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# Natriuretic Peptides for the Diagnosis and Prognosis of Heart Failure

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*Inova Heart and Vascular Institute*

# Disclosures

Research support to Inova: Abbott Diagnostics, FujiRebio, Quidel/Ortho Diagnostics, Randox, Roche Diagnostics, Siemens Healthineers
Consulting/Honorarium: Abbott Diagnostics, FujiRebio, Quidel/Ortho Diagnostics, Pathfast, Roche Diagnostics, Siemens Healthineers
Royalties: UpToDate

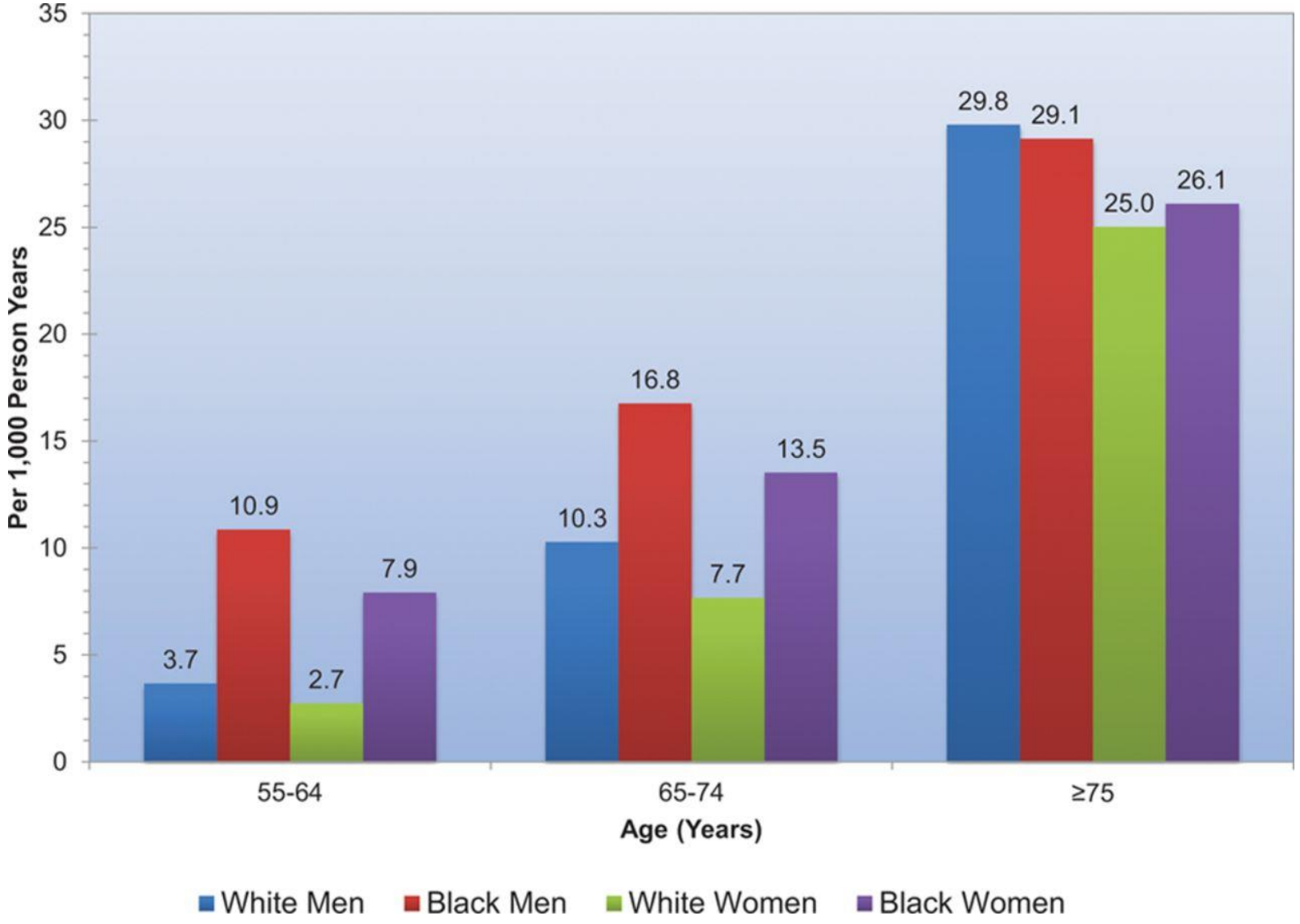
# Learning Objectives

- 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 level with or without a diagnosis of HF
- 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 is patients presenting with dyspnea
  - ICON Reloaded
  - Considerations in patients with known heart failure
- Determining prognosis with natriuretic peptides
- Emerging use of NT-proBNP to guide optimization of medical therapy post acute heart failure hospitalization

# First acute decompensated heart failure annual event rates

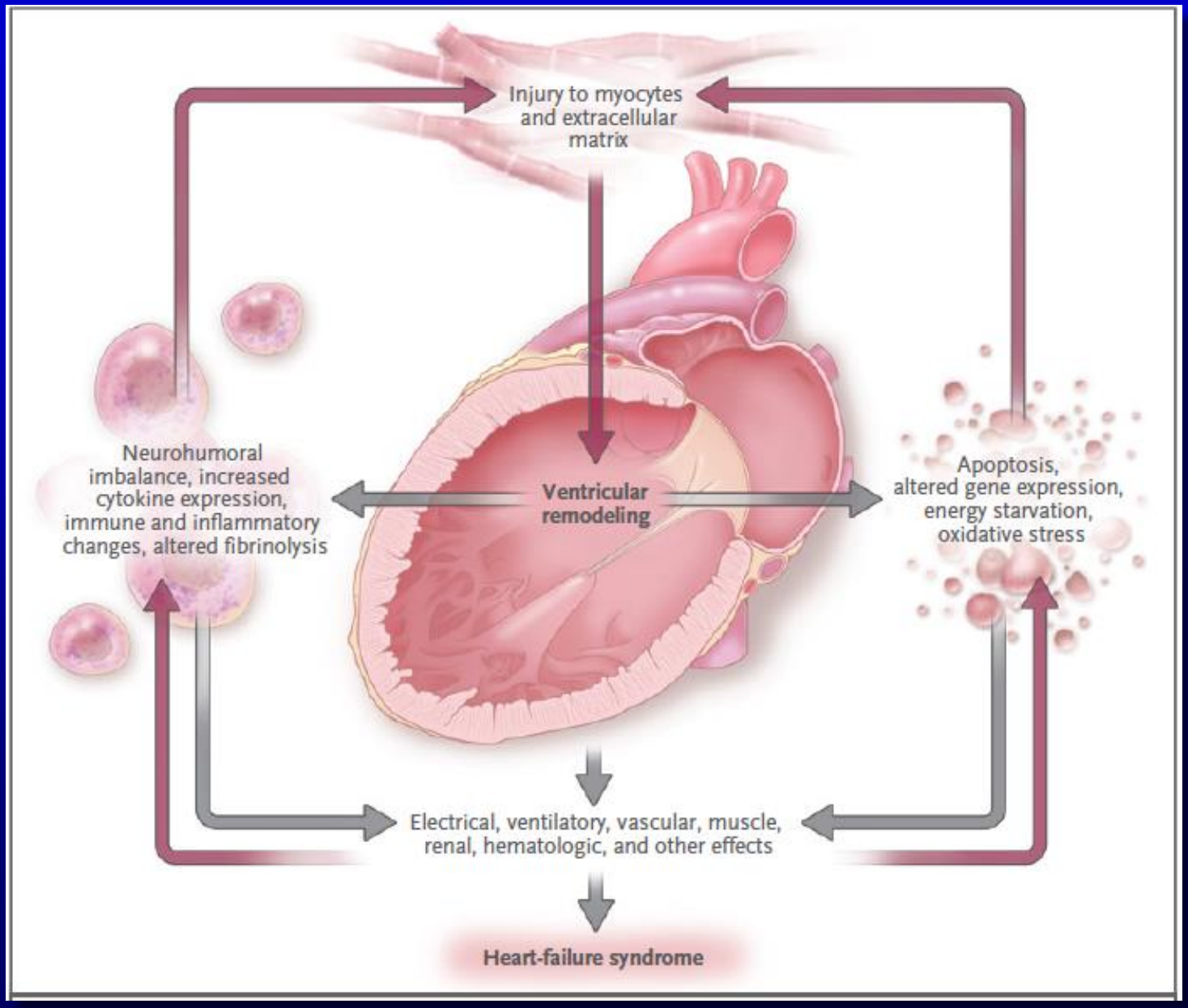



(per 1000 from ARIC community surveillance [2005–2011])

American Heart Association.

Dariush Mozaffarian et al. Circulation. 2015;131:e29-e322

# Pathophysiology of Systolic Heart Failure




N Engl J Med 2010;362:228-38

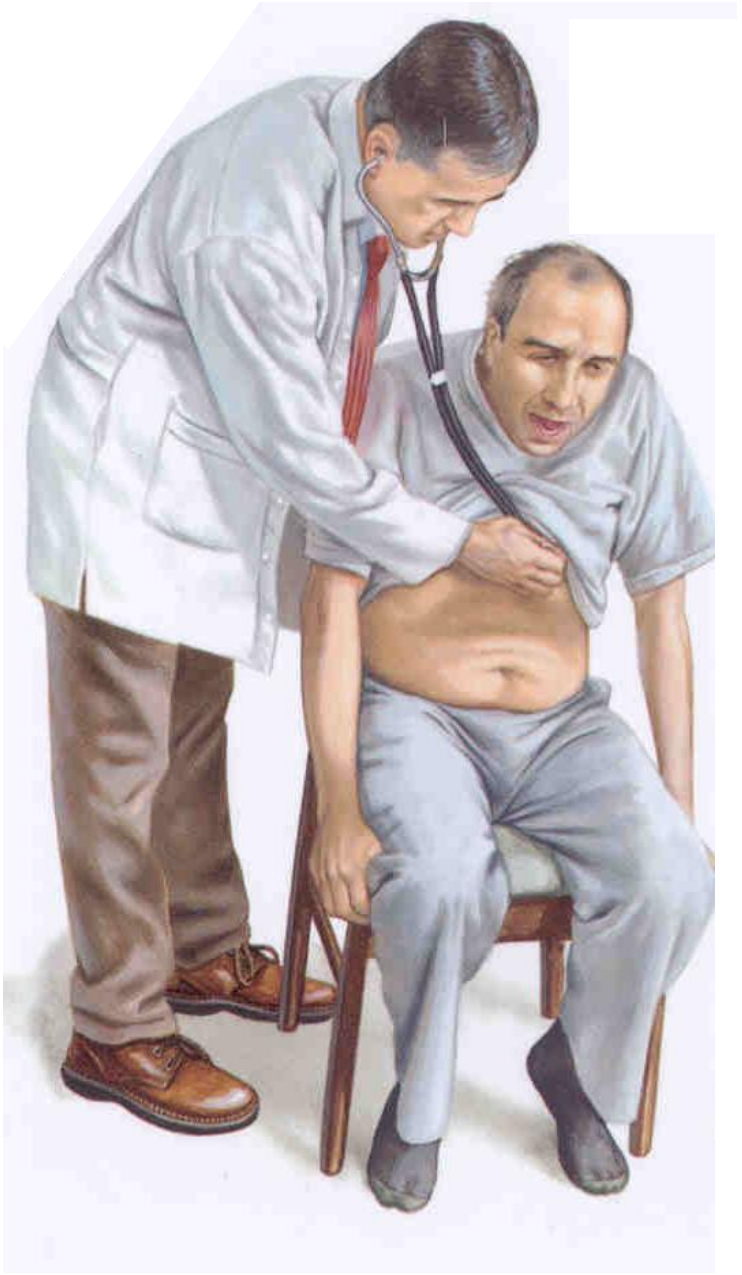
# A New Cough

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.*

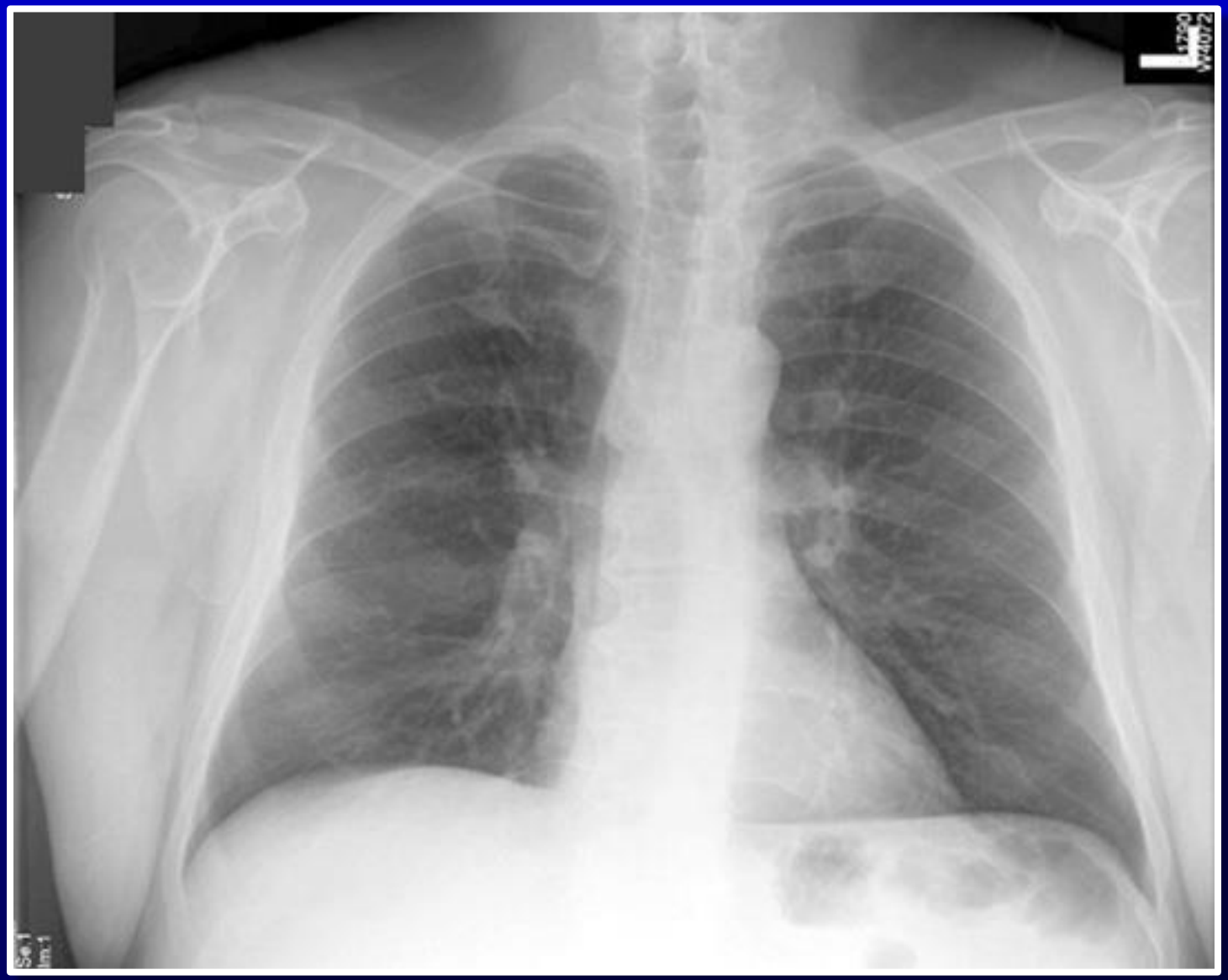
| |
|---|
| **Major Criteria** |
| Paroxysmal nocturnal dyspnea or orthopnea |
| Neck-vein distention |
| Rales |
| Cardiomegaly |
| Acute pulmonary edema |
| $S_3$ gallop |
| Increased venous pressure ->16 cm of water |
| Circulation time ≥25 sec |
| Hepatojugular reflux |
| **Minor Criteria** |
| Ankle 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

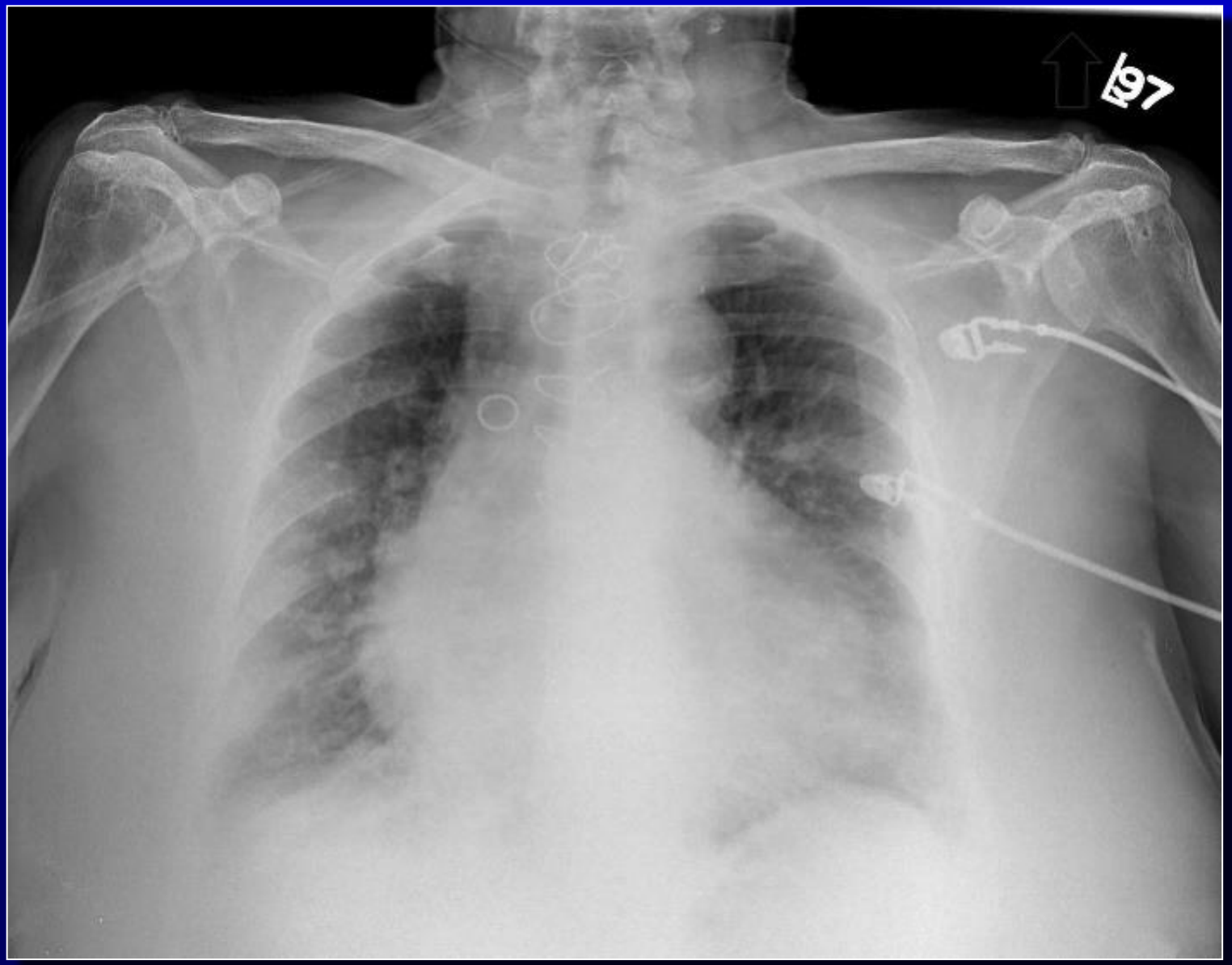
McKee PA et al. N Engl J Med 1971;285:1441-1446

# Normal
## Chest X-ray

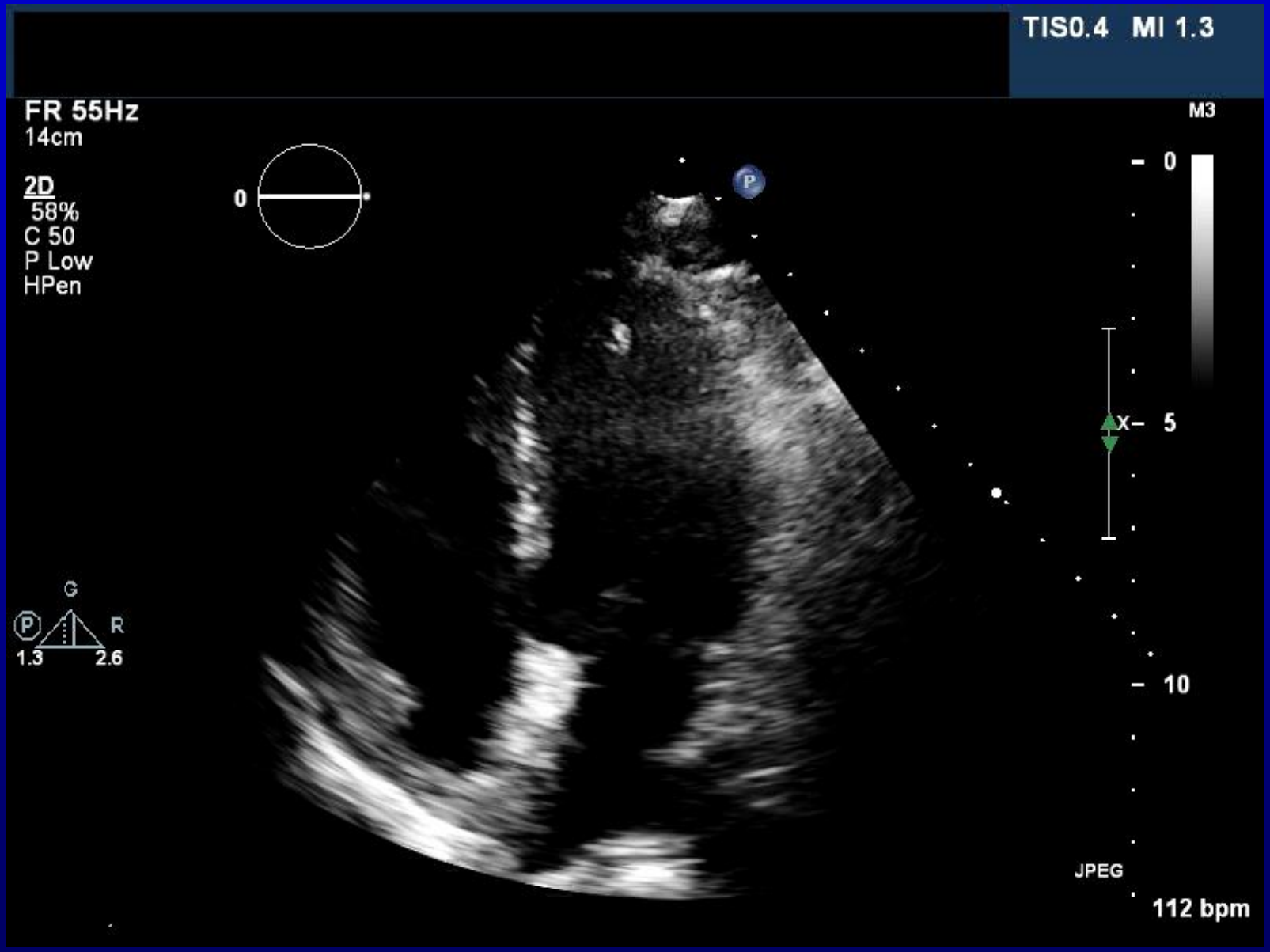


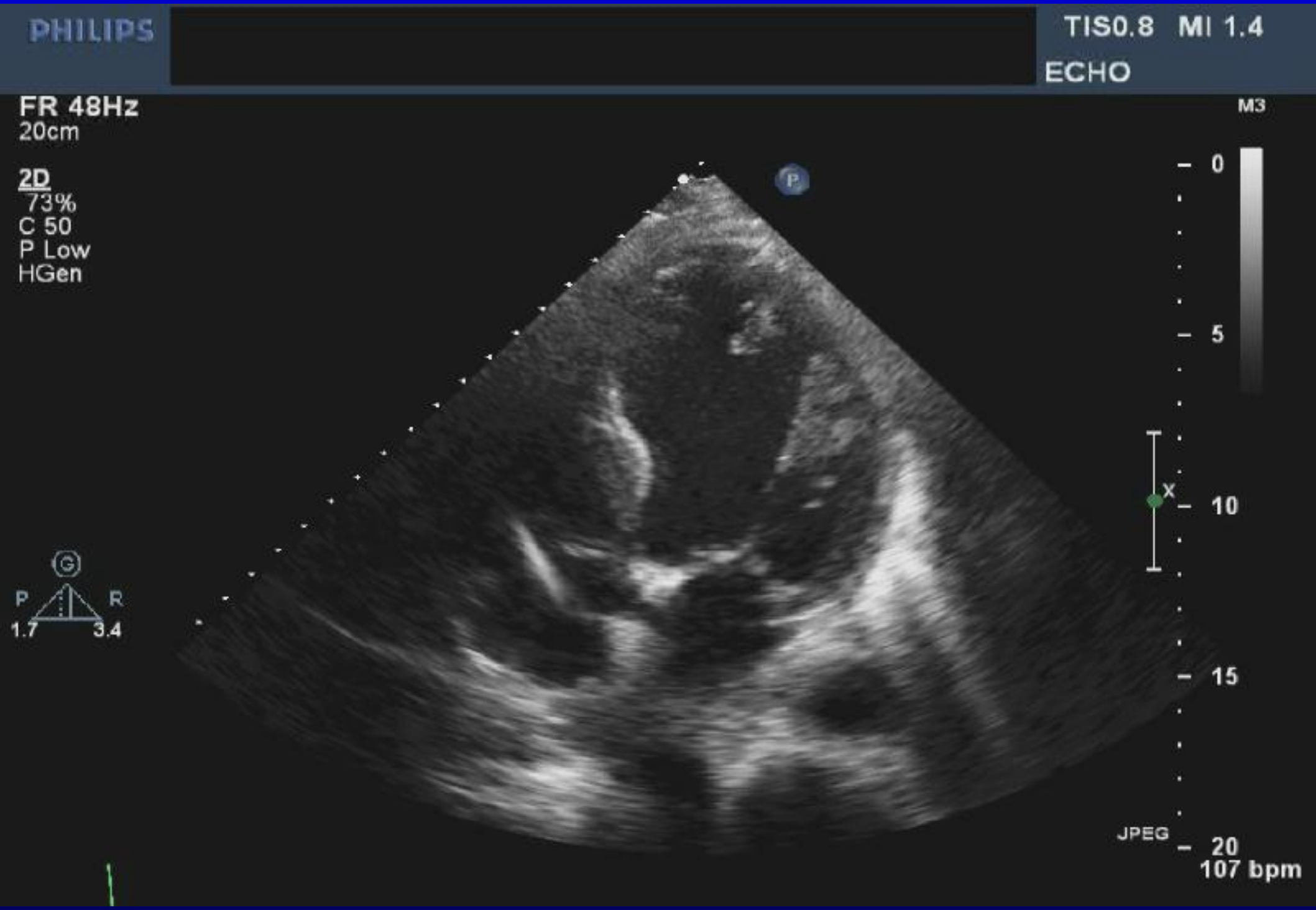
# Case Presentation

## Chest X-ray



# Normal echocardiogram




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

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# Poll Question #1

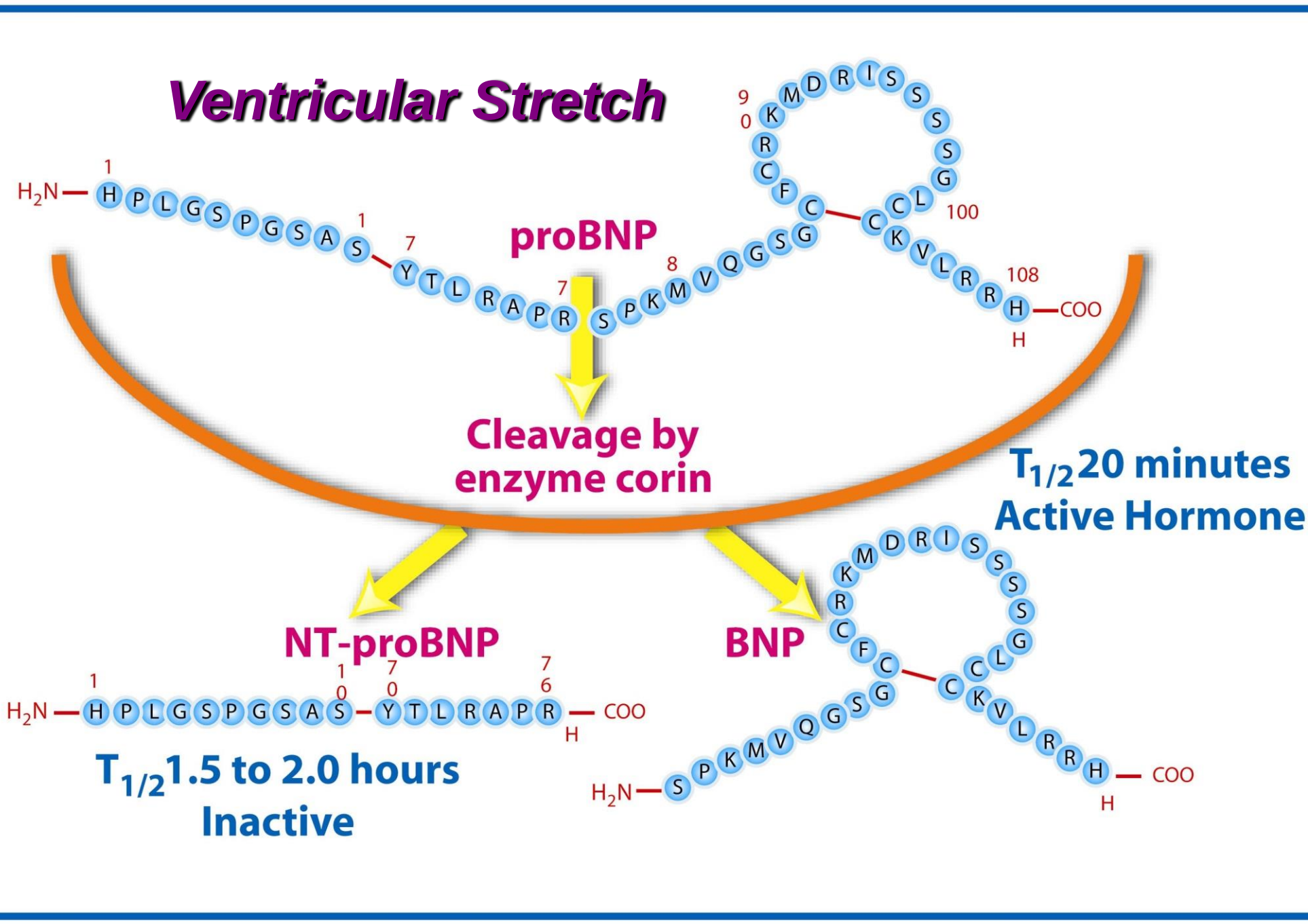
## How is NT-proBNP best used to diagnose acute heart failure?

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

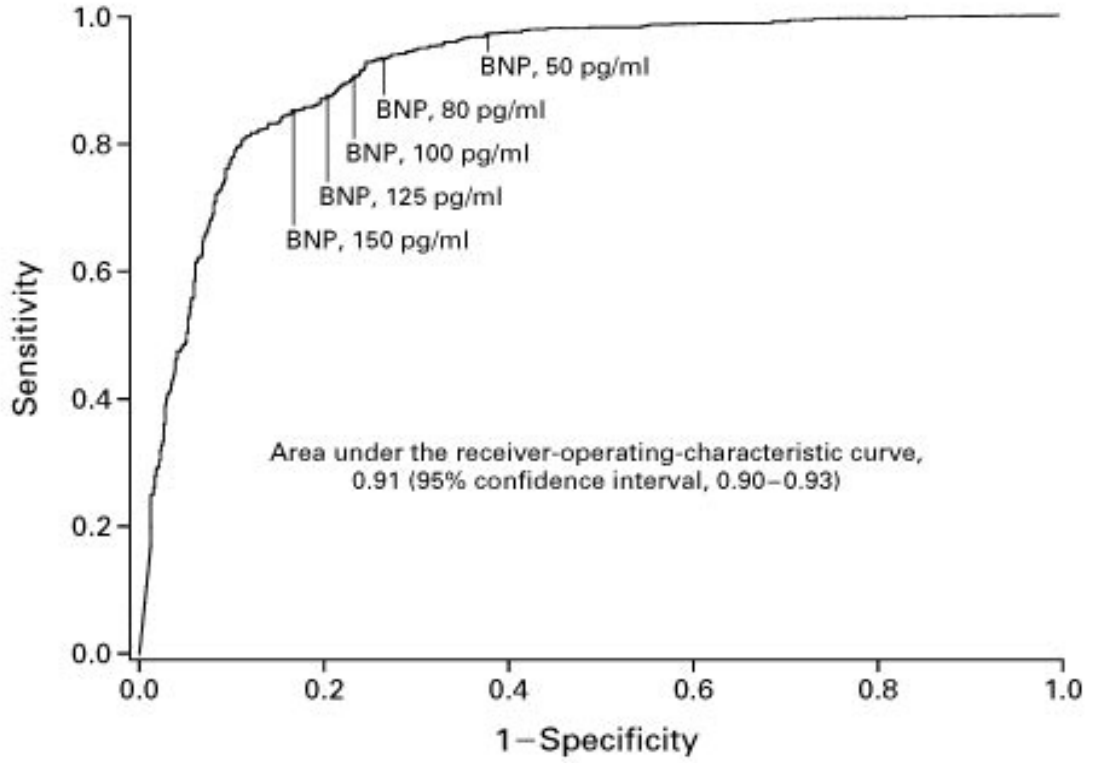
b) Age specific cut-offs to “rule-in” heart failure and a single cut-off to “rule-out” Heart failure

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

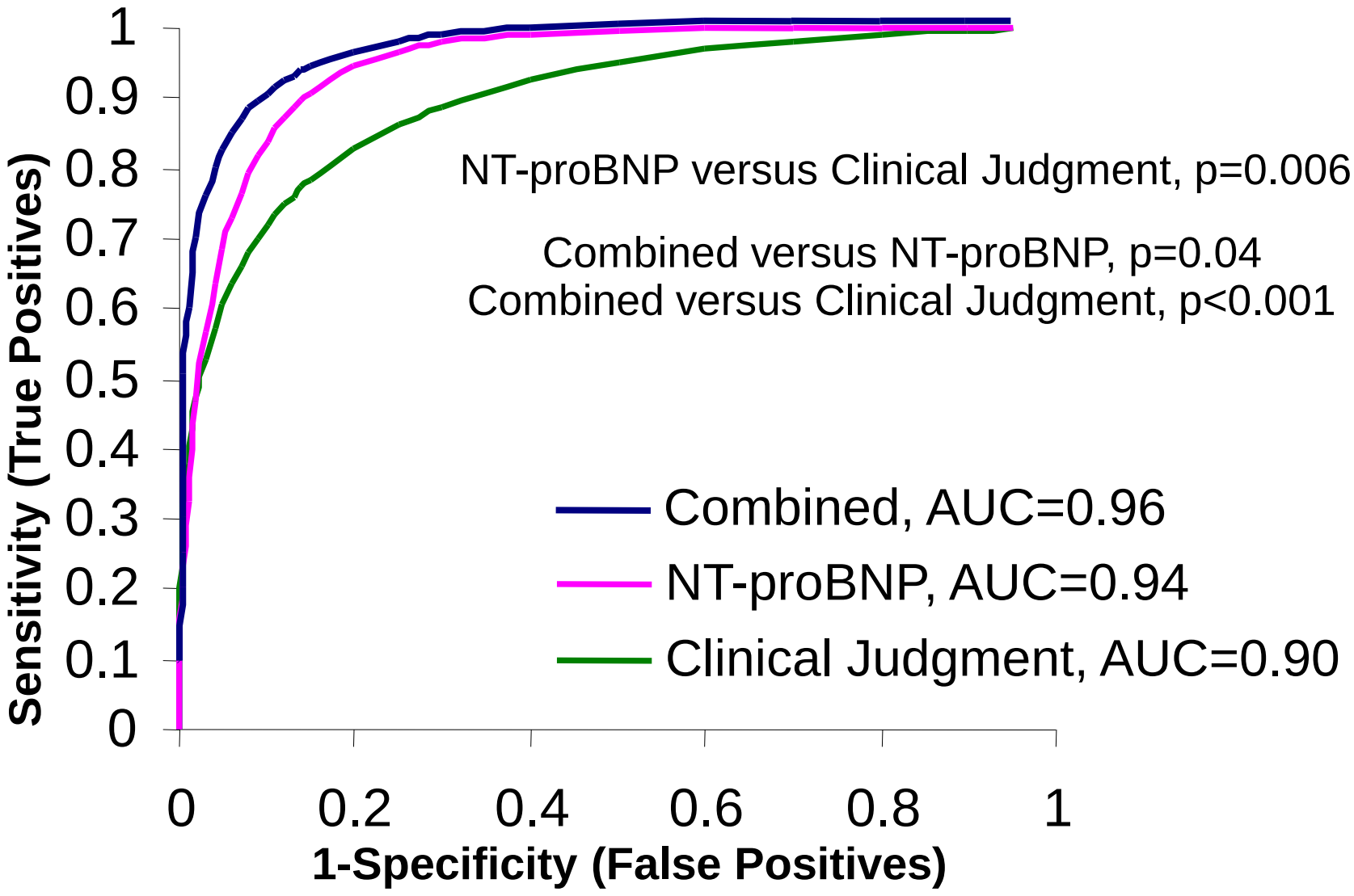



| BNP pg/ml | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value | Accuracy |
|---|---|---|---|---|---|
| | | (95 percent confidence interval) | | | |
| 50 | 97 (96–98) | 62 (59–66) | 71 (68–74) | 96 (94–97) | 79 |
| 80 | 93 (91–95) | 74 (70–77) | 77 (75–80) | 92 (89–94) | 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 |

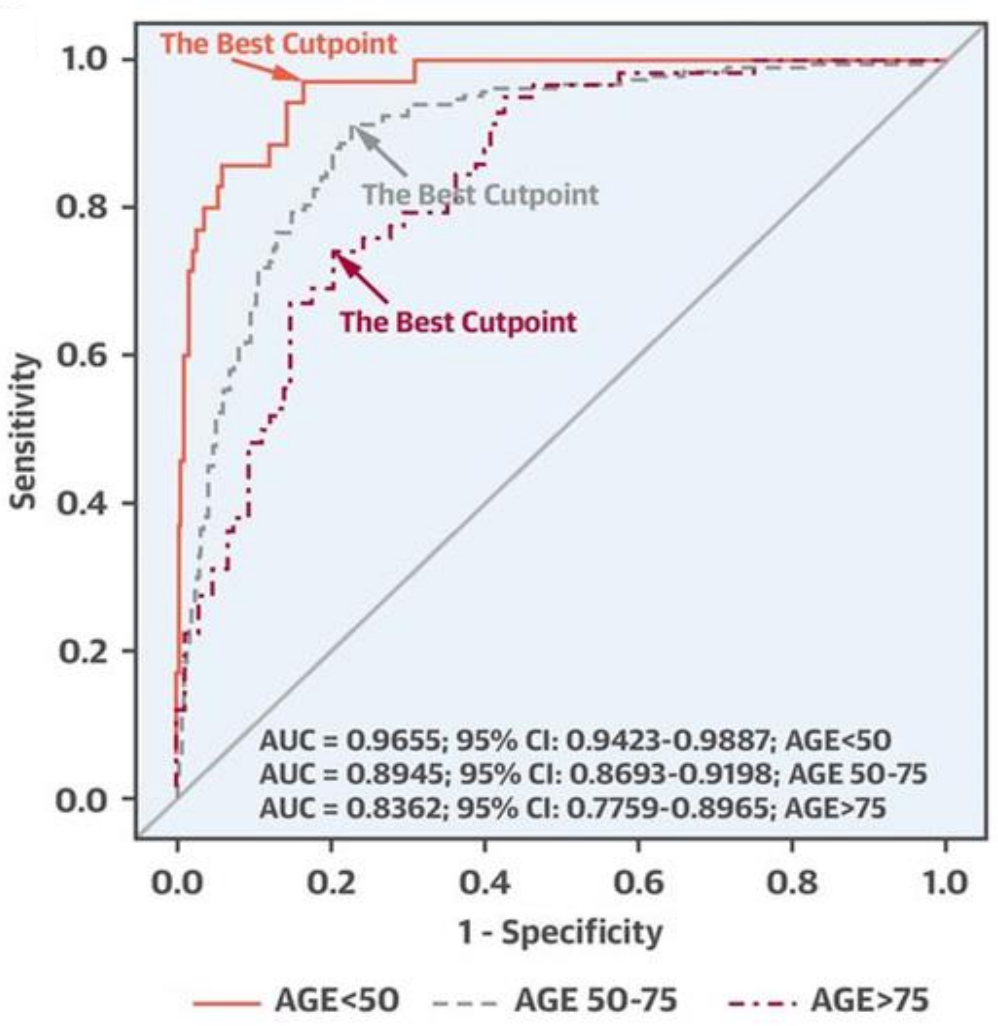
The NEW ENGLAND JOURNAL of MEDICINE

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

# Results: Primary Endpoint



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



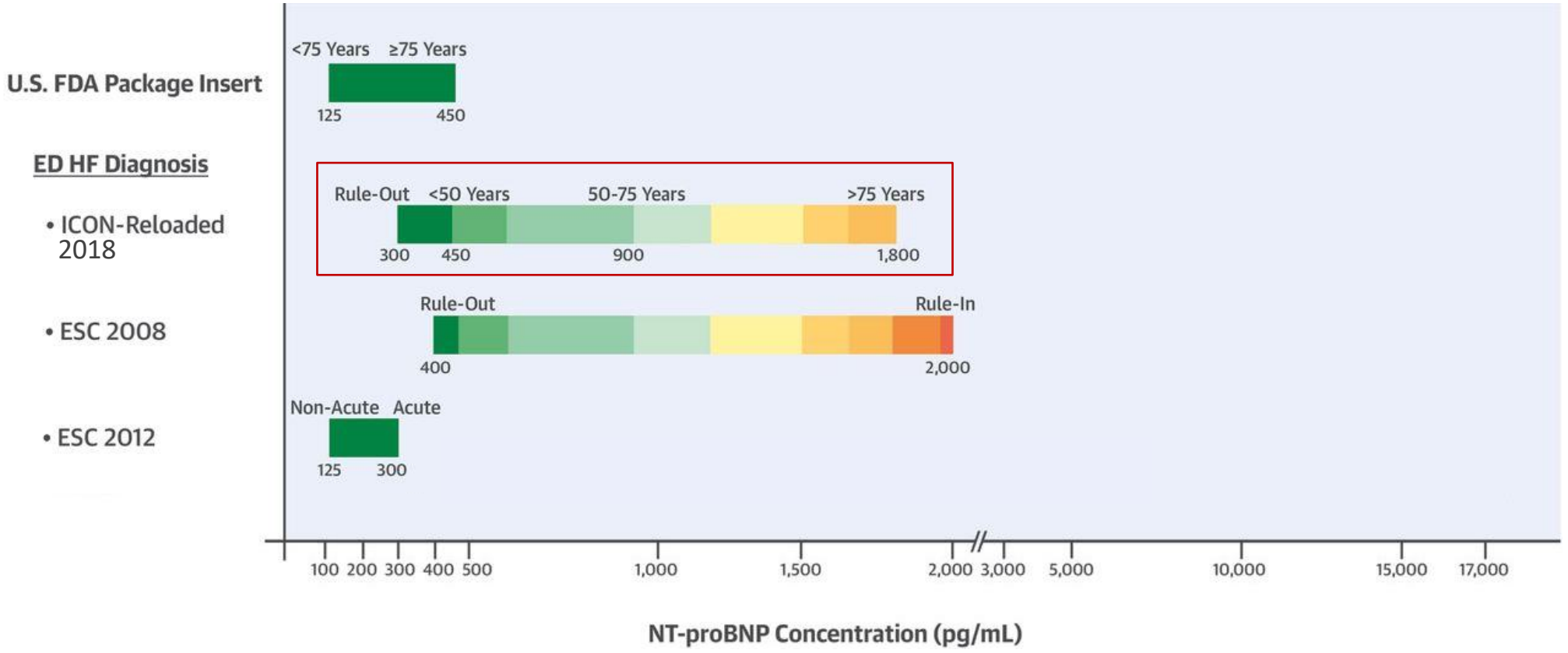

| | AUC | p Value for Difference in AUC |
|---|---|---|
| 1.73 $m^2$ | 0.872 | 0.12 |
| 1.73 $m^2$ | 0.907 | |

| | 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

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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 heart failure exacerbation is a cause of worsening shortness of breath

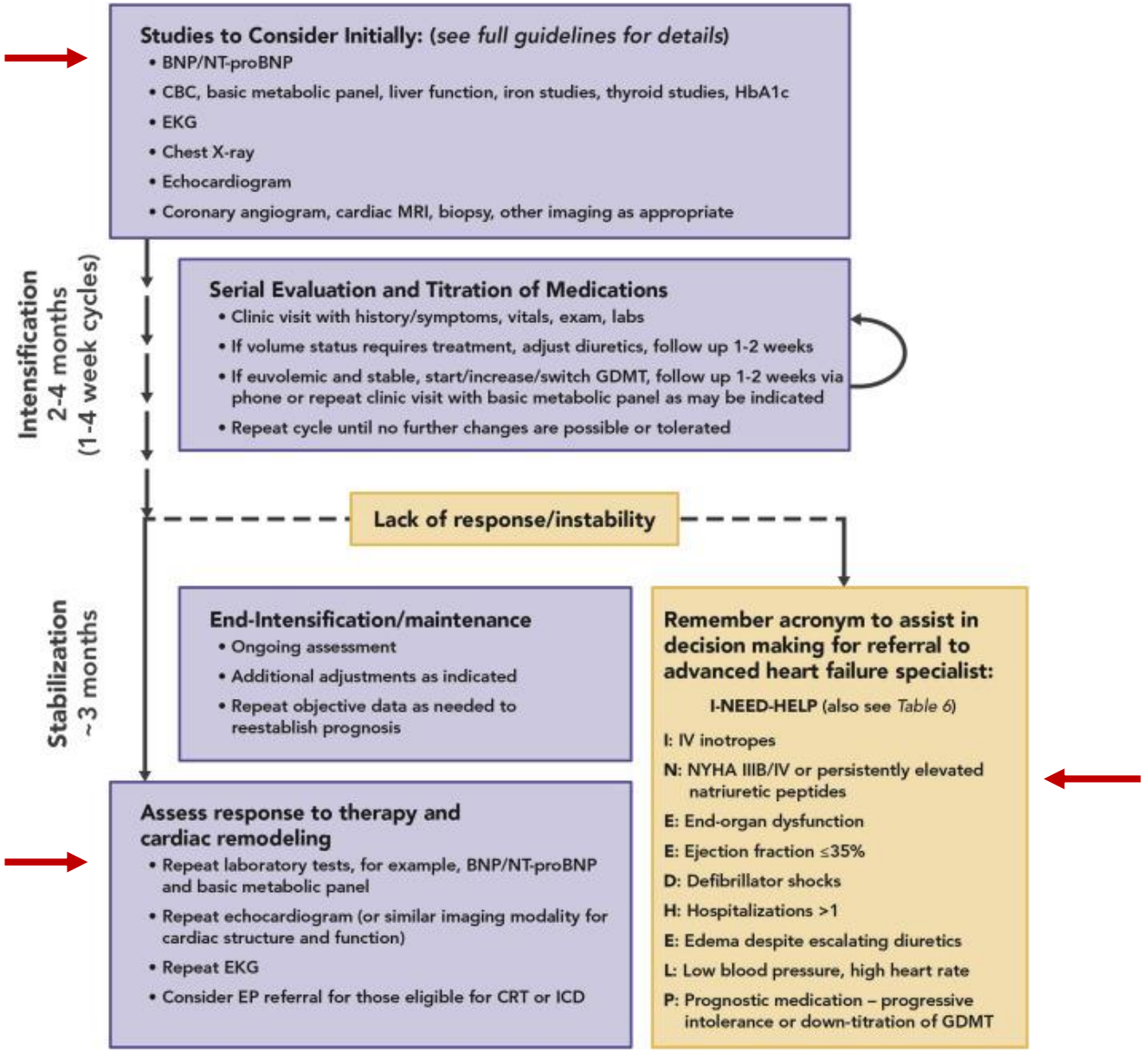
b) BNP and NT-proBNP levels can change in the opposite direction depending on the type of medical therapy limiting the use of BNP for the diagnosis of a heart failure exacerbation

c) Knowing a baseline level of BNP or NT-proBNP in a stable outpatient with 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

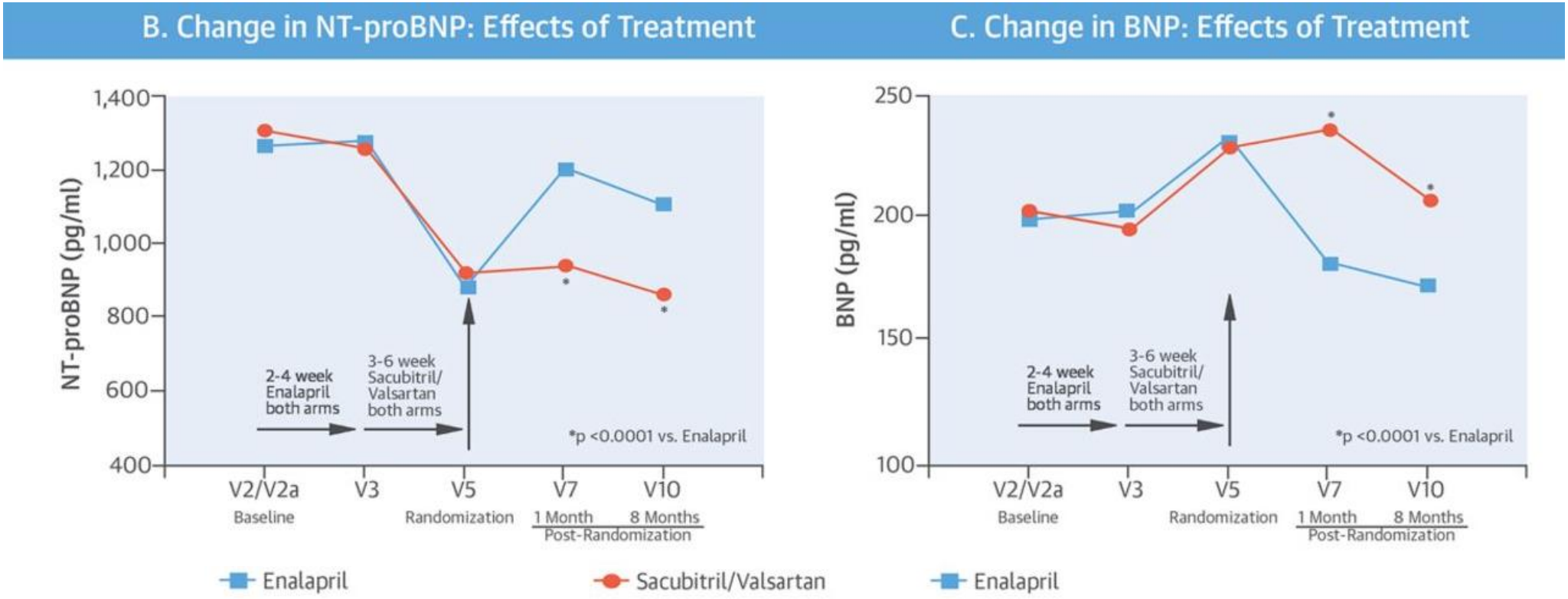
# ACC Expert Consensus Decision Pathway for HF Treatment

## The role of BNP/NT-proBNP testing in outpatients




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

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



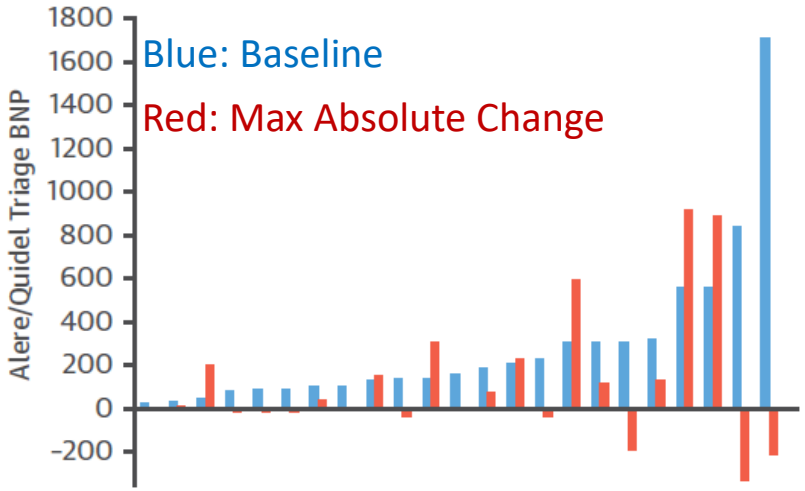

Zile et al. JACC 2016;68:2425-2436

# Never Simple!

## Changes in BNP level after starting Entresto can depend on the patient and the assay

**TABLE 4** Percent Change in Various Biomarker Concentrations as a Function Of Maximum Achieved Dose of Sacubitril/Valsartan

| Final Visit Biomarker (% Change) vs. Maximum Dose | None (n = 2) | Sacubitril/Valsartan 24/26 mg (n = 5) | Sacubitril/Valsartan 49/51 mg (n = 9) | Sacubitril/Valsartan 97/103 mg (n = 7) | p Value |
|---|---|---|---|---|---|
| Abbott Architect BNP | −1 (−32 to +166) | −36 (−71 to +28) | +39 (−20 to +104) | −22 (−37 to +134) | 0.38 |
| Alere/Quidel Triage BNP | +36 (−28 to +110) | −14 (−28 to +12) | +39 (−0 to +158) | −11 (−18 to +165) | 0.16 |
| Siemens Centaur BNP | +15 (−16 to +224) | −11 (−20 to +29) | +41 (+9 to +118) | +9 (−23 to +161) | 0.64 |
| Roche NT-proBNP | −13 (−52 to +31) | −25 (−35 to 0) | +5 (−19 to +22) | −21 (−54 to +12) | 0.69 |




Ibrahim et al. JACC 2019:1273-84

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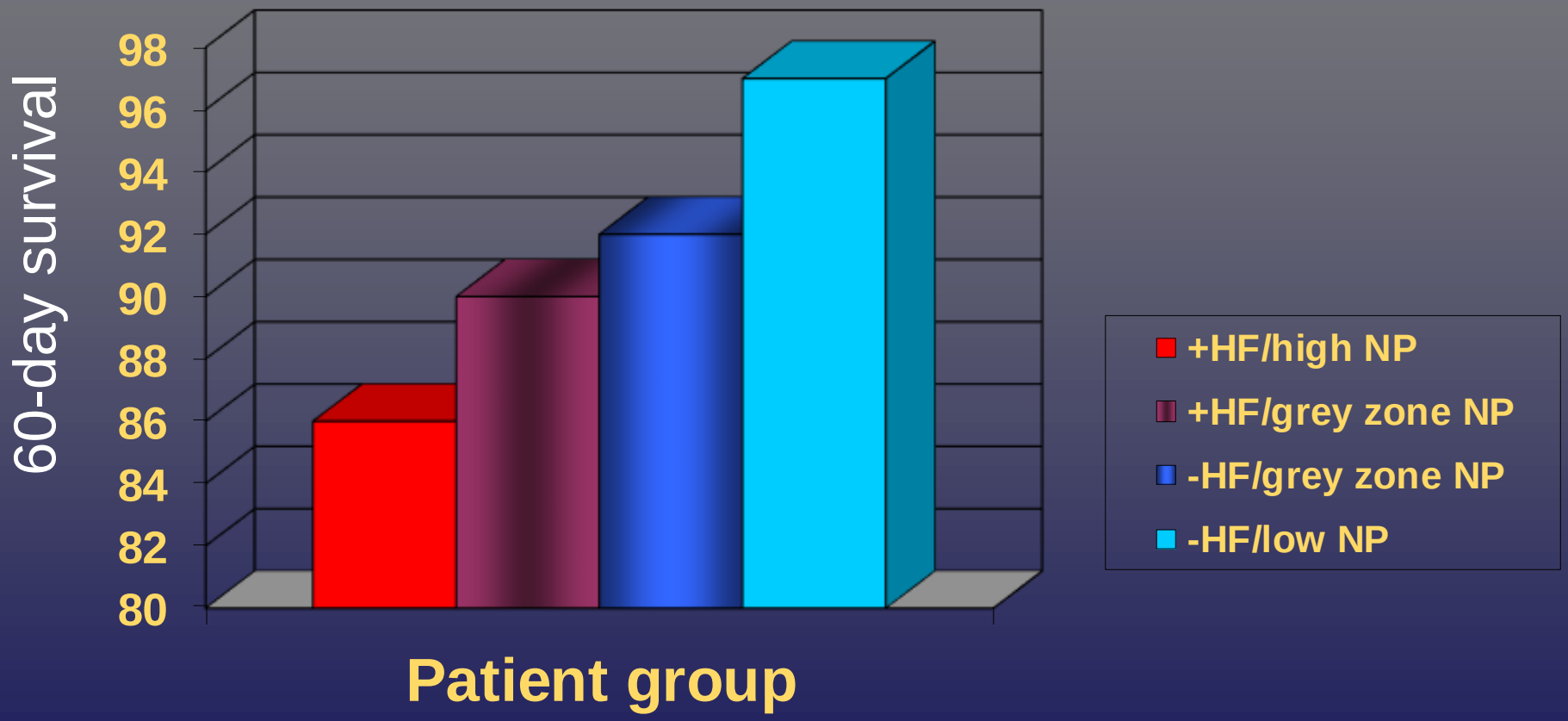
# Prognosis for the dyspnea patient

## Diagnosis, NT-proBNP and the "grey zone"



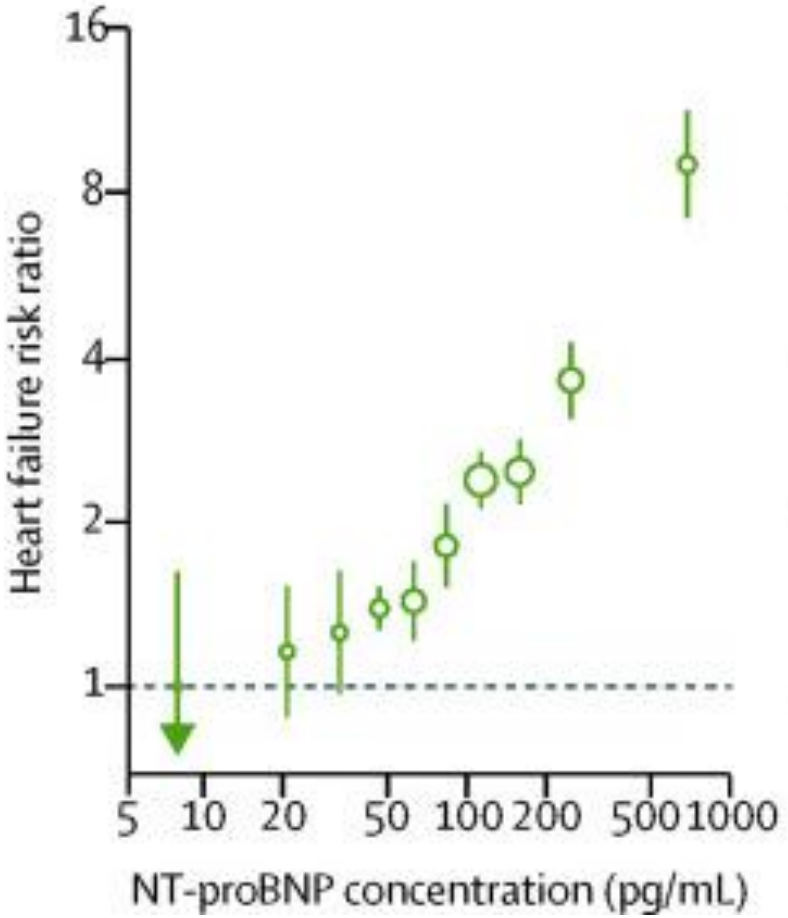

"Grey Zone" NT-proBNP is between 300 pg/ml and age adjusted rule-in cut-off

Van Kimmenade. Am J cardiol 2006;98:386

# 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

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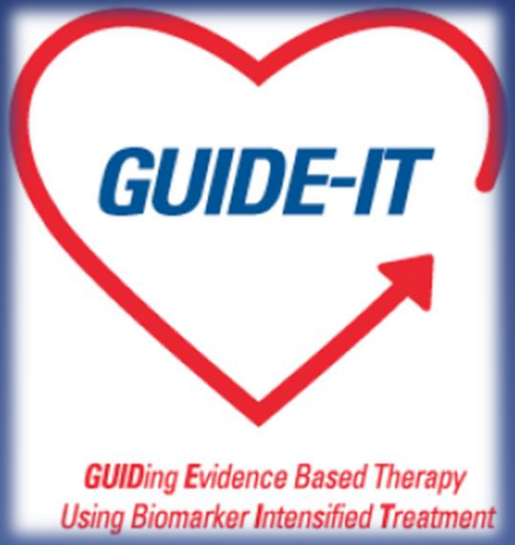
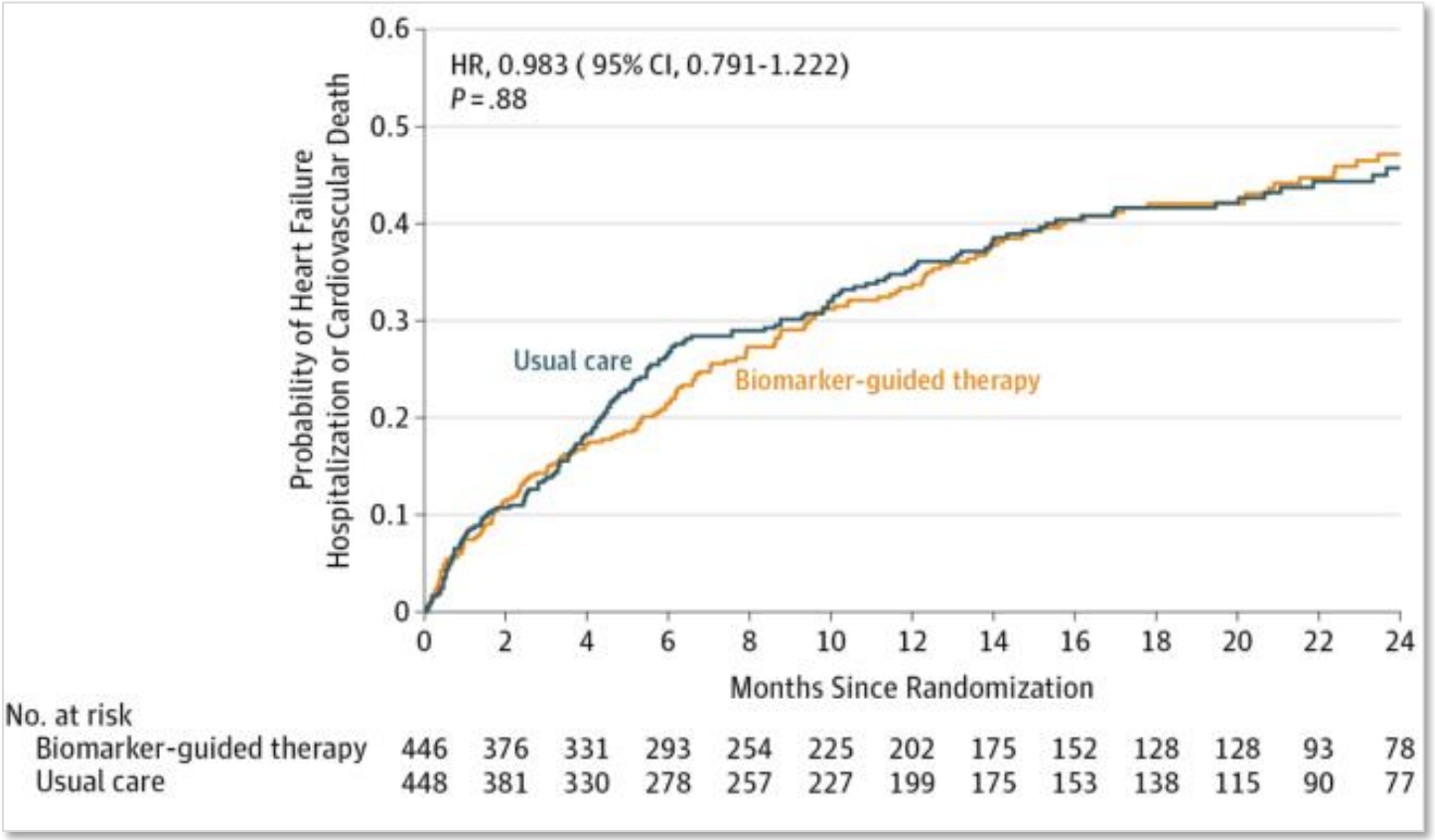



## Primary Hypothesis of NIH GUIDE-IT trial

- 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

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

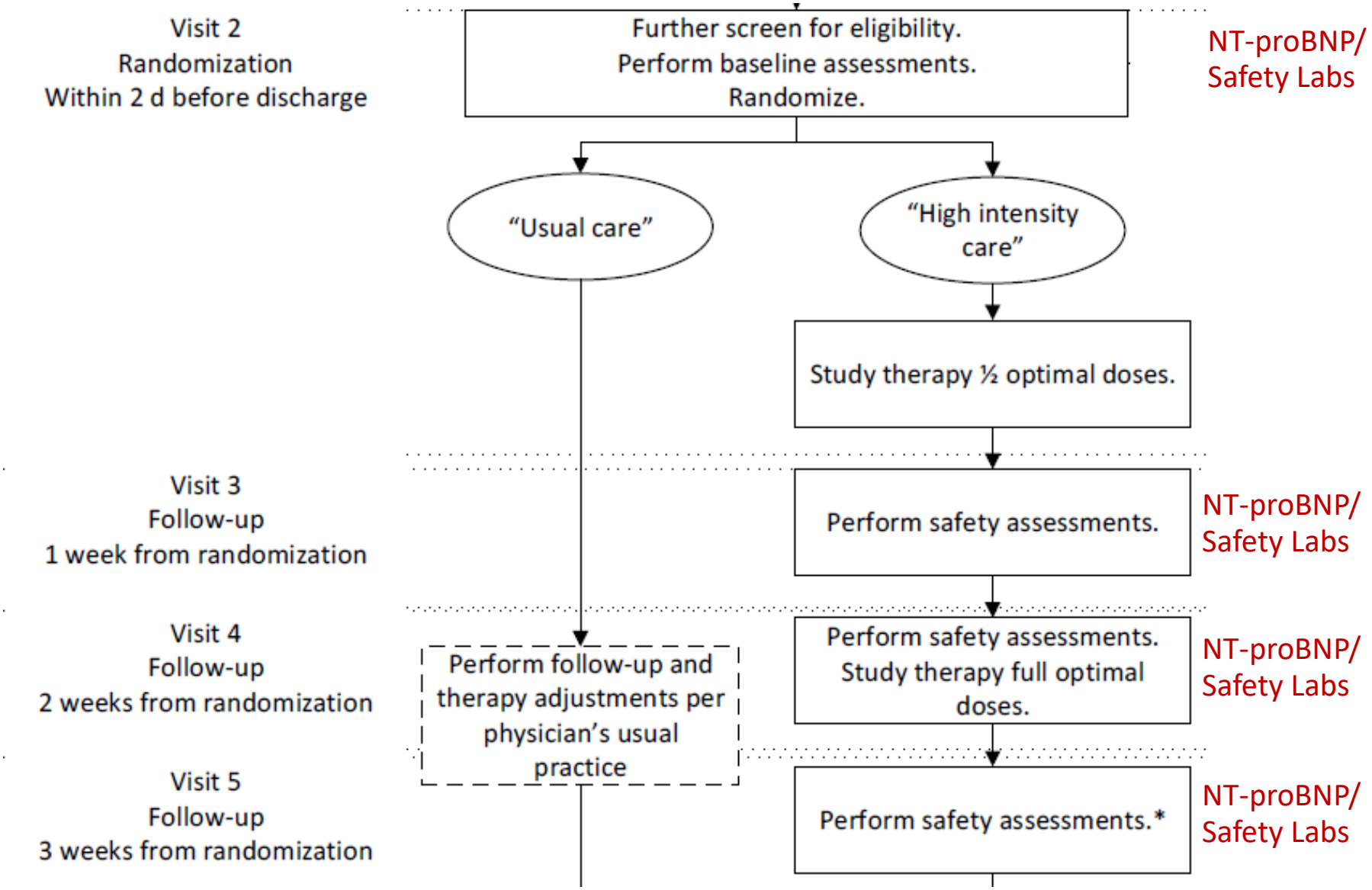
*Alexandre Mebazaa, Beth Davison, Ovidiu Chioncel, Alain Cohen-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski, Karen Sliwa, Adriaan A Voors, Christopher Edwards, Maria Novosadova, Koji Takagi, Albertino Damasceno, Hadiza Saidu, Etienne Gayat, Peter S Pang, Jelena Celutkiene,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

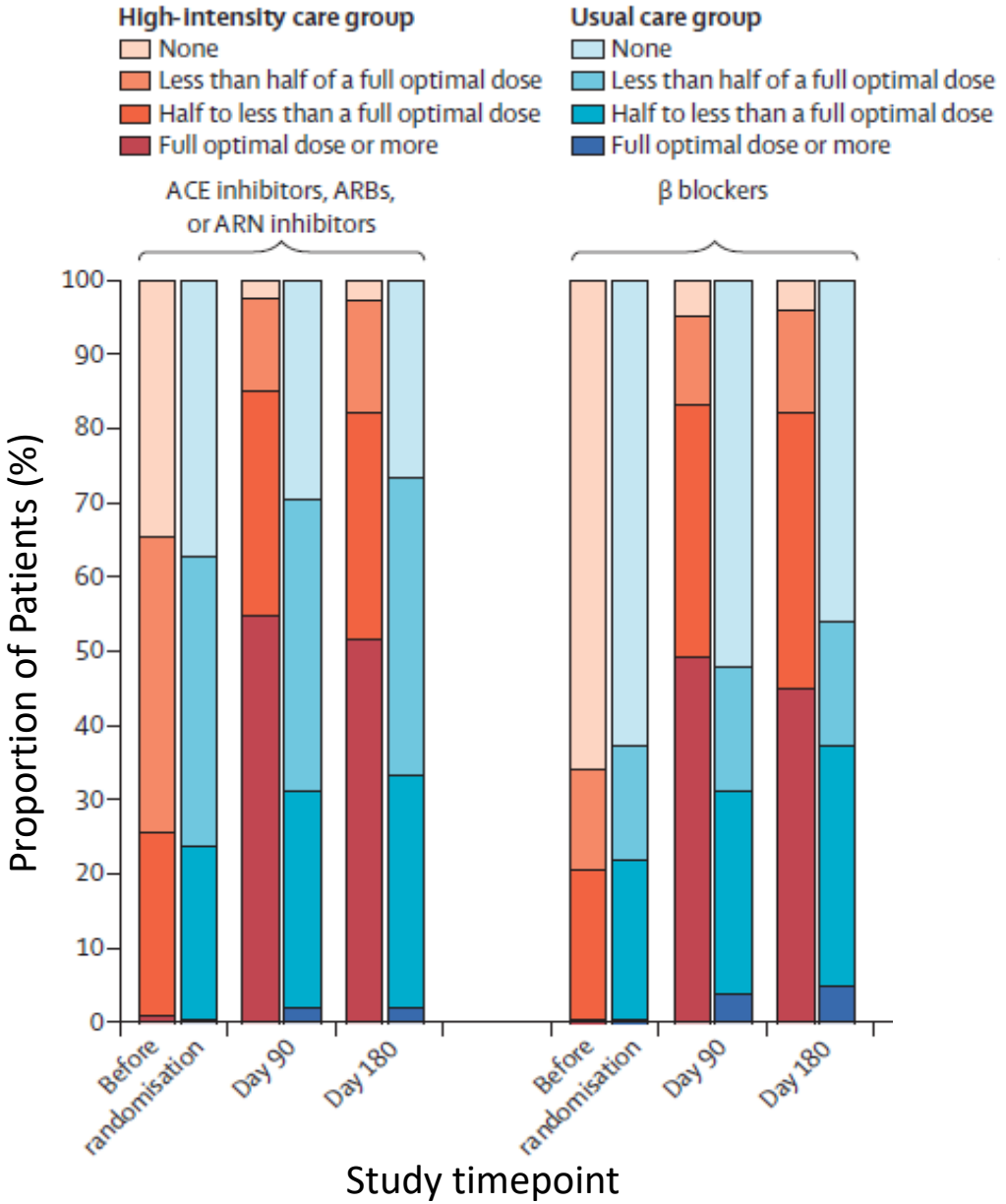
# STRONG-HF

## Strategy and Protocol



# Strong-HF

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

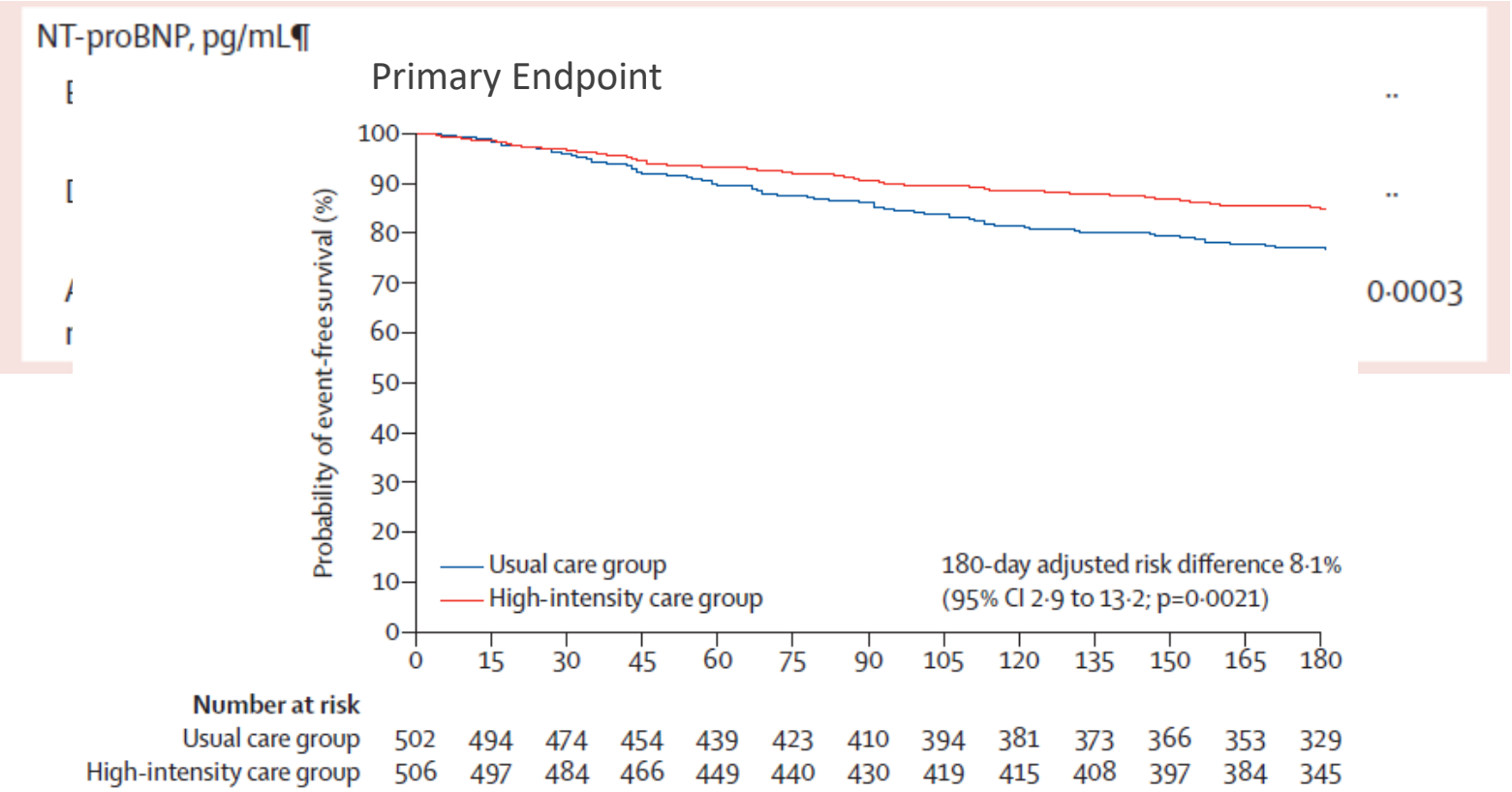



*Lancet* 2022; 400: 1938–52

# STRONG-HF

## Change in NT-proBNP and subsequent clinical outcomes

| | High-intensity care group (n=542) | Usual care group (n=536) | Adjusted treatment effect (95% CI) | Adjusted risk ratio (95% CI) | p value |
|---|---|---|---|---|---|
| **Primary endpoint** | | | | | |
| All-cause death or heart failure readmission by day 180* | 74/506 (15·2%) | 109/502 (23·3%) | 8·1 (2·9 to 13·2) | 0·66 (0·50 to 0·86) | 0·0021 |
| **Secondary endpoints** | | | | | |
| Change from baseline to day 90 in EQ-5D VAS† | 10·72 (0·88) | 7·22 (0·90) | 3·49 (1·74 to 5·24) | NA | <0·0001 |
| All-cause death by day 180* | 39/506 (8·5%) | 48/502 (10·0%) | 1·6 (−2·3 to 5·4) | 0·84 (0·56 to 1·26) | 0·42 |



# Role of Natriuretic Peptides in CVD

## Conclusions

- NT-proBNP now has clearly defined values based on age for the diagnosis of HF in patients presenting with shortness-of-breath with possible HF
- NT-proBNP can assist with prognosis and can be repeated in the ambulatory setting to gauge the need for referral to a HF specialist
- NT-proBNP is emerging as a potentially important adjunct to optimize medical treatment post acute HF hospitalization