

Biomarkers in Heart Disease

Felix J. Rogers, DO, FACOI

April 29, 2018

Biomarkers

- NIH:
 - A biomarker is a “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”

Biomarkers

- NIH:
 - A biomarker is a “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”
- Intended uses:
 - screening
 - diagnostic
 - prognostic

Cardiac Biomarkers

- Neurohormones (Epi, norEpi)
- Extracellular matrix remodeling
- Inflammatory mediators
 - CRP
 - Toll-like receptors
 - Cytokines
- Myocyte injury and stress
 - Troponin
 - BNP, NT-proBNP
- BIOSTAT-CHF Trial measured 161 biomarkers!!

Cardiac Biomarkers

- ~~Neurohormones (Epi, norEpi)~~ Impractical
- ~~Extracellular matrix remodeling~~ Postulated
- Inflammatory mediators
 - CRP
 - ~~Toll-like receptors~~ Potential
 - ~~Cytokines~~ Unavailable
- Myocyte injury and stress
 - Troponin
 - BNP, NT-proBNP

Cardiac Biomarkers

- Neurohormones (Epi, norEpi)
- Extracellular matrix remodeling
- Inflammatory mediators
 - Hs-CRP
 - Toll-like receptors
 - Cytokines
- Myocyte injury and stress
 - Troponin
 - BNP, NT-proBNP

C-reactive protein

CRP is known to be involved in the immune response, as a mediator of inflammation as well as a marker of the presence of an inflammatory process.

C-reactive protein

CRP is known to be involved in the immune response, as a mediator of inflammation as well as a marker of the presence of an inflammatory process.

Elevated levels of CRP predict future vascular events, even out to 20 years

C-reactive protein

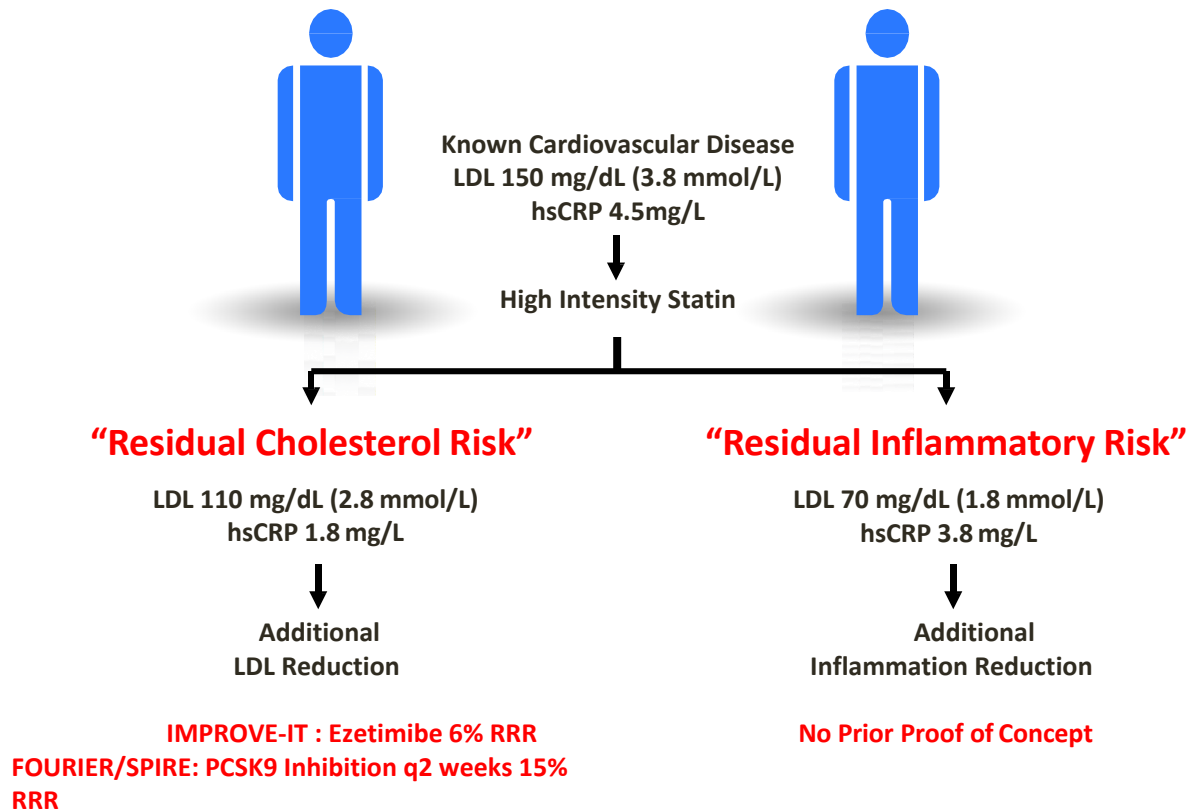
CRP is known to be involved in the immune response, as a mediator of inflammation as well as a marker of the presence of an inflammatory process.

Elevated levels of CRP predict future vascular events, even out to 20 years

However, CRP elevation is not independent of other markers, is not uniformly prognostic and it does not respond to treatment, except for statins, which has not resulted in improved outcomes

Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22

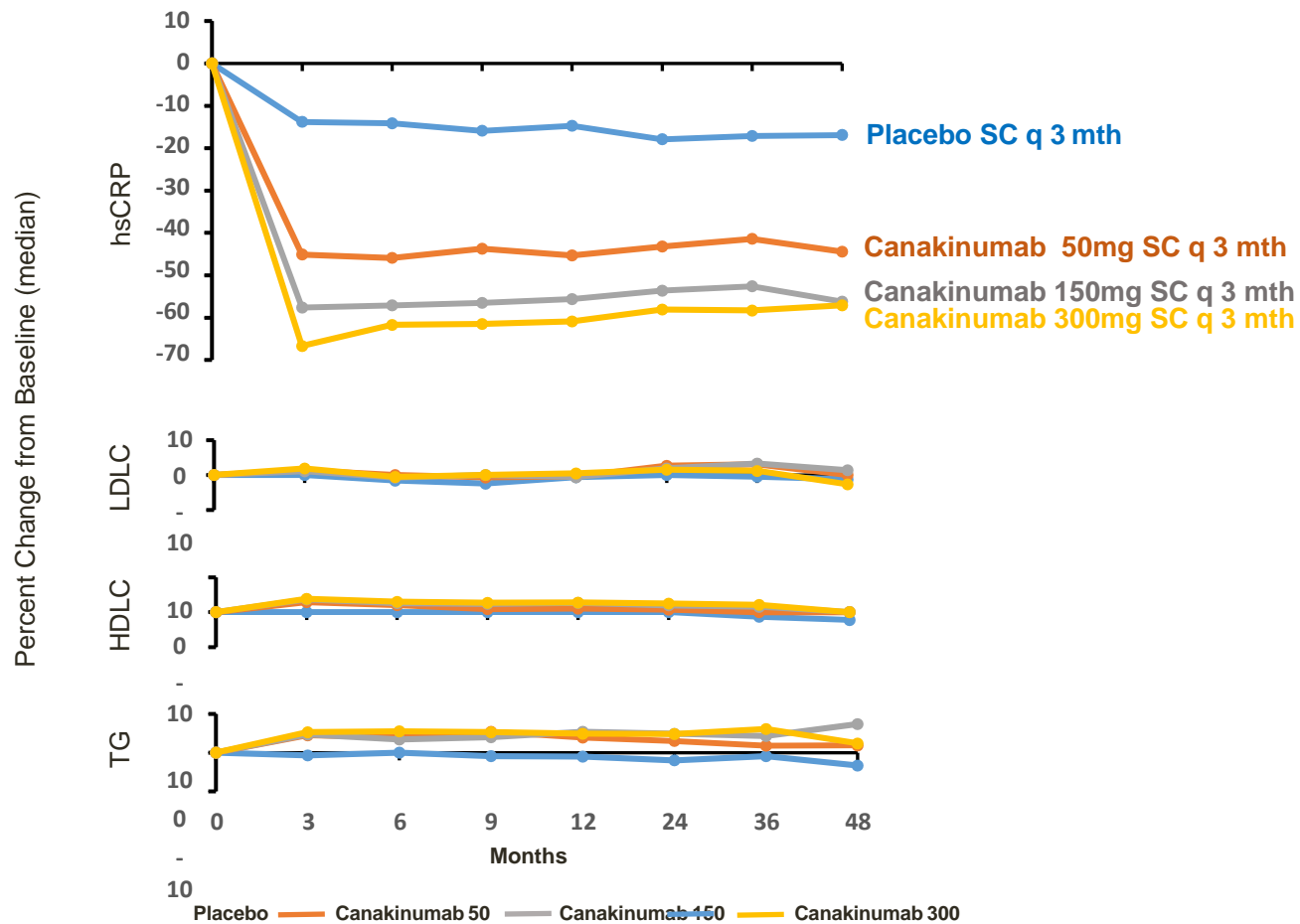


Canakinumb

(Novartis)

-
- **high-affinity human monoclonal anti-human interleukin-1b (IL-1b) antibody currently indicated for the treatment of IL-1b driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)**
 - **designed to bind to human IL-1b and functionally neutralize the bioactivity of this pro-inflammatory cytokine**
 - **long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months**

CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)



Let's try a case

Patient No. 1

- This 29 year old woman had a C-Section complicated by severe bleeding. She had emergency hysterectomy. This was complicated by pneumonia, shock and severe anemia.
- Additional medical issues: BMI 45.3, smoker

Patient No. 1

- This 29 year old woman had a C-Section complicated by severe bleeding. She had emergency hysterectomy. This was complicated by pneumonia, shock and severe anemia.
- Additional medical issues: BMI 45.3, smoker
- From the cardiology consult:
 - No chest pain
 - BNP 468, trop 0.52
 - Hb at 11:32 PM - 5.2 g/dL
 - Echocardiogram normal
 - Conclusion: Elevated troponin due to Type 2 MI
- ECG - normal

What's wrong with this picture?

What's wrong with this picture?

How long did it take you to notice what's wrong here?



Patient No. 1

- This 29 year old woman had a C-Section complicated by severe bleeding. She had emergency hysterectomy. This was complicated by pneumonia, shock and severe anemia.
- Additional medical issues: BMI 45.3, smoker
- From the cardiology consult:
 - No chest pain
 - BNP 468, trop 0.52
 - Hb at 11:32 PM - 5.2 g/dL
 - Echocardiogram normal
 - Conclusion: Elevated troponin due to Type 2 MI
- ECG - normal

Universal Definition of Myocardial Infarction

Definition of myocardial infarction
<p>Criteria for acute myocardial infarction</p> <p>The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:</p> <ul style="list-style-type: none"> • Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: <ul style="list-style-type: none"> ♦ Symptoms of ischaemia. ♦ New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). ♦ Development of pathological Q waves in the ECG. ♦ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. ♦ Identification of an intracoronary thrombus by angiography or autopsy. • Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. • Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values ($>5 \times 99^{\text{th}}$ percentile URL) in patients with normal baseline values ($\leq 99^{\text{th}}$ percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. • Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. • Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values ($>10 \times 99^{\text{th}}$ percentile URL) in patients with normal baseline cTn values ($\leq 99^{\text{th}}$ percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. <p>Criteria for prior myocardial infarction</p> <p>Any one of the following criteria meets the diagnosis for prior MI:</p> <ul style="list-style-type: none"> • Pathological Q waves with or without symptoms in the absence of non-ischaemic causes. • Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause. • Pathological findings of a prior MI.

Universal Definition of Myocardial Infarction

- Simplified version
- Rise and/or fall of troponin and at least one of the following:
 - Symptoms of ischemia (chest pain)
 - New or presumed new ST-T changes, or new LBBB
 - New Q waves on the ECG (except in lead 3)
 - Evidence on imaging study of new loss of viable myocardium, or of new wall motion abnormality
 - Identification of intra coronary thrombus on cath or at autopsy

Universal Classification of MI

Table 2 Universal classification of myocardial infarction

Type 1: Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischaemic imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values $>5 \times 99^{\text{th}}$ percentile URL in patients with normal baseline values ($\leq 99^{\text{th}}$ percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99^{th} percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values $>10 \times 99^{\text{th}}$ percentile URL in patients with normal baseline cTn values ($\leq 99^{\text{th}}$ percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Classification of MI, simplified

Type 1. Spontaneous MI

Type 2. MI secondary to ischemic imbalance

Type 3. MI with death, but no biomarkers available

Type 4a. MI related to PCI

Type 4b. MI related to stent thrombosis

Type 5. MI related to CABG

Universal Classification of MI

- Simplified version
 - **Type 2 MI** – Myocardial necrosis caused by a condition other than CAD when a mismatch between myocardial oxygen supply and demand occurs, e.g. when there is excessive tachycardia, hypoxemia, hypotension, hypertension (with or without LVH)

Proper diagnosis

- Non-MI troponin elevation

Troponin release

- Screening
 - Emergency department
- Prognosis

High Sensitivity Troponin

- Hs-cTn
 - Assays that detect troponin at levels 10-100 fold lower than contemporary assays
 - Characteristics
 - 1) Coefficient of variance <10% of the 99th percentile for the reference healthy population
 - 2) Concentrations above the assay's limit of detection are measurable in >50% of healthy individuals

High Sensitivity Troponin

Advantages

1. Increased sensitivity and better early discrimination of AMI compared to contemporary assays
2. Allows shorter period for “rule-out” AMI (1-3 hours)
3. Excellent negative predictive values (~99%) for events at 1 hour; allows facilitated throughput of patients in ED
4. Very low values rule out MI with a single blood draw
5. Test is best employed when patient does not have chest pain of new onset, no associated ECG changes or high risk characteristics

High Sensitivity Troponin

- How to define the reference population?
- 99th percentile = 14 micrograms/L for Hs-cTn based on 616 healthy people, mean age 44
- However, 10% of healthy men >65 had hs-cTn greater than MI threshold

Sample of contemporary hs-cTn

Analytic Comparisons of Contemporary High-Sensitivity Cardiac Troponin Assays*

Limit of Detection (ng/L)		99% (CV) (ng/L)	10% CV (ng/L)	
Hs-cTn-T				
Roche Elecsys		5.0	14 (13%)	13
Hs-cTn-I				
Abbot ARCHITECT	1.2	16 (5.6%)	3.0	
Beckman ACCESS	2 to	3	8.6 (10%)	8.6
Mitsubishi Pathfast	8.0	29 (5%)	14	
Nanosphere		0.2	2.8 (9.5%)	0.5
Radiometer AQT90	9.5	23 (17.7%)	39	
Singulex Erenna		0.09	10.1 (9.0%)	0.88
Siemens Vista		0.5	9 (5.0%)	3
Siemens Centaur		6.0	40 (10%)	30

CV indicates coefficient of variance; Hs-cTn-T, high-sensitivity cardiac troponin T

Excerpt From: "High-Sensitivity Troponin Assays: Evidence, Indications, and Reasonable Use."
iBooks.

Troponin and Heart Failure

- Serum troponin is associated with worse clinical outcome in patients with acute decompensated heart failure and chronic stable HF
- The mechanisms triggering the release of circulating cardiac troponin without manifest ischemia are not clear. Possible factors include
 - underlying CAD
 - subendocardial ischemia
 - increased wall stress
 - left ventricular hypertrophy

Troponin and Heart Failure

- Serum hs-cTn is associated with a risk for subsequent development of heart failure.
- This association applies equally to the high-risk and the general population, and is independent of conventional CVD risk factors and natriuretic peptide levels.

hs-cTn and heart failure

- Systematic review and meta-analysis of 67,063 patients with 4,165 incident heart failure events (*JACC Heart Failure*, March 2018: 187-97)
- Average age 57, 47% women
- Results: participants in the top third compared to those in the bottom third had a hazard risk of 2.09 ($p < 0.001$)
- Hazard ratios were similar in men and women, for troponin T and I, and were independent of conventional risk factors and BNP levels.

hs-cTn and HF

- High sensitivity troponin may be a useful means of targeting echocardiographic screening for HF in high-risk subjects to identify asymptomatic LV dysfunction and allow early treatment.

Another consideration for non-MI troponin release

- Association between post-op troponin levels and 30 day mortality.
- *JAMA*, June 6, 2012, No.21, p. 2295-2304
- 15,133 patients, cTnT measured 6-12 hours, 1, 2 & 3 days after surgery.

Surgical group

- Major orthopedic 20.4 %
- Major general 20.3 %
- Low-risk surgery 39.4 %

24.2% were > 75 years old

51.5% were women

HTN 50.9%, DM 19.5%, Cancer 26.5%

Surgical group

- Major orthopedic 20.4 %
- Major general 20.3 %
- Low-risk surgery 39.4 %

24.2% were > 75 years old

51.5% were women

HTN 50.9%, DM 19.5%, Cancer 26.5%

cTnT values ≥ 0.02 occurred in 11.6% of pt.

30 day mortality with troponin release

Troponin value	30 day mortality	
≤ 0.01	1.0 %	
0.02	4.0 %	(1 in 25 pt.)
0.03 – 0.29	9.3 %	(1 in 11 pt.)
≥ 0.3	16.9 %	(1 in 6 pt.)

Cardiac biomarkers in HF

- Markers of inflammation
- Markers of fibrosis, extracellular matrix remodeling
- Markers of biochemical strain
- Markers of neurohormonal activation
- Markers of cardiomyocyte injury

Cardiac biomarkers in HF

- Markers of inflammation
 - C-reactive protein
- Markers of fibrosis, extracellular matrix remodeling
- Markers of biochemical strain
 - Natriuretic peptides
- Markers of neurohormonal activation
- Markers of cardiomyocyte injury
 - Cardiac troponins

Cardiac biomarkers in HF

- Markers of inflammation
 - C-reactive protein
- Markers of fibrosis, extracellular matrix remodeling
- Markers of biochemical strain
 - Natriuretic peptides
- Markers of neurohormonal activation
- Markers of cardiomyocyte injury
 - Cardiac troponins

Cardiac biomarkers in HF

- Markers of inflammation
 - C-reactive protein
- Markers of fibrosis, extracellular matrix remodeling
- Markers of biochemical strain
 - Natriuretic peptides
- Markers of neurohormonal activation
- Markers of cardiomyocyte injury
 - Cardiac troponins
- Don't overlook serum creatinine!!!

B-type natriuretic peptide

- BNP is produced as a prohormone
- Processed to proBNP
- Cleaved by corin to produce biologically active BNP and inactive NT-proBNP
- BNP (but not NT-proBNP) is cleaved by neprilysin
- Although BNP is a natriuretic agent, sodium retention and edema still occur in patients with HF

B-type natriuretic peptide

- Control of NP release
 - Continuously released from the heart
 - Atrial muscle stretch augments ANP and BNP release.
 - Mechanism not known – atrial dimension? atrial pressure?
 - ANP is elevated in patients with SVT and A Fib without HF
- ANP is released mainly from the atria. BNP resides mainly in ventricular muscle.
- BNP is cleared more slowly from the circulation than ANP.
- Confounding issues:
 - Asian and Black patients have higher NP levels than White and Hispanic patients
 - Obese patients have low circulating NP levels

Current indications for NP measurements in HF

Diagnosis in patients with dyspnea (acute)	I-A
Diagnosis in patients with dyspnea (ambulatory)	I-A
Prognosis in patients with known HF (acute)	I-A
Prognosis in patients with known HF (ambulatory)	I-A
Achieving guideline-directed medical therapy	IIa-B
Natriuretic peptide guided therapy for chronic HF	IIb-B
Lack strong recommendation: ACS	
A Fib	
Valvular heart disease	

Diagnosing CHF in the ED

What emergency department physicians want

- “When we set out to find a blood test (BNP) that would allow physicians to diagnose heart failure in the ED, they wanted a test that would have a cut off for normal – so if it was 99, they sent the patient home, but if it was 101, they would intubate the patient.”

Alan Maisel, MD



BNP

- Breathing Not Properly Trial, *NEJM* 2002
- 1586 patients presenting to the ED with dyspnea
 - CHF 744 44%
 - LVD, but not CHF 72 5%
 - No CHF 770 49%
- Diagnostic accuracy BNP 100 83%
- Negative predictive value BNP 50 96%

BNP

- Breathing Not Properly Trial, *NEJM* 2002
- 1586 patients presenting to the ED with dyspnea
 - CHF 744 44%
 - LVD, but not CHF 72 5%
 - No CHF 770 49%
- Diagnostic accuracy BNP 100 83%
- Negative predictive value BNP 50 96%
- Sensitivity BNP 100 90%
- Specificity BNP 100 76%

BNP- Rule In

- BNP Rule in MI 400 pg/ml

NT-proBNP in the ED

- PRIDE (ProBNP Investigation of Dyspnea) *AJC* 2005;95: 948-54
- Partition values for diagnosis of HFrEF.
 - NT-proBNP:

• Age < 50	450
• Age 50-75	900
• Age > 75	1800
- Confounders

Age
Obesity
ACS, PE & renal disease

NT-proBNP in the ED

- Januzzi, et al *JACC* 2018;71:1191-200
- Dyspneic patients presenting to 19 EDs in North America
- Of 1,461 patients, 277 (19%) were adjudicated to have acute HF
- Sensitivity for age-stratified cutoffs

450 pg/ml	85.7%
900 pg/ml	79.3%
1,800 pg/ml	75.9%

Rule-out NT-proBNP < 300 pg/ml strongly excludes the presence of acute HF

NT-proBNP in the ED. Dealing with gray zones

- FDA package insert

- Age < 75 > 125 pg/ml
- Age > 75 > 450 g/ml

- ESC 2008 Guidelines

- Rule-out < 400 pg/ml
- Rule-in > 2,000 pg/ml

- ESC 2012

- Acute/worsening Sx Rule-out <300 pg/ml
- Non-acute Sx Rule-out <125 pg/ml

Partition values, HFpEF

- Diagnosis of HFpEF
 - BNP > 100
 - NT-proBNP ≥ 800

Diagnosis in outpatients

Patients are typically less symptomatic, less hemodynamically decompensated

So, diagnostic thresholds to establish the diagnosis are lower to avoid false negative results

Anticipate a single value for BNP, but age adjustment for NT-proBNP.

ESC: Screen with BNP/NT-proBNP and perform echo in patients with elevated values

Estimating prognosis in patients with known HF

- NP are powerful prognostic markers in all forms of HF:

HFrEF

HFpEF

Acute HF

However, establishing risk is of marginal clinical benefit unless it affects treatment in a meaningful way

Can natriuretic peptides be used to guide clinical care?

NP: markers of prognosis

- Chronic heart failure
- Increases in BNP and NT-proBNP parallel the heart failure severity , NYHA class, increased LV filling pressures and adverse hemodynamics
- Each increase in BNP by 100 carries a 35% increase in relative risk of mortality.
- (Detectable hs-cTn predicts worse outcomes, including mortality at 2 years)

Summary of BNP and HF (AHA 2017)

- Acute decompensated heart failure
 - Helpful to assess prognosis and disease severity
 - Pre-discharge BNP and NT-proBNP are stronger markers of post-discharge outcomes
- Outpatient management of heart failure
 - “uncertain benefit” use of BNP to guide treatment
 - NT-proBNP is not an adequate surrogate to guide sacubitril/valsartan (Entresto) treatment
- Management of in-hospital care
 - Not established
 - Values after treatment may be useful for prognosis

BNP in outpatient management

- Ouwerkerk, et al. *JACC* 2018; 71: 386-98, Jan 30, 2018
- 2,516 patients with worsening heart failure from the BIOSTAT-CHF study compared with 3 theoretical treatment scenarios
 - A. All patients up-titrated to >50% of recommended doses
 - B. Patients up-titrated according to biomarker selection model
 - C. No patient is up-titrated to >50% of recommended doses
- Outcome measures: death or heart failure hospitalization
- Assessment: 161 biomarkers

BNP in outpatient management

- Results
- Guideline-based up titration
 - ACEi/ARB Prevent 9.8 events per 100 pt at 24 months
 - B Blocker Prevent 1.3 events
 - MRA Prevent 12.3 events
- Biomarker based up titration
 - ACEi/ARB Prevent 9.9 events
 - B Blocker Prevent 4.7 events
 - MRA Prevent 13.1 events

Guideline based targets (AHA, ESC)

- ACEi
 - Enalapril 10-20 mg BID
 - Lisinopril 20-40 mg daily (ESC 20-35)
- ARB
 - Losartan 150 mg
- Beta blocker
 - Metoprolol succ. 200 mg
- MRA
 - Spironolactone 50 mg

- Results
 - A biomarker-based treatment up titration choice in patients with heart failure was favorable over up titration to >50% recommended ACEi/ARB and beta blocker and over $\geq 50\%$ MRA
- However, differences were small between the 2 up titration groups.
- RECOMMENDATION. Up titration should always be attempted in heart failure patients

NP as biomarkers of treatment response in clinical trials of HF

- Vaduganathan et al, *JACC Heart Failure* 2018
- Do treatment-related changes in NPs predict long term therapeutic effects in trials of HF?
- 18 trials from 1987 to 2013. 48,844 patients

Results

No correlation with all-cause mortality

Modest correlation with HF hospitalization

Correlation improved with trials conducted in last decade, using NT-proBNP and evaluating MRA