Correlation of novel cardiac marker and mortality in EGAT population.

Soluble ST2

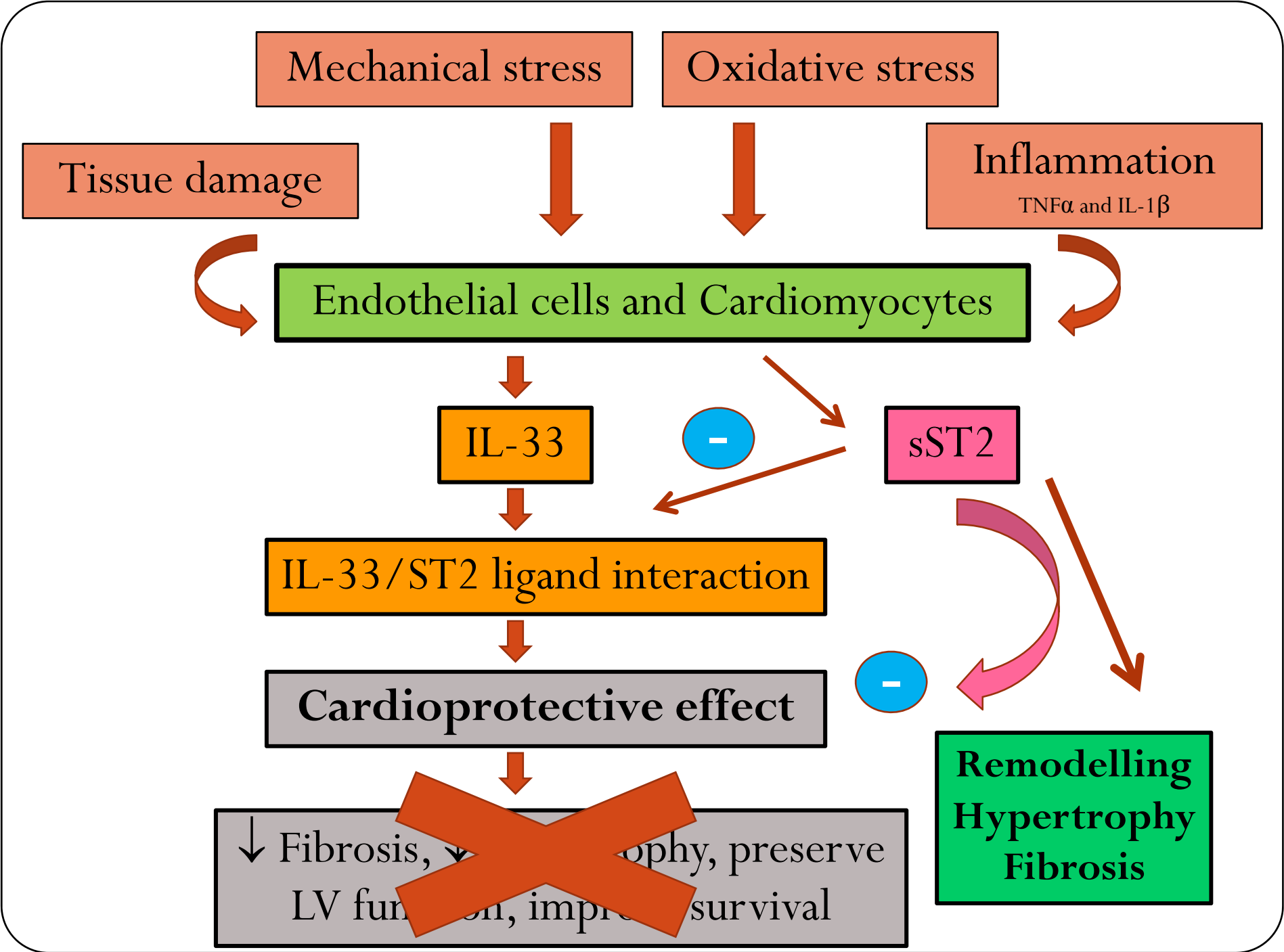hsCRP

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Background

- hsCRP - the most widely studied biomarker in general populations.

- Secreted by liver and reflect inflammation from a variety of causes.

- hsCRP>3 mg/L predicts a higher risk for CHD events in asymptomatic subjects independent of Framingham risk factors

Background

- **What is ST2?**

- ST2 is a member of the interleukin-1 (IL-1) receptor family

- The *ST2 gene* encodes two isoforms:
  - ST2 ligand (ST2L)- transmembrane form
 - Soluble ST2 (sST2) - circulating in human plasma

sST2 vs hsCRP

- More specific with cardiovascular system

- More information
  - Mechanical stress
  - Myocardial damage
  - Inflammation
  - Remodelling (fibrosis, hypertrophy)

- Therapeutic implication (aldosterone antagonist?)

Distribution and Clinical Correlates of the Interleukin Receptor Family Member Soluble ST2 in the Framingham Heart Study

Erin E. Coglianese,[1] Martin G. Larson,[2,3,4] Ramachandran S. Vasan,[2,5] Jennifer E. Ho,[6] Anahita Ghorbani,[6] Elizabeth L. McCabe,[3] Susan Cheng,[2,7] Michael G. Fradley,[6] Dana Kretschman,[8] Wei Gao,[3] George O'Connor,[8] Thomas J. Wang,[2,6] and James L. Januzzi[6*]

Age

Male

sST2

DM

HT
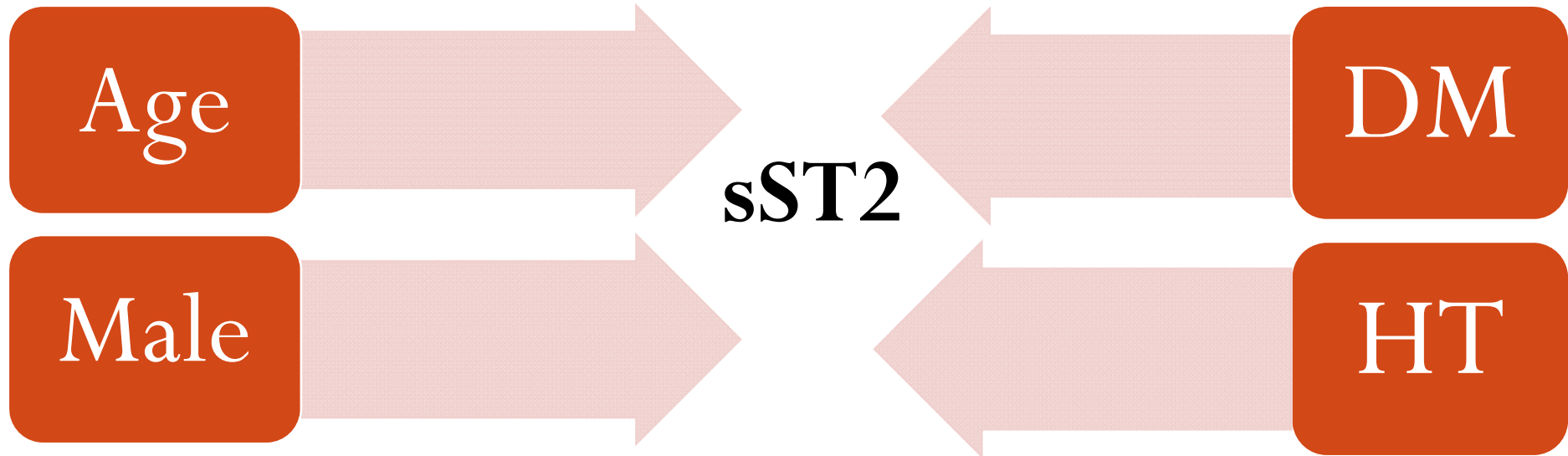
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Table 3. Reference limits for sST2 (ng/mL) by sex and age.

| Age group, years	Men, percentile				Women, percentile			
	2.5th	50th	97.5th	99th	2.5th	50th	97.5th	99th
Empirical reference limits								
35–44	10.6	22.9	47.6	49.3	10.4	17.1	33.2	45.9
45–54	11.5	22.3	43.7	64.4	9.8	17.7	30.7	36.7
55–64	12.4	22.7	43.3	46.4	9.9	17.5	34.3	39.3
65–74	13.2	24.5	45.2	54.7	9.3	19.2	45.1	53.0
Quantile regression reference limits								
35–44	10.3	21.3	46.5	46.7	10.2	16.6	29.4	29.5
45–54	11.2	22.0	45.8	48.7	10.0	17.2	31.2	34.0
55–64	12.1	22.8	45.2	50.8	9.8	17.8	33.2	39.3
65–74	13.1	23.6	44.6	53.0	9.6	18.5	35.3	45.3

Soluble ST2 Is Associated with All-Cause and Cardiovascular Mortality in a Population-Based Cohort: The Dallas Heart Study

Lu Q. Chen,[1] James A. de Lemos,[1,2] Sandeep R. Das,[1,2] Colby R. Ayers,[2,3] and Anand Rohatgi[1,2*]

- sST2 concentrations do not correlate strongly with age or other traditional risk factors except for male sex.

- sST2 concentrations are remarkably higher in African Americans.

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Race

Male

sST2

Genetic factors

All cause Mortality
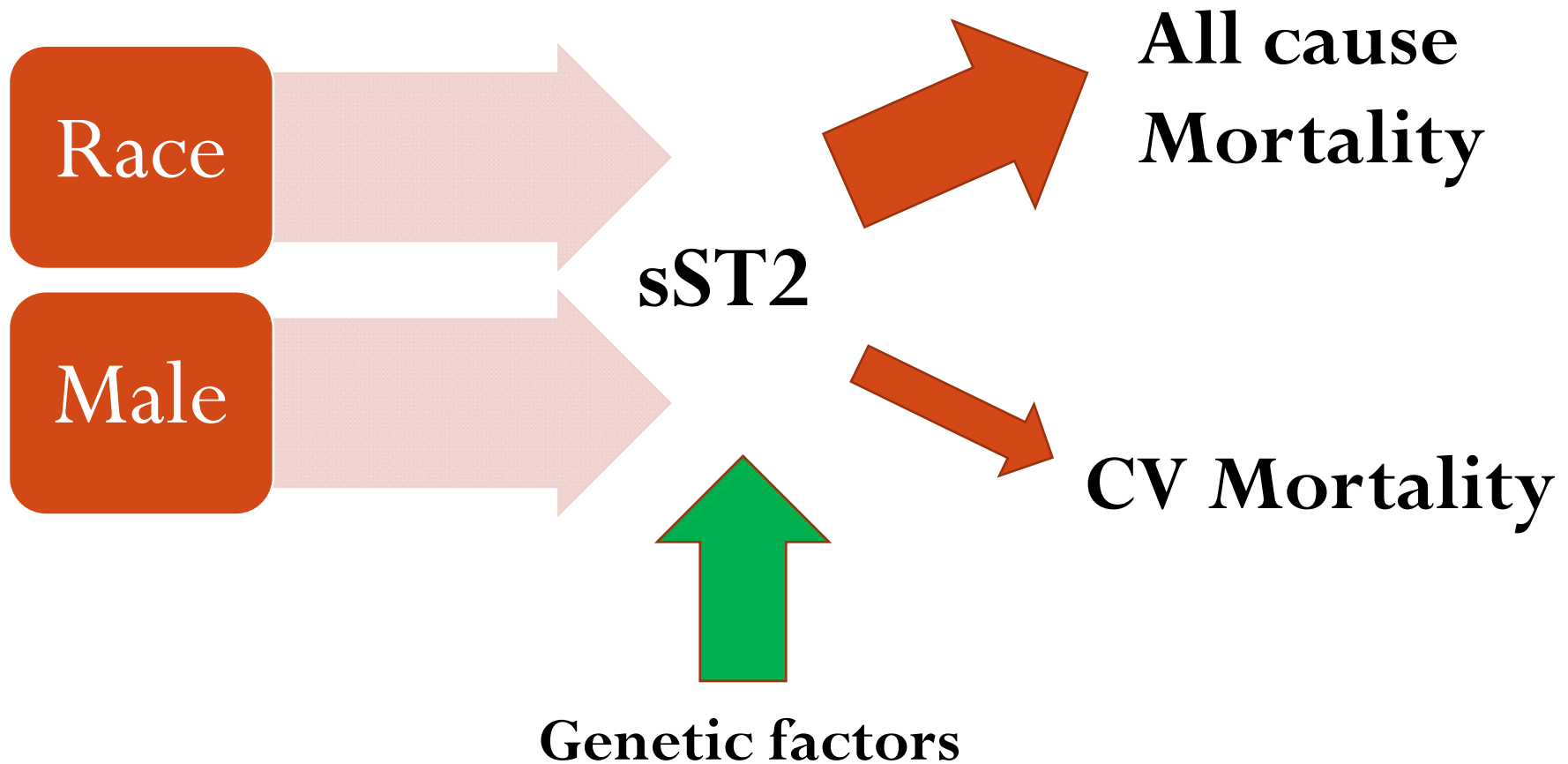
CV Mortality

Research Questions

- Can sST2 and hsCRP predict mortality in EGAT population ?

Primary objective

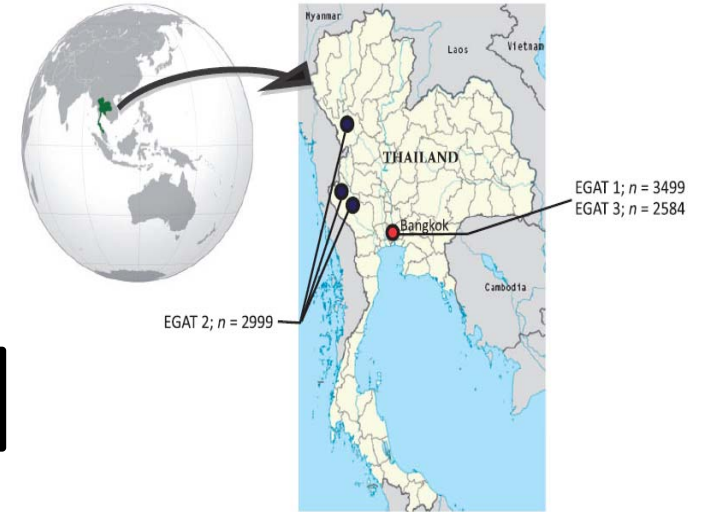- To evaluate sST2 and hsCRP as a biomarker for mortality in EGAT population.

Secondary objective

- To evaluate the prognostic value of sST2 and hsCRP in CV death and CV events (MI, stroke, HF, revascularization) in EGAT population.
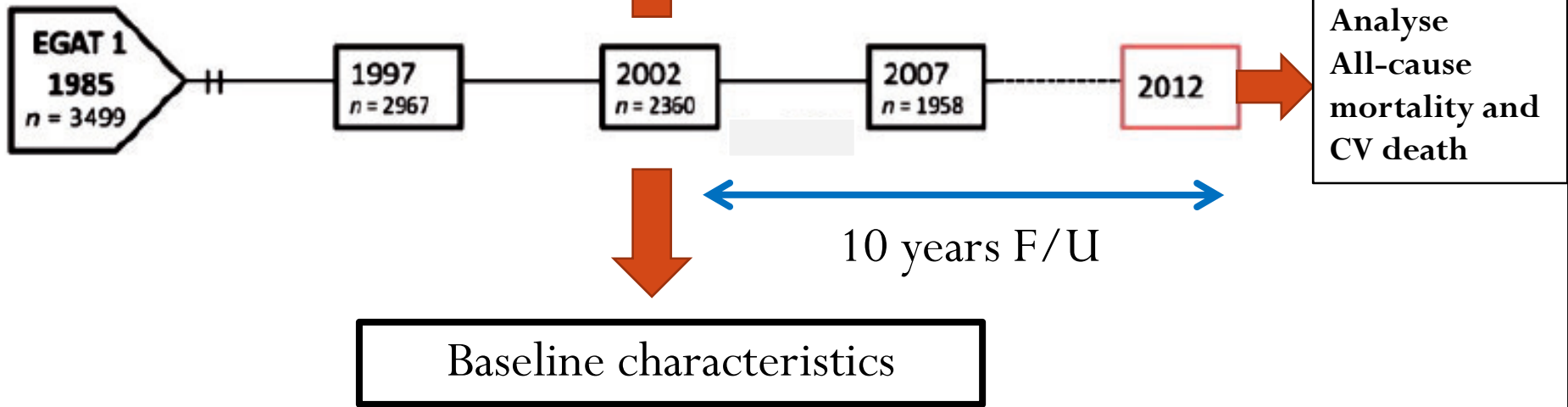
Types of the research designs

- Retrospective cohort from EGAT study

Research methodology

- Participants in EGAT 1/3 in 2002

- N = 2,200

- Evaluate sST2 by a high-sensitivity assay for sST2 (Presage®, Critical Care Diagnostics, Inc., New York, NY, USA)

- Evaluate hsCRP by N high-sensitivity latex-enhanced immunonephelometric (BN 100 nephelometer, Dade Behring)

Inclusion criteria

- Participants from EGAT1/3 study

- Have frozen blood for measure both sST2 and hsCRP

- Have baseline characteristic data and general cardiovascular risk factors measurements.

Exclusion criteria

- Missing data such as inadequate frozen blood samples

STATISTICAL ANALYSIS

- The participants will grouped into quatile according to levels of hsCRP and sST2.

- Compared demographic and clinical variables across increasing sST2 categories.

- Survival analysis: Kaplan-Meier

- Cox proportional hazards models to assess associations between sST2 , hsCRP and outcome.

- ROC curve: Compare with previous risk factors

RAMA-EGAT Score

Score	-2	0	2	3	4	5	6	8	10
Age (year)	35-39	40-44	45-49		50-54		55-59	60-65	≥ 65
Gender		Female		Male					
Cholesterol (mg/dl)		<280				>280 or drug therapy			
Smoking		No	Yes						
Diabetes		No				Yes			
Hypertension		No		Yes					
Waist circumference*		Below		Above					

* Waist circumference: male ≥ 36 inches, female ≥ 32 inches

Prevalence of CAD by RAMA-EGAT Score and CAVI
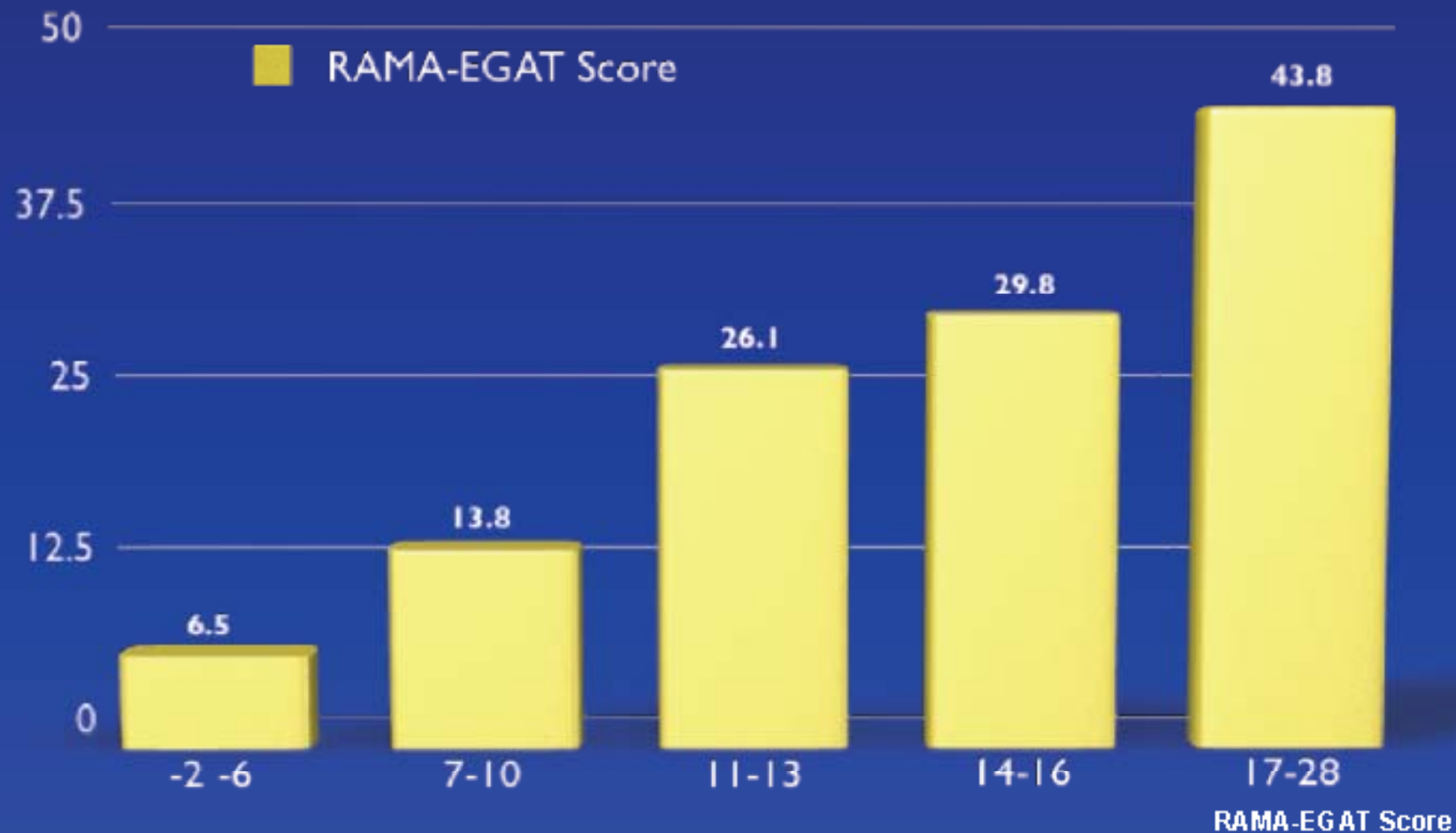
Table 1. Baseline Characteristics

Characteristic	Total (n=2058)
Age	58.9±4.9
Male	1,559 (75.8%)
HT	661 (32.1%)
DM	308 (14.9%)
DLP	984 (47.8%)
Smoking	1,111 (54.0%)
Alcohol	1,047 (50.9%)
Weight (Kg.)	65.1±11.5
Waist circumference (cm.)	88.3±12.6
sST2 (median)	18.3±9.2 ng/ml
hsCRP (median)	1.5±7.4 mg/L

Figure1
sST2 & hsCRP concentrations in EGAT population

Distribution of sST2 in EGAT population

N = 2,058

Median of sST2 = 18.3 ng/ml

Mean sST2 19.8 ng/ml, SD 9.2

Distribution of hsCRP in EGAT population

N = 2,058

Median hsCRP = 1.5 mg/L

Mean hsCRP = 3.1 mg/L, SD 7.4
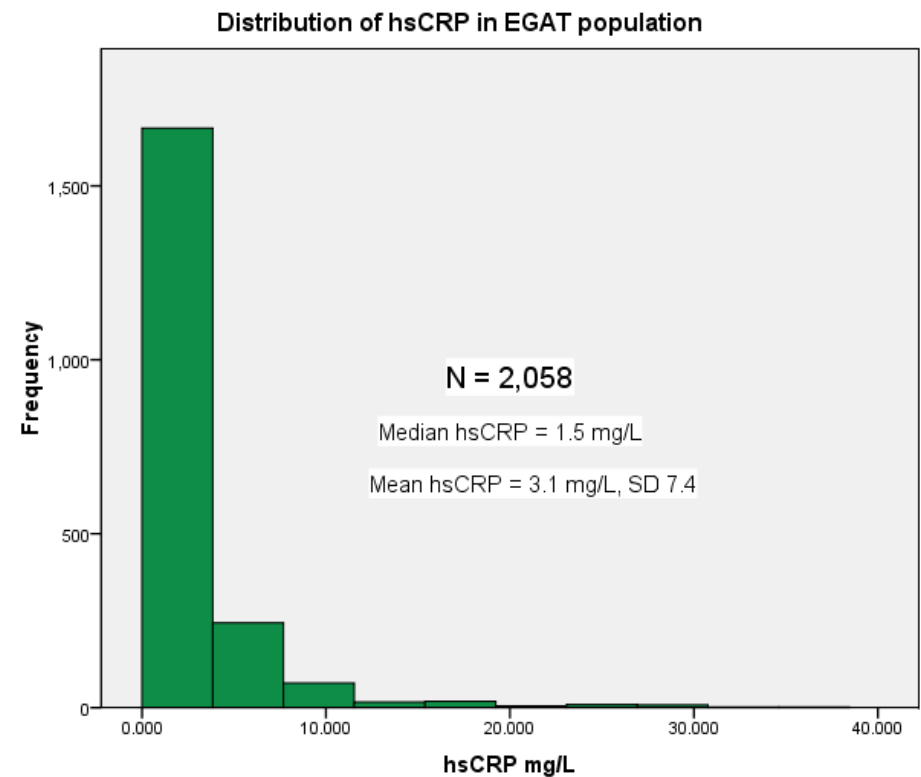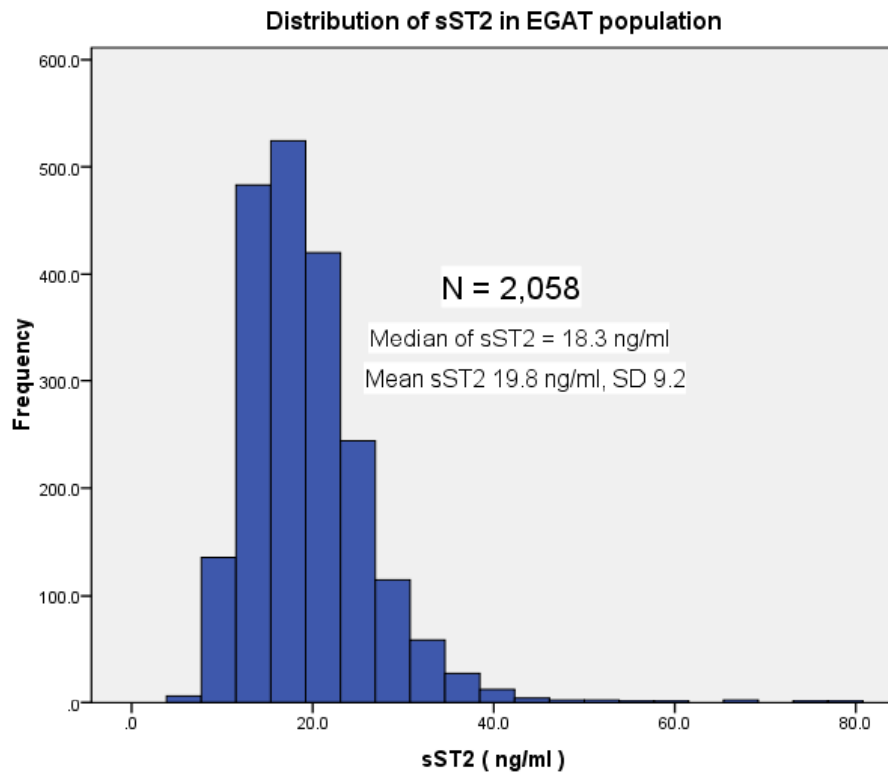
Spearman's rho	
Correlation coefficient between sST2 and hsCRP	0.007

Table 2.
sST2 concentrations in men and women

Median sST2 (age 55–64)	Male	Female
EGAT	19.1	15.8
Framingham	22.7	17.5

Median hsCRP	Male	Female
EGAT	1.3	1.6
Framingham	1.81	2.38

Table 3.
Clinical correlates with higher sST2 and hsCRP

Underlying	sST2
Male gender	*P=0.008*
History of diabetes	*P=0.008*
History of hypertension	*P=0.131*
History of dyslipidemia	*P=0.508*
History of smoking	*P< 0.001*

Table 4.
Demographic characteristics across increasing quatiles of sST2

sST2	Q1	Q2	Q3	Q4	*P*
FBS (mg/dl)	104.6	108.2	108.3	115.8	*<0.001*
SBP (mmHg)	126.4	128.3	128.6	130.5	*0.012*
Weight (kg.)	63.2	64.8	65.8	66.7	*<0.001*
Waist circumference (cm.)	86.9	88.0	88.4	89.7	*0.006*
Creatinine (mg/dl)	0.96	1.00	1.04	1.10	*<0.001*
LDL (mg/dl)	154.5	156.1	149.5	151.7	*0.097*
HDL (mg/dl)	55.2	54.4	53.7	54.3	*0.439*

Table 5.
Demographic characteristics across increasing quatiles of hsCRP

sST2	Q1	Q2	Q3	Q4	P
FBS (mg/dl)	103.4	107.4	109.5	116.7	<0.001
SBP (mmHg)	125.4	127.0	130.0	131.8	<0.001
Weight (kg.)	62.4	65.1	65.7	67.3	<0.001
Waist circumference (cm.)	85.1	87.7	89.1	91.2	<0.001
Creatinine (mg/dl)	1.03	1.02	1.02	1.03	0.792
LDL (mg/dl)	152.0	151.8	154.9	153.1	0.5
HDL (mg/dl)	58.8	54.4	53.1	51.2	<0.001
Triglyceride (mg/dl)	131.3	153.6	162.5	163.9	<0.001
Cholesterol (mg/dl)	238.4	237.8	244.4	241.4	0.06

Table 5. Incident events after 10 years follow up

Events		N
Death	All-cause death	**192 (9.3%)**
	Cardiovascular death (18.8%)	**36 (1.7%)**
	Non cardiovascular death (81.2%) Malignancy (37.5%) Infection (13.4%)	**156 (7.6%)**
Combine CV events (Stroke, MI, CHF, CAG, Revascularization)		**177 (8.6%)**
Coronary Intervention	Coronary angiography	**106 (5.2%)**
	Coronary revascularization	**95 (4.6%)**

Table 6. Incident events (%) by sST2 categories

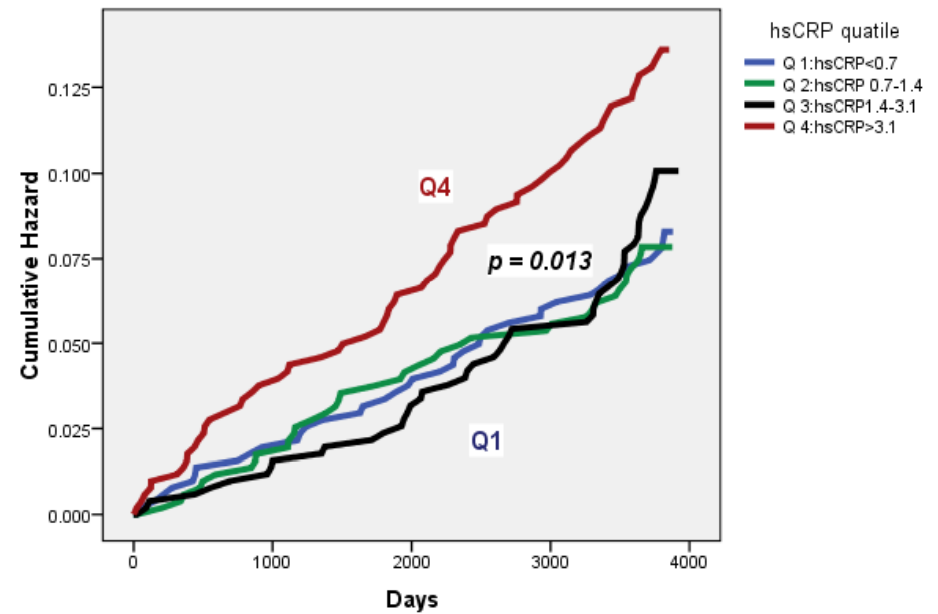| Quatiles of sST2						
	n	Q1 5.7-14.7	Q2 14.7-18.3	Q3 18.3-22.9	Q4 22.9-166.8	P value
All-cause death	192	31 (16.1%)	42 (21.9%)	42 (21.9%)	77 (40.1%)	*<0.001*
Cardiovascular death	36	3 (8.3%)	9 (25%)	8 (22.2%)	16 (44.4%)	*0.021*
Noncardiovascular death	156	28 (17.9%)	33 (21.2%)	34 (21.8%)	61 (39.1%)	*<0.001*

Table 7. Incident events (%) by hsCRP categories

Quatiles of hsCRP						
	n	Q1 0.16-0.7	Q2 0.7-1.4	Q3 1.4-3.1	Q4 3.1-168	P value
All-cause death	192	39 (20.3%)	39 (20.3%)	49 (25.5%)	65 (39.9%)	*0.014*
Cardiovascular death	36	2 (5.6%)	11 (30.6%)	11 (30.6%)	12 (33.3%)	0.058
Noncardiovascular death	156	37 (23.7%)	28 (17.9%)	38 (24.4%)	33 (34.0%)	*0.028*

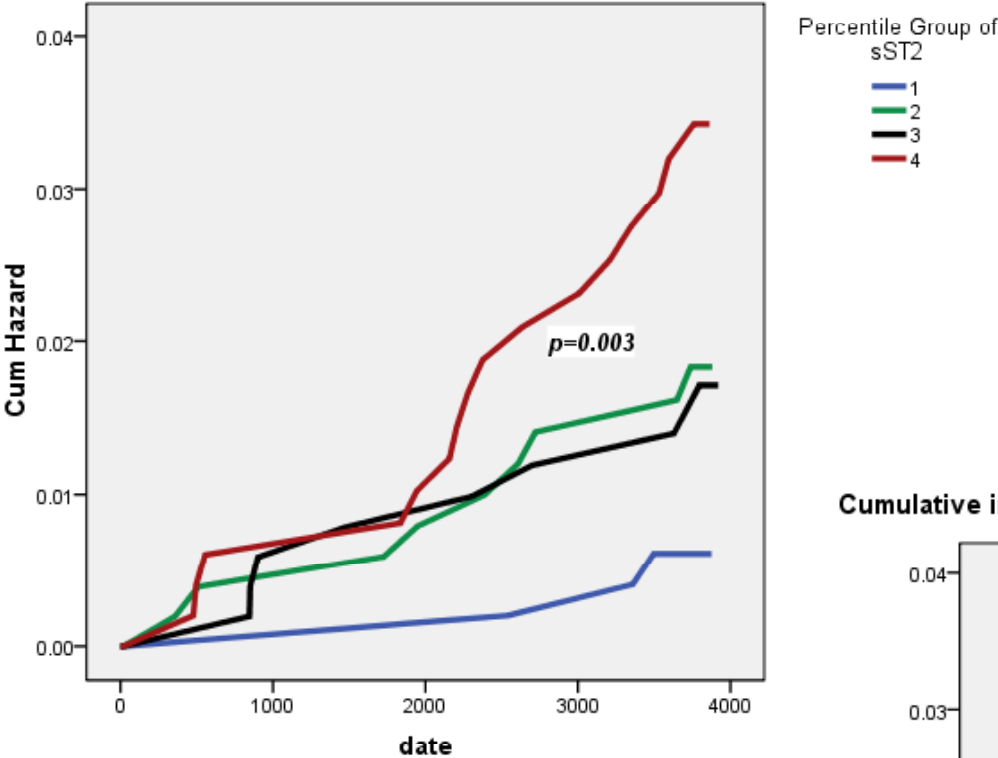Cumulative incidence of death according to quatile of sST2

sST2quatile
- Q 1: sST2<14.7
- Q 2: sST2 14.7-18.3
- Q 3: sST2 18.3-22.9
- Q 4: sST2>22.9

Q 4   p < 0.001

Q1
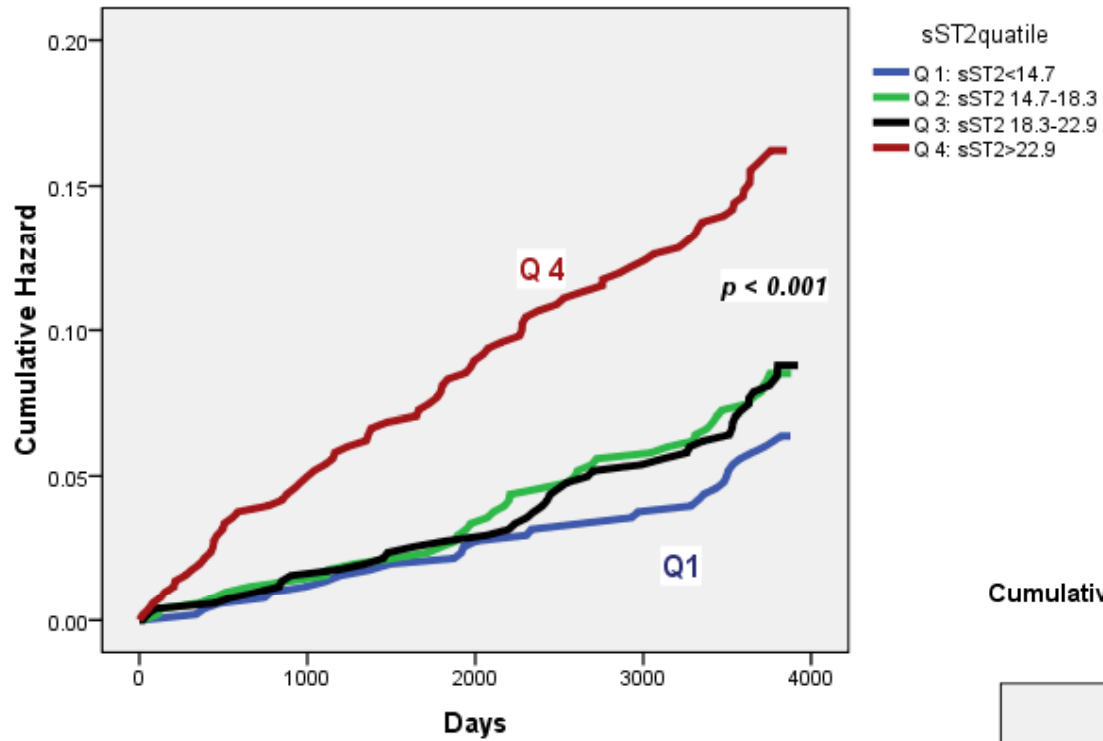
All Cause death

Cumulative incidence of death according to quatile of hsCRP

hsCRP quatile
- Q 1:hsCRP<0.7
- Q 2:hsCRP 0.7-1.4
- Q 3:hsCRP1.4-3.1
- Q 4:hsCRP>3.1

Q4   p = 0.013

Q1

Cumulative incidence of CV death according to quatile of sST2
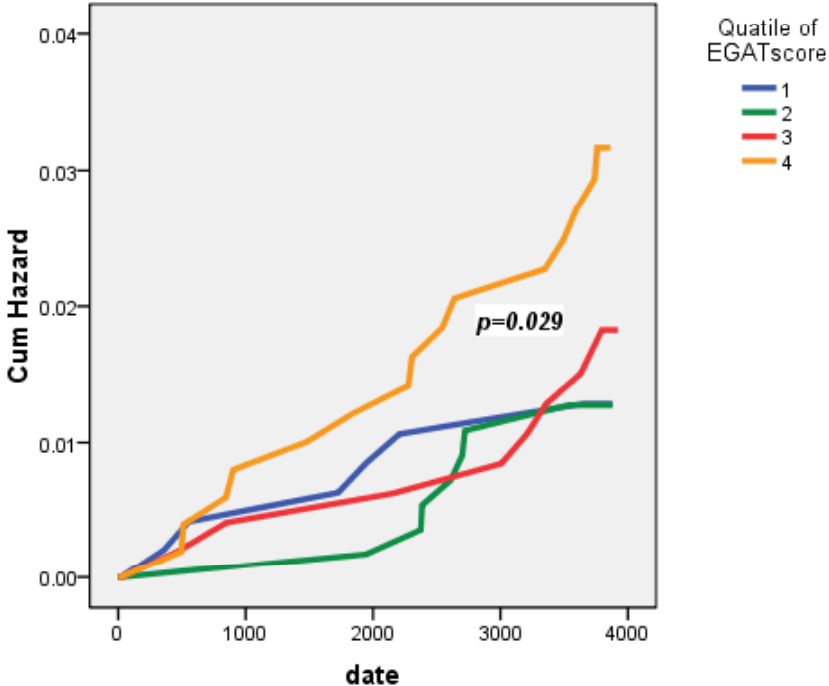
CV death

Cumulative incidence of CV death according to quatile of EGAT score

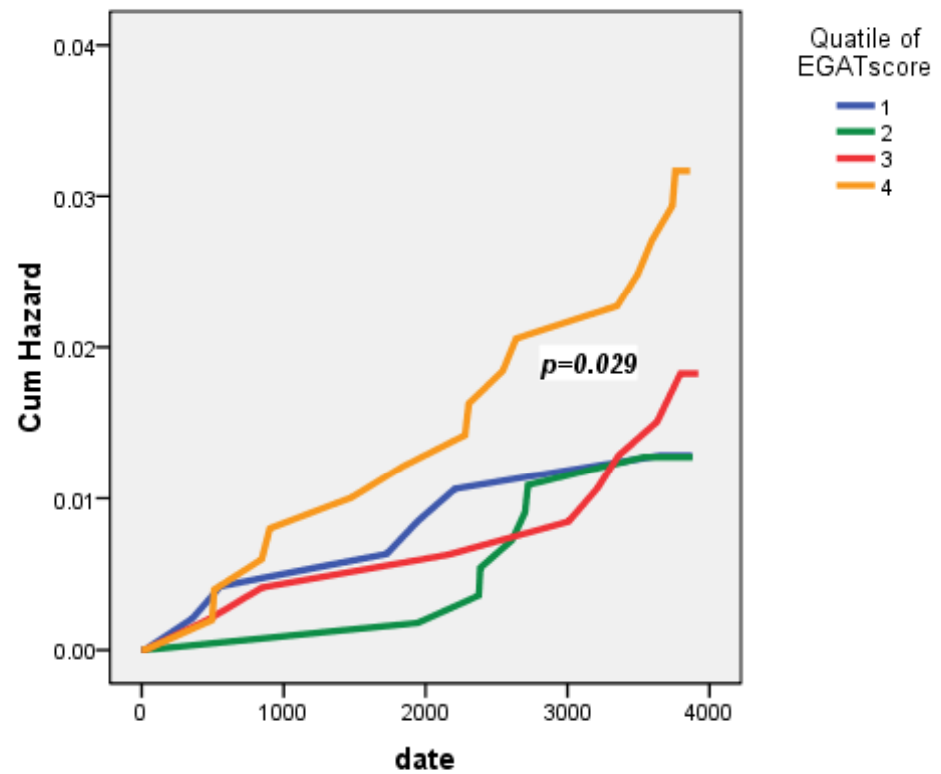Cumulative incidence of death according to quatile of EGAT score

Quatile of EGATscore
- Q1 EGAT Score 4-12
- Q3 EGAT Score 13-16
- Q3 EGAT Score 17-20
- Q4 EGAT Score 21-31

$p < 0.001$

Cum Hazard

date
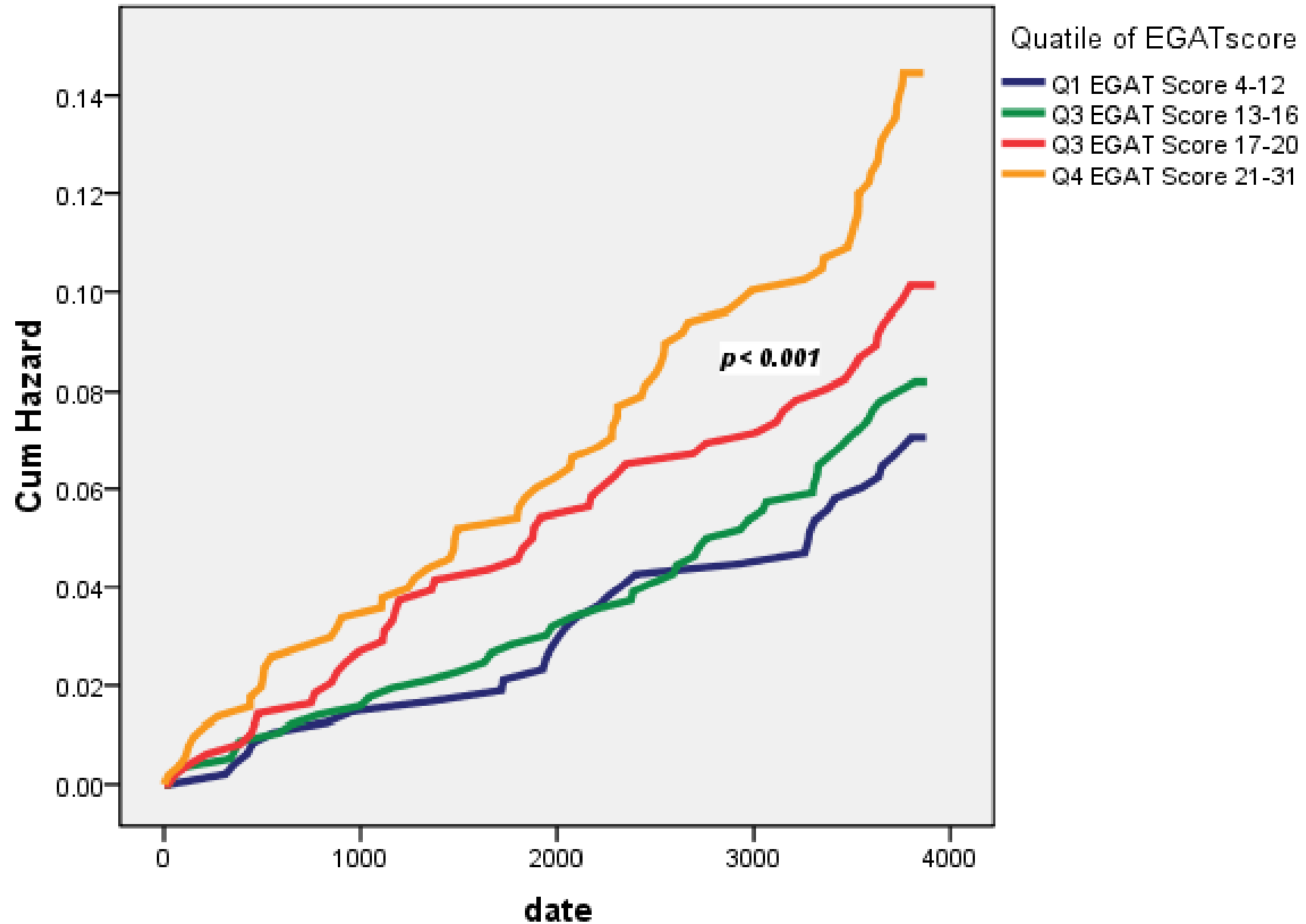
Cumulative incidence of CV death according to quatile of EGAT score

Table 8. Multivariable-Adjusted Hazard Ratio

Independent variable	Death	*p*	CV death	*p*
Age>64	1.61 (1.2-2.2)	*0.004*	1.60 (0.8-3.2)	*0.193*
Male gender	1.25 (0.8-2.1)	*0.385*	0.74 (0.3-2.0)	*0.544*
Smoking	1.67 (1.1-2.4)	*0.007*	1.20 (0.5-2.7)	*0.653*
Weight>72Kg.	0.97 (0.6-1.6)	*0.901*	1.17 (0.4-3.3)	*0.770*
Waist>95cm.	0.86 (0.53-1.4)	*0.530*	0.81 (0.3-2.3)	*0.692*
Underlying DM HT	1.65 (1.2-2.4) 1.20 (0.9-1.7)	*0.005* *0.280*	1.78 (0.9-3.7) 1.59 (0.8-3.2)	*0.124* *0.192*
hsCRP>3.1mg/L	1.22 (0.9-1.7)	*0.250*	1.08 (0.5-2.3)	*0.832*
sST2>23 ng/ml	1.81 (1.3-2.5)	*0.000*	2.28 (1.2-4.5)	*0.018*

Table 9. Multivariable-Adjusted Hazard Ratio

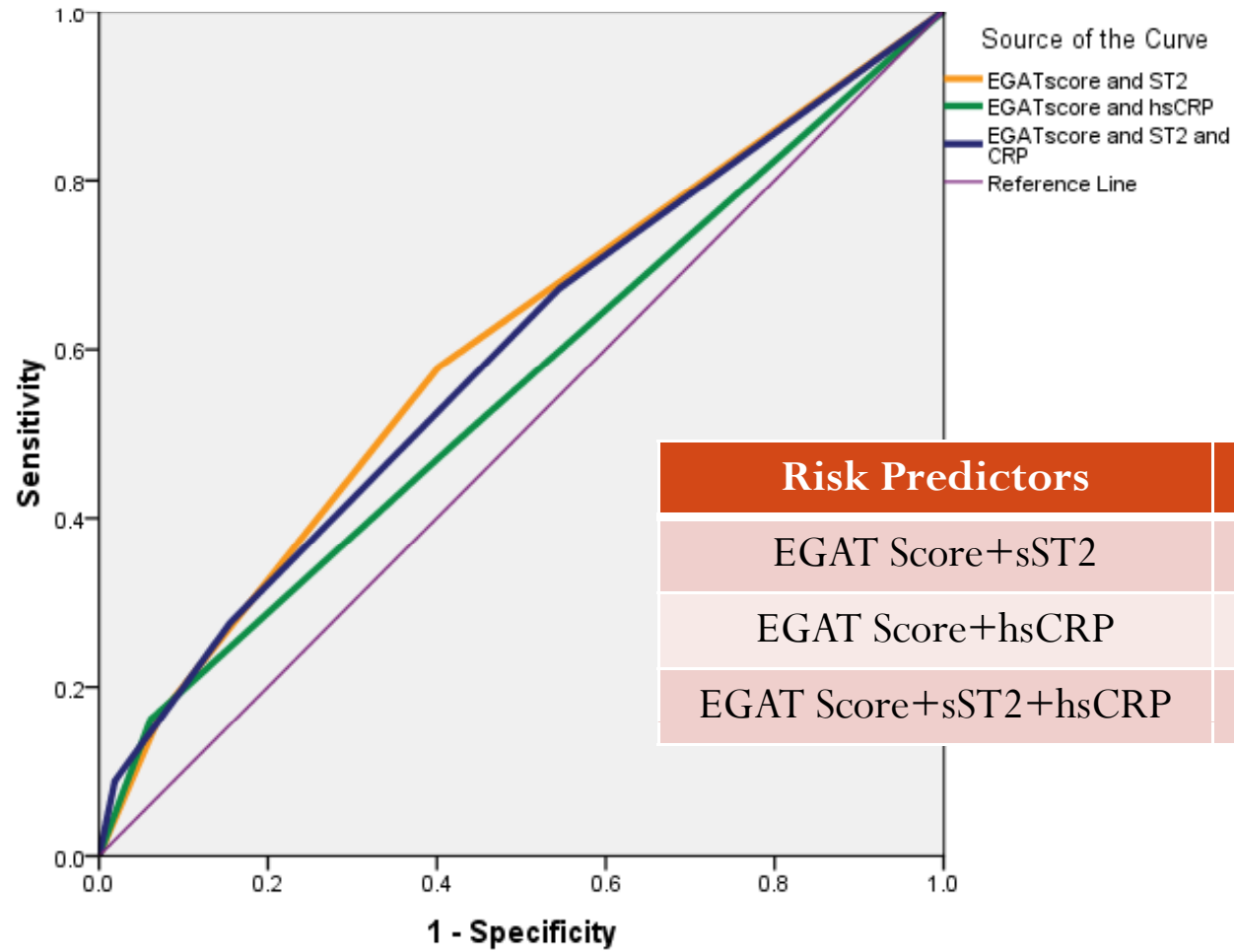| Independent variable	Combine CV Event*	p
Age>64	0.99 (0.7-1.4)	0.964
Male gender	1.64 (1.0-2.6)	**0.036**
Smoking	1.03 (0.7-1.5)	0.867
Underlying DM HT	1.08 (0.7-1.6) 1.38 (1.0-1.9)	0.683 **0.046**
hsCRP>3.1mg/L	1.18 (0.8-1.6)	0.340
sST2>23 ng/ml	0.87 (0.6-1.2)	0.448

Combine CV Event: Stroke, HF, MI, CAG, Revascularization
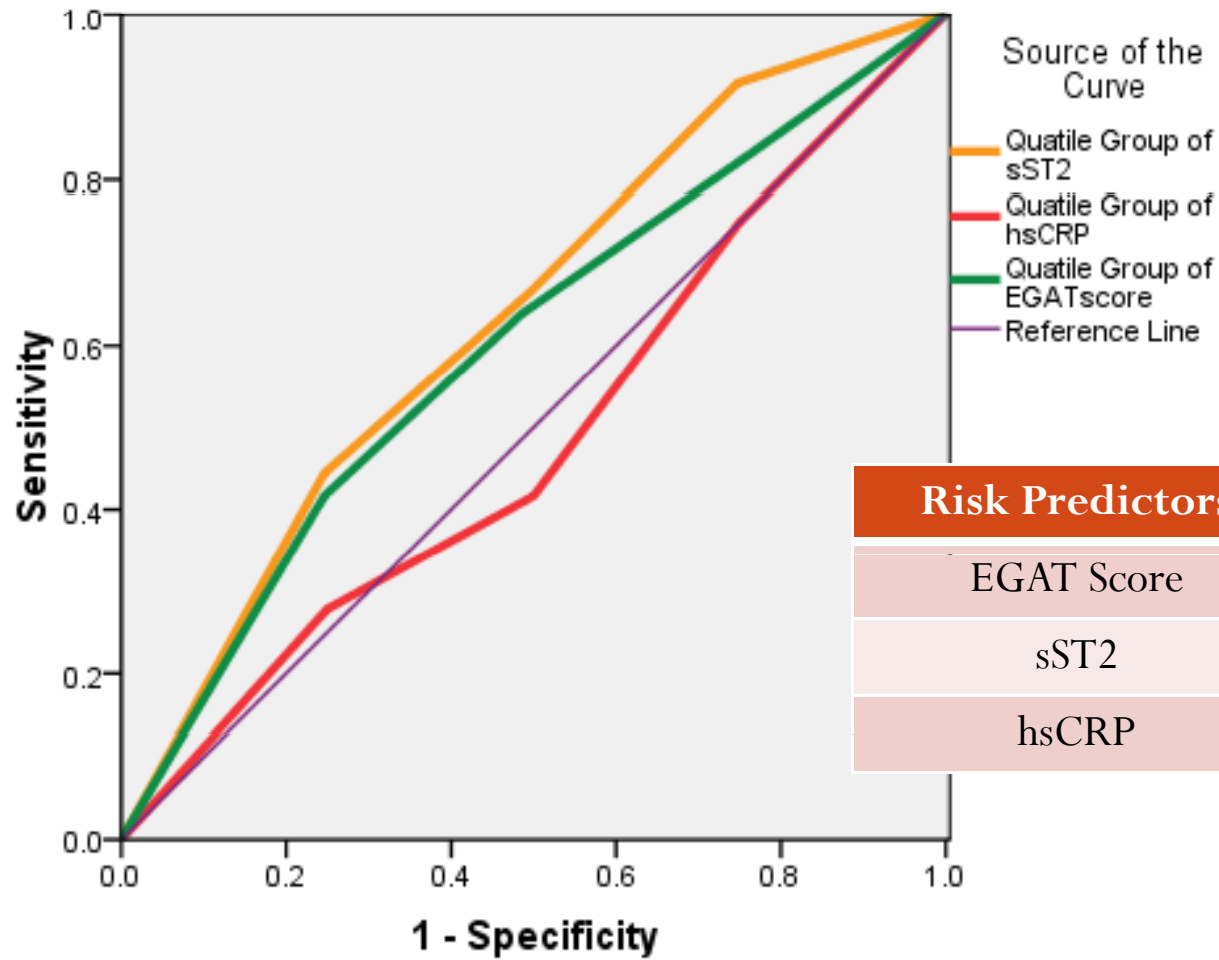
All cause mortality

ROC Curve

Risk Predictors	AUC
EGAT Score	0.581
sST2	0.582
hsCRP	0.485

All cause mortality

Risk Predictors	AUC
EGAT Score+sST2	0.601
EGAT Score+hsCRP	0.553
EGAT Score+sST2+hsCRP	0.591

Cardiovascular death

ROC Curve

Risk Predictors	AUC
EGAT Score	0.598
sST2	0.634
hsCRP	0.486

Cardiovascular death

ROC Curve

Risk Predictors	AUC
EGAT Score+sST2	0.640
EGAT Score+hsCRP	0.568
EGAT Score+sST2+hsCRP	0.630
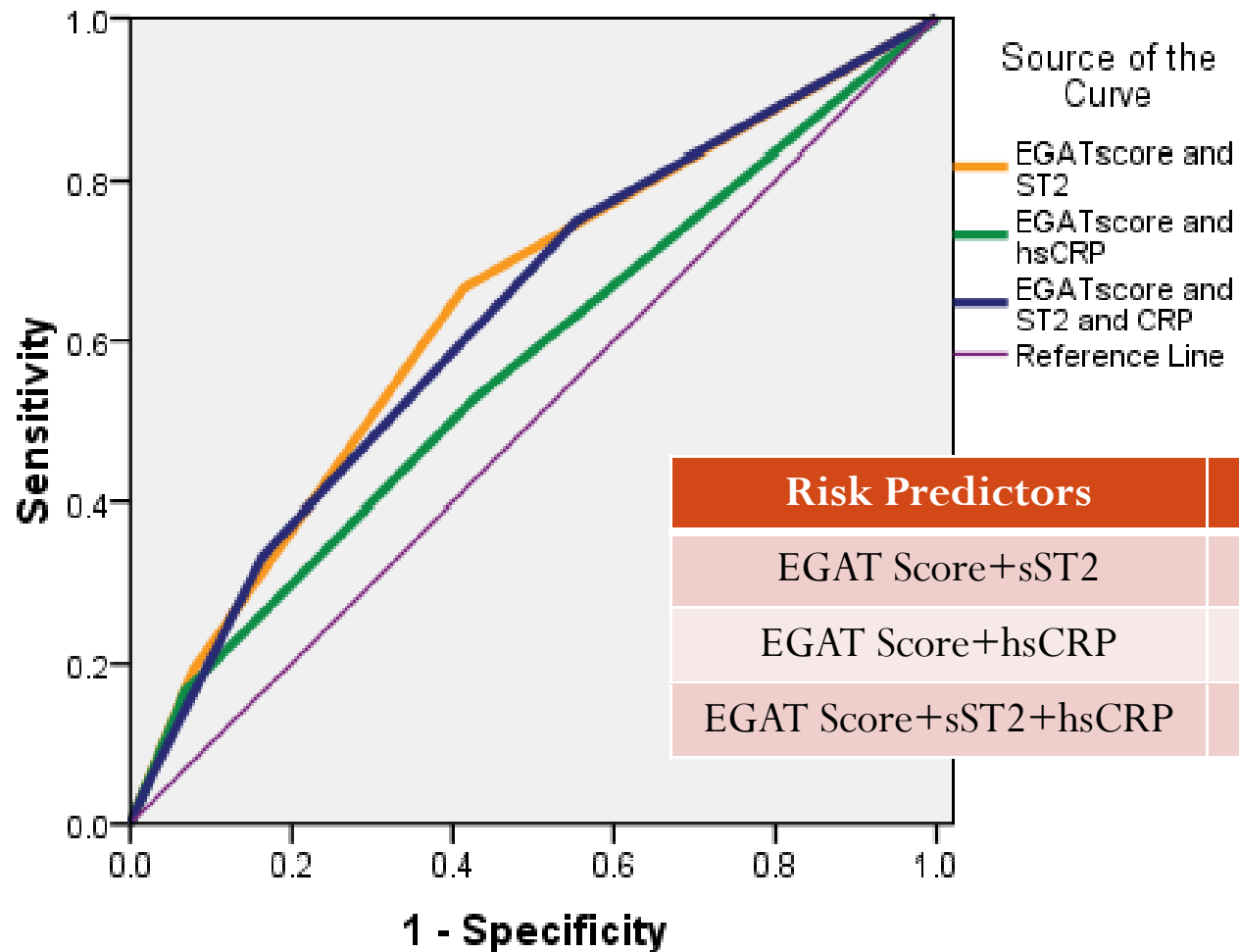
Combine CV death and CV event

ROC Curve

Risk Predictors	AUC
sST2	0.538
hsCRP	0.517
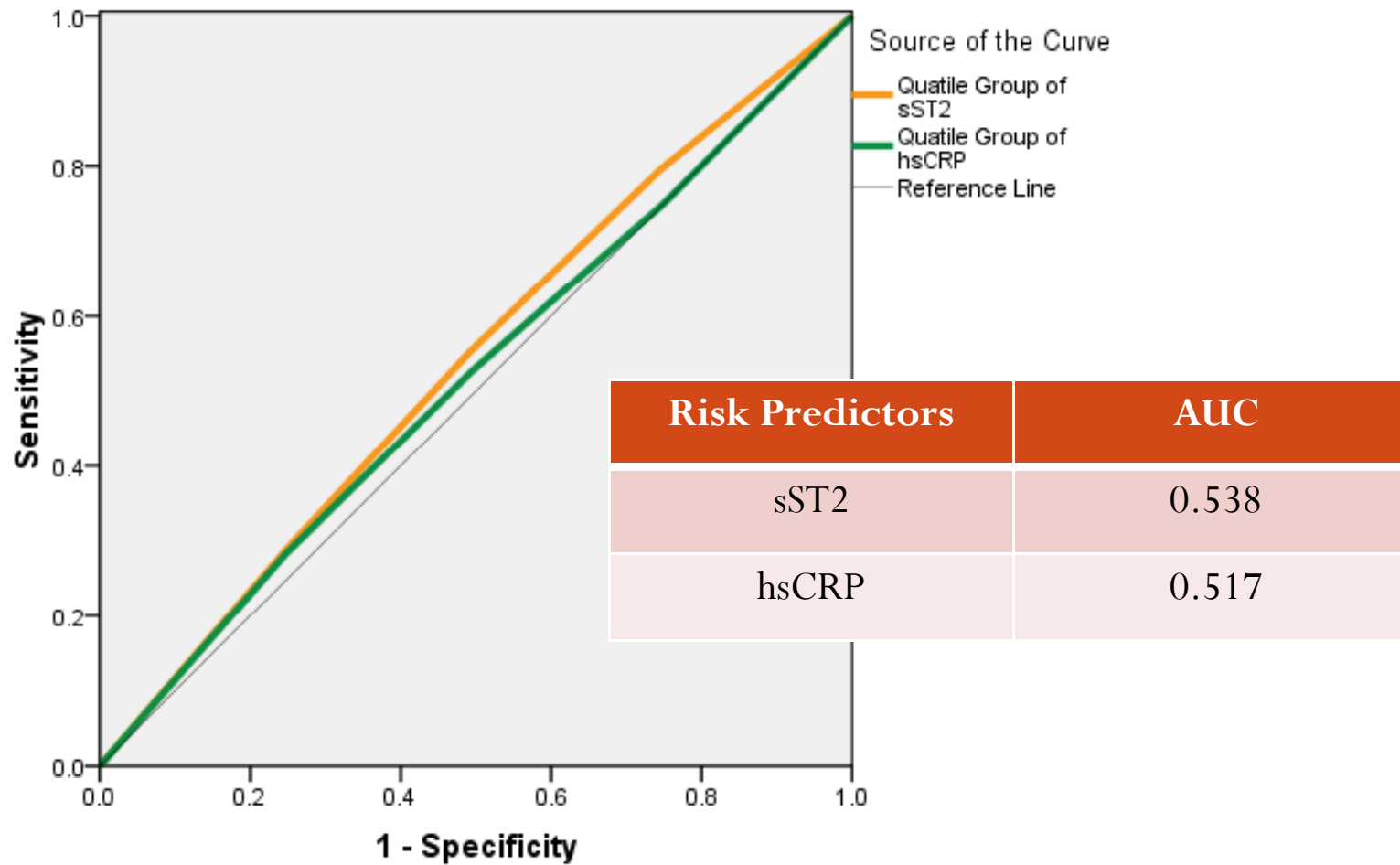
Conclusion

- DM, smoking, body weight, waist circumference and serum creatinine correlate with sST2 levels.

- sST2 appeared to be a better predictor of cardiovascular and all-cause mortality in Thai population than hsCRP.

- No correlation between sST2 and hsCRP.

- Multiple biomarkers for risk prediction is not indicated.

Thank you for your attention.

Background

- Guidelines recommends **against th**e use of **CRP** as a risk marker in the <u>general population</u> for risk prediction. (Class III, Level of Evidence C).

- Men > 50, women with moderate risk for CVD are candidates. (Class, Level of Evidence A).

- LDL mg/dL and **hsCRP > 2 mg/L**, fixed intensive-dose reduced the CVD events by 44% compared with placebo.
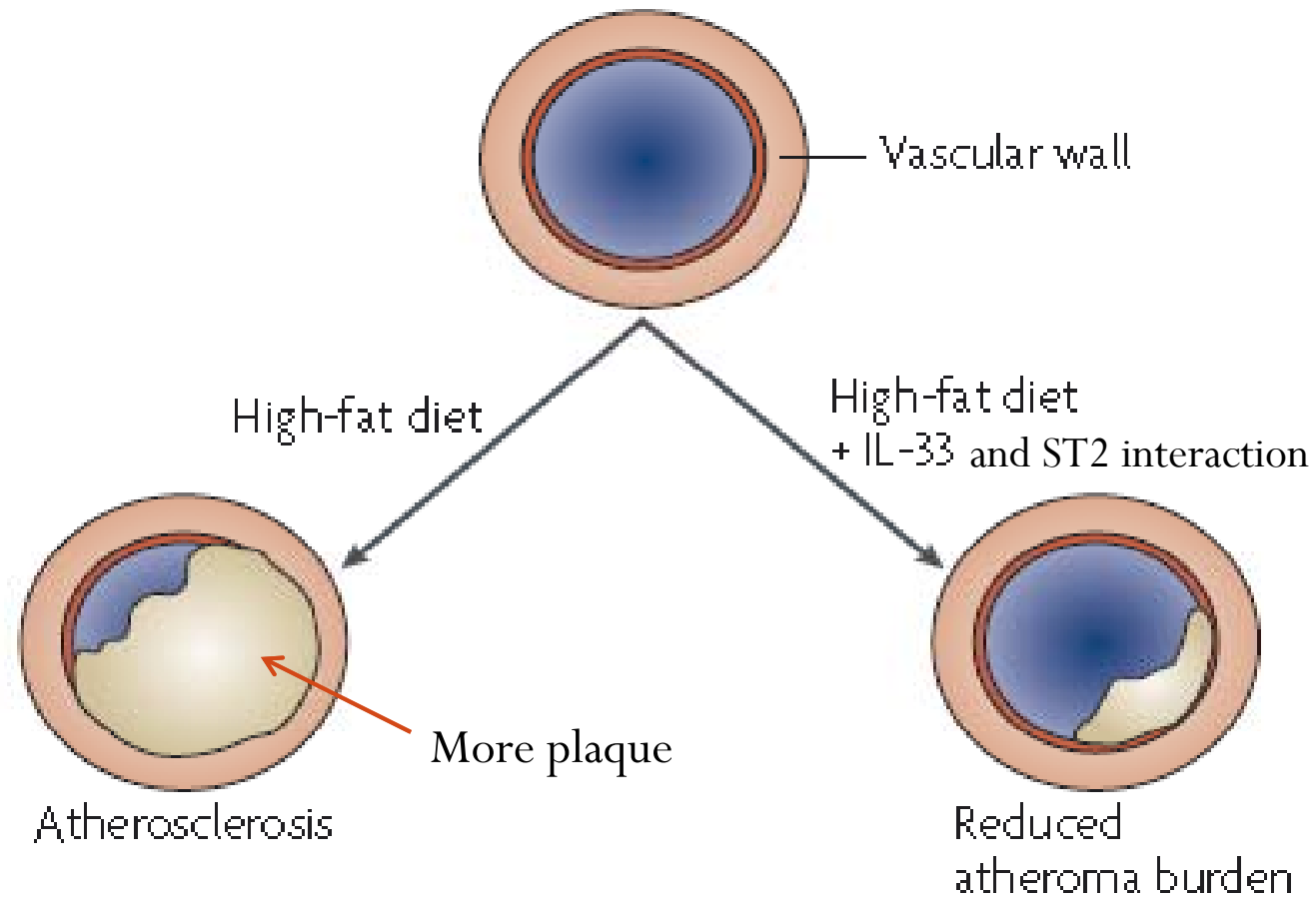
Elevation of CRP lack specificity.

Circulation. 2003; 107:499-511

Can J Cardiol 2009;25(10): 567-579.

ACC/AHA 2013 Blood Cholesterol Guideline.

sST2 – Inflammation - Atherosclerosis

Background

- Novel biomarker should
  - More specific to cardiovascular system
  - Add another biological information
  - Add another clinical information
  - Potential new therapeutic approach

Soluble ST2