Biomarkers in Heart Failure: The Old and The New

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Case

- RM is a 56 yo male. He was admitted to the hospital 2 weeks ago with his first episode of HF, and is sent to you for post-discharge f/u.
- Non-ischemic, LVEDD 69 mm, EF 25%, normal RV fxn
- ECG with NSR@102 bpm, LVH, QRS 100 ms
- On ASA, lisinopril 10, metoprolol succinate 12.5, simvastatin
- Weight 105 kg, BP 124/76, HR 96, JVP 16 cm H2O, 2/6 HSM, +S3
- BUN 18, Creatinine 1.2, eGFR 56

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- BUN 18, Creatinine 1.2, eGFR 56
- NT-proBNP 2200
- sST2 44

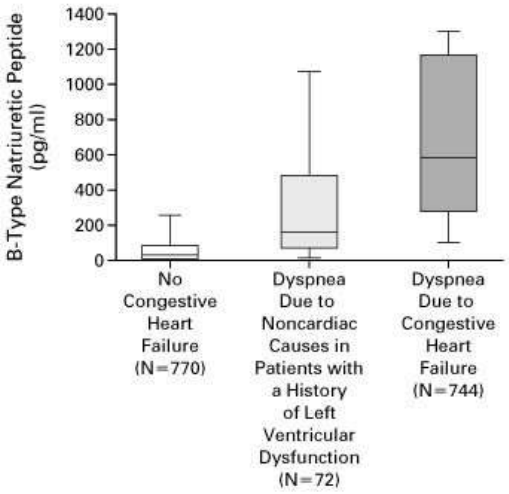
What Makes a Good Biomarker?

- A measurable phenomenon that allows:
  - Detection of Preclinical Disease
  - Diagnosis
  - Risk Stratification
  - Treatment Selection and Monitoring

The Promise of Biomarker Guided Tx

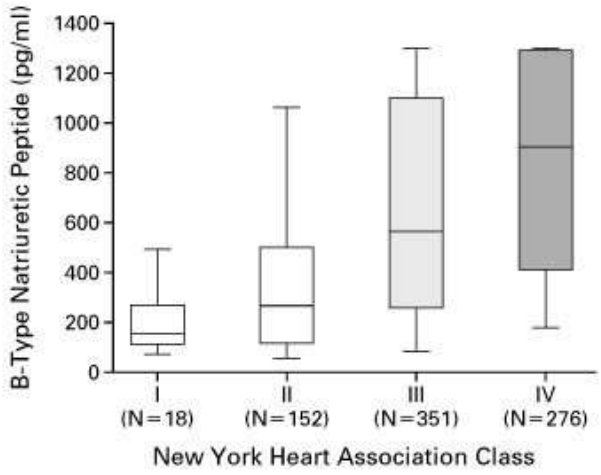
- Instead of empiric uptitration of therapy, if a physiologic target or marker could be used, we might be more able to prescribe the right therapy, at the right time, at the right dose, in the right patient

The Breathing Not Properly Study



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

The Breathing Not Properly Study



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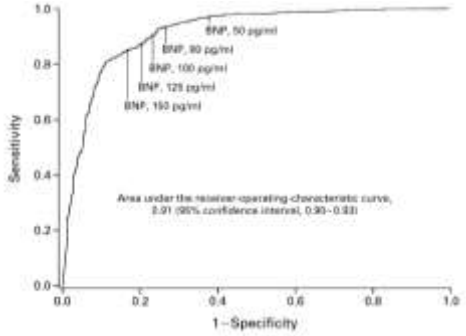

BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
		(95 percent confidence interval)			
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	78 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	82 (80–85)	85 (83–88)	84

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

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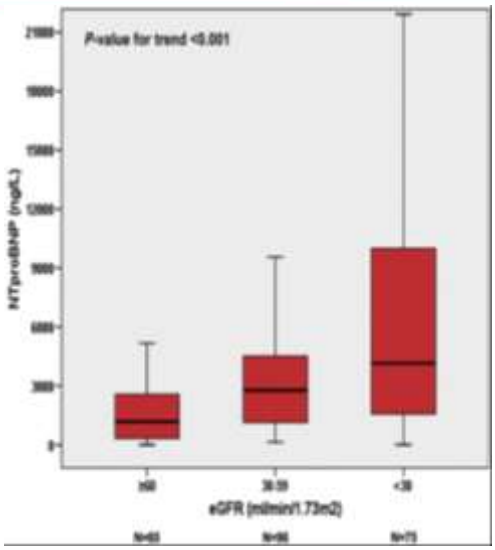
Assay Characteristics



Bayes-Genis et al, Am J Cardiol p3A

What Makes a Good Biomarker?

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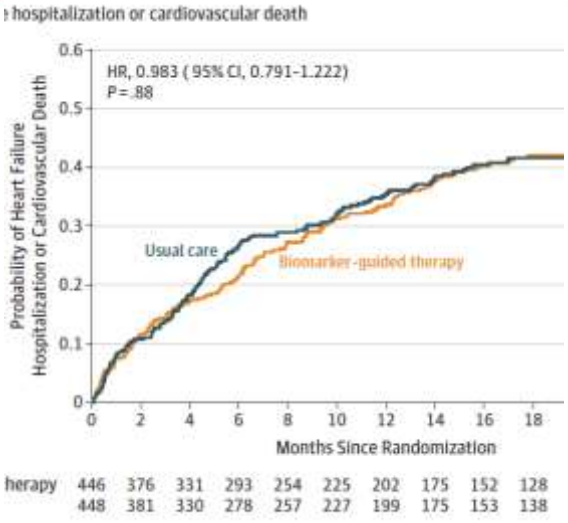
Guide-IT

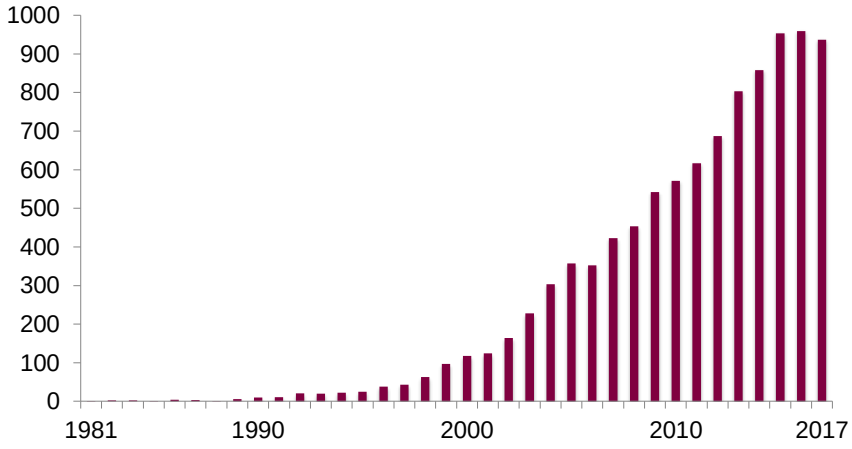


Felker et al, JAMA 2017; 318:713-720

BNP as a Biomarker

	Y	N
Detection of Preclinical Disease		X
Diagnosis	✓	
Risk Stratification	✓	
Treatment Selection and Monitoring		X

Biomarker Studies



Defining New biomarkers

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STATE-OF-THE-ART PAPER

Charting a Roadmap for Heart Failure Biomarker Studies

Tariq Ahmad, MD, MPH,*† Mona Fiuzat, PharmD,*† Michael J. Pencina, PhD,* Nancy L. Geller, PhD,‡ Faiez Zannad, MD, PhD,§ John G.F. Cleland, MD,‖ James V. Snider, PhD,¶ Stephan Blankenberg, MD,# Kirkwood F. Adams, MD,** Rita F. Redberg, MD, MPH,†† Jae B. Kim, MD,‡‡ Alice Mascette, MD,§§ Robert J. Mentz, MD,* Christopher M. O'Connor, MD,*† G. Michael Felker, MD, MHS,*† James L. Januzzi, MD*‖‖

TABLE 1 Evaluation of Heart Failure Biomarkers

Method
The method by which a novel biomarker is judged should be thorough: novel tests should be evaluated across a wide range of patients typical of the diagnosis for which the biomarker will be applied, and the statistical methods used to evaluate the biomarker should be contemporary, rigorous, standardized, and fair.

Measurement
Measurement of a novel heart failure biomarker should be easily achieved within a short period of time and provide acceptable accuracy. Assays for its measurement should have defined biological variation and low analytical imprecision.

Mechanism
The biomarker should primarily reflect important pathophysiological processes involved in heart failure presence and progression. Use of a biomarker that is reflective of heart disease but originates outside the myocardium is acceptable as long as such a biomarker provides independently useful information involved in the diagnosis, prognosis, progression, or therapy of heart failure syndromes.

Clinical Information
The biomarker must provide clinically useful information for caregivers and patients to facilitate more swift and reliable diagnosis accurate estimation of prognosis and to inform more successful therapeutic strategies. The information from such a biomarker should not recapitulate clinical information already available at the bedside and must be additional to information provided by established biomarkers.

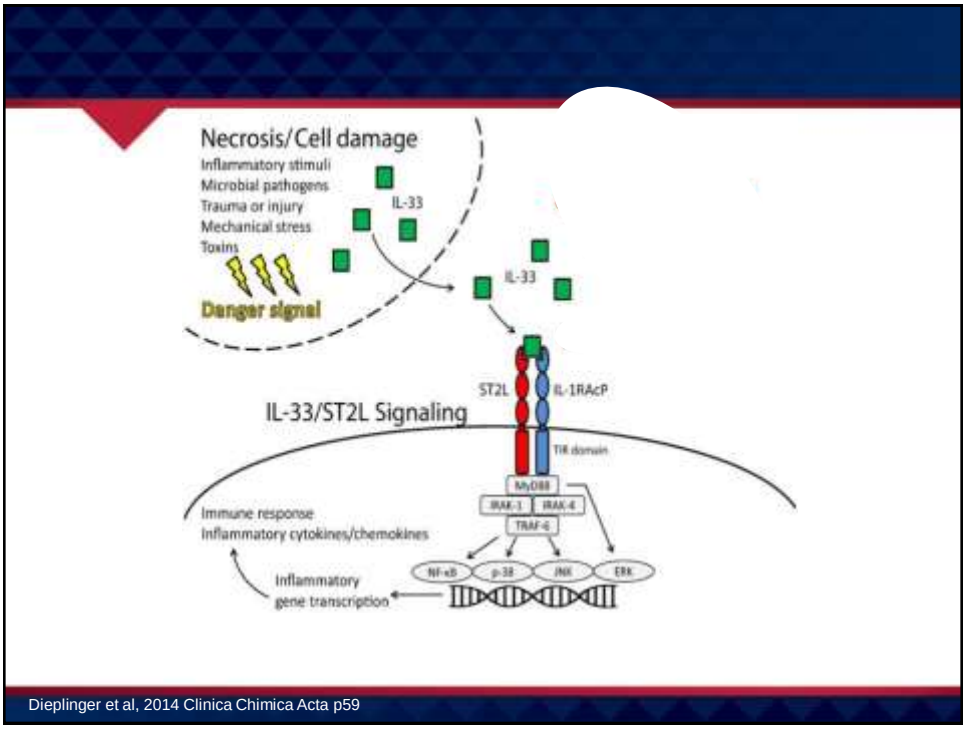
Ahmad et al, JACC:HF 2014, adapted from van Kimmenade and Januzzi

Risk Stratification

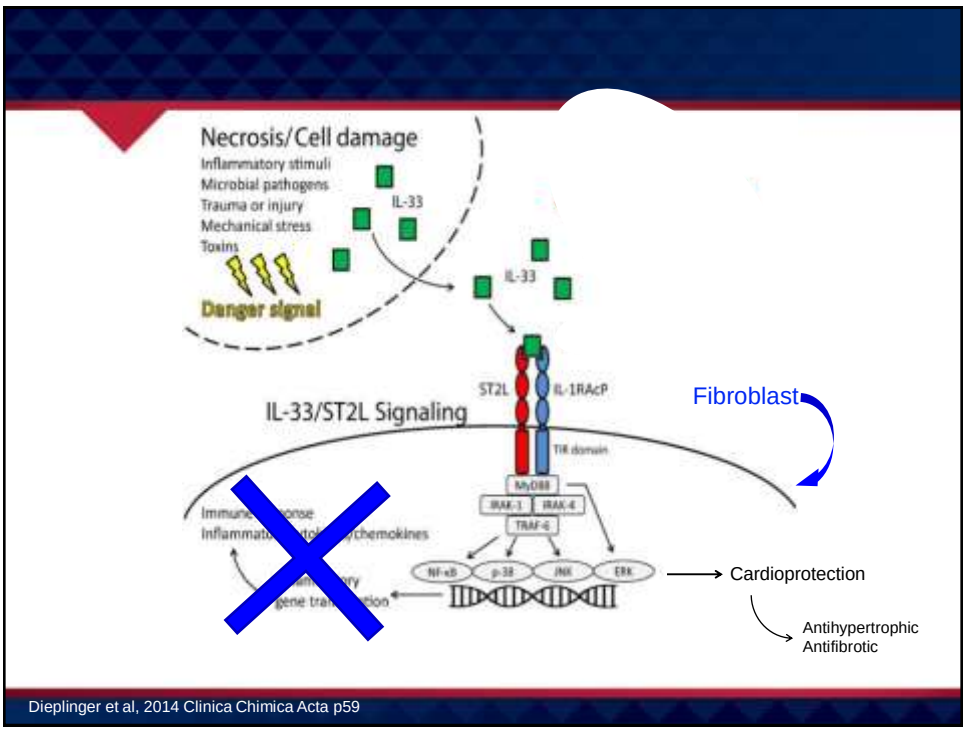
- 100s of biomarkers with demonstrated association with event risk in HF
- Rarely significantly better than BNP
- Almost none with any ability to guide therapeutic decisions

ST2

- Suppression of Tumorigenicity 2 (ST2)
- Member of the IL-1 receptor-like family of proteins
- Immune biology worked out in the 1990s
- Comes in 2 forms – membrane bound (ST2L) and soluble, circulating form (sST2)
- 2002: ST2 the most highly-induced gene in response to mechanical strain a microarray screen



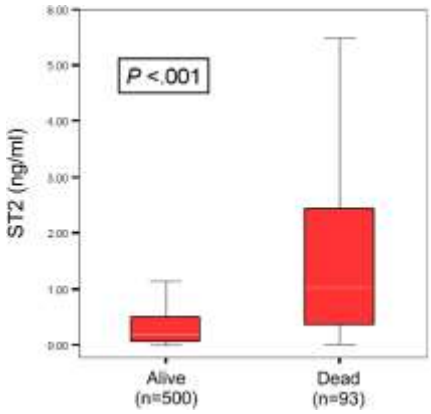
Dieplinger et al, 2014 Clinica Chimica Acta p59



Dieplinger et al, 2014 Clinica Chimica Acta p59

ST2 Risk Stratification in Acute HF

- PRIDE study
- 599 patients presenting to the MGH ED with dyspnea
- 35% adjudicated to have dyspnea due to HF
- Non-HF dx included COPD, pneumonia, ACS, PE, bronchitis, other

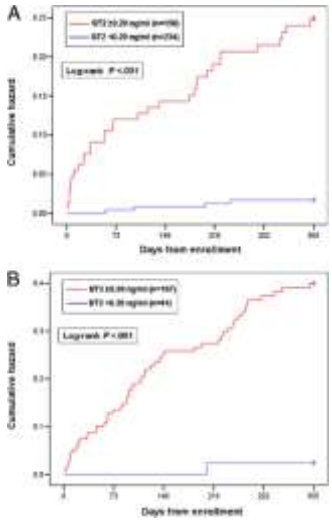


Januzzi JL et al, 2007 JACC p607

Risk Stratification in Acute HF

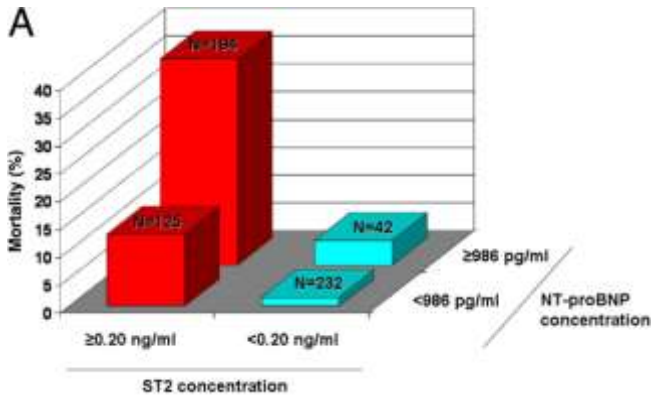
Dyspnea Due to HF

Dyspnea Without HF



Januzzi JL et al, 2007 JACC p607

Risk Stratification in Acute HF



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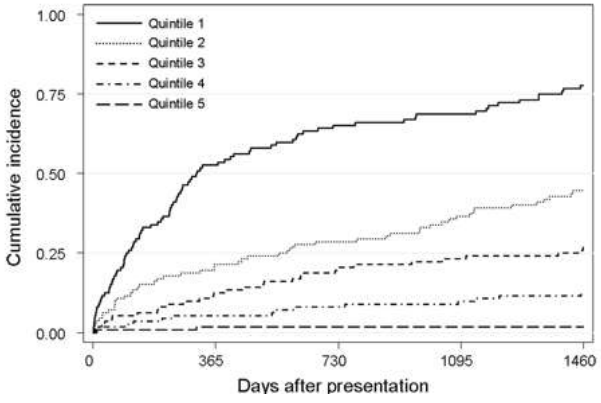
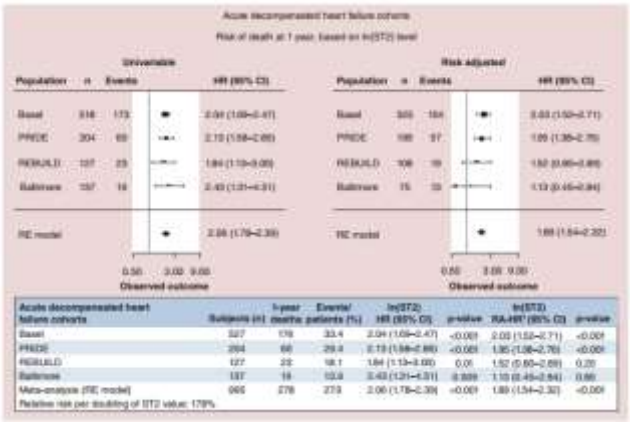
Risk Stratification in Acute HF



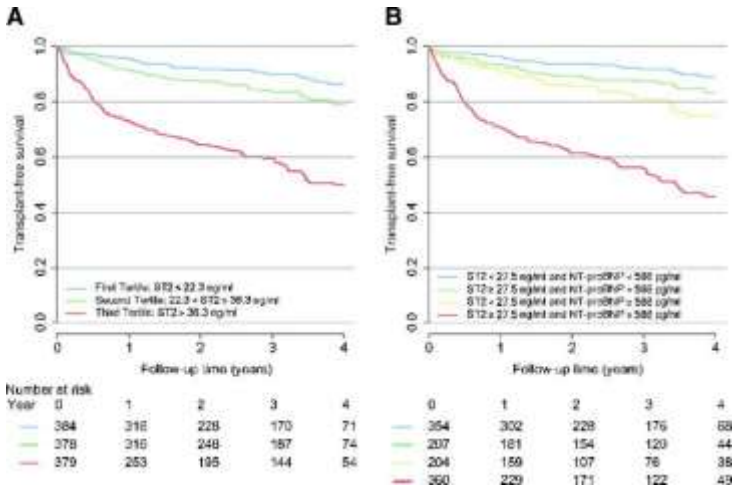
Januzzi JL et al, 2010 Clin Chem p1814

Risk Stratification in Acute HF



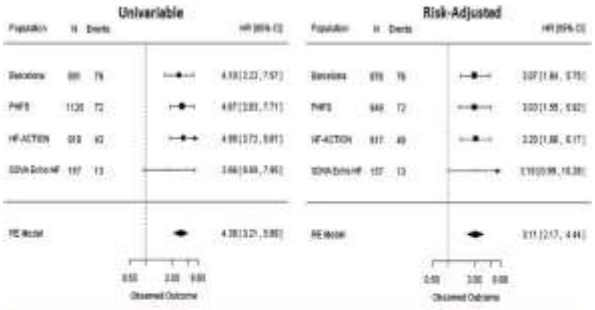
Daniels LB & Bayes-Genis A, 2014 Future Med p525

Risk Stratification in Chronic HF



Ky B et al, 2010 CircHF p180

Risk Stratification in Chronic HF

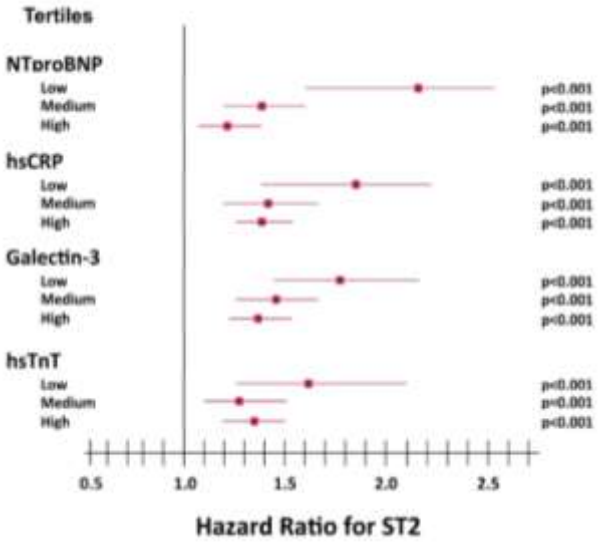


Chronic Heart Failure Cohorts	Subjects (n)	1-Year Deaths	Events/ Patients	>35 ng/mL HR (95% CI)	p	>35 ng/mL RA-HR*(95% CI)	p
Barcelona	876	78	8.7%	4.33 (2.22–7.57)	<0.001	3.07 (1.66–5.73)	<0.001
PHFS	949	72	7.6%	4.67 (2.83–7.71)	<0.001	3.03 (1.55–5.93)	0.001
HF-ACTION	817	40	4.9%	6.95 (2.72–9.01)	<0.001	3.20 (1.66–6.15)	<0.001
EDVA	257	13	5.1%	2.66 (1.09–7.01)	0.07	3.18 (0.39–10.28)	0.28
Meta-Analysis (Random Effects Model)	2799	203	7.2%	4.38 (3.21–5.98)	<0.001	3.11 (2.17–4.44)	<0.001

*Risk-adjusted hazard ratio, adjusted for age, sex, NYHA functional class, left ventricular ejection fraction, estimated glomerular filtration rate, diabetes, hypertension, and smoking.

Bayes-Genis et al, Am J Cardiol p3A

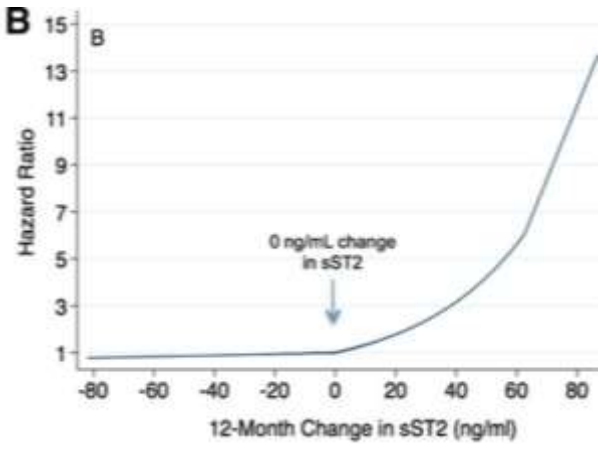
Risk Stratification – Multiple



Bayes-Genis et al, 2014 J Card Fail p25

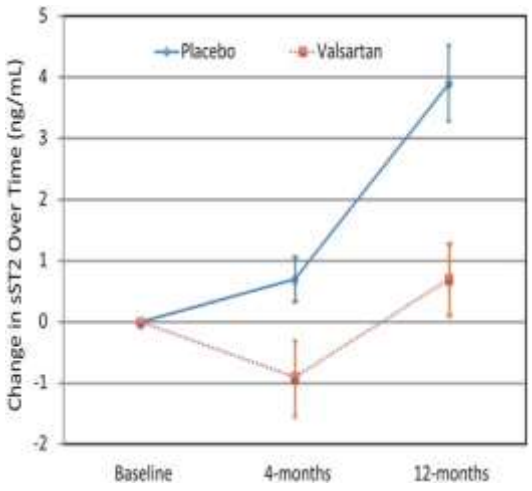
Monitoring HF Treatment

ST2 in Treatment Monitoring



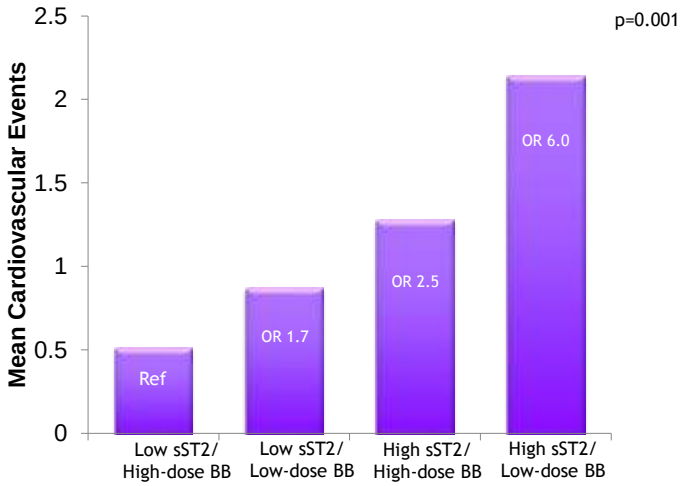
Anand IS et al, 2014 CircHF p418

ST2 in Therapy



Anand IS et al, 2014 CircHF p418

ST in Treatment Monitoring



Januzzi JL et al, 2015 Am J Cardiol p4A

ST2 and Reverse Remodeling

Biomarker	Reverse Remodeling N=104	No reverse remodeling N=200	Univariable Logistic Regression			Multivariable Logistic Regression		
			OR	95% CI	P	OR	95% CI	p
Galectin-3, ng/mL	16.3 (12.6-20.2)	16.5 (13.2-22.8)	0.77	0.42-1.42	0.406	-	-	-
NT-proBNP, ng/L	1307 (703-2772)	2390 (1044-4298)	0.74	0.61-0.91	0.005	0.77	0.55-1.07	0.12
Hs-cTnT, ng/L	21.4 (7.5-32.8)	28.8 (14.5-48.5)	0.62	0.47-0.81	<0.001	0.95	0.65-1.38	0.78
ST2, NG/mL	38.3 (32-47.5)	43.8 (33-59.9)	0.71	0.56-0.9	0.004	0.69	0.5-0.94	0.02

- Reverse remodeling defined as LVEF increase ≥ 15% or LVEF increase ≥ 10% + LVESDi reduction ≥ 20% or LVESVi reduction ≥ 40%.
- R2 group had HR 0.36 for death + HF hosp

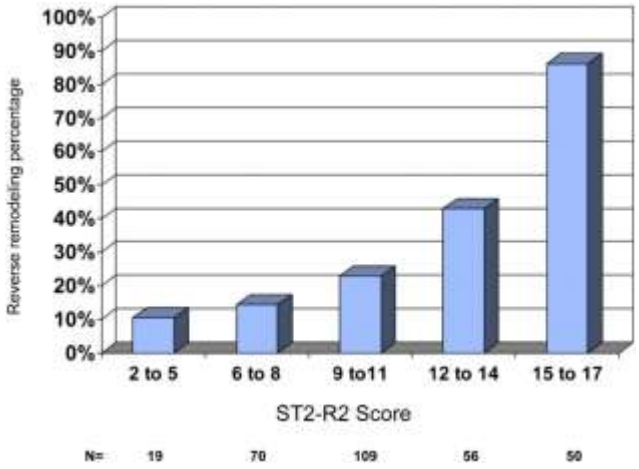
Lupon J et al, 2015 Int J Cardiol p337

ST2 and Reverse Remodeling

	Multivariate logistic regression (N = 304)				
	OR	95% CI	p	β	Points
Non-ischemic etiology	6.33	3.52–11.39	< 0.001	1.845	5
No LBBB	5.56	2.37–13.05	< 0.001	1.716	4
ST2 < 48 ng/mL	2.96	1.62–5.39	< 0.001	1.084	3
Duration of HF < 12 months	2.13	1.18–3.84	0.01	0.754	2
β-Blocker treatment	1.89	0.52–6.86	0.34	0.634	2
Baseline LVEF < 24%	1.52	0.81–2.88	0.20	0.421	1

Lupon J et al, 2015 Int J Cardiol p337

ST2-R2 Score



Lupon J et al, 2015 Int J Cardiol p337

BNP as a Biomarker

	BNP	ST2
Detection of Preclinical Disease		
Diagnosis	✓	
Risk Stratification	✓	✓
Treatment Selection and Monitoring		✓

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TABLE 3 Proposed Tier System for Quality of Biomarker Studies: The Paris Criteria

Improved Diagnosis and Prognostication	Tailoring Therapeutics
Tier 1 • Satisfies criteria for tiers 2 and 3 • Interaction testing of subgroups • Influence of therapeutics on predictive abilities	Tier 1 • Satisfies criteria for tiers 2 and 3 • Randomized, controlled trial in which biomarker levels determine therapeutic choices
Tier 2 • Satisfies criteria for tier 3 • Compares multiple biomarkers concomitantly • Validates results in a representative cohort	Tier 2 • Satisfies criteria for tier 3 • Validates results in a representative cohort
Tier 3 • Follows STARD statement • Pathophysiological link to heart failure • Confirms association with well-defined outcomes in a representative cohort of patients with heart failure after controlling for clinical factors and natriuretic peptides • Reports AUC with and without addition of biomarker and shows that there is statistically significant improvement with the addition of the biomarker • Demonstrates that addition of the new biomarker improves the classification of those who had the biomarker event	Tier 3 • Shows differential effect of treatment based on biomarker levels in a retrospective analysis of randomized, controlled trials

AUC = area under the receiver-operating characteristic curve; STARD = Standards for Reporting of Diagnostic Accuracy.

Ahmad T et al, 2014. JACC:HF 2014;2:477–88

Sarver Heart Center

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