On behalf of the investigators of the SYNTAXES, FREEDOM, PRECOMBAT, and BEST trial

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Individualized Decision Making between Percutaneous and Surgical Revascularization in Patients with Complex Coronary Artery Disease: Redevelopment and Validation of the SYNTAX score II 2020

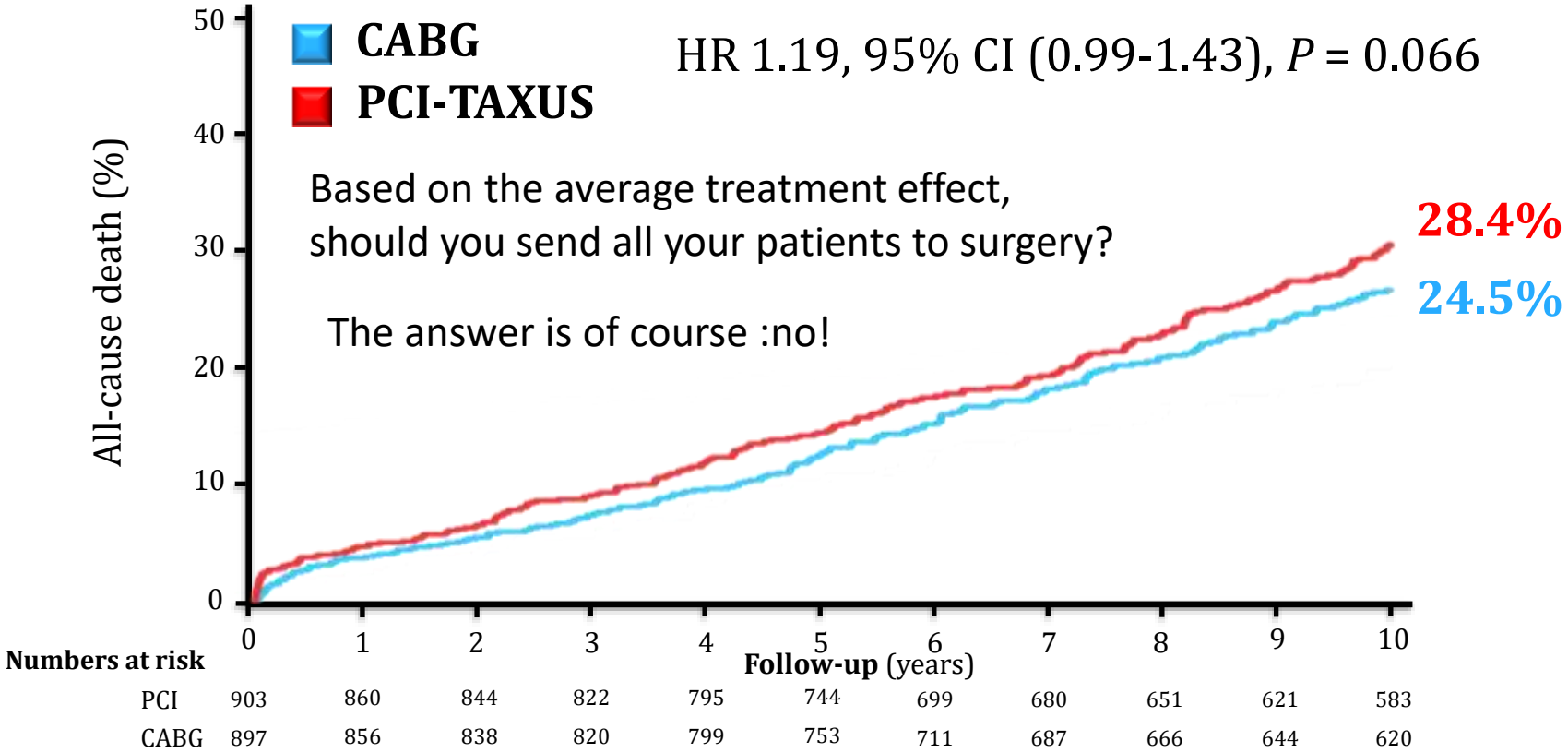
In press in the LANCET

BACKGROUND

- **RCT ‘s are the gold standard** for testing the effectiveness of novel treatment .
- **Average treatment effect** are typically reported in RCT’s
- However**, treatment effectiveness** can **vary across individual patients**.
- **Average treatment effect may be suboptimal** for decision-making in **individual patients**[1,2]..
- The **SYNTAX score II (**2013**)** derived from 2 angiographic and 6 clinical variables, provides an **individualized decision-making based on 4-year all-cause death** after either CABG or PCI [3].
- Using the data of the 10 years F/uP of **SYNTAX Extended Survival (SYNTAXES**) [4], we sought to :
- (i) **update the SS II** (version 2020) for prediction of **10-year Mortality** and **5-year MACCE**
- (ii) to **externally validate** (FREEDOM,BEST,PRE-COMBAT) the SS II 2020 for its ability to predict treatment benefit in **mortality** and in **MACCE.**

- **1. Rothwell et al. Lancet 1995; 345 (8965): 1616-9. 2. Kent et al. BMJ 2018; 363: k4245**
  3. Farooq et al. Lancet 2013; 381 (9867): 639-50. 4. Thuijs et al. Lancet 2019

Average Treatment Effect as a Summary Result for 10-year All-cause Death in the SYNTAXES

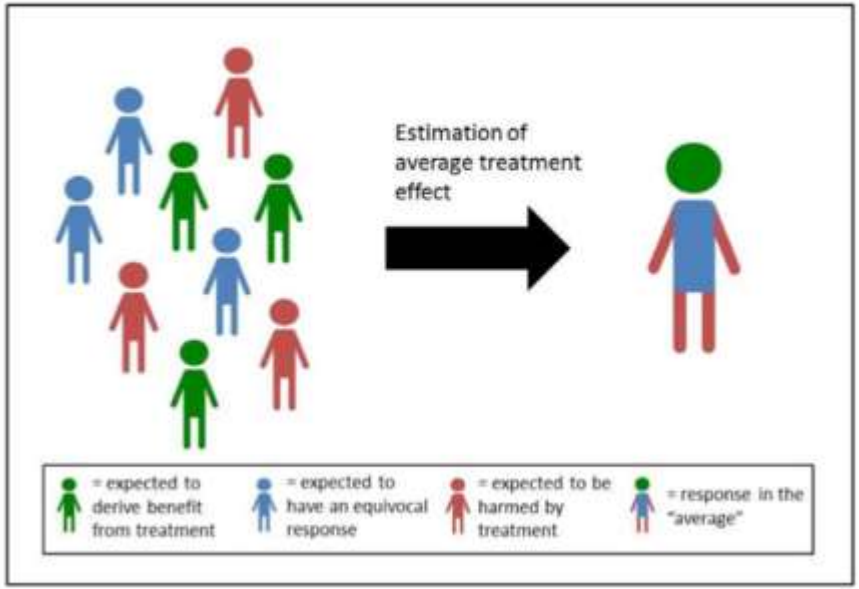


Thuijs et al. Lancet. 2019 Oct 12;394(10206):1325-1334.

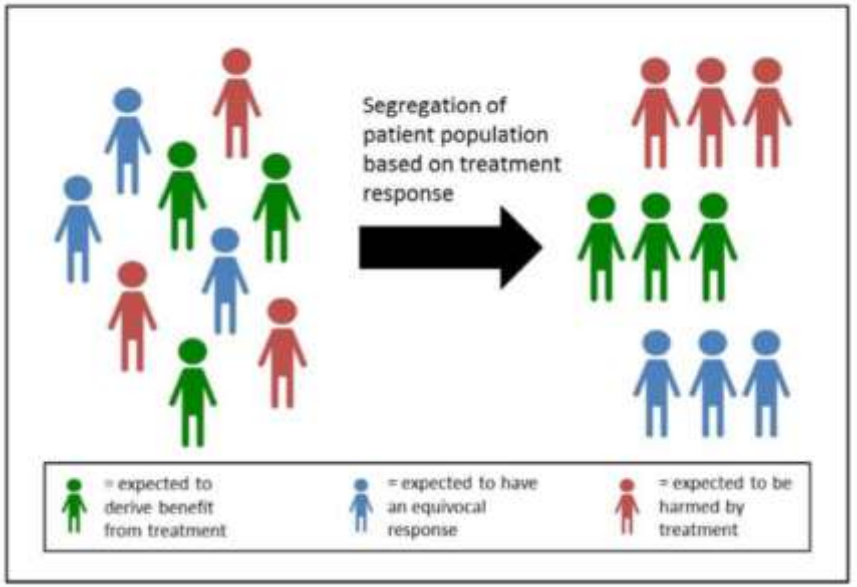
Decision Tools to Improve Personalized Care in Cardiovascular Disease

Moving the Art of Medicine Toward Science

A Average Treatment Effect Assessed in a Heterogeneous Population



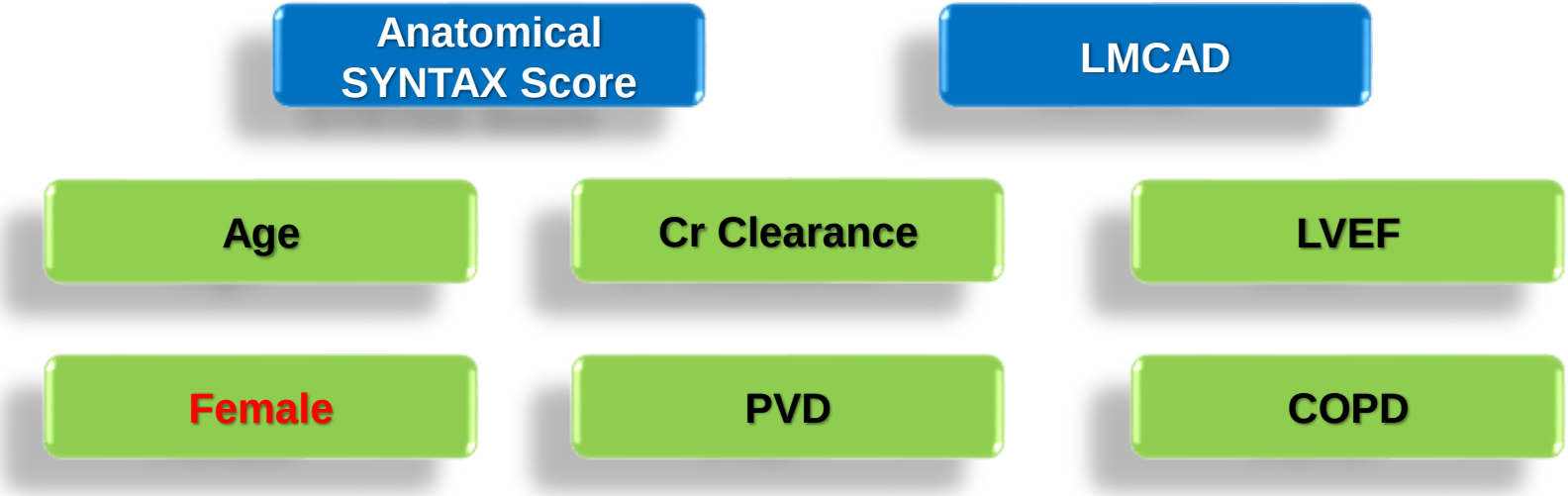
B Identification of Heterogeneous Responses to Treatment



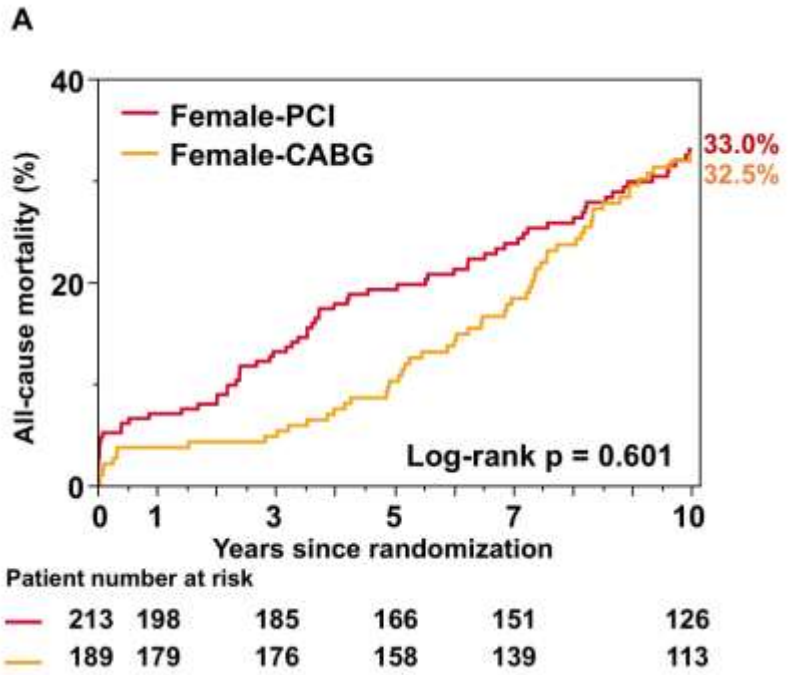
Yeh et al. Circulation 2017;135:1097-1100

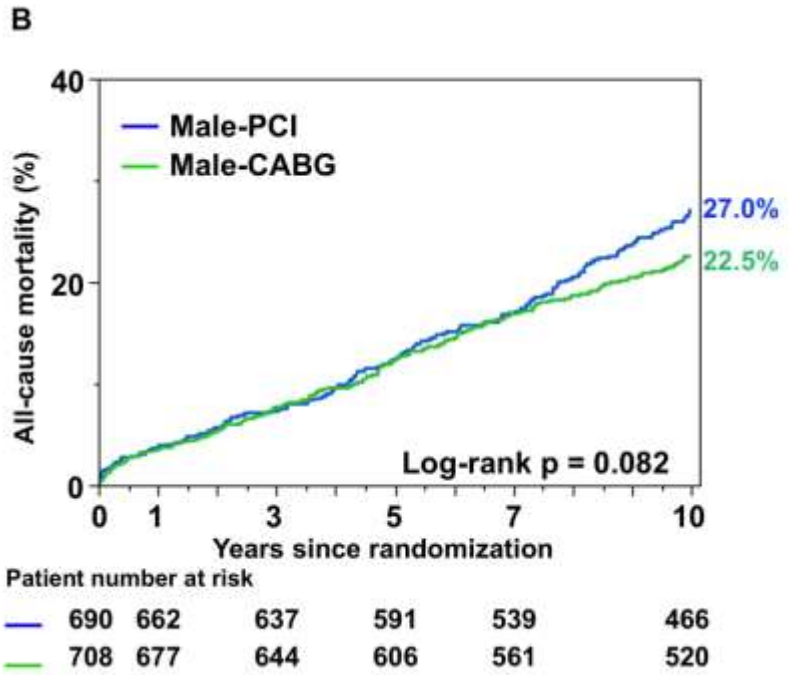
SYNTAX Score II (2013)

SYNTAX Score II was developed by applying a Cox proportional hazards model to the 4-year results of SYNTAX trial resulting in a combination of 6 clinical and 2 anatomical independent predictors of 4 years all-cause mortality:



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





At four year F/uP , females randomized to CABG had a lower all-cause mortality than females randomized to PCI

At ten years all cause mortality rates in females (PCI or CABG)were identical.

In male (PCI vs CABG) all cause mortality started to diverge after 7 years

SYNTAX Score II 2020

SYNTAX Score II 2020 was redeveloped to predict 10-year mortality and 5-year MACE in the SYNTAX(ES) trial and externally validated in the FREEDOM, BEST, and PRECOMBAT trials:

Anatomical SYNTAX Score	Disease type (3VD or LMCAD)	Current smoking
Age	Cr Clearance	LVEF
Diabetes	PVD	COPD

Pr (10-year mortality) = 1 - exp(-0.243 * exp (0.99 * (0.72 * Age/10 - 0.07 * min(CrCl, 90)/10 - 0.31 * Min(LVEF, 50)/10 + 0.48 * COPD + 0.73 * PVD + 0.20 * Medically treated diabetes + 0.46 * on insulin + 0.66 * Current smoking) - 0.10 * LMCAD - 0.40 * CABG * 3VD + 0.02 * CABG * LMCAD + 0.16 * PCI * (SYNTAX Score - 29)/10 - 2.80)).

SYNTAX Score II 2020

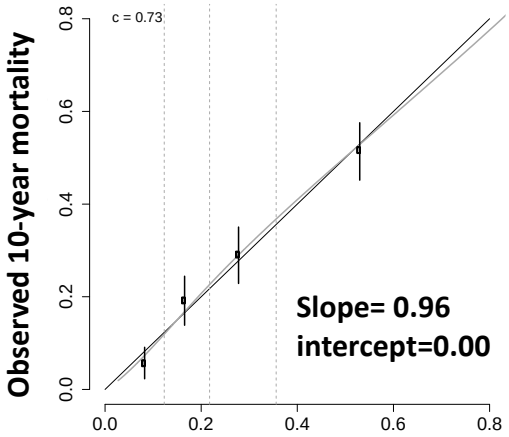
SYNTAX Score II 2020 was redeveloped to predict 10-year mortality and 5-year MACE in the SYNTAX(ES) trial and externally validated in the FREEDOM, BEST, and PRECOMBAT trials:

Anatomical SYNTAX Score	Disease type (3VD or LMCAD)	Current smoking
Age	Cr Clearance	LVEF
Diabetes	PVD	COPD

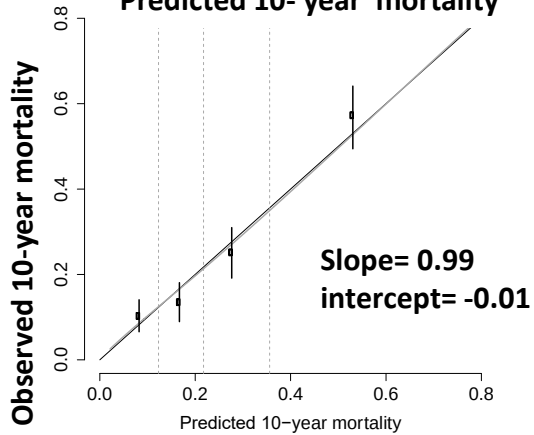
Pr (5-year MACE) = 1 - exp (-0.175 * exp(0.74 * (0.72 * Age/10 - 0.07 * min(CrCl, 90)/10 - 0.31 * min(LVEF, 50)/10 + 0.48 * COPD + 0.73 * PVD + 0.2 * Medically treated diabetes + 0.46 * On insulin + 0.66 * Current smoking) - 0.23 * LMCAD - 0.48 * CABG * 3VD + 0.13 * CABG * LMCAD + 0.19 * PCI * (SYNTAX Score - 29)/10 – 2.00)).

Cross validation of the 10 years mortality in the SYNTAXES (1800 patients)

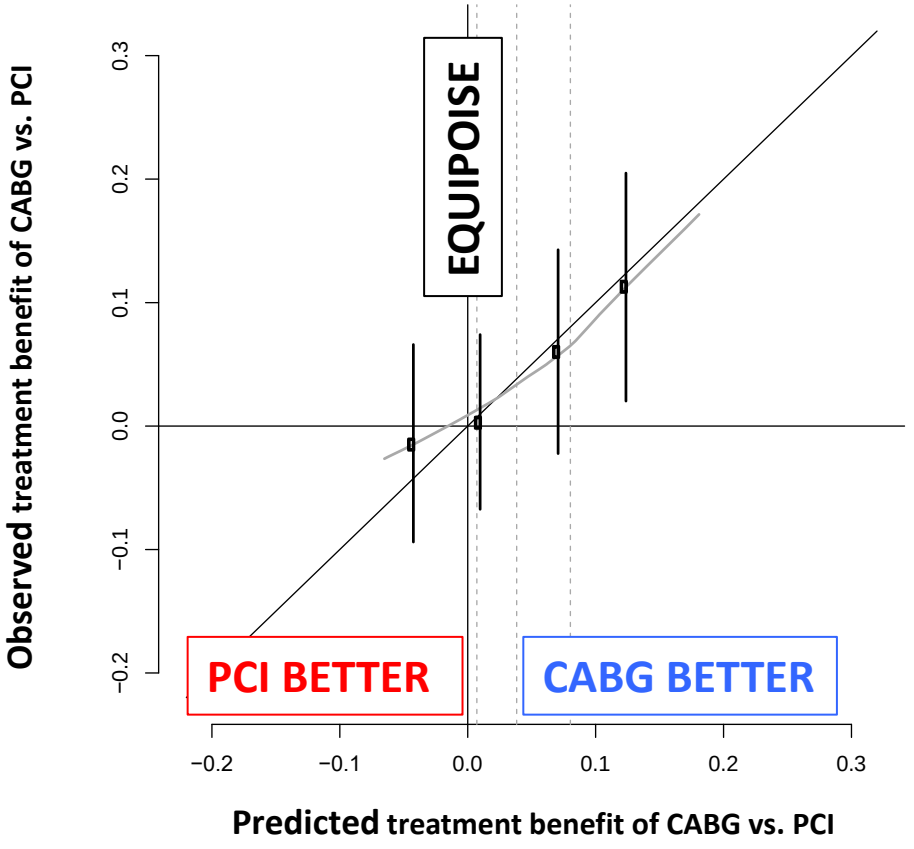
PCI



CABG



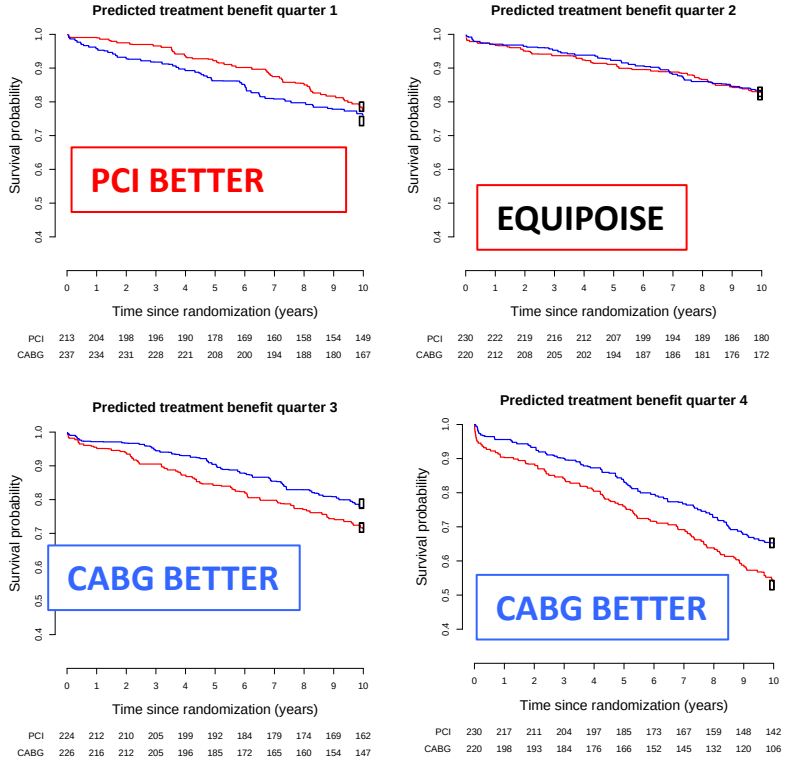
Difference in 10-year mortality called "Treatment benefit" of CABG vs. PCI for mortality



Cross validation of the 10 years mortality in the SYNTAXES (1800 patients)

Kaplan-Meier curves by quartiles

Predicted risk of 10-year mortality with PCI
Predicted risk of 10-year mortality with CABG



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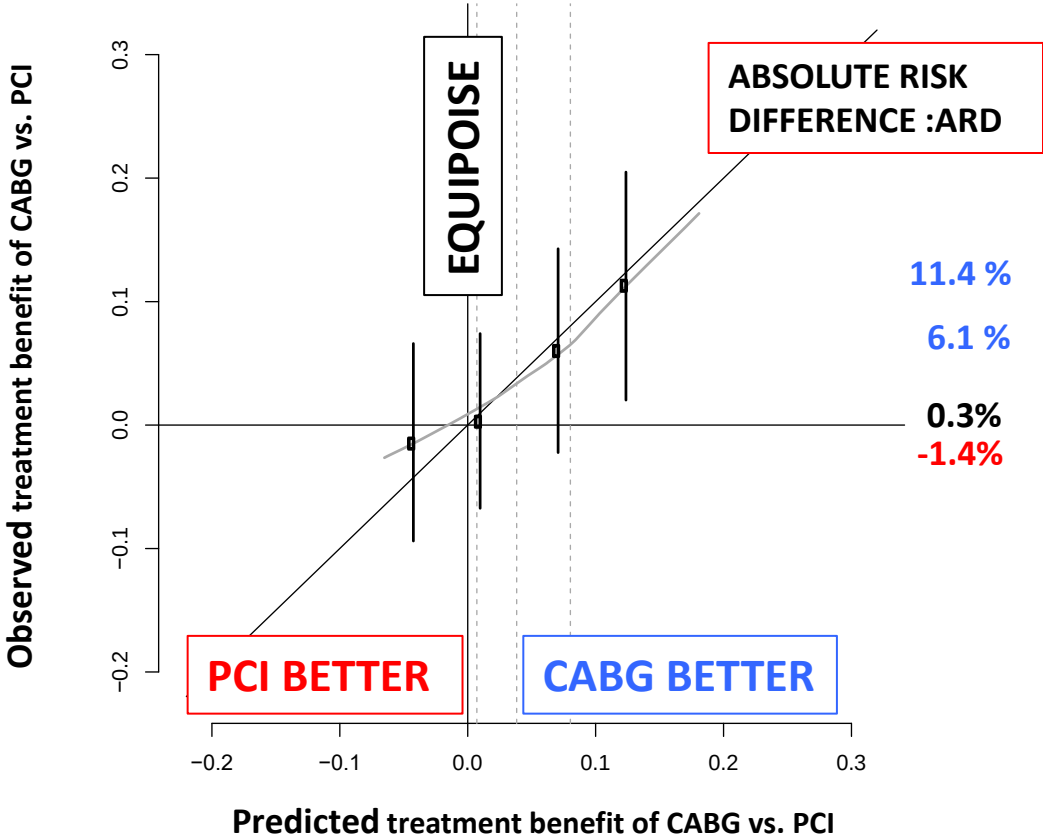
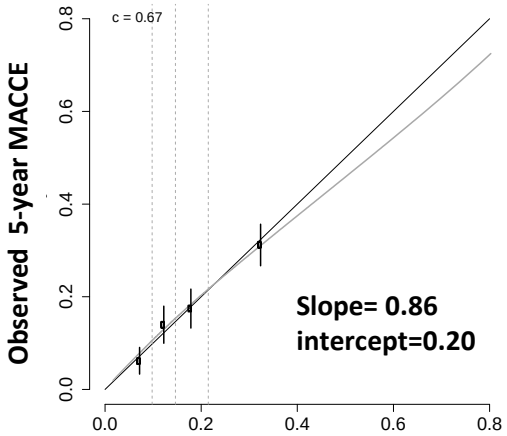
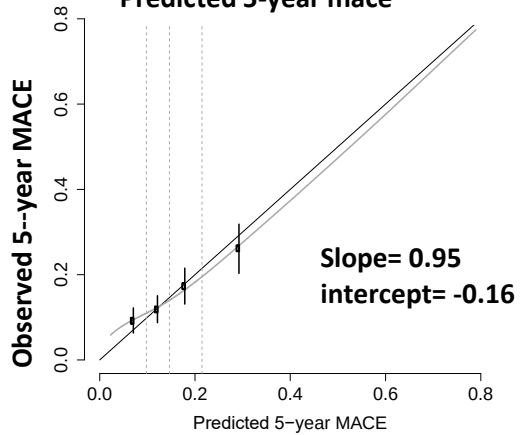


External Validation of the 5-year MACE model in the FREEDOM, BEST, and PRECOMBAT trials (n= 3,380 patients)

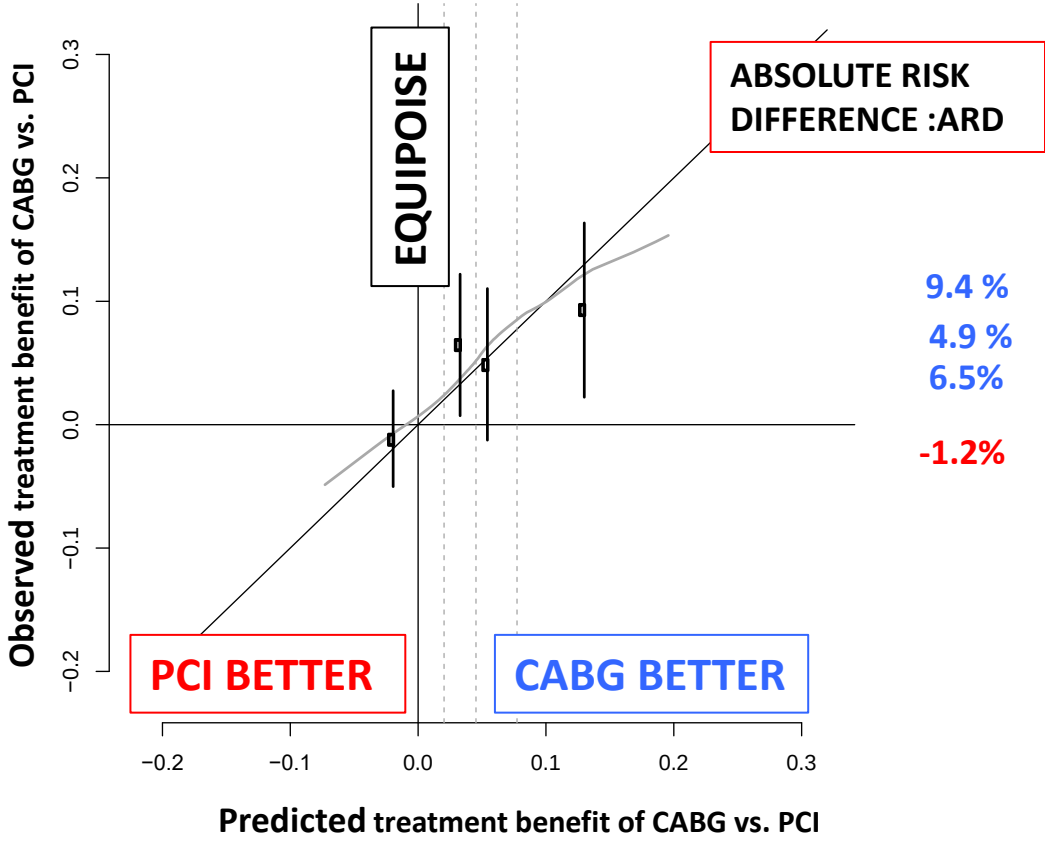
PCI



CABG

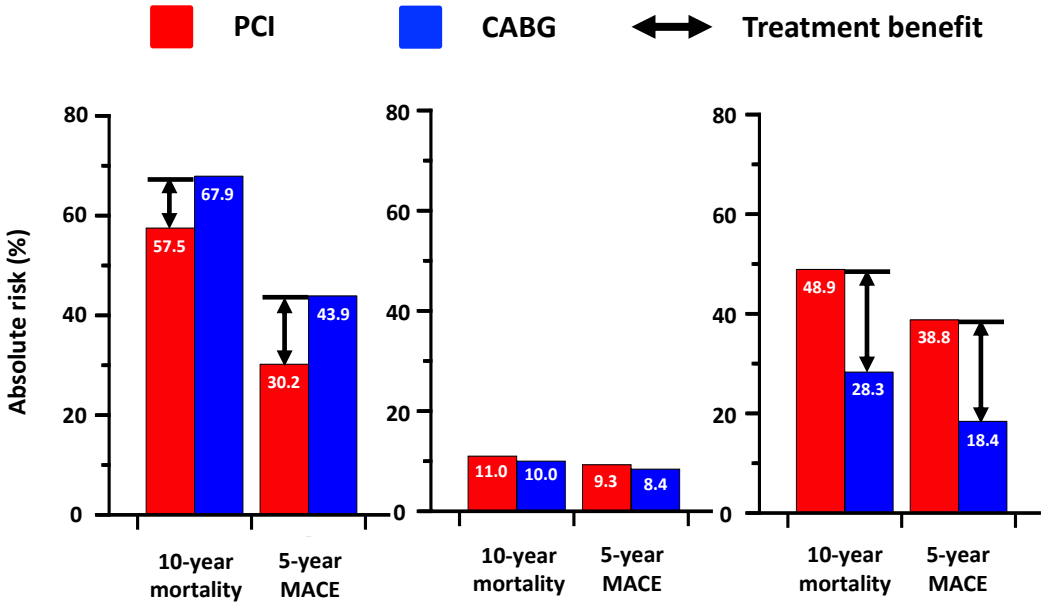


Difference in 5-year MACCE called "Treatment benefit" of CABG vs. PCI fo rMACCE



SYNTAX Score II 2020 for Individualized Decision Making

Baseline characteristics at the time of decision-making	*Case 1*	*Case 2*	*Case 3*
Age (years):	**74**	**59**	**69**
Diabetes:	-	**Yes**	**Yes**
On insulin:	-	-	**Yes**
CrCl (ml/min/1.73m^2):	**38.6**	**67.6**	**72.5**
LVEF (%):	**40**	**67**	**55**
COPD:	-	-	-
PVD:	-	-	-
Current smoking:	**Yes**	-	-
3VD or LMCAD:	**LMCAD**	**3VD**	**3VD**
Anatomical SYNTAX score:	**11**	**10**	**50**



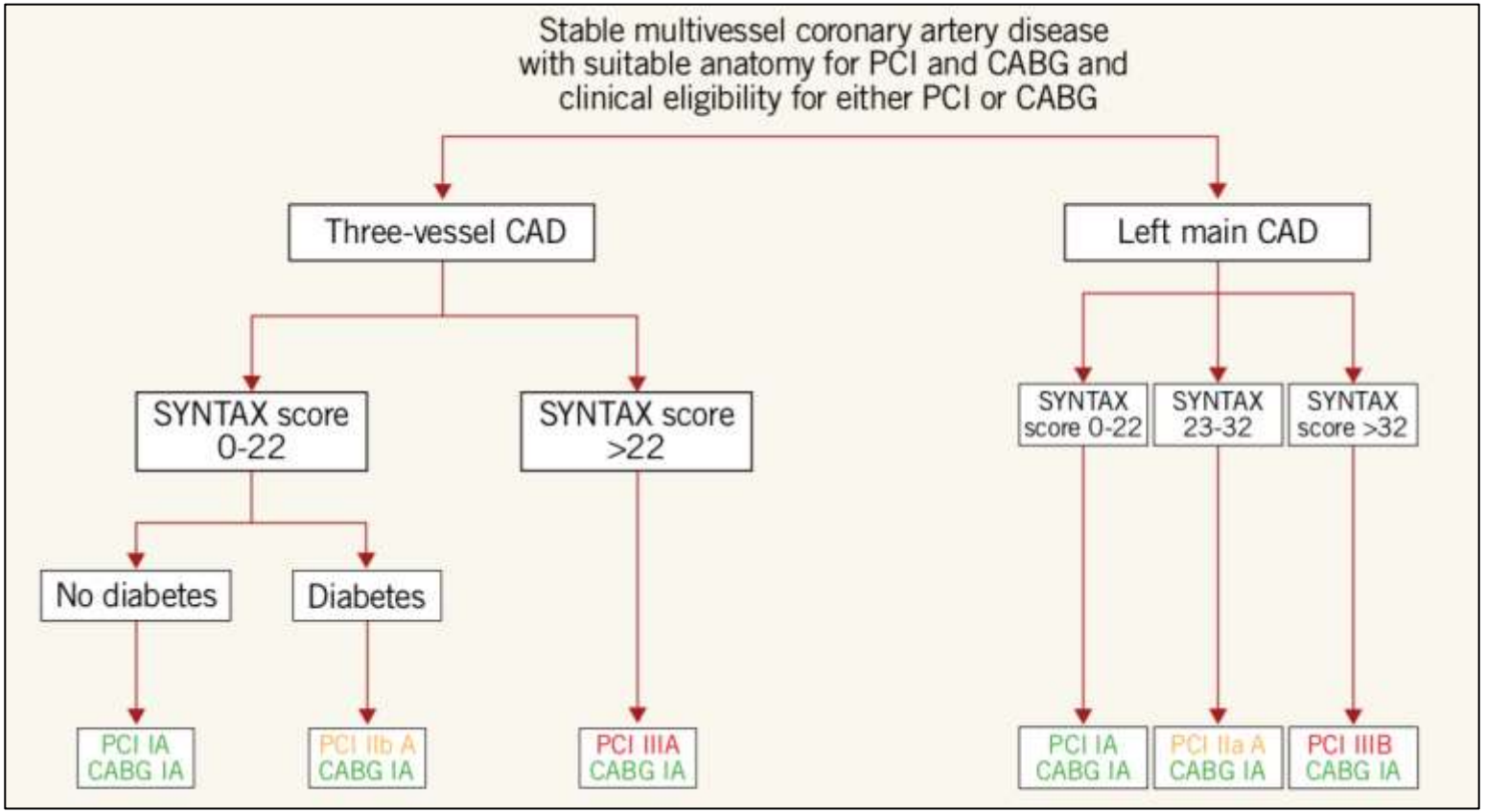
Conclusions

- **Using data from the randomized SYNTAX(ES) trial, we have updated and externally validated the SS II 2020, a personalized predictive model based on 7 prognostic factors and 2 pre-specified effect modifiers _disease type (3VD or LMCAD) and_ the anatomical SS to predict 10-year all-cause death and 5-year MACE for patients treated with either PCI or CABG.**
- **By providing expected probabilities of 5- and 10-year outcomes, this model may improve the ability of the Heart Team to inform patients and their families regarding the risks and benefits of alternative treatments for complex CAD and support a more transparent shared decision-making process.**

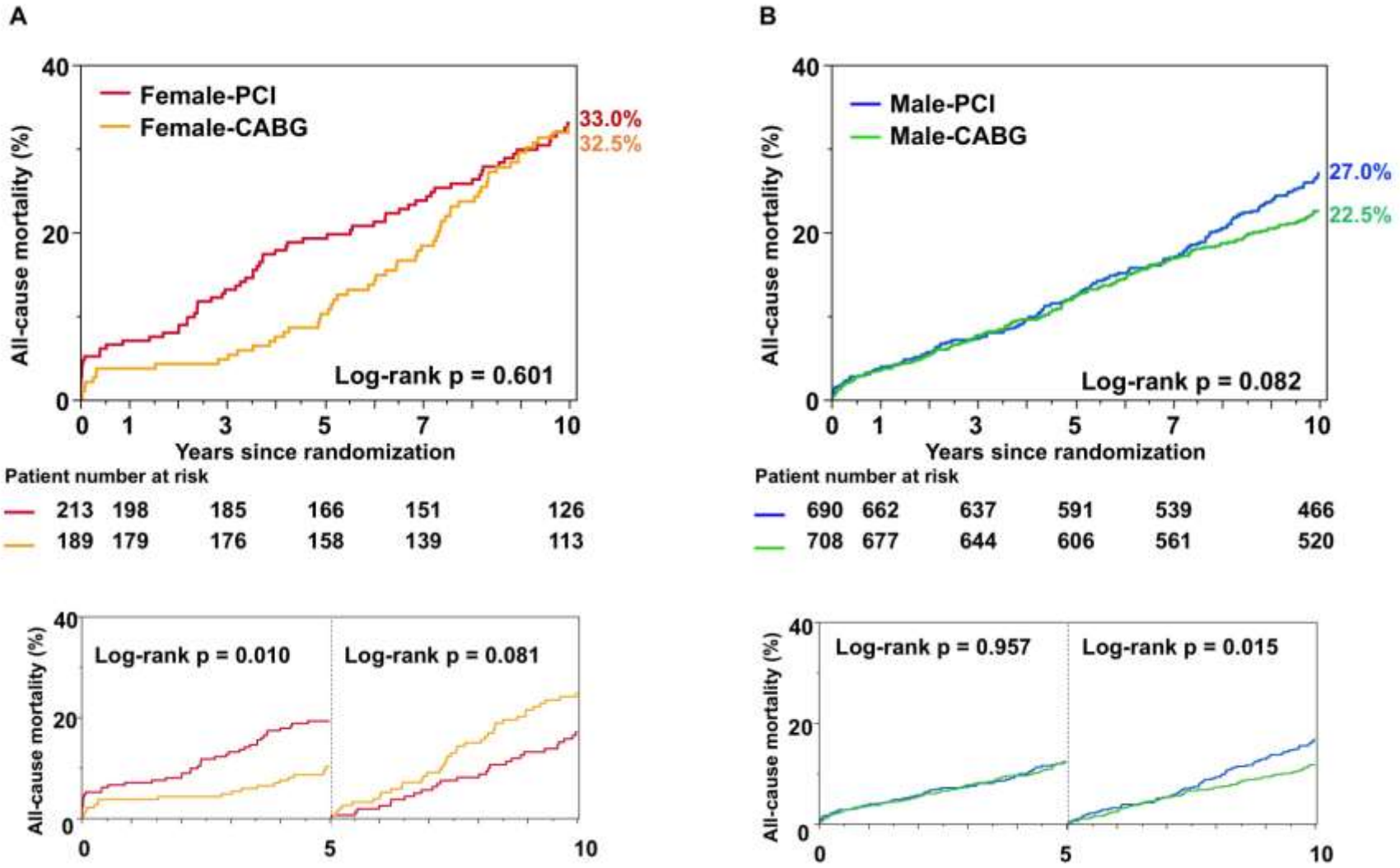
Limitations

- The SYNTAX trial was conducted between 2005 and 2007 with a default use of the first-generation DES for treatment with PCI, whereas the newer generation DES may improve outcomes. However, it is unavoidable that the findings from long-term follow-up data are inherently based on somewhat outdated technology and method of treatment, whereas evidence derived from implementation of contemporary technology and best practice can be derived only from short-term follow-up studies.
- The SYNTAXES study evaluated vital status up to 10 years and did not assess other outcomes, and thus a prediction model for MACE beyond 5 years could not be constructed.

Algorithm to guide the choice of revascularization procedure across major categories in patients with 3VD or LMCAD



Windecker et al. Eur Heart J. 2019 Jan 7;40(2):204-212.
Glineur et al. EuroIntervention. 2019 Feb 20;14(14):1429-1433.


A
All-cause mortality (%)
Female-PCI
Female-CABG
33.0%
32.5%
Log-rank p = 0.601
Years since randomization
Patient number at risk
213 198 185 166 151 126
189 179 176 158 139 113
Log-rank p = 0.010
Log-rank p = 0.081
B
Male-PCI
Male-CABG
27.0%
22.5%
Log-rank p = 0.082
690 662 637 591 539 466
708 677 644 606 561 520
Log-rank p = 0.957
Log-rank p = 0.015