Biomarkers Now and in the Future of Emergency Medicine- TIME TO USE sST2

Alan S. Maisel MD FACC
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Chest Pain, Shortness of breath: We Need Rapid and Accurate Diagnosis, Risk Stratification, and Treatment

Where do biomarkers fit in?

Objectives of Biomarker Testing in Heart Disease

Diagnosis[1]

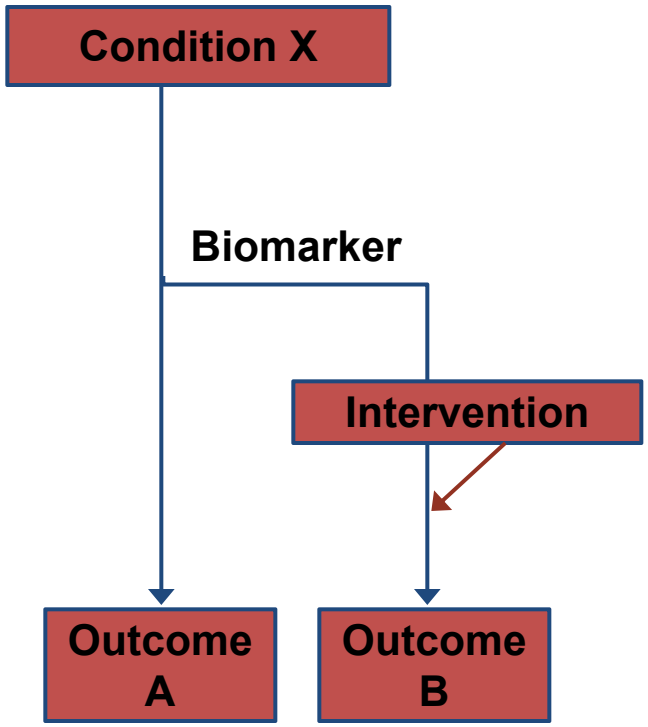
- To establish or refute a diagnosis

Risk Stratification

- Who should be admitted/who can go home

Monitoring/Therapeutic Guidance[1]

- To facilitate selection of an appropriate therapeutic intervention
- to guide or monitor responses to treatment



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

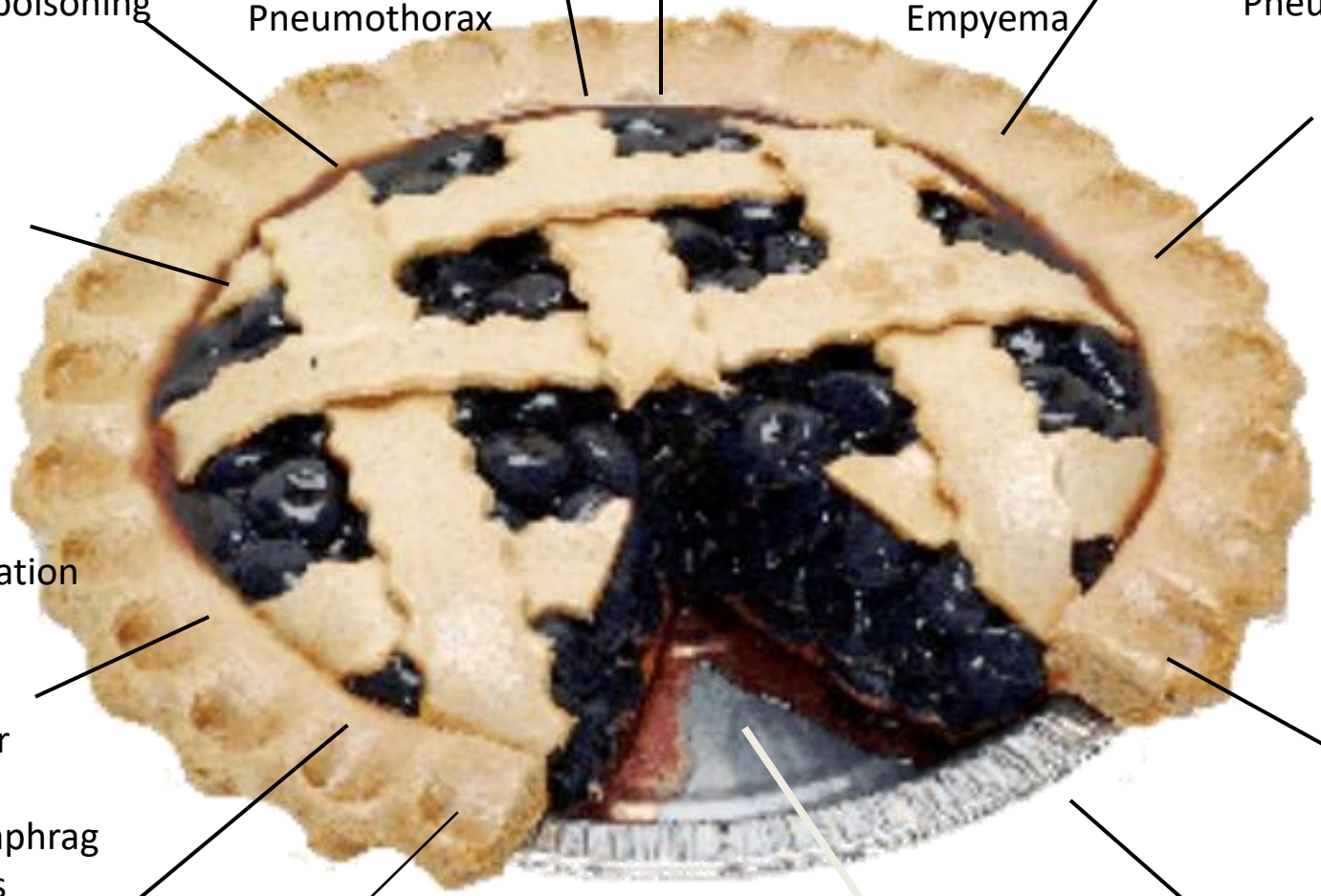
Getting it right is important

- Accuracy counts

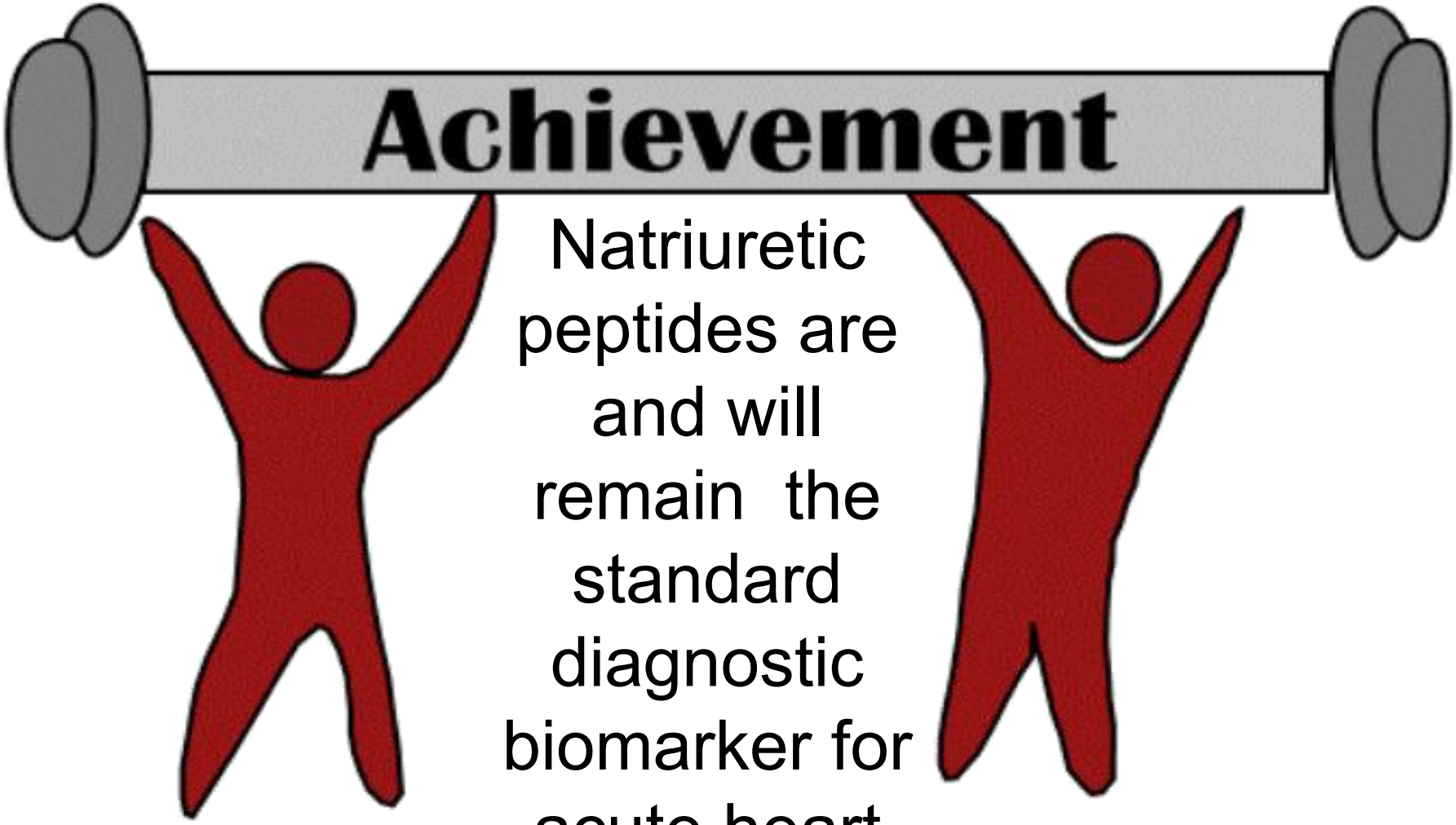
Acute Heart Failure

- First make a rapid and accurate diagnosis

The Short of Breath Pie


Musculoskeletal Pain
Pneumomediastinum
Mediastinitis
IVDA Pulm Infarction
Anxiety
Pulmonary Embolus
Panic Attack
Cyanide poisoning
Pneumothorax
Empyema
Pneumonia
MetHgb
Tietze's disease
Mondor's Syndrome
DKA
Metabolic acidosis
Asthma
COPD exacerbation
FB Aspiration
Breast Cancer
Chemical Exposure
Subdiaphrag Abcess
Anemia
Heart Failure
Lung Cancer
Amniotic Fluid Embolus
Anaphylaxis

Raising the bar



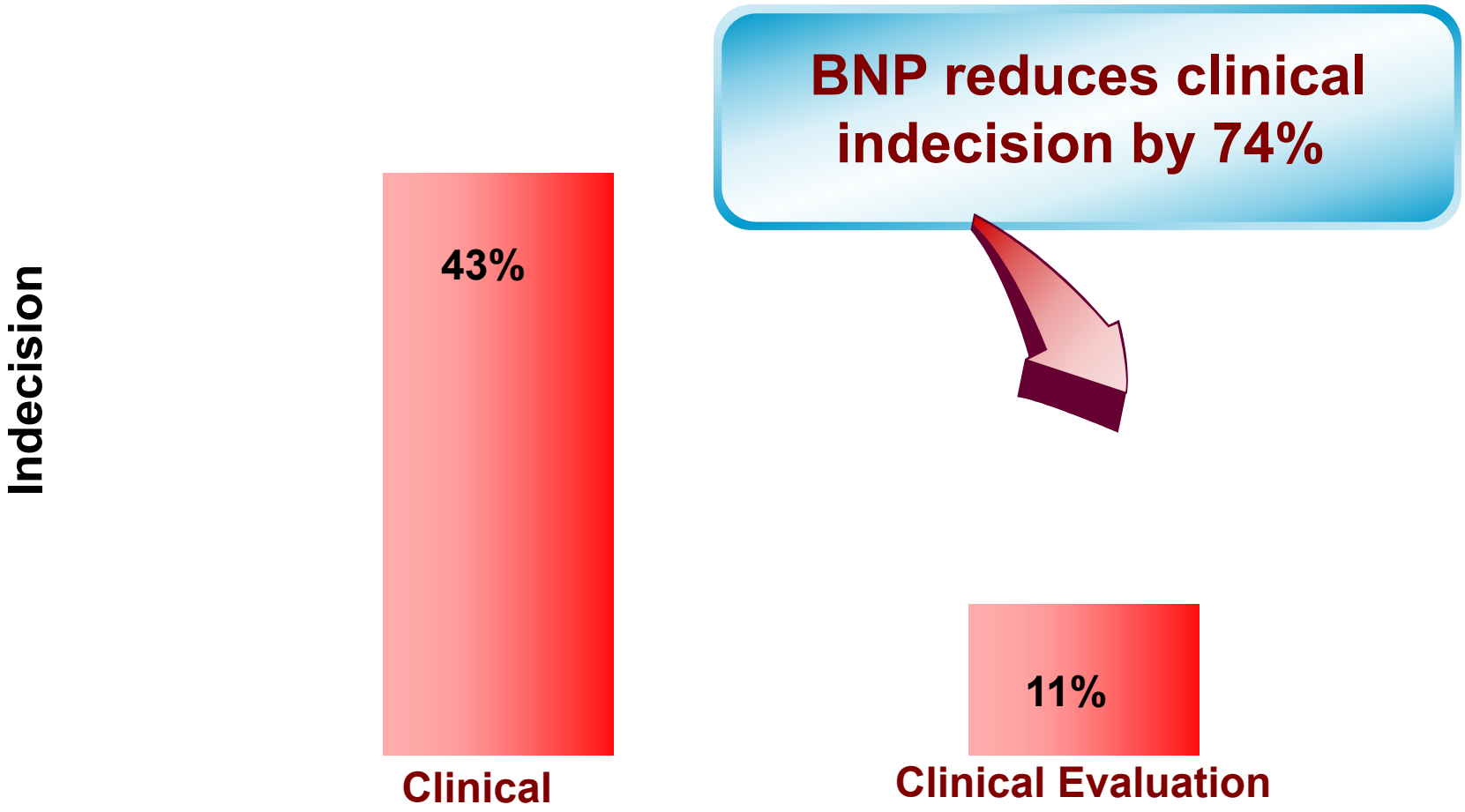
Natriuretic peptides are and will remain the standard diagnostic biomarker for acute heart failure

Biomarkers

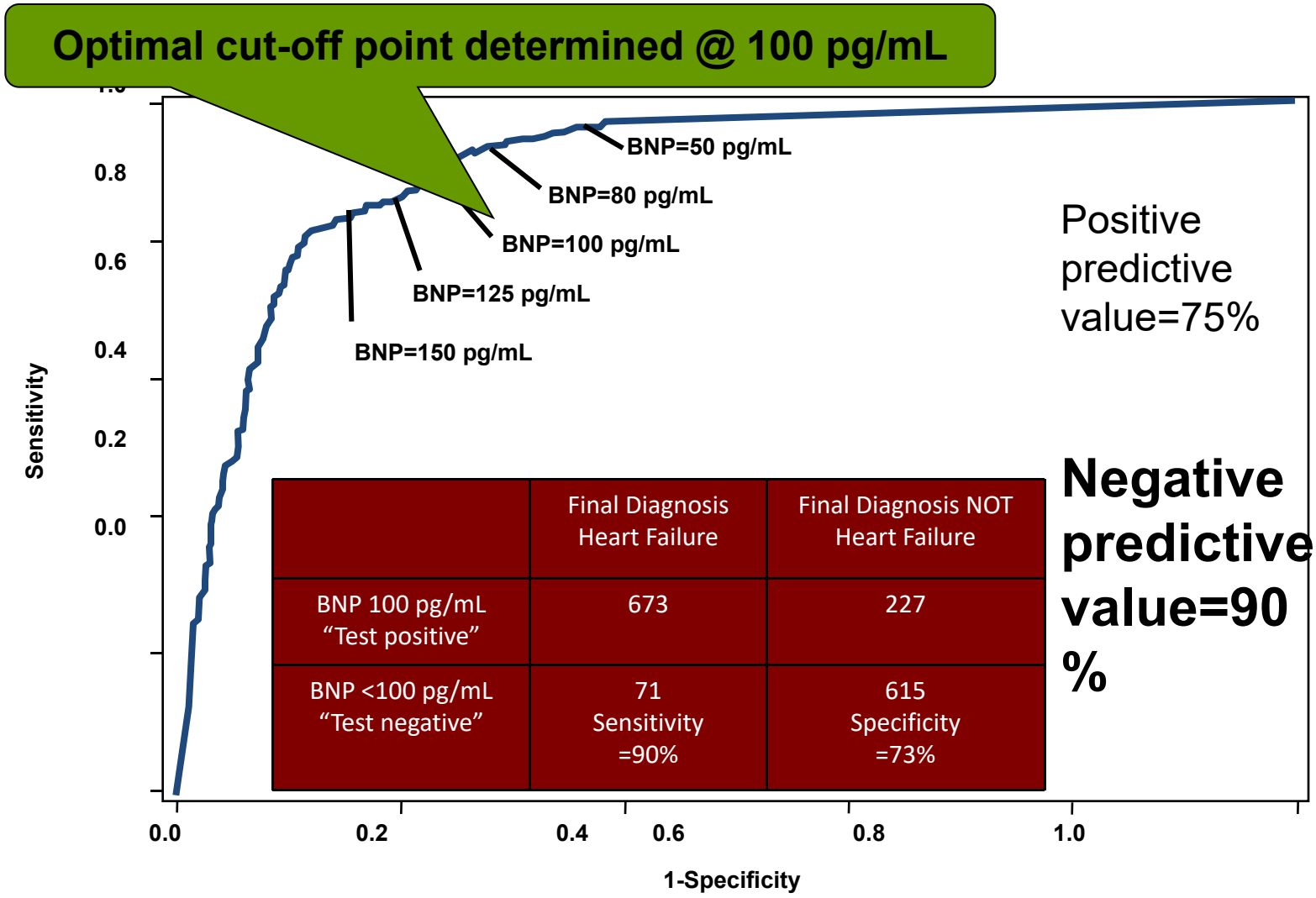
Biomarkers for Diagnosis

COR	LOE	Recommendation	Comment/ Rationale
I	A	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF.	MODIFIED: 2013 acute and chronic recommendations have been combined into a diagnosis section.

Clarification of Diagnosis & BNP



Accuracy is 90%



	Final Diagnosis Heart Failure	Final Diagnosis NOT Heart Failure
BNP 100 pg/mL "Test positive"	673	227
BNP <100 pg/mL "Test negative"	71 Sensitivity =90%	615 Specificity =73%

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

NtproBNP cut-offs

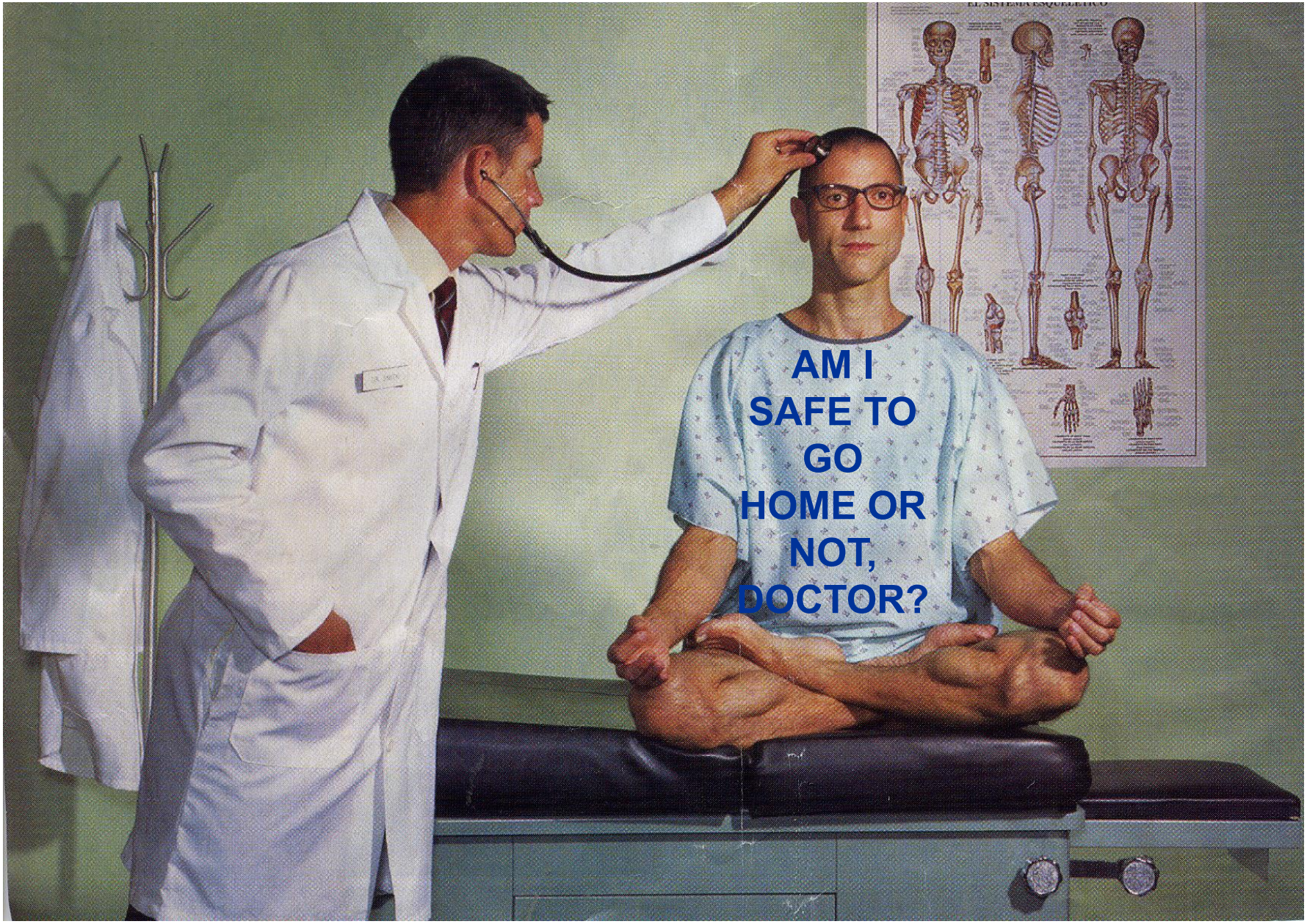
- 1. 125 < 75 y.o. and 450 > 75 yo
- 2. 450, 900, 1800 based on age
- 3. 300 to rule out.

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

ADD-00056845

But once we make the diagnosis

- That is only half the battle.
  - There is another problem


AM I
SAFE TO
GO
HOME OR
NOT,
DOCTOR?

Heart failure is mainly a clinical diagnosis

But how can you tell which one of these men is likely to be dead in a month?

Into the hospital, obs unit or home?

They say “I feel well.” You think “They look okay”

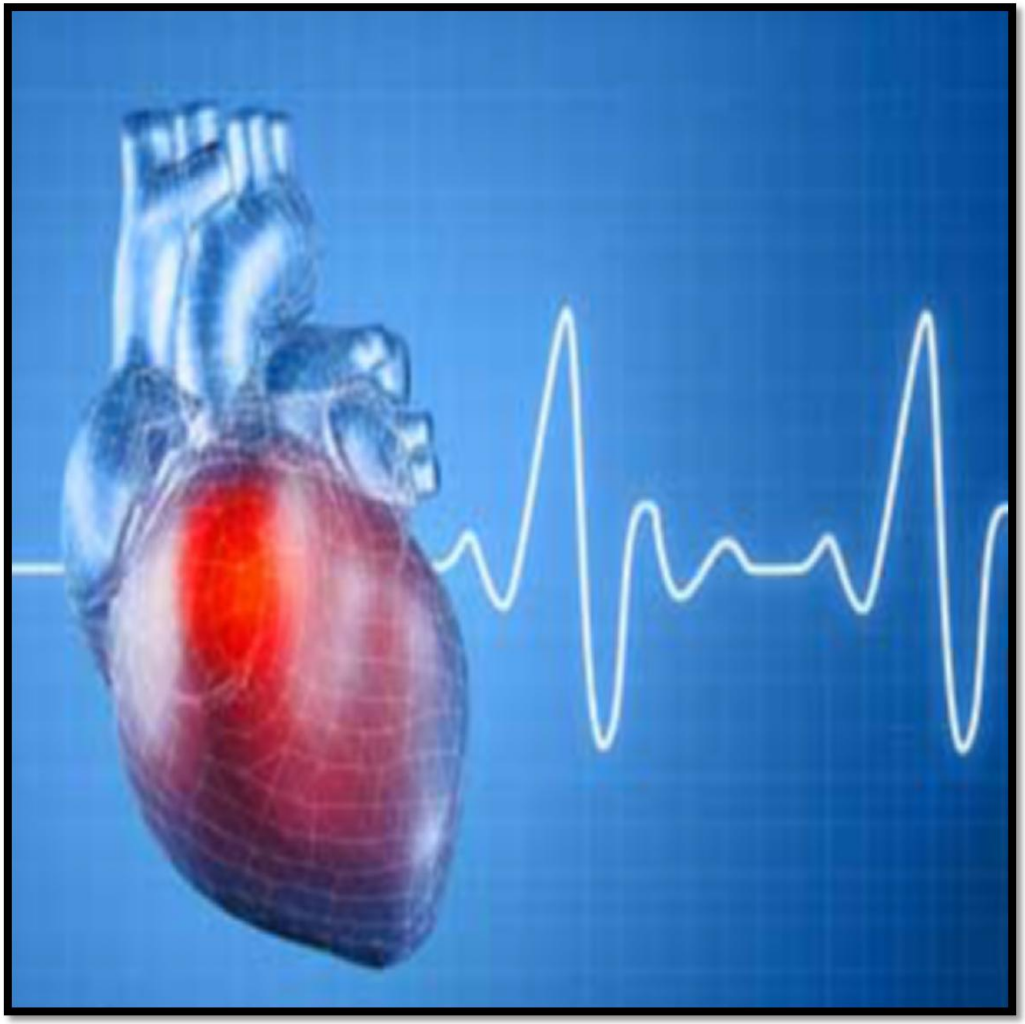
But you could be wrong

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

When ED docs don't know the answer…….



They are admitted (at least in usa) why?

WELL

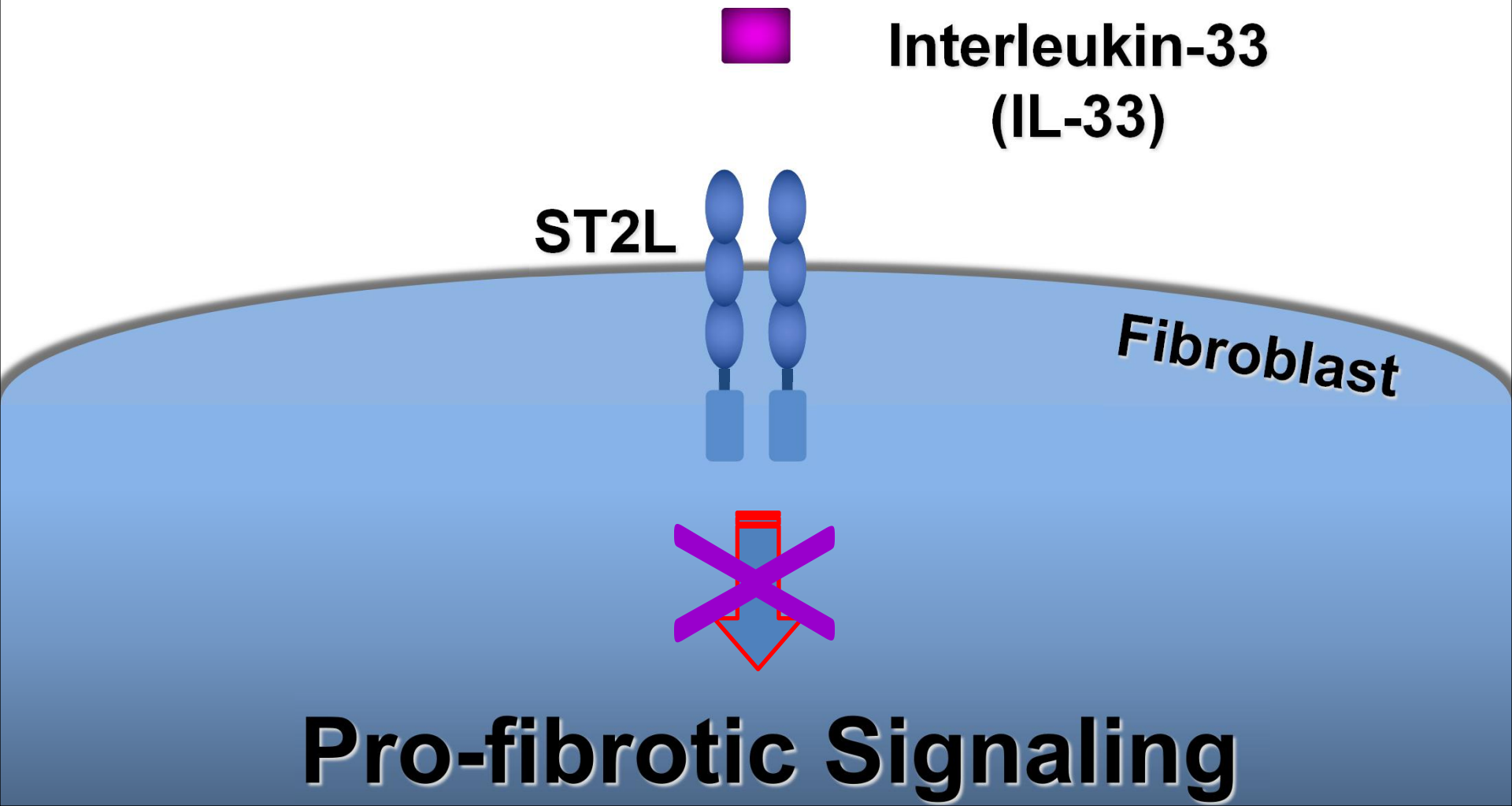
I think we finally found the answer

sST2

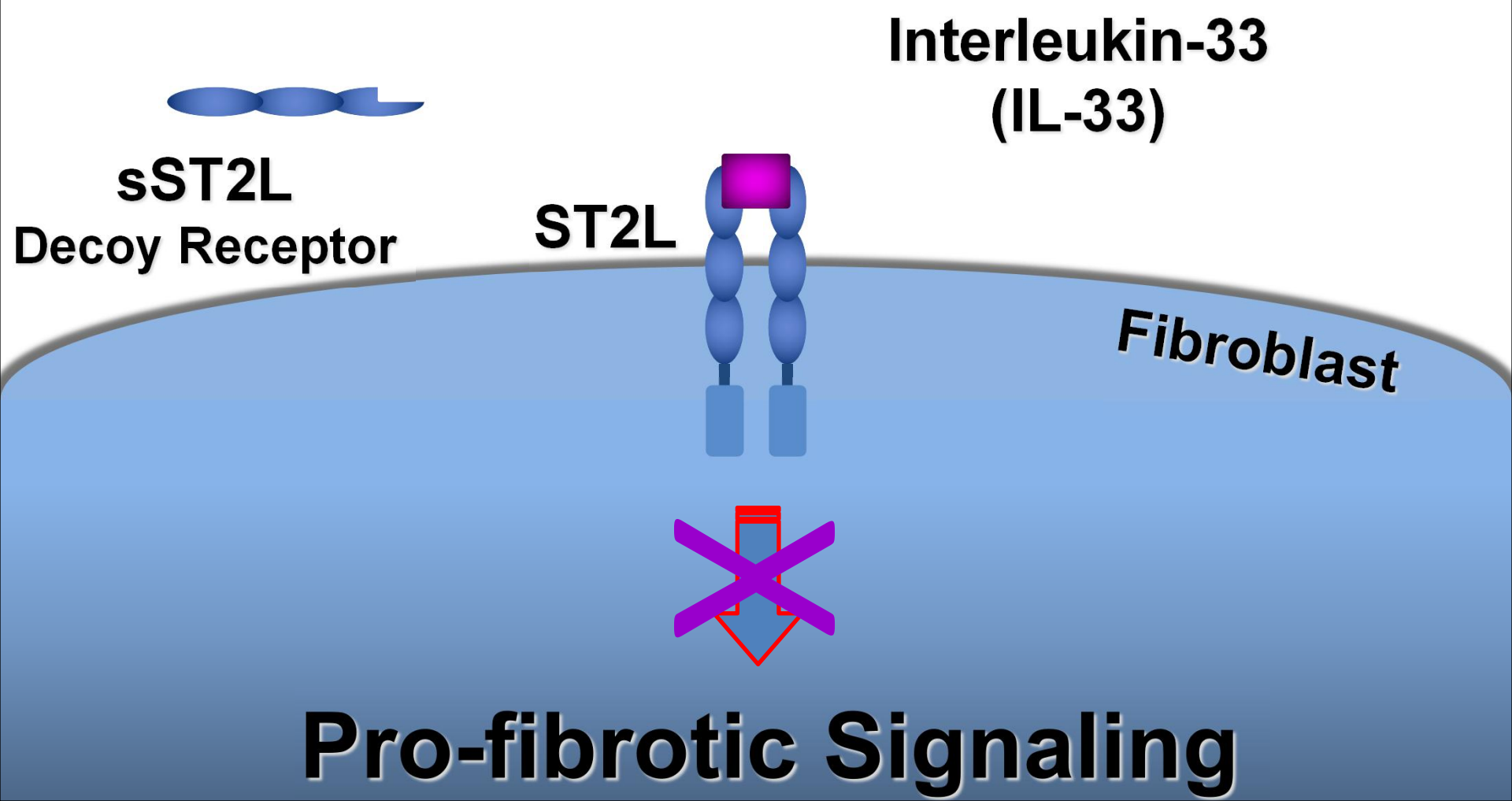
sST2- has evolved to be an ED test as an arbitrator of high risk

Soluble ST – 2

ST-2: Suppressor of tumorigenicity 2 (IL-1 receptor-like-1)
Member of Interleukin-1 receptor family
membrane bound receptor: ST-2L (Profibrotic signaling)
soluble truncated form: sST-2 (Decoy receptor)



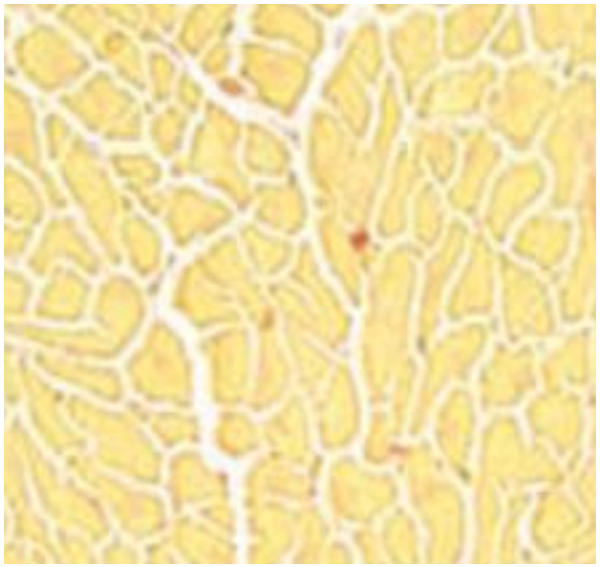
↑ sST-2 binds IL-33 &
↓ inhibition of ST-2L profibrotic signaling
↑ Fibrosis



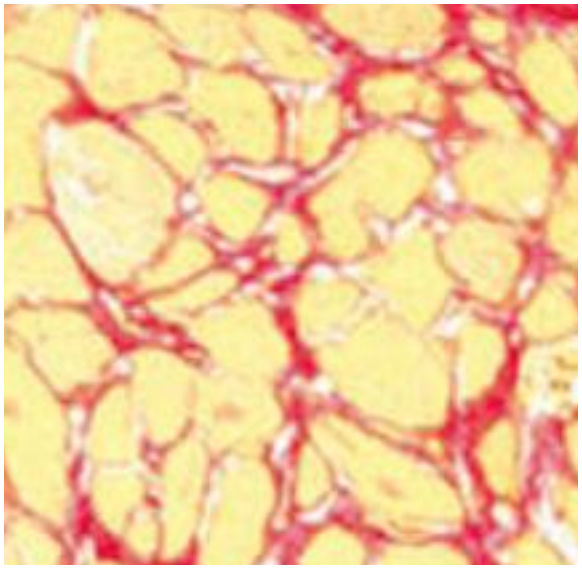
ST2 plays a role in reducing cardiomyocyte hypertrophy and fibrosis

Abnormalities in ST2 experimentally result in severe cardiac remodeling and heart failure

Intact sST2



sST2 knock out



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

Wu, 2013, accepted Am. Heart J.

SOLID CUTPOINTS

- **➢70**

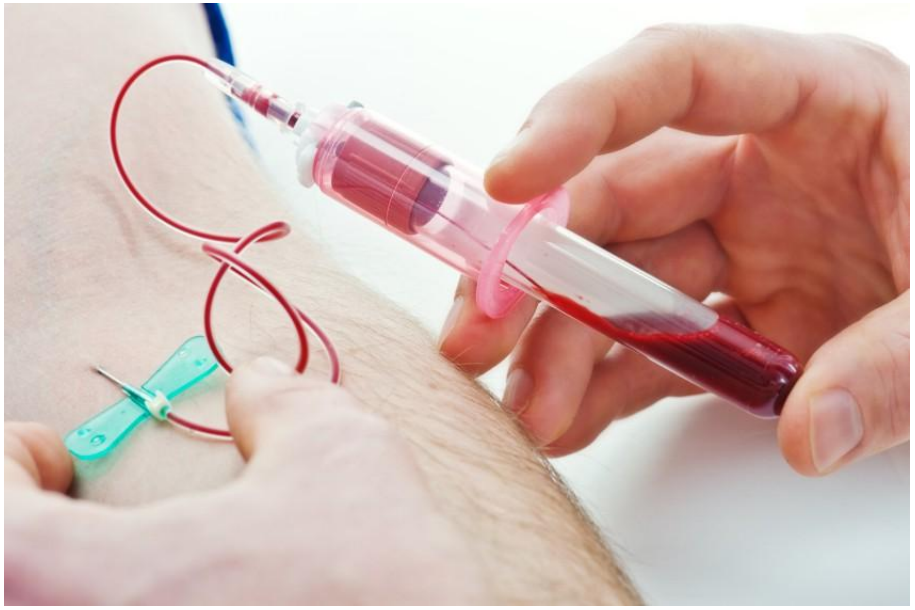
  NG/ML

- ➢HIGH

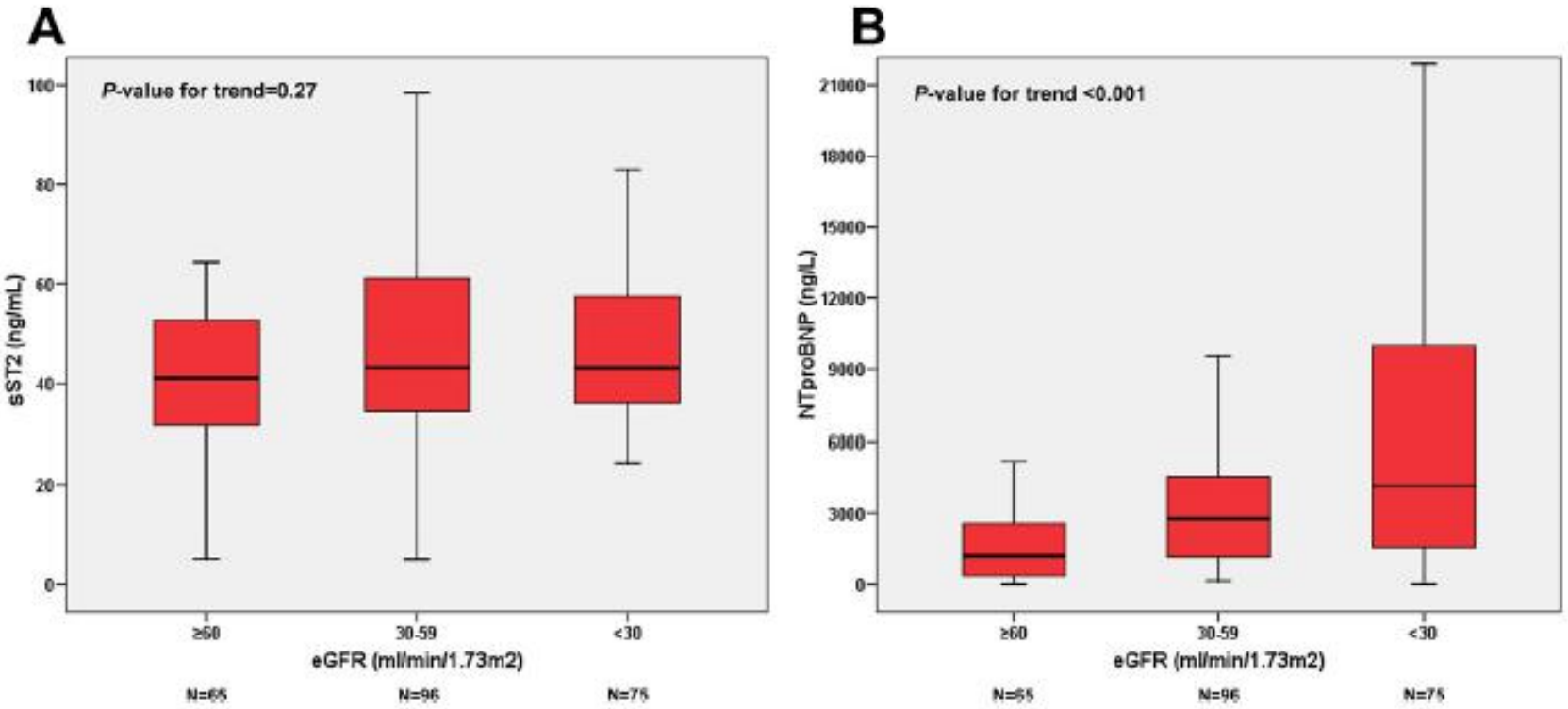
  RISK ED

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

sST2 is NOT a diagnostic marker of AHF

sST2 elevated in other conditions

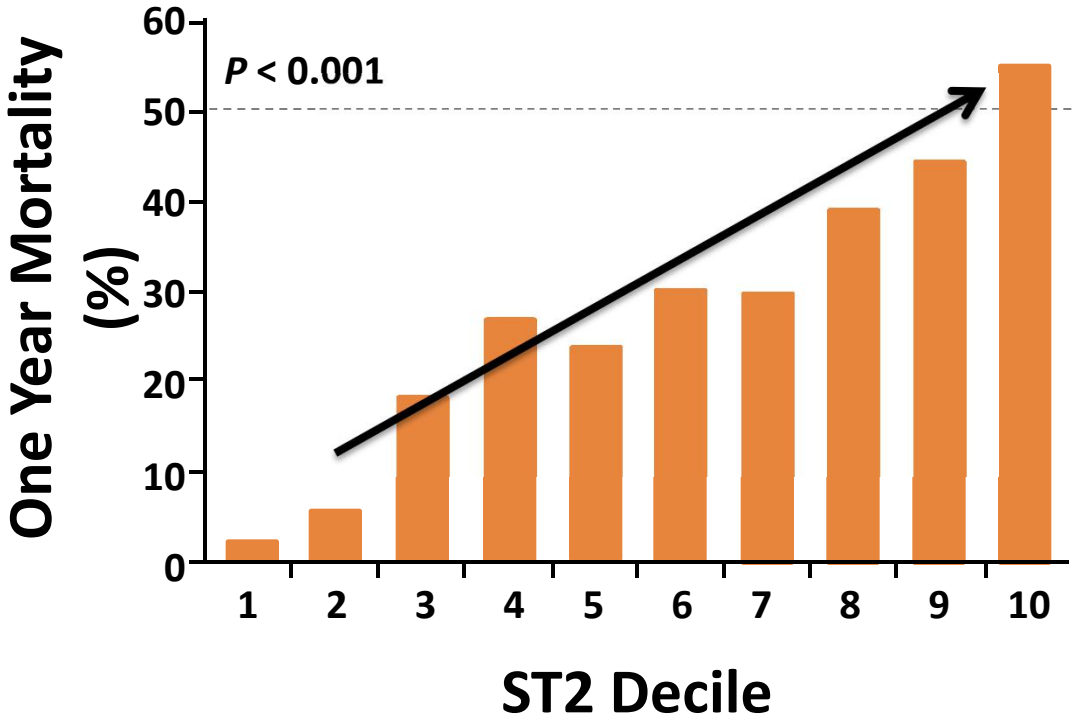
- Severe sepsis
- Inflammatory disease
- Disseminated cancer
- Liver or other organ fibrosis

It is elevated in 90% of patients with AHF

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

Mortality Risk Increases With ST2 Levels

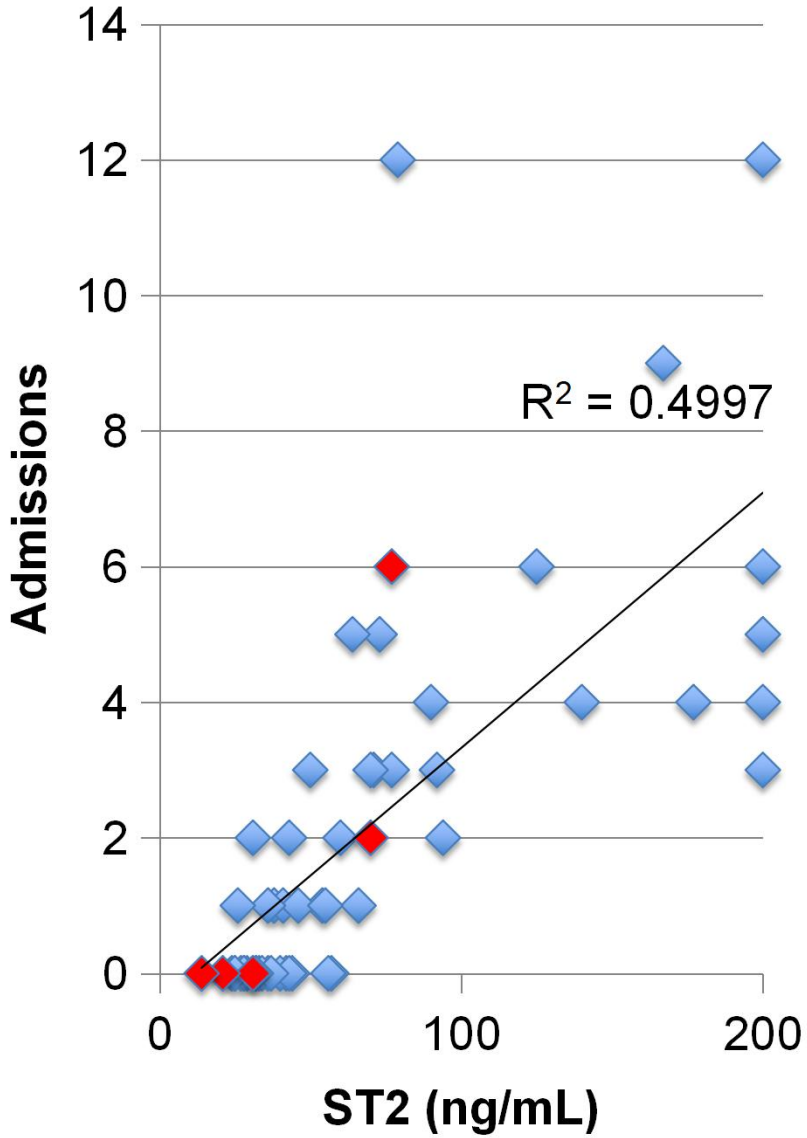
One-year mortality exceeded 50% in the highest decile.



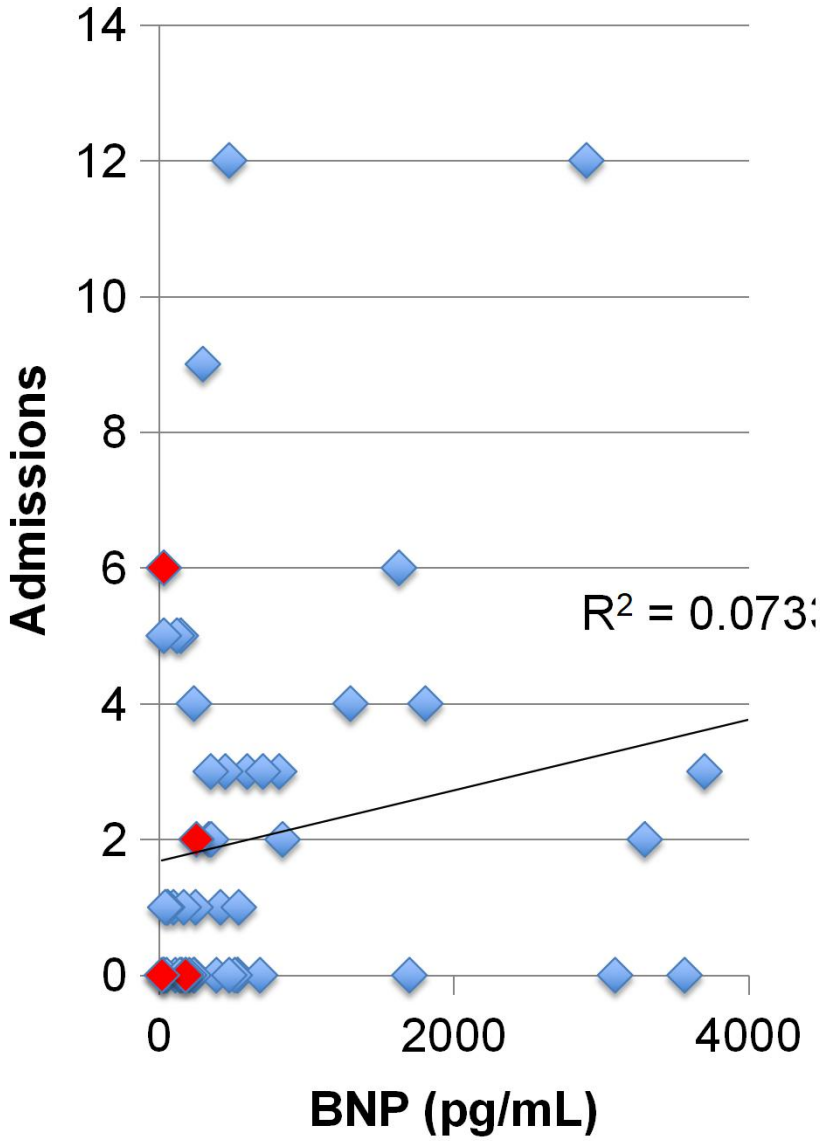
Rehman SU, Mueller T, Januzzi JL et al. *J Am Coll Cardiol*. 2008;52:1458-65.

How I got ST2 into my hospital

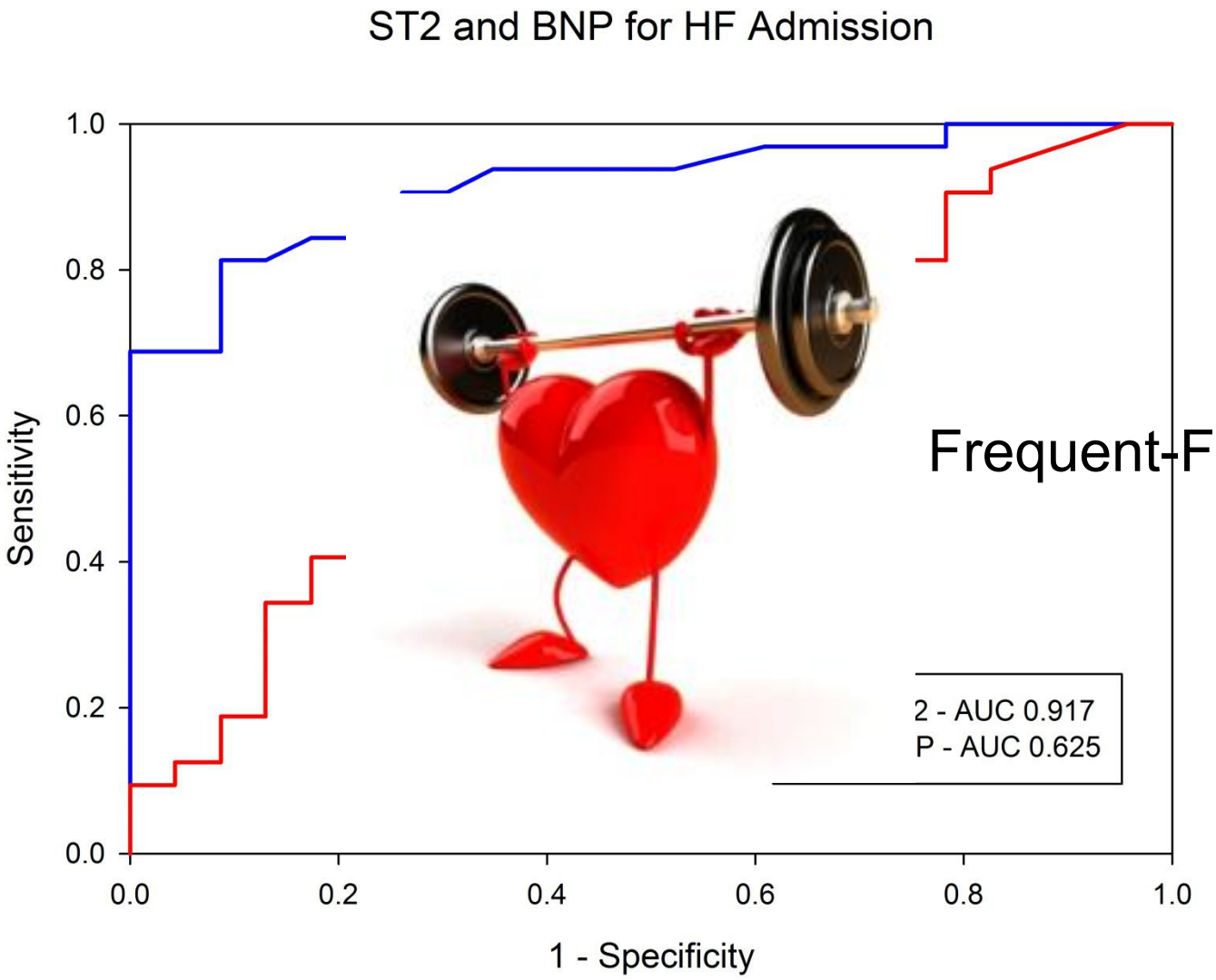
ST2 and Admissions Over 6 Months



BNP and Admissions Over 6 Months



Wetterson, Maisel AJM-2016



Frequent-Flyer Index


ST2, ST2, ST2

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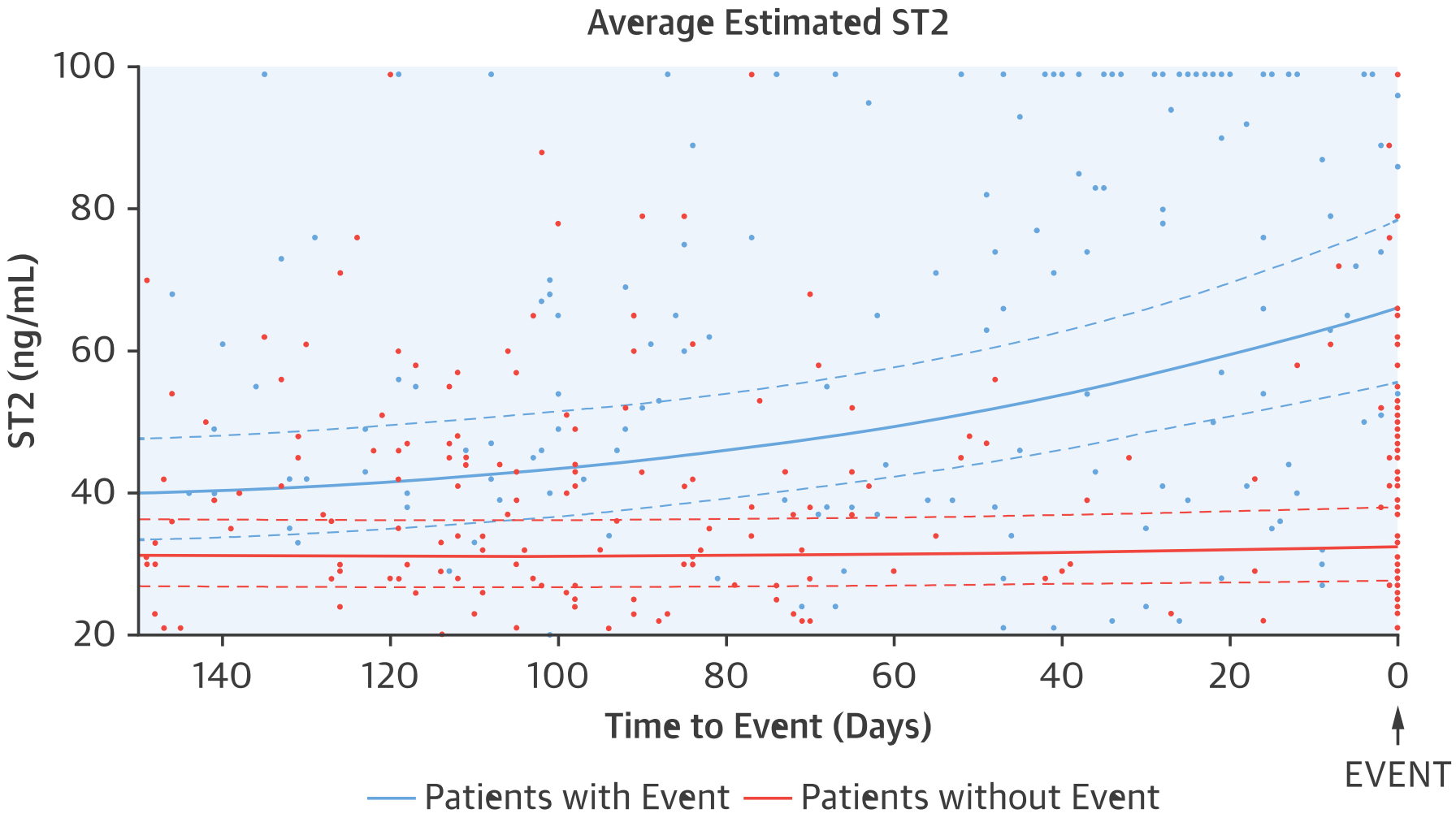
ISSN 0735-1097/$36.0
https://doi.org/10.1016/j.jacc.2017.09.02

PUBLISHED BY ELSEVIER

Prognostic Value of Serial ST2 Measurements in Patients With Acute Heart Failure

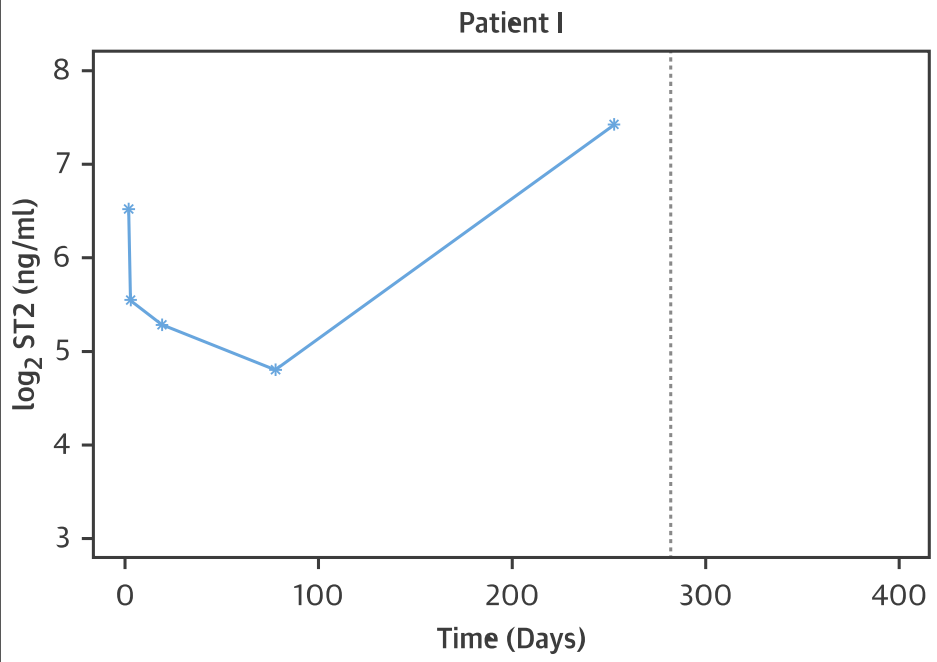
Laura C. van Vark, MD,[a,b] Ivonne Lesman-Leegte, PhD,[c] Sara J. Baart, MSc,[a,b] Douwe Postmus, PhD,[c] Yigal M. Pinto, MD, PhD,[d] Joke G. Orsel, PhD,[e] B. Daan Westenbrink, MD, PhD,[c] Hans P. Brunner-la Rocca, MD, PhD, Addy J.M. van Miltenburg, MD, PhD,[g] Eric Boersma, PhD,[a,b] Hans L. Hillege, MD, PhD,[c] K. Martijn Akkerhuis, MD, PhD,[a,b] for the TRIUMPH Investigators

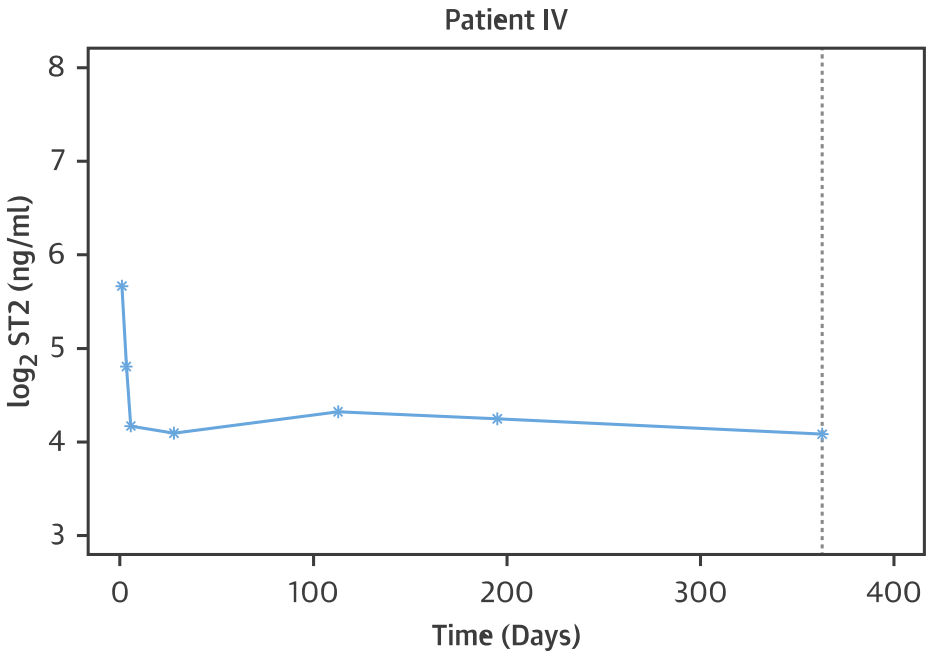
Serial ST2 Predicts Mortality and HF Hospitalization



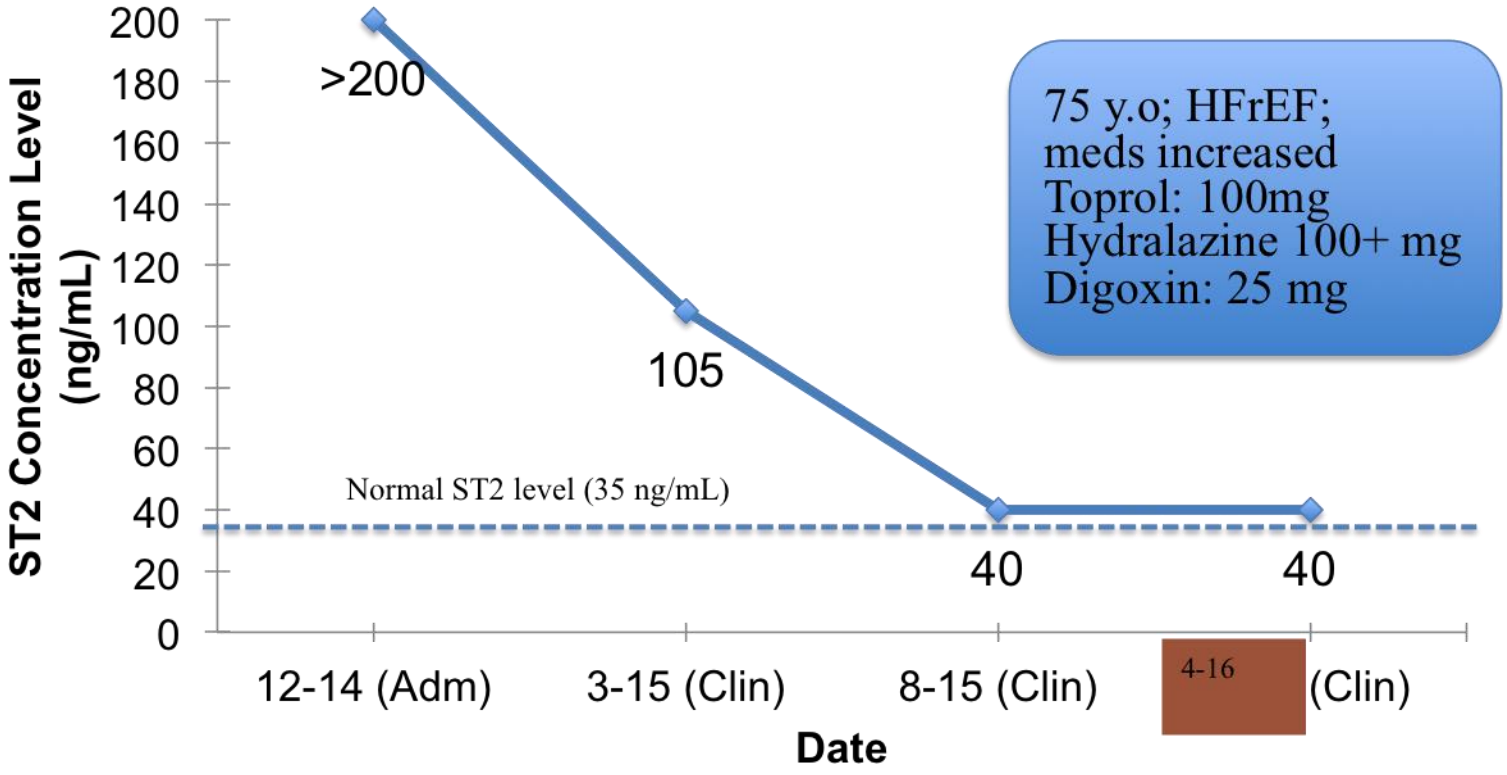
van Vark, L.C. et al. J Am Coll Cardiol. 2017;70(19):2378-88.

Are You a U or a J?



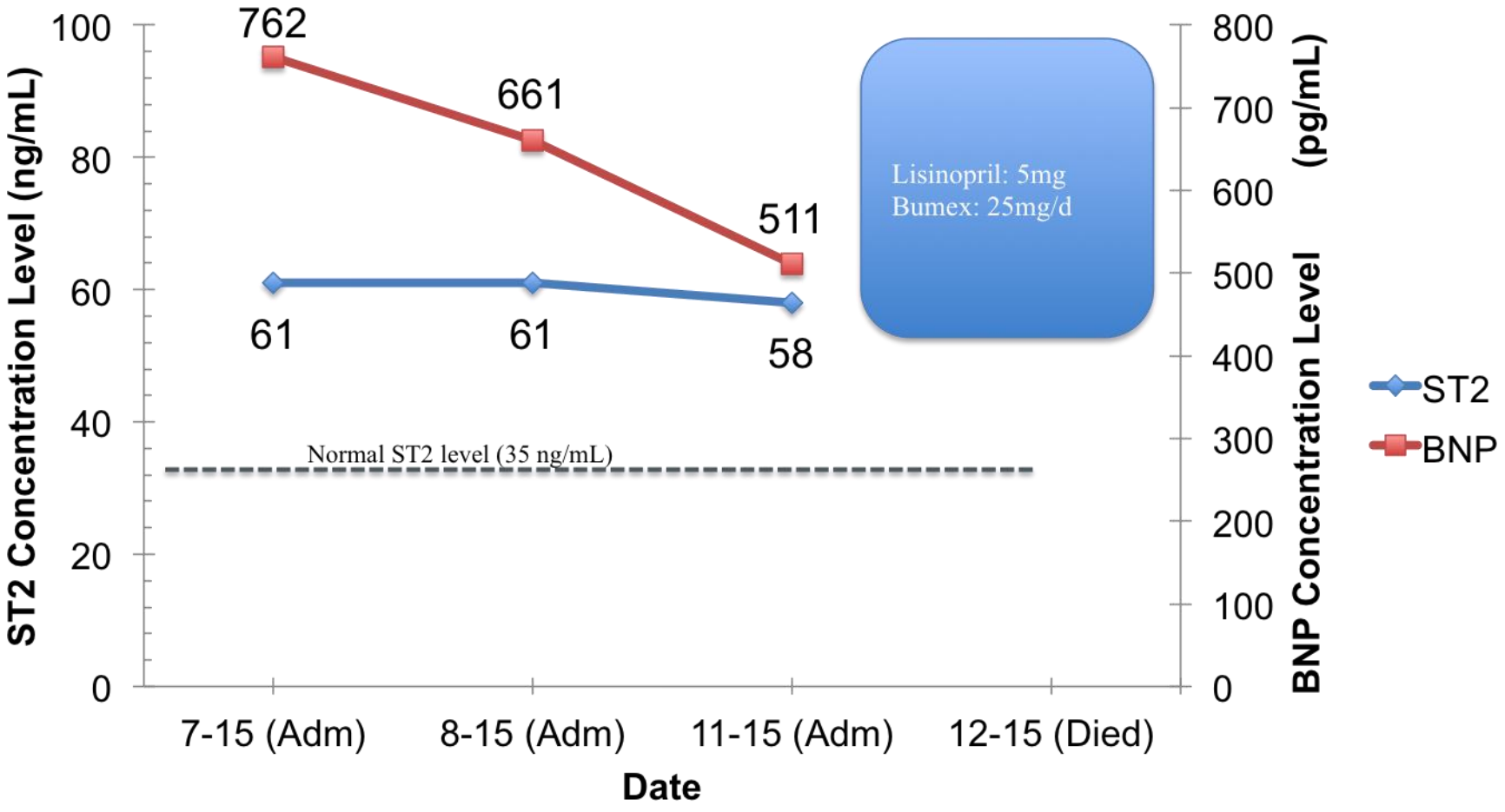


Patient: H.V.



No readmissions over **One Year**

Patient: B.H.



BNP dropped, but not ST-2

JACC: HEART FAILURE VOL. 5, NO. 4, 2017

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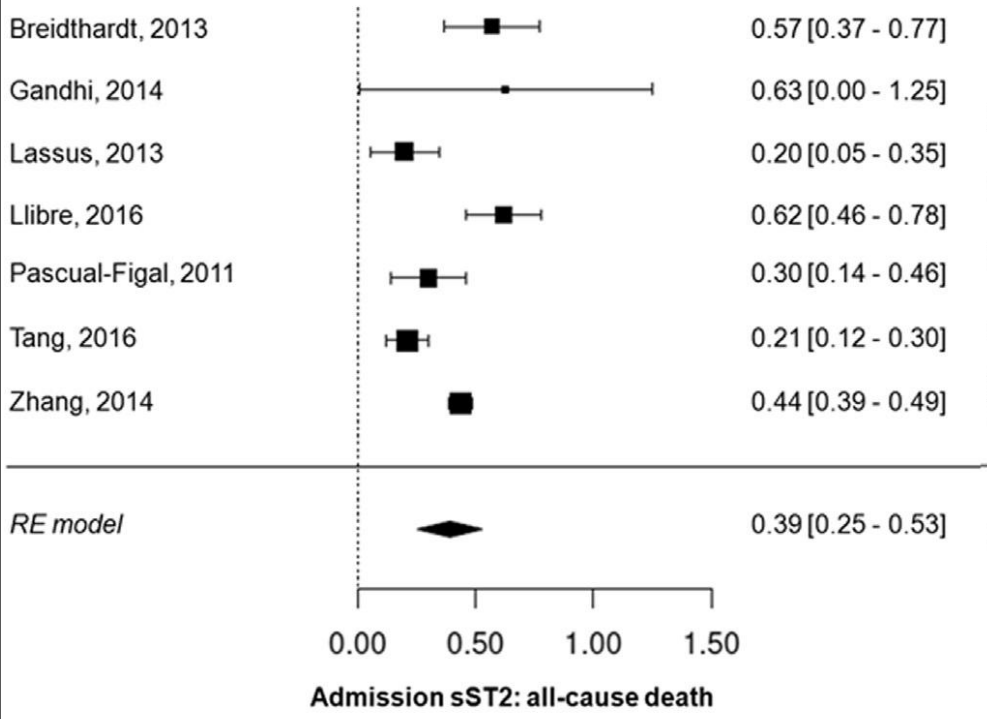
Meta-Analysis of Soluble Suppression of Tumorigenicity-2 and Prognosis in Acute Heart Failure

Alberto Aimo, MD,[a] Giuseppe Vergaro, MD,[a,b] Andrea Ripoli, EngD,[b] Antoni Bayes-Genis, MD, PhD,[c] Domingo A. Pascual Figal, MD, PhD,[d] Rudolf A. de Boer, MD,[e] Johan Lassus, MD, PhD,[f] Alexandre Mebazaa, MD, PhD,[g] Etienne Gayat, MD, PhD,[g] Tobias Breidthardt, MD,[h] Zaid Sabti, MD,[h] Christian Mueller, MD,[h] Hans-Peter Brunner-La Rocca, MD,[i] W.H. Wilson Tang, MD,[j] Justin L. Grodin, MPH,[k] Yuhui Zhang, MD,[l] Paulo Bettencourt, MD,[m] Alan S. Maisel, MD,[n] Claudio Passino, MD,[a,b] James L. Januzzi, MD,[o] Michele Emdin, MD, PhD[a,b]

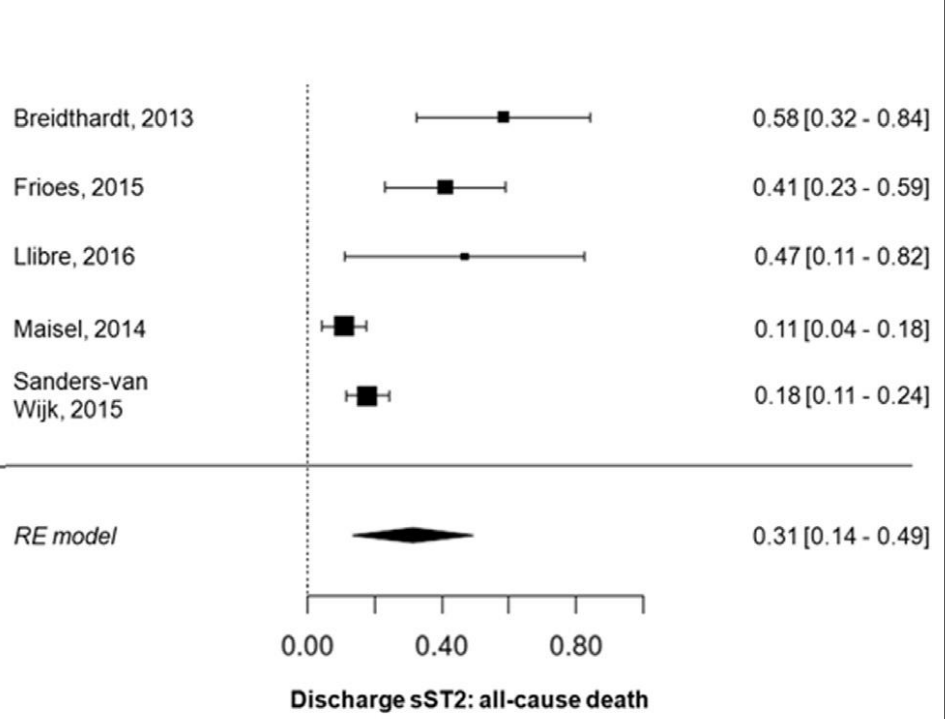
ST2 Predicts All-cause Death in Acute HF

Admission



Hazard Ratio = 2.46

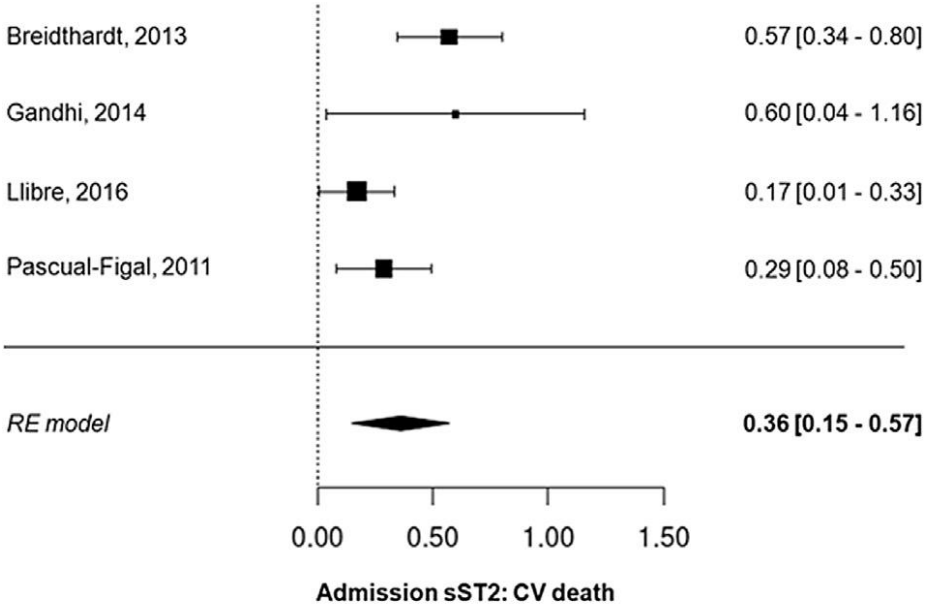
Discharge



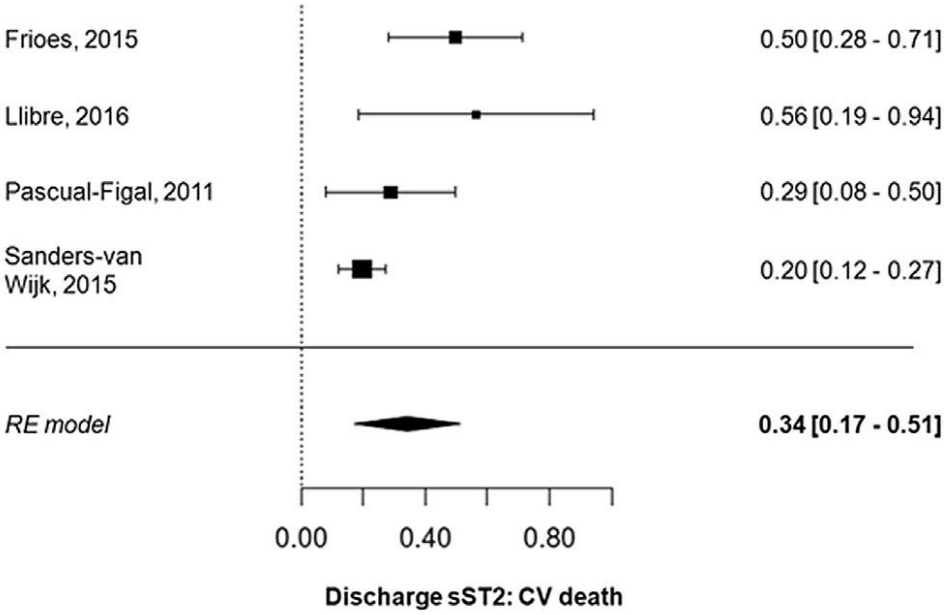
Hazard Ratio = 2.06

ST2 Predicts Cardiovascular Death in Acute HF

Admission



Discharge

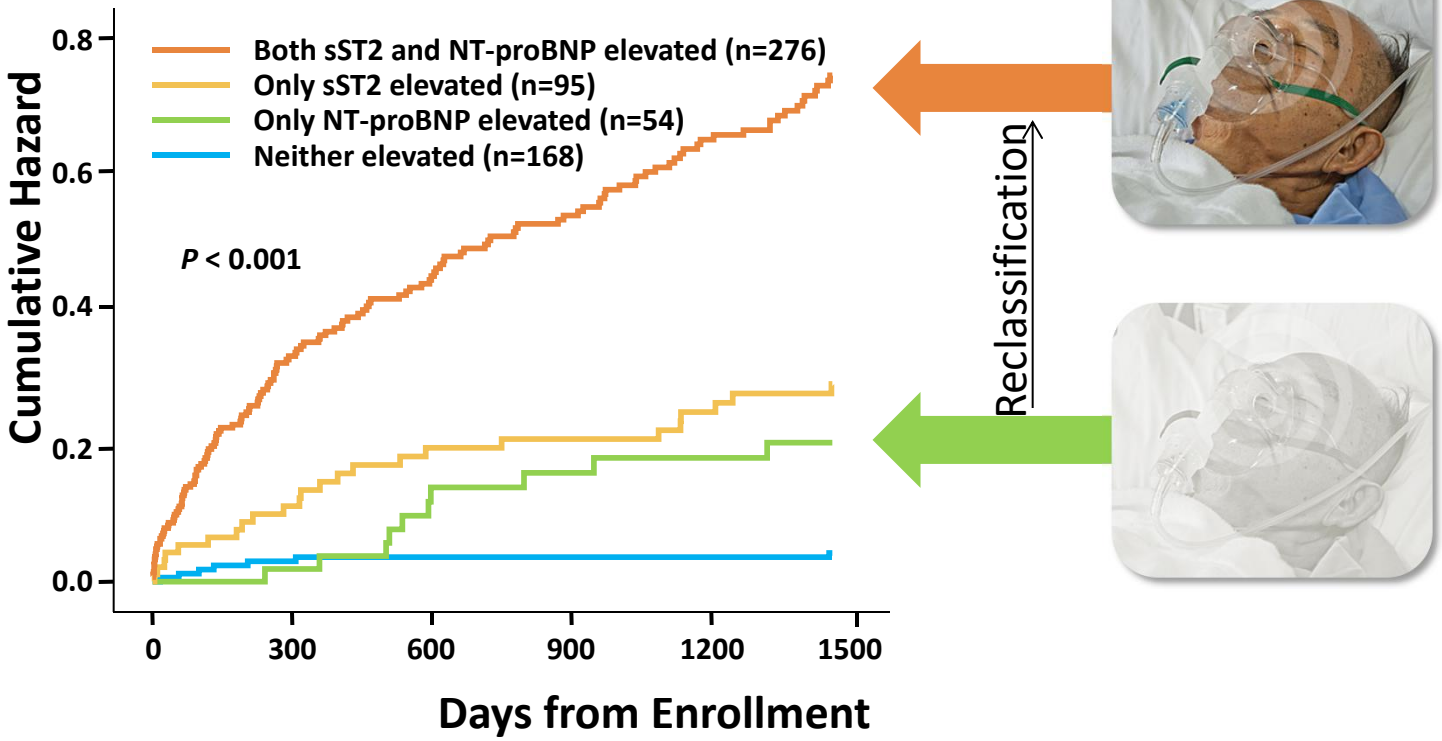


Hazard Ratio = 2.29

Hazard Ratio = 2.20

sST2 the ultimate death marker?

Additive Value of ST2 to NT-proBNP:Acute HF



Patient would have been classified as moderate risk with only NT-proBNP, but is considered high risk with the addition of ST2.

Rehman SR, van Kimmenade RR, Januzzi JL. *Circulation.* 2008;118:S_871.

Combined Measurement of Soluble ST2 and Amino-Terminal Pro-B-Type Natriuretic Peptide Provides Early Assessment of Severity in Cardiogenic Shock Complicating Acute Coronary Syndrome

Heli Tolppanen, MD[1–3]; Mercedes Rivas-Lasarte, MD[1,4]; Johan Lassus, MD, PhD[3]; Malha Sadoune, MSc[1]; Etienne Gayat, MD, PhD[1,5]; Kari Pulkki, PhD[6]; Mattia Arrigo, MD[1,5,7,8]; Evguenia Krastinova, MD, PhD[1,9]; Alessandro Sionis, MD[4]; John Parissis, MD, PhD[10]; Jindrich Spinar, MD, PhD[11,12]; James Januzzi, MD, PhD[13]; Veli-Pekka Harjola, MD, PhD[14]; Alexandre Mebazaa, MD, PhD[1,5,15]; for the CardShock Study Investigators and the GREAT Network

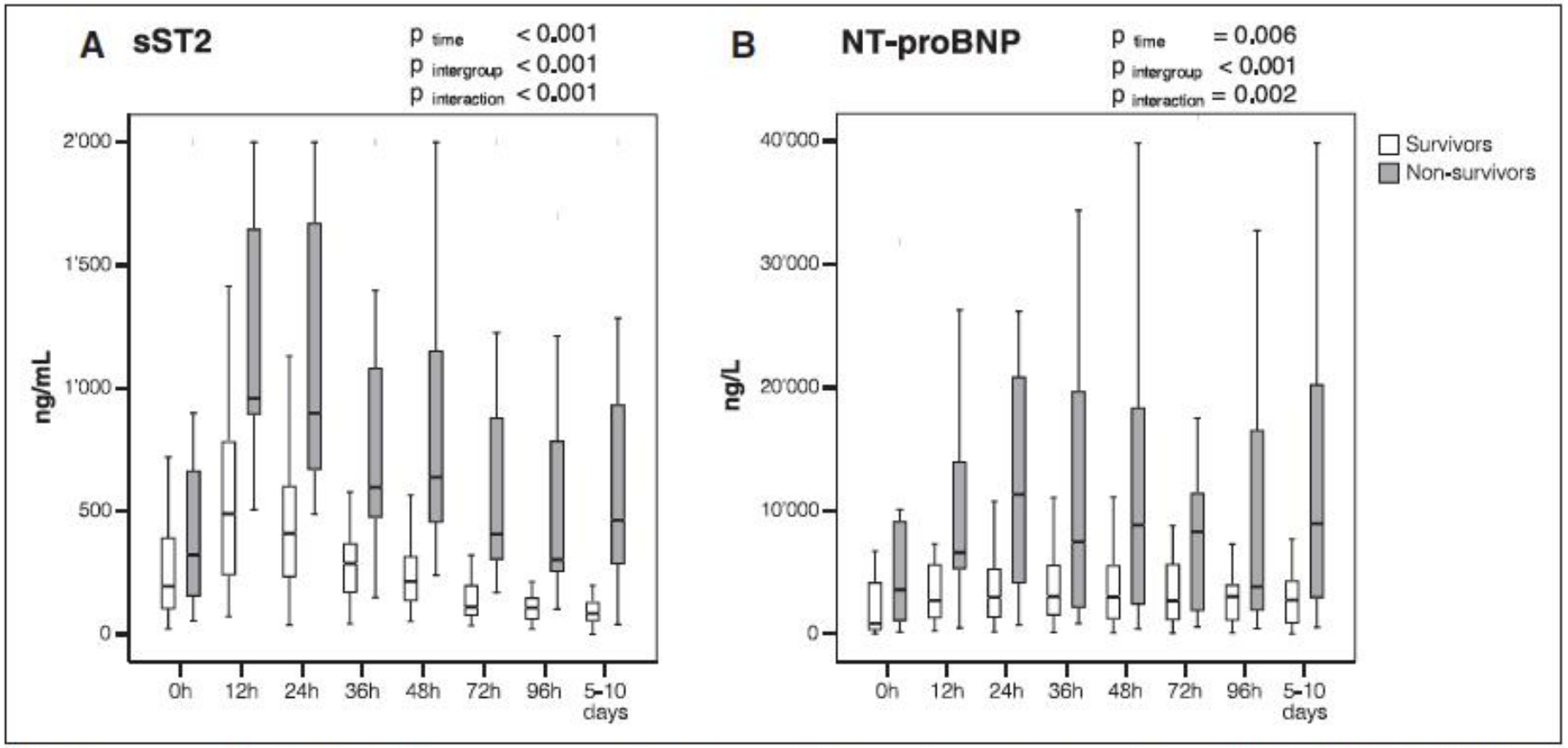
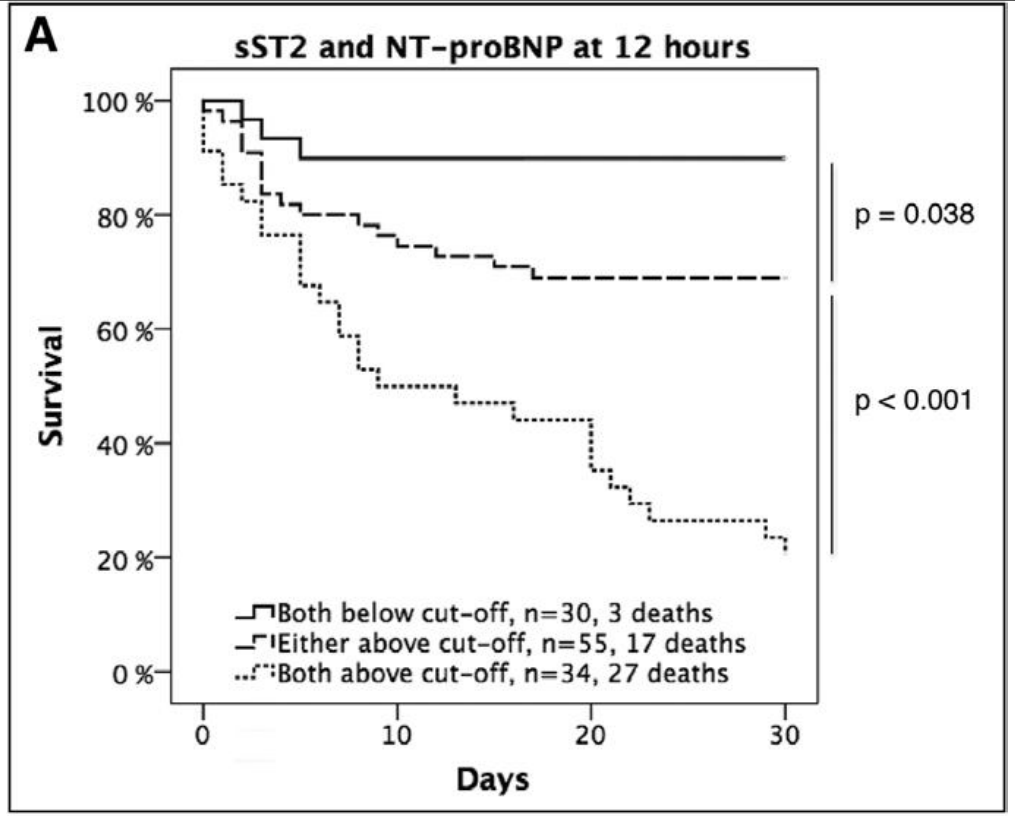
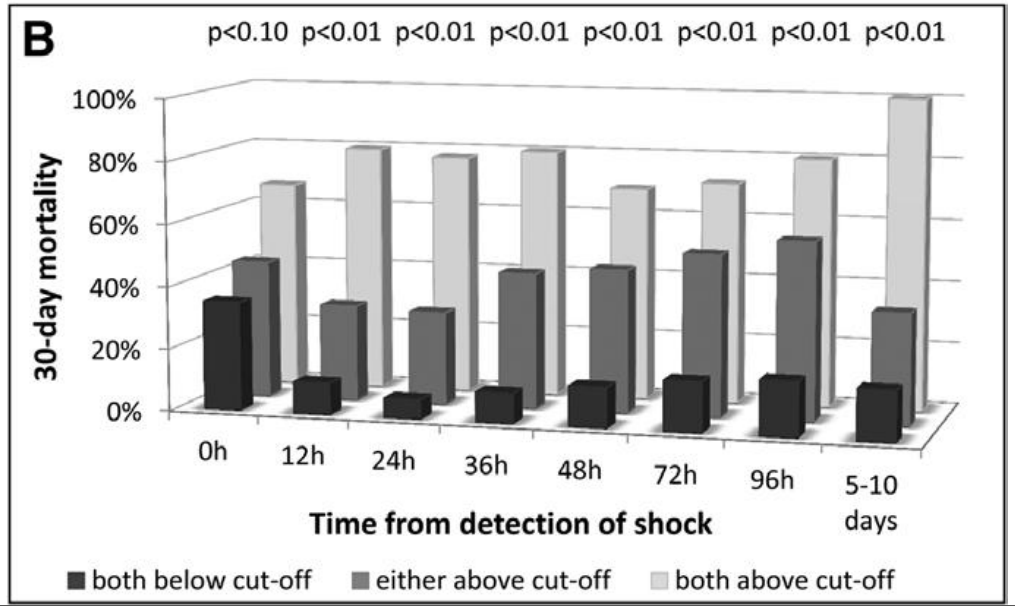


Figure 1. Kinetics of soluble ST2 (sST2) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP). Levels of sST2 (**A**) and NT-proBNP (**B**) in 30-d survivors (*white boxes*) and nonsurvivors (*gray boxes*) in time course. *Central line* represents median, *box* represents interquartile range, and *whiskers* represent fifth and 95th percentile.


A
sST2 and NT-proBNP at 12 hours
100 %
80 %
60 %
40 %
20 %
0 %
Survival
0
10
20
30
Days
p = 0.038
p < 0.001
Both below cut-off, n=30, 3 deaths
Either above cut-off, n=55, 17 deaths
Both above cut-off, n=34, 27 deaths


B
p<0.10 p<0.01 p<0.01 p<0.01 p<0.01 p<0.01 p<0.01 p<0.01
100%
80%
60%
40%
20%
0%
30-day mortality
0h
12h
24h
36h
48h
72h
96h
5-10 days
Time from detection of shock
both below cut-off
either above cut-off
both above cut-off

sST2: ACUTE HF

High NP Levels

<35

DIAGNOSIS*
Very unusual (10%)

INTERPRETATION
Question the Dx

ACTION
Consider other causes of increase in BNP

*DOES NOT REPLACE NP

35-70

DIAGNOSIS*
Fairly common (40%)

INTERPRETATION
Associated with mild to moderate HF

ACTION
May be able to go home after diuretic

>70

DIAGNOSIS*
Fairly common (40%)

INTERPRETATION
Associated with sigficant neurohormonal and fibrotic pathways

ACTION
1. Admission
2. Use spironolac

“High Sensitivity Troponin”

What Does it Mean?
What Should I Do?

Famous lies throughout history

1600's You can't burn a witch

1700's Night air causes pneumonia

1800's Tomatoes will kill you

1900's Stop that or you'll go blind

(my mother)

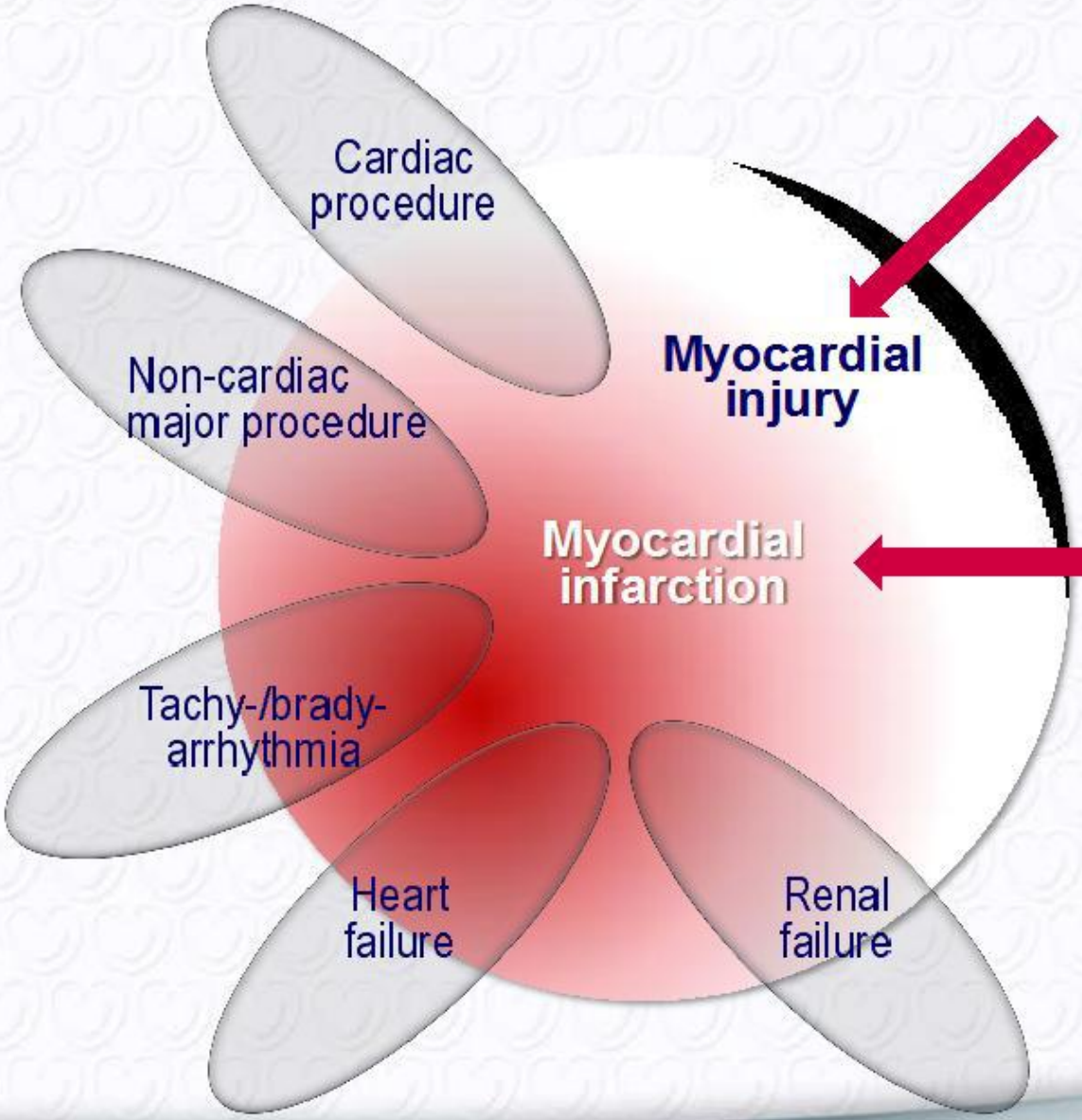
2010's Those are just false positive troponins

(~a bunch of very famous cardiologists)

There are really Dr's out there that don't believe in hscTn???

TROPONIN IS A MARKER OF MYOCARDIAL ~~INFARCTION~~

INJURY



Myocardial injury with cell death market by cardiac troponin elevation

Clinical evidence of acute myocardial ischaemia with rise and/or fall of cardiac troponin

www.escardio.org/guidelines

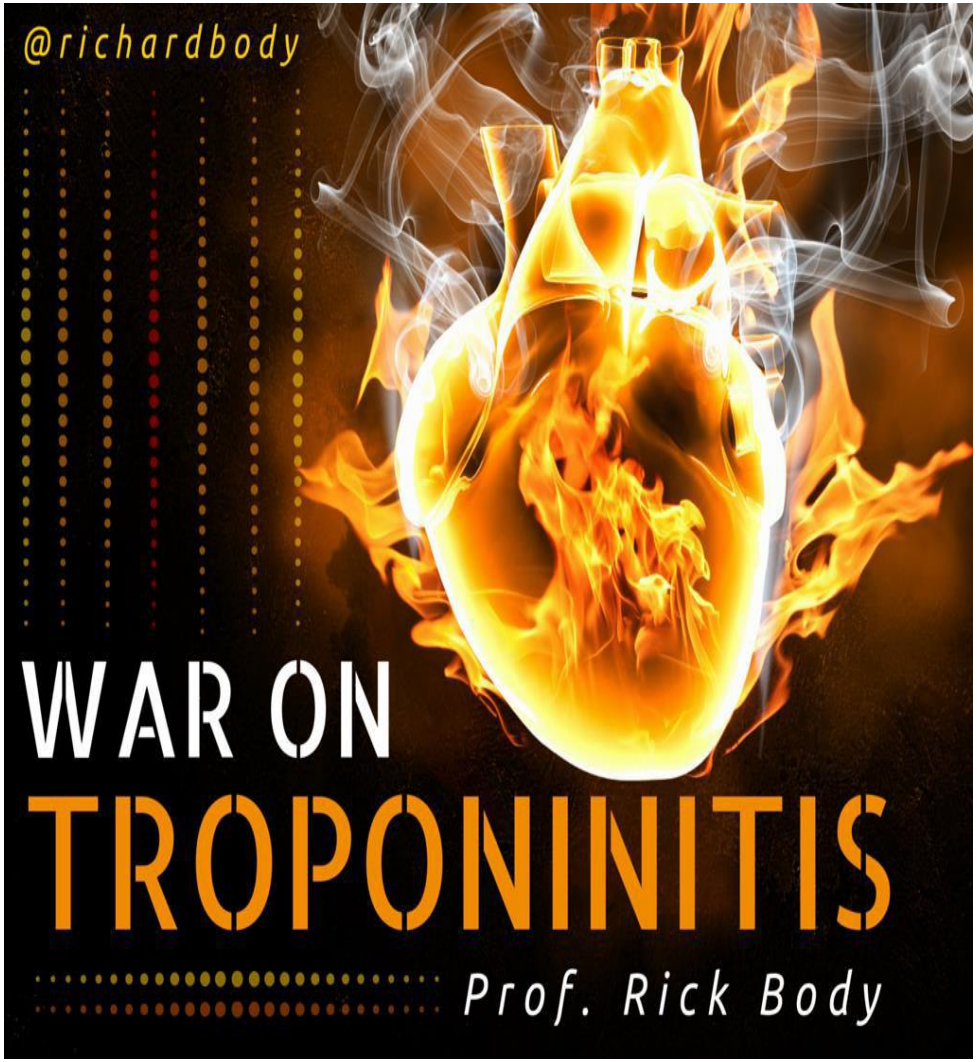
European Heart Journal (2012) 33: 2551–2567
doi:10.1093/eurheartj/ehs184

EUROPEAN SOCIETY OF CARDIOLOGY®

Contemporary troponin

Glasses vs no-glasses

- ALMOST ALL SPECIALTIES BELIEVE THAT INCREASED ACCURACY IS BETTER
  - WHAT IS UP WITH THE CARDIOLOGISTS?


@richardbody
WAR ON
TROPONINITIS
Prof. Rick Body

You know you're a cardiologist when….

- You have made up a vernacular to denigrate small troponin increases, **as if they are unimportant**

- Troponinitis
- Troponinosis
- Troponenemia
- Troponin leak

I call BS

Not only is this unacceptable, its irresponsible

Have you ever heard any other specialists say?

Nephrologist

- Creatinemia
- Creatinine leak
- Creatinitis
- Creatinenosis

Neurologist

- Its just a little brain leak
- Brainitis
- Brainosis
- Brainemia

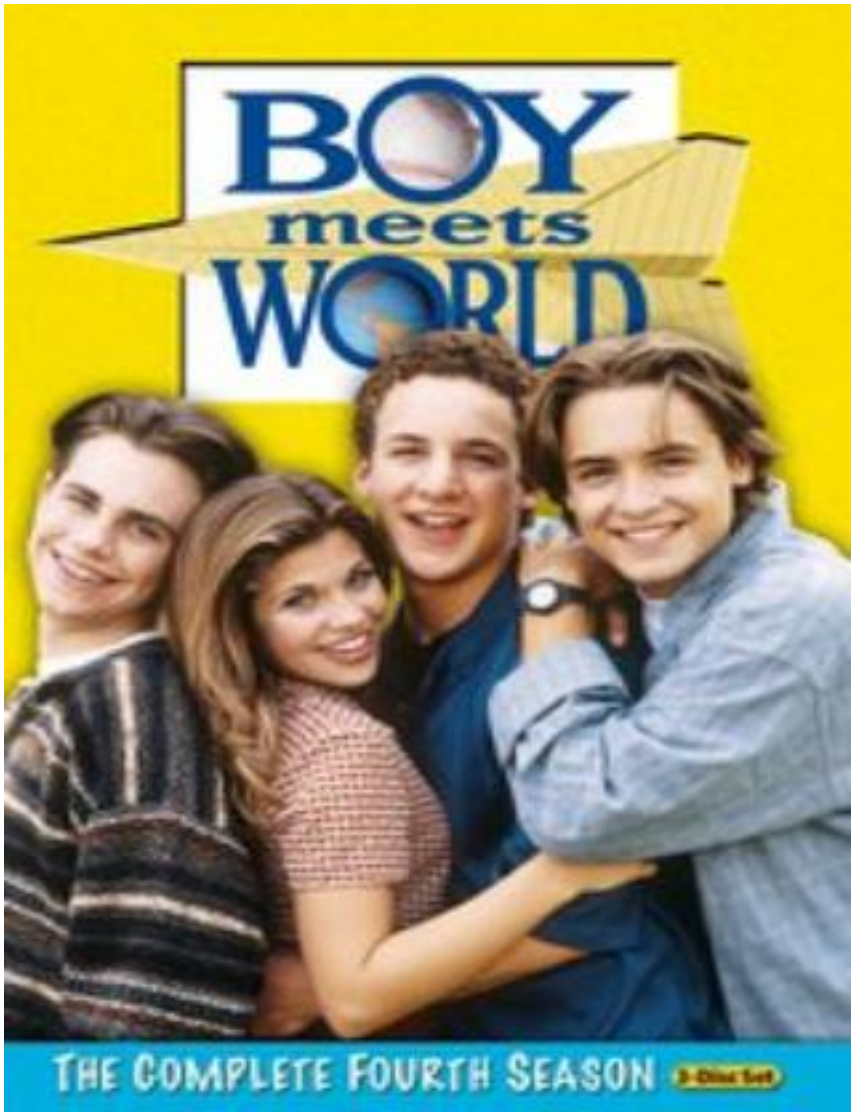
“Its just a little brick leak”

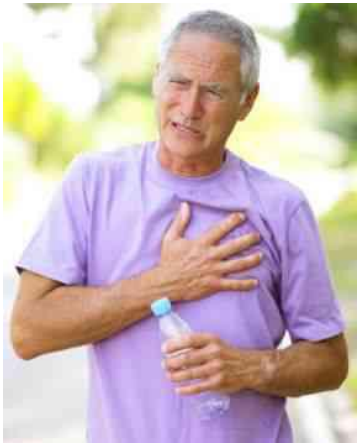
Small troponin leak

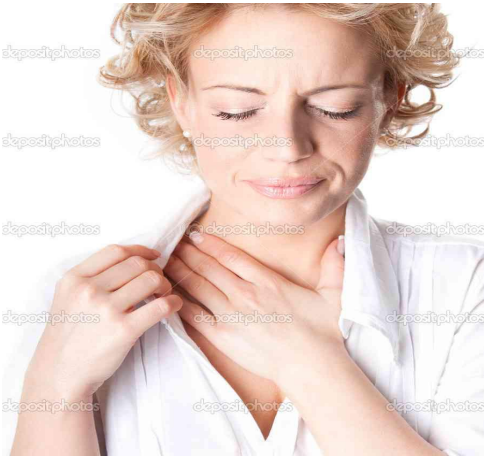
Are they really false positives when the elevation gives you greater risk?

- BUT HOW DO WE ARBITRATE THAT RISK OF ELEVATED TROPONIN IN A TYPE II MI?

sST2 in the future of Emergency Medicine- Coming of Age



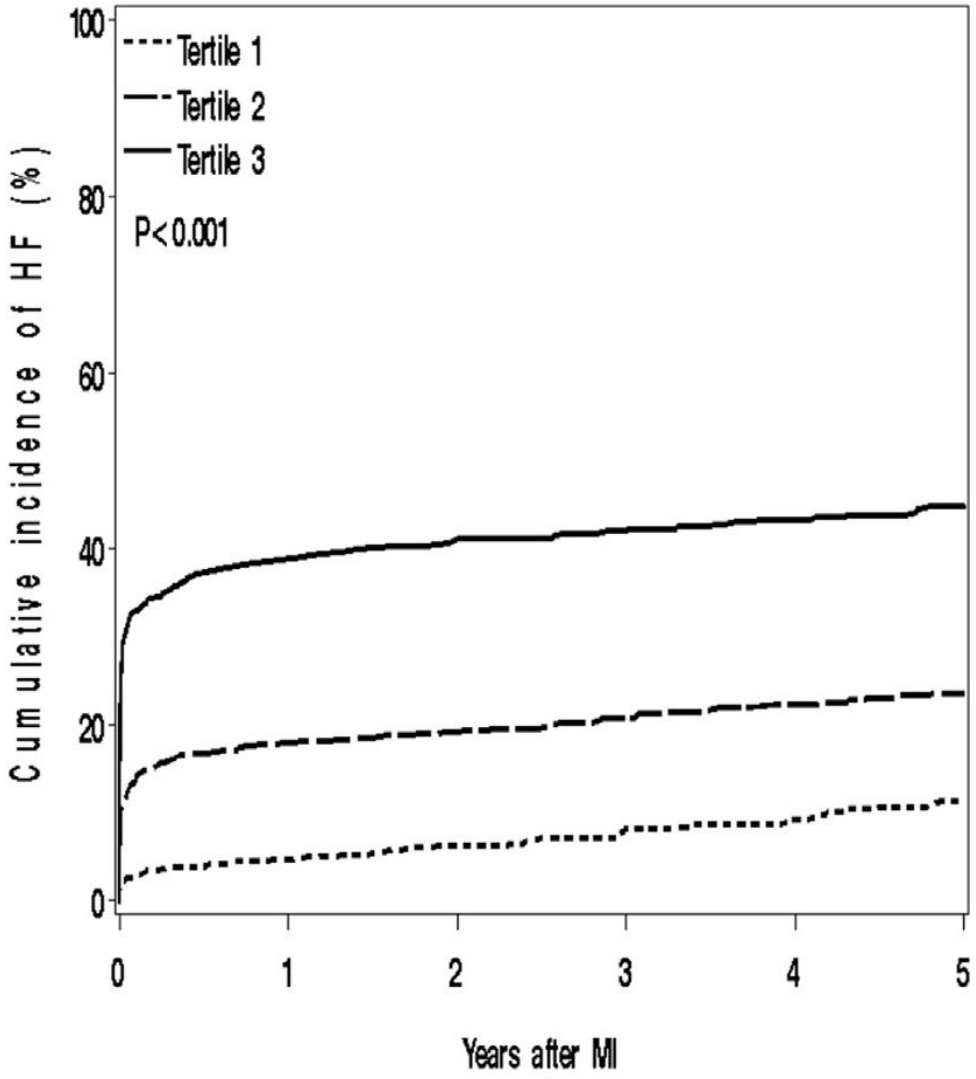




The Multiple Causes of Troponin Elevation

Cardiac contusion	Heart failure	Aortic dissection	HOCM
Takotsubo	Arrhythmias or heart block	Pulmonary embolism	Renal failure
SAH	Myocarditis	Critical illness	Burns
Extreme exertion	Type 1 myocardial infarction	Type 2 myocardial infarction	Normal biological variation

sST2 levels Predict HF post-MI



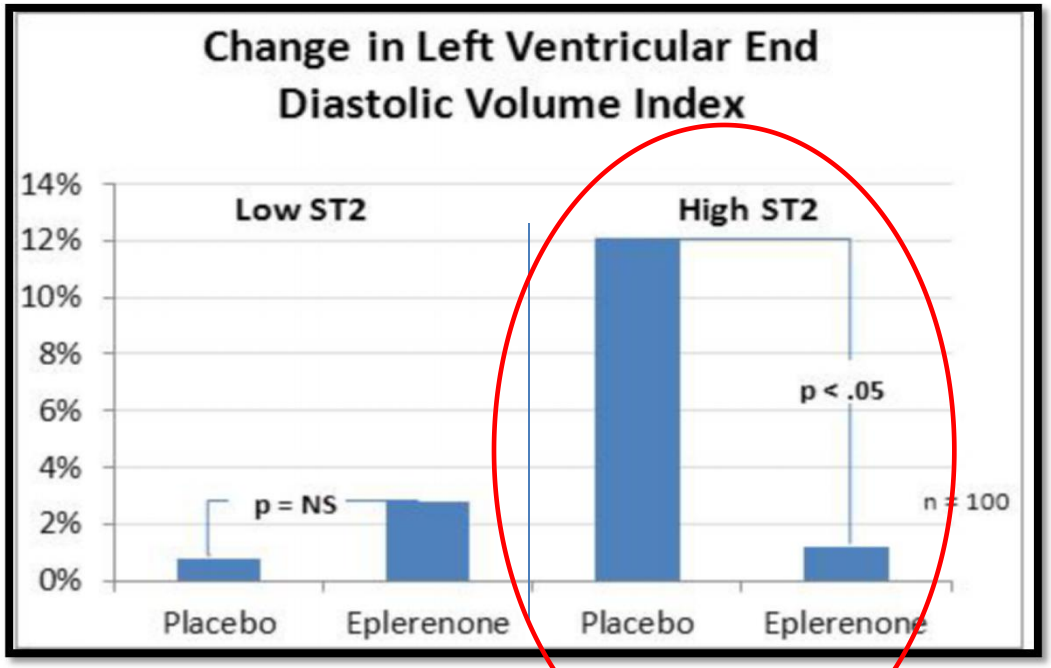
HR 2.88

HR 1.67

Jenkins, Am J Med. 2017 Sep;130(9):1112.e9-1112.e15

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

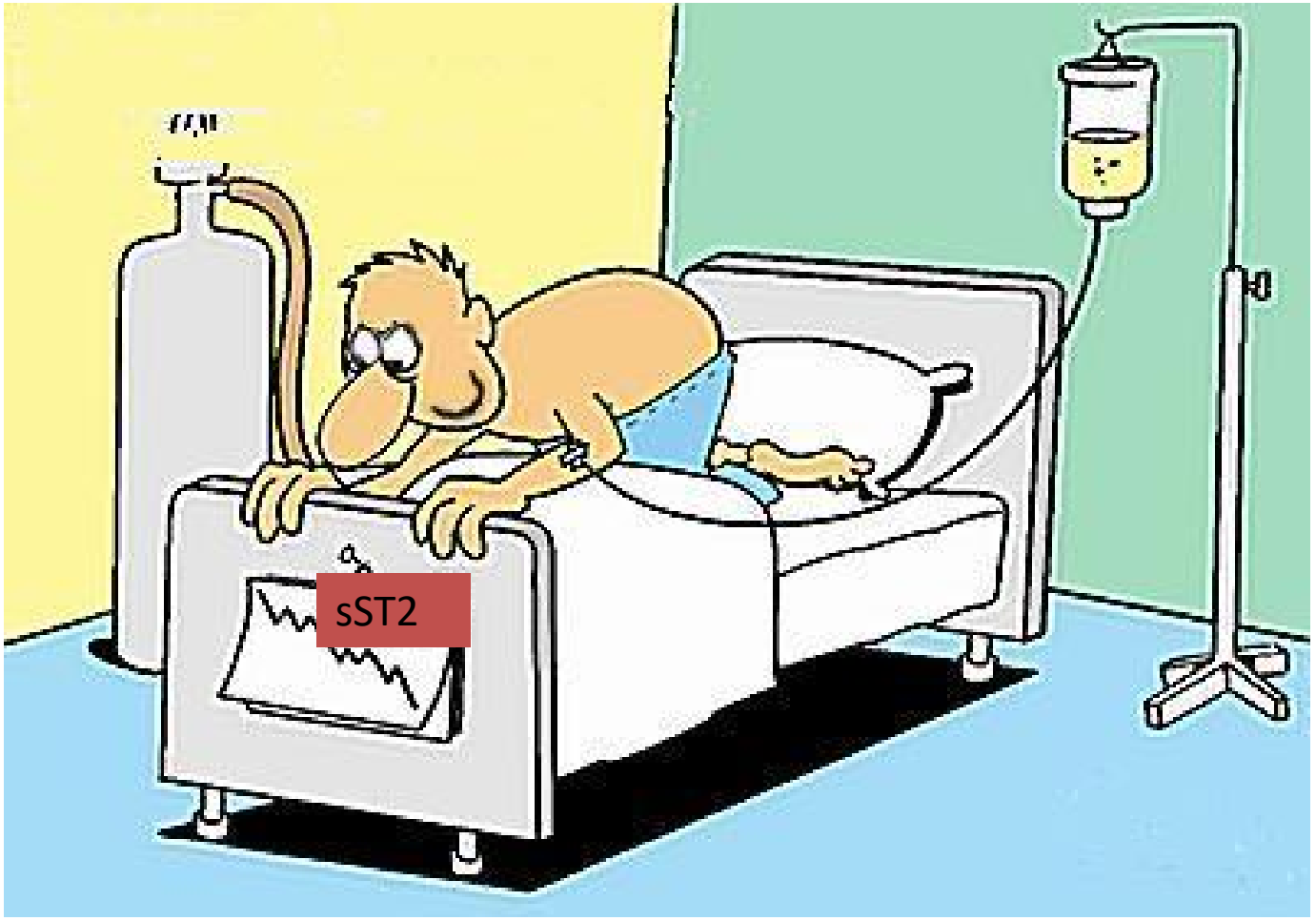


High and low ST2 separated at median.

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

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

Alogorithms for Type One and Type II MI utilizing sST2



sST2: TYPE I MI

<35	35-70	>70
DIAGNOSIS* No activation of fibrotic pathways INTERPRETATION Adverse remodeling unlikely ACTION Standard of care	DIAGNOSIS* Moderate activation of fibrotic pathways INTERPRETATION Adverse remodeling likely ACTION ACE, BB; consider spiranolactone or	DIAGNOSIS* Fairly common (40%) INTERPRETATION Associated with sigficant neurohormonal and fibrotic pathways, HF likely ACTION 1. Aggressive anti-

*DOES NOT REPLACE NP

SST2: TYPE II MI

Troponin levels elevated

<35	35-70	>70
DIAGNOSIS* No activation of fibrotic pathways INTERPRETATION Adverse remodeling unlikely ACTION Mild disease consider follow up after discharge	DIAGNOSIS* Fairly common (40%) INTERPRETATION Adverse remodeling likely ACTION Treat underlying cause: HTN,HF, Afib, +/- admission	DIAGNOSIS* Fairly common INTERPRETATION Significant neurohormonal and fibrotic pathways, HF likely ACTION 1. Admission 2. Aggressive workup and Rx HTN, HF, Afib, etc. 3. Ischemia w/u in

*DOES NOT REPLACE NP

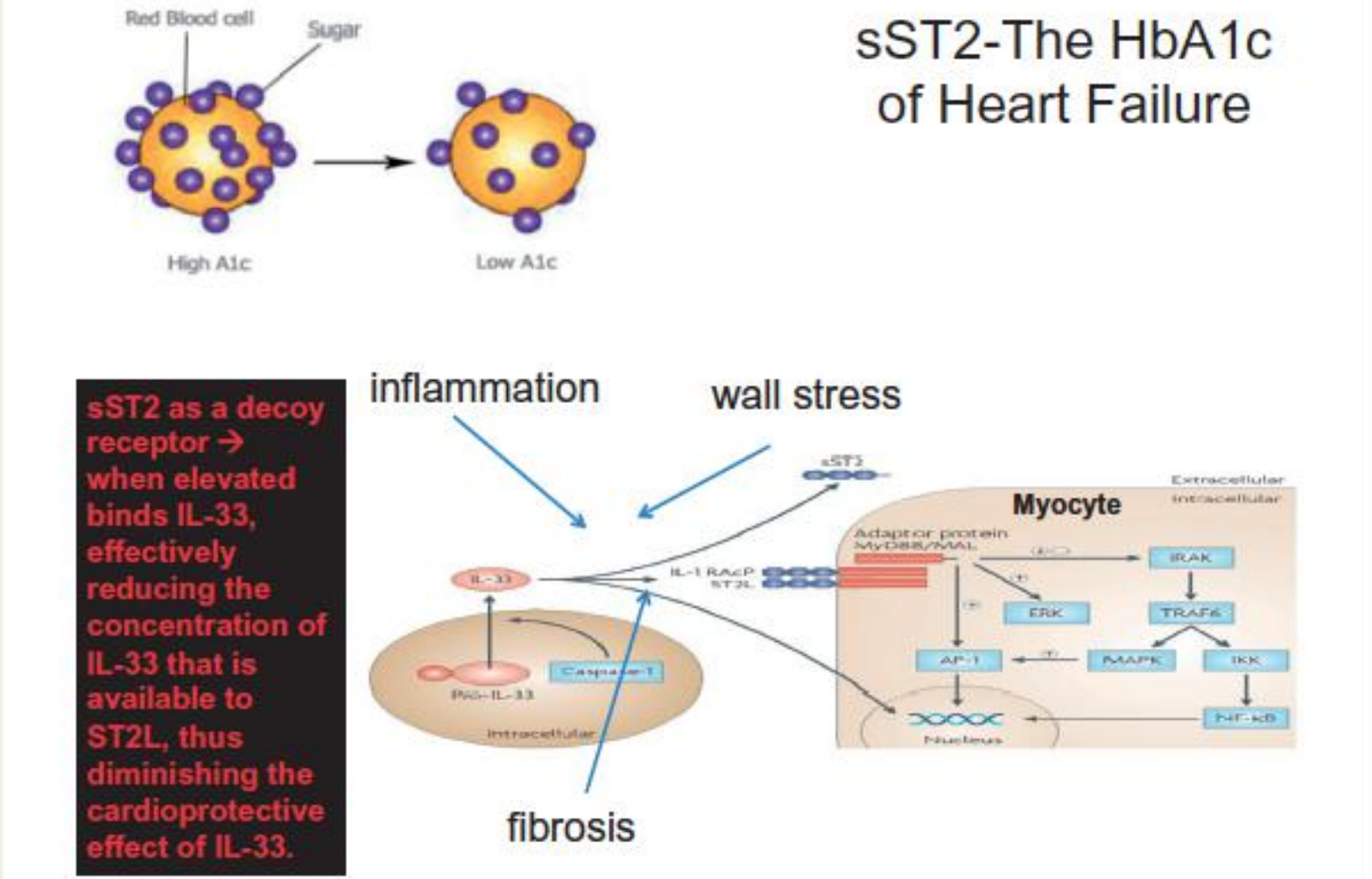
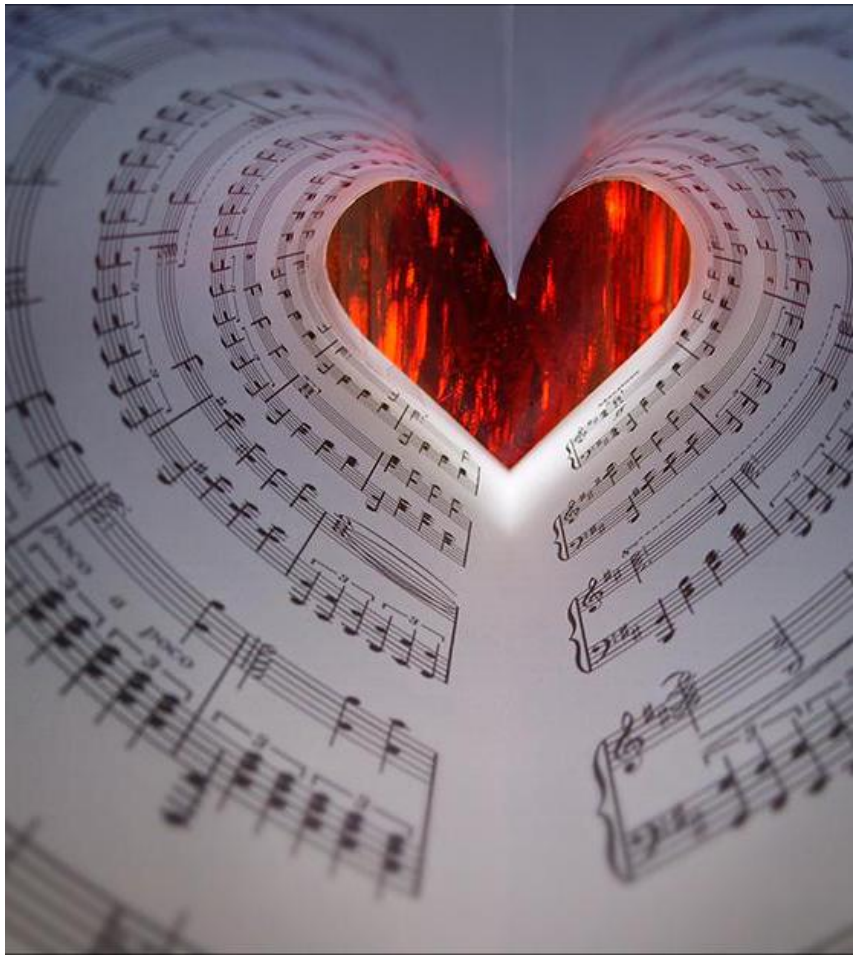


Figure 1 sST2 the HbA1c of heart failure.

The Science merged with the ART



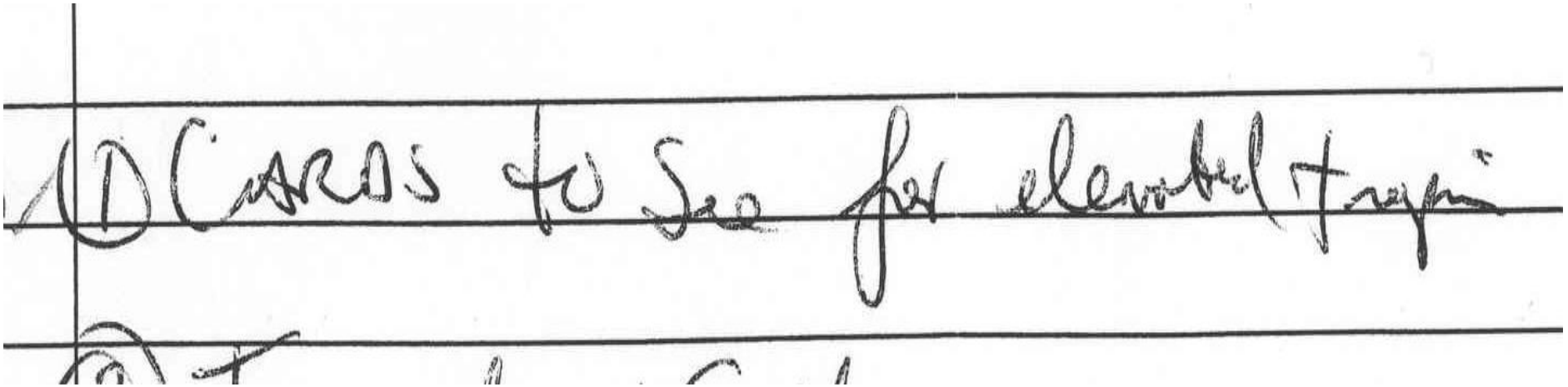

Biomarkers will
Make bad
doctors worse
and good
doctors better!

A First Warning

- The use of Biomarkers for diagnosis and guiding therapy is always secondary to clinical judgment

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!!!