The Clinical Evolution of NT-proBNP: From Diagnosis and Prognosis to Guiding Therapy

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Inova Schar Heart and Vascular

Disclosures

Consulting/Advisory Board: Abbott Diagnostics, FujiRebio, QuidelOrtho,
Roche Diagnostics
Endpoint adjudication: Siemens Healthineers, Tosoh
Speaker: PathFast/PolyMedco
Royalties: UpToDate

The Three Aims of In-Vitro Diagnostic Tests

The Three Aims of In-Vitro Diagnostic Tests

Prognosis

The Three Aims of In-Vitro Diagnostic Tests

Prognosis

Diagnosis

The Three Aims of In-Vitro Diagnostic Tests

Prognosis

Diagnosis

Prediction/Guidance
Effect Measure Modification
Precision Medicine

Learning Objectives

- Explain the signs and symptoms of HF
- Discuss the optimal diagnostic thresholds for NT-proBNP to diagnose HF
- Explain the prognostic implications of an elevated natriuretic peptide levels and their role for staging HF
- Review American Diabetic Association guidelines for measuring NT-proBNP to risk stratify asymptomatic patients with diabetes
- Identify potential confounders whether they be medical comorbidities or treatments for HF that may influence natriuretic peptides and recognize if these might impact the threshold to diagnose HF
- Evaluate how NT-proBNP levels may be used along with clinical judgement to optimize HF medical management

The Role for Natriuretic Peptides in Cardiovascular Disease

- Review of acute decompensated heart failure
  - Epidemiology
  - Pathophysiology
  - Clinical presentation
- Diagnosis of heart failure in patients presenting with dyspnea
  - ICON Reloaded
  - Considerations in patients with known heart failure
- Staging heart failure with natriuretic peptides
- NT-proBNP for screening for HF risk
- Emerging use of NT-proBNP to guide optimization of medical therapy post acute heart failure hospitalization

Heart Failure in the United States

Population group	Prevalence, 2017–2020, ≥20 y of age	Mortality, 2021, all ages*	Hospital discharges, 2020, all ages	Cost, 2012†
Both sexes	6 700 000 (2.3%) [95% CI, 1.9%–2.8%]	85 037	1 111 500	$30.7 billion
Males	3 700 000 (2.7%)	40 344 (47.4%)‡		…
Females	3 000 000 (1.9%)	44 693 (52.6%)‡		…
NH White males	2.9%	31 993	…	…
NH White females	1.6%	35 873	…	…
NH Black males	3.8%	4902	…	…
NH Black females	3.3%	5208	…	…

American Heart Association.

Martin et al. *Circulation*. 2024;149:e347–e913. DOI: 10.1161/CIR.0000000000001209

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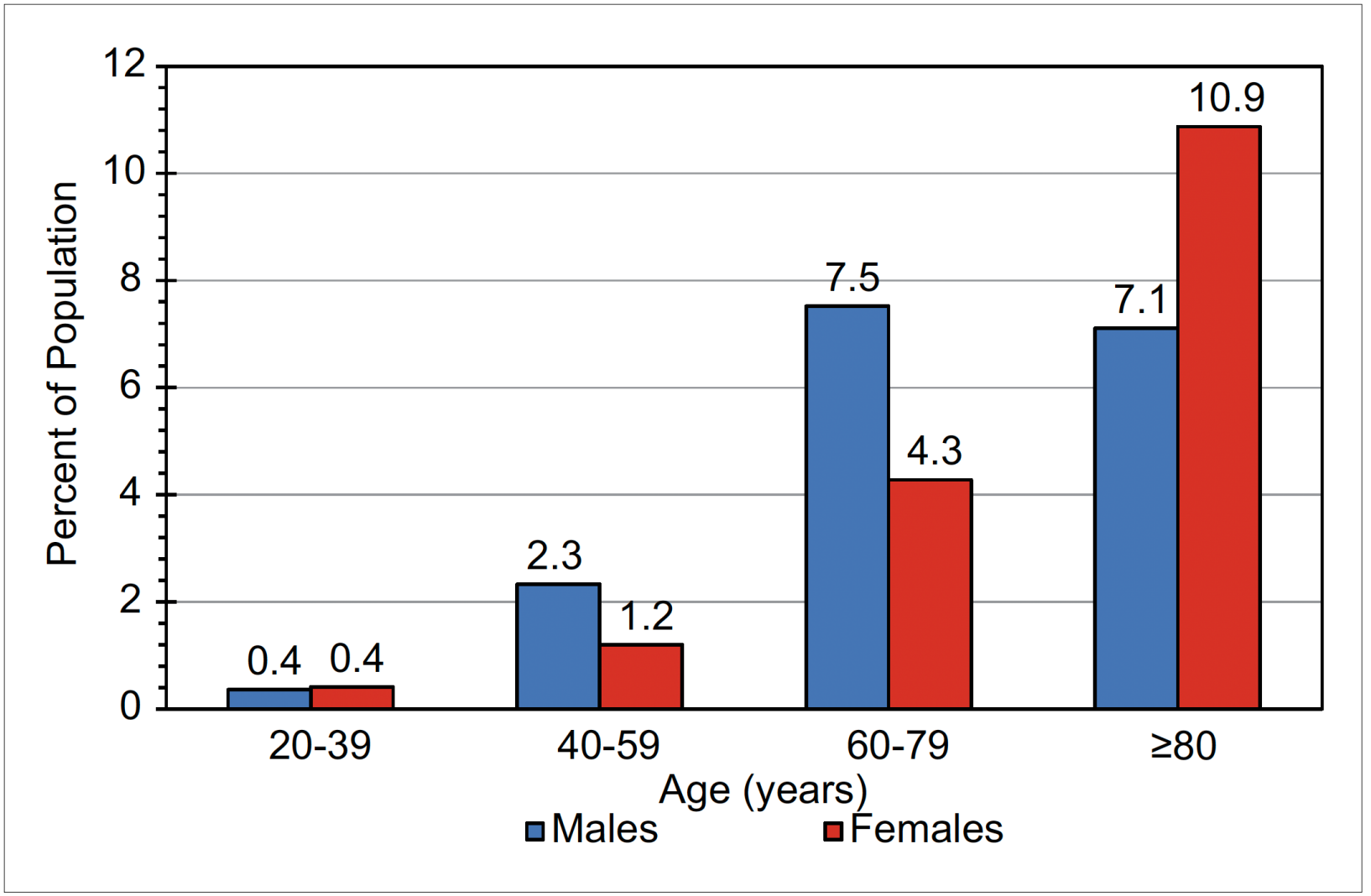
Prevalence of Heart Failure Among US Adults
(NHANES 2017-2020)



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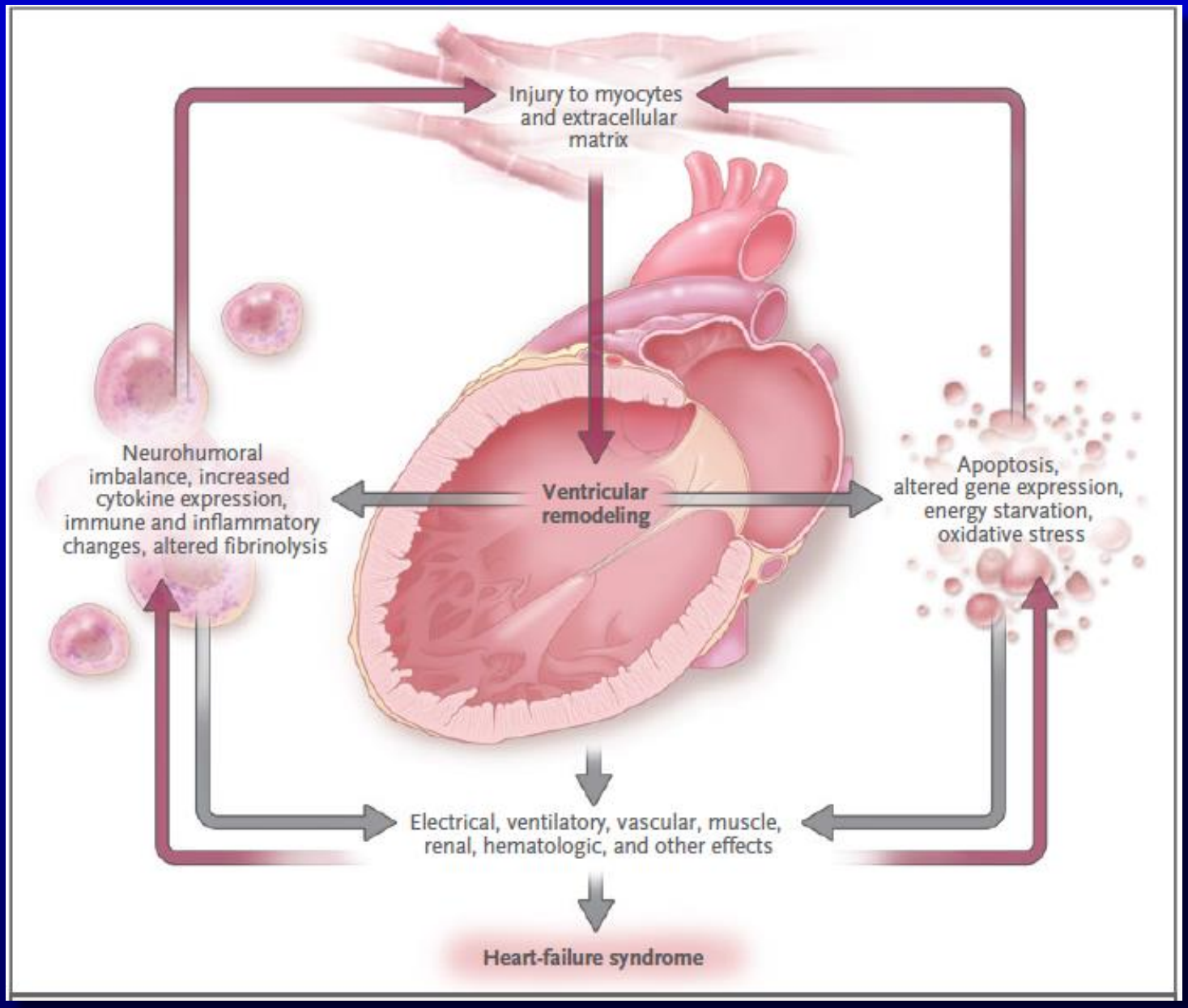
Pathophysiology of Systolic Heart Failure



N Engl J Med 2010;362:228-38

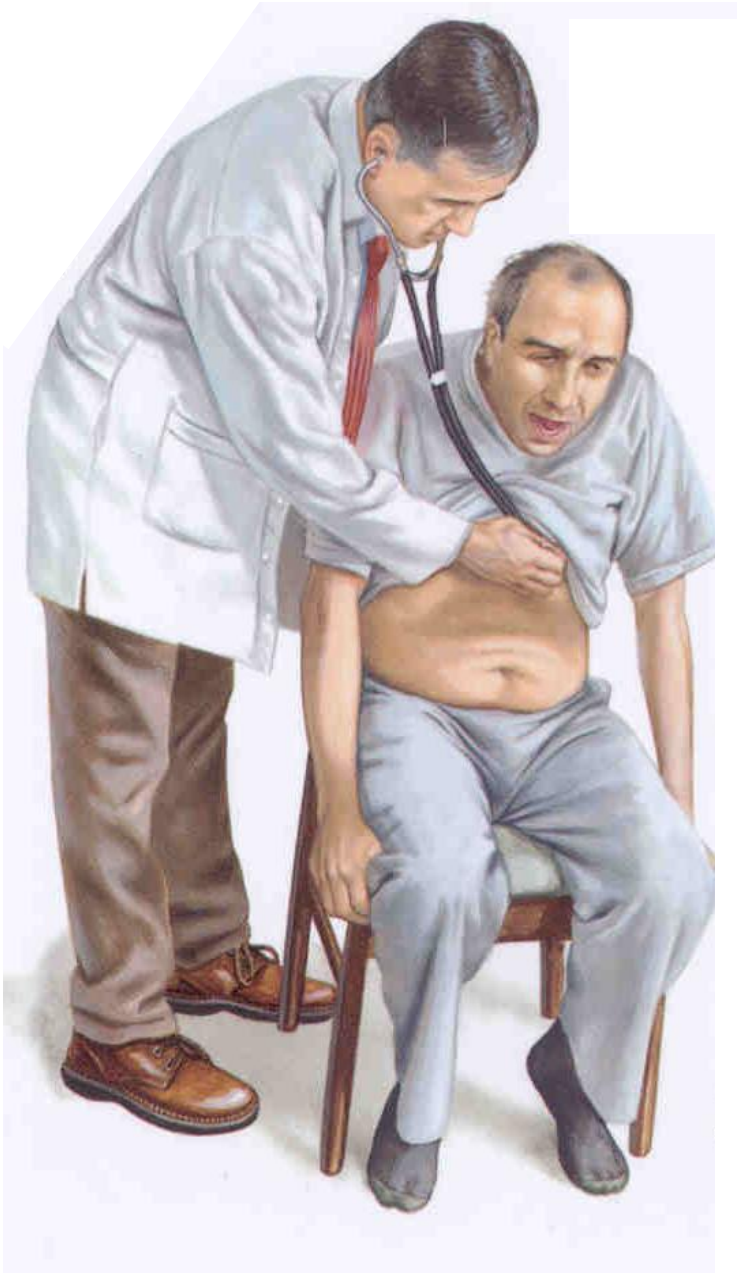
A New Cough

Netter's cardiology, 2004

Case Presentation

- 73 year male with 10 days of cough productive of yellow-green phlegm.
- 1-2 days of increased dyspnea with exertion, and now at rest. At baseline he could climb a flight of stairs and walk several blocks
- Positive for orthopnea, and paroxysmal nocturnal dyspnea.
- No fever or chills, chest pain, diaphoresis or nausea.
- Past history:
  - CABG and MI 10 years ago
  - HTN, diabetes and hyperlipidemia

Physical Findings



Netter’s cardiology, 2004

Case Presentation

- Pulse 92 beats/min and regular
- Blood pressure 121/74 mm Hg
- There is jugular venous distension
- Lateral displacement of the cardiac apical beat on the left side of the chest
- Edema of the lower limbs
- The lung examination is normal

Criteria for Heart Failure

Table 1. Criteria of CHF.*

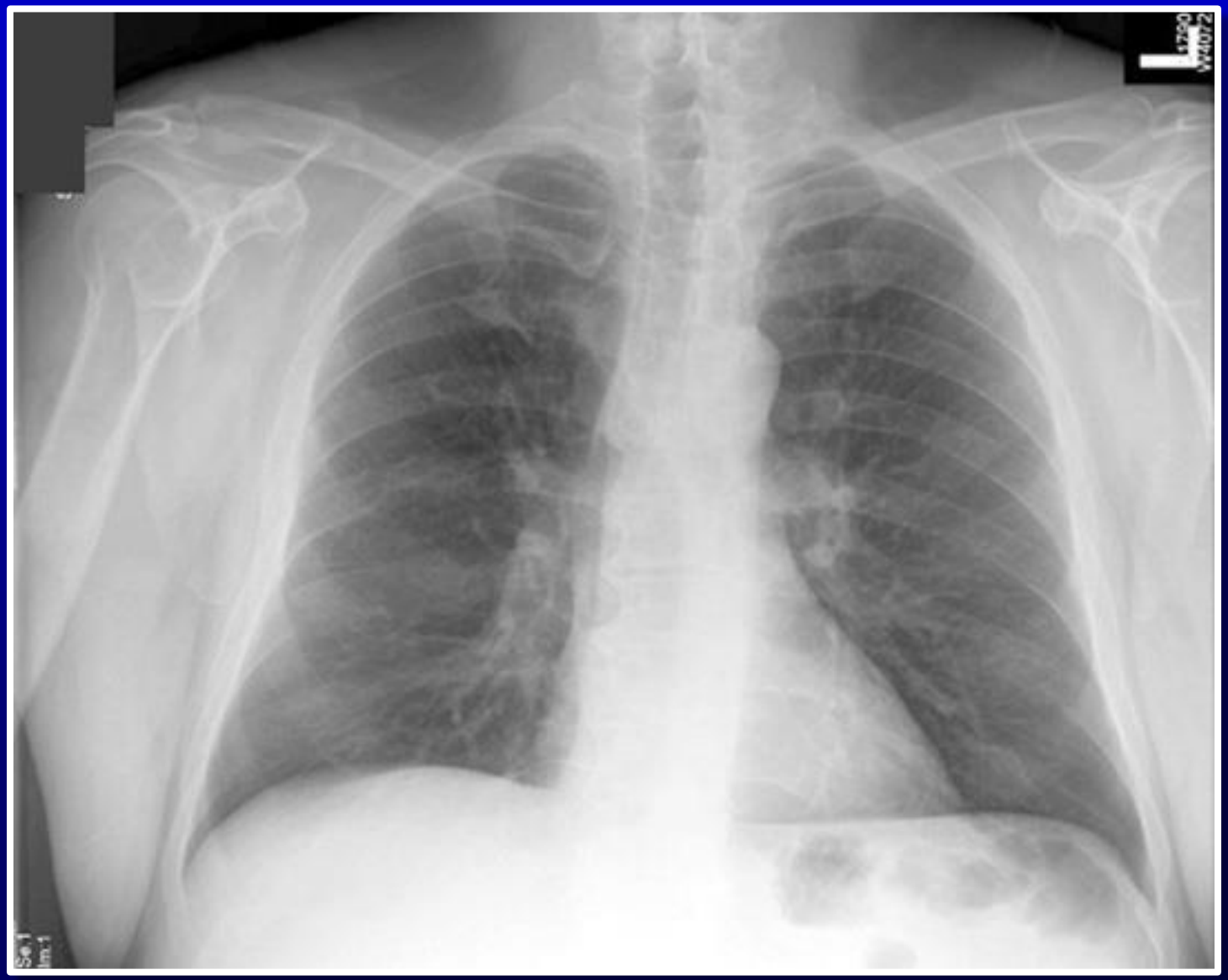
Major Criteria
Paroxysmal nocturnal dyspnea or orthopnea
Neck-vein distention
Rales
Cardiomegaly
Acute pulmonary edema
S_3 gallop
Increased venous pressure ->16 cm of water
Circulation time ≥25 sec
Hepatojugular reflux
Minor Criteria
Ankle edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity ↓ ⅓ from maximum
Tachycardia (rate of ≥120/min)
Major or Minor Criterion
Weight loss ≥4.5 kg in 5 days in response to treatment

*For establishing a definite diagnosis of congestive heart failure in this study, 2 major or 1 major & 2 minor criteria had to be present concurrently.

The NEW ENGLAND JOURNAL of MEDICINE

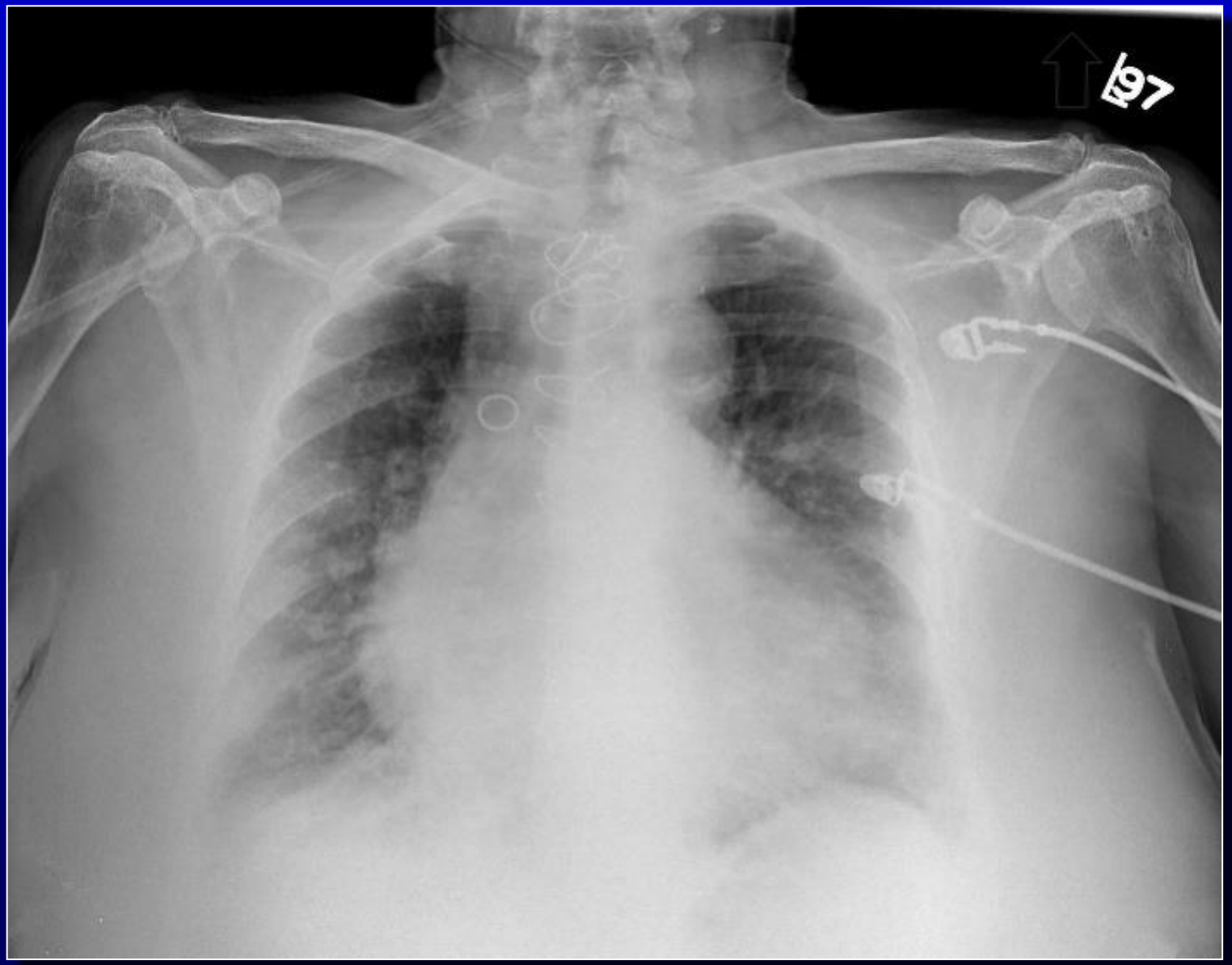
McKee PA et al. N Engl J Med 1971;285:1441-1446

Normal
Chest X-ray

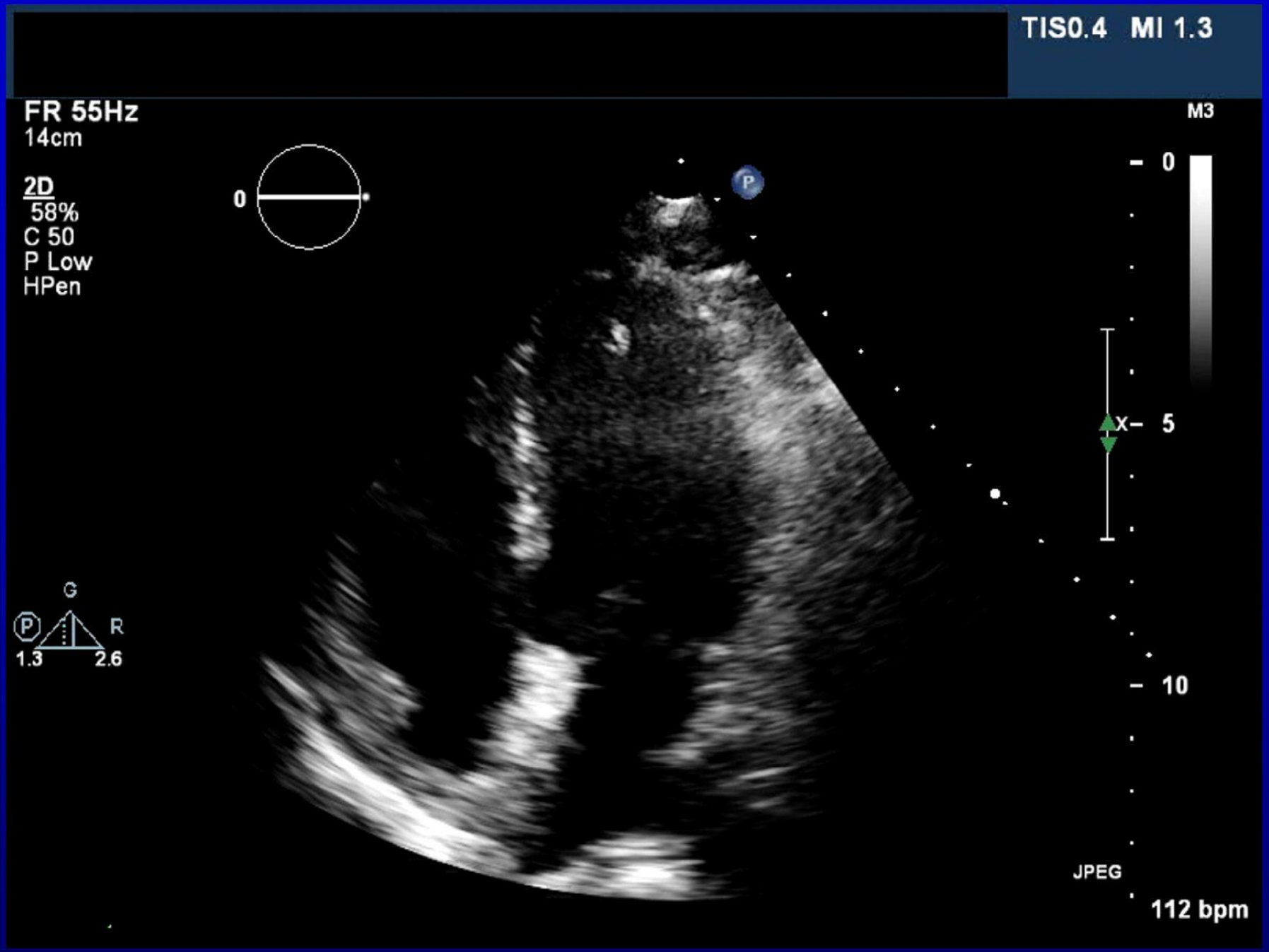


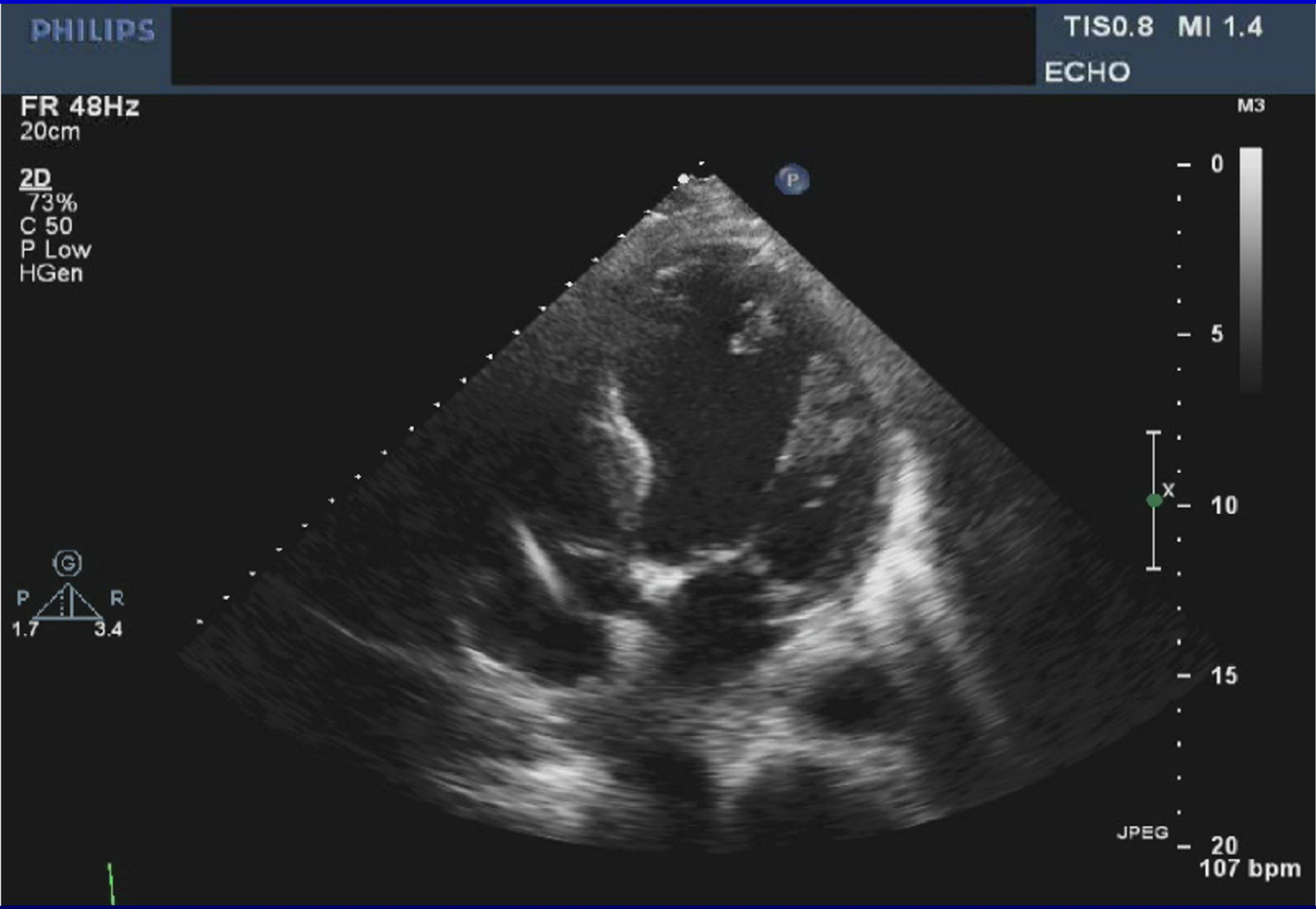
Case Presentation

Chest X-ray



Normal echocardiogram




PHILIPS
TIS0.8 MI 1.4
ECHO
FR 48Hz
20cm
M3
2D
73%
C 50
P Low
HGen
P
0
5
10
15
20
X
G
P
R
1.7
3.4
JPEG
107 bpm

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Poll Question #1

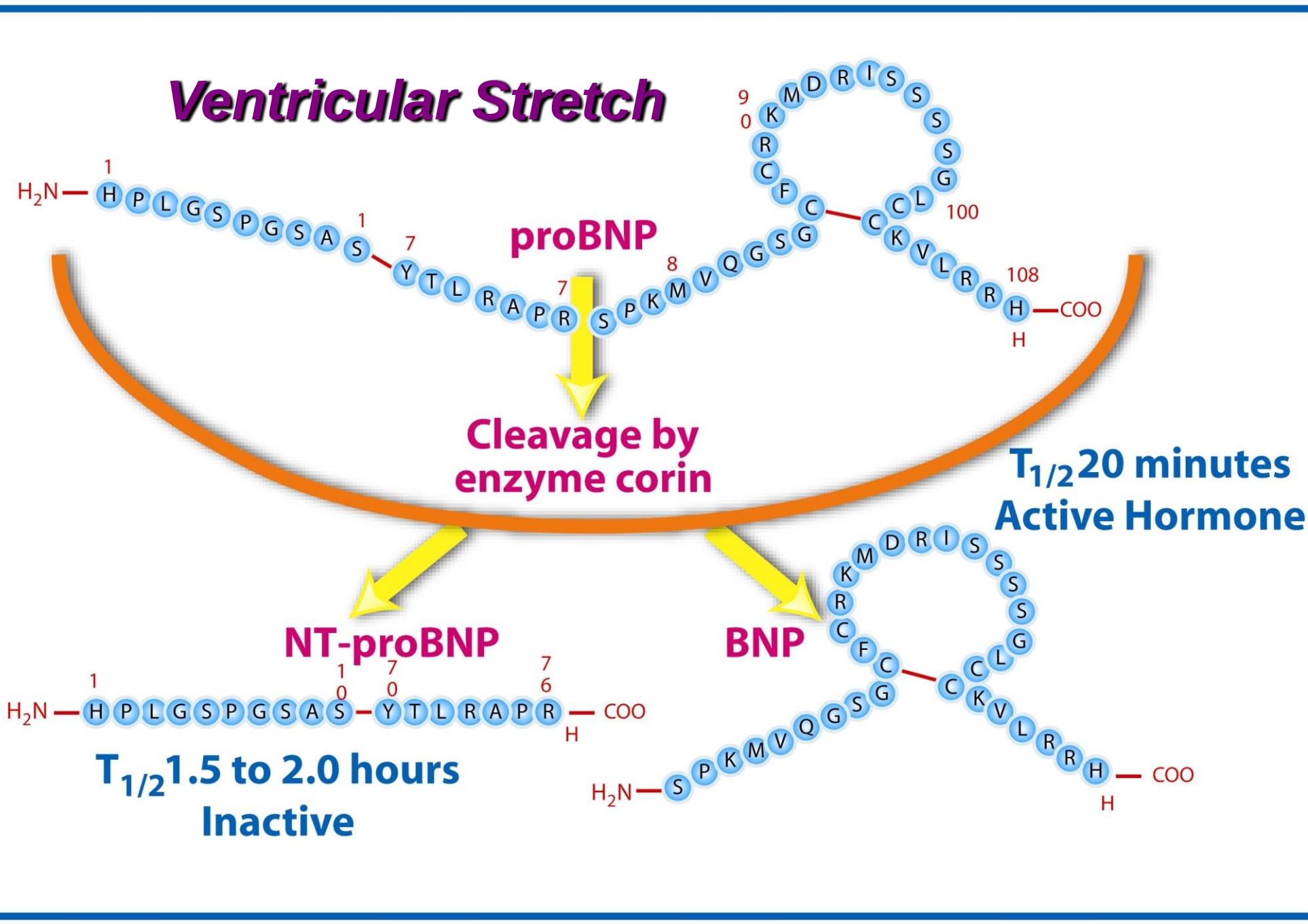
How is NT-proBNP best used to diagnose acute heart failure?

a) Single cut-off for all patients being presenting with dyspnea (shortness of breath) of uncertain etiology

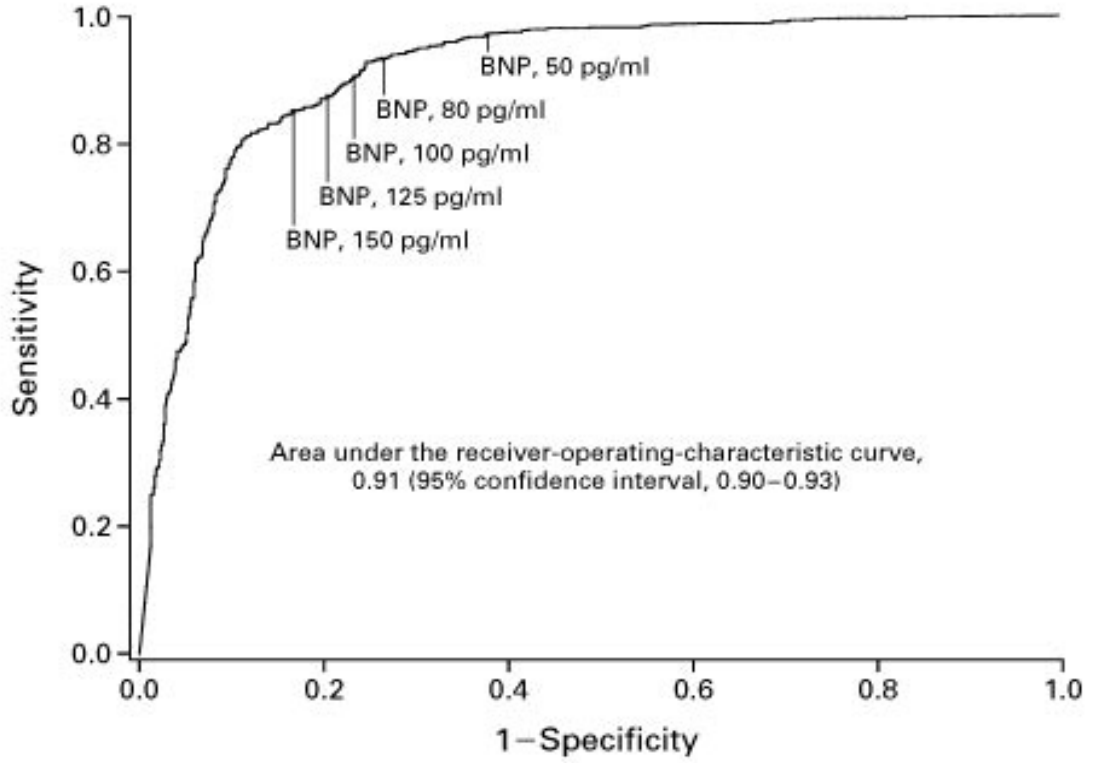
b) Age specific cut-offs to “rule-in” heart failure and a single cut-off to “rule-out” Heart failure

c) Gender specific cut-offs to “rule-in” and “rule-out” heart failure

d) Renal function specific cut-offs (i.e. above and below an eGFR of 60 mL/min/1.73m^2) to “rule-in” and “rule-out” heart failure


Ventricular Stretch
proBNP
Cleavage by enzyme corin
NT-proBNP
BNP
T1/2 20 minutes
Active Hormone
T1/2 1.5 to 2.0 hours
Inactive

Receiver-Operating-Characteristic Curve for Various Cutoff Levels of BNP in Differentiating between Dyspnea Due to Heart Failure or Due to Other Causes



BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

The NEW ENGLAND JOURNAL of MEDICINE

Maisel AS et al. N Engl J Med 2002;347:161-167

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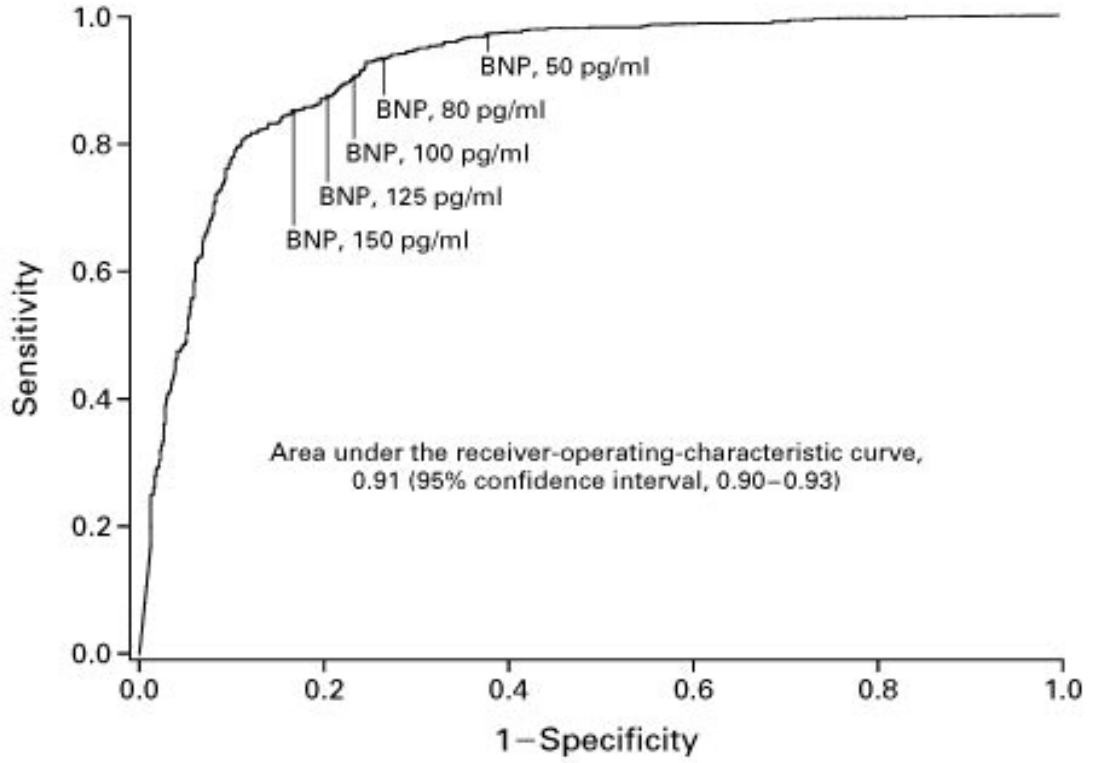

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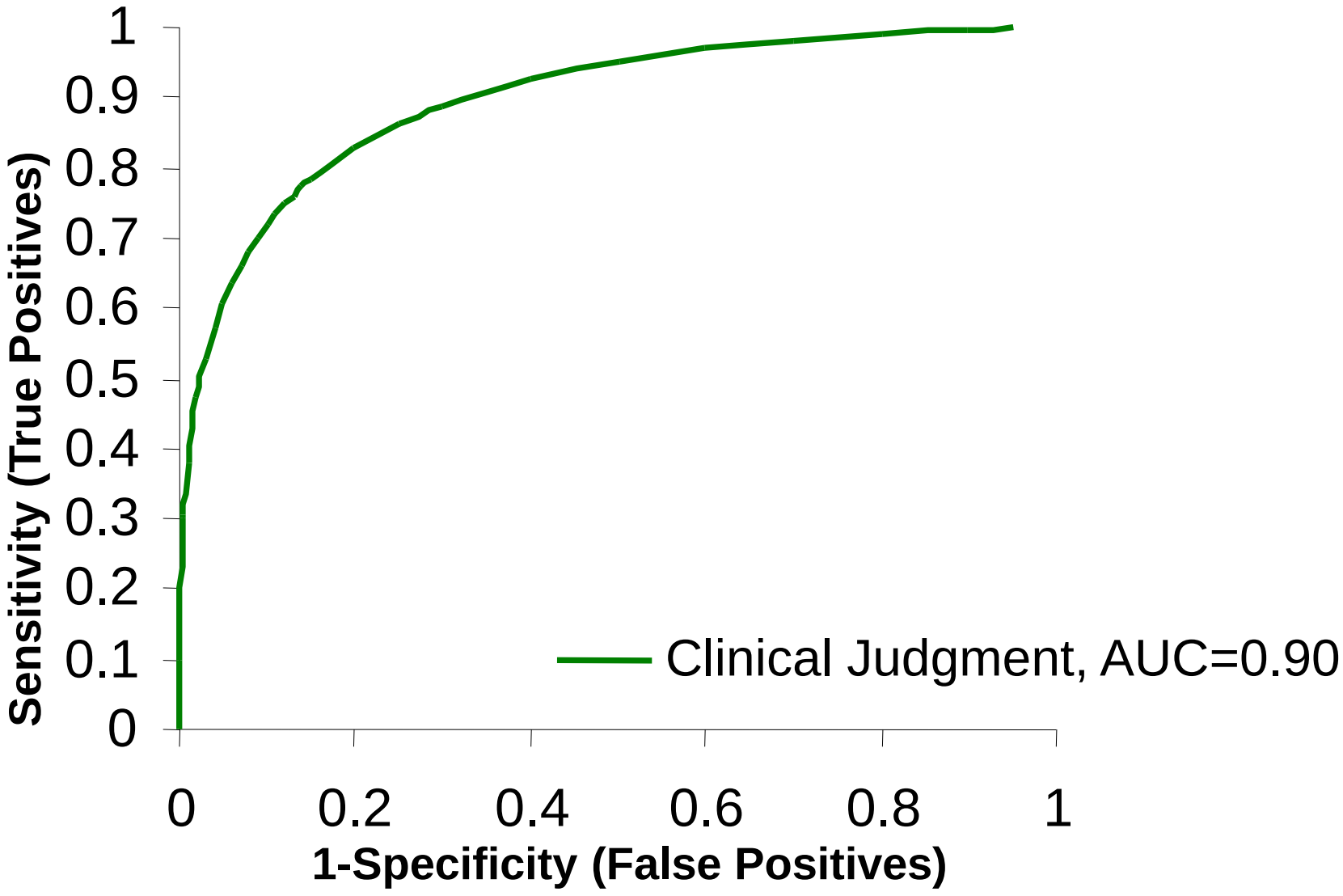
Results: Primary Endpoint



Januzzi I et al. Am J Cardiol. 2005;958:948-54

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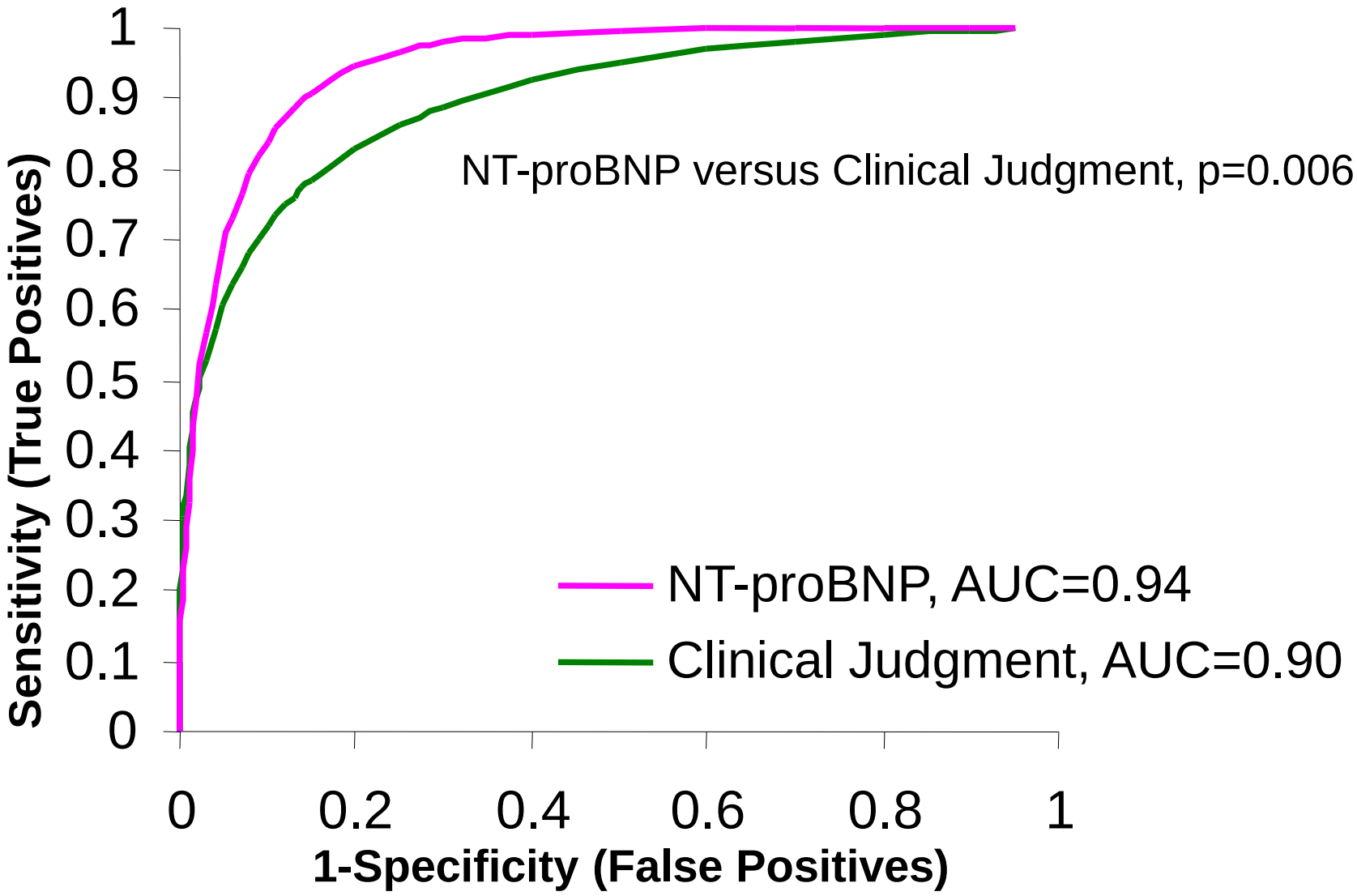

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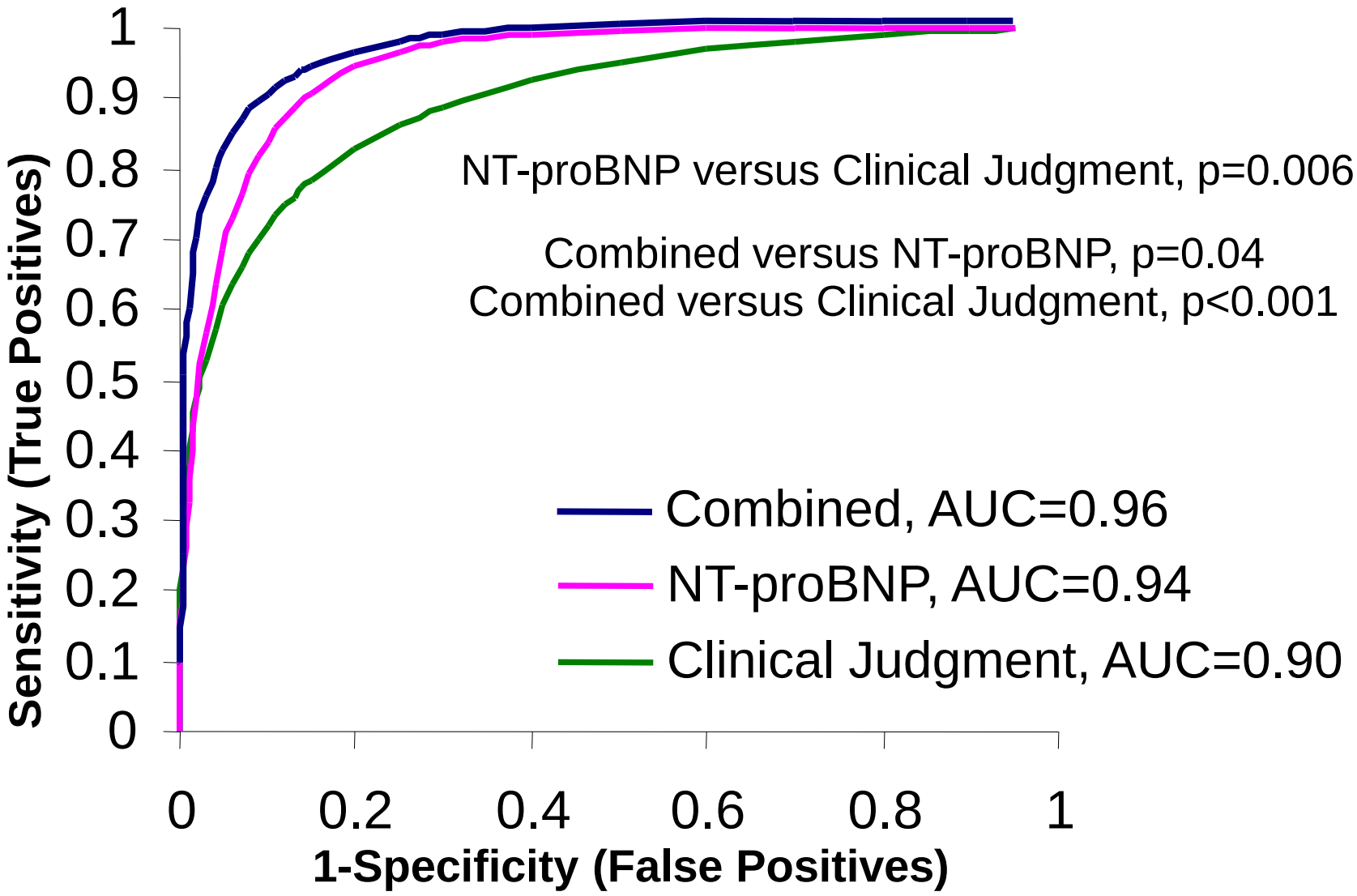

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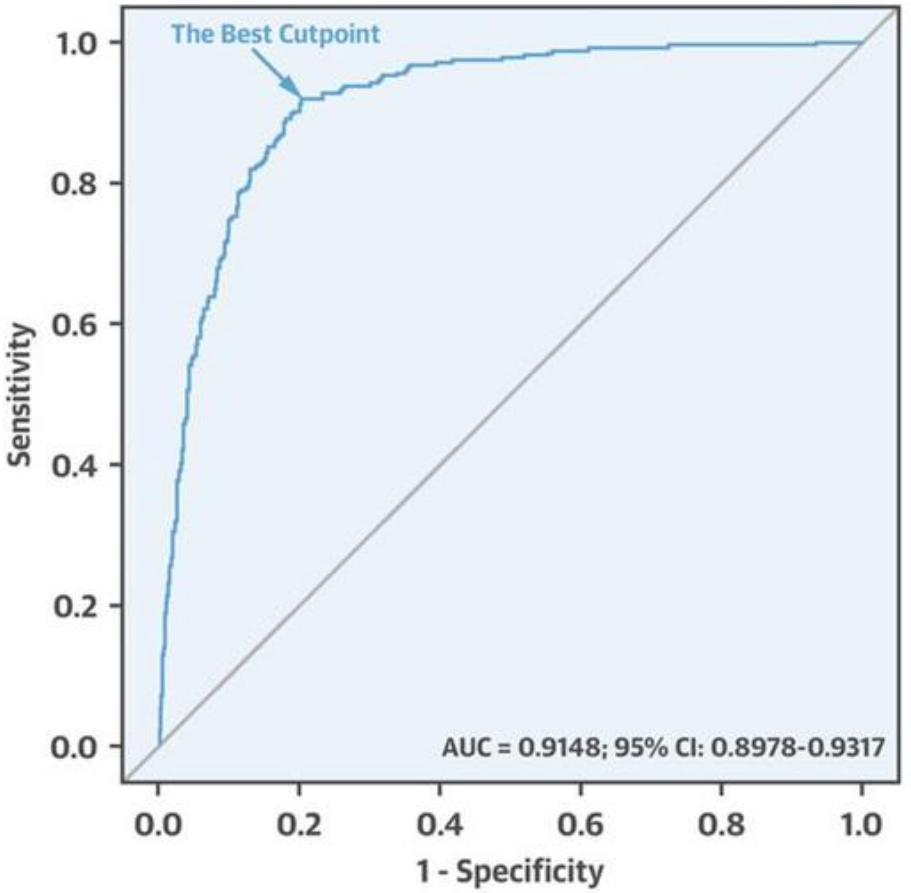
NT-proBNP for diagnosis of acute heart failure in patients with shortness of breath (ICON-RELOADED)

The Icon Reloaded Study



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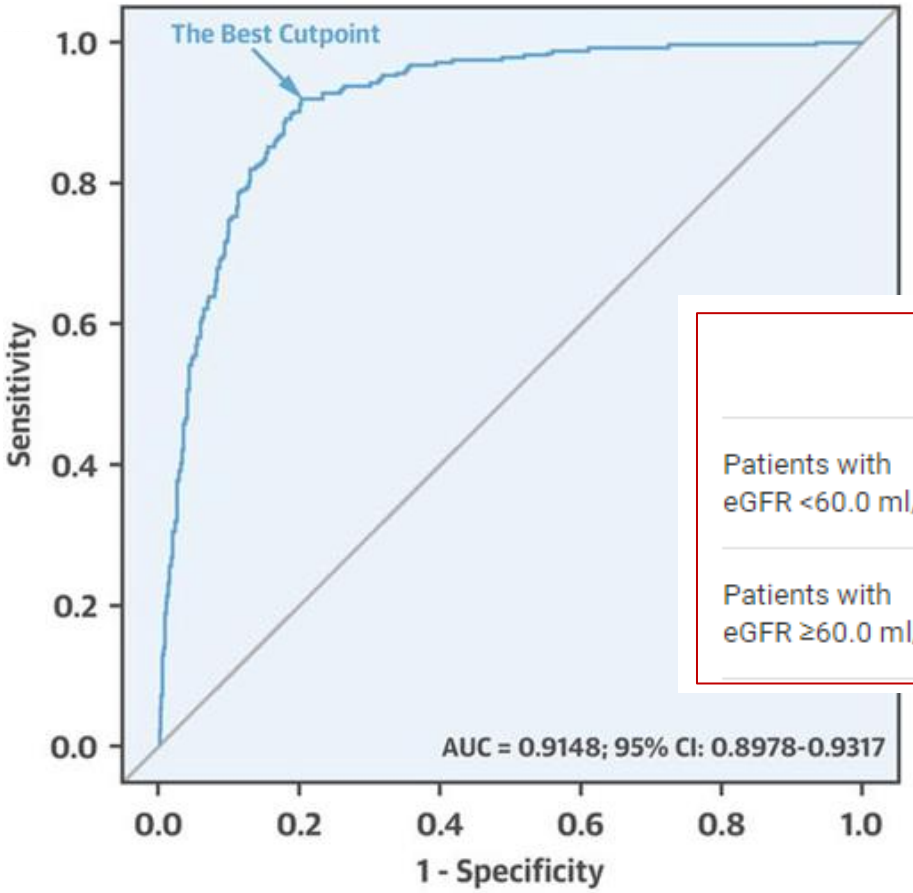
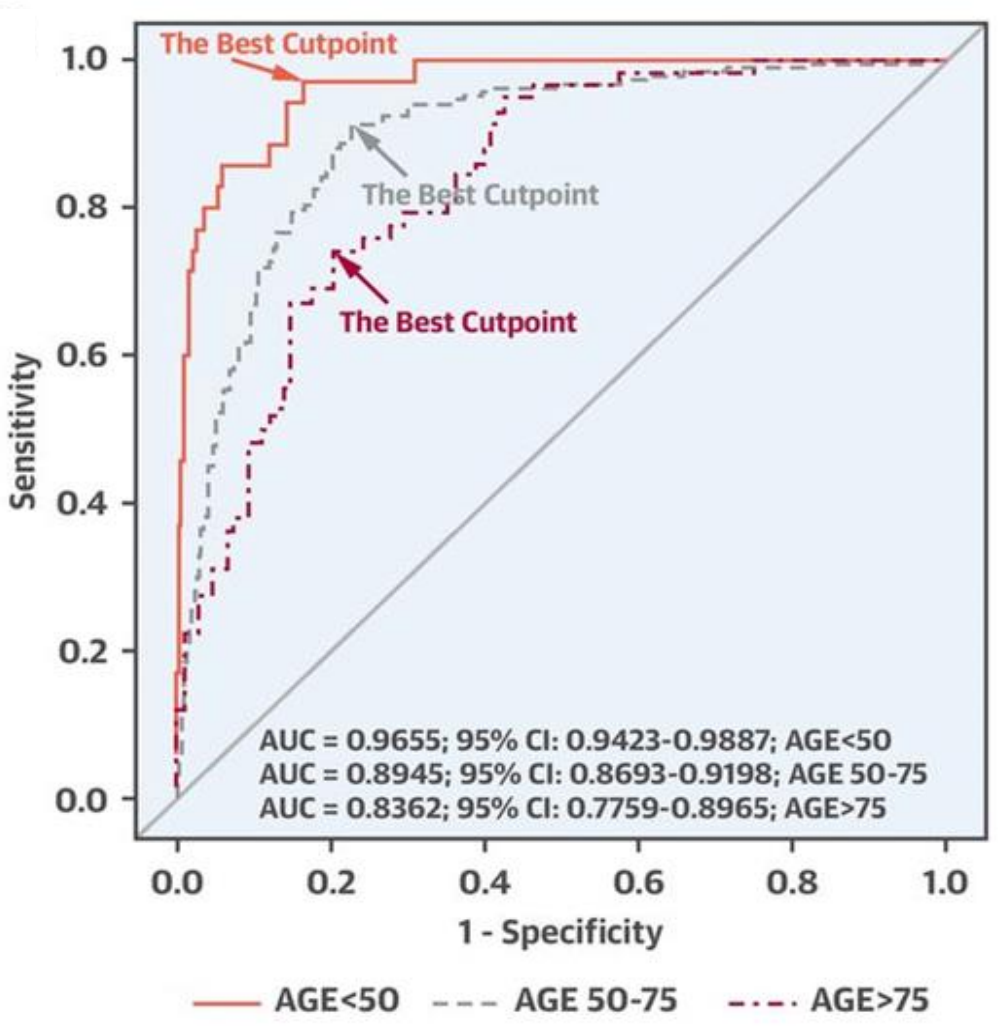


	AUC	p Value for Difference in AUC
Patients with eGFR <60.0 ml/min/1.73 m^2	0.872	0.12
Patients with eGFR ≥60.0 ml/min/1.73 m^2	0.907	

Januzzi, JL et al. J Am Coll Cardiol 2018;71:1191-1200

NT-proBNP for diagnosis of acute heart failure in patients with shortness of breath (ICON-RELOADED)

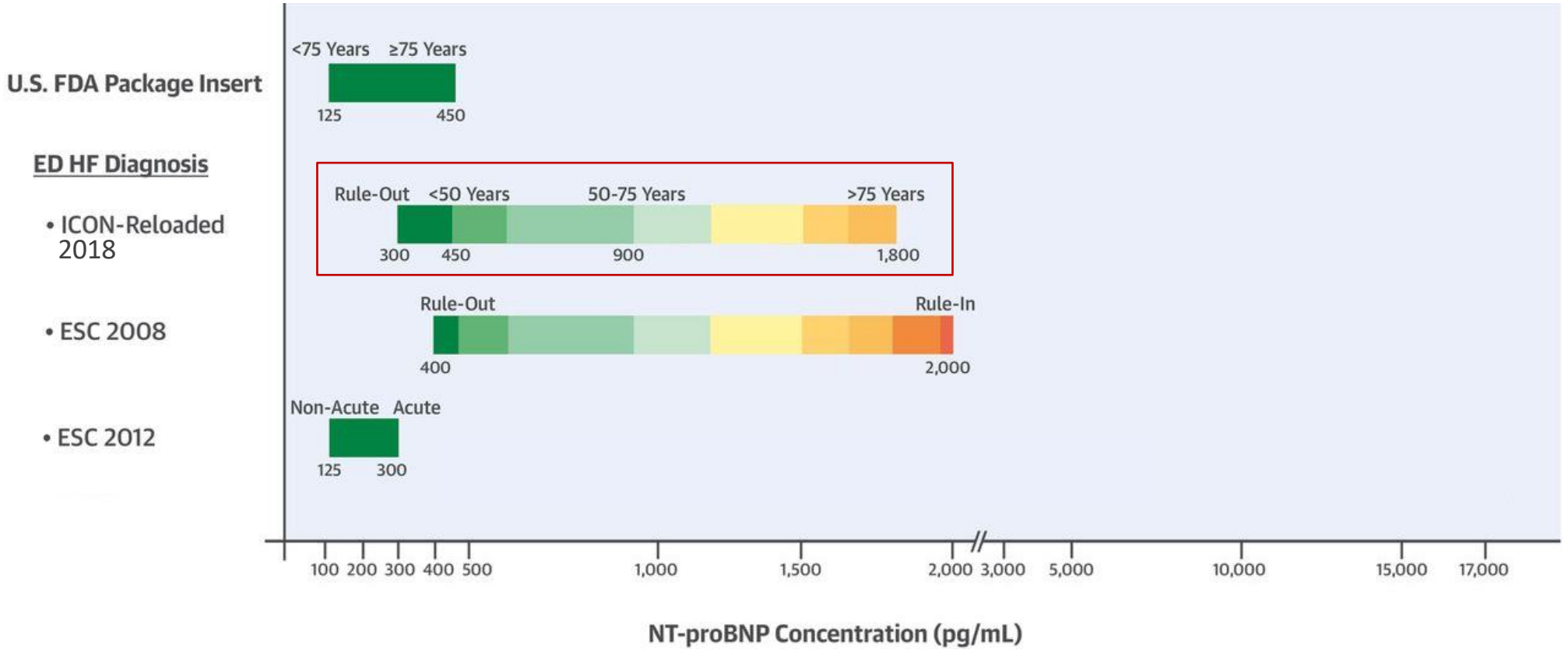


	Age <50	Age 50-75	Age ≥75
Sensitivity	97.1% (95% CI 91.6%-100.0%)	91.3% (95% CI 87.2%-95.4%)	74.1% (95% CI 62.9%-85.4%)
Specificity	83.6% (95% CI 80.1%-87.1%)	77.0% (95% CI 73.8%-80.3%)	79.6% (95% CI 72.0%-87.2%)
PPV	32.7% (95% CI 28.0%-37.7%)	53.0% (95% CI 49.3%-56.7%)	66.2% (95% CI 56.6%-74.5%)
NPV	99.7% (95% CI 98.1%-100.0%)	96.9% (95% CI 95.1%-98.0%)	85.1% (95% CI 78.6%-90.0%)
Accuracy	84.6% (95% CI 81.3%-87.9%)	80.2% (95% CI 77.5%-82.9%)	77.7% (95% CI 71.4%-84.0%)

Januzzi, JL et al. J Am Coll Cardiol 2018;71:1191-1200

Diagnostic threshold for acute heart failure with NT-proBNP

Diagnostic Recommendations Heterogeneity



J Am Coll Cardiol 2018;71:1201-1203

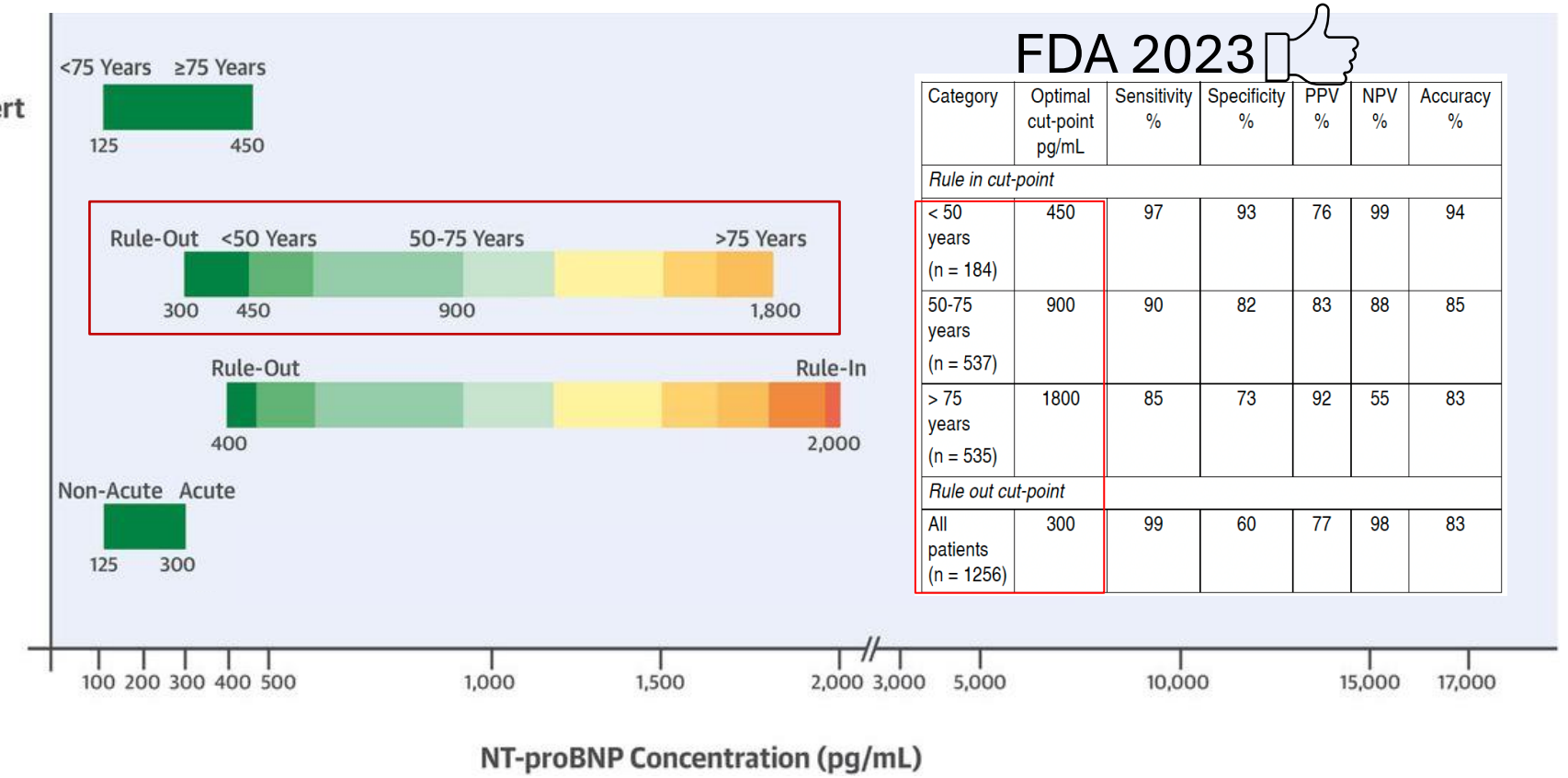
Diagnostic threshold for acute heart failure with NT-proBNP

Diagnostic Recommendations Heterogeneity

U.S. FDA Package Insert

ED HF Diagnosis

- ICON-Reloaded 2018
- ESC 2008
- ESC 2012



FDA 2023

Category	Optimal cut-point pg/mL	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Rule in cut-point						
< 50 years (n = 184)	450	97	93	76	99	94
50-75 years (n = 537)	900	90	82	83	88	85
> 75 years (n = 535)	1800	85	73	92	55	83
Rule out cut-point						
All patients (n = 1256)	300	99	60	77	98	83

J Am Coll Cardiol 2018;71:1201-1203

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Poll Question #2

For outpatients with heart failure, are there special considerations for BNP and NT-proBNP interpretation?

a) Expect levels of both BNP and NT-proBNP to be always elevated and therefore can't be used to diagnose if a heart failure exacerbation is a cause of worsening shortness of breath

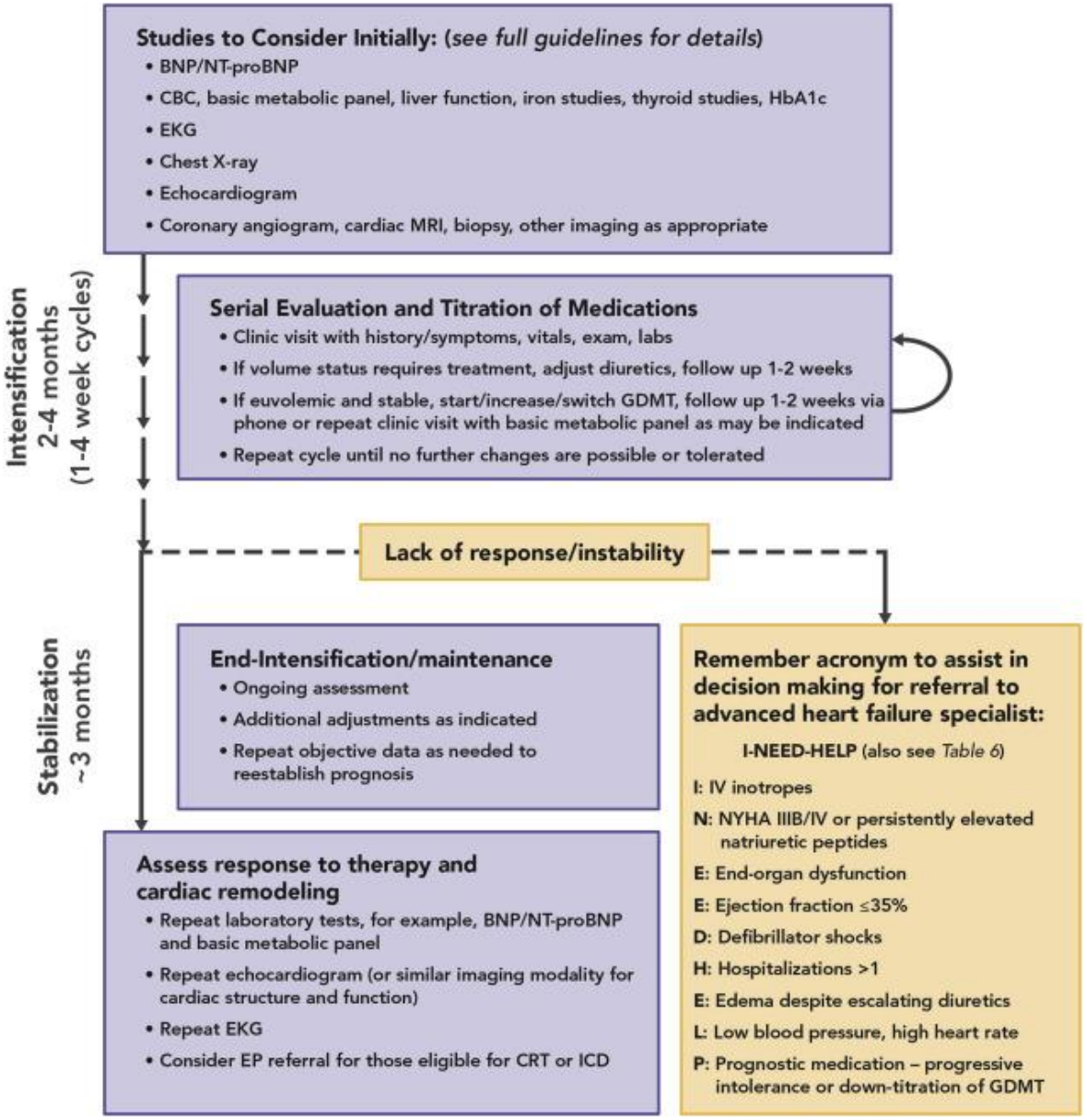
b) BNP and NT-proBNP levels can change in the opposite direction depending on the type of medical therapy limiting the use of BNP for the diagnosis of a heart failure exacerbation

c) Knowing a baseline level of BNP or NT-proBNP in a stable outpatient with symptomatic heart failure is recommended

d) Following serial NT-proBNP levels could be an effective way of determining if patients are on optimal medical treatment to prevent hospitalizations and death

ACC Expert Consensus Decision Pathway for HF Treatment

The role of BNP/NT-proBNP testing in outpatients



Yancy et al. J Am Coll Cardiol 2018;71:201-230

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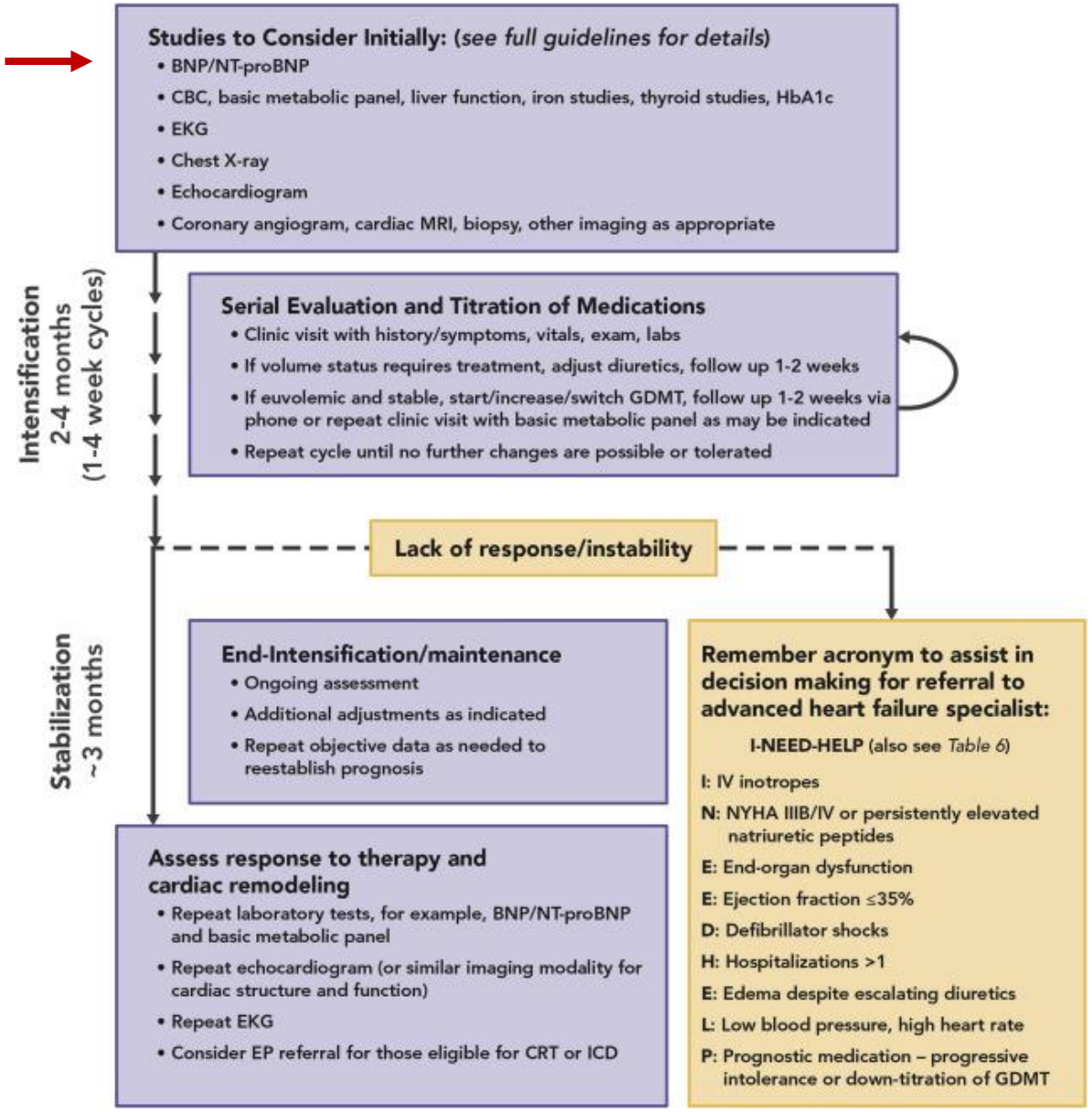

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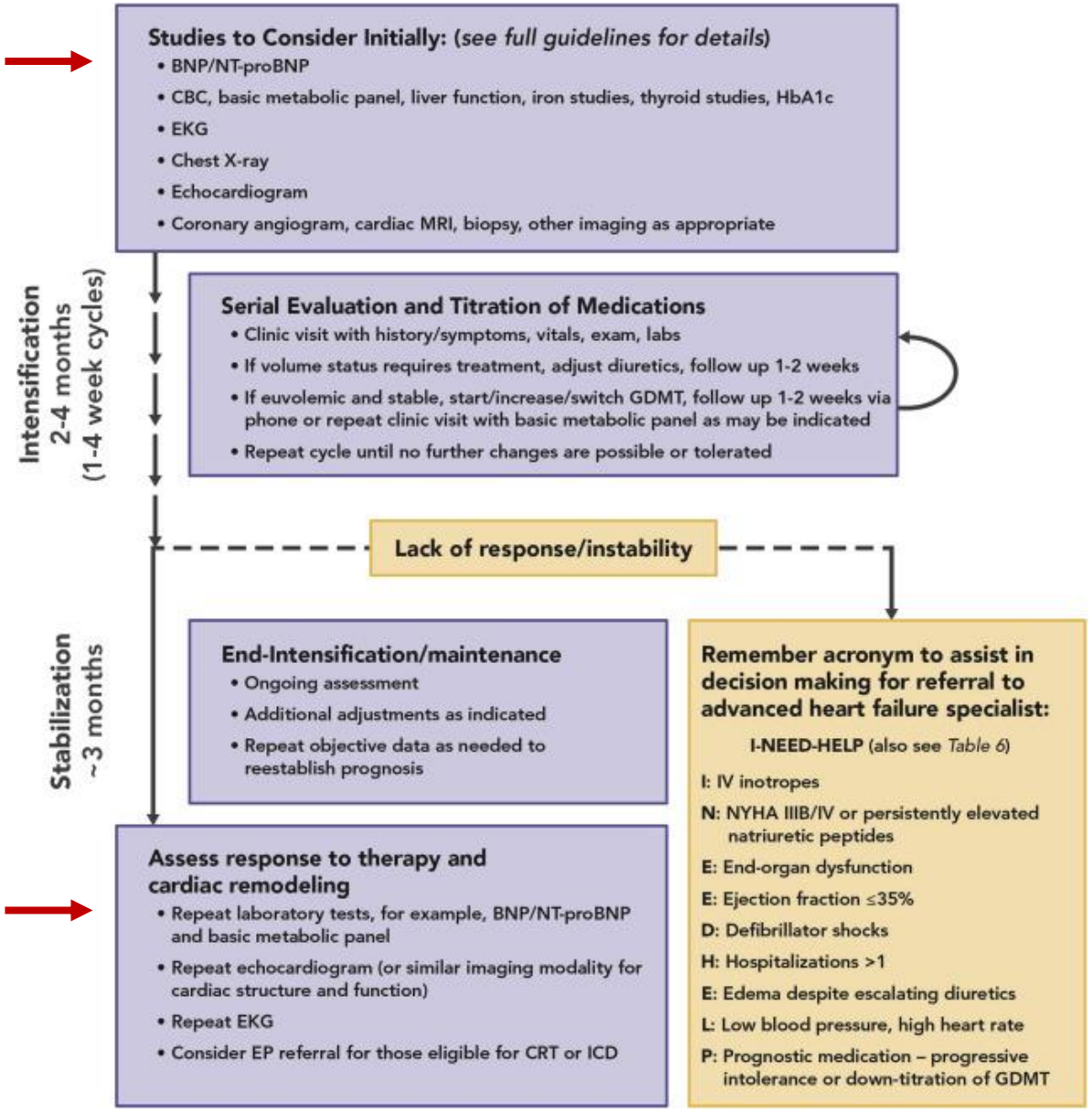

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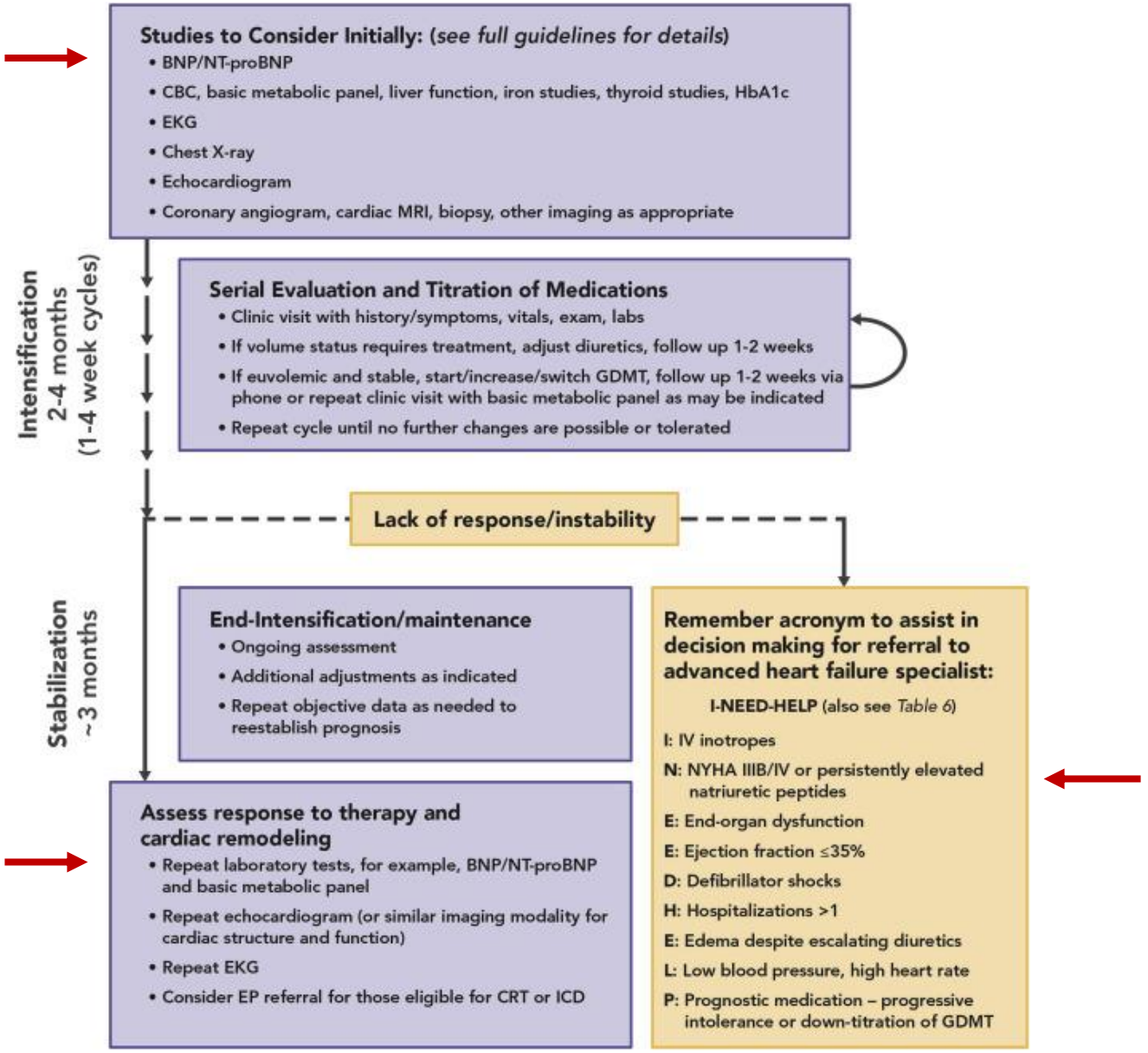

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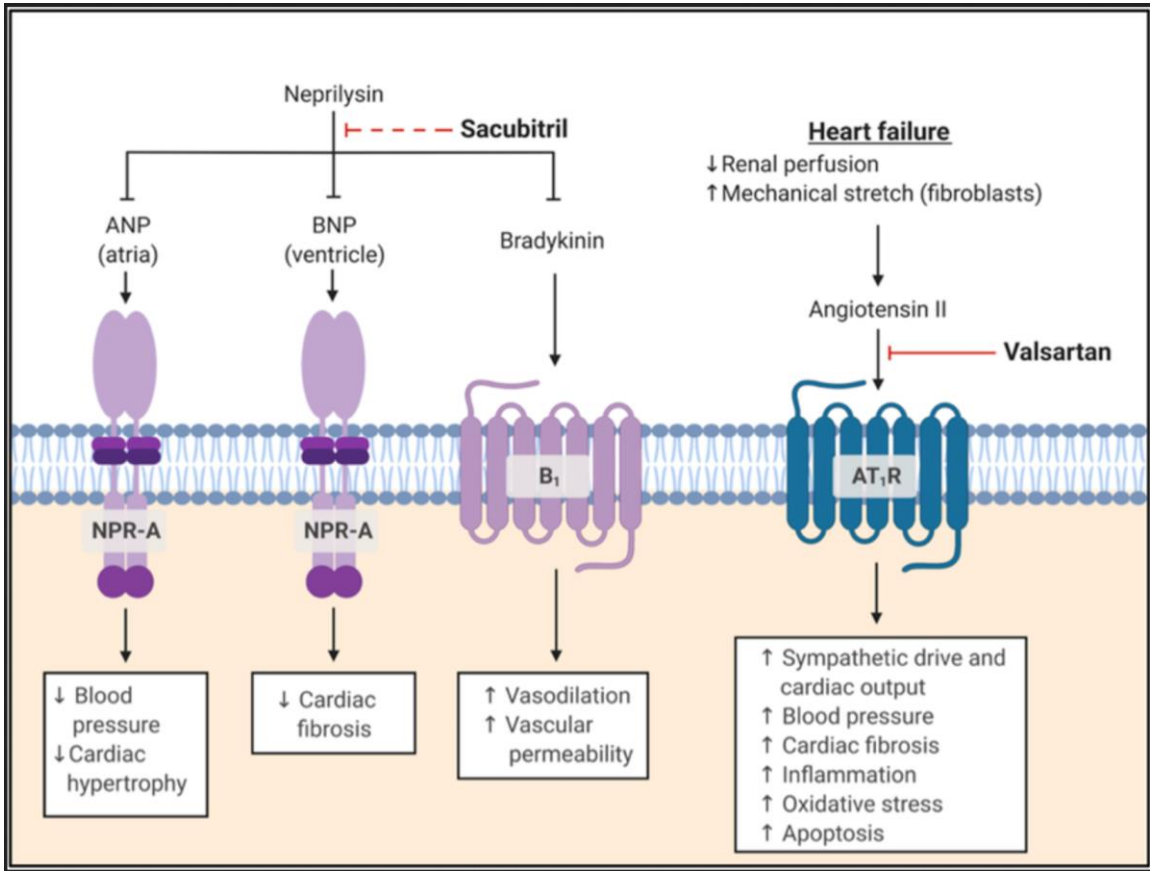
Changes in NT-proBNP and BNP
Patients With HF treated with Sacubitril/Valsartan (Entresto)
PARIDIGM-HF



Zile et al. JACC 2016;68:2425-2436

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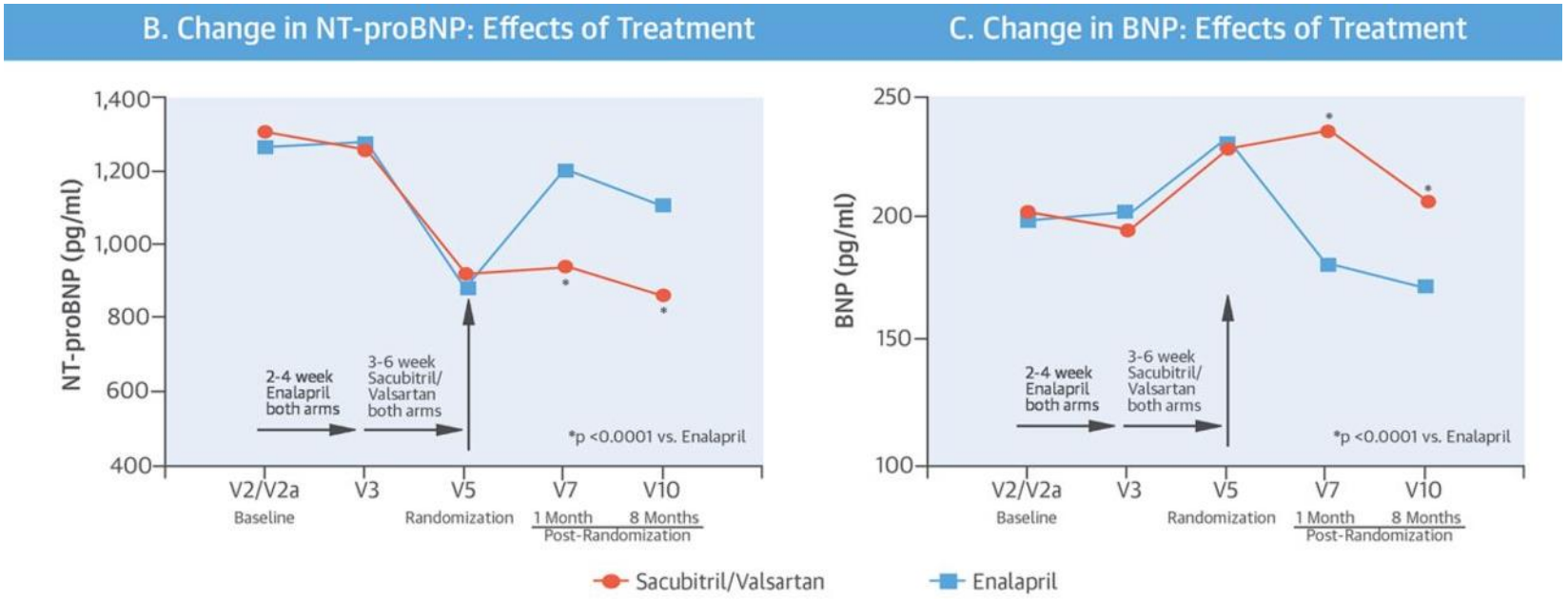

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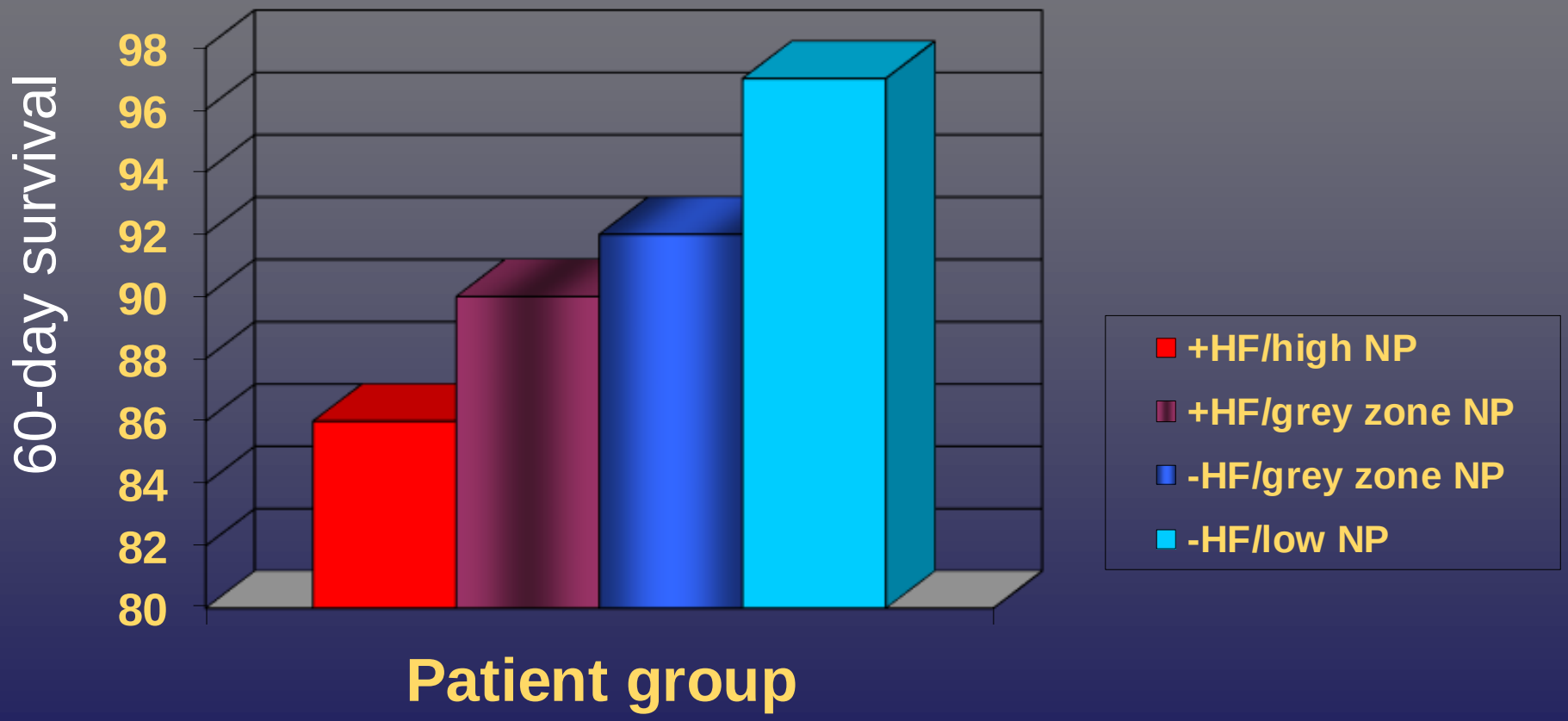
Prognosis for the dyspnea patient

Diagnosis, NT-proBNP and the "grey zone"

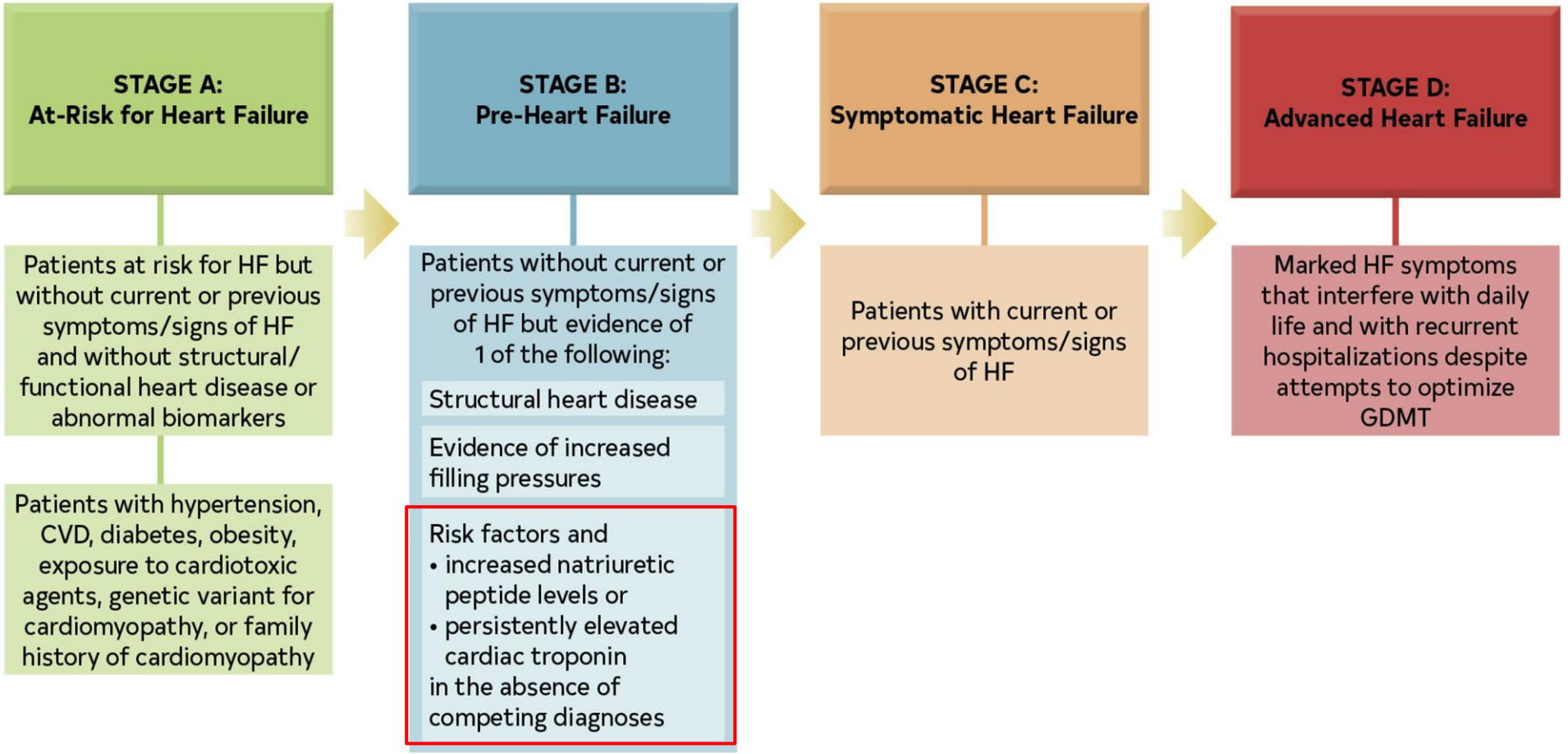


"Grey Zone" NT-proBNP is between 300 pg/ml and age adjusted rule-in cut-off

Van Kimmenade. Am J cardiol 2006;98:386

Incorporation of Biomarkers to Define Pre-Symptomatic Heart Failure

ACC/AHA/HFSA 2022 Guidelines

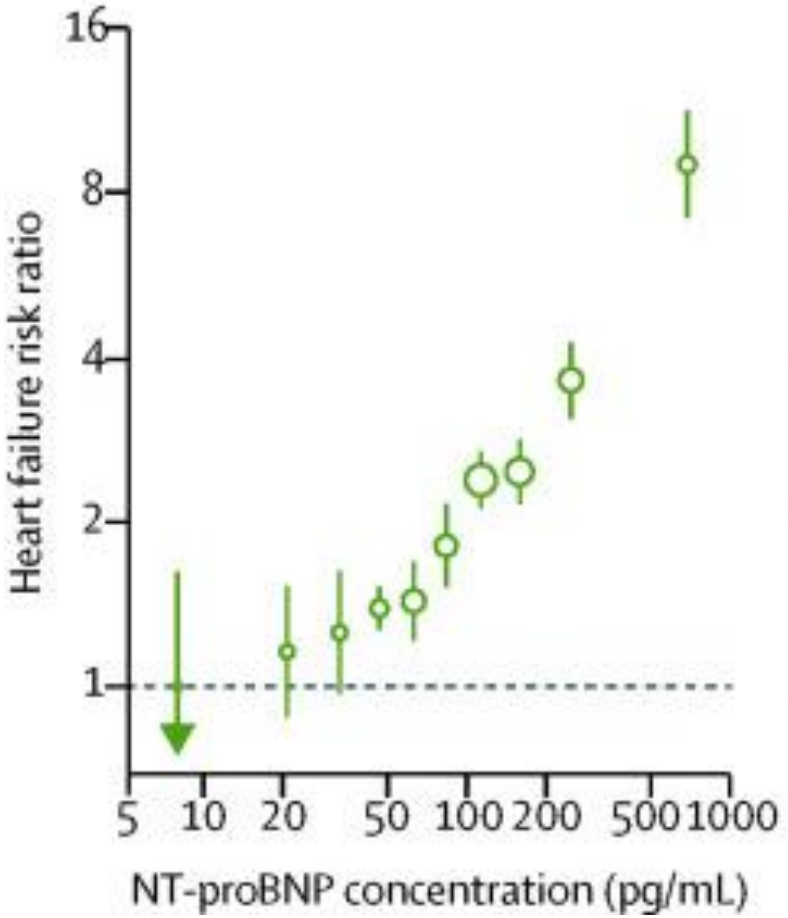


Heidenreich P et al. J Am Coll Cardiol. 2022 doi.org/10.1016/j.jacc.2021.12.012

Natriuretic peptides and integrated risk assessment for HF

An individual-participant-data meta-analysis of 16 general population cohorts without HF to predict future incident HF

- Risk ratio = top third/bottom third
- Median follow-up 7.8 years
- 2212 incident heart failure outcomes

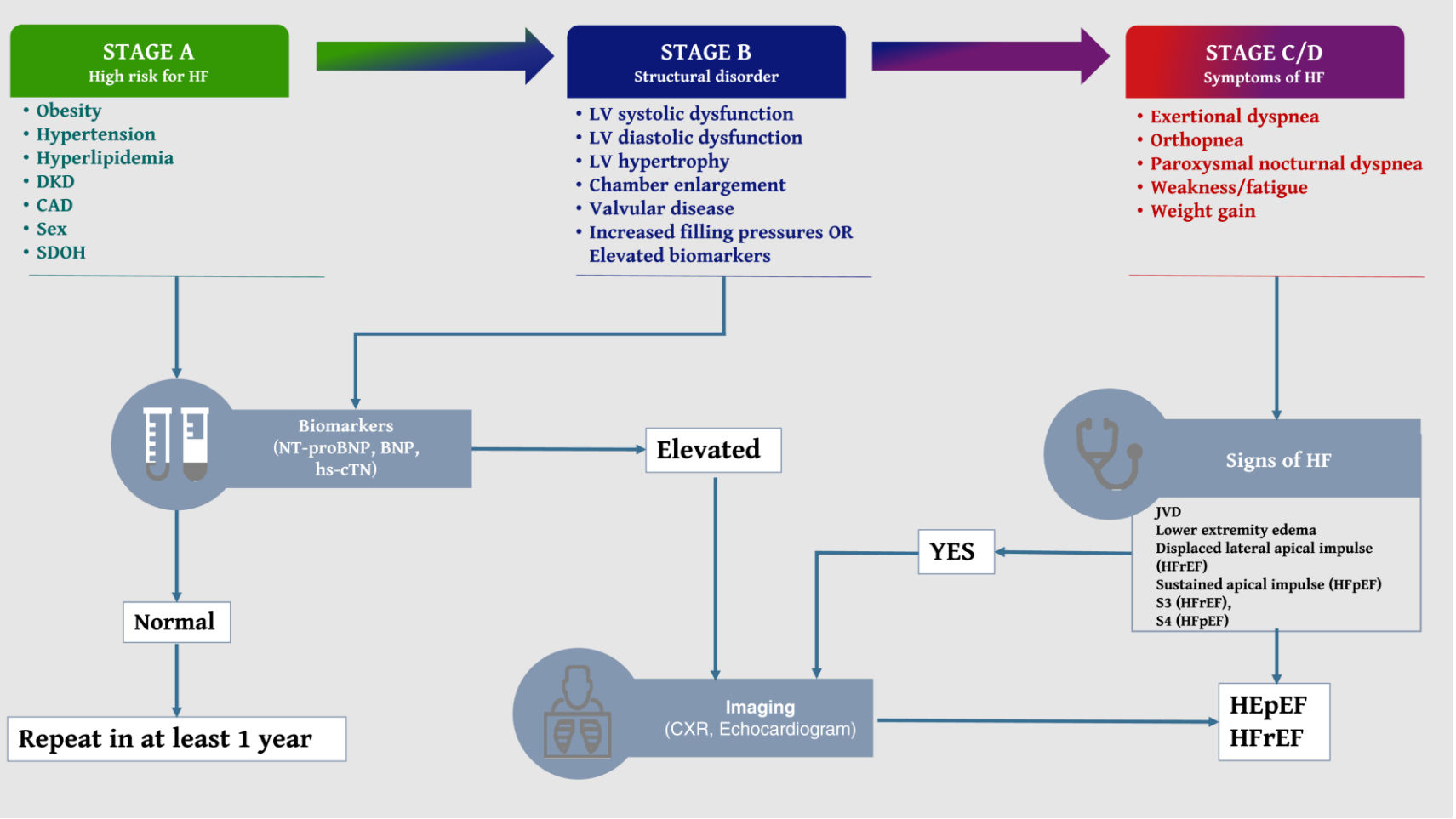


Willet P. Lancet Diab Endo 2016;4:840-849

American Diabetes Association®

Stepwise approach for screening and diagnosis across HF stages

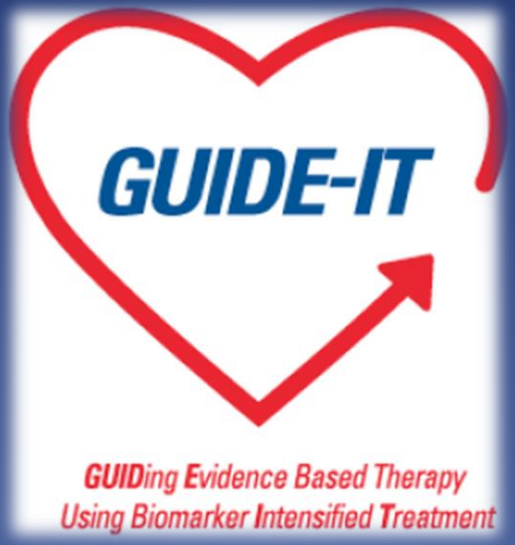
Recommendations for Diabetics



Diabetes Care. 2022;45(7):1670-1690. doi:10.2337/dci22-0014

The Role for Natriuretic Peptides in Cardiovascular Disease

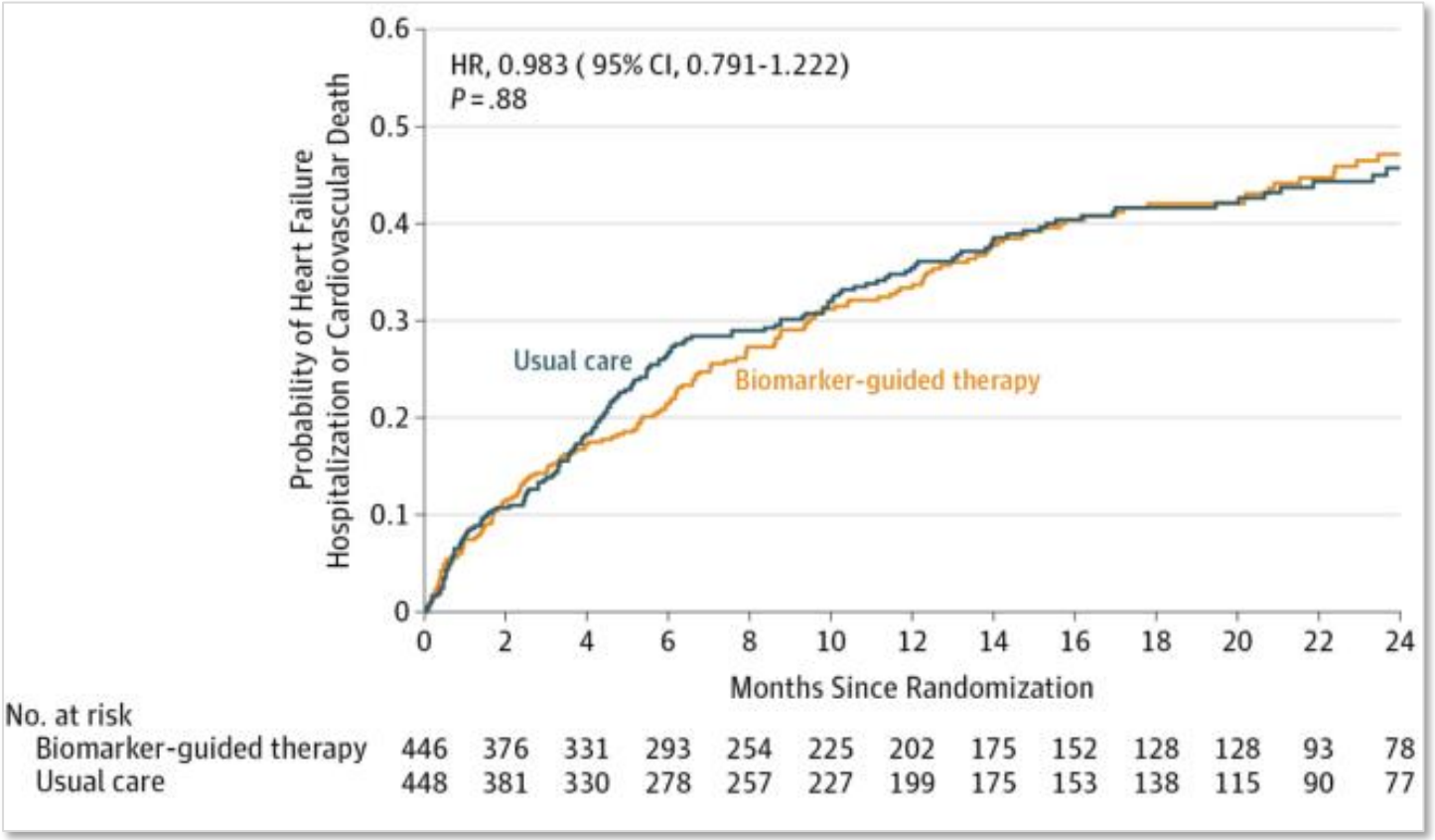
- ✓ Review of acute decompensated heart failure
  - – Epidemiology
  - – Pathophysiology
  - – Clinical presentation
- ✓ Diagnosis of heart failure in patients presenting with dyspnea
  - ✓ ICON Reloaded
  - ✓ Considerations in patients with known heart failure
- ✓ Staging heart failure with natriuretic peptides
- ✓ NT-proBNP for screening for HF risk
- Emerging use of NT-proBNP to guide optimization of medical therapy post acute heart failure hospitalization



Primary Hypothesis of NIH GUIDE-IT trial

- In high risk heart failure patients with LV systolic dysfunction, a strategy of titrating medical therapy based on minimizing natriuretic peptide levels will be superior to usual care with regard to the composite endpoint of heart failure hospitalizations or CV mortality

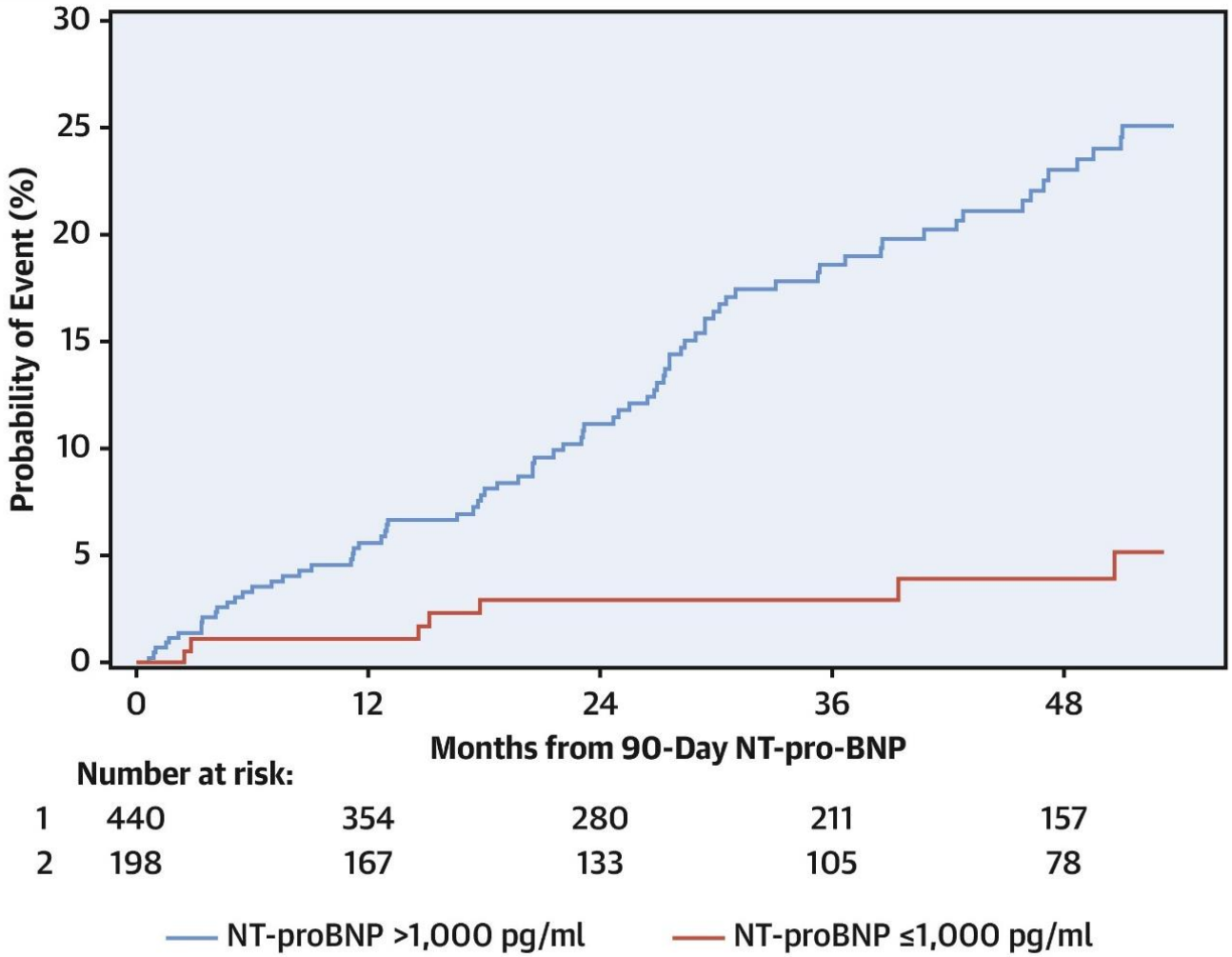
GUIDE-IT Primary Endpoint
First HF Hospitalization or Cardiovascular Death



Felker et al. JAMA. 2017;318:713-720

GUIDE-IT Outcomes Based on 90-day NT-proBNP Level

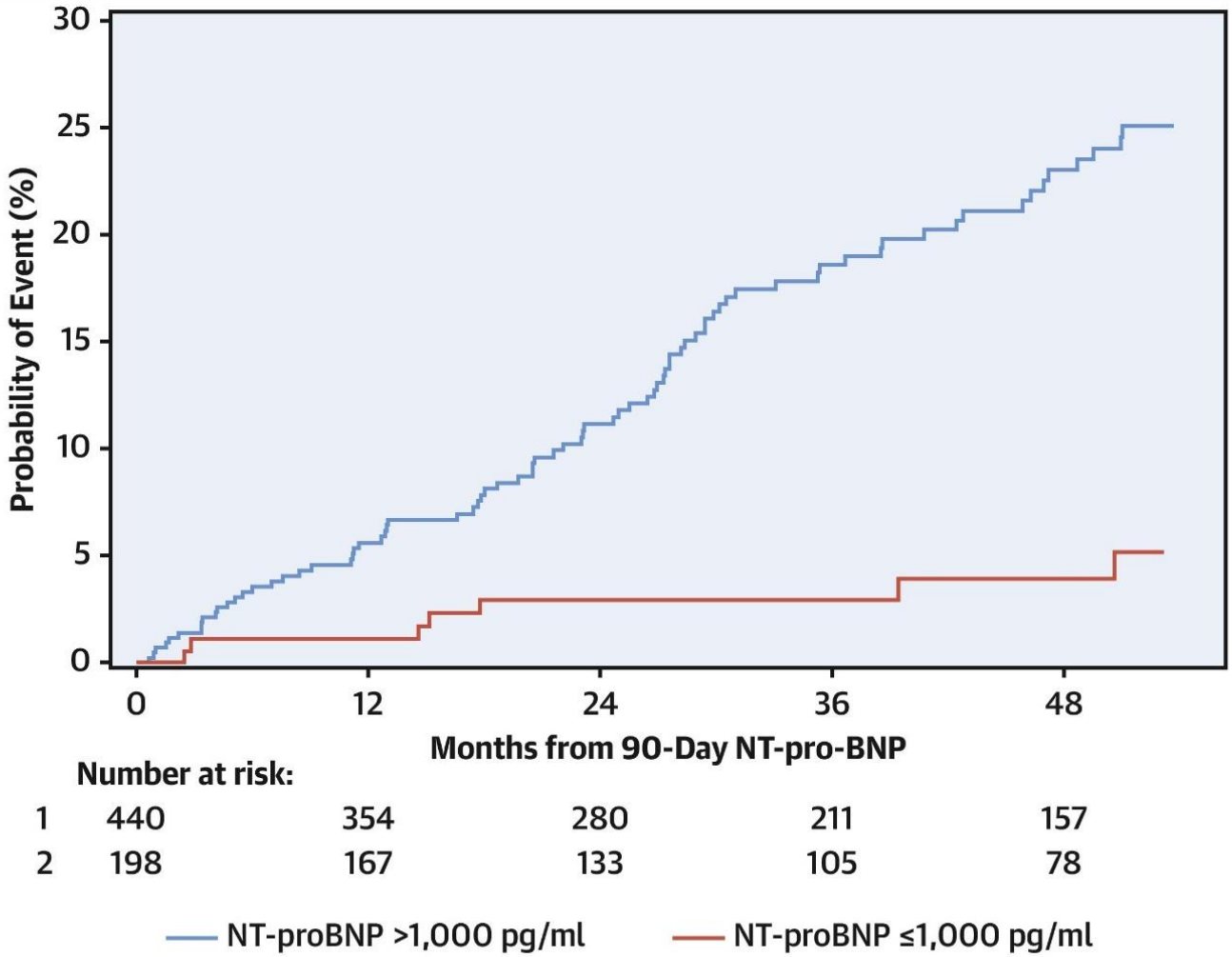
First HF Hospitalization or Cardiovascular Death



Januzzi J et al. J Am Coll Cardiol. 2018;74:1205-17

GUIDE-IT Outcomes Based on 90-day NT-proBNP Level

First HF Hospitalization or Cardiovascular Death



Findings independent of treatment strategy!

Januzzi J et al. J Am Coll Cardiol. 2018;74:1205-17

Safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

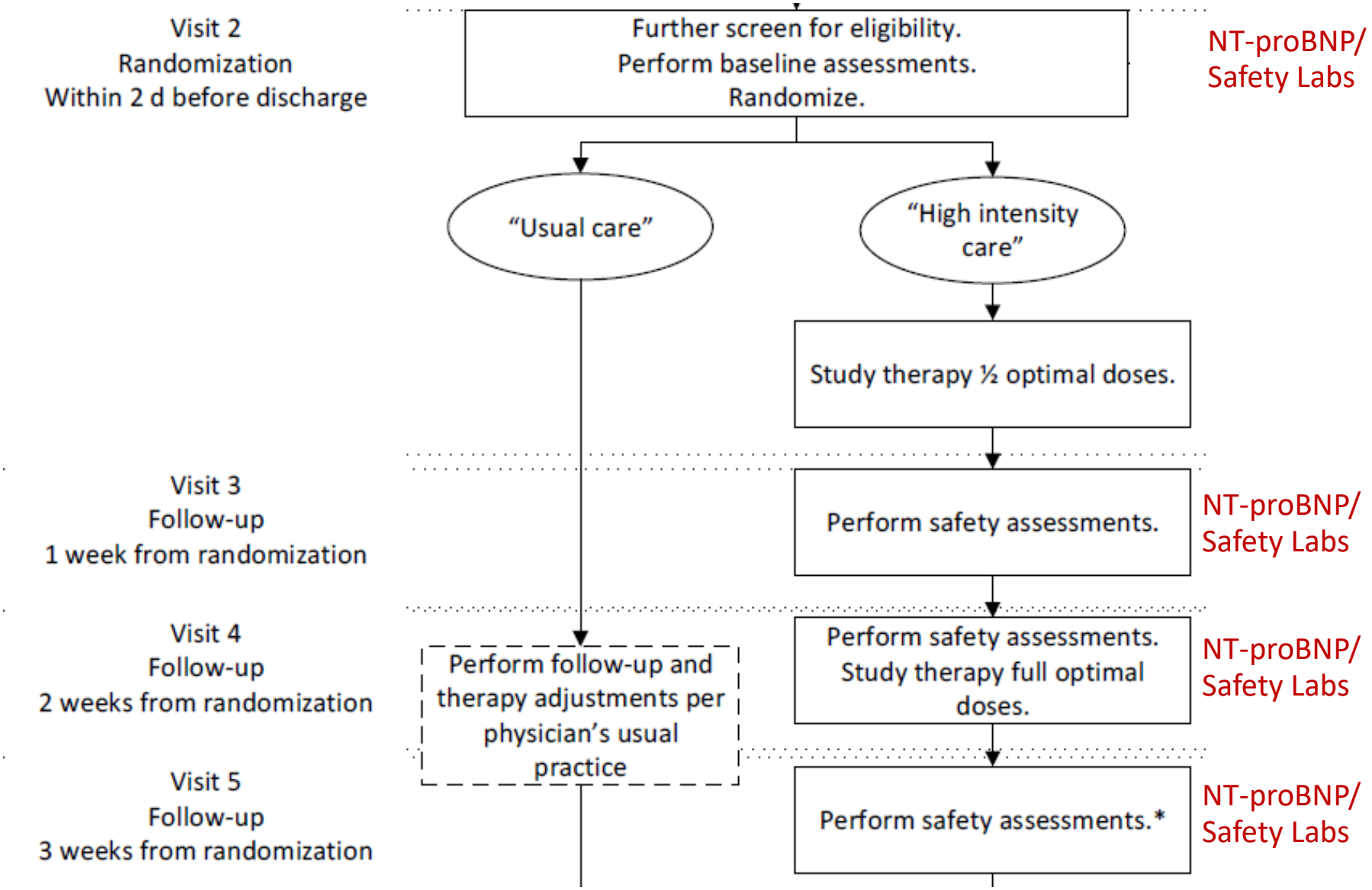
Alexandre Mebazaa, Beth Davison, Ovidiu Chioncel, Alain Cohen-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski, Karen Sliwa, Adriaan A Voors, Christopher Edwards, Maria Novosadova, Koji Takagi, Albertino Damasceno, Hadiza Saidu, Etienne Gayat, Peter S Pang, Jelena Celutkiene, Gad Cotter

Background **There is a paucity of evidence for dose and pace of up-titration of guideline-directed medical therapies after admission to hospital for acute heart failure.**

Lancet 2022; 400: 1938–52

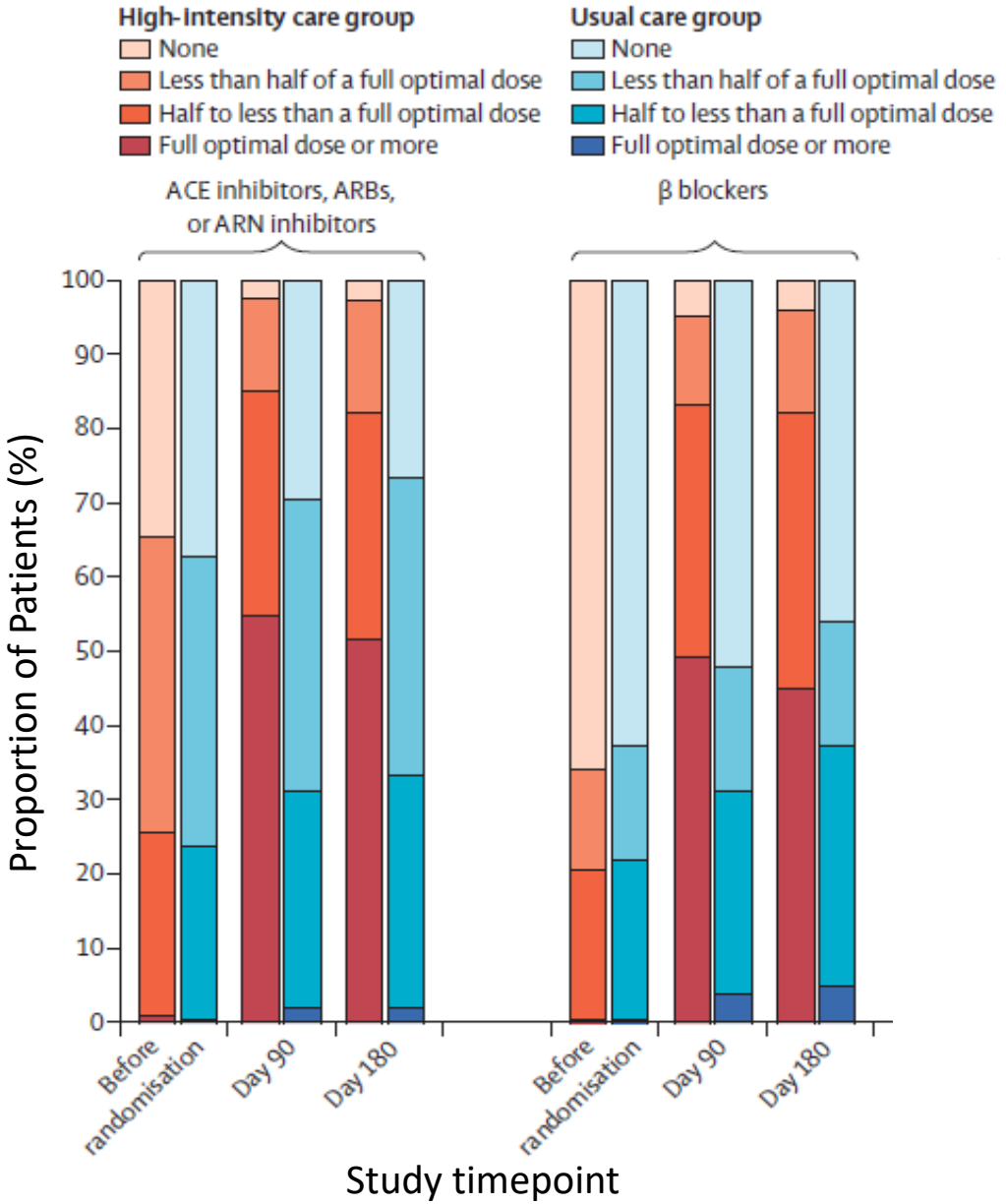
STRONG-HF

Strategy and Protocol



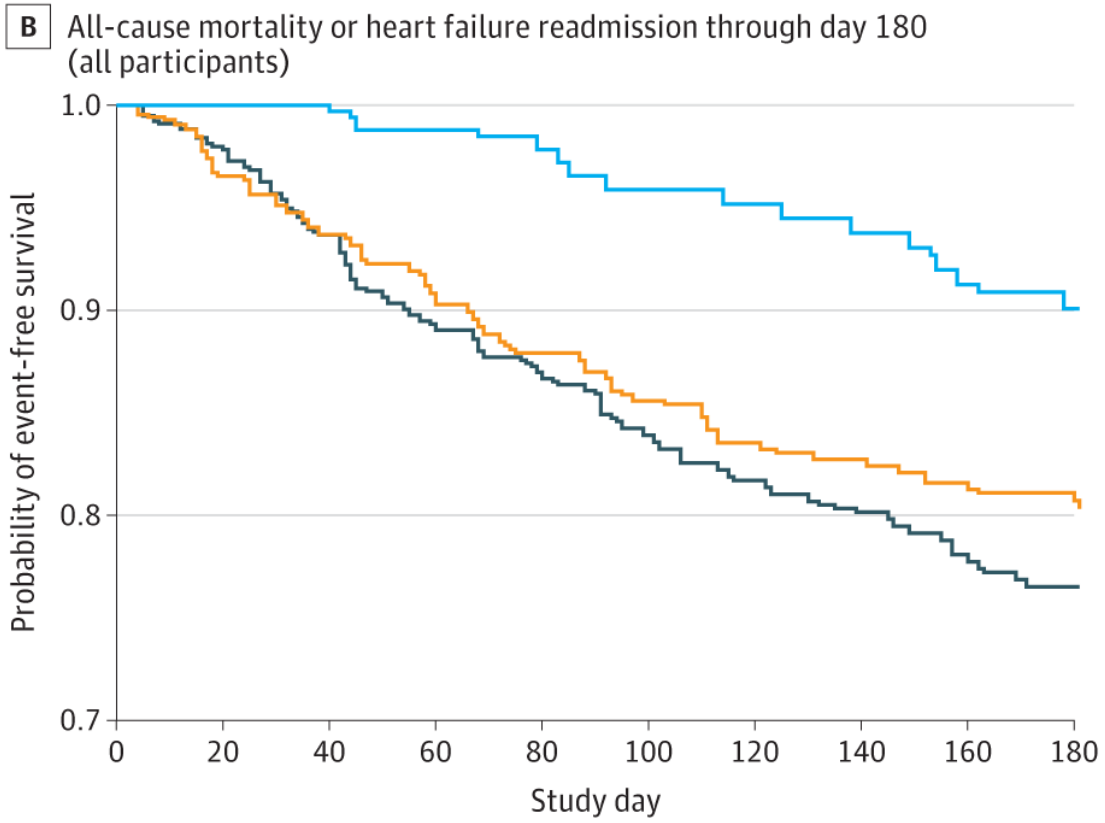
Strong-HF

Oral guideline-directed medical therapies for heart failure prescribed, in high-intensity care and usual care groups by visit



Lancet 2022; 400: 1938–52

Optimization of Heart Failure Medications in 2 Weeks After an Acute Heart Failure Admission Association with Heart Failure Admission or Death



Average % of optimal doses of HF Medications by 2-Weeks

≥90% 50-<90% <50%

JAMA Cardiol. 2024;9(2):114-124. doi:10.1001/jamacardio.2023.4553

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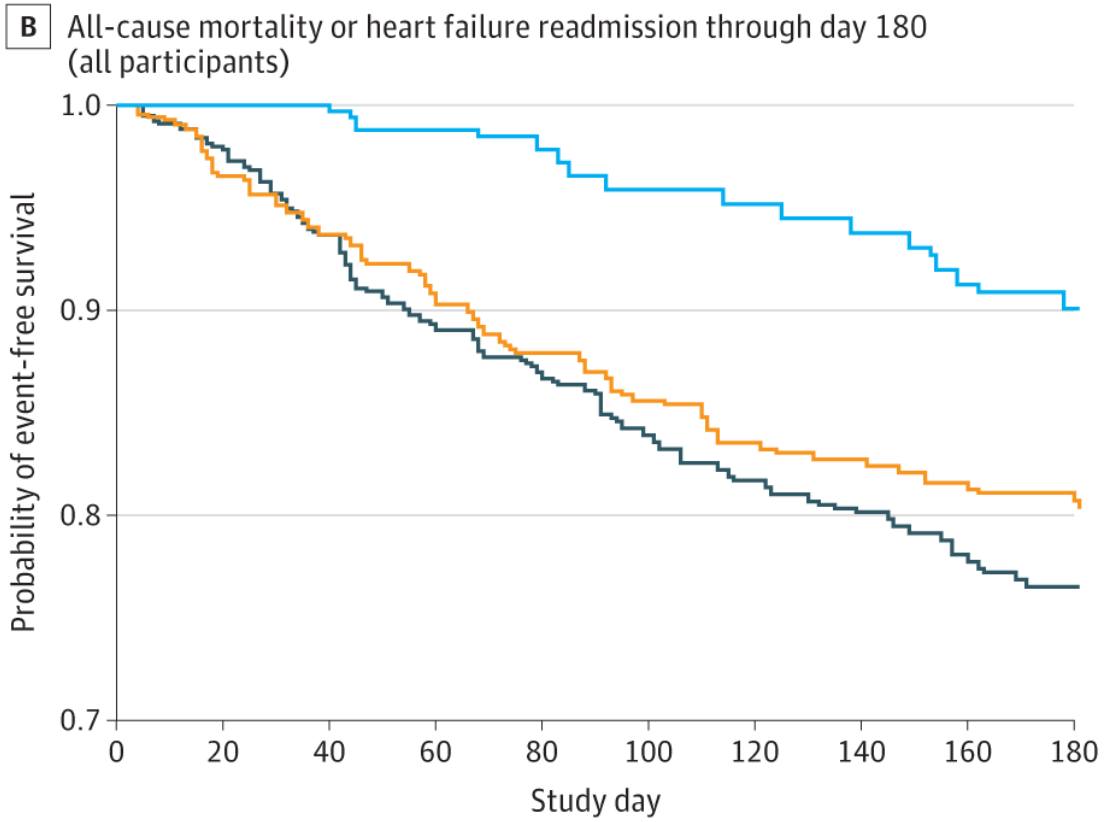

Average % of optimal doses of HF Medications by 2-Weeks

	≥90%	50-<90%	<50%
Patients per Category	43%	49%	8%

JAMA Cardiol. 2024;9(2):114-124. doi:10.1001/jamacardio.2023.4553

Role of Natriuretic Peptides in HF

Conclusions

- NT-proBNP now has clearly defined values based on age for the diagnosis of Heart Failure in patients presenting with shortness-of-breath with clinical suspicion for Heart Failure
- NT-proBNP can assist with prognosis and in the absence of symptoms defines an early stage of a Heart Failure (stage B) that at least for diabetics warrents further evaluation
- NT-proBNP is an important adjunct to optimize medical treatment post acute Heart Failure hospitalization