10 years evaluation of soluble ST2 level and incidence of diastolic dysfunction in EGAT study population

Wisuit Katekao, MD
Prin Vathesatogkit, MD
Oraporn See, MD
Sukit Yamwong, MD
Piyamitr Sritara, MD

Background

- **ST2 (also known as IL1RL1, or Interleukin 1 Receptor-Like 1) is a member of the interleukin 1 receptor family.**

IL1RL1 interleukin 1 receptor-like 1 [*Homo sapiens*]

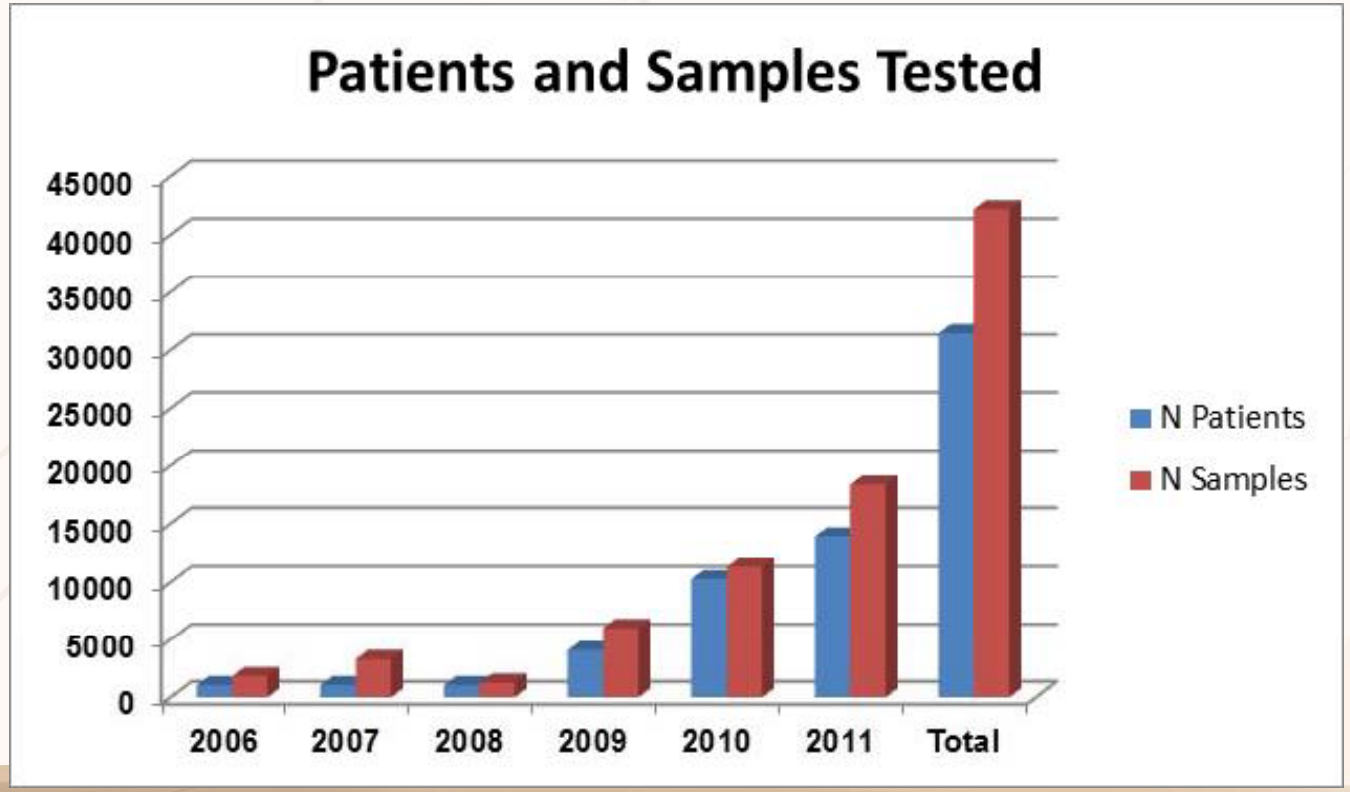
Gene ID: 9173, updated on 9-Dec-2012

Summary

Official Symbol	IL1RL1 provided by HGNC
Official Full Name	interleukin 1 receptor-like 1 provided by HGNC
Primary source	HGNC:5998
See related	Ensembl:ENSG00000115602; HPRD:03123; MIM:601203; Vega:OTTHUMG00000130782
Gene type	protein coding
RefSeq status	REVIEWED
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	T1; ST2; DER4; ST2L; ST2V; FIT-1; IL33R
Summary	The protein encoded by this gene is a member of the interleukin 1 receptor family. Studies of the similar gene in mouse suggested that this receptor can be induced by proinflammatory stimuli, and may be involved in the function of helper T cells. This gene, interleukin 1 receptor, type I (IL1R1), interleukin 1 receptor, type II (IL1R2) and interleukin 1 receptor-like 2 (IL1RL2) form a cytokine receptor gene cluster in a region mapped to chromosome 2q12. Alternative splicing of this gene results in multiple transcript variants. [provided by RefSeq, Jul 2008]

Background

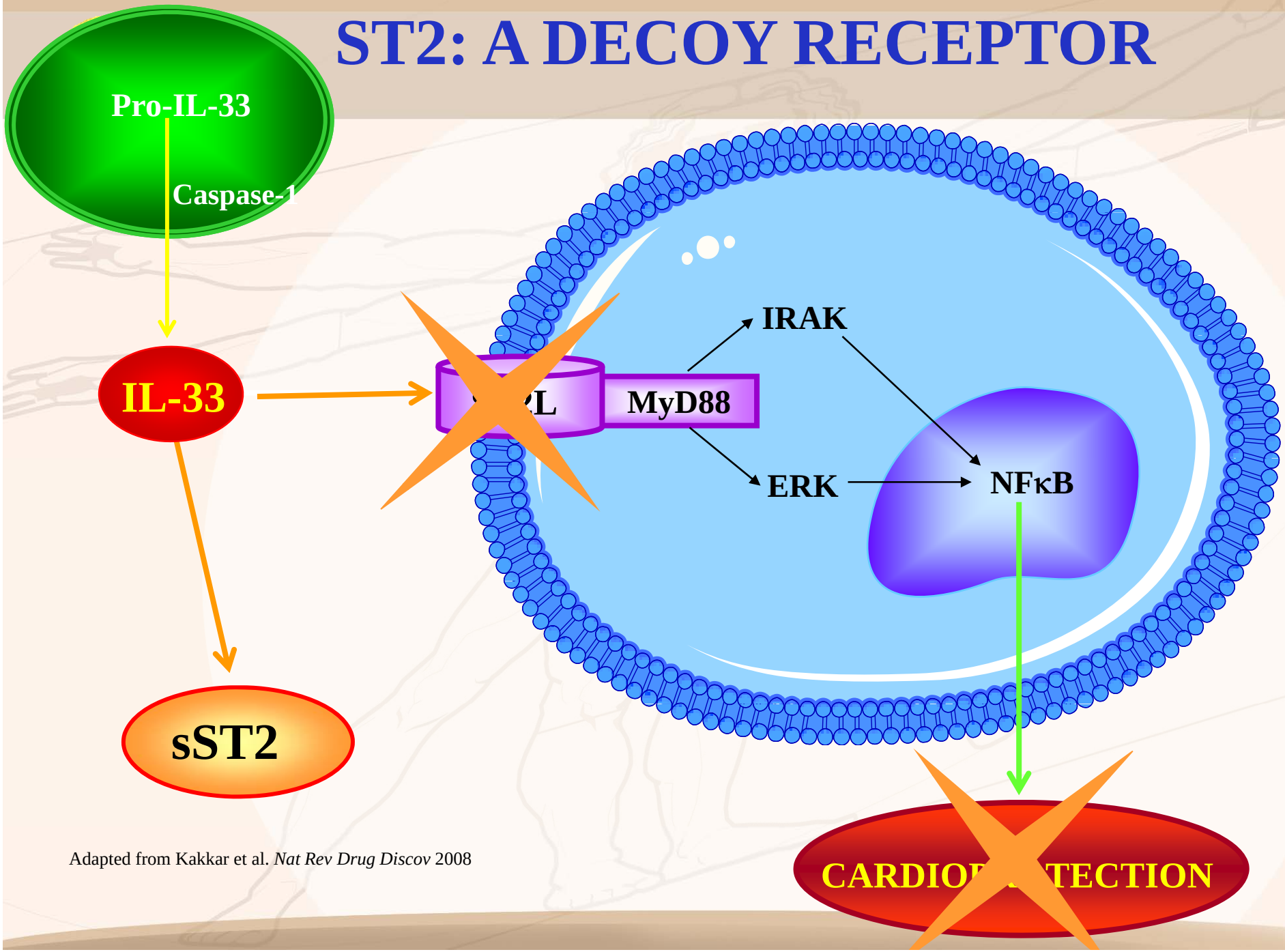
Studies		Patients	Samples
dysnea	5	1,994	2,031
heart failure	24	11,845	18,490
ACS/CAD	10	9,395	13,000
other	10	8,234	8,668
Total	49	31,468	42,189



Background

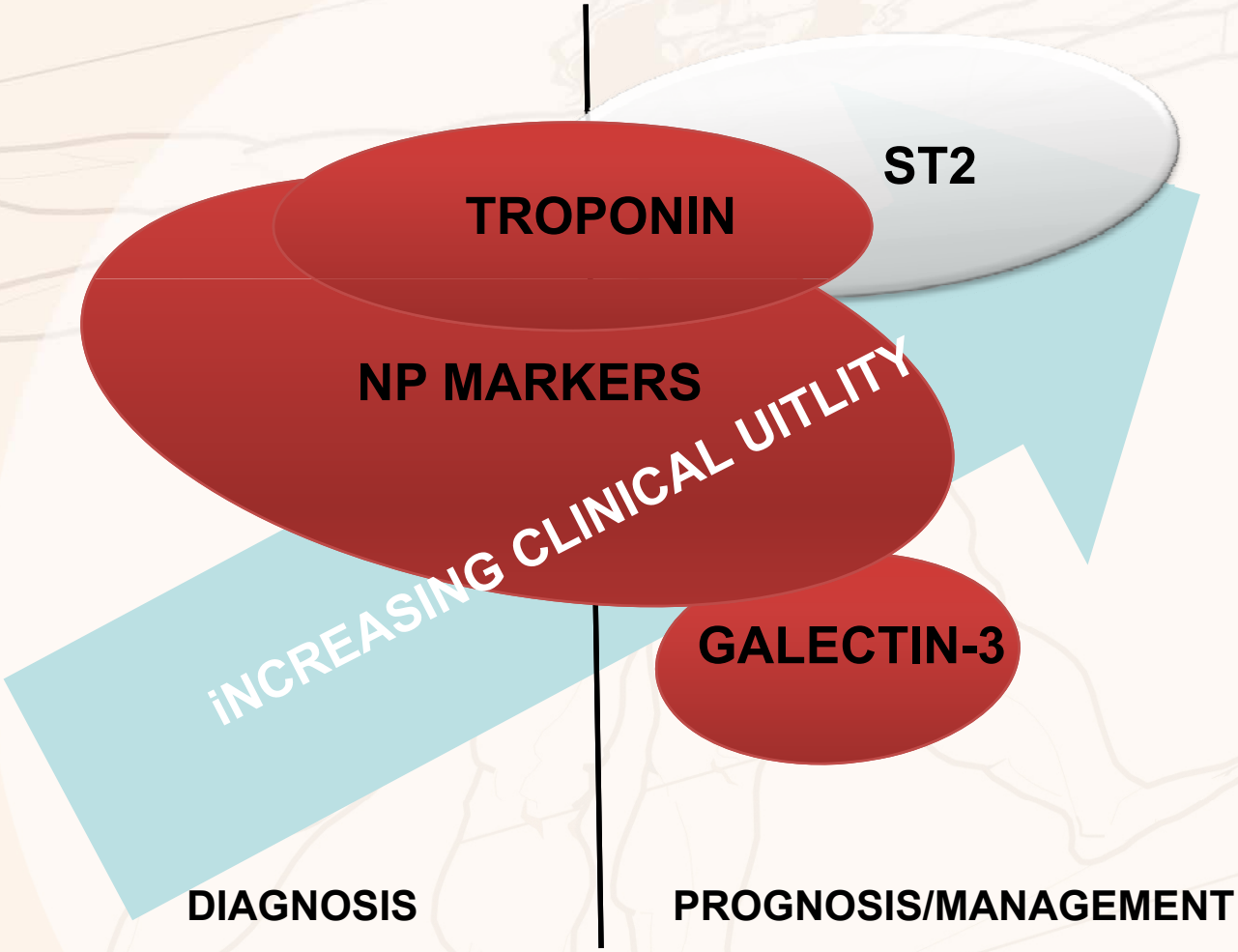
- **Mechanism**
  1. **Cardioprotection or conversely remodeling (fibrosis) and hypertrophy**
  2. **Immune response and inflammatory signaling**

ST2: A DECOY RECEPTOR



Adapted from Kakkar et al. *Nat Rev Drug Discov* 2008

ST2 Well Positioned Relative to Other Biomarkers in Cardiac Disease



- **The Presage ST2 Assay is *not* a *diagnostic assay*. Its use is in *prognosis*, *treatment selection/monitoring* and *disease prevention*.**

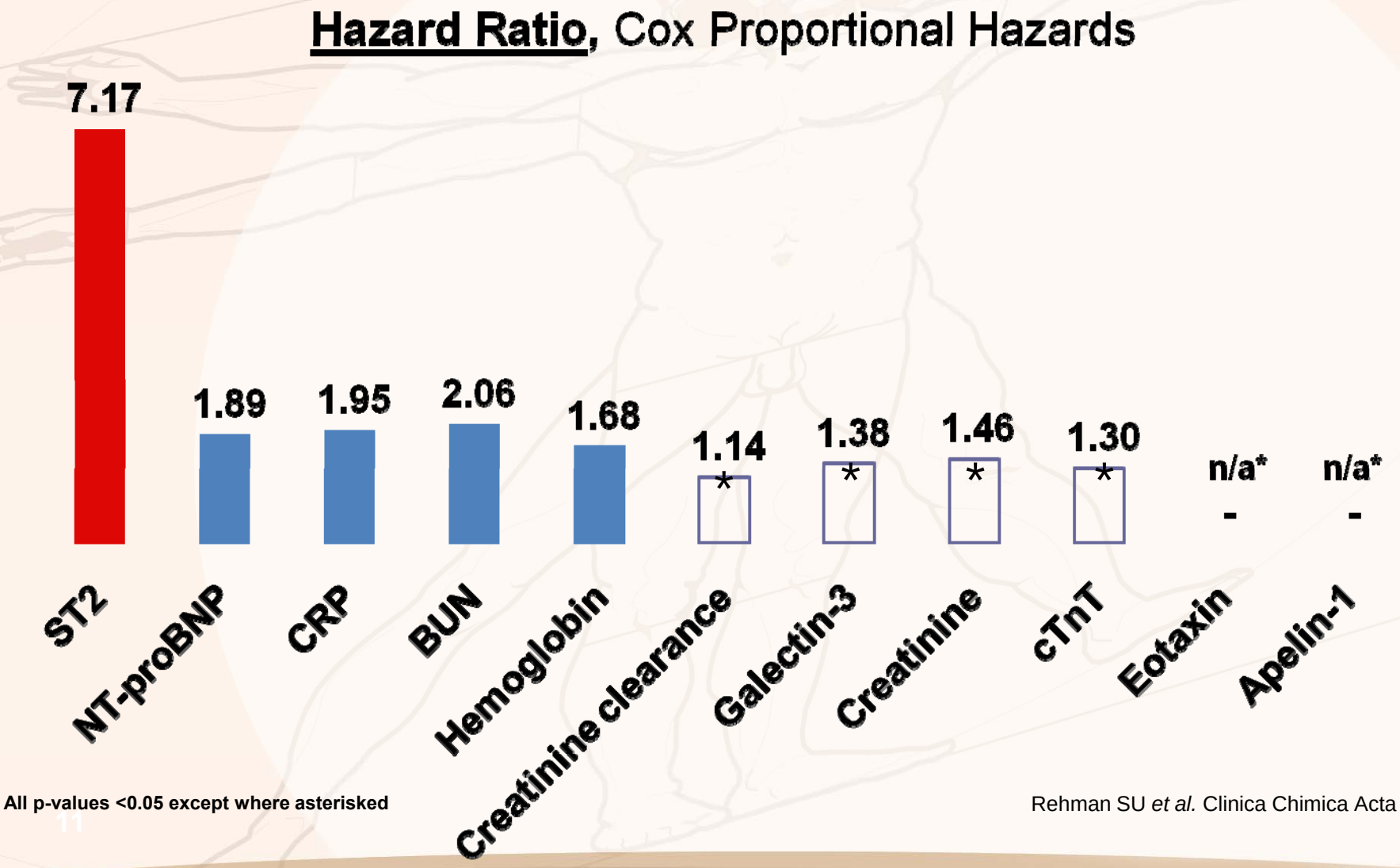
- **ST2 levels change in response to therapies that improve outcomes.**

The Impact of ST2 in Patient Management

- **ST2 have the highest prognostic accuracy OVER ALL OTHER MARKERS *(BNP, NT-proBNP, Gal-3…)***

PRIDE: 1 Yr Mortality Risk Stratification

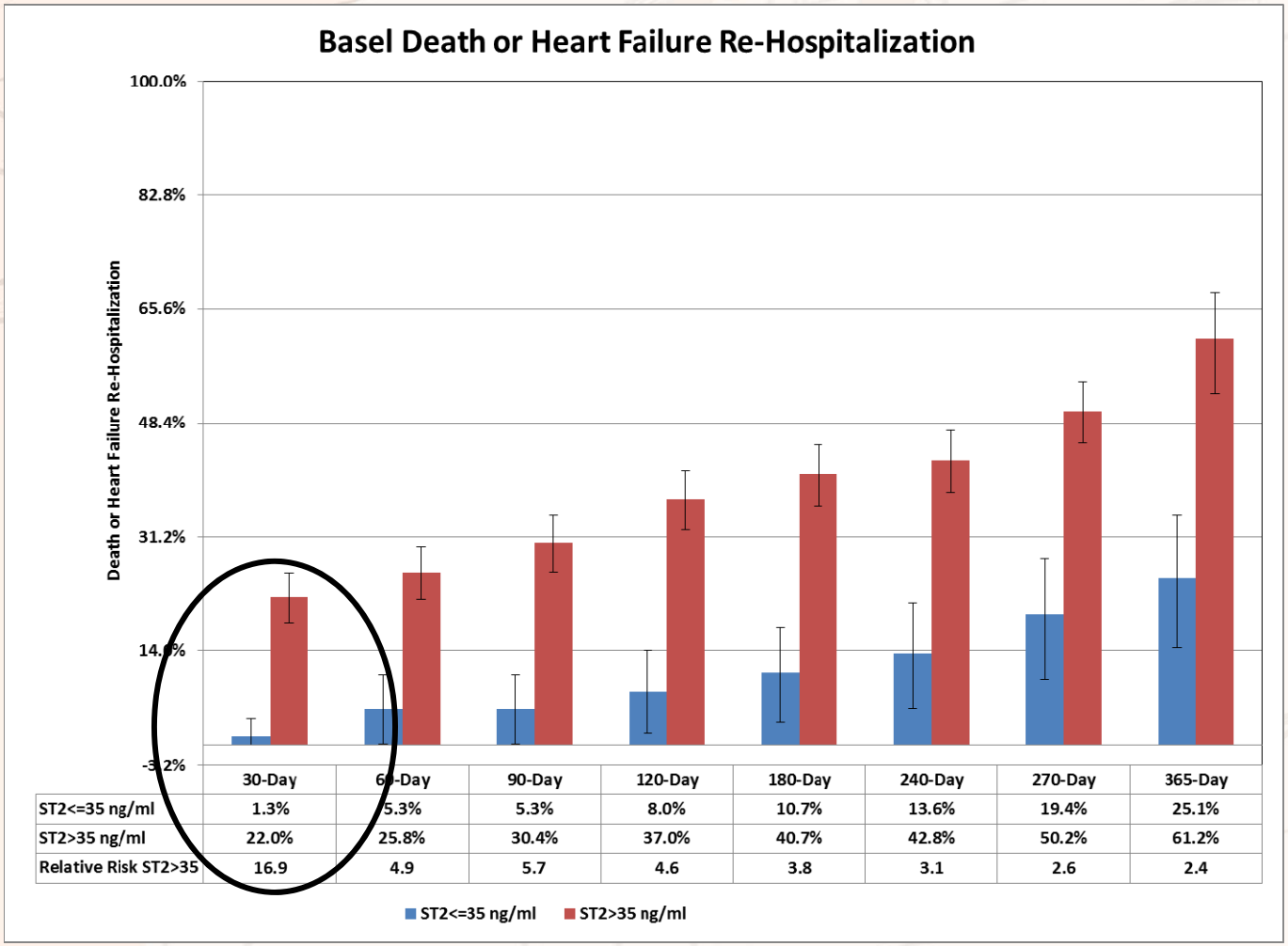
Dyspnea: ST2 Has Strongest Prognostic Hazard Ratio



All p-values <0.05 except where asterisked

Rehman SU *et al.* Clinica Chimica Acta 2008

Cumulative Adverse Event Rates For ST2 Values >35 ng/ml for Death or Heart Failure Re-hospitalization

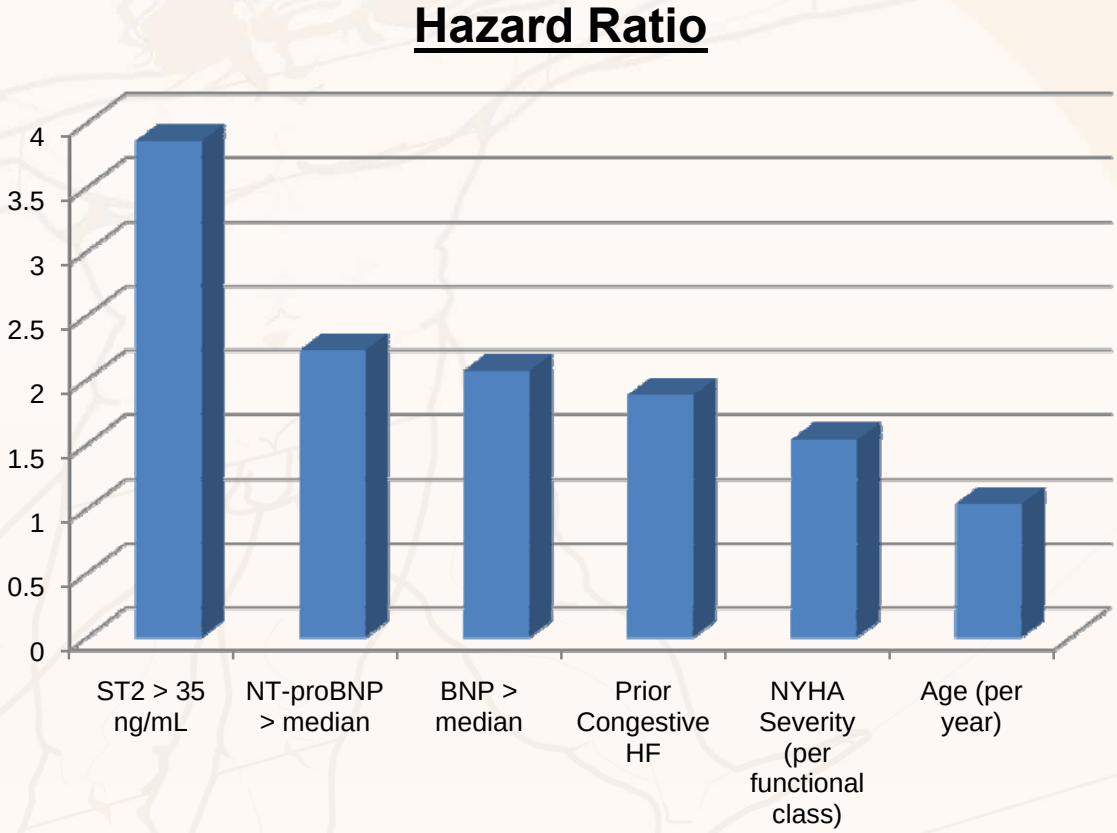


	30-Day	60-Day	90-Day	120-Day	180-Day	240-Day	270-Day	365-Day
ST2<=35 ng/ml	1.3%	5.3%	5.3%	8.0%	10.7%	13.6%	19.4%	25.1%
ST2>35 ng/ml	22.0%	25.8%	30.4%	37.0%	40.7%	42.8%	50.2%	61.2%
Relative Risk ST2>35	16.9	4.9	5.7	4.6	3.8	3.1	2.6	2.4

Example from FDA submission

Acute HF: Other Tools are Inadequate… ST2 Most Predictive of Mortality Risk

- **ST2 predicted mortality better than other demographic variables and biomarkers**
- **ST2 provides valuable information not available from existing tools**
  - **Hypertension, CAD, Diabetes, Ejection Fraction, and Smoking were not significant predictors of mortality, but were evaluated.**

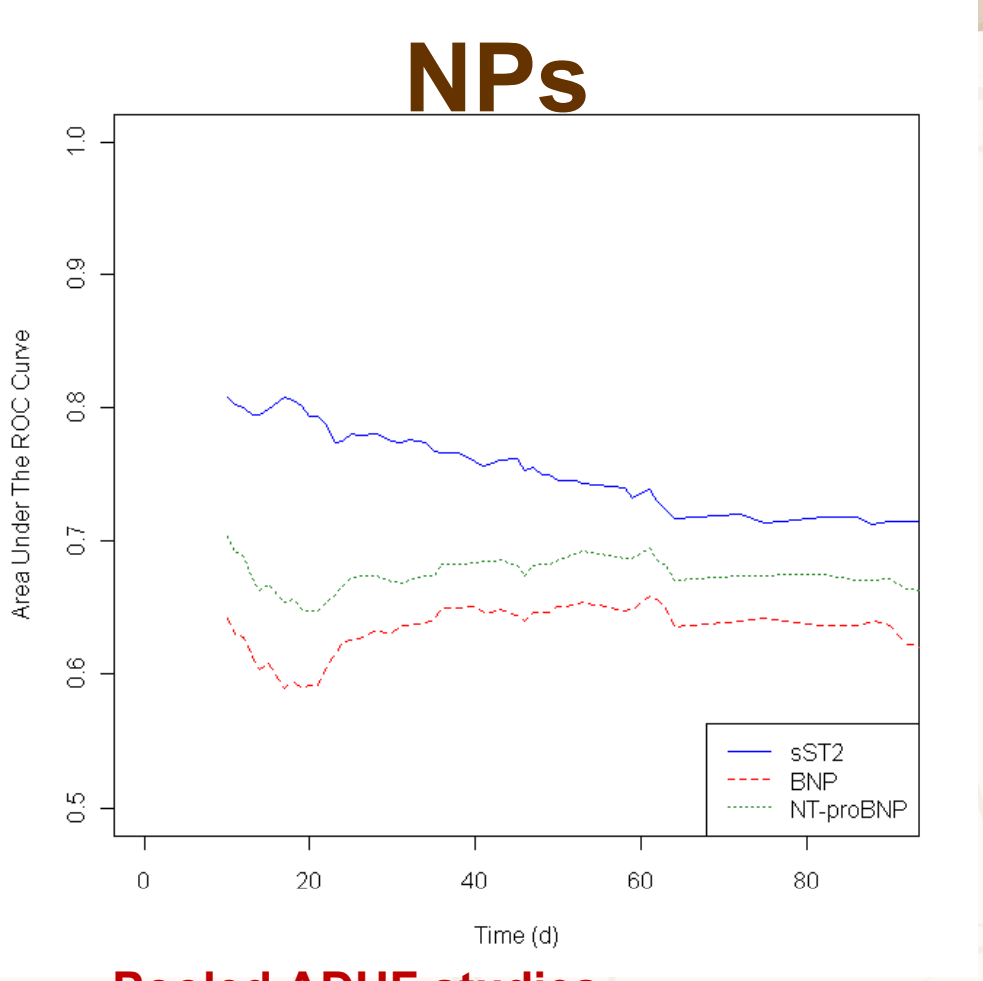


***HR shown if p<.05; univariate HRs are given. ST2 HR is forST2>35 ng/mL from PRIDE dataset; additional data provided by investigators to Critical Diagnostics. For ST2 > median, HR is 2.85.**

Rehman S, et al.. **Characteristics of the Novel Interleukin Family Biomarker ST2 in Patients with Acute Heart Failure.** *J. Am. Coll. Cardiol*. 2008;52(18):1458-1465.

Januzzi JL Jr, et al. **Importance of Biomarkers for Long-term Mortality Prediction in Acutely Dyspneic Patients.** *Clin Chem*. 2010 Dec; 56(12):1814-21. Epub 2010 Oct 4.

ST2 Provides an Earlier Signal For Short Term Adverse Events than NPs



- **Pooled ADHF studies**
- **Isn't an Earlier Signal, By Definition, A More Clinically Useful Signal?**

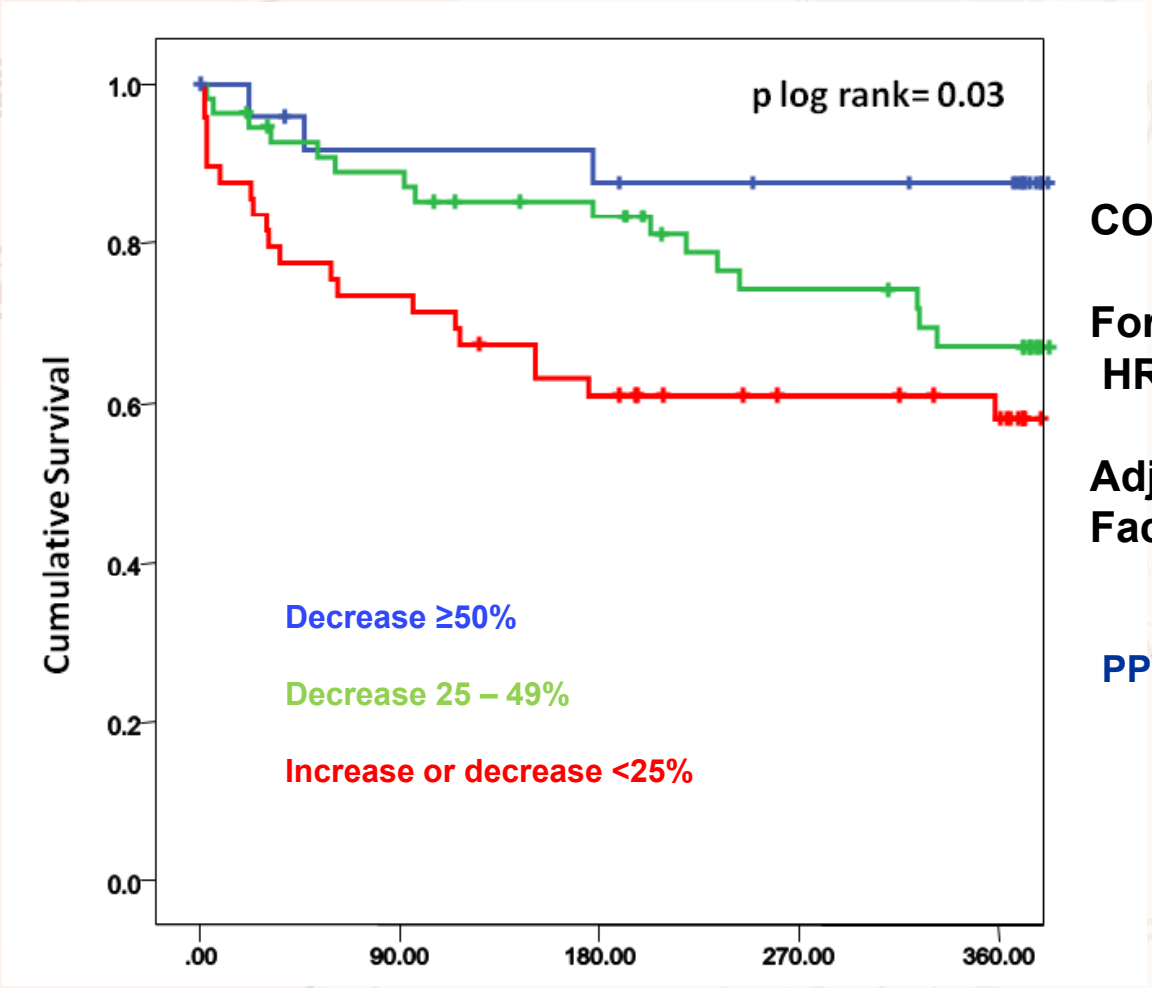
ST2 and NT-proBNP are Additive for Risk

Category	Death Rate	HR (95% CI)	p
ST2 ≤35 ng/ml NT-proBNP ≤median	9.0%	1	NA
ST2 ≤35 ng/ml NT-proBNP >median	23.3%	2.87 (1.9 – 4.32)	<0.001
ST2 >35 ng/ml NT-proBNP ≤median	22.2%	2.70 (1.25 – 5.84)	0.0115
ST2 >35 ng/ml NT-proBNP >median	38.9%	5.59 (3.61 – 8.66)	<0.001

Results from HF-ACTION chronic, ambulatory HF study cohort
Median NT-proBNP concentration is 852 pg/ml in this study.
Study follow-up period of 4 years.

- **Elevated ST2 identifies high risk patients missed by NT-proBNP, almost 25%!!**
- **Risk is higher if either marker is elevated and highest if both makers are elevated**

Serial ST2 Measurements Categorize Responder Status



COX Regression Analysis

For every 10% ST2 change HR 1.04, p=0.03

Adjustment for ADHERE Risk Factors and BNP change.

PPV for Survival for 92%

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Prognostic Utility of Novel Biomarkers of Cardiovascular Stress

The Framingham Heart Study

Thomas J. Wang, MD*; Kai C. Wollert, MD*; Martin G. Larson, ScD; Erin Coglianese, MD; Elizabeth L. McCabe, MS; Susan Cheng, MD; Jennifer E. Ho, MD; Michael G. Fradley, MD; Anahita Ghorbani, MD, MPH; Vanessa Xanthakis, PhD; Tibor Kempf, MD; Emelia J. Benjamin, MD, ScM; Daniel Levy, MD; Ramachandran S. Vasan, MD*; James L. Januzzi, MD*

Table 3. Multimarker Score and Prediction of Future Events

	Death	Heart Failure	Major Cardiovascular Events
Score, per 1-unit increment	1.80 (1.64–1.98)	1.83 (1.55–2.16)	1.43 (1.28–1.61)
P	<0.001	<0.001	<0.001
By quartile of score			
Quartile 1	Referent	Referent	Referent
Quartile 2	1.26 (0.82–1.92)	1.52 (0.57–4.06)	1.01 (0.67–1.53)
Quartile 3	1.55 (1.04–2.30)	2.19 (0.88–5.42)	1.10 (0.74–1.63)
Quartile 4	3.20 (2.18–4.70)	6.25 (2.63–14.82)	1.87 (1.28–2.73)
P for trend	<0.001	<0.001	<0.001
c Statistics			
Best-fit clinical model	0.787	0.846	0.780
Best-fit clinical model+multimarker score	0.810	0.870	0.791
P	<0.001	0.002	0.005
IDI	0.05 (0.04–0.07)	0.04 (0.02–0.06)	0.02 (0.01–0.03)
P	<0.001	<0.001	<0.001
NRI(>0)* vs best-fit clinical model	0.42 (0.31–0.54)	0.39 (0.21–0.57)	0.21 (0.08–0.34)
P	<0.001	<0.001	0.001

IDI indicates integrated discrimination improvement; NRI: net reclassification improvement. Values for continuous score and quartile are hazards ratios (95% confidence intervals) from multivariable models adjusted for age, sex, body mass index, systolic blood pressure, hypertension therapy, diabetes mellitus, cigarette smoking, total cholesterol, high-density lipoprotein cholesterol, atrial fibrillation (heart failure and death analyses only), major cardiovascular disease (heart failure and death analyses), ECG left ventricular hypertrophy (heart failure and death analyses), and heart murmur (heart failure analysis only).

*NRI(>0) denotes category-free NRI using a threshold of 0% for the minimum change in predicted risk necessary to change classification. Values for NRI(>0.01) and NRI(>0.02) correspond to category-free NRI with thresholds of 1% and 2% and are shown in the text.

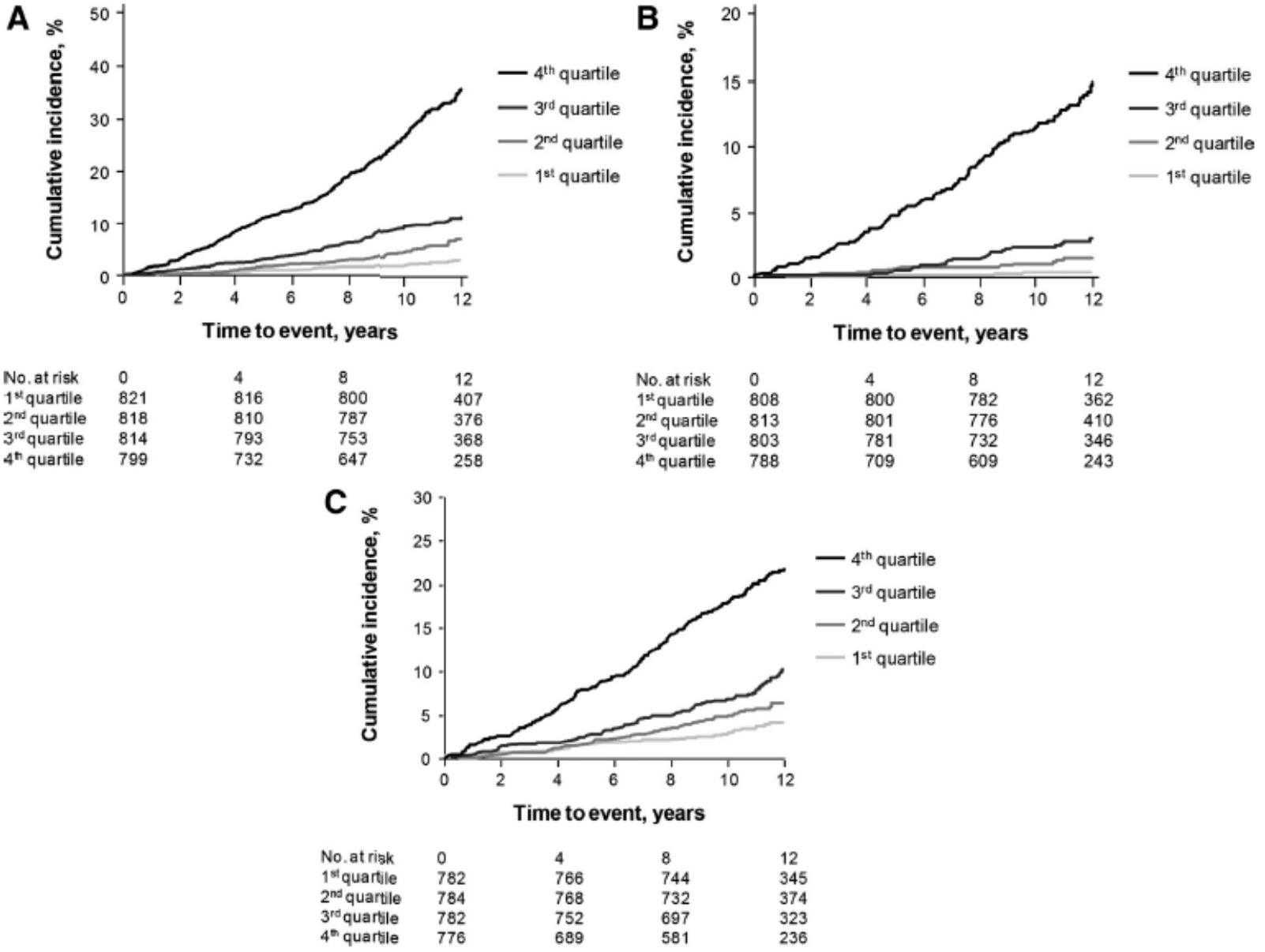


Figure. Cumulative incidence of death (**A**), heart failure (**B**), and first major cardiovascular events (**C**) according to quartile of a multimarker score consisting of soluble ST2, growth differentiation factor-15, high-sensitivity troponin I, B-type natriuretic peptide, and high-sensitivity C-reactive protein. Curves for heart failure and major cardiovascular events are adjusted for the competing risk of death.

- อย่างไรก็ตาม ยังมีการศึกษาระหว่าง Structural heart disease กับค่า soluble ST2 level ว่าเกี่ยวข้องกันหรือไม่

Research Question

- **Does sST2 level can predict an incidence of diastolic dysfunction in elderly patient ?**

Circ Heart Fail. 2009 Jul;2(4):311-9. Epub 2009 May 14.

Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea.

Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL.

Department of Medicine, Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA.

Abstract

BACKGROUND: ST2, a biomarker of cardiomyocyte stretch, powerfully predicts poor outcomes in patients with acute dyspnea, but nothing is known about associations between soluble ST2 (sST2) and cardiac structure and function, or whether sST2 retains prognostic meaning in the context of such measures.

METHODS AND RESULTS: One hundred thirty-four dyspneic patients with and without decompensated heart failure had echocardiography during index admission and vital status was ascertained at 4 years. Echocardiographic and clinical correlates of sST2 as well as independent predictors of death at 4 years were identified. sST2 correlated with left ventricular end-systolic dimensions/volumes and left ventricular ejection fraction. sST2 was inversely associated with right ventricular fractional area change (rho=-0.18; P=0.046), higher right ventricular systolic pressure (rho=0.26; P=0.005), and right ventricular hypokinesis (P<0.001) and was correlated with tissue Doppler Ea wave peak velocity, but not to other indices of diastolic function. In multivariate regression, independent predictors of sST2 included right ventricular systolic pressure (t=2.29; P=0.002), left ventricular ejection fraction (t=-2.15; P=0.05) and dimensions (end systolic, t=2.57; end diastolic, t=2.98; both P<0.05), amino-terminal pro-B-type natriuretic peptide (t=3.31; P=0.009), heart rate (t=2.59; P=0.01), and presence of jugular venous distension (t=2.00; P=0.05). In a Cox proportional hazards model that included echocardiographic results and other biomarkers, sST2 independently predicted death at 4 years (hazard ratio=2.70; P=0.003).

CONCLUSIONS: Among dyspneic patients with and without acute heart failure, sST2 concentrations are associated with prevalent cardiac abnormalities on echocardiography, a more decompensated hemodynamic profile and are associated with long-term mortality, independent of echocardiographic, clinical, or other biochemical markers of risk.

Clin Chem. 2011 Jun;57(6):874-82. Epub 2011 Apr 22.

Prognostic utility of ST2 in patients with acute dyspnea and preserved left ventricular ejection fraction.

Shah KB, Kop WJ, Christenson RH, Diercks DB, Henderson S, Hanson K, Li SY, deFilippi CR.

Division of Cardiology, Virginia Commonwealth University, Richmond, VA, USA.

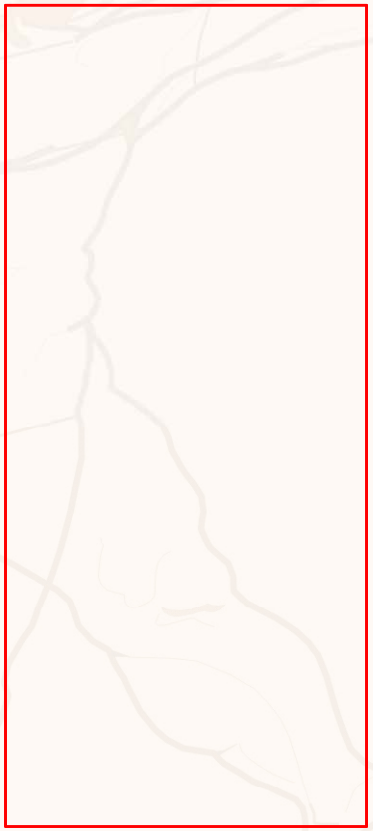
Abstract

BACKGROUND: Soluble ST2 (sST2), an interleukin-1 receptor family member, is an emerging risk indicator for patients with cardiovascular disease. We evaluated the prognostic role of sST2 for patients presenting to the emergency department with acute dyspnea, with a focus on those with preserved left ventricular ejection fraction (LVEF ≥50%), as risk stratification is often most complex in this subgroup.

METHODS: We conducted a post hoc analysis of 387 patients [39% female, mean (SD) age 57.6 (14.5) years] presenting to the emergency department with dyspnea and followed for 1 year (97% complete follow-up). We examined clinical data, concentrations of serum biomarkers [sST2, amino-terminal pro-B-type natriuretic peptide (NT-proBNP)], and transthoracic echocardiography.

RESULTS: Patients had a median sST2 concentration of 38.4 U/mL [interquartile range (IQR) 25.5-64 U/mL]. Forty-six patients (12%) died during follow-up. Log sST2 [hazard ratio (HR) (95% CI) 2.85 (2.04-3.99), P < 0.001rsqb] and log NT-proBNP [1.28 (1.13-1.45), P < 0.001] concentrations were significant predictors of mortality at 1 year. After multivariate adjustment, only sST2 remained predictive of mortality [per log: 2.14 (1.37-3.38), P = 0.001]. In the subpopulation of individuals with normal systolic function (n = 200), only sST2 continued to predict mortality after multivariate adjustment [per log: 2.57 (1.12-5.91), P = 0.03]. Only NT-proBNP, but not sST2, concentrations correlated with multiple echocardiographic indices of left ventricular diastolic function.

CONCLUSIONS: sST2 is a strong predictor of mortality in patients presenting with acute dyspnea, particularly those with preserved LVEF, and may be useful for triage and risk stratification of this challenging group.



Abstract

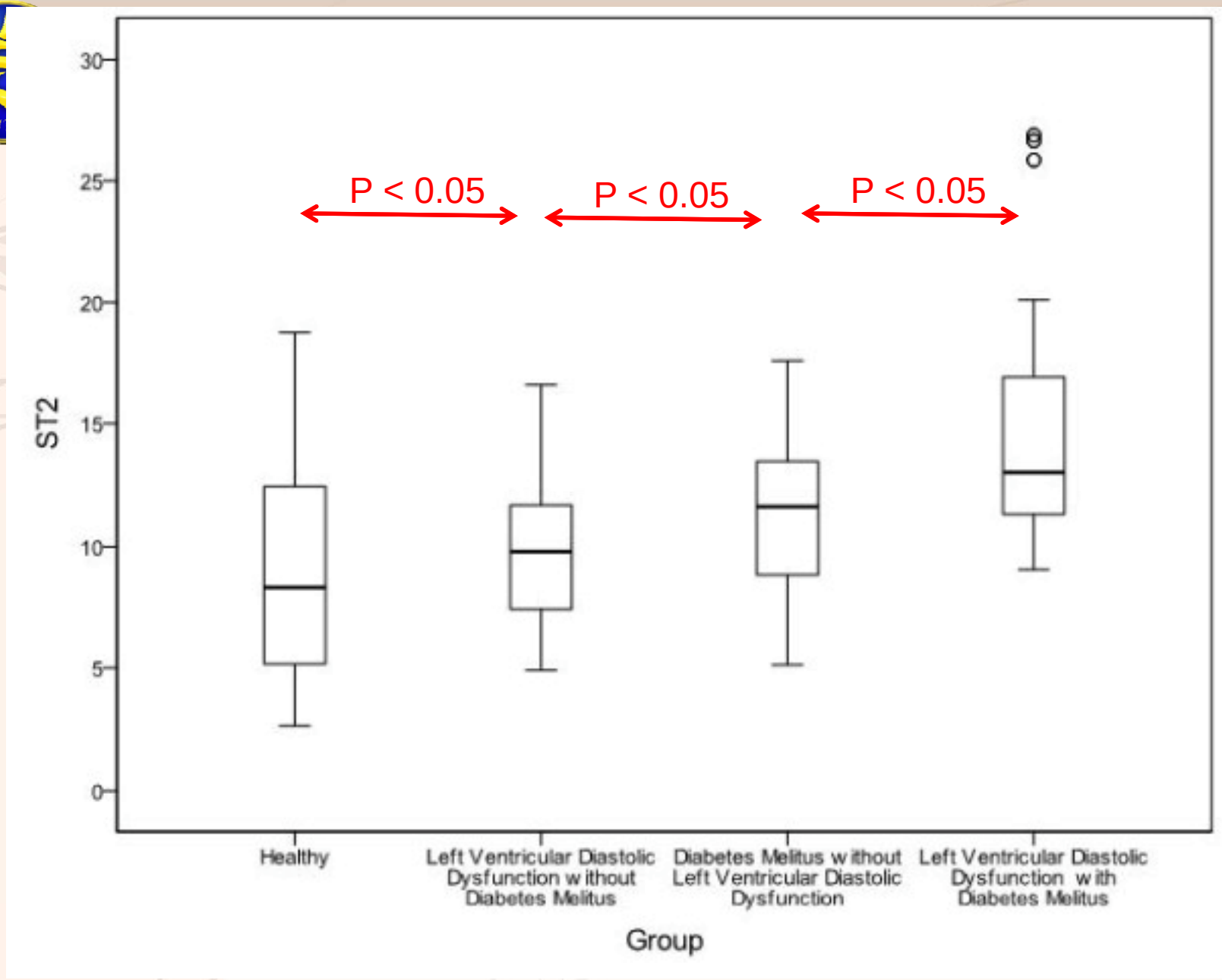
Background: Soluble ST2, a member of the of the To predictive value in heart failure and myocardial infarct Soluble ST2 is considered a decoy receptor of IL 33 th atherosclerosis and cardiac remodeling. In the present ST2, BNP and hs-CRP between healthy controls and p diastolic dysfunction. A secondary aim was to investig 2 diabetes, such as HbA1c.

Methods: 158 volunteers were recruited and underwe systolic & diastolic cardiac function. All subjects with e was divided in 4 groups as follows: A: 42 healthy controls, B: 18 subjects without diabetes with LVDD, C: 48 patients with type 2 diabetes without LVDD & D: 50 patients with type 2 diabetes & LVDD. ELISA technique was performed to measure sST2 levels. Statistical analysis was performed with Kruskal-Wallis & Mann-Whitney test (continuous variables), chi squared & Fischer exact test (discrete variables), Spearman coefficient (univariate analysis) and step-wise backward method (multivariate analysis).

Results: Patients with type 2 diabetes with ($p < 0.001$) or without LVDD ($p = 0.007$) had higher serum ST2 levels compared to healthy controls, state found also for hs-CRP levels but not for the corresponding BNP levels ($p = 0.213$ & $p = 0.207$ respectively). Patients with type 2 diabetes & LVDD had higher serum ST2 in relation to diabetic patients without LVDD ($p = 0.001$). In multivariate analysis HbA1c positively and independently correlated with sST2 levels in both groups of patients with type 2 diabetes.

Conclusions: Patients with type 2 diabetes exhibit higher sST2 levels compared to healthy controls. The presence of LVDD in patients with type 2 diabetes is associated with even higher sST2 levels. A significant correlation between glycemic control and sST2 levels was also revealed.

Keywords: Soluble ST2, BNP, hs-CRP, type 2 diabetes, diastolic dysfunction


P < 0.05
P < 0.05
P < 0.05
ST2
30
25
20
15
10
5
0
Healthy
Left Ventricular Diastolic Dysfunction without Diabetes Melitus
Diabetes Melitus without Left Ventricular Diastolic Dysfunction
Left Ventricular Diastolic Dysfunction with Diabetes Melitus
Group

SEEGAT

- ดังนั้นการใช้ ST2 สามารถที่จะบอก prognosis และบอกถึงสภาพของหัวใจที่ผิดปกติได้
  - LVEF, RVSP, RV function, Ea wave
  - Diastolic function & sST2 in outpatient setting = no data available !!!

SEEGAT

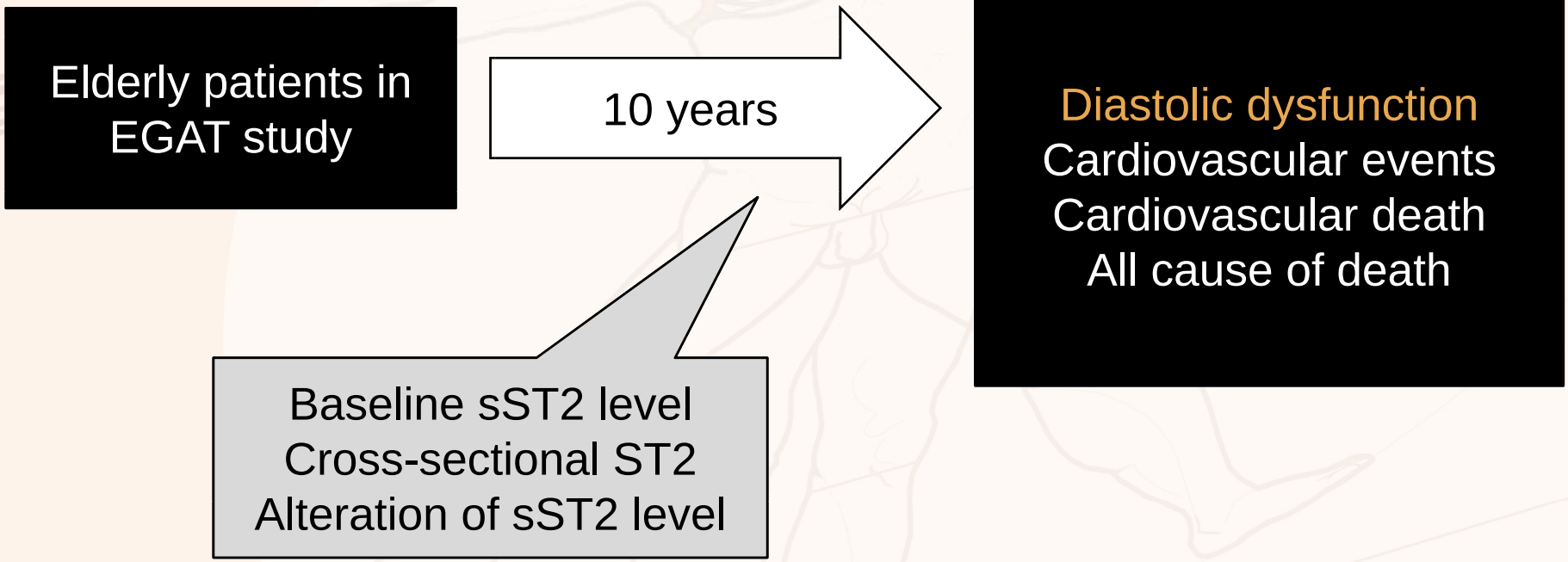
- To compare baseline/change in sST2
- Primary Outcome
  - Incidence of diastolic dysfunction in elderly outpatient setting

SEEGAT

- **Secondary Outcome**
  - **Death from cardiovascular causes**
  - **All-causes mortality**
  - **Major adverse cardiovascular event**

- ในการติดตามศึกษาระยะยาว อาจจะสามารถใช้เพิ่มเป็นอีก 1 ข้อใน Risk stratification of RAMA-EGAT score !!!

Conceptual Framework

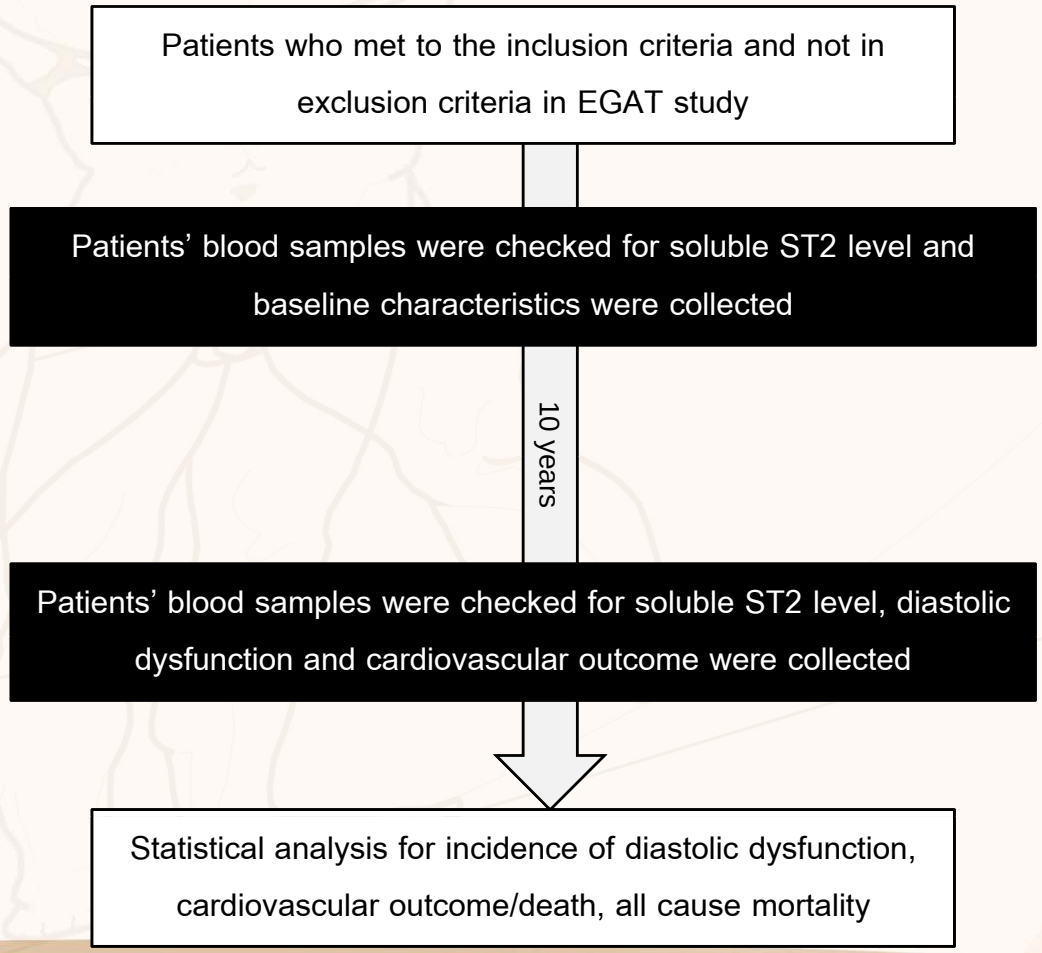


Research Methodology

- **Observational cohort study**

Inclusion criteria:
- Age more than 60 years
- Blood samples were available for sST2 evaluation at 0, 10 years

Exclusion criteria:
- Patients are participated in others double blind clinical controlled trial
- Loss to follow-ups at 10 years
- Has an incomplete data for baseline characteristics, echocardiography or cardiovascular outcomes



Dummy Baseline

	Low ST2	High ST2	*P*-value
Age, year			
Male, %			
Obesity (BMI ≥ 25), %			
Cerebrovascular disease, %			
Cardiovascular disease, %			
Peripheral artery disease, %			
Smoking, %			
Hypertension, %			
Diabetes mellitus, %			
Hypercholesterolemia, %			
Family history of premature cardiac death, %			

Dummy Outcome

	Low ST2	High ST2	*P*- value
Incidence of diastolic dysfunction			
✓ E/e’			
✓ LA volume index			
✓ LV strain pattern			
History of recurrent cardiovascular event, %			
✓ Cerebral infarction, %			
✓ Myocardial infarction, %			
✓ Peripheral arterial disease, %			
Cardiovascular death, %			
All cause of death, %			

Chi-square test,
Fisher exact test,
Odd ratio, 95% CI
Spearmen’s correlation

Kaplan meier’s
Cox-regression hazard ratio

Time schedule

Year	2012					2013											2014
Month	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1
Revised proposal																		
Data collection																		
Analysis																		
Writing final report																		
Present paper																		

ACC – SF dec12

ESC – HL feb13

Expect benefit and application

- Be the first study to show a correlation of New-onset diastolic dysfunction and sST2 level in outpatient setting

- To add sST2 level into RAMA-EGAT score for more accuracy of risk stratification

Acknowledgement

Prin Vathesatogkit, MD

Oraporn See, MD

Sukit Yamwong, MD

Piyamitr Sritara, MD