

Biomarkers In The Management Of Heart Failure

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What is a Biomarker: NIH Definition

“A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or the response to a therapeutic intervention.”

Atkinson et al, Clin Pharmacol Ther 2001

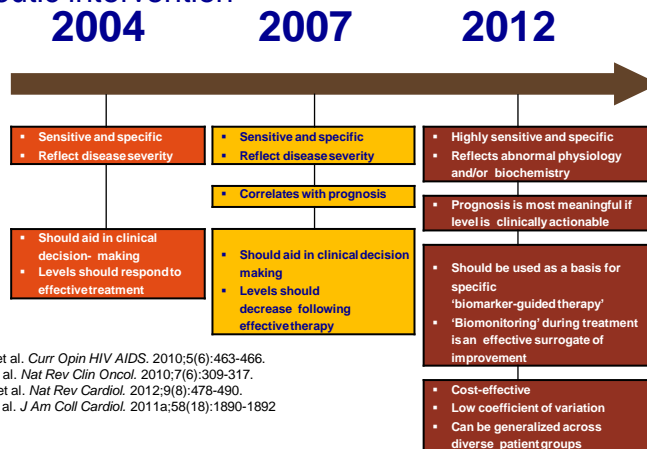
Biomarkers and Heart Failure

Agenda

- Overview
- Biomarkers of Myocardial Strain
- Biomarkers of Myocardial Injury
- Novel Biomarkers in Heart Failure
- Biomarkers of Inflammatory Processes
- Biomarkers of Neurohormonal Activation

Biomarkers: Overview

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention



1. Strimbu K, et al. *Curr Opin HIV AIDS*. 2010;5(6):463-466.
2. Buyse M, et al. *Nat Rev Clin Oncol*. 2010;7(6):309-317.
3. Maisel AS, et al. *Nat Rev Cardiol*. 2012;9(8):476-490.
4. Maisel A, et al. *J Am Coll Cardiol*. 2011a;58(18):1890-1892

Biomarkers Related To Myocyte Strain, Remodeling And Injury

MARKERS OF CARDIAC MYOCYTE STRAIN

- BNP
- NT-proBNP
- MR-proANP



MARKERS OF CARDIAC MYOCYTE REMODELING

- ST2
- Galectin-3
- GDF-15

MARKERS OF CARDIAC MYOCYTE INJURY

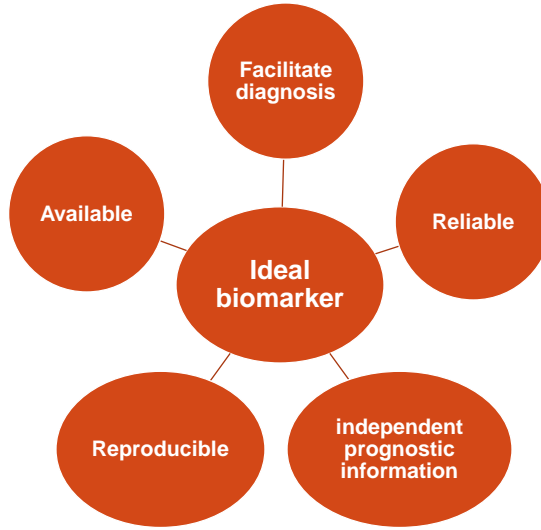
- High Sensitivity Troponins

Cardiovasc Diagn Ther 2012;2(2):147-164

Clinical Value of Cardiac Biomarkers

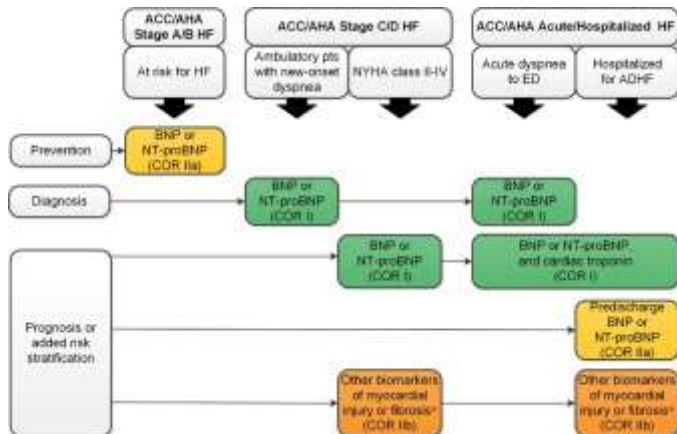
- Screening for preclinical disease in asymptomatic subjects
- Diagnosis of clinical disease in patients with uncertain symptoms
- Risk stratification in patients with clinical disease
- Therapeutic guidance in selection or titration of agents in patient with know disease

Characteristics of an ideal marker for HF



Bozkurt B *Circulation* 2003;107: 1231-1233

Biomarkers Indications for Use



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

ACC indicates American College of Cardiology; AHA, American Heart Association; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; COR, Class of Recommendation; ED, emergency department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and pts, patients.



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Biomarkers in Heart Failure

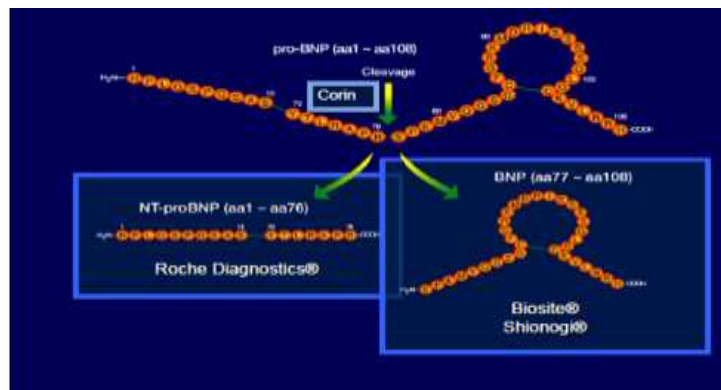
From Very Long List

- Established for HF
 - Natriuretic Peptides (NTproBNP, BNP)

- Established for other conditions
 - High sensitivity troponins

- FDA approved but optimal use uncertain
 - ST2
 - Galectin-3

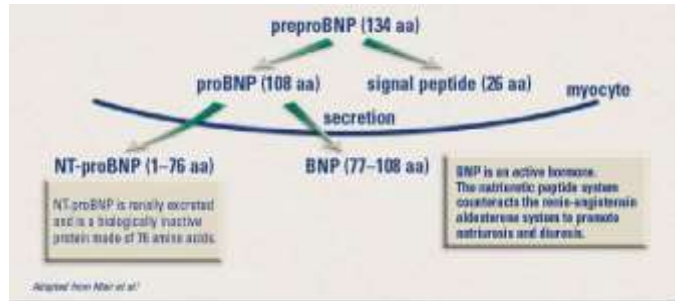
Natriuretic Peptides



- The natriuretic peptide system has complex genetic regulation
- Synthesis of an intracellular precursor, proBNP₁₋₁₀₈, precedes release of BNP₁₋₃₂ and NT-proBNP₁₋₇₆
- The kidneys clear NT-proBNP and BNP equally

European Journal of Heart Failure 2008; 10: 824-839.

BNP, NT-proBNP Secretion



- **BNP:**
 - secreted from cardiomyocytes
 - an active hormone providing compensatory response to the overload in the ventricles
 - released in order decrease fluid volume and reduce overload
- **NT-proBNP :**
 - secreted from cardiomyocytes at the same time as BNP
 - Not a hormone, does not assist in decreasing fluid volume
 - Inactive protein, requires adequate kidney function for clearance from the bloodstream making it questionable for patients with coexisting renal insufficiency

Clearance

BNP is cleared by:

1. Binding to natriuretic peptide receptors



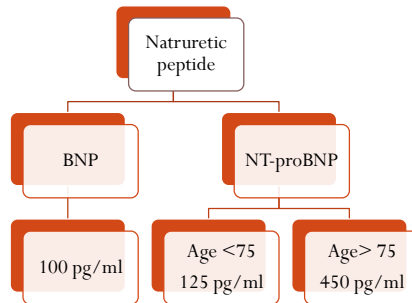
2. Enzymatic degradation

NT-proBNP is cleared:

1. Through the kidneys and is treated as a waste product



Diagnostic Cut Points For Natriuretic Peptides In Acute Dyspnea



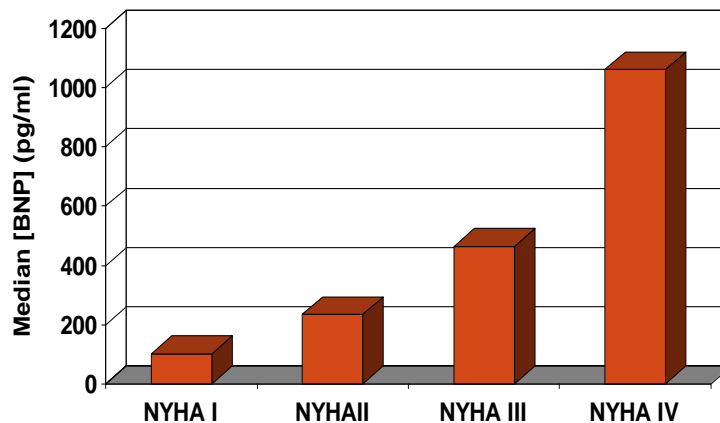
Important points

- Sensitivity is greater than specificity (false positive is greater than false negatives)
- High BNP suggests but does not prove heart failure diagnosis

Maisel et al, New Eng J Med (2002) 347:161-167.

BNP Relationship to NYHA

Objective Vs. Subjective Evaluation
Linear Range 5 pg/ml-5000 pg/ml



Januzzi et al, - EurHeart J (2006) 27: 330-337.

Troponin As Biomarker In Heart Failure

Am Heart J, 1999 Oct;138(4 Pt 1):646-53.

Cardiac troponins in congestive heart failure.

Del Carlo CH, O'Connor CM.

Duke Clinical Research Institute, Duke University Medical Center, Durham, NC 27710, USA.

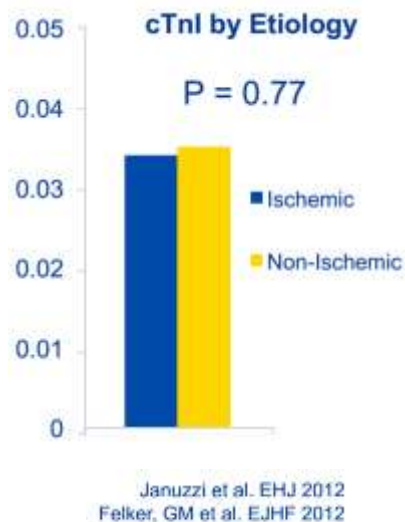
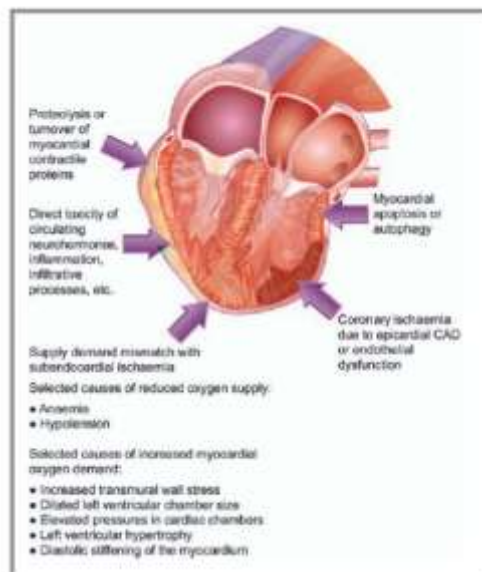
Abstract

BACKGROUND: We sought to assess the release of cardiac troponins in congestive heart failure (CHF).

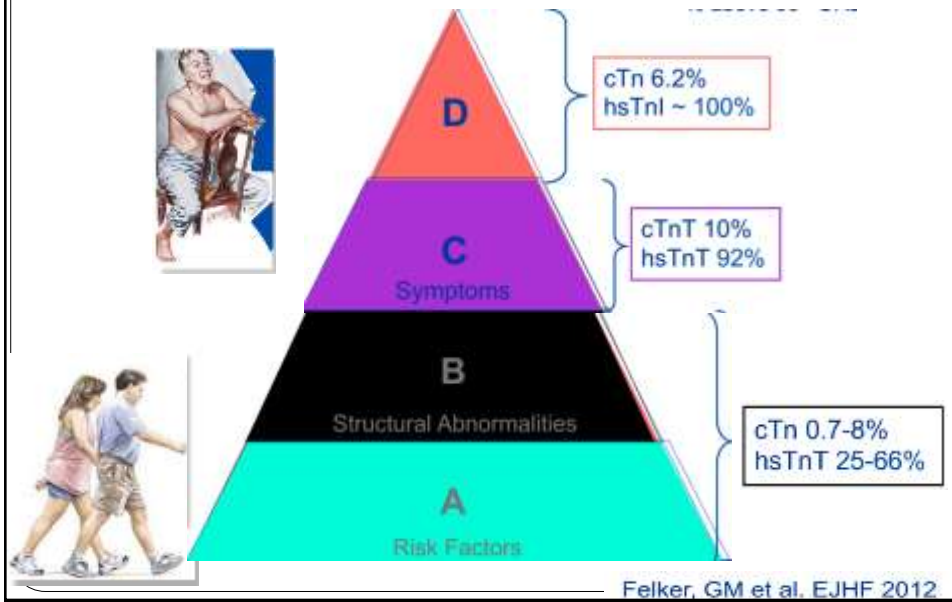
METHODS AND RESULTS: We performed a computer-assisted search of the English language literature (MEDLINE database) followed by a manual search of the reference list of pertinent articles retrieved. Studies evaluating the release of cardiac troponins (T and I) in patients with CHF were screened for review. Studies investigating cardiac troponins in patients with ischemic coronary syndromes that reported the rate of CHF were also selected. Available data on the release of cardiac troponins in ischemic and nonischemic CHF were summarized. Possible mechanisms of cell death in the progression to end-stage CHF were discussed.

CONCLUSIONS: Cardiac troponins were detected in patients with advanced CHF. These markers correlated with the severity of CHF and suggest an association with worse prognosis. Possible mechanisms for the release of cardiac troponins T and I in advanced CHF may include the following: ventricular remodeling, presence of coronary artery disease in CHF, abnormalities of coronary microcirculation, and reduced coronary reserve. Further studies will be necessary to elucidate the actual mechanism and determine the clinical significance of cardiac troponins in CHF.

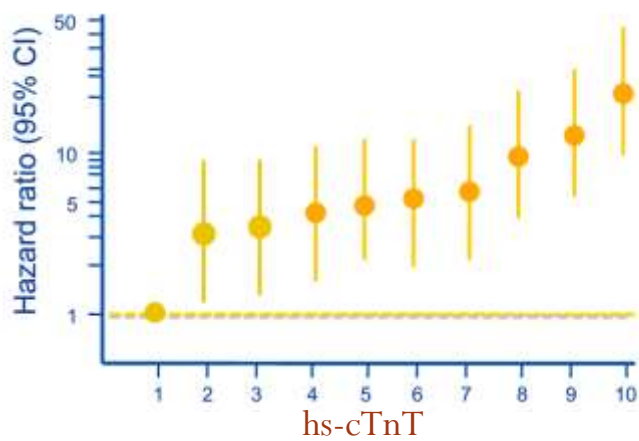
Causes Of Troponin Release



Stages Of Heart Failure And Troponin Levels



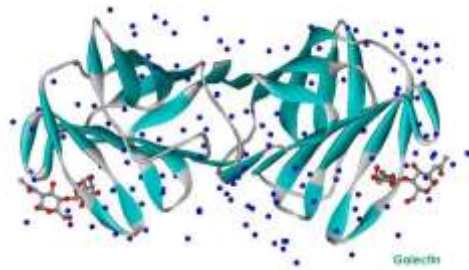
hs-cTnT & risk of death: GISSI HF



Masson, Circ 2012

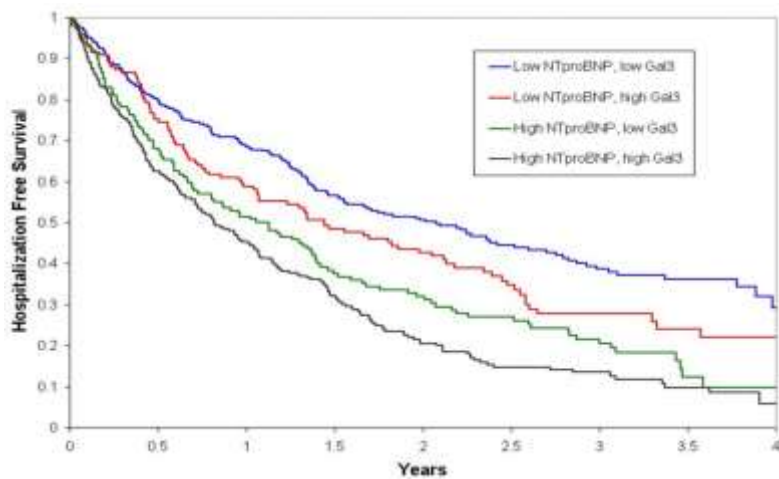
Galectin-3 Biology

- Beta-galactoside binding lectin
- Secreted by macrophages
- Mechanistic role in fibrosis
- Anti-apoptotic
- The (switch) that turns quiescent fibroblasts into activated, matrix secreting myofibroblasts



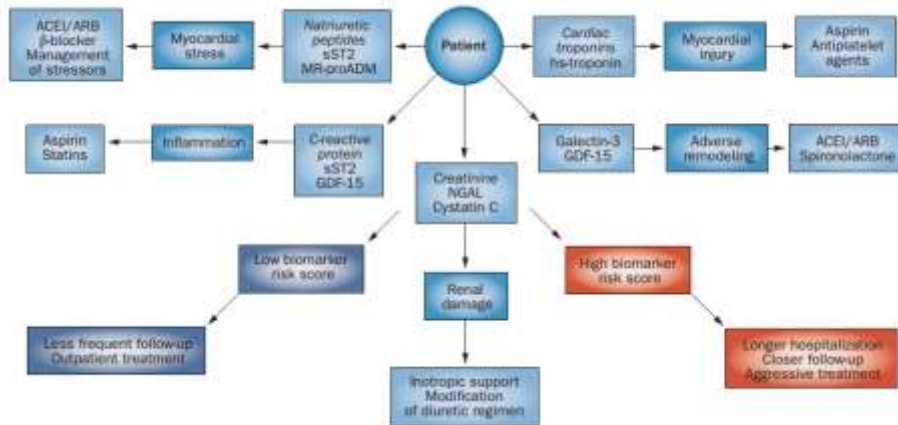
Felker et al. Circ HF 2010

Galectin-3 and NTproBNP in Chronic HF



Felker et al. Circ HF 2010

Future Strategies For Biomarker Guided Therapy In Heart Failure



Ahmad, T. et al. Nat. Rev. Cardiol. 9, 347–359 (2012)

Thank You