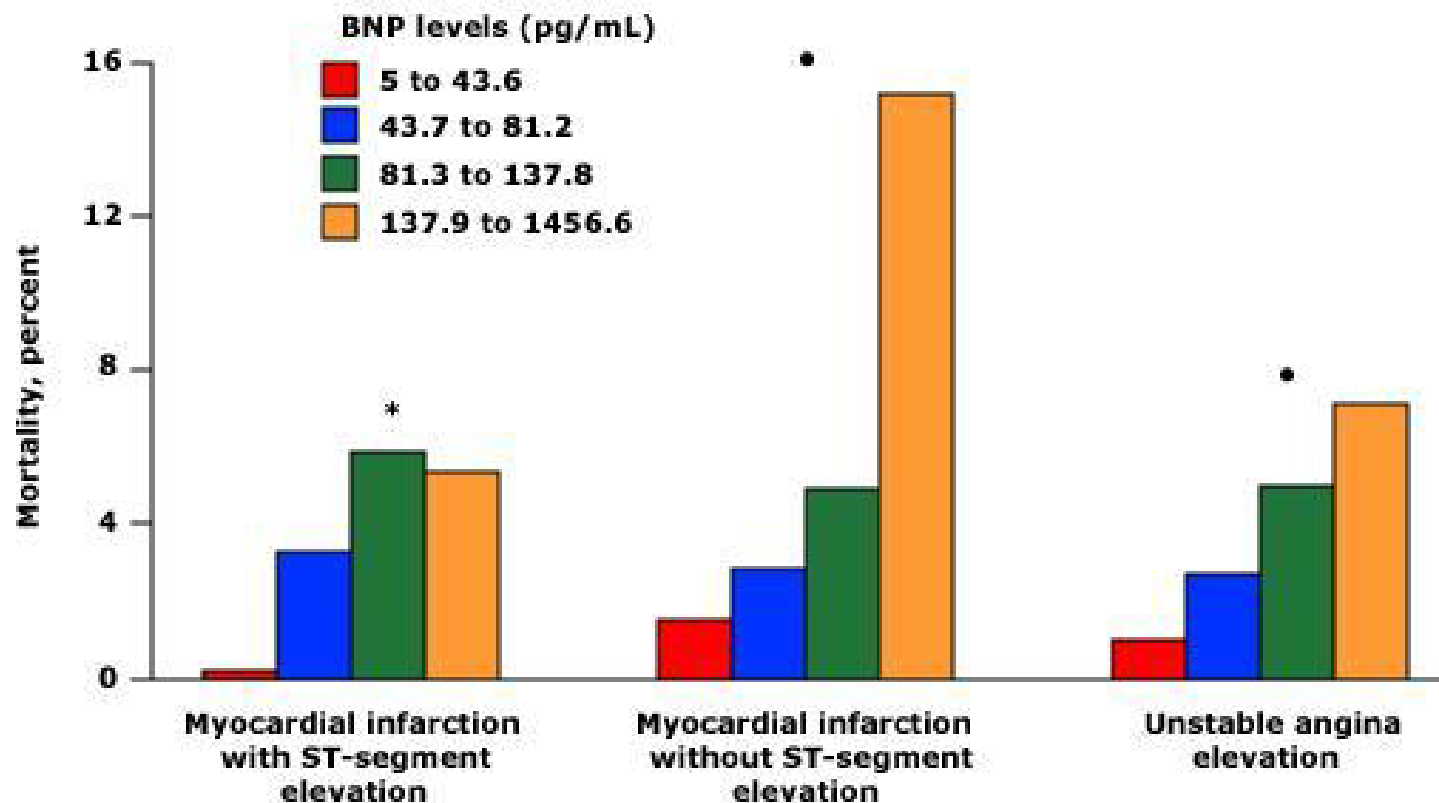


PLASMA BNP IN OTHER SETTINGS

- NP levels may be predictors of the development of HF or other cardiovascular events, in asymptomatic patients without HF (Framingham Heart Study)
- Elevated plasma BNP is associated with increased mortality in patients with an acute coronary syndrome (ACS).

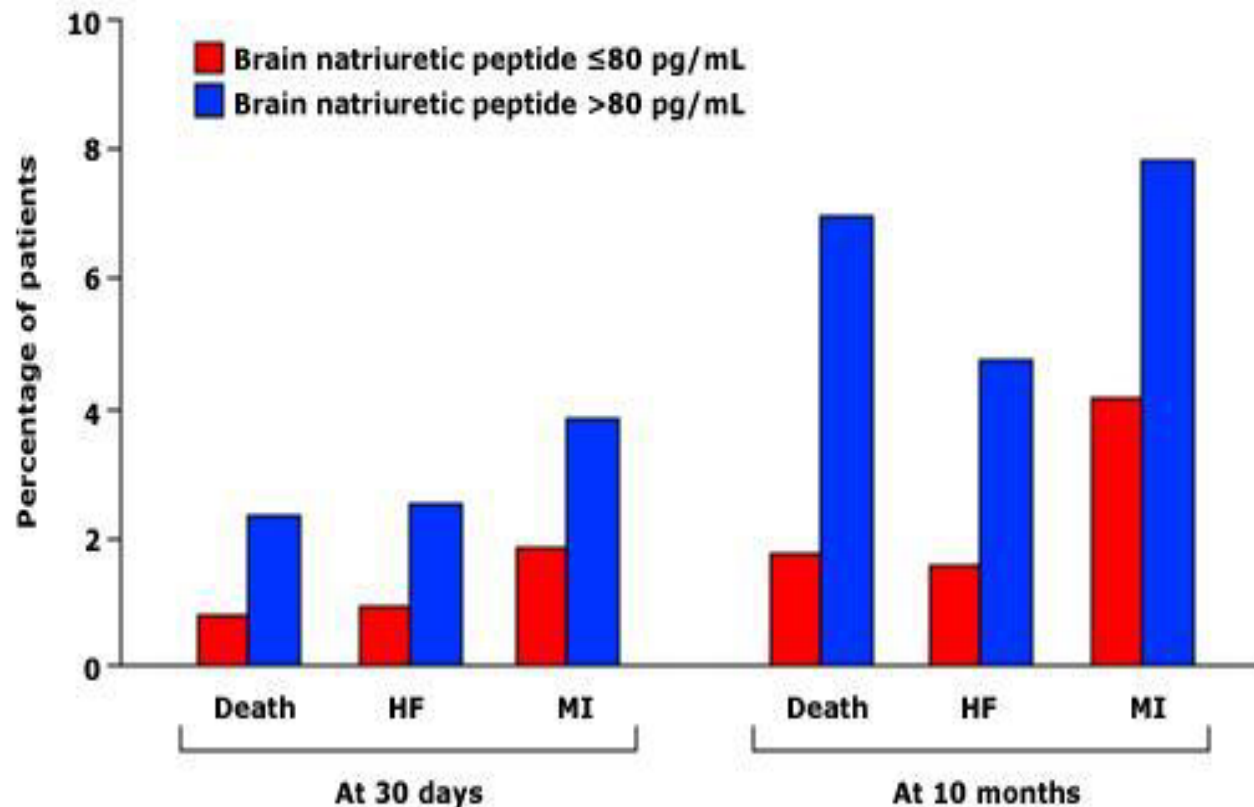


Levels of brain natriuretic peptide predict mortality in patients with an acute coronary syndrome



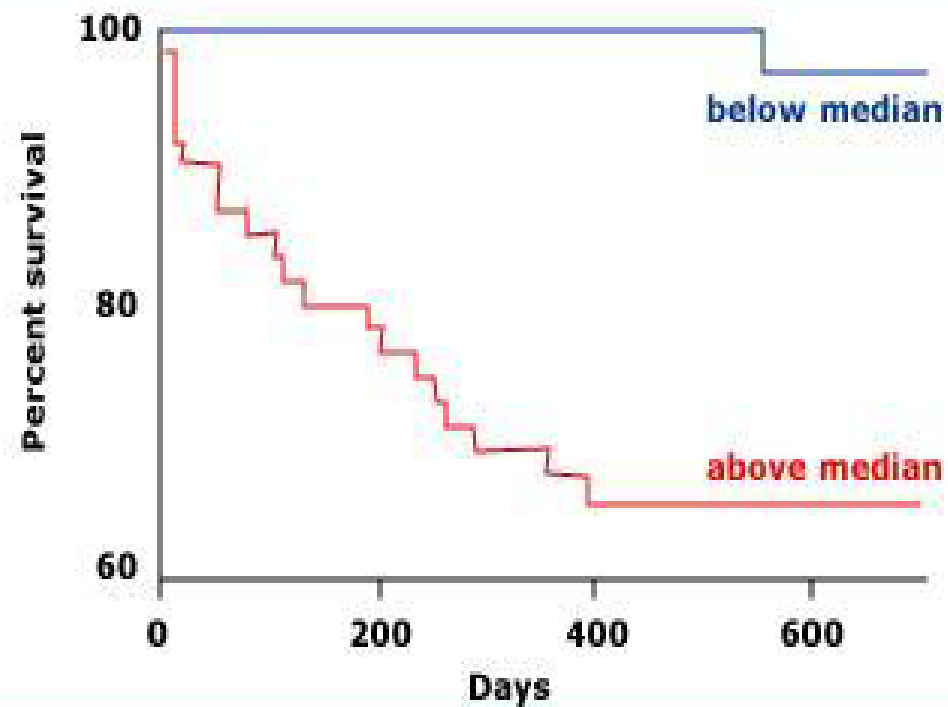


Levels of brain natriuretic peptide predict cardiac events in patients with an acute coronary syndrome





N-BNP predicts survival after acute MI





PLASMA BNP IN OTHER SETTINGS

- Plasma BNP concentrations have prognostic value in patients with stable angina
- Serum BNP may have prognostic value in patients with chronic mitral regurgitation
- In a report of six patients with constrictive pericarditis and five with restrictive cardiomyopathy, BNP was markedly elevated in the latter group (825 versus 128 pg/mL)
- In AS, NPs may be useful to identify patients with equivocal symptoms who are at risk for rapid progression
- In low gradient AS, BNP levels may predict prognosis and may be helpful to differentiate true AS from pseudostenosis



Comparison of BNP and Npro-BNP

- A study of 164 patients hospitalized with decompensated heart failure found that admission and discharge NT-pro-BNP and BNP levels predicted cardiac mortality and all-cause mortality at 90 day follow-up
- NT-pro-BNP had greater prognostic value than BNP levels for all-cause mortality.
- Waldo SW J Am Coll Cardiol. 2008



NESIRITIDE

- Recombinant human brain natriuretic peptide (BNP 1-32).



NESIRITIDE: effect on hemodynamics and symptoms

- RCT of 489 patients vs nitroglyceride (GTN) vs placebo for 3 hours
- Better reduction of PWP but no improvement of symptoms compared to GTN
- Concerns of possible deleterious effects on mortality vs non-inotropic vasodilators
- There is a concern about a possible deleterious effect of renal function
- Should be limited to patients who are hospitalized for severe HF (but not hypotensive or in cardiogenic shock) and who remain symptomatic with dyspnea despite intravenous loop diuretics
- Plasma BNP should NOT be used for clinical assessment during the administration of nesiritide
- N-pro-BNP does not detect nesiritide



Conclusions

- NP levels are helpful in screening to identify or exclude cardiovascular disease
- They aid the differential diagnosis of symptoms that might be due to HF
- Very good prognostic tool
- The clinician should become familiar with at least one of the assays
- Levels should be interpreted in the context of the clinical setting and in conjunction with a test of renal function
- Serial measurement determines whether a patient's prognosis has changed in response to therapy but it is not yet clear whether and how it should be used to guide treatment