Validation of the updated logistic clinical SYNTAX score for all-cause mortality in the GLOBAL LEADERS trial

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KEYWORDS

- drug-eluting stent
- miscellaneous
- risk stratification

Abstract

Aims: The aim of this study was the external validation of the updated logistic clinical SYNTAX score for two-year all-cause mortality after PCI in the GLOBAL LEADERS trial.

Methods and results: The GLOBAL LEADERS trial was an investigator-initiated, prospective randomised, multicentre, open-label trial comparing two strategies of antiplatelet therapy in 15,991 patients undergoing PCI. As a predefined analysis, we studied the first 4,006 consecutive patients enrolled between July 2013 and April 2014 for whom the anatomic SYNTAX scores were calculated by an independent core lab. The updated logistic clinical SYNTAX score was available in 3,271 patients. Patients were divided into quintiles according to the score. The C-statistic of the updated logistic clinical SYNTAX score for two-year all-cause mortality was 0.71 (95% confidence interval [CI]: 0.64-0.77). The updated logistic clinical SYNTAX score identified patients at very high risk for two-year all-cause mortality after PCI. Although it systematically overestimated two-year all-cause mortality, predicted and observed two-year all-cause mortality in the majority of the patients (four out of five quintiles) were in agreement.

Conclusions: Overall discrimination for two-year all-cause mortality of the updated logistic clinical SYNTAX score is either borderline acceptable or possibly helpful. Calibration in the majority of patients is appropriate. The score is potentially useful in selecting enriched high-risk populations.

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Abbreviations

ACS	acute coronary syndrome
BARC	Bleeding Academic Research Consortium
BMS	bare metal stents
CABG	coronary artery bypass grafting
CrCl	creatinine clearance
DES	drug-eluting stents
LCSS	logistic clinical SYNTAX score
LVEF	left ventricular ejection fraction
NACE	net adverse clinical events
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
POCE	patient-oriented composite endpoints
PVD	peripheral vascular disease
STEMI	ST-segment elevation myocardial infarction

Introduction

The logistic clinical SYNTAX score (LCSS) was developed and internally validated in a pooled database from seven stent trials with more than 6,000 patients[1]. By combining age, creatinine clearance (CrCl), left ventricular ejection fraction (LVEF) and anatomic SYNTAX score in a core model, the LCSS predicted one-year all-cause mortality after percutaneous coronary intervention (PCI). An extended model was developed by including six variables in the core model. The LCSS has been revised and updated to predict all-cause mortality at one and two years[2].

To date, no external validation in an all-comers population has been performed. Only two studies evaluating its performance are limited to patients with acute coronary syndrome (ACS) or left main lesions[3,4]. Notably, with the improvement in PCI outcomes over time, it is uncertain whether the score is still up to date. Therefore, we aimed to validate the updated LCSS externally in the real-world population of a large contemporary PCI trial.

Methods

The GLOBAL LEADERS trial was a randomised, open-label trial comparing two strategies of antiplatelet therapy in all-comer patients undergoing PCI at 130 sites in 18 countries (NCT01813435). The design of the trial has been described previously[5] and is summarised in **Supplementary Appendix 1**.

This present analysis was pre-specified in the protocol and aimed at predicting two-year all-cause mortality in the first 4,006 consecutive patients with an available anatomic SYNTAX score in the early phase of the trial to verify the correctness of the assumed two-year all-cause mortality - a major component of the primary composite endpoint. The anatomic SYNTAX score was analysed off-line by an independent core lab (Cardialysis, Rotterdam, the Netherlands) blinded to the treatment allocation[6]. Patients with prior coronary artery bypass grafting (CABG) were excluded from this analysis as they were not included in the developmental cohort of the LCSS. In cases of ST-segment elevation myocardial infarction (STEMI), the anatomic SYNTAX score was calculated using the angiogram performed prior to wiring, as described previously[7].

The GLOBAL LEADERS trial was approved by the institutional review board at each participating institution. All patients provided informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practice.

UPDATED LOGISTIC CLINICAL SYNTAX SCORE

The updated LCSS and the predicted two-year all-cause mortality were calculated using the method described previously by our group[2]. The updated LCSS combined the prognostic value of the anatomic SYNTAX score with clinical characteristics and comorbidities including age, CrCl, LVEF, body mass index, diabetes, peripheral vascular disease (PVD) and SYNTAX-like characteristics to predict two-year all-cause mortality after PCI. Patients with missing variables required to calculate the score were excluded. Details and definitions of the variables used in this study are shown in **Supplementary Table 1**.

OBJECTIVE AND STUDY ENDPOINTS

The primary objective was to evaluate the predictive performance of the updated LCSS for two-year all-cause mortality. The primary endpoint was all-cause mortality. Definitions of other outcomes reported in this study are shown in **Supplementary Appendix 2**.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation (SD) or median and interquartile range (IQR) according to the distribution, while categorical variables are expressed as counts and percentages. Baseline characteristics of the patients in the present study were compared with the population in the developmental cohort of the updated LCSS. Independent t-tests or Mann-Whitney U tests were used to compare continuous variables and chi-square tests were used to compare categorical variables.

Baseline characteristics and outcomes are reported for each quintile of the patients categorised according to the updated LCSS. Testing for linear trend between quintiles was performed by the Cochran-Armitage test for categorical variables and the generalised linear model with updated LCSS class as a co-variable for continuous variables. The Kaplan-Meier method was used to estimate the cumulative rates of clinical events in the quintiles and the log-rank test was performed to examine the differences between quintiles.

The area under the receiver-operating characteristic curve, which equals the C-statistic when the outcome is binary, was calculated for all-cause mortality and other outcomes. In general, the discrimination is considered outstanding if the C-statistic is ≥0.9, excellent if the C-statistic is ≥0.8 and <0.9, acceptable if the C-statistic is ≥0.7 and <0.8, poor if the C-statistic is >0.5 and <0.7, and no discrimination if the C-statistic=0.5[8]. A more recent approach refers to a C-statistic <0.60 as poor discrimination, 0.60 to 0.75 as possibly helpful discrimination, and more than 0.75 as clearly useful discrimination[9].

Agreement between observed and expected (predicted) all-cause mortality was assessed by calibration plot. Quintiles of the patients were depicted in the calibration plot augmented by

a locally weighted scatterplot smoothing over the logical range of predicted probability[10]. Calibration-in-the-large (model intercept) and calibration slope were evaluated by fitting the calculated linear predictor in all patients with all-cause mortality as the outcome in the logistic regression model. Intercept of 0 and slope of 1 indicate perfect prediction[10]. Negative and positive intercepts indicate overestimation and underestimation, respectively.

The Brier score was reported as an overall measure of performance. A Brier score of 0 reflects a perfect model whereas a score of 0.25 suggests a non-informative model[10]. The predictive performance was evaluated in the overall population, high or non-high-risk patients according to the anatomic SYNTAX score (>22 or ≤22), and in patients with clinical and angiographic characteristics meeting the inclusion criteria of the TWILIGHT study (NCT02270242) **(Supplementary Table 2)**. Statistical analyses were performed in R, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

PATIENTS AND BASELINE CHARACTERISTICS

In the first 4,006 consecutive patients, six patients withdrew consent and requested data deletion from the database, 32 patients did not receive PCI, and 275 patients had previous CABG, leaving 3,693 coronary angiograms to be forwarded to the core lab for evaluation of the anatomic SYNTAX score. From these, the anatomic SYNTAX score could be calculated in 3,473 cases; in the remaining 220 patients, the non-target vessel was not documented. After excluding 202 patients with incomplete clinical information, the updated LCSS was available in 3,271 patients with a mean age of 64.3 years (SD 10.5), mean anatomic SYNTAX score of 12.0 (SD 8.3), median CrCl of 88.8 ml/min with an interquartile range of 70.2 to 112.2 ml/min, mean LVEF of 54.8% (SD 10.7), and mean body mass index of 28.1 kg/m^2 (SD 4.5). The prevalence of diabetes, established PVD and SYNTAX-like population was 22.9%, 6.1%, 22.2%, respectively. These variables were used for the updated LCSS calculation.

In comparison with the developmental cohort, age and frequency of female gender, diabetes, hypertension, and hypercholesterolaemia were similar, whereas the frequency of previous stroke, previous MI, established PVD and current smoking was lower in the present study **(Table 1)**. CrCl was higher while the LVEF and anatomic SYNTAX score were lower in the present study. There were higher rates of patients with STEMI and unstable angina, and lower rates of patients with stable angina and NSTEMI in the developmental cohort than in the population in the present study. Baseline clinical characteristics according to updated LCSS quintiles are shown in **Supplementary Table 3**.

Table 1. Baseline characteristics of patients in the present study and developmental cohort.

Baseline characteristics	Present study (N=3,271)	Developmental cohort (N=6,321)	*p*-value
Age, years (mean±SD)	64.3±10.5	63.8±10.8	0.0513
CrCl, ml/min (median, IQR)	88.8 (70.2-112.2)	86.4 (67.1-109.3)	<0.0001
LVEF, % (mean±SD)	54.8±10.7	56.3±12.1	<0.0001
Anatomic SYNTAX score (mean±SD)	12.0±8.3	17.0±11.0	<0.0001
Female	23.6 (772)	24.7 (1,564)	0.2264
Body mass index, kg/m^2 (mean±SD)	28.1±4.5	27.7±4.4	<0.0001
Diabetes mellitus	22.9 (748)	23.2 (1,460)	0.7091
Hypertension	69.7 (2,276)	69.4 (4,349)	0.7944
Hypercholesterolaemia	66.9 (2,128)	65.2 (4,073)	0.1075
Previous stroke	2.3 (76)	4.9 (182)	<0.0001
Previous MI	20.9 (683)	30.7 (1,752)	<0.0001
Previous PCI	28.6 (935)	21.4 (1,237)	<0.0001
Established PVD	6.1 (201)	7.5 (288)	0.0306
Known COPD	5.6 (183)	NA	NA
History of previous bleeding	0.6 (19)	NA	NA
Currently smoking	27.9 (913)	31.5 (1,706)	0.0004
Cardiac arrest at presentation	0.5 (17)	NA	NA
Clinical presentation			
Stable angina	47.0 (1,536)	41.3 (2,368)	<0.0001
Unstable angina	12.0 (394)	22.1 (1,268)	
NSTEMI	25.3 (827)	14.3 (819)	
STEMI	15.7 (514)	22.2 (1,274)	
SYNTAX-like patient	22.2 (725)	NA	NA

Values shown are % (n) unless otherwise indicated.

DISCRIMINATION AND CALIBRATION

The C-statistic of the updated LCSS for two-year all-cause mortality after PCI was 0.71 (95% confidence interval [CI]: 0.64-0.77). Discriminative ability is poor or non-existent for other outcomes **(Supplementary Table 4)**.

The updated LCSS systematically overestimates two-year all-cause mortality as demonstrated by the negative intercept **(Figure 1)**. The calibration slopes indicate a weaker association between predicted and observed two-year all-cause mortality in the validation cohort compared with the developmental population. In the first to fourth quintile, predicted probabilities of two-year all-cause mortality (ranging from 1 to 4%) are close to the line of identity for the agreement between predicted and observed two-year all-cause mortality. The Brier score of the updated LCSS for two-year all-cause mortality is 0.0247.

The C-statistic of the updated LCSS for two-year all-cause mortality in the high-risk population according to anatomic SYNTAX score or TWILIGHT's inclusion criteria is higher than the non-high-risk population, whereas the Brier score is lower (and thus better) in the non-high-risk than in the high-risk population **(Figure 2)**.

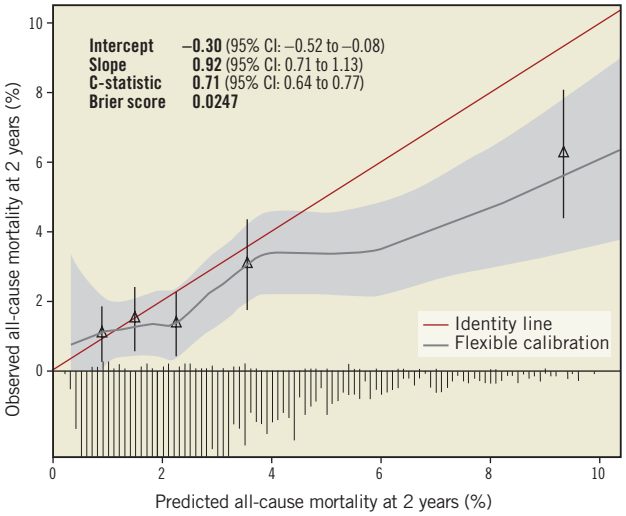


Figure 1. *Calibration plot for the updated logistic clinical SYNTAX score for all-cause mortality at two years after PCI. Triangles represent five quintiles of patients with mean predicted probability and mean observed all-cause mortality with 95% confidence interval. The distribution of the predicted probabilities is displayed in the histogram.*

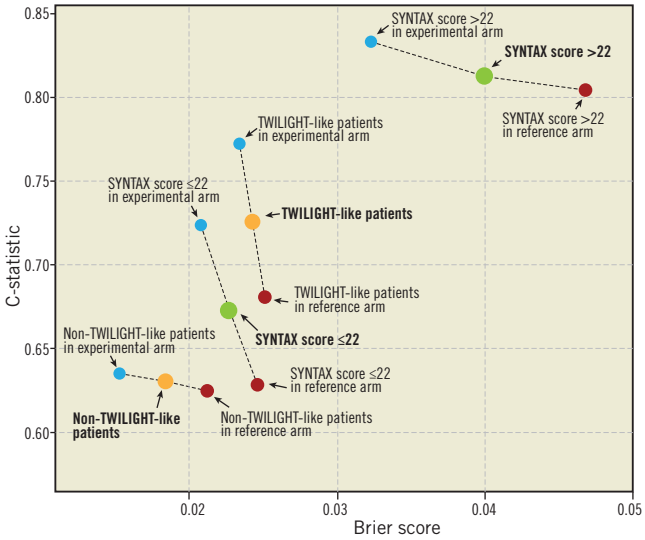


Figure 2. *C-statistic and Brier score of the updated logistic clinical SYNTAX score in high-risk patients versus non-high-risk patients according to the treatment strategy.*

OUTCOMES ACCORDING TO QUINTILES AT TWO YEARS

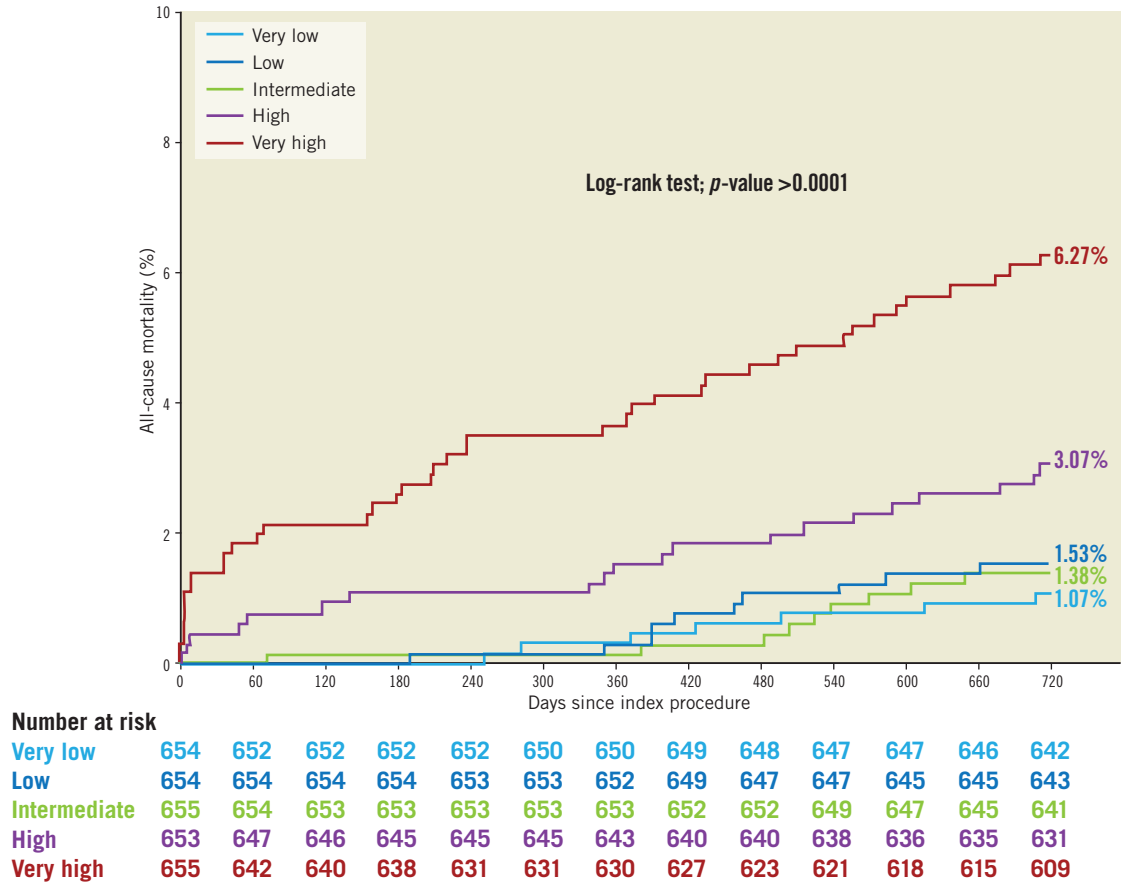
All-cause mortality at two years was 2.66% (87 patients). The updated LCSS discriminates all-cause mortality, net adverse clinical events (NACE) and patient-oriented composite endpoints (POCE) in the very high quintiles at two years **(Figure 3, Supplementary Figure 1)**. However, the cumulative curves of survival, NACE and POCE among the very low, low, intermediate and high score quintiles are almost superimposed and not discriminated. **Table 2** shows other outcomes at two years in each quintile.

Discussion

The main findings are as follows. 1) The overall discriminative ability of the updated LCSS for two-year all-cause mortality is either borderline acceptable according to the general cut-off proposed by Hosmer et al[8], or possibly helpful according to the recent

Table 2. Clinical outcomes at 2 years after index PCI according to updated logistic clinical SYNTAX quintiles.

Updated logistic clinical SYNTAX score	Updated logistic clinical SYNTAX score quintiles					
	Very low (–2.29146 to –0.93821) (N=654)	Low (–0.93706 to –0.51604) (N=654)	Intermediate (–0.51549 to –0.08958) (N=655)	High (–0.08894 to 0.44314) (N=653)	Very high (0.44351 to 3.90466) (N=655)	*p*-value
Observed all-cause death, % (n)	1.07 (7)	1.53 (10)	1.38 (9)	3.07 (20)	6.27 (41)	<0.0001
Observed all-cause death in experimental arm, % (n)	0.91 (3)	1.23 (4)	0.31 (1)	3.21 (11)	5.94 (19)	<0.0001
Observed all-cause death in reference arm, % (n)	1.24 (4)	1.82 (6)	2.40 (8)	2.91 (9)	6.58 (22)	0.0004
Expected all-cause death, %						
Mean, %	0.88	1.49	2.24	3.54	9.33	NA
Observed/expected mortality ratio	1.22	1.03	0.62	0.87	0.67	NA
Any stroke, % (n)	0.93 (6)	0.62 (4)	0.93 (6)	0.94 (6)	2.36 (15)	0.0289
Any myocardial infarction, % (n)	2.94 (19)	2.94 (19)	3.24 (21)	3.44 (22)	4.87 (31)	0.2906
Any repeat revascularisation, % (n)	8.70 (56)	9.45 (61)	9.74 (63)	10.07 (64)	12.05 (76)	0.3481
Definite or probable stent thrombosis, % (n)	0.77 (5)	0.46 (3)	1.23 (8)	1.40 (9)	1.25 (8)	0.4179
Bleeding Academic Research Consortium type 3 or 5, % (n)	0.93 (6)	1.39 (9)	2.62 (17)	2.50 (16)	5.16 (33)	<0.0001
Patient-oriented composite endpoints, % (n)	10.99 (71)	12.35 (80)	12.17 (79)	14.15 (91)	20.18 (131)	<0.0001
Net adverse clinical events, % (n)	11.89 (77)	13.12 (85)	14.02 (91)	15.40 (99)	23.56 (153)	<0.0001



Number at risk

Very low	654	652	652	652	652	650	650	649	648	647	647	646	642
Low	654	654	654	654	653	653	652	649	647	647	645	645	643
Intermediate	655	654	653	653	653	653	653	652	652	649	647	645	641
High	653	647	646	645	645	645	643	640	640	638	636	635	631
Very high	655	642	640	638	631	631	630	627	623	621	618	615	609

Figure 3. *Kaplan-Meier curves for all-cause mortality at two years according to the updated logistic clinical SYNTAX score quintiles.*

approach by Alba et al[9]: by stratifying patients using quintiles, the score can identify patients at very high risk for two-year all-cause mortality after PCI. 2) Although the score systematically overestimated two-year all-cause mortality in the GLOBAL LEADERS population, calibration in the first four quintiles of the patients, who had a predicted two-year all-cause mortality ranging from 1 to 4% in four of the five quintiles, is appropriate and close to the identity line between the observed and predicted all-cause mortality.

Two issues may be responsible for the findings. First, the outcomes after PCI in the GLOBAL LEADERS trial were different from the developmental cohort of the LCSS.

The updated LCSS was developed from patient-level data from seven coronary stent trials (SIRTAX, ARTS-II, STRATEGY, MULTISTRATEGY, LEADERS, SYNTAX, RESOLUTE all-comers)[2] which had a pooled two-year all-cause mortality of 4.6%, which is higher than the overall two-year all-cause mortality (2.99%) seen in the GLOBAL LEADERS trial[5]. Contemporary improvements in PCI techniques and post-procedural medications may have led to this reduced mortality. Optimal pharmacological treatment following PCI, such as using potent antiplatelet therapy (ticagrelor) and guideline-directed medical therapy (high-intensity statin and risk factor control), have been shown to reduce mortality[11,12]. In the developmental cohort, clopidogrel was the main $P2Y_{12}$ inhibitor used in dual antiplatelet therapy after PCI, whereas in the GLOBAL LEADERS trial the majority of patients received ticagrelor either as monotherapy or as part of standard dual antiplatelet therapy. In the GLOBAL LEADERS trial, more than 90% of patients received statin on discharge and statin usage remained as high as 90% at two years, while in the SYNTAX trial 81% and 78% of patients received statin therapy at discharge and at one year, respectively[13]. The developmental cohort was recruited before 2008 when new-generation drug-eluting stents (DES), fractional flow reserve and image-guided PCI were not yet recommended in the guidelines or universally reimbursed. In the developmental cohort, the majority of populations were still treated with bare metal stents (BMS) or first-generation DES, and the same biolimus A9-eluting stent was only used in one of the seven trials. Second-generation DES have been shown to reduce adverse events after PCI when compared with BMS or first-generation DES[14]. However, it may be argued that compared with BMS they have not demonstrated a mortality benefit.

Second, there were differences in the clinical characteristics and comorbidities of the patients enrolled in the developmental cohort and the present study: the prevalence of poor prognostic features

such as prior stroke, previous MI, and a clinical presentation of STEMI was higher in the developmental cohort. Although these features were not included in the updated LCSS, they have been associated with poor outcomes including mortality after PCI[15,16]. The mean anatomic SYNTAX score in the present study was comparable to other all-comer PCI trials **(Supplementary Table 5)**; however, it was lower than the mean anatomic SYNTAX score in the developmental cohort.

IMPACT OF THE UPDATED LOGISTIC CLINICAL SYNTAX SCORE IN CURRENT PRACTICE

Unbiased, evidence-based and reliable information is mandatory for the informed consent before PCI[17]. Precision medicine is growing and will reach the patient community. The updated LCSS is a quantified instrument which serves this purpose well by providing the objective risk of the individual patient undergoing PCI.

In clinical practice, the patients undergoing PCI vary from a young adult with a single lesion to an elderly patient with poor renal function, low LVEF, multiple comorbidities and complex lesions. The mortality risk in these patients can range from very low to extremely high. Patients at very high risk need more intensive pharmacological therapy and aggressive risk factor modification than patients at lower risk. The updated LCSS can objectively stratify the risk and consequently optimal care should be delivered to these patients.

A dedicated impact study to evaluate the effect of the LCSS in guiding tailor-made care in patients undergoing PCI could fill this evidence gap.

POTENTIAL TRIAL IMPACT OF A RISK MODEL IN A LARGE ONGOING TRIAL

In our study, the patients in the highest updated LCSS quintile had many high-risk clinical features and comorbidities such as advanced age, female gender, established PVD, diabetes, chronic kidney disease, left main and multivessel coronary artery disease which correspond roughly to the inclusion criteria of the TWILIGHT study. In the very high-risk quintile, the two-year all-cause mortality was 6.27% with a POCE and NACE rate of 20.18% and 23.56%, respectively. By selecting clinical variables and anatomic SYNTAX score in the highest risk quintile of the updated LCSS, those patients at highest risk can be identified to provide an enriched population where the benefits of novel therapies or strategies could be more easily demonstrated in a clinical trial. Of note, in the present study, we did not see any differences between the experimental and reference treatment arms in terms of all-cause mortality, POCE and NACE.

The updated LCSS derived from baseline characteristics obtained at enrolment from the first quarter of patients enrolled consecutively in the trial provided the initial estimated overall mortality of the GLOBAL LEADERS population. The sample size of the trial was derived from the composite rate of all-cause mortality and new Q-wave MI of 5% at two years in the LEADERS study[5]. The overall two-year all-cause mortality in the LEADERS study was 4.86%. Since the observed two-year all-cause mortality among the 3,271 patients enrolled in the present study was 2.66% **(Figure 4)**, the GLOBAL LEADERS trial was at risk of being statistically underpowered. If the two-year mortality had been evaluated after enrolment of one fourth of the cohort using the updated LCSS, the anticipated two-year all-cause mortality would have been 3.50%, which would have been an incentive for recalculating the sample size or prolonging follow-up until the appropriate expected event rate was reached, thereby lessening the risk of an underpowered trial. In addition, other strategies such as extending the follow-up period until achievement of the desired event rate or even modifying the primary endpoints as in the ISCHEMIA study (NCT01471522) might have been considered. In the GLOBAL LEADERS trial, the steering committee was nevertheless reassured by the somewhat high incidence of new Q-wave MI that compensated for the lower than predicted all-cause mortality.

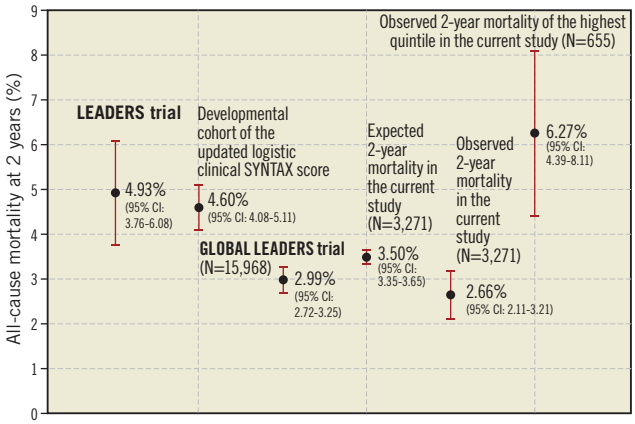


Figure 4. *All-cause mortality at two years among the population in the LEADERS trial, developmental cohort of the updated logistic clinical SYNTAX score and the present study.*

Limitations

Our analysis was performed in the first 3,271 consecutive patients out of 15,991 patients in the GLOBAL LEADERS trial. However, the consecutiveness of the enrolled patients with anatomic SYNTAX score calculation performed by an independent core lab blinded to the outcomes should have avoided serious selection bias in this population.

Differences in clinical characteristics between the first quarter of the study population and the last three quarters led to consideration of an adjustment. However, we restrained ourselves from performing this because, in a study with sequential cohorts, time is the main confounding factor that cannot be intrinsically and properly adjusted.

The effect of the antiplatelet strategies was not taken into account given that in the present cohort there was no statistical difference in all-cause mortality at two years between patients in

the experimental and reference treatment arms (experimental vs reference; 2.3% vs 3.0%, p-value 0.23).

Conclusions

The overall discriminative ability of the updated LCSS for two-year all-cause mortality is either borderline acceptable or possibly helpful. The score can identify patients at very high risk of two-year all-cause mortality after PCI. Calibration in the majority of patients is appropriate. The score is potentially useful in selecting enriched high-risk populations.

Impact on daily practice

The overall discriminative ability of the updated logistic clinical SYNTAX score for long-term mortality in an all-comers PCI population is either borderline acceptable or possibly helpful. The predicted mortality for the majority of the patients was in relatively good agreement with the observed mortality. The score may help in tailored risk assessment of coronary artery disease patients undergoing PCI.

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Conflict of interest statement

P. Chichareon reports receiving a grant from Biosensors, outside the submitted work. Y. Onuma reports being a member of the advisory board of Abbott Vascular. R. Modolo has received research grants from Biosensors outside the submitted work and from the Sao Paulo Research Foundation (FAPESP – grant number 2017/22013-8). R.J. van Geuns reports receiving grants and personal fees from Abbott Vascular, and grants from Boston Scientific, outside the submitted work. J.J. Piek reports non-financial support from membership of the medical advisory board of Abbott Vascular, personal fees and non-financial support for being a consultant for Philips/Volcano, outside the submitted work. E. Spitzer reports institutional grants from the European Cardiovascular Research Institute, during the conduct of the study. P. Jüni serves as an unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company. C.W. Hamm serves on the advisory board of and reports speaker's fees from Medtronic. G. Steg reports grants and personal fees from Servier, during the conduct of the study, grants and personal fees from Bayer/Janssen, Merck, Sanofi, and Amarin, and personal fees from Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Pfizer, Novartis, Regeneron, Lilly, and AstraZeneca, outside the submitted work. P. Vranckx has received personal fees from AstraZeneca and The Medicines Company during the conduct of the study and personal fees from Bayer Health Care, Terumo, and Daiichi Sankyo outside the submitted work. M. Valgimigli has received personal fees from Abbott, AstraZeneca, Chiesi, Bayer, Daiichi Sankyo, Terumo, Alvi Medical, and Amgen, and grants from the Swiss National Foundation, Terumo, Medicure, Abbott, and AstraZeneca, outside the submitted work. S. Windecker's institution has research contracts with Abbott, Amgen, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, St. Jude Medical, Symetis SA, and Terumo outside the submitted work. P.W. Serruys reports personal fees from Abbott Laboratories, Biosensors, Cardialysis, Medtronic, Micell Technologies, Sinomedical Sciences Technology, Stentys, Svelte Medical Systems, Philips/Volcano, Xeltis, StentIt, and HeartFlow outside the submitted work. The other authors have no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

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Supplementary data

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Supplementary data

Supplementary Appendix 1. Summary of the treatment strategies and endpoint in the GLOBAL LEADERS trial

In the experimental treatment strategy, patients received aspirin 75-100 mg once daily in combination with ticagrelor 90 mg twice daily for one month, followed by ticagrelor 90 mg twice daily alone for 23 months (irrespective of the clinical presentation). In the reference treatment strategy, patients received aspirin 75-100 mg daily in combination with either clopidogrel 75 mg once daily in patients with stable coronary artery disease or ticagrelor 90 mg twice daily in patients with ACS for one year, followed by aspirin 75-100 mg once daily alone for the following 12 months (from 12 to 24 months after PCI). Biolimus A9-eluting stents along with bivalirudin were used uniformly in the enrolled patients.

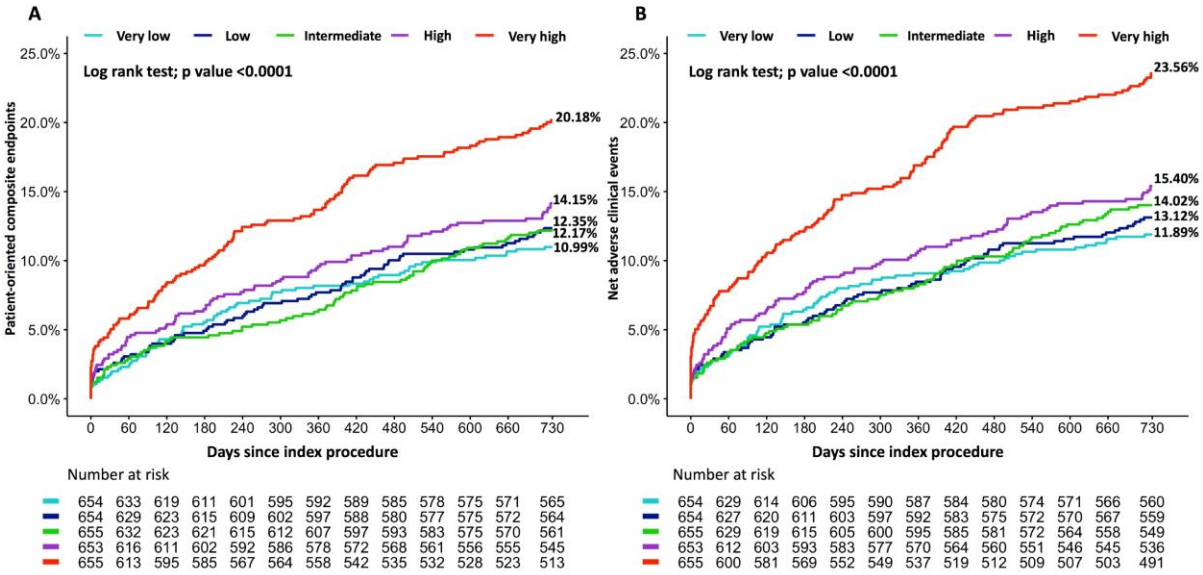
A total of 15,991 patients were enrolled between July 2013 and November 2015 into the GLOBAL LEADERS trial without restriction regarding clinical presentation, lesion complexity or the number of stents used – the "all comers" concept. The primary endpoint was the composite of all-cause mortality and new Q-wave myocardial infarction (MI) within two years. All-cause mortality is an indisputable event which requires no adjudication, whilst a new Q-wave MI was assessed by the independent core lab. The survival status of patients lost to follow-up, or those who withdrew consent was obtained through public civil registries such that more than 99.9% of the vital status at two years was available. Although there was no central adjudication for other outcomes, the completeness and consistency of the site-reported endpoints were checked by medical monitors.

Supplementary Appendix 2. Outcomes reported in the present study

Patient-oriented composite endpoints (POCE) included all-cause mortality, any stroke, any MI and any revascularisation.

Net adverse clinical events (NACE) included POCE plus Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding.

Each itemised component of the composite outcomes as well as definite or probable stent thrombosis according to the Academic Research Consortium definition.



Supplementary Figure 1. Kaplan-Meier curves for patient-oriented composite endpoints (A) and net adverse clinical events (B) at two years according to the updated logistic clinical SYNTAX score quintiles.

Supplementary Table 1. Definition of the variables used in the updated logistic clinical SYNTAX score calculation in the present study.

Variables	Definition
Creatinine clearance	The Cockcroft-Gault formula was used to derive the creatinine clearance. Serum creatinine used in the calculation was the value closest to the procedure since the trial included a substantial proportion of STEMI patients in whom the creatinine was not known at the time of the emergency procedure
Left ventricular ejection fraction	Pre-PCI LVEF value was primarily used for the updated logistic clinical SYNTAX score calculation whereas post-PCI LVEF value was used in case of missing information on pre-PCI LVEF
SYNTAX-like patient	SYNTAX-like patients were defined as the patients who met the inclusion criteria of the SYNTAX trial (left main disease in isolation or associated with one-, two- or three-vessel disease or three-vessel disease alone)
Peripheral vascular disease	Extracardiac arteriopathy with one or more of the following: 1) claudication, 2) carotid occlusion or >50% stenosis, 3) amputation for arterial disease, 4) previous or planned intervention on the abdominal aorta, limb arteries or carotids
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease (COPD) was defined as chronic lung disease with long-term use of bronchodilators or steroids for lung disease

Regression formula to calculate predicted risk of mortality at two years after PCI [2].

Log hazard (death) = 0.0187*SXscore + 0.0425*age + 0.0522*$(50\text{-LVEF})_+$ + 0.0174*$(90\text{-CrCl})_+$ + 0.1667*SYNTAX-like + 0.0312*BMI + 0.3463*Diabetes + 0.5700*PVD – 4.5210

Risk of 2-year death = 1 – exp [-0.0306*exp (log hazard [death])]

SXscore	= SYNTAX score
Age	= age (years)
LVEF	= left ventricular ejection fraction
CrCl	= creatinine clearance (ml/min)
SYNTAX-like	= three-vessel or left main disease (Yes=1/No= 0)
BMI	= body mass index (kg/m^2)
Diabetes	= diabetes, either not insulin-treated or insulin-treated
PVD	= peripheral vascular disease (Yes=1/No=0)
$(50\text{-LVEF})_+$	indicates 50-LVEF for positive values, 0 for negative values
$(90\text{-CrCl})_+$	indicates 90-CrCl for positive values, 0 for negative values

Supplementary Table 2. TWILIGHT study enrolment criteria and criteria of a TWILIGHT-like patient in the present study.

Inclusion criteria of TWILIGHT study	**Criteria of TWILIGHT-like patient in the present study**
Clinical criteria (must meet at least one)	**Clinical criteria (must meet at least one)**
Adult patients ≥65 years of age	Adult patients ≥65 years of age
Female gender	Female gender
Troponin positive acute coronary syndrome	Troponin positive acute coronary syndrome
Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularisation	Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularisation
Diabetes mellitus treated with medications (oral hypoglycaemic therapy or subcutaneous insulin)	Diabetes mellitus
Chronic kidney disease defined as an estimated glomerular filtration rate <60 ml/min/1.73 m² or creatinine clearance <60 ml/min	Chronic kidney disease defined as creatinine clearance <60 ml/min
Angiographic criteria (must meet at least one)	**Angiographic criteria (must meet at least one)**
Multivessel coronary artery disease	Multivessel coronary artery disease
Target lesion requiring total stent length >30 mm	Total stent length >30 mm
Thrombotic target lesion	
Bifurcation lesions with Medina X,1,1 classification requiring at least 2 stents	Bifurcation PCI requiring at least 2 stents
Left main (≥50%) or proximal LAD (≥70%) lesion	Left main (≥50%) or proximal LAD (≥70%) lesion
Calcified target lesion(s) requiring atherectomy	

For the present analysis, patients with prior stroke or patients with STEMI presentation were excluded as in the TWILIGHT study.

Supplementary Table 3. Baseline characteristics according to updated logistic clinical SYNTAX score quintiles.

Baseline characteristics according to updated logistic clinical SYNTAX score quintiles

Updated logistic clinical SYNTAX score	Very low (-2.29146 to -0.93821) (N=654)	Low (-0.93706 to -0.51604) (N=654)	Intermediate (-0.51549 to -0.08958) (N=655)	High (-0.08894 to 0.44314) (N=653)	Very high (0.44351 to 3.90466) (N=655)	*p*-value*
Age (years), mean±SD	51.40±5.93	59.89±5.65	65.01±6.43	70.08±6.84	75.05±7.61	<0.0001
CrCl (ml/min), median (IQR)	111.93 (96.62-132.74)	100.74 (86.25-122.66)	88.09 (76.35-107.99)	75.57 (64.71-94.08)	60.43 (47.39-74.08)	<0.0001
Left ventricular ejection fraction (%), mean±SD	57.85±7.70	56.97±8.50	55.71±9.39	54.62±10.05	48.67±14.05	<0.0001
Anatomic SYNTAX score, mean±SD	8.03±5.18	10.21±6.48	11.37±7.20	13.28±8.34	17.20±10.50	<0.0001
Female	13.76 (90)	18.35 (120)	23.05 (151)	27.26 (178)	35.57 (233)	<0.0001
BMI (kg/m^2), mean±SD	27.54±4.01	28.41±3.98	28.49±4.59	28.28±4.96	28.02±4.61	0.1308
Diabetes	3.06 (20)	13.61 (89)	25.19 (165)	30.17 (197)	42.29 (277)	<0.0001
Hypertension	50.77 (331)	66.16 (432)	71.45 (468)	78.99 (515)	80.92 (530)	<0.0001
Hypercholesterolaemia	62.32 (397)	66.35 (424)	71.41 (452)	69.07 (440)	65.15 (415)	0.1558
Previous stroke more than 30 days ago	0.31 (2)	1.68 (11)	2.29 (15)	3.68 (24)	3.66 (24)	<0.0001
Previous MI	18.04 (118)	17.48 (114)	20.46 (134)	20.98 (137)	27.48 (180)	<0.0001
Previous PCI	22.02 (144)	26.91 (176)	29.16 (191)	30.93 (202)	33.89 (222)	<0.0001
Established PVD	0.15 (1)	1.68 (11)	4.43 (29)	7.66 (50)	16.79 (110)	<0.0001
Known COPD	3.06 (20)	5.66 (37)	4.59 (30)	7.67 (50)	7.08 (46)	0.0004
History of major bleeding or previous predisposition to bleeding	0.46 (3)	0.61 (4)	0.31 (2)	0.46 (3)	1.07 (7)	0.2556
Currently smoking	49.08 (321)	34.10 (223)	23.51 (154)	18.07 (118)	14.81 (97)	<0.0001
Cardiac arrest at presentation	0.76 (5)	0.15 (1)	0.92 (6)	0.46 (3)	0.31 (2)	0.4911
Clinical presentation						
Stable angina	38.69 (253)	47.40 (310)	51.45 (337)	50.38 (329)	46.87 (307)	0.0017
Unstable angina	13.30 (87)	11.62 (76)	10.99 (72)	13.17 (86)	11.15 (73)	0.4913
Non-STEMI	28.75 (188)	26.15 (171)	23.36 (153)	22.51 (147)	25.65 (168)	0.0676
STEMI	19.27 (126)	14.83 (97)	14.20 (93)	13.94 (91)	16.34 (107)	0.1336
SYNTAX-like patient	9.48 (62)	14.83 (97)	18.93 (124)	25.42 (166)	42.14 (276)	<0.0001

Values shown are n (%) unless otherwise indicated.
*Testing for linear trend between quintiles was performed by the Cochran-Armitage test for categorical variables and generalised linear model with logistic clinical SYNTAX score class as a co-variable for continuous variables.
BMI: body mass index; COPD: chronic obstructive pulmonary disease; CrCl: creatinine clearance; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; STEMI: ST-segment elevation myocardial infarction

Supplementary Table 4. **Discriminative ability of the updated logistic clinical SYNTAX score for all-cause mortality and other outcomes at two years.**

Outcomes at 2 years	C-statistic (95% confidence interval)
All-cause death	0.71 (0.64-0.77)
Any stroke	0.62 (0.53-0.72)
Any myocardial infarction	0.56 (0.50-0.62)
Any repeat revascularisation	0.53 (0.50-0.56)
Bleeding Academic Research Consortium type 3 or 5	0.67 (0.61-0.73)
Definite or probable stent thrombosis	0.58 (0.48-0.68)
Patient-oriented composite endpoints	0.57 (0.54-0.60)
Net adverse clinical events	0.58 (0.56-0.61)

Supplementary Table 5. Mean anatomic SYNTAX score in various all-comer PCI trials.

Trial	Anatomic SYNTAX score (mean±SD)
Current study (N=3,271)	12.0±8.3
LEADERS trial (N=1,397)	13.5±8.7
RESOLUTE All Comers	
Zotarolimus-eluting stent (N=1,140)	14.8±9.3
Everolimus-eluting stent (N=1,152)	14.6±9.2
AIDA	
Scaffold group (N=924)	13.2±8.6
Stent group (N=921)	12.6±8.4
BIOSCIENCE (N=2,041)	14±11.4