21st CardioVascular Summit

TCTAP 2016 April 26-29, 2016
Coex, Seoul, Korea

SYNTAX SCORE
SYNTAX SCORE II

Boston Scientific

CARDIALYSIS

Individual long-term mortality prediction following either coronary stenting or bypass surgery in patients with multivessel and/or unprotected left-main disease: An external validation of the SYNTAX score II model in the 1480 patients of BEST and PRECOMBAT randomized controlled trials

April 26 5:00-5:10 pm

Yoshinobu Onuma, MD, PhD
Erasmus MC, Rotterdam , The Netherlands

Yohei Sotomi, MD; Rafael Cavalcante, MD. PhD.;
David van Klaveren, MSc; Jung-Min Ahn, MD.; Cheol Whan Lee, MD;
Ewout W Steyerberg, PhD; Robbert J. de Winter, MD, PhD;
Joanna J. Wykrzykowska, MD, PhD;
Seung-Jung Park, MD. PhD.; Patrick W Serruys MD. PhD.

Background

- In patients with multivessel coronary disease and/or unprotected left main disease, the choice of the best revascularization strategy is not simple.

- **The SYNTAX score II** is a tool created using the predictors of 4 years mortality after both treatments in the landmark all-comers SYNTAX trial. It takes into account not only the **anatomic complexity of the disease (SYNTAX SCORE)**, but also **clinical co-morbidities** that were shown to impact mortality in that trial. This score provides an individualized estimation of long-term mortality after **both PCI and CABG.** This prediction model is already recommended for risk stratification in the European guidelines as class IIa.

SYNTAX Score II variables

SYNTAX Score II was developed by applying a Cox proportional hazards model to the results of SYNTAX trial obtaining a combination of clinical and anatomical independent predictors of 4 years all-cause mortality:

ANATOMICAL SYNTAX SCORE	LM
AGE	Cr Clearance	LVEF
Gender	PVD	COPD

Farooq V et al. Lancet 2013; 381: 639–50

Chapter 8

Statistical Models for Prognostication

By: Ewout W. Steyerberg, PhD, Department of Public Health, Erasmus University Rotterdam, the Netherlands, and Prof. Frank E. Harrell Jr, PhD, Department of Health Evaluation Sciences, University of Virginia, Charlottesville, VA.

Erasmus MC
Universitair Medisch Centrum Rotterdam

UNIVERSITY of VIRGINIA

Circulation

Special Report

Use and Misuse of the Receiver Operating Characteristic Curve in Risk Prediction

Nancy R. Cook, ScD
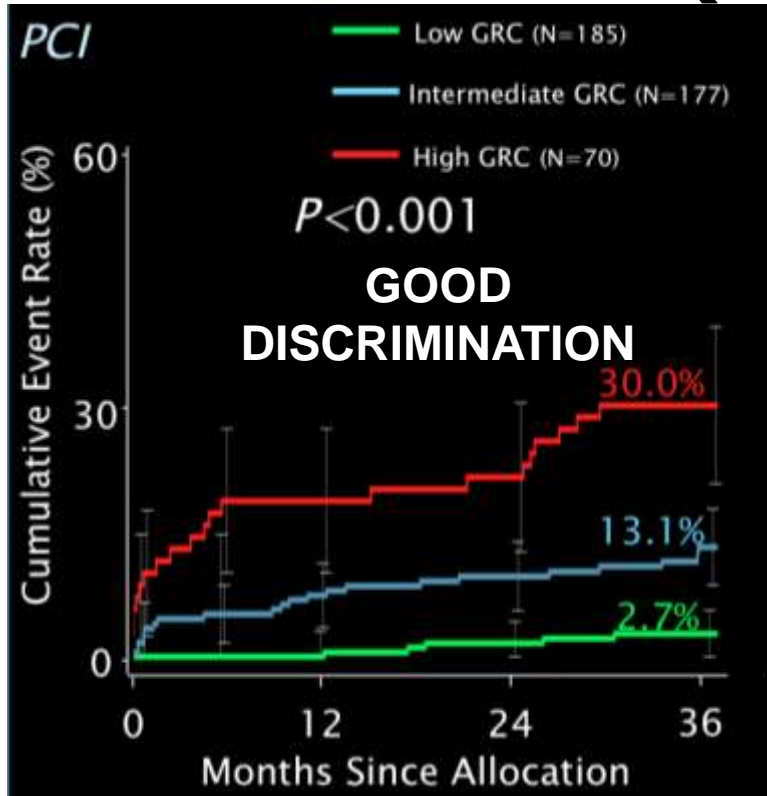
"As novel risk factors are discovered, sole reliance on the c-statistic to evaluate their utility as risk predictors thus seems ill-advised..."

DISCRIMINATION
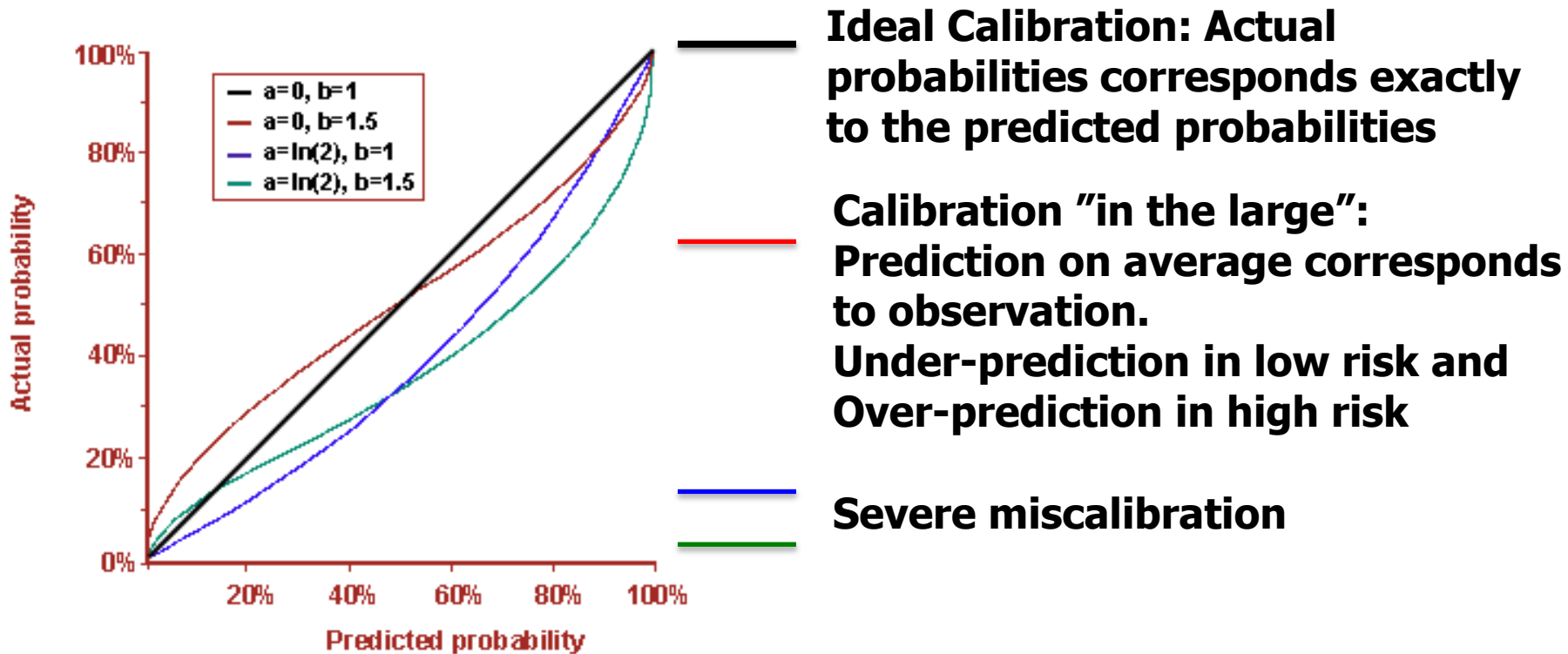## **C-Statistics (area under ROC curve)**

$$\text{Sensitivity} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}}$$

$$\text{Specificity} = \frac{\text{True Negative}}{\text{True Negative} + \text{False Positive}}$$

Discrimination refers to the ability to distinguish high risk subjects from low risk subjects, and is commonly quantified by a measure of concordance, the c statistic. For binary outcomes, c is identical to the area under the receiver operating characteristic curve

Calibration

Calibration refer to whether the predicted probabilities agree with the observed probabilities.

Ideal Calibration: Actual probabilities corresponds exactly to the predicted probabilities

Calibration "in the large": Prediction on average corresponds to observation. Under-prediction in low risk and Over-prediction in high risk

Severe miscalibration

"There is, in fact, a trade-off between discrimination and calibration and a model typically cannot be perfect in both."

CALIBRATION Of SYNTAX SCORE II in the DELTA [LM] and CREDO KYOTO [3VD] registries

Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II
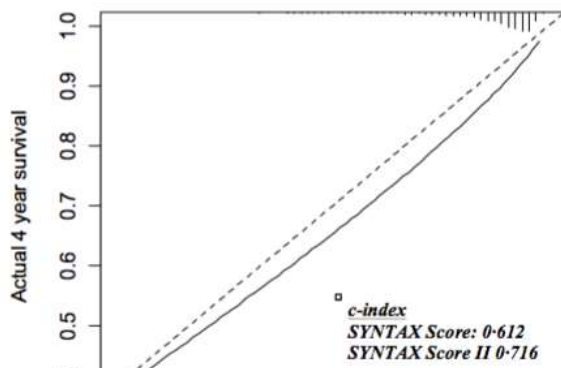
Predictive Performance of SYNTAX Score II in Patients With Left Main and Multivessel Coronary Artery Disease — Analysis of CREDO-Kyoto Registry —

Carlos M. Campos, MD; David van Klaveren; Javaid Iqbal, MD, PhD; Yoshinobu Onuma, MD, PhD; Yao-Jun Zhang, MD, PhD; Hector M. Garcia-Garcia, MD, PhD; Marie-Angele Morel, BSc; Vasim Farooq, MD, PhD; Hiroki Shiomi, MD; Yutaka Furukawa, MD; Yoshihisa Nakagawa, MD; Kazushige Kadota, MD; Pedro A. Lemos, MD, PhD; Takeshi Kimura, MD; Ewout W. Steyerberg, PhD; Patrick W. Serruys, MD, PhD
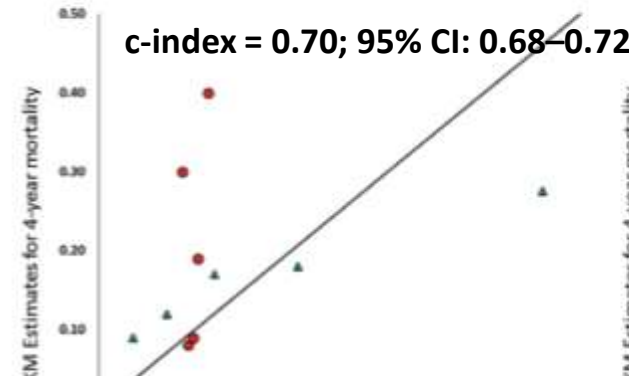
DELTA registry

CREDO KYOTO registry

b) Validation Plot SYNTAX Score II: DELTA Registry

c-index
SYNTAX Score: 0·612
SYNTAX Score II 0·716

A PCI group — c-index = 0.70; 95% CI: 0.68–0.72

B CABG group — c-index = 0.75, 95% CI: 0.72–0.78

Anatomical SYNTAX Score
SYNTAX Score II
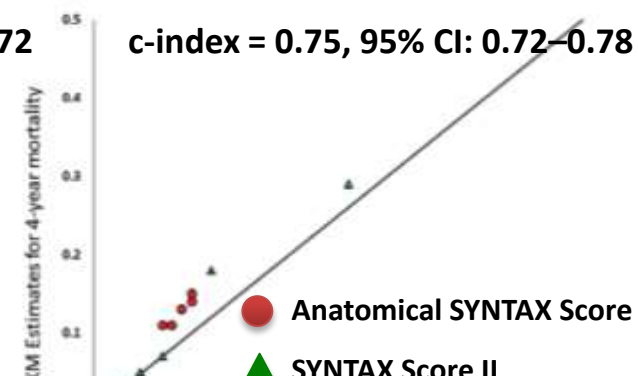
However, Syntax II has been never validated in the context of Randomized trial...

Methods

Our primary objective was to assess the prediction and discrimination performance of the Syntax score II for PCI and CABG to appropriately stratify the risk of all-cause mortality in patients with severe coronary artery disease from largest Asian RCTs: BEST and PRECOMBAT trials.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease

Seung-Jung Park, M.D., Ph.D., Jung-Min Ahn, M.D., Young-Hak Kim, M.D., Duk-Woo Park, M.D., Sung-Cheol Yun, Ph.D., Jong-Young Lee, M.D., Soo-Jin Kang, M.D., Seung-Whan Lee, M.D., Cheol Whan Lee, M.D., Seong-Wook Park, M.D., Suk Jung Choo, M.D., Cheol Hyun Chung, M.D., Jae Won Lee, M.D., David J. Cohen, M.D., Alan C. Yeung, M.D., Seung Ho Hur, M.D., Ki Bae Seung, M.D., Tae Hoon Ahn, M.D., Hyuck Moon Kwon, M.D., Do-Sun Lim, M.D., Seung-Woon Rha, M.D., Myung-Ho Jeong, M.D., Bong-Ki Lee, M.D., Damras Tresukosol, M.D., Guo Sheng Fu, M.D., and Tiong Kiam Ong, M.D., for the BEST Trial Investigators*

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Randomized Trial of Stents Versus Bypass Surgery for Left Main Coronary Artery Disease

5-Year Outcomes of the PRECOMBAT Study

Jung-Min Ahn, MD,* Jae-Hyung Roh, MD,* Young-Hak Kim, MD,* Duk-Woo Park, MD,* Sung-Cheol Yun, PhD,† Pil Hyung Lee, MD,* Mineok Chang, MD,* Hyun Woo Park, MD,* Seung-Whan Lee, MD,* Cheol Whan Lee, MD,* Seong-Wook Park, MD,* Suk Jung Choo, MD,* CheolHyun Chung, MD,* JaeWon Lee, MD,* Do-Sun Lim, MD,‡ Seung-Woon Rha, MD,§ Sang-Gon Lee, MD,‖ Hyeon-Cheol Gwon, MD,¶ Hyo-Soo Kim, MD,# In-Ho Chae, MD,** Yangsoo Jang, MD,†† Myung-Ho Jeong, MD,‡‡ Seung-Jea Tahk, MD,§§ Ki Bae Seung, MD,‖‖ Seung-Jung Park, MD*

BEST trial

a randomized trial conducted at 27 sites in South Korea, China, Malaysia, and Thailand that included 880 patients with multivessel coronary artery disease

PRECOMBAT trial

a randomized trial conducted at 13 sites in Korea that included 600 patients with documented unprotected left main coronary artery (ULMCA) stenosis

Study Population

n = 1480
BEST n = 880
PRECOMBAT n = 600

Missing data
n = 106
BEST n = 12
PRECOMBAT n = 94

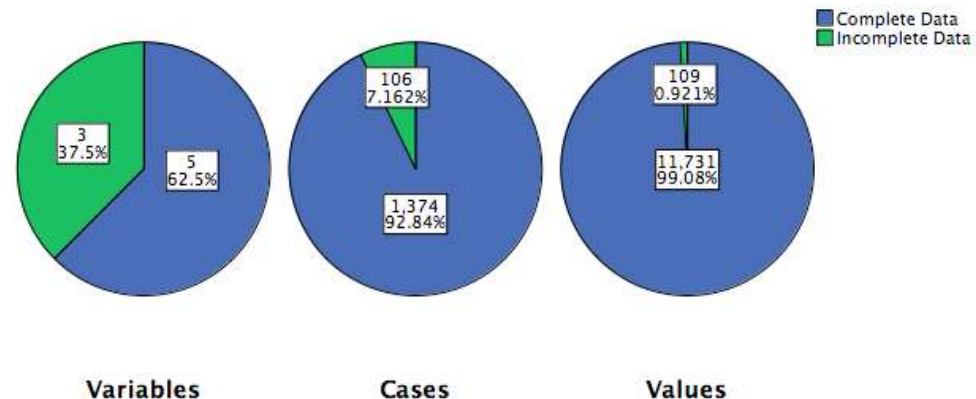Multiple imputation (5 times)
for Syntax II variables

n = 1480
BEST n = 880
PRECOMBAT n = 600

Number of Missing Values

	PRECOMBAT (n=600)	BEST (n=880)
Syntax score	34	0
CrCl	19	12
LVEF	44	0
UPLMD	0	0
Age	0	0
Gender	0	0
PVD	0	0
COPD	0	0

Overall Summary of Missing Values

Complete Data
Incomplete Data

3
37.5%

5
62.5%

106
7.162%

1,374
92.84%

109
0.921%

11,731
99.08%

Variables   Cases   Values

Validation for SYNTAX score II in BEST and PRECOMBAT trials

- ## *Discrimination performance*

Receiver-operating characteristic (ROC) curve was used to compare the prognostic ability (discrimination performance) of SYNTAX score II to predict the rates of all-cause death in the whole population, UPLMD disease population, and multivessel disease population. Discrimination was studied with the ***concordance (C) index***, which is identical to the area under the ROC curve. The C-index estimates the probability that, of two randomly chosen patients, the patient with the more favorable prognostic score will outlive the patient with the less favorable prognostic score, and ranges from 0.5 (no discrimination) to a theoretical maximum of 1.

- ## *Calibration performance*

The calibration performance of the Syntax score II was evaluated using ***Calibration plots*** in the same populations. Calibration refers to the agreement between observed and predicted outcomes. The possible over- or underestimation of the predicted risks were graphically assessed with validation plots.

Results: Patient characteristics (1/3)

	CABG (n=742)	PCI (n=738)
Age (years)	65 [57-71]	64 [56-70]
Male gender, n (%)	556 (74.9)	532 (72.1)
Height (cm)	164 [158-169]	164 [158-169]
Bodyweight (kg)	65.7 [58.6-72.4]	65.7 [59.0-72.0]
SYNTAX Score II variables		
Anatomical SYNTAX Score	25 [18-31]	24 [18-30]
Creatinine clearance (ml/min)	73.0 [58.4-89.9]	72.3 [56.4-89.6]
UPLMD, n (%)	300 (40.4)	300 (40.7)
Left ventricular ejection fraction (%)	60 [57-65]	60 [57-65]
Chronic obstructive pulmonary disease, n (%)	16 (2.2)	14 (1.9)
Peripheral vascular disease, n (%)	19 (2.6)	30 (4.1)
Treatment recommendation by SYNTAX Score II		
PCI	17 (2.3)	33 (4.5)
Equipoise	474 (63.9)	489 (66.3)
CABG	251 (33.8)	216 (29.3)

Results: Patient characteristics (2/3)

	CABG (n=742)	PCI (n=738)
Clinical presentation *		
Silent myocardial ischemia, n (%)	74 (10.0)	84 (11.4)
Stable angina, n (%)	330 (44.7)	366 (49.7)
Unstable angina, n (%)	277 (37.5)	232 (31.5)
Unstable angina and recent acute myocardial infarction, n (%)	58 (7.8)	55 (7.5)
Hypertension, n (%)	456 (61.5)	452 (61.2)
Diabetes, n (%)	275 (37.1)	282 (38.2)
Current smoker, n (%)	172 (23.2)	177 (24.0)
Hypercholesterolemia, n (%)	342 (46.1)	366 (49.6)
Previous myocardial infarction, n (%)	48 (6.5)	38 (5.1)
Previous PCI, n (%)	76 (10.2)	68 (9.2)
Previous cerebrovascular accident, n (%) †	33 (7.5)	37 (8.4)
Proximal LAD disease, n (%) ‡	545 (73.5)	563 (76.3)
Median follow-up duration (days)	1800 [1428-1800]	1800 [1403-1800]

Results: Patient characteristics (3/3)

	CABG (n=742)	PCI (n=738)
Procedural data		
CABG		
Off-pump CABG, n (%) [§]	407 (65.1)	
Number of total conduit (n) [§]	3.0 [2.0-3.0]	
Number of arterial conduit (n) [§]	2.0 [1-3.0]	
Number of venous conduit (n) [§]	1.0 [0-1.0]	
Use of LIMA, n (%) [¶]	612 (97.1)	
PCI		
Number of stents (n) [#]		3.0 [2.0-4.0]
Total stent length (mm) [††]		74 [50-102]
Mean stent diameter (mm) [#]		3.2 [3.0-3.4]
Stent type, n (%)		
Sirolimus-eluting stent		300 (40.7)
Everolimus-eluting stent		438 (59.3)
Complete revascularization**	506 (70.6)	420 (57.5)

Calibration Plots at Cross-Validation of SYNTAX score II in the entire population

n = 1480

(%)

Underestimation

Overestimation of Mortality in high SxSII group

0.66

0.95

The SYNTAX score II has good calibration but only moderate discrimination ability for the 4 years mortality prediction in whole population.

0.93

Kaplan-Meier
4 years mortality

0.86

0.85

c-index = 0.683

Overestimation

SYNTAX score II   (%)
Predicted 4 years mortality
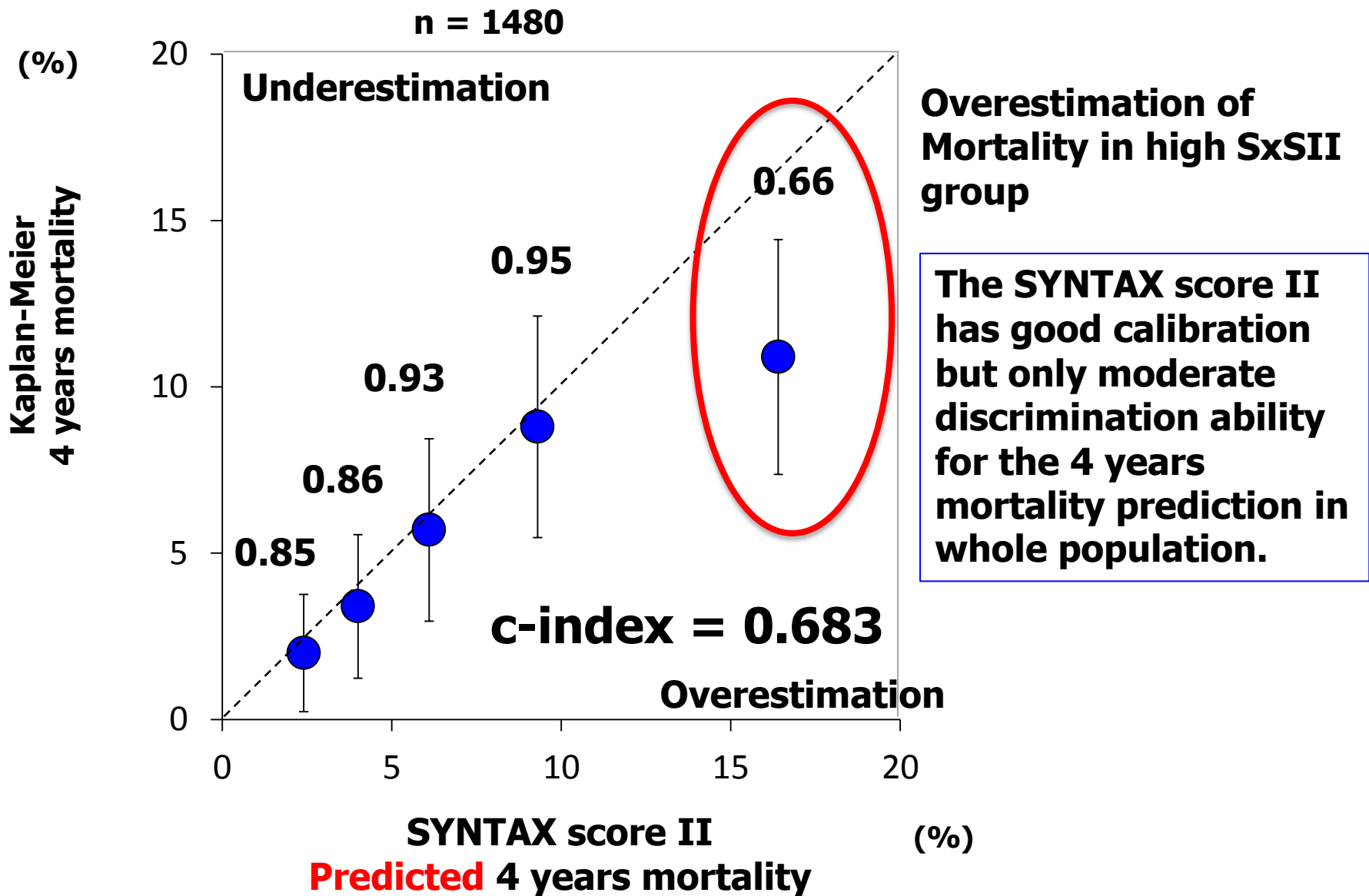
Calibration Plots at Cross-Validation of SYNTAX score II in subgroups

Whole population

PCI

CABG
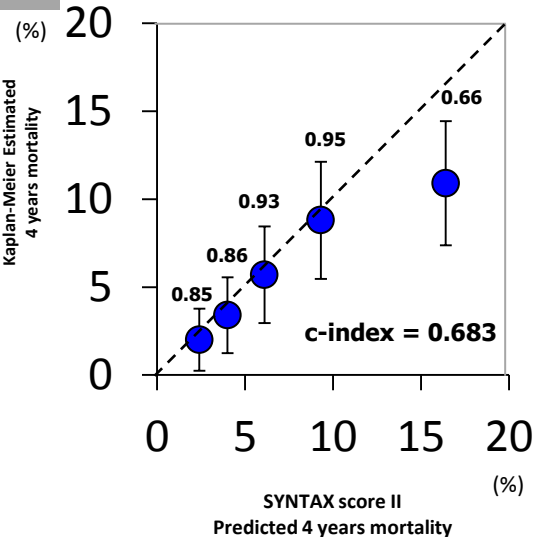
Left Main

Multi-vessel

A — n = 1480, c-index = 0.683

B — n = 300, c-index = 0.718

C — n = 300, c-index = 0.662

D — n = 438, c-index = 0.700

E — n = 442, c-index = 0.661
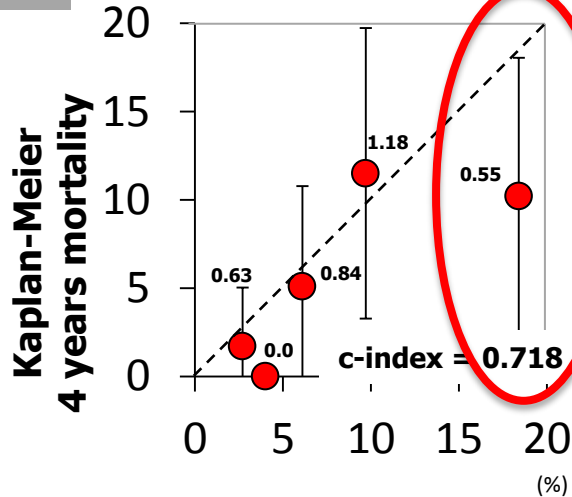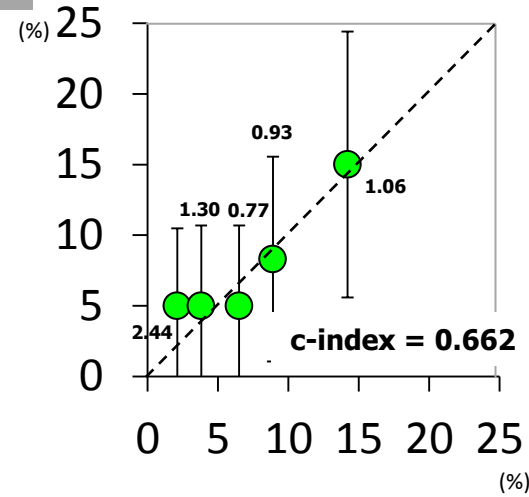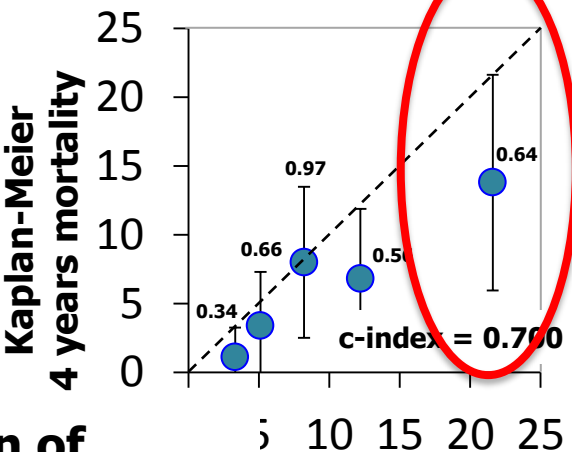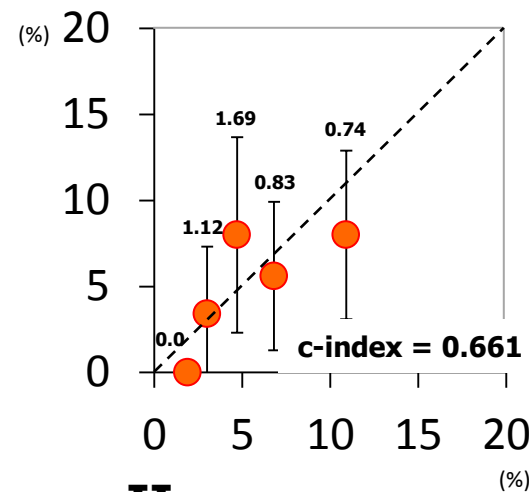
Overestimation of Mortality in high SxSII group

SYNTAX score II Predicted 4 years mortality

Summary

- **The validity of the recommendation for PCI or CABG by SYNTAX score II model was supported for patients with multivessel and/or unprotected left-main coronary artery disease.**

- **The SYNTAX II score model showed good calibration but only moderate discrimination for the individual prediction of 4 years all-cause mortality after PCI and CABG in this population.**

- **In the highest Syntax II quintiles there was overestimation of 4-year mortality.**

What is the potential cause of overestimation of mortality especially in high Syntax II score group ?

Stent type used in the three trials

	SYNTAX	PRECOMBAT	BEST
Stent type	TAXUS	CYPHER	XIENCE

Dangas et al. JACC Cardiovasc Interv 2013.
Kaul et al. N Engl J Med 2015.

1. **SYNTAX Score II was established in the SYNTAX trial using TAXUS stent, while in the validation population (PRECOMBAT and BEST) Cypher and Xience stent were used. Mortality rate in TAXUS > SES/EES ??**

2. **In highest Syntax Score II group, complete revascularization rate were less in PCI, which could confound mortality prediction**

Syntax II Score	CABG arm	PCI arm
1st quintile	74.20%	76.40%
2nd quintile	65.90%	64.30%
3rd quintile	70.30%	52%
4th quintile	67.70%	51.30%
5th quintile	74.70%	52.50%

NO CHANGE **DECREASE**

What is the potential cause of overestimation of mortality especially in high Syntax II score group ?

Gender effect may play a role...
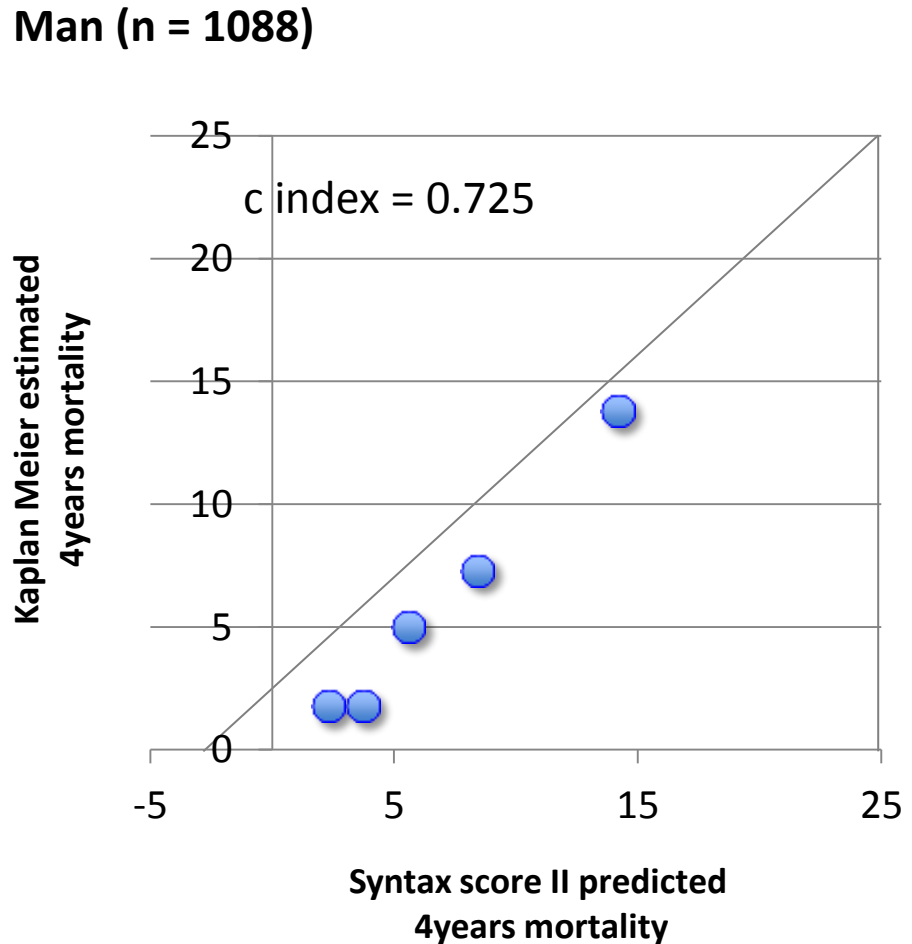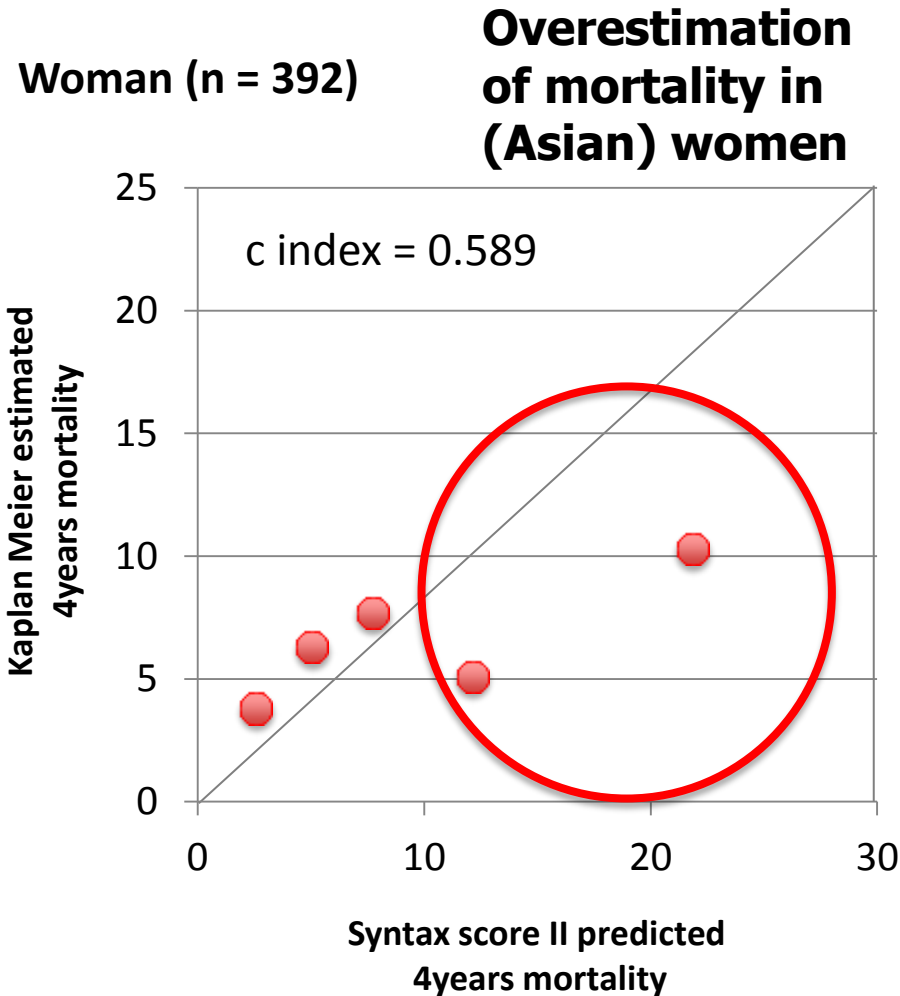
Woman (n = 392)

Overestimation of mortality in (Asian) women

Man (n = 1088)

c index = 0.589

c index = 0.725

What is the potential cause of overestimation of mortality especially in high Syntax II score group ?

Gender effects are different amongst SYNTAX, PRECOMBAT, and BEST trials
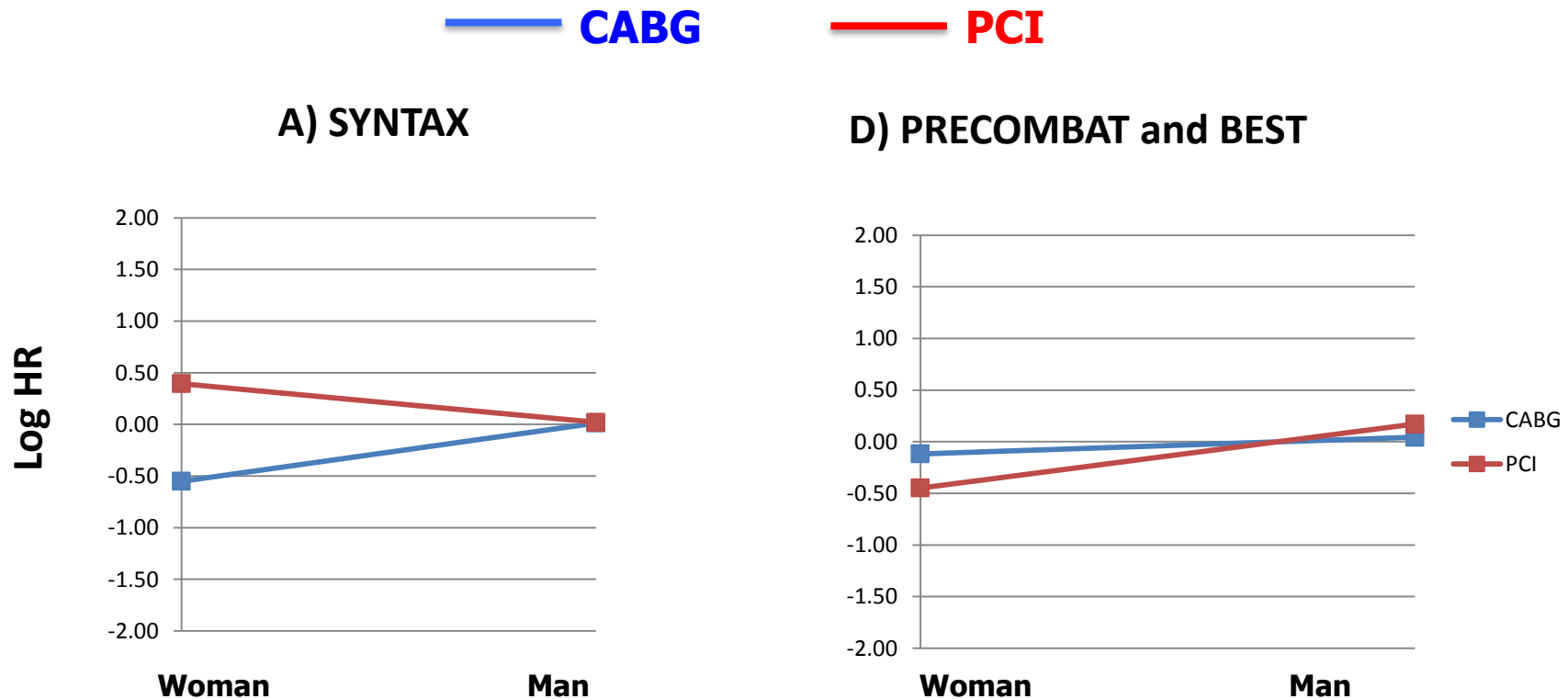
In the SYNTAX trial (A), female gender favors CABG compared to PCI, while in the PRECOMBAT (B), BEST (C), and their combined database (D), female gender favors PCI rather than CABG.

Conclusions

- **The SYNTAX score II has good calibration but only moderate discrimination ability for the 4 years mortality prediction after PCI and CABG in patients with multivessel and/or unprotected left-main disease in the populations as randomized for BEST and PRECOMBAT trials.**

- **This score provides an important tool to help guide the Heart Team decision-making process regarding the selection of the best revascularization strategy for this patient population.**

- **The observed heterogeneity of treatment effect in women warrants further investigations involving the global geometry.**

SYNTAX Score II Online calculator
Coming soon !!!

The SYNTAX Score is a tool developed in connection with the SYNTAX Trial, a trial comparing PCI and Cardiac Surgery in complex, high-risk LM and/or 3VD patients. It is important to note that **the safety and effectiveness of drug-eluting stents have not been established in these high risk patients**, and physicians are strongly encouraged to review the indications, contraindications, warnings and instructions included in the products' Directions for Use.

The SYNTAX Score and related materials should not represent any medical advice or guidance as to appropriate treatment strategies. Individual patient risk and benefits should be carefully considered for each patient taking into account all available data and treatment options and physicians and other healthcare providers should always exercise their own clinical judgment for any given situation. In cases where SYNTAX Score and related materials are

Yes, I have fully read the Important Information above.

Proceed with SYNTAX Score I

Proceed with SYNTAX Score II

Close calculator

Thank You!