This article is a CME / ABIM MOC / CE certified activity. To earn credit for this activity visit: http://www.medscape.org/viewarticle/881184

Supported by an independent educational grant from
Roche Diagnostics

Heart Failure and Biomarkers: Practical Strategies and Protocols CME / ABIM MOC / CE

Javed Butler, MD, MPH, MBA; Carolyn Su Ping Lam, MBBS, PhD, MRCP; A. Mark Richards, MD, PhD; Adriaan A. Voors, MD, PhD

Posted: 11/10/2017

Medscape EDUCATION

the heart.org from NEJM

Heart Failure and Biomarkers

Practical Strategies and Protocols

Moderator
Javed Butler, MD, MPH, MBA
Professor of Medicine
Professor of Physiology and Biophysics
Director, Division of Cardiovascular Medicine
Co-Director, Heart Institute
Stony Brook University
Stony Brook, New York

Heart Failure and Biomarkers: Practical Strategies and Protocols

Medscape EDUCATION

the heart.org

Panelists

Carolyn Su Ping Lam, MBBS, PhD, MRCP
Professor and Senior Consultant
Duke-National University of Singapore
Graduate Medical School
Senior Consultant
National Heart Centre
Chairperson
Asia Pacific Association of Women's Cardiovascular Disease
Singapore

Adriaan A. Voors, MD, PhD
Professor of Cardiology
University Medical Center
Groningen, Netherlands

A. Mark Richards, MD, PhD
Professor, Department of Medicine
University of Otago
Director
Christchurch Heart Institute
Christchurch, New Zealand
Professor
Department of Medicine
Director
Cardiovascular Research Institute
National University of Singapore
Singapore

Panelists

Learning Objectives

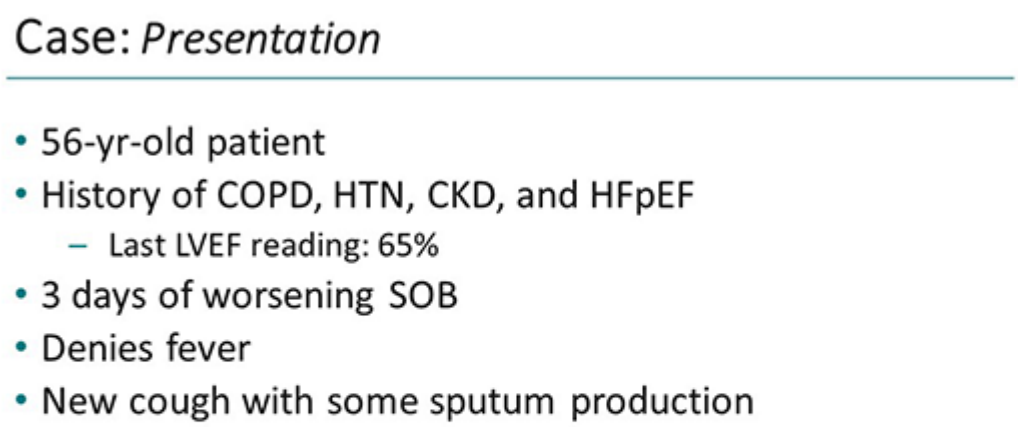
Increased knowledge regarding:

- Latest clinical guideline recommendations on the use of biomarkers in patients with HF

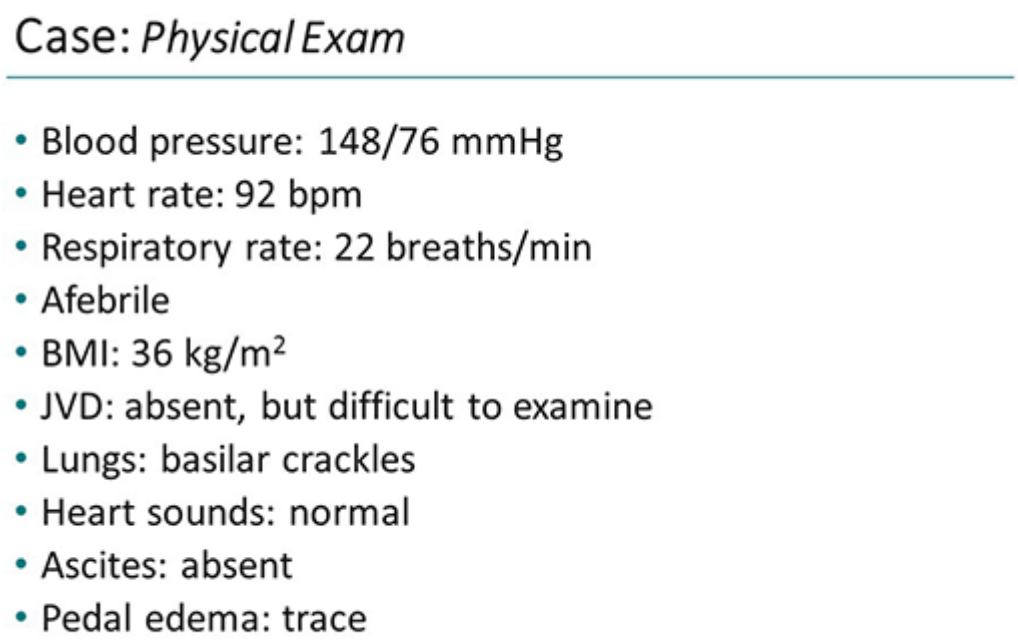
Greater competence related to:

- Clinical interpretation of biomarker results in HF
- Practical strategies to use NT-proBNP to guide therapy for patients with HF, both during and outside of hospitalization

Learning Objectives



Case: Presentation



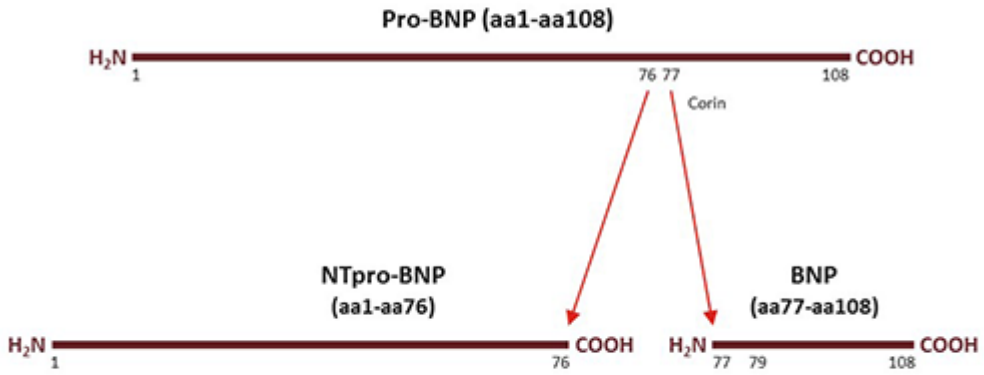
Case: Physical Exam

Case: *Laboratory Findings*

- Sodium: 139 mEq/L
- Potassium: 4.8 mEq/L
- Blood urea nitrogen: 42 mg/dL
- Creatinine: 1.9 mg/dL
- Hemoglobin and Hematocrit: normal
- NT-proBNP: 1272 pg/mL
- Previous baseline labs: unavailable

Case: Laboratory Findings

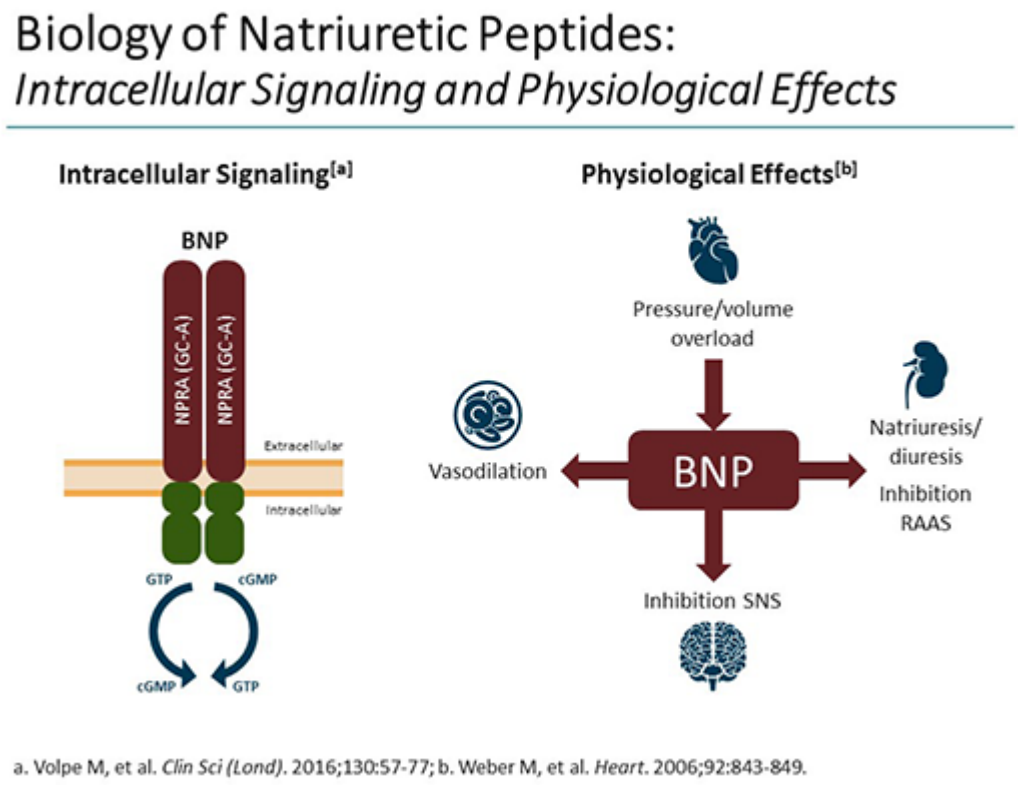
Biology of Natriuretic Peptides: *Processing*



Lam C, et al. *J Am Coll Cardiol*. 2007;49:1193-1202.

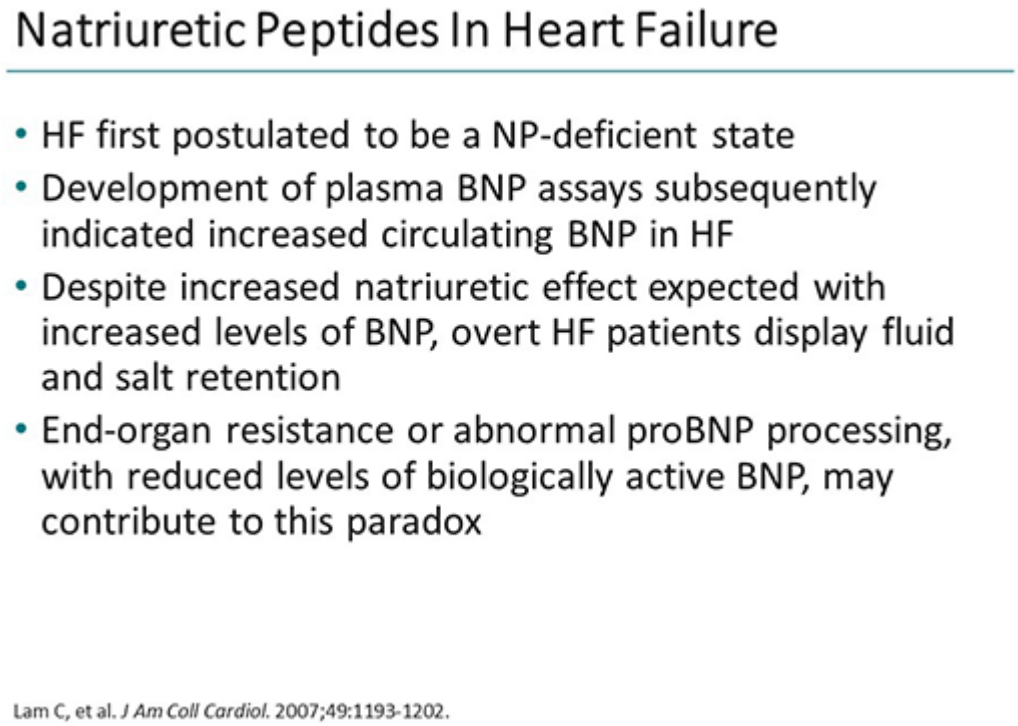
Biology of Natriuretic Peptides: Processing[1]

- B-type natriuretic peptide (BNP) is synthesized in cardiomyocytes as pre-proBNP
- Pre-proBNP is cleaved to form pro-BNP
- Upon release into the circulation, proBNP is cleaved into BNP and the N-terminal (NT) fragment, NT-proBNP
- Half-life of BNP is 22 min and NT-proBNP is 70 min



Biology of Natriuretic Peptides: Intracellular Signaling and Physiological Effects[2,3]

- BNP elicits its physiological responses mostly through natriuretic peptide receptor type A (NPR-A) binding
- This activates guanylate cyclase, producing cyclic guanosine monophosphate (cGMP)
- cGMP is an intracellular second messenger



Natriuretic Peptides In Heart Failure[1]

- In patients treated with valsartan/sacubitril, NT-proBNP should be measured instead of BNP because:
  - Neprilysin inhibits the breakdown of BNP, resulting in increased levels of BNP

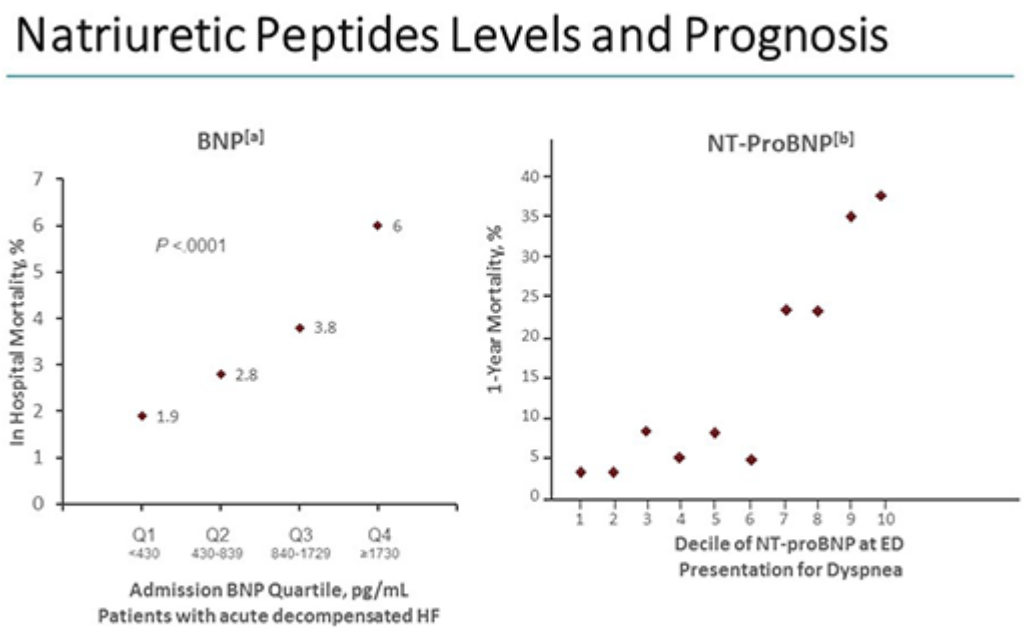
Cut-off Values for BNP and NT-proBNP for Diagnosis of HF

	Age, y	Rule-Out HF Unlikely	Rule-In HF Likely
BNP[a]	All	<100 pg/mL	>500 pg/mL
NT-proBNP[b]	<50	<300 pg/mL	>450 pg/mL
	50 to 75	<300 pg/mL	>900 pg/mL
	>75	<300 pg/mL	>1800 pg/mL

a. Maisel A, et al. *N Engl J Med.* 2002;347:161-167; b. Januzzi J, et al. *Eur Heart J.* 2006;27:330-337.

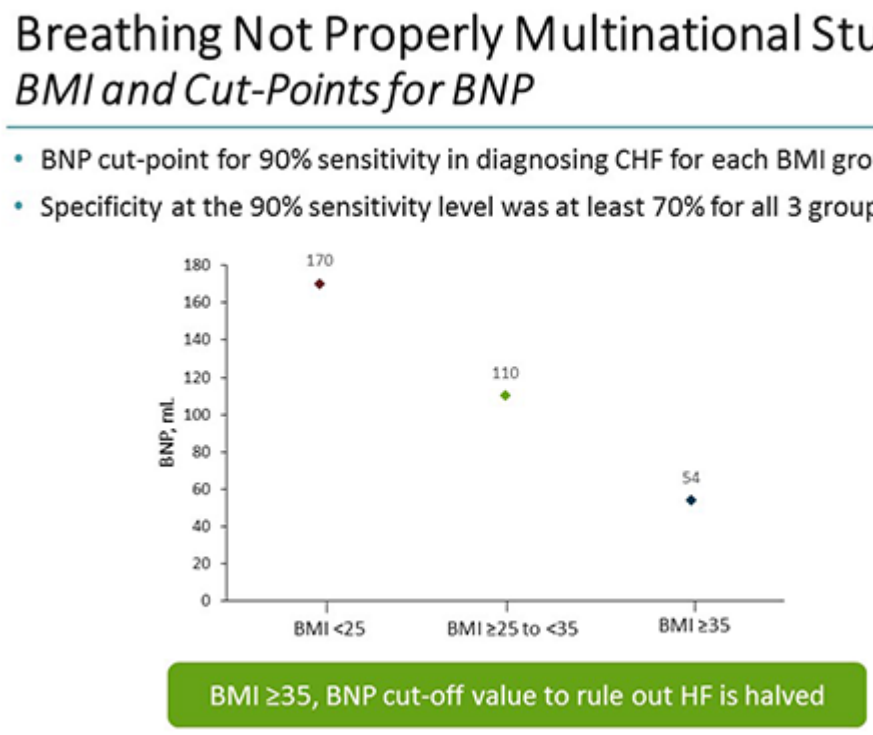
Cut-off Values for BNP and NT-proBNP for Diagnosis of HF[4,5]

- Factors that may affect plasma NP levels:
  - Age
  - Renal dysfunction
  - Body mass index (BMI)
  - Atrial fibrillation (AF)
- Increasing age and presence of AF increase NP levels while obesity suppresses NP levels



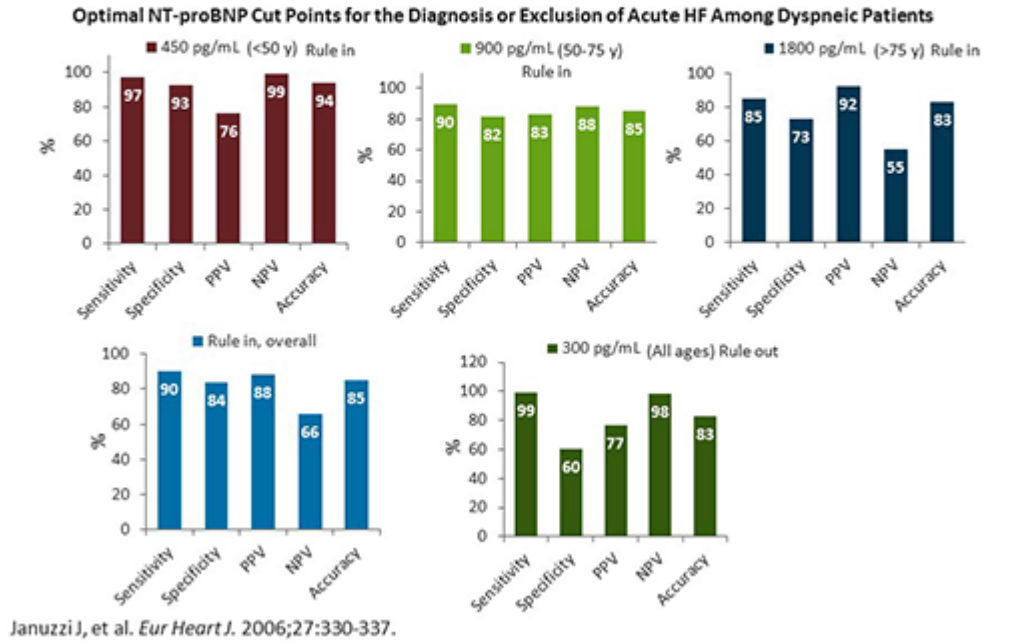
Natriuretic Peptides Levels and Prognosis[6,7]

- Higher NP levels are associated with worse prognosis, regardless of comorbidities and preserved or reduced ejection fraction



Breathing Not Properly Multinational Study: BMI and Cut-Points for BNP[8]

NT-proBNP Cut-Points By Age: *Sensitivity/Specificity*



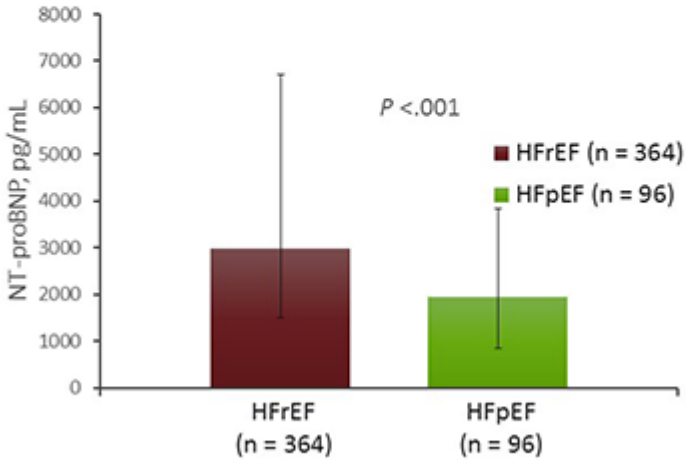
Januzzi J, et al. *Eur Heart J.* 2006;27:330-337.

NT-proBNP Cut-Points By Age: Sensitivity/Specificity[5]

- Age stratification
  - Improves diagnostic sensitivity for younger patients
  - Preserves specificity for older patients

NT-proBNP Higher in HFrEF vs HFpEF

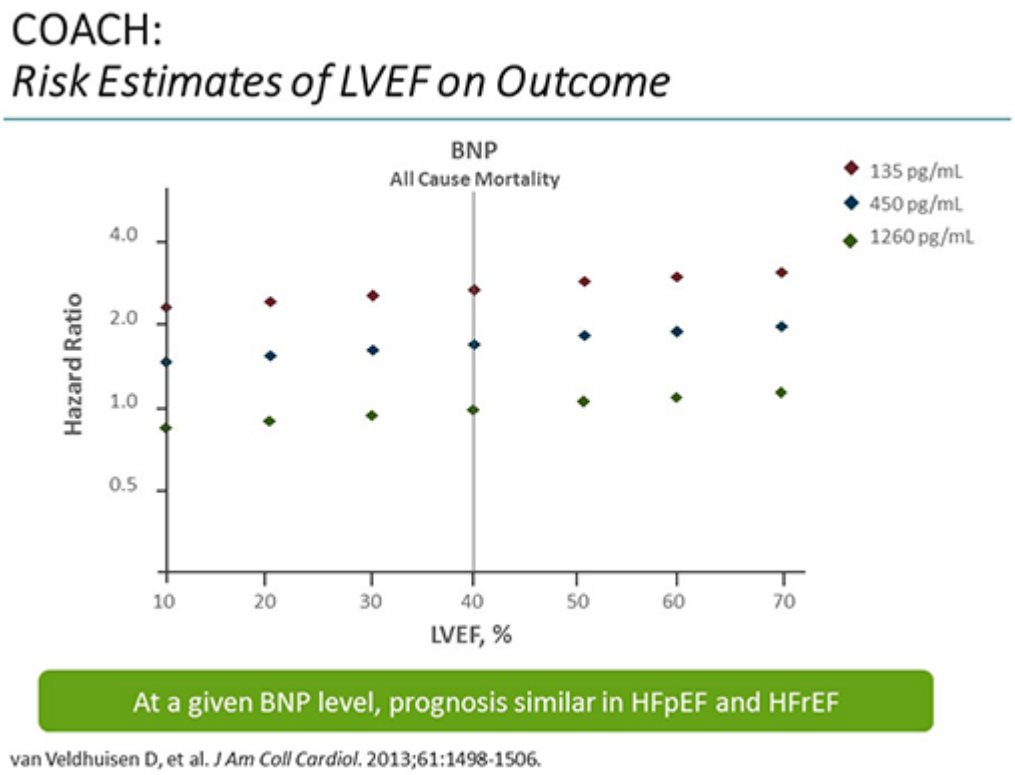
- Measured at discharge after hospitalization for acute HF



Tromp J, et al. *J Am Heart Assoc.* 2017;6:e003989.

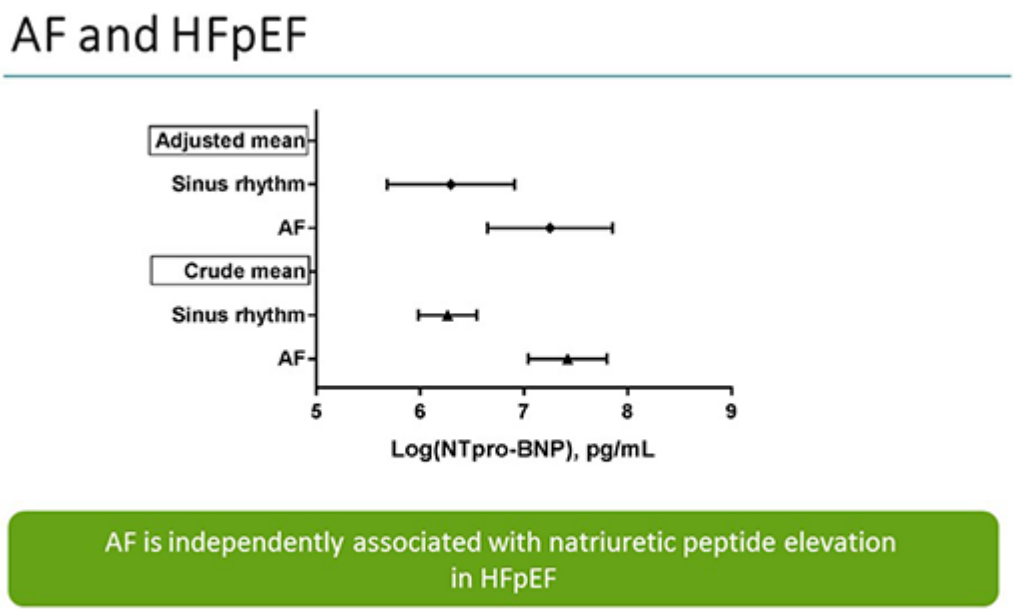
NT-proBNP Higher in HFrEF vs HFpEF[9]

- Heart failure with preserved ejection fraction (HFpEF) is associated with inflammation and angiogenesis-associated interactions
- Heart failure with reduced ejection fraction (HFrEF) is associated with mainly cardiac stretch-associated interactions
- Cardiac stretch-associated interactions lead to an increase in NP levels



COACH: Risk Estimates of LVEF on Outcome[10]

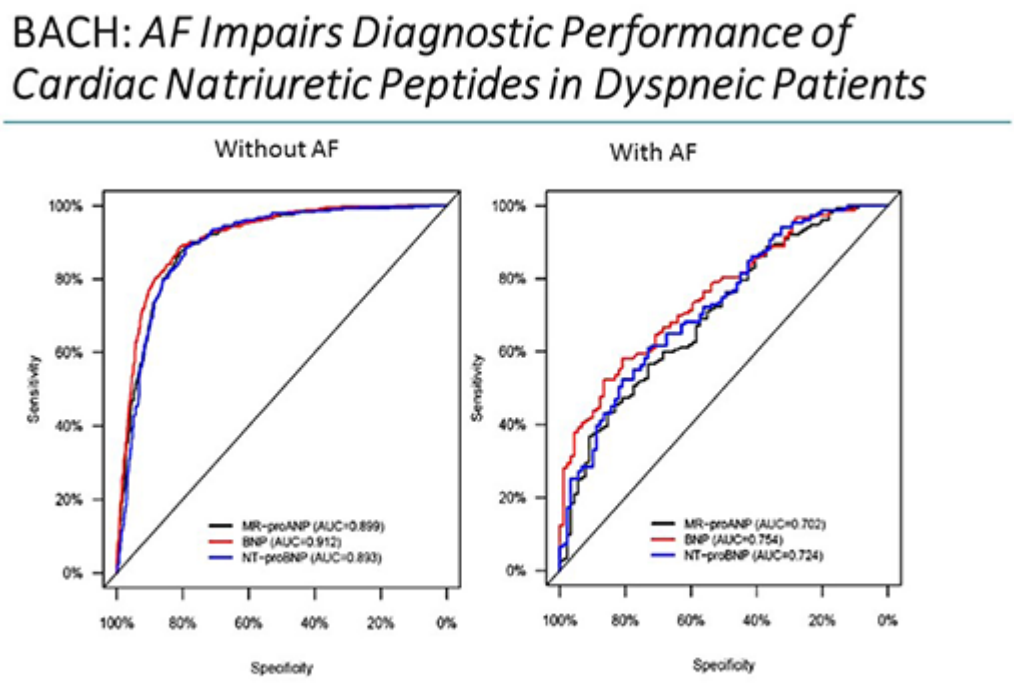
- No statistically significant changes in prognostic value of BNP with increasing left ventricular ejection fraction (LVEF)



Reprinted from *JACC Heart Fail*, 5, Lam CS, et al., Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction Association With Exercise Capacity, Left Ventricular Filling Pressures, Natriuretic Peptides, and Left Atrial, 5, 92-98., Copyright 2017, with permission from Elsevier.

AF and HFpEF[11]

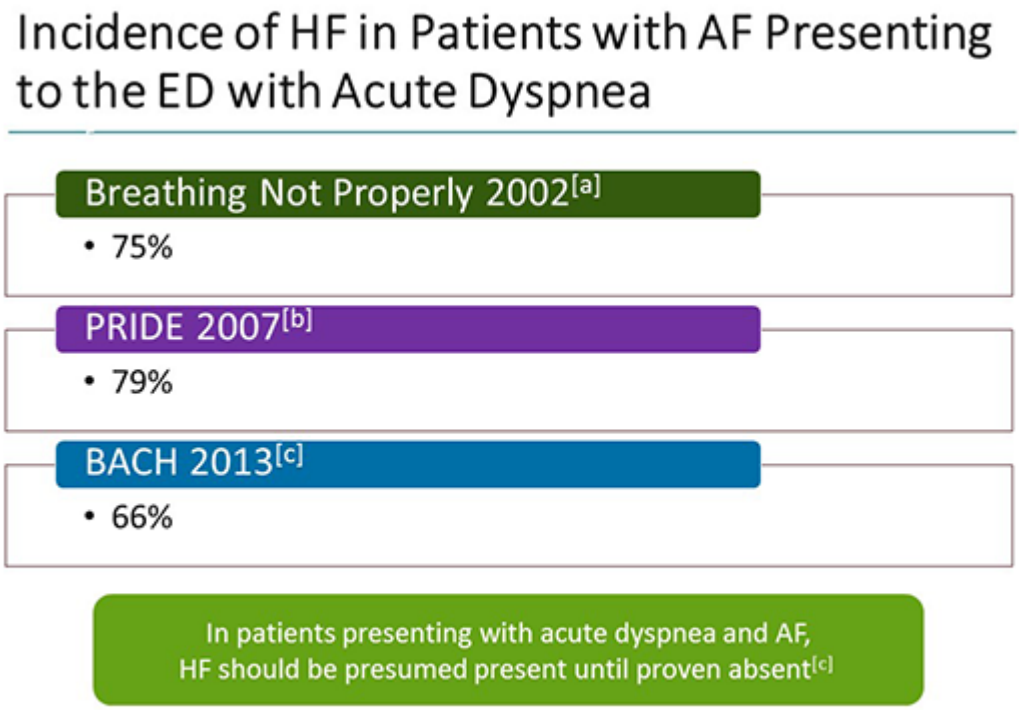
- Patients with AF have higher NT-proBNP levels independent of LV filling pressures and presence of HF
- Higher cutoff for NT-proBNP used in presence of AF



Reprinted from *JACC Heart Fail*, 1, Richards M, et al., Atrial Fibrillation Impairs the Diagnostic Performance of Cardiac Natriuretic Peptides in Dyspneic Patients Results From the BACH Study (Biomarkers in Acute Heart Failure), 192-199., Copyright 2013, with permission from Elsevier.

BACH: AF Impairs Diagnostic Performance of Cardiac Natriuretic Peptides in Dyspneic Patients[12]

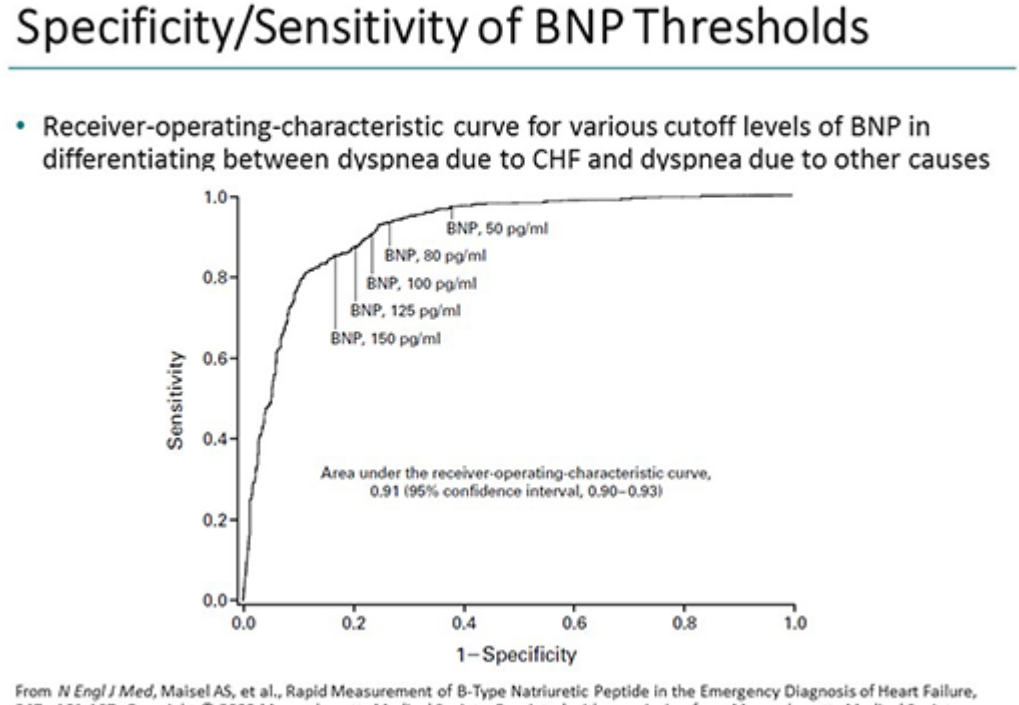
- Makes the diagnosis of HF difficult
- Patient work-up is important
- Absence of echocardiographic criteria to guide diagnosis



a. Maisel A, et al. *N Engl J Med.* 2002;347:161-167; b. Morello A, et al. *Am Heart J.* 2007;153:90-97; c. Richards M, et al. *JACC Heart Fail.* 2013;1:192-199.

Incidence of HF in Patients with AF Presenting to the ED with Acute Dyspnea[4,12,13]

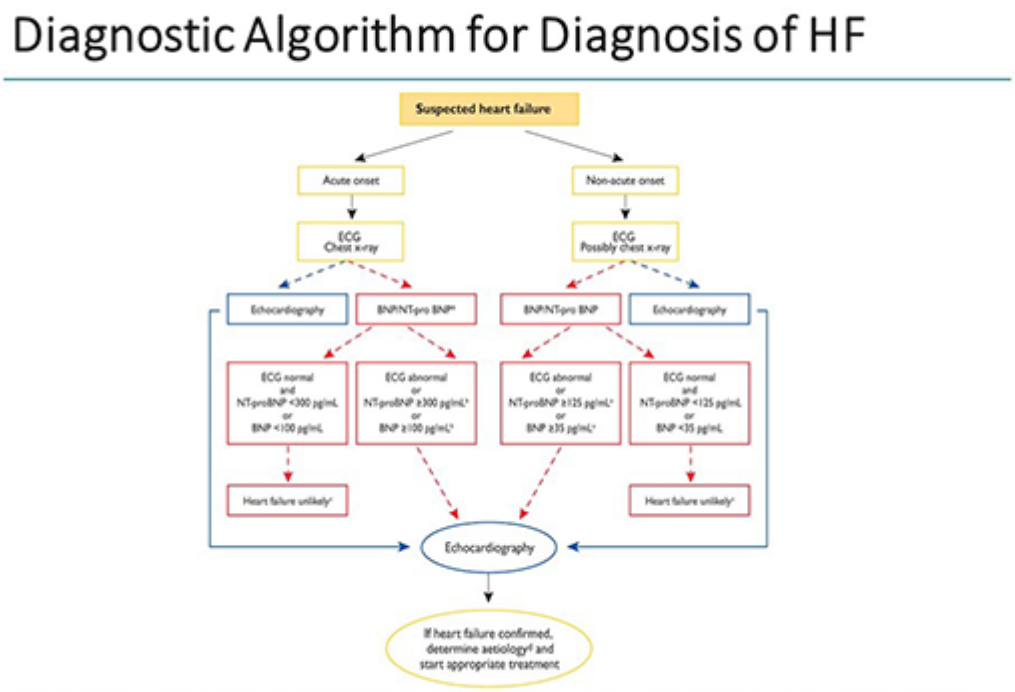
- 75% to 80% had a final diagnosis of acute HF



From *N Engl J Med*, Maisel AS, et al., Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure, 347., 161-167. Copyright © 2002 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Specificity/Sensitivity of BNP Thresholds[4]

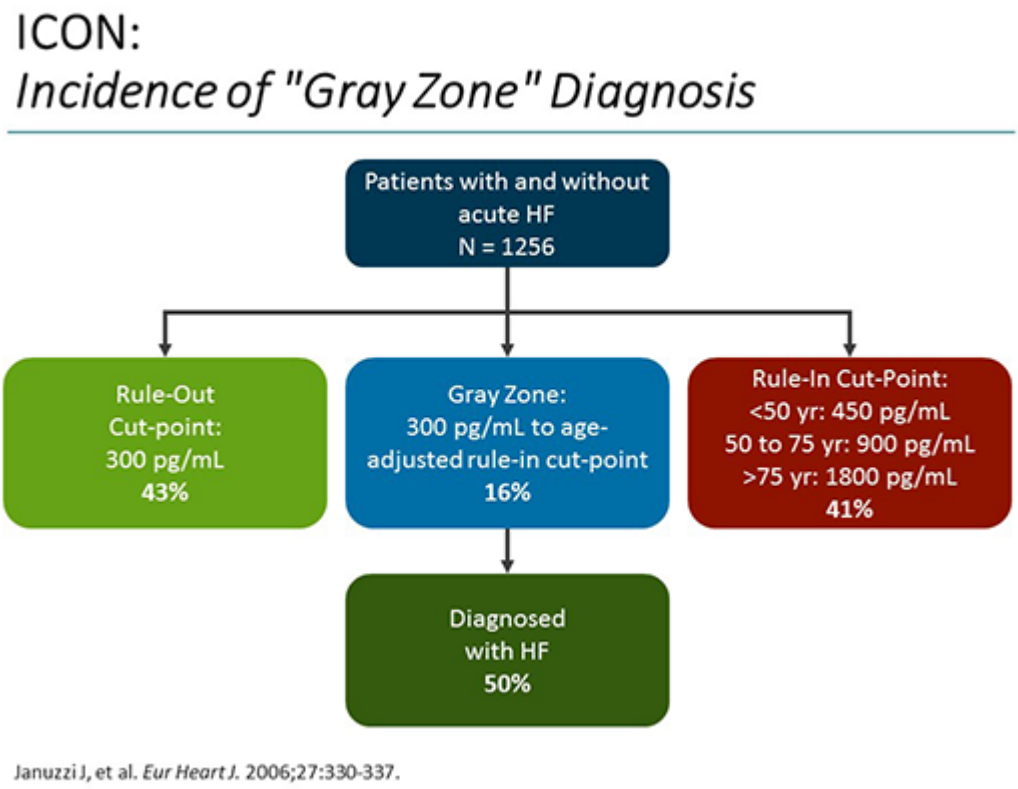
- Sensitivity is high and specificity low at the area under the curve (AUC), ie, the optimal point



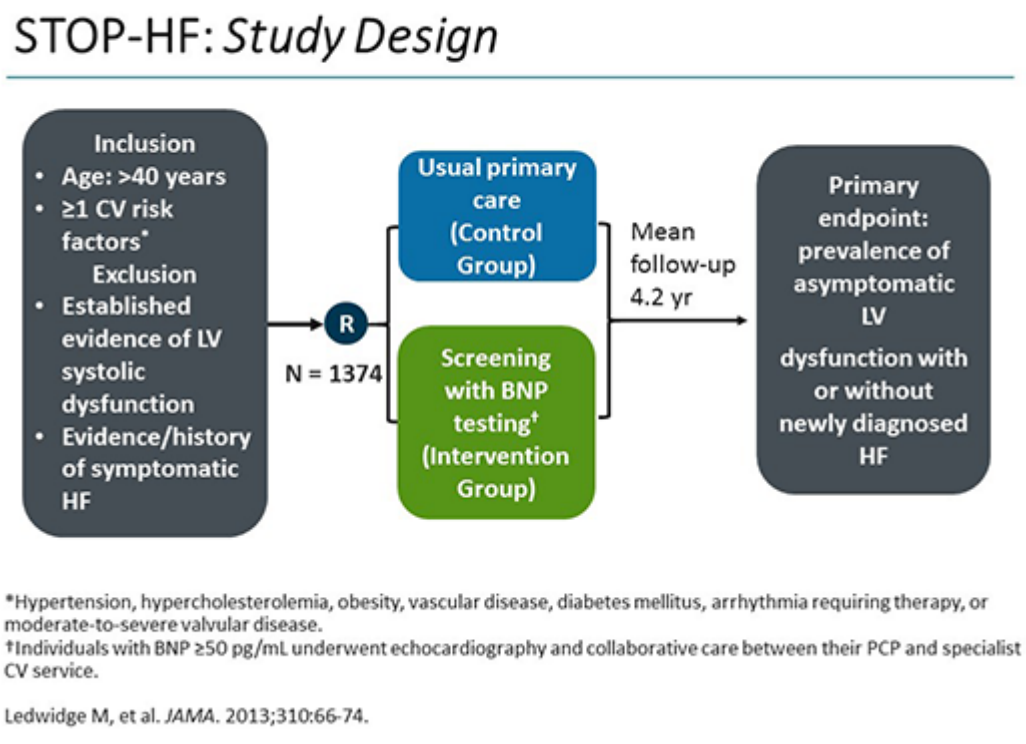
McMurray JJ, et al. *Eur J Heart Fail*. 2012;14:803-869. Published on behalf of the European Society of Cardiology. All rights reserved. © 2012 the Authors.

Diagnostic Algorithm for Diagnosis of HF[14]

- NP thresholds provided by guidelines
  - Are for ruling out HF
  - Have negative predictive value of about 99%
  - Does not suggest that values above threshold are diagnostic of HF
- Rule-in thresholds are much higher
- Values between rule-out and rule-in thresholds are in the "gray zone"
  - Need additional information and additional diagnostic criteria for ruling in HF

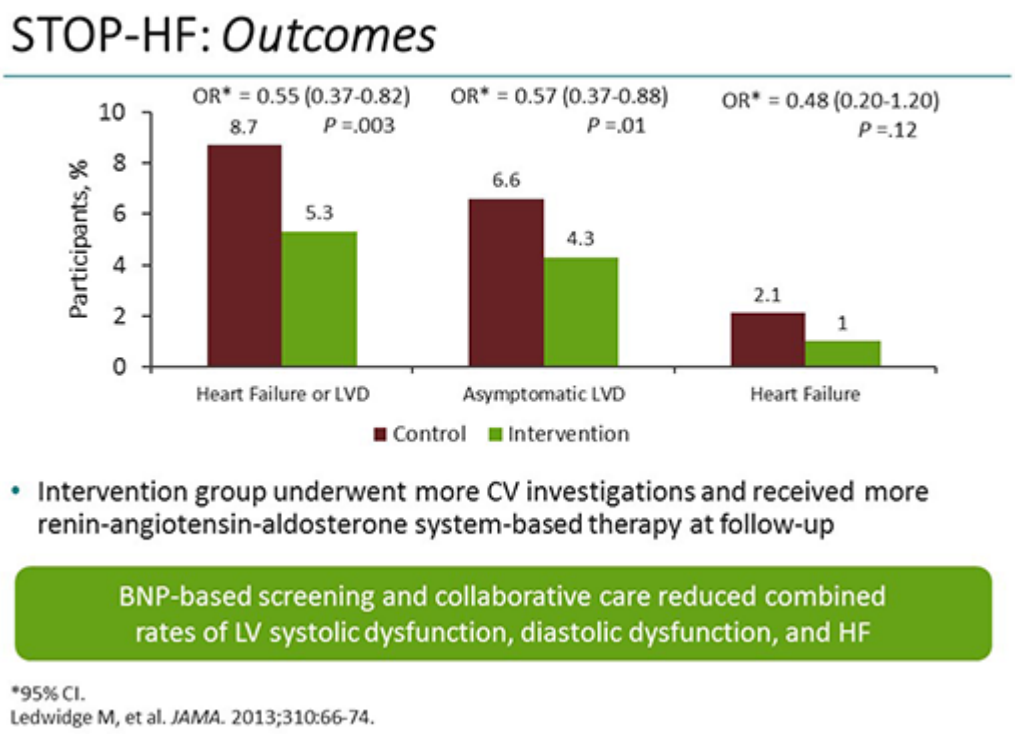


ICON: Incidence of "Gray Zone" Diagnosis[5]

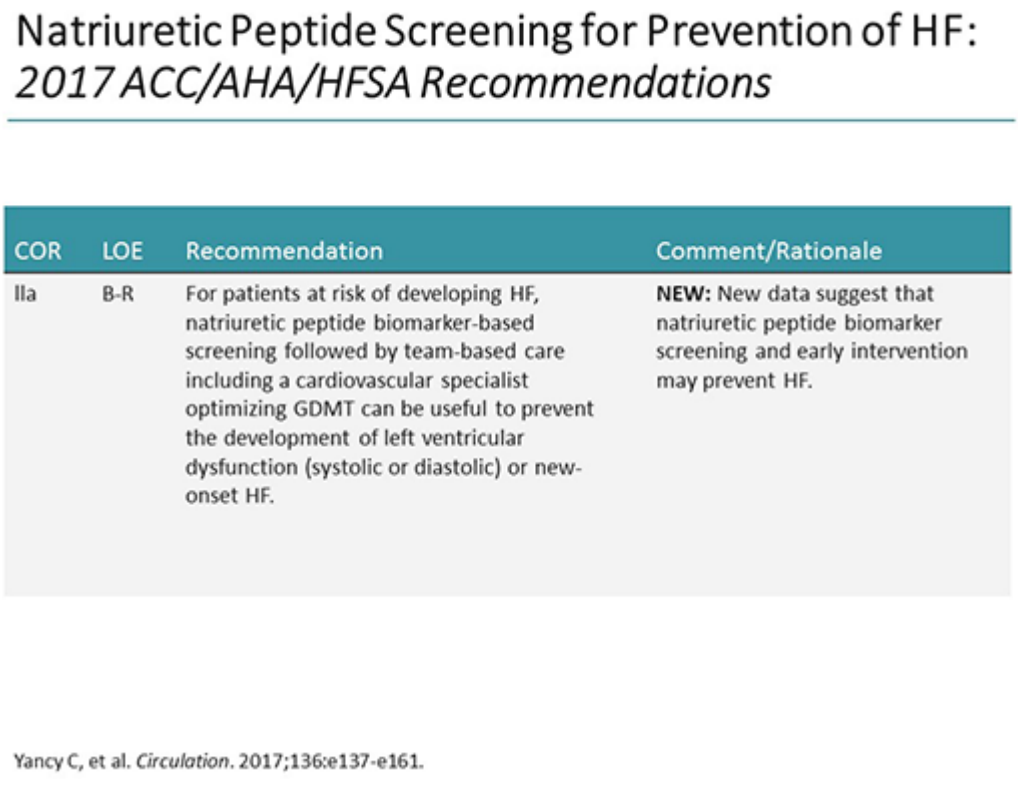


STOP-HF: Study Design[15]

- Determined the efficacy of a screening program using BNP and collaborative care in high-risk patients in reducing:
  - Newly diagnosed HF
  - Prevalence of LV systolic and/or diastolic dysfunction



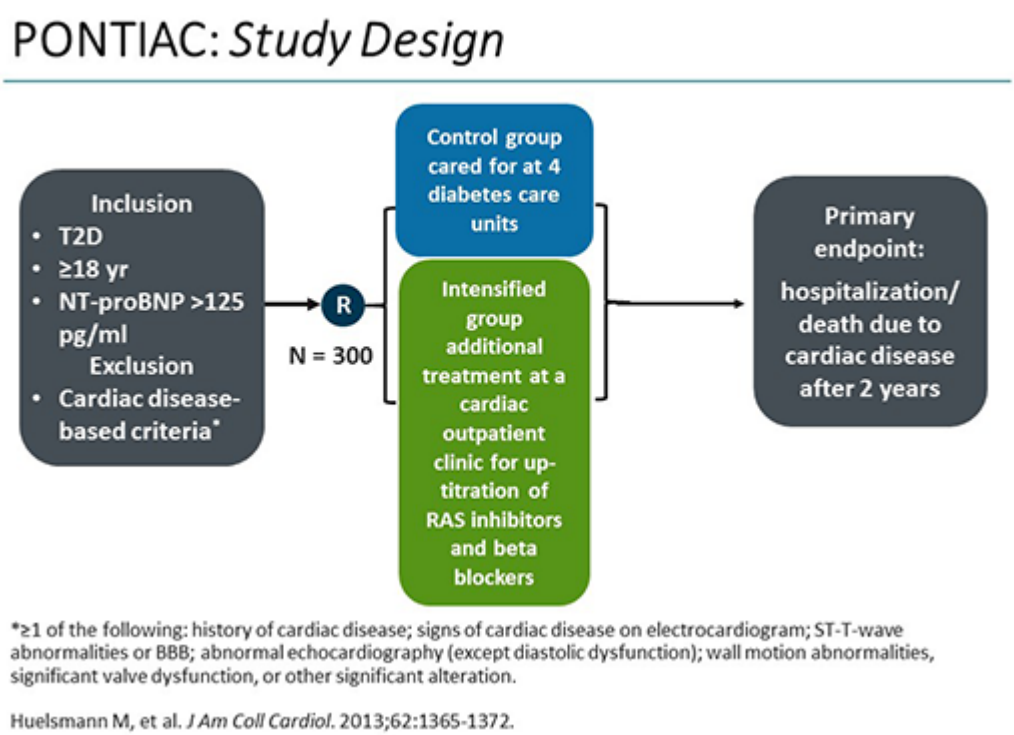
STOP-HF: Outcomes[15]



Natriuretic Peptide Screening for Prevention of HF: 2017 ACC/AHA/HFSA Recommendations[16]

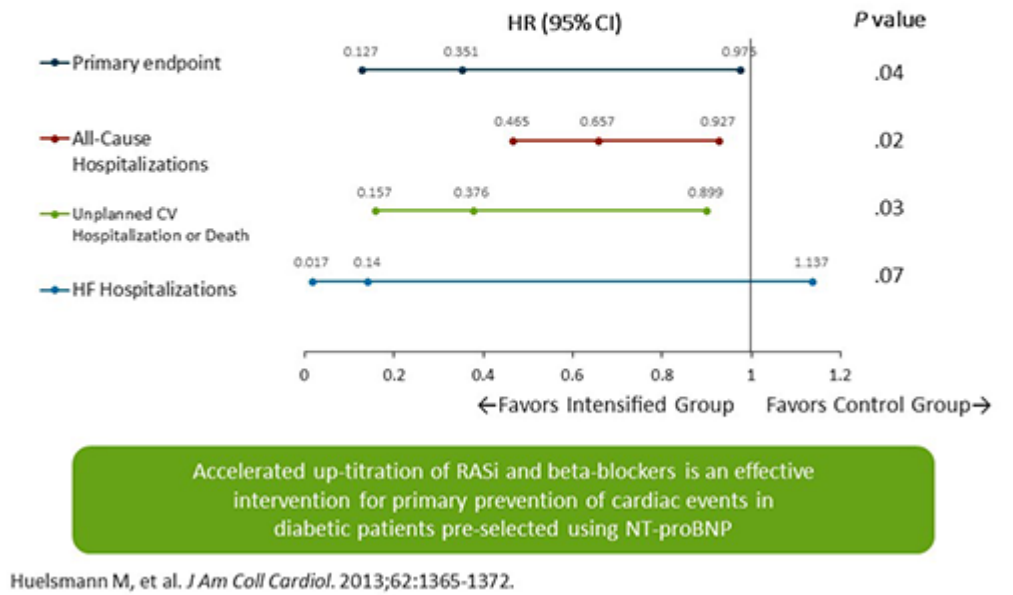
- Collaborative care is key to prevention
- Challenge to translate trial into clinical practice
    - Need to disseminate message to general practitioners (GPs)

- GPs are first to encounter patients at risk for developing HF

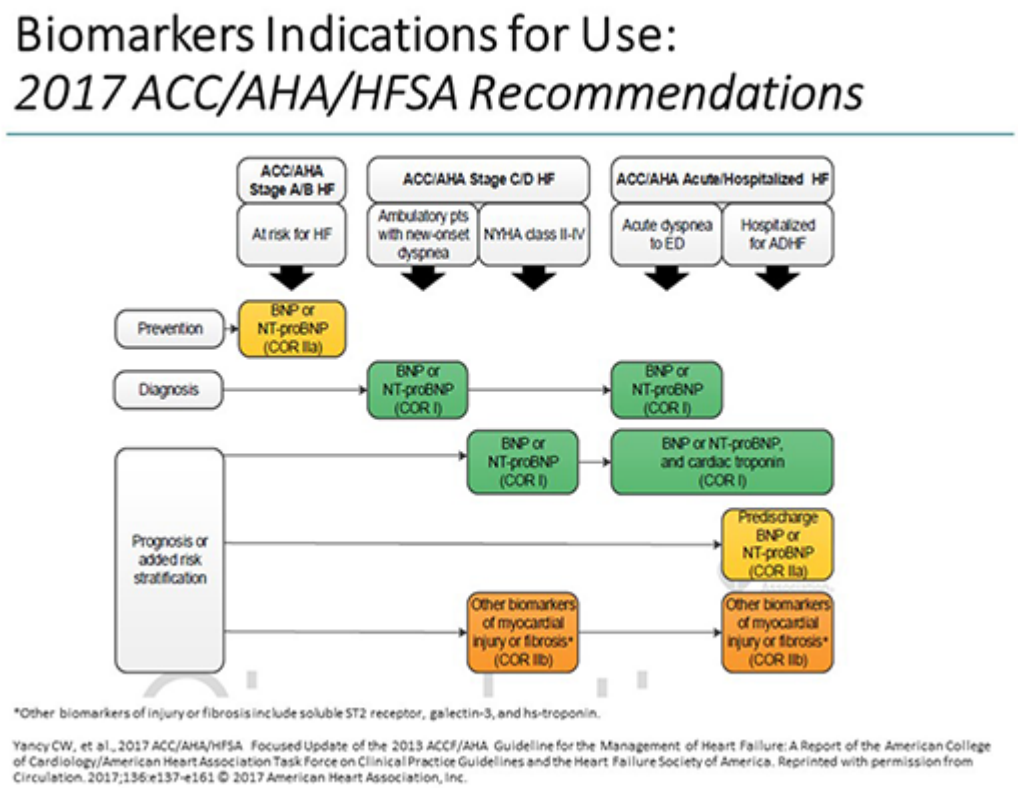


PONTIAC: Study Design[17]

- Assessed primary preventive effect of neurohumoral therapy in high-risk diabetic patients selected by NT-proBNP level

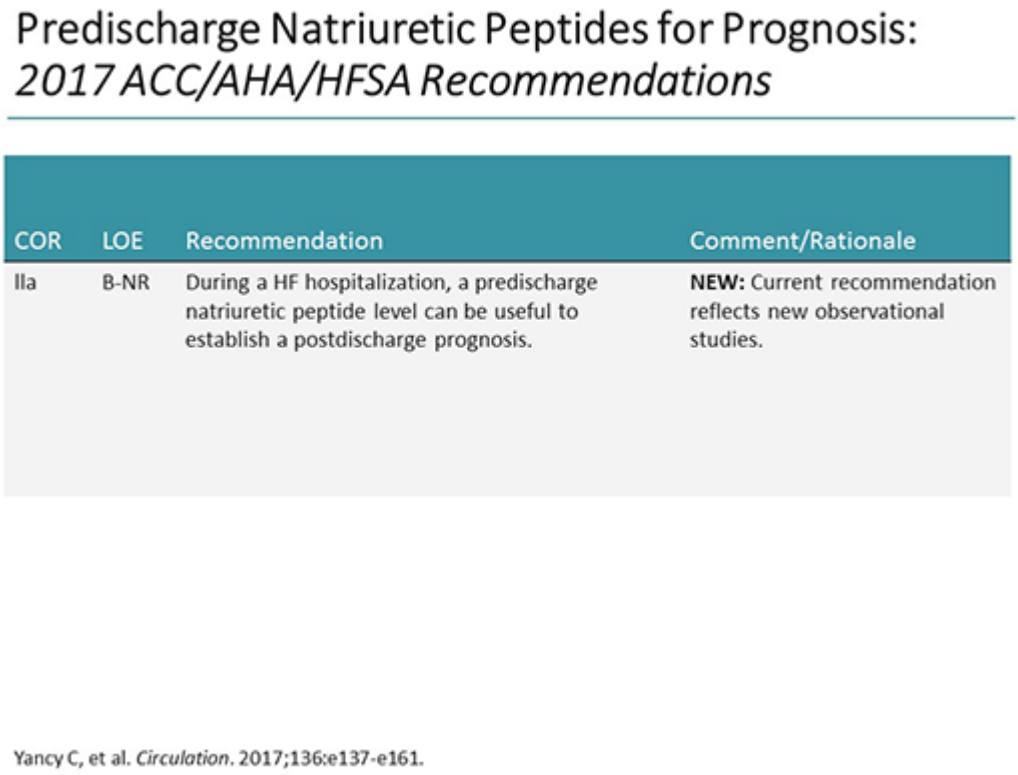


PONTIAC: Outcomes[17]



Biomarkers Indications for Use: 2017 ACC/AHA/HFSA Recommendations[16]

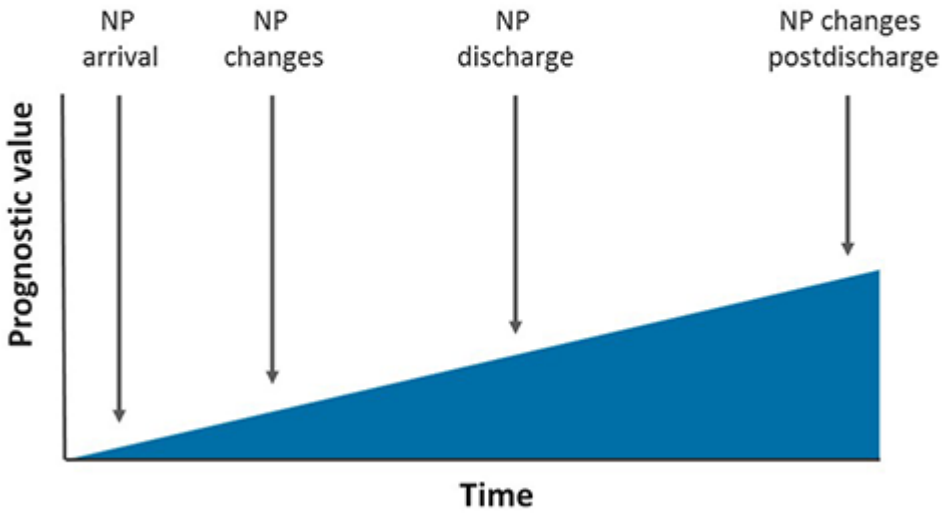
- NPs are one of the best-established markers of prognosis
- They are particularly strong markers in the chronic setting



Predischarge Natriuretic Peptide for Prognosis: 2017 ACC/AHA/HFSA Recommendations[16]

- Predischarge NP level may guide
  - Therapy intensification
  - Close vs distant follow-up
  - Follow-up frequency

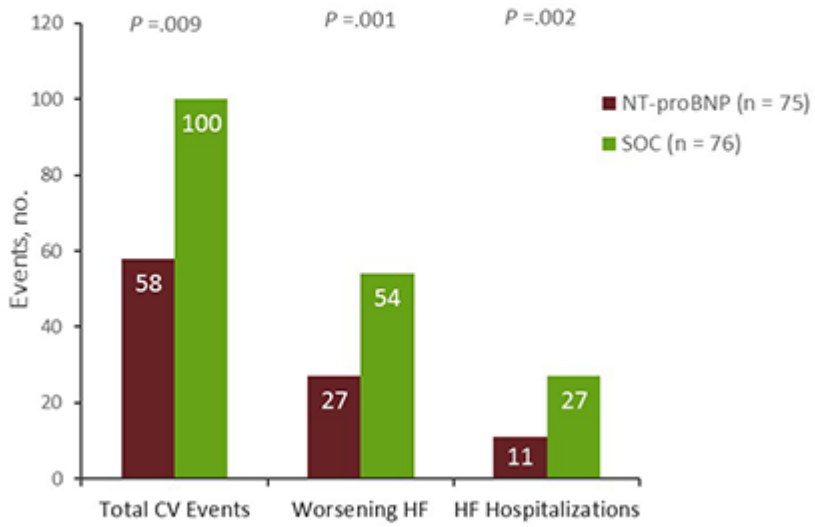
Natriuretic Peptide Sampling for Outcome: *The Later the Better*



Natriuretic Peptide Sampling for Outcome: The Later The Better

- The more recent the NP sampling, the greater its prognostic value

PROTECT: *NT-proBNP-Guided Therapy in Patients with Chronic LVSD*



Januzzi J Jr, et al. *J Am Coll Cardiol*. 2011;58:1881-1889.

PROTECT: NT-proBNP-Guided Therapy in Patients with Chronic LVSD[18]

- At least 14 trials of NT-guided therapy to date
- Trials have been heterogeneous in sample size, average age, comorbidity burden, and treatment targets
- No single trial showed a definitive, clear-cut, positive outcome, with the exception of PROTECT
- In PROTECT, NT-proBNP-guided therapy was superior to standard of care

Benefits of Natriuretic Peptide-Guided Therapy: *Individual Patient Meta-Analysis*

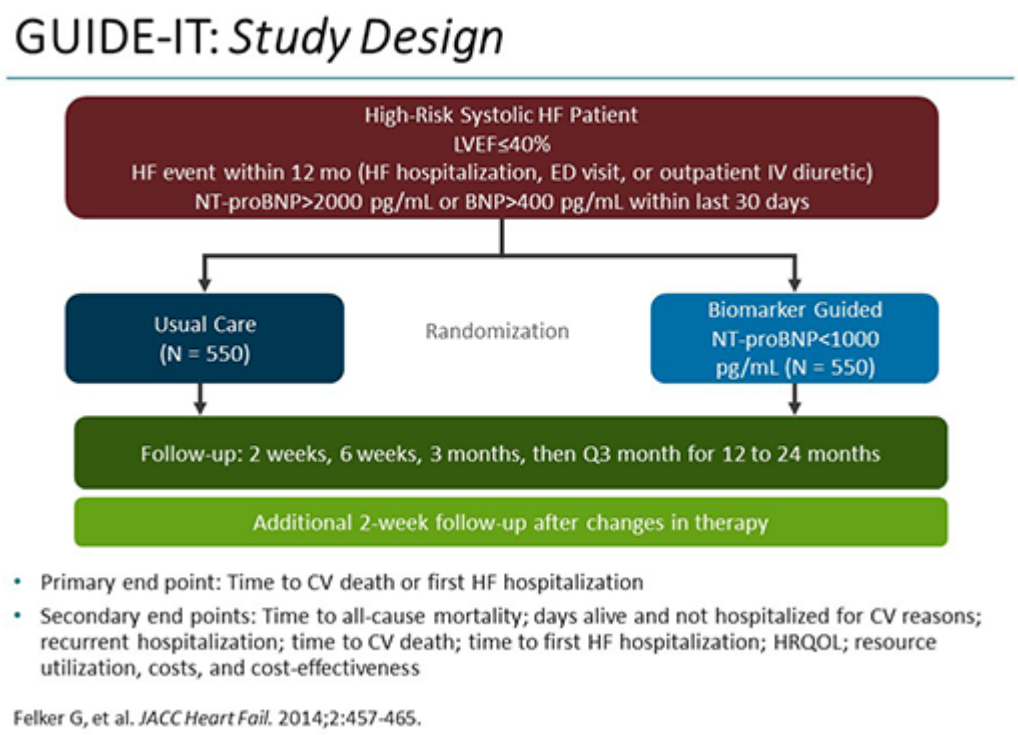
Endpoint	HR (95% CI) NP- vs Clinically-Guided Care	*P*
All-cause mortality	0.62 (0.45, 0.86)	.004
HF hospitalization	0.80 (0.67, 0.94)	.009
CV Hospitalization	0.82 (0.67, 0.99)	.048

- 2000 patients from 9 studies; clinically guided care (N = 994) and NP-guided care (N = 1006)
- Lower mortality in the NP-guided group
  - No heterogeneity between studies (*P* =.57)
  - No LVEF interaction
  - Age interaction (*P* =.028); survival benefit seen in younger patients (<75 yrs), but not older patients (≥75 yrs)

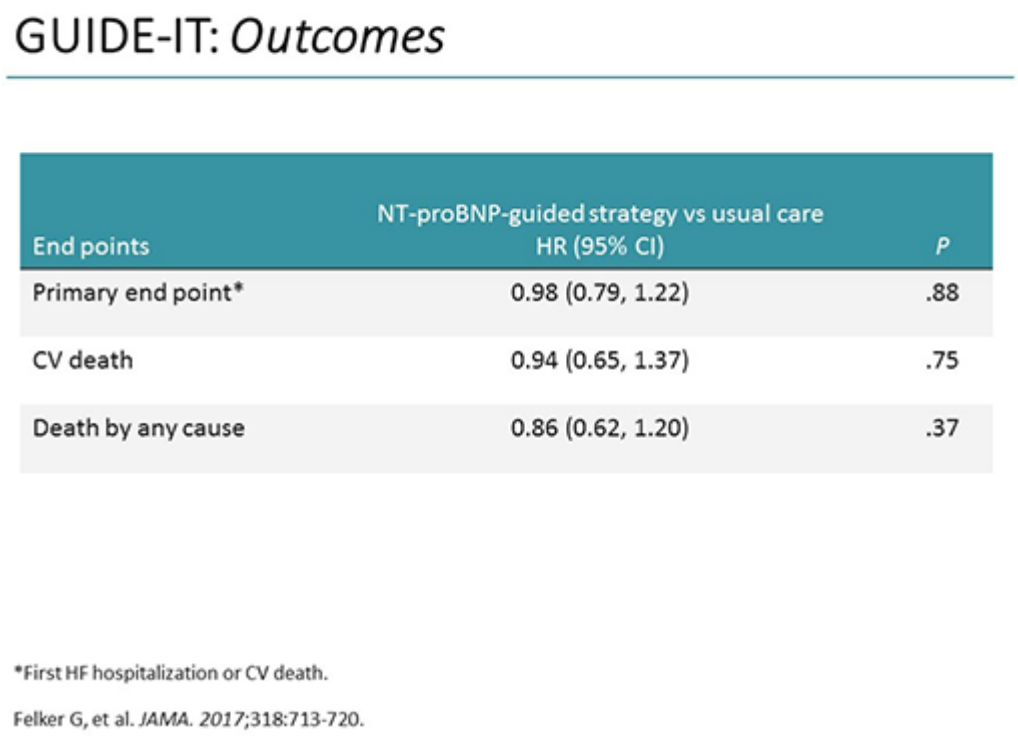
Troughton R, et al. *Eur Heart J*. 2014;35:1559-1567.

Benefits of Natriuretic Peptide-Guided Therapy: Individual Patient Meta-Analysis[19]

- Meta-analyses have shown positive outcomes with NP-guided therapy



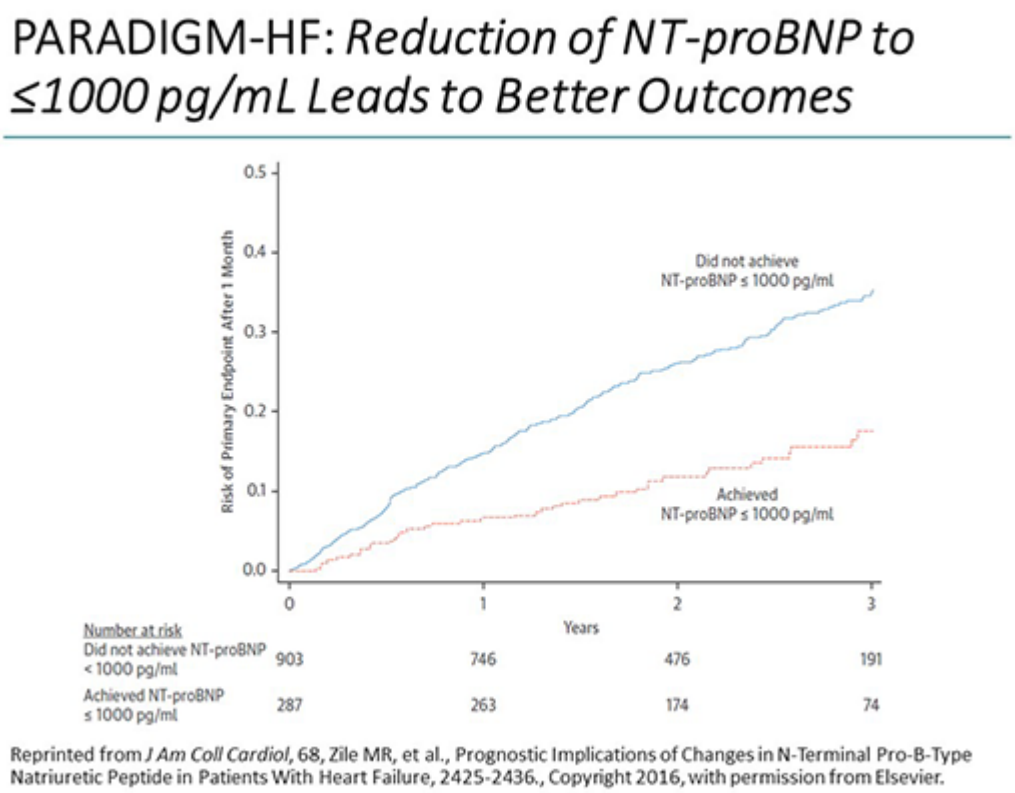
GUIDE-IT: Study Design[20]



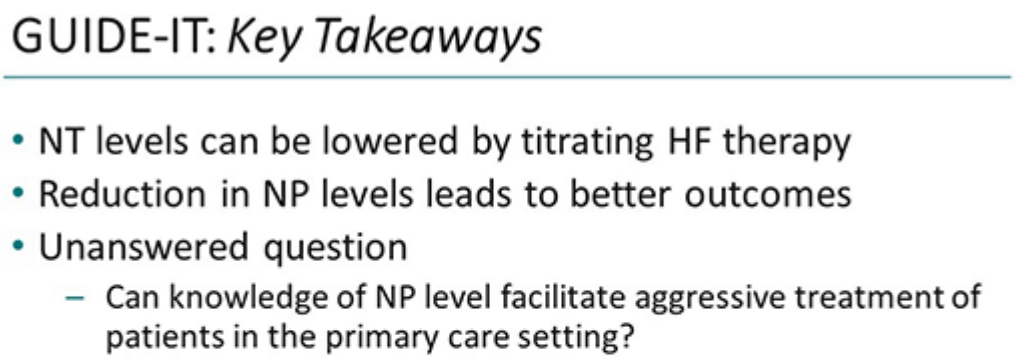
GUIDE-IT: Outcomes[21]

- Study terminated after enrollment of 894 patients because of futility
- At 12 months, study arms did not differ in achieved NT-proBNP levels or in achieved dosages of guidelines-recommended drugs
- Between 6 and 10 months, survival curves diverged in favor of NT-proBNP-guided strategy
- Despite null result, study showed lowering of NT-proBNP to <1000 pg/mL leads to better outcomes

- About 40% of patients in both arms achieved target NT-proBNP level <1000 pg/mL at 12 months

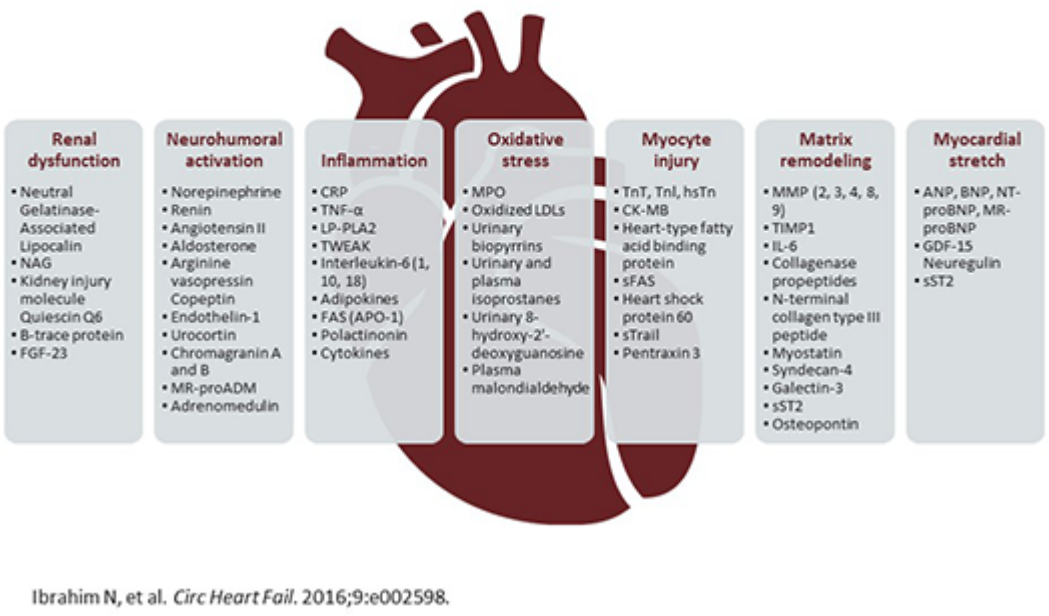


PARADIGM-HF: Reduction of NT-proBNP to ≤1000 pg/mL Leads to Better Outcomes[22]



GUIDE-IT: Key Takeaways

- Strategy trials should be cluster randomized trials, ie, study sites should be randomized, not individuals



Ibrahim N, et al. *Circ Heart Fail*. 2016;9:e002598.

Other Cardiac Biomarkers in HF[23]

- Cardiac troponins are the next most commonly used biomarker in HF
- High sensitivity troponins are
  - Predictive of hospitalization and mortality
  - Additive to natriuretic peptide levels in their prognostic value

Summary

- NPs assist in the diagnosis or exclusion of HF in both chronic and acute decompensated settings, especially when the cause of dyspnea is unclear
- NP levels are also useful in risk stratification and prognosis
- NP values can be influenced by age and comorbidities, including
  - Obesity
  - Renal dysfunction
  - Atrial fibrillation
- NP screening and early intervention may prevent HF
- NT levels can be lowered by titrating HF therapy
- Reduction in NP levels leads to better outcomes

Summary

Medscape EDUCATION

the heart.org

Thank you for participating in this activity.

To proceed to the online CME test, click on the **Earn Credit** link on this page.

Thank You

This content has been condensed for improved clarity.

Abbreviations

ACC = American College of Cardiology
AF = atrial fibrillation
AHA = American Heart Association
ANP = atrial natriuretic peptide
AUC = area under the curve
BBB = bundle branch block
BMI = body mass index
bpm = beats per minute
cGMP = cyclic guanosine monophosphate
CHF = congestive heart failure
CI = confidence interval
CKD = chronic kidney disease
CK-MB = creatinine kinase-MB fraction
COPD = chronic obstructive pulmonary disease
COR = class of recommendation
CRP = C-reactive protein
CV = cardiovascular
ED = emergency department
FGF = fibroblast growth factor
GC-A = guanylate cyclase type A
GDF-15 = growth differentiating factor 15
GDMT = guideline-directed medical therapy
GTP = guanosine triphosphate
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction

HFSA = Heart Failure Society of America
HR = hazard ratio
HRQoL = health-related quality of life
hs = high-sensitivity
HTN = hypertension
IL = interleukin
JVD = jugular venous extension
LDL = low density lipoprotein
LOE = level of evidence
LP-PLA2 = lipoprotein associated phospholipase 2
LV = left ventricular
LVD = left ventricular dysfunction
LVEF = left ventricular ejection fraction
LVSD = left ventricular systolic dysfunction
MMP = matrix metalloproteinase
MPO = myeloperoxidase
MR-proADM = mid regional-pro adrenomedullin
NAG = N-acetyl beta-D gluosaminidase
NPR-A = Natriuretic peptide receptor A
NPV = negative predictive value
NR = nonrandomized
NT-proBNP = N-terminal pro B-type natriuretic peptide
OR = odds ratio
PCP = primary care provider
PPV = positive predictive value
R = randomized
RAAS = renin-angiotensin-aldosterone system
RAS = renin-angiotensin system
RASi = RAS inhibitor
sFAS = soluble tumor necrosis super family member 6
SNS = sympathetic nervous system
SOB = shortness of breath
SOC = standard of care
ST2 = interleukin-1 receptor family member
T2D = type 2 diabetes
TIMP = tissue inhibitor of metalloproteinases
TNF-α = tumor necrosis factor alpha
TWEAK = tumor necrosis factor-like weak inducer of apoptosis

中文字幕

中文专家评论

这个评论项目是一大型培训活动的一部分. 加入之后, 请回 到 **Heart Failure and Biomarkers: Practical Strategies and Protocols,** 便可访问所有相关的培训内容.

中文文字稿

Download the pdf.

Download Now

References

1. Lam CS, Burnett JC Jr, Costello-Boerrigter L, et al. Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population. J Am Coll Cardiol. 2007;49:1193-1202. Abstract
2. Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. Clin Sci (Lond). 2016;130:57-77. Abstract
3. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart. 2006;92:843-849. Abstract
4. Maisel AS, Krishnaswamy P, Nowak RM, et al; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347:161-167. Abstract
5. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J. 2006;27:330-337. Abstract
6. Fonarow GC, Peacock WF, Phillips CO, et al; ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol. 2007;49:1943-1950. Abstract
7. Januzzi JL Jr, Sakhuja R, O'Donoghue M, et al. Utility of amino-terminal pro-brain natriuretic peptide testing

for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. Arch Intern Med. 2006;166:315-320. Abstract
8. Daniels LB, Clopton P, Bhalla V, et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. Am Heart J. 2006;151:999-1005. Abstract
9. Tromp J, Khan MA, Klip IT, et al. Biomarker Profiles in Heart Failure Patients With Preserved and Reduced Ejection Fraction. J Am Heart Assoc. 2017;6:e003989.
10. van Veldhuisen DJ, Linssen GC, Jaarsma T, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. J Am Coll Cardiol. 2013;61:1498-1506. Abstract
11. Lam CS, Rienstra M, Tay WT, et al. Atrial fibrillation in heart failure with preserved ejection fraction: association with exercise capacity, left ventricular filling pressures, natriuretic peptides, and left atrial volume. JACC Heart Fail. 2017;5:92-98. Abstract
12. Richards M, Di Somma S, Mueller C, et al. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH Study (Biomarkers in ACute Heart Failure). JACC Heart Fail. 2013;1:192-199. Abstract
13. Morello A, Lloyd-Jones DM, Chae CU, et al. Association of atrial fibrillation and amino-terminal pro-brain natriuretic peptide concentrations in dyspneic subjects with and without acute heart failure: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. Am Heart J. 2007;153:90-97. Abstract
14. McMurray JJ, Adamopoulos S, Anker SD, et al; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur J Heart Fail. 2012;14:803-869. Abstract
15. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA. 2013;310:66-74. Abstract
16. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137-e161. Abstract
17. Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol. 2013;62:1365-1372. Abstract
18. Januzzi JL Jr, Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol. 2011;58:1881-1889. Abstract
19. Troughton RW, Frampton CM, Brunner-La Rocca HP, et al. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur Heart J. 2014;35:1559-1567. Abstract
20. Felker GM, Ahmad T, Anstrom KJ, et al. Rationale and design of the GUIDE-IT study: Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure. JACC Heart Fail. 2014;2:457-465. Abstract
21. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2017;318:713-720. Abstract
22. Zile MR, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol. 2016;68:2425-2436. Abstract
23. Ibrahim NE, Gaggin HK, Konstam MA, et al. Established and emerging roles of biomarkers in heart failure clinical trials. Circ Heart Fail. 2016;9:e002598.

This article is a CME / ABIM MOC / CE certified activity. To earn credit for this activity visit: http://www.medscape.org/viewarticle/881184