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

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## Heart Failure and Biomarkers

## Practical Strategies and Protocols

#### Moderator

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Heart Failure and Biomarkers: Practical Strategies and Protocols





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## Carolyn Su Ping Lam, MBBS, PhD, MRCP

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#### **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

- 56-yr-old patient
- · History of COPD, HTN, CKD, and HFpEF
  - Last LVEF reading: 65%
- · 3 days of worsening SOB
- Denies fever
- New cough with some sputum production

Case: Presentation

### Case: Physical Exam

Blood pressure: 148/76 mmHg

· Heart rate: 92 bpm

• Respiratory rate: 22 breaths/min

Afebrile

• BMI: 36 kg/m<sup>2</sup>

• JVD: absent, but difficult to examine

Lungs: basilar cracklesHeart sounds: normal

· Ascites: absent

· Pedal edema: trace

Case: Physical Exam

### Case: Laboratory Findings

Sodium: 139 mEq/LPotassium: 4.8 mEq/L

· Blood urea nitrogen: 42 mg/dL

Creatinine: 1.9 mg/dL

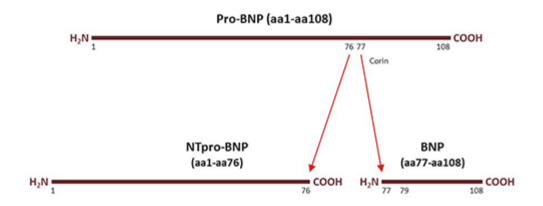
· Hemoglobin and Hematocrit: normal

• NT-proBNP: 1272 pg/mL

Previous baseline labs: unavailable

Case: Laboratory Findings

## Biology of Natriuretic Peptides: Processing

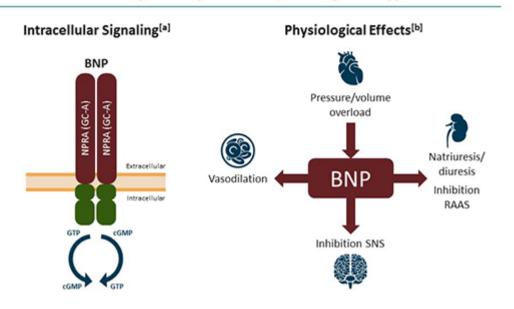


Lam C, et al. J Am Coll Cardiol. 2007;49:1193-1202.

## Biology of Natriuretic Peptides: Processing<sup>[1]</sup>

- 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



a. Volpe M, et al. Clin Sci (Lond). 2016;130:57-77; b. Weber M, et al. Heart. 2006;92:843-849.

#### Biology of Natriuretic Peptides: Intracellular Signaling and Physiological Effects<sup>[2,3]</sup>

- 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

- · HF first postulated to be a NP-deficient state
- Development of plasma BNP assays subsequently indicated increased circulating BNP in HF
- Despite increased natriuretic effect expected with increased levels of BNP, overt HF patients display fluid and salt retention
- End-organ resistance or abnormal proBNP processing, with reduced levels of biologically active BNP, may contribute to this paradox

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

Natriuretic Peptides In Heart Failure<sup>[1]</sup>

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

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

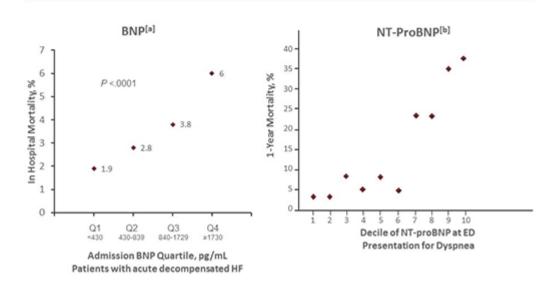
		Rule-Out	Rule-In
	Age, y	HF Unlikely	HF Likely
BNP[a]	All	<100 pg/mL	>500 pg/mL
NT-proBNP <sup>[b]</sup>	<50	<300 pg/mL	>450 pg/mL
	50 to 75	<300 pg/mL	>900 pg/mL
	>75	<300 pg/mL	>1800 pg/mL

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<sup>[4,5]</sup>

- 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



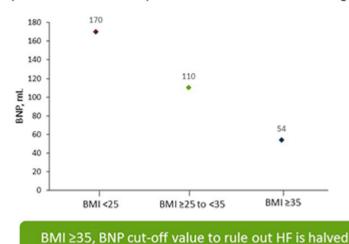
a. Fonarow G, et al. J Am Coll Cardiol. 2007;49:1943-1950; b. Januzzi J Jr, et al. Arch Intern Med. 2006;166:315-320.

#### Natriuretic Peptides Levels and Prognosis<sup>[6,7]</sup>

• 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

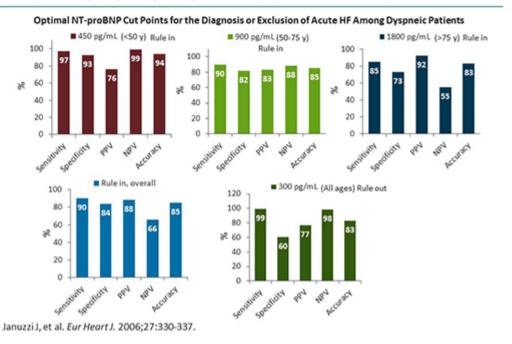
- · BNP cut-point for 90% sensitivity in diagnosing CHF for each BMI group
- Specificity at the 90% sensitivity level was at least 70% for all 3 groups



Daniels L, et al. Am Heart J. 2006;151:999-1005.

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

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

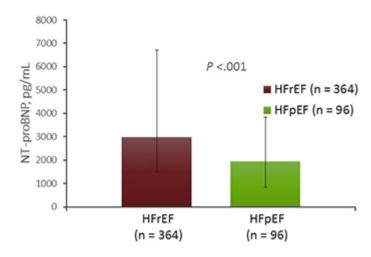


### NT-proBNP Cut-Points By Age: Sensitivity/Specificity<sup>[5]</sup>

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

## NT-proBNP Higher in HFrEF vs HFpEF

· Measured at discharge after hospitalization for acute HF

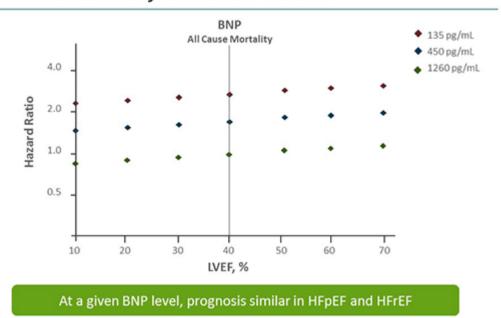


Tromp J, et al. J Am Heart Assoc. 2017;6:e003989.

NT-proBNP Higher in HFrEF vs HFpEF<sup>[9]</sup>

- 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

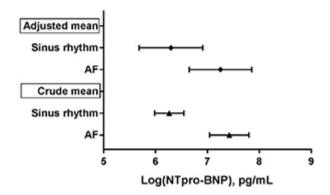


van Veldhuisen D, et al. J Am Coll Cardiol. 2013;61:1498-1506.

### COACH: Risk Estimates of LVEF on Outcome<sup>[10]</sup>

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

## AF and HFpEF



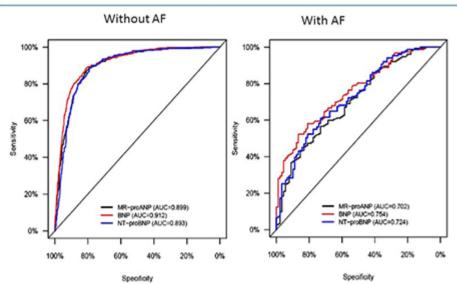
AF is independently associated with natriuretic peptide elevation in HFpEF

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<sup>[11]</sup>

- 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

## BACH: AF Impairs Diagnostic Performance of Cardiac Natriuretic Peptides in Dyspneic Patients

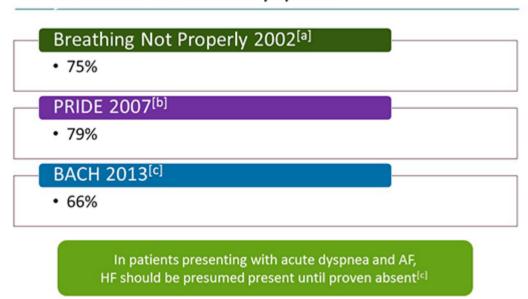


Reprinted from JACC Heart Fail, 1, Richards M, et al., Atrial Fibrillation Impairs the Diagnostic Performance of Cardiac Natriuretic Peptides in Dyspneic Patients Results From the BACH Study (Biomarkers in Acute Heart Failure), 192-199., Copyright 2013, with permission from Elsevier.

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

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

## Incidence of HF in Patients with AF Presenting to the ED with Acute Dyspnea



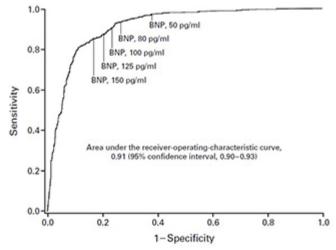
a. Maisel A, et al. N Engl J Med. 2002;347:161-167; b. Morello A, et al. Am Heart J. 2007;153:90-97; c. Richards M, et al. JACC Heart Fail. 2013;1:192-199.

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

## Specificity/Sensitivity of BNP Thresholds

 Receiver-operating-characteristic curve for various cutoff levels of BNP in differentiating between dyspnea due to CHF and dyspnea due to other causes

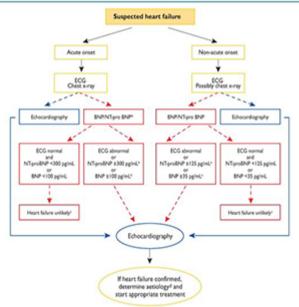


From N Engl J Med, Maisel AS, et al., Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure, 347., 161-167. Copyright © 2002 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

#### Specificity/Sensitivity of BNP Thresholds<sup>[4]</sup>

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

## Diagnostic Algorithm for Diagnosis of HF

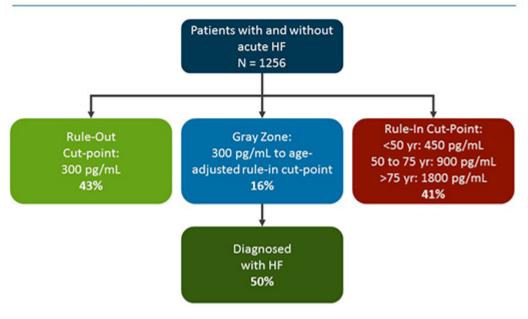


McMurray JJ, et al. Eur J Heart Fail. 2012;14:803-869. Published on behalf of the European Society of Cardiology. All rights reserved. © 2012 the Authors.

### Diagnostic Algorithm for Diagnosis of HF<sup>[14]</sup>

- 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

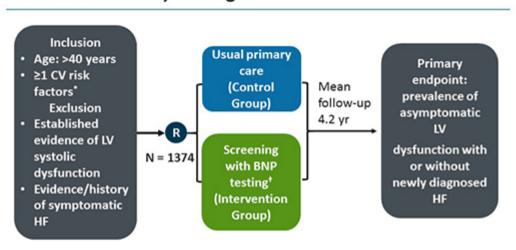
# ICON: Incidence of "Gray Zone" Diagnosis



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

ICON: Incidence of "Gray Zone" Diagnosis<sup>[5]</sup>

## STOP-HF: Study Design



<sup>\*</sup>Hypertension, hypercholesterolemia, obesity, vascular disease, diabetes mellitus, arrhythmia requiring therapy, or moderate-to-severe valvular disease.

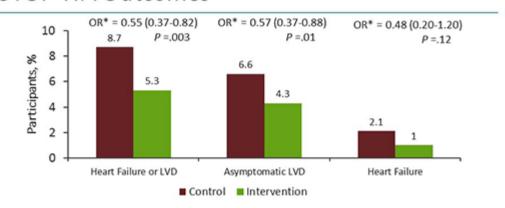
Ledwidge M, et al. JAMA. 2013;310:66-74.

### STOP-HF: Study Design<sup>[15]</sup>

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

<sup>†</sup>Individuals with BNP ≥50 pg/mL underwent echocardiography and collaborative care between their PCP and specialist CV service.

#### STOP-HF: Outcomes



 Intervention group underwent more CV investigations and received more renin-angiotensin-aldosterone system-based therapy at follow-up

BNP-based screening and collaborative care reduced combined rates of LV systolic dysfunction, diastolic dysfunction, and HF

\*95% CI.

Ledwidge M, et al. JAMA. 2013;310:66-74.

STOP-HF: Outcomes[15]

## Natriuretic Peptide Screening for Prevention of HF: 2017 ACC/AHA/HFSA Recommendations

COR	LOE	Recommendation	Comment/Rationale
lla	B-R	For patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care including a cardiovascular specialist optimizing GDMT can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or newonset HF.	<b>NEW:</b> New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF.

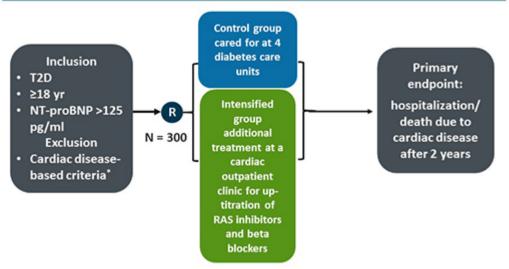
Yancy C, et al. Circulation. 2017;136:e137-e161.

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

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

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

## PONTIAC: Study Design



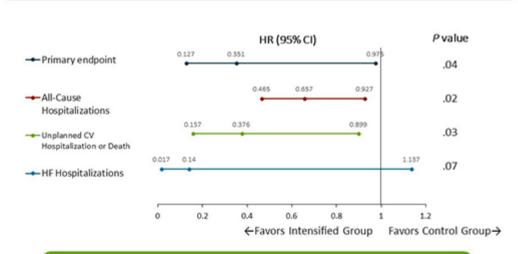
\*>1 of the following: history of cardiac disease; signs of cardiac disease on electrocardiogram; ST-T-wave abnormalities or BBB; abnormal echocardiography (except diastolic dysfunction); wall motion abnormalities, significant valve dysfunction, or other significant alteration.

Huelsmann M, et al. J Am Coll Cardiol. 2013;62:1365-1372.

#### PONTIAC: Study Design[17]

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

#### **PONTIAC:** Outcomes

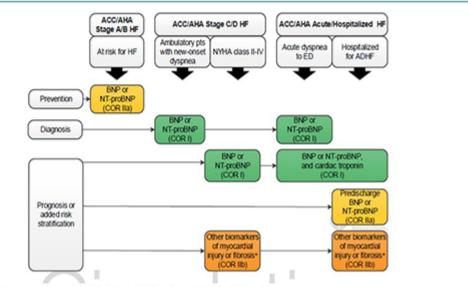


Accelerated up-titration of RASi and beta-blockers is an effective intervention for primary prevention of cardiac events in diabetic patients pre-selected using NT-proBNP

Huelsmann M, et al. J Am Coll Cardiol. 2013;62:1365-1372.

PONTIAC: Outcomes<sup>[17]</sup>

# Biomarkers Indications for Use: 2017 ACC/AHA/HFSA Recommendations



\*Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and hs-troponin.

Yancy CW, 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. Reprinted with permission from Circulation. 2017;136:e137-e161 © 2017 American Heart Association, Inc.

#### Biomarkers Indications for Use: 2017 ACC/AHA/HFSA Recommendations<sup>[16]</sup>

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

## Predischarge Natriuretic Peptides for Prognosis: 2017 ACC/AHA/HFSA Recommendations

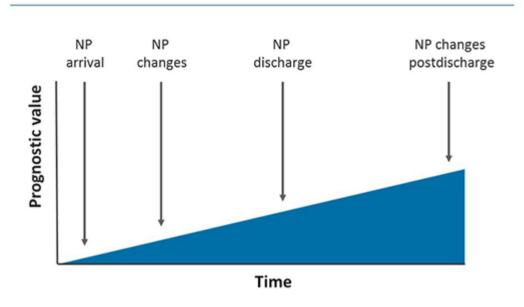
COR	LOE	Recommendation	Comment/Rationale
lla	B-NR	During a HF hospitalization, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis.	<b>NEW:</b> Current recommendation reflects new observational studies.

Yancy C, et al. Circulation. 2017;136:e137-e161.

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

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

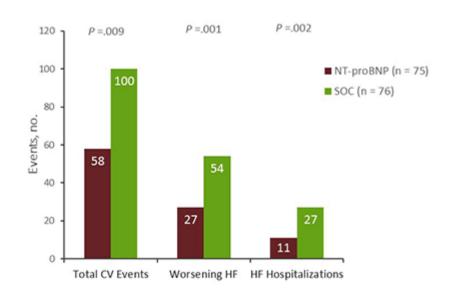
## Natriuretic Peptide Sampling for Outcome: The Later the Better



#### 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<sup>[18]</sup>

- 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

	HR (95% CI)	
Endpoint	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

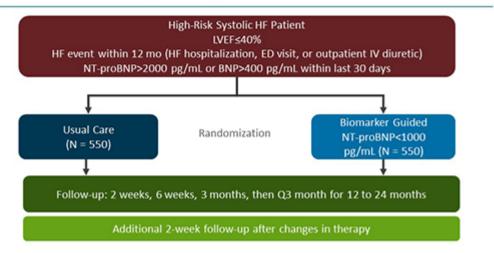
- 2000 patients from 9 studies; clinically guided care (N = 994) and NP-guided care (N = 1006)
- · Lower mortality in the NP-guided group
  - No heterogeneity between studies (P =.57)
  - No LVEF interaction
  - Age interaction (P =.028); survival benefit seen in younger patients (<75 yrs), but not older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

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

## Benefits of Natriuretic Peptide-Guided Therapy: Individual Patient Meta-Analysis<sup>[19]</sup>

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

## GUIDE-IT: Study Design



- · Primary end point: Time to CV death or first HF hospitalization
- Secondary end points: Time to all-cause mortality; days alive and not hospitalized for CV reasons; recurrent hospitalization; time to CV death; time to first HF hospitalization; HRQOL; resource utilization, costs, and cost-effectiveness

Felker G, et al. JACC Heart Fail. 2014;2:457-465.

#### GUIDE-IT: Study Design<sup>[20]</sup>

### **GUIDE-IT:** Outcomes

End points	NT-proBNP-guided strategy vs usual care HR (95% CI)	Р
Primary end point*	0.98 (0.79, 1.22)	.88
CV death	0.94 (0.65, 1.37)	.75
Death by any cause	0.86 (0.62, 1.20)	.37

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

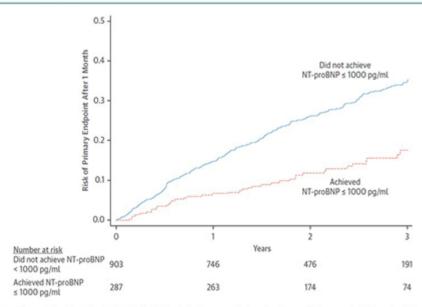
#### GUIDE-IT: Outcomes<sup>[21]</sup>

- 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 guidelinesrecommended 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

<sup>\*</sup>First HF hospitalization or CV death.

• 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



Reprinted from J Am Coll Cardiol, 68, Zîle MR, et al., Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure, 2425-2436., Copyright 2016, with permission from Elsevier.

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

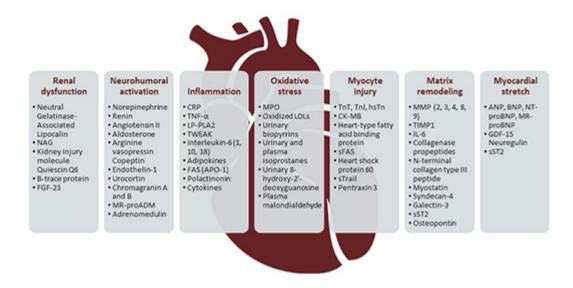
### GUIDE-IT: Key Takeaways

- NT levels can be lowered by titrating HF therapy
- Reduction in NP levels leads to better outcomes
- Unanswered question
  - Can knowledge of NP level facilitate aggressive treatment of patients in the primary care setting?

#### **GUIDE-IT: Key Takeaways**

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

### Other Cardiac Biomarkers in HF



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

#### Other Cardiac Biomarkers in HF<sup>[23]</sup>

- 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





# 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- $\alpha$  = 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

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   Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347:161-167. Abstract
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