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Impact of the CABG SYNTAX score on all-cause death at 10 years: a SYNTAX Extended Survival (SYNTAXES) substudy

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Introduction

The anatomical SYNTAX score (SS) has been considered an important tool in the quantitative assessment of the complexity of coronary artery disease (CAD) and in facilitating the risk stratification of patients undergoing revascularisation. However, the anatomical SS, obtained prior to revascularisation, has been shown not to be associated with short- and long-term clinical outcomes in patients who received coronary artery bypass grafting (CABG). These findings prompted the development of the CABG SS, assessing native residual stenotic lesions, taking into account the extent of revascularisation by bypass grafting, with the aim of helping to identify patients at higher risk of future adverse events. The primary report about the CABG SS, assessed at 15 months after surgical revascularisation in 115 patients enrolled in the SYNTAX-LE MANS substudy, demonstrated the feasibility (98.3%, n=113) and reproducibility of the score[1], and evaluated clinical outcomes up to five years.

The SYNTAX Extended Survival (SYNTAXES) trial has recently reported vital status up to 10 years in patients enrolled in the original SYNTAX trial[2]. The aim of this study is therefore to update our previous findings concerning the impact of the CABG SS on 10-year all-cause death in patients with previous CABG.

Methods

Details of the trial design of the SYNTAX trial and the pre-specified SYNTAX-LE MANS substudy have been reported previously[1] and are summarised in **Supplementary Appendix 1**. The methodology of the CABG SS has been reported previously[1] and is described briefly in **Figure 1** and **Supplementary Appendix 1**.

Results

Vital status at 10-year follow-up was complete in 110 (97.3%) patients. The median duration of follow-up was 11.3 years (interquartile range: 10.1-12.0) overall, 11.3 years (10.5-11.9) in the low CABG SS group, and 11.4 years (7.3-12.0) in the high CABG SS group. Baseline characteristics according to the CABG SS are summarised in **Supplementary Table 1**. Medication status is presented in **Supplementary Table 2**. Although clinical characteristics were comparable between the low and high CABG SS groups, the high CABG SS group had more complex CAD with a higher anatomical SS, resulting in a lower rate of complete revascularisation. A representative case of the CABG SS is shown in **Figure 1**.

The discriminative ability of the CABG SS for predicting all-cause death at 10 years and at maximum follow-up showed

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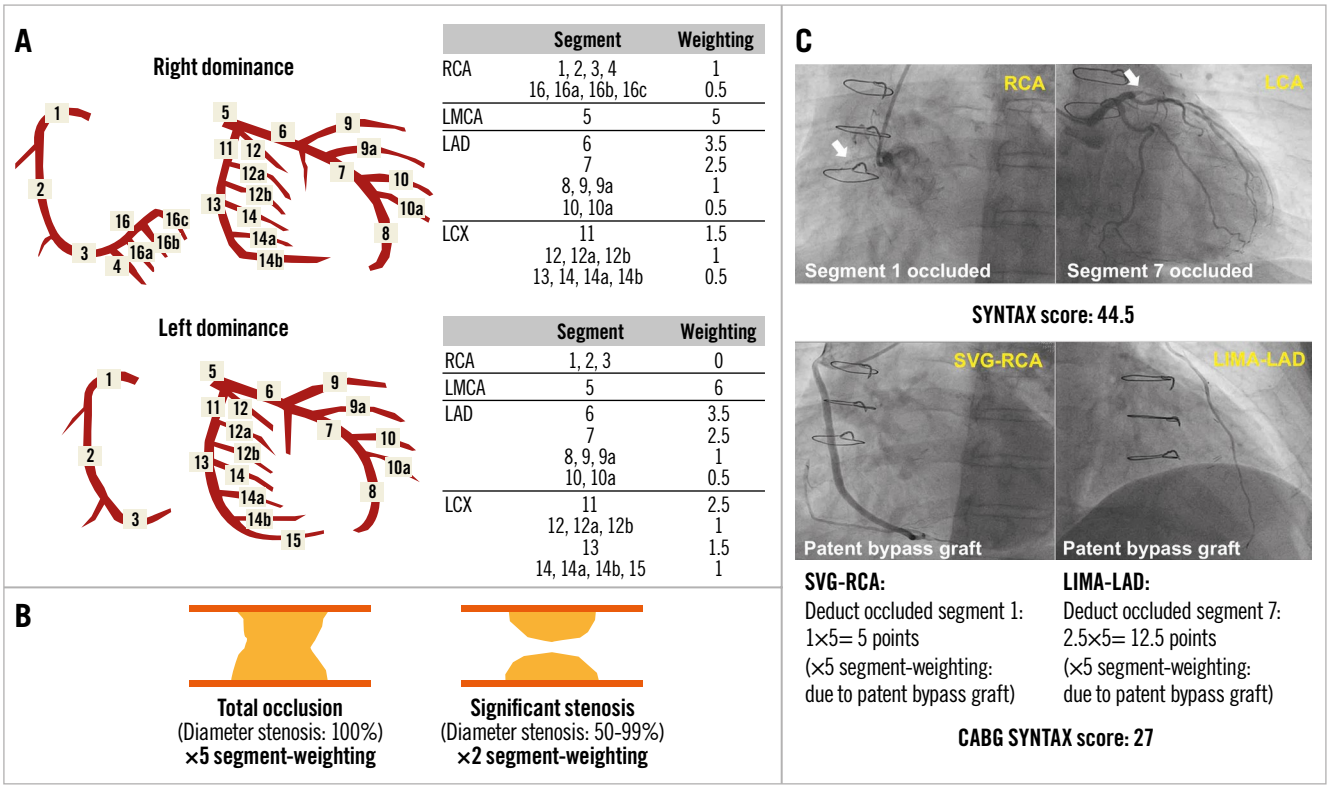

Figure 1. *A representative case of the CABG SS. Coronary segment-weighting derived from the Leaman score (A), and segment-weighting multiplication factors depending on the severity of the lesion (B). These were used to calculate points for deduction from the SS. C) The SS was 44.5 points (upper panel). A patent LIMA to LAD without obstructive disease (lower right panel) resulted in the deduction of 2.5×5 points (×5 segment-weighting due to occluded native coronary artery) from the SS. A patent SVG to RCA without obstructive disease (lower left panel) resulted in deduction of 1×5 points. Thus, the CABG SS was 44.5–(12.5+5)=27 points. An arrow indicates the occluded native coronary artery. CABG: coronary artery bypass grafting; LCA: left coronary artery; LIMA: left internal mammary artery; RCA: right coronary artery; SS: SYNTAX score; SVG: saphenous vein graft*

a c-statistic of 0.60 and 0.67, respectively **(Supplementary Table 3)**, which suggests a possibly helpful discrimination. Cumulative incidences of all-cause death according to the CABG SS are presented in **Figure 2**. A higher CABG SS was associated with an increased risk of all-cause death at 10 years (27.8% vs 14.0%; hazard ratio [HR] 2.24, 95% confidence interval [CI]: 0.95-5.30; log-rank p=0.058) and at maximum follow-up (40.6% vs 14.0%; HR 3.11, 95% CI: 1.38-7.02; log-rank p=0.004) **(Supplementary Table 4)**.

Discussion

The CABG SS has been proposed for objective quantification of the residual disease and level of revascularisation in patients with previous CABG and thereby to help identify patients at higher risk of future adverse events[1]. The present study demonstrated that the CABG SS was possibly helpful: it identified patients with a more than threefold increase in mortality among those with prior CABG.

To improve clinical outcomes in patients with previous CABG, optimal medical therapy (OMT) is of paramount importance to mitigate disease progression in both the native coronary artery and bypass graft, given that the use of OMT was achieved infrequently in patients who underwent CABG compared to those with PCI[3]. The CABG SS might potentially help to identify patients in whom a more aggressive risk factor control with OMT could maximise its benefit.

Despite these secondary prevention therapies after revascularisation, patients with previous CABG sometimes undergo repeat revascularisation in the long term due to late graft failure and atherosclerotic progression of native coronary arteries. For instance, saphenous vein grafts (SVGs) have been shown to be protective in the first seven years, while, beyond that time, mortality increases significantly as SVGs lose their patency in patients who have received CABG[4]. In such cases, they are usually referred for PCI because of concomitant comorbidities and re-operative risks. A recent retrospective study demonstrated the prognostic value of the CABG SS in patients with prior CABG[5]. Additionally, an incremental prognostic benefit of the post-PCI CABG SS over the sole CABG SS in patients with previous CABG who underwent PCI was observed as attested by net reclassification improvement of 0.306 for all-cause death at five years[5]. These findings suggest a prognostic utility of the CABG SS in patients with previous CABG in the long term.

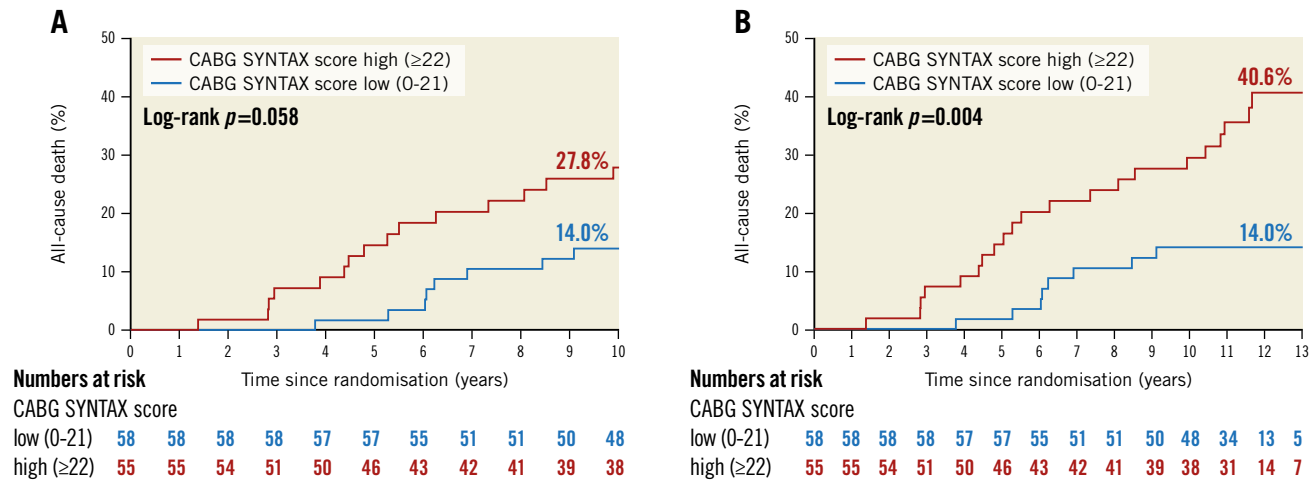

Figure 2. *All-cause death according to the CABG SYNTAX score subdivided into low and high score groups by the median. A) At 10 years. B) At maximum follow-up.*

Limitations

In addition to the *post hoc* nature of the present study, the pre-specified sample size was limited in this analysis. The SYNTAX-LE MANS substudy mandated a 15-month coronary angiogram by protocol, so that the CABG SS was calculated at 15 months after the surgical procedure. In addition, the score does not take into account the type of graft anastomosed and the characteristics of the graft disease. Thus, prospective, large-scale investigations are warranted to evaluate the value of the CABG SS in the long term.

Conclusion

The present study assessed 10-year all-cause death according to the CABG SS in patients with prior CABG, showing a numerically higher risk of all-cause death in the high versus low CABG SS groups.

Impact on daily practice

The anatomical SS, as assessed before the index revascularisation, has been shown not to have any prognostic impact in patients with CABG. In contrast, the CABG SS may aid in long-term risk stratification of patients at high risk of future adverse events.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Table 1. Baseline characteristics according to the CABG SYNTAX score.

Supplementary Table 2. Medication status at discharge and five years according to the CABG SYNTAX score.

Supplementary Table 3. Discriminative ability of the SYNTAX score and the CABG SYNTAX score.

Supplementary Table 4. Clinical outcomes according to the CABG SYNTAX score.

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Supplementary data

Supplementary Appendix 1. Methods

Study population

The overall trial design of the SYNTAX trial (NCT00114972) and the SYNTAX-LE MANS substudy have been reported previously. In brief, the SYNTAX-LE MANS study was a pre-specified substudy of the SYNTAX trial, enrolling patients with unprotected left main coronary artery disease (isolated or associated with one-, two- or three-vessel disease). These patients were prospectively assigned to undergo a 15-month coronary angiogram after the index revascularisation. The SYNTAX trial completed patient follow-up up to five years and has been reinitiated as the SYNTAXES study (NCT03417050) to evaluate vital status up to 10 years. Vital status was confirmed by electronic healthcare record review and national death registry checks [2]. The pre-specified primary endpoint was all-cause death at 10 years. The pre-specified secondary endpoint was all-cause death at maximum follow-up.

The CABG SS

The CABG SS is calculated by determining the baseline anatomical SS in the native coronary vessels and deducting points based on the importance of the diseased coronary artery segments (Leaman score) that have a functioning bypass graft anastomosed distally [1]. Points related to intrinsic coronary disease, such as bifurcation disease or calcification, remain unchanged **(Figure 1)**. In the present analysis, the CABG SS was calculated at 15 months after surgical revascularisation by a panel of three interventional cardiologists blinded to the result of the baseline anatomical SS analysed by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) [1].

Statistical analysis

Continuous variables are reported as mean±standard deviations (SD) or median and interquartile range (IQR) and are compared using Student's t-tests or the Mann-Whitney U test, depending on the distribution and the number of groups. Categorical variables are reported as percentages and numbers and are compared using the chi-square or Fisher's exact test as appropriate.

The predictive performance of the SS II is evaluated with the c-statistic. The cumulative incidence of all-cause death according to the CABG SS at 10 years or at maximum follow-up is estimated using the Kaplan-Meier method and compared using the log-rank test. The hazard ratio (HR) with 95% confidence interval (CI) is estimated in a Cox regression model. In addition, the five-year landmark analysis is performed to assess late outcomes according to the CABG SS. All tests are two-sided and a p-value of <0.05 is considered to be statistically significant. All analyses are performed using SPSS Statistics, Version 25 (IBM Corp., Armonk, NY, USA).

Supplementary Table 1. Baseline characteristics according to the CABG SYNTAX score.

	CABG SYNTAX score		
	High (n=55)	Low (n=58)	*p*-value
Age, years	66.6±10.1	63.2±9.5	0.066
Sex			0.695
Male	85.5 (47)	82.8 (48)	
Female	14.5 (8)	17.2 (10)	
Body mass index, kg/m^2	27±5.2	27.8±4.0	0.379
Medically treated diabetes	23.6 (13)	19.0 (11)	0.544
On insulin	9.1 (5)	10.3 (6)	0.822
Metabolic syndrome	26.0 (13)	42.9 (21)	0.077
Hypertension	56.4 (31)	60.3 (35)	0.668
Dyslipidaemia	74.1 (40)	74.1 (43)	0.994
Current smoking	14.8 (8)	27.6 (16)	0.100
Previous myocardial infarction	23.6 (13)	24.1 (14)	0.950
Previous cerebrovascular disease	9.3 (5)	12.1 (7)	0.631
Previous stroke	1.9 (1)	3.4 (2)	0.601
Previous transient ischaemic attack	1.9 (1)	5.2 (3)	0.344
Previous carotid artery disease	5.5 (3)	5.2 (3)	0.947
Peripheral vascular disease	7.3 (4)	8.6 (5)	0.791
Chronic obstructive pulmonary disease	7.3 (4)	8.6 (5)	0.791
Creatinine clearance (ml/min)	86.7±36.0	93.7±26.6	0.258
Left ventricular ejection fraction (%)	59.7±10.0	55.9±14.3	0.200
Congestive heart failure	5.5 (3)	7.0 (4)	0.733
Clinical presentation			0.564
Silent ischaemia	12.7 (7)	12.1 (7)	
Stable angina	52.7 (29)	62.1 (36)	
Unstable angina	34.5 (19)	25.9 (15)	
EuroSCORE	3.7±2.7	3.3±2.1	0.312
Parsonnet score	9.7±7.5	6.5±5.5	0.013
Number of lesions	4.6±1.7	2.9±1.8	<0.001
Anatomical SYNTAX score	38.1±10.7	25.2±12.4	<0.001
Anatomical SYNTAX score tercile			
Low (0-22)	9.1 (5)	50.0 (29)	<0.001
Intermediate (23-32)	18.2 (10)	20.7 (12)	0.736
High (≥33)	72.7 (40)	29.3 (17)	<0.001
CABG SYNTAX score	30.2±7.4	12.7±6.3	<0.001
Any total occlusion	23.6 (13)	5.2 (3)	0.005
1 total occlusion	20.0 (11)	3.4 (2)	
2 total occlusions	3.6 (2)	1.7 (1)	
Any bifurcation	85.5 (47)	60.3 (35)	0.003
Off-pump CABG	16.4 (9)	12.1 (7)	0.513
Use of LIMA	92.7 (51)	94.8 (55)	0.643

Total number of conduits	2.7±0.7	2.4±0.8	0.128
Number of arterial conduits	1.5±0.6	1.3±0.5	0.228
Number of venous conduits	1.2±0.9	1.1±0.9	0.654
Complete revascularisation *	50.9 (28)	79.3 (46)	0.002

Data are presented as mean±standard deviation or percentage (number).

* Complete revascularisation was defined by the protocol as the treatment of any lesion with more than 50% diameter stenosis in vessels ≥1.5 mm as estimated on the diagnostic angiogram during the local Heart Team conference. Outcomes were documented by the operator based on whether the intended equivalent anatomic revascularisation was achieved.

CABG: coronary artery bypass grafting; LIMA: left internal mammary artery

Supplementary Table 2. Medication status at discharge and five years according to the CABG SYNTAX score.

	CABG SYNTAX score		
	High (n=55)	Low (n=58)	*p*-value
At discharge			
Optimal medical therapy *	27.3 (15)	31.0 (18)	0.660
Any antiplatelet therapy	94.5 (52)	100.0 (58)	0.071
Aspirin	92.7 (51)	96.6 (56)	0.365
Thienopyridine	18.2 (10)	22.4 (13)	0.577
Statin	76.4 (42)	82.8 (48)	0.399
Beta-blocker	74.5 (41)	77.6 (45)	0.705
ACEI or ARB	49.1 (27)	51.7 (30)	0.780
ACEI	41.8 (23)	48.3 (28)	0.491
ARB	9.1 (5)	3.4 (2)	0.214
At 5 years			
Optimal medical therapy *	50.0 (27)	31.0 (18)	0.041
Any antiplatelet therapy	87.0 (47)	96.6 (56)	0.064
Aspirin	81.5 (44)	93.1 (54)	0.063
Thienopyridine	11.1 (6)	8.6 (5)	0.658
Statin	85.2 (46)	86.2 (50)	0.877
Beta-blocker	74.1 (40)	53.4 (31)	0.024
AECI or ARB	75.9 (41)	65.5 (38)	0.227
ACEI	59.3 (32)	50.0 (29)	0.326
ARB	16.7 (9)	15.5 (9)	0.869

Data are presented as mean±standard deviation or percentage (number).

* Optimal medical therapy was defined as the combination of at least one antiplatelet therapy, statin, β-blocker, and ACEI/ARB.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; OMT: optimal medical therapy

Supplementary Table 3. Discriminative ability of the SYNTAX score and the CABG SYNTAX score.

	c-statistic (95% CI)	*p*-value
At 10 years		
SYNTAX score	0.53 (0.41-0.65)	0.625
CABG SYNTAX score	0.60 (0.47-0.74)	0.125
At maximum follow-up		
SYNTAX score	0.60 (0.48-0.72)	0.112
CABG SYNTAX score	0.67 (0.56-0.79)	0.005

CABG: coronary artery bypass grafting; CI: confidence interval; HR: hazard ratio

Supplementary Table 4. Clinical outcomes according to the CABG SYNTAX score.

	CABG SYNTAX score			
	High (n=55)	Low (n=58)	HR (95% CI)	*p*-value
At 5 years	14.5 (8)	1.7 (1)	8.96 (1.12-71.67)	0.012
Between 5 and 10 years	15.6 (7)	12.5 (7)	1.25 (0.44-3.56)	0.678
At 10 years	27.8 (15)	14.0 (8)	2.24 (0.95-5.30)	0.058
Between 5 years and maximum follow-up	30.5 (13)	12.5 (7)	2.25 (0.90-5.65)	0.075
At maximum follow-up	40.6 (21)	14.0 (8)	3.11 (1.38-7.02)	0.004

Data are presented as percentage (number of deaths).

CABG: coronary artery bypass grafting; CI: confidence interval; HR: hazard ratio