Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation

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ABSTRACT

Background

Randomised controlled trials are considered the gold standard for testing the efficacy of novel therapeutic interventions, and typically report the average treatment effect as a summary result. As the result of treatment can vary between patients, basing treatment decisions for individual patients on the overall average treatment effect could be suboptimal. We aimed to develop an individualised decision making tool to select an optimal revascularisation strategy in patients with complex coronary artery disease.

Methods

The SYNTAX Extended Survival (SYNTAXES) study is an investigator-driven extension follow-up of a multicentre, randomised controlled trial done in 85 hospitals across 18 North American and European countries between March, 2005, and April, 2007. Patients with de-novo three-vessel and left main coronary artery disease were randomly assigned (1:1) to either the percutaneous coronary intervention (PCI) group or coronary artery bypass grafting (CABG) group. The SYNTAXES study ascertained 10-year all-cause deaths. We used Cox regression to develop a clinical prognostic index for predicting death over a 10-year period, which was combined, in a second stage, with assigned treatment (PCI or CABG) and two prespecified effect-modifiers, which were selected on the basis of previous evidence: disease type (three-vessel disease or left main coronary artery disease) and anatomical SYNTAX score. We used similar techniques to develop a model to predict the 5-year risk of major adverse cardiovascular events (defined as a composite of all-cause death, non-fatal stroke, or non-fatal myocardial infarction) in patients receiving PCI or CABG. We then assessed the ability of these models to predict the risk of death or a major adverse cardiovascular event, and their differences (ie, the estimated benefit of CABG versus PCI by calculating the absolute risk difference between the two strategies) by cross-validation with the SYNTAX trial (n=1800 participants) and external validation in the pooled population (n=3380 participants) of the FREEDOM, BEST, and PRECOMBAT trials. The concordance (C)-index was used to measure discriminative ability, and calibration plots were used to assess the degree of agreement between predictions and observations.

Findings

At cross-validation, the newly developed SYNTAX score II, termed SYNTAX score II 2020, showed a helpful discriminative ability in both treatment groups for predicting 10-year all-cause deaths (C-index=0.73 [95% CI 0.69–0.76] for PCI and 0.73 [0.69–0.76]

for CABG) and 5-year major adverse cardiovascular events (C-index=0.65 [0.61–0.69] for PCI and C-index=0.71 [0.67–0.75] for CABG). At external validation, the SYNTAX score II 2020 showed helpful discrimination (C-index=0.67 [0.63–0.70] for PCI and C-index=0.62 [0.58–0.66] for CABG) and good calibration for predicting 5-year major adverse cardiovascular events. The estimated treatment benefit of CABG over PCI varied substantially among patients in the trial population, and the benefit predictions were well calibrated.

Interpretation

The SYNTAX score II 2020 for predicting 10-year deaths and 5-year major adverse cardiovascular events can help to identify individuals who will benefit from either CABG or PCI, thereby supporting heart teams, patients, and their families to select optimal revascularisation strategies.

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INTRODUCTION

Myocardial revascularisation is one of the most studied fields in medicine, with more than 20 randomised controlled trials testing the efficacy and safety of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) in approximately 15 000 patients to date.[1] Nevertheless, the optimal revascularisation strategy for individual patients with complex coronary artery disease is still debated. By contrast with previous randomised controlled trials, which enrolled highly selected populations, the Synergy Between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial was a landmark study comparing CABG with PCI (using first-generation drug-eluting stents) in all-comer patients with de-novo three-vessel disease or left main coronary artery disease, or both.[2–5] Following the publication of the primary results of the SYNTAX trial and subgroup analyses in 2009,3 the 2010 European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularisation introduced an algorithm based on the type (three-vessel disease or left main coronary artery disease), extent, and severity of coronary artery disease, as assessed by the anatomical SYNTAX score.[6–8] This stratification has been maintained in the 2018 version of the guidelines.[1] However, as noted in the guidelines, these subgroup analyses merely provide the heart team with an anatomical stratification of treatment recommendations, and do not consider major clinical characteristics and comorbidities.[9–11]

Conventional subgroup analyses evaluate the heterogeneity of a treatment effect by comparing groups of patients who differ in only one single variable (eg, male vs female or age <70 years vs ≥70 years) and do not account for multiple variables that might simultaneously influence outcomes (eg, young male vs old male vs young female vs old female). As such, conventional subgroup analyses do not represent the broader heterogeneity of patients who clinicians treat in daily practice.[12–19] In addition, conventional subgroup analyses usually divide the overall population into smaller groups, resulting in reduced statistical power for detecting a differential treatment effect (ie, false-negative findings) and an increased risk for false-positive findings due to multiple comparisons.[13–21] Finally, clinical interpretation of subgroup analyses is hampered by the fact that the average treatment effect is usually presented on a relative scale (eg, as odds ratios or hazard ratios [HRs]), whereas the absolute risk difference is the most important scale for clinical decision making.[15–19]

To move beyond conventional subgroup analyses, multivariable risk predictive models have been proposed to simultaneously account for multiple patient characteristics that influence treatment effects. Such an approach can readily estimate

treatment benefits on the basis of multiple individual patient characteristics, enabling personalised decision making for each patient.[13–19] We previously developed the SYNTAX score II to predict 4-year mortality in individual patients given CABG or PCI, to support more evidence-based decision making by the heart team.[11] The SYNTAX score II included eight prognostic factors and their interactions with treatment assignment. However, simulations have shown that data-driven inclusion of interactions overestimated the heterogeneity of the treatment effect.[22] In 2019, the SYNTAX Extended Survival (SYNTAXES) study reported 10-year all-cause death in patients with de-novo three-vessel disease or left main coronary artery disease, or both, who were randomly assigned to receive either CABG or PCI in the original SYNTAX trial.[23] Therefore, the aims of the present study were to redevelop the SYNTAX score II for predicting the benefit of CABG versus PCI over a 10-year period, and to externally validate the updated score (termed the SYNTAX score II 2020) for its ability to predict treatment benefit, further supporting its potential usefulness in clinical care.

Research in context

Evidence before this study

We searched PubMed on Feb 20, 2020, using the search terms "percutaneous coronary intervention", "coronary artery bypass grafting", and "score". We searched for studies on multivariable risk predictive models that had been developed for individualised decision making between percutaneous coronary intervention (PCI) and coronary artery bypass (CABG) in patients with complex coronary artery disease, published in English from database inception up to Feb 20, 2020. We identified 936 potential studies, which were checked manually. Several randomised controlled trials have been done to identify an optimal revascularisation strategy in patients with complex coronary artery disease. However, these trials report an average treatment effect as a summary result of a trial, and treatment effect has been shown to vary among individual patients. Therefore, basing treatment decisions for individual patients on the overall average treatment effect could be suboptimal. Among the 936 studies identified through the literature search, we identified only two studies that had developed a score, based on the predicted risk of long-term adverse events from CABG or PCI as a decision-making tool to guide the selection of an optimal revascularisation strategy for individual patients. One study was on the development of the original SYNTAX score II, which aimed to improve the individualised decision making process by estimating the risk difference in 4-year death between CABG and PCI in patients with three-vessel disease or left main coronary artery disease, or both. The other study developed the FREEDOM score, which estimated the 5-year

risk of having a major adverse cardiovascular event and the 1-year risk of angina in patients with diabetes and multivessel coronary artery disease.

Added value of this study

Using the SYNTAX Extended Survival (SYNTAXES) study, which reported 10-year all-cause death in patients with de-novo three-vessel disease or left main coronary artery disease, or both, who were randomly assigned to receive either CABG or PCI in the original SYNTAX trial, we redeveloped the SYNTAX score II (termed SYNTAX score II 2020), with two prespecified effect-modifiers selected on the basis of previous evidence for predicting the 10-year death risk and 5-year risk of having a major adverse cardiovascular event. The primary results of the SYNTAXES study showed that there was no significant difference in 10-year all-cause death between the PCI group and the CABG group. However, the SYNTAX score II 2020 disentangled the results of this pivotal study and identified patients who gained the most benefit from CABG over PCI, or vice versa, in terms of 10-year all-cause mortality.

Implications of all the available evidence

The SYNTAX score II 2020 provides individuals with a predicted treatment benefit of CABG over PCI, in terms of the 10-year death risk and 5-year risk of having a major adverse cardiovascular event, based on key angiographic and clinical variables obtained at the time of decision making. This model enables more individualised and patient-centred care to be delivered during multidisciplinary heart team discussions for patients and their families.

METHODS

Study design and participants

The study design, and the primary and final 5-year results of the SYNTAX trial (NCT00114972), have been reported previously.[2–5] In brief, the SYNTAX trial is an international, multicentre, randomised controlled trial done in 85 centres across 18 North American and European countries between March, 2005, and April, 2007. Based on clinical judgment and consensus of a heart team (consisting of a cardiothoracic surgeon and interventional cardiologist) at each centre, all patients with three-vessel disease or left main coronary artery disease who were considered to achieve a clinical equipoise between CABG and PCI were randomly assigned (1:1) to either the CABG group (n=897) or the PCI group (n=903), with paclitaxel-eluting stents. The SYNTAX trial completed patient follow-up at 5 years,[5] and the SYNTAXES study (NCT03417050) ascertained all-cause deaths at 10 years.[23]

No randomised trials with 10-year follow-up data in patients with three-vessel disease or left main coronary artery disease, or both (ie, a SYNTAX-like population), are available, thus precluding external validation of the SYNTAX score II 2020 model. However, we extracted patient-level data from three trials involving patients with multivessel disease or left main coronary artery disease treated with PCI and CABG to externally validate the SYNTAX score II 2020 model for predicting 5-year all-cause deaths and 5-year major adverse cardiovascular events, defined as a composite of all-cause death, non-fatal stroke, or non-fatal myocardial infarction. These trials included the Future Revascularisation Evaluation in Patients with Diabetes Mellites: Optimal Management of Multivessel Disease trial (FREEDOM; NCT00086450),[24] the Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease trial (BEST; NCT00997828), and the BYPASS Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease trial (PRECOMBAT; NCT00422968).

The study design, and the primary and final 5-year follow-up results of the FREEDOM trial have been published previously.[24] Briefly, the FREEDOM trial, which was done at 140 international centres between 2005 and 2010, randomly assigned (1:1) 1900 patients with diabetes and multivessel disease to either the CABG group (n=947) or the PCI group (n=953), in which patients received first-generation drug-eluting stents.[24] The FREEDOM trial has reported the primary results at 5 years of follow-up.[24] In 2019, an extended follow-up report of the trial was published, which presents all-cause mortality at 8 years in approximately half of the original trial cohort.[25]

The BEST trial is a multicentre randomised trial done at 27 centres in Asia (South Korea, China, Malaysia, and Thailand) between July, 2008, and September, 2013, that randomly assigned (1:1) 880 patients with multivessel disease to either the CABG group (n=442) or the PCI group (n=438), in which patients received everolimus-eluting stents.[26] The BEST trial has completed patient follow-up for up to 5 years, with 10-year follow-up ongoing.

The PRECOMBAT trial is a multicentre randomised trial, done at 13 centres in Korea between April, 2004, and August, 2009, which randomly assigned (1:1) 600 patients with left main coronary artery disease to either the CABG group (n=300) or the PCI group (n=300), in which patients received a sirolimus-eluting stent.[27,28] The 10-year follow-up results from the PRECOMBAT trial were published in 2020.[29]

All randomised trials included in this study were approved by the ethics committees at each investigating centre, and all patients provided written informed consent before participating in the trial.

Procedures

We contacted the principal investigators of the included trials to request the patient-level data for the external validation of the SYNTAX score II 2020. Data on three randomised trials (FREEDOM, BEST, and PRECOMBAT) were already available, and two investigators (KT and DvK) independently checked the data and compared them with the original publications for completeness and consistency. The principal investigators of these trials were contacted if queries arose during the data checks. A clinical event committee masked to randomisation adjudicated all clinical adverse events of each study. Unless specified, previously reported definitions in each study were used for variables.

We extracted data on age, sex, body-mass index, smoking status (ie, whether they smoked at the time of enrolment), creatinine clearance (according to the Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] formula), and left ventricular ejection fraction, whether they had chronic obstructive pulmonary disease (COPD), peripheral vascular disease, medically treated diabetes, or had received insulin therapy, and whether they had a history of myocardial infarction or stroke.

We developed a predictive model for the prespecified primary endpoint of the SYNTAXES study, 10-year all-cause death, which is the most robust endpoint for both patients and physicians. In addition, we developed a predictive model for 5-year major adverse cardiovascular events, because patients valued stroke or myocardial infarction as an equally or even more important endpoint than death, and they valued other endpoints (eg, repeat revascularisation or readmission to hospital) as substantially less important.[30]

Statistical analysis

In the original SYNTAX trial, results for most of the baseline variables were available for more than 98% of the trial population, whereas data on left ventricular ejection fraction was 98.4% complete as a categorical variable (defined as good [≥50%], moderate [30–49%], and poor [<30%]), and 62.6% complete as continuous variable. Data on serum creatinine was 91% complete. During the development of the original SYNTAX score II, the Cockcroft-Gault formula was used to calculate creatinine clearance.[11] This formula is no longer recommended for clinical use, as it does not adjust for body surface area and overestimates creatinine clearance.[31] We therefore used

the CKD-EPI formula to estimate creatinine clearance, as endorsed by consensus guidelines.[32–34] Similar to the development of the original SYNTAX score II, multiple imputation (20 times) of missing values was done, based on the correlation between all potential predictors, to make efficient use of the available data without introducing bias under the missing at random assumption.[35,36]

Following the recommendations of the Predictive Approaches to Treatment effect Heterogeneity statement,[18,19] published in 2019, we first used Cox regression for the SYNTAXES study data (n=1800 participants) to develop a clinical prognostic index for predicting 10-year all-cause deaths, while masked to treatment assignment.[37] Since the ultimate goal of model development was to inform the choice of a revascularisation strategy, only variables available at the time of decision making were included. Candidate variables were selected a priori on the basis of published data and clinical experience. We then fitted a Cox model, which included treatment assignment, the prognostic index, and two prespecified effect-modifiers: disease type (three-vessel disease or left main coronary artery disease) and anatomical SYNTAX score. We used an analogous approach to develop a model to predict the 5-year risk of major adverse cardiovascular events by use of data from the SYNTAX trial.

The predictive performance of the SYNTAX score II 2020 was internally validated in the development cohort of the SYNTAXES trial by use of a 10-fold cross-validation approach, fitting regression models to 90% of the patients, and calculating predictions for the remaining 10% of patients. The SYNTAX score II 2020 was then externally validated in the combined FREEDOM, BEST, and PRECOMBAT trial cohorts. In addition, we compared the external predictive performance of the SYNTAX score II 2020 with the original SYNTAX score II, calibrated to 5-year deaths, in the FREEDOM, BEST, and PRECOMBAT trial cohort. This calibrated original SYNTAX score II was derived by fitting calibration slopes for patients in the CABG and PCI groups of the SYNTAXES study separately, to update the association between the SYNTAX score II and 5-year deaths.

For each of these validation analyses, the discriminative ability of the SYNTAX score II 2020 for outcome risk was assessed in the separate treatment groups by use of Harrell's C statistic.[38] Calibration for outcome risk in separate treatment groups was also assessed visually by use of calibration plots (ie, agreement between observed vs predicted risk). We added a smooth calibration curve to each calibration plot on the basis of a Cox model that fitted outcomes to a restricted cubic spline of the predictions. Calibration is optimal when the smooth calibration curve is close to the

identity line (ie, diagonal), also reflected by a calibration intercept close to 0 and a calibration slope close to 1.

For models intended to predict treatment benefit, it is important to validate predicted benefits, not just predicted outcomes.[18,19] Thus, we assessed the agreement between predicted and observed benefit of treatment with CABG over PCI by use of a benefit calibration plot, which displays observed versus predicted treatment benefit in quarters of predicted treatment benefit.[39] We estimated the observed benefit of treatment with CABG over PCI by calculating the difference in Kaplan-Meier estimates between the CABG group and the PCI group.[39] We added a smooth calibration curve to each benefit calibration plot on the basis of local polynomial regression between observed and predicted treatment benefit in small groups of 40 patients with increasing predicted benefit.

Continuous variables were reported as the mean (SD), compared by use of Student's *t* tests, or median (IQR), compared by use of Mann-Whitney U tests. Categorical variables were reported as percentages and numbers, and were compared by use of χ^2 or Fisher's exact test, as appropriate. Clinical outcomes are analysed by use of the Kaplan-Meier estimates and compared with the log-rank test. HRs with 95% CIs were estimated by use of a Cox proportional hazards model.

All tests were two-sided, and a p value of less than 0.05 was considered to indicate a significant difference. The analyses were done in accordance with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement.[40] All statistical analyses were done in R, version 3.5.3.

Role of the funding source

All randomised trials included in our study were investigator-initiated, and the funders of each trial and of this report had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author (PWS), first author (KT), and last author (DvK) had full access to the data and had final responsibility for the decision to submit for publication.

RESULTS

In the SYNTAX trial,[5] 1800 patients at 85 European and US hospitals were enrolled between March, 2005, and April, 2007, and randomly assigned to either the CABG group (n=897) or the PCI group (n=903), in which they received paclitaxel-eluting

stents. At 10 years' follow-up, 460 deaths had occurred among all 1800 patients. 212 (24%) patients in the CABG group had died compared with 248 (28%) patients in the PCI group, with no significant difference in deaths observed between the two groups (HR 1.19 [95% CI 0.99–1.43], log-rank p value=0.066). By contrast, at 5 years follow-up (IQR 4.7–5.0), 185 (21%) of 903 patients in the PCI group had had a major adverse cardiovascular event compared with 140 (17%) of 897 patients in the CABG group, with a significant difference observed between the two groups (HR 1.27 [95% CI 1.02–1.59], log-rank p value=0.030).[5]

Baseline characteristics of patients grouped by 10-year all-cause deaths and 5-year incidence of major adverse cardiovascular events are summarised (table 1). Compared with those who were still alive at 10 years' follow-up, patients who had died were older (ie, those who were still alive had a mean age of 63.5 years compared with 69.9 years in those who had died), and were more likely to be female, to have comorbidities (ie, medically treated diabetes, dyslipidaemia, COPD, peripheral vascular disease, lower left ventricular ejection fraction, lower creatinine clearance, and receiving insulin), and more complex coronary artery disease, as indicated by the anatomical SYNTAX score (30.7 [SD 11.7] in those who had died vs 28.1 [11.2] in those who had not, p<0.0001). Compared with patients who had not had a major adverse cardiovascular event at 5 years' follow-up, those who had were older and were more likely to have comorbidities (ie, COPD, peripheral vascular disease, a previous myocardial infarction, lower left ventricular ejection fraction, lower creatinine clearance, and receiving insulin), and a higher anatomical SYNTAX score (30.9 [11.7] in those who had a major adverse cardiovascular event *vs* 28.3 [11.3] in those who had not, p<0.0001; table 1).

For predicting the risk of 10-year all-cause death, the prognostic index consisted of eight clinical predictors of death (age, creatinine clearance, left ventricular ejection fraction, smoking status, and whether they have medically treated diabetes, are receiving insulin, have COPD, and have peripheral vascular disease; table 2). The predictive model for this outcome included the prognostic index, initial revascularisation strategy, and two treatment interactions (three-vessel disease or left main coronary artery disease and anatomical SYNTAX score). CABG was, on average, found to be beneficial in patients with three-vessel disease (HR 0.67 [95% CI 0.53–0.86]), but not in patients with left main coronary artery disease (1.02 [0.77–1.36], $p_{interaction}$=0.028), and anatomical SYNTAX score was only associated with increased risk of death in patients who received PCI (HR per 10 points 1.17 [1.06–1.30]), but not CABG (1.00 [0.89–1.12], $p_{interaction}$=0.039). The SYNTAX score II 2020 showed helpful discriminative ability for both treatment groups for predicting 10-year all-cause

Table 1: Baseline characteristics of patients grouped by all-cause death at 10 years and major adverse cardiovascular events at 5 years

	10-year all-cause death (n=1800)			5-year incidence of a major adverse cardiovascular event (n=1800)*		
	Yes (n=460)	No (n=1340)	P value	Yes (n=328)	No (n=1472)	P value
Study group	..	..	0.063	..	..	0.012
PCI	258 (53.9%)	655 (48.9%)	..	185 (56.4%)	718 (48.8%)	..
CABG	212 (46.1%)	685 (51.1%)	..	143 (43.6%)	754 (51.2%)	..
Age (years)	69.9 (8.8)	63.5 (9.5)	<0.0001	68.8 (9.1)	64.3 (9.7)	<0.0001
Sex	..	..	0.004	..	..	0.400
Male	335 (72.8%)	1063 (79.3%)	..	249 (75.9%)	1149 (78.1%)	..
Female	125 (27.2%)	277 (20.7%)	..	79 (24.1%)	323 (21.9%)	..
Body-mass index (kg/m²)	27.8 (5.0)	28.1 (4.6)	0.280	27.6 (4.7)	28.1 (4.7)	0.074
Medically treated diabetes	152 (33.0%)	300 (22.4%)	<0.0001	96 (29.3%)	356 (24.2%)	0.055
Receiving insulin	75 (16.3%)	107 (8.0%)	<0.0001	47 (14.3%)	135 (9.2%)	0.0051
Hypertension	310 (67.4%)	886 (66.1%)	0.618	226 (68.9%)	970 (65.9%)	0.297
Dyslipidaemia	332 (73.0%)	1059 (79.6%)	0.0031	243 (74.5%)	1148 (78.7%)	0.103
Creatinine clearance (mL/min per 1.73 m²)	72.9 (20.7)	81.3 (17.4)	<0.0001	74.8 (21.1)	80.1 (17.9)	<0.0001
Left ventricular ejection fraction	55.3% (14.2)	59.4% (12.4)	<0.0001	55.1% (14.4)	59.1% (12.6)	<0.0001
Chronic obstructive pulmonary disease	64 (13.9%)	90 (6.7%)	<0.0001	44 (13.4%)	110 (7.5%)	0.0050
Peripheral vascular disease	89 (19.3%)	88 (6.6%)	<0.0001	58 (17.7%)	119 (8.1%)	<0.0001
Current smoker	105 (22.8%)	259 (19.3%)	0.107	74 (22.6%)	290 (19.7%)	0.244
Previous myocardial infarction	164 (36.2%)	421 (31.7%)	0.080	124 (38.2%)	461 (31.7%)	0.025
Previous stroke	27 (5.9%)	51 (3.8%)	0.057	17 (5.3%)	61 (4.2%)	0.380
Clinical presentation	..	..	0.003	..	..	0.061
Silent ischaemia	83 (18.0%)	177 (13.2%)	..	53 (16.2%)	207 (14.1%)	..
Stable angina	233 (50.7%)	794 (59.3%)	..	168 (51.2%)	859 (58.4%)	..

Table 1: Baseline characteristics of patients grouped by all-cause death at 10 years and major adverse cardiovascular events at 5 years (continued)

	10-year all-cause death (n=1800)			5-year incidence of a major adverse cardiovascular event (n=1800)*		
Unstable angina	144 (31.3%)	369 (27.5%)	..	107 (32.6%)	406 (27.6%)	..
Disease type	..	..	0.012	..	..	0.017
Left main coronary artery disease only	12 (2.6%)	79 (5.9%)	..	6 (1.8%)	85 (5.8%)	..
Left main coronary artery disease plus one-vessel disease	45 (9.8%)	93 (6.9%)	..	26 (7.9%)	112 (7.6%)	..
Left main coronary artery disease plus two-vessel disease	62 (13.5%)	156 (11.6%)	..	48 (14.6%)	170 (11.6%)	..
Left main coronary artery disease plus three-vessel disease	74 (16.1%)	184 (13.7%)	..	57 (17.4%)	201 (13.7%)	..
Three-vessel disease only	267 (58.0%)	828 (61.8%)	..	191 (58.2%)	904 (61.4%)	..
SYNTAX score	30.7 (11.7)	28.1 (11.2)	<0.0001	30.9 (11.7)	28.3 (11.3)	0.0002
SYNTAX score tertile	..	..	0.0006	..	..	0.028
Low (0–22)	119 (25.9%)	455 (34.0%)	..	86 (26.2%)	488 (33.2%)	..
Intermediate (23–32)	155 (33.7%)	460 (34.3%)	..	114 (34.8%)	501 (34.0%)	..
High (≥33)	186 (40.4%)	425 (31.7%)	..	128 (39.0%)	483 (32.8%)	..

Data are presented as n (%) or mean (SD). PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. *Defined as a composite of all-cause death, non-fatal stroke, or non-fatal myocardial infarction.

mortality (concordance [C]-index=0.73 [95% CI 0.69–0.76] for PCI and 0.73 [0.69–0.76] for CABG), with excellent calibration between deaths predicted by the SYNTAX score II 2020 and the observed 10-year deaths in the SYNTAXES trial (figure 1A, B). The predicted treatment benefit of CABG over PCI was also well calibrated in cross-validation of the model in the SYNTAXES study (figure 1C).

The SYNTAX score II 2020, developed for predicting 10-year all-cause death, showed similar cross-validated performance in predicting 5-year all-cause death for both PCI and CABG groups in the SYNTAX trial (C-index 0.74 [95% CI 0.69–0.78] for the PCI group and 0.72 [0.67–0.77] for the CABG group), and good agreement between observed and predicted 5-year deaths (appendix p 2). Calibration of the observed versus predicted 5-year treatment benefit of CABG over PCI was excellent (appendix p 2).

Table 2: Model for predicting risk of all-cause death at 10 years

	Coefficient	HR (95% CI)	P value
Prognostic index			
Age, per 10 years	0.72	2.05 (1.81–2.33)	<0.0001
Creatinine clearance, per 10 mL/min per 1.73 m²*	–0.07	0.93 (0.88–0.99)	0.0279
Left ventricular ejection fraction, per 10%†	–0.31	0.73 (0.63–0.84)	<0.0001
Chronic obstructive pulmonary disease	0.48	1.62 (1.24–2.12)	0.0004
Peripheral vascular disease	0.73	2.08 (1.63–2.62)	<0.0001
Medically treated diabetes	0.20	1.22 (0.95–1.57)	0.1251
Receiving insulin	0.46	1.58 (1.14–2.19)	0.0055
Current smoker	0.66	1.93 (1.52–2.45)	<0.0001
Predictive model			
Prognostic index	0.99	2.69 (2.42–3.01)	<0.0001
CABG × three-vessel disease	–0.40	0.67 (0.53–0.86)	0.0014
CABG × left main coronary artery disease	–0.08	0.92 (0.72–1.19)	0.5466
PCI × left main coronary artery disease	–0.10	0.90 (0.70–1.17)	0.4418
PCI × (SYNTAX score - 29)/10	0.16	1.17 (1.06–1.30)	0.0024

Table shows the estimated Cox regression coefficients for the prognostic index with seven variables, and for the predictive model with the predictive index and two predefined treatment interactions (three-vessel disease or left main coronary artery disease and anatomical SYNTAX score) entered into the SYNTAX II 2020 for predicting 10-year all-cause death. The formula used to predict this outcome is as follows: predicted probability of all-cause death at 10 years=1 – exp(–0.243 × exp[0.99 × {0.72 × age - 0.07 × creatinine clearance - 0.31 × left ejection fraction + 0.48 × chronic obstructive pulmonary disease + 0.73 × peripheral vascular disease + 0.20 × medically treated diabetes + 0.46 × on insulin + 0.66 × current smoker} - 0.40 × CABG × three-vessel disease - 0.08 × CABG × left main coronary artery disease - 0.10 × PCI × left main coronary artery disease + 0.16 × PCI × {SYNTAX score - 29}/10 - 2.80]), where age is expressed in years per 10 years, the creatinine clearance is expressed per 10 mL/min per 1.73 m² (capped at 90 per 10 mL/min per 1.73 m²), and the left ventricular ejection fraction is expressed per 10% (capped at 50 per 10%). CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. *Capped at 90 per 10 mL/min per 1.73 m². -Capped at 50 per 10%. HR=hazard ratio.

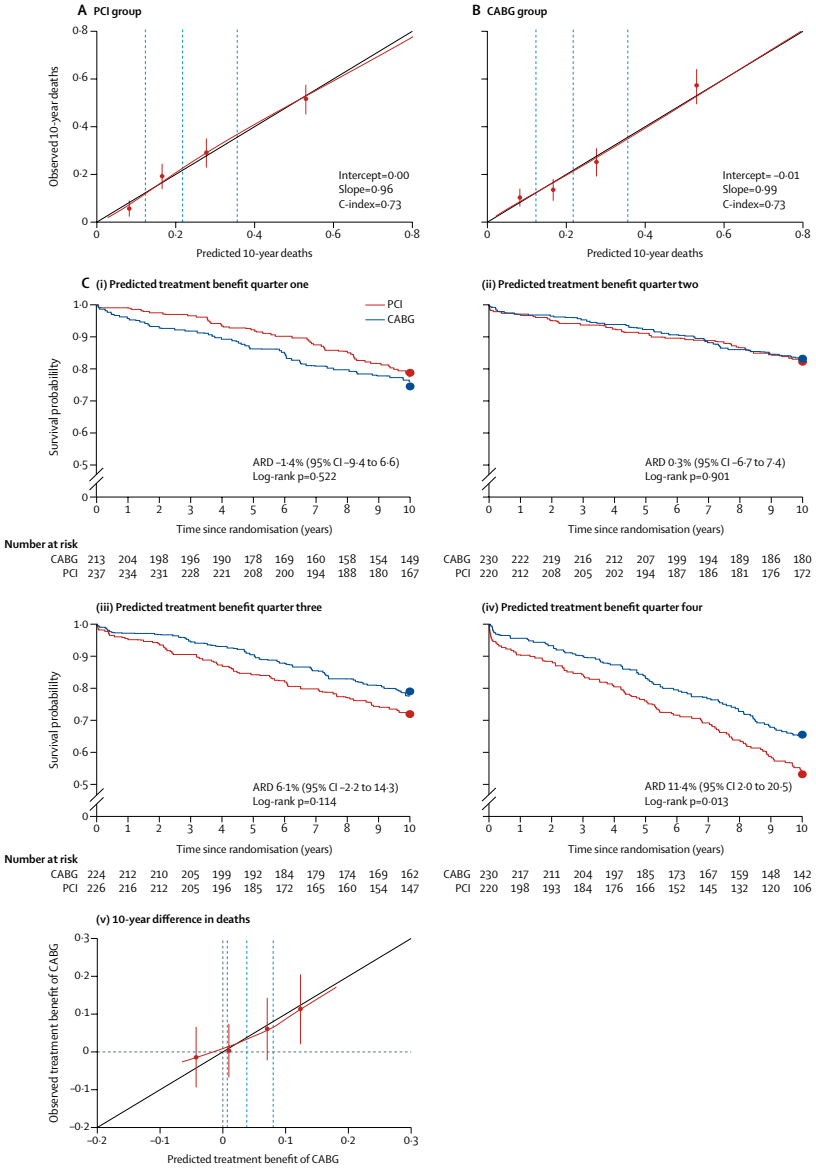

Figure 1: Cross-validation of the SYNTAX score II 2020 for predicting 10-year death in patients with three-vessel disease or left main coronary artery disease in the SYNTAX trial (n=1800)

Calibration plots showing the observed versus predicted 10-year death according to the SYNTAX score II 2020 in the PCI group (A) and in the CABG group (B). (C) Kaplan-Meier plots showing the observed versus predicted treatment benefit of CABG over PCI according to the SYNTAX score II 2020 in predicted benefit quarters (i-iv), and a calibration plot showing the observed versus predicted treatment benefit of CABG over PCI, in terms of 10-year death (v). A positive ARD represents an increase in treatment benefit of CABG over PCI. Vertical dashed lines in the calibration plots represent the quartiles of 10-year death. In the Kaplan-Meier plots, blue circles represent predicted risk of death at 10 years for CABG and red circles represent the predicted risk of death at 10 years for PCI. PCI=percutaneous coronary intervention. C-index=concordance index. CABG=coronary artery bypass grafting. ARD=absolute risk difference.

By use of data from the FREEDOM, BEST, and PRECOMBAT trials, external validation of the SYNTAX score II 2020 model showed helpful discriminative ability for 5-year all-cause death in the PCI and CABG groups (C-index=0.70 [95% CI 0.67–0.74] in the PCI group and 0.70 [0.66–0.74] in the CABG group), with excellent calibration (figure 2A, B). The SYNTAX score II 2020 model also showed good calibration for the predicted treatment benefit of CABG over PCI in this population, in terms of 5-year all-cause death (figure 2C).

The SYNTAX score II 2020 model for predicting the 5-year risk of major adverse cardiovascular events included the same prognostic index and the same two treatment effect-modifiers (ie, disease type [three-vessel disease or left main coronary artery disease] and anatomical SYNTAX score) as the 10-year death model (table 3). Cross-validation of this model with the SYNTAX trial provided a C-index of 0.65 (95% CI 0.61–0.69) in the PCI group and 0.71 (0.67–0.75) in the CABG group, with good agreement between the observed and predicted 5-year risk of major adverse cardiovascular events (appendix p 3). The model also showed excellent calibration for treatment benefit of CABG over PCI (appendix p 3). In the pooled patient cohort from the FREEDOM, BEST, and PRECOMBAT trials, the SYNTAX score II 2020 model for predicting 5-year risk of major adverse cardiovascular events showed helpful discrimination in both treatment groups (C-index=0.67 [95% CI 0.63–0.70] for PCI and 0.62 [0.58–0.66] for CABG) and good calibration (figure 3A, B). The model also showed good calibration for the observed versus predicted treatment benefit of CABG over PCI in the FREEDOM, BEST, and PRECOMBAT trials (figure 3C).

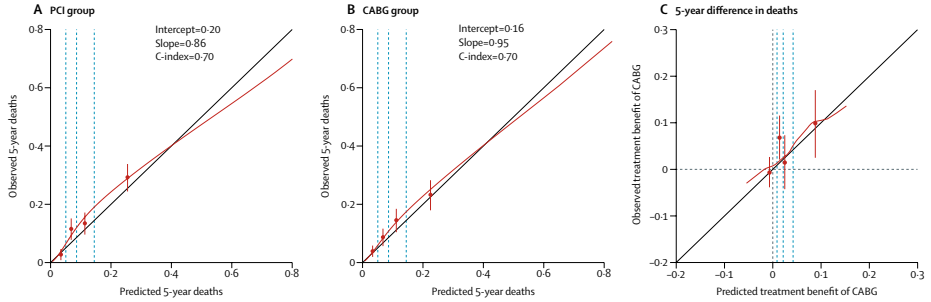

Figure 2: External validation of the 10-year death model of the SYNTAX score II 2020 for predicting 5-year all-cause death in patients with multivessel disease or left main coronary artery disease in the FREEDOM, BEST, and PRECOMBAT trials (n=3380)

Calibration plots showing the observed versus predicted 5-year deaths according to the SYNTAX score II 2020 in the PCI group (A) and CABG group (B). Vertical dashed lines represent quartiles of predicted 5-year deaths. (C) Calibration plot showing the observed versus predicted treatment benefit of CABG, according to the SYNTAX score II 2020. Vertical dashed lines represent quartiles of predicted treatment benefit of CABG. PCI=percutaneous coronary intervention. C-index=concordance index. CABG=coronary artery bypass grafting.

Table 3: Model for predicting the risk of a major adverse cardiovascular event at 5 years

	Coefficient	HR (95% CI)	P value
Prognostic index	0.74	2.10 (1.84–2.39)	<0.0001
CABG × three-vessel disease	–0.48	0.62 (0.46–0.83)	0.0012
CABG × left main coronary artery disease	–0.10	0.91 (0.67–1.22)	0.5117
PCI × left main coronary artery disease	–0.23	0.80 (0.59–1.08)	0.1397
PCI × (SYNTAX score - 29)/10	0.19	1.21 (1.07–1.37)	0.0021

Table shows the coefficients for the prognostic index, with the same seven variables as used for the 10-year all-cause death model, and two predefined treatment interactions (three-vessel disease or left main coronary artery disease and anatomical SYNTAX score), derived from a Cox multivariable model for predicting the risk of a major adverse cardiovascular event at 5 years. The predicted risk of this outcome can be calculated by use of the following formula: predicted probability of major adverse cardiovascular event at 5 years=1 – exp(–0.175 × exp[0.74 × {0.72 × age - 0.07 × creatinine clearance - 0.31 × left ejection fraction + 0.48 × chronic obstructive pulmonary disease + 0.73 × peripheral vascular disease + 0.20 × medically treated diabetes + 0.46 × on insulin + 0.66 × current smoker} - 0.48 × CABG × three-vessel disease - 0.10 × CABG × left main coronary artery disease - 0.23 × PCI × left main coronary artery disease + 0.19 × PCI × {SYNTAX score - 29} / 10 - 2.00]), where age is expressed in years per 10 years, the creatinine clearance is expressed per 10 mL/min per 1.73 m² (capped at 90 per 10 mL/min per 1.73 m²), and the left ventricular ejection fraction is expressed per 10% (capped at 50 per 10%). HR=hazard ratio. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention.

The SYNTAX score II 2020 was better able to discriminate 5-year all-cause deaths than the calibrated original SYNTAX score II in patients randomly assigned to CABG and PCI groups in the external validation cohort of the FREEDOM, BEST, and PRECOMBAT trials (figure 2, appendix p 4). Of note, the SYNTAX score II 2020 was superior to the calibrated original SYNTAX score II for predicting treatment benefit of CABG over PCI in terms of 5-year all-cause death (figure 2, appendix p 4).

DISCUSSION

In this study, we used data from the original SYNTAX trial[5] and the SYNTAXES trial[23] to develop two risk models; one to predict all-cause death at 10 years and the second to predict the risk of major adverse cardiovascular events at 5 years. The SYNTAX score II 2020 contains eight prognostic factors and two prespecified effect-modifiers (disease type and anatomical SYNTAX score). A significant treatment interaction with disease type was observed, and the anatomical SYNTAX score was only associated with death in patients who received PCI, but not in those who received CABG. We found that being female was not an independent predictor of all-cause death over the 10-year follow-up period of the SYNTAXES study. The SYNTAX score II 2020 was internally validated for its ability to predict 10-year death. In addition, we found that the SYNTAX score II 2020 was able to predict 5-year all-cause death and benefit of CABG over PCI in both internal and external validation cohorts. Using the same variables as the 10-year all-cause death model, we developed a model to predict the

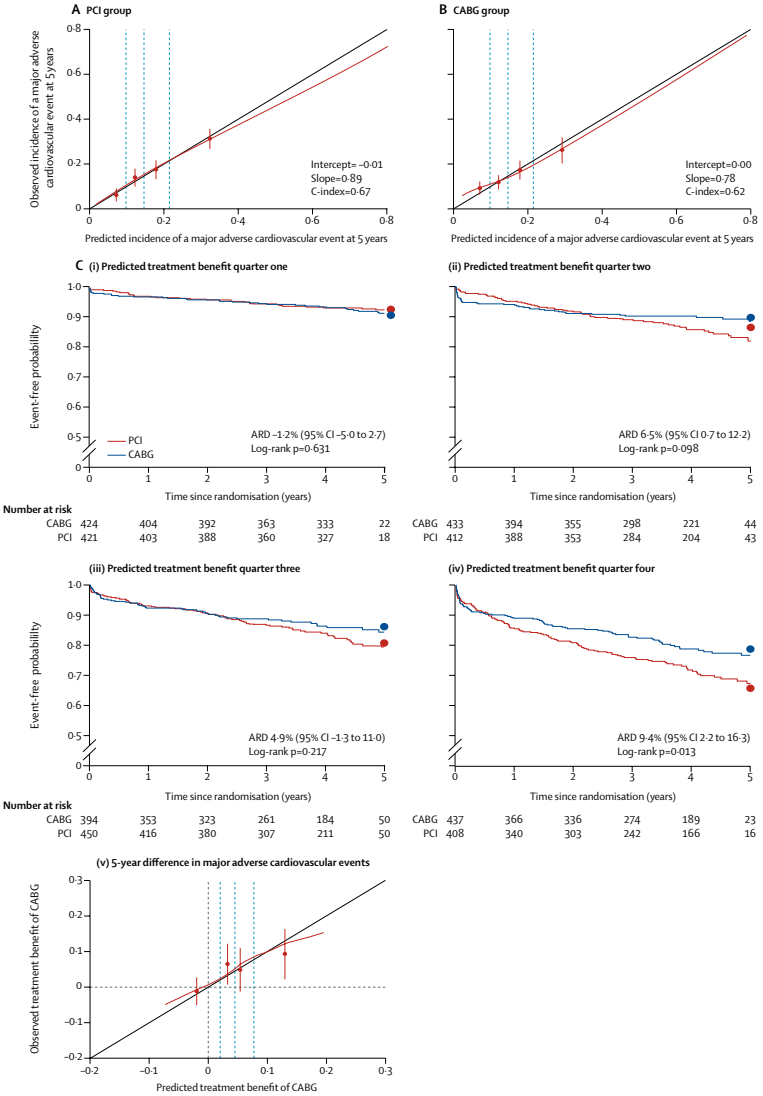

Figure 3: External validation of the SYNTAX score II 2020 for predicting major adverse cardiovascular events at 5 years in patients with multivessel or left main coronary artery disease in the FREEDOM, BEST, and PRECOMBAT trials (n=3380)

Calibration plots showing the observed versus predicted 5-year incidence of major adverse cardiovascular events in the PCI group (A), and the CABG group (B). (C) Kaplan-Meier plots showing the observed versus predicted treatment benefit of CABG over PCI according to the SYNTAX score II 2020 in quarters of predicted treatment benefit (i-iv), and a calibration plot showing the observed versus predicted treatment benefit of CABG over PCI, in terms of the incidence of major cardiovascular adverse events at 5 years (v). A positive ARD represents treatment benefit of CABG over PCI. In the calibration plots, vertical dashed lines represent quartiles of predicted major adverse cardiovascular events at 5 years. In the Kaplan-Meier plots, blue circles represent predicted 5-year major adverse cardiovascular events for CABG, and red circles represent predicted 5-year major cardiovascular events for PCI. PCI=percutaneous coronary intervention. C-index=concordance index. CABG=coronary artery bypass grafting. ARD=absolute risk difference.

	Case 1	Case 2	Case 3
Age, years	74	59	69
Diabetes	No	Yes	Yes
Receiving insulin	No	No	Yes
Creatinine clearance, mL/min per 1·73 m²	38·6	67·6	72·5
Left ventricular ejection fraction	40%	67%	55%
Chronic obstructive pulmonary disease	No	No	No
Peripheral vascular disease	No	No	No
Current smoker	Yes	No	No
Three-vessel disease or left main coronary artery disease	Left main coronary artery disease	Three-vessel disease	Three-vessel disease
Anatomical SYNTAX score	11	10	50

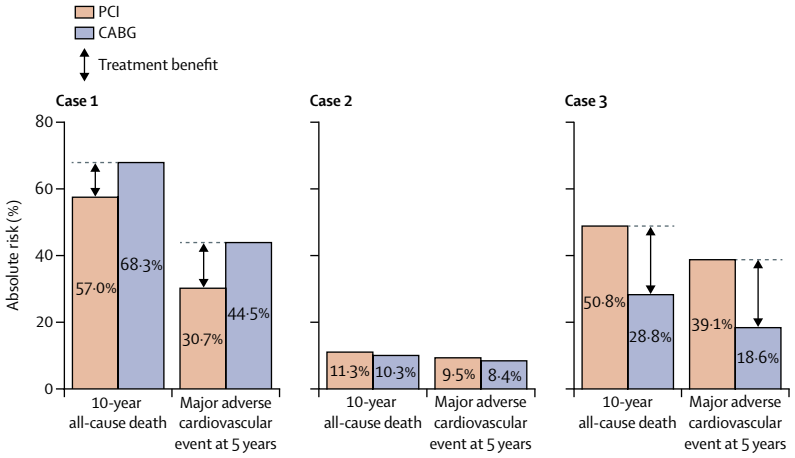

Figure 4: Use of the SYNTAX score II 2020 for individualised decision making
The bar graphs show three representative case scenarios in which the SYNTAX score II 2020 model, for predicting 10-year death and the risk of a major cardiovascular event at 5 years, can provide individualised predictions for these outcomes in different patients depending on the treatment given (PCI or CABG). In the first scenario, a male aged 74 years with left main coronary artery disease, a low left ventricular ejection fraction, and a low creatinine clearance, the model predicts a 10-year all-cause death risk of 68.3% with CABG versus 57.0% with PCI, and 5-year risk of having a major adverse cardiovascular event of 44.5% with CABG versus 30.7% with PCI. As a result, the predicted absolute treatment benefit of PCI over CABG is 11.3% for 10-year death and 13.8% for the 5-year risk of a major adverse cardiovascular event. The second scenario involves a women aged 59 years with three-vessel disease and who had medically treated diabetes, but had a low anatomical SYNTAX score. For this patient, the model predicts a 10-year all-cause death risk of 10.3% with CABG versus 11.3% with PCI, and a 5-year risk of having a major adverse cardiovascular event of 8.4% with CABG versus 9.5% with PCI. The predicted absolute treatment benefit of CABG over PCI is 1.0% for 10-year death and 1.1% for the 5-year risk of a major adverse cardiovascular event. The third scenario involves a male aged 69 years with three-vessel disease, who was given insulin and had a high anatomical SYNTAX score. For this patient, the model predicts a 10-year all-cause death risk of 28.8% with CABG versus 50.8% with PCI, and a 5-year risk of having a major adverse cardiovascular event of 18.6% with CABG versus 39.1% with PCI. The predicted absolute treatment benefit of CABG over PCI is 22.0% for 10-year death and 20.5% for the 5-year risk of having a major adverse cardiovascular event. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention.

5-year risk of major adverse cardiovascular events. This model was also internally and externally validated for its ability to predict major adverse cardiovascular events at 5 years, and showed a good calibration for treatment benefit of CABG over PCI. Finally, the SYNTAX score II 2020 showed better discrimination and calibration for outcome risk and treatment benefit of CABG over PCI compared with the original SYNTAX score II (even with recalibration).

In medicine, randomised controlled trials have been considered the gold standard for comparing the efficacy and safety of alternative therapies. When interpreting and applying the trial results to individual patients, it has generally been assumed that the average treatment effect shown by the trial applies equally to all patients involved in the trial, and among similar future patients who meet the inclusion and exclusion criteria of the trials. However, several reports have suggested that these average treatment effects might obscure considerable variation in individual treatment effects, and individual patients enrolled in clinical trials are heterogeneous with respect to baseline characteristics and consequently to the absolute risk of an outcome of interest. Thus, the application of an average relative risk to individual patients is challenging.[13–19]

To provide individual patients with the best treatment, and to make effective use of limited medical resources, there has been an increasing interest in so-called personalised medicine. To achieve a more personalised approach in patients with complex coronary artery disease, we used data from landmark clinical trials5,23 to develop a predictive model that explicitly considers baseline outcome risk, such that we can distinguish between patients who benefit from CABG and those who could benefit from PCI.[13,21] Indeed, the SYNTAXES study showed no significant difference in 10-year all-cause death between patients in the PCI group compared with those in the CABG group.[23] By contrast, our predictive model provides a more nuanced interpretation of the results of this pivotal study, as it identifies patients who derive substantial survival benefit from CABG over PCI, and those in whom there is little expected difference between the two strategies in terms of 10-year death.

During the development of the original SYNTAX score II, diabetes was not identified as an independent predictor of 4-year all-cause death in the SYNTAX trial, nor an important effect-modifier for 4-year death.[11] Conversely, multivariable analyses done in our study showed that medically treated diabetes, especially among patients taking insulin, was an independent predictor of 10-year all-cause death in both CABG and PCI groups. One possible explanation for these contradictory results could be related to the modest size of the population of patients with diabetes enrolled in

the SYNTAX trial (n=452), which provided only modest statistical power to examine this association. Indeed, a recent large-scale, nationwide, population-based study[41] involving 39 235 participants showed that Kaplan-Meier curves for all-cause death in patients with type II diabetes versus those without undergoing CABG only started to diverge a few years after the surgical procedure and that this divergence increased over time.

Regarding the female sex as a variable of the SYNTAX score II, the results of the SYNTAX trial[5] suggested that women who underwent PCI had a higher adjusted risk of all-cause death at 4 years compared with men (HR 1.70 [95% CI 1.11–2.60]), whereas the risk in those who underwent CABG was similar between the two sexes (0.59 [0.32–1.10], $p_{interaction}$=0.0059). This favourable treatment benefit from CABG over PCI in women led to the inclusion of female sex as a variable in the original SYNTAX score II.[11] However, similar findings with respect to the sex–treatment interaction for all-cause death were not observed in other randomised trials.[42] The absence of a sex–treatment interaction in a diverse spectrum of patients with multivessel disease or with left main coronary artery disease again underscores a difficulty in applying the results of an underpowered subgroup analysis (ie, male *vs* female), and underlines the need for a more sophisticated statistical approach in the choice of revascularisation strategies in patients with complex coronary artery disease.[13–21]

More recently, investigators in the FREEDOM trial developed a model for predicting the 5-year risk of major adverse cardiovascular events and the 1-year angina status to support individualised treatment decisions between CABG and PCI in patients with diabetes and multivessel disease.[43] The investigators showed that the discriminative ability of the 5-year risk of major adverse cardiovascular events model and the 1-year angina status model was the same (C-statistic 0.67) in both PCI and CABG groups in the derivation cohort.[43] To interpret the performance of a newly developed multivariable predictive model, Alba and colleagues[44] rightly classified a C-index range of 0.60–0.75 as possibly helpful, because a C-index in this range is only helpful when the model is able to separate substantial groups of patients across meaningful risk thresholds and when the model is calibrated. As our SYNTAX score II 2020 model is adequately calibrated over the range of predictions encompassed by the study population, and is helpful for discriminating between patients with high and low treatment benefit, we considered our model to be helpful.

Nevertheless, one might be concerned about the applicability of our new model to daily clinical practice, given that the SYNTAX trial was done using an outdated technology and strategy for treatment with PCI or CABG. The paclitaxel-eluting

stent used to treat patients in the PCI group (TAXUS Express) is no longer commercially available, and the SYNTAX II trial showed that contemporary, best practice PCI, including the use of current-generation drug-eluting stents, physiology-guided treatment, and intravascular ultrasound-mediated optimisation of stent deployment, definitely improved clinical outcomes.[45,46] Similarly, contemporary CABG, as executed in the EXCEL trial, offered superior outcomes when compared with CABG in the SYNTAX trial in a propensity-matched analysis.[47] However, contemporary randomised data are not currently available for the construction of a multivariable predictive model. In addition, physiology-guided PCI and intracoronary imaging devices are not routinely used in our daily clinical practice. When the SYNTAX score II 2020 was externally validated to compare CABG with PCI (with the everolimus-eluting durable polymer stent [Xience]) in patients with multivessel disease from the BEST trial, the predicted treatment benefit of CABG over PCI was well calibrated (appendix p 5). Therefore, we consider that our new model is worthy of testing in clinical practice.

In our study, the treatment benefit of CABG over PCI was defined as the absolute risk difference between CABG and PCI. One might conclude that patients in the fourth quarter had a significant treatment benefit of CABG over PCI in terms of 10-year all-cause death. Similar grouped outcomes can be visually illustrated by Kaplan-Meier curves. However, we consider that one treatment (CABG) is not globally superior, inferior, or equal to another treatment (PCI), but that a specific treatment is superior, inferior, or equal for a specific patient. For this individualised decision making, the SYNTAX score II 2020 generates a prediction of treatment benefit for individual patients based on their own angiographic and clinical variables. To visualise the ability of our model to predict a treatment benefit, it is crucial to use calibration plots. Lastly, the benefit threshold of 7.9% between the third and fourth quarter is highly dependent on how the cohort is grouped to display the calibration plot (ie, by tertiles, quartiles, or quintiles), and physicians rarely agree on a specific threshold at which one treatment over the other should be initiated[48] because thresholds are influenced by many factors, such as the potential risks and benefits of a particular treatment, physician or patient preferences, and economic considerations.[17]

Physician preference has traditionally played a major role in selecting a revascularisation strategy for individual patients.[49] Surgeons and interventional cardiologists provide their patients with vastly different information on myocardial revascularisation treatment options, with a bias toward a specific strategy,[50] which is exemplified by varying ratios of PCI versus CABG, not only across various European countries with a similar economic status, but also among the same geographical regions within

a country.[51,52] Many physicians in these regions might guide revascularisation strategies on the basis of subjective assessments according to their experience, specialty, or background, which do not always represent guideline recommendations,[53,54] and could potentially result in an inaccurate risk assessment[55,56] and the patient receiving inappropriate treatments with suboptimal outcomes.[56] To avoid this physician-related bias, the multidisciplinary heart team should use the SYNTAX score II 2020 in the decision making process to choose the best revascularisation strategy for each patient, thus enabling more individualised and patient-centred care in those with complex coronary artery disease. Figure 4 shows three example case scenarios in which the SYNTAX score II 2020 was applied. Using the evidence-based predicted treatment benefits of CABG over PCI that this model provides, in terms of 10-year all-cause death and 5-year risk of major adverse cardiovascular events, patients and their families can make a final decision based on their preference,[49,57] since most patients prefer PCI over CABG,[58] even if the subsequent risk of ischaemic events after PCI is much greater when compared with CABG.[59,60]

This study has several limitations. First, the SYNTAX trial5 collected baseline information on death, and the present analysis accounted for such baseline information in Cox multivariable models; however, relevant but unmeasured variables (eg, B-type natriuretic peptide) could not be included in the model. Second, the SYNTAXES study[23] evaluated vital status up to 10 years and did not assess other outcomes; thus a predictive model for estimating the risk of major adverse cardiovascular events beyond 5 years could not be constructed. Given that mean age of patients in the SYNTAX trial was 65 years at the time of randomisation, and the overall life expectancy of patients has been increasing worldwide, a predictive model for the 10-year risk of major adverse cardiovascular events could be informative to further guide the optimal revascularisation strategy in patients with complex coronary artery disease.

Using data from the SYNTAX trial[5] and the extended follow-up SYNTAXES study,[23] we have updated, and externally validated the SYNTAX score II 2020, a personalised predictive model based on eight prognostic factors and two prespecified effect-modifiers, to predict 10-year all-cause death and the 5-year risk of major adverse cardiovascular events for patients treated with either PCI or CABG. By providing the expected probabilities of 5-year and 10-year outcomes, this model could improve the ability of the heart team to inform patients and their families about the risks and benefits of these treatments for complex coronary artery disease and support a more transparent and shared decision making process. Further adequately powered, randomised trials of PCI versus CABG, with 5–10 years' follow-up, which employ

contemporary revascularisation techniques, devices, and adjunctive medical therapy, should be done to prospectively validate the SYNTAX score II 2020 model.

Contributors

PWS and KT conceived, designed, and interpreted data, drafted the manuscript, and revised and approved the final version of the manuscript for submission. DvK analysed and interpreted data, and revised and approved the final version of the manuscript for submission. VF, MEF, JAS, DJC, S-JP, D-WP, J-MA, APK, SJH, DJFMT, YO, DMK, and EWS interpreted data, and revised and approved the final version of the manuscript for submission.

Declaration of interests

PWS reports personal consultancy fees from Biosensors, Medtronic, Micell, Sino Medical Sciences Technology, Philips Volcano, Xeltis, and Heartflow, outside the submitted work. MEF reports research grants from Amgen, Novartis, and Novo Nordisk, outside the submitted work. JAS reports an equity interest in Health Outcomes Sciences; ownership of the Seattle Angina Questionnaire; consulting services to United Healthcare, Amgen, Bayer, Novartis, Janssen, Myokardia, and Janssen; a research grant from Abbott Vascular; and serving on the Board of Directors of Blue Cross Blue Shield of Kansas City, all outside the submitted work. DJC reports institutional research grants and personal fees from Medtronic, Boston Scientific, and Abbott Vascular, outside the submitted work. APK and SJH are employees of Medtronic, outside the submitted work. All other authors declare no competing interests.

Data sharing

All data, including study participant data, the data dictionary, the statistical analysis plan, and informed consent, will not be shared.

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