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Coronary Atherosclerotic Burden Assessed by SYNTAX Scores and Outcomes in Surgical, Percutaneous, or Medical Strategies: a retrospective cohort study

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Running head: Coronary atherosclerotic burden and treatment strategies

Abstract

Objectives Coronary atherosclerotic burden and SYNTAX score (SS) are predictors of cardiovascular events. This study aimed to investigate the value of SYNTAX scores (SS, SSII and residual SS [rSS]) for predicting cardiovascular events in patients with multivessel coronary artery disease (CAD).

Design A retrospective cohort study.

Setting A single tertiary cardiology hospital in São Paulo, Brazil.

Paticipants A total of 1,719 patients with stable multivessel CAD and preserved left ventricular ejection fraction (LVEF) were included. Eligible patients were selected between January 2002, and December 2015 from the Medicine, Angioplasty or Surgery Study (MASS) database.

Intervention Patients with multivessel CAD who had undergone CABG, PCI, or MT.

Primary and secondary outcomes The primary endpoint was death from any cause at 5 years. Secondary outcomes included major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of all-cause death, myocardial infarction, stroke, and subsequent coronary revascularization.

Results A total of 1,719 patients, whose mean age was 60.74±8.78 years, underwent PCI (n = 573), CABG (n = 572), or MT (n = 574) alone. The SS was not considered an independent predictor of 5-year death and MACCE in the PCI, CABG and MT cohorts. The SSII (low, intermediate and high SSII, 3.6% vs. 7.9% vs. 10.5%, respectively, p <0.001) was associated with a higher risk of death in the overall population. Within each treatment strategy, SSII was associated with a significant incidence in death at 5 years, especially in CABG patients with intermediate and high SSII (p = 0.004) and in MT patients with high SSII (p = 0.031). SSII demonstrated a better predictive accuracy for death compared with SS and rSS.

Conclusions In patients with multivessel CAD, coronary atherosclerotic burden alone was not associated with significantly increased risk of death and MACCE. The SSII better discriminates the risk for death.

Strengths and limitations of this study

- This is the only study that concomitantly evaluated the three SYNTAX scores (SS, SSII and rSS) in patients with multivessel CAD undergoing one of three treatment strategies (CABG, PCI or MT).
- The data were collected in a single center, which may limit the external validation of the analysis. Nevertheless, the patients were treated homogeneously by a team of cardiologists experienced in the management of patients with CAD.
- This was a retrospective study, with the intrinsic biases associated with this type of study. However, predictors and outcome variables were collected prospectively.
- Revascularization strategies and standards of practice changed over time. The stent types used in the MASS database were either first- and second-generation DES or BMS. These changes occurred in all study patients, irrespective of the therapeutic group they were placed in at the initiation of the study.
- The sample size of our study is limited leading to issues of the reduced power to detect important differences.

INTRODUCTION

Historically, the number of diseased vessels as well as the location and extension of the coronary atherosclerotic lesions have been considered predictors of cardiovascular events in the short- and long-term [1] among patients with stable coronary artery disease (CAD). In fact, studies have shown that as the coronary atherosclerosis burden rises, a continued increase in coronary events occurs [2].

The SYNTAX score (SS) was proposed to quantify the complexity and extent of CAD. The score became a surrogate of atherosclerotic burden and a tool to help selecting candidates for percutaneous or surgical treatment [3]. The residual SYNTAX Score (rSS) was derived from the SS to quantify the atherosclerotic burden of residual CAD after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and has been validated as an independent predictor of clinical adverse events [4,5]. More recently, the SYNTAX score II (SSII) was developed to increase the prognostic predictive accuracy with the addition of clinical variables [6]. These three scores have not been evaluated concomitantly among patients with coronary artery disease undergoing a coronary revascularization procedure or only medical therapy (MT). The aim of the present study was to assess the prognostic value of coronary atherosclerotic burden through the calculation of the SYNTAX scores (SS, rSS and SSII) in patients with stable multivessel CAD undergoing PCI, CABG, or MT alone.

METHODS

STUDY DESIGN. This is a single-center retrospective study that enrolled patients from the Medicine, Angioplasty or Surgery Study (MASS) unit database at the Heart Institute of the

University of Sao Paulo, Brazil. Patients with multivessel CAD (defined as stenosis ≥ 70% in at least 2 of the 3 main coronary arteries) and preserved LVEF who underwent coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or medical treatment (MT) between January 2002 and December 2015 were included in this study.

DATA COLLECTION AND CRITERIA. SS and SSII were calculated by scoring all coronary lesions with a diameter stenosis ≥ 50%, in vessels with a diameter ≥ 1.5 mm, using the SS algorithm, which is described in full elsewhere [3,7]. Two experienced clinical cardiologists and two interventional cardiologists blinded to clinical outcomes calculated the SS retrospectively for each patient. Clinical data were obtained from the medical records for the calculation of SSII. Intraobserver and interobserver variability for the SS were performed for 100 coronary angiograms according to the kappa [k] coefficient.

For the SS and SSII calculation of the MT group, we used the CABG group as a reference. This option assumed that surgery is the strategy that provides the most complete revascularization in patients with multivessel CAD. The residual SYNTAX Score (rSS) was calculated for each coronary lesion that was evaluated with the SS but was not treated [8]. The coronary angiogram performed immediately after the percutaneous intervention or the surgical report of the CABG patients was used to calculate the rSS. For the MT group, the rSS is similar to the SS. A higher value of rSS suggests that more CAD lesions were untreated. Finally, patients were categorized within each score as low, intermediate, and high (see **Supplementary material online, Table S1**).

TREATMENT. Patients were categorized according to three coronary revascularization strategies: MT, PCI and CABG. Patients in the three groups received intensive secondary prevention with lifestyle and pharmacologic interventions, using "treat-to-target" algorithms. All patients were treated according to the current guidelines at the time of study enrollment.

Among patients undergoing PCI, target-lesion revascularization was always attempted, and complete revascularization was performed as clinically appropriate. Subjects in the PCI group received plain bare metal stents (BMS), or drug eluting stents (DES), as available. A successful PCI was defined as a normal coronary artery flow or less than 20% stenosis in the luminal diameter after coronary stent implantation, as assessed by visual estimation of the angiograms before and after the procedure. Clinical success was defined as angiographic success plus the absence of in-hospital myocardial infarction (MI), emergency CABG, or death.

CABG was performed in accordance with the best current practices. The use of cardiac extracorporeal circulation was defined at the discretion of the surgical team, but the surgical team had experience in both on-pump and off-pump surgery.

STUDY ENDPOINTS. The primary endpoint was death from any cause at 5 years. Secondary endpoint was major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of all-cause death, MI, stroke, and subsequent coronary revascularization measured.

STATISTICAL ANALYSIS. Continuous variables were summarized as mean ± SD and compared using the Student unpaired *t* test or the Mann-Whitney test, as appropriate. The normality assumption for continuous variables was evaluated using the Kolmogorov-Smirnov test. Categorical variables were summarized as counts and percentages and compared with the chi-square test when appropriate. Otherwise, the Fisher exact test was used. Cox regression analysis was used to find independent predictors of mortality in the PCI, CABG, and MT groups. The variables with a probability value of <0.20 in the univariate analyses were included in the backward stepwise multivariable model. Only variables with statistical significance (p <0.05) remained in the Cox multivariable model. No correction was made for multiple tests. Receiver-operating characteristic (ROC) curves were created to evaluate the capacity of each score to discriminate MACCE in the PCI, CABG, and MT groups. Survival curves were constructed using Kaplan-Meier estimates and compared by using the log-rank test at 5 years of follow-up. A 2-sided p-value <0.05 was considered statistically significant. All analyses were conducted using the statistical package SPSS 25.0 (IBM®) software for Windows.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

OVERVIEW OF PATIENT CHARACTERISTICS

From January 2002 to December 2015, 2,176 patients with stable multivessel CAD were screened and 1,719 were included in this study. The reasons for exclusion of the remaining 457 patients are listed in **Figure S1 in the Supplementary material online**. A total of 573 patients underwent PCI, 572 underwent CABG, and 574 received MT alone. The overall clinical, laboratory, and angiographic characteristics of the 3 groups are depicted in **Table 1**. Compared to the PCI and MT patients, those who underwent CABG were more frequently smokers, had more peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), presented more frequently with a positive treadmill test, and had more left main coronary artery disease (LMCAD). The SS was significantly higher in the CABG group compared to the MT and PCI groups (24.18±8.20 vs. 17.22±6.55 vs. 19.46±7.56, respectively, p <0.001). Conversely, the SSII was significantly higher in the PCI and CABG groups compared to the MT group (28.13±7.97 vs. 25.03±10.52 vs. 21.69±8.53, respectively, p <0.001). The rSS was significantly higher in the MT group compared to the PCI and CABG groups (19.46±7.56 vs. 8.43±6.39 vs. 4.31±4.92, respectively, p <0.001).

Table 1 Baseline and Procedure Variables in PCI, CABG, and MT Patient Groups.

	PCI (n = 573)	CABG (n = 572)	MT (n = 574)	p Value
Age at randomization, yr	59.78 ± 8.8	61.75 ± 8.97	60.69 ± 8.59	0.222
Male	378 (66.0)	397 (69.4)	383 (66.7)	0.428
Current smoker	124 (21.6)	163 (28.5)	126 (22.0)	<0.001
Hypertension	488 (85.2)	469 (82.0)	453 (78.9)	0.023
Diabetes	292 (51.0)	294 (51.4)	334 (58.2)	0.023
Previous MI	269 (46.9)	242 (42.3)	222 (38.7)	0.018
COPD	4 (0.7)	26 (4.5)	15 (2.6)	<0.001
PAD	15 (2.6)	64 (11.2)	19 (3.3)	<0.001
BMI, kg/m^2	27.74 ± 4.55	27.70 ± 4.09	27.92 ± 4.41	0.547
Total cholesterol, mg/dL	197.85 ± 55.16	197.50 ± 50.92	194.60 ± 49.28	0.466
LDL cholesterol, mg/dL	122.30 ± 43.30	122.48 ± 42.35	120.69 ± 42.64	0.684
HDL cholesterol, mg/dL	38.57 ± 10.25	39.46 ± 10.66	40.06 ± 11.40	0.068

Triglycerides, mg/dL	183.71 ± 151.51	176.55 ± 109.93	172.67 ± 123.99	0.175
Glucose, mg/dL	131.07 ± 52.70	131.08 ± 55.66	138.10 ± 61.32	0.147
Glycated hemoglobin, %	6.81 ± 1.70	6.70 ± 1.64	7.01 ± 1.81	0.004
Creatinine, mg/dL	1.04 ± 0.26	1.07 ± 0.26	1.07 ± 0.40	0.107
LVEF, %	61.3 ± 9.3	61.1 ± 8.7	60.9 ± 9.8	0.725
Positive treadmill test	391 (68.2)	378 (66.1)	347 (60.5)	<0.001
Angina CCS class				
I	69 (12.0)	60 (10.5)	124 (21.6)	<0.001
II	293 (51.2)	367 (64.2)	314 (54.7)	
III	193 (33.7)	121 (21.2)	127 (22.1)	
IV	18 (3.1)	24 (4.2)	9 (1.6)	
Coronary anatomy				
2-vessel disease	229 (40.0)	135 (23.6)	155 (27.0)	<0.001
3-vessel disease	344 (60.0)	437 (76.4)	419 (73.0)	
LAD disease	535 (93.4)	547 (95.6)	557 (97.0)	0.012
LMCAD	20 (3.5)	158 (27.6)	13 (2.3)	<0.001
SYNTAX score	17.22 ± 6.55	24.18 ± 8.20	19.46 ± 7.56	<0.001
SYNTAX score II	28.13 ± 7.97	25.03 ± 10.52	21.69 ± 8.53	<0.001
Residual SYNTAX score	8.43 ± 6.39	4.31 ± 4.92	19.46 ± 7.56	<0.001
SRI	54.07 ± 26.20	81.85 ± 21.22	0	<0.001
Surgery off-pump	NA	249 (43.7)	NA	-
Left internal thoracic artery	NA	559 (97.7)	NA	-
BMS use	369 (64.4)	NA	NA	-
DES use	204 (35.6)	NA	NA	-
No. of graft vessels	NA	2.9 ± 0.7	NA	-

Total number of stents	2.1 ± 1.0	NA	NA	-

Values are presented as mean ± SD or number (%).
Legend: BMI = body mass index; BMS = bare metal sent; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; DES = drug eluting stent; HDL = high-density lipoprotein cholesterol; LAD = left anterior descending artery; LDL = low-density lipoprotein cholesterol; LMCAD = left main coronary artery disease; LVEF = left ventricular ejection function; MI = myocardial infarction; PAD = peripheral artery disease; SRI = SYNTAX revascularization index (SRI= (1-[rSS/SS]) ×100); NA = not available.

The degree of agreement for intraobserver and interobserver reproducibility according to the tertile analysis (≤22, 23 to 32, ≥33) of the SS was substantial (k=0.606, 95% CI 0.456-0.741, p<0.001, and k=0.656, 95% CI 0.498-0.811, p<0.001, respectively).

Compared to the other revascularization groups, patients in the MT group were more likely to have diabetes and patients of the CABG group, a positive treadmill test. The distribution of SYNTAX score categories according to the treatment strategies is shown in **Table 2**.

Table 2 Distribution of SYNTAX Scores Categories According to the Treatment Strategy.

Syntax Score	**Subgroups**	**Treatment**						**p Value**
		PCI		**CABG**		**MT**		
		n	**%**	**n**	**%**	**n**	**%**	
SS	<22	433	75.6	230	40.2	367	63.9	<0.001
	22-33	133	23.2	266	46.5	176	30.7	
	>33	7	1.2	76	13.3	31	5.4	
SSII	<18.7	59	10.3	167	29.2	219	38.2	<0.001
	18.7-25.7	197	34.4	155	27.1	170	29.6	

	>25.7	317	55.3	250	43.7	185	32.2	
	<4	137	23.9	302	52.8	0	0.0	
rSS	4-8	189	33.0	159	27.8	20	3.5	<0.001
	>8	247	43.1	111	19.4	554	96.5	

Legend: SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; MT = medical treatment.

MORTALITY IN THE OVERALL COHORT ACCORDING TO THE SYNTAX SCORES

In the overall cohort, there were not statistically significant differences in mortality between low, intermediate and high SS (7.5%, 7.5% and 12.3%, respectively, p = 0.148, **Figure 1A**) at 5 years. Compared to patients with low SSII, those with intermediate and high SSII (**Figure 1B**) had a higher incidence of death at 5 years (3.6% vs. 7.9% vs. 10.5%, respectively, p <0.001). Higher rSS as well as higher SS also did not significantly increase the mortality rate (low: 7.5%, intermediate: 7.5%, and high: 8.2%, p = 0.990, **Figure 1C**).

MORTALITY IN THE PCI, CABG AND MT GROUPS ACCORDING TO DIFFERENT SYNTAX SCORES CATEGORIES

No statistically significant difference for death was observed among patients in the three SS groups within the PCI, CABG, and MT cohorts (**Figure 2A to C**). There was a higher incidence of death in PCI (1.7% with low, 4.6% with intermediate and 8.9% with high SSII, p = 0.046) and MT (5.0% with low, 4.7% with intermediate and 10.8% with high SSII, p = 0.031) patients with higher SSII values compared to those with lower SSII values. Additionally, the rate of death was lower in CABG patients with low SSII than those with intermediate and high SSII (1.8%, 9.7% and 10.0%, respectively, p = 0.004) (**Figure 2D to F**). The incidence of death was lower in patients of CABG group with low rSS than intermediate and high rSS (5.0%, 10.1% and 10.8%, respectively, p = 0.048), with no differences in the PCI and MT cohorts (**Figure 2G to I**).

LONG-TERM FOLLOW-UP PREDICTORS OF MORTALITY IN PCI, CABG, AND MT GROUPS

In multivariate analysis of the PCI cohort, diabetes (hazard ratio [HR]: 5.50; 95% confidence interval [CI]: 1.23 to 24.54; p = 0.025) was independent predictor of mortality at 5 years (**Table 3**).

In the CABG group, after adjustment for potential confounding biases by multivariate logistic Cox regression, intermediate SSII (hazard ratio [HR]: 3.93; 95% confidence interval [CI]: 1.21 to 12.78; p = 0.023) and high rSS (hazard ratio [HR]: 3.48; 95% confidence interval [CI]: 1.32 to 9.17; p = 0.012) were independent risk factors for mortality at 5 years (**Table 3**).

In the MT group, diabetes (hazard ratio [HR]: 2.14; 95% confidence interval [CI]: 1.04 to 4.38; p = 0.037) and high SSII (hazard ratio [HR]: 2.35; 95% confidence interval [CI]: 1.10 to 5.02; p = 0.026) were independently associated with mortality at 5 years (**Table 3**).

Table 3 Multivariable Cox Model for Death in the PCI, CABG, and MT groups.

Predictor	HR (95% CI)	p Value
PCI		
Diabetes Mellitus	5.50 (1.23-24.54)	0.025

Positive treadmill test	5.74 (0.75-43.92)	0.092
CABG		
Intermediate SSII	3.93 (1.21-12.78)	0.023
High SSII	2.79 (0.91-8.57)	0.072
Intermediate rSS	2.50 (0.97-8.57)	0.056
High rSS	3.48 (1.32-9.17)	0.012
MT		
Diabetes Mellitus	2.14 (1.04-4.38)	0.037
High SSII	2.35 (1.10-5.02)	0.026

Legend: DM = diabetes mellitus; SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score.

SSII combining clinical and anatomical variables had better discrimination ability compared with that of SS and rSS to predict death in patients with multivessel CAD (**Figure 3A**). The area under curve (AUC) in the PCI group was 0.486, 0.640 and 0.443 for SS, SSII and rSS, respectively (**Figure 3B**). In the CABG group, the AUC was 0.601, 0.615 and 0.625 for SS, SSII and rSS, respectively (**Figure 3C**). And in the MT group, the AUC was 0.488, 0.625 and 0.488 for SS, SSII and rSS, respectively (**Figure 3D**).

MACCE IN THE PCI, CABG AND MT GROUPS ACCORDING TO SYNTAX SCORES CATEGORIES

No statistically significant differences in MACCE were observed among patients in the three SS groups within the PCI, CABG, and MT cohorts. No differences were observed in the incidence of MACCE among patients in the three SSII groups within the PCI and MT population. Patients in the lower SSII categories treated with CABG experienced lower incidence of MACCE at 5 years (11.4% vs. 20.0% vs. 20.4% in the low, intermediate and high SSII groups, respectively, p = 0.042). The incidence of MACCE was similar among all rSS categories, regardless of the revascularization strategy. There was a higher incidence of stroke among patients of the PCI group with high SS (2.4% vs. 3.8% vs. 28.6% with low, intermediate, and high SS category, respectively, p <0.001). The rates of subsequent revascularization and myocardial infarction were similar in all SS, SSII and rSS categories of the PCI, CABG and MT groups (see **Supplementary material online, Table S2**).

DISCUSSION

This study evaluated the impact of the coronary atherosclerotic burden on cardiovascular events through the application of SYNTAX scores in patients with stable multivessel CAD who underwent CABG, PCI, or MT alone. The main finding of this study is that atherosclerotic burden alone was not able to discriminate the occurrence of death in these patients at a follow-up of 5 years regardless of the therapeutic strategy while the SSII predicted mortality as angiographic and clinical variables were taken into account.

Even in the MT group atherosclerotic burden was not associated with increased risk of death and cardiovascular events. Moreover, most of our patients (70%) had documented myocardial ischemia and even in this high-risk population the burden of coronary disease was not associated with a worse cardiovascular prognosis. These findings support the hypothesis that in patients with stable CAD, a conservative strategy with optimized medical therapy is associated with good long-term cardiovascular prognosis, particularly in patients with preserved left ventricular ejection fraction, as shown by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [9].

The maximum expression of the myocardium at risk observed in the MT group did not reflect a worse prognosis when MT was compared with the CABG or PCI. Our findings are in line with the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial that did not find differences in cardiovascular outcomes among patients with documented moderate or severe myocardial ischemia and stable CAD who underwent invasive or conservative treatment [10]. In concordance with Garzillo and colleagues, our results showed that regardless of the therapeutic strategy applied, the presence of documented myocardial ischemia and distinct atherosclerotic burden were not associated with an increased occurrence of cardiovascular events in patients with multivessel CAD [11].

Recently, a substudy of the ISCHEMIA trial showed a greater association of more severe CAD with increased risk of death and MI [12]. However, the assessment of atherosclerotic burden was performed only through the number of compromised vessels, and not through the anatomical complexity and extent.

The addition of clinical variables to the SS has provided a significant improvement in the process of risk stratification. The SSII had moderate predictive accuracy for death, clinical characteristics were important predictors of cardiovascular events and death and were more suitable to predict death in patients with stable CAD. These results found with SSII suggested that angiographic variables alone did not suffice to accurately stratify the risk of cardiovascular outcomes in this population. In fact, recent studies have also shown a better prognostic value of SSII compared to SS for the risk of mortality and MACE [13-16].

Of note, the presence of DM was associated with a higher incidence of death in PCI and MT groups. This finding is in agreement with a recent analysis by Tam et al. that showed better long-term survival and decreased risk of MACCE in diabetic patients with multivessel CAD undergoing CABG compared to PCI [17]. Regarding completeness of revascularization, we found similar incidence of death even with higher tertiles of rSS, except in CABG patients with intermediate and high rSS who presented a higher rate of death. These findings possibly reflect the stability of CAD, previously confirmed by the The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial [18] and more recently, by the ISCHEMIA trial [10] and are in agreement with those found by Kobayashi et al. in patients from the FFR-guided PCI cohort of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial [19].

In light of the complexity of coronary disease, and with the results observed in this study, we can infer that death and MACCE were not directly related to the atherosclerotic burden. Therefore, it may be that the development of a myocardial infarction and its consequences depend more on the vulnerability of the plaque, and less on the overall atherosclerotic burden or myocardial ischemia. These variables must be considered as aggravating conditions. Myocardial infarction is often associated with the local characteristics of the atherosclerotic plaque. However, the hypothesis that plaque rupture and its consequences are more frequent and accentuated in the presence of more extensive coronary disease is questionable. Symptoms of angina, frequently related to plaque instability, emerge in this intricate pathophysiological mechanism. The instability of the plaque, however, cannot be assessed by the SS.

Finally, the current analysis indicates that the CAD stability, the strict control of symptoms of angina with optimized MT, and preserved left ventricular function contributed to the favorable long-term results. In addition, the atherosclerotic burden alone did not influence the incidence of death and MACCE. Clinical characteristics are probably more important for clinical decision-making in patients with multivessel CAD.

CONCLUSION

In patients with multivessel CAD and preserved ventricular function, the addition of clinical variables to anatomical information by means of the SSII significantly impacted the accuracy of predicting long-term prognosis. The coronary atherosclerotic burden evaluated by the SS alone was not able to predict mortality and MACCE in patients undergoing PCI, CABG or MT.

DATA SHARING STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENTS

PATIENT CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL

This study was approved by our Institutional Review Board and was only initiated after it (CAAE: 88738618.6.000.0068). Patients agreeing to participate will sign an informed consent form before entering the study.

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CONTRIBUTORS

TLS contributed to data collection, data analysis and writing of the article. WH, MEF, PCR, and, JAFR, RKF, and LCG contributed to the writing of the article. AGL participated in analysis of data. EBM helped collect data. All authors revised the manuscript and eventually approved it for publication. WH was responsible for the overall content as guarantor who accepted full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish.

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FIGURES

Figure 1 Kaplan-Meier Survival Curves for All-cause Mortality According to SYNTAX Scores.

Kaplan-Meier curves for mortality stratified by SS (2A), SSII (2B), and rSS (2C) regardless of strategy of treatment (PCI, CABG, or MT).

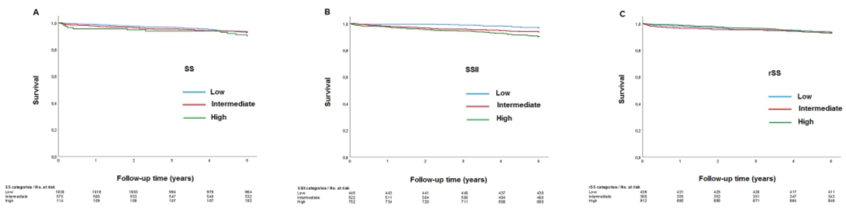
Figure 2 Kaplan-Meier Curves for 5-year All-Cause Mortality.

Kaplan-Meier estimates for death in patients assigned to MT, PCI or CABG over 5 years of follow-up according to SYNTAX scores (SS: PCI [A], CABG [B] and MT [C]; SSII: PCI [D], CABG [E] and MT [F]; rSS: PCI [G], CABG [H] and MT [I]).

Figure 3 ROC Curves SYNTAX Scores for Discrimination of All-Cause Mortality in the PCI, CABG, and MT Groups.

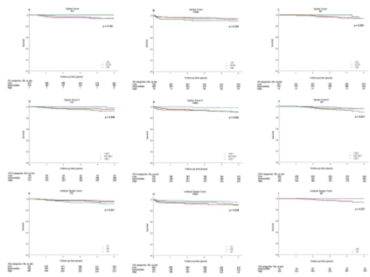
ROC curves SYNTAX scores for Mortality in MASS database (A), PCI group (B), CABG group (C), and MT group (D).

* In the MT group, SS has the same value as rSS. Therefore, the ROC curves are superimposed (Figure 3D).

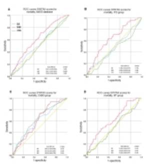


Kaplan-Meier curves for mortality stratified by SS (2A), SSII (2B), and rSS (2C) regardless of strategy of treatment (PCI, CABG, or MT).

758x376mm (300 x 300 DPI)



Kaplan-Meier estimates for death in patients assigned to MT, PCI or CABG over 5 years of follow-up according to SYNTAX scores (SS: PCI [A], CABG [B] and MT [C]; SSII: PCI [D], CABG [E] and MT [F]; rSS: PCI [G], CABG [H] and MT [I]).



ROC curves SYNTAX scores for Mortality in MASS database (A), PCI group (B), CABG group (C), and MT group (D).
* In the MT group, SS has the same value as rSS. Therefore, the ROC curves are superimposed (Figure 3D).

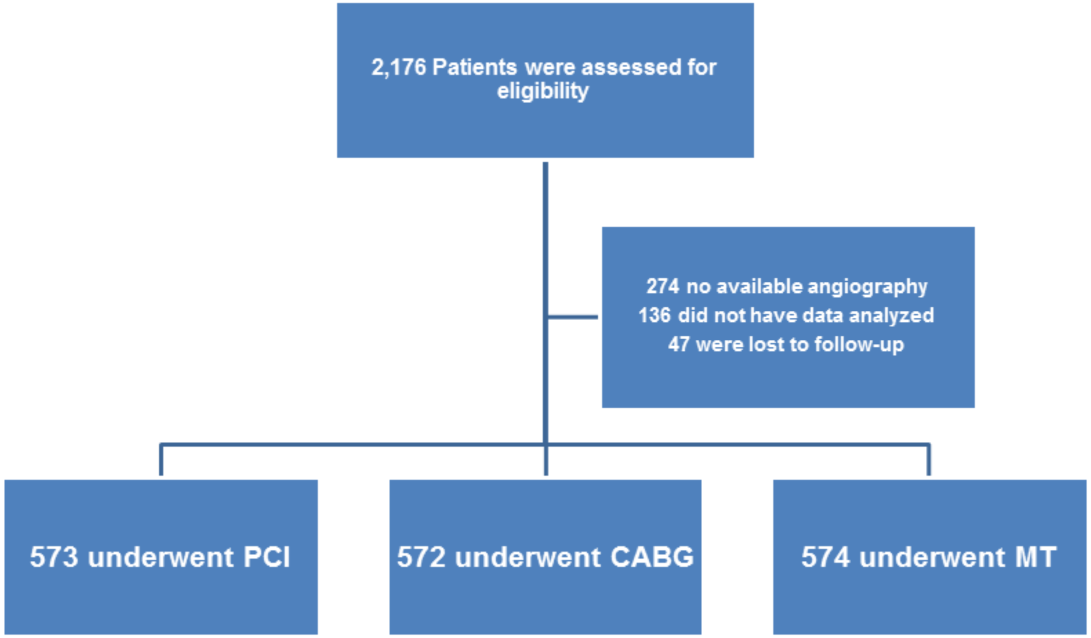
Supplementary Material

Figure S1. **Enrollment of Patients With Coronary Artery Disease in the MASS Database.**

Table S1. **SYNTAX scores subgroups definition.**

Table S2. **Kaplan-Meier Estimates of Events at 5 Years by SYNTAX Scores Categories and Treatment Arm.**

Figure S1. **Enrollment of Patients With Coronary Artery Disease in the MASS Database.**



Flowchart for patients included in the MASS database SYNTAX scores analysis. CABG = coronary artery bypass graft; MT = medical treatment; PCI = percutaneous coronary intervention.

Table S1. **SYNTAX scores subgroups definition.**

SYNTAX scores	**Low**	**Intermediate**	**High**
SS	≤22	23 to 32	≥33
SSII	<18.7	18.7 to 25.7	>25.7
rSS	0 to 4	>4 to 8	>8

Legend: SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score.

Table S2. **Kaplan-Meier Estimates of Events at 5 Years by SYNTAX Scores Categories and Treatment Arm.**

	SS											
	PCI				**CABG**				**MT**			
	Low	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**
Death	6.5	6.8	4.3	0.745	5.7	8.0	12.1	0.194	6.8	6.9	6.5	0.993
MACCE	27.1	34.8	42.9	0.122	15.9	19.1	20.3	0.620	24.3	28.5	25.8	0.580
Cardiac death	2.1	3.1	0	0.746	1.8	2.3	0	0.429	2.5	2.9	6.4	0.463
MI	5.7	9.4	0	0.268	7.2	6.3	1.3	0.208	7.2	9.7	6.5	0.510
Stroke	2.4	3.8	28.6	<0.001	2.7	4.7	7.4	0.257	1.9	3.5	3.2	0.550
Further revascularization	18.6	22.6	14.3	0.549	5.5	5.6	1.5	0.353	18.0	18.2	19.8	0.981
	SSII											
	PCI				**CABG**				**MT**			
	Low	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**
Death	1.7	4.6	8.9	0.046	1.8	9.8	10.2	0.004	5.0	4.7	10.8	0.031
MACCE	18.7	28.4	31.4	0.132	11.6	20.3	20.8	0.042	23.3	24.7	29.2	0.447
Cardiac death	0	2.0	2.9	0.381	0	1.3	3.3	0.052	1.8	3.0	4.0	0.468
MI	6.9	5.6	6.9	0.884	4.3	6.9	6.7	0.540	6.0	9.5	9.0	0.375
Stroke	1.7	1.6	4.3	0.185	1.8	5.6	5.2	0.200	1.4	1.8	4.5	0.114
Further revascularization	15.4	20.3	19.6	0.687	6.2	5.5	3.8	0.601	19.1	19.9	15.2	0.468
	rSS											
	PCI				**CABG**				**MT**			
	Low	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**
Death	9.5	4.8	6.5	0.241	5.1	10.1	11.2	0.051	-	0	7.1	0.227
MACCE	27.8	29.8	29.3	0.916	15.1	19.7	23.1	0.164	-	10.0	26.2	0.121
Cardiac death	2.4	1.6	2.9	0.686	1.0	2.0	3.8	0.195	-	0	2.9	0.440
MI	8.3	7.4	5.0	0.416	6.5	4.6	6.6	0.725	-	5.0	8.1	0.624
Stroke	3.1	4.3	2.1	0.410	3.8	4.1	5.7	0.680	-	5.0	2.4	0.465
Further revascularization	16.7	20.5	20.0	0.669	4.9	5.5	4.6	0.964	-	10.0	17.4	0.331

Values are presented as %.
Legend: MI = myocardial infarction; SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score.

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Coronary Atherosclerotic Burden Assessed by SYNTAX Scores and Outcomes in Surgical, Percutaneous, or Medical Strategies: a retrospective cohort study

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Coronary Atherosclerotic Burden Assessed by SYNTAX Scores and Outcomes in Surgical, Percutaneous, or Medical Strategies: a retrospective cohort study

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Running head: Coronary atherosclerotic burden and treatment strategies

Abstract

Introduction Coronary atherosclerotic burden and SYNTAX score (SS) are predictors of cardiovascular events.

Objectives To investigate the value of SYNTAX scores (SS, SSII and residual SS [rSS]) for predicting cardiovascular events in patients with coronary artery disease (CAD).

Design Retrospective cohort study.

Setting Single tertiary centre.

Paticipants Medicine, Angioplasty or Surgery Study (MASS) database patients with stable multivessel CAD and preserved ejection fraction.

Interventions CAD patients undergoing coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), or medical treatment (MT) alone from January 2002 to December 2015.

Primary and secondary outcomes Primary: 5-year all-cause mortality. Secondary: composite of all-cause death, myocardial infarction, stroke, and subsequent coronary revascularization at 5 years.

Results A total of 1,719 patients underwent PCI (n = 573), CABG (n = 572), or MT (n = 574) alone. The SS was not considered an independent predictor of 5-year mortality in the PCI (low, intermediate and high SS 6.5%, 6.8% and 4.3%, respectively, p=0.745), CABG (low, intermediate and high SS 5.7%, 8.0% and 12.1%, respectively, p=0.194) and MT (low, intermediate and high SS 6.8%, 6.9% and 6.5%, respectively, p=0.993) cohorts. The SSII (low, intermediate and high SSII, 3.6% vs. 7.9% vs. 10.5%, respectively, p <0.001) was associated with a higher mortality risk in the overall population. Within each treatment strategy, SSII was associated with a significant 5-year mortality rate, especially in CABG patients with higher SSII (low, intermediate and high SSII, 1.8%, 9.7% and 10.0%, respectively, p = 0.004) and in MT patients with high SSII (low, intermediate and high SSII, 5.0%, 4.7% and 10.8%, respectively, p = 0.031). SSII demonstrated a better predictive accuracy for mortality compared with SS and rSS (c-index = 0.62).

Conclusions Coronary atherosclerotic burden alone was not associated with significantly increased risk of all-cause mortality. The SSII better discriminates the risk of death.

Strengths and limitations of this study

- This is the only study that evaluated the three SYNTAX scores (SS, SSII and rSS) in patients with multivessel CAD undergoing one of three treatment strategies (CABG, PCI or MT).
- This analysis focused on the evaluation of atherosclerotic burden through the SYNTAX scores as a predictor of cardiovascular events.
- The addition of clinical variables to SS-II discriminated increased risk of death in this sample.
- The main limitations of this study were the small sample size and the involvement of a single center.

INTRODUCTION

Historically, the number of diseased vessels as well as the location and extension of the coronary atherosclerotic lesions have been considered predictors of cardiovascular events in the short- and long-term [1] among patients with stable coronary artery disease (CAD). In fact, studies have shown that as the coronary atherosclerosis burden rises, a continued increase in coronary events occurs [2].

The SYNTAX score (SS) was proposed to quantify the complexity and extent of CAD. The score became a surrogate of atherosclerotic burden and a tool to help selecting candidates for percutaneous or surgical treatment [3]. The residual SYNTAX Score (rSS) was derived from the SS to quantify the atherosclerotic burden of residual CAD after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and has been validated as an independent predictor of clinical adverse events [4,5]. More recently, the SYNTAX score II (SSII) was developed to increase the prognostic predictive accuracy with the addition of clinical variables [6]. These three scores have not been evaluated concomitantly among patients with coronary artery disease undergoing a coronary revascularization procedure or only medical therapy (MT). The aim of the present study was to assess the prognostic value of coronary atherosclerotic burden through the calculation of the SYNTAX scores (SS, rSS and SSII) in patients with stable multivessel CAD undergoing PCI, CABG, or MT alone.

METHODS

STUDY DESIGN. This is a single-center retrospective study that enrolled patients from the Medicine, Angioplasty or Surgery Study (MASS) unit database at the Heart Institute of the University of Sao Paulo, Brazil. Patients with multivessel CAD (defined as stenosis ≥ 70% in at least 2 of the 3 main coronary arteries) and preserved LVEF who underwent coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or medical treatment (MT) between January 2002 and December 2015 were included in this study see **(Supplementary material online, Table S1)**.

DATA COLLECTION AND CRITERIA. SS and SSII were calculated by scoring all coronary lesions with a diameter stenosis ≥ 50%, in vessels with a diameter ≥ 1.5 mm, using the SS algorithm, which is described in full elsewhere [3,7]. Two experienced clinical cardiologists and two interventional cardiologists blinded to clinical outcomes calculated the SS retrospectively for each patient. Clinical data were obtained from the medical records for the calculation of SSII. Intraobserver and interobserver variability for the SS were performed for 100 coronary angiograms according to the kappa [k] coefficient. Coefficients ranging from 0.21 to 0.40 are considered fair, from 0.41 to 0.60 moderate, from 0.61 to 0.80 substantial, and over 0.81 excellent. For ordinal variables, the weighted kappa coefficient was used to express the degree of agreement inter-observer and intra-observer.

For the SS and SSII calculation of the MT group, we used the CABG group as a reference. This option assumed that surgery is the strategy that provides the most complete revascularization in patients with multivessel CAD. The residual SYNTAX Score (rSS) was calculated for each coronary lesion that was evaluated with the SS but was not treated [8]. The coronary angiogram performed immediately after the percutaneous intervention or the surgical report of the CABG patients was used to calculate the rSS. For the MT group, the rSS is similar to the SS. A higher value of rSS suggests that more CAD lesions were untreated. Finally, patients were categorized within each score as low, intermediate, and high (see **Supplementary material online, Table S2**).

TREATMENT. Patients were categorized according to three coronary revascularization strategies: MT, PCI and CABG. Patients in the three groups received intensive secondary prevention with lifestyle and pharmacologic interventions, using "treat-to-target" algorithms. All patients were treated according to the current guidelines at the time of study enrollment.

Among patients undergoing PCI, target-lesion revascularization was always attempted, and complete revascularization was performed as clinically appropriate. Subjects in the PCI group received plain bare metal stents (BMS), or drug eluting stents (DES), as available. A successful PCI was defined as a normal coronary artery flow or less than 20% stenosis in the luminal diameter after coronary stent implantation, as assessed by visual estimation of the angiograms before and after the procedure. Clinical success was defined as angiographic success plus the absence of in-hospital myocardial infarction (MI), emergency CABG, or death.

CABG was performed in accordance with the best current practices. The use of cardiac extracorporeal circulation was defined at the discretion of the surgical team, but the surgical team had experience in both on-pump and off-pump surgery.

STUDY ENDPOINTS. The primary endpoint was death from any cause at 5 years. Secondary endpoint was major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of all-cause death, MI, stroke, and subsequent coronary revascularization measured.

STATISTICAL ANALYSIS. Continuous variables were summarized as mean ± SD and compared using the Student unpaired *t* test or the Mann-Whitney test, as appropriate. The normality assumption for continuous variables was evaluated using the Kolmogorov-Smirnov test. Categorical variables were summarized as counts and percentages and compared with the chi-square test when appropriate. Otherwise, the Fisher exact test was used. Cox regression analysis was used to find independent predictors of mortality in the PCI, CABG, and MT groups. The variables with a probability value of <0.20 in the univariate analyses were included in the backward stepwise multivariable model. Only variables with statistical significance ($p < 0.05$) remained in the Cox multivariable model. No correction was made for multiple tests. Receiver-operating characteristic (ROC) curves were created to evaluate the capacity of each score to discriminate MACCE in the PCI, CABG, and MT groups. Survival curves were constructed using Kaplan-Meier estimates and compared by using the log-rank test at 5 years of follow-up. A 2-sided p-value <0.05 was considered statistically significant. All analyses were conducted using the statistical package SPSS 25.0 (IBM®) software for Windows.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

OVERVIEW OF PATIENT CHARACTERISTICS

From January 2002 to December 2015, 2,176 patients with stable multivessel CAD were screened and 1,719 were included in this study. The reasons for exclusion of the remaining 457 patients are listed in **Figure S1 in the Supplementary material online**. A total of 136 patients were lost to follow-up. A total of 573 patients underwent PCI, 572 underwent CABG, and 574 received MT alone. The overall clinical, laboratory, and angiographic characteristics of the 3 groups are depicted in **Table 1**. Compared to the PCI and MT patients, those who underwent CABG were more frequently smokers, had more peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), presented more frequently with a positive treadmill test, and had more left main coronary artery disease (LMCAD). The SS was significantly higher in the CABG group compared to the MT and PCI groups (24.18±8.20 vs. 17.22±6.55 vs. 19.46±7.56, respectively, $p < 0.001$). Conversely, the SSII was significantly higher in the PCI and CABG groups compared to the MT group (28.13±7.97 vs. 25.03±10.52 vs. 21.69±8.53, respectively, $p < 0.001$). The rSS was significantly higher in the MT group compared to the PCI and CABG groups (19.46±7.56 vs. 8.43±6.39 vs. 4.31±4.92, respectively, $p < 0.001$).

Table 1 Baseline and Procedure Variables in PCI, CABG, and MT Patient Groups.

	PCI (n = 573)	CABG (n = 572)	MT (n = 574)	p Value
Age at randomization, yr	59.78 ± 8.8	61.75 ± 8.97	60.69 ± 8.59	0.222
Male	378 (66.0)	397 (69.4)	383 (66.7)	0.428
Current smoker	124 (21.6)	163 (28.5)	126 (22.0)	<0.001
Hypertension	488 (85.2)	469 (82.0)	453 (78.9)	0.023
Diabetes	292 (51.0)	294 (51.4)	334 (58.2)	0.023
Previous MI	269 (46.9)	242 (42.3)	222 (38.7)	0.018
COPD	4 (0.7)	26 (4.5)	15 (2.6)	<0.001
PAD	15 (2.6)	64 (11.2)	19 (3.3)	<0.001
BMI, kg/m^2	27.74 ± 4.55	27.70 ± 4.09	27.92 ± 4.41	0.547
Systolic blood pressure, mm Hg	126.4 ± 16.1	127.8 ± 16.0	128.0 ± 15.4	0.487
Diastolic blood pressure, mm Hg	72.7 ± 10.7	73.1 ± 10.6	74.2 ± 11.0	0.097
Heart rate, bpm	69.5 ± 11.3	68.7 ± 10.7	69.0 ± 10.8	0.234

Total cholesterol, mg/dL	197.85 ± 55.16	197.50 ± 50.92	194.60 ± 49.28	0.466
LDL cholesterol, mg/dL	122.30 ± 43.30	122.48 ± 42.35	120.69 ± 42.64	0.684
HDL cholesterol, mg/dL	38.57 ± 10.25	39.46 ± 10.66	40.06 ± 11.40	0.068
Triglycerides, mg/dL	183.71 ± 151.51	176.55 ± 109.93	172.67 ± 123.99	0.175
Glucose, mg/dL	131.07 ± 52.70	131.08 ± 55.66	138.10 ± 61.32	0.147
Glycated hemoglobin, %	6.81 ± 1.70	6.70 ± 1.64	7.01 ± 1.81	0.004
Creatinine, mg/dL	1.04 ± 0.26	1.07 ± 0.26	1.07 ± 0.40	0.107
LVEF, %	61.3 ± 9.3	61.1 ± 8.7	60.9 ± 9.8	0.725
Positive treadmill test	391 (68.2)	378 (66.1)	347 (60.5)	<0.001
Angina CCS class				
I	69 (12.0)	60 (10.5)	124 (21.6)	<0.001
II	293 (51.2)	367 (64.2)	314 (54.7)	
III	193 (33.7)	121 (21.2)	127 (22.1)	
IV	18 (3.1)	24 (4.2)	9 (1.6)	
Coronary anatomy				
2-vessel disease	229 (40.0)	135 (23.6)	155 (27.0)	<0.001
3-vessel disease	344 (60.0)	437 (76.4)	419 (73.0)	
LAD disease	535 (93.4)	547 (95.6)	557 (97.0)	0.012
LMCAD	20 (3.5)	158 (27.6)	13 (2.3)	<0.001
SYNTAX score	17.22 ± 6.55	24.18 ± 8.20	19.46 ± 7.56	<0.001
SYNTAX score II	28.13 ± 7.97	25.03 ± 10.52	21.69 ± 8.53	<0.001
Residual SYNTAX score	8.43 ± 6.39	4.31 ± 4.92	19.46 ± 7.56	<0.001
Surgery off-pump	NA	249 (43.7)	NA	-
Left internal thoracic artery	NA	559 (97.7)	NA	-

BMS use	369 (64.4)	NA	NA	-
DES use	204 (35.6)	NA	NA	-
No. of graft vessels	NA	2.9 ± 0.7	NA	-
Total number of stents	2.1 ± 1.0	NA	NA	-

Values are presented as mean ± SD, median (interquartile range), or number (%).
Legend: BMI = body mass index; BMS = bare metal sent; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; DES = drug eluting stent; HDL = high-density lipoprotein cholesterol; LAD = left anterior descending artery; LDL = low-density lipoprotein cholesterol; LMCAD = left main coronary artery disease; LVEF = left ventricular ejection function; MI = myocardial infarction; PAD = peripheral artery disease; NA = not available.

The degree of agreement for intraobserver and interobserver reproducibility according to the tertile analysis (≤22, 23 to 32, ≥33) of the SS was substantial (k=0.606, 95% CI 0.456-0.741, p<0.001, and k=0.656, 95% CI 0.498-0.811, p<0.001, respectively). The intra-observer and inter-observer weighted kappa scores according to SS tertile (≤22, 23 to 32, ≥33) were 0.68 and 0.61, respectively, indicating a substantial agreement.

Compared to the other revascularization groups, patients in the MT group were more likely to have diabetes and patients of the CABG group, a positive treadmill test. The distribution of SYNTAX score categories according to the treatment strategies is shown in **Table 2**.

Table 2 Distribution of SYNTAX Scores Categories According to the Treatment Strategy.

Syntax Score	Subgroups	Treatment						p Value
		PCI		CABG		MT		
		n	%	n	%	n	%	
	<22	433	75.6	230	40.2	367	63.9	

	22-33	133	23.2	266	46.5	176	30.7	
SS	>33	7	1.2	76	13.3	31	5.4	<0.001
	<18.7	59	10.3	167	29.2	219	38.2	
SSII	18.7-25.7	197	34.4	155	27.1	170	29.6	<0.001
	>25.7	317	55.3	250	43.7	185	32.2	
	<4	137	23.9	302	52.8	0	0.0	
rSS	4-8	189	33.0	159	27.8	20	3.5	<0.001
	>8	247	43.1	111	19.4	554	96.5	

Legend: SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; MT = medical treatment.

MORTALITY IN THE OVERALL COHORT ACCORDING TO THE SYNTAX SCORES

In the overall cohort, there were not statistically significant differences in mortality between low, intermediate and high SS (7.5%, 7.5% and 12.3%, respectively, p = 0.148, **Figure 1A**) at 5 years. Compared to patients with low SSII, those with intermediate and high SSII (**Figure 1B**) had a higher incidence of death at 5 years (3.6% vs. 7.9% vs. 10.5%, respectively, p <0.001). Higher rSS as well as higher SS also did not significantly increase the mortality rate (low: 7.5%, intermediate: 7.5%, and high: 8.2%, p = 0.990, **Figure 1C**).

MORTALITY IN THE PCI, CABG AND MT GROUPS ACCORDING TO DIFFERENT SYNTAX SCORES CATEGORIES

No statistically significant difference for death was observed among patients in the three SS groups within the PCI, CABG, and MT cohorts (**Figure 2A to C**). There was a higher incidence of death in PCI (1.7% with low, 4.6% with intermediate and 8.9% with high SSII, p = 0.046) and MT (5.0% with low, 4.7% with intermediate and 10.8% with high SSII, p = 0.031) patients with higher SSII values compared to those with lower SSII values. Additionally, the rate of death was lower in CABG patients with low SSII than those with intermediate and high SSII (1.8%, 9.7% and 10.0%, respectively, p = 0.004) (**Figure 2D to F**). The incidence of death was lower in patients of CABG group with low rSS than intermediate and high rSS (5.0%, 10.1% and 10.8%, respectively, p = 0.048), with no differences in the PCI and MT cohorts (**Figure 2G to I**).

LONG-TERM FOLLOW-UP PREDICTORS OF MORTALITY IN PCI, CABG, AND MT GROUPS

In multivariate analysis of the PCI cohort, diabetes (hazard ratio [HR]: 5.50; 95% confidence interval [CI]: 1.23 to 24.54; p = 0.025) was independent predictor of mortality at 5 years (**Table 3**).

In the CABG group, after adjustment for potential confounding biases by multivariate logistic Cox regression, intermediate SSII (hazard ratio [HR]: 3.93; 95% confidence interval [CI]: 1.21 to 12.78; p = 0.023) and high rSS (hazard ratio [HR]: 3.48; 95% confidence interval [CI]: 1.32 to 9.17; p = 0.012) were independent risk factors for mortality at 5 years (**Table 3**).

In the MT group, diabetes (hazard ratio [HR]: 2.14; 95% confidence interval [CI]: 1.04 to 4.38; p = 0.037) and high SSII (hazard ratio [HR]: 2.35; 95% confidence interval [CI]: 1.10 to 5.02; p = 0.026) were independently associated with mortality at 5 years (**Table 3**).

Table 3 Multivariable Cox Model for Death in the PCI, CABG, and MT groups.

Predictor	HR (95% CI)	p Value
PCI		
Diabetes Mellitus	5.50 (1.23-24.54)	0.025
Positive treadmill test	5.74 (0.75-43.92)	0.092
CABG		
Intermediate SSII	3.93 (1.21-12.78)	0.023
High SSII	2.79 (0.91-8.57)	0.072
Intermediate rSS	2.50 (0.97-8.57)	0.056
High rSS	3.48 (1.32-9.17)	0.012
MT		
Diabetes Mellitus	2.14 (1.04-4.38)	0.037
High SSII	2.35 (1.10-5.02)	0.026

Legend: DM = diabetes mellitus; SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score.

SSII combining clinical and anatomical variables had better discrimination ability compared with that of SS and rSS to predict death in patients with multivessel CAD (**Figure 3A**). The area under curve (AUC) in the PCI group was 0.486 (CI 95% 0.393-0.579, p=0.758), 0.640 (CI 95% 0.559-0.720, p=0.002) and 0.443 (CI 95% 0.352-0.534, p=0.207) for SS, SSII and rSS, respectively (**Figure 3B**). In the CABG group, the AUC was 0.601 (CI 95% 0.519-0.684, p=0.019), 0.615 (CI 95% 0.543-0.687, p=0.008) and 0.625 (CI 95% 0.545-0.705, p=0.004) for SS, SSII and rSS, respectively (**Figure 3C**). And in the MT group, the AUC was 0.488 (CI 95% 0.398-0.577, p=0.046), 0.625 (CI 95% 0.542-0.710, p=0.043) and 0.488 (CI 95% 0.398-0.577, p=0.046) for SS, SSII and rSS, respectively (**Figure 3D**).

MACCE IN THE PCI, CABG AND MT GROUPS ACCORDING TO SYNTAX SCORES CATEGORIES

No statistically significant differences in MACCE were observed among patients in the three SS groups within the PCI, CABG, and MT cohorts. No differences were observed in the incidence of MACCE among patients in the three SSII groups within the PCI and MT population. Patients in the lower SSII categories treated with CABG experienced lower incidence of MACCE at 5 years (11.4% vs. 20.0% vs. 20.4% in the low, intermediate and high SSII groups, respectively, $p = 0.042$). The incidence of MACCE was similar among all rSS categories, regardless of the revascularization strategy. There was a higher incidence of stroke among patients of the PCI group with high SS (2.4% vs. 3.8% vs. 28.6% with low, intermediate, and high SS category, respectively, $p <0.001$). The rates of subsequent revascularization and myocardial infarction were similar in all SS, SSII and rSS categories of the PCI, CABG and MT groups (see **Supplementary material online, Table S3**).

DISCUSSION

This study evaluated the impact of the coronary atherosclerotic burden on cardiovascular events through the application of SYNTAX scores in patients with stable multivessel CAD who underwent CABG, PCI, or MT alone. The main finding of this study is that atherosclerotic burden alone was not able to discriminate the occurrence of death in these patients at a follow-up of 5 years regardless of the therapeutic strategy while the SSII predicted mortality as angiographic and clinical variables were taken into account.

Even in the MT group atherosclerotic burden was not associated with increased risk of death and cardiovascular events. Moreover, most of our patients (70%) had documented myocardial ischemia and even in this high-risk population the burden of coronary disease was not associated with a worse cardiovascular prognosis. These findings support the hypothesis that in patients with stable CAD, a conservative strategy with optimized medical therapy is associated with good long-term cardiovascular prognosis, particularly in patients with preserved left ventricular ejection fraction, as shown by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [9].

The maximum expression of the myocardium at risk observed in the MT group did not reflect a worse prognosis when MT was compared with the CABG or PCI. Our findings are in line with the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial that did not find differences in cardiovascular outcomes among patients with documented moderate or severe myocardial ischemia and stable CAD who underwent invasive or conservative treatment [10]. In concordance with Garzillo and colleagues, our results showed that regardless of the therapeutic strategy applied, the presence of documented myocardial ischemia and distinct atherosclerotic burden were not associated with an increased occurrence of cardiovascular events in patients with multivessel CAD [11].

Recently, a substudy of the ISCHEMIA trial showed a greater association of more severe CAD, assessed by coronary computed tomographic angiography, with increased risk of death and MI [12]. However, the assessment of atherosclerotic burden was performed only through the number of compromised vessels, and not through the anatomical complexity and extent.

The addition of clinical variables to the SS has provided a significant improvement in the process of risk stratification. The SSII had moderate predictive accuracy for death, clinical characteristics were important predictors of cardiovascular events and death and were more suitable to predict death in patients with stable CAD. These results found with SSII suggested that angiographic variables alone did not suffice to accurately stratify the risk of cardiovascular outcomes in this population. In fact, recent studies have also shown a better prognostic value of SSII compared to SS for the risk of mortality and MACE [13-16].

Of note, the presence of DM was associated with a higher incidence of death in PCI and MT groups. This finding is in agreement with a recent analysis by Tam et al. that showed better long-term survival and decreased risk of MACCE in diabetic patients with multivessel CAD undergoing CABG compared to PCI [17]. Additionally, a recent study conducted by Kurtul et al identified a strong correlation between diabetic retinopathy and atherosclerotic burden measured by the SYNTAX Score [18]. Regarding completeness of revascularization, we found similar incidence of death even with higher tertiles of rSS, except in CABG patients with intermediate and high rSS who presented a higher rate of death. These findings possibly reflect the stability of CAD, previously confirmed by the The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial [19] and more recently, by the ISCHEMIA trial [10] and are in agreement with those found by Kobayashi et al. in patients from the FFR-guided PCI cohort of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial [20].

In light of the complexity of coronary disease, and with the results observed in this study, we can infer that death and MACCE were not directly related to the atherosclerotic burden. Therefore, it may be that the development of a myocardial infarction and its consequences depend more on the vulnerability of the plaque, and less on the overall atherosclerotic burden or myocardial ischemia. These variables must be considered as aggravating conditions. Myocardial infarction is often associated with the local characteristics of the atherosclerotic plaque. However, the hypothesis that plaque rupture and its consequences are more frequent and accentuated in the presence of more extensive coronary disease is questionable. Symptoms of angina, frequently related to plaque instability, emerge in this intricate pathophysiological mechanism. However, the instability of the plaque cannot be assessed by the SS.

Finally, the current analysis indicates that the CAD stability, the strict control of symptoms of angina with optimized MT, and preserved left ventricular function contributed to the favorable long-term results. In addition, the atherosclerotic burden alone did not influence the incidence of death and MACCE. Clinical characteristics are probably more important for clinical decision-making in patients with multivessel CAD.

LIMITATIONS

This study has a few limitations that need to be acknowledged. First, this was a retrospective study, with the intrinsic biases associated with this type of study. However, predictors and outcome variables were collected prospectively. Second, revascularization strategies and standards of practice changed over time. These changes occurred in all study patients, irrespective of the therapeutic group they were placed in at the initiation of the study. Third, the sample size of our study is limited, which may compromise statistical power. Last, the data were collected in a single center, which may limit the generalizability of our results. Nevertheless, the homogeneity of treatment reduces the limitations of the present study.

CONCLUSION

In patients with multivessel CAD and preserved ventricular function, the addition of clinical variables to anatomical information by means of the SSII significantly impacted the accuracy of predicting long-term prognosis. The coronary atherosclerotic burden evaluated by the SS alone was not able to predict mortality and MACCE in patients undergoing PCI, CABG or MT.

DATA SHARING STATEMENT

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.4f4qrfjfv

ETHICS STATEMENTS

The Ethics Committee of the Heart Institute of the University of São Paulo Medical School, São Paulo, SP, Brazil, approved the trial (CAAE: 88738618.6.000.0068). All procedures were performed in accordance with the Declaration of Helsinki.

PATIENT CONSENT FOR PUBLICATION

The MASS-Trials database includes randomized clinical trials (MASS-II; MASS-III and MASS-V) and non-randomized patients (registry). All patients provided written informed consent and were assigned to a treatment group.

ETHICS APPROVAL

The Ethics Committee of the Heart Institute of the University of São Paulo Medical School, São Paulo, SP, Brazil, approved the trial. All procedures were performed in accordance with the Declaration of Helsinki.

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CONTRIBUTORSHIP STATEMENT

TLS contributed to data collection, data analysis and writing of the article. WH, MEF, PCR, and, JAFR, RKF, and LCG contributed to the writing of the article. AGL participated in analysis of data. EBM helped collect data. All authors revised the manuscript and eventually approved it for publication. WH was responsible for the overall content as guarantor who accepted full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish.

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COMPETING INTERESTS

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FIGURES

Figure 1 Kaplan-Meier Survival Curves for All-cause Mortality According to SYNTAX Scores.

Kaplan-Meier curves for mortality stratified by SS (2A), SSII (2B), and rSS (2C) regardless of strategy of treatment (PCI, CABG, or MT).

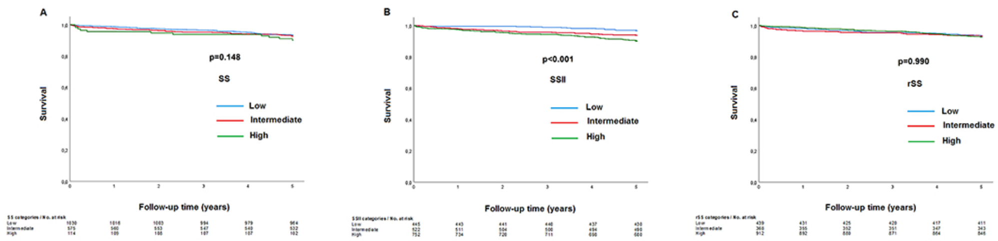
Figure 2 Kaplan-Meier Curves for 5-year All-Cause Mortality.

Kaplan-Meier estimates for death in patients assigned to MT, PCI or CABG over 5 years of follow-up according to SYNTAX scores (SS: PCI [A], CABG [B] and MT [C]; SSII: PCI [D], CABG [E] and MT [F]; rSS: PCI [G], CABG [H] and MT [I]).

Figure 3 ROC Curves SYNTAX Scores for Discrimination of All-Cause Mortality in the PCI, CABG, and MT Groups.

ROC curves SYNTAX scores for Mortality in MASS database (A), PCI group (B), CABG group (C), and MT group (D).

* In the MT group, SS has the same value as rSS. Therefore, the ROC curves are superimposed (Figure 3D).



Kaplan-Meier curves for mortality stratified by SS (2A), SSII (2B), and rSS (2C) regardless of strategy of treatment (PCI, CABG, or MT).

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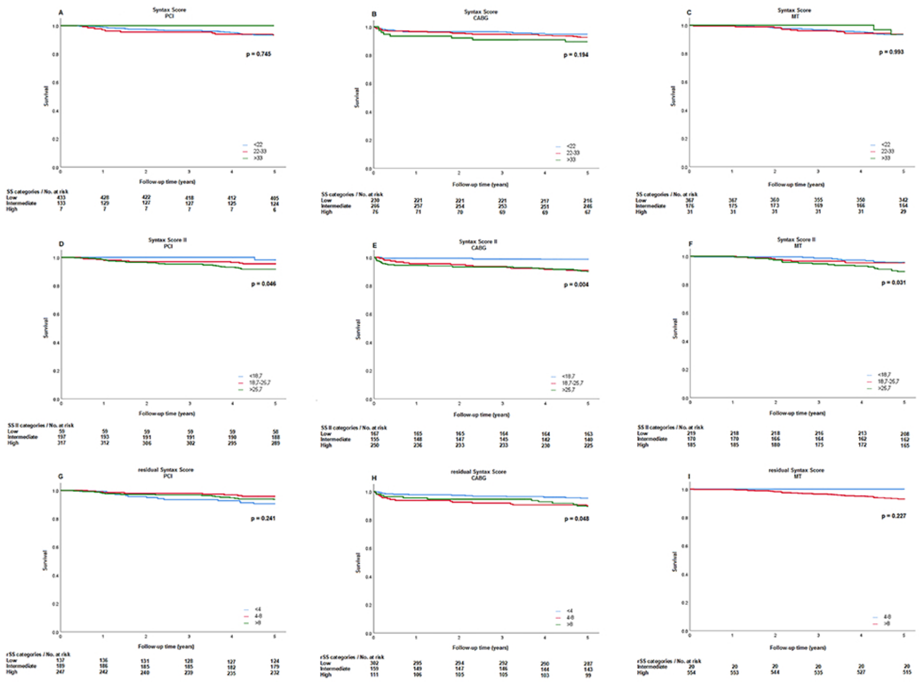

Kaplan-Meier estimates for death in patients assigned to MT, PCI or CABG over 5 years of follow-up according to SYNTAX scores (SS: PCI [A], CABG [B] and MT [C]; SSII: PCI [D], CABG [E] and MT [F]; rSS: PCI [G], CABG [H] and MT [I]).

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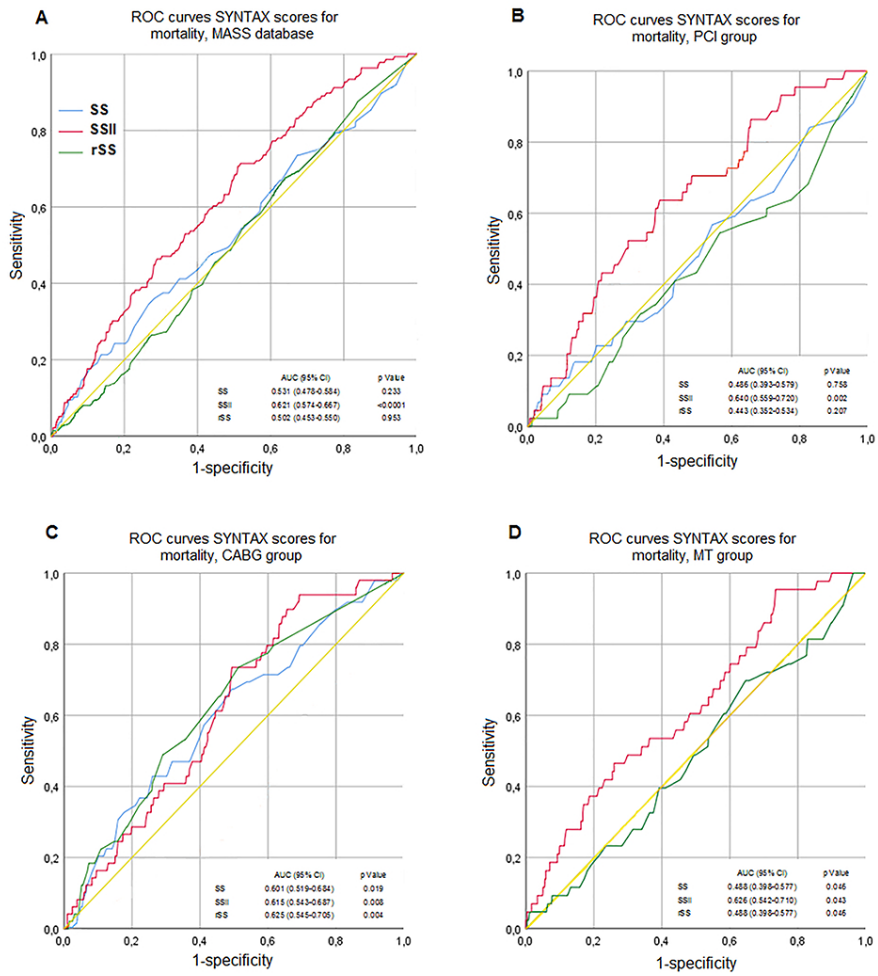


ROC curves SYNTAX scores for Mortality in MASS database (A), PCI group (B), CABG group (C), and MT group (D). * In the MT group, SS has the same value as rSS. Therefore, the ROC curves are superimposed (Figure 3D).

228x228mm (118 x 118 DPI)

Supplementary Material

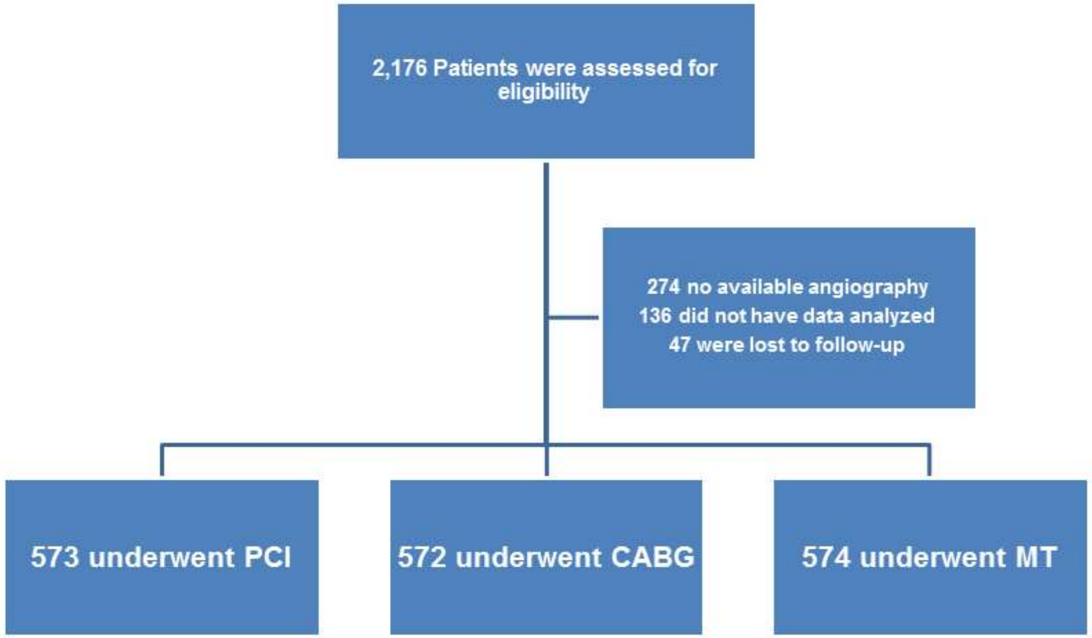
Figure S1. **Enrollment of Patients With Coronary Artery Disease in the MASS Database.**

Table S1. **Inclusion and Exclusion Criteria.**

Table S2. **SYNTAX scores subgroups definition.**

Table S3. **Kaplan-Meier Estimates of Events at 5 Years by SYNTAX Scores Categories and Treatment Arm.**

Figure S1. **Enrollment of Patients With Coronary Artery Disease in the MASS Database.**



Flowchart for patients included in the MASS database SYNTAX scores analysis. CABG = coronary artery bypass graft; MT = medical treatment; PCI = percutaneous coronary intervention.

Table S1. **Inclusion and exclusion criteria.**

Inclusion criteria	
•	Multivessel CAD (defined as stenosis ≥ 70% in at least 2 of the 3 main coronary arteries)
•	Preserved LVEF
•	Stable CAD
Exclusion criteria	
•	Refractory angina or acute MI requiring emergency revascularization
•	Ventricular aneurysm requiring surgical repair
•	Left ventricular ejection fraction of <40%
•	Previous PCI or CABG
•	Single-vessel CAD
•	History of congenital heart disease, valvular heart disease, or cardiomyopathy
•	Patients unable to understand or cooperate with the protocol requirements
•	Left main coronary artery stenosis of ≥50%
•	Suspected or known pregnancy
•	Another coexisting condition that was a contraindication to CABG or PCI.

Table S2. **SYNTAX scores subgroups definition.**

SYNTAX scores	Low	Intermediate	High
SS	≤22	23 to 32	≥33
SSII	<18.7	18.7 to 25.7	>25.7
rSS	0 to 4	>4 to 8	>8

Legend: SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score.

Table S3. **Kaplan-Meier Estimates of Events at 5 Years by SYNTAX Scores Categories and Treatment Arm.**

	SS											
	PCI				**CABG**				**MT**			
	Low	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**
Death	6.5	6.8	4.3	0.745	5.7	8.0	12.1	0.194	6.8	6.9	6.5	0.993
MACCE	27.1	34.8	42.9	0.122	15.9	19.1	20.3	0.620	24.3	28.5	25.8	0.580
Cardiac death	2.1	3.1	0	0.746	1.8	2.3	0	0.429	2.5	2.9	6.4	0.463
MI	5.7	9.4	0	0.268	7.2	6.3	1.3	0.208	7.2	9.7	6.5	0.510
Stroke	2.4	3.8	28.6	<0.001	2.7	4.7	7.4	0.257	1.9	3.5	3.2	0.550
Further revascularization	18.6	22.6	14.3	0.549	5.5	5.6	1.5	0.353	18.0	18.2	19.8	0.981
	SSII											
	PCI				**CABG**				**MT**			
	Low	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**
Death	1.7	4.6	8.9	0.046	1.8	9.8	10.2	0.004	5.0	4.7	10.8	0.031
MACCE	18.7	28.4	31.4	0.132	11.6	20.3	20.8	0.042	23.3	24.7	29.2	0.447
Cardiac death	0	2.0	2.9	0.381	0	1.3	3.3	0.052	1.8	3.0	4.0	0.468
MI	6.9	5.6	6.9	0.884	4.3	6.9	6.7	0.540	6.0	9.5	9.0	0.375
Stroke	1.7	1.6	4.3	0.185	1.8	5.6	5.2	0.200	1.4	1.8	4.5	0.114
Further revascularization	15.4	20.3	19.6	0.687	6.2	5.5	3.8	0.601	19.1	19.9	15.2	0.468
	rSS											
	PCI				**CABG**				**MT**			
	Low	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**	**Low**	**Intermediate**	**High**	**Log-rank p Value**
Death	9.5	4.8	6.5	0.241	5.1	10.1	11.2	0.051	-	0	7.1	0.227
MACCE	27.8	29.8	29.3	0.916	15.1	19.7	23.1	0.164	-	10.0	26.2	0.121
Cardiac death	2.4	1.6	2.9	0.686	1.0	2.0	3.8	0.195	-	0	2.9	0.440
MI	8.3	7.4	5.0	0.416	6.5	4.6	6.6	0.725	-	5.0	8.1	0.624
Stroke	3.1	4.3	2.1	0.410	3.8	4.1	5.7	0.680	-	5.0	2.4	0.465
Further revascularization	16.7	20.5	20.0	0.669	4.9	5.5	4.6	0.964	-	10.0	17.4	0.331

Values are presented as %.
Legend: MI = myocardial infarction; SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Retrospective cohort study in title and abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found See abstract
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Page 4
Methods		
Study design	4	Present key elements of study design early in the paper Pages 4 and 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Pages 5 and 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Pages 5 and 6
Bias	9	Describe any efforts to address potential sources of bias Page 6
Study size	10	Explain how the study size was arrived at All available patients were included
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Pages 6 and 7 (Method of handling variables was reported. The criteria for selecting groups were detailed).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 7
		(*b*) Describe any methods used to examine subgroups and interactions Page 7
		(*c*) Explain how missing data were addressed Page 8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed

	Page 8 *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(e) Describe any sensitivity analyses Pages 7, 12, 13, Figure 3

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 8
		(b) Give reasons for non-participation at each stage Page 8
		(c) Consider use of a flow diagram Figure S1 in the Supplement
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) Page 8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Pages 11 and 12. Figures 1 and 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Pages 11-13, Table 3
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Pages 16 and 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results Pages 16 and 17
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based The study was not funded.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.