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# Impact of non-respect of SYNTAX score II recommendation for surgery in patients with left main coronary artery disease treated by percutaneous coronary intervention: an EXCEL substudy

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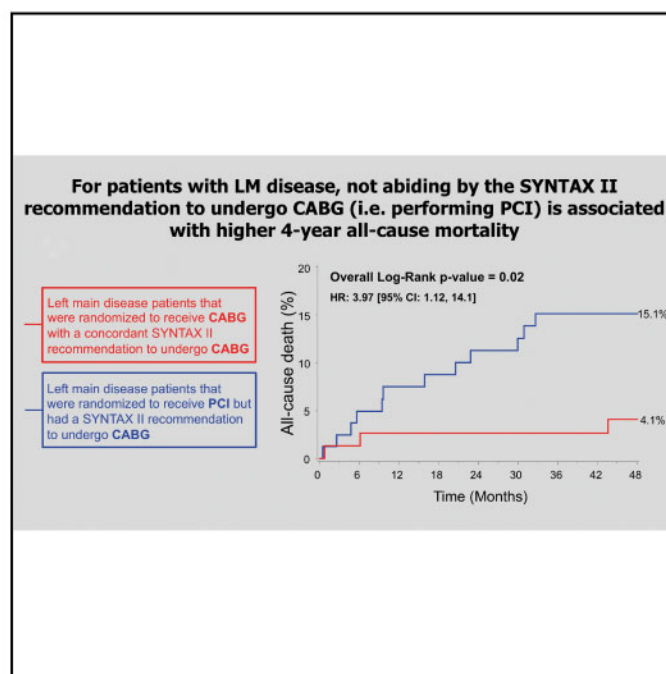
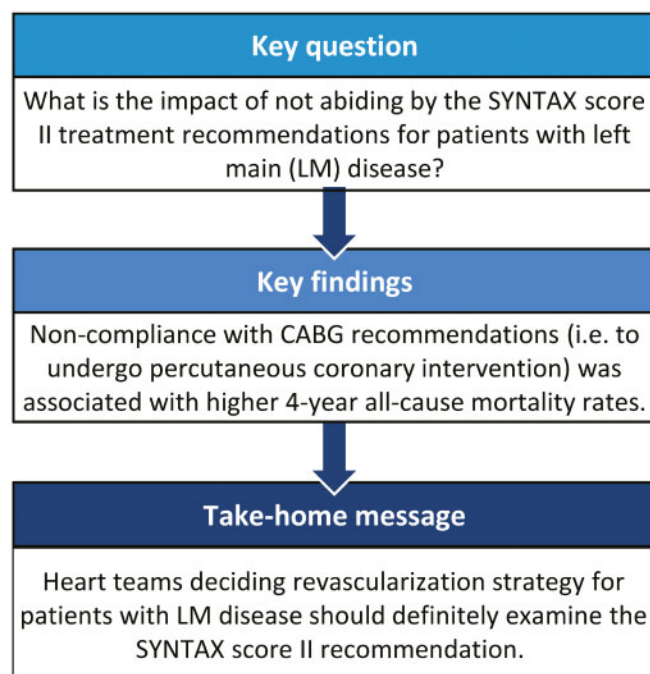
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## Abstract

**OBJECTIVES:** The SYNTAX score II (SSII) was developed from the SYNTAX trial to predict the 4-year all-cause mortality after left main or multivessel disease revascularization and to facilitate the decision-making process. The SSII provides the following treatment recommendations: (i) coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) (equipoise risk), (ii) CABG preferred (excessive risk for PCI) or (iii) PCI preferred (excessive risk for CABG). We sought to externally validate SSII and to investigate the impact of not abiding by the SSII recommendations in the randomized EXCEL trial of PCI versus CABG for left main disease.

**METHODS:** The calibration plot of predicted versus observed 4-year mortality was constructed from individual values of SSII in EXCEL. To assess overestimation versus underestimation of predicted mortality risk, an optimal fit regression line with slope and intercept was determined. Prospective treatment recommendations based on SSII were compared with actual treatments and all-cause mortality at 4 years.

**RESULTS:** SSII variables were available from EXCEL trial in 1807/1905 (95%) patients. For the entire cohort, discrimination was possibly helpful (*C* statistic = 0.670). SSII-predicted all-cause mortality at 4 years overestimated the observed mortality, particularly in the highest-risk percentiles, as confirmed by the fit regression line [intercept 2.37 (1.51–3.24), *P* = 0.003; slope 0.67 (0.61–0.74), *P* < 0.001]. When the SSII-recommended treatment was CABG, randomized EXCEL patients treated with PCI had a trend towards higher mortality compared with those treated with CABG (14.1% vs 5.3%, *P* = 0.07) in the as-treat population. In the intention-to-treat population, patients randomized to PCI had higher mortality compared with those randomized to CABG (15.1% vs 4.1%, *P* = 0.02), when SSII recommended CABG.

**CONCLUSIONS:** In the EXCEL trial of patients with left main disease, the SSII-predicted 4-year mortality overestimated the 4-year observed mortality with a possibly helpful discrimination. Non-compliance with SSII CABG treatment recommendations (i.e. randomized to PCI) was associated with higher 4-year all-cause mortality.

**Keywords:** Coronary artery bypass grafting • Left main coronary artery disease • Drug-eluting stents • SYNTAX score

### ABBREVIATIONS

3VD	3-Vessel disease
CABG	Coronary artery bypass grafting
CI	Confidence interval
EXCEL	Evaluation of XIENCE vs Coronary Artery Bypass Grafting for Effectiveness of Left Main Revascularization
HR	Hazard ratio
ITT	Intention-to-treat
LM	Left main
PCI	Percutaneous coronary intervention
RCTs	Randomized controlled trials
SS	SYNTAX score
SSII	SYNTAX score II
SYNTAX	Synergy between PCI with Taxus and Cardiac Surgery

## INTRODUCTION

The anatomical Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score (SS) is a practical tool that uses coronary anatomy to objectively guide the decision-making process for revascularization treatment in patients with complex coronary artery disease [left main (LM) disease or 3-vessel disease (3VD)] [1, 2]. Studies have demonstrated the utility of the anatomical SS to help guide selection of revascularization mode between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) [3–5], and it is therefore advocated by contemporary guidelines [6–8].

The SYNTAX score II (SSII) was subsequently developed from the SYNTAX trial to further improve decision-making between CABG and PCI in patients with complex coronary artery disease [9]. The SSII combines anatomic and clinical factors, allowing for more individualized decision-making between PCI and CABG. The SSII gives a clear recommendation based on the predicted 4-year mortality for both CABG and PCI: (i) CABG only; (ii) PCI

only; or (iii) equipoise, meaning the mortality risk is equal for PCI and CABG. SSII has been externally validated in 2 real-world registries [9, 10] and in pooled randomized trial populations [11, 12].

As recommended by the guidelines, heart teams should indicate the best revascularization treatment for patients with 3VD and LM disease based on anatomy and clinical conditions [13]. In the single-arm SYNTAX II study, outcomes of patients with complex coronary artery disease undergoing PCI were compared with a historical surgical comparator matched by similar SSII [14, 15]; however, randomized clinical trials (RCTs) assessing revascularization strategies (PCI or CABG) for 3VD or LM performed to date have not taken into account integrated risk score recommendation such as that from the SSII. As such, RCTs have assigned patients to PCI in whom SSII may have otherwise recommended CABG and vice-versa. Thus, RCTs may be uniquely suited for assessing the mortality impact associated with the lack of concordance between SSII recommendations and actual treatment. We therefore sought to externally validate SSII and to determine the mortality impact of not abiding by the SSII recommendations in the setting of a large-scale contemporary RCT comparing PCI and CABG for the treatment of LM stem disease.

## METHODS

### Trial design and study population

The present study is a *post-hoc* analysis of patients randomized to CABG or PCI in the EXCEL (Evaluation of XIENCE vs Coronary Artery Bypass Grafting for Effectiveness of Left Main Revascularization) trial [16]. The EXCEL trial methodology and main results have been previously published [16]. Briefly, EXCEL was an international, open-label, multicentre randomized trial that compared PCI with everolimus-eluting stents with CABG in patients with LM disease and an investigator-reported anatomical SS  $\leq 32$  (i.e. low or intermediate). Eligible patients (*n* = 1905),

recruited from 2010 to 2014, were assigned to undergo either PCI with everolimus-eluting stents (XIENCE, Abbott Vascular, Santa Clara, CA, USA,  $n = 948$ ) or CABG ( $n = 957$ ). Key inclusion criteria were LM stenosis  $\geq 70\%$  by visual estimation or haemodynamically significant stenosis of 50% to  $<70\%$  by either invasive or non-invasive testing. All patients were considered by a local heart team to be suitable for revascularization with either PCI or CABG. Calibration and discrimination were assessed in the as-treated population. Guideline-directed medical therapy was recommended for all patients. The trial was conducted in accordance with ethical principles for medical research involving human subjects of the World Medical Association (Declaration of Helsinki). Its protocol was approved by the ethics committee at each participating centre, and all patients signed informed consent. Follow-up is ongoing through 5 years, with all patients having completed 4-year follow-up at the time of this report.

## The SYNTAX score II

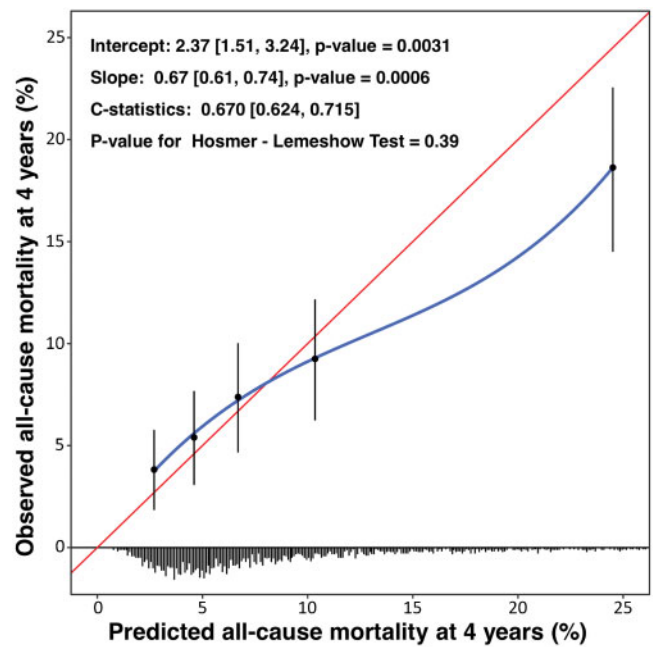
The SSII has been previously described [9]. Briefly, it combines data from the coronary anatomy (anatomical SS and the presence of unprotected LM disease) with clinical characteristics (sex, age, creatinine clearance, left ventricular ejection fraction, chronic obstructive pulmonary disease and peripheral vascular disease) allowing for 4-year all-cause mortality predictions to be made following revascularization with either CABG or PCI. Based on treatment effect interactions for PCI and CABG, the SSII provides different scores with their correspondent estimated mortalities for each of the revascularization strategies. Thus, patients are recommended for CABG if the predicted mortality for PCI is statistically higher (with 95% of confidence), and likewise are recommended for PCI if the predicted risk of mortality following CABG is higher (with 95% of confidence). If the predicted mortality rates are not statistically different between PCI and CABG, patients are recommended for either treatment (equipoise risk). In summary, SSII affords a personalized recommendation for: (i) only CABG; (ii) only PCI; or (iii) equipoise between CABG and PCI. In the EXCEL trial, the anatomic SS was measured at an independent angiographic core laboratory (Cardiovascular Research Foundation, New York, NY, USA) [17]. The core laboratory-assessed SS measures were used for the SSII calculation given the tendency of sites to under-estimate the anatomic SS [2, 17, 18].

## End points

The primary end point in the present study was all-cause mortality at 4 years, the measure for which the SSII was developed and validated. Mortality was confirmed by an independent Clinical Events Committee by review of original source documents.

## Statistical analysis

Continuous data are presented as mean  $\pm$  standard deviation or median and interquartile range and were compared with the Student's  $t$ -test or Wilcoxon rank sum test as appropriate. Categorical data are presented as percentages (counts) and were compared with the  $\chi^2$  test or Fisher's exact test. Clinical event rates are presented as Kaplan–Meier estimates in time-to-first-event analyses and were compared with the log-rank test. Calibration between observed and expected mortality at 4 years



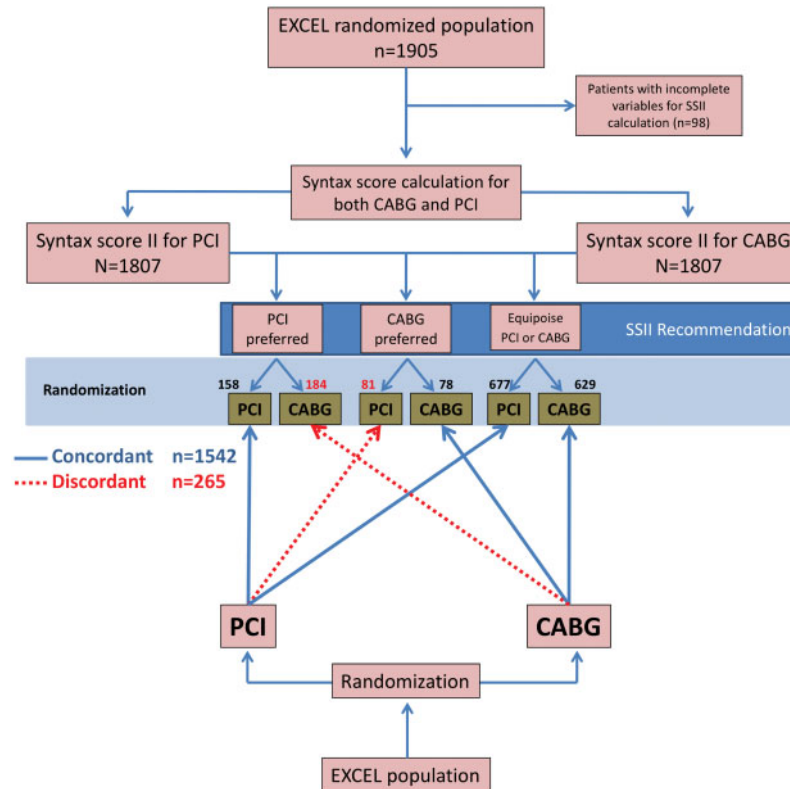
**Figure 1:** Flexible calibration plot of observed versus SYNTAX score II predicted 4-year mortality of the entire population from the EXCEL trial with available SYNTAX score II measures. Red line represents the identity line.

based on SSII was investigated in quintiles of the EXCEL population. A linear regression model was fit between observed and predicted all-cause mortality in each quintile, and the intercept, slope and  $R^2$  from the model result were determined. Discrimination was assessed using C statistics, also represented by the receiver-operating characteristic curve (since the outcome is binary), and using the Brier score [19, 20]. Calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test. The Kaplan–Meier method was used to estimate the cumulative rates of clinical events in the quintiles. Cox proportional-hazards regression models were used to calculate hazard ratios (HRs) in the subgroups based on SSII score recommendation and to test for interactions. If the assumptions were not satisfied, a logistic regression was performed and the odds ratios with its 95% confidence interval (CI) reported along. All analyses to test the impact of not abiding by the SSII recommendation were performed according to the: (i) randomization of the patients (intention-to-treat population–ITT) to either CABG or PCI and (ii) treatment that the patients actually received (PCI or CABG)—i.e. the as-treated population; and results are presented for both populations. A 2-sided  $P$ -value of 0.05 or less was considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### Discrimination and calibration

Out of the 1905 patients randomized in EXCEL, 1807 had all the variables for the retrospective calculation of SSII, representing the present study population. Within 4 years, 156 patients died (Kaplan–Meier estimated rate 8.9%). The calibration plot for the observed versus expected overall 4-year mortality rates is presented in Fig. 1. The C statistic for the SSII prediction for the



**Figure 2:** Flow of the patients in the EXCEL trial. From top down—the calculation of the SSII and its personalized recommendation. From bottom up—the randomization process of the trial. The blue lines show the path of patients who received a treatment concordant with the SSII recommendation. Red dashed lines show the path of patients who received a treatment other than the one recommended by the SSII. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; SSII: SYNTAX score II.

entire EXCEL population was 0.670 (95% CI 0.624–0.715,  $P < 0.0001$ ), which is considered a possibly helpful discrimination. The fit regression line showed a slope of 0.67 (95% CI 0.61–0.74,  $P = 0.0006$ ) and intercept of 2.37 (95% CI 1.51–3.24,  $P = 0.0031$ ). The slope of  $< 1$  with a positive intercept evidences the overestimation of the prediction model in the higher scores and underestimation in the lower scores. The Brier score for the prediction was 0.077. A Brier score of zero would represent a perfect model, whereas a score of 0.25 is considered non-informative [19, 20]. Model calibration was good ( $\chi^2 = 8.56$ ;  $P_{HL} = 0.38$ ).

The median (interquartile range) SSII measure of randomized patients undergoing PCI versus CABG in EXCEL was 28.47 (23.41–35.57) versus 31.10 (25.00–37.40), respectively,  $P = 0.0006$ . In this population, by 4 years 92 and 64 PCI and CABG patients had died, respectively (Kaplan–Meier estimated rates of 10.26% and 7.40%). The C statistic (95% CI) for SSII prediction of 4-year mortality after PCI was 0.661 (0.600–0.721) and the C statistic for CABG was 0.695 (0.628–0.762), and model calibration was good for each ( $\chi^2 = 6.68$ ;  $P_{HL} = 0.57$  and  $\chi^2 = 7.05$ ;  $P_{HL} = 0.53$ , respectively).

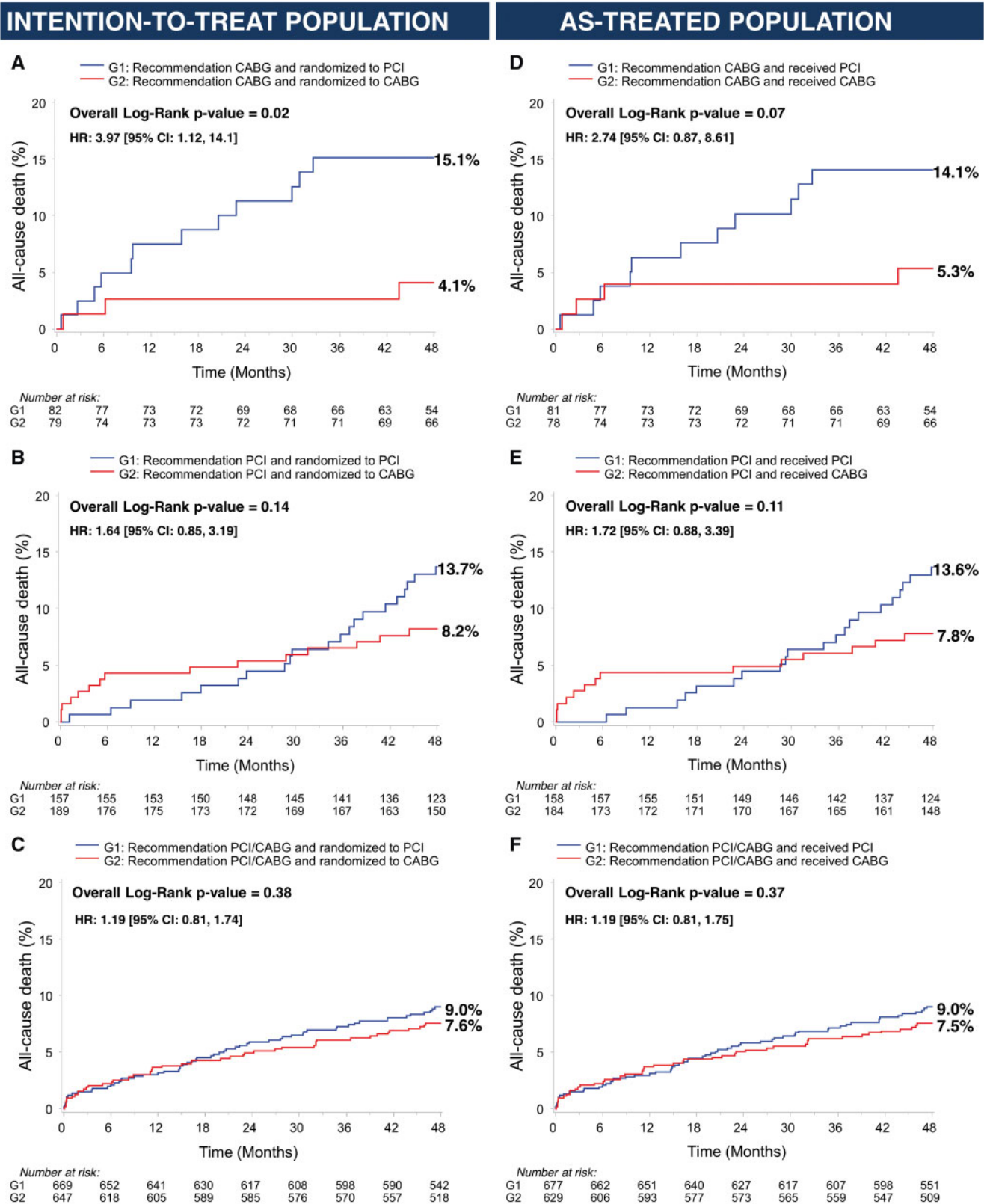
### Concordance and discordance with the SYNTAX score II recommendation

Among the 1807 study patients, SSII recommended ‘PCI only’ in 342 patients (18.9%), ‘CABG only’ in 159 (8.8%) and ‘CABG or PCI’ in 1306 patients (72.3%). Baseline characteristics and medication intake in each SSII recommendation group are shown in the [Supplementary Material](#). CABG was performed in 184/342 (52.9%) patients in whom SSII recommended PCI only, and PCI

was performed in 81/159 (50.9%) patients in whom SSII recommended CABG only (Fig. 2). The actual treatment was thus at variance (discordant) with the SSII recommendation in 265/1807 patients (14.7%). If the SSII recommendation was for ‘PCI or CABG’, there was no difference in mortality at 4 years if the patient received either treatment (9.0% for PCI vs 7.5% for CABG, HR 1.19, 95% CI 0.81–1.75;  $P = 0.37$ ). If the SSII recommendation was ‘PCI only’, 4-year mortality was also not significantly different in patients treated with PCI versus CABG (13.6% for PCI vs 7.8% for CABG, HR 1.72, 95% CI 0.88–3.39;  $P = 0.11$ /odds ratio 1.86, 95% CI 0.91–3.80;  $P = 0.09$ ); however, if the SSII recommendation was to undergo ‘CABG only’, the 4-year rate of all-cause death was higher in those treated with PCI compared with those undergoing CABG (14.1% vs 5.3%, HR 2.74, 95% CI 0.87–8.61;  $P = 0.07$ , respectively) (Fig. 3). In order to use an ‘unbiased’ population, we performed the same analysis on the ITT population, i.e. patients grouped as they were randomized. In the ITT population, in patients with an SSII recommendation ‘PCI only’, 4-year mortality was not significantly different between patients randomized to PCI versus CABG (13.7% for PCI vs 8.2% for CABG,  $P = 0.14$ ); however, in patients with an SSII recommendation ‘CABG only’, the 4-year rate of all-cause death was significantly higher in those randomized to PCI compared with those randomized to CABG (15.1% vs 4.1%,  $P = 0.02$ , respectively) (Fig. 3 and [Supplementary Figure 1](#)).

### DISCUSSION

The main findings of the present study are as follows: (i) The SSII has now been externally validated in a randomized population



**Figure 3:** Time-to-event curves for all-cause death. (A–C) Refers to the intention-to-treat population and (D–E) refers to the as-treated population. (A) Shows the patients who received a SYNTAX score II (SSII) recommendation to undergo CABG and were randomized to PCI (blue line) or CABG (red line). (B) Shows the patients who received an SSII recommendation to undergo PCI and were randomized to PCI (blue line) or CABG (red line). (C) Shows the patients who received an SSII recommendation of equipoise risk (CABG or PCI) and were randomized to PCI (blue line) or CABG (red line). (D) Shows the patients who received an SSII recommendation to undergo CABG and underwent PCI (blue line) versus CABG (red line). (E) Shows the patients who received an SSII recommendation to undergo PCI and underwent PCI (blue line) versus CABG (red line). (F) Shows the patients who received an SSII recommendation of equipoise risk (CABG or PCI) and underwent PCI (blue line) versus CABG (red line). CABG: coronary artery bypass grafting; CI: confidence interval; HR: hazard ratio; PCI: percutaneous coronary intervention.

with LM disease, demonstrating possibly helpful discrimination (C statistic = 0.670) and good calibration; (ii) non-respect of the SSII treatment recommendation for CABG in the EXCEL trial (i.e. performance of PCI instead) was associated with a trend towards greater mortality compared with performance of CABG as recommended; and (iii) no significant differences in 4-year mortality between PCI and CABG were observed when the SSII recommendation was to perform PCI or noted equipoise between PCI and CABG.

The present study is the first to validate the SSII in a randomized LM disease population for the performance of CABG versus PCI, and the results are in keeping with the original validation upon development of SSII [9]. The internal validation of SSII in the index SYNTAX trial [1] showed a C statistic of 0.725, whereas the external validation performed in the DELTA registry [21] cohort of non-randomized patients resulted in a C statistic of 0.716—both possibly helpful and somewhat similar to what we observed in the randomized EXCEL population (0.670).

The current 4-year data from the EXCEL trial allow for the first time a proper validation of the discrimination ability of the SSII. With regard to definition, discrimination is considered outstanding if C statistic  $\geq 0.9$ , excellent if  $\geq 0.8$  and  $< 0.9$ , acceptable if  $\geq 0.7$  and  $< 0.8$ , poor if  $> 0.5$  and  $< 0.7$  and absent if C statistic = 0.5 [22]. In a more recent definition, a C statistic  $< 0.60$  defines a poor discrimination, 0.60–0.75 a possibly helpful discrimination and  $> 0.75$  a clearly useful discrimination [23]. Therefore, our results can define the discrimination ability of SSII as poor or possibly helpful.

Worthy of mentioning from our analysis is the overestimation of 4-year mortality from that predicted in SSII and observed in EXCEL, particularly in the highest quintile of predicted mortality (Fig. 1). The likely explanation for this discordance is the fact that SSII was developed in an earlier period at the time of the SYNTAX trial. In this regard we have previously shown that there has been an improvement in surgical outcomes from SYNTAX to EXCEL [24]. As to PCI, the stent used in the SYNTAX trial was the first-generation paclitaxel-eluting thick-strut TAXUS stent. In EXCEL, the second-generation everolimus-eluting XIENCE stent was used, which has thinner struts and a more biocompatible polymer and drug, resulting in improved late outcomes [14].

The SSII was created to fulfil the need for objective and individualized guidance for decision-making between PCI and CABG in patients with complex coronary artery disease [9]. The heart team concept is currently the proper approach for such patients, and non-compliance to guidelines may result in inappropriate revascularization [13, 25, 26]. It has been previously demonstrated that applying the SSII affords high agreement with heart team revascularization decisions [27]. The present study is the first to demonstrate a potential harmful effect of not complying with the SSII recommendation. Interestingly this negative effect was largely confined to the CABG recommendation, i.e. when the patient was referred to PCI even though there was a clear SSII recommendation for CABG (Fig. 3). In such cases a sustained separation of the Kaplan–Meier curves was evident favouring CABG. Paradoxically, a trend favouring surgery was also observed when the recommendation was for the patient to undergo PCI, although it was statistically not different.

Another important message arising from these data is that when the recommendation derived from SSII was for 'CABG or PCI' (i.e. equipoise was present), the 4-year mortality rates for either CABG or PCI were indeed equivalent ( $P = 0.37$ ). Worthy of note for the heart teams evaluating LM disease patients is that

the observed mortality rates of patients undergoing CABG was similar in those with an SSII recommendation for 'PCI only' compared with an SSII recommendation for 'CABG or PCI'. Thus, even if a patient has a PCI recommendation, the heart team could choose CABG based on other clinical reasons (e.g. doubtful dual antiplatelet therapy adherence) without apparent impact on 4-year mortality.

In the single-arm SYNTAX II study, the anatomical recommendation of the European Society of Cardiology (ESC) was not applied; however, the ethical aspect of the recommendation treatment was maintained since the patient could only be included if the SSII recommendation was for equipoise ('CABG or PCI'). This was accomplished by an exploratory comparison of the PCI population with the surgical cases of the original SYNTAX trial using only a population matched for the SSII, which resulted in similar event rates [14].

## Limitations

This study has limitations inherent in a non-prespecified retrospective analysis. A prospective analysis of the predictive ability of SSII would be preferred. Nevertheless, the fact that we assessed patients who were randomized without considering the SSII recommendation was a strength for the present analysis, as it allowed us to assess the impact of non-compliance to the SSII treatment recommendation. In addition, it would be unethical to assign a patient to a treatment arm with the belief that, by the SSII prediction, the patient would have worse outcomes. Of note, in the present study of patients with LM disease the SSII recommended 'CABG only' in only 8.8% of patients; however, patients with a site-assessed anatomical SS  $> 32$  were excluded from randomization in the EXCEL trial. By core lab analysis  $\sim 25\%$  of enrolled patients had, in fact, an anatomical SS  $> 32$ . Nonetheless, further studies are required to validate the SSII in patients with high anatomic SS in whom CABG is more frequently recommended. Despite the numerically higher all-cause 4-year mortality in patients receiving PCI amongst those with 'CABG only recommendation by SSII' (as-treated population), the CI for the HR was wide thus not allowing for a better conclusion to be drawn on the effect of undergoing PCI in discordance with the SSII recommendation. Nevertheless, when analysing the 'unbiased' ITT population, the mortality was significantly higher when performing PCI, instead of the recommended CABG. Finally, the SSII was developed for patients with 3VD and/or LM disease from the SYNTAX trial, whereas the present study was restricted to the treatment of LM disease with or without additional diseased vessels.

## CONCLUSIONS

For patients with LM disease enrolled in the EXCEL trial, the predicted 4-year mortality based on the SSII overestimated the 4-year observed mortality, with possibly helpful overall discrimination. Non-compliance with the SSII recommendation to undergo CABG (i.e. treating the patient with PCI—as-treated population) was associated with a trend towards higher 4-year all-cause mortality, i.e. a numerically large difference that did not reach statistical significance, whereas, in the ITT population, randomization of patients to PCI in discordance with the SSII recommendation (CABG only) resulted in significantly higher 4-year

all-cause mortality as compared with patients randomized to CABG. These results are merely hypothesis-generating due to the small sample size of the population with discordance in recommendation/treatment. Additional larger studies involving patients with multivessel disease with or without LM involvement are warranted for more conclusive findings on the harmful effect of not abiding by the SYNTAX II recommendation.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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**Conflict of interest:** Rodrigo Modolo: Received research grant from Biosensors, not related to the present work. Ply Chichareon: Received research grant from Biosensors, not related to the present work. Joseph F. Sabik III: Consultant—Medtronic, Edwards and Sorin. Advisory board—Medtronic Cardiac Surgery. Yoshinobu Onuma: Employee at Cardialysis. Arie Pieter Kappetein: Employee—Medtronic. Gregg W. Stone reports that his employer, Columbia University, receives royalties from sale of the MitraClip manufactured by Abbott Vascular. Patrick W. Serruys: Consultant—Abbott, Biosensors, Medtronic, Micell Technologies, QualiMed, SINOMED, St. Jude Medical, Stentys, Svelte, Philips/Volcano, Xeltis. All other authors declared no conflict of interest.

## Author contributions

**Rodrigo Modolo:** Conceptualization; Investigation; Methodology; Supervision; Validation; Visualization; Writing - Original Draft; Writing - Review & Editing. **Ply Chichareon:** Methodology; Supervision; Validation; Visualization; Writing - Original Draft; Writing - Review & Editing. **David van Klaveren:** Investigation; Methodology; Writing - Review & Editing. **Ovidiu Dressler:** Data curation; Formal analysis; Investigation; Writing - Review & Editing. **Yiran Zhang:** Formal analysis; Writing - Review & Editing. **Joseph Sabik:** Conceptualization; Investigation; Writing - Review & Editing. **Yoshinobu Onuma:** Writing - Review & Editing. **Arie Pieter Kappetein:** Conceptualization; Investigation; Writing - Review & Editing. **Gregg W. Stone:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Validation; Writing - Original Draft; Writing - Review & Editing. **Patrick W. Serruys:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Validation; Writing - Original Draft; Writing - Review & Editing.

## REFERENCES

- Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961–72.
- Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP *et al.* Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;5:50–6.
- Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G *et al.* Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv* 2009;2:731–8.
- Farooq V, Head SJ, Kappetein AP, Serruys PW. Widening clinical applications of the SYNTAX score. *Heart* 2014;100:276–87.
- Garg S, Sarno G, Serruys PW, Rodriguez AE, Bolognese L, Anselmi M *et al.* Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a substudy of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) trials. *JACC Cardiovasc Interv* 2011;4:66–75.
- Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG *et al.* 2011 ACCF/AHA Guideline for coronary artery bypass graft surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;124:2610–42.
- Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B *et al.* 2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44–122.
- Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87–165.
- Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A *et al.* 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. *Lancet* 2013;381:639–50.
- Campos CM, van Klaveren D, Iqbal J, Onuma Y, Zhang YJ, Garcia-Garcia HM *et al.* Predictive performance of SYNTAX score II in patients with left main and multivessel coronary artery disease-analysis of CREDO-Kyoto registry. *Circ J* 2014;78:1942–9.
- Cavalcante R, Sotomi Y, Mancone M, Whan Lee C, Ahn JM, Onuma Y *et al.* Impact of the SYNTAX scores I and II in patients with diabetes and multivessel coronary disease: a pooled analysis of patient level data from the SYNTAX, PRECOMBAT, and BEST trials. *Eur Heart J* 2017;38:1969–77.
- Sotomi Y, Cavalcante R, van Klaveren D, Ahn JM, Lee CW, de Winter RJ *et al.* 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 1,480 patients of the BEST and PRECOMBAT randomized controlled trials. *JACC Cardiovasc Interv* 2016;9:1564–72.
- Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes DR Jr *et al.* The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. *Eur Heart J* 2013;34:2510–8.
- Escaned J, Collet C, Ryan N, De Maria GL, Walsh S, Sabate M *et al.* Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J* 2017;38:3124–34.
- Luscher TF. Optimizing percutaneous coronary interventions: heart Team, SYNTAX II Score, physiology and imaging guidance, modern stents, and guideline-based medication. *Eur Heart J* 2017;38:3109–13.
- Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J *et al.* Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med* 2016;375:2223–35.
- Généreux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R *et al.* SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv* 2011;4:553–61.
- Garg S, Girasis C, Sarno G, Goedhart D, Morel MA, Garcia-Garcia HM *et al.* The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. *Catheter Cardiovasc Interv* 2010;75:946–52.
- Serruys PW, Farooq V, Vranckx P, Girasis C, Brugaletta S, Garcia-Garcia HM *et al.* A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. *JACC Cardiovasc Interv* 2012;5:606–17.

- [20] Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. New York, NY: Springer, 2008.
- [21] Chieffo A, Meliga E, Latib A, Park SJ, Onuma Y, Capranzano P *et al.* Drug-eluting stent for left main coronary artery disease. The DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv* 2012;5:718–27.
- [22] Hosmer DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. New York: John Wiley and Sons, Inc., 2013.
- [23] Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ *et al.* Discrimination and calibration of clinical prediction models: users' guides to the medical literature. *JAMA* 2017;318:1377–84.
- [24] Modolo R, Chichareon P, Kogame N, Dressler O, Crowley A, Ben-Yehuda O *et al.* Contemporary outcomes following coronary artery bypass graft surgery for left main disease. *J Am Coll Cardiol* 2019;73:1877–86.
- [25] Hannan EL, Racz MJ, Gold J, Cozzens K, Stamato NJ, Powell T *et al.* Adherence of catheterization laboratory cardiologists to American College of Cardiology/American Heart Association guidelines for percutaneous coronary interventions and coronary artery bypass graft surgery: what happens in actual practice? *Circulation* 2010;121:267–75.
- [26] Stanetic BM, Ostojic M, Campos CM, Marinkovic J, Farooq V, Kovacevic-Preradovic T *et al.* Appropriateness of myocardial revascularization assessed by the SYNTAX score II in a country without cardiac surgery facilities; PROUST study. *Int J Cardiol* 2017;227:478–84.
- [27] Campos CM, Stanetic BM, Farooq V, Walsh S, Ishibashi Y, Onuma Y *et al.* Risk stratification in 3-vessel coronary artery disease: applying the SYNTAX score II in the Heart Team Discussion of the SYNTAX II trial. *Catheter Cardiovasc Interv* 2015;86:E229–38.