# ΠΑΛΑΙΑ ΚΑΙ ΝΕΑ ΝΑΤΡΙΟΥΡΗΤΙΚΑ ΠΕΠΤΙΔΙΑ

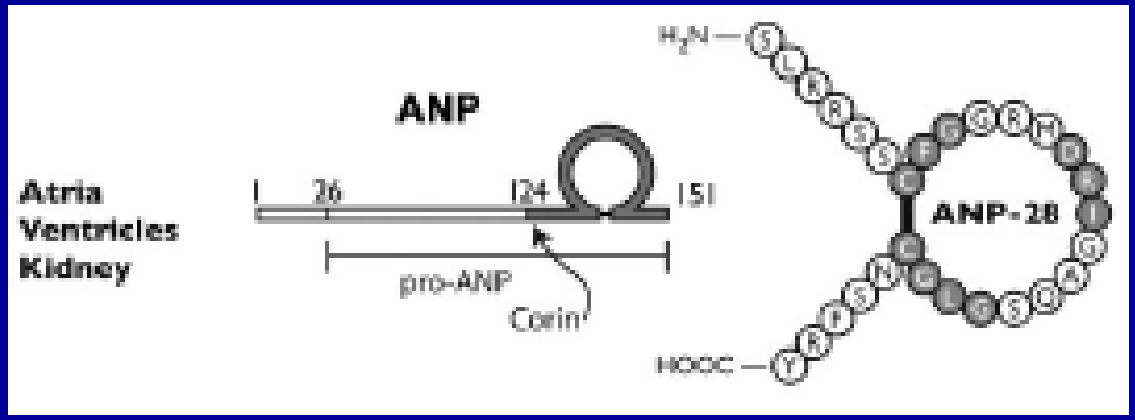
ΝΙΝΙΟΣ ΒΛΑΣΙΟΣ
ΚΛΙΝΙΚΗ ΑΓΙΟΣ ΛΟΥΚΑΣ
ΘΕΣΣΑΛΟΝΙΚΗ 2010

# NATRIURETIC PEPTIDES

- ANP
- BNP
- CNP

# ANP

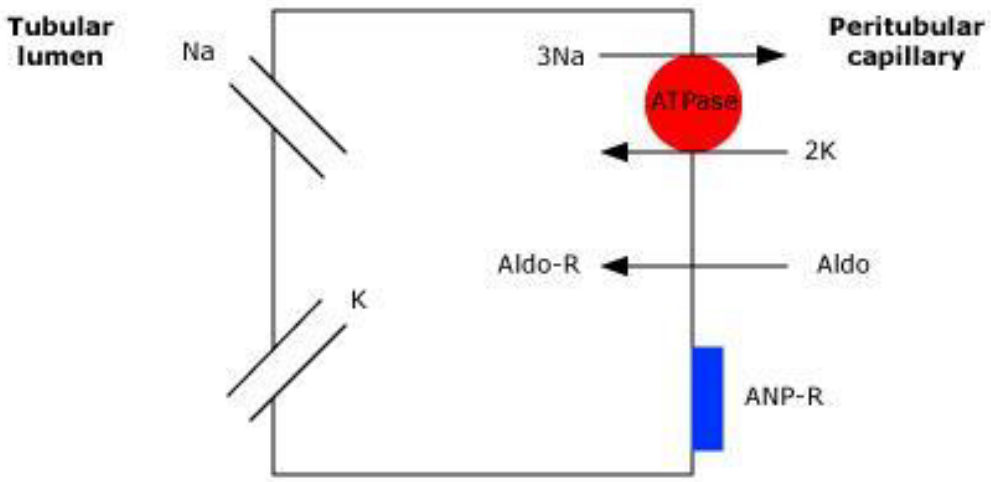
- First described by De Bold in 1981
- released from myocardial cells in the atria and in some cases the ventricles

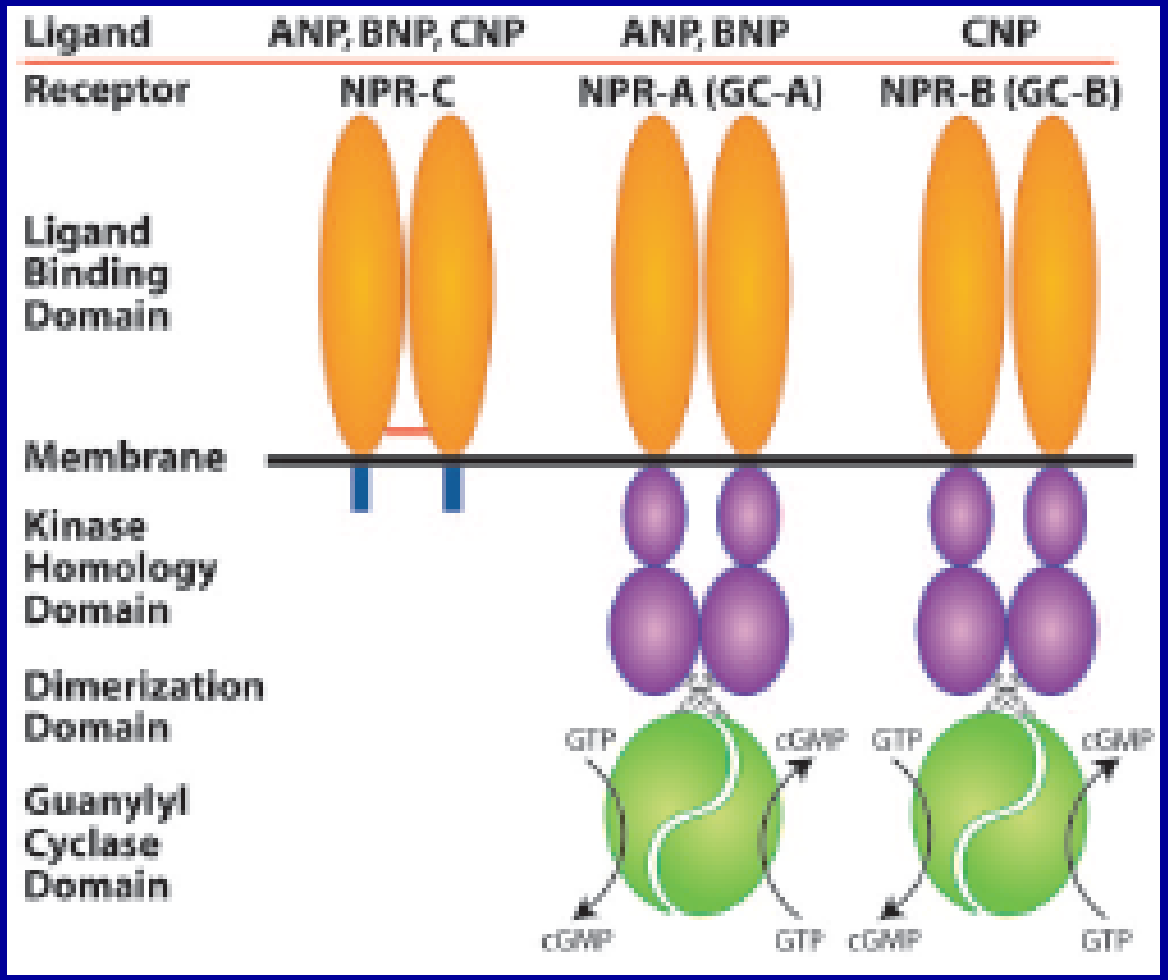

ANP
Atria
Ventricles
Kidney
26
124
151
pro-ANP
Corin
H2N —
HOOC —
ANP-28

# 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




Ligand
ANP, BNP, CNP
ANP, BNP
CNP
Receptor
NPR-C
NPR-A (GC-A)
NPR-B (GC-B)
Ligand Binding Domain
Membrane
Kinase Homology Domain
Dimerization Domain
Guanylyl Cyclase Domain
GTP
cGMP
cGMP
GTP
GTP
cGMP
cGMP
GTP

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

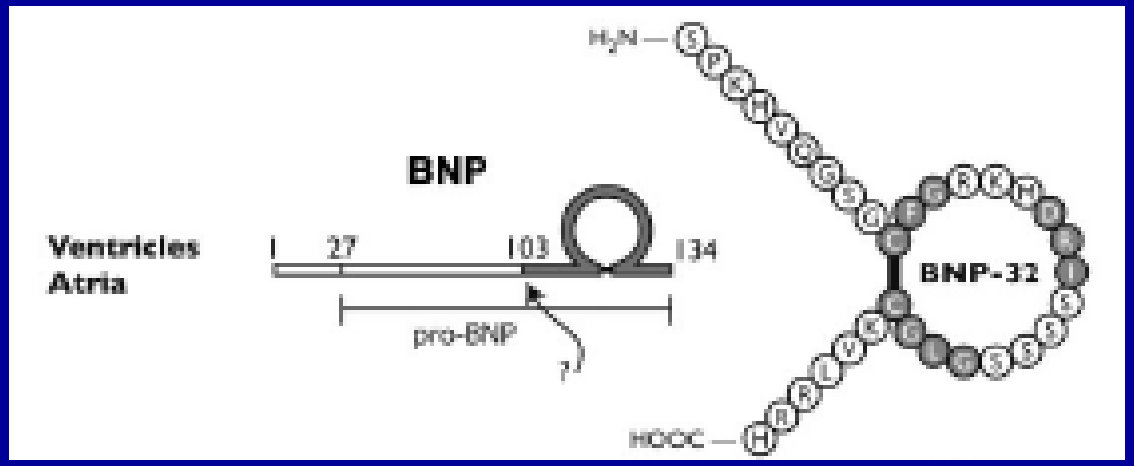
# Urodilatin

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

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

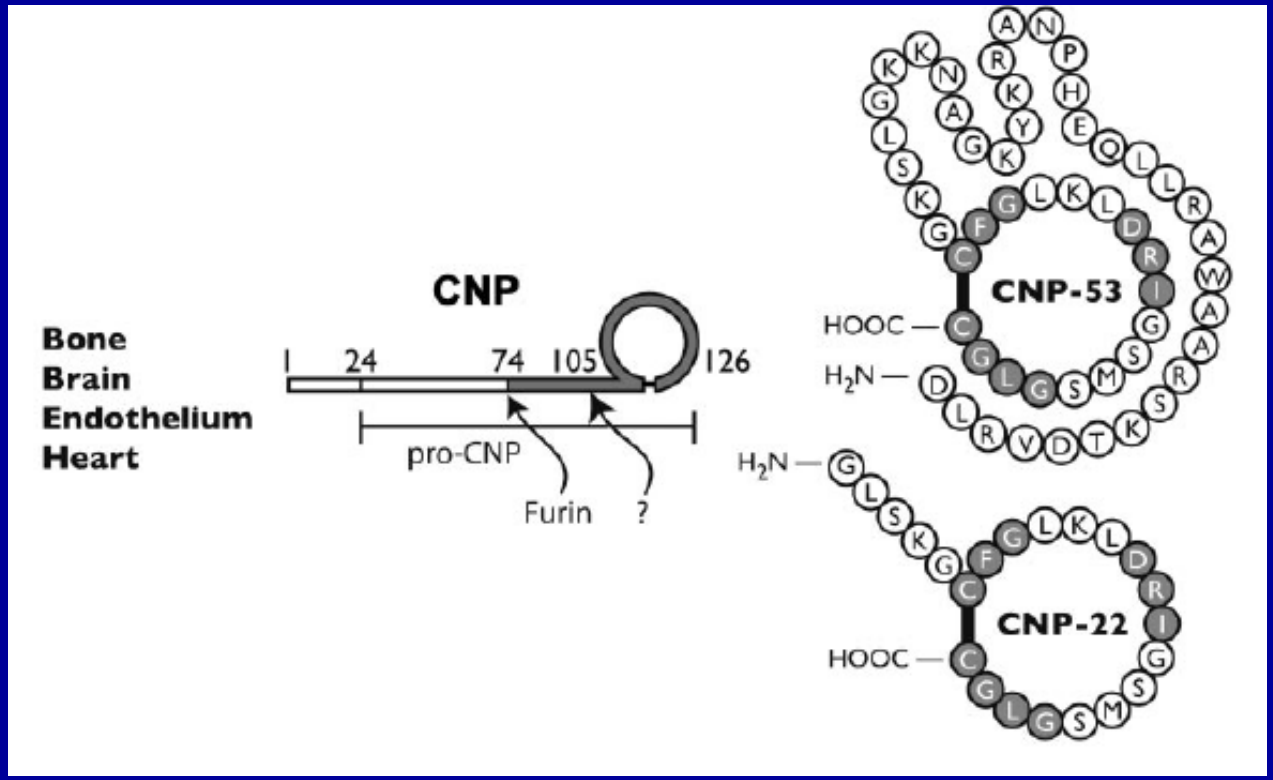
- More stable in vivo or ex vivo than ANP
- Levels increase proportionally with NYHA class
- It appears that it is also a powerful predictor of mortality like pro-BNP
- **Biomarkers in Acute Heart Failure** (BACH) trial showed that it may enhance the diagnostic ability of the BNPs for patients in the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


CNP
Bone
Brain
Endothelium
Heart
1
24
74
105
126
pro-CNP
Furin
?
CNP-53
HOOC —
H2N —
H2N —
CNP-22
HOOC —

# 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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European Journal of Heart Failure 10 (2008) 824–839

The European Journal of Heart Failure

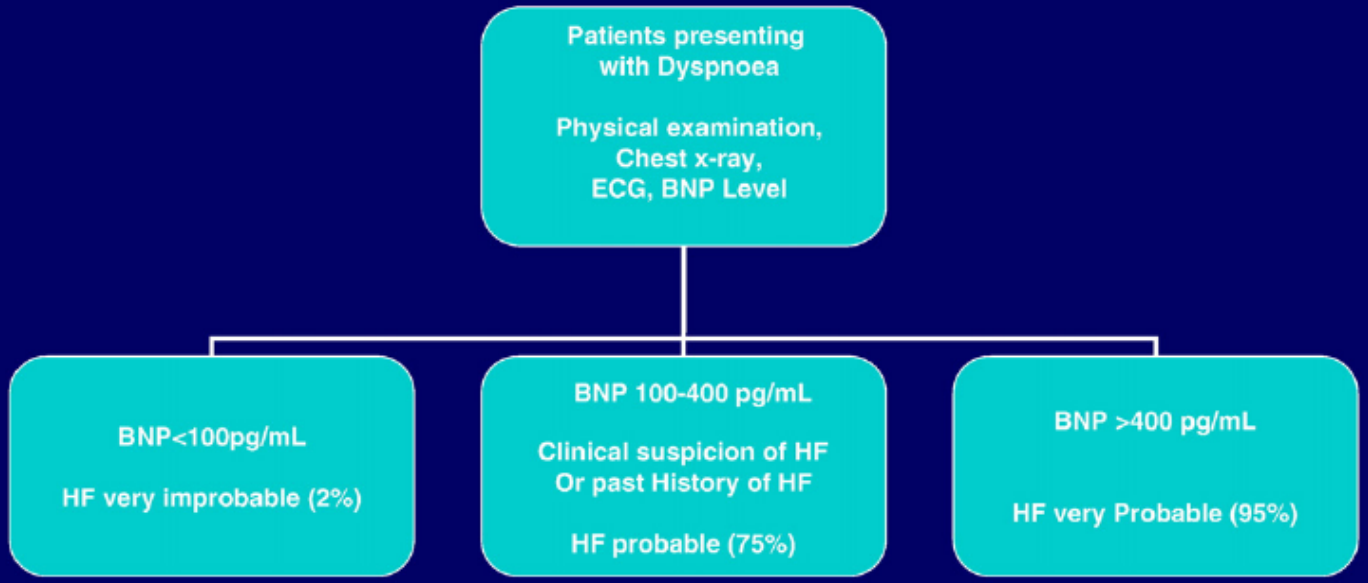
www.elsevier.com/locate/ejheart

Review

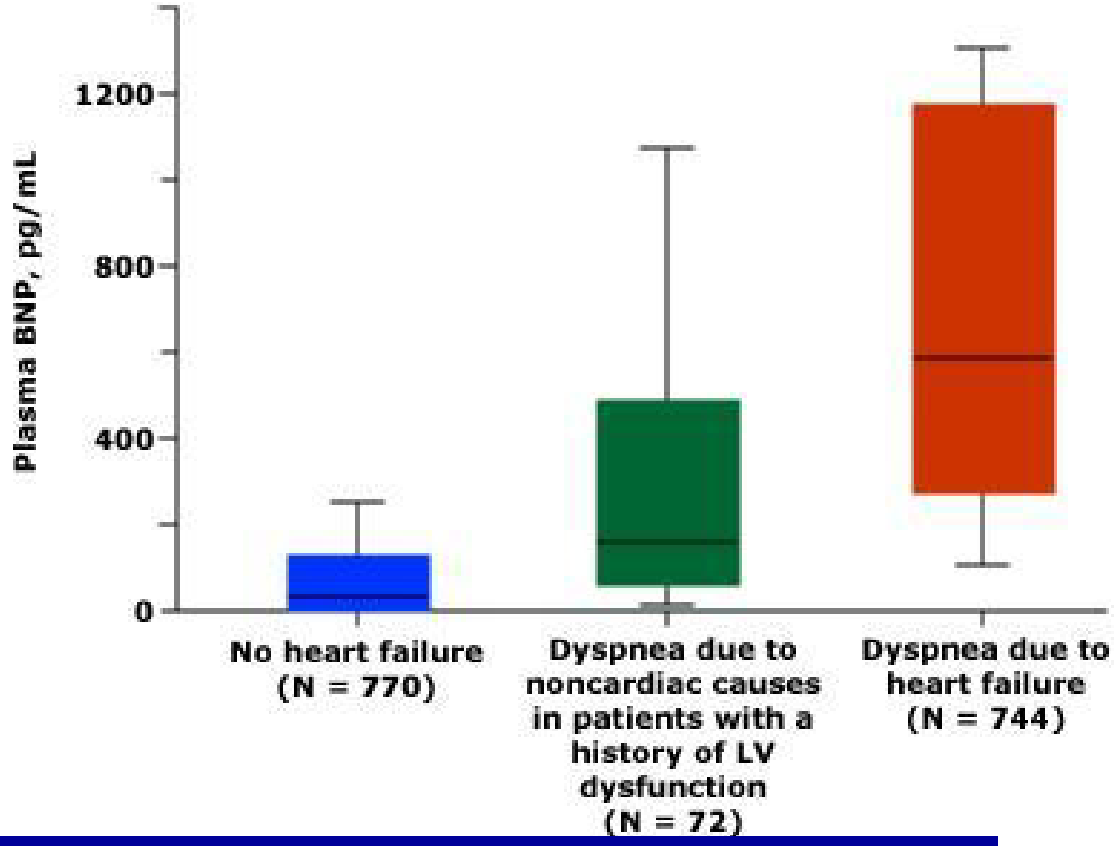
# State of the art: Using natriuretic peptide levels in clinical practice

Alan Maisel [a,i,*], Christian Mueller [b], Kirkwood Adams Jr. [c], Stefan D. Anker [d], Nadia Aspromonte [e], John G.F. Cleland [f], Alain Cohen-Solal [g], Ulf Dahlstrom [h], Anthony DeMaria [i], Salvatore Di Somma [j], Gerasimos S. Filippatos [k], Gregg C. Fonarow [l], Patrick Jourdain [m], Michel Komajda [n], Peter P. Liu [o], Theresa McDonagh [p], Kenneth McDonald [q], Alexandre Mebazaa [r], Markku S. Nieminen [s], W. Frank Peacock [t], Marco Tubaro [u], Roberto Valle [v], Marc Vanderhyden [w], Clyde W. Yancy [x], Faiez Zannad [y], Eugene Braunwald [z]

# 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, Circulation2007

| BNP [28] | NT-proBNP [27] |
| --- | --- |
| 100–400 pg/ml | <50 years old 300 450 pg/ml<br>50–75 years 300–900 pg/ml<br>>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.
- BNP<350–400 pg/ml or NT-proBNP <4000 pg/ml at the time of discharge, especially in the setting of optivolaemia,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 Karmpaliotis D, Chest 2007;

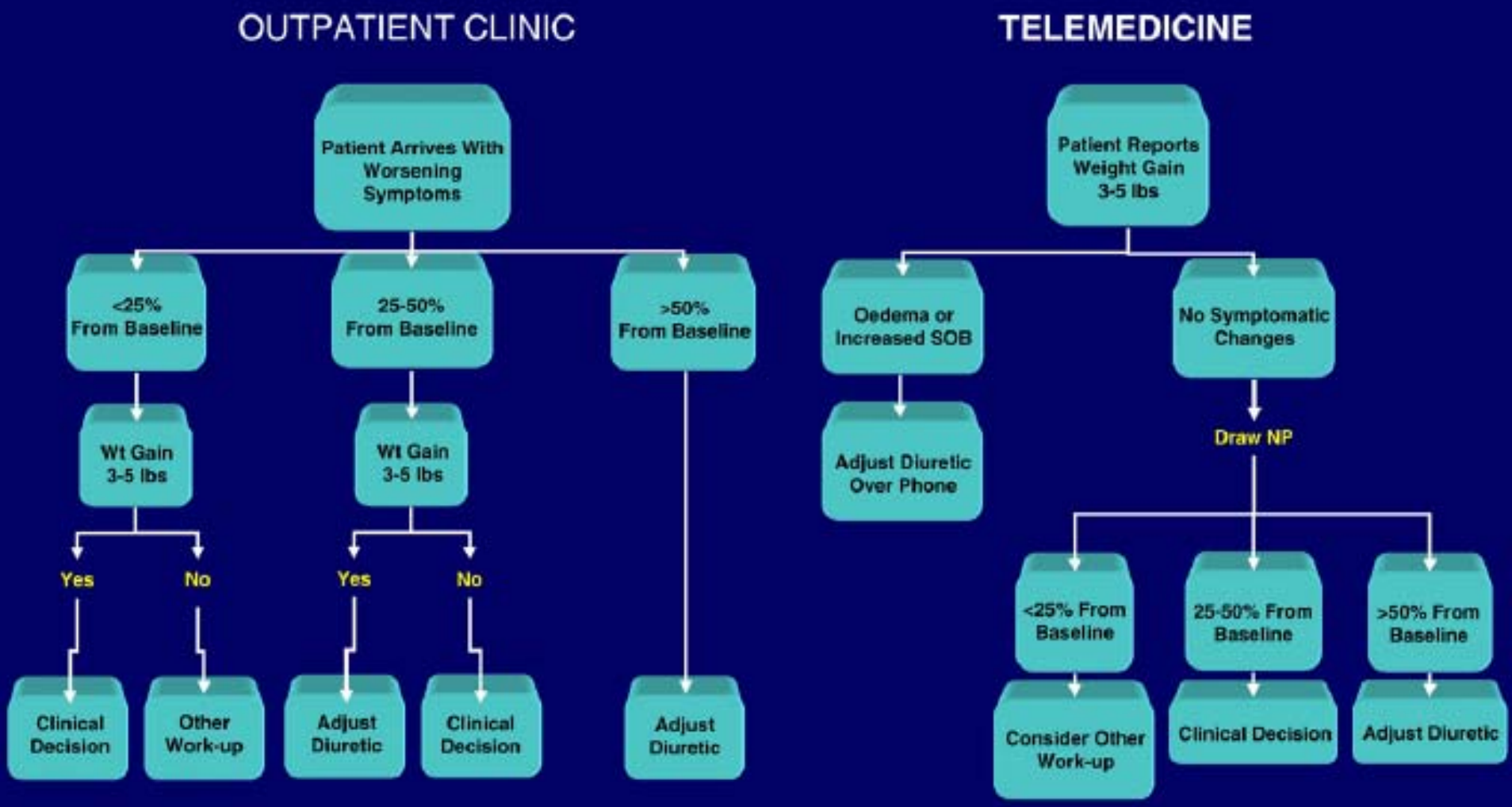
2 Tung RH, Crit Care Med20043

3 Mekontso-Dessap A, Intensive CareMed 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



# 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

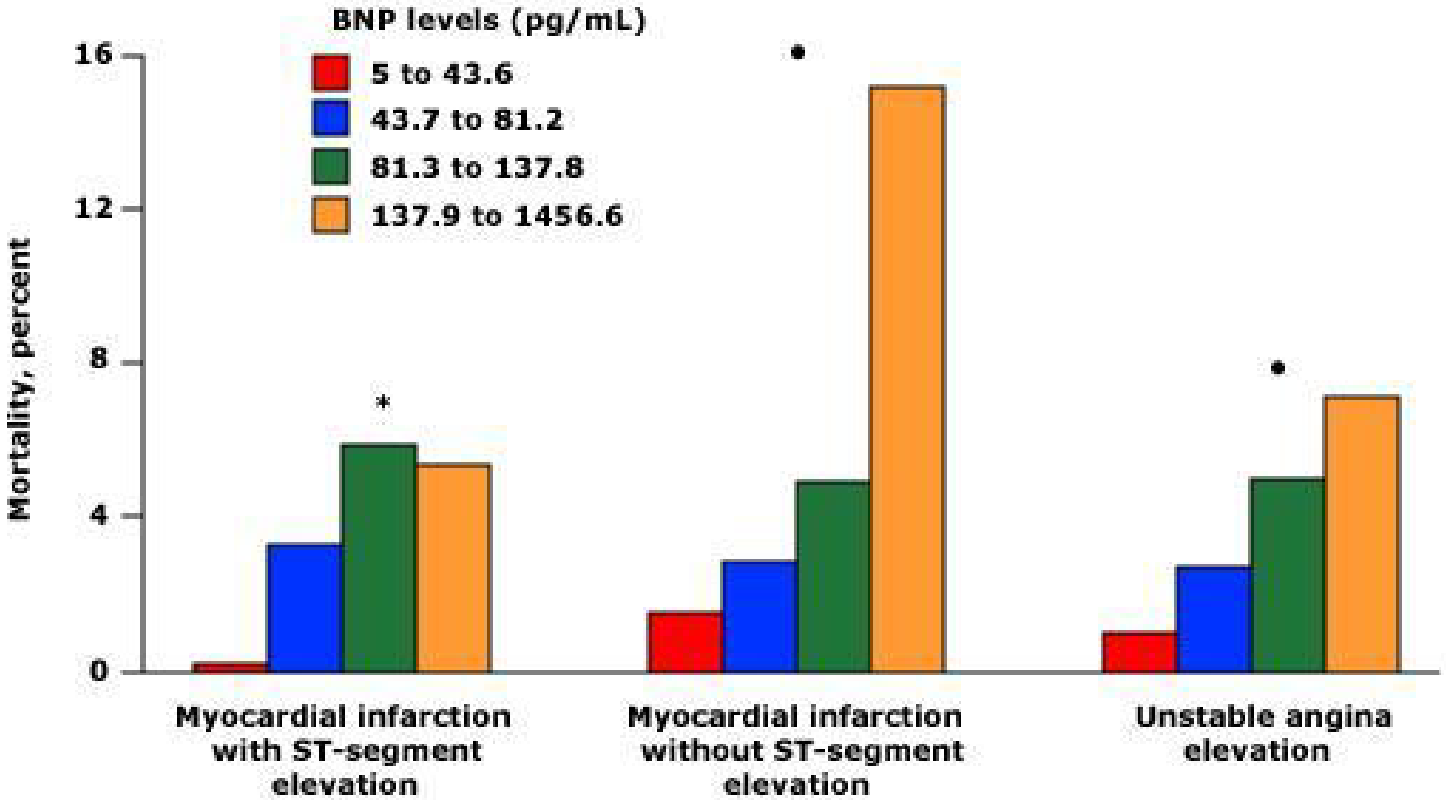
# Prognostic importance of NP levels

- 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

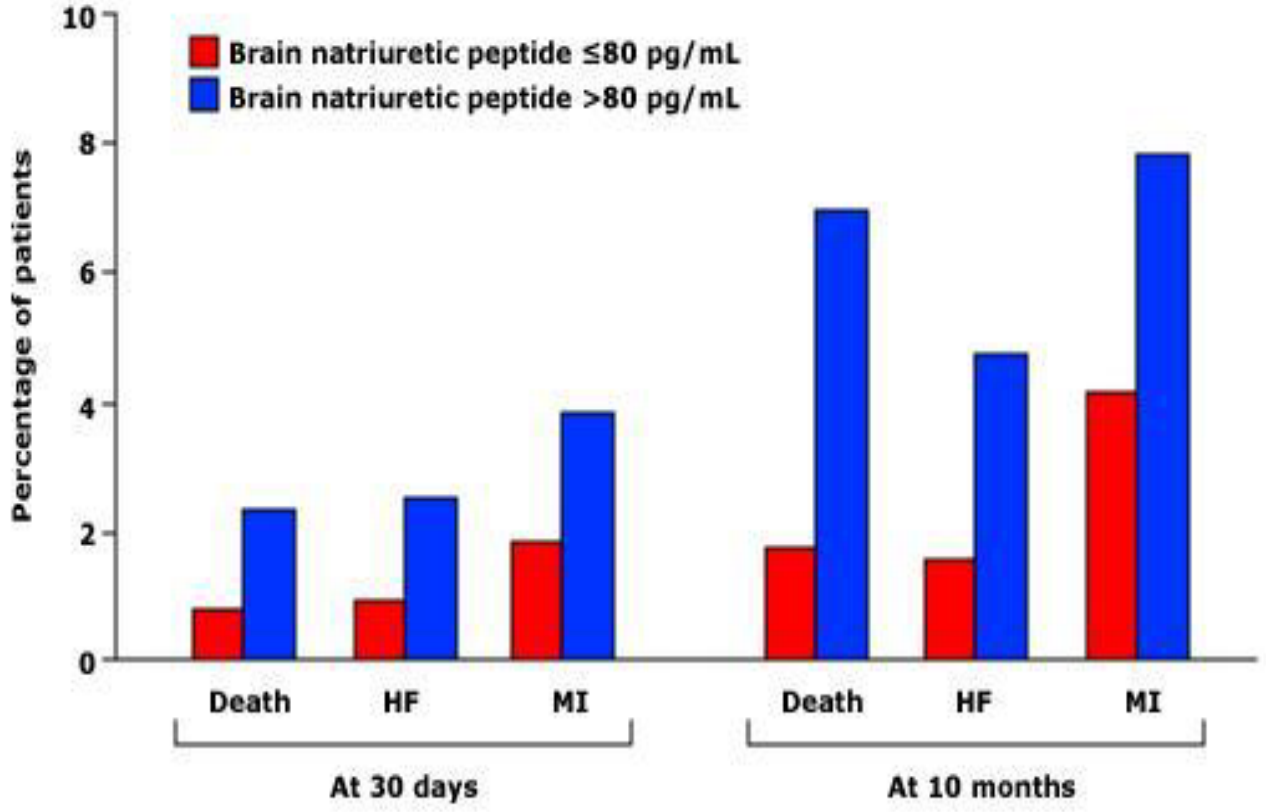
# PLASMA BNP IN OTHER SETTINGS

- 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).

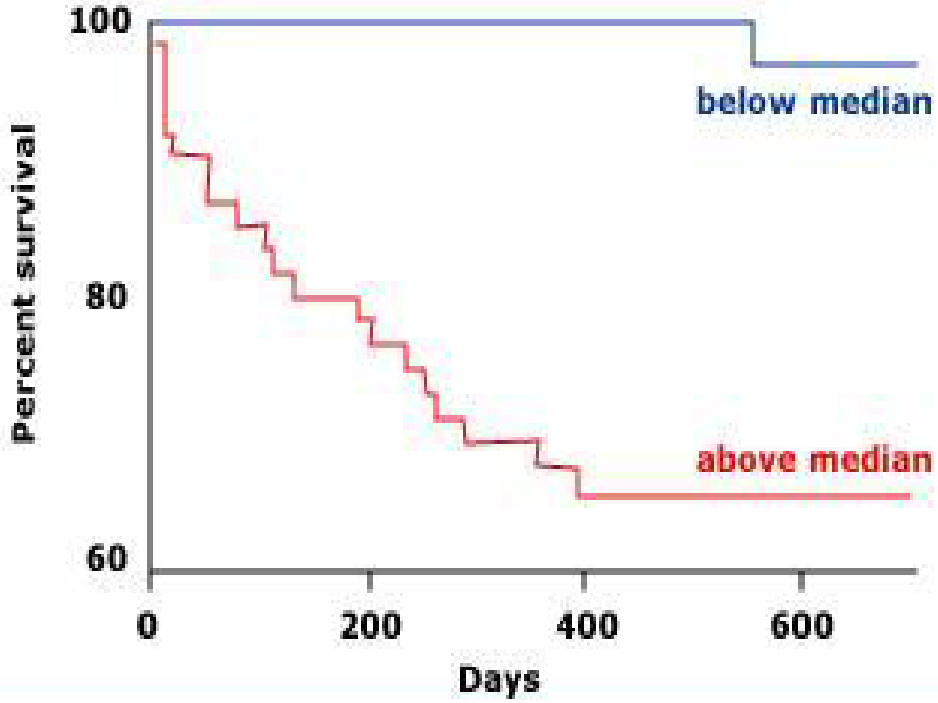
# Levels of brain natriuretic peptide predict mortality in patients with an acute coronary syndrome



# 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 identity 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 lenels 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