Cardiac Safety Research Consortium

Diagnostic Devices
(e.g. troponins, other biomarkers)

CSRC and MDEpiNet Thinktank Meeting: "The Role of Endpoint Adjudication in Medical Device Clinical Trials"

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Disclosures

- I disclose the following relationships with industry that are relevant to my talk:
  - Employment: Harvard Clinical Research Institute
  - Grants: Roche Diagnostics, Singulex, Thermo-Fisher, Prevencio
  - Consulting: Roche Diagnostics, Critical Diagnostics, Amgen, Novartis, Radiometer, Boeringer-Ingelheim, Phillips, Janssen
  - CEC/DSMB: Boeringer-Ingelheim, Janssen, Novartis, Amgen
- I may discuss off-label use of biomarkers

Introduction

- Biomarkers are frequently used in the execution of clinical trials.
  - Inclusion/exclusion
  - As an endpoint
  - Safety/toxicity monitor (DSMB)
  - As an adjudication tool to identify an endpoint (CEC)
- Each application has its drawbacks

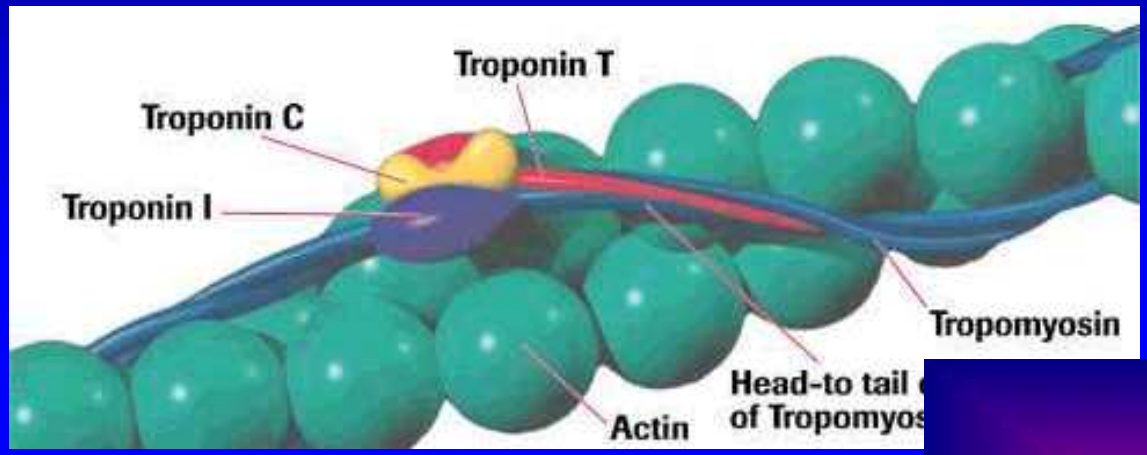
Biomarkers as tools to adjudicate presence of disease/endpoint

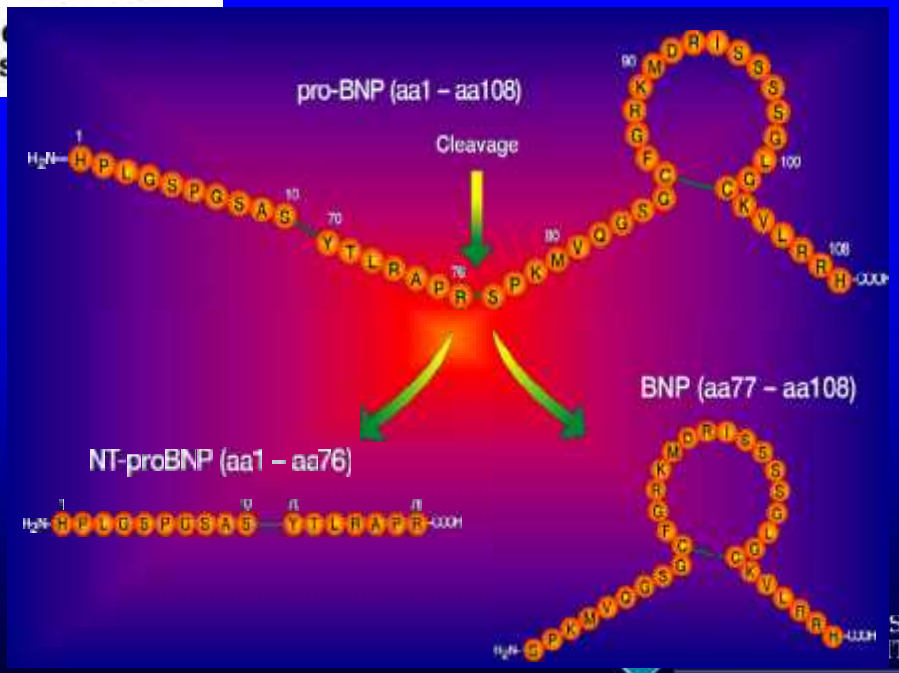
- Adjudicating using biomarkers
  - As the device itself
  - To identify endpoints in trials of other devices

Biomarkers as tools to adjudicate presence of disease/endpoint

- Requirements
  - Sensitivity for disease
  - Specificity for disease
  - Appropriate timing for detection of disease

Biomarkers as tools to adjudicate presence of disease/endpoint





An example of how complex it can get…

(in handwritten scrawl):

"The patient is a 76 year old man with diabetes, hypertension, and prior coronary disease. They presented with chest discomfort at rest and ST segment depression. Hemoglobin returned at 8. Troponin was 0.15".

Does this patient have an MI? And what type?

EXPERT CONSENSUS DOCUMENT

Third Universal Definition of Myocardial Infarction

Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman and Harvey D. White: the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction

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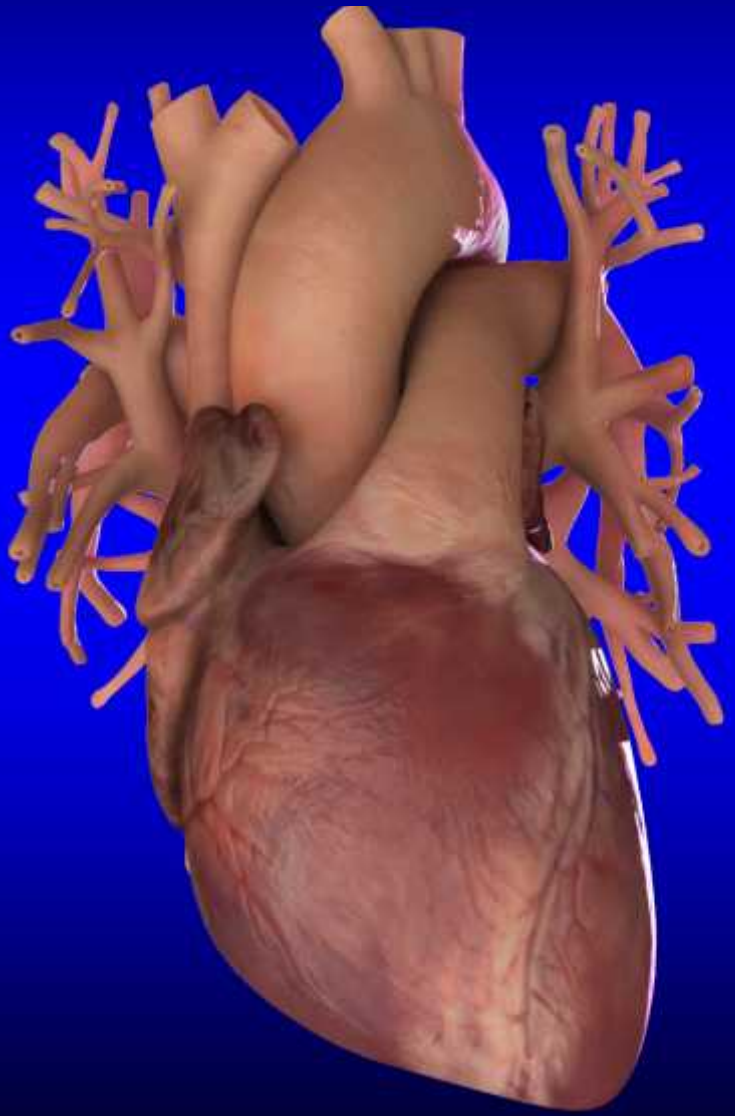
Differentiation of MI types 1 and 2 based on coronary artery condition



Plaque Rupture with Thrombus

MI Type 1

Vasospasm or Endothelial Dysfunction

MI Type 2

Fixed Atherosclerosis and Supply-Demand Imbalance

MI Type 2

Supply-Demand Imbalance Alone

MI Type 2

Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-2035.

An example of how complex it can get…

(in handwritten scrawl):

and ST segment depression. Hemoglobin returned at 8. Troponin was 0.15 .

Does this patient have an MI?

The wide world of troponins

Assay	LLD	99th Percentile	WHO-ROC Cutoff	10%* CV
Abbott ARCH	0.009	0.012	0.3	0.032
AxSYM *ADV*	0.02	0.04	0.4	0.16
**I-STAT	0.02	0.08 (WB)	ND	0.1
Bayer Centaur	0.02	0.1	1.0	0.35
Ultra	0.006	0.04	0.9	0.03
Beckman Accu	0.01	0.04	0.5	0.06
**Biosite Triage	0.05	<0.05	0.4	NA
bioMerieux Vds	0.001	0.01	0.16	0.11
Dade RxL	0.04	0.07	0.6-1.5	0.14
**CS	0.03	0.07	0.6-1.5	0.06
DPC Immulite	0.1	0.2	1.0	0.6
MKI Pathfast	0.006	0.01	0.06	0.06
Ortho Vitros	0.02	0.08	0.4	0.12
ES (R&D)	0.012	0.032	0.12	0.053
**Response	0.03	< 0.03 (WB)	ND	0.21
Roche Elecsys	0.01	<0.01	0.03	0.03
**Reader	0.05	<0.05 (WB)	0.1	ND
Tosoh AIA	0.06	0.06	0.31-0.64	0.06

•*Per manufacturer; ** POC Assay
•Adapted - Apple Am Heart J 2002

LLD = lower limit of detection

99th percentile = cut-point corresponding to value below which 99/100 normals will have

WHO-ROC cutoff = optimized to CK-MB

10% CV cutoff = lowest level that the assay can measure with 10% imprecision

Diagnosis

Third universal definition of myocardial infarction

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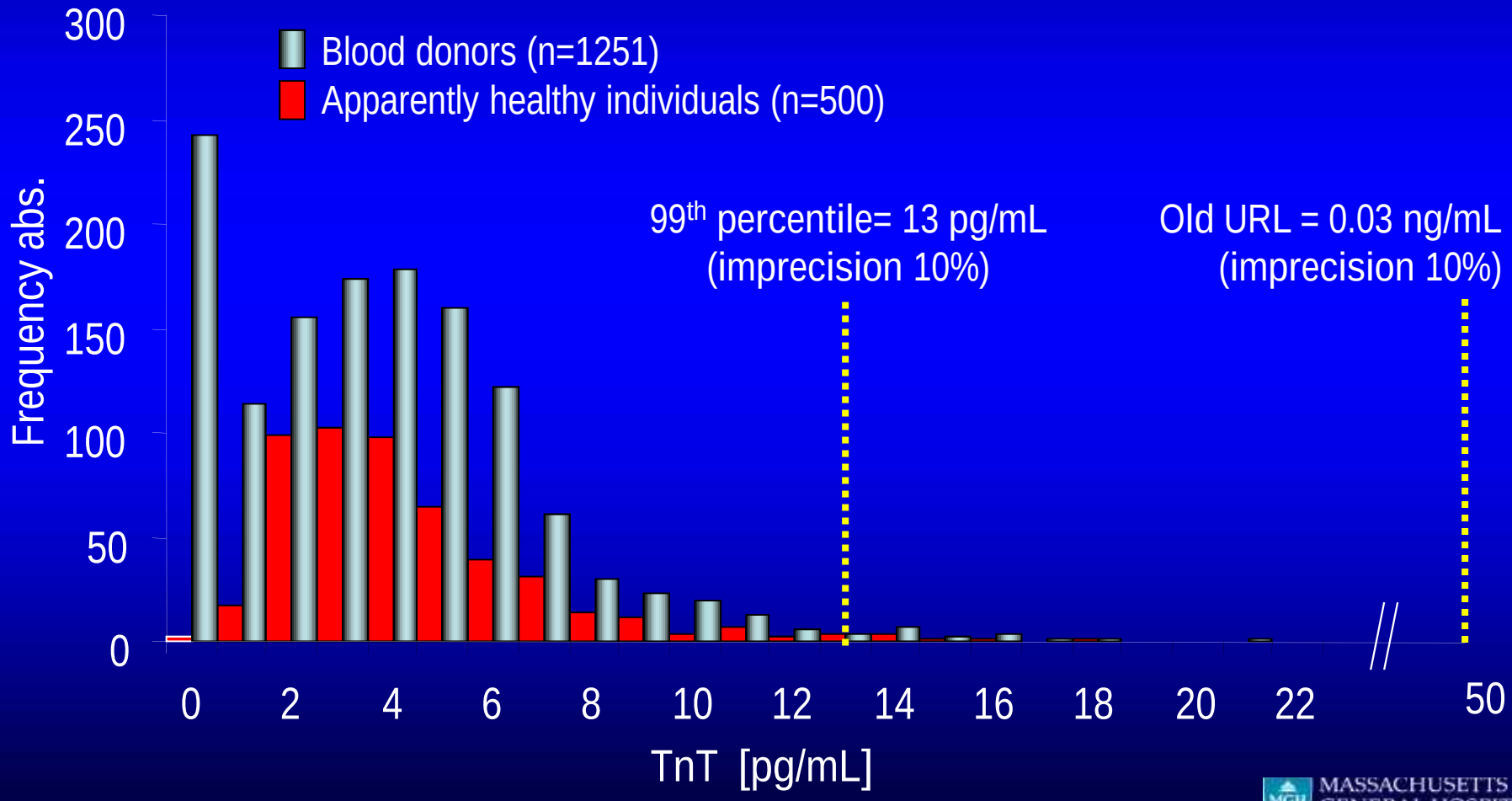
- **Detection of *rise and/or fall of troponin* with at least one value >99th percentile of the URL (or the lowest cut-point delivering <10% imprecision) together with evidence of myocardial ischemia with at least one of the following:**
  - ***Symptoms***
  - ***ECG changes***
  - ***Imaging evidence of new loss of myocardium or new RMWA***

99th Percentile for Troponin T



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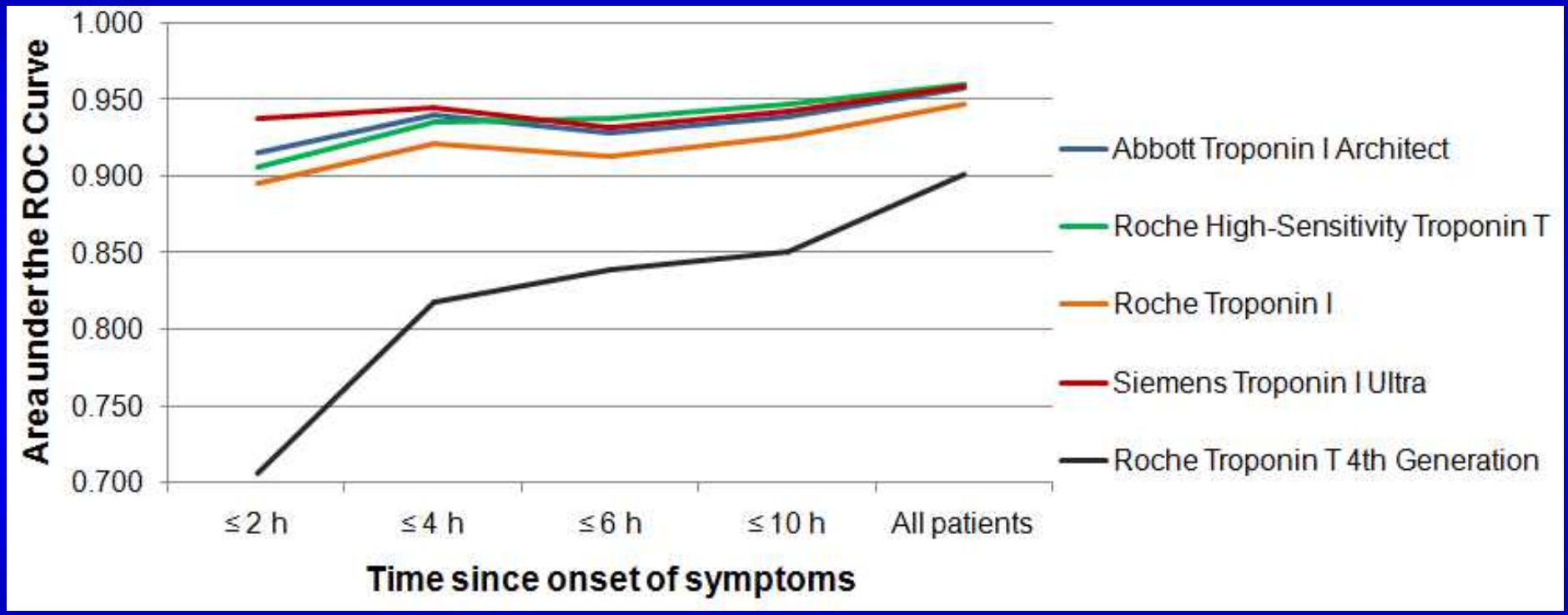
Sensitive Troponins improve the early diagnosis of AMI (at presentation!)



N ENGL J MED 361;9 NEJM.ORG AUGUST 27, 2009

hsTroponin is 30% more sensitive for detection of MI (reclassifies UAP to MI)

Changing the gold standard

- 30% of ACS have abnormally elevated hsTn c/w cTn
  - Are these MI?
  - How to adjudicate?
- Not all hsTn methods are comparably sensitive

Comparing Contemporary cTn vs. hs-cTn Assays

Manufacturer – assay	Measurable values >LoD, %	%CV at 99th URL Total Imprecision
Abbott ARCHITECT – hs-cTnI	96%	5.6%
Abbott ARCHITECT – cTnI	2%	14%
Beckman Access 2 – hs-cTnI	80%	10%
Beckman Access 2 – cTnI	35%	14%
Siemens Dimension Vista – hs-cTnI	100%	5.0%
Siemens Dimension Vista - cTnI	1%	10%
Roche Elecsys – hs-cTnT	25%	8%
Roche Elecsys Gen 4 - cTnT	0%	20%

Apple FS, Collinson PO. Clin Chem 2012; Apple FS, Ler R, Murakami MM. Clin Chem 2012.

An example of how complex it can get…

(in handwritten scrawl):

"The patient is a 76 year old man with diabetes, hypertension, and prior coronary disease. They presented with dyspnea at rest and a BNP of 200".

Does this patient have HF?

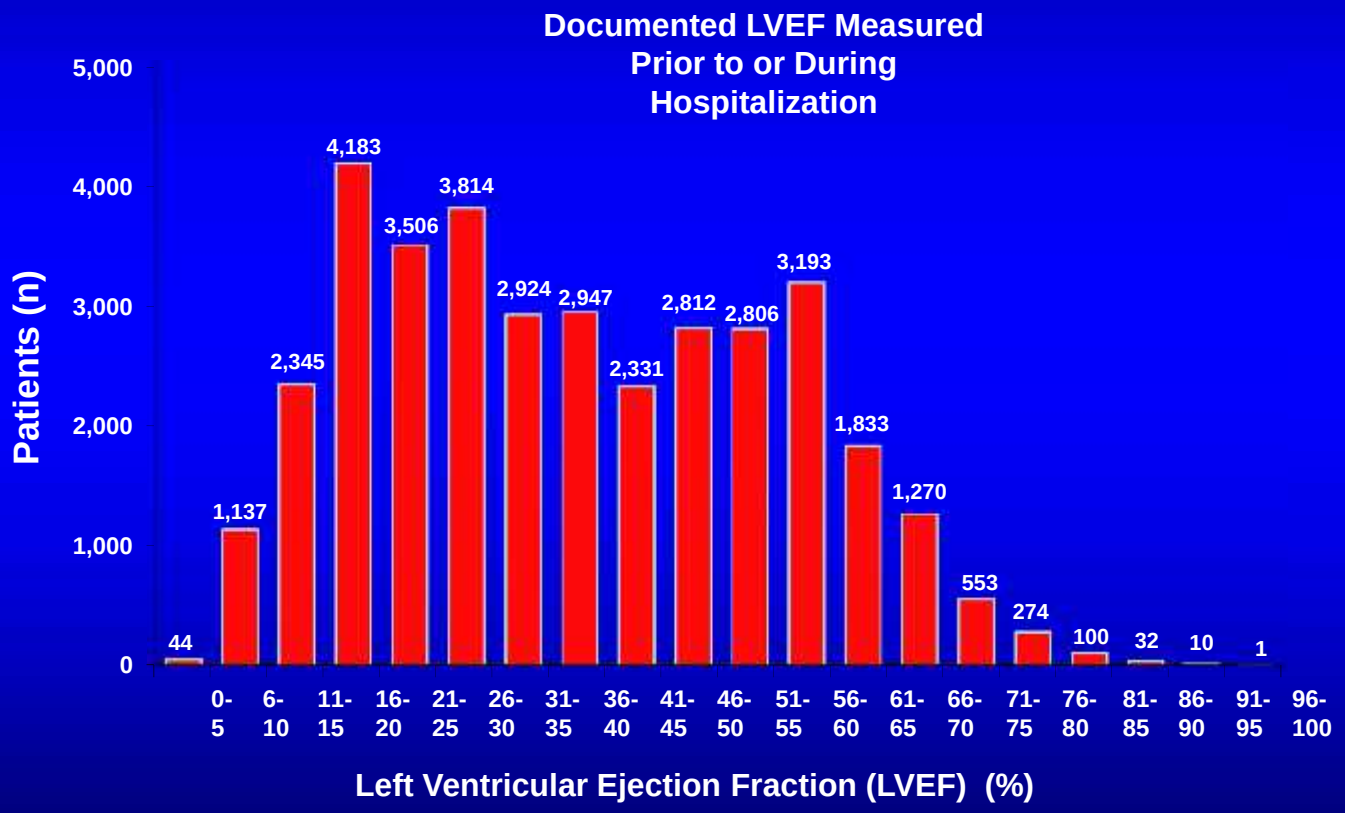
Correlations of Natriuretic Peptides with Cardiac Structure and Function

- Left ventricle
  - Size
  - Systolic function
  - Diastolic function
- Right ventricle
  - Size
  - Systolic function
- Atrial size and pressure
- Valve disease
  - Aortic
  - Mitral
  - Tricuspid
- Heart rhythm
- Ischemic heart disease
- Pericardial disease

Clinical correlates of elevated NPs

- Heart failure
- ACS
- Heart muscle disease
- Pericardial disease
- Valvular heart disease
- Atrial fibrillation
- Pulmonary hypertension
- Myocarditis
- Cardiac surgery
- Congenital heart disease
- Cardioversion
- Advancing age
- Anemia
- Pulmonary embolism
- Sleep apnea
- Critical illness
- Sepsis
- Burns
- Toxic-metabolic insults
- Renal failure

Distribution of LVEF in Patients Hospitalized With a Primary Discharge Diagnosis of HF



Stough W, et al. *J Am Coll Cardiol*. 2006;47:47A.

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What doesn't work well today

- Missing data, incomplete data, incorrect sampling
  - Time points matter for biomarkers
  - Required source data must be defined prospectively and all efforts should be made to obtain complete information when diagnosis is ambiguous
- Lack of standardization between troponin assays
- Delay in adoption of hsTn methods
- Application of accepted standards for biomarker use in adjudication

Priorities

- Troponin
  - Arrival of hsTn globally
  - Harmonization of cut offs
  - Establishment of SOPs for use of troponin in clinical trial adjudication
- BNP/NT-proBNP
  - More widespread use to facilitate adjudication of HF endpoints
  - Establishment of SOPs for use of BNP/NT-proBNP in clinical trial adjudication

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(e.g. troponins, other biomarkers)

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