Biomarkers & Treatment Guidance

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San Diego VA Medical Center

The Epidemic of Heart Failure

Prevalence	Incidence	Mortality	Hospital Discharges	Outpatient Visits	Cost
5,100,000	670,000	50% at five years	1,023,000	12-15 million	$39.8 billion

- Heart failure is common, costly, and deadly
- Prevention, diagnosis, risk stratification, monitoring, and managing heart failure is challenging
- There has been great interest in the clinical role of biomarkers in heart failure

American Heart Association. *2013 Heart and Stroke Statistical Update.* Dallas, Tex: American Heart Association; 2013.

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BACON
SWEET & SALTY FRIED BUTTER COMBO
BOTH FOR

Walk the Dog For Exercise


Exhibit

Where do biomarkers fit in?

Objectives of Biomarker Testing in Heart Disease

Diagnosis[1]

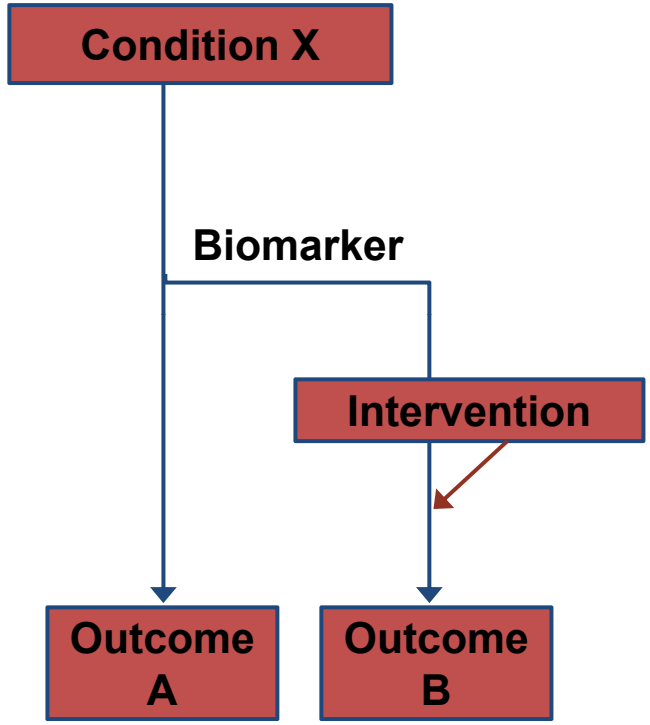
- To establish or refute a diagnosis
- To understand the underlying pathophysiologic processes

Risk Stratification/Screening[1]

- To determine the presence or severity of disease
- To detect adverse consequences

Monitoring/Therapeutic Guidance[1]

- To facilitate selection of an appropriate therapeutic intervention

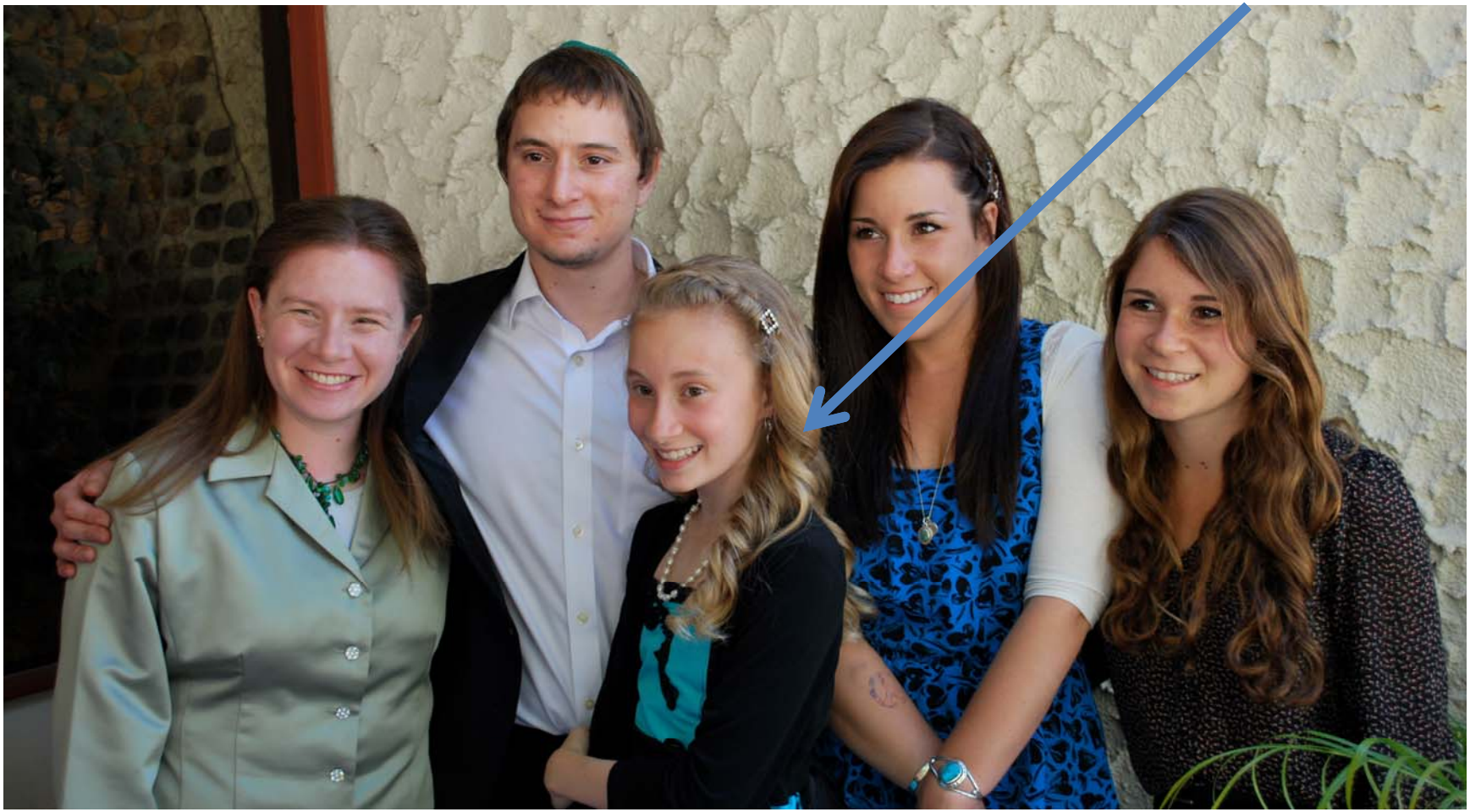


Many biomarkers may be risk factors themselves; therefore, may be potential targets of therapy[2]

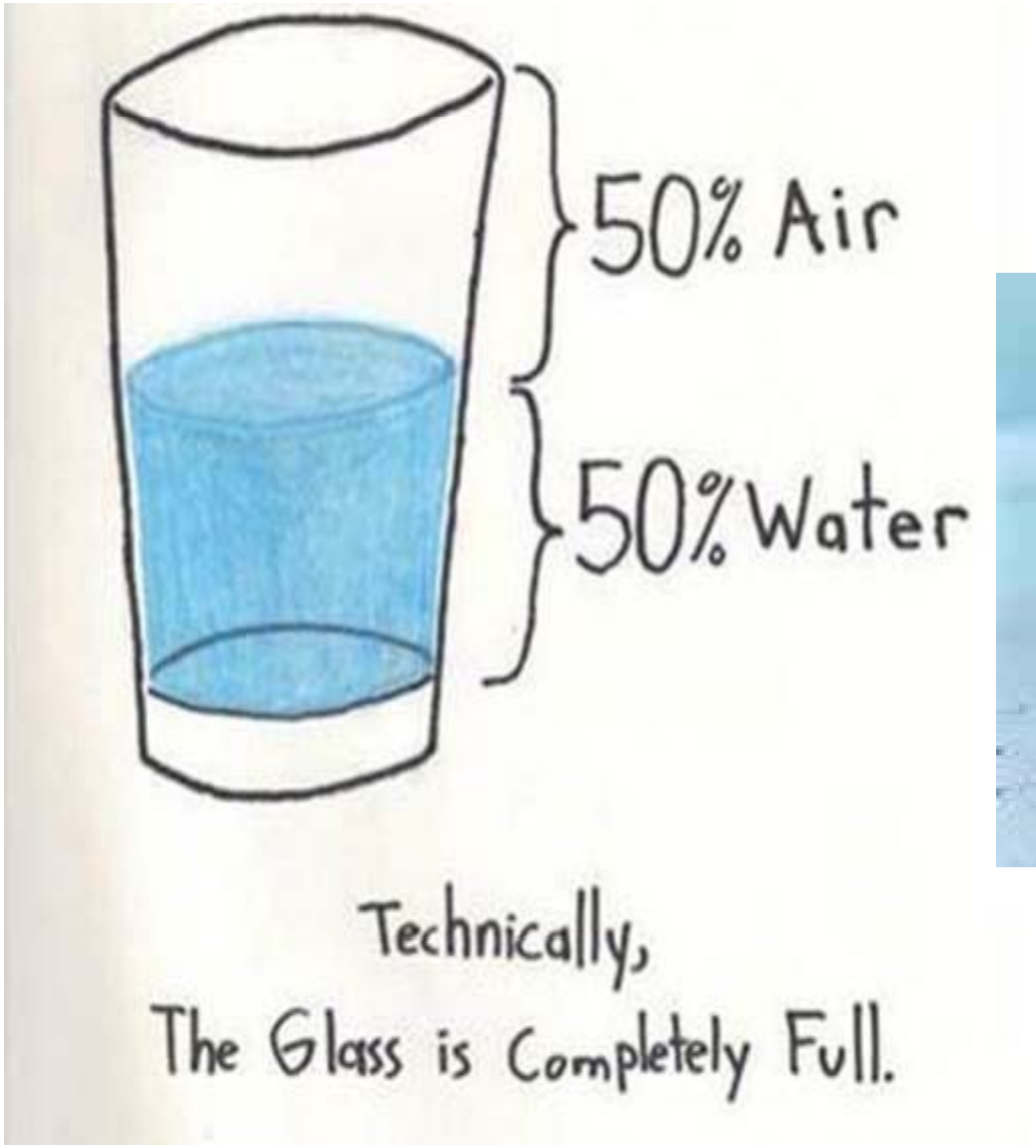
HF, heart failure.

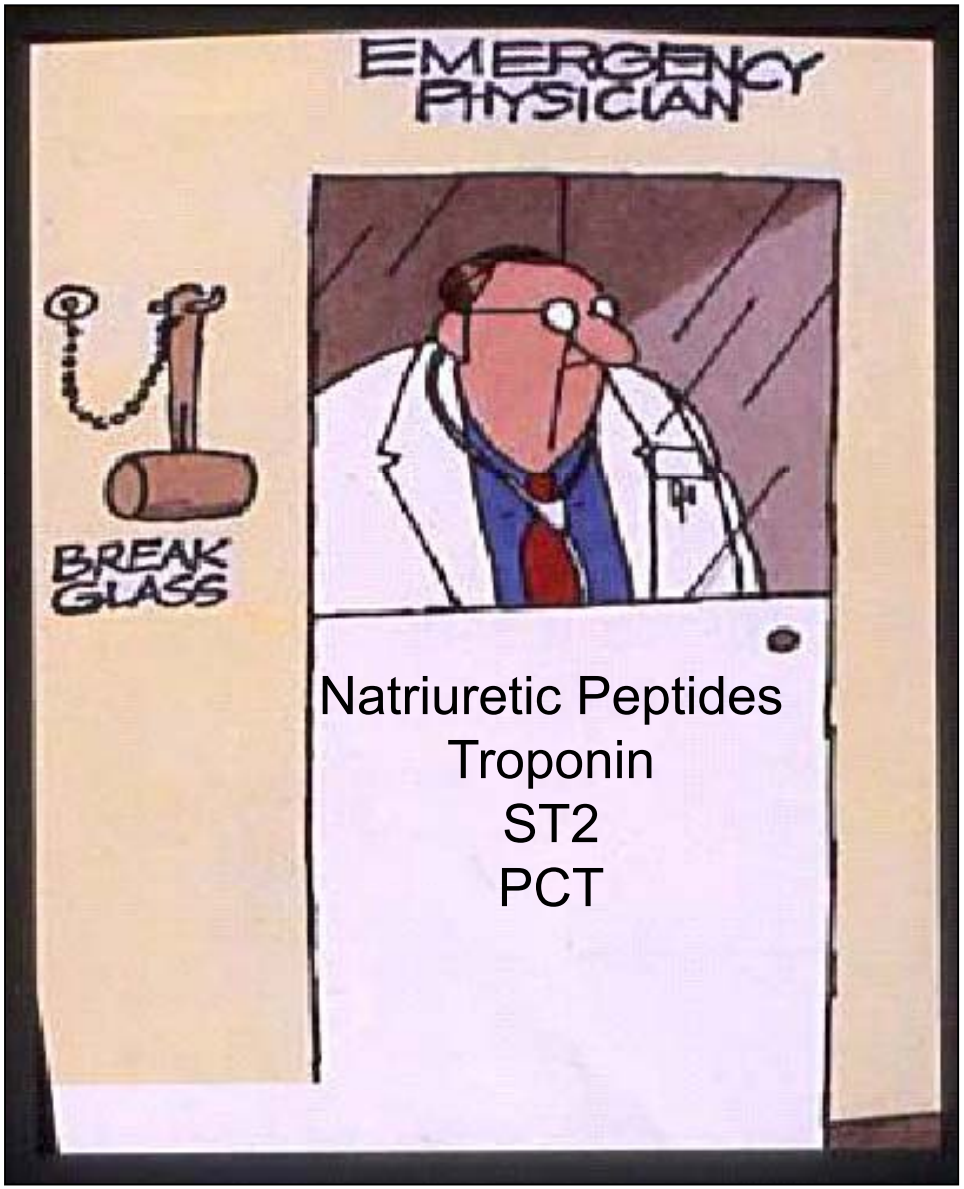
1. Morrow DA, et al. *Circulation.* 2007;115:949-952.
2. Kalogeropoulos AP, et al. *Prog Cardiovasc Dis.* 2012;55(1):3-13.

Is the cup half-empty or half-full?
My youngest daughter and I argued this point until one day after her physics class, she explained something to me.

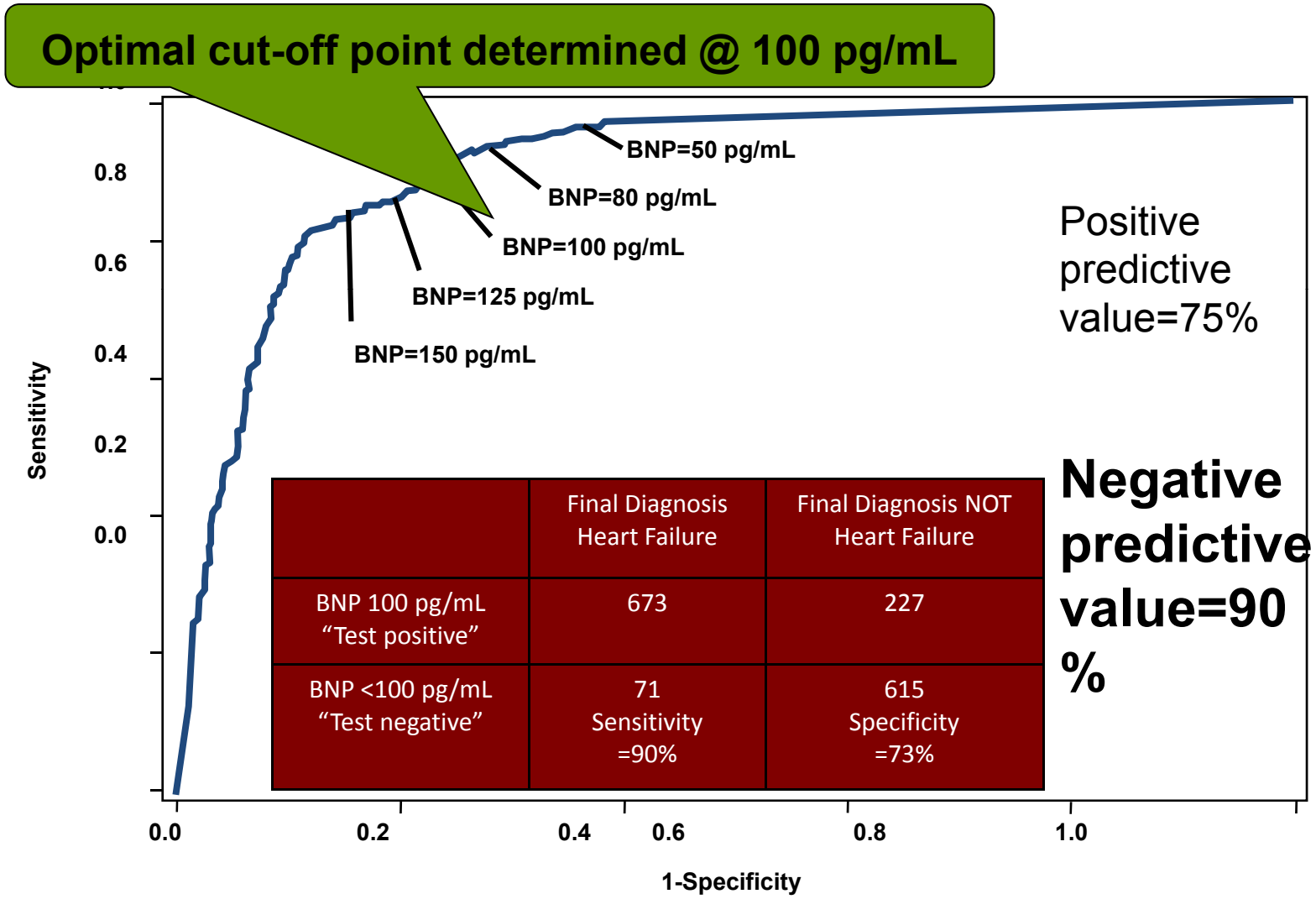


Biomarkers are here to stay!



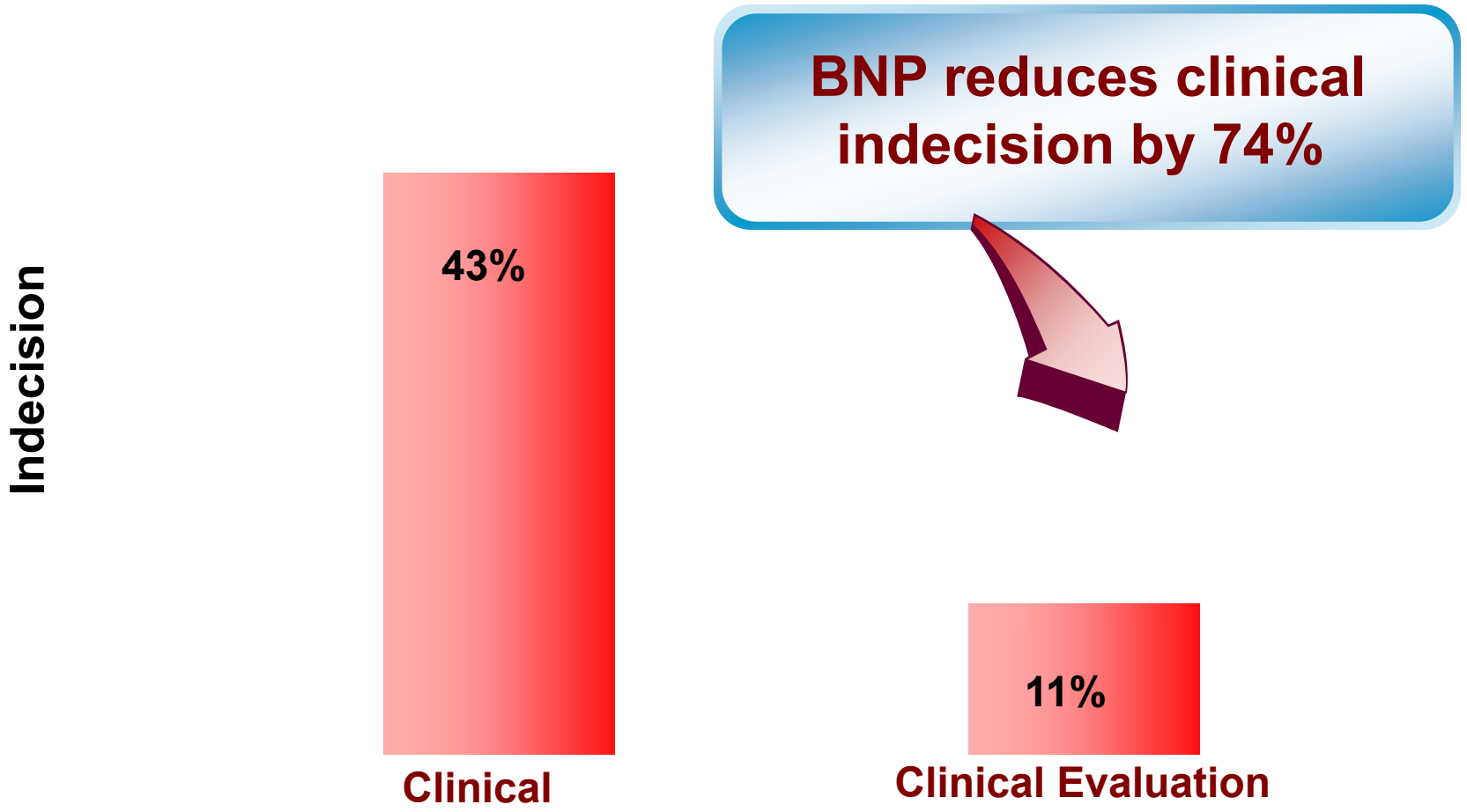

EMERGENCY PHYSICIAN
BREAK GLASS
Natriuretic Peptides
Troponin
ST2
PCT

Accuracy is 90%

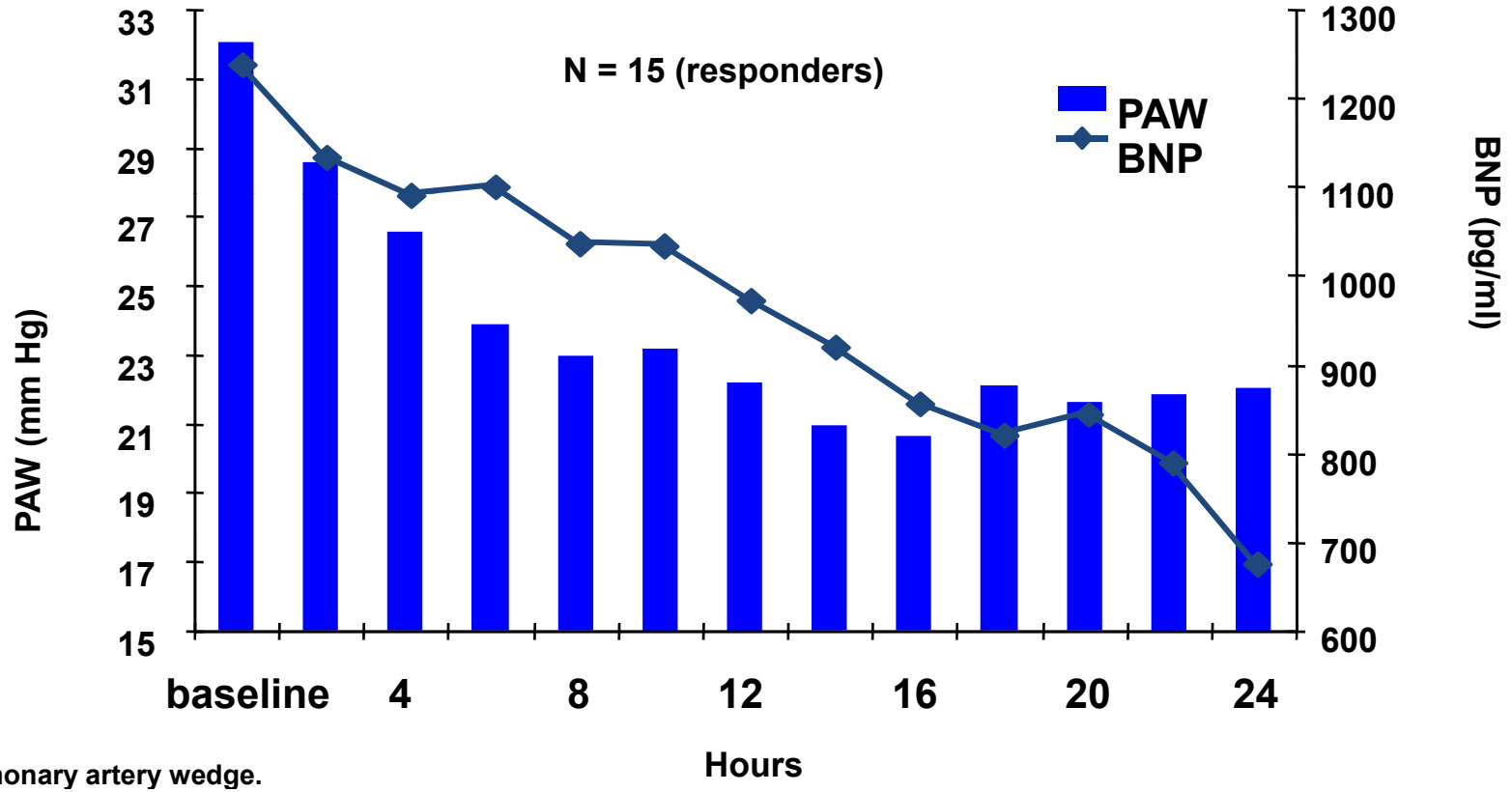


Maisel AS et al. *N Engl J Med.* 2002;347:161-167.

Clarification of Diagnosis & BNP



Changes in BNP Mirror changes in PAW* During Treatment of Acute Heart Failure

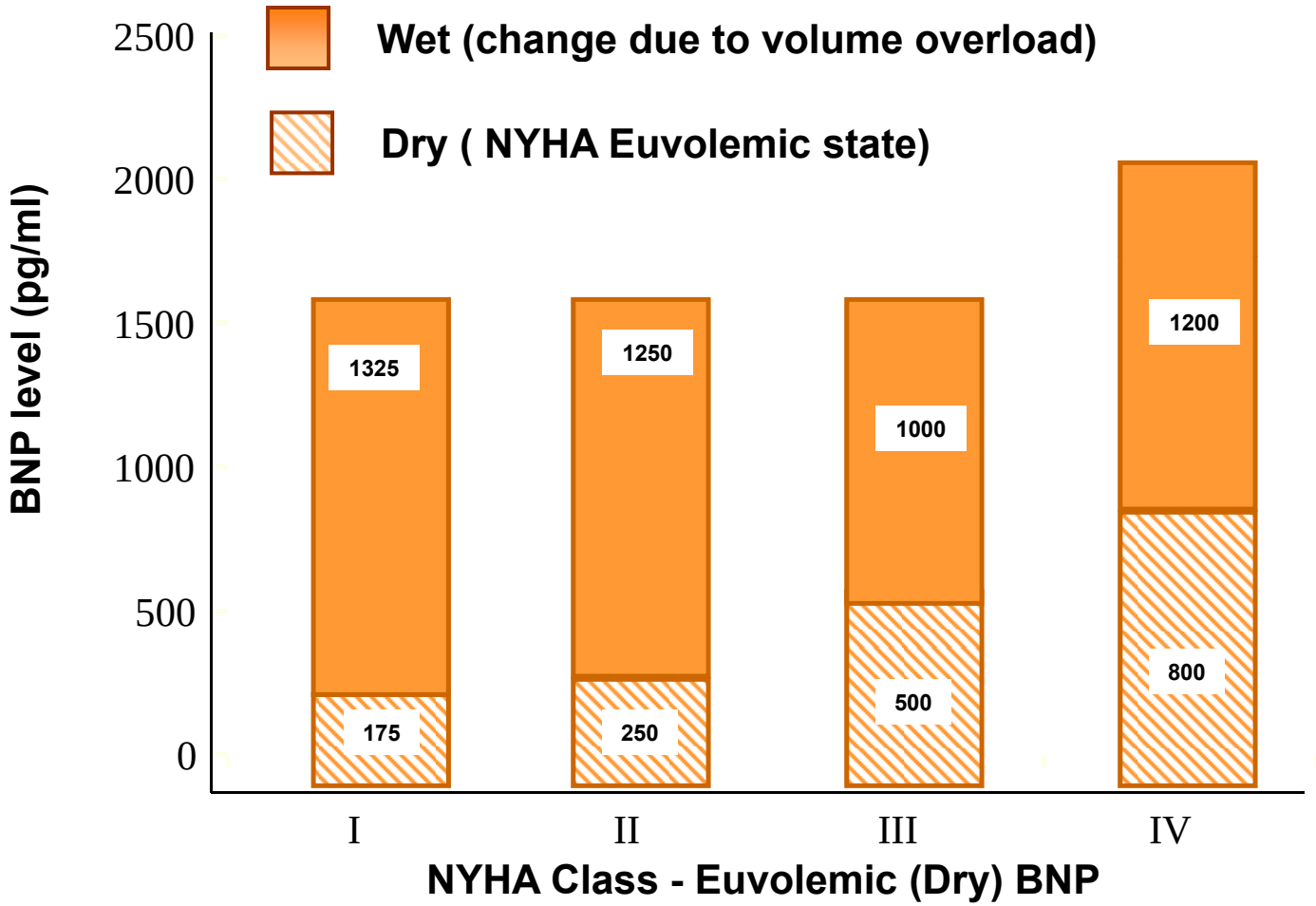


*Pulmonary artery wedge.

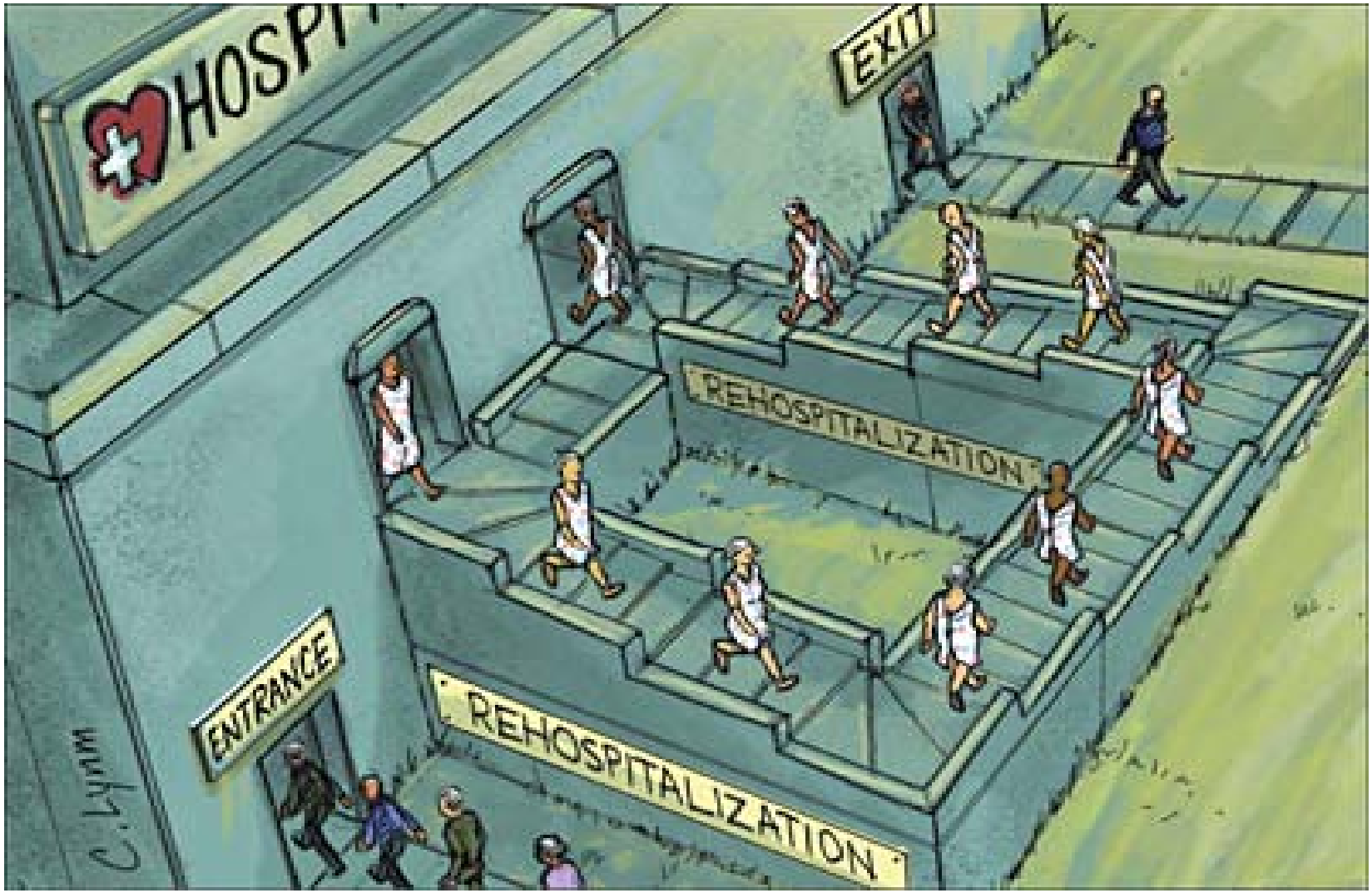
Kazenegra, Maisel, A. et al. *J Cardiac Failure,* Vol. 7, No. 1, 2001

In volume overloaded patients:

NP level = baseline NP (dry) + change due to increased volume (wet)



Heart Failure Admissions- The Revolving Door



In my shop, most of the the ADHF patients are being treated the same way

- Tune up with diuretics-iv for 2-3 days, then a new oral dose
- A bit of education
- Push patient out the door & wave good-bye

Traditional Heart Failure Admission

Changes one might consider on the basis of a Biomarkers prior to discharge

- Extra hospital time
- One week follow up
- Home nursing
- Telemonitoring
- More aggressive titration of medications

Surely they can’t be as expensive as other tests.

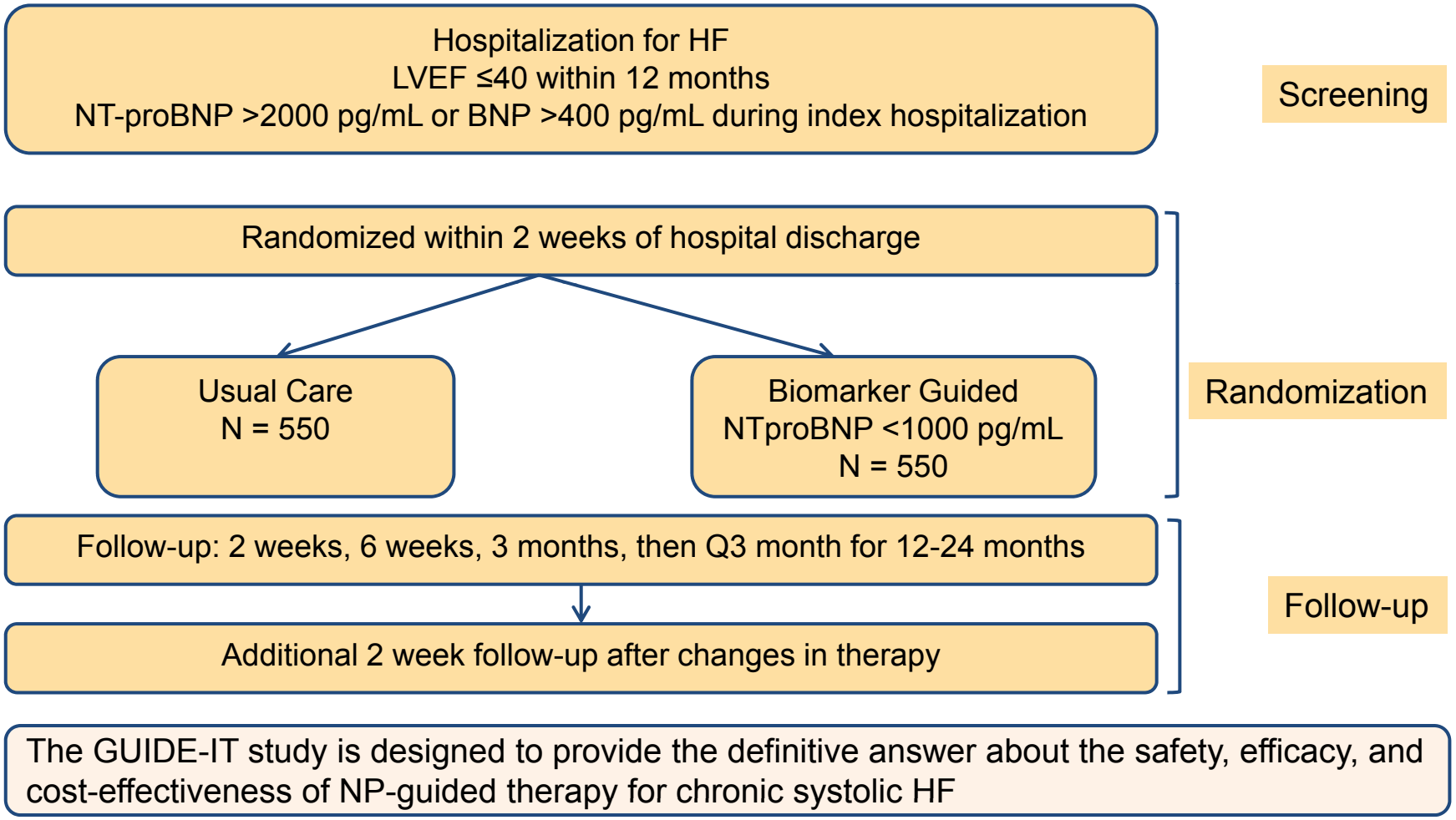
"Who's been fooling around with these x-rays?"

“Well, Bob, it looks like a paper cut, but just to be sure. Let’s get an echo.”


GUIDE-IT

NP Guided Therapy

GUIDE-IT Trial



The GUIDE-IT study is designed to provide the definitive answer about the safety, efficacy, and cost-effectiveness of NP-guided therapy for chronic systolic HF

HF, heart failure; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; Q3, every 3 months.

Felker GM. et al. *JACC Heart Fail.* 2014;2(5):457-465.

STOP-HF trial

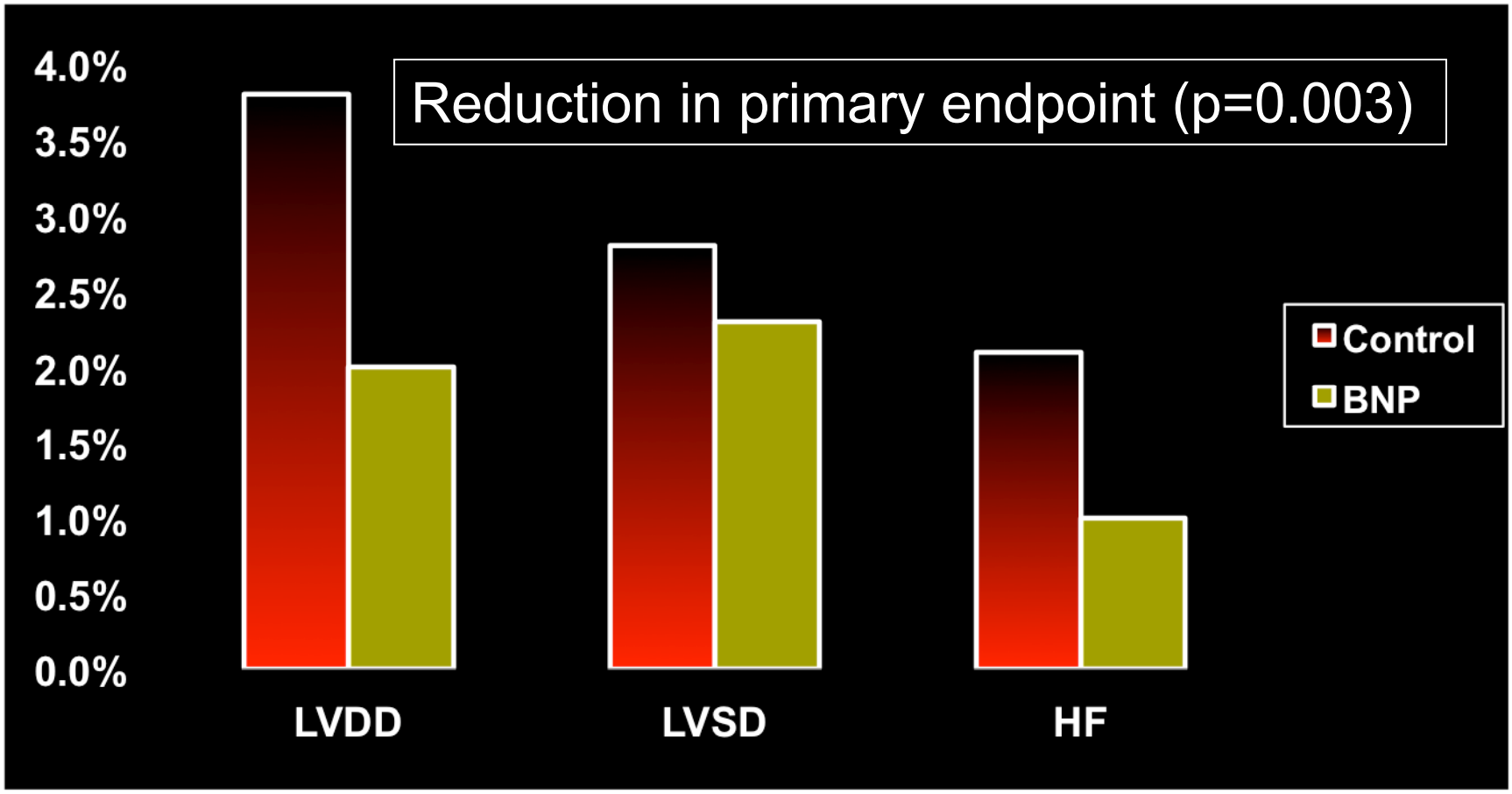
St Vincent's Screening to Prevent Heart Failure Study

Routine care (n=677)	Vs.	BNP-directed care (n=697)
Routine PCP care		Annual BNP check
Cardiology care PRN		*If BNP >50 pg/ml at any time: cardiology consult, echo, nurse-coaching*

1° Endpoint: LV systolic or diastolic dysfunction, or heart failure
2° Endpoints: Emergency hospitalization for arrhythmia, TIA, stroke, MI, PE/DVT, HF

Ledwidge et al. JAMA 2013

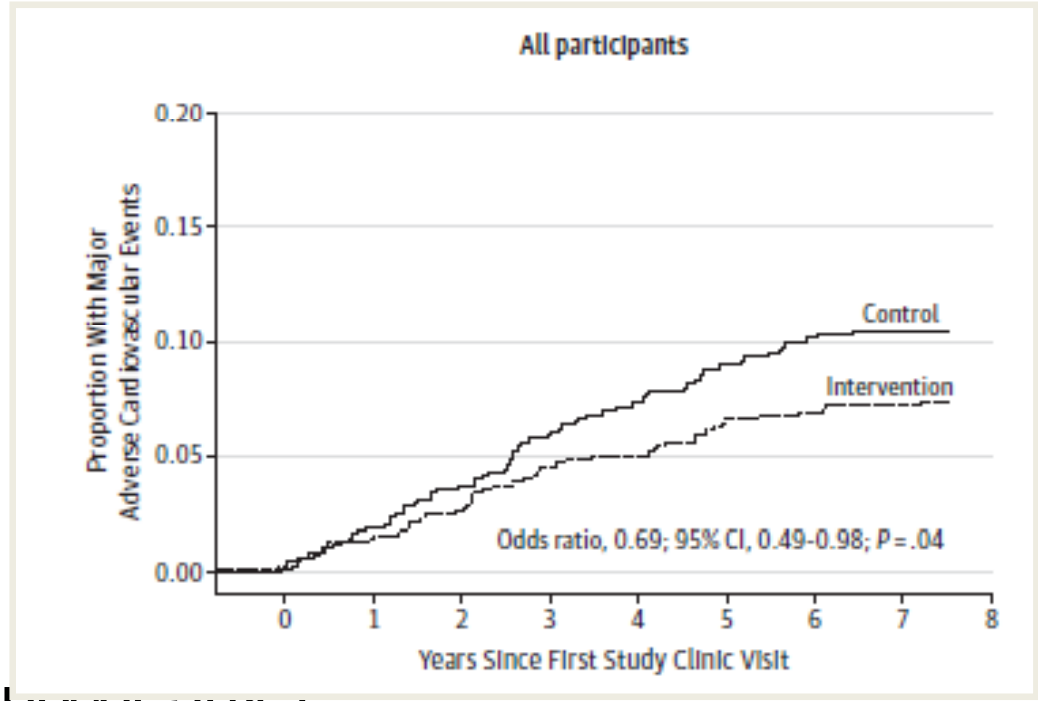
STOP-HF trial: results



Ledwidge et al. JAMA 2013

STOP-HF

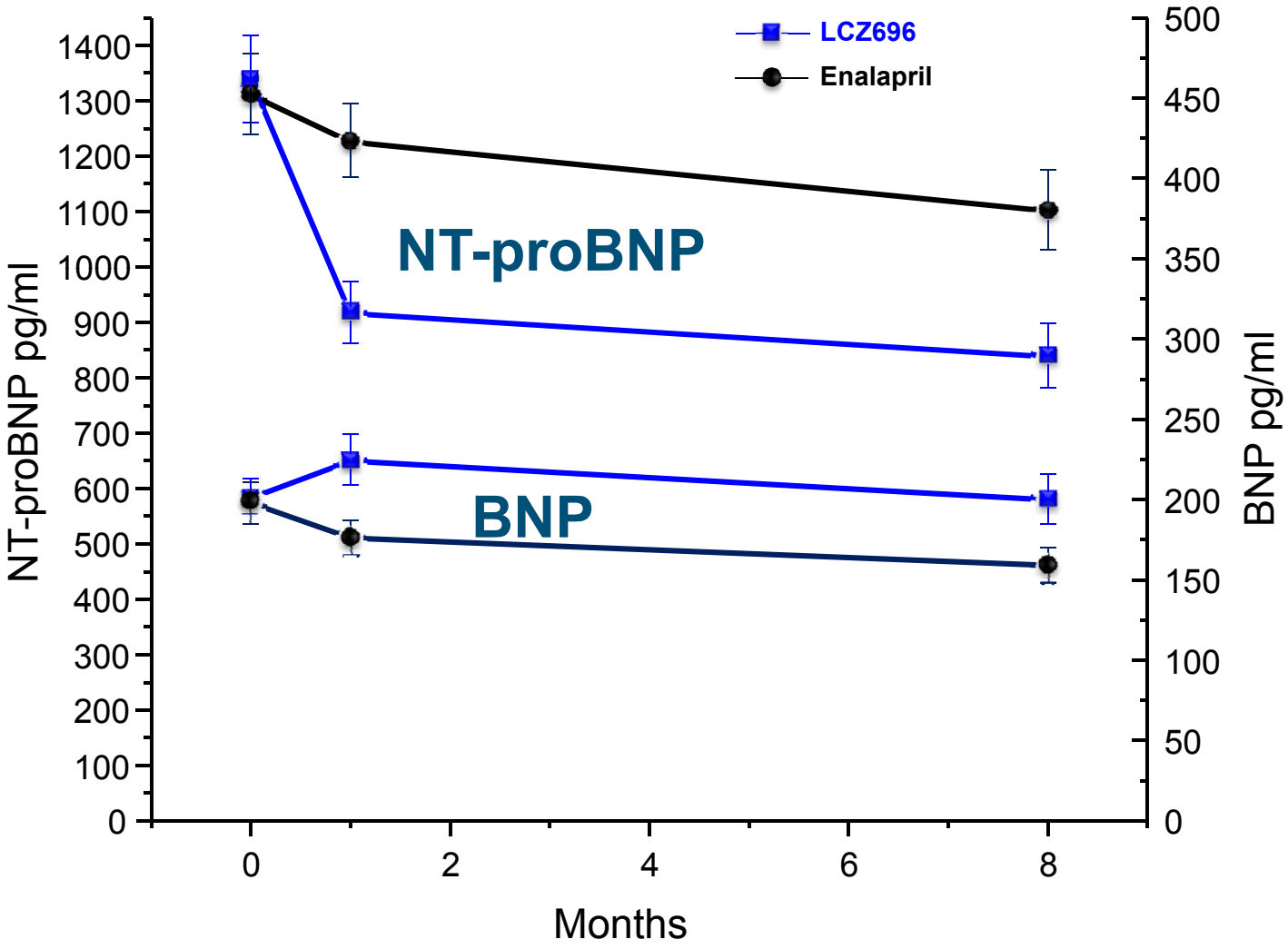
- Also reduced emergency hospitalizations for MACE
- BNP group received ↑ renin-angiotensin-aldosterone system-based therapy

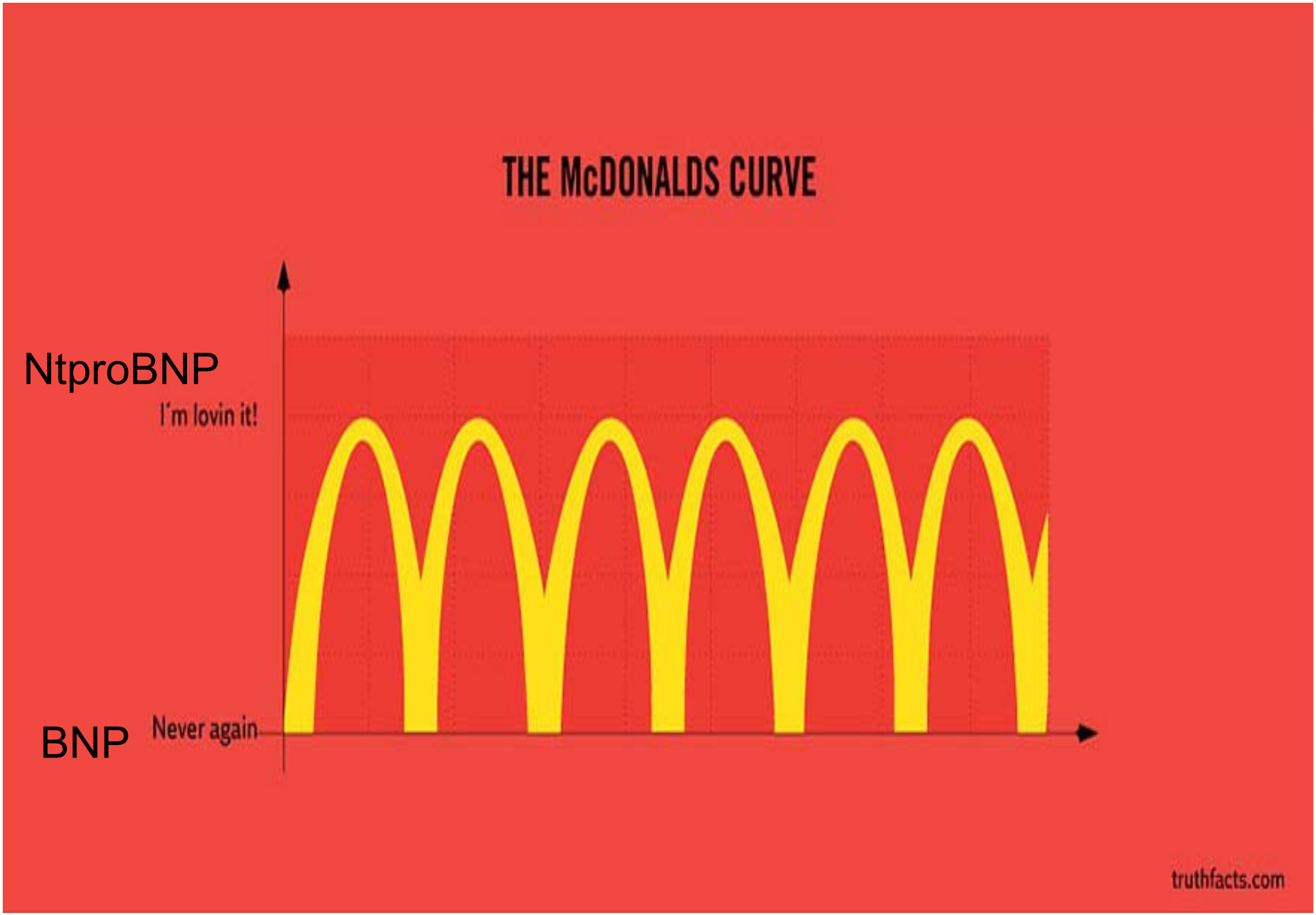


Ledwidge et al. JAMA 2013

Which peptide with Sacubitril/ Valsartan? NT-proBNP? BNP?

PARADIGM-HF: NT-proBNP and BNP




THE McDONALDS CURVE
NtproBNP
I'm lovin it!
BNP
Never again
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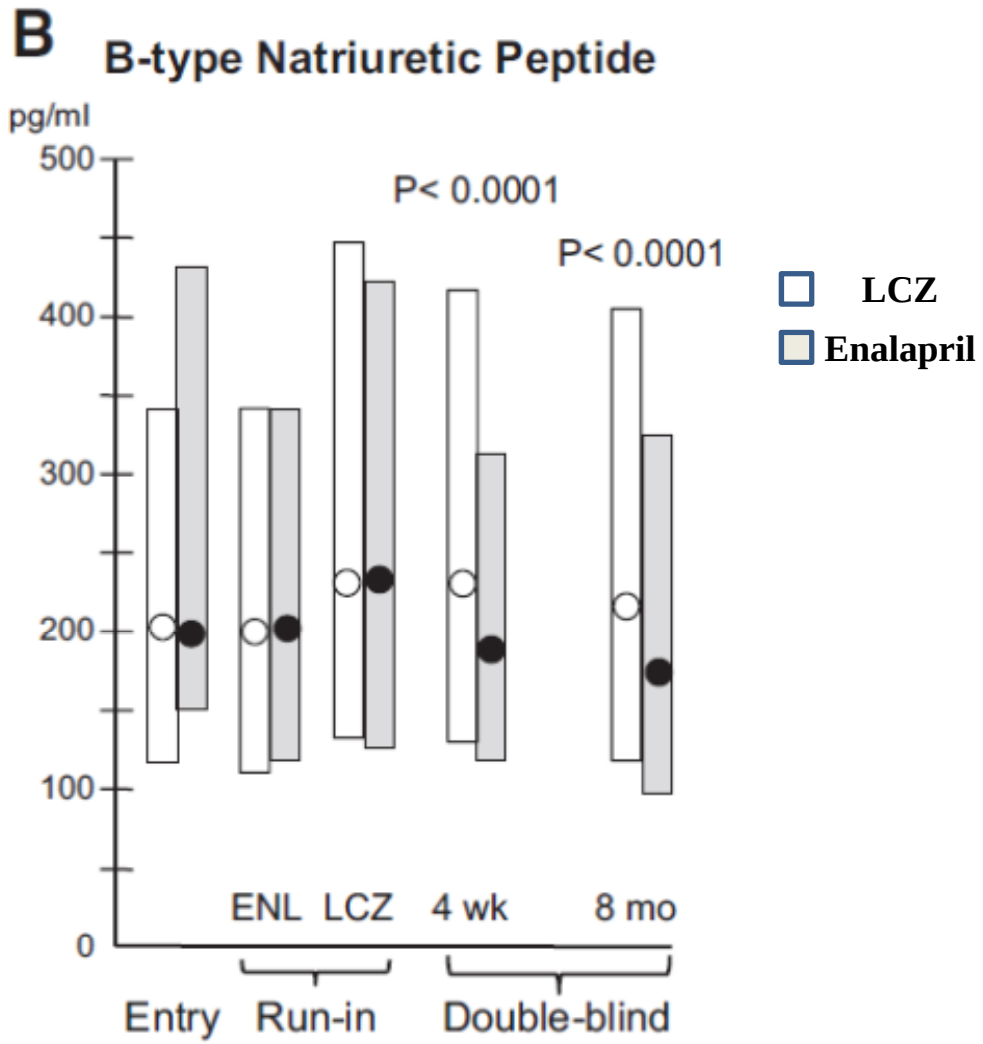
whoops
BNP

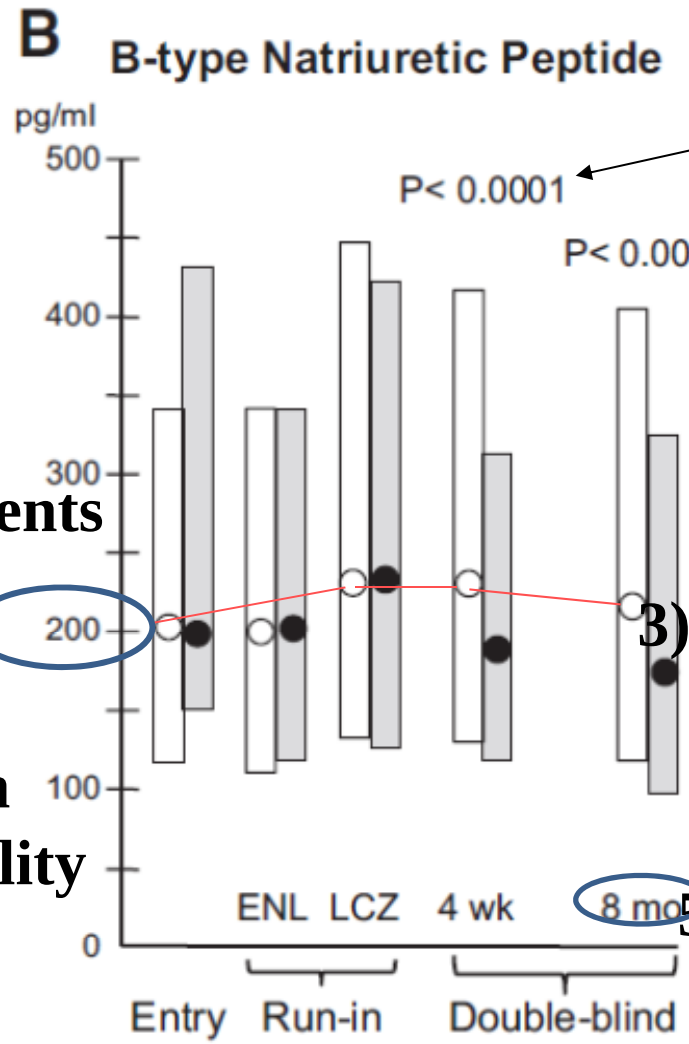
You may hear: « Based on PARADIGM, BNP is useless » !



ADD-00056847

Packer M et al Circulation 2015

You may hear: « Based on PARADIGM, BNP is useless » ! This is wrong !



2) LCZ versus Enalapr
intra-group differenc

Only 27 % of the patients had NPs measured

3) LCZ does not alter BN

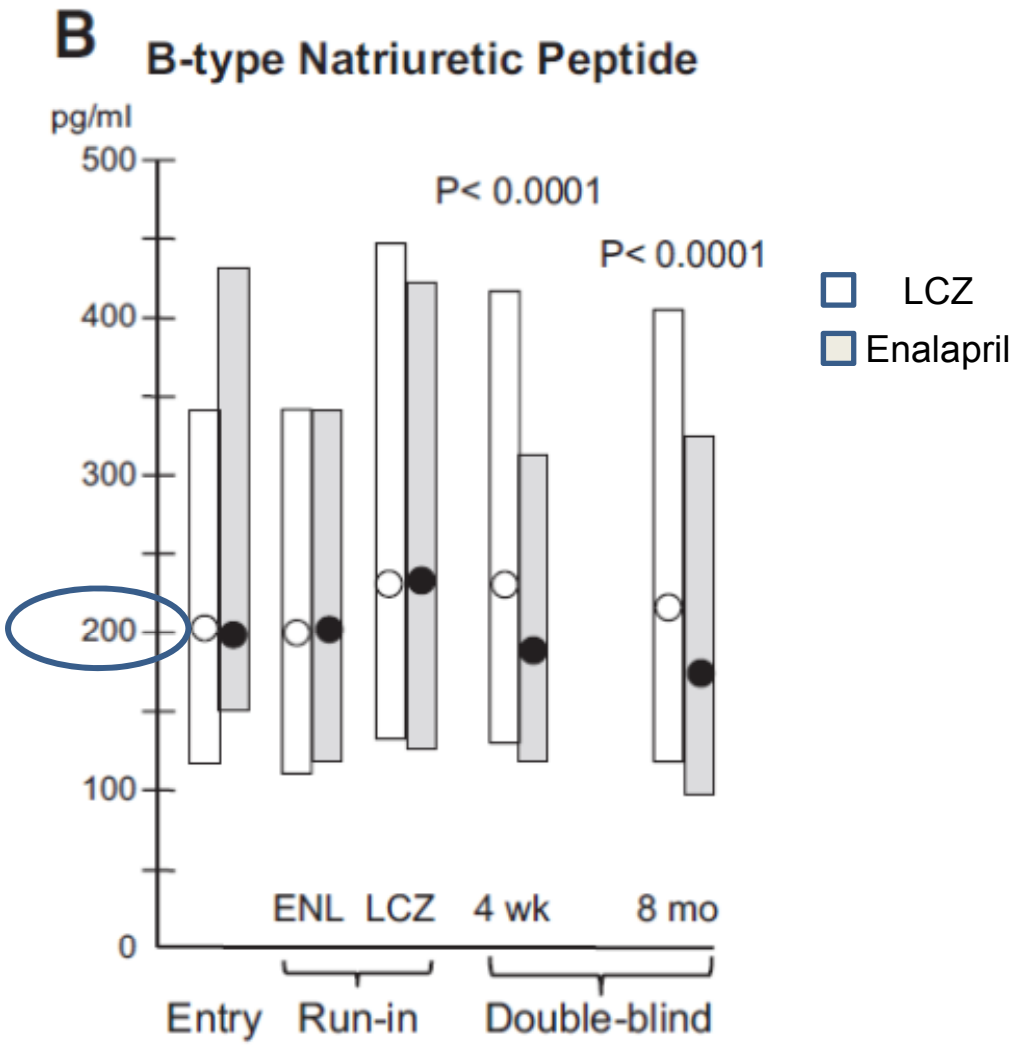
4) Changes are within ıtra-individual variability

5) Cardiovascular deatl similar at 8 mo

ADD-00056847

Packer M et al Circulation 2015

Furthermore, levels of BNP are much below those measured in Acute Heart Failure



Packer M et al Circulation 2015

Confounders of NP interpretation

Higher NP levels than expected	Lower NP levels than expected
Increasing age*	Obesity
ACS*	Flash pulmonary edema
Renal insufficiency	Pericarditis/Tamponade
RV dysfunction*	Genetic polymorphisms
Atrial fibrillation	“Burned-out” Cardiomyopathy
Pulmonary hypertension*	
Pulmonary embolism*	
Anemia/high output states*	
Sepsis	
Mitral Regurgiation*	

* Delineates likely elevation from Ventricular stretch


PCT
PCT
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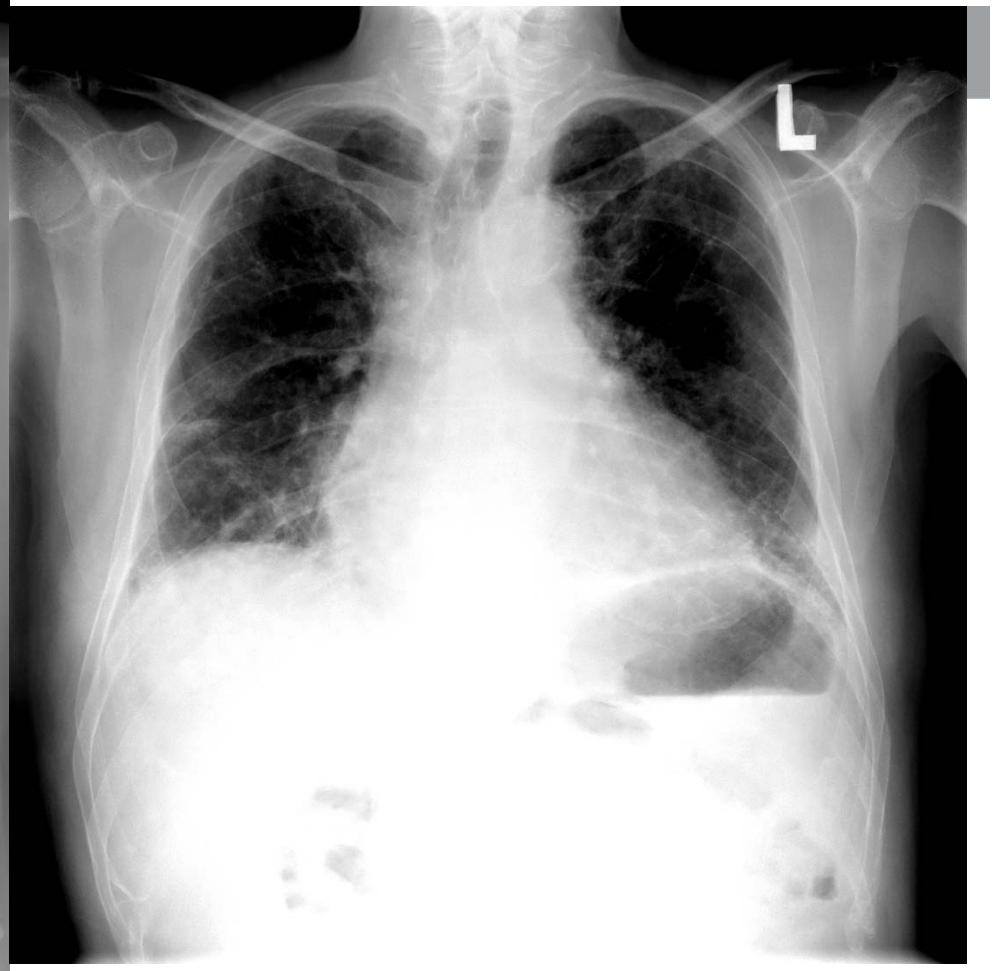
Heart Failure + Infection

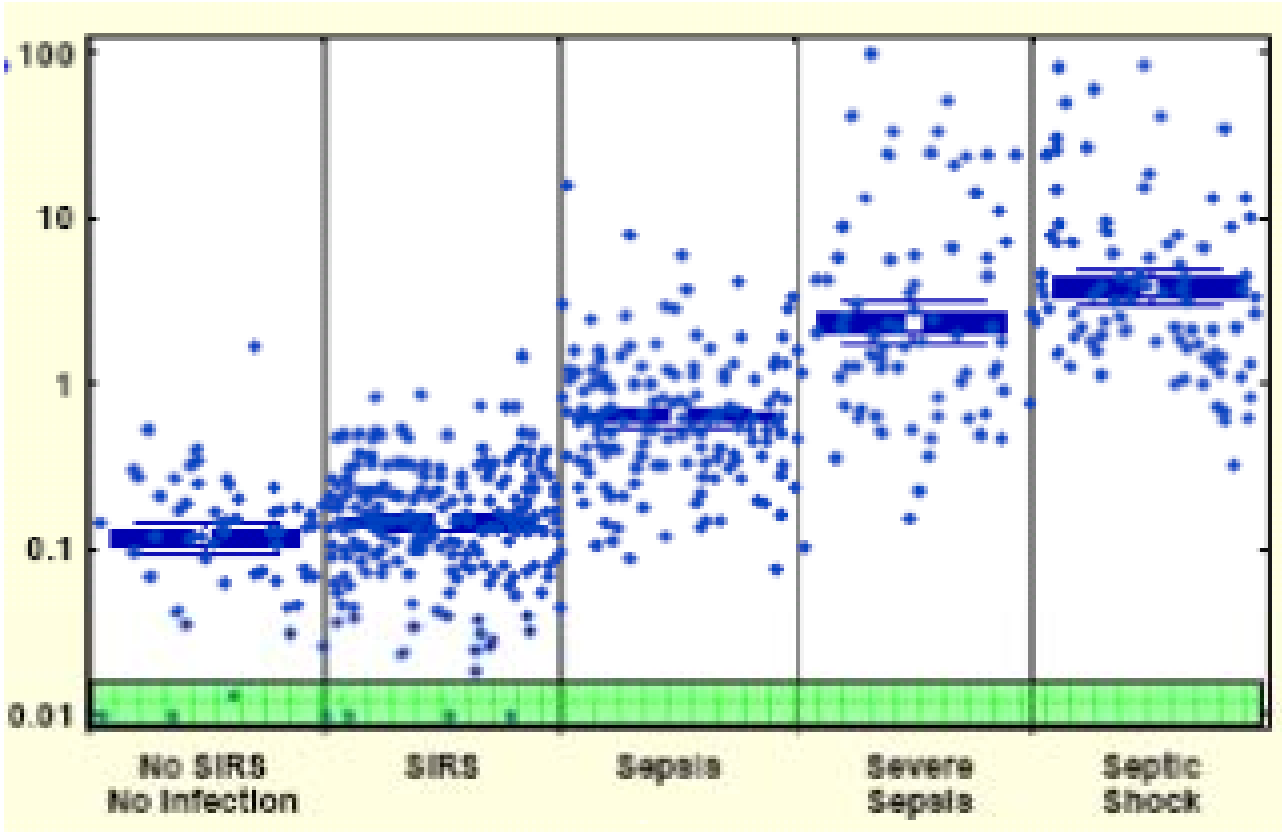
- 20% of hospitalized AHF patients.
- If pneumonia untreated, hospital mortality may be up to 20% (versus 5%)



24 h later after decongestion

Patient presents with dyspnea, chest x-ray: Only congestion or additional pneumonia?

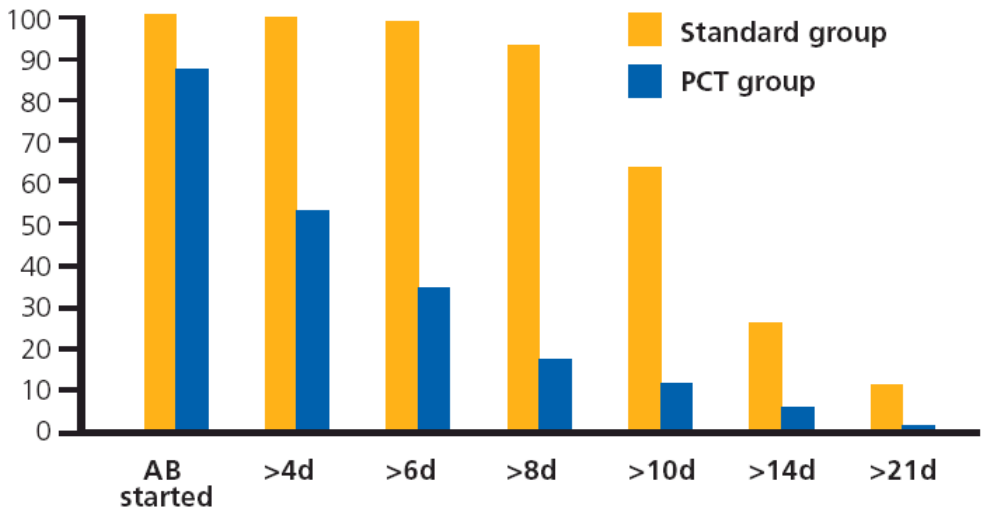
The likelihood and severity of bacterial infection increase with increasing PCT levels



Müller B. et al., Crit.Care Med. 2000

PCT in "Antibiotic Stewardship":
-> Reducing Duration of Antibiotic Therapy in patients with CAP

Prospective interventional trial: 302 patients



Tailoring of antibiotics treatment to the individual patient needs

Reduction of average treatment duration from 12 to 5 days.

Same outcome! (Safety)

Christ-Crain M et al. Am J Respir Crit Care Med. 2006 Apr 7

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European Journal of Heart Failure (2012) **14**, 278–286
doi:10.1093/eurjhf/hfr177

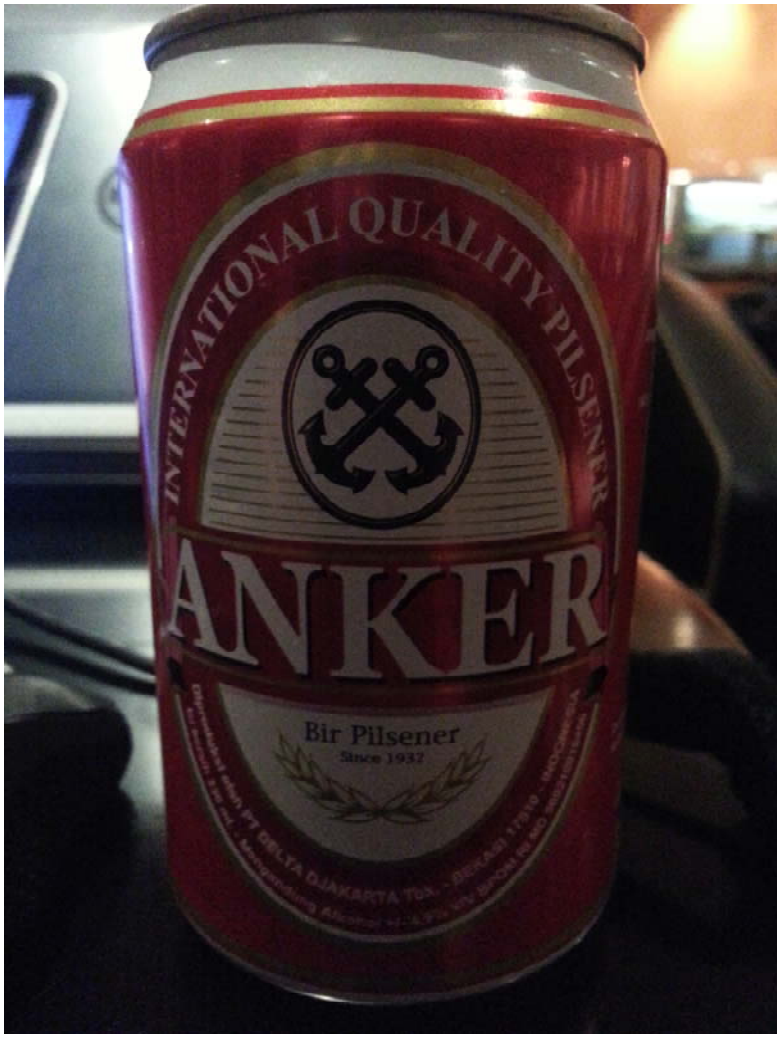
Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial

Alan Maisel[1,2]*, Sean-Xavier Neath[2], Judd Landsberg[1,2], Christian Mueller[3], Richard M. Nowak[4], W. Frank Peacock[5], Piotr Ponikowski[6], Martin Möckel[7], Christopher Hogan[8], Alan H.B. Wu[9], Mark Richards[10], Paul Clopton[1], Gerasimos S. Filippatos[11], Salvatore Di Somma[12], Inder Anand[13], Leong L. Ng[14], Lori B. Daniels[9], Robert H. Christenson[15], Mihael Potocki[3], James McCord[4], Garret Terracciano[16], Oliver Hartmann[17], Andreas Bergmann[18], Nils G. Morgenthaler[7], and Stefan D. Anker[7,19]

[1]VA San Diego Healthcare System, San Diego, CA, USA; [2]University of California, San Diego, CA, USA; [3]University Hospital Basel, Basel, Switzerland; [4]Henry Ford Health System, Detroit, MI, USA; [5]The Cleveland Clinic, Cleveland, OH, USA; [6]Medical University, Faculty of Public Health, Wroclaw, Poland; [7]Charite, Campus Virchow-Klinikum, Berlin, Germany; [8]Virgina Commonwealth University, Richmond, VA, USA; [9]University of California, San Francisco, CA, USA; [10]University of Otago, Christchurch, New Zealand; [11]Athens University Hospital Attikon, Athens, Greece; [12]Sant'Andrea Hospital, University La Sapienza, Rome, Italy; [13]VA Minneapolis, MN, USA; [14]University of Leicester, and Leicester NIHR Cardiovascular Biomedical Research Unit, Leicester, UK; [15]University of Maryland School of Medicine, Baltimore, MD, USA; [16]University of California, San Diego School of Medicine, San Diego, CA, USA; [17]BRAHMS GmbH, Biotechnology Centre Hennigsdorf/Berlin, Germany; [18]Waltraut Bergmann Foundation, Hohen Neuendorf, Germany; and [19]Centre for Clinical and Basic Research IRCCS San Raffaele, Roma, Italy

Received 3 September 2011; revised 5 November 2011; accepted 12 December 2011; online publish-ahead-of-print 2 February 2012


Maisel's Weisse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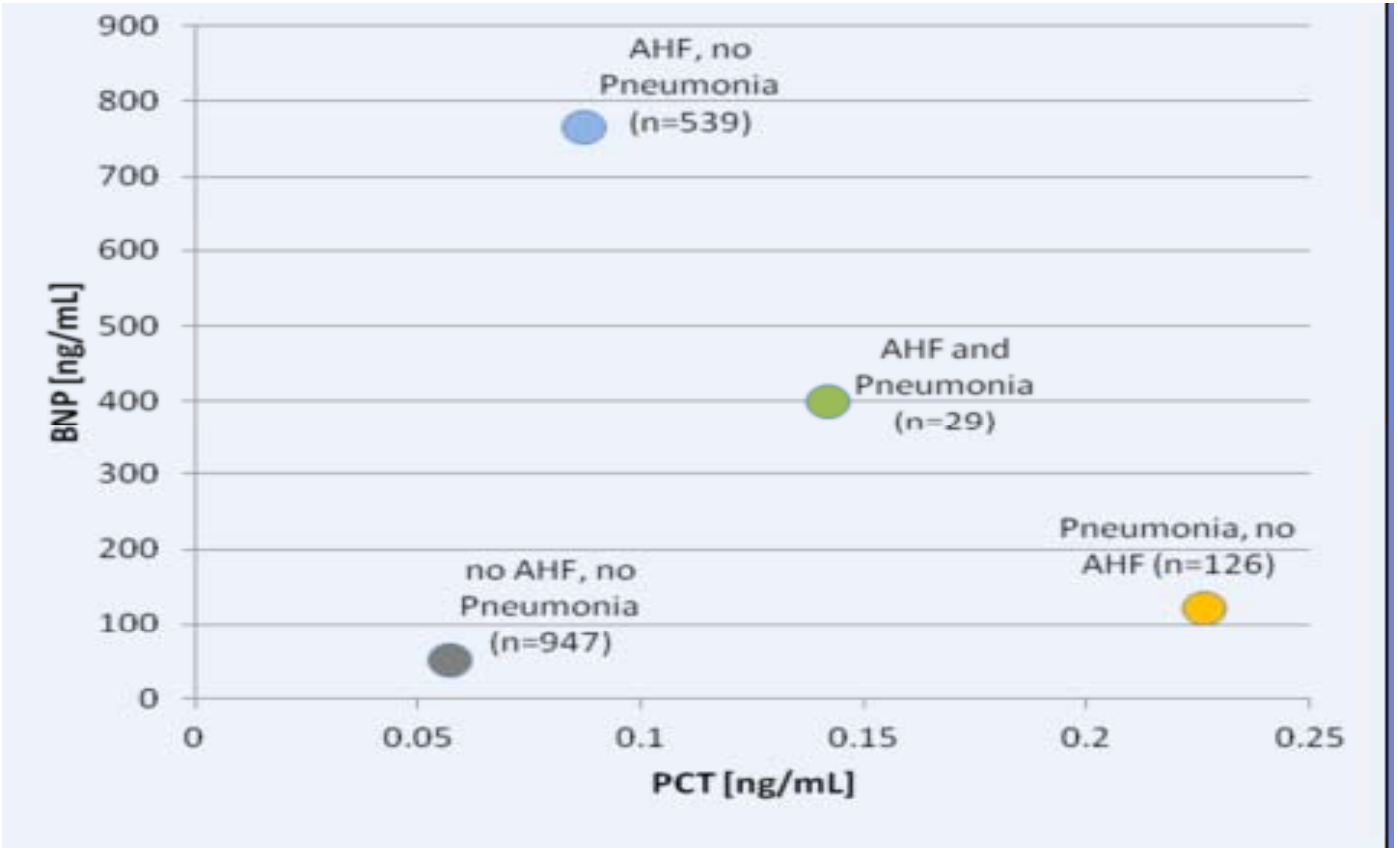
A combination of Natriuretic Peptide and PCT can be used to better diagnose dyspneic patients

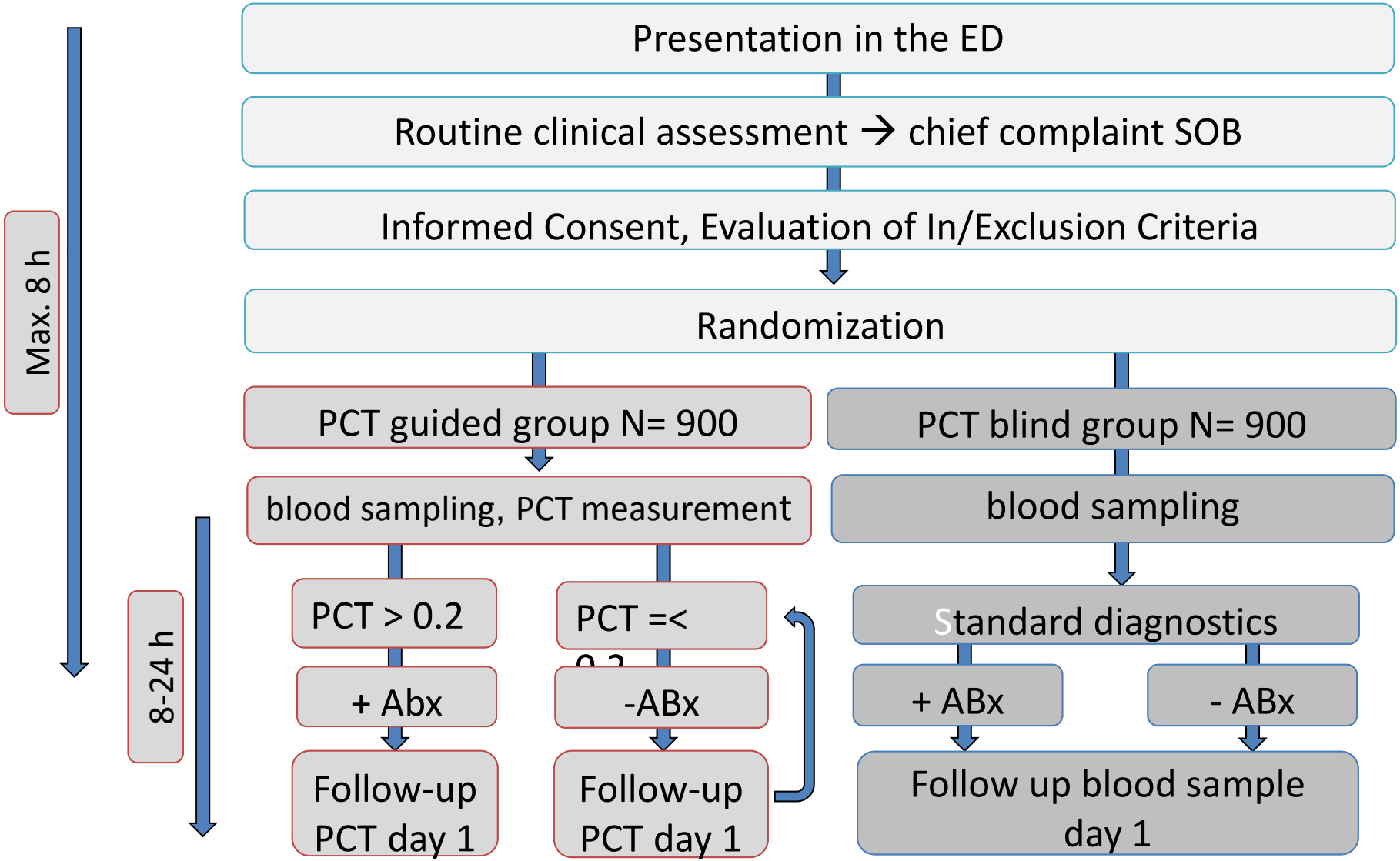


Maisel Eur J HF 2012

IMPACT

Improved Management of heart failure with ProcAlCiTonin

IMPACT-EU


Max. 8 h
8-24 h
Presentation in the ED
Routine clinical assessment → chief complaint SOB
Informed Consent, Evaluation of In/Exclusion Criteria
Randomization
PCT guided group N= 900
PCT blind group N= 900
blood sampling, PCT measurement
blood sampling
PCT > 0.2
PCT =<
+ Abx
-ABx
Follow-up PCT day 1
Follow-up PCT day 1
Standard diagnostics
+ ABx
- ABx
Follow up blood sample day 1

European Heart Journal

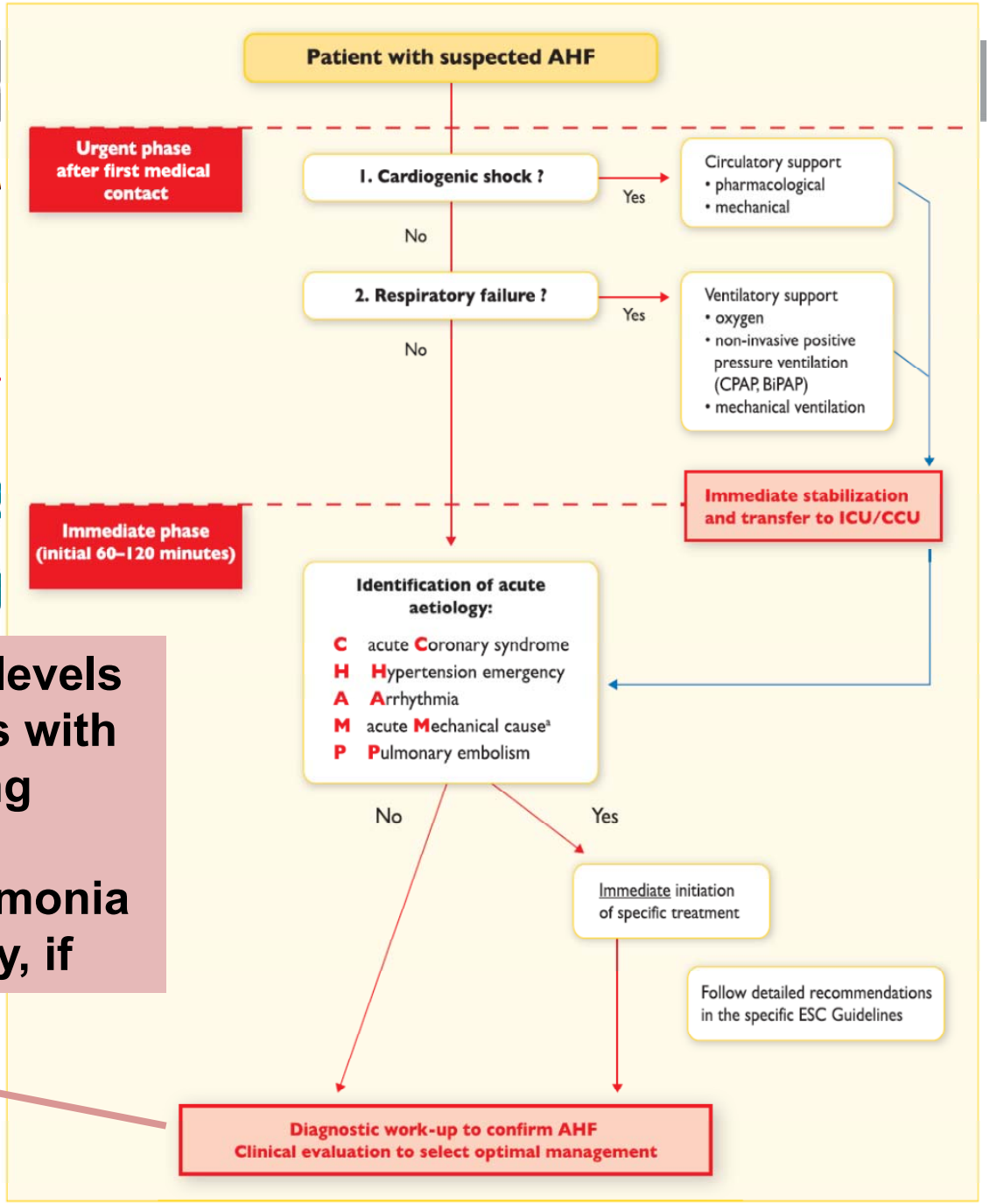
European Heart Journal
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines

treatment of acute a

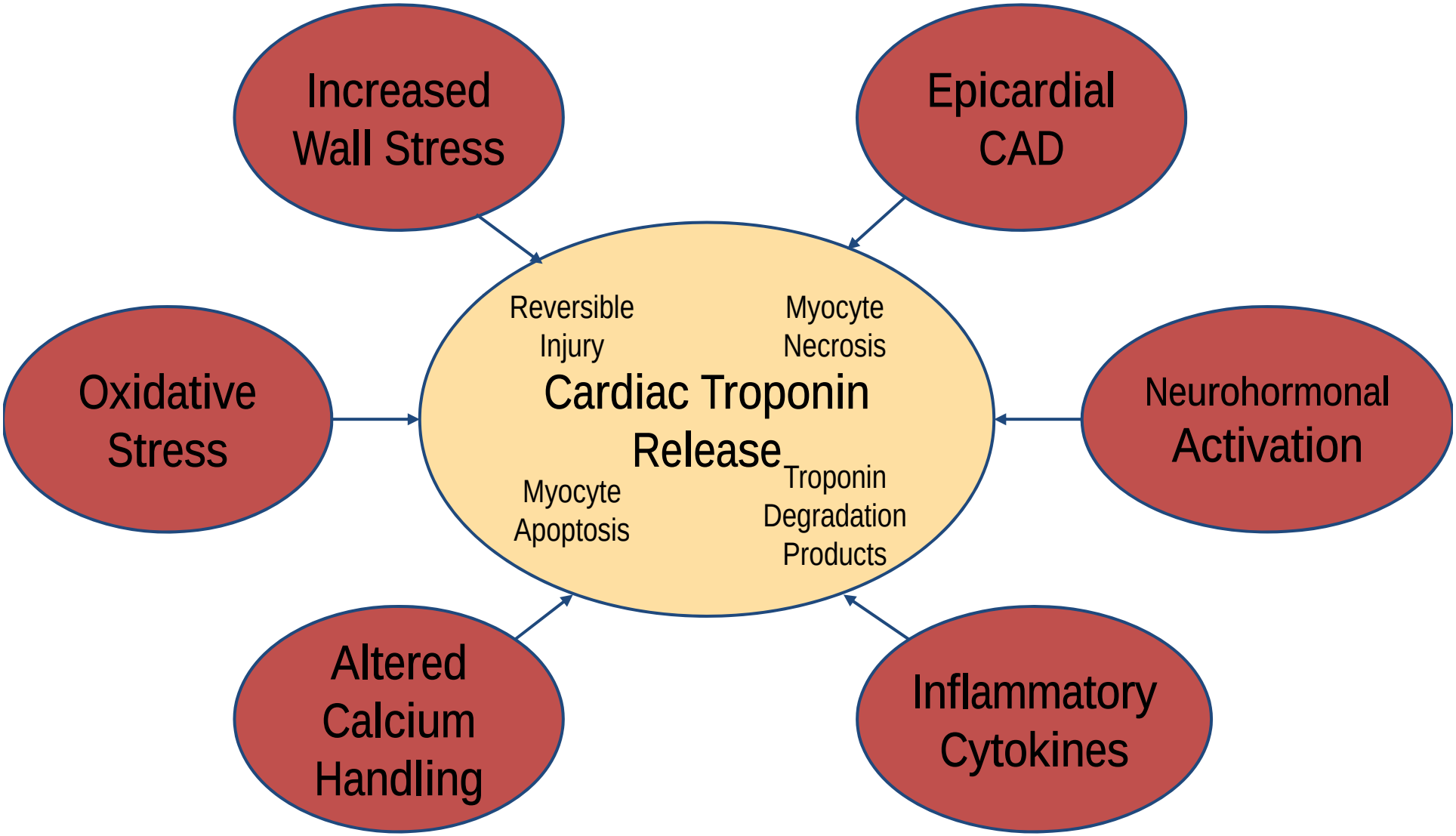
Assessment of procalcitonin levels may be considered in patients with AHF with suspected coexisting infection, particu-larly for the differential diagnosis of pneumonia and to guide antibiotic therapy, if considered. (IIb, B)

European Heart Journal
doi:10.1093/eurheartj/ehw128



Cardiac Troponins

Overview and Mechanism of Troponin Release



Choose: 1 or 2?

When faced with an AHF patient with a ‘positive’ troponin, the ER will….

Choose: 1 or 2?

When faced with an AHF patient with a ‘positive’ troponin, the ER will….

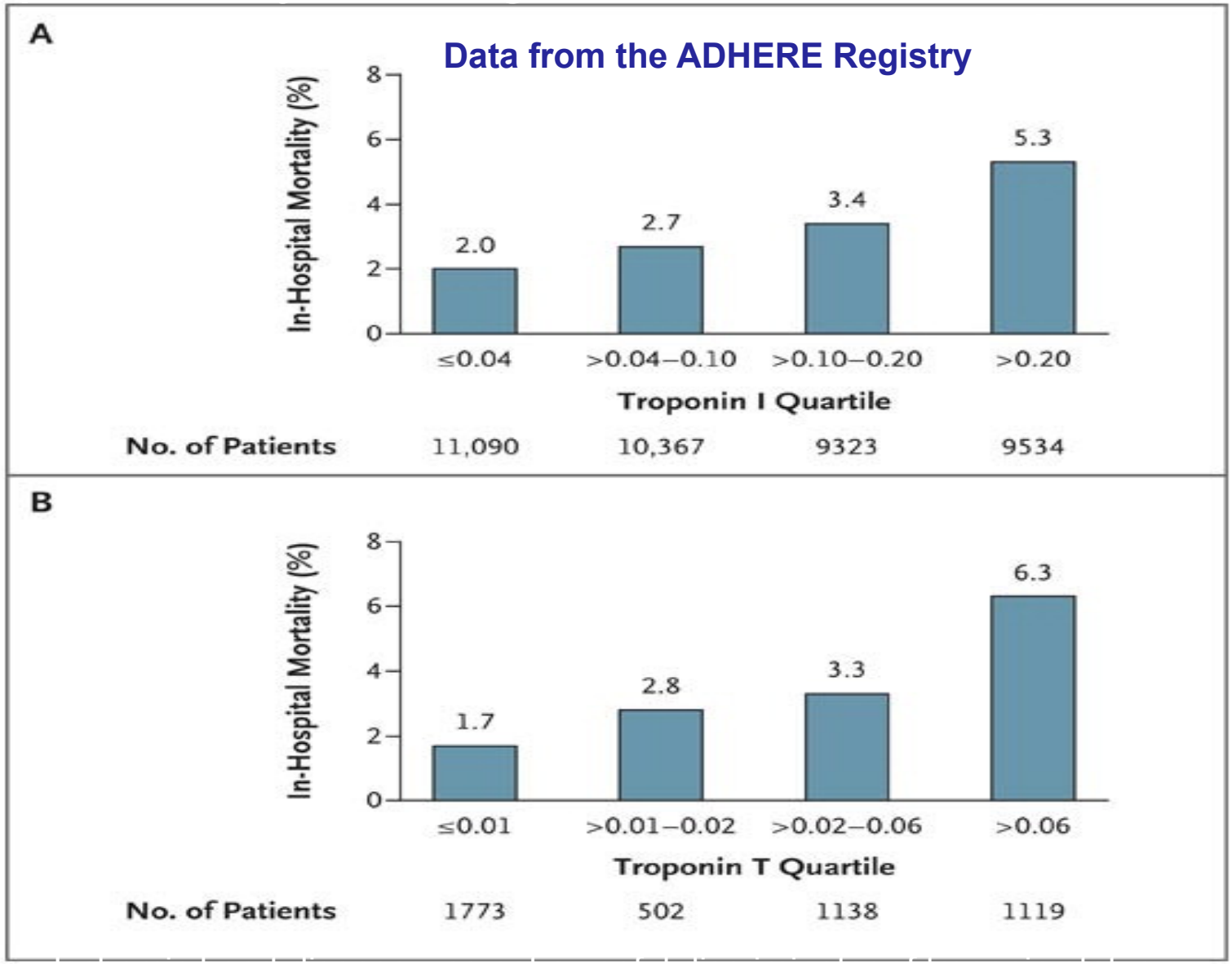
1. Carefully consider the clinical context, review all past records, discuss with the cardiologist or primary care physician of record and in consideration of the patients other co-morbid conditions, determine whether admission or discharge with early follow up is best.

Choose: 1 or 2?

When faced with an AHF patient with a ‘positive’ troponin, the ER will….

1. Carefully consider the clinical context, review all past records, discuss with the cardiologist or primary care physician of record and in consideration of the patients other co-morbid conditions, determine whether admission or discharge with early follow up is best.
2. Admit the patient

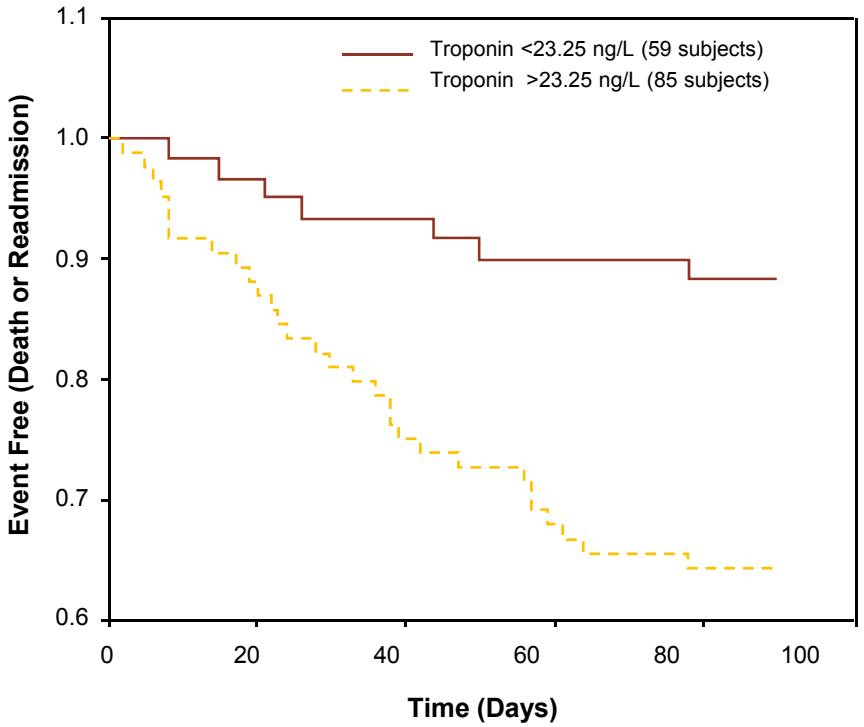
Data from the ADHERE Registry



Cardiac Troponins

Role in Prognosis

90-day Mortality and HF-related Readmissions by Discharge Troponin I Levels[2]

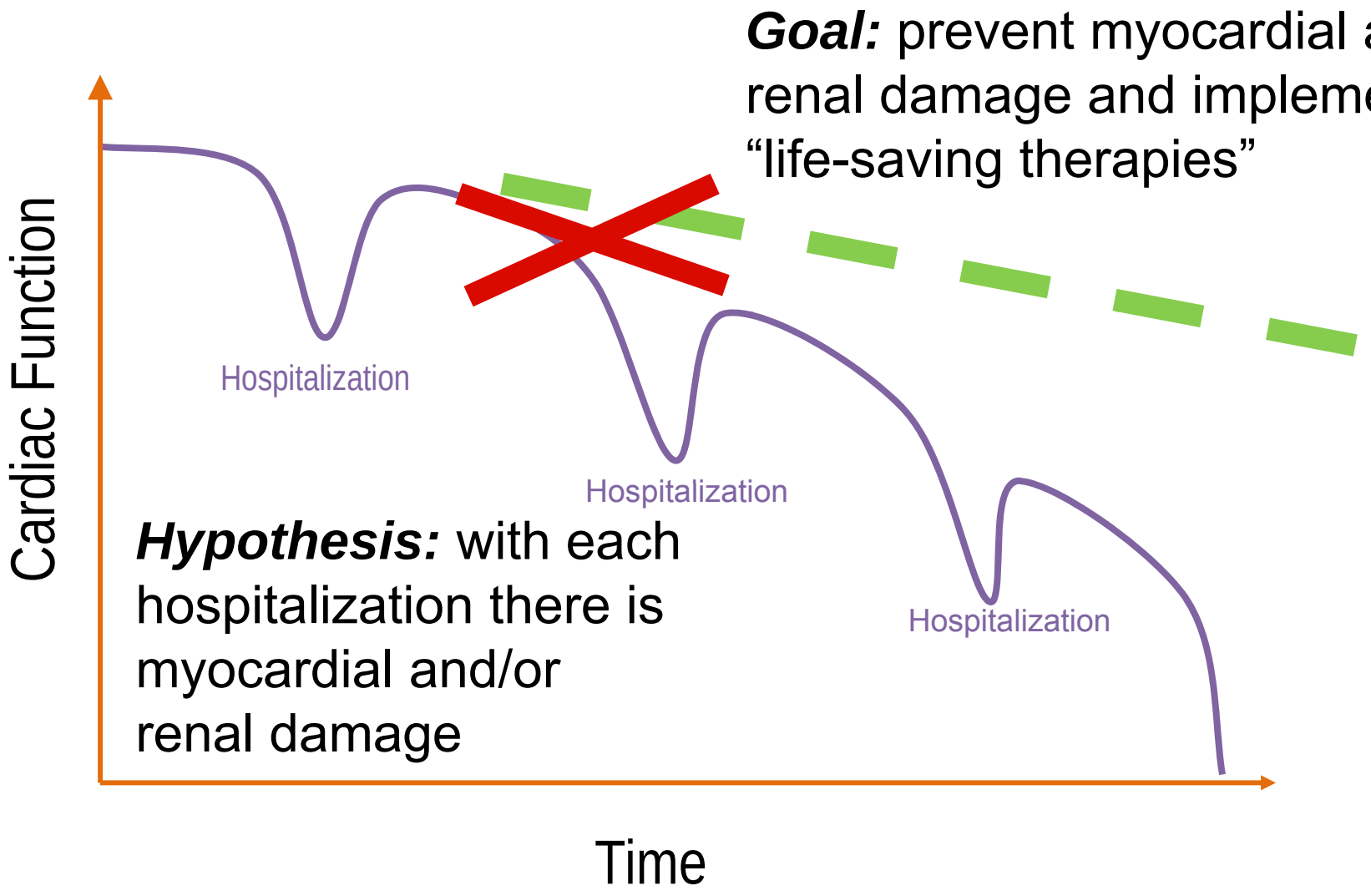


Patients with a discharge TnI >23.25 ng/L had significantly higher 90-day mortality and HF-related readmissions than patients with a discharge TnI <23.25 ng/L (*P*=0.003, HR, 3.547)[2]

ACS, acute coronary syndrome; AHF, acute heart failure; CHF, chronic heart failure; HR, hazard ratio; hs-cTnT, high-sensitive cardiac troponin T; TnI, troponin I.

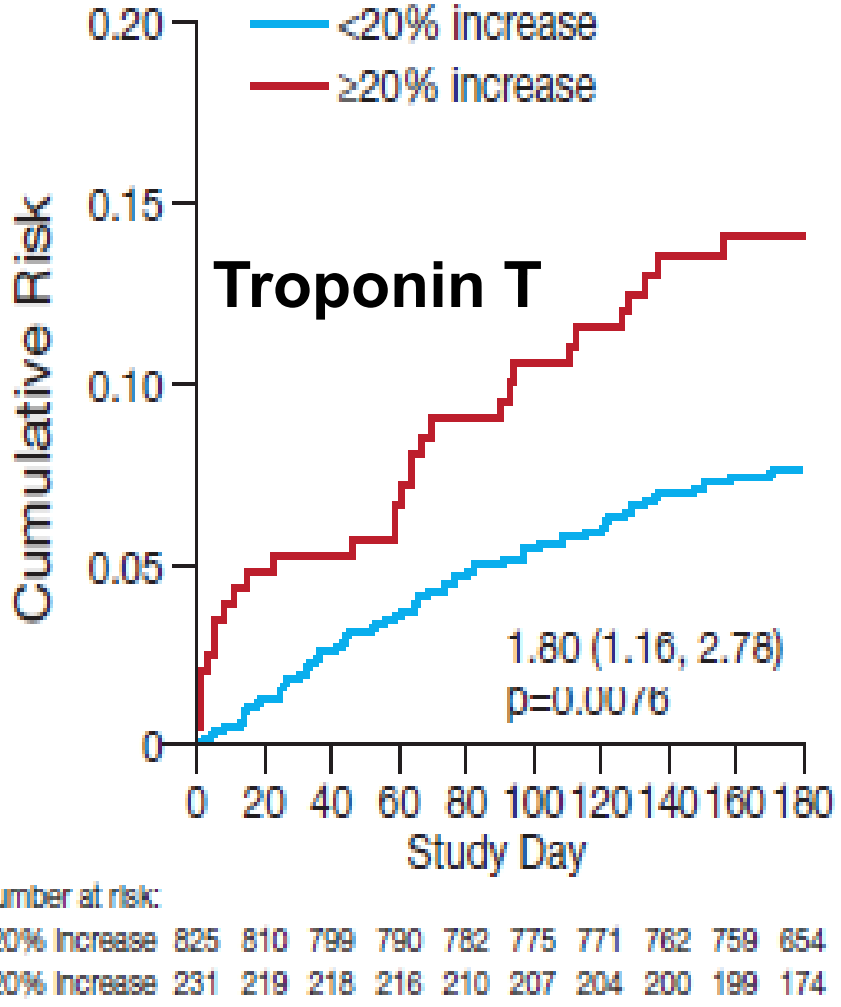
1. Maisel. et al. *Circulation.* 2007;116(5):e99-109.
2. .

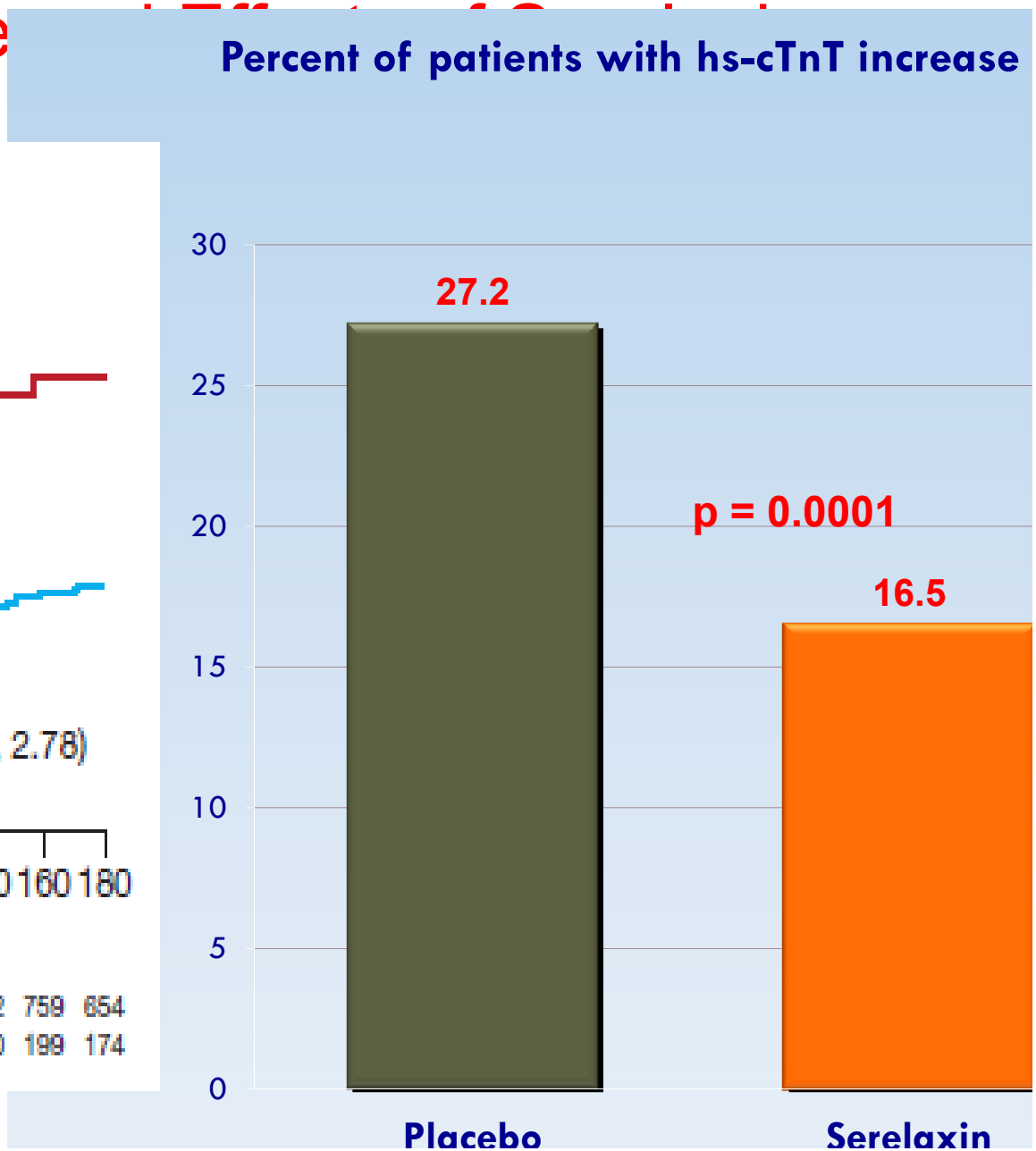
AHF Contributes to the Progression of HF



Gheorghiade et al. Am J Cardiol 2005;96(6A):11G–17G

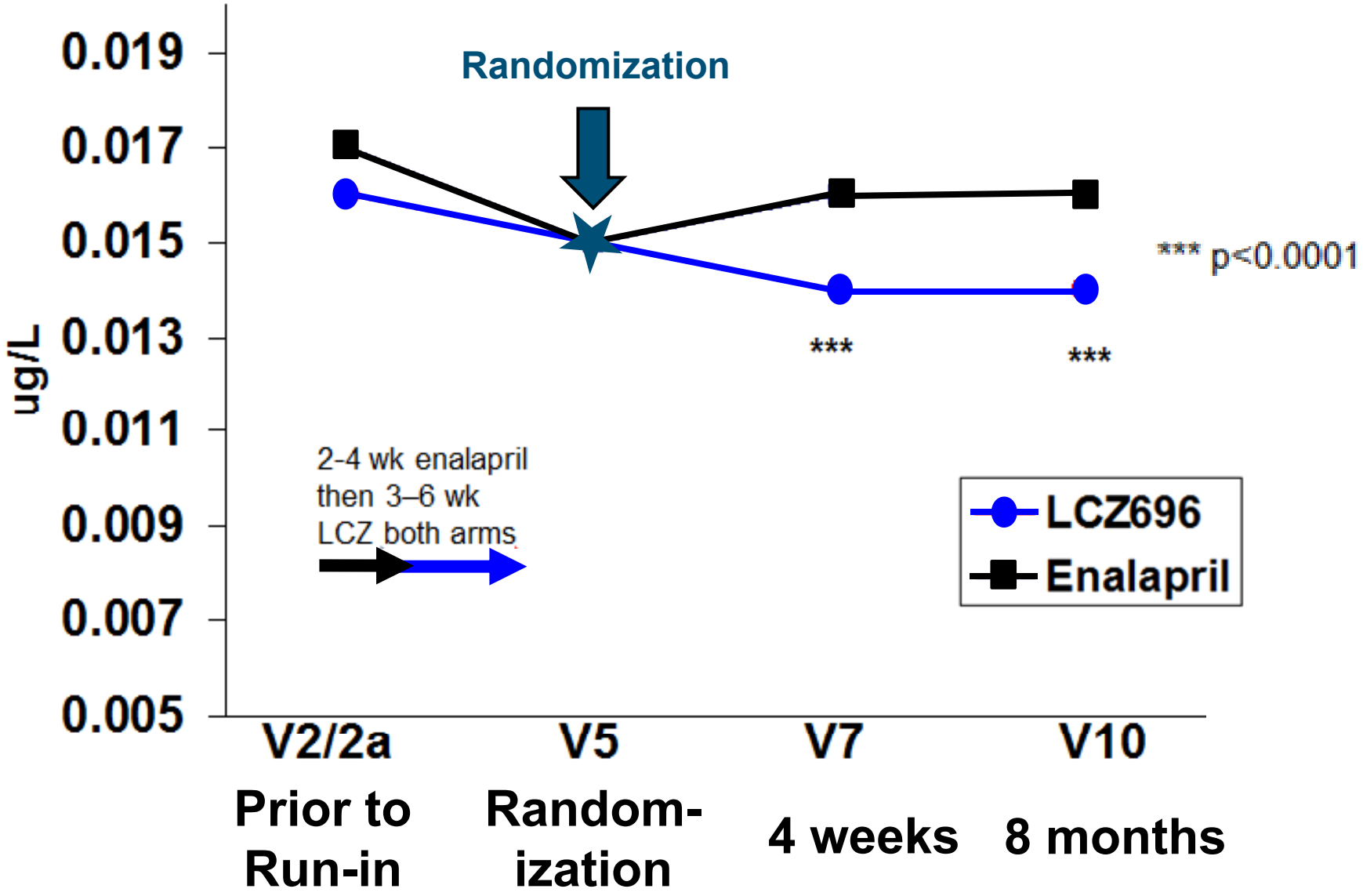
Prognostic Value of a ≥20% hs-cTnT Increase From Baseline





Metra et al. JACC 2013

PARADIGM-HF: median hs-TnT (µg/l) concentration by visit



Recommendations for using troponin in Acute Heart Failure

Clinical update

Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: *Heart Failure Section*

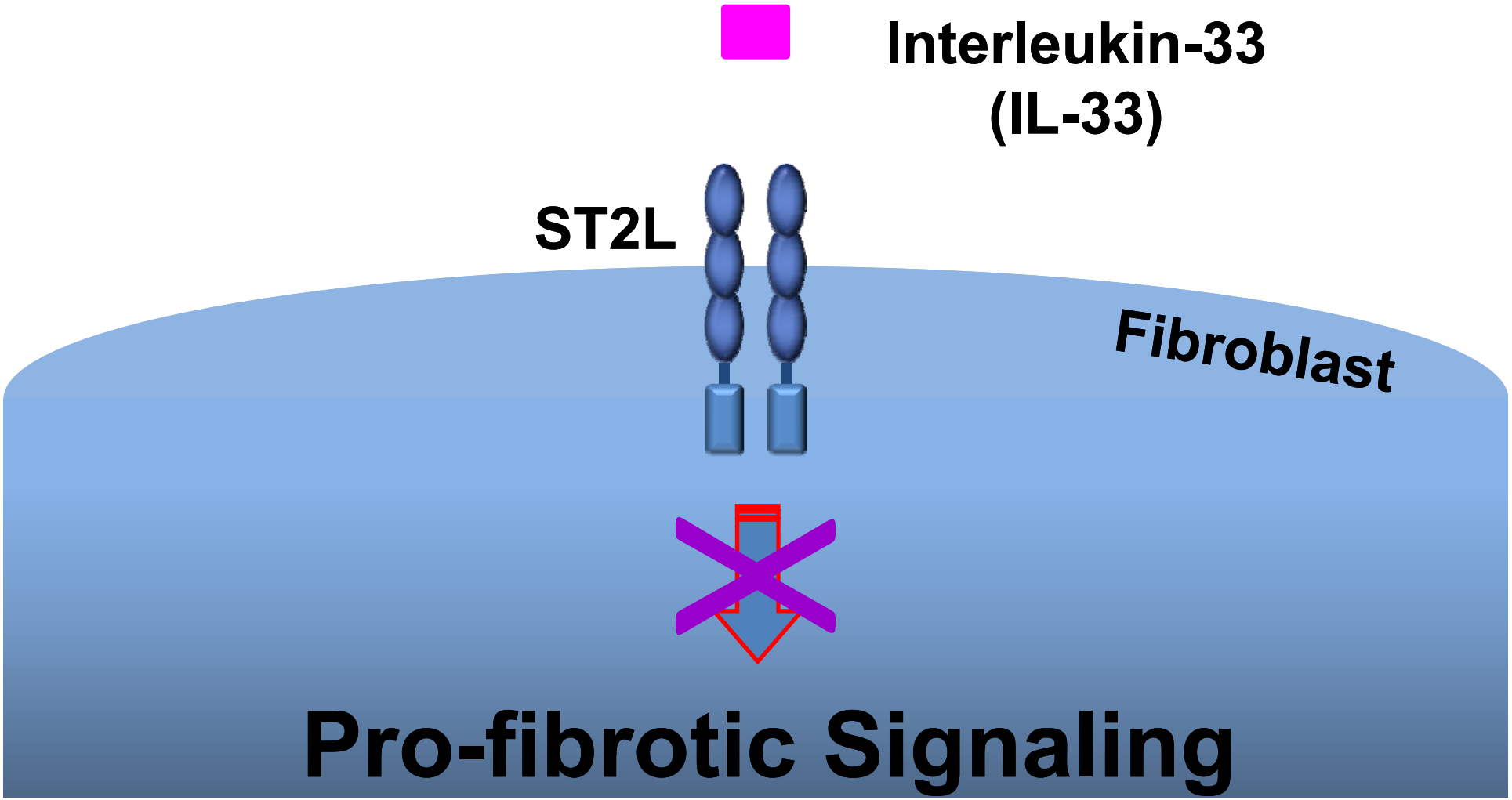
James L. Januzzi Jr[1]*, Gerasimos Filippatos[2], Markku Nieminen[3] and Mihai Gheorghiade[4]

- Exclude type I MI (ACS)
  - Rising/falling pattern
  - Signs/symptoms of ischemia
  - Imaging evidence
- May rise and fall even without MI
  - ADHF→ rise; treatment of HF → fall
- Tn >99th percentile → worse outcome
  - Regardless of type I MI/ACS

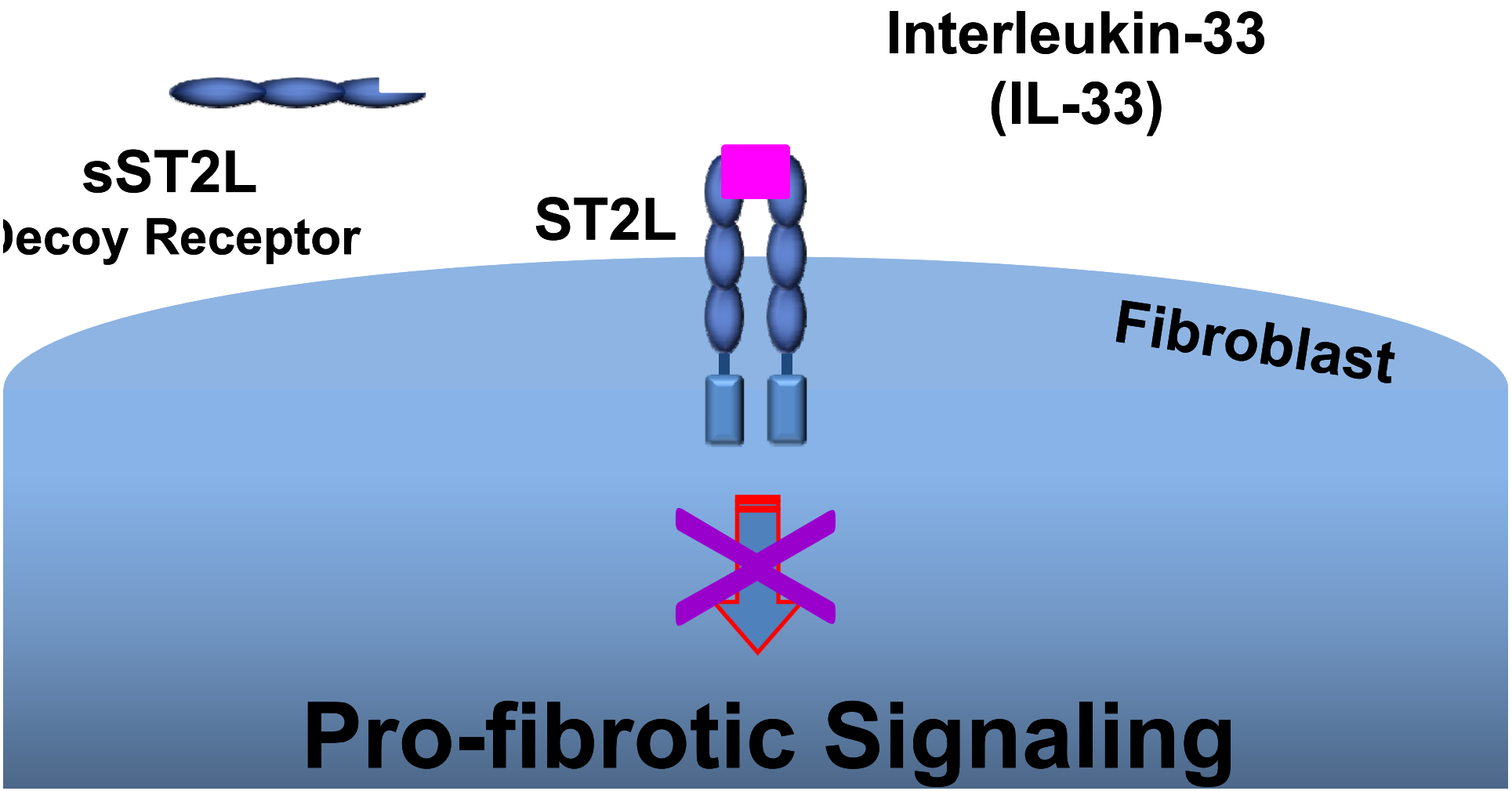
sST2- has evolved to be a useful marker

Soluble ST – 2

ST-2: Suppressor of tumorigenicity 2 (IL-1 receptor-like-1)
Member of Interleukin-1 receptor family
***ST2* gene encodes isoforms by alternative promotor splicing**
membrane bound receptor: ST-2L (Profibrotic signaling)
soluble truncated form: sST-2 (Decoy receptor)
IL-33: Interleukin 33, Binds to ST-2L & Inhibits Profibrotic signaling



↑ sST-2 binds IL-33 &
↓ inhibition of ST-2L profibrotic signaling
↑ Fibrosis



Biological Variation Summary

Marker	Duration	CV_I	RCV
CK	2 mths	30%	82%
BNP	2 mths	50%	138%
NT-proBNP	2 mths	33%	92%
hs-cTnI	2 mths	14%	63%
hs-cTnI	9 mths	28%	73%
hs-cTnT	1 mths	31%	87%
Gal-3	2 mths	20%	61%
sST2	1.5 mths	10.5%	30%
sST2	2 mths	11%	30%

- **sST2 has the lowest intra-individual variation and smallest relative change value compared to other biomarkers**

Wu, 2013, accepted Am. Heart J.

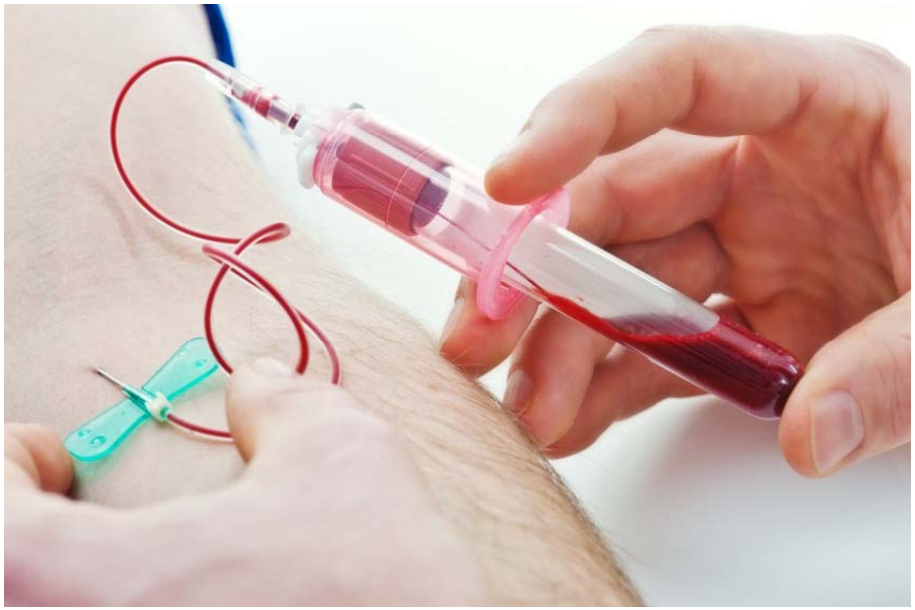
Reference Analysis and Cut-point Selection

Level	Primary Reference Cohort	Confirmation Reference Cohort
Mean (SD)	20.9 (9.3)	22.4 (8.7)
Min	1.8	3.2
25th percentile	14.5	16.7
50th percentile (median)	18.8	20.9
75th percentile	25.2	26.1
90th percentile	34.2	32.9
95th percentile*	**37.9**	**37.3**
99th percentile	49.7	51.0
Max	66.3	119.6
N	490	3,450

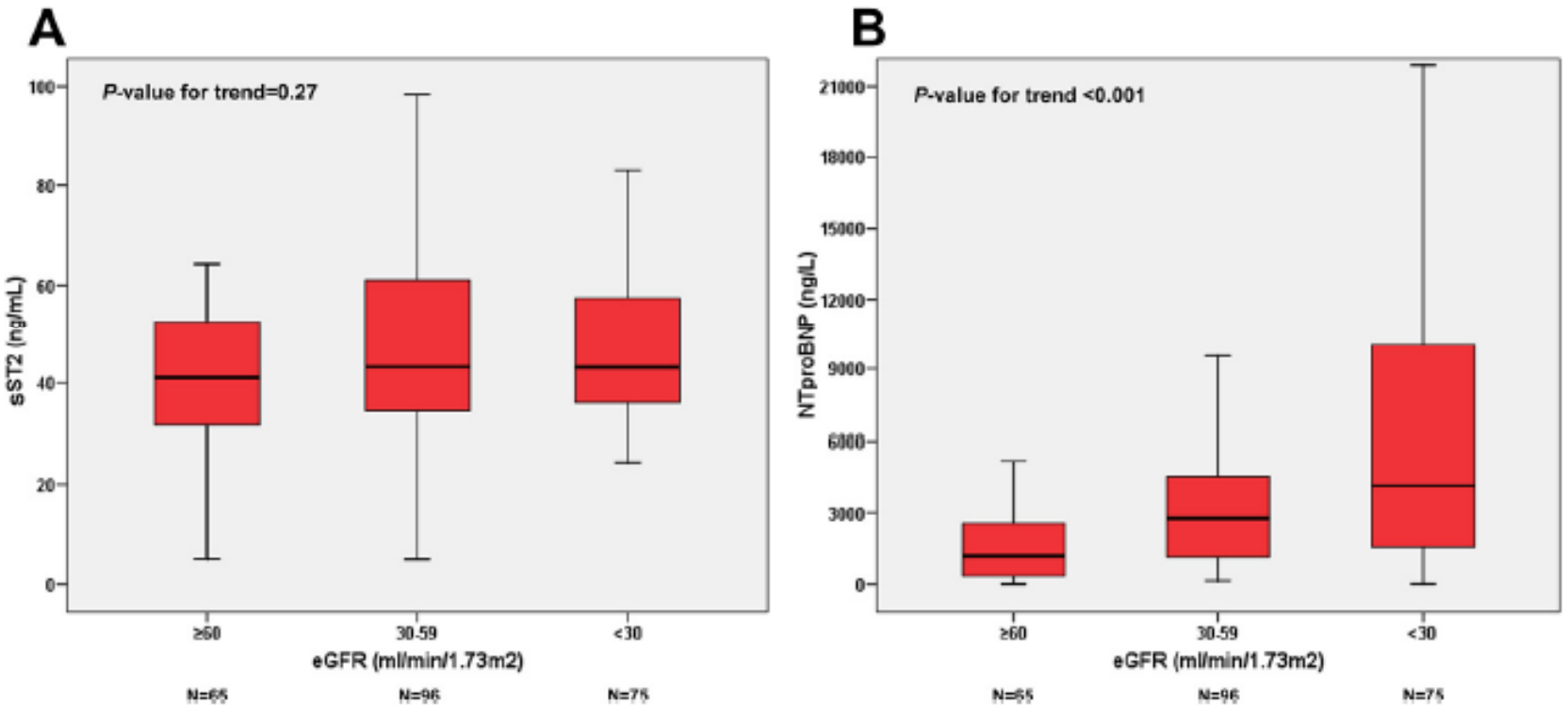
Single ST2 Cut-point:

ST2 not effected by

- Age
- Sex
- BMI
- Etiology of HF
- Atrial Fibrillation
- Anemia



ST2 Not Correlated with Renal Function



In a cohort of 879 heart failure patients ST2 did not show any correlation with renal function whereas NT-proBNP concentrations increased significantly with decreasing renal function.

Bayes-Genis et al. 2013 JCF

ST2 in Acute Heart Failure

sST2 is NOT a diagnostic marker of AHF

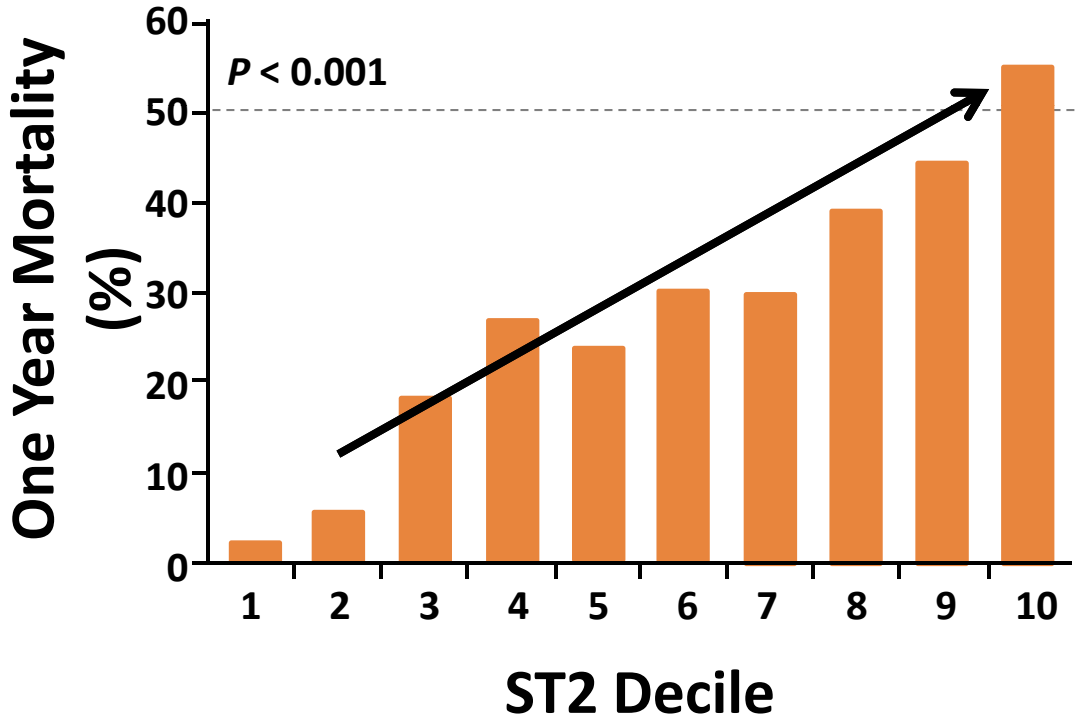
- Severe sepsis
- Inflammatory disease
- Disseminated cancer
- Liver or other organ fibrosis

- It is elevated in almost everyone with AHF
- It is very prognostic in AHF
  - Short-term
  - Long-term
- Risk can be mitigated by lowering level

sST2 the ultimate death marker?

Mortality Risk Increases With ST2 Levels

One-year mortality exceeded 50% in the highest decile.



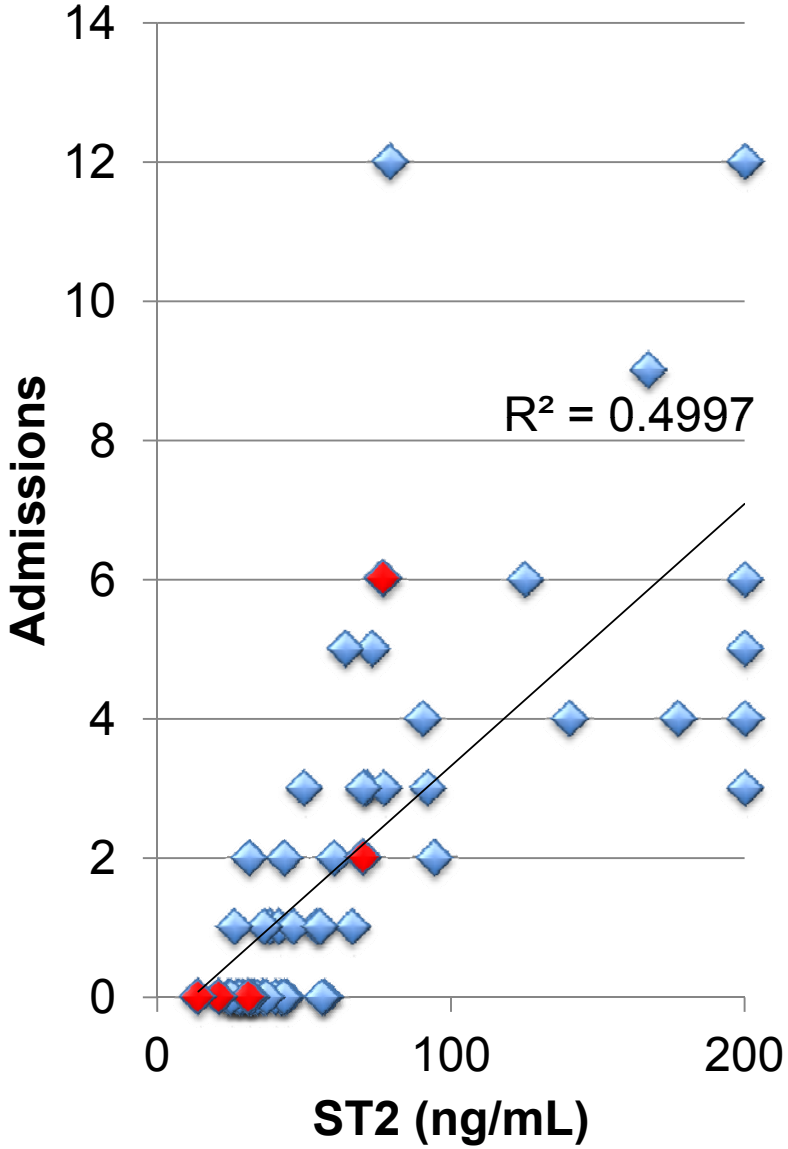
Rehman SU, Mueller T, Januzzi JL et al. *J Am Coll Cardiol*. 2008;52:1458-65.

How I got ST2 into my hospital

Measured levels of ST2 and BNP on consecutive admissions for AHF

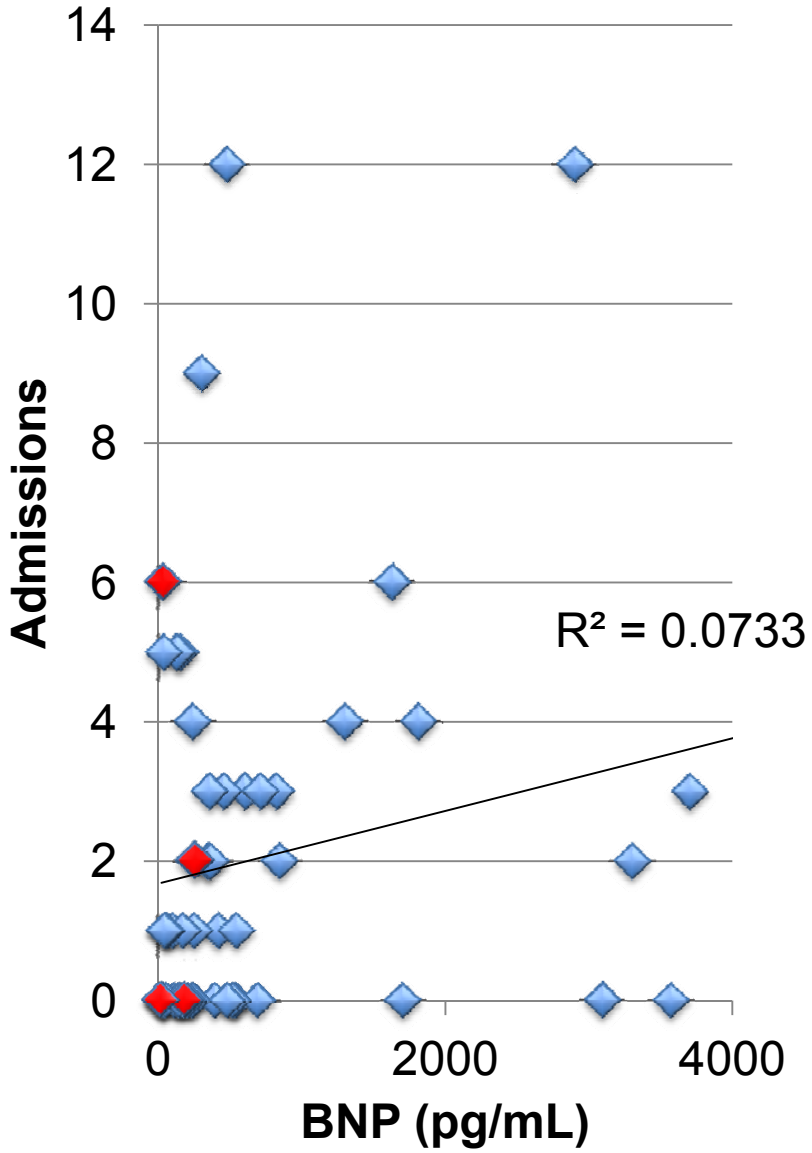
- Looked at admissions in previous 3 months
- Looked at admissions in the 3 months following discharge
- Related ST2 and BNP levels to total number of admissions
- ROC curve analysis to predict probability of other admissions when they come to hospital (ie readmission risk)

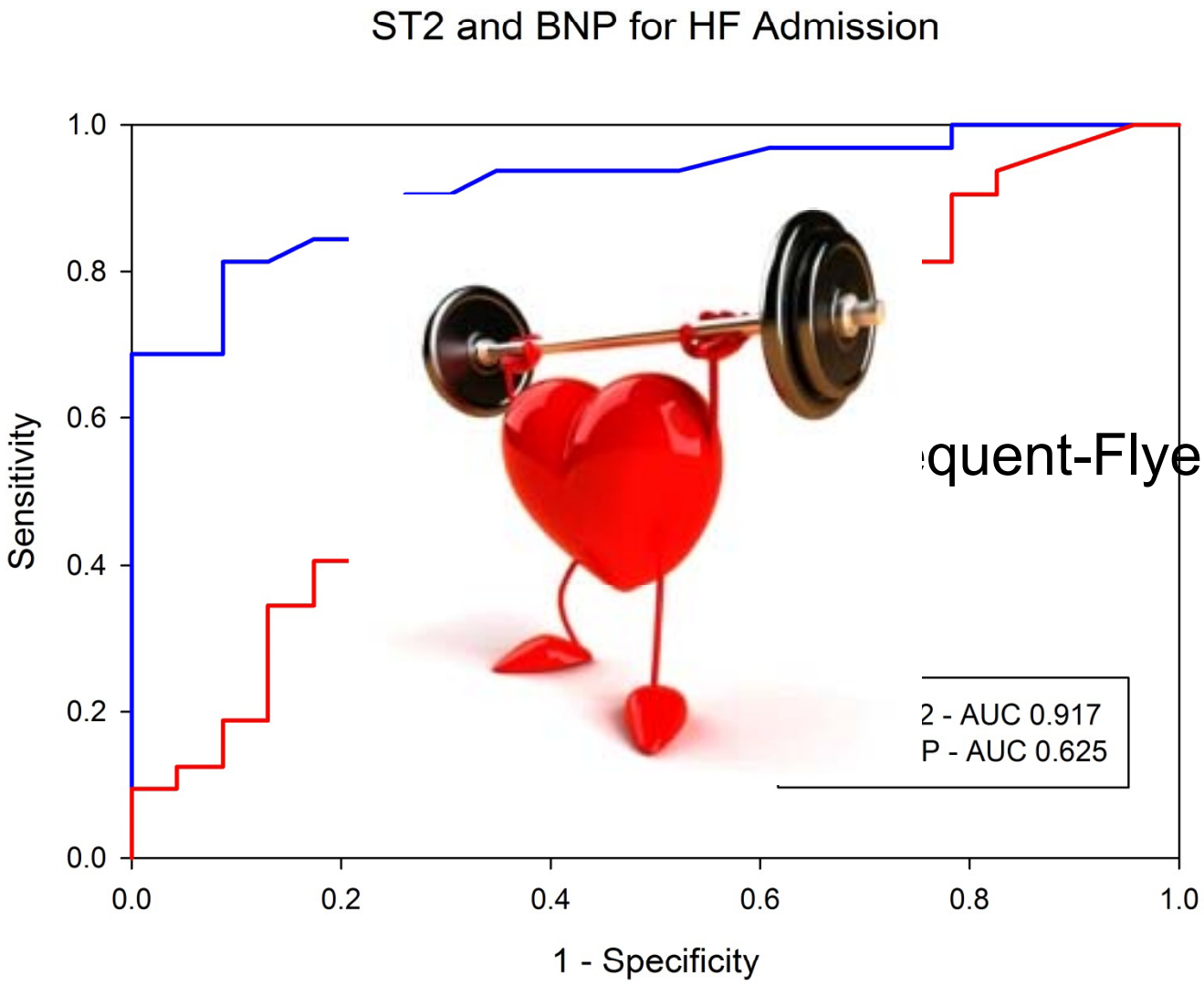
ST2 and Admissions Over 6 Months



Wetterson, Maisel AJM-2016

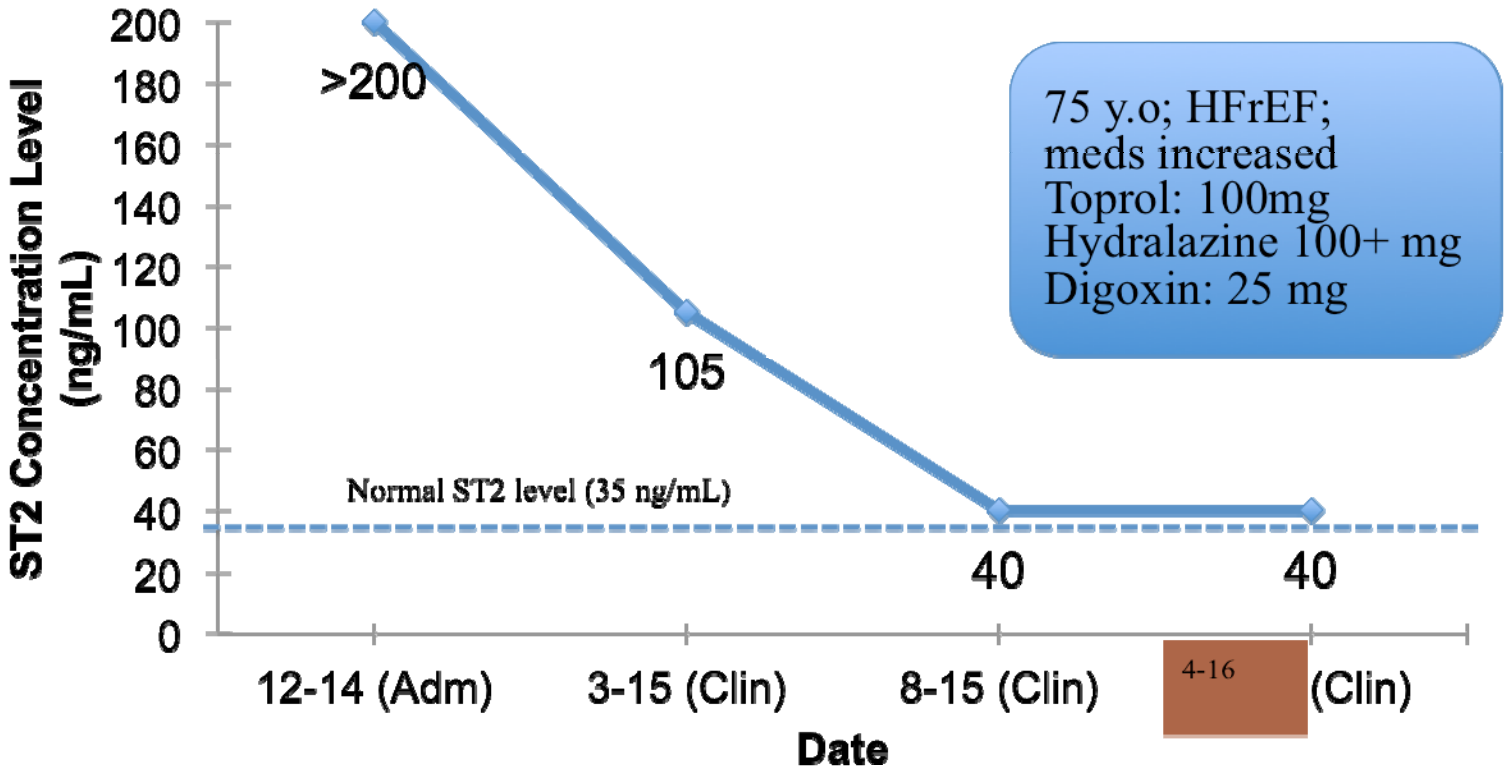
BNP and Admissions Over 6 Months





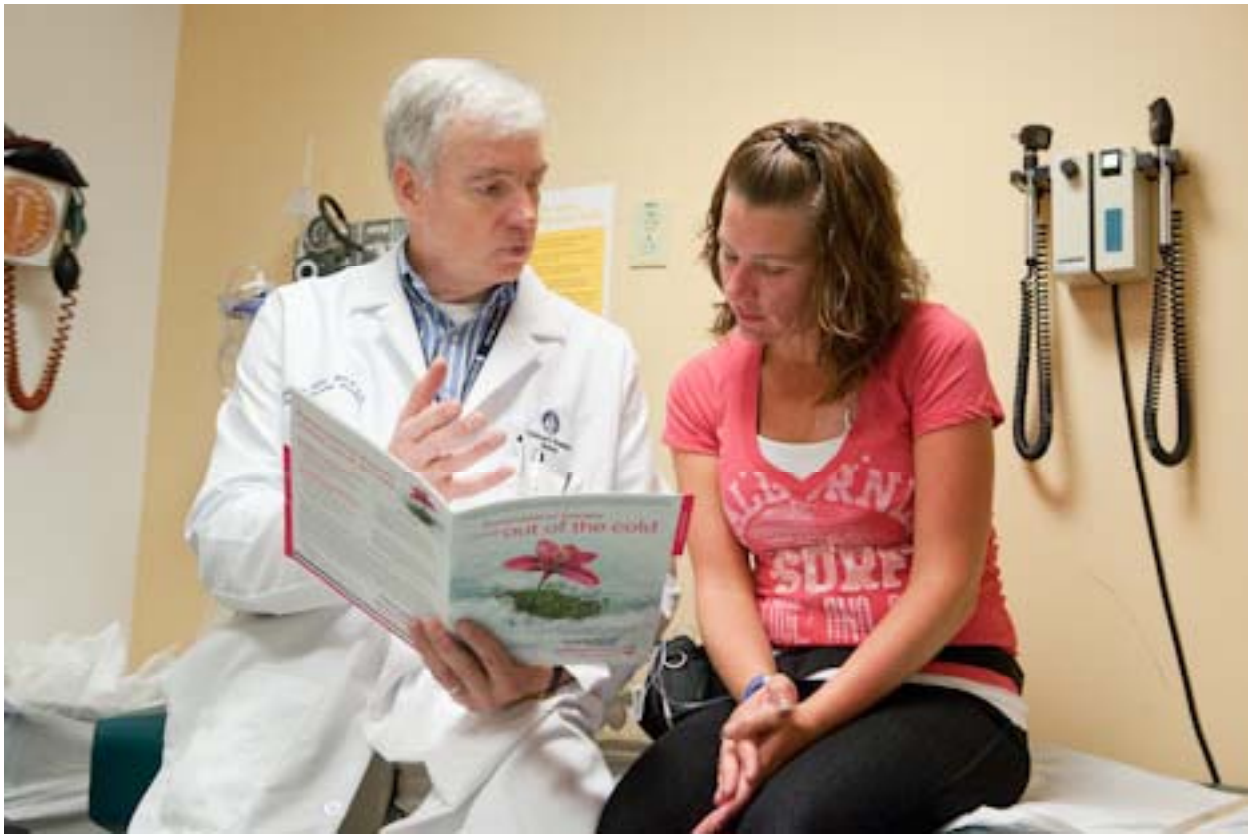
quent-Flyer Index

Patient: H.V.

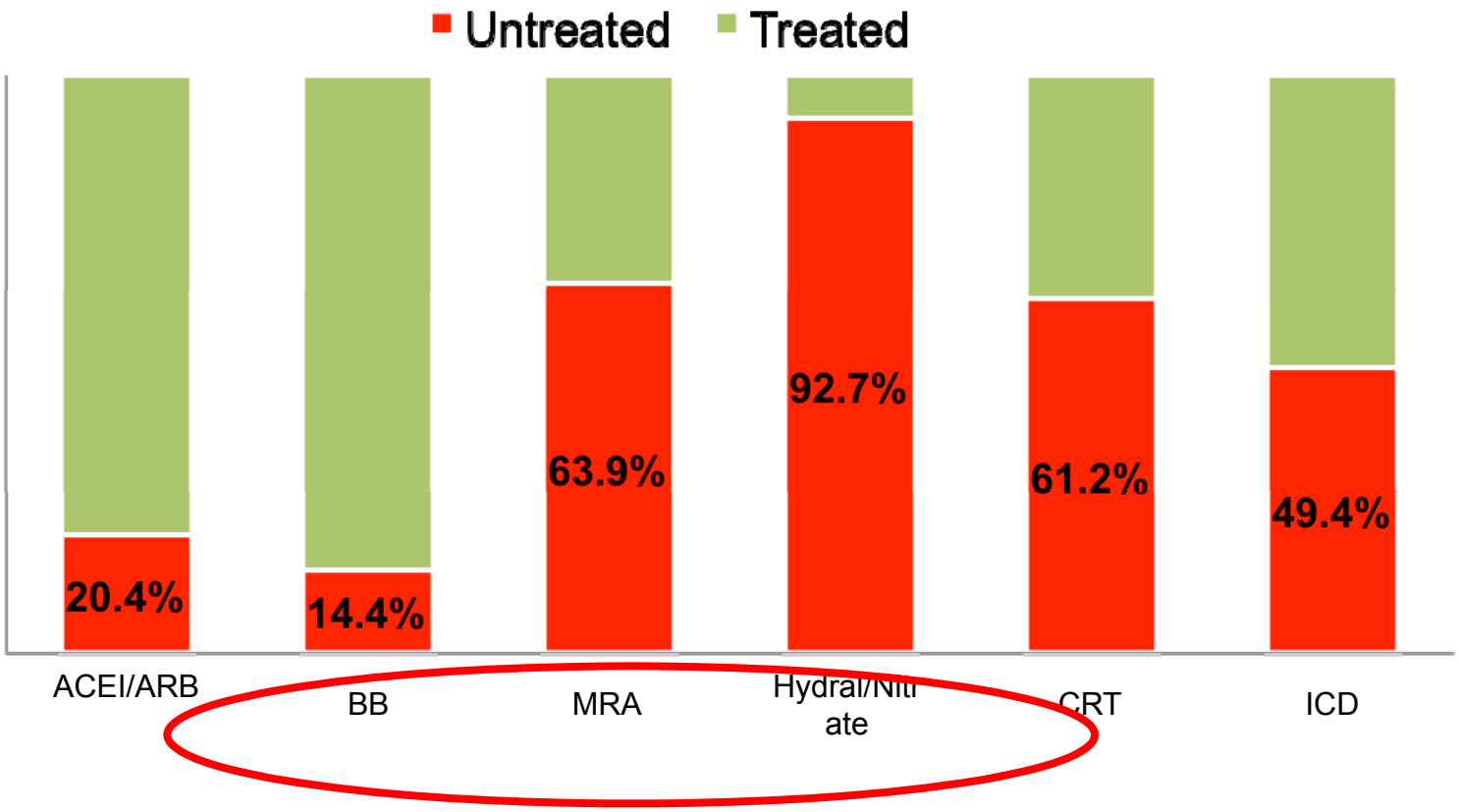


No readmissions over **One Year**

ST2 in Ambulatory Heart Failure



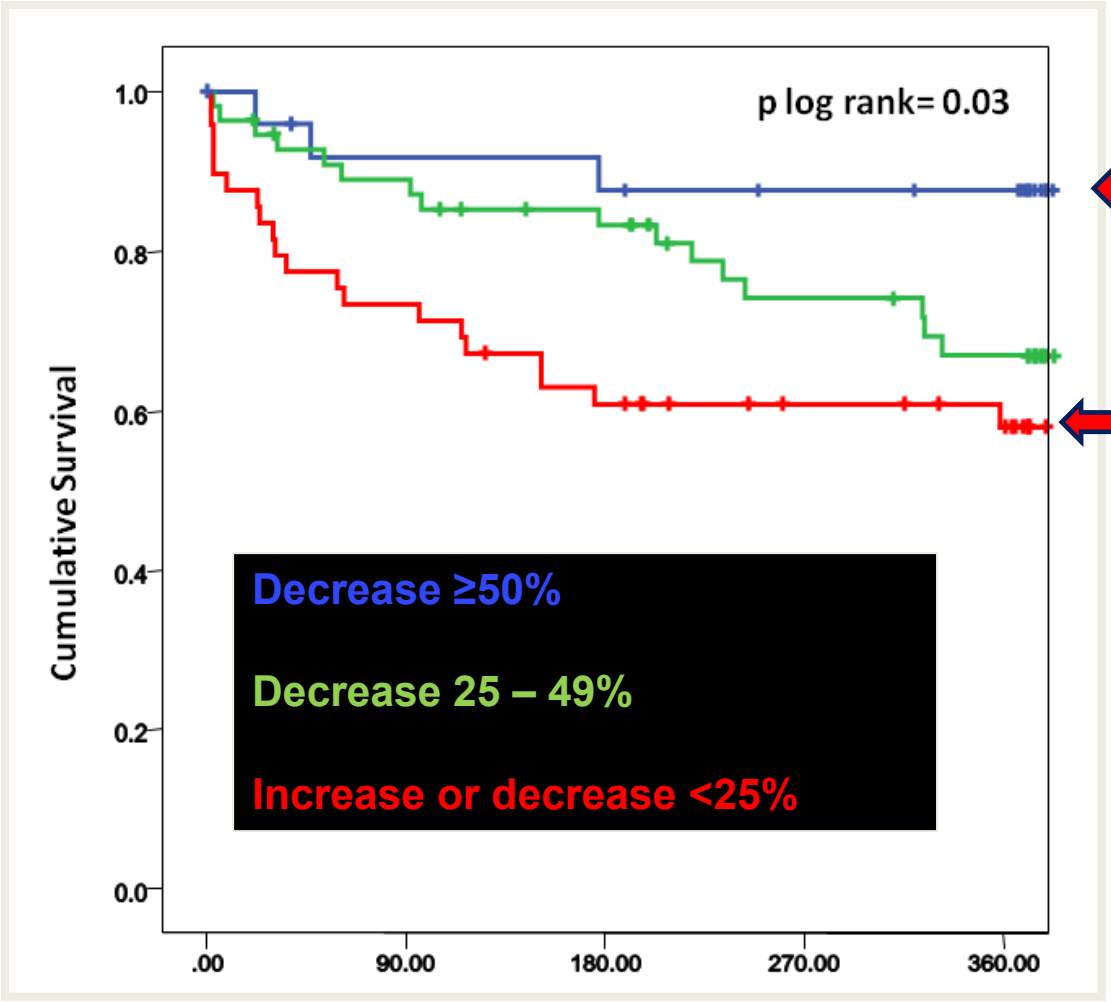
A Large Number of Eligible Patients are Untreated



Number of Eligible Patients	2,459,644	2,512,560	603,014	150,754	326,151	1,725,732

Fonarow et al. Am Heart J 2011

Serial ST2 Measurements Categorize Responder Status



ST2 "Responders"

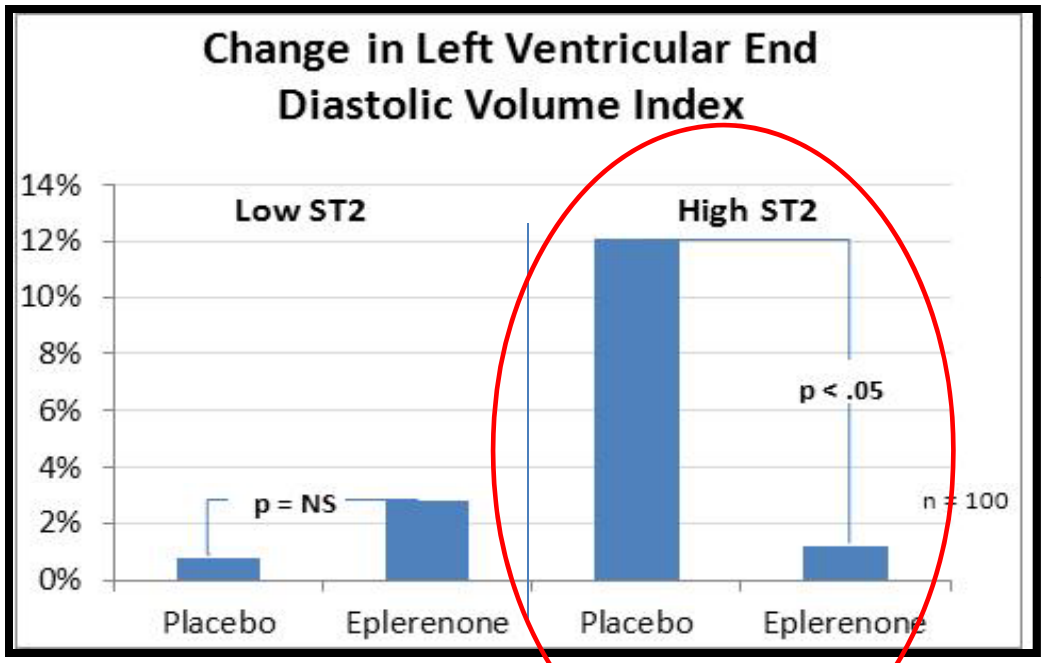
ST2 "Non-Responders"

Adjusted for ADHERE Risk Factors and BNP change.

Basel ADHF cohort

ST2 Predicts Response to Treatment: Aldosterone Blockade in STEMI

- Eplerenone prevents adverse ventricular remodeling
- ST2 predicts which pts are most at risk…
- AND which pts will benefit most from aldosterone blockade



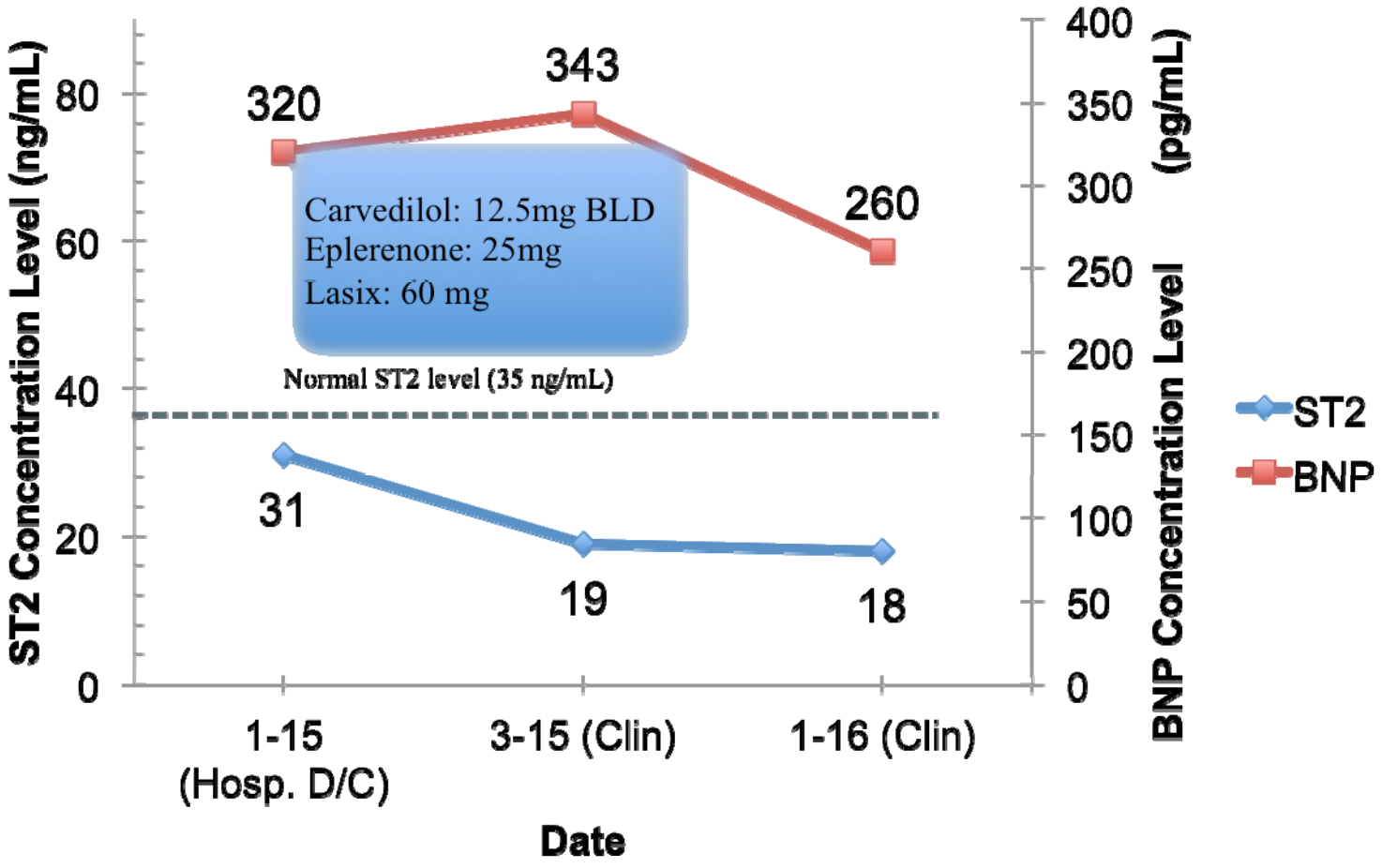
High and low ST2 separated at median.

→ Eplerenone attenuates remodeling more in pts with higher baseline ST2.

Weir AP, et al. J. Am. Coll. Cardiol. 2010;55;243-250.

ST2 Levels: Monitoring and Response to Treatment

Patient: K.E.

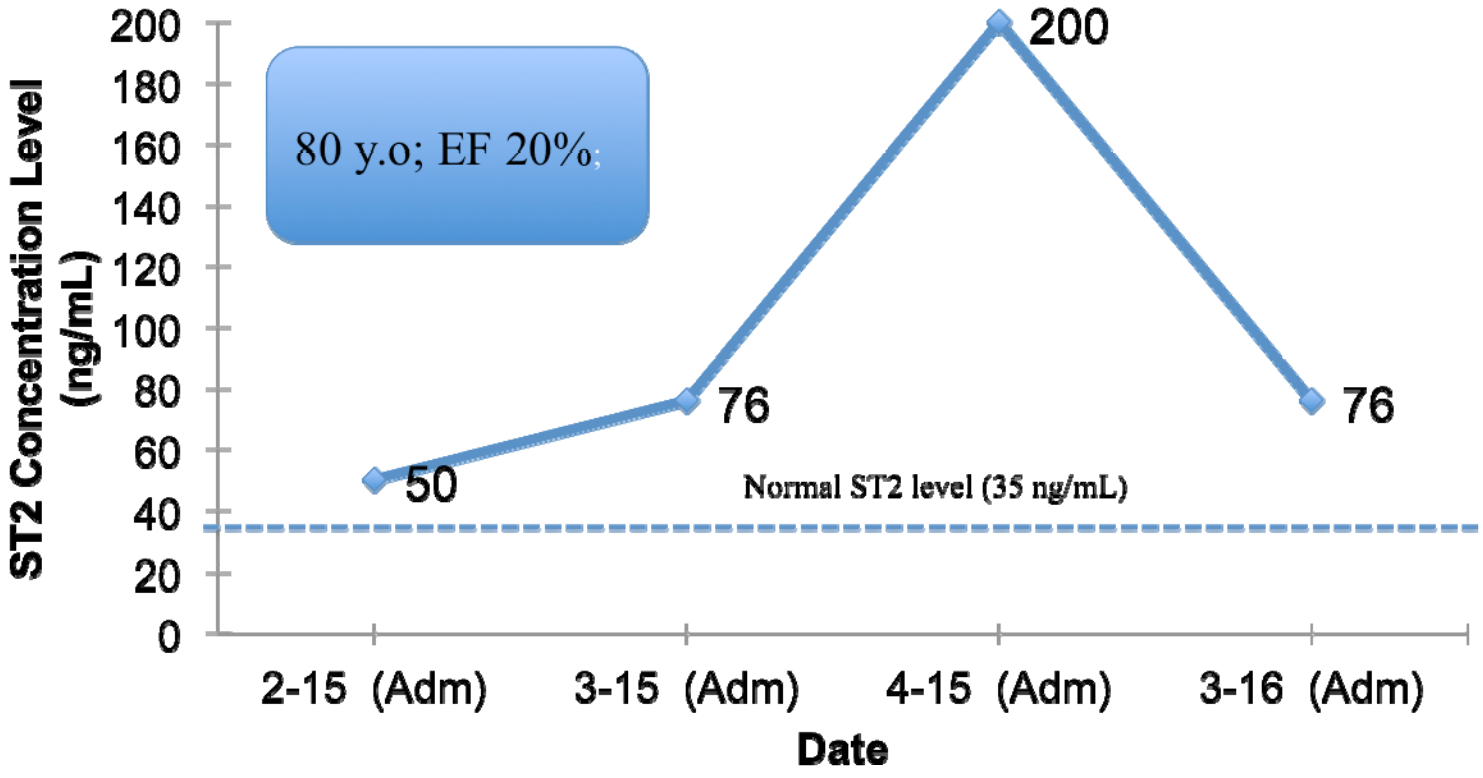


BNP still high but ST2 low-No readmissions in one year

ST-2 in the clinic

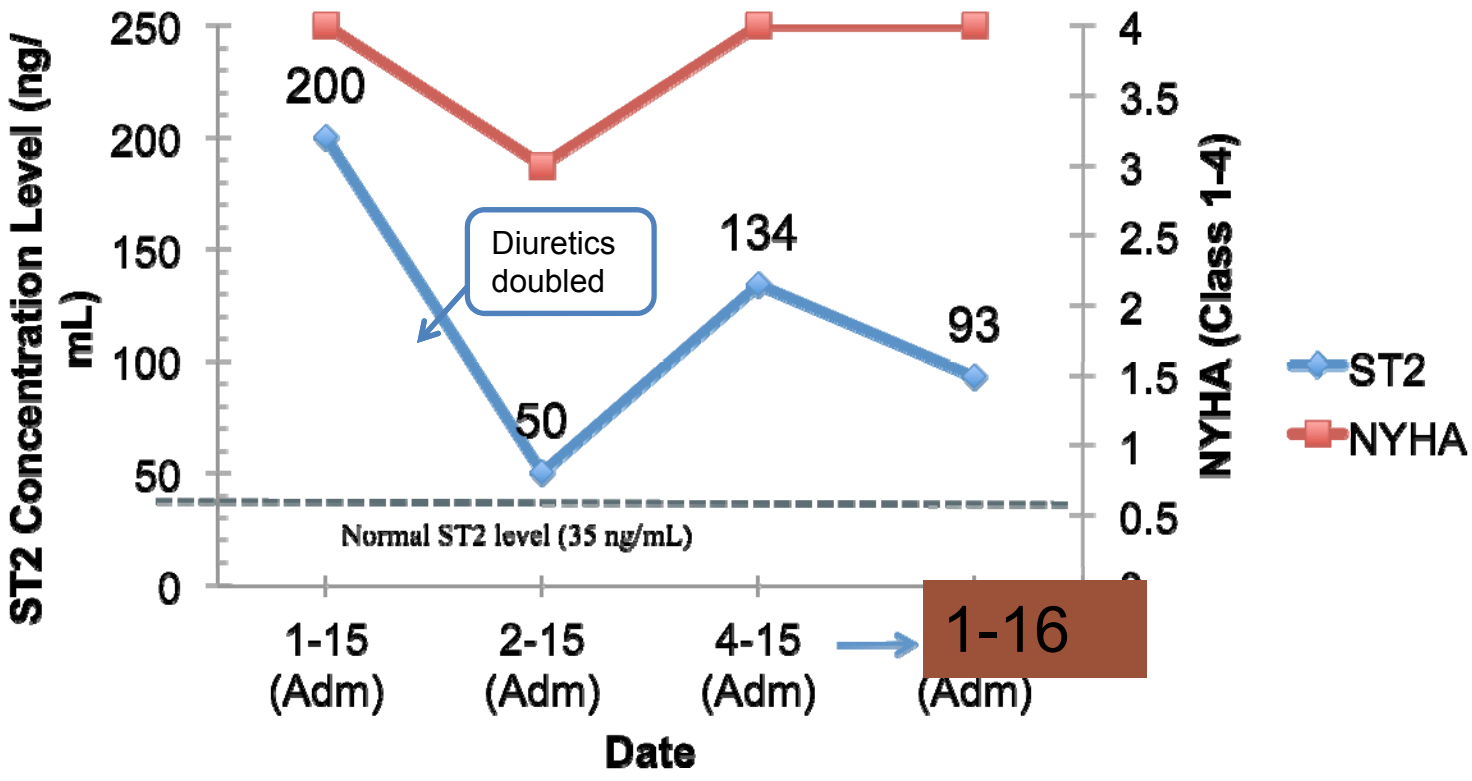
Non-responders are often sicker

Patient: H.H.



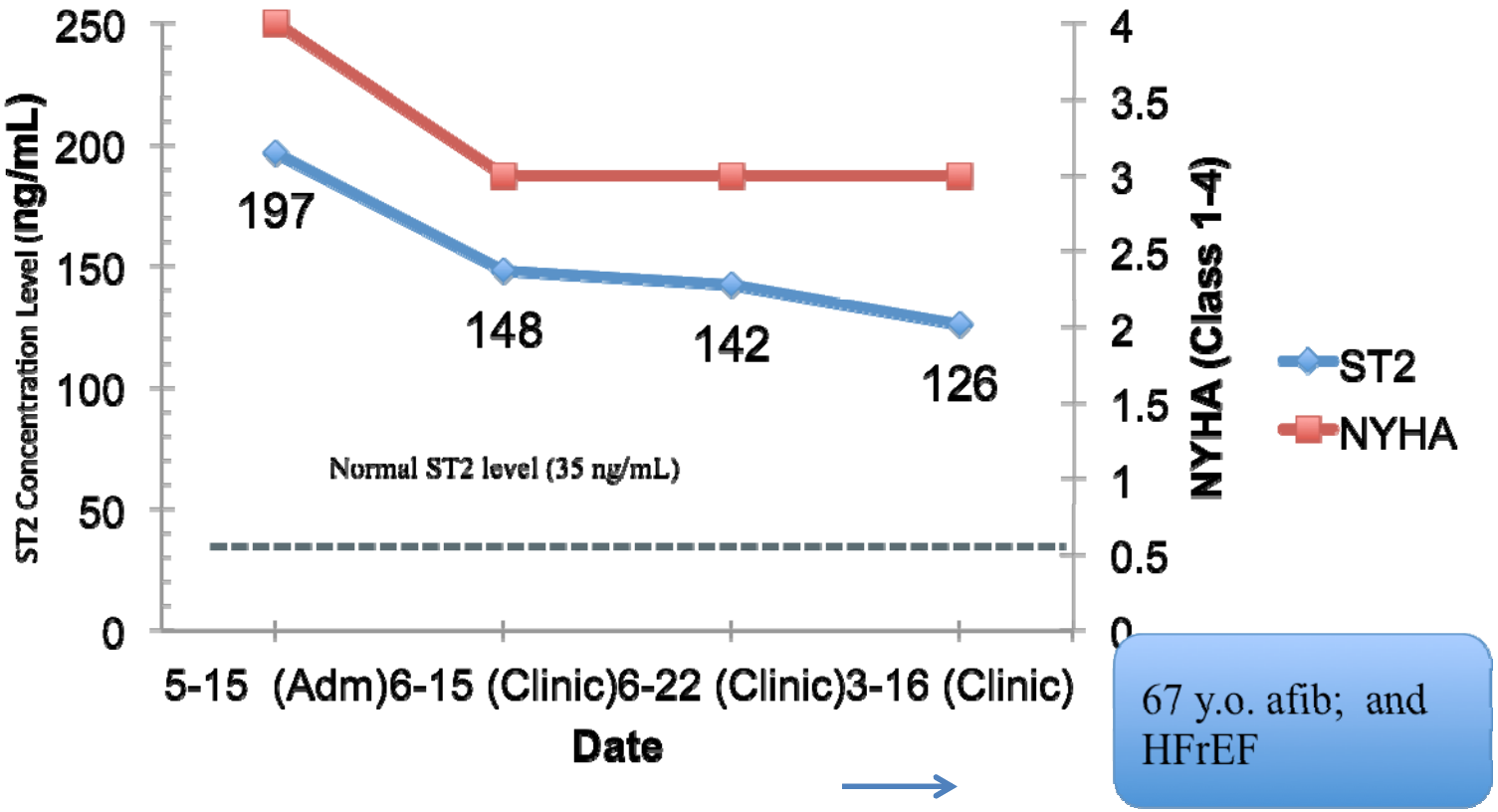
Lived in mexico- poor diet and med compliance

Patient: M.O.



Only transient decrease in ST2- too hypotensive to increase medications

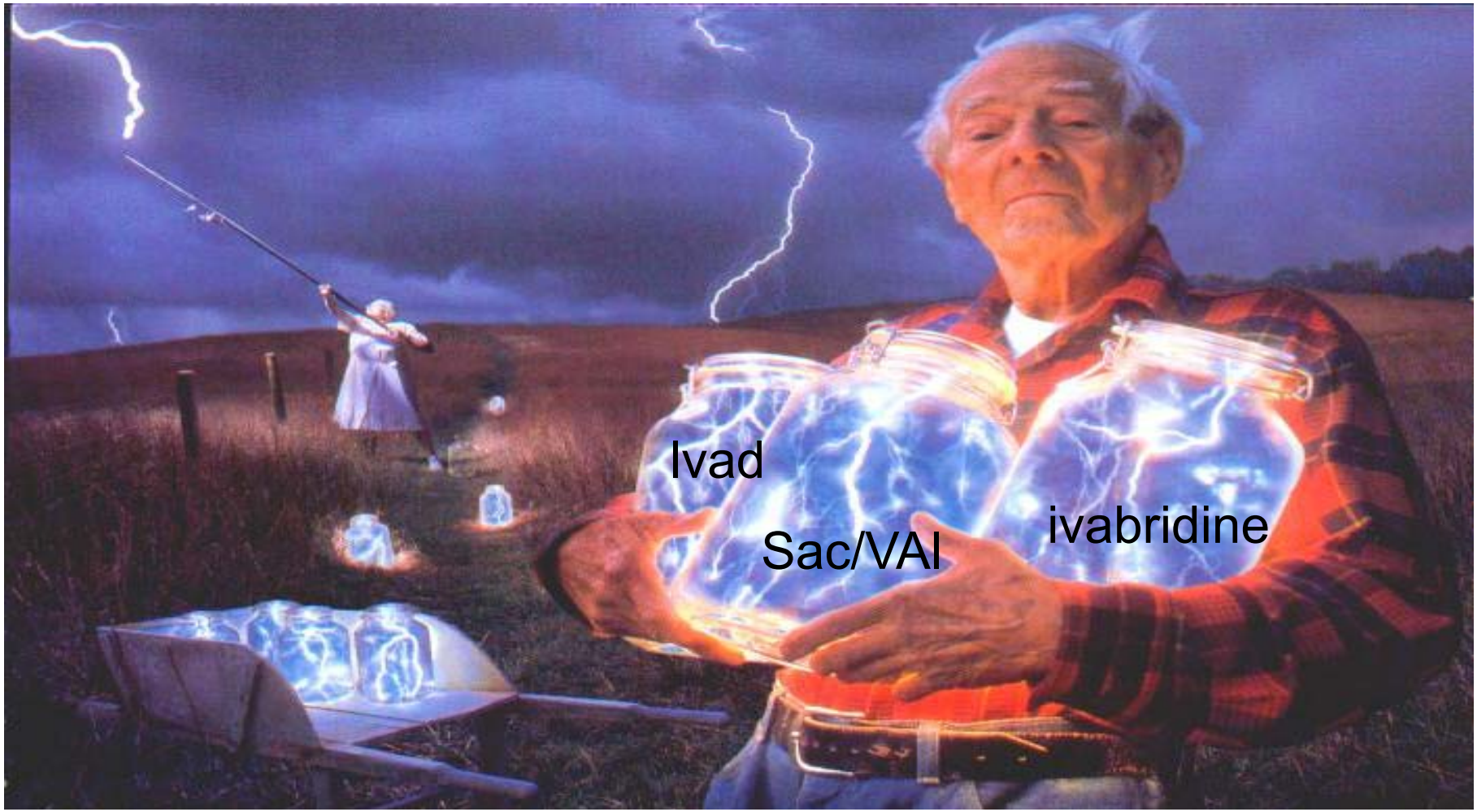
Patient: M.L.



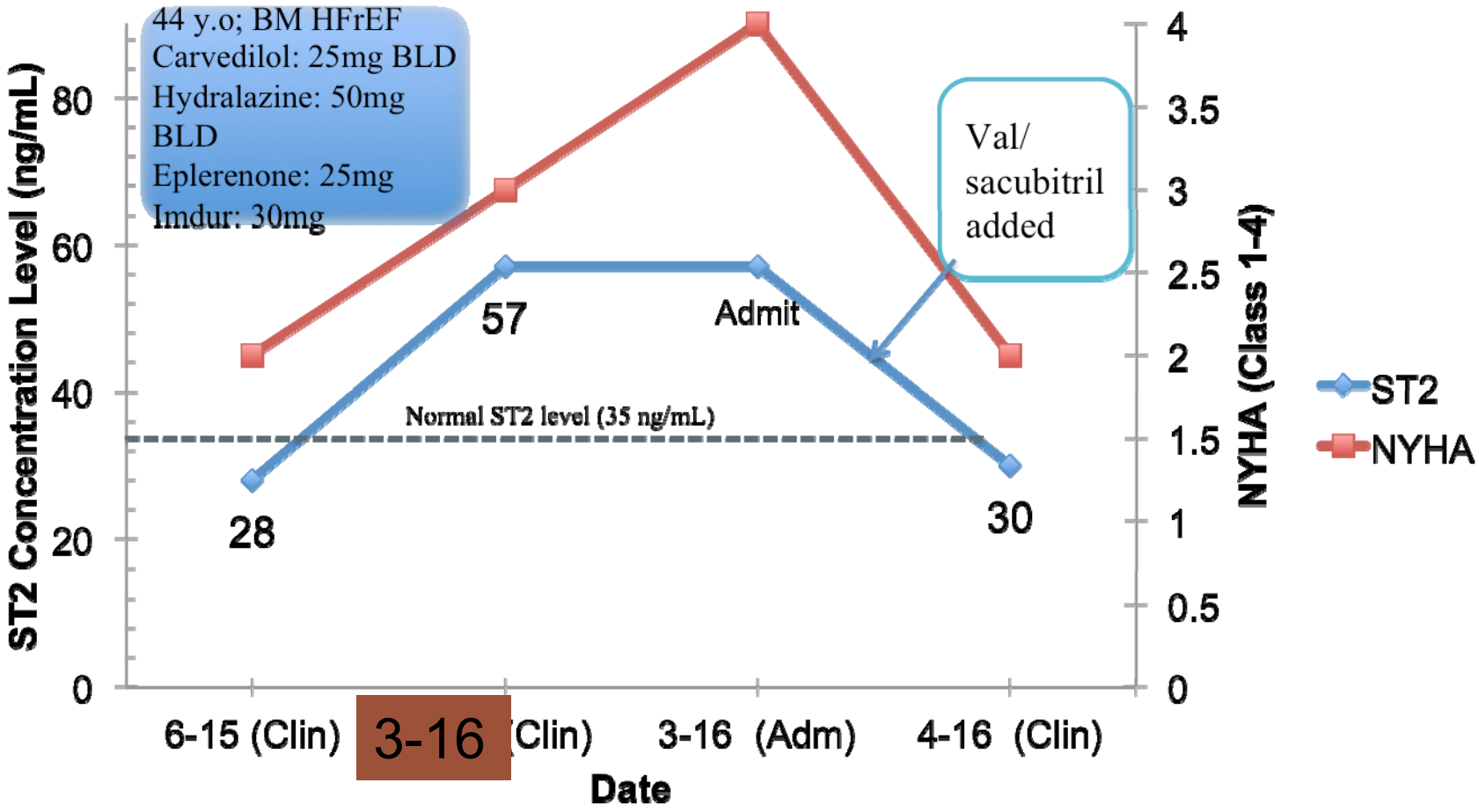
Working the st2 down-doesn't tolerate meds well keeping out of hospital

ST-2 in the clinic

Non-responders to traditional medications may get newer therapies



Patient: C.B.


44 y.o; BM HFrEF
Carvedilol: 25mg BLD
Hydralazine: 50mg BLD
Eplerenone: 25mg
Imdur: 30mg
Val/ sacubitril added
57
Admit
28
30
Normal ST2 level (35 ng/mL)
ST2 Concentration Level (ng/mL)
NYHA (Class 1-4)
0
20
40
60
80
0
0.5
1
1.5
2
2.5
3
3.5
4
6-15 (Clin)
3-16
(Clin)
3-16 (Adm)
4-16 (Clin)
Date
ST2
NYHA

Old biomarkers become new "guided treatment" biomarkers

- Sodium
- Potassium
- Pulmonary pressure
- Heart rate

- Tolvaptan
- New K drugs
- CardioMems
- Ivabridine

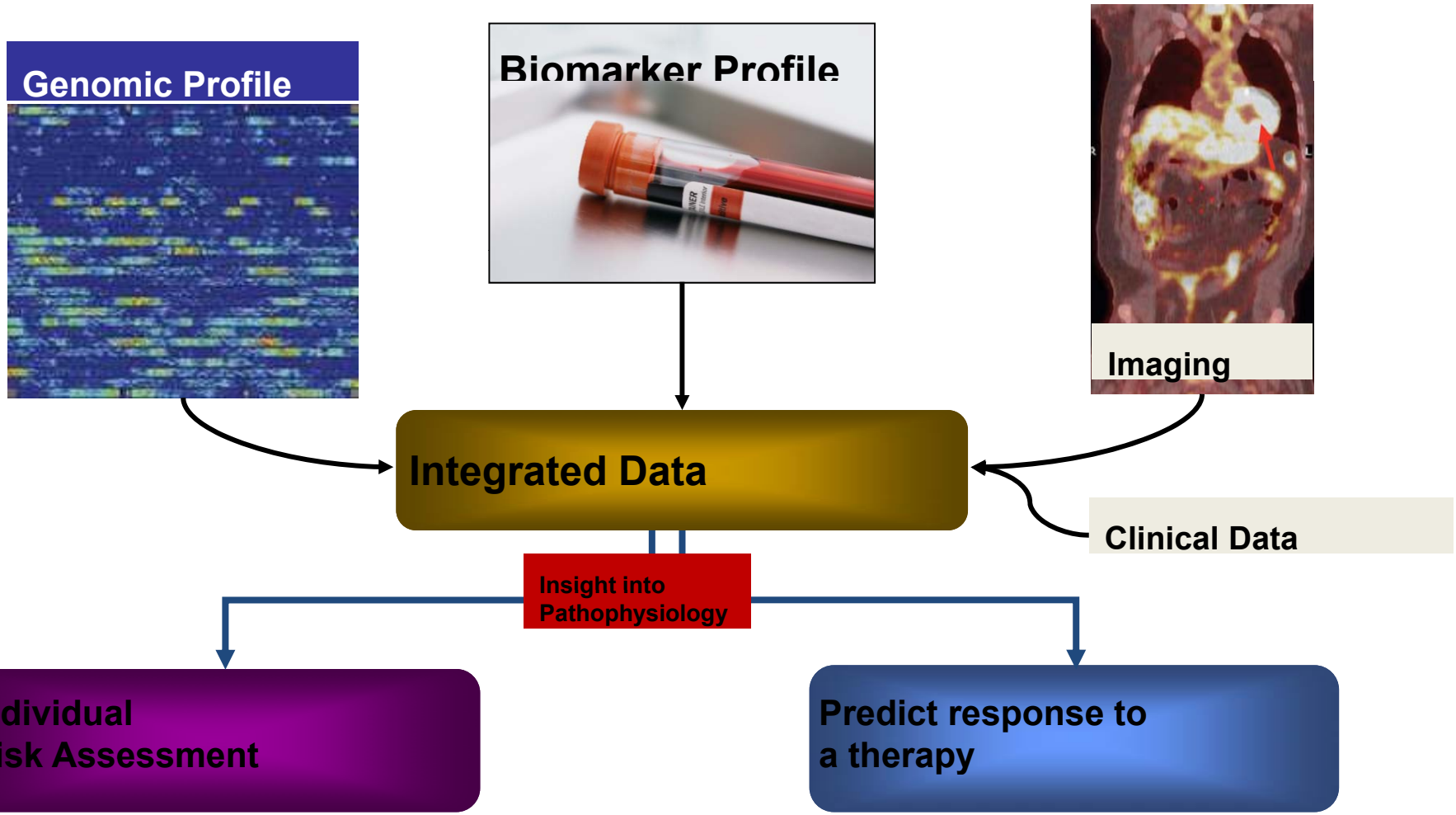
EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Zirconium Cyclosilicate for Treatment of Hyperkalemia

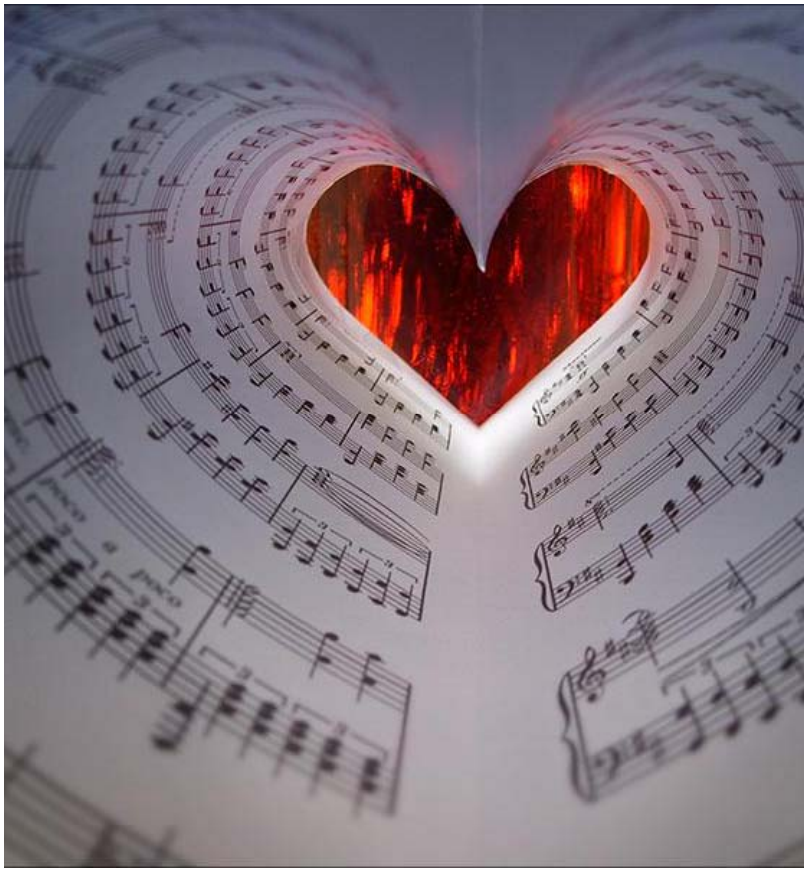
Bradley S. Dixon, MD

The Promise of Personalized Medicine

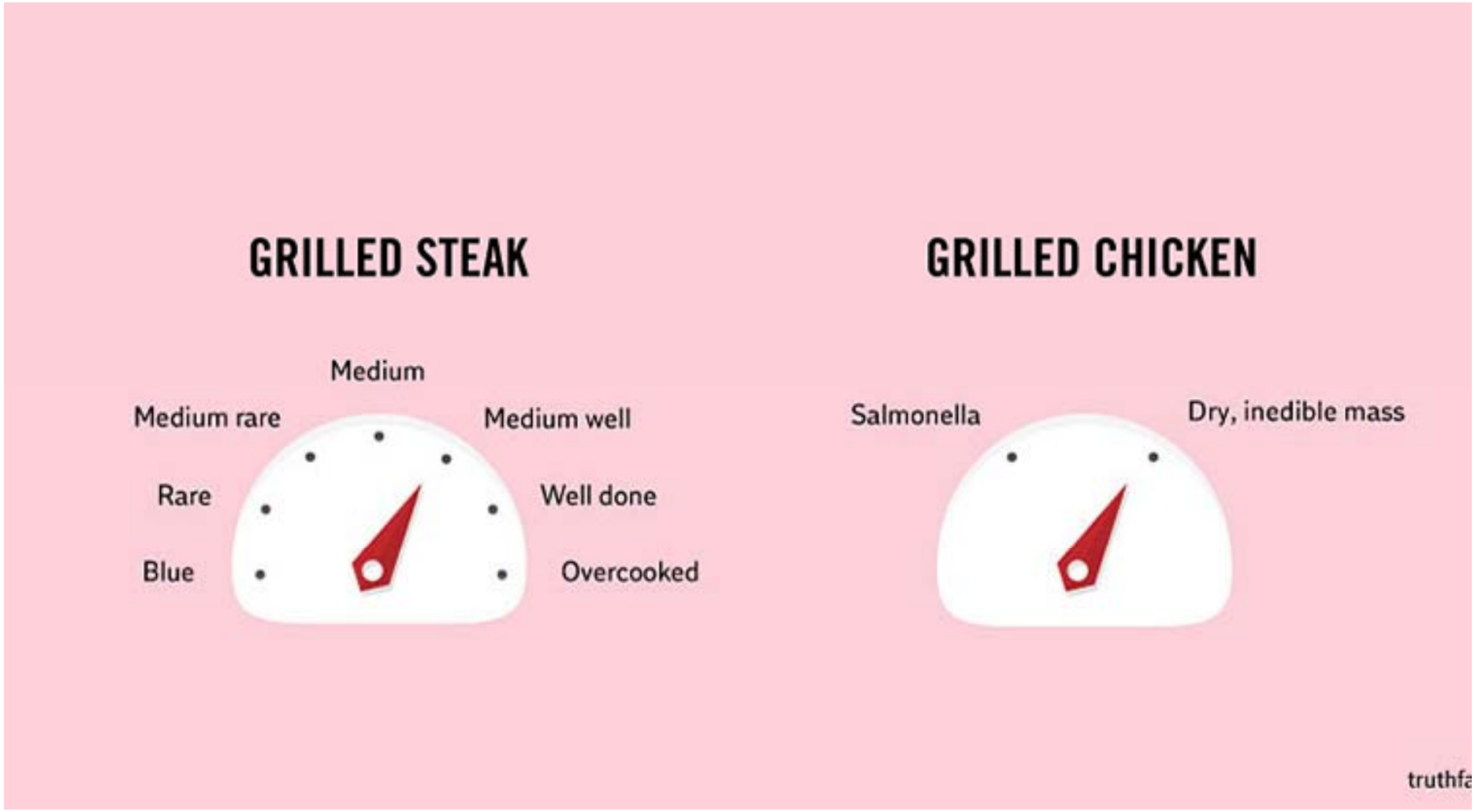


Morrow DA ESC 2007; Adapted from West et al. Genome Research 2006; 16:559-566

The Science merged with the ART



There is more ways to grill steak than chicken

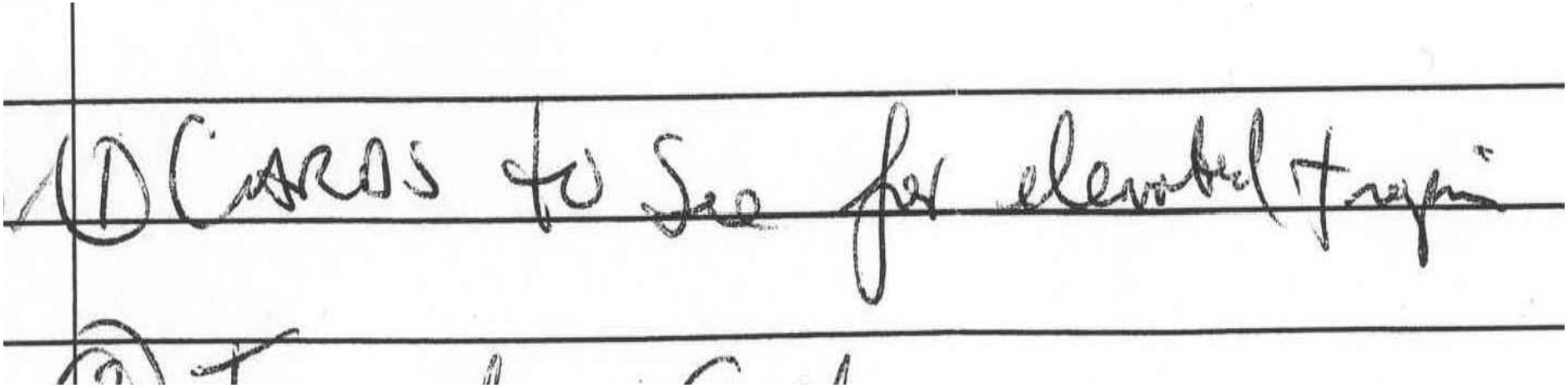


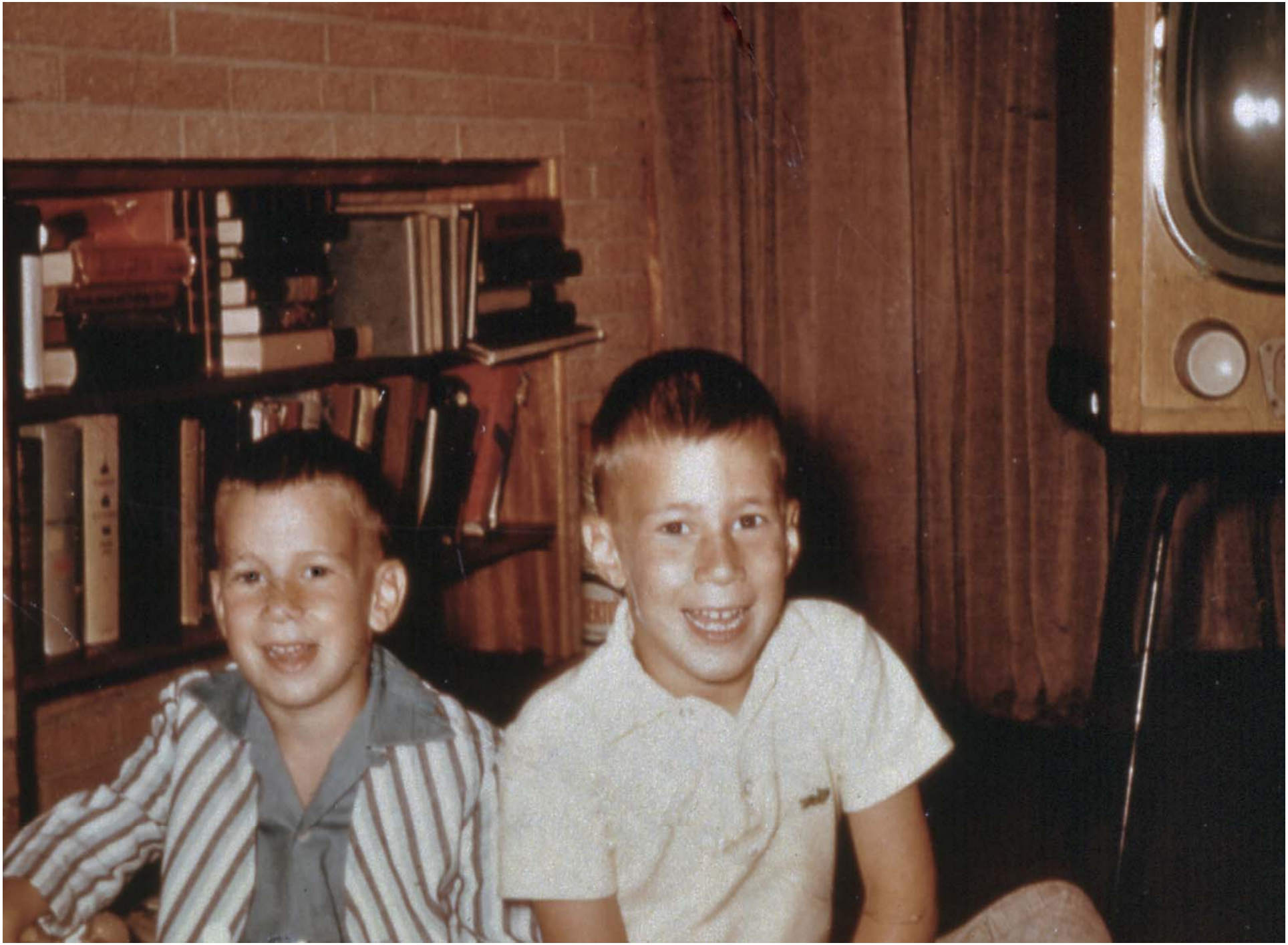
Having biomarkers around is more like grilling steak- than chicken more opportunites!


Biomarkers will
Make bad
doctors worse
and good
doctors better!

When aTroponin is “elevated” in the ED, many think their job is over!!

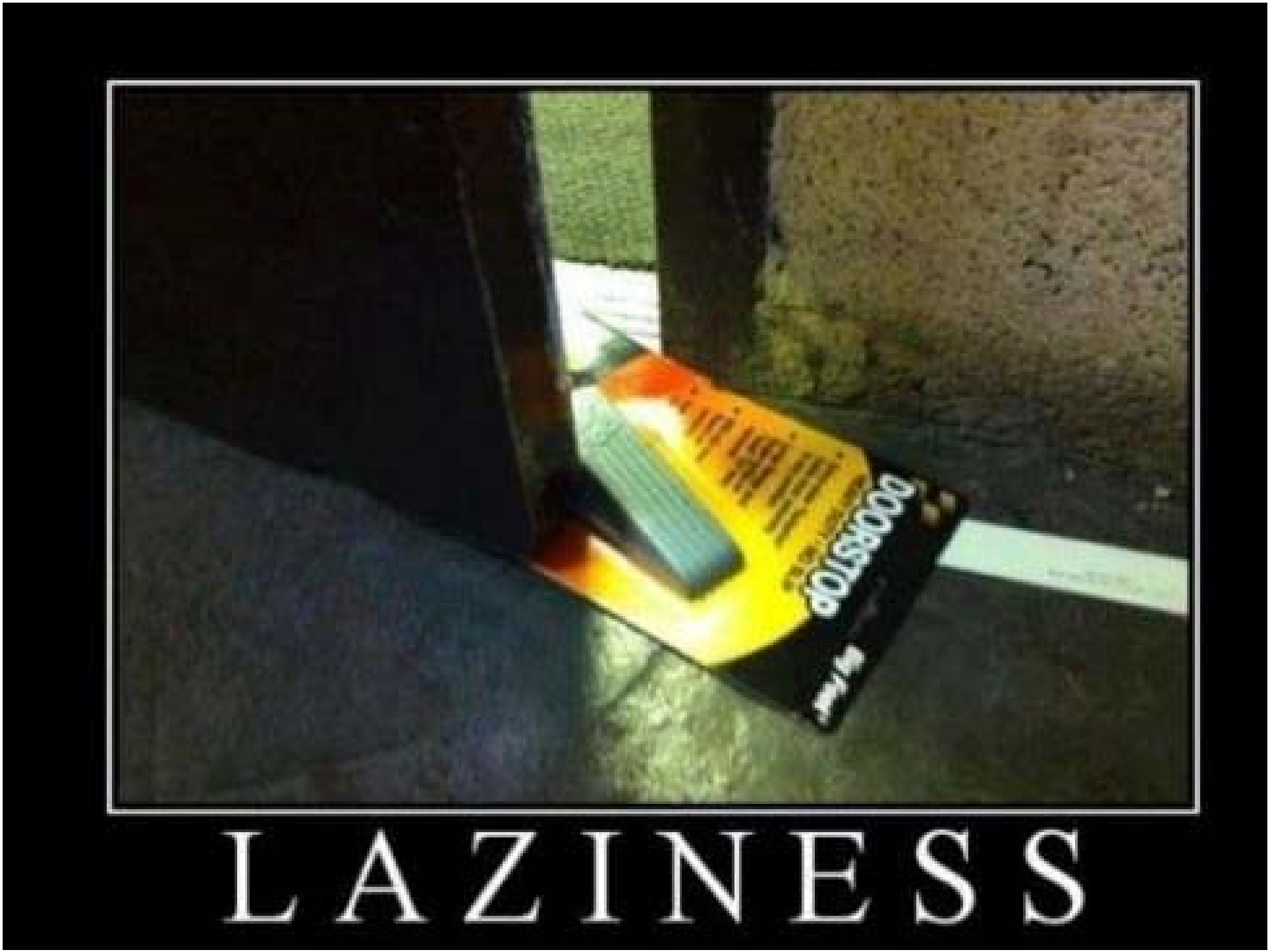
“Cards to See for Elevated Troponin”





There is still no substitute for a “Hands on” open-ended history and physical exam- all the while , demonstrating compassion and empathy


The Music Of Love


LAZINESS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Thank You!!!