NT-proBNP in Pediatric Cardiology 2009 update

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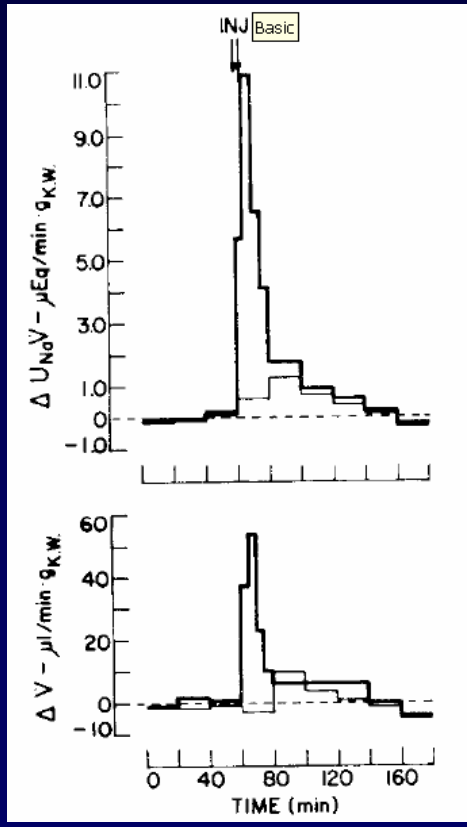
The Natriuretic Peptides History

- 1981 - Extract of rat atria produced powerful natriuresis, diuresis and hypotension (de Bold et al.)

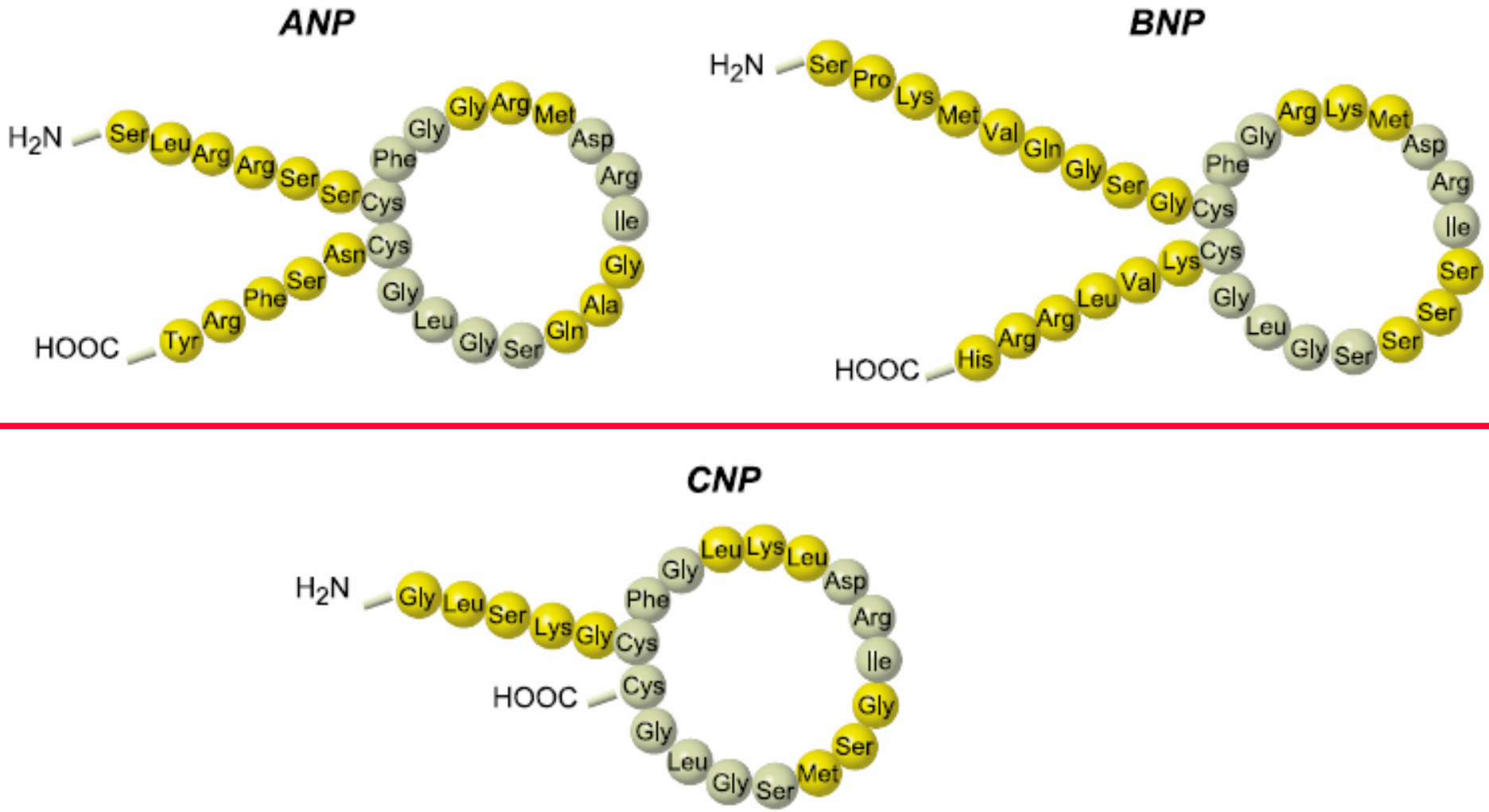
  Atrial natriuretic factor - ANF - later ANP
- 1988 – Similar peptide isolated from porcine brain

  Brain (B)- type natriuretic peptide – BNP (Sudoh et al.)
- 1990 – C- type natriuretic peptide – CNP (Furuya et al.)



De Bold et al.
Life Sci. 28: 89–94,1981

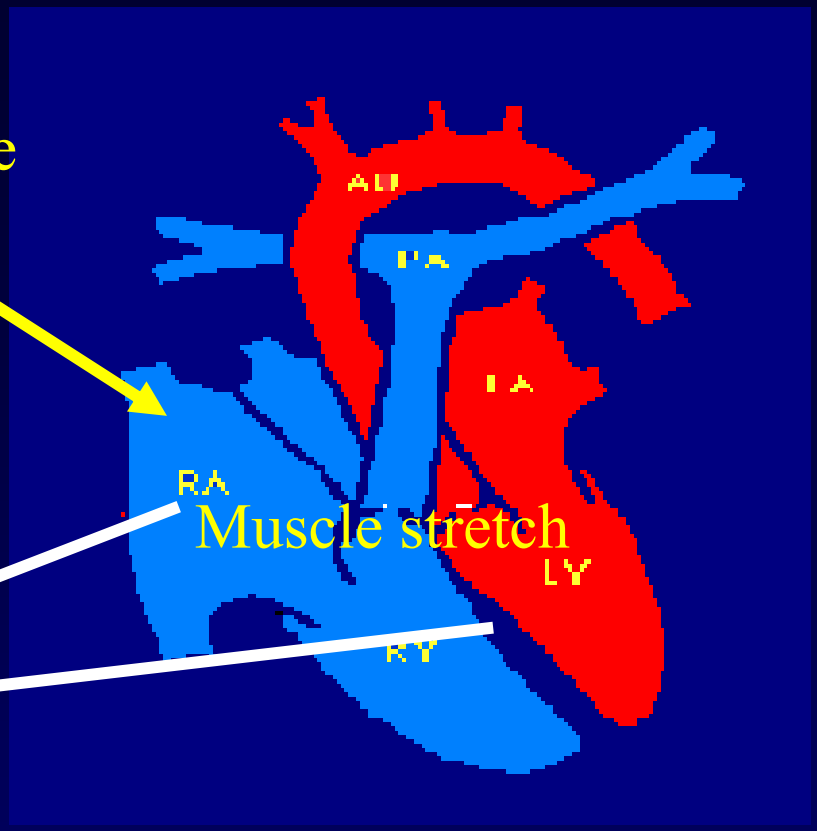
The Natriuretic Peptides



Abassi et al. Pharmacology & Therapeutics 2004

The natriuretic peptides play an important role in volume homeostasis

volume / pressure overload



ANP

diuresis
natriuresis
vasodilatation

BNP

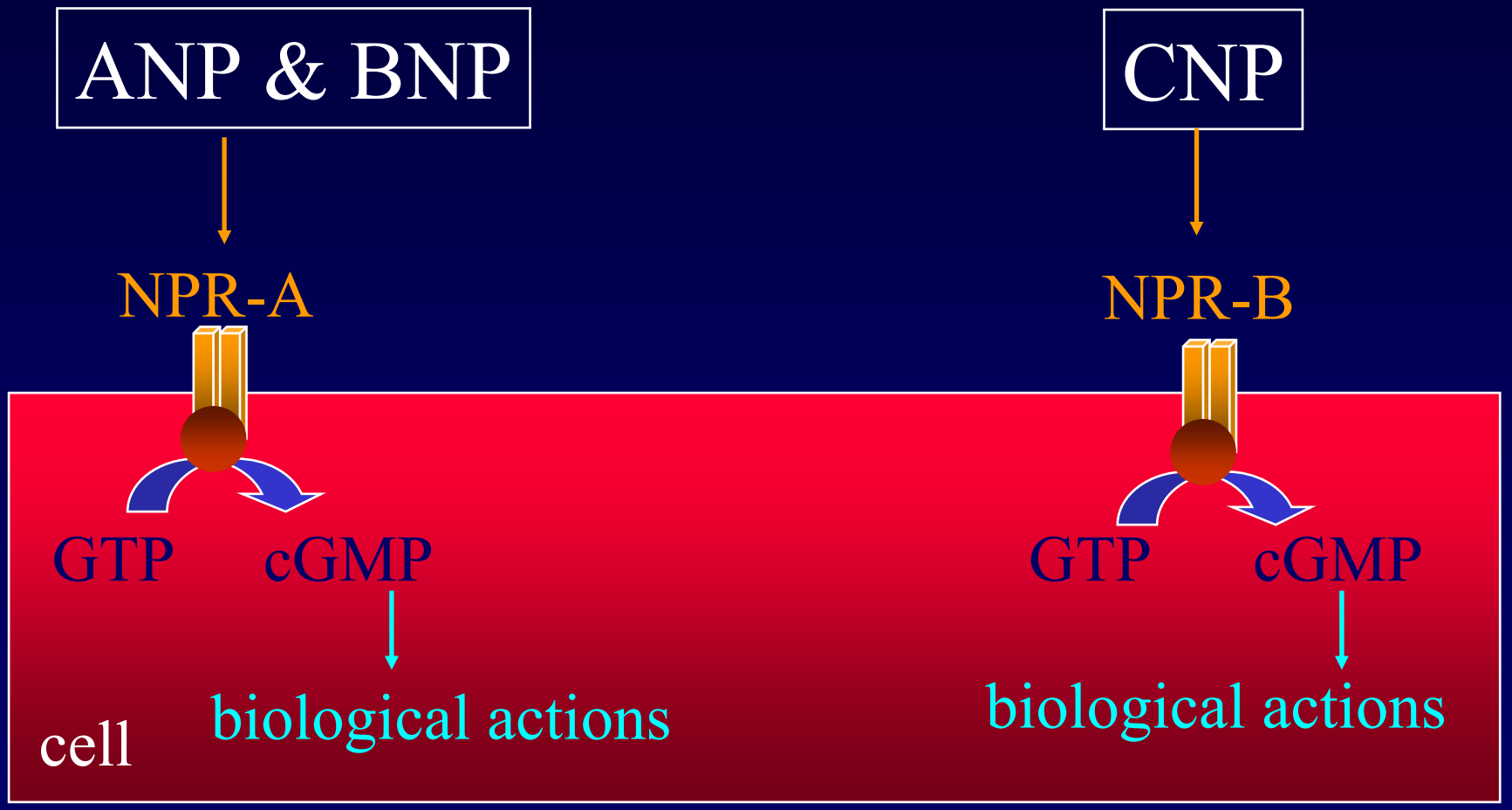
↓ renin-angiotensin-aldosterone
↓ sympathetic tone
↓ endothelin

The natriuretic peptides as volume regulators

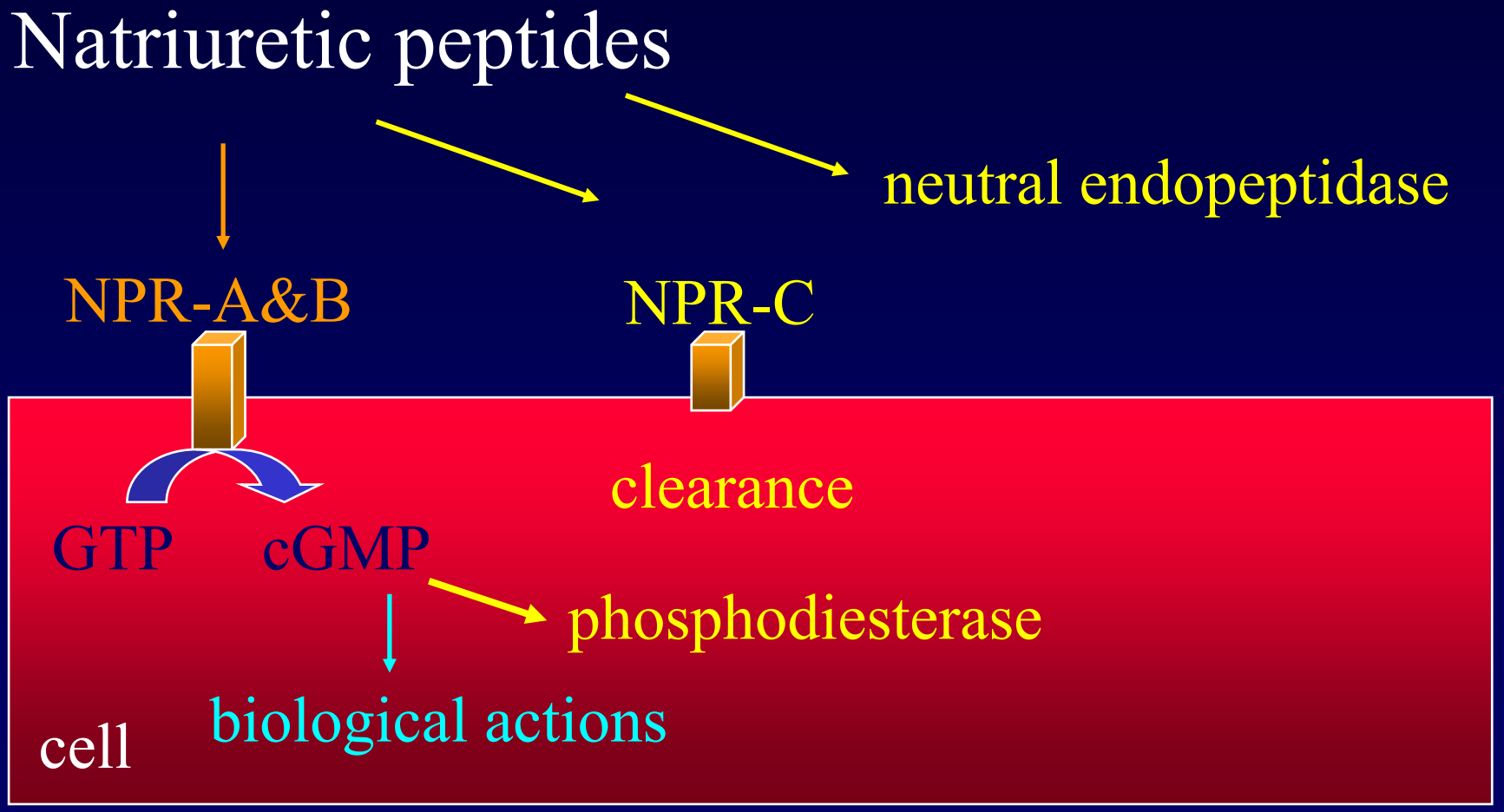
Hemodynamic Actions of the Natriuretic Peptides

- Unloading of the heart
  - Vasodilation
  - Volume reduction (diuresis & natriuresis)
  - Counteracting stress factors

Natriuretic Peptides Active Receptors



Natriuretic Peptides Degradation

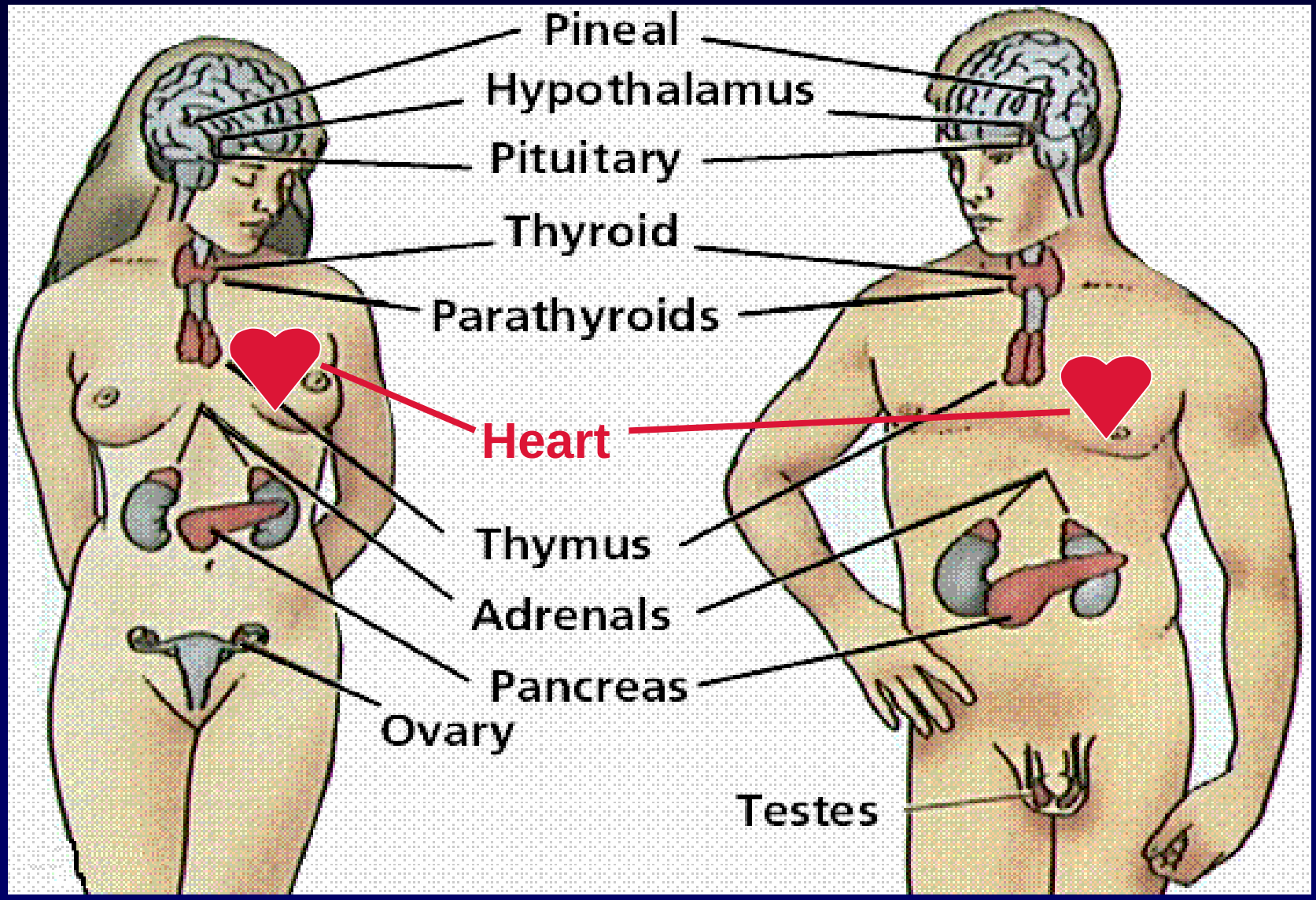


Direct Cardiac Actions of the Natriuretic Peptides

- Counteract
  - hypertrophy
  - proliferation
  - fibrosis
- Improve diastolic function
- Suppress TGF-β mediated pathway
- Possible negative feedback

- ANP is the predominant natriuretic peptide in physiological conditions
- BNP predominates in pathological conditions

Endocrine glands



Clinical Applications

- Therapy
- Markers for heart disease

Plasma levels of the natriuretic peptides are elevated in heart disease

BNP was found to be superior to ANP as a marker for heart disease

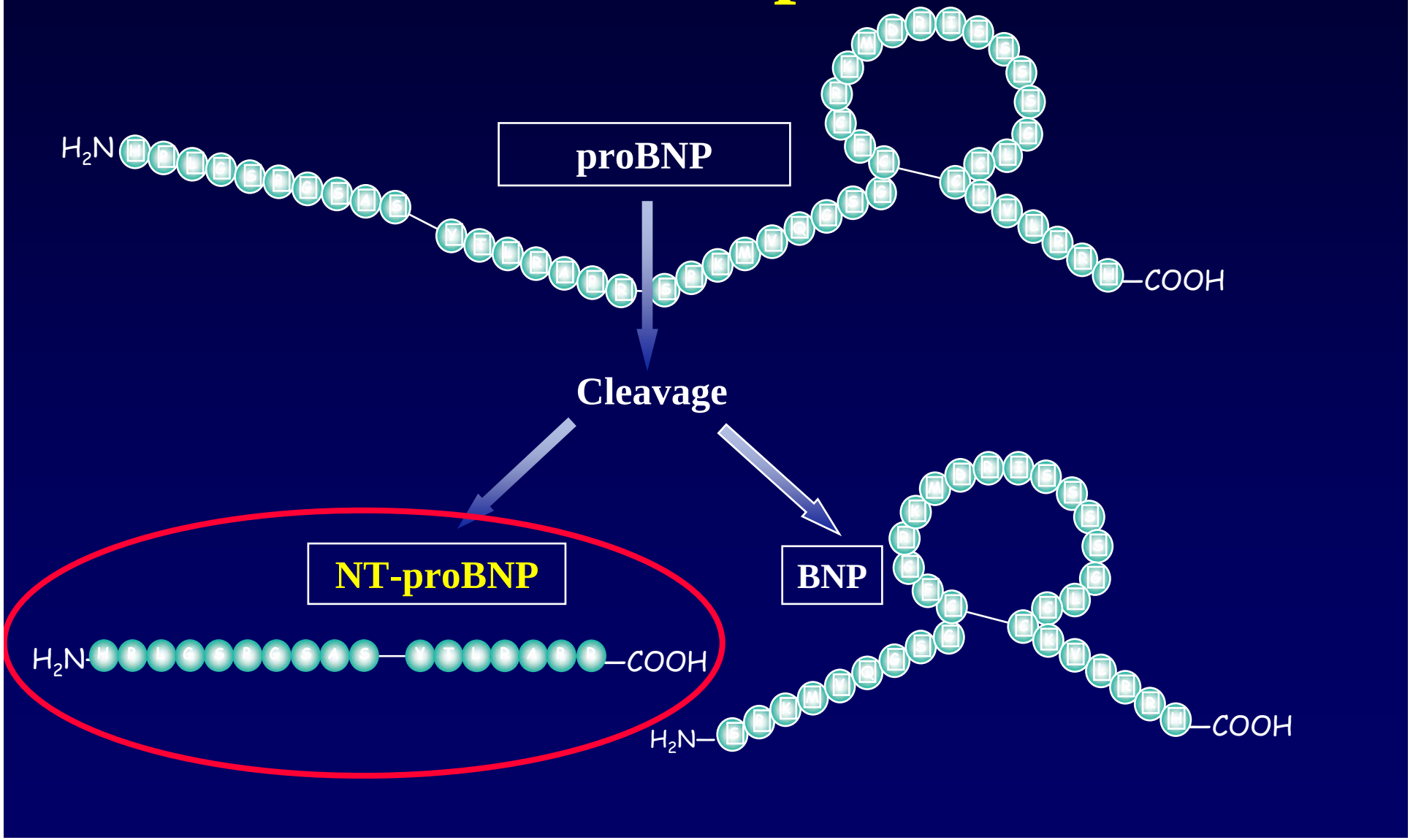
Present guidelines and practice

- More than 80% of hospitals in the US use some type of natriuretic peptide testing

Maisel A. J Am Coll cardiol 2006;47:61

- Most of the recent national and international guidelines of heart failure management have incorporated recommendations on the use of these markers

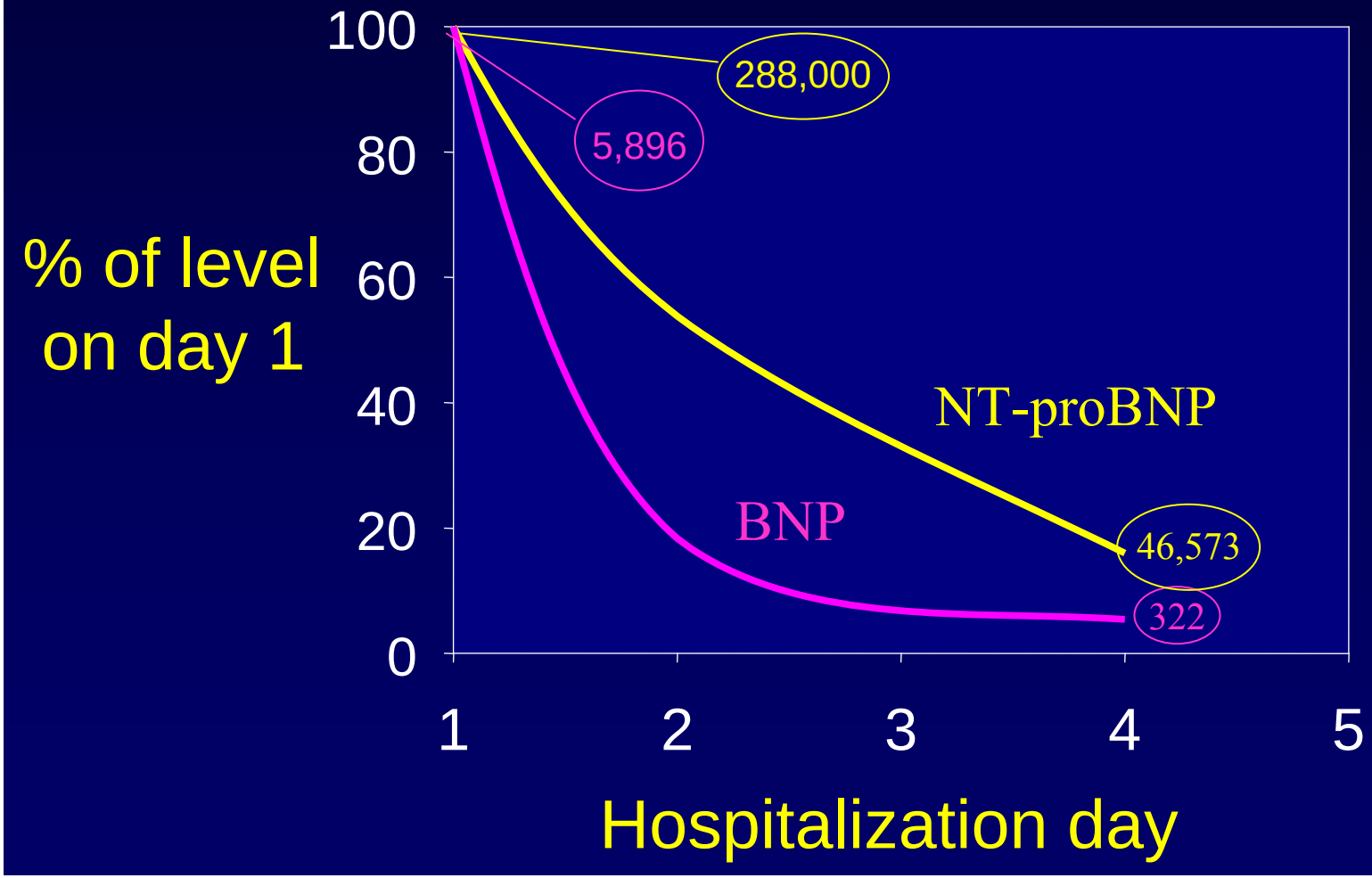
Intracellular Production
BNP & NT-proBNP



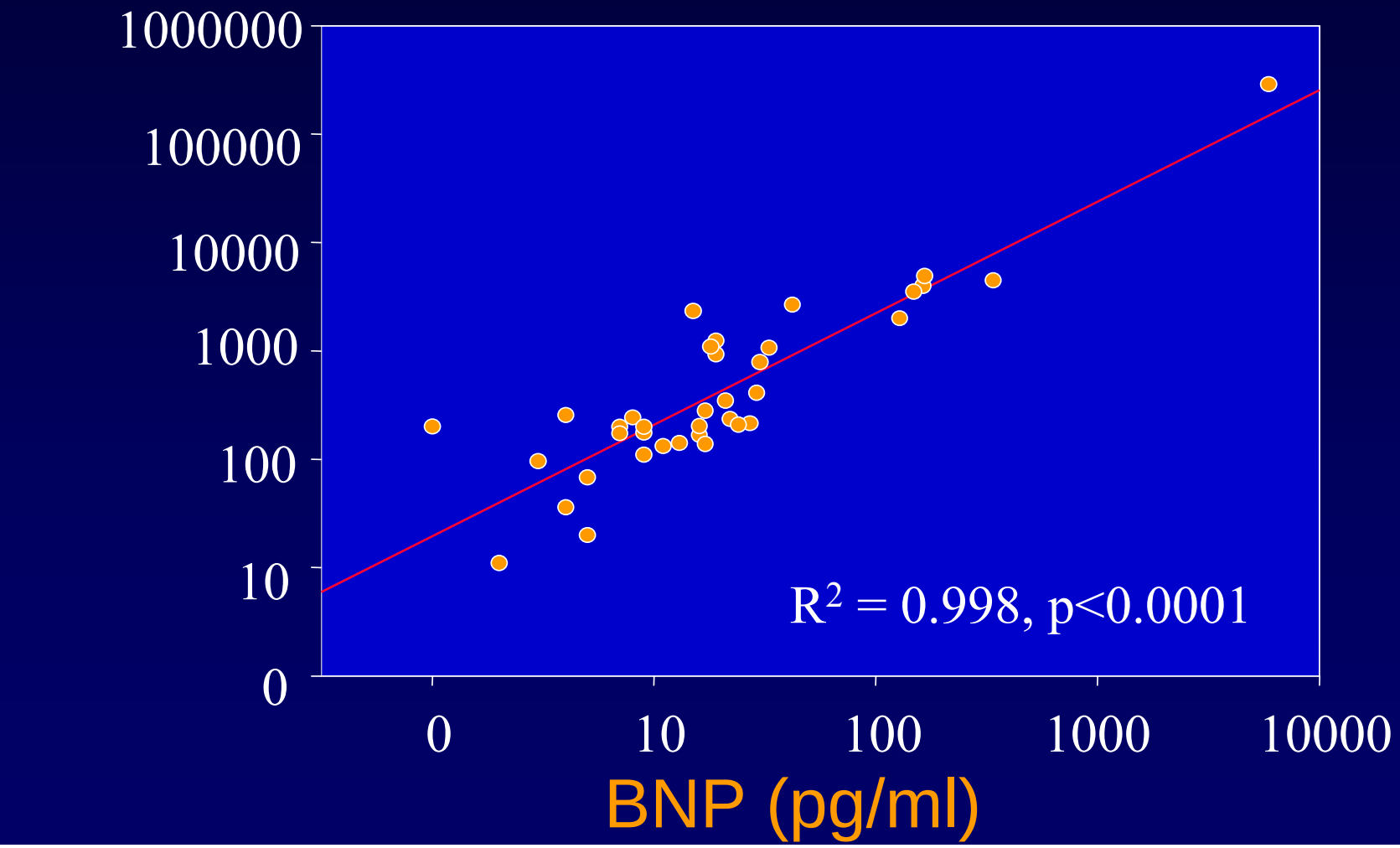
NT-proBNP Vs BNP

- NT-proBNP
  - Longer half life (3h Vs 20 min)
  - Higher plasma concentrations
  - More stable – Slower changes

BNP and NT-proBNP in a baby with acute myocarditis



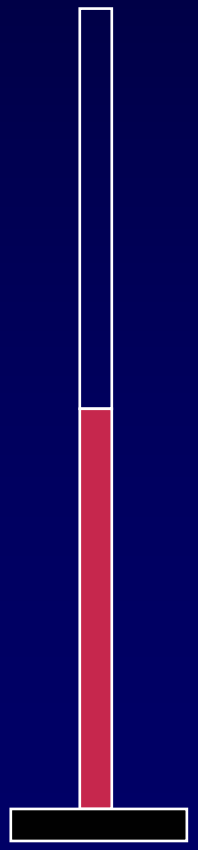
BNP and NT-proBNP in children with and without heart disease



BNP is Elevated in Many Heart Diseases

- Cardiac dysfunction
  - Systolic
  - Diastolic
  - Hypertrophic
- Ischemic heart disease
- Allograft rejection following heart transplantation
- Right heart failure – pulmonary disease
- Pediatrics – congenital and acquired heart disease

BNP is the Sedimentation Rate of the Heart



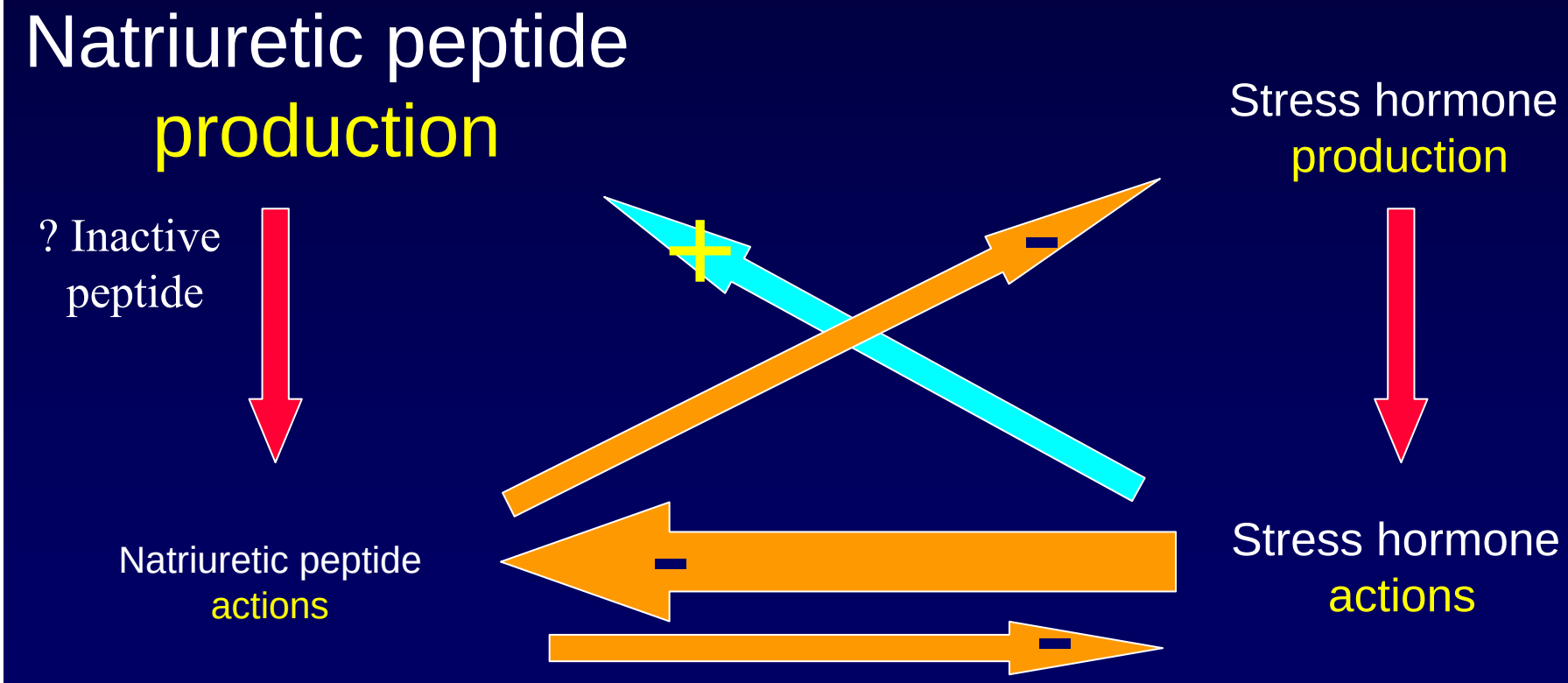
The Paradox

- Natriuretic peptides are good for the failing heart
- High plasma natriuretic peptides = heart disease

Heart Failure Syndrome

- Decreased perfusion pressure causes activation of
  - Renin-angiotensin-aldosterone
  - Sympathetic tone
  - Endothelin

Cross-talk Between the Natriuretic Peptides and Stress Hormones



Clinical Use for BNP as a Marker in Adult Cardiology

- Screening for ventricular dysfunction in asymptomatic people
- Identifying heart failure in patients with dyspnea or other symptoms suggesting heart disease
- Monitoring effectiveness of heart failure therapy
- Predicting prognosis

Screening for Left Ventricular Systolic Dysfunction

area under the ROC curve

Table 8 AUCs for NTpBNP and BNP to screen for LVSD

Natriuretic peptide	Definition of LVSD	AUC	Population studied	Number of subjects	References
NTpBNP	LVEF 40–50%	0.75	High-risk subjects	86	Hammerer-Lercher *et al.*[29]
NTpBNP	LVEF <45%	0.87	General population	1360	Ng *et al.*[30]
NTpBNP	LVEF <40%	0.92	General population	307	Hobbs *et al.*[20]
NTpBNP	LVEF <40%	0.84	High-risk subjects	133	Hobbs *et al.*[20]
NTpBNP	LVEF <35%	0.81	General population	1360	Ng *et al.*[30]
BNP	LVEF 40–50%	0.78	High-risk subjects	86	Hammerer-Lercher *et al.*[29]
BNP	LVEF <45%	0.93	General population	1360	Ng *et al.*[30]
BNP	LVEF <45%	0.79	High-risk subjects	466	Yamamoto *et al.*[31]
BNP	LVEF <40%	0.79	General population males	1470	Vasan *et al.*[8]
BNP	LVEF <40%	0.85	General population females	1707	Vasan *et al.*[8]
BNP	LVEF <40%	0.89	General population males	984	Redfield *et al.*[32]
BNP	LVEF <40%	0.92	General population females	1058	Redfield *et al.*[32]
BNP	LVEF <35%	0.94	General population	1360	Ng *et al.*[30]
BNP	LVEF < 30%	0.88	General population	1252	McDonagh *et al.*[19]

Galasko et al. European Heart Journal 2005; 26, 2269–2276

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BNP in the Diagnosis of Heart Failure in Adults Presenting with Dyspnea

- 452 patients who presented with acute dyspnea
  - 227 standard diagnosis

    (Hx, PE, O_2 Sat, Blood w/u, CXR)
  - 225 standard + rapid bedside BNP assay
  - Very similar characteristics

Mueller et al. N Engl J Med 2004;350:647

BNP in the Diagnosis of Heart Failure in Adults Presenting with Dyspnea

	BNP	No BNP
• Time to treatment (min)	63	90
• Hospitalization days	8	11
• Hospitalization %	75	85
• Total cost ($)	5410	7264

Mueller et al. N Engl J Med 2004;350:647

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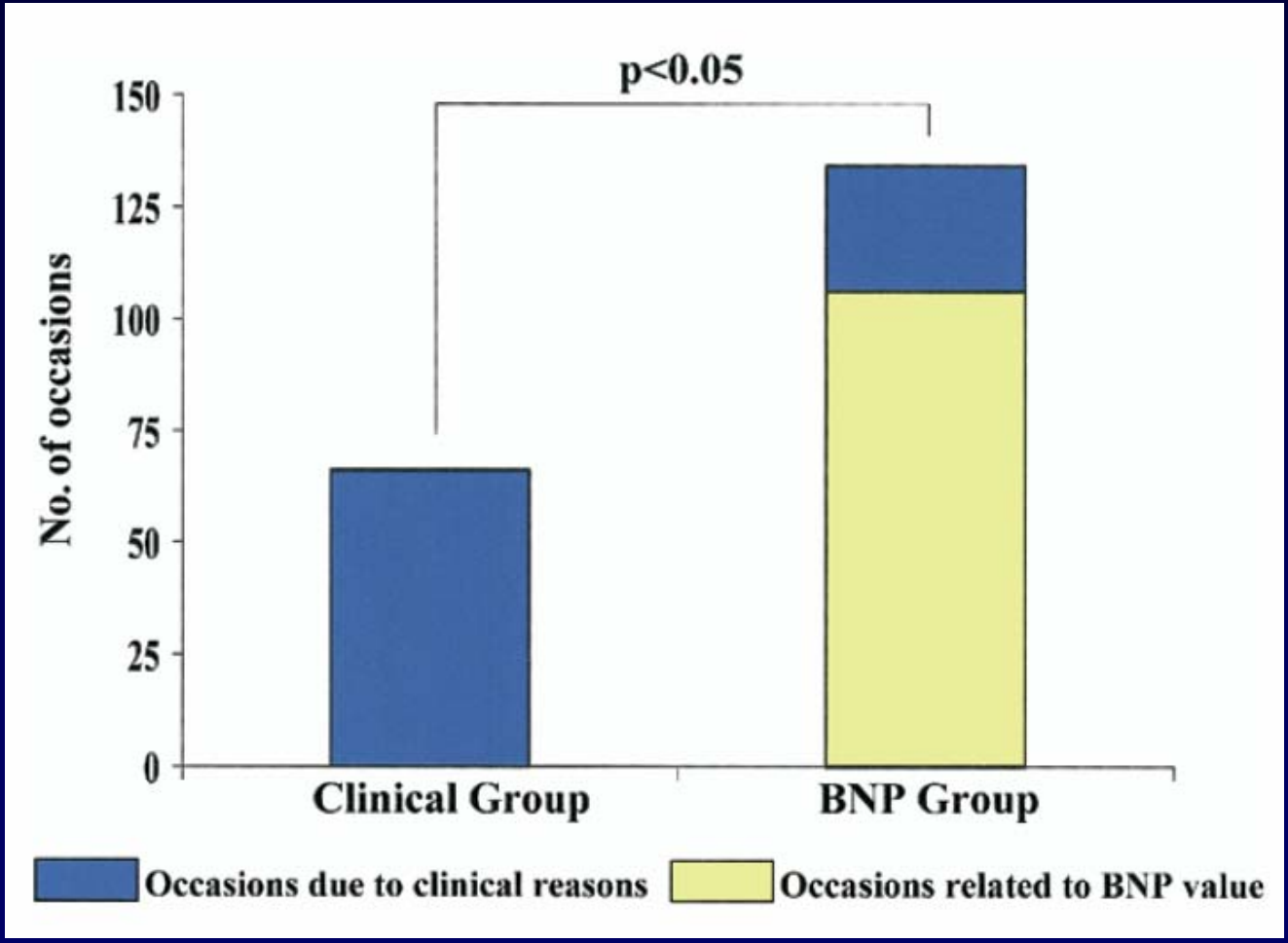
BNP-Guided Chronic Heart Failure Therapy

- 220 patients
- BNP group
- medical therapy was increased with the aim of lowering plasma BNP levels (target < 100 pg/ml)
- Clinical group
- medical therapy was adjusted according physical examination and usual laboratory parameters. The investigators were not allowed to measure plasma BNP

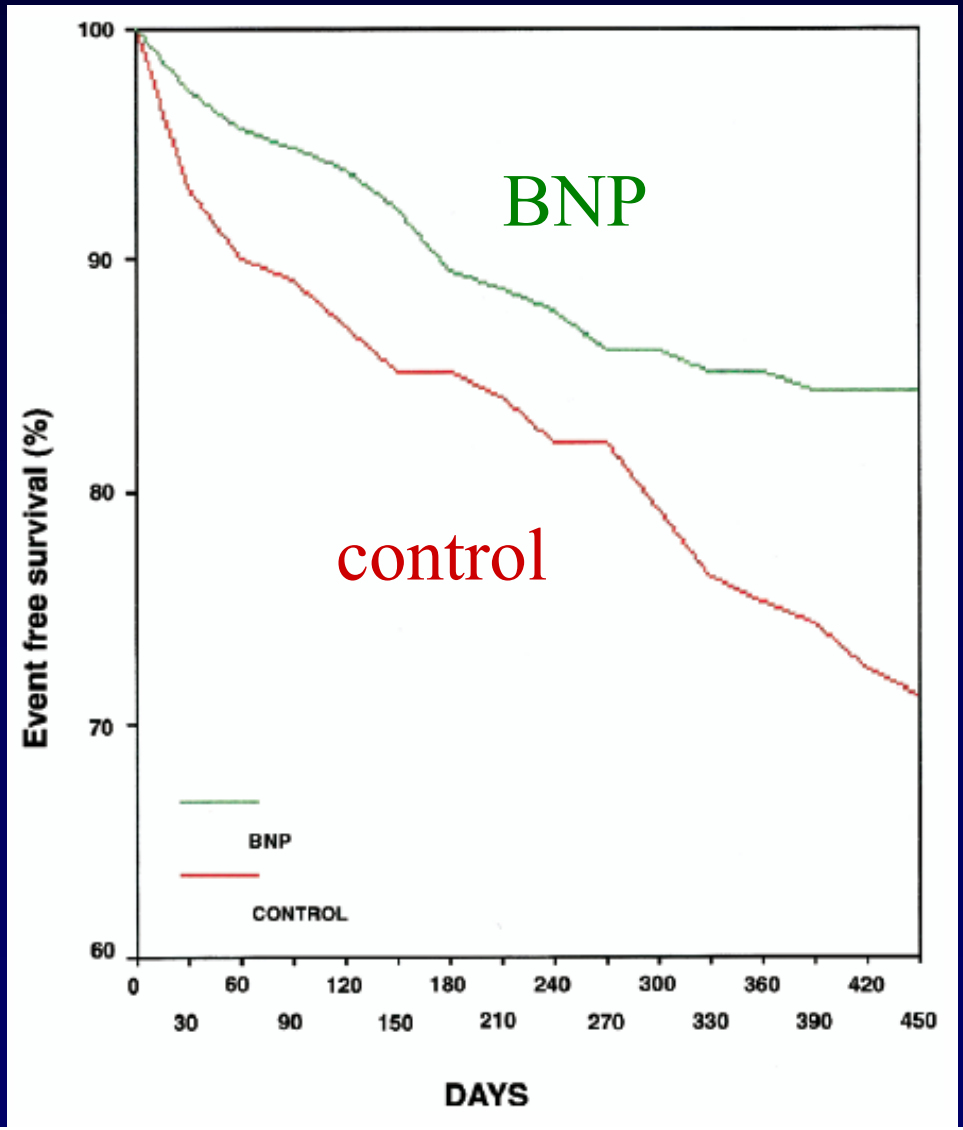
Jourdain et al. J Am Coll Cardiol 2007;49:1733

Number of change in medications during the 1st 3 months



Jourdain et al. J Am Coll Cardiol 2007;49:1733

Hospitalizations or Death Related to Heart Failure



Jourdain et al.
J Am Coll Cardiol
2007;49:1733

NT-proBNP-Guided Therapy for Heart Failure

- 69 patients randomized to drug treatment based on:

•plasma levels of NT-proBNP

•clinical criteria

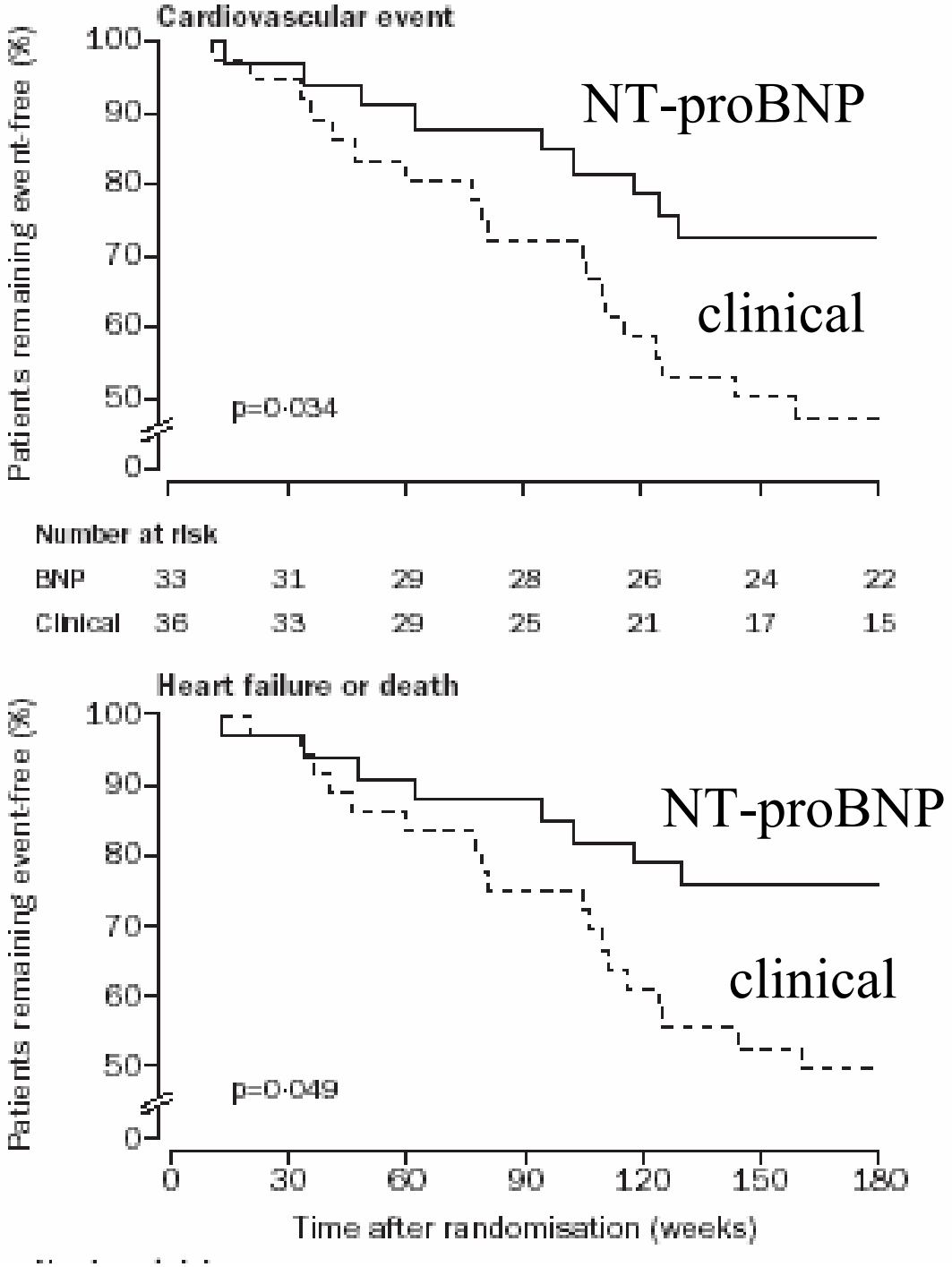
Symptom	Value
Orthopnoea	0·5
Paroxysmal nocturnal dyspnoea	1·0
Reduction in exercise tolerance	0·5
Resting sinus tachycardia (>100/min)	0·5
Jugular venous pressure >4 cm	0·5
Hepatojugular reflex positive	1·0
Third heart sound present	1·0
Basal crackles	1·0
Hepatomegaly	0·5
Peripheral oedema	0·5

Decompensated heart failure indicated by total score ⩾2.

Table 1: **Standardised heart-failure scoring system**

Troughton et al, Lancet 2000

NT-proBNP as Guide for Heart Failure Therapy



Troughton et al, Lancet 2000

Clinical Use for BNP as a Marker in Adult Cardiology

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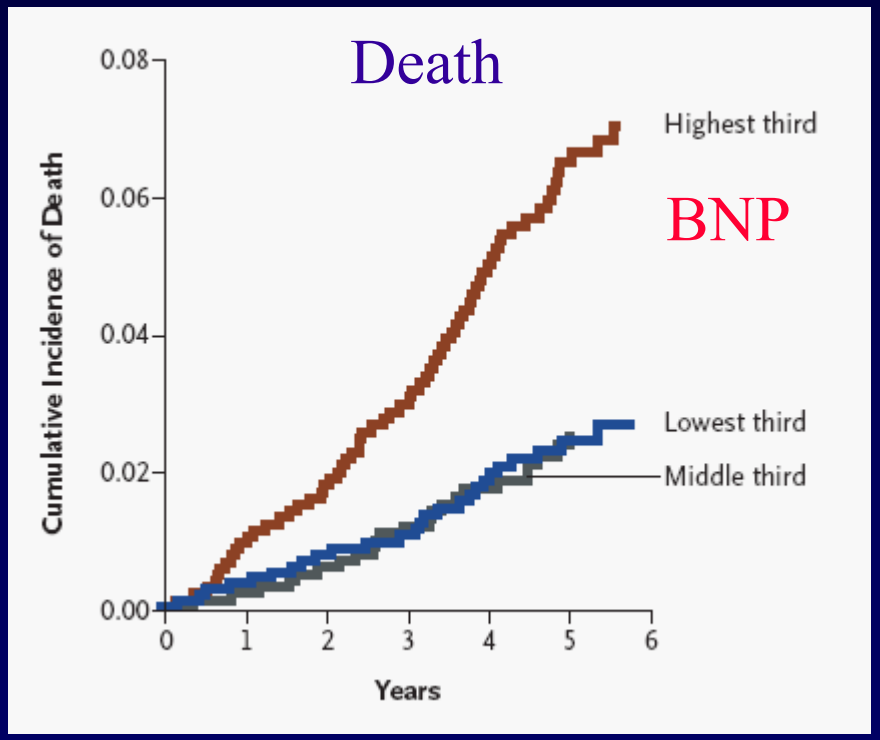
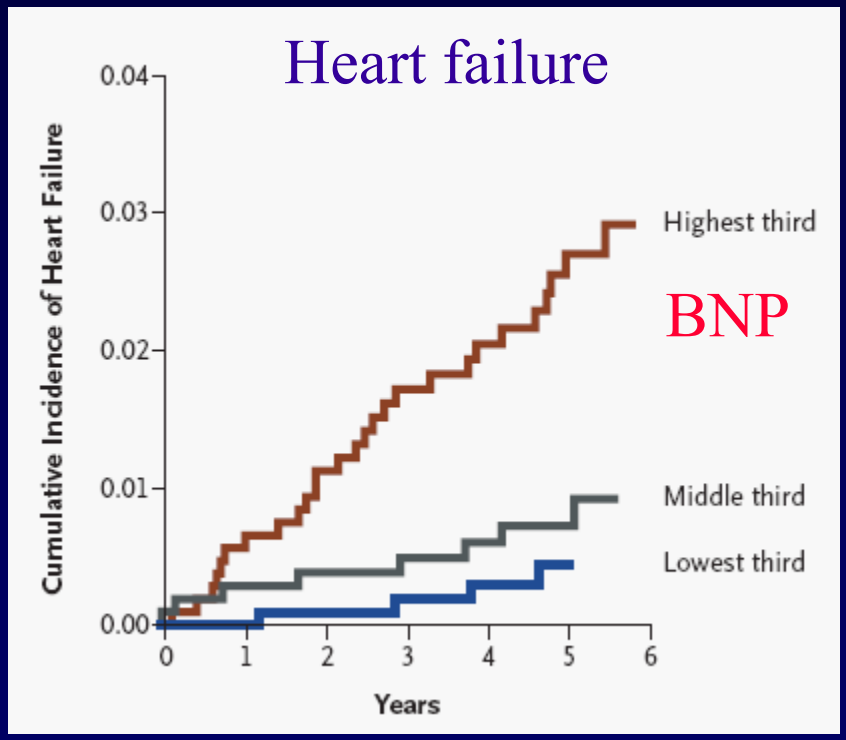
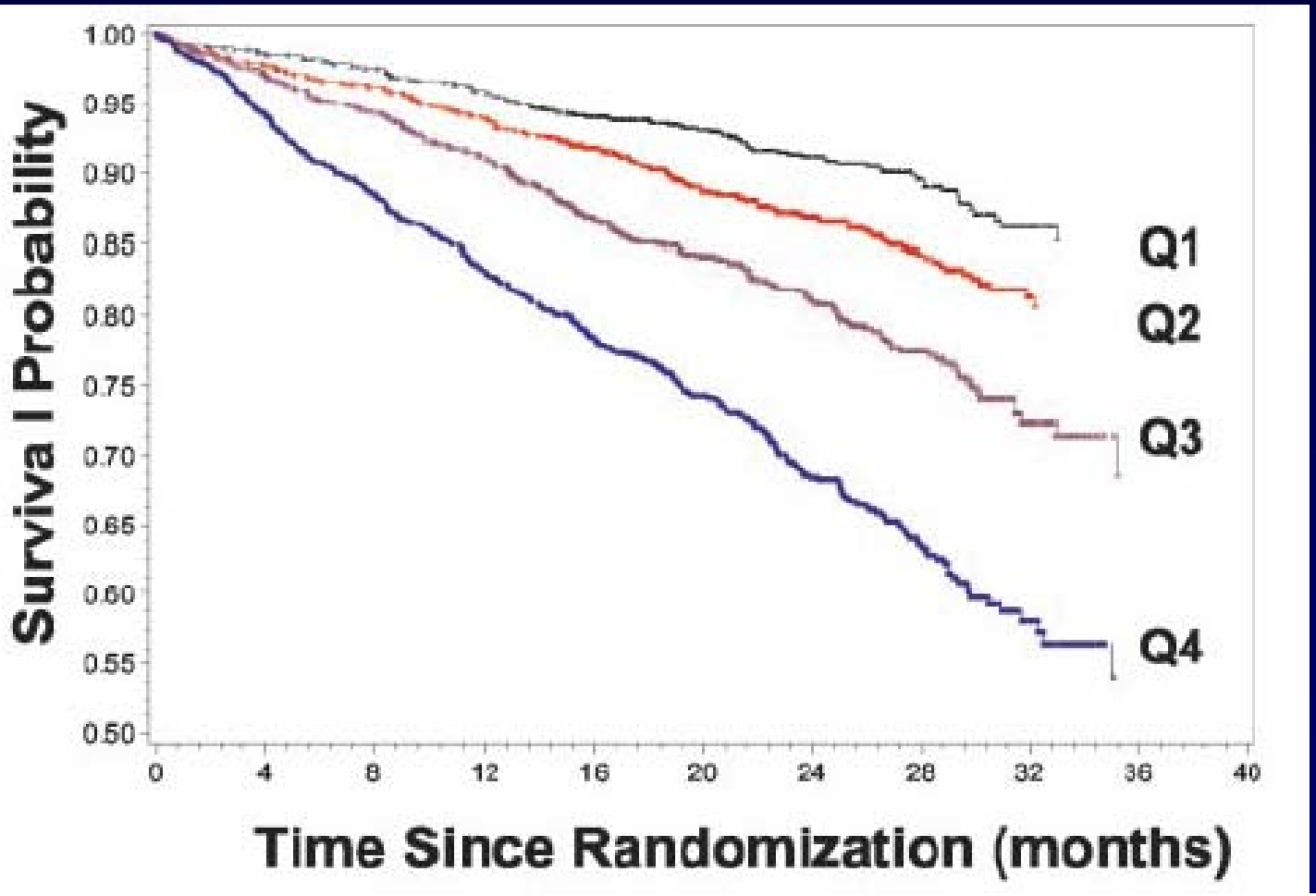
BNP and Risk for Death or Heart Failure in 3346 Adults (age ~60y) Without Heart Failure





Wang et al. Framingham Heart Study, N Engl J Med 2004;350:655-63

BNP and Prognosis of 4300 Patients with Heart Failure



Valsartan heart failure trial
Anand et al.
Circulation 2003

BNP and NT-proBNP in Pediatrics

Normal values

Reference values, range and upper limits, of NT-proBNP in infants and children

Analysis of combined data from 4 studies

Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, Koch A, Falkenberg J, Mir TS

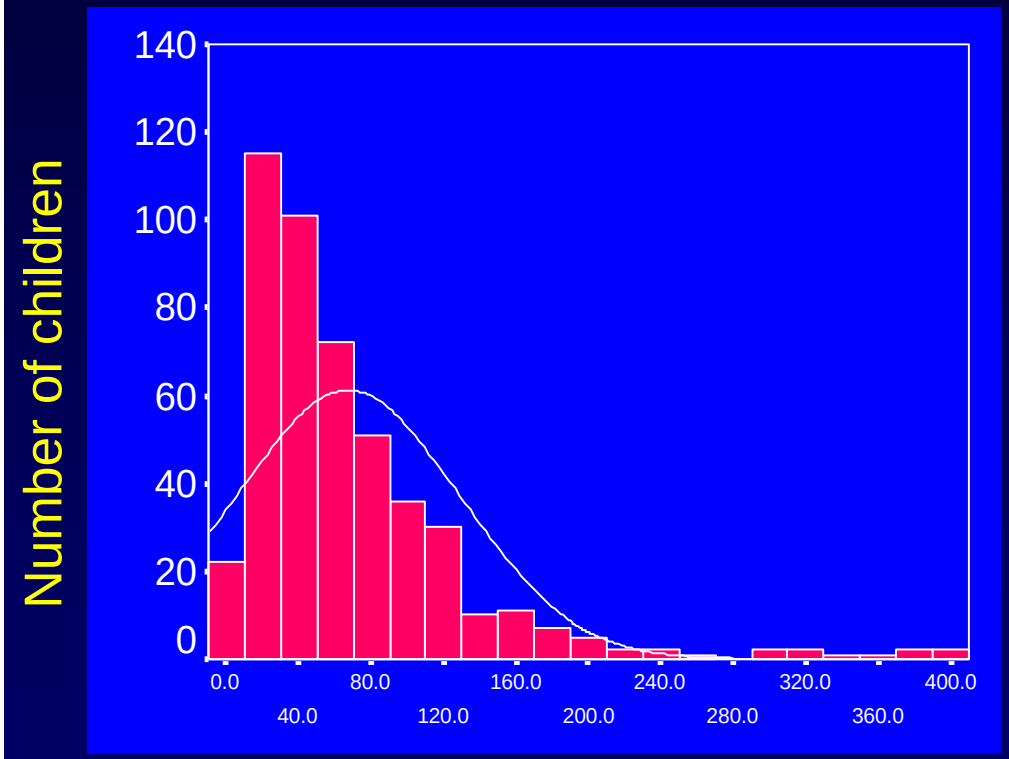
Shaare Zedek Medical Center, Jerusalem, Israel
University Clinic of the Saarland, Homburg/Saar, Germany
University Clinic Erlangen, Erlangen, Germany
Hadassah, Hebrew University Medical Center, Jerusalem, Israel
University Duesseldorf, Duesseldorf, Germany
University Heart center University Hamburg, Germany

Pediatr Cardiol. 2009;30:3-8

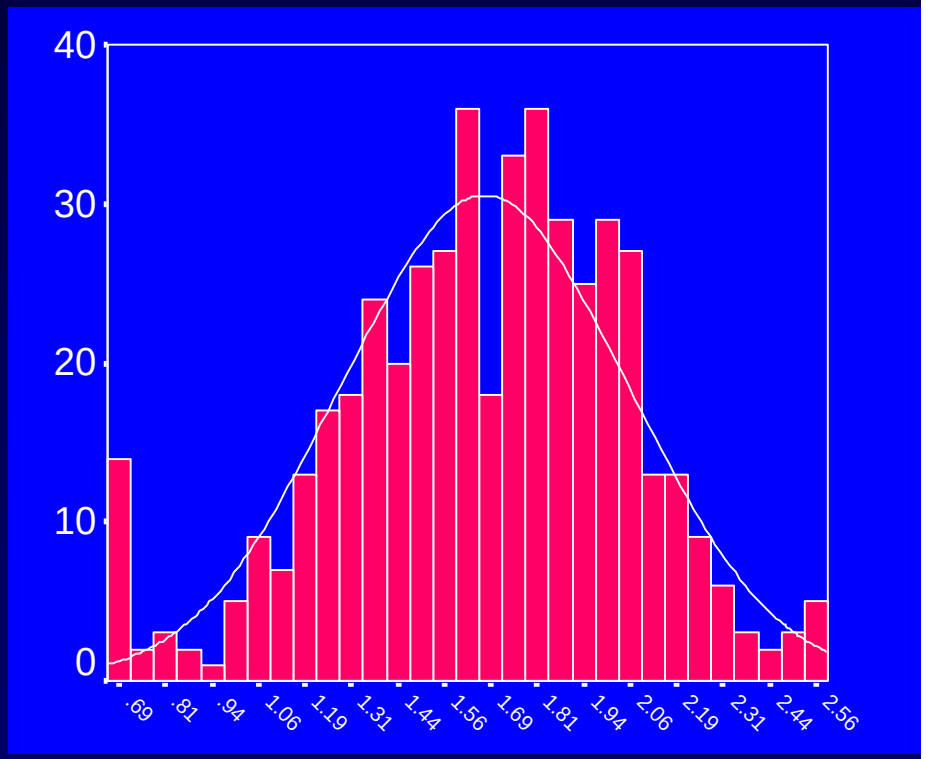
690 subjects, 47% males

NT-proBNP distribution

Normality test failed

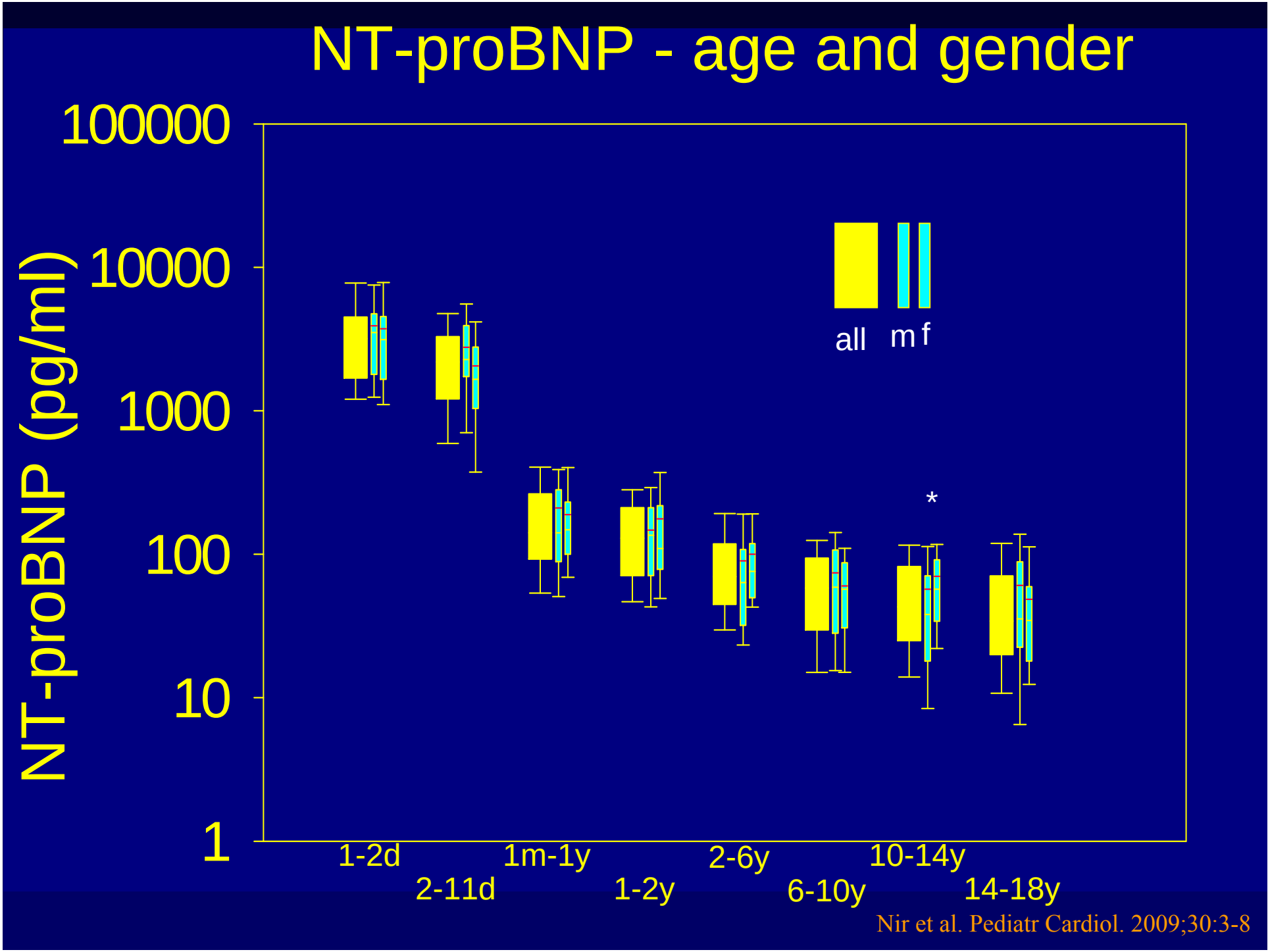


Normality test passed



Nir et al. Pediatr Cardiol. 2009;30:3-8

NT-proBNP - age and gender



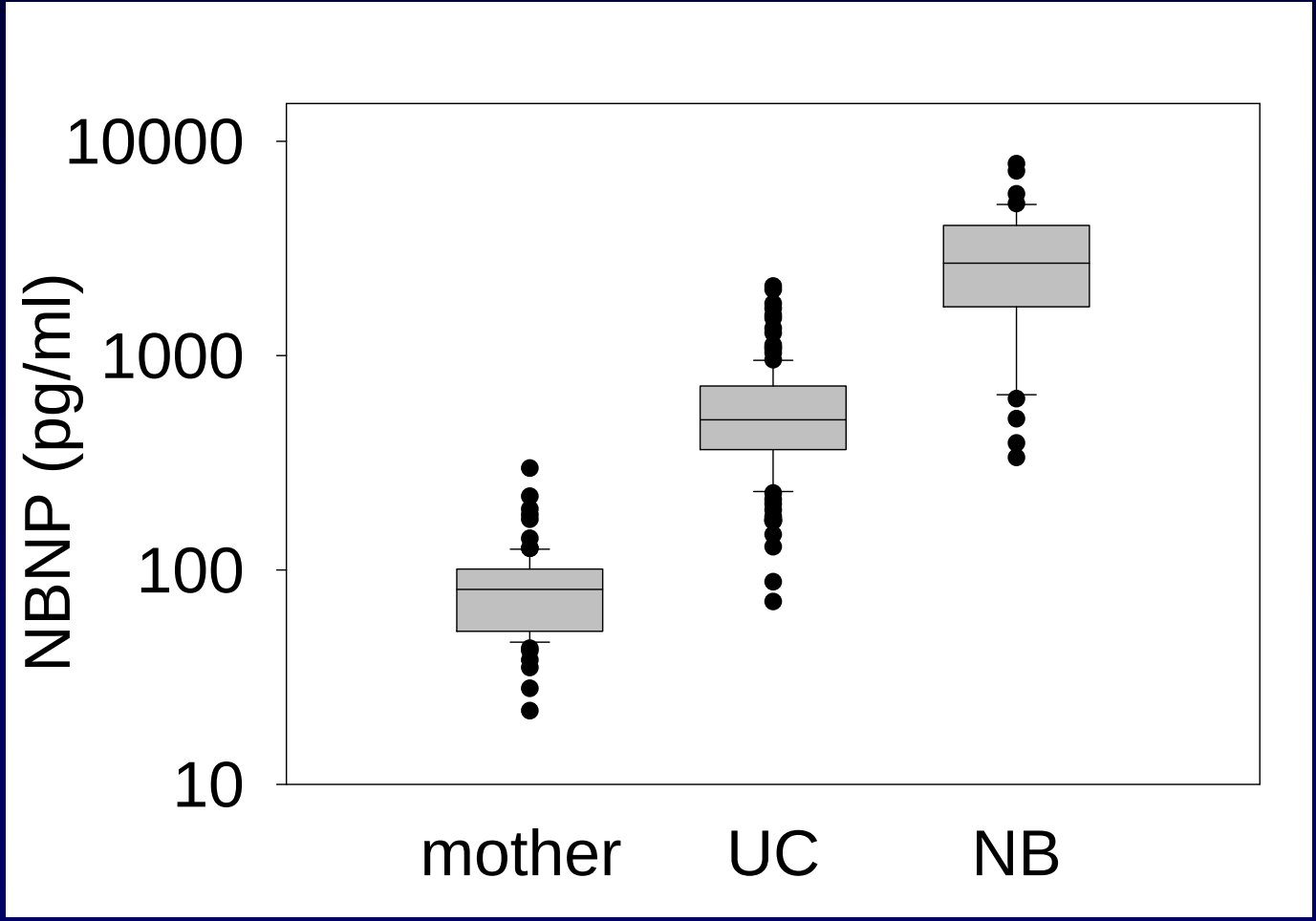
Nir et al. Pediatr Cardiol. 2009;30:3-8

NT-proBNP – Normal Values

Age interval	n	Median (pg/ml)	Range (pg/ml)	5%tile	95%tile
0-2d	43	3138	260-13224	321	11987
3-11d	84	2210	28-7250	263	5918
1m - 1y	50	141	5-1121	37	646
1y - 2y	38	129	31-675	39	413
1y – 6y	81	70	5-391	23	289
6y - 14y	278	52	5-391	10	157
14y - 18y	116	34	5-363	6	158

Nir et al. Pediatr Cardiol. 2009;30:3-8

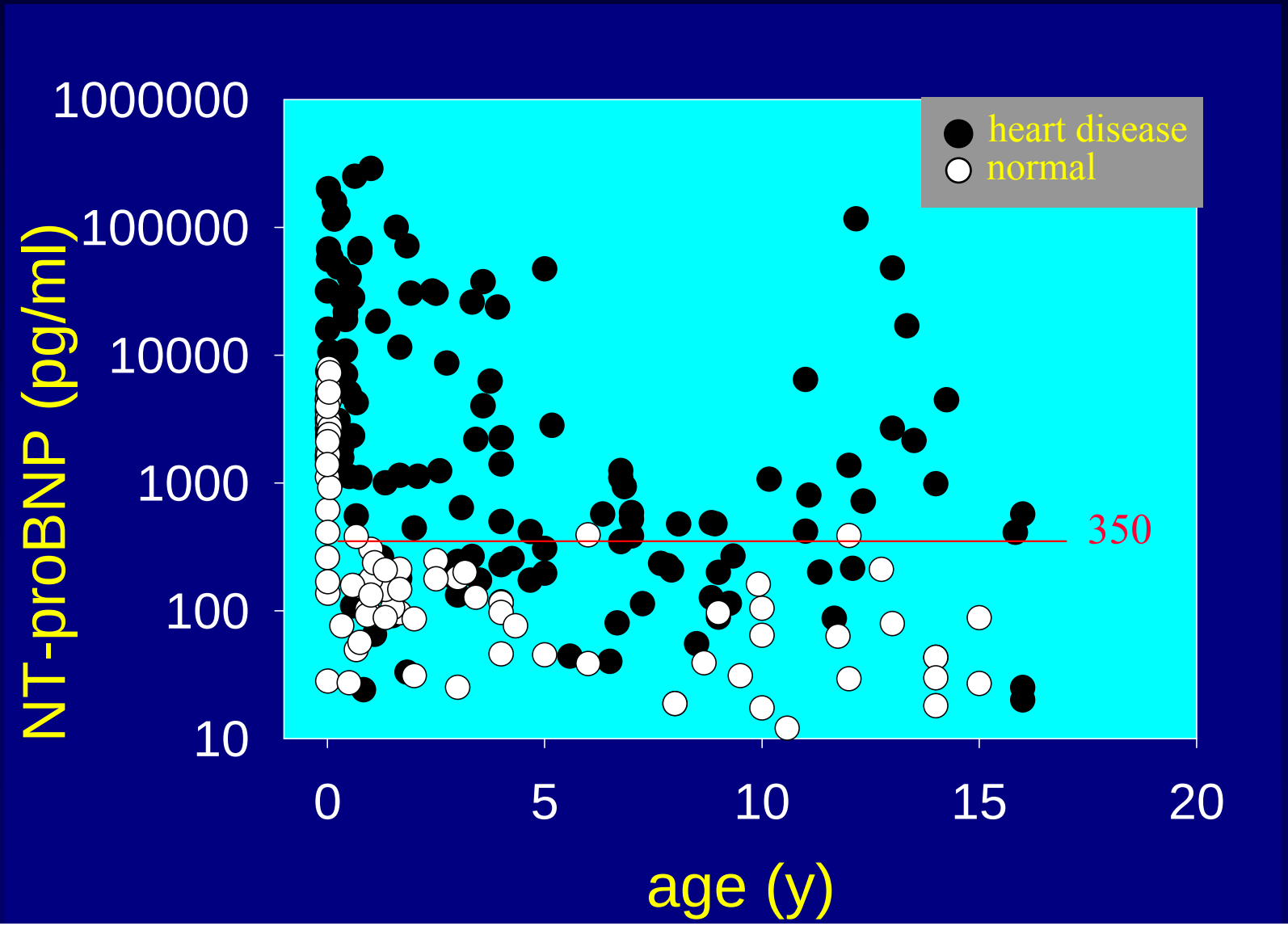
NT-proBNP in mothers and newborns



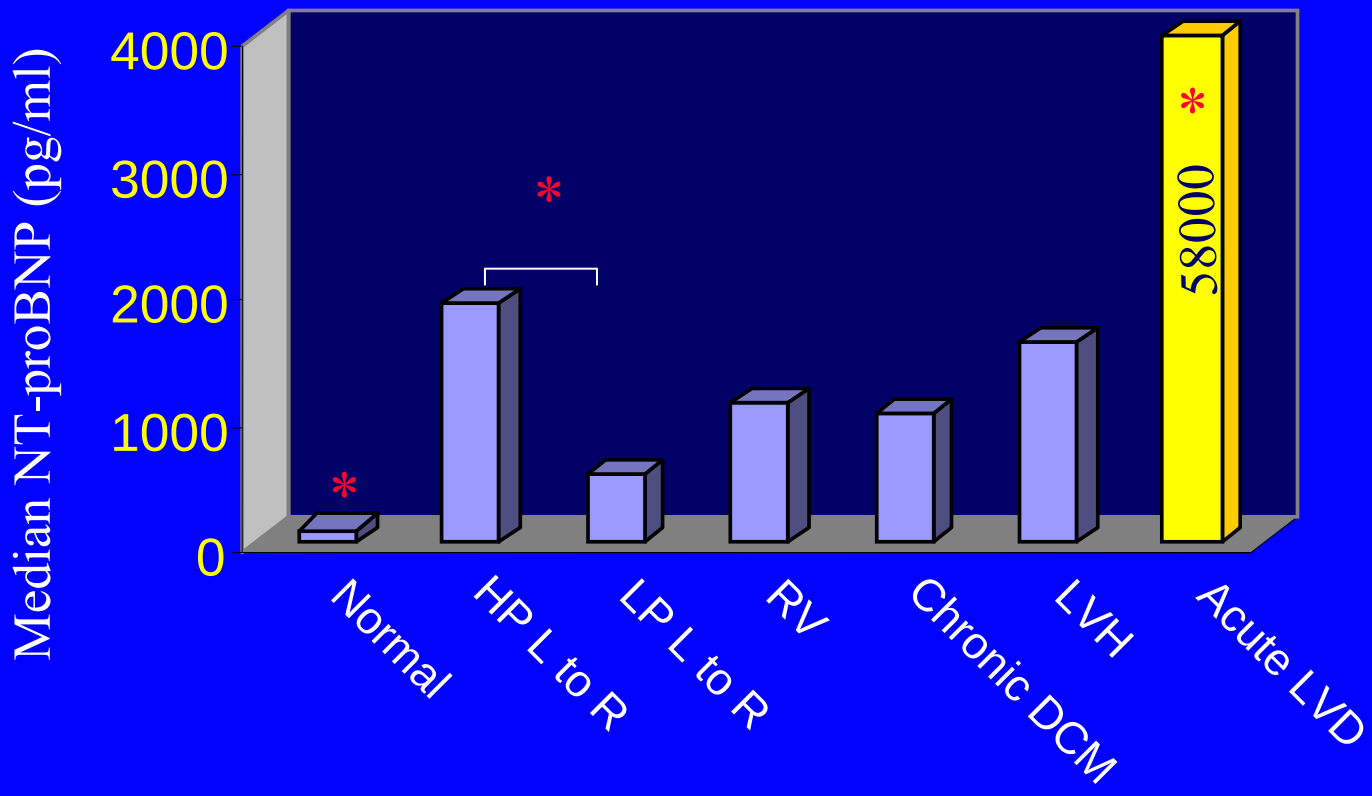
Bar-Oz B, Lev-Sagie A, Arad I, Salpeter L, Nir A. Clin Chem 51:926-7,2005

BNP in various pediatric heart diseases

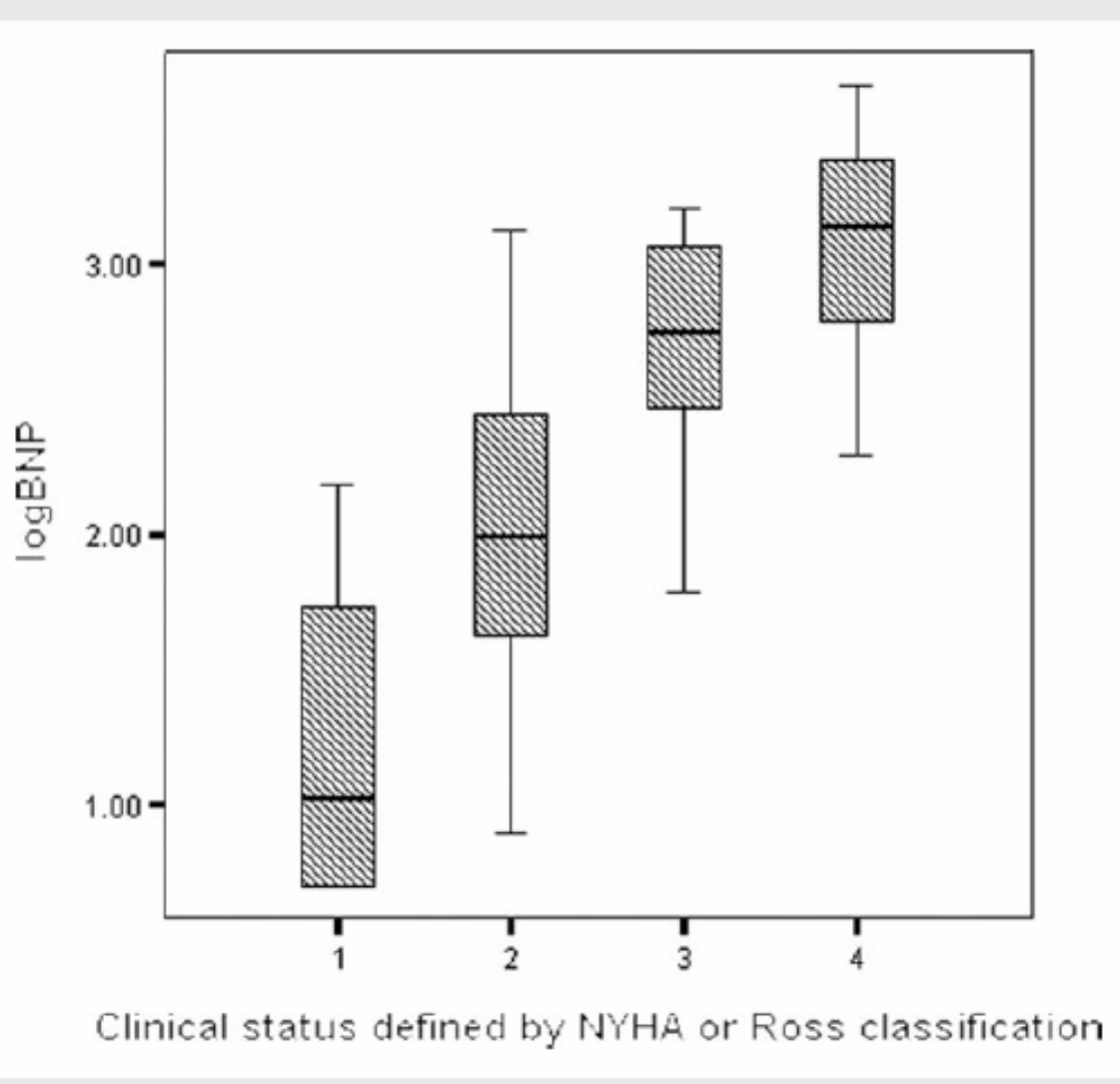
Plasma NT-proBNP in Infants and Children with and without Heart Disease



NT-proBNP in Children with Heart Diseases



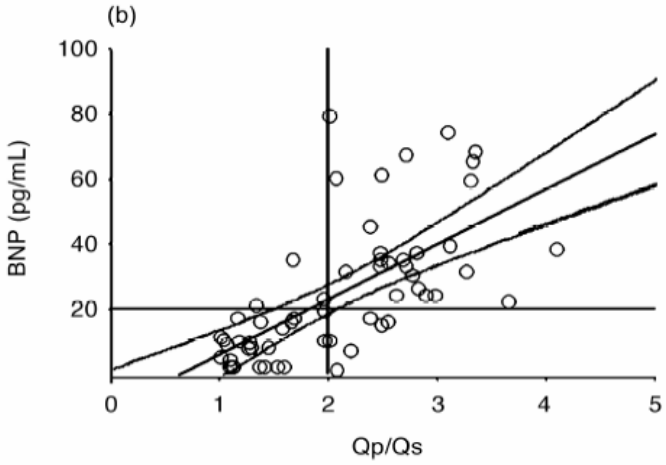
BNP in 48 pediatric patients with dilated cardiomyopathy



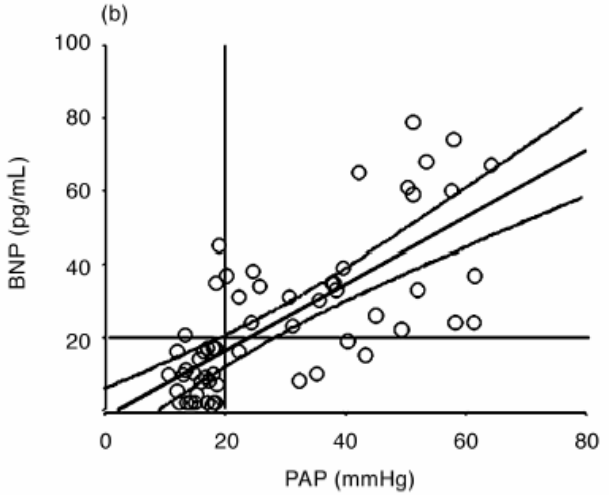
Mangat et al.
(Great Ormond Street)
Eu J. HF, 2009;11, 48

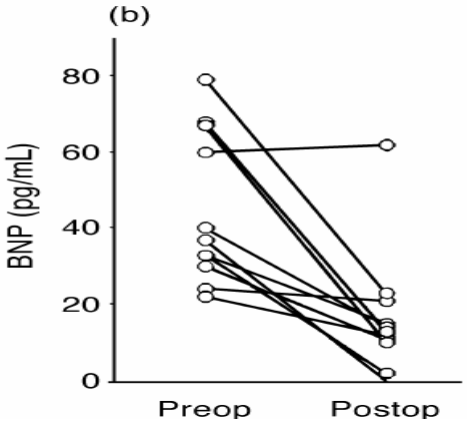
BNP in patients with Ventricular Septal Defect

Qp/Qs



Pulmonary artery pressure





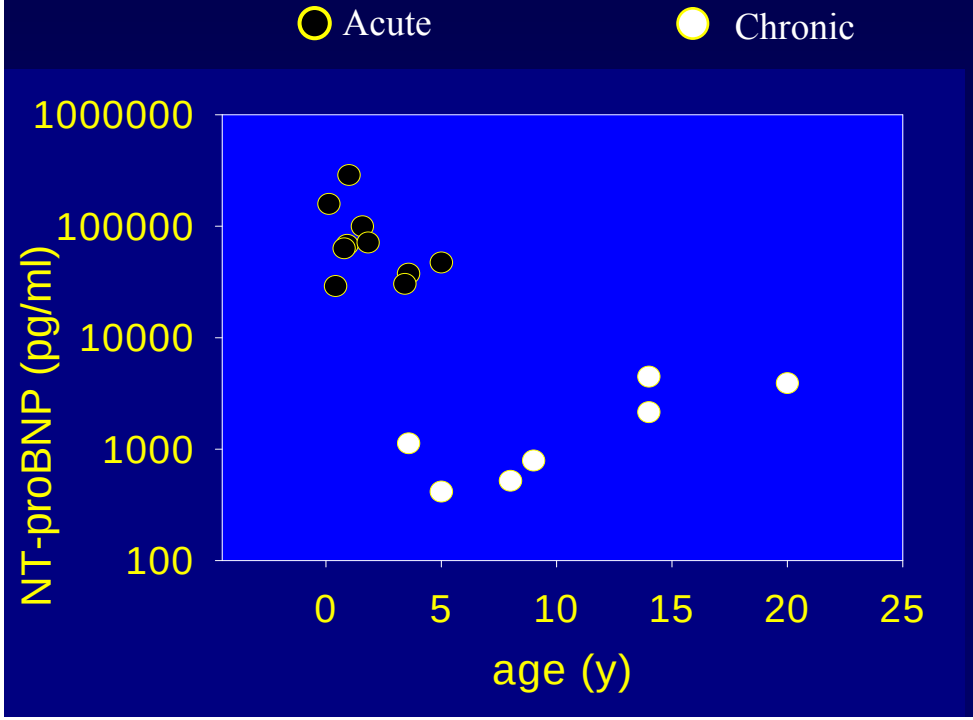
Suda et al. Pediatr Int 2003

N-TERMINAL PRO-B–TYPE NATRIURETIC PEPTIDE LEVELS IN ACUTE VERSUS CHRONIC LEFT VENTRICULAR DYSFUNCTION

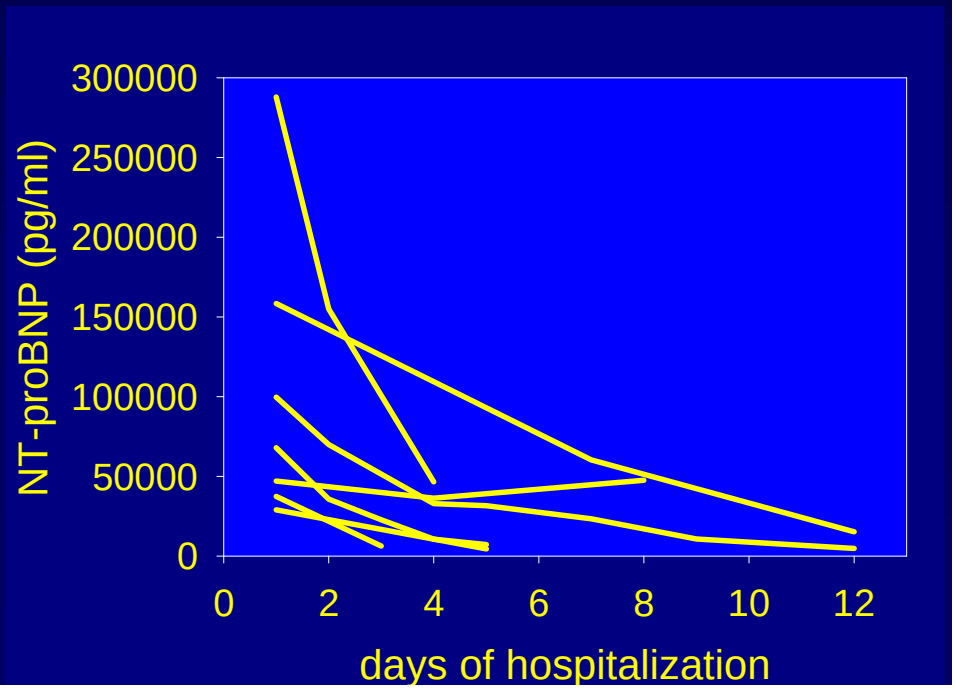
IRIS FRIED, MD, BENJAMIN BAR-OZ, MD, ZEEV PERLES, MD, AZARIA JJT REIN, MD, ZEEV ZONIS, MD, AND AMIRAM NIR, MD

J Pediatr 2006;149:28-31

acute and equivalent
Chronic cardiac dysfunction

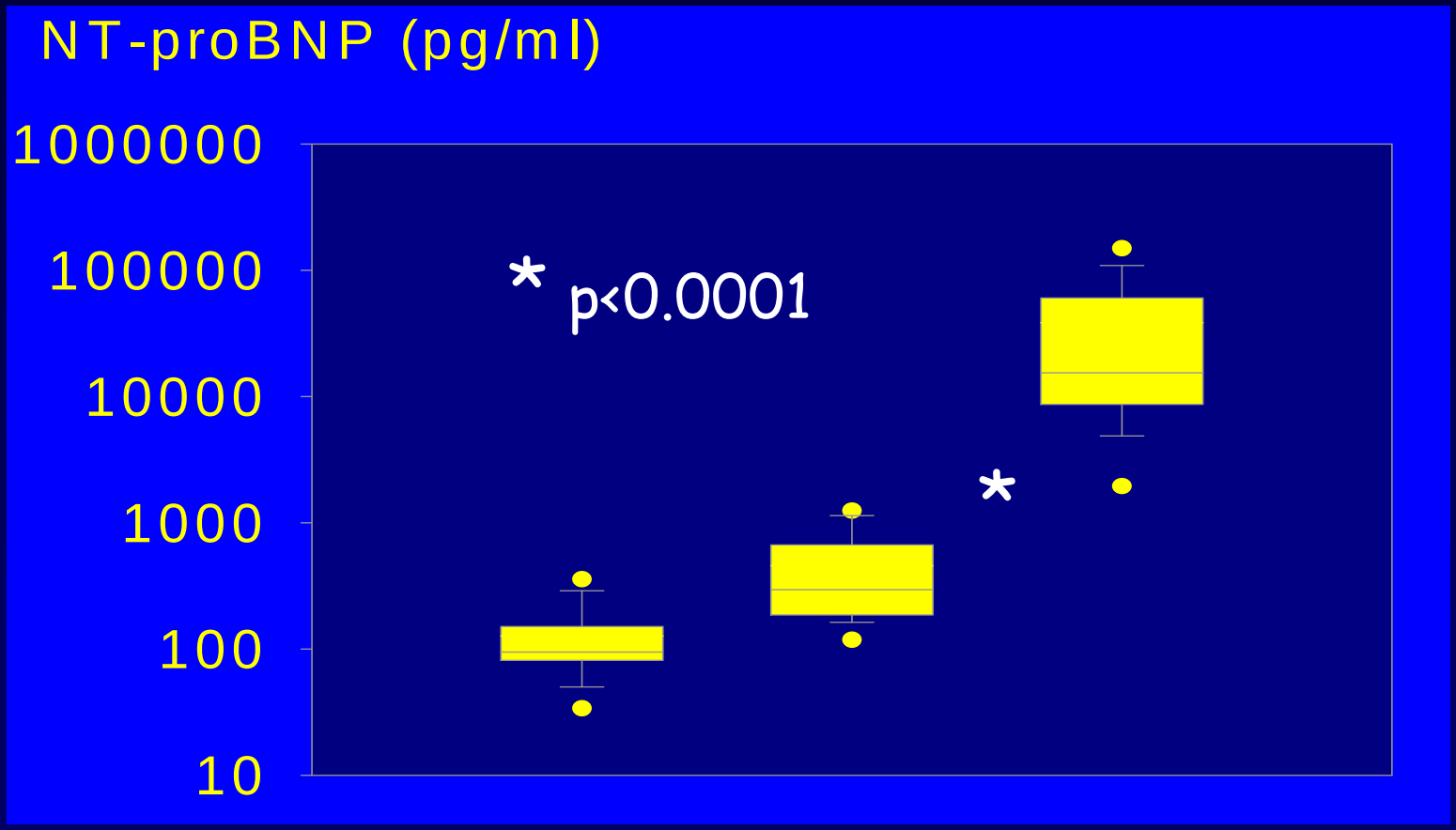


time course in acute
cardiac dysfunction



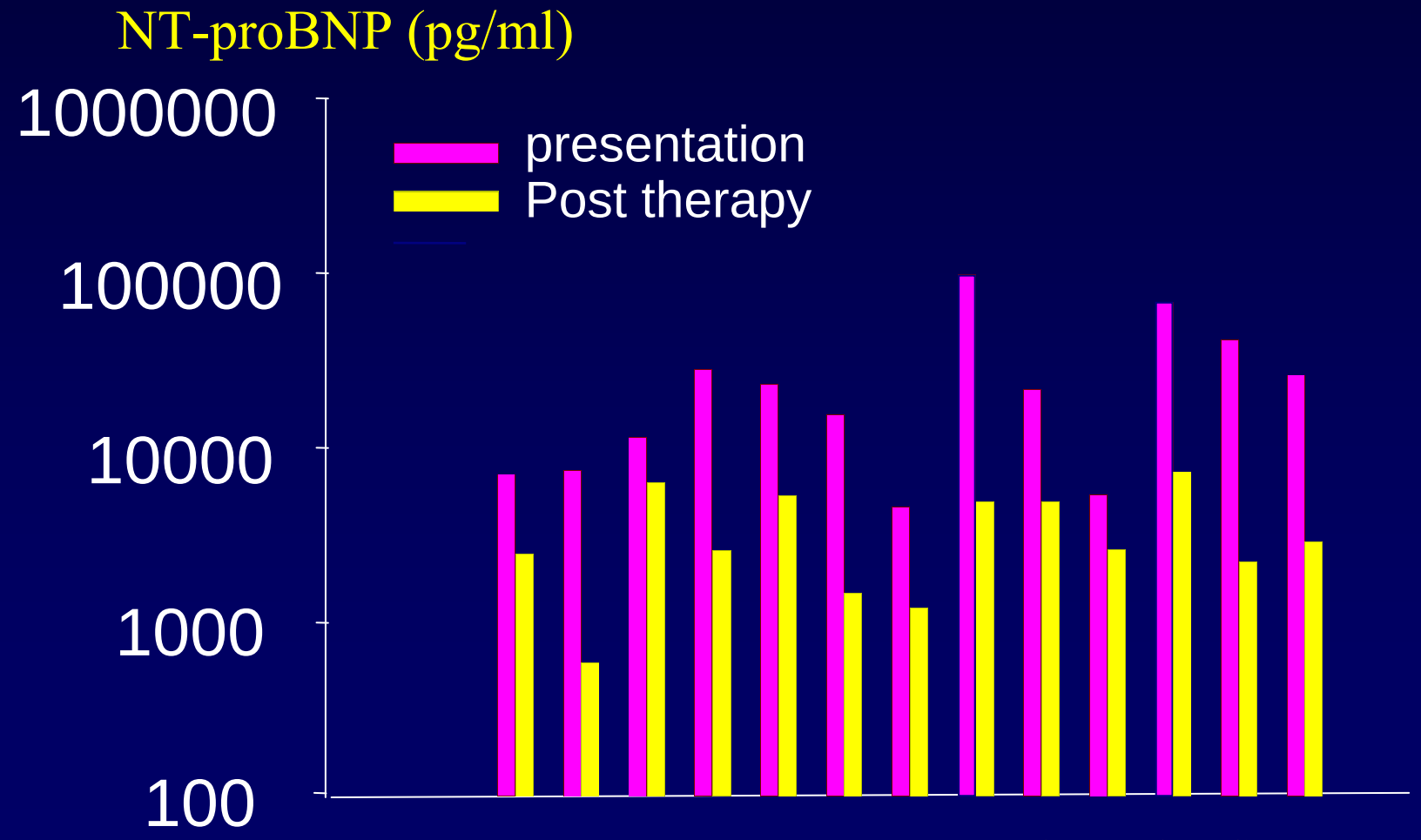
Identifying heart disease

NT-proBNP as a Marker for Heart Disease in Infants with Respiratory Distress



Cohen et al. Pediatrics 2005;115:1347-50

The Effect of Medical Therapy on NT-proBNP in Infants with Respiratory Distress due to Heart Disease

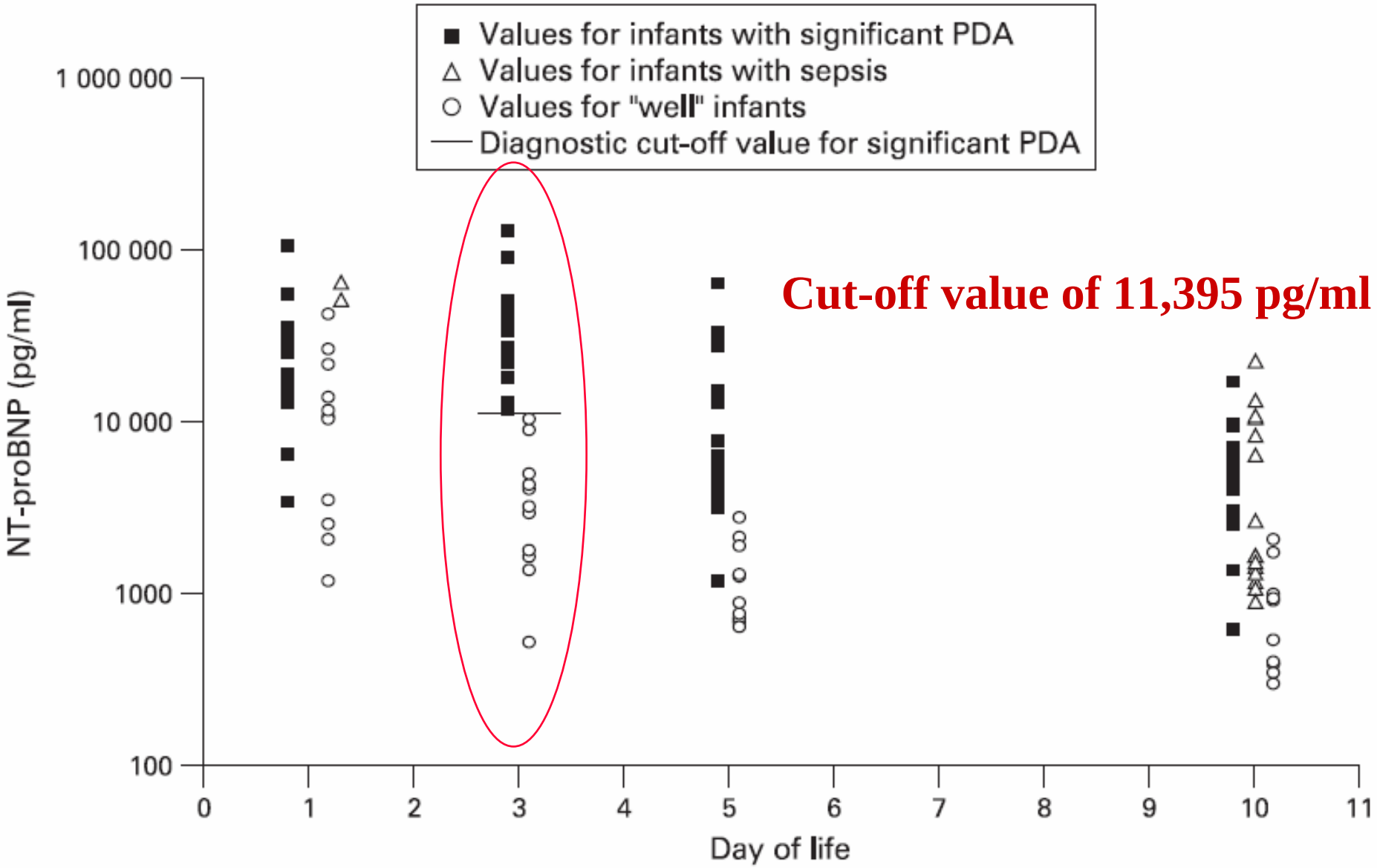


Cohen et al. Pediatrics 2005;115:1347-50

NT-proBNP and PDA

- 49 Premies
  - Gestational age range 24–33 weeks
  - Birth weight range 550–1950 gram
- NT-proBNP levels were measured on days 1, 3, 5 and 10 with simultaneous echo
- Hemodinamically significant PDA:
  - large ductal flow
  - >1.6 mm PDA
  - clinical features of PDA
- 18/49 had hemodynamically significant PDA

Farombi-Oghuvbu et al. *Arch. Dis. Child. Fetal Neonatal Ed.* 2008;93;F257-F260;

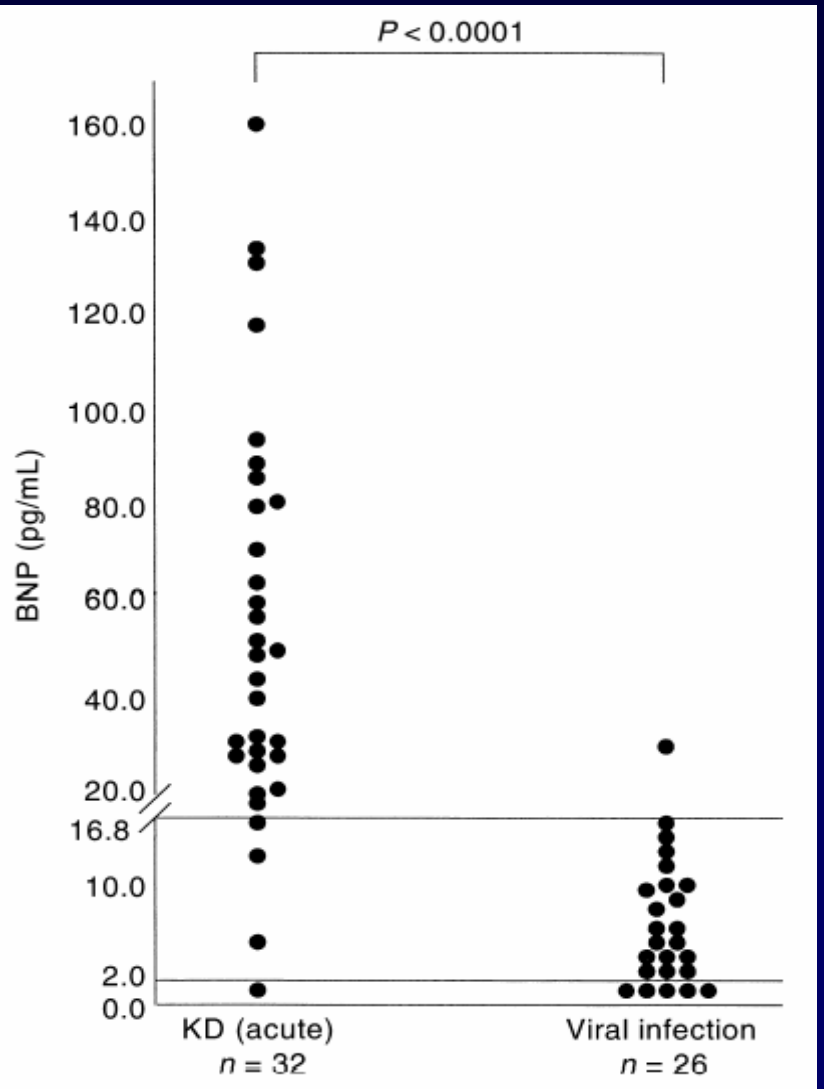


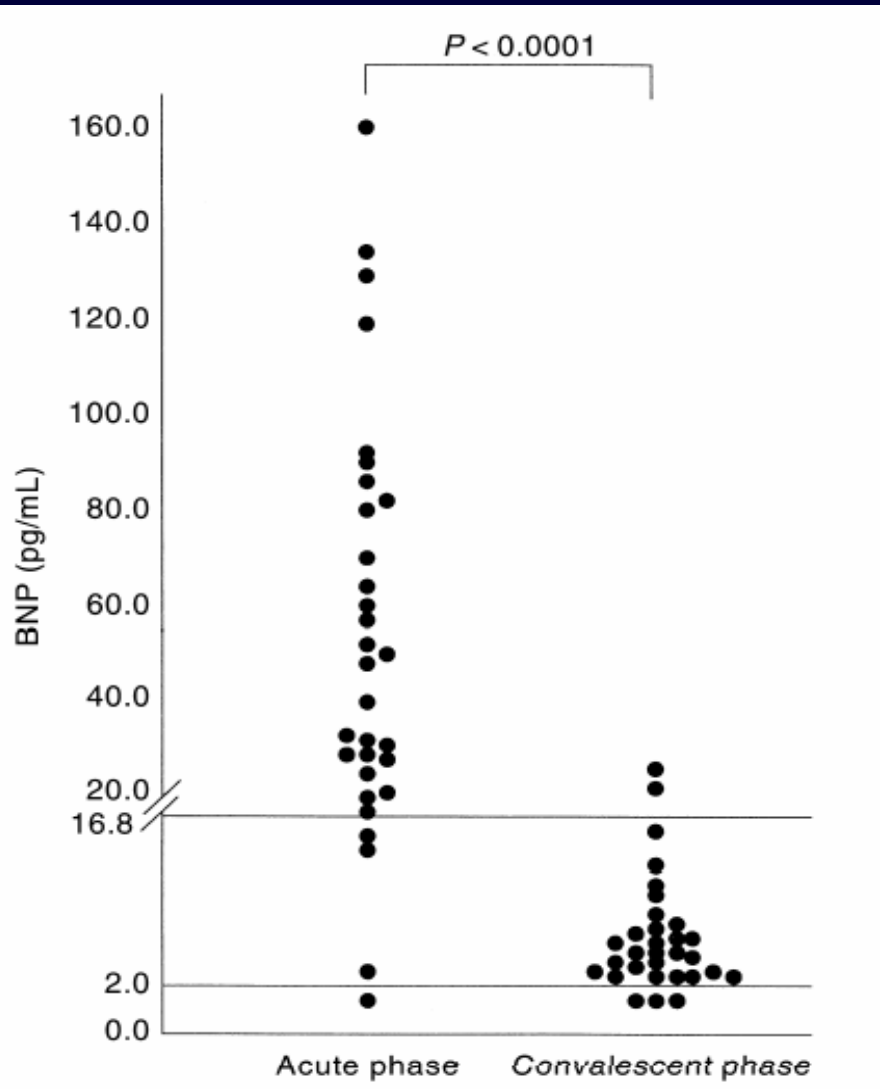
Cut-off value of 11,395 pg/ml

Farombi-Oghuvbu et al. *Arch. Dis. Child. Fetal Neonatal Ed.* 2008;93;F257-F260;

BNP in Kawasaki's Dis

(Kawamura et al. Ped Int 2000)

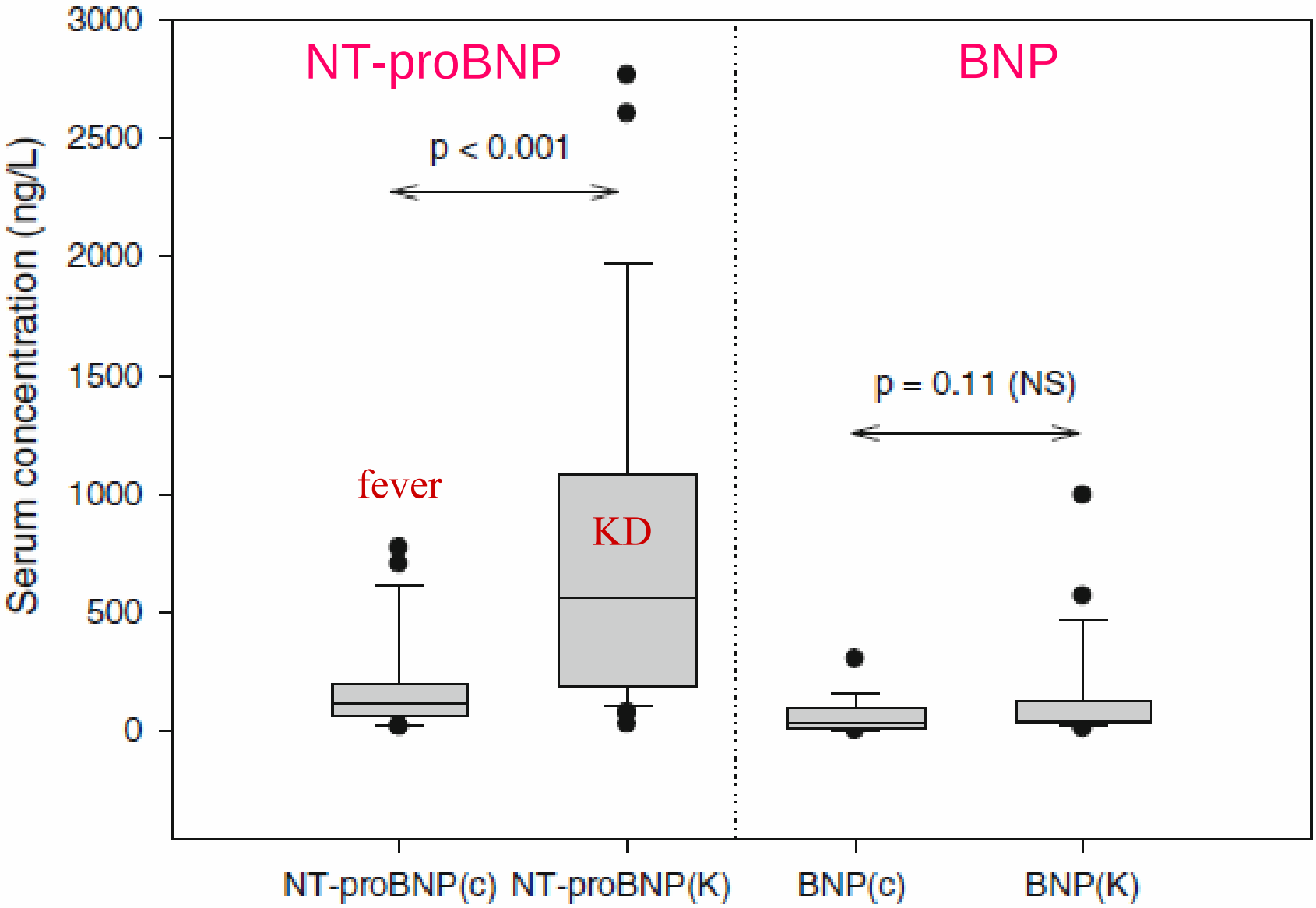




BNP and NT-proBNP in Kawasaki's disease

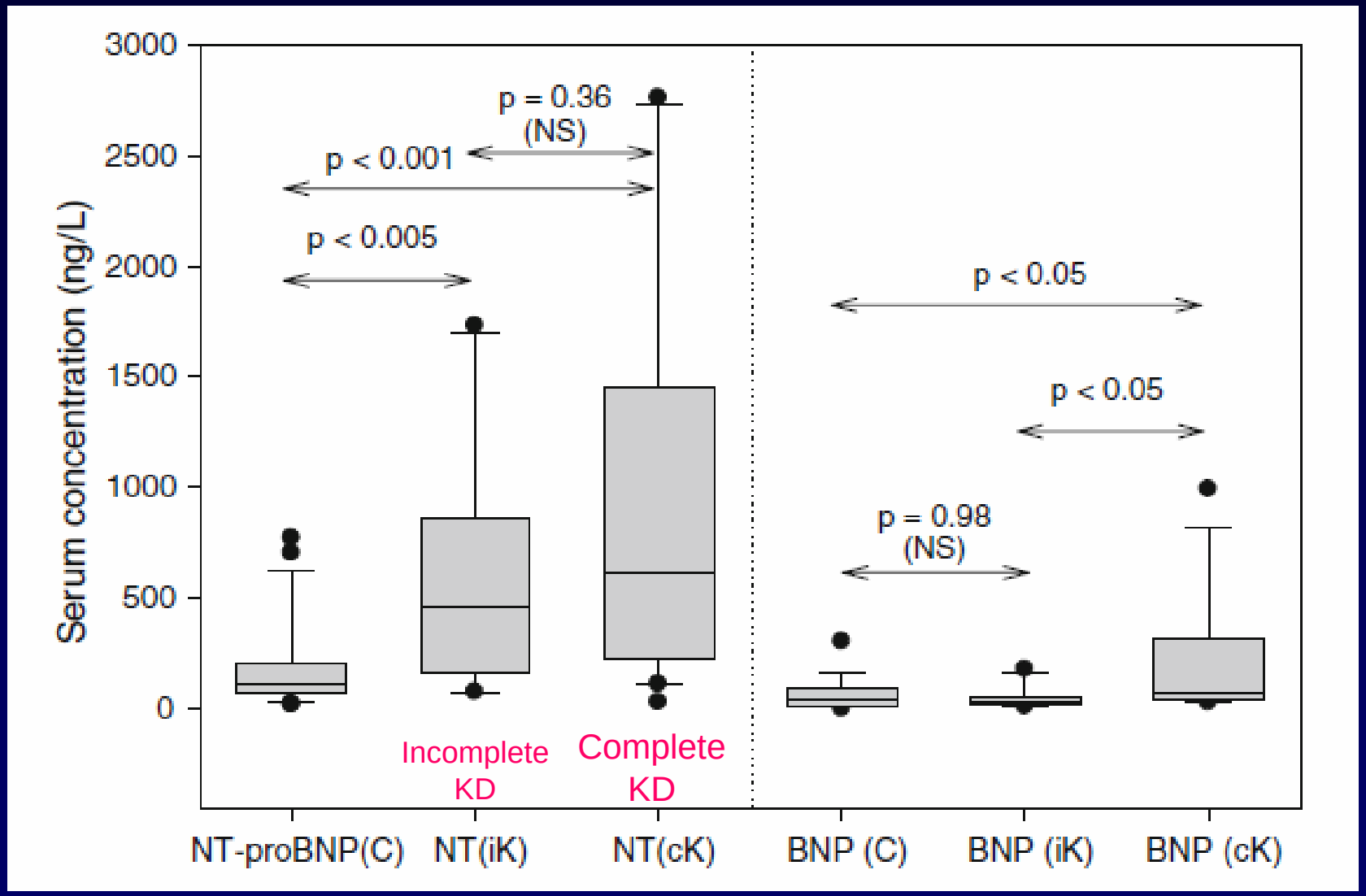
- Prospective study
  - 43 Newly diagnosed KD patients
  - 19 Non-KD febrile illness controls

Dahdah et al. (Montreal) Pediatr. Cardiol, Apr. 2009



Dahdah et al. (Montreal) Pediatr. Cardiol, Apr. 2009

Complete and incomplete KD



Dahdah et al. (Montreal) Pediatr. Cardiol, Apr. 2009

NT-proBNP cutoff in KD

- NT-proBNP cutoff value 170 ng/L
  - sensitivity of 78%
  - specificity of 63%

Dahdah et al. (Montreal) Pediatr. Cardiol, Apr. 2009

	n	NT-proBNP median	NT-proBNP range
Febrile non-cardiac	138	162	5-2891

Inbar Navo (avodat gemer, same assay)

BNP Is a Sensitive Screening Test for Acute Rejection in Pediatric Heart Transplant Patients

- 86 patients underwent a total of 560 endomyocardial biopsies.
- 59 episodes of acute rejection
- BNP levels were higher in patients with acute rejection
- In patients >1 year post-transplant, a BNP level of <100 pg/ml correlates with a 1% chance of acute rejection and may obviate the need for EMB in some cases.

Rossano, Towbin, MD, Dreyer,
J Heart Lung Transplant 2008;27:649 –54.

NT-proBNP as a Marker for Acute Anthracycline Cardiotoxicity in Children

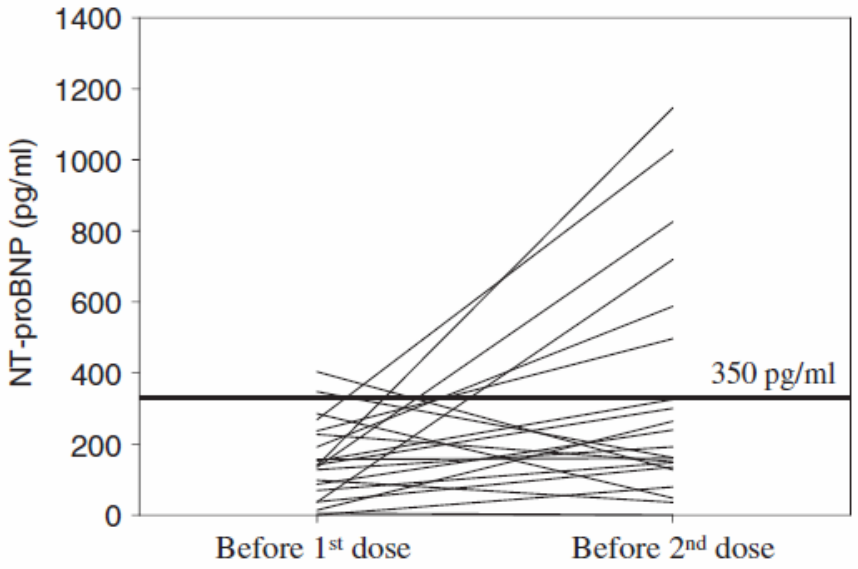


FIGURE 1. NT-proBNP (pg/mL) before the first and second anthracycline dose in pediatric oncology patients.

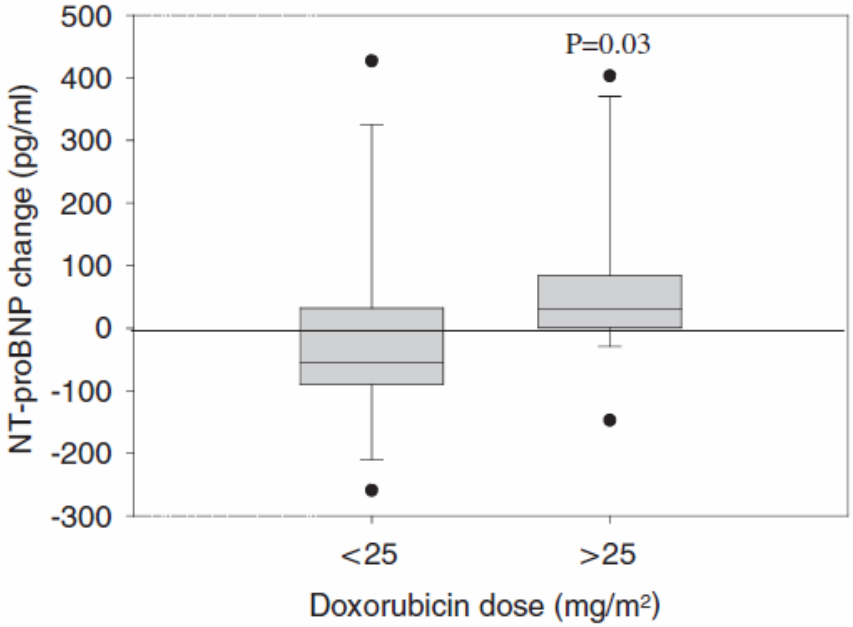


FIGURE 2. Relationship between first anthracycline dose and NT-proBNP differences (the change in NT-proBNP from baseline to after the first anthracycline dose).

Ekstein S, Nir A, Rein AJJT, Perles Z, Bar-Oz B, Salpeter L, Algur N, Weintraub M
J Pediatr Hematol Oncol 2007;29:440–444

“Prediction is very difficult, especially about the future"

Niels Bohr

Nobel price winner, physics 1922

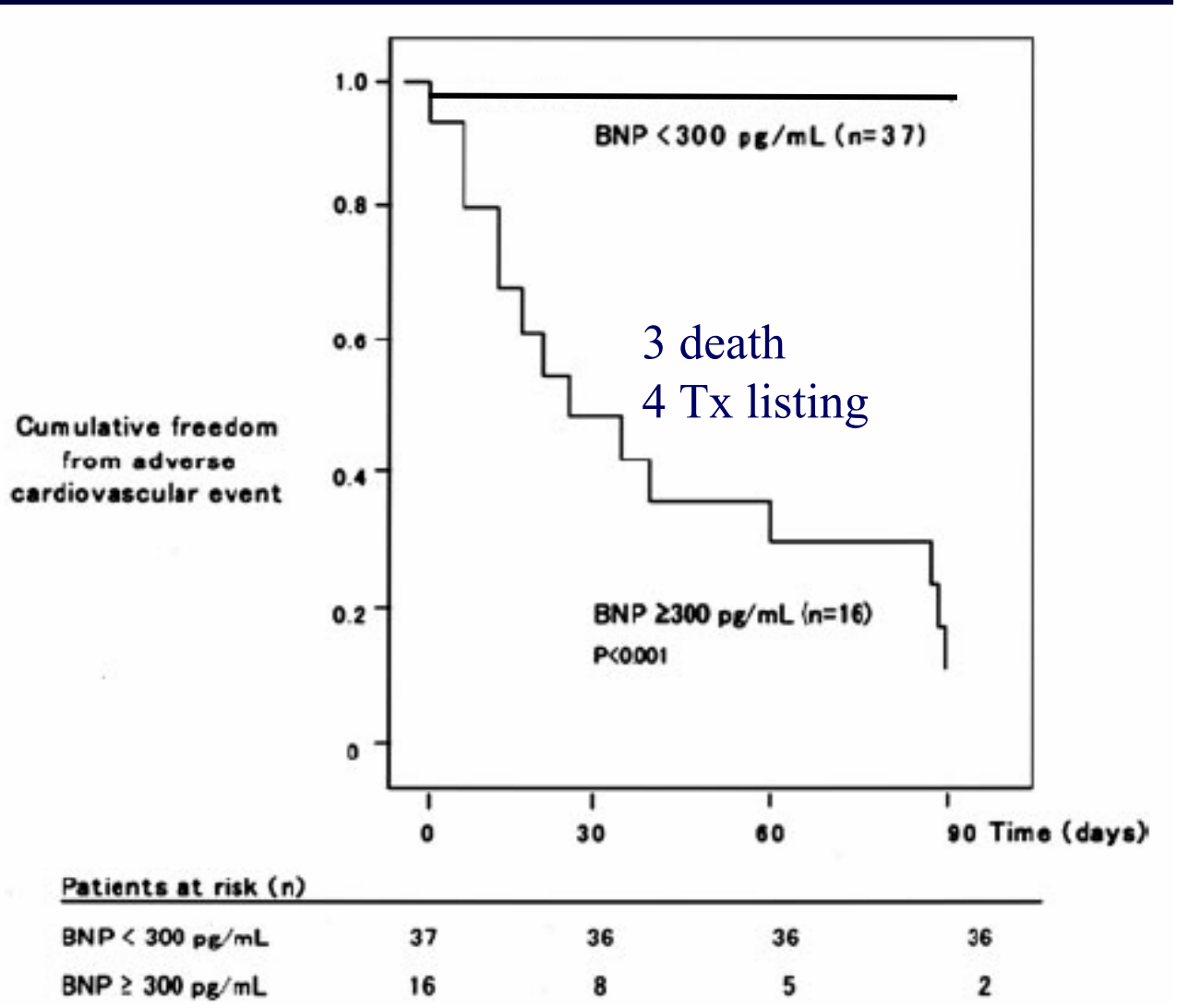
BNP predicts prognosis in pediatric chronic left ventricular dysfunction

- 53 children with chronic left ventricular systolic dysfunction
  - biventricular hearts
  - ejection fraction <50%
  - 3 months since diagnosis
- 90 days follow-up
- Adverse cardiovascular event
  - cardiac death
  - cardiac-related hospitalization
  - listing for cardiac transplantation

Price et al. *Circulation* 2006;114;1063

BNP predicts prognosis in pediatric chronic left ventricular dysfunction

adjusted hazard ratio
63.6; $P<0.0001$



Price et al.
Circulation 2006;114;1063

BNP and prognosis of pediatric chronic left ventricular dysfunction

- BNP had a better predictive value than
  - Heart failure signs and symptoms
  - Echocardiography
    - Left ventricular systolic function (LVEF)
    - Left ventricular dilatation (LVEDD)
    - Measures of diastolic dysfunction (MV E/Ea, MPI)

Price et al. *Circulation* 2006;114;1063

BNP in pediatric dilated cardiomyopathy

- Retrospective review of all BNP levels taken from 48 patients over a 2-year period
- Minimum follow-up 90 days
- 20 patients (42%) reached the combined endpoint
  - Death
  - Transplantation
  - listing for transplantation.

Mangat et al. (Great Ormond Street)
European Journal of Heart Failure, 2009;11, 48–52

BNP (1 month after acute episode) in pediatric dilated cardiomyopathy

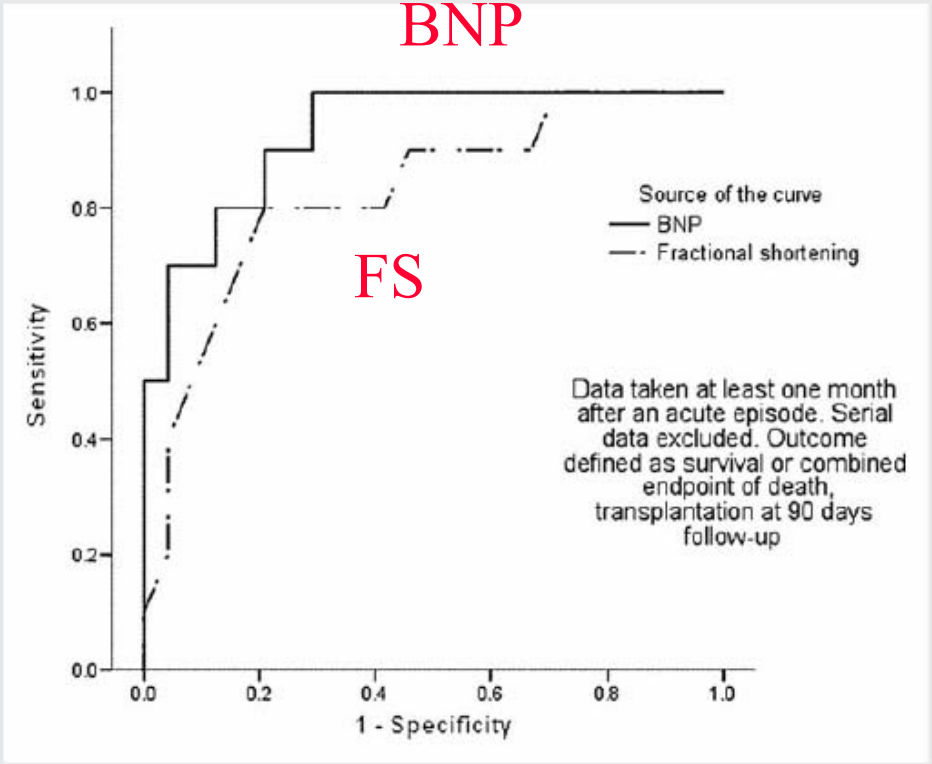


Figure 2 Receiver-operating characteristic curve 1 comparing brain natriuretic peptide to fractional shortening as predictors of outcome in chronic heart failure.

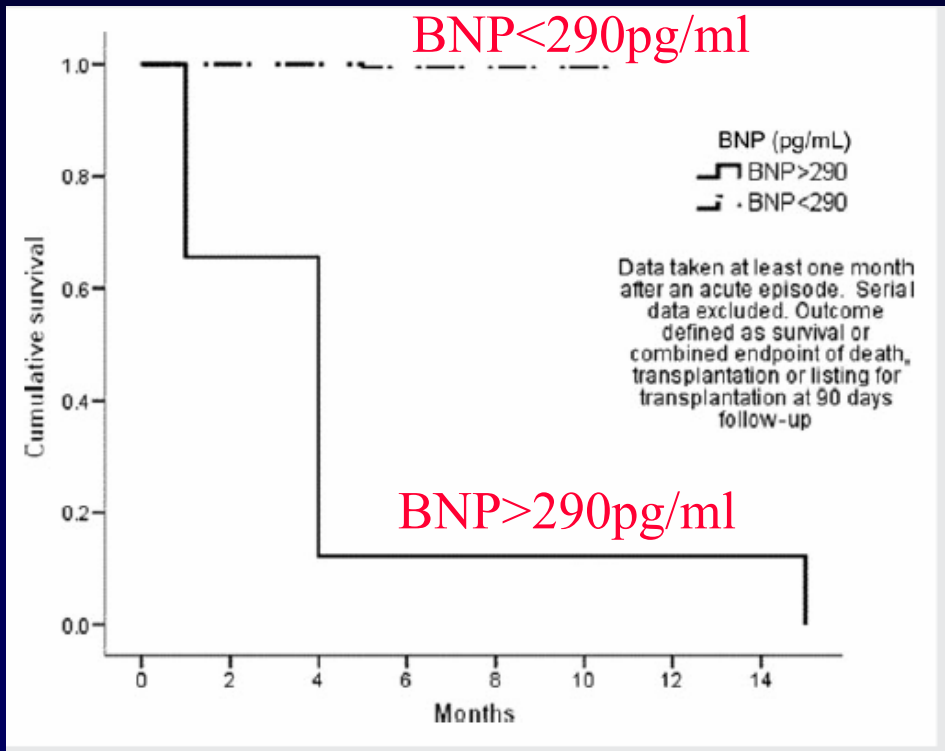


Figure 3 Cox regression analysis in chronic heart failure. Comparison of survival in patients with brain natriuretic peptide above or below 290 pg/mL at mean of covariates. Covariates include age, fractional shortening, clinical status, and tissue Doppler Lateral Sa.

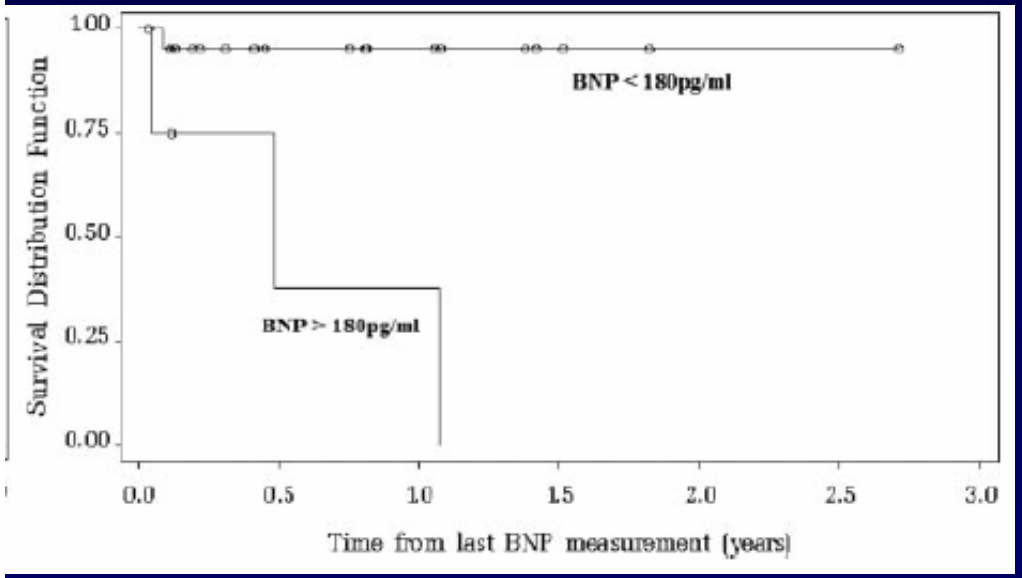
Mangat et al. Eu. J. Heart Failure, 2009;11, 48–52

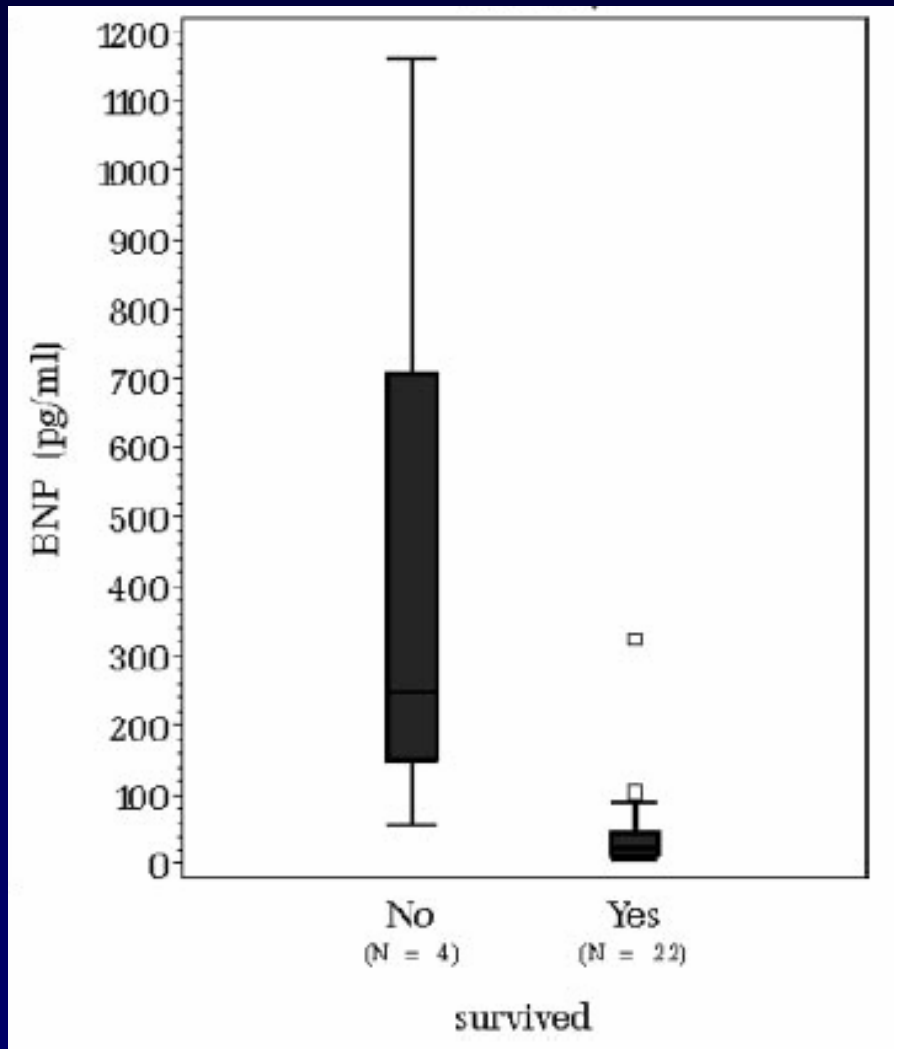
BNP in children with primary pulmonary hypertension

- BNP levels in patients with PHT
- 26/78 had primary PHT

Bernus et al. CHEST 2009; 135:745–751

Last BNP and survival in pediatric primary PHT





Bernus et al. CHEST 2009; 135:745–751

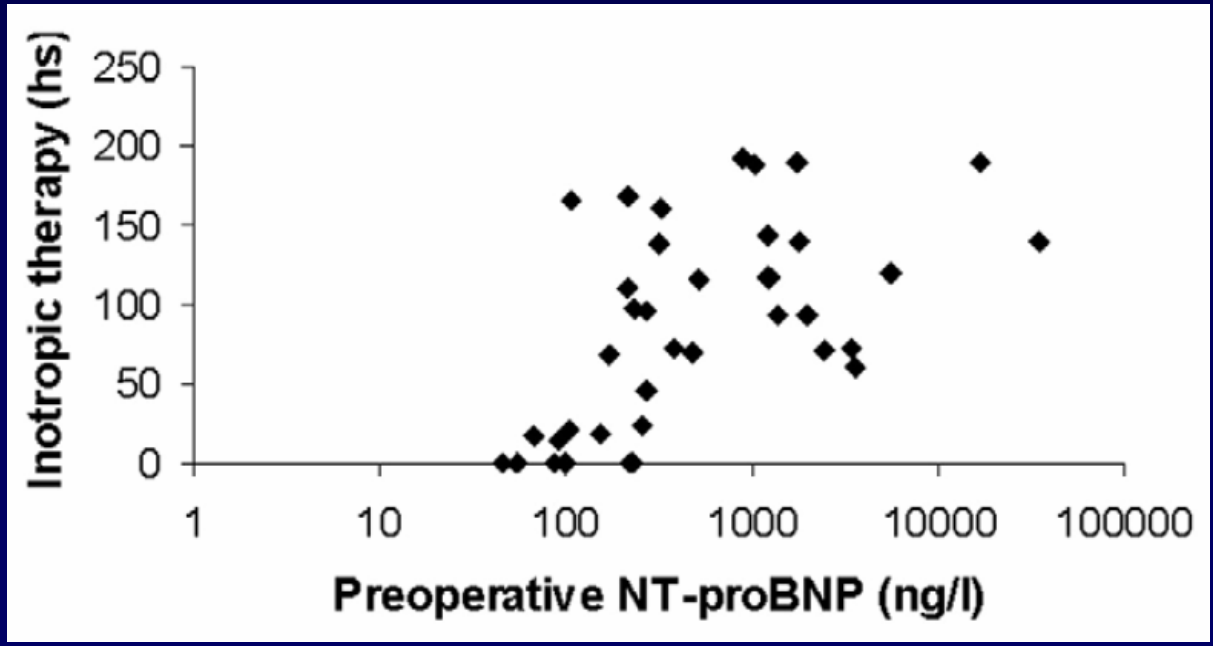
Prognostic value of NT-proBNP for cardiac surgery

- 40 children undergoing open heart surgery for congenital heart disease
- Potential pre-op predictors
  - NT-proBNP
  - Troponin T
  - Lactate
  - CRP
  - WBC

Gessler et al. *J Pediatr 2006;148:372*

Prognostic value of NT-proBNP

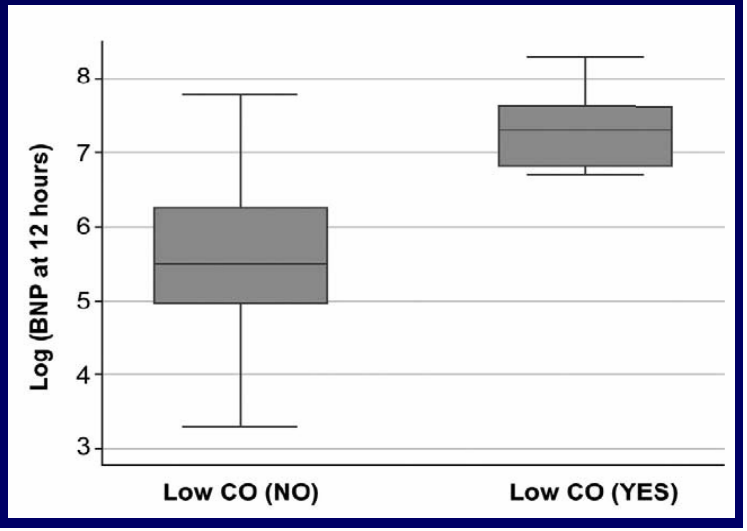
- NT-proBNP was the only predictor for the duration and score of post-operative inotropic support



Gessler et al. *J Pediatr 2006;148:372*

Post operative BNP predicts low cardiac output

- 51 infants and children undergoing surgery for congenital heart disease
- Elevated BNP 12 h post-op predicted low cardiac output state within 48 hours after surgery
  - sensitivity 87%
  - specificity of 90%



Shih et al. J Thorac Cardiovasc Surg 2006;131:632

BNP to Predict Ductus Intervention in Infants <28 Weeks

- 67 preterm infants < 28 wk (median 26)
- BNP on the second day of life in a prospective blinded study
- 24 patients received treatment
- Logistic stepwise regression analysis (gestational age, birthweight, BNP level, and LA/Ao-ratio) showed that BNP and LA/Ao-ratio were independent predictors of ductus intervention with a positive predictive value of 91%.

Czernik et al. ***Pediatr Res* 64: 286–290, 2008**

למה BNP גבוה מראה על שיבוש?

- ביוון העתיקה האמינו שיש 4 מרות / נוזלי גוף
  - מרה לבנה (Phlegm) - אדישות, עצלות
  - מרה שחורה - עצב, מלנכוליה
  - מרה צהובה (choleric) – כעס
  - דם (sanguine) – אופטימיות, שמחת חיים

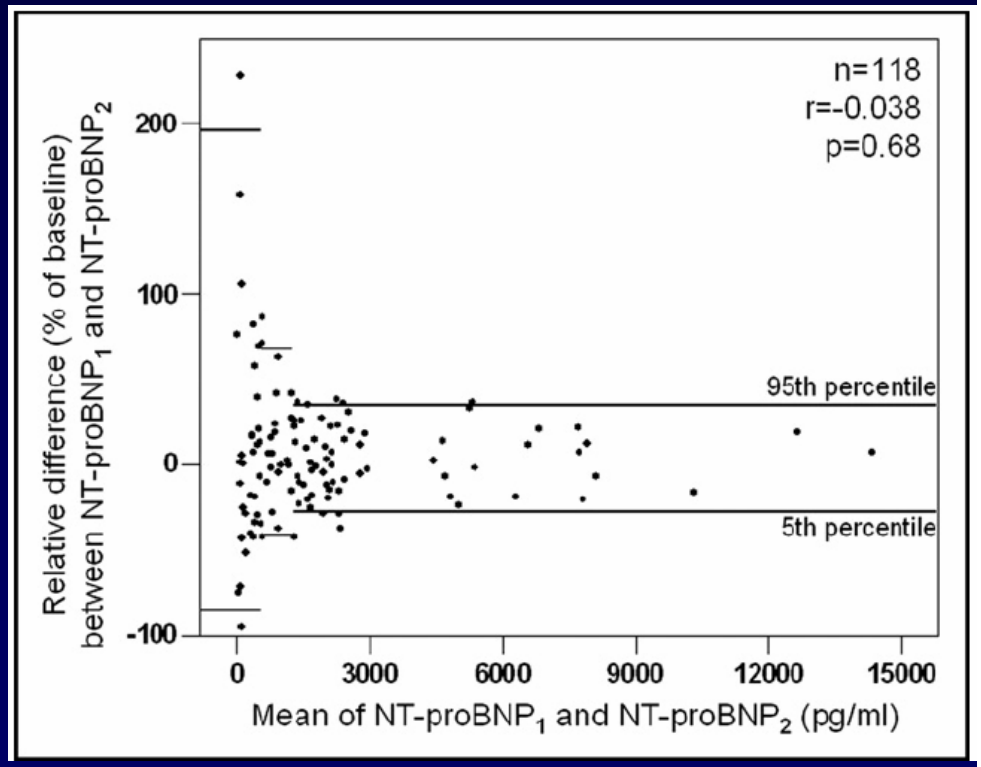
- חוסר איזון (dyskrasia) בין המרות מביא למחלה
- האם BNP הוא מדד לדיסקרזיה בלב?

Markham DW and de Lemos JA, European Heart Journal (2005)

False positive and false negative

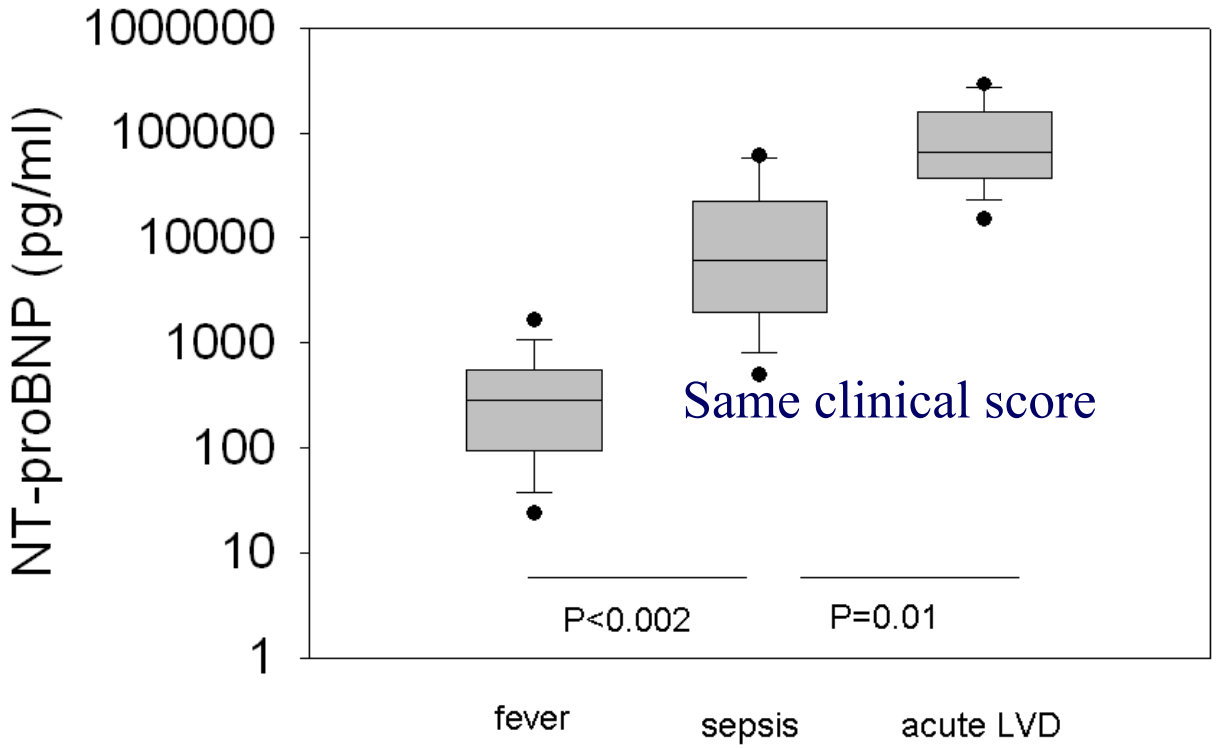
Intra-individual variations of NT-proBNP

- **Adults with chronic, stable HF**
- **3-week intervals**
- **If NT-proBNP >1,300 pg/ml, variations 30%-40% can be expected without clinical change**



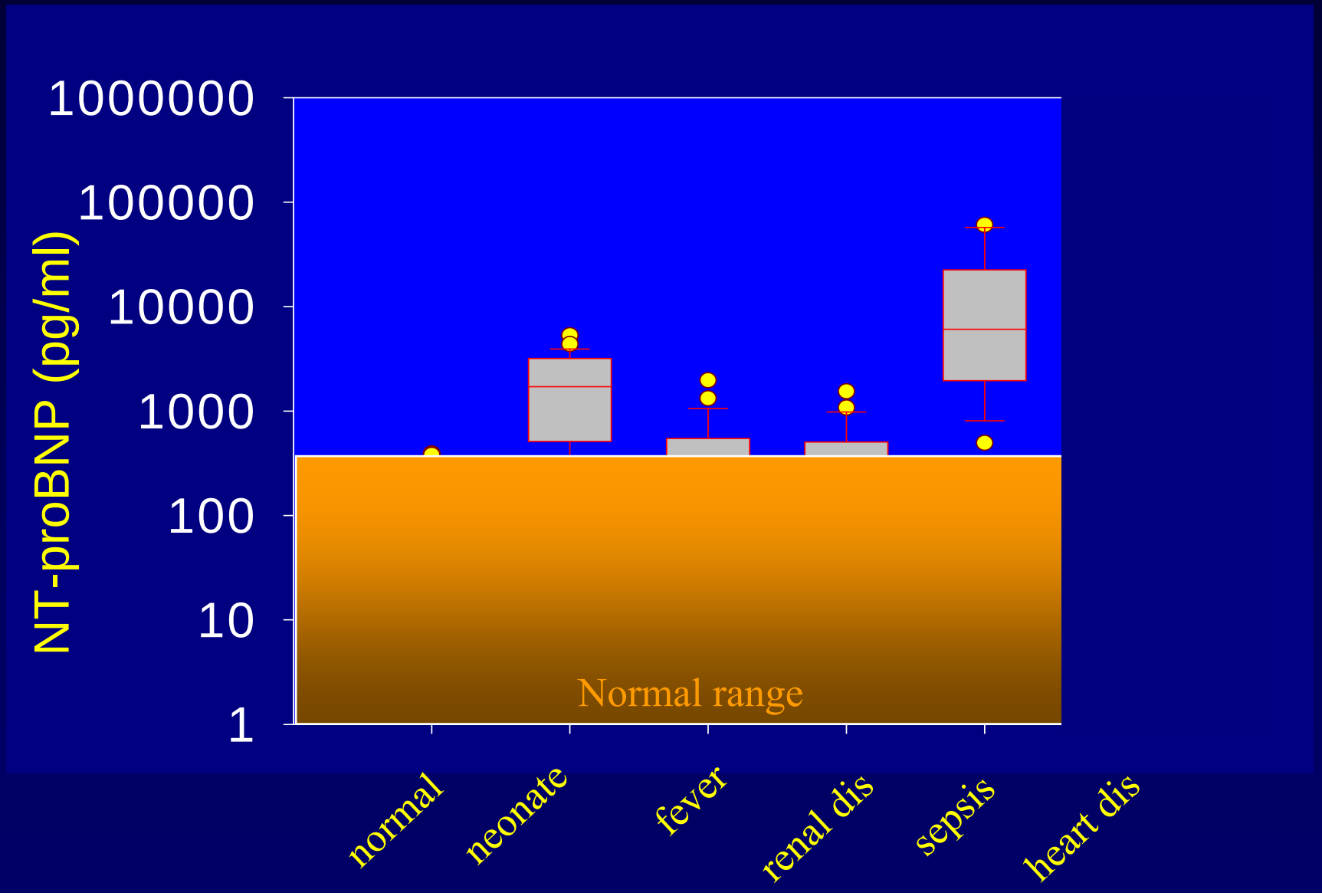
Araújo et al. **Am J Cardiol 2006;98:1248**

NT-proBNP in infants and children with sepsis



Fried et al. Pediatrics 118:e1165-8, 2006

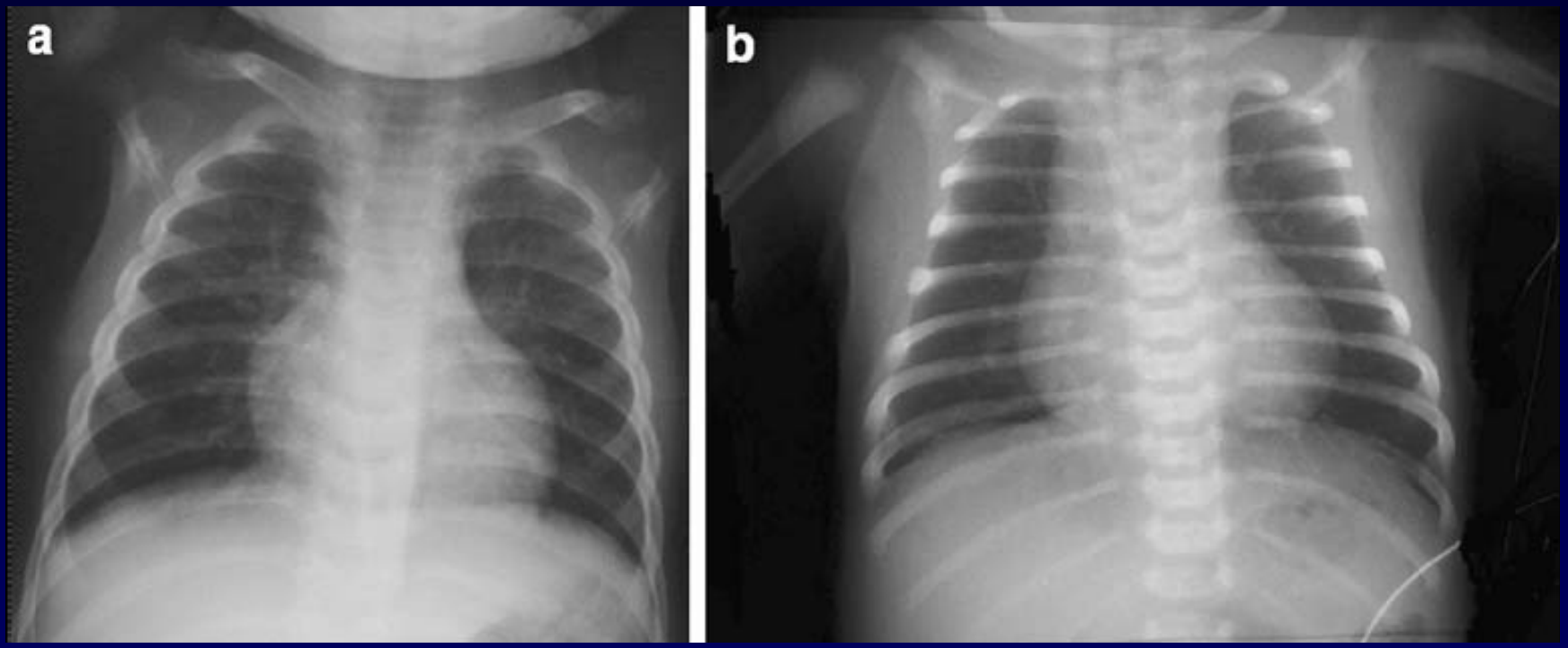
NT-proBNP may also be elevated in non-cardiac diseases



Natriuretic Peptide levels are affected by

- Age
- Gender (adult)
- Exercise
- Assay / Kit
- Disease
  - Renal
  - Liver
  - Endocrine
  - Fever

Chest X ray in infants and children



normal Hypoplastic left heart syndrome

5 pediatric radiologists with > 100 years of collective experience
71% accuracy to distinguish CHD from normal

Laya et al. Pediatr Radiol (2006) 36: 677–681

Practical points

- BNP is stable in whole blood at room temperature for at least 24 h
- NT-proBNP is stable in whole blood at room temperature for at least 72 h
- Both BNP and NT-proBNP are stable during freeze and thaw processes

Commercial kits

- Lab platforms
  - AxSYM BNP, Abbot
  - ADVIA centaur BNP, Bayer
  - Elecsys NT-proBNP, Roche Diagnostics
- Bedside
  - Triage BNP, Biosite
  - Cardiac Reader NT-proBNP, Roche Diagnostics
- Values are not comparable
- No conversion factor from BNP to NT-proBNP

So what does this mean?

- NT-proBNP use may improve the cardiac evaluation of infants and children
- It is not a "stand-alone" test
- It should not replace Hx, PE, or clinical judgment

Investigators and collaborators

- Nurit Algur
- Zvi Argaman
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- Shlomo Cohen
- Sivan Ekstein
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- Azaria JJT Rein
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- Lea Salpeter
- Chaim Springer
- Ori Wand
- Zeev Zonis
- Sagui Gavri