Higher Syntax Score is not Predictive of Late Mortality in "Real-World" Patients with Multivessel Coronary Artery Disease Undergoing Coronary Artery Bypass Grafting

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ABSTRACT:
Background: The Syntax score (SS) is a helpful tool for determining the optimal revascularization strategy regarding coronary artery bypass surgery (CABG) vs. percutaneous coronary intervention (PCI) in patients with complex coronary disease. While an association between higher SS and mortality was found for PCI patients, no such association was found for CABG patients.

Objectives: To assess whether the SS predicts late mortality in patients undergoing CABG in a real-world setting.

Methods: The study included 406 consecutive patients referred for CABG over a 2 year period. Baseline and clinical characteristics were collected. Angiographic data SS were interpreted by an experienced angiographer. Patients were divided into three groups based on SS tertiles: low ≤ 21 (n=205), intermediate 22–31 (n=138), and high ≥ 32 (n=63). Five year mortality was derived from the National Mortality Database.

Results: Compared with low SS, patients with intermediate and high scores were significantly older ($P = 0.02$), had lower left ventricular ejection fraction (64% vs. 52% and 48%, $P < 0.001$) and greater incidence of acute coronary syndrome, left main disease, presence of chronic total occlusion of the left anterior descending and/or right coronary artery, and a higher EuroSCORE (5% vs. 5% and 8%, $P < 0.01$). Patients with intermediate and high SS had higher 5 year mortality rates (18.1% and 19%, respectively) compared to patients with low score (9.8%, $P = 0.04$). On multivariate analysis, SS was not an independent predictor of late mortality.

Conclusion: Patients with lower SS had lower mortality after CABG, which is attributable to lower baseline risk. SS is not independently predictive of late mortality in patients with multi-vessel coronary artery disease undergoing CABG.

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KEY WORDS: coronary artery disease (CAD), coronary artery bypass surgery (CABG), Syntax score (SS)

S everal randomized control studies and registries have previously shown that coronary artery bypass surgery (CABG) is the preferred mode of revascularization in patients with multi-vessel and/or left main coronary artery disease [1-4]. The most recent large randomized study, Synergy between percutaneous coronary intervention (PCI) with TAXUS and cardiac surgery (SYNTAX), also confirmed this observation even when percutaneous revascularization was performed using drug-eluting stents [5,6]. However, the SYNTAX trial was able to show that in patients with low anatomic risk for PCI, e.g., lowest tertile of Syntax score (SS) [5], PCI may be comparable to CABG in all aspects including target vessel revascularization. The SYNTAX study confirmed that the Syntax score is correlated with outcome only in patients undergoing PCI but failed to show the same correlation in patients undergoing CABG [5,6]. The SYNTAX trial selected patients who were suitable for both PCI and CABG according to the heart team and therefore may not represent "real-world" patients who are routinely referred to CABG. The SS represents the extent of coronary artery disease with respect to the complexity of PCI, e.g., lesion calcifications, chronic total occlusion (CTO), etc. However, a higher SS does represent a challenge to the cardiac surgeon aiming to achieve complete revascularization, such as CTO with ideal target for bypass or diffuse coronary disease. Therefore, in patients with multi-vessel disease who are not suitable for PCI and are referred to CABG, a higher SS may be an independent predictor of worse outcome due to incomplete revascularization and technical surgical challenges. The aim of the present study was to evaluate the prognostic value of the Syntax score in patients with left main and/or multi-vessel disease undergoing CABG in a "real-life" setting.

PATIENTS AND METHODS

The study included 406 consecutive patients who underwent angiography at the Sheba Heart Center catheterization laboratory and were referred for and underwent CABG during the 2 year period from January 2006 through December 2007 [7]. The study was approved by the institutional review board.

Clinical data regarding socio-demographic characteristics, clinical and co-morbid conditions, and left ventricular (LV) function as assessed by echocardiography during the month prior to surgery were collected from the hospital database.

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Angiographic data were interpreted off-line by a single experienced angiographer. Additional angiographic data included the number of diseased coronary arteries (defined as diameter stenosis ≥ 50%), and the complexity of coronary disease expressed as Syntax score, which was calculated using the online calculator (www.syntaxscore.org) [8-10]. Surgical data regarding number and type of bypass graft used and information regarding which vessels were bypassed were collected directly from the surgical reports. EuroSCORE, a measure of surgical risk, was calculated for each patient using the online calculator (www.euroscore.org). Patients were divided into three groups according to tertiles of Syntax scores as previously described [5-9].

The end-point of this study was 5 year all-cause mortality. Individual mortality data and time of death were derived from the Israeli national population registry of the Ministry of the Interior.

Continuous parameters were compared with Student's *t*-test, and discrete variables were compared using the chi-square test or the Fisher's exact test, as appropriate. The Kaplan-Meier method was used to calculate the survival function over time, and Hazard ratios (HR) from Cox regression analysis were used to analyze the effects of covariates (age, gender, creatinine, left ventricular ejection fraction, Syntax score) on survival. Analysis was performed separately for Syntax score tertiles and for Syntax score as a continuous variable. The log rank test was used to test the significance of difference between survival functions in the Cox regression. The critical value of $P < 0.05$ was used for statistical significance. All analyses were performed with IBM SPSS v20.0 (SPSS, Chicago, IL, USA).

RESULTS

Included in the study were 406 consecutive patients who underwent CABG at Sheba Medical Center during the years 2006–2007. Patients were classified according to the predefined Syntax score tertiles [5-10]. Baseline characteristics for patients according to their Syntax score are shown in Table 1. Patients with the highest Syntax score were older, suffered more from peripheral vascular disease, had significantly lower left ventricular ejection fraction (LVEF), and greater EuroSCORE. Other baseline characteristics were similar between the groups.

As shown in Figure 1, the crude, 5 year, all-cause mortality rate was lower in patients with the lowest Syntax score tertile (9.8% as compared to 18.1% and 19% in the intermediate and higher tertiles, respectively, $P = 0.04$). Figure 2 shows unadjusted Kaplan-Meier curves for 5 year mortality according to Syntax tertiles.

After multivariate analysis, independent predictors for all-cause 5 year mortality were age, preoperative systolic pulmonary artery pressure > 30 mmHg, postoperative rise in creatinine, and the presence of chronic obstructive pulmonary disease (COPD) [Table 2]. Intermediate and high Syntax scores, as well as Syntax score as a continuous variable were not

Table 1. Baseline characteristics according to the original SYNTAX score categories

	Syntax 0–22 (n=205)	Syntax 23–32 (n=138)	Syntax ≥ 33 (n=63)	P value
Age (mean ± SD)	64 ± 11	66 ± 11	69 ± 9	0.02
Male gender (%)	83	81	80	0.79
Diabetes mellitus (%)	36	34	35	0.52
Hypertension (%)	66	62	65	0.76
Dyslipidemia (%)	60	63	54	0.48
Creatinine (mean ± SD)	1.2	1.3	1.3	0.11
Peripheral vascular disease (%)	13	11	22	0.08
COPD (%)	3	8	10	0.09
Previous stroke (%)	4	9	6	0.27
Previous myocardial infarction (%)	32	32	32	0.34
Previous PCI (%)	29	20	17	0.08
Previous cardiac surgery (%)	1.5	1.4	0	0.75
Clinical setup Stable angina (%) Acute coronary syndrome (%)	36 64	35 65	19 81	0.04
Congestive heart failure (%)	5	11	8	0.16
Atrial fibrillation (%)	8	7	8	0.95
LVEF (mean ± SD)	55 ± 10	52 ± 12	48 ± 13	‹ 0.001
SPAP (mean ± SD)	33 ± 9.5	34 ± 10.4	38 ± 14.0	0.09
Mitral regurgitation › 1 (%)	8	10	16	0.14
IABP use (%)	5	5	6	0.90
Logistic EuroSCORE (%), median (IQR)	3.1 (1.5–5.8)	3.3 (1.8–7.2)	6.1 (2.4–10.5)	0.003

COPD = chronic obstructive pulmonary disease, PCI = percutaneous coronary intervention, LVEF = left ventricular ejection fraction, SPAP = systolic pulmonary arterial pressure, IABP = intra-aortic balloon pump, IQR = interquartile range

Figure 1. Five year crude all-cause mortality rates according to SYNTAX tertiles
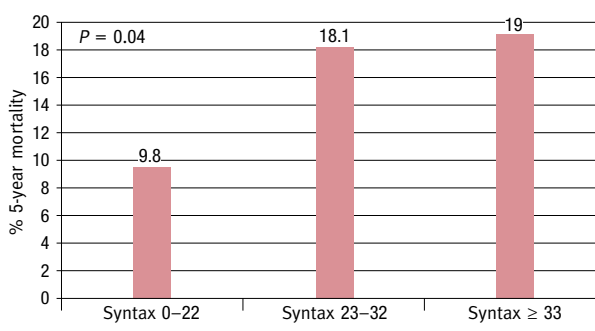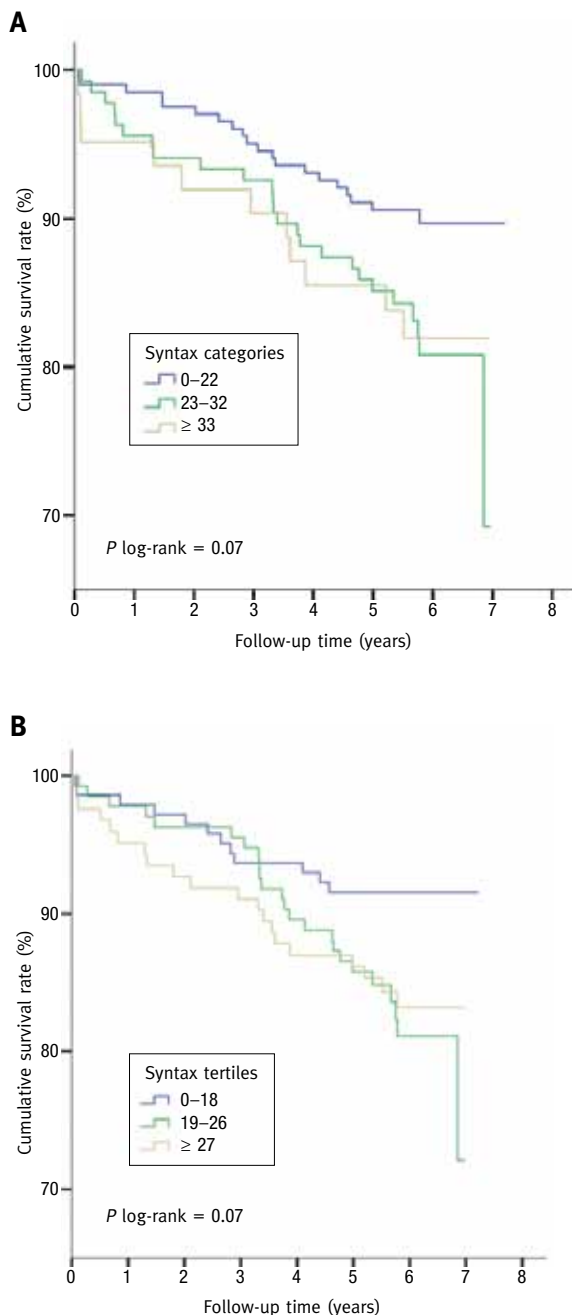

found to be independent predictors for long-term mortality in patients undergoing CABG.

DISCUSSION

The main finding of the present study was that in a real-life setting the Syntax score does not independently identify patients at high long-term risk after CABG. Although patients with

Figure 2. Unadjusted K-M curves for 5 year all-cause mortality. **[A]** According to original Syntax tertiles, **[B]** according to tertiles obtained from our study

A

B

Table 2. Multivariate independent predictor for 5 year all-cause mortality*

	Hazard ratio	95%CI	P value
Age (per 1 year increase)	1.08	1.05–1.12	‹ 0.001
Gender	0.98	0.50–1.91	0.95
Pulmonary hypertension › 30 mmHg	2.64	1.11–6.32	0.03
Post-operative creatinine (per 0.3 increase)	1.77	1.26–2.51	0.001
Chronic obstructive pulmonary disease	2.60	1.16–5.80	0.02
Syntax score 0–22 23–32 ≥ 33	 Reference 1.65 1.03	 0.86–3.17 0.45–2.36	 0.13 0.94

*The model was also adjusted to left ventricular ejection fraction, clinical presentation (acute coronary syndrome vs. stable angina), a history of previous percutaneous coronary intervention, and peripheral vascular disease (all non-significant)

The randomized SYNTAX study included a selection of patients with multi-vessel coronary disease who were suitable for both CABG and PCI. Although Syntax score was a powerful predictor of outcome in patients undergoing PCI, it was not found to be an independent predictor in the same manner in patients undergoing CABG [4,5]. This observation is feasible since the complexity of the treated lesion, as assessed by the Syntax score, is usually not relevant when grafting is performed distal to the diseased segment. A similar observation was shown by Lemesle et al. [11] who examined the role of the Syntax score among 320 patients undergoing CABG. In that study, patients were divided not according to the predefined score but to tertiles obtained from their analysis (< 24.5, 24.5–34, and < 34), and still no differences were observed in the 1 year composite end-point of death/myocardial infarction/stroke (9.4% vs. 7.5% vs. 10.4%, respectively) [11]. However, a different study in a subset of patients with left main disease undergoing CABG was able to show that the Syntax score was the best single discriminator between patients with and without major 1 year adverse events, with a discrimination level of 36.5 [12]. Our study is unique in several ways. First, we show the significance of the Syntax score on long-term (5 year) all-cause mortality; second, we used the predefined Syntax score tertiles; and third, the study included real-life, all-comer consecutive patients.

The Syntax score includes parameters that are mainly relevant to the complexity of PCI, namely, characteristics of chronic total occlusions, type of bifurcations, degree of calcifications, etc. [8,9]. If the distal target vessel for bypass anastomosis is free of disease, and of large caliber, these parameters are not necessarily relevant to the complexity of bypass surgery. Other parameters included in the Syntax score are relevant to CABG, such as the existence of diffuse disease and the number of affected vessels requiring more conduits, which require the use of vein grafts and are associated with a higher rate of graft failure. Therefore, a modified Syntax score may be needed for

higher Syntax score have increased crude long-term mortality rates, this is due to higher risk profile including higher age, higher logistic EuroSCORE, and lower LVEF, and is not correlated to the complexity of coronary lesions as manifested by the Syntax score.

patients who are candidates for bypass surgery, allocating more "points" to parameters such as visibility of target vessel, diffuse disease, and number of conduits needed.

Unlike the randomized trial, the SYNTAX registry included patients who can undergo CABG only, mainly due to complex coronary anatomy not suitable for PCI or chronic total occlusion untreatable with PCI. Mean Syntax score in this group was 37.8 with 56.4% of patients having chronic total occlusion [13]. Unlike the PCI registry, 3 year major adverse cardiac and cerebral events were similar between Syntax score tertiles (9%, 13.8%, and 18.3%, respectively).

It is speculated whether the Syntax score may be a surrogate for a generalized increased atherosclerotic burden. Ikeda and collaborators [14] examined the relationship between carotid intima-media thickness and plaque score with the severity of the Syntax score. Both mean intima-media thickness and plaque score correlated well with the Syntax score. The odds ratios associated with the mean intima-media thickness and the plaque score for the prediction of an intermediate or high Syntax score were 1.24 and 1.31, respectively. It is reasonable to take the Syntax score one step forward, and attempts to combine the Syntax score with other physiological or imagined measures have been described. A sub-analysis of the FAME study determined functional Syntax (FSS) score by only counting ischemia-producing lesions (fractional flow reserve < 0.8). FSS demonstrated a better predictive accuracy for major adverse cardiac and cerebral events compared with Syntax score only [15]. Furthermore, the combination of intra-coronary imaging by near-infrared spectroscopy and the Syntax score may help identify high risk plaques and estimate the risk of peri-procedural myocardial necrosis and future adverse events. In a small study that examined the combination of intra-coronary imaging (assessing lipid core burden index, LCBI) and the angiographic Syntax score, upon linear regression analysis LCBI was an independent predictor of the overall SS ($P = 0.004$). LCBI was significantly differently distributed across patients categorized by SS tertiles ($P = 0.009$); in particular, patients with the highest SS exhibited the highest LCBI as compared to patients with the lowest SS ($P = 0.001$) [16,17].

Our study has some limitations. First, the small number of patients in each Syntax score tertiles may not be powerful enough to assess for outcome. Second, our cohort includes real-life patients who would have been candidates for both the randomized SYNTAX study and the registries. Third, the decision to refer each patient for CABG was at the discretion of the operator or heart team, with no specific criteria or guidelines. However, since our study reflects common practice, the Syntax score might be useful as a tool for everyday practice when attempts are made to assess the long-term risk of patients with multi-vessel coronary disease.

In summary, in real-life patients undergoing CABG, the Syntax score does not independently predict long-term outcome. Intermediate and high Syntax scores do identify high risk patients with increased crude mortality rates. A dedicated CABG Syntax score, or combined score with physiological and imaging parameters, may be necessary to more accurately assess patients who are referred for bypass surgery.

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