The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

Experience of Biomarker Usage in Heart Failure: Indonesian Real Data

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Disclosure

- Supported Symposia by Roche Diagnostics

Out line

- Biomarkers on Heart Failure and Recommendations in The guidelines
- Natriuretic Peptide ; BNP and Nt-Pro BNP
- Experience of Biomarker Usage in Heart Failure at Dr. Sardjito Hospital.

Preface

- ✓Biomarkers in heart failure have been thoroughly studied to reflect different pathophysiological processes ; such as fibrosis, inflammation, myocardial injury, and remodeling. There are several biomarkers that reflect this condition
- ✓Several guidelines (AHA/ACC, ESC, JCS) have recommended biomarkers in heart failure for the diagnosis, prognosis, risk stratification and screening of heart failure ; especially natriuretic peptite (NT-pro BNP , BNP)
- ✓There are still problems in using biomarkers (NT-pro BNP) in the management of heart failure in Indonesia

Biomarkers in Heart Failure

Established and emerging biomarkers in HF

Main group	Subgroup	Biomarker
Myocardial insult	**Myocyte stretch**	**ANP, BNP,[a] NT-proBNP,[a] MR-proANP** , GDF-15, neuregulin
	Myocardial injury	**Troponin T,[a] Troponin I,[a] hsTN,** heart type fatty acid protein, myosin light-chain kinase 1, creatinine kinase MB fraction
	Oxidative stress	Myeloperoxidase, **MR-proADM**, oxizidized low-density lipoprotein, urinary biopyrrins, plasma malondialdehyde
Neurohormonal-Activation	Renin-angiotensin system	Renin, angiotensin II, aldosterone
	Sympathetic nervous system	Norepinephrine, chromogranin A
	Arginine vasopressin system	Arginine vasopressin, Copeptin
	Endothelin	**Endothelin-1,** big proET-1
		Chromogranin A and B
Myocardial-Remodeling	**Inflammation**	**C-reactive protein**, **TNF-α,** Fas (APO-1,=), **interleukins 1,6**, **and 18**, cytokines, procalcitonin, adipokines, adiponectin
	Hypertrophy/fibrosis	**Soluble ST2,[a] Galectin-3**,[a] matrix metalloproteinases (MMP), collagen peptide

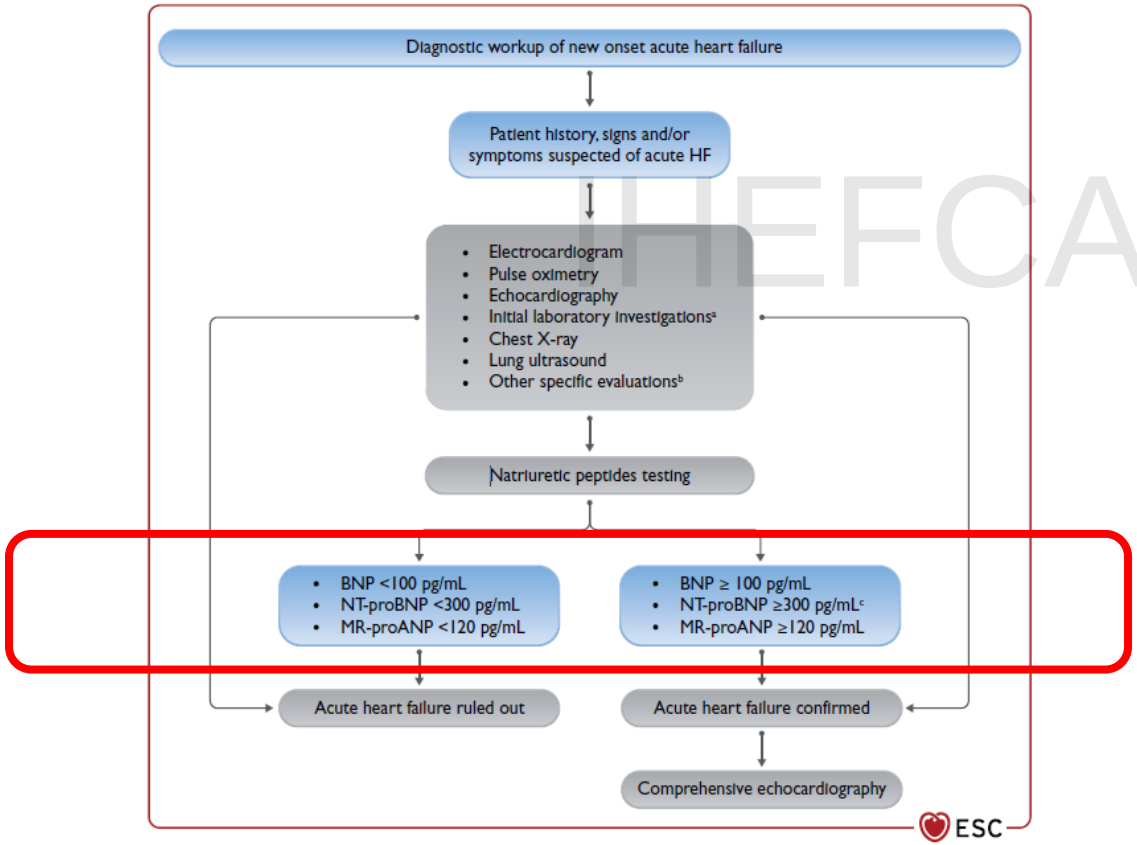
ANP atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *GDF-15* growth differentiation factor 15, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *MR-pro*ANP mid-regional pro atrial natriuretic peptide, *MR-proADM* mid-regional pro-adrenomedullin. *TNF-α* tumor necrosis factor

[a] Established biomarkers

Natriuretic Peptides are incorporated in HF Management by Major Guidelines

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

ESC Guidelines



2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Recommendations for Use of Biomarkers for Prevention, Initial Diagnosis, and Risk Stratification
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients presenting with dyspnea, measurement of B-type natriuretic peptide (BNP) or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) is useful to support a diagnosis or exclusion of HF (1-12).
1	A	2. In patients with chronic HF, measurements of BNP or NT-proBNP levels are recommended for risk stratification (11,13-29).
1	A	3. In patients hospitalized for HF, measurement of BNP or NT-proBNP levels at admission is recommended to establish prognosis (11,13-19).
2a	B-R	4. In patients at risk of developing HF, BNP or NT-proBNP–based screening followed by team-based care, including a cardiovascular specialist, can be useful to prevent the development of LV dysfunction or new-onset HF (30,31).
2a	B-NR	5. In patients hospitalized for HF, a predischarge BNP or NT-proBNP level can be useful to inform the trajectory of the patient and establish a postdischarge prognosis (14,17,20-29).

European Heart Journal (2021) 00, 1-128. doi:10.1093/eurheartj/ehab368
J Am Coll Cardiol. (2022). 145: e895-e1032. doi: 10.1161/CIR.0000000000001063

Table 1. Recommendations for measurement of BNP or NT-proBNP in heart failure guidelines

	Recommendations	Class	Evidec
2022 AHA/ACC/HFSA	In patients presenting with dyspnea, measurement of BNP or NT-proBNP is useful to support **a diagnosis or exclusion of HF**	**I**	**A**
	In patients with **chronic HF,** measurements of BNP or NT-proBNP levels are recommended for. **risk stratification.**	**I**	**A**
	In patients **hospitalized for HF**, measurement of BNP or NT-proBNP levels **at admission** is recommended **to establish prognosis**	**I**	**A**
	In patients at **risk of developing HF**, BNP or NT-proBNP-based **screening** followed by team-based care, including a cardiovascular specialist, can be useful to **prevent the development of LV dysfunction or new-onset HF.**	IIa	B-R
	In patients hospitalized for HF, **a predischarge BNP or NT-proBNP** level can be useful to inform **the trajectory** of the patient and establish a post discharge prognosis.	IIa	B-NR
2021 ESC	Plasma concentrations of **NP** are recommended as **initial diagnostic** tests in patients with symptoms suggestive of HF **to rule out the diagnosis**. Elevated concentrations support a diagnosis of HF, are useful for **prognostication,** and may guide further cardiac investigation.	**I**	**B**
2017 JCS/JHFS	Confirm the diagnosis of HF	**I**	**A**
	Assess the severity of HF	**I**	**A**
	Assess the prognosis of HF	**I**	**A**
	Monitor the efficacy of HF treatment	IIa	B
	Screen patients susceptible to HF	IIa	C

BNP, B-type natriuretic peptide; HF, heart faiure; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Is it something new?

Yancy et al 2013 ACCF/AHA Heart Failure Guideline

Table 9. Recommendations for Biomarkers in HF

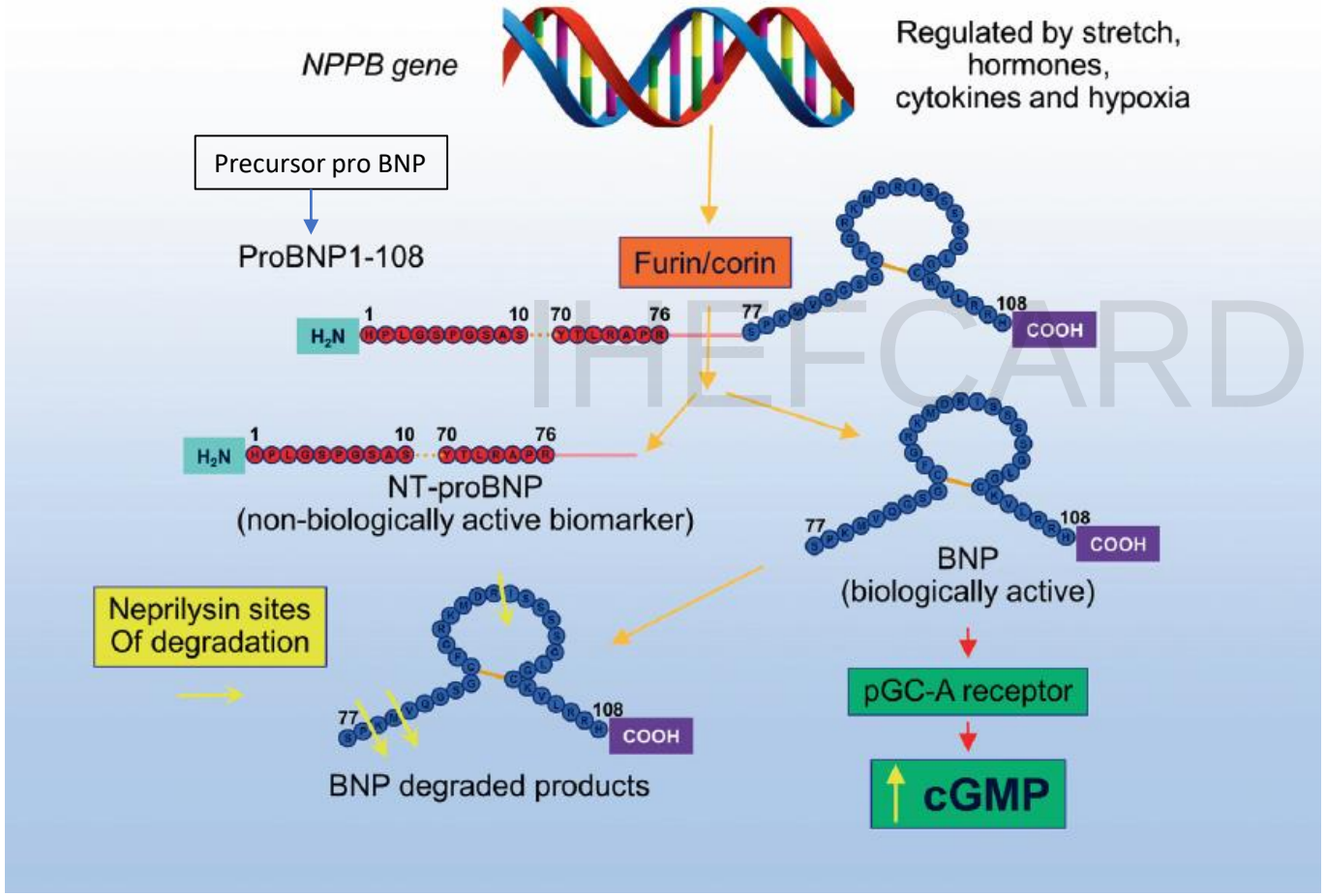
Biomarker, Application	Setting	COR	LOE	References
Natriuretic peptides				
Diagnosis or exclusion of HF	Ambulatory, Acute	I	A	212, 217–223, 245–250
Prognosis of HF	Ambulatory, Acute	I	A	222, 224–229, 248, 251–258
Achieve GDMT	Ambulatory	IIa	B	230–237
Guidance for acutely decompensated HF therapy	Acute	IIb	C	259, 260
Biomarkers of myocardial injury				
Additive risk stratification	Acute, Ambulatory	I	A	238–241, 248, 253, 256–267
Biomarkers of myocardial fibrosis				
Additive risk stratification	Ambulatory	IIb	B	242–244
	Acute	IIb	A	248, 253, 256, 258–260, 262, 264–267

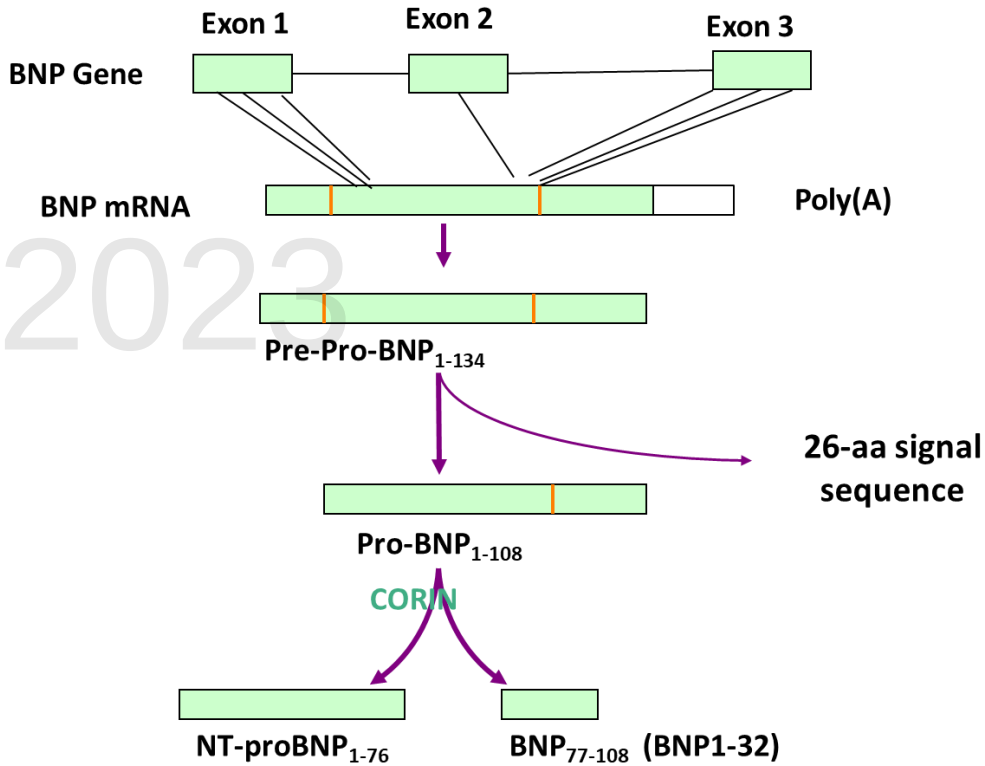
COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.

Class IA recommendation in HF guideline for ~10 years

What are natriuretic peptides (NPs)?

BNP and NT-proBNP

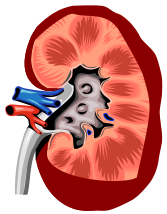




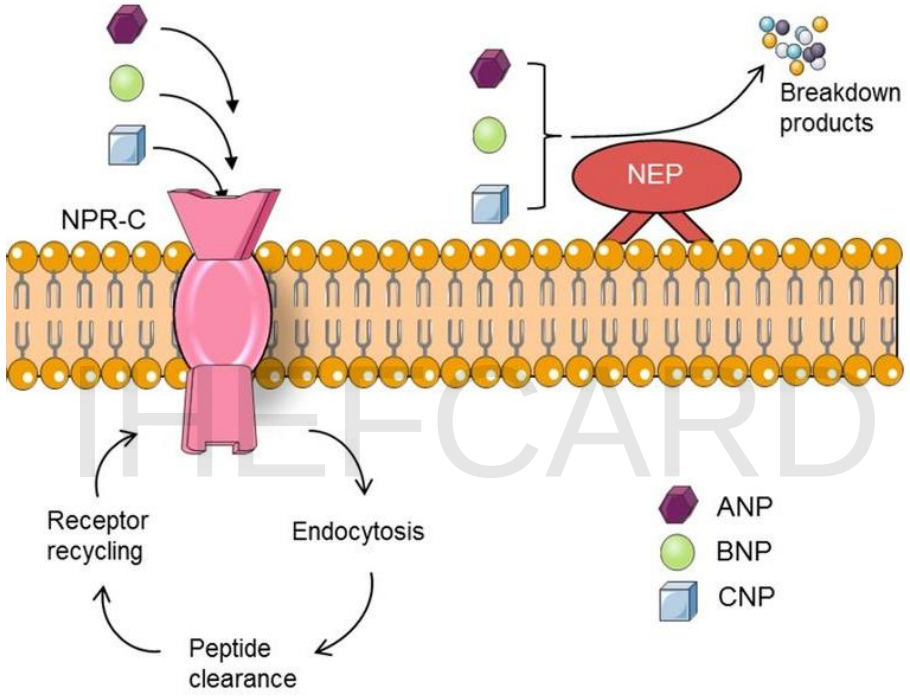
J Am Coll Cardiol. 2016 Dec 6;68(22):2437-2439.

Metabolism of BNP and NT-proBNP

NT-proBNP$_{1-76}$

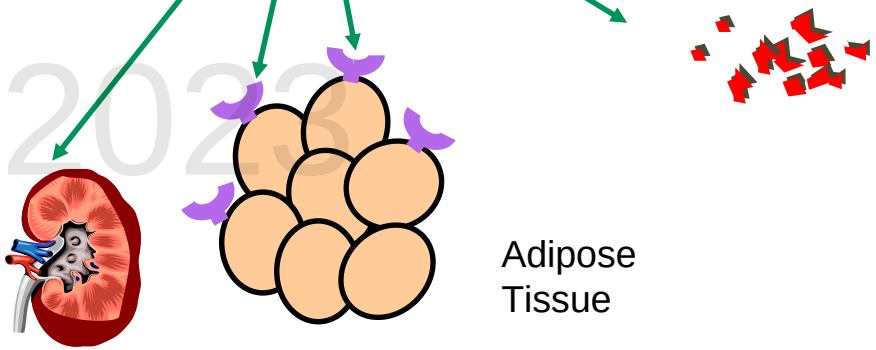


$T_{1/2}$= 120 min



BNP$_{77-108}$

Neutral Endopeptidase (Neprilysin)



$T_{1/2}$= 20 min

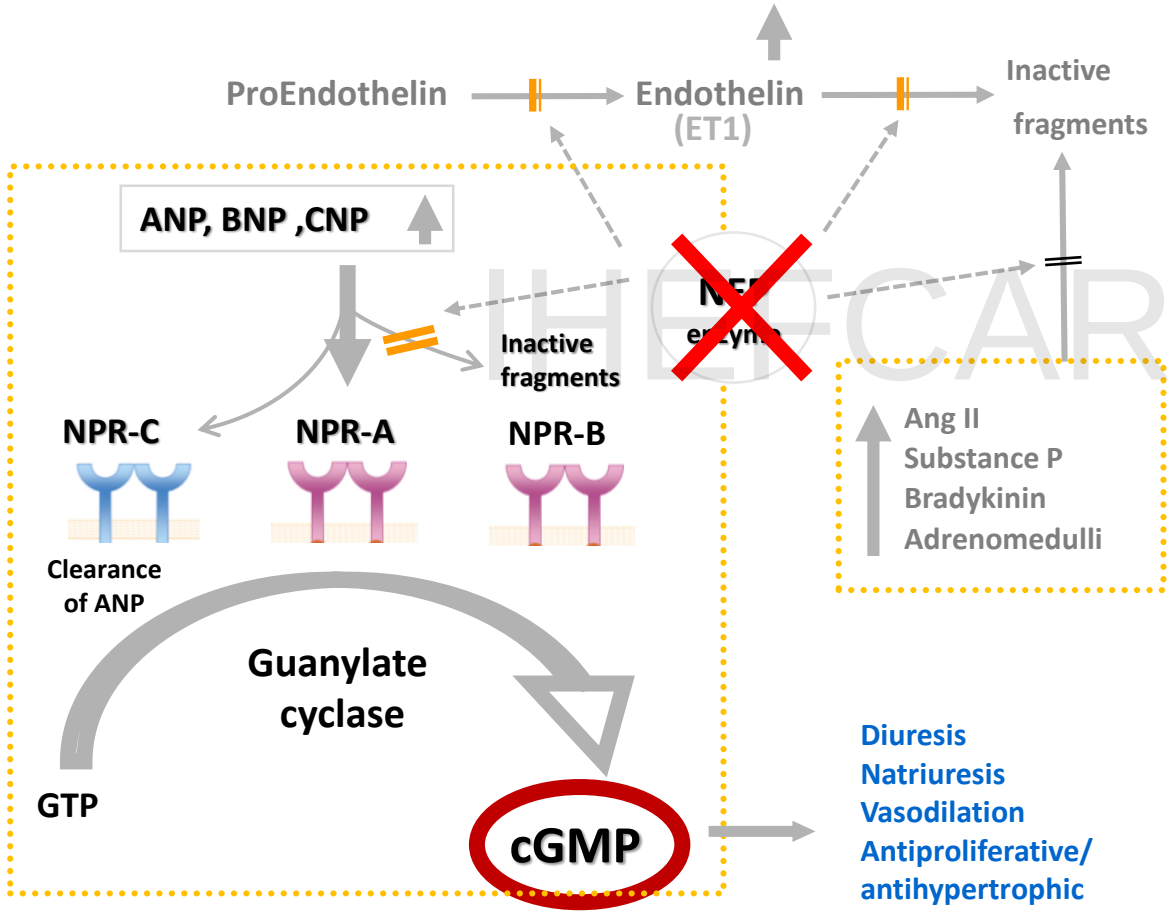
***NT-proBNP**: Kidney clearance*

***BNP**: NEP metabolism becomes the dominant clearance pathway in HF, when clearance via the NPR-C pathway becomes saturated*

Handb Exp Pharmacol. 2009 ; (191): 341–366. doi:10.1007/978-3-540-68964-5_15

Neprilysin inhibition enhances the effects of NPs

Metabolism of ANP and other peptide hormones by NEP [1-4]



Neprilysin (NEP) is the major enzyme responsible for degrading NPs [5]

BNP, not NT-proBNP, is a NEP substrate [6]

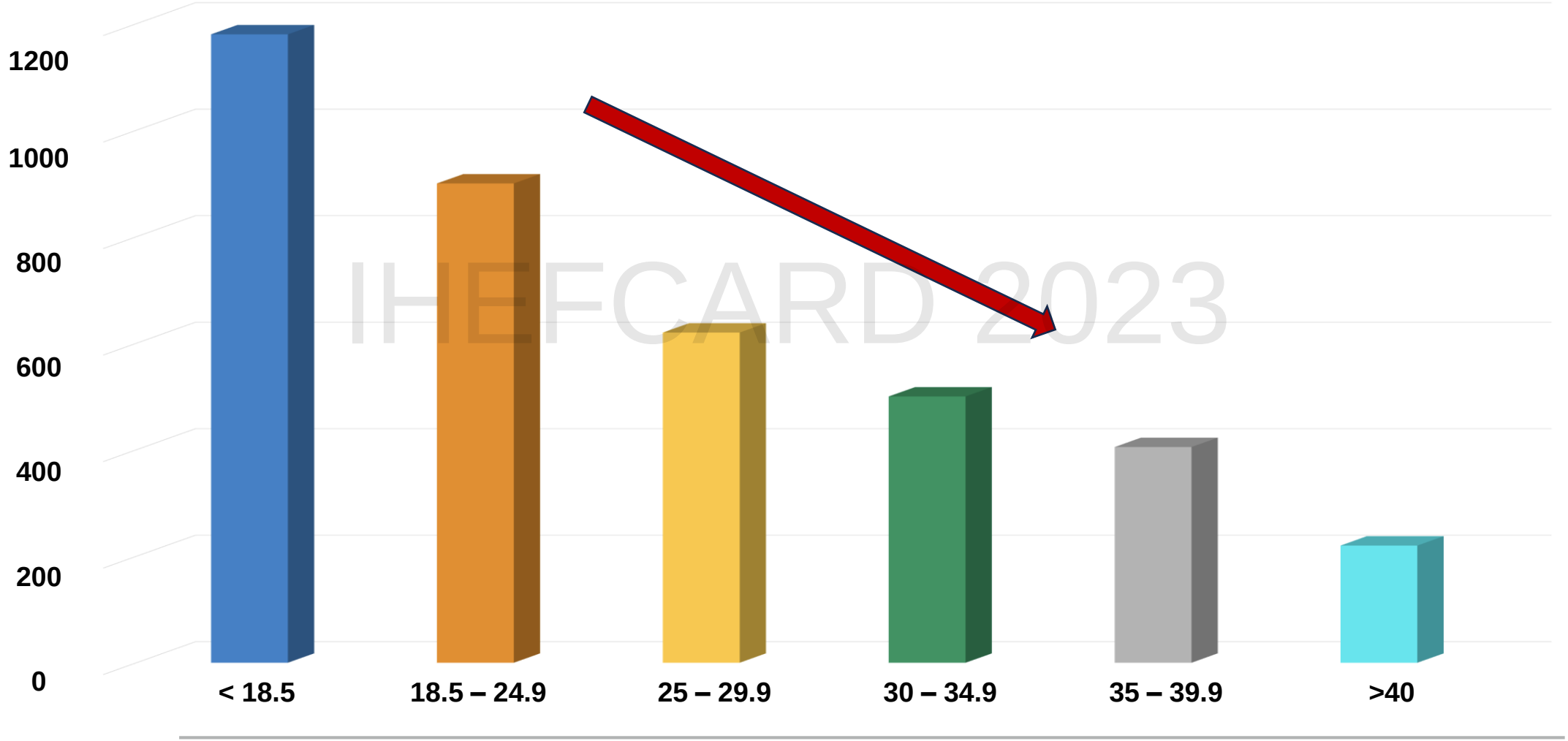
Inhibition of NEP enhances the effects of NPs [7]

Effects of NEP inhibition alone= offset by increase Ang II [2,5,7]

1. Erdos, Skidgel. FASEB J 1989;3:145–51; 2. Levin et al. N Engl J Med 1998;339;321–8; 3. Murphy et al. Br J Pharmacol 1994;113:137–42; 4. Jiang et al. Hypertens Res 2004;27:109–17; 5. Ferro et al. Circulation 1998;97:2323–30; 6. Martinez-Rumayor et al. Am J Cardiol 2008;101[suppl]:3A-8A; 7. Richards et al. J Hypertens 1993;11:407–16

Physiological factors affect BNP and NT-proBNP levels

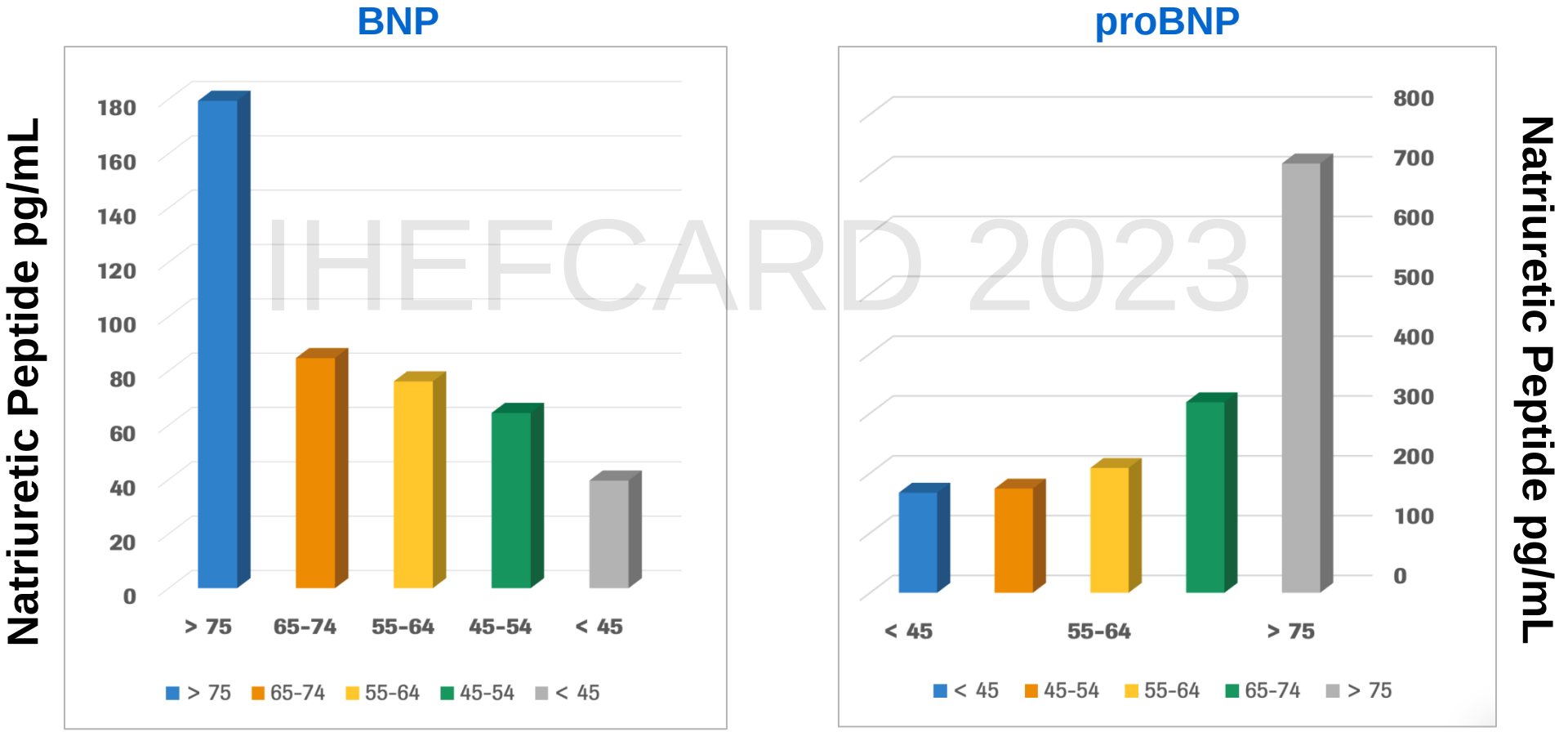
***Obesity**: 30% reduction in Body Mass Index over 30*



BMI, body mass index
Mundy, et al, JACC: 158a, 2003

Physiological factors affect BNP and NT-proBNP levels

Age affects both BNP and NT-proBNP likely reflects age-related decreases in left ventricular compliance



Data taken from Package Insert for Biosite BNP (4/26/04), and Roche Diagnostics NT-proBNP (2005 v.2)

Analytical affect BNP and NT-proBNP levels

Pre-analytic issues

Factors known to influence

- Physical exercise
  Extreme exercise affects
  BNP and NT-proBNP concentrations[1,2]
- Circadian variation
  Daily BNP levels can vary
  up to 20%, less so with NT-proBNP[3]

Factors lacking influence

- Posture
  - NT-proBNP is less influenced with posture changes[4]
- Storage
  - NT-proBNP levels are stable under a variety of conditions
  - For BNP, stability is dependent on the specific assay and storage temperatures[5]

1. Kjaer. et al., (2004). Eur J Heart Fail. 6: 29
2. Scharhag. et al., (2005). Am Heart J. 150: 1128
3. Bruins. et al., (2004). Clin Chem. 50: 2052
4. Boomsma. et al., (2001). Clin Chem. 47: 963
5. Christenson. et al., (2007). Clin Chim Acta. 384:

Comparison between BNP and NT-proBNP

Characteristics	NT-proBNP	BNP
Amino acids	76	32
Molecular mass	8.5 kDa	3.5 kDa
Hormonally active	No	Yes
Half-life	**90-120 minutes**	**20 minutes**
Test tube	EDTA, serum, heparinized	EDTA
Sample stability	72 hours	varies (4-20 hours)
Interference with recombinant BNP therapy	No	Yes
Assay standardization	Yes	No

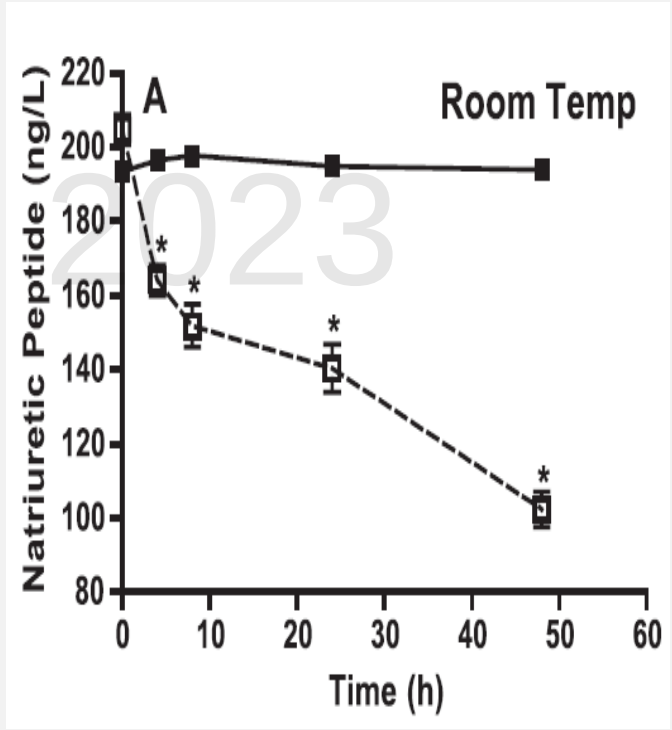
Singh JSS, et al. Heart 2017;103:1569–1577

Advantages of NT-proBNP over BNP

NT-proBNP has longer half-time

- Circulating concentrations of NT-proBNP are, therefore, higher than those of BNP.
- The longer half life of NT-proBNP might make it a better marker of steady state left ventricular function because blood levels are less subject to short-term physiologic alterations

NT-proBNP levels are stable under a variety of conditions.



1. Yeo, (2003). 338: 107-115
2. Christenson. (2007). 384:

The diagnostic accuracy of BNP and NT-proBNP: NT-proBNP has better sensitivity for HF diagnosis

Natriuretic peptide (threshold)	No of studies	No	No of cases	Sensitivity %	Specificity %	Positive predictive value	Negative predictive value	I^2 (%)
B type natriuretic peptide:								
≤100 ng/L	19	6950	3049	0.95 (0.93 to 0.96)	0.63 (0.52 to 0.73)	0.67 (0.63 to 0.75)	0.94 (0.90 to 0.96)	98
100-500 ng/L	20	4543	2160	0.85 (0.81 to 0.88)	0.86 (0.79 to 0.91)	0.85 (0.78 to 0.90)	0.86 (0.82 to 0.89)	97
≥500 ng/L	4	283	145	0.35 (0.17-0.56) to 0.83 (0.69-0.92)*	0.78 (0.56-0.93) to 1.00 (0.91-1.00)*	0.89 (0.75-0.96) to 1.0 (0.63-1.0)*	0.55 (0.69-0.80) to 0.69 (0.48-0.84)*	—
N terminal probrain natriuretic peptide:								
≤300 ng/L	10	3349	1695	0.99 (0.97 to 1.00)	0.43 (0.26 to 0.62)	0.64 (0.57 to 0.73)	0.98 (0.89 to 1.0)	94
300-1800 ng/L	13	3223	1652	0.90 (0.86 to 0.93)	0.76 (0.69 to 0.82)	0.80 (0.74 to 0.84)	0.88 (0.82 to 0.92)	97
≥1800 ng/L	3	840	444	0.67 (0.60-0.73) to 0.87 (0.81-0.92)*	0.72 (0.63-0.80) to 0.95 (0.91-0.98)*	0.80 (0.73-0.86) to 0.94 (0.89-0.97)*	0.71 (0.65-0.76) to 0.82 (0.73-0.89)*	—
Mid-regional proatrial natriuretic peptide:								
≤120 pmol/L	2	1892	705	0.95 (0.90-0.98) to 0.97 (0.95-0.98)*	0.56 (0.47-0.65) to 0.60 (0.57-0.63)*	0.56 (0.53-0.59) to 0.72 (0.65-0.79)*	0.90 (0.80-0.96) to 0.97 (0.96-0.98)*	—
>120 pmol/L	3	916	406	0.84 (0.77-0.89) to 0.98 (0.94-1.00)*	0.40 (0.34-0.46) to 0.84 (0.77-0.90)*	0.41 (0.35-0.47) to 0.86 (0.79-0.91)*	0.82 (0.74-0.88) to 0.98 (0.93-1.00)*	—

Emmert Roberts et al. BMJ 2015

NT-proBNP has better sensitivity than BNP in HF diagnosis

Study	True positive	False positive	False negative	True negative	Threshold	Sensitivity (95% CI)
B type natriuretic peptide ≤100 ng/L						
Blonde-Cynober 2011	23	12	3	26	100	
Logeart 2002	110	33	5	15	100	
Maisel 2010	543	409	25	664	100	
Maisel 2002	670	202	74	640	100	
Lokuge 2010	252	166	22	172	101	
Lainchbury 2003	68	69	2	66	104	
Davis 1994	26	2	6	18	100	
Dao 2001	91	9	6	144	100	
Chung 2006	72	42	0	29	100	
Wang 2010	46	23	3	12	100	
Sanz 2006	43	3	2	27	100	
Rogers 2009	353	115	15	257	100	
Ray 2004	127	68	14	99	100	
Parab 2005	45	17	2	6	100	
Mueller 2005	132	44	5	70	100	
Chenevier-Gobeaux 2010	114	155	1	108	100	
Barcase 2004	55	4	2	37	100	
Alibay 2005	59	53	1	47	100	
Arques 2005	31	14	1	24	100	

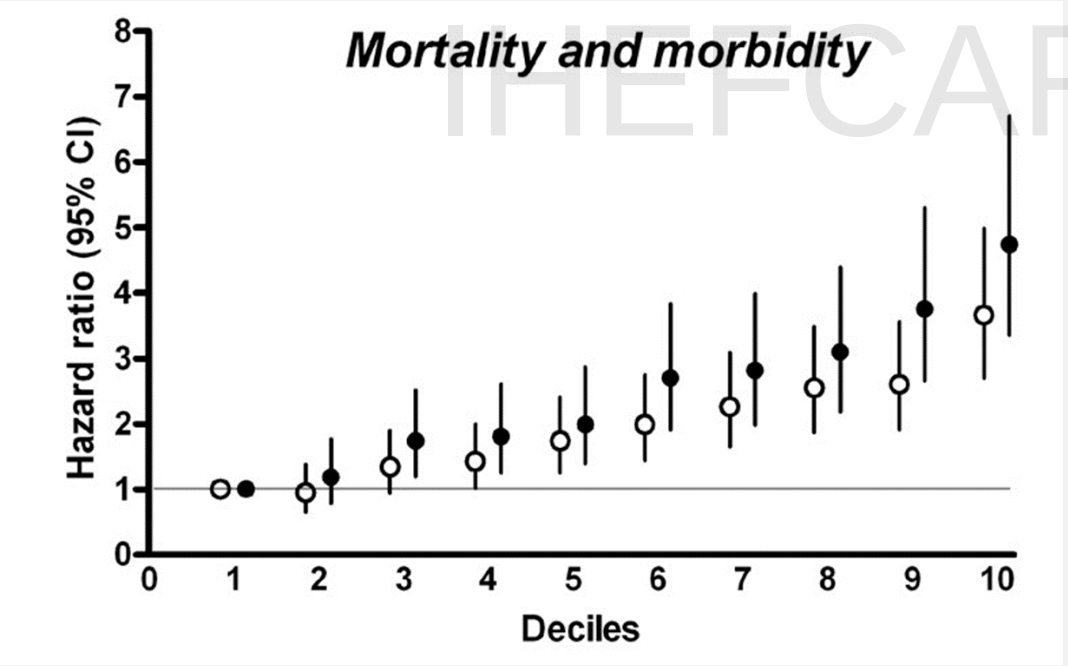
Study	True positive	False positive	False negative	True negative	Threshold	Sensitivity (95% CI)
N terminal probrain natriuretic peptide ≤300 ng/L						
Januzzi 2006	713	214	7	322	300	
Shaikh 2011	72	12	0	9	300	
Sanz 2006	45	15	0	15	300	
Mueller 2005	130	54	7	60	292	
Nazerian 2009	63	63	1	18	300	
Alibay 2005	60	95	0	5	280	
Chenevier-Gobeaux 2010	115	192	0	71	300	
Behnes 2009	117	145	5	134	300	
Gargani 2008	118	2	4	25	298	
Klemen 2009	236	93	2	110	300	

When converted to absolute patient numbers the use of BNP rather than NTproBNP in an acute care setting **potentially increased the false negative test results by between 8 and 31 more people per 1000 people** (assuming a prevalence ranging from 0.23 to 0.82, the range in the included study cohorts).

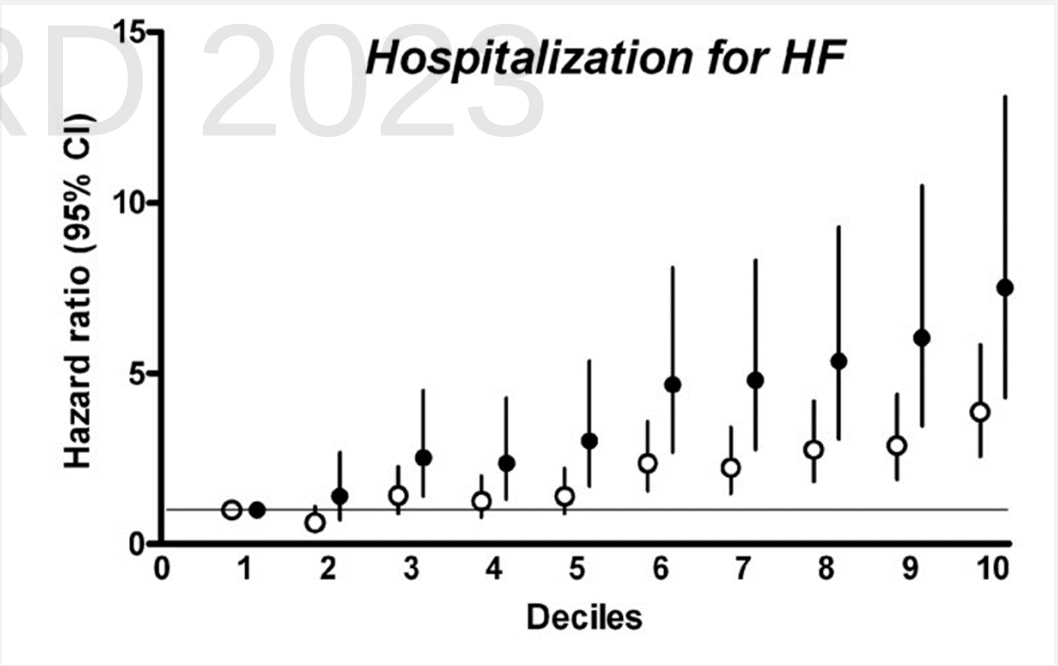
Emmert Roberts et al. BMJ 2015

Superiority of NT-proBNP over BNP for predicting the risk of hospitalization for patients with HF across the whole range of concentrations

HR (hazard ratio)
NT-proBNP vs BNP
4.74 (3.36–6.70) vs 3.67 (2.70–4.98)



RR (relative risk) of hospitalization in the tenth decile
NT-proBNP vs BNP
7.51 (4.30–13.11) vs 3.86 (2.56–5.84)



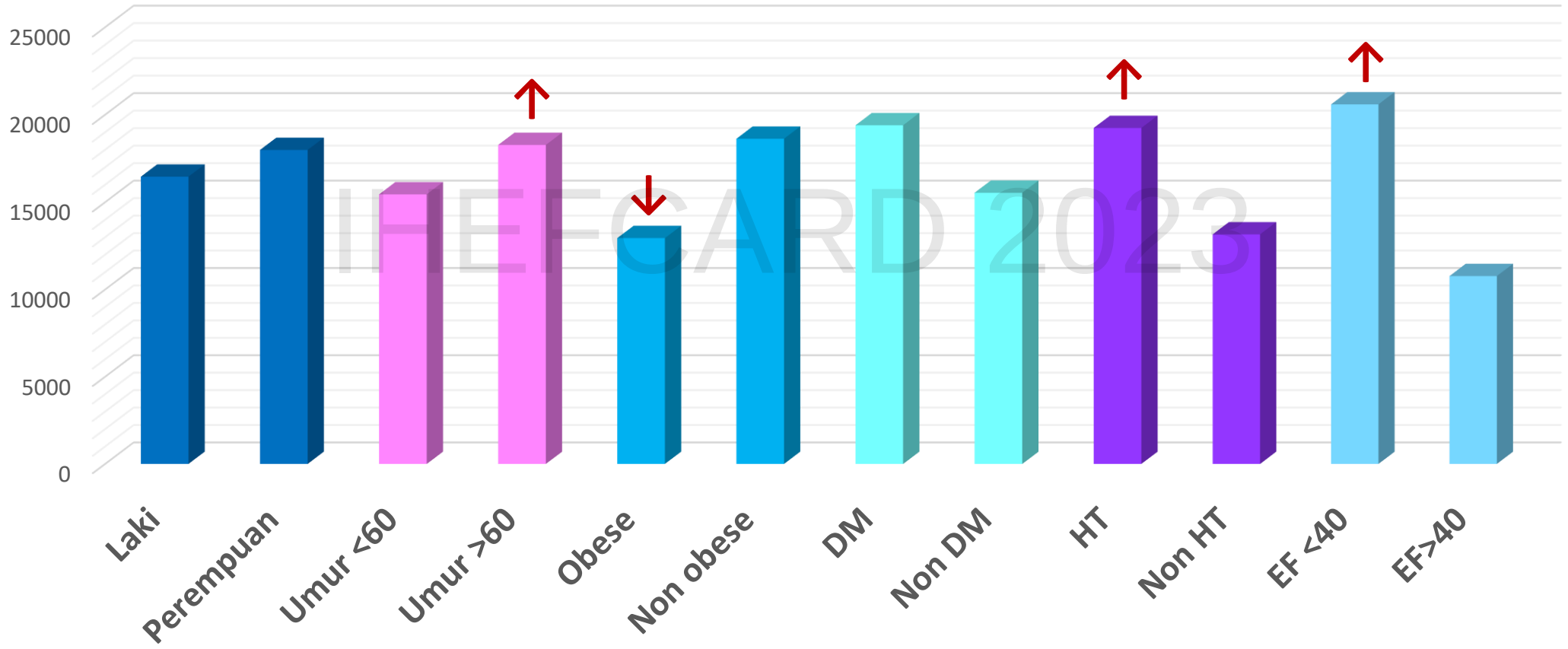
Surge Masson et al. Clin Chem 2006

Indonesia Real Data ; DR. Sardjito Hospital

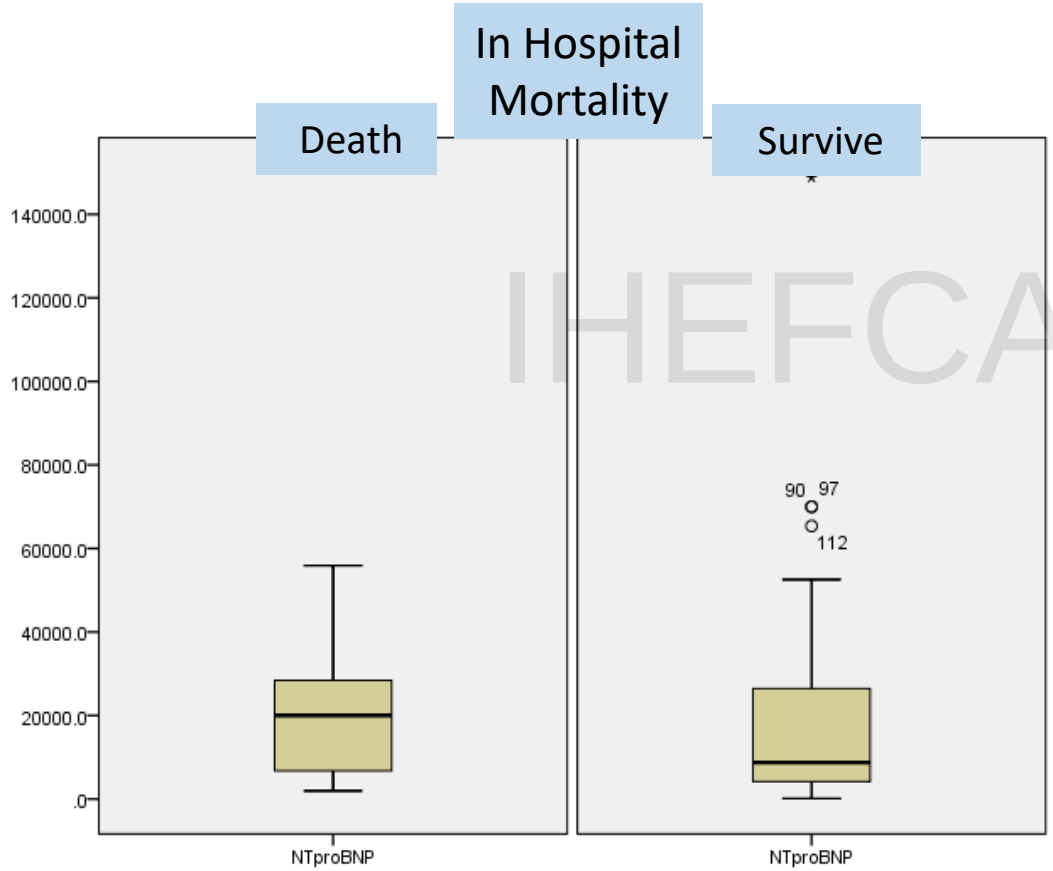
1. Registry Heart Faillure 2021
2. Registry Acute care in CVCU 2022
3. Trial Nt-ProBNP in heart failure 2019
4. Adeste Study ; control subject
5. Tesis : Hubungan Strain Atrium Kiri, Nt-proBNP Dengan Derajat Disfungsi Diastolik Ventrikel Kiri Pada Pasien Gagal Jantung Di RSUP Dr. Sardjito

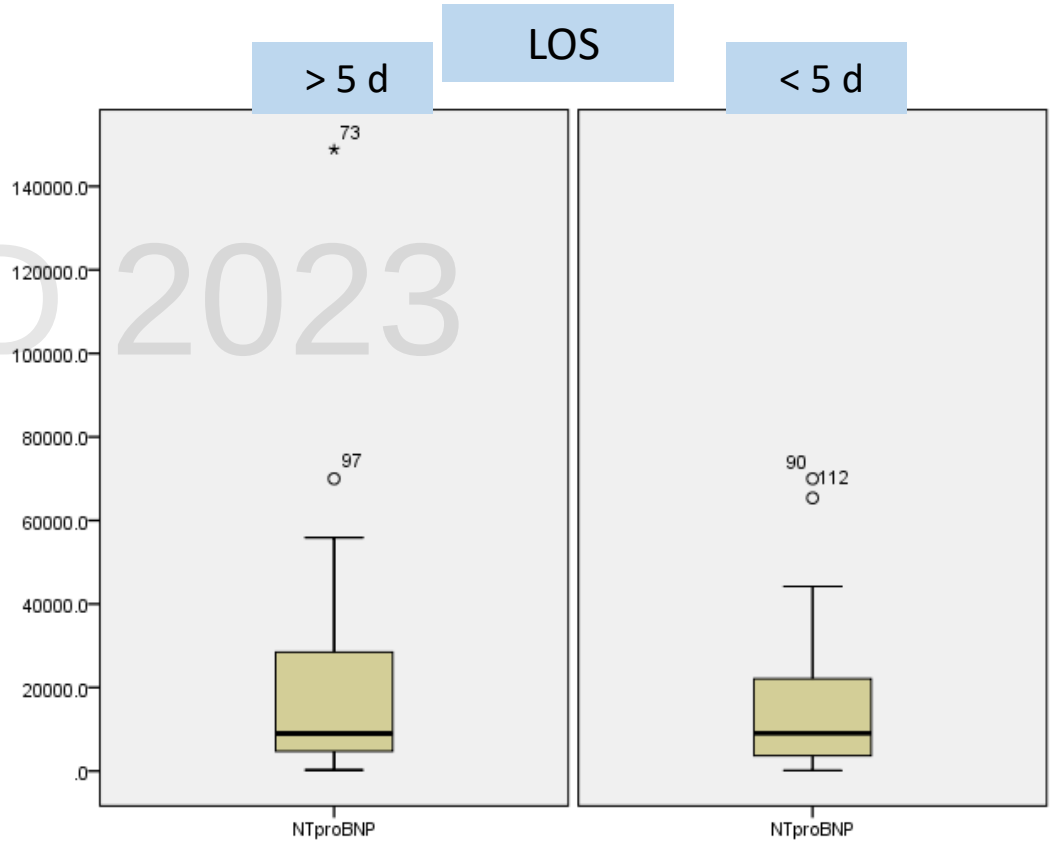
1. Registry HF Sardjito Hospital – 132 subyek , 2022

Nt-pro BNP in Hospitalized Heart Failure Patients



Nt-pro BNP and Outcomes in Hospitalized Heart Failure Patients





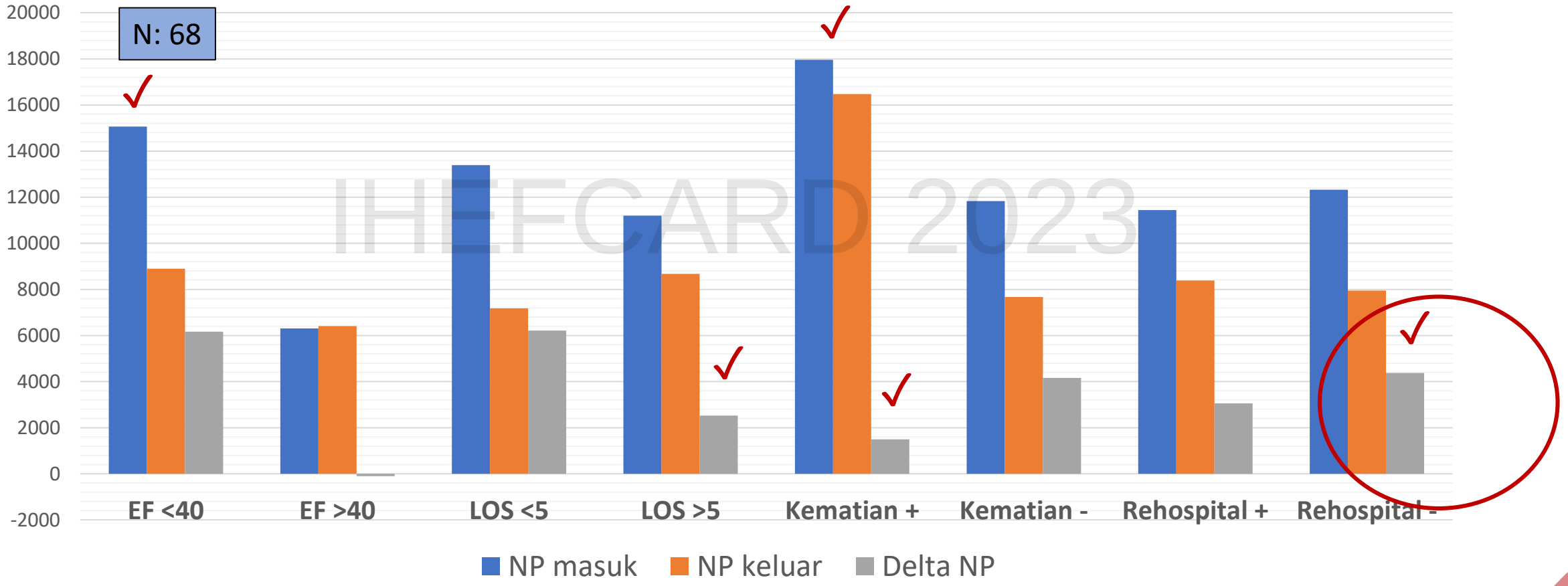
2. Registry AHF di ICCU Sardjito Hospital – 132 subyek , 2022

Nt-ProBNP in Acute Heart Failure ; CVCU RSUP Sardjito

Variabel	Mean NT Pro BNP	n, %	P	Min-max (median)
Forrester Classification				
I	17922	1 (0.9%)		(17.922)
II	**16476**	63 (61.7%)	0.191	335-70.000 (10.748)
III	12415	4 (3.9%)		2.708-35.000 (5.977)
IV	**26423**	34 (33.3%)		698-70.000 (24.051)
LOS; > 5	17545	19 (18.6%)	0.747	335-35.000 (16.370)
< 5	20127	83 (81.3%)		367-70.000 (14.421)
Kematian				
Meninggal	**24508**	26 (25.5%)	0.167	335-70.000 (18.830)
Tidak Meninggal	17983	76 (74.5%)		367-70.000 (11.616)
Hemodinamik				
Syok	**24323**	37 (36.3%)	0.44	698-70.000 (20.121)
Tidak Syok	16984	65 (63.7%)		335-70.000 (10.644)
EF ; > 40	18479	43 (42.1%)	0.139	335-70.000 (10.644)
< 40	**20498**	59 (57.9%)		418-70.000 (16.152)
Usia: > 60	19420	56 (54.9%)	0.162	335-70.000 (12.901)
< 60	19923	46 (45.1%)		367-70.000 (14.557)

3. Study Nt-Pro BNP in Acute heart failure Sardjito Hospital (2020) ; Dyah AK, Hasanah M)

Nt-pro BNP Admission and Pre-discharge in Heart Failure Patients : Out-comes mortality, Rehospitalisation



Delta Nt-Pro BNP pada terapi HF selama perawatan

	Terapi	Mean Δ Nt-Pro BNP	N 68
	Beta bloker	3079	56 (82.3%)
	Tanpa beta bloker	8547	12 (17.7%)
	ACE-i	5864	26 (38.2%)
	ARB	3679	33 (48.5%)
	Tanpa ACE/ ARB	120	9 (13.2%)
	Dengan ACE/ARB	4642	59 (86.8%)

4. Control subjects in ADESTE Study – site Dr. Sardjito Hospital, 2020

Biomarkers and Serious Adverts Evens (SAE) ; Adeste study

Budi Hartopo

	SAE(s) group (n=4) ↑	No SAE(s) group (n=6)	p value
Baseline NT-proBNP (pg/mL) mean±SEM	13684 ± 2486 ↑	9432 ± 3250	0.3737
Baseline hsTropI (ng/L) median (Q1-Q3)	211.4 (n=3) (38.00 – 349.00) ↑	17.40 (n=5) (10.55 – 2515)	0.2500
NT-proBNP at discharge (pg/mL) mean±SEM	13467 ± 7287 ↑	6186 ± 2976	0.3193
hsTropI at discharge (ng/L) median (Q1-Q3)	174.1 (n=3) (28.50 – 560.7)	15.60 (n=5) (10.00 – 1372)	0.5714
Length of stay (days) median (Q1-Q3)	6.000 (6.000 – 7.500)	7.000 (5.750 – 8.250)	0.5571

Tesis:

Hubungan Antara Strain Atrium Kiri, Kadar Penanda Nt-proBNP dengan Derajat Disfungsi Diastolik Ventrikel Kiri pada Pasien Gagal Jantung Di RSUP Dr. Sardjito

Kuswardhana. N,C, Mumpuni. H, Hariawan. H.

- Inklusi:
  - Usia ≥18 tahun
  - Penderita gagal jantung yang dirawat inap dan terdapat disfungsi diastolik yang dikonfirmasi dari hasil TTE
  - Memiliki pemeriksaan NT-ProBNP dan dengan irama sinus sebagai irama dasar

- Eksklusi:
  - Penyakit jantung katup yang signifikan (lebih dari derajat ringan baik regurgitasi maupun stenosis pda katup mitral atau aorta)
  - Penderita dengan rekaman TTE yang sulit untuk dilakukan penilaian
  - Penderita dengan fibrilasi atrium
  - Disfungsi diastolik *indeterminate*
  - Gagal ginjal kronis.

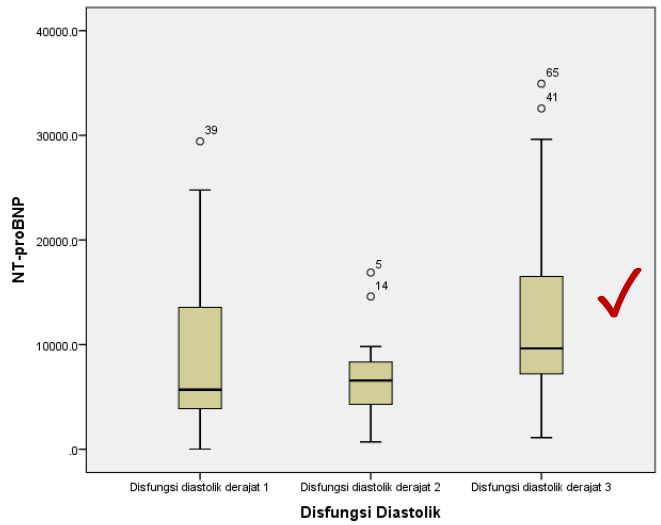
Hubungan Strain Atrium Kiri, Kadar NT-proBNP dengan Derajat Disfungsi Diastolik LV

Parameter	derajat disfungsi diastolik 1	derajat disfungsi diastolik 2	derajat disfungsi diastolik 3	Nilai p
Strain atrium kiri	11,05 (4,72-30,38)	8,87 (2,47-26)	4,6 (1,84-15,31)	< 0,001*
Kadar NT-proBNP	8520,5 (14,4-35000)	9077,5 (703,6-35000)	13583(1110-35000)	0,523

↑ ↑↑

Hubungan Nt-proBNP (Kelompok < 35000 Pg/Ml) dengan Derajat Disfungsi Diastolik (N =65)

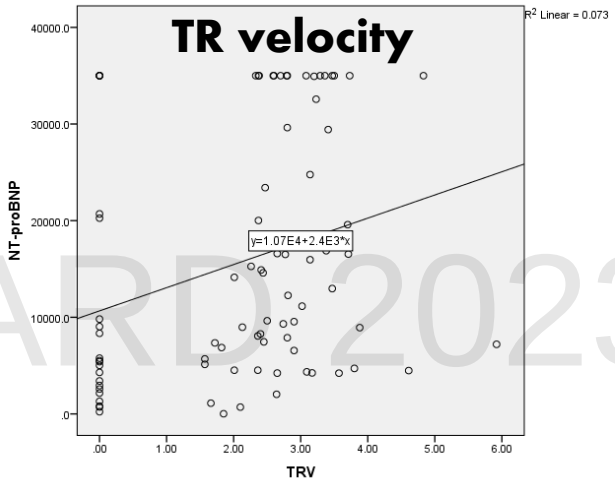
Parameter	derajat disfungsi diastolik 1	derajat disfungsi diastolik 2	derajat disfungsi diastolik 3	Nilai p
kadar NT-proBNP	5693 (14,4-29424)	6563 (703,6-16881)	**9640** (1110-34934)	0,069

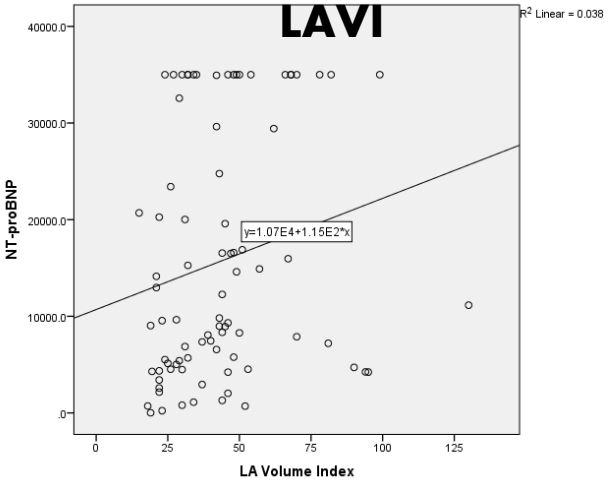


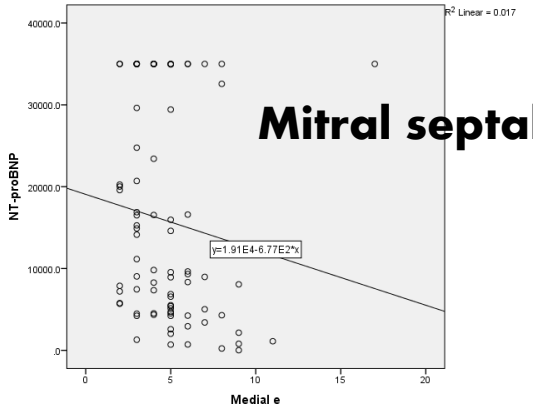
Analisis Hubungan Kadar NT-proBNP Dengan Parameter Ekokardiografi Disfungsi Diatolik

Tabel 12. Analisis hubungan kadar NT-proBNP dengan parameter ekokardiografi disfungsi diastolik

Parameter	kadar NT-proBNP (n=84)	
	r	p
LVEF (%)	- 0,239	0,029*
LVMI (g/m^2)	0,053	0,633
RWT	0,054	0,623
LA diameter (mm)	0,199	0,070
LAVI (ml/m^2)	0,279	0,010*
TR *velocity* (m/s)	0,340	0,002*
Mitral E *wave velocity*	-0,04	0,710
Mitral E/A *ratio*	0,162	0,142
Mitral lateral *e'*	- 0,243	0,026*
Mitral septal *e'*	- 0,290	0,007*
Mitral E/e' *average ratio*	0,054	0,626
Laju jantung saat TTE	0,023	0,839

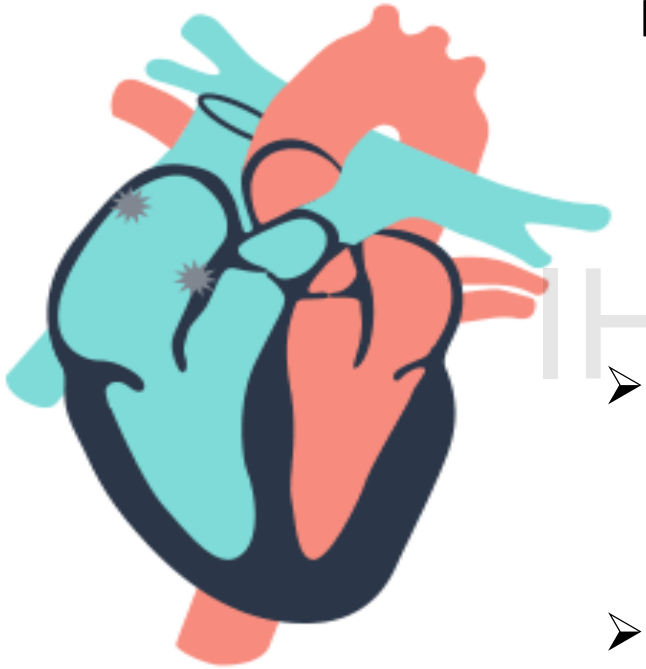






Interval Koefisien	Tingkat Hubungan
0,00 – 0,199	Sangat rendah
0,20 – 0,399	Rendah
0,40 – 0,599	Cukup
0,60 – 0,799	Kuat
0,80 – 1,000	Sangat kuat

Summary



- Natriuretic peptides (NPs) are produced in response to the ventricular wall stress, among which BNP and NT-proBNP were incorporated in different major guidelines for heart failure management.
- NT-proBNP is potentially superior to BNP for heart failure management because
  - NT-proBNP is more stable with longer half life
  - NT-proBNP not affected by neprilysin inhibitor
  - NT-proBNP has better sensitivity for HF diagnosis
  - NT-proBNP has better prognostic value than BNP
- Data in Indonesia (Yogyakarta); NT-pro BNP in heart failure in addition to diagnosis and exclusion, is useful for risk stratification related to several clinical parameters, echocardiography, and assessing prognosis and therapy.
- It is necessary to increase the use of NT-pro BNP in the management of heart failure and **research for** screening of people with risk factors for heart failure.

Thank you