Chronic Heart Failure: Pathophysiology and Treatment in a nutshell and Natriuretic peptides in Heart Disease

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Heart Failure

- Final common pathway for many cardiovascular diseases whose natural history results in symptomatic or asymptomatic left ventricular dysfunction
- Cardinal manifestations of heart failure include dyspnea, fatigue and fluid retention
- Risk of death is 5-10% annually in patients with mild symptoms and increases to as high as 30-40% annually in patients with advanced disease

Main causes

- Coronary artery disease
- Hypertension
- Valvular heart disease
- Cardiomyopathy
- Cor pulmonale

New classification of heart failure

- **Stage A: Asymptomatic with no heart damage but have risk factors for heart failure**
- **Stage B: Asymptomatic but have signs of structural heart damage**
- **Stage C: Have symptoms and heart damage**
- **Stage D: Endstage disease**

ACC/AHA guidelines, 2001

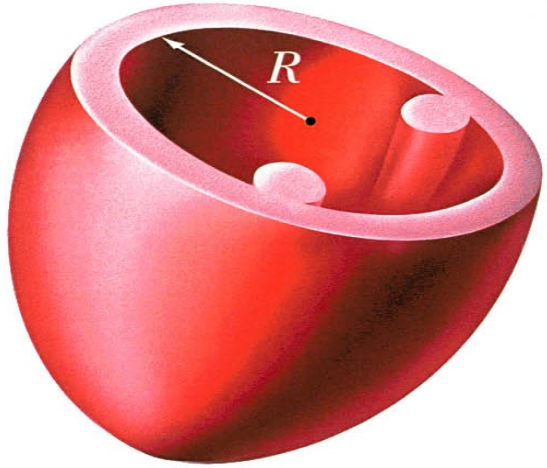
Types of heart failure

- Diastolic dysfunction or diastolic heart failure
- Systolic dysfunction or systolic heart failure

Inability of Heart to Pump enough Blood

Systolic- Large dilated heart with low EF

Diastolic- Limited by filling of heart



Factors aggravating heart failure

- Myocardial ischemia or infarct
- Dietary sodium excess
- Excess fluid intake
- Medication noncompliance
- Arrhythmias
- Intercurrent illness (eg infection)
- Conditions associated with increased metabolic demand (eg pregnancy, thyrotoxicosis)
- Administration of drug with negative inotropic properties or fluid retaining properties (e. NSAIDs, corticosteroids)
- Alcohol

NYHA Classification of heart failure

- Class I: No limitation of physical activity
- Class II: Slight limitation of physical activity
- Class III: Marked limitation of physical activity
- Class IV: Unable to carry out physical activity without discomfort

Compensatory changes in heart failure

- Activation of SNS
- Activation of RAS
- Increased heart rate
- Release of ADH
- Release of atrial natriuretic peptide
- Chamber enlargement
- Myocardial hypertrophy

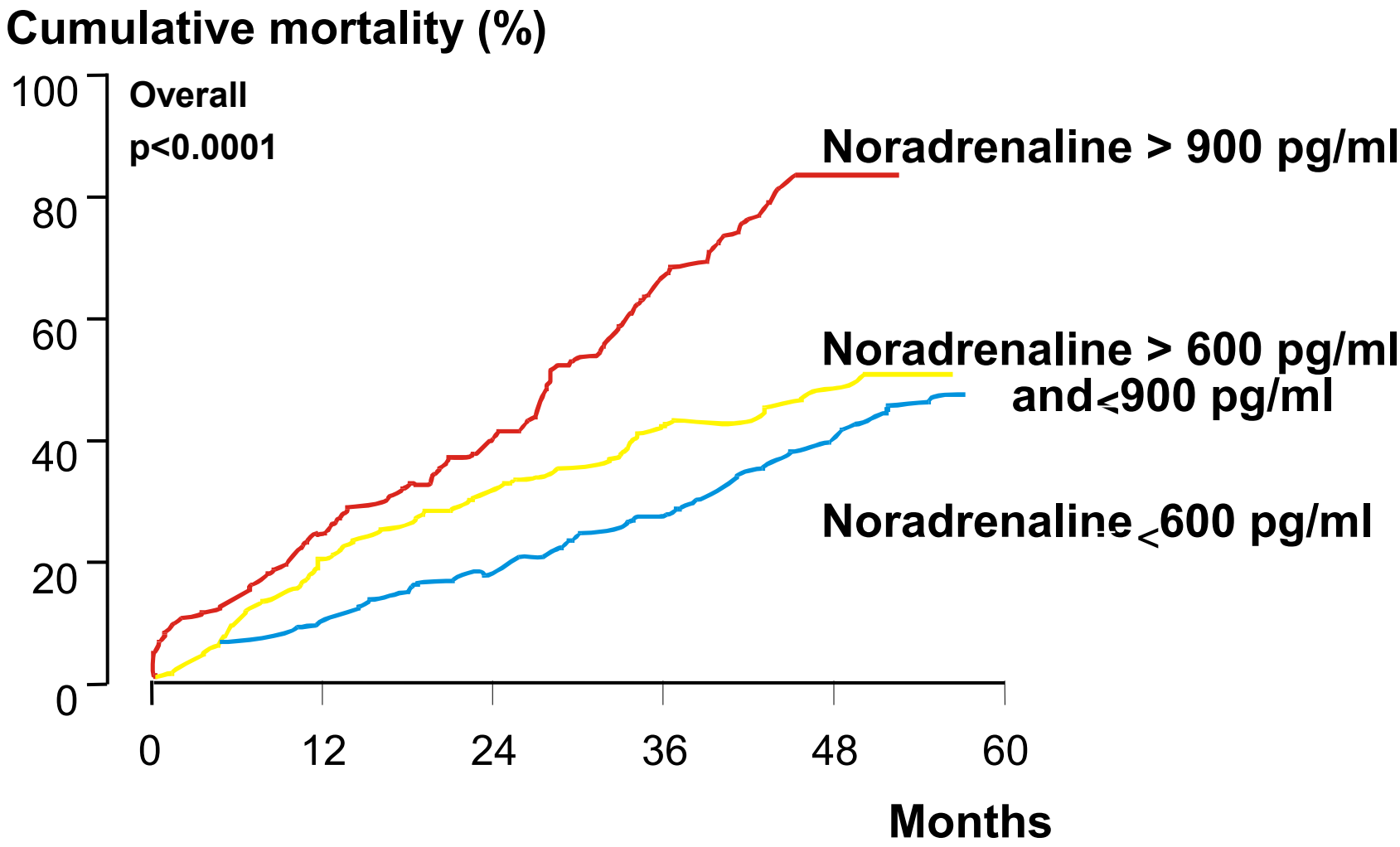
Effects of SNS Activation in Heart Failure

- **Dysfunction/death of cardiac myocytes**
- **Provokes myocardial ischemia**
- **Provokes arrhythmias**
- **Impairs cardiac performance**

These effects are mediated via stimulation of β and α_1 receptors

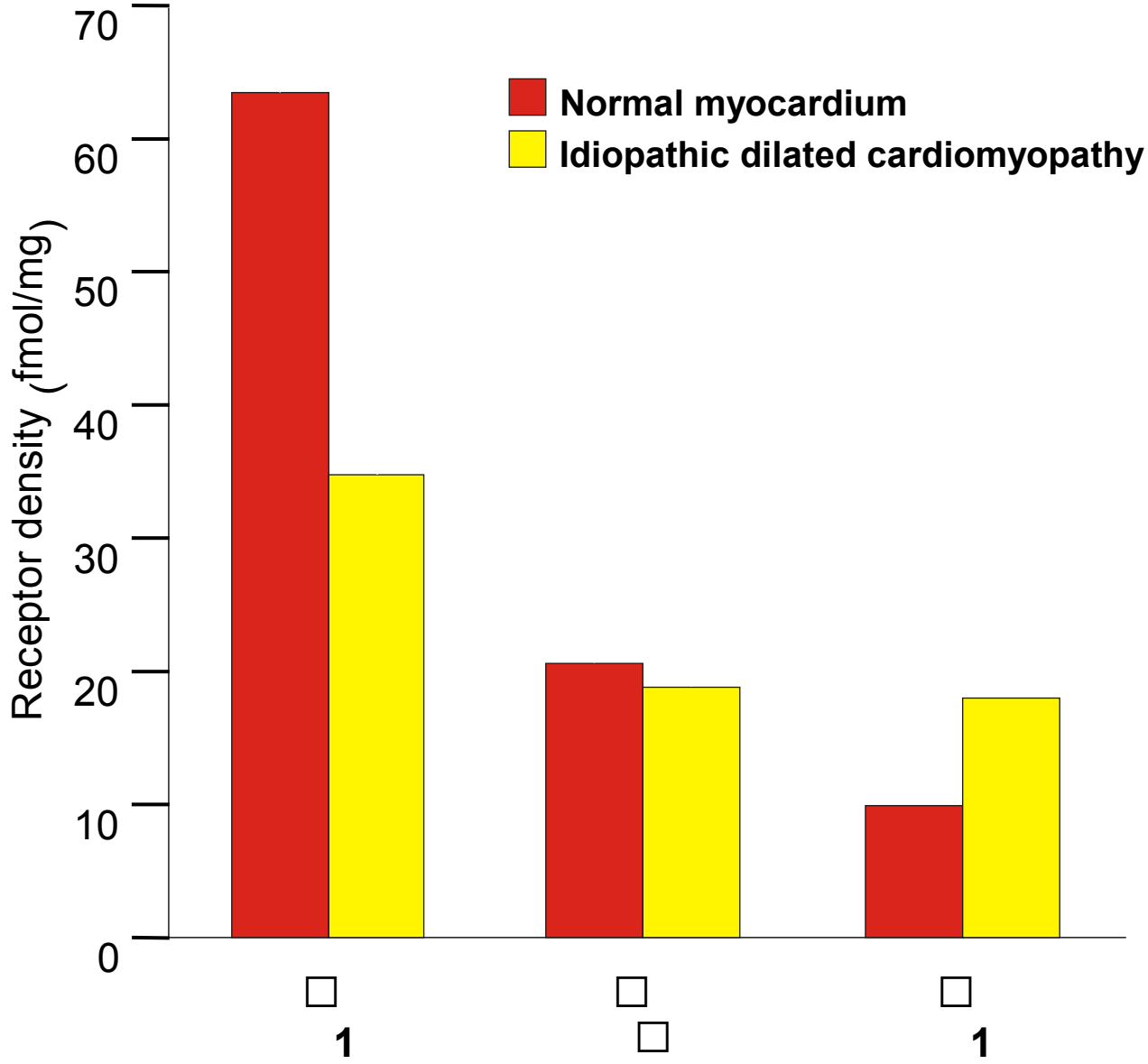
Am J Hypertens 1998; 11: 23S-37S

Relation between plasma noradrenaline and mortality in patients with heart failure



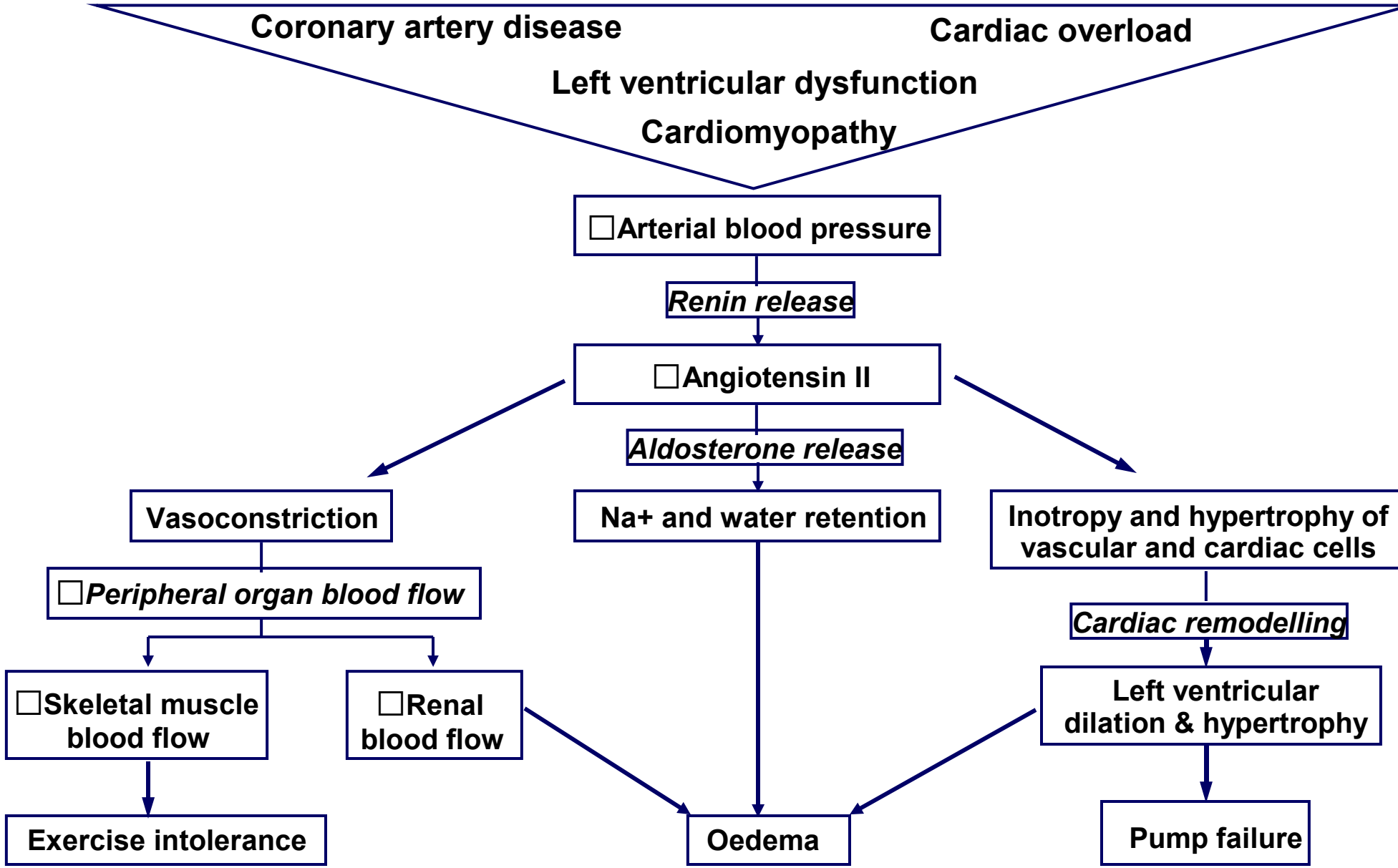
NEJM 1984; 311: 819-823

Receptor densities in human left ventricular myocardium

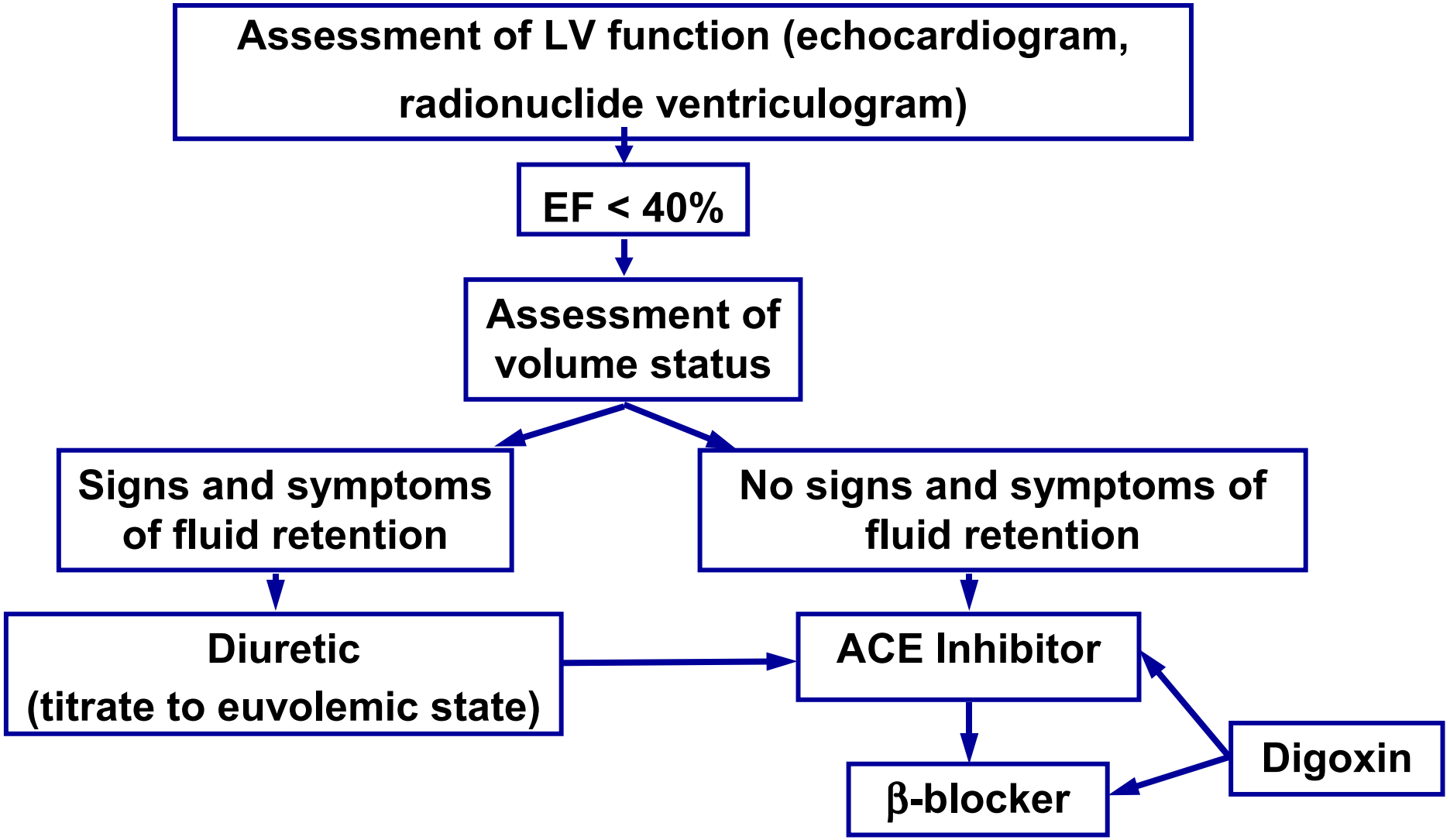


Scand Cardiovasc J 1998; Suppl 47:45-55

The role of angiotensin II in the progression of heart failure



Approach to the Patient with Heart Failure



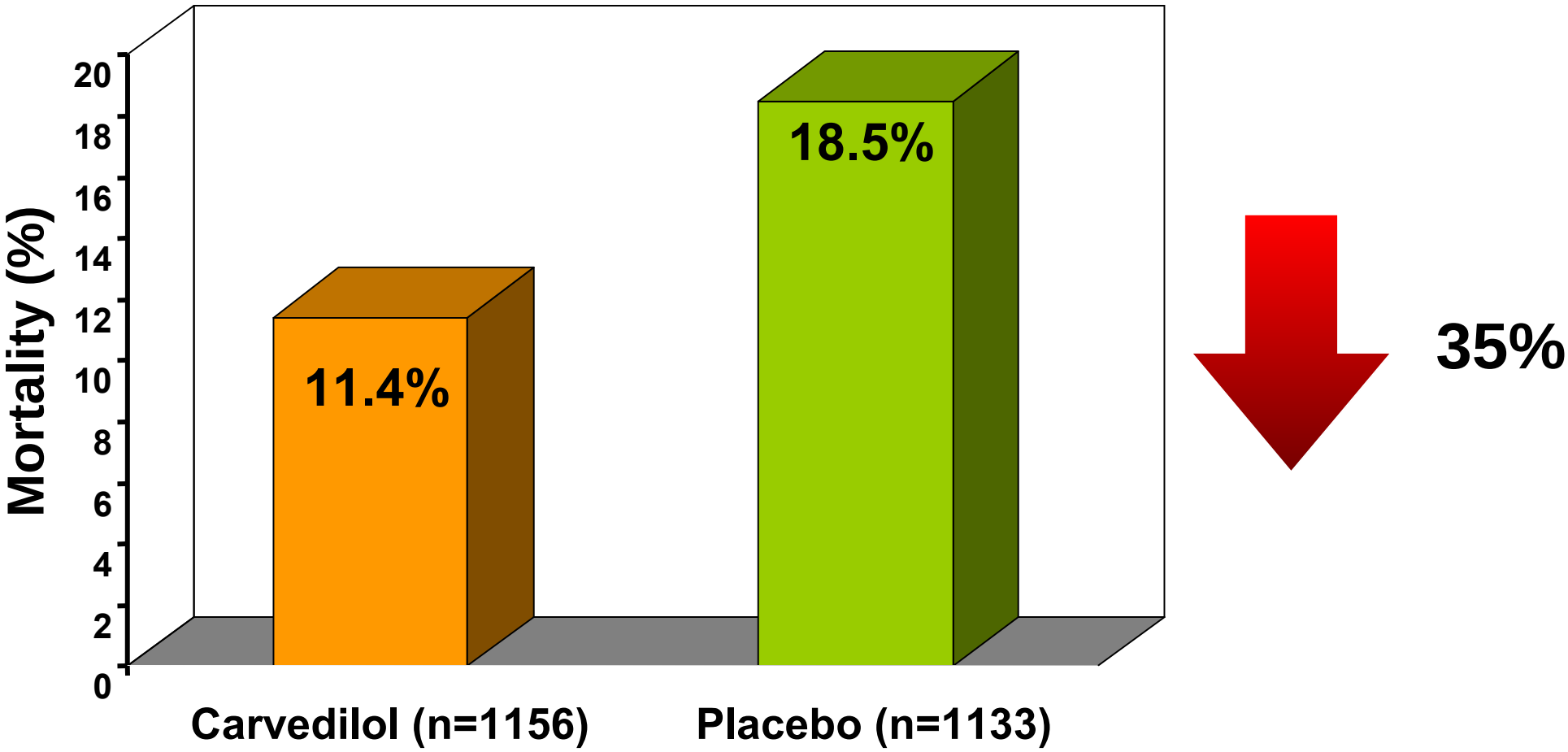
Goals of treatment

- To improve symptoms and quality of life
- To decrease likelihood of disease progression
- To reduce the risk of death and need for hospitalisation

Summary of drug treatment for CHF

Asymptomatic LV dysfunction	Mild to moderate CHF	Moderate to severe CHF
ACE inhibitor	Digoxin	Digoxin
Beta blocker	Diuretics	Diuretics
	ACE inhibitor	ACE inhibitor
	Beta blocker	Beta blocker
		Spironolactone

COPERNICUS: Effect on Mortality



22nd Congress of European Society of Cardiology, August 2000

Carvedilol in Heart Failure

- **Effective receptor-blockade approach to heart failure**
- **Negative inotropic effect counteracted by vasodilation**
- **Provides anti-proliferative, anti-arrhythmic activity and inhibition of apoptosis**
- **Prevents renin secretion**

Drugs of Today 1998; 34 (Suppl B): 1-23.

Dosage guidelines for Carvedilol in heart failure

Patient selection

- **Stable on background medications (diuretics, digoxin and/or ACE inhibitors)**
- **Not in a fluid-overload state**
- **Not hypotensive**

3.125 mg bid

2 weeks

Doubled every 2 weeks

Max dose 25 mg bid (<85 kg); 50 mg bid (>85 kg)

Before dose increase
Evaluate for

- **Worsening heart failure**
- **Vasodilation**
- **Bradycardia**

After each new dose initiation

- **Observe for signs of dizziness or light headedness for one hour**

Management of Complications

Transient worsening of heart failure (e.g. increasing dyspnea, decreasing exercise capacity)

- Increase dose of diuretic and/or ACE inhibitor
- If necessary, reduce carvedilol dose and/or prolong titration interval
- Search for other possible causes (e.g. thyroid malfunction, infection, non-compliant drug intake, excessive liquid intake, etc.)

Vasodilatory Symptoms (dizziness, light headedness, symptomatic hypotension)

- Decrease diuretic dose and, if necessary, ACE inhibitor dose
- If the cessation of both is not successful, reduce carvedilol dose and/or prolong titration interval

Management of Complications *(Contd.)*

Bradycardia (Pulse rate below 55 beats/min)

- Check and eventually reduce digitalis dose
- If necessary, reduce carvedilol dose and/or prolong titration interval
- Withdraw carvedilol only in the event that hemodynamics are affected

Symptoms of Bronchial obstruction

- Search for other possible causes (e.g., concurrent infection, subacute pulmonary edema)
- Reduce dose of, or withdraw, carvedilol only after possible causes for symptoms have been ruled out

Asymptomatic Patients

Enalapril (SOLVD Prevention Trial)

Patients with EF<35%

↓ HF progression, ↓ hospitalization

Captopril (SAVE, GISSI-3, ISIS-4)

Post MI patients with EF <40%

↓ overall mortality, ↓ re-infarction

↓ hospitalization, ↓ HF progression

Symptomatic Patients

Hydralazine + Isosorbide dinitrate

VHeFT-I: ↓ mortality, improved functional class as compared with use of digoxin and diuretics

VHeFT-II: proved less effective than enalapril

AIRE

- AIRE Study demonstrated efficacy of ramipril on mortality and morbidity in CHF post-MI NYHA class I-III patients
- 2006 patients enrolled in a double-blind, randomized, placebo-controlled study
- 27% reduction in the risk of death
- 23% decrease in progression to severe / resistant heart failure

Lancet 1993; 342:821-828

ACE Inhibitors: physiologic benefits

Arteriovenous Vasodilatation

- ↓ pulmonary arterial diastolic pressure
- ↓ pulmonary capillary wedge pressure
- ↓ left ventricular end-diastolic pressure
- ↓ systemic vascular resistance
- ↓ systemic blood pressure
- ↓ maximal oxygen uptake (MVO_2)

ACE Inhibitors: physiologic benefits

- ↑ LV function and cardiac output
- ↑ renal, coronary, cerebral blood flow
- No change in heart rate or myocardial contractility
- no neurohormonal activation
- resultant diuresis and natriuresis

ACE Inhibitors: clinical benefits

- Increases exercise capacity
- improves functional class
- attenuation of LV remodeling post MI
- decrease in the progression of chronic HF
- decreased hospitalization
- enhanced quality of life
- improved survival

Guidelines to ACE Inhibitor Therapy

- Contraindications
  - Renal artery stenosis
  - Renal insufficiency (relative)
  - Hyperkalemia
  - Arterial hypotension
  - Cough
  - Angioedema
- Alternatives: Hydralazine + ISDN, ARB

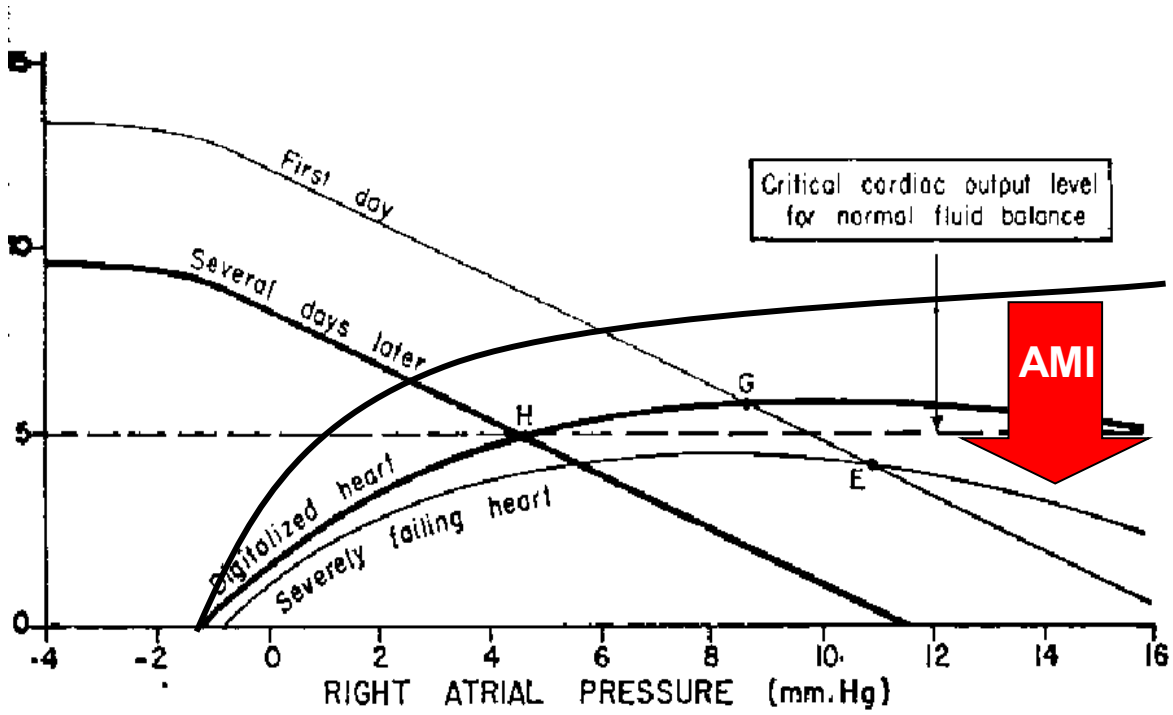
Guidelines to ACE Inhibitor Therapy

- All patients with symptomatic heart failure and those in functional class I with significantly reduced left ventricular function should be treated with an ACE inhibitor, unless contraindicated or not tolerated
- ACE inhibitors should be continued indefinitely
- It is important to titrate to the dosage regimen used in the clinical trials … in the absence of symptoms or adverse effects on end-organ perfusion
- In very severe heart failure, hydralazine and nitrates added to ACE inhibitor therapy can further improve cardiac output

Diuretics

- Indicated in patients with symptoms of heart failure who have evidence of fluid retention
- Enhance response to other drugs in heart failure such as beta-blockers and ACE inhibitors
- Therapy initiated with low doses followed by increments in dosage until urine output increases and weight decreases by 0.5-1kg daily

Effect of treatment and some spontaneous recovery on cardiac and vascular function curve



Guyton AC.Textbook of Medical Physiology, 5th Ed. 1976 p343

Digoxin

- Enhances LV function, normalizes baroreceptor-mediated reflexes and increases cardiac output at rest and exercise
- Recommended to improve clinical status of patients with heart failure due to LV dysfunction and should be used in conjunction with diuretics, ACE inhibitors and beta-blockers
- Also recommended in patients with heart failure with AF
- Digoxin initiated and maintained at a dose of 0.25 mg daily
- Adverse effects include cardiac arrhythmias, GI symptoms and neurological complaints (eg. visual disturbances, confusion).

Anemia and Mortality in Heart Failure Patients

A Systematic Review and Meta-Analysis

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Groningen and Deventer, the Netherlands; and Boston, Massachusetts

J Am Coll Cardiol 2008;52:818–27

Results

Anemia was defined by criteria used in the original articles. Of the 153,180 CHF patients, 37.2% were anemic.

After a minimal follow-up of 6 months, 46.8% of anemic patients died compared with 29.5% of nonanemic patients. Crude mortality risk of anemia was odds ratio 1.96 (95% confidence interval: 1.74 to 2.21, $p<0.001$).

Lower baseline hemoglobin values were associated with increased crude mortality rates ($r=-0.396$, $p=0.025$). Adjusted hazard ratios showed an increased adjusted risk for anemia (hazard ratio 1.46 [95% confidence interval: 1.26 to 1.69, $p<0.001$]). Subgroup analysis showed no significant difference between mortality risk of anemia in diastolic or systolic CHF.

Methods

A systematic literature search in MEDLINE (through November 2007) for English language articles was performed.

In addition, a manual search was performed. We included cohort studies and retrospective secondary analyses of randomized controlled trials whose primary objective was to analyze the association between anemia and mortality in CHF. Of a total of 1,327 initial studies, we included 34 studies, comprising 153,180 patients.

Information on study design, patient characteristics, outcome, and potential confounders were extracted.

Conclusions

Anemia is associated with an increased risk of mortality in both systolic and diastolic CHF. Anemia should, therefore, be considered as a useful prognosticator, and therapeutic strategies aimed to increase hemoglobin levels in CHF should be investigated.

(J Am Coll Cardiol 2008;52:818–27)

Table 3 Definitions of Anemia Used in the Original Articles

Definition of Anemia	Author (Ref. #)
WHO	Elabbassi et al. (8), Maraldi et al. (11), De Silva et al. (42), Go et al. (3), Komajda et al. (10), Formiga et al. (18), Hebert et al. (25), O'Meara et al. (36), Felker et al. (13), Ralli et al. (16), Grigorian Shamagian et al. (14), Rosolova et al. (35), Gardner et al. (19), Ezekowitz et al. (24), van der Meer et al. (30), Kerzner et al. (40), Mozaffarian et al. (37), Schou et al. (17)
Hb <11.5 g/dl	Kalra et al. (26)
Hb <12.0 g/dl	Varadarajan et al. (6), Anand et al. (1), Szachniewicz et al. (33), Tanner et al. (32)
Hb <12.3 g/dl	Horwich et al. (9)
Hb <13.0 g/dl	Sharma et al. (34)
Hb <11.0 g/dl in women and Hb <12.0 g/dl in men	Maggioni et al. (Val-HeFT) (5), Maggioni et al. (IN-CHF) (5)
Hb <11.5 g/dl in women and <13.0 g/dl in men	Berry et al. (7), Newton and Squire (15)
Ht <35%	Al-Ahmad et al. (12)
Ht ≤37%	Kosiborod et al. 2003 (39), McClellan et al. (38)
Ht <37%	Terrovitis et al. (31)
Ht <37% in women and <40% in men	Kosiborod et al. 2005 (4)

Table 5 Definitions of Systolic and Diastolic HF Used in the Original Articles

	LVEF (%)
Systolic CHF	
Mozaffarian et al. (37), Anand et al. (1)	<30
Komajda et al. (10), Terrovitis et al. (31)	<35
Sharma et al. (34), Ralli et al. (16), Maggioni et al. (5), Kerzner et al. (40), Kosiborod et al. (4), O'Meara et al. (36), Felker et al. (13)	<40
Schou et al. (17)	<45
Diastolic CHF	
Kerzner et al. (40), Kosiborod et al. (4), O'Meara et al. (36), Felker et al. (13)	>40
Grigorian Shamagian et al. (14)	>50

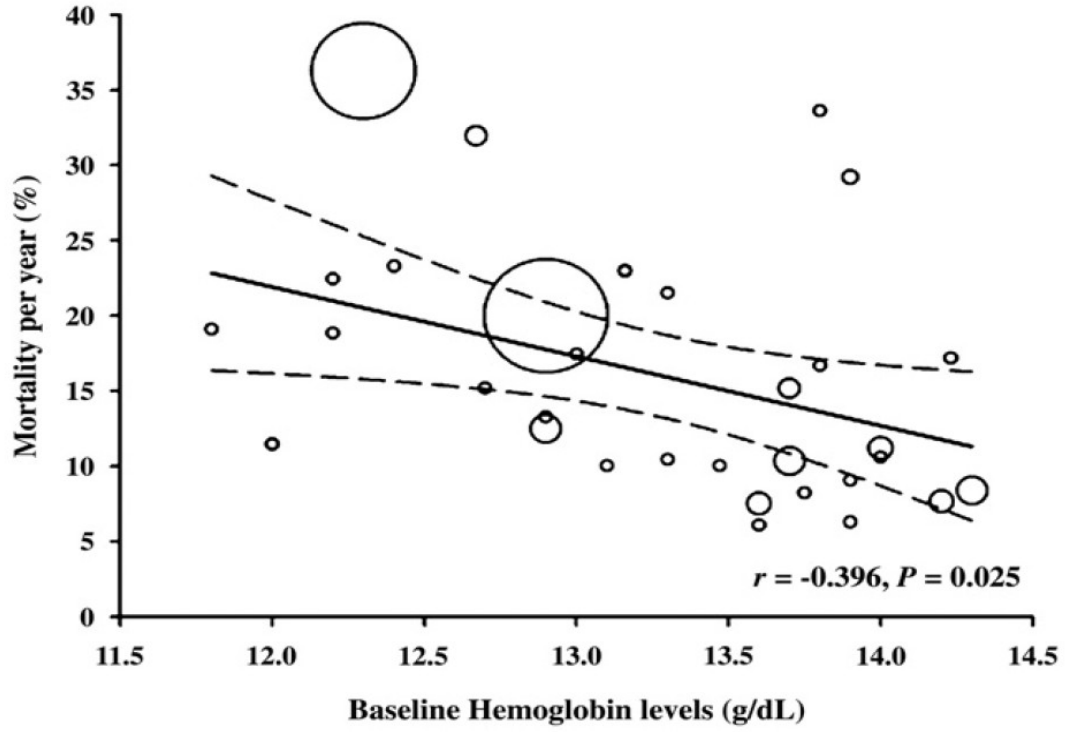


Figure 4 **Relationship Between Baseline Hemoglobin and Annual Mortality**

***Findings from intervention studies*. Considering the increased mortality risk caused by anemia, in heart failure as well as renal failure, trials have been designed in which patients receive erythropoiesis-stimulating proteins (ESPs) to increase Hb levels. The first intervention study to address the efficacy of EPO in CHF patients was performed by Silverberg et al. in 32 patients. Correction of anemia with EPO and intravenous iron led to a significant increase in left ventricular ejection fraction and decrease in NYHA functional class, which was reflected by almost 90% reduction in the number of hospitalizations. A similar study showed that EPO treatment significantly increased peak oxygen consumption and exercise duration in patients with moderate-to-severe CHF.**

Recently, 2 substantially larger multicenter phase II studies evaluated the effects of darbepoetin (a long-acting ESP) on surrogate cardiovascular end points. Treatment with darbepoetin was safe and effectively raised Hb.

Moreover, it significantly improved clinical status; however, no significant improvement in exercise tolerance could be observed.

However, recently several studies showed a potentially harmful effect of ESP treatment in patients with kidney disease and malignancies. A meta-analysis in patients with cancer-associated anemia showed an increased risk in venous thromboembolism and mortality associated with recombinant EPO and darbepoetin administration.

Furthermore, concerns about the cardiovascular safety of ESP in patients with kidney disease have been raised. Two separate studies showed that patients targeted to a higher Hb level had an increased incidence of cardiovascular events. However, in these studies, no placebo groups were included. These studies were all performed in patients with severe renal failure, and only a minority of patients suffered from heart failure. Consequently, the results of the studies mentioned in the preceding text cannot be extrapolated to the CHF population.

Conclusions

Anemia is present in one-third of the CHF population and is an independent risk prognosticator for mortality in subjects so affected, irrespective of a systolic versus diastolic etiology of CHF. Further research is needed to assess the effect of correcting anemia in CHF patients.

Natriuretic Peptides: The Heart as a Secretory Organ

- Atrial stretch receptors link blood volume to renal function
- Distension of a balloon catheter in atria of dogs resulted in diuresis

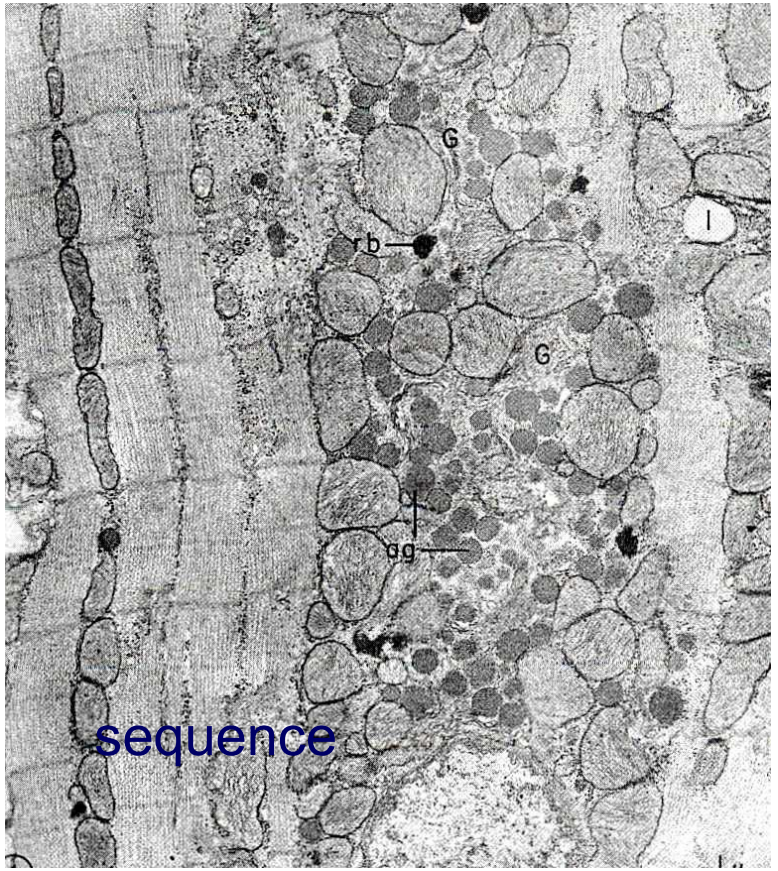
Henry et al (1956)

- Secretory granules discovered in the atria

Kisch (1956)

Jamieson and Palade (1964)

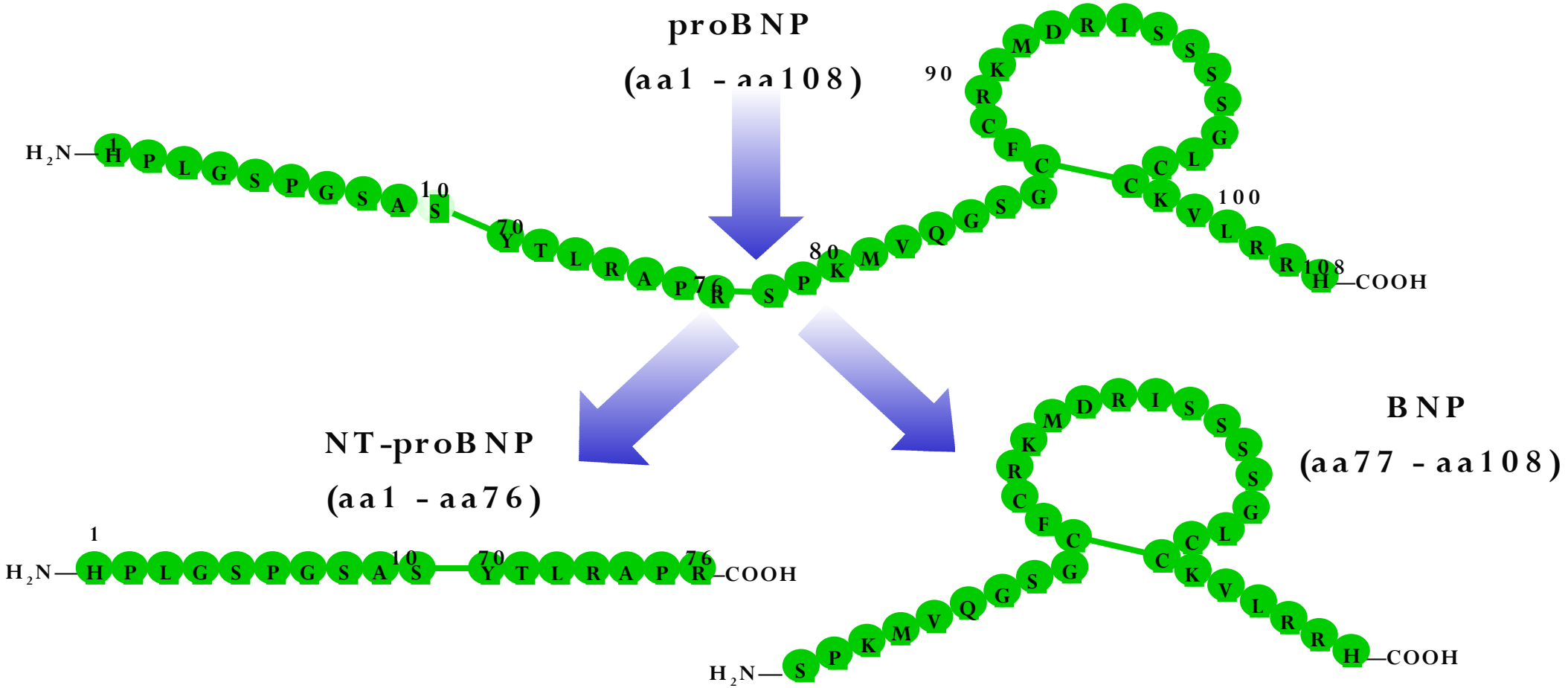
- BNP was characterized by amino acid and DNA clones



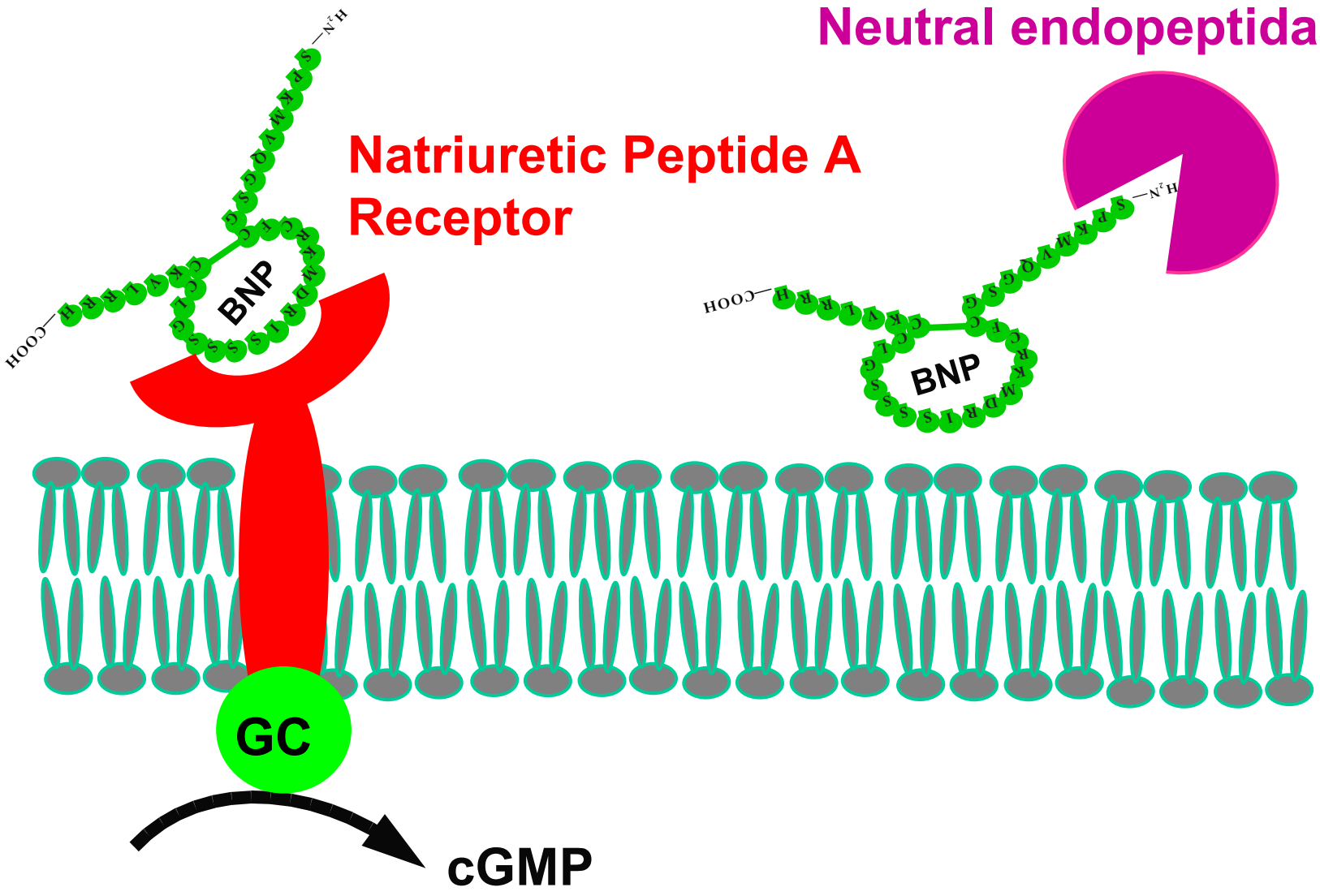
sequence

Jamieson and Palade. *J Cell Biol.* 1964;23:151.

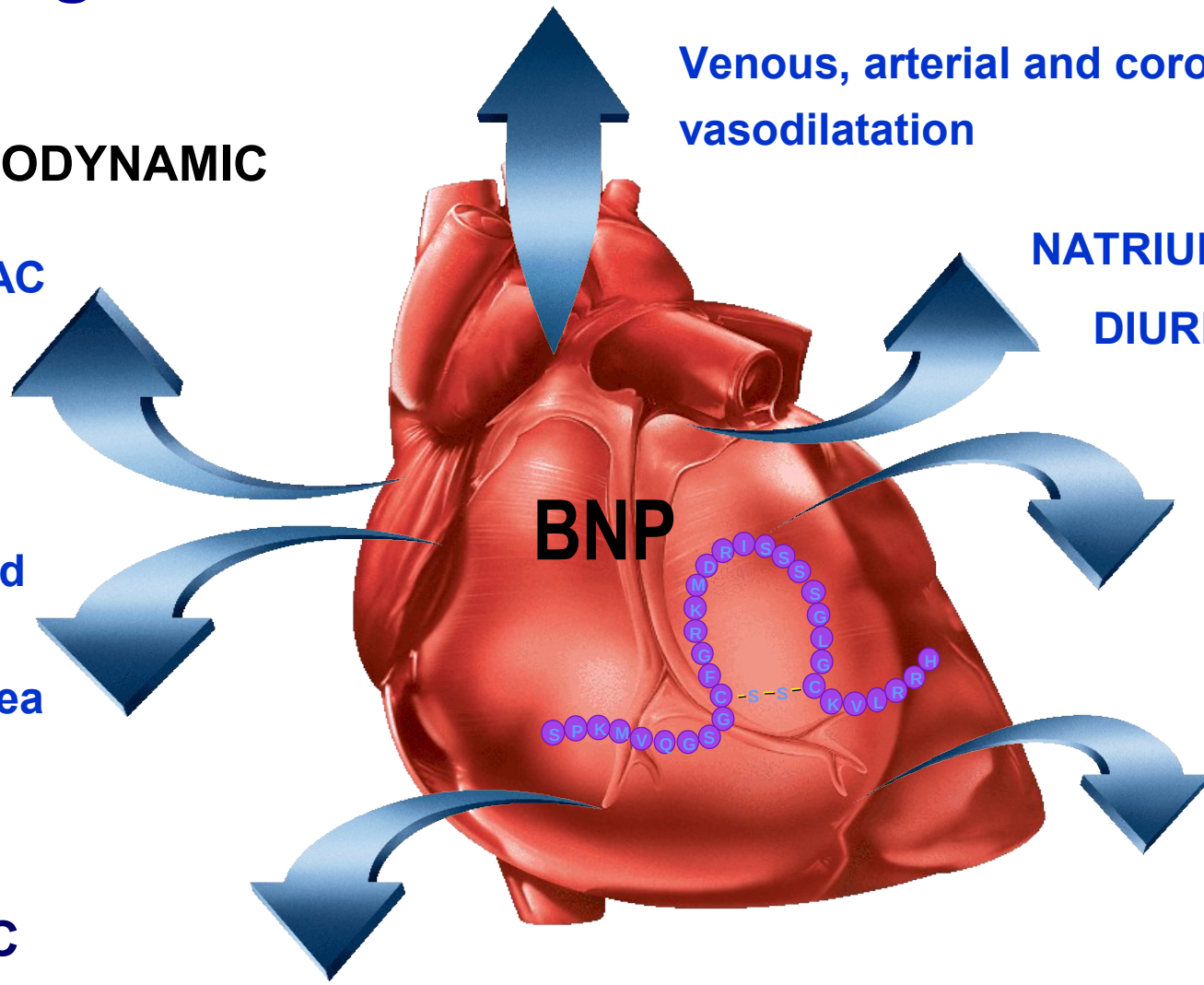
Enzymatic Cleaving of proBNP



Physiology of receptors and elimination of BNP



Physiologic effects of BNP



HEMODYNAMIC

Venous, arterial and coronary vasodilatation

CARDIAC INDEX

Preload

Afterload

PCWP

Dyspnoea

RENAL

NATRIURESIS

DIURESIS

Fluid volume

Preload

Diuretic usage

CARDIAC

Lusitropic effect

No increase in HR

Not proarrhythmic

Aldosterone

Endothelin

Norepinephrine

SYMPATHETIC AND NEUROHORMONAL SYSTEMS

Introduction

The heart is an extremely efficient and resilient pump, but is also an important endocrine organ that functions together with other physiological systems to control .fluid volume

The natriuretic peptides are natural antagonists for the sympathetic nervous system and the renin- .(angiotensin-aldosterone system (RAAS

BNP Consensus Panel 2004. Congestive Heart Failure 2004; 10(5)

Physiologic purpose of BNP

The main physiological function of the natriuretic peptides is homeostasis and protection of the cardiovascular and other systems from the effects of .volume overload

BNP Consensus Panel 2004. Congestive Heart Failure 2004; 10(5)

BNP Elevations- not only with left HF

Right sided heart failure

- Cor pulmonale: 200-500 pg/mL
- Primary pulmonary hypertension: 200-500 pg/mL
- Acute pulmonary embolism: 150-500 pg/mL

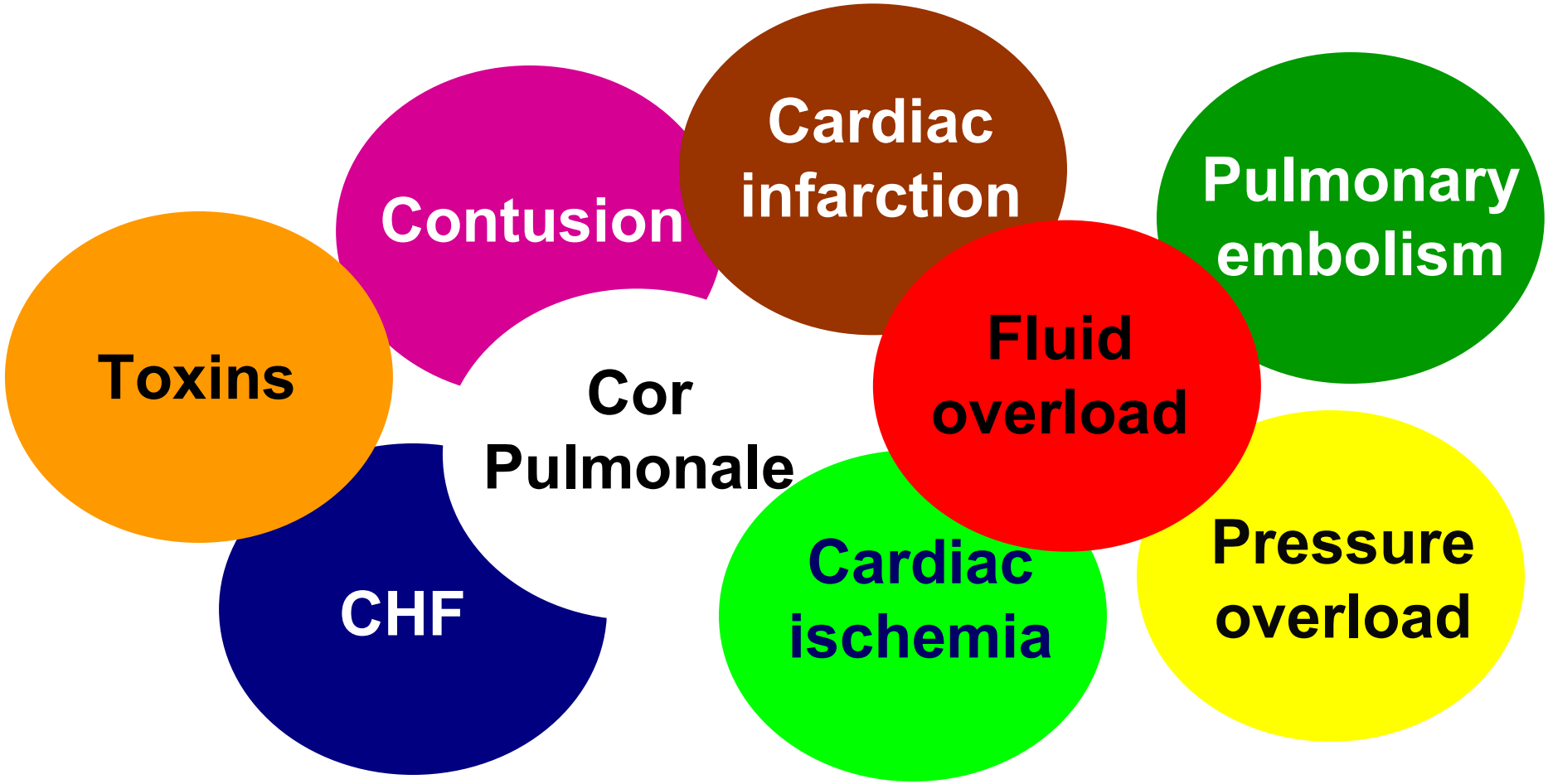
Non heart failure elevations

- Acute coronary syndromes: 40 - 400 pg/mL
- Acute myocardial infarction: 40 - >1300 pg/mL
- End-stage renal disease: 80 - >1300 pg/mL

BNP is a *specific marker* of cardiac disease. Its level is augmented in any condition involving myocardial stress.

It does not point to the specific cause of heart strain.

BNP or NT-proBNP level is augmented in any condition involving myocardial stress



Elevated levels of BNP and NT-proBNP in heart failure: A diagnostic opportunity

The BNP and NT-proBNP are established assays used to diagnose and rule out HF in the emergency room.

Their negative predictive value is > 95%, and the assays are incorporated in diagnostic algorithms.

BNP level increases following volume or pressure load on the myocardium or a portion of it regardless of cause.

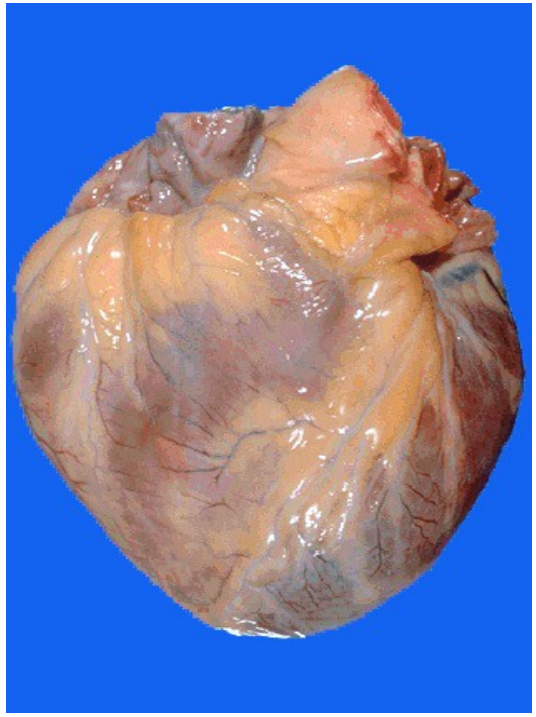
BNP is the cardiac stress hormone and a specific marker of cardiac disease.

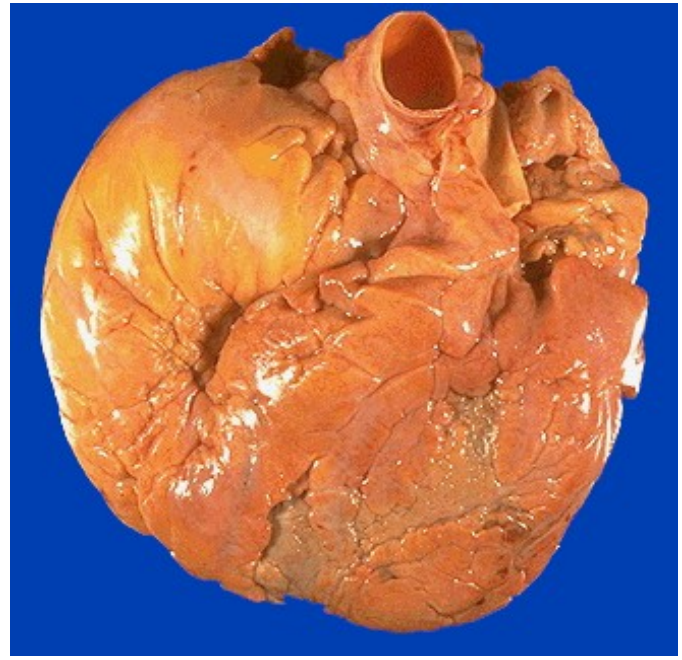
It does not point to the specific cause of heart strain.

Elevated levels of BNP and NT-proBNP in heart failure

A diagnostic opportunity

Chronic heart failure: magnitude of the problem





Diastolic heart failure: Elevated Natriuretic peptide

The left ventricle is markedly thickened in this patient with severe hypertension that was untreated for years.

The myocardial fibers have undergone hypertrophy.

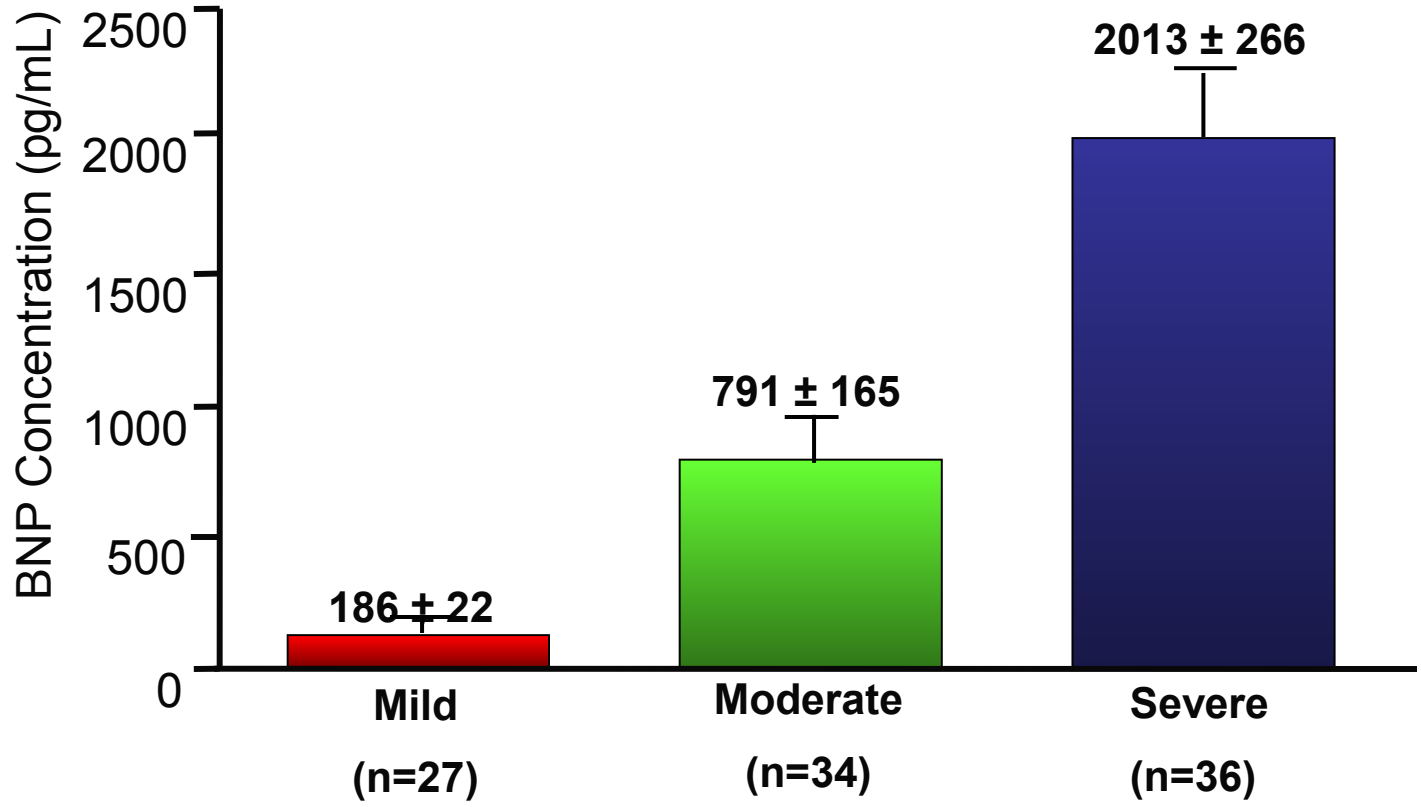
Accuracy of BNP in Detection of Left Ventricular Systolic Dysfunction

Group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Participants aged 25 -74				
All study participants	77	87	16	97.5
Participants w/ Ischemic (Heart Disease (IHD	84	76	30	97.5
Age>55 All Study participants	89	71	18	99.2
/Participants w Ischemic (Heart Disease (IHD	92	72	32	98.5

McDonagh et al. Lancet 1998;351:9-13

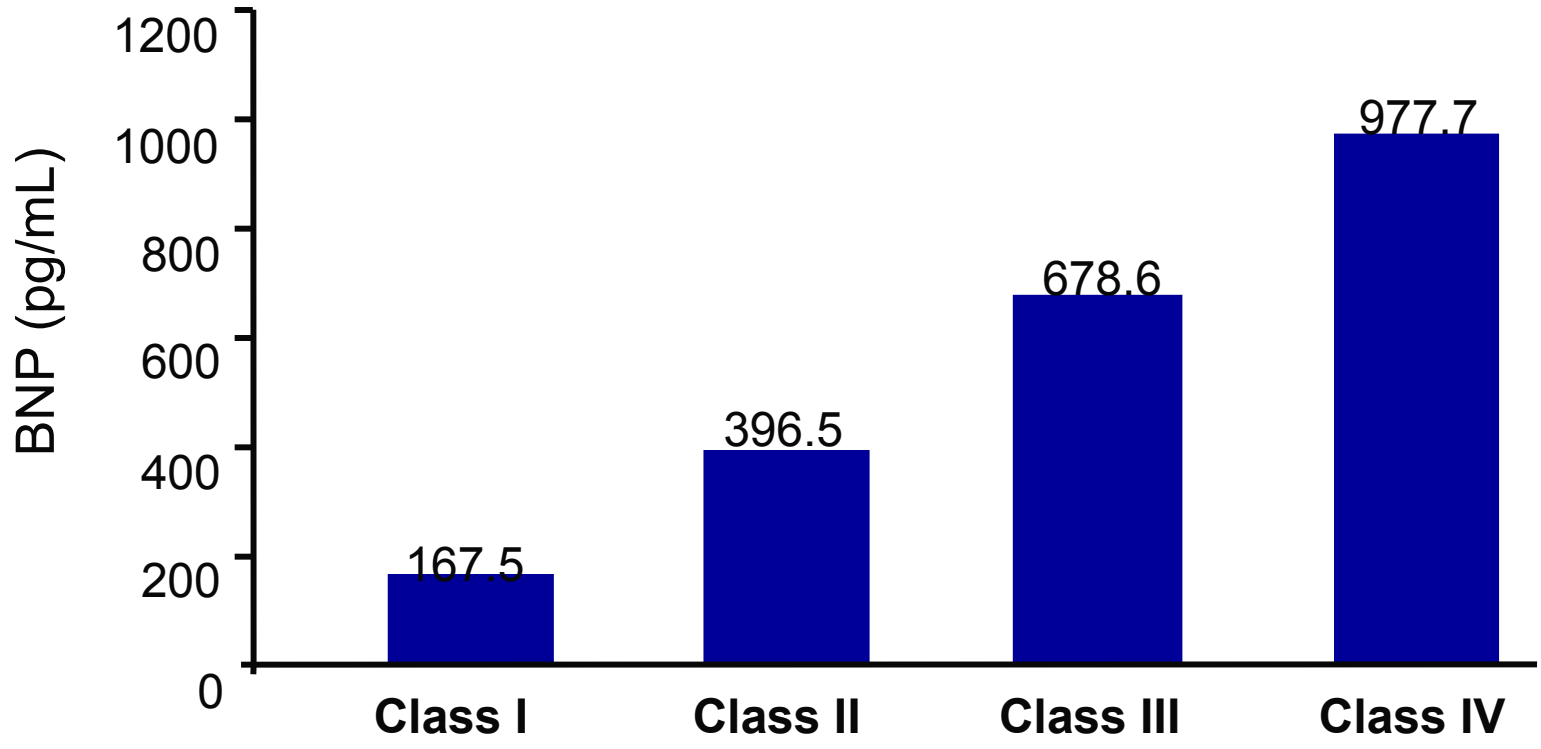
$$NPV = \frac{TN}{TN + FN}$$

BNP Concentration for the degree of CHF Severity



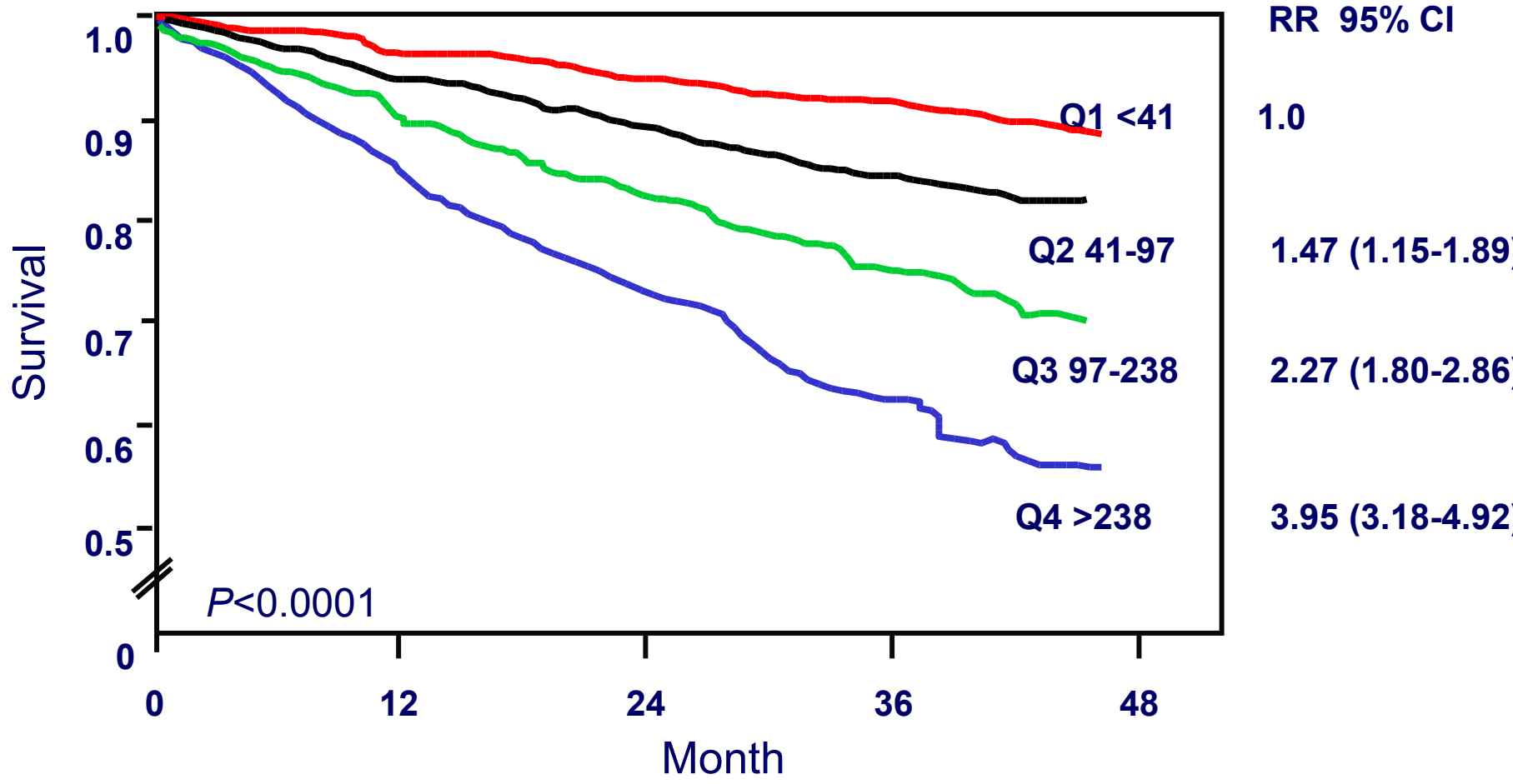
Dao Q, Maisel A, et al. *J. Am Coll Cardiol.* 2001;37(2):379-385.

Relationship of BNP and NYHA Classification



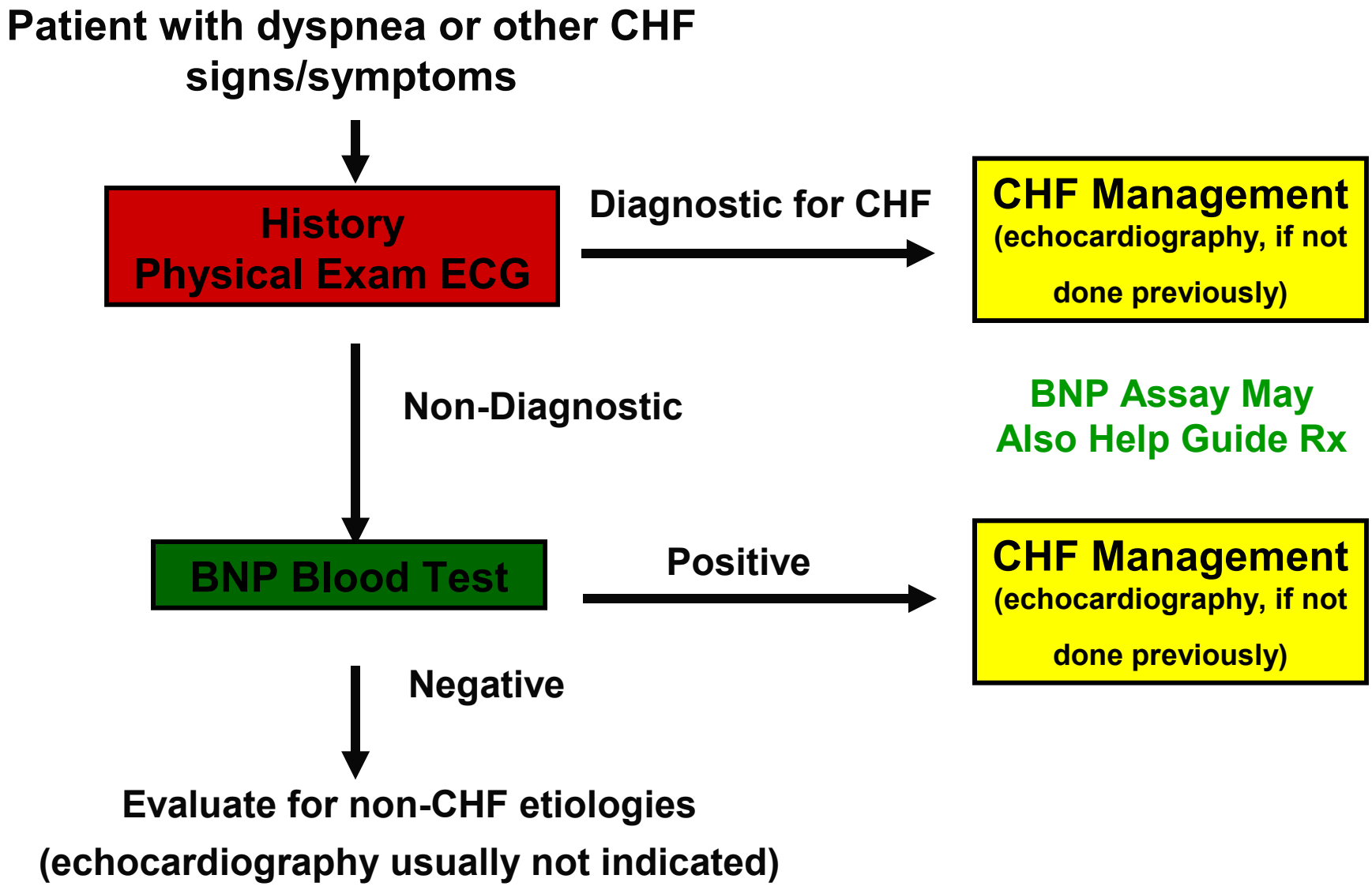
Triage® BNP package insert. Data on File at Biosite Diagnostics Inc.

Baseline BNP and Mortality in HF:Val-HeFT Study

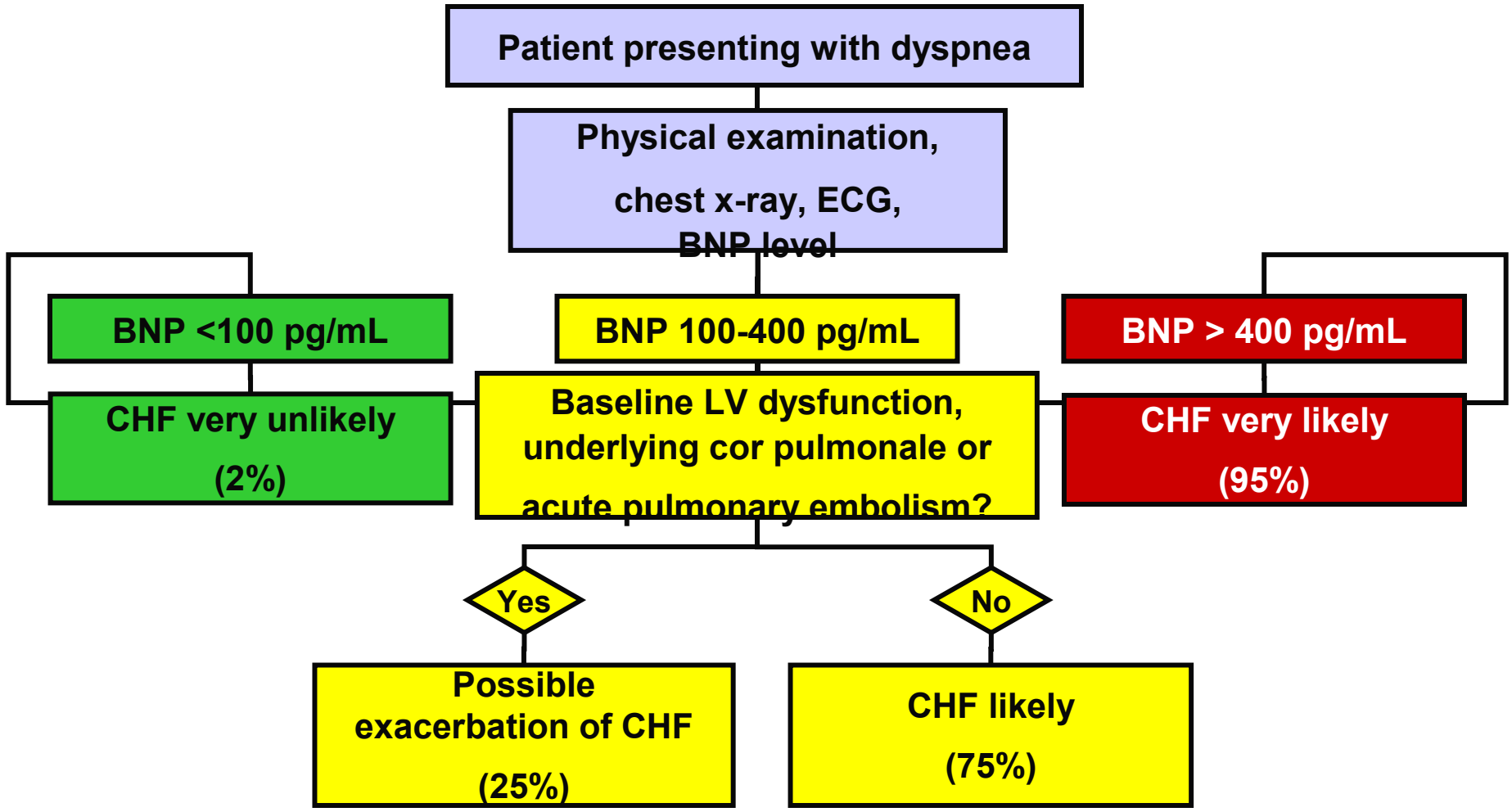


Anand IS et al. *Circulation.* 2003;107:1276-1281.

Heart Failure Diagnostic Algorithm



Heart Failure Diagnostic Algorithm



Maisel A. *Rev Cardiovasc Med*. 2002;3(suppl 4):S13.

BNP4EVER Study

מכתבי האיגוד הקרדיולוגי בישראל

הפפטיד הנתריורטי המוחי (Brain-type Natriuretic Peptide): שימושים אפשריים ברפואת הלב

שמחה מיזל
מכון הלב, מרכז רפואי הלל יפה

דב פריימרק
מכון הלב, מרכז רפואי ע"ש חיים שיבא

הקדמה

הפפטיד הנתריורטי המוחי הוא הורמון המיוצר על ידי תאי שריר לב כתגובה לעומס לחץ או נפח. לפפטיד זה פוטנציאל לשמש כתבחין מעבדתי לשם אבחנה, הערכת טיפול ולקביעת פרוגנוזה בחולים עם מחלת לב ממגוון אטיולוגיות. בעשור האחרון התפרסמו, לכן, מחקרים רבים הדנים בהיבטים הקליניים והמעבדתיים של הפפטיד הנטריורטי המוחי. בנייר עבודה זה ביקשנו לסווג את אפשרויות השימוש של ההורמון בזירה

BNP4EVER Study

BNP for EValuation in the Emergency Room (BNP4EVER): Assessing the acutely dyspneic patient in the emergency room

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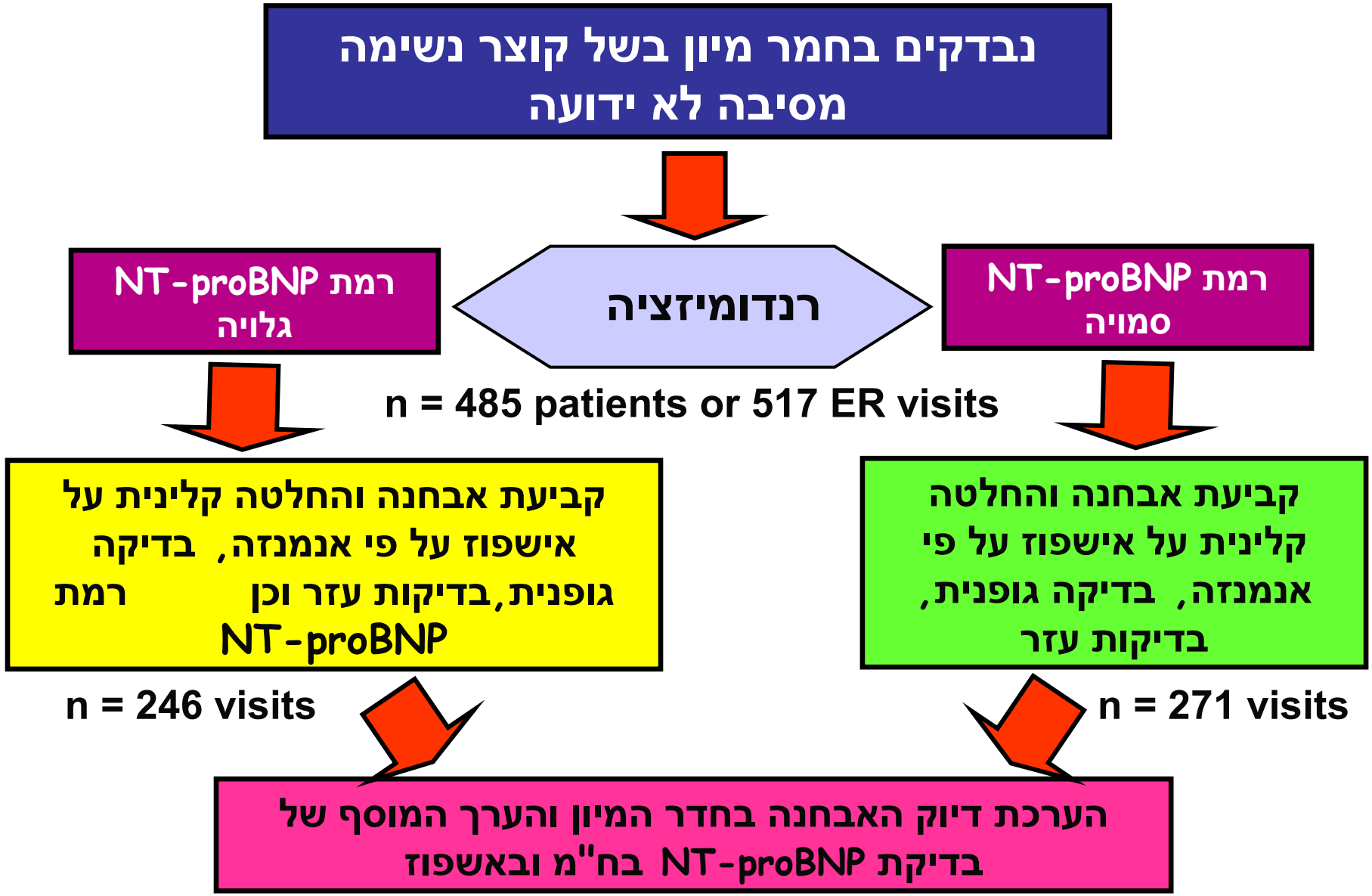
Aim of study

To evaluate the effect of the NT-proBNP test performed in central lab on admission rate of patients presenting to the ED with dyspnea, and on the accuracy of diagnosis of AHF in the patients admitted to medical departments.

In addition, we intended to assess the impact of correct diagnosis on mortality and event-free survival following index admission.

BNP4EVER Study design



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Age-stratified cutpoints for the diagnosis of CHF

Patient age	NT-proBNP values (pg/ml)		
	Group A	Group B	Group C
< 50	< 300	300-450	> 450
50-75	< 300	300-900	> 900
> 75	< 300	300-1800	> 1800
Interpretation	CHF is unlikely	Acute CHF less likely, alternative causes must be considered	Acute CHF likely, Consider confounding factors

Januzzi JL. JACC 2005;45:140 Suppl A

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Participating hospitals

Assaf Harofeh Medical Center Zerifin

Hillel Yaffe Medical Center Hadera

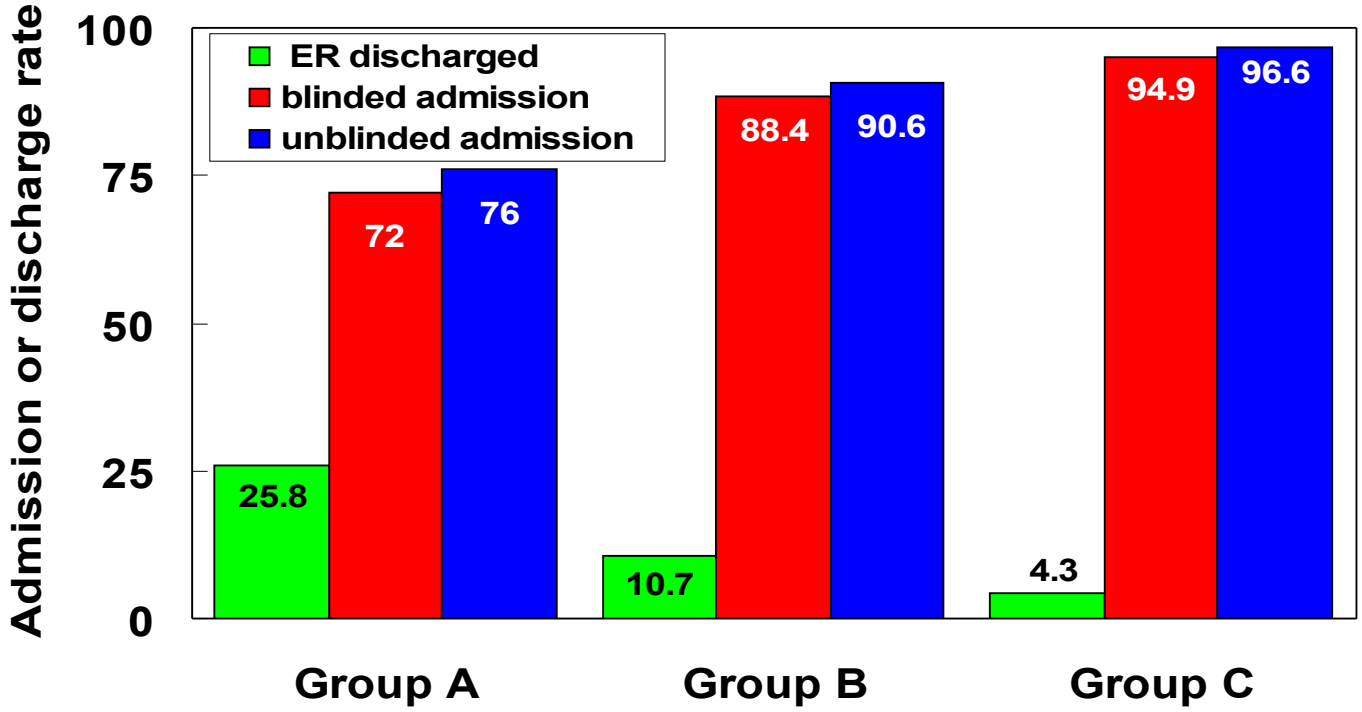
Study population

Hillel Yaffe Medical Center (10/05-3/07): 386 patients and 416 referrals to the ER. Assaf Harofeh Medical Center (3/06-1/07): 99 patients with 101 referrals to the ER.

Overall, 484 patients and 517 presentations to the ER.
261 Females (74.4±12.4, median-72), and 249 males (70.5±13.4, median-77)

Results

Percentage of patients discharged home from ER and admitted according to blinding status in all groups



There was a significant difference between but not within groups.

The central lab NT-proBNP assay did not affect admission rate.

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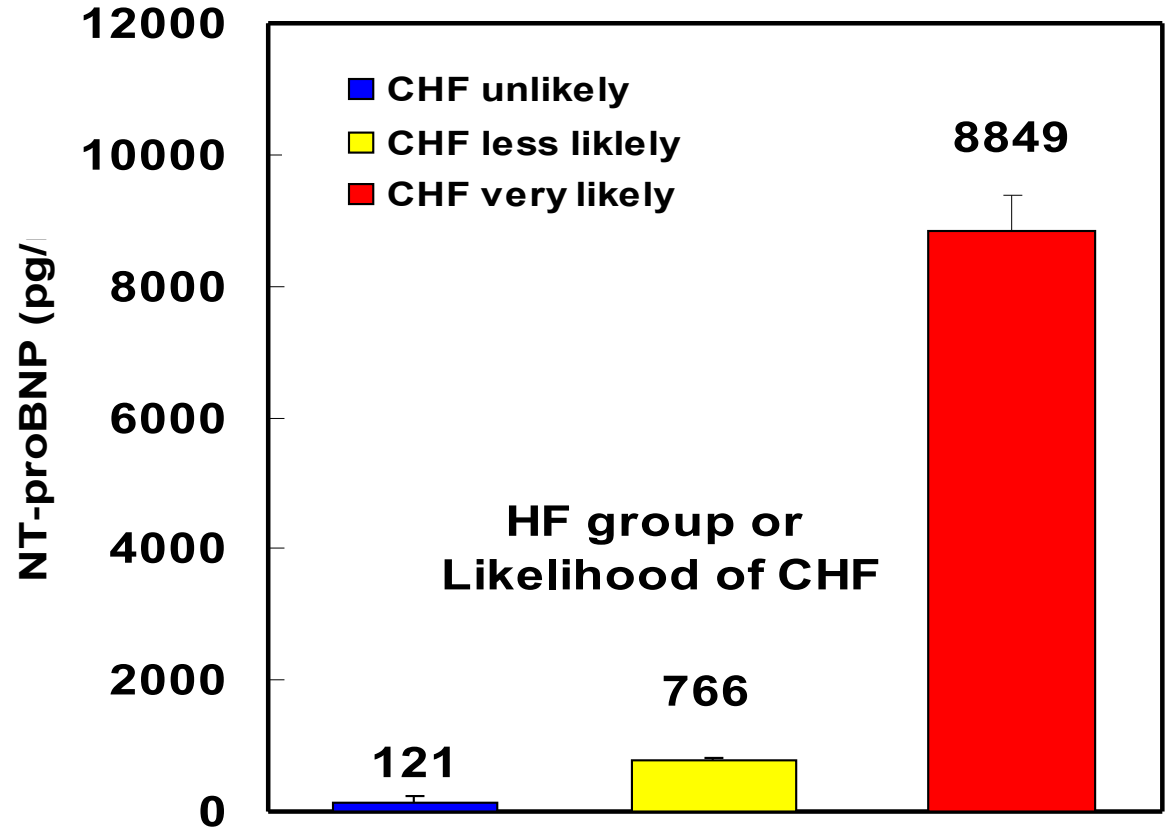

#Patients in each group	84	123	302
%Patients	17%	24%	59%
ER diagnosis of HF	18%	54.5%	75%
Admission rate	74%	88.6%	96.3%
Discharge Dx of HF	10.8%	24%	66%

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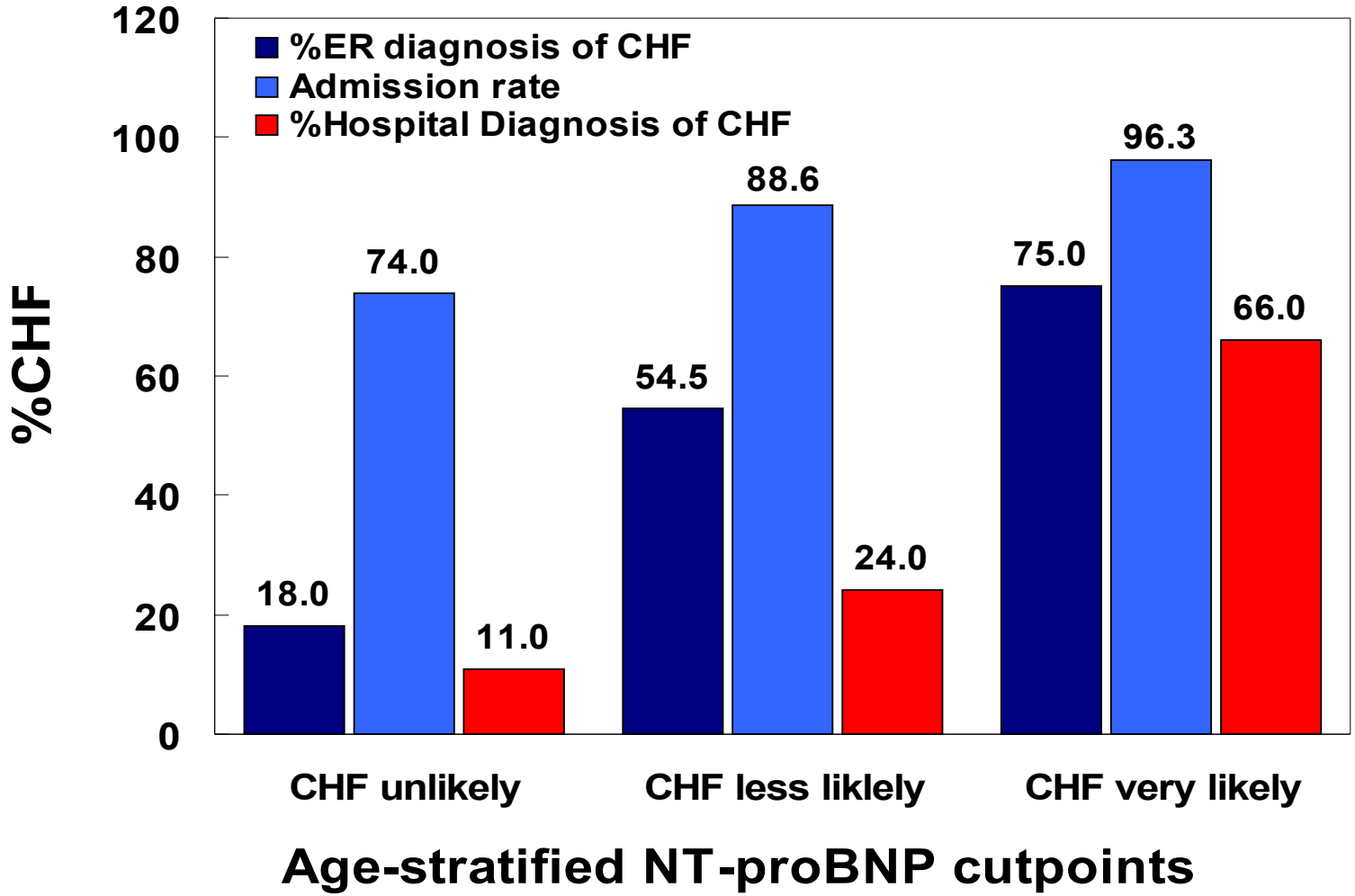
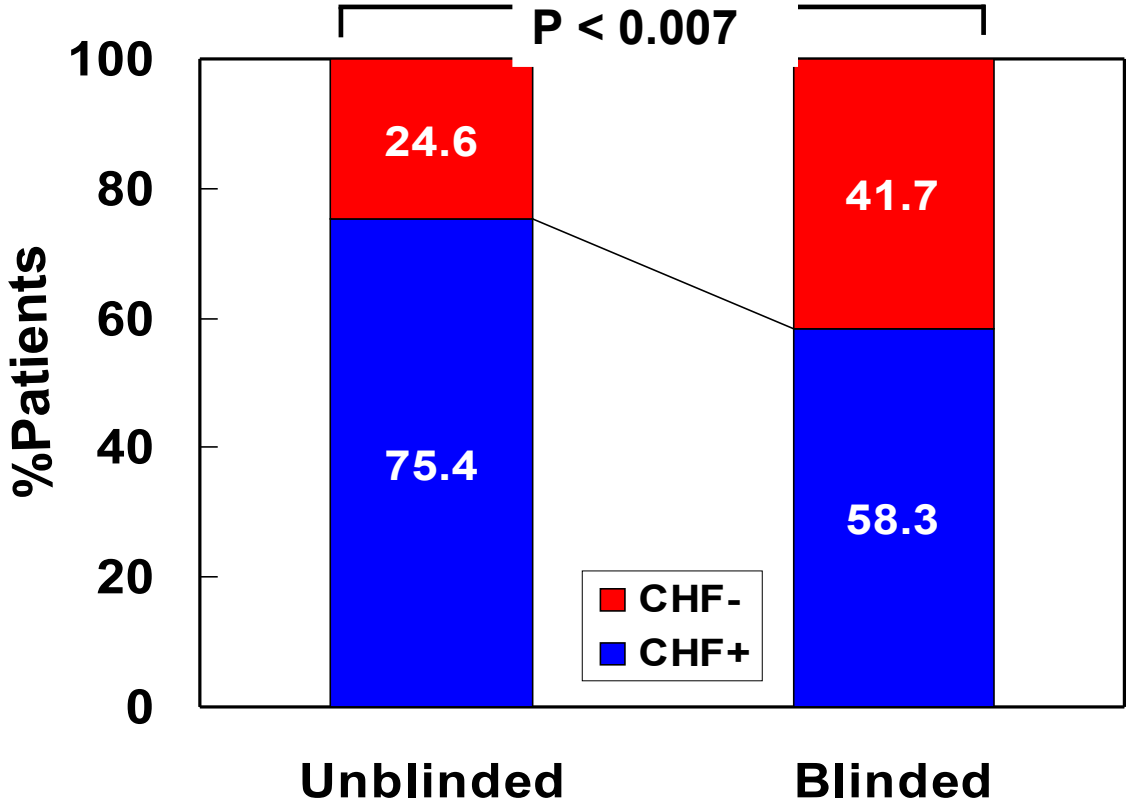
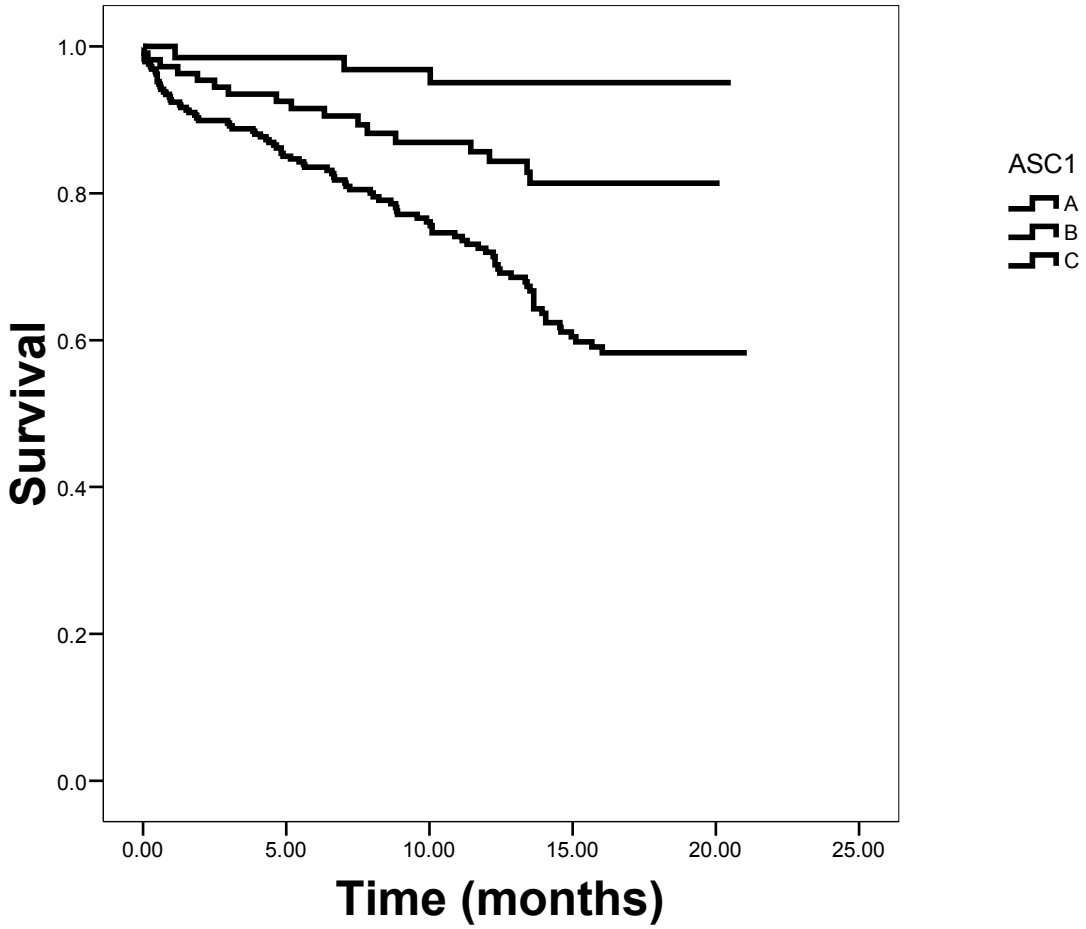


All admitted HF-likely (age-stratified group C) patients according to test blinding



The pro-BNP test improved, despite test assimilation period, the accuracy of acute heart failure diagnostic on discharge in patients admitted for clinically significant dyspnea.

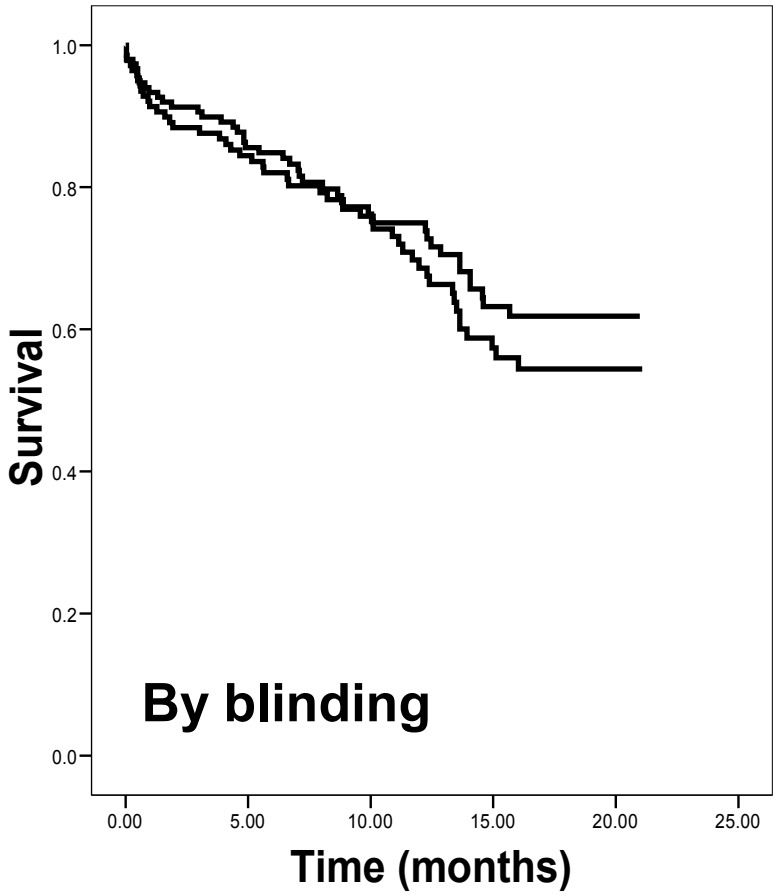
Survival in all study patients according to ASC group

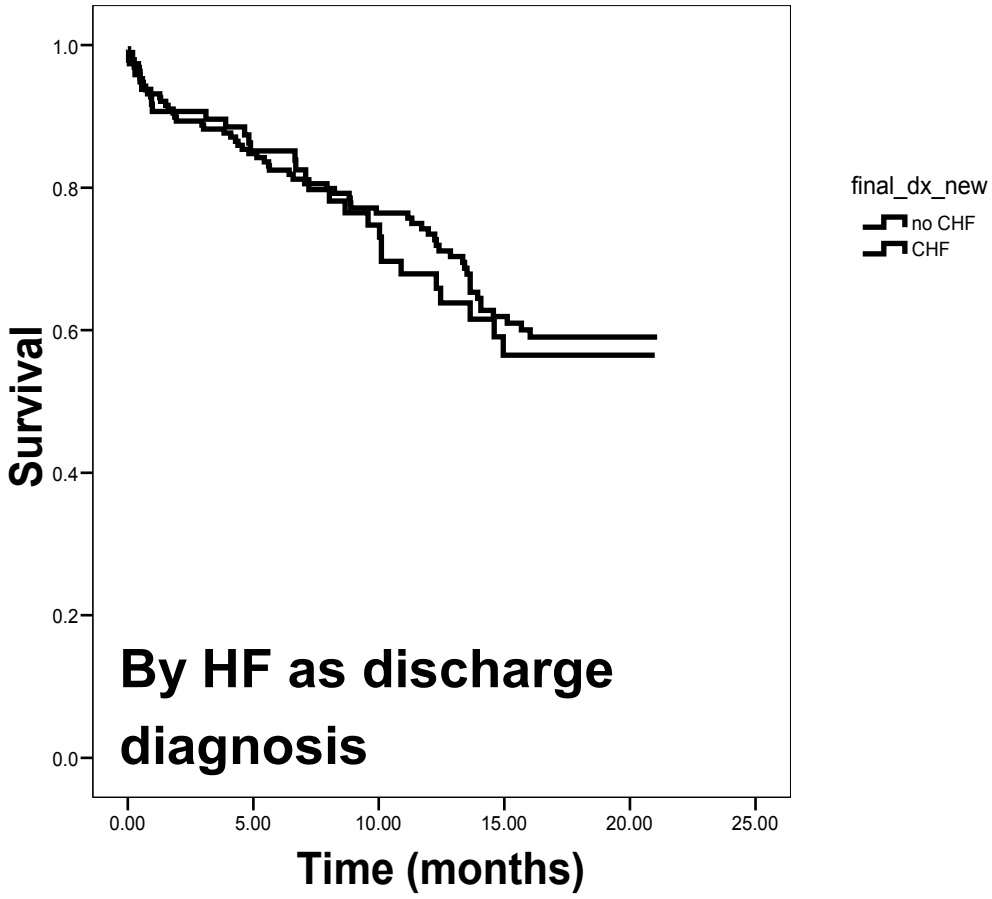


Life table analysis of mortality in HF-likely HYMC patients (group C): No difference according to blinding or final diagnosis of HF

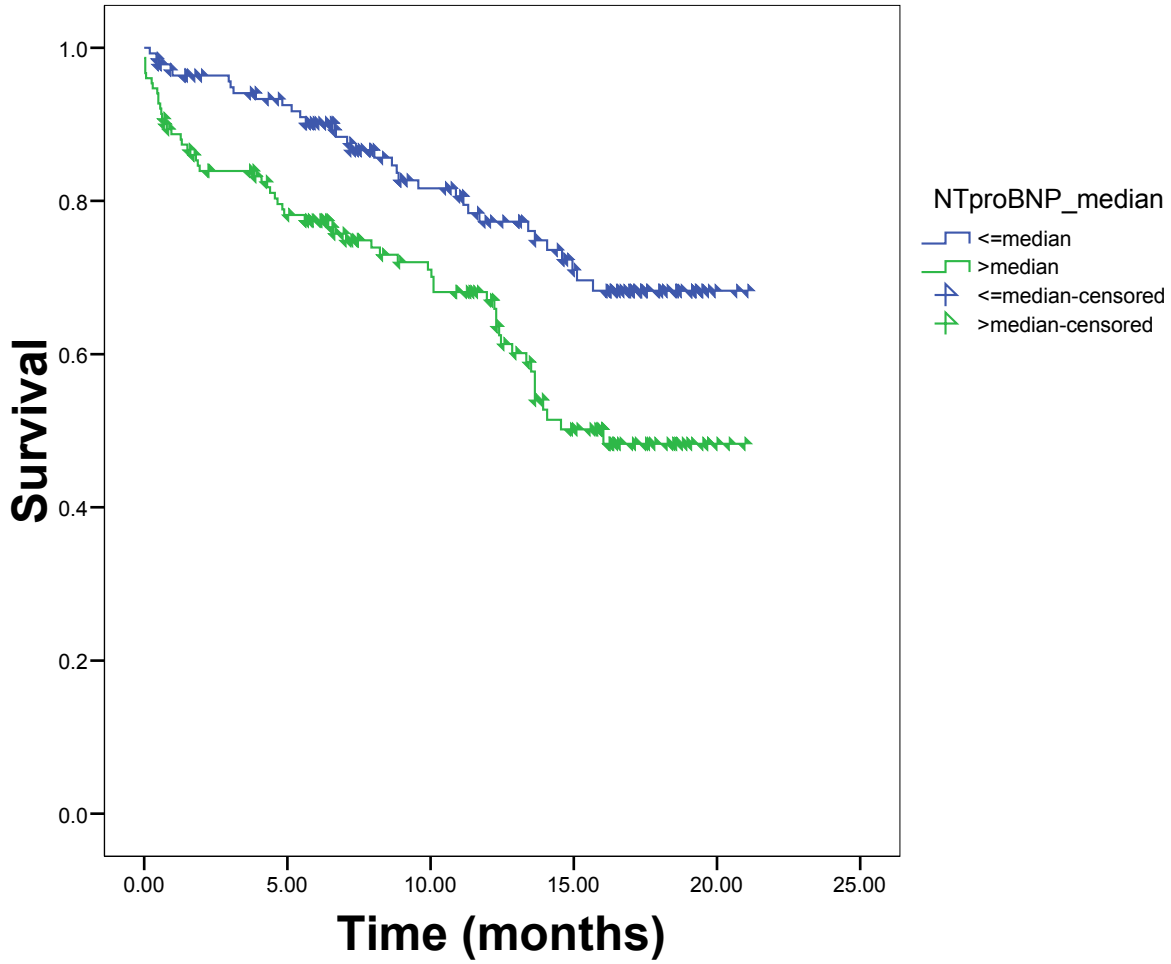
HF-diagnosed patients

HF-undiagnosed patients





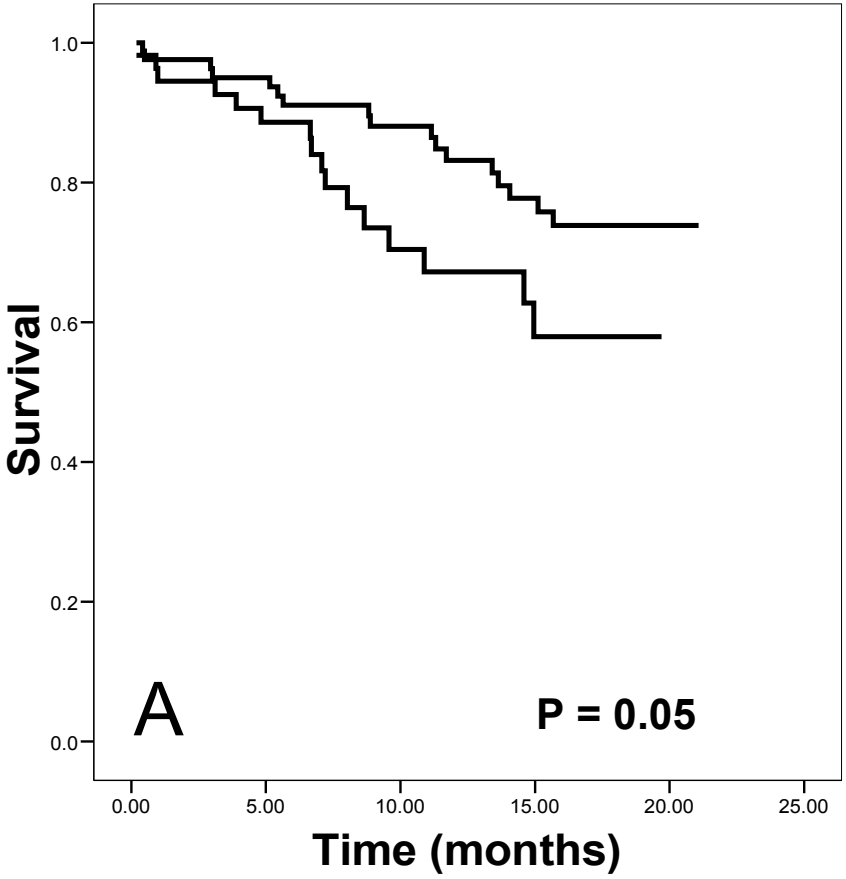
NT-proBNP levels in HF patients (group C) according to median value

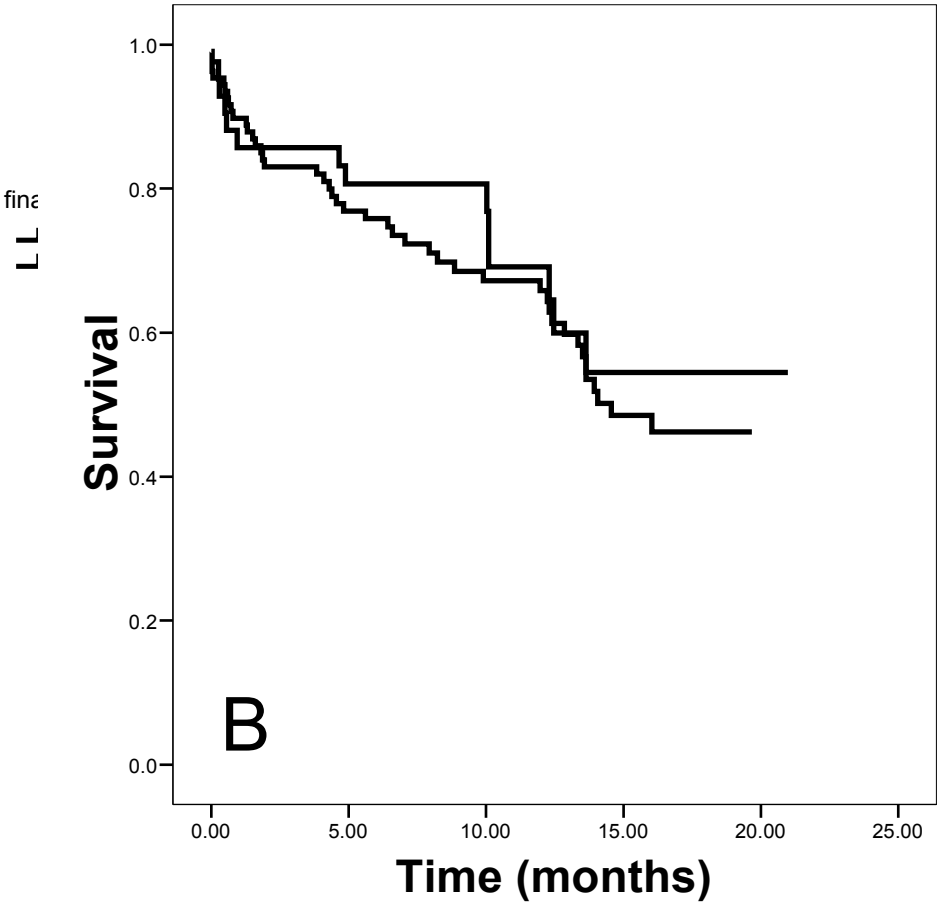


Survival in HF-likely patients (group C) with NT-proBNP < 5000 (A) and > 5000 pg/ml (B) according to discharge diagnosis

HF-diagnosed patients

HF-undiagnosed patients





Study group	N	NT-proBNP Mean ±SE Median (Interquartile Range)	Survival 21 Months%	BB%	Treatment intensity Mean ± std Median	AA%	Treatment intensity mean ± std (median)
Blinded	151	8335 ± 660.7 5093 (2611-10798)	62	31	1.61 ± 0.71 (1.0)	58.2	2.03 ±0.56 (2.0)
Unblinded	140	8695 ± 723.4 5168 (2961, 11807)	54	32	1.44 ± 0.55 (1.0)	55.0	1.88 ± 0.56 (2.0)
Patients undiagnosed as AHF	97	6970 ± 714 * 4444 (2433-8212)	57	14.4	1.71 ± 0.73 (2.0)	50.5	1.92 ± 0.61 (2.0)
Patients diagnosed as AHF	192	9337 ± 637.7 * 6149 (2970-12,456)	59	40.1	1.49 ± 0.62 (1.0)	59.9	1.98 ± 0.55 (2.0)
NT-proBNP < median undiagnosed as AHF	55	2825 ±160 2780 (1849- 3878)	58	9.1	1.8 ± 0.84 (2.0)	56.3	1.94 ± 0.63 (2.0)
NT-proBNP < median diagnosed as AHF	84	2891 ± 116 2897 (1992-3783)	74 *	31.0	1.5 ± 0.58 (1.5)	66.6	2.0 ± 0.47 (2.0)
NT-proBNP > median undiagnosed as AHF	42	12398 ± 1202 8982 (7159-14,551)	55	21.4	1.67 ± 0.71 (2.0)	42.9	1.89 ± 0.58 (2.0)
NT-proBNP > median diagnosed as AHF	108	14350 ± 863 11517 (7723-17,385)	46	47.2	1.47 ± 0.65 (1.0)	54.7	1.97 ± 0.62 (2.0)

*p=0.019

Conclusions

- **The NT-proBNP test did not affect ER admission rate.**

(2) The NT-proBNP test improved the accuracy of the diagnosis of AHF on discharge.

(3) Accurate diagnosis based on the NT-proBNP resulted in improved mid-term (20 months) overall mortality in patients with< 5000 pg/ml, but not in those with > 5000 pg/ml.

(4) Undertreatment and treatment effect.