



Original Article

Long-term outcomes following left main bifurcation stenting in Indian population—Analysis based on SYNTAX I and II scores



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ABSTRACT

Background: Syntax 1 and recently Syntax 2 (SS2) scores are validated risk prediction models in coronary disease.

Objectives: To find out the long term outcomes following stenting for unprotected left main bifurcation disease (LMD) and to validate and compare the performance of the SYNTAX scores 1 and 2 (SS1 and SS2 PCI) for predicting major adverse cardiac events (MACE) in Indian population.

Methods: Single-center, retrospective, observational study involving patients who underwent percutaneous coronary intervention (PCI) with at least one stent implanted for the LMD. Discrimination and calibration models were assessed by ROC curve and the Hosmer-Lemeshow test.

Results: Data of 103 patients were analyzed. The mean SS1 and SS2 scores were 27.9 and 30.7 and MACE was 16.5% at 4 years. The target lesion revascularization (TLR) rate at 4 years was 11 (10.7%). There were 4 deaths (3.8%). The mean left ventricular ejection fraction (LVEF) was the only variable in SS2, which predicted cardiac events. ROC curve analysis showed both models to be accurate in predicting TLR and mortality following LM PCI. SS2 score showed a better risk prediction than SS1 with AUC for TLR (SS1 0.560 and SS2PCI 0.625) and AUC for mortality (SS1 0.674 and SS2PCI 0.833). Hosmer-Lemeshow test validated the accuracy of both the risk models in predicting the events.

Conclusions: Both risk models were applicable for Indian patients. The SS2 score was a better predictor for mortality and TLR. In the SS2 score, the LVEF was the most useful predictor of events after LM PCI.

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1. Introduction

Left main disease (LMD) is seen in up to 15% cases subjected for angiography.¹ It is considered as a potentially lethal entity and requires early revascularization either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Unprotected LMD is associated with poor prognosis when medically treated.^{2,3} CABG is the gold standard treatment.^{4–9} But of late, PCI with drug eluting stents has shown non-inferiority to CABG in ostial and shaft LMD.^{7,10} More than 80% of lesions in left main (LM) in clinical practice tend to involve the bifurcation and the long – term outcomes following left main bifurcation stenting has always been a concern. But recent trials have even shown that even with bifurcation LMD, the results of PCI may be superior to CABG.^{8,10} Large-scale trials and meta-analysis support that survival

is at least similar for both CABG and PCI up to 5 years in LMD.^{10–12} This consistent non-inferiority has been reflected in the current European revascularization guidelines with PCI of the LMD being upgraded to a class I and IIa for patients with a low and intermediate SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score, respectively.^{1–3} Given the fact that LMD often co-exists with multivessel coronary artery disease (CAD), the outcomes vary and are completely different in such situations.^{11–14} Mortality following revascularization is a subject of research in multivessel disease with various risk scores being published.^{3,6,7,14} The most popular being the SYNTAX scores.^{1–3} While the SYNTAX I (SS1) scoring focused only on angiographic severity of coronary lesions, in SYNTAX II (SS2), both angiographic and clinical variables are included in predicting the outcomes following PCI versus CABG in the setting of complex multivessel disease.¹² Nevertheless, selecting the optimal revascularization strategy remains challenging. Despite the inherent limitations, risk stratification tools are useful adjuncts for decision-making particularly in a heart team setting. While the data based on these risk models are available in

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European and North American population, data from the Indian sub continent is scarce in this regard. We therefore analyzed the long-term outcomes and major cardiac events in patients with LMD following PCI based on the syntax scores. The SS1 was created as part of the SYNTAX trial in order to objectively characterize the severity of CAD, stratifying patients into low (SS1 <22), intermediate (SS1 23–32) and high (SS1 >33) risk tertiles. Within this population, the 5-year follow-up supports PCI as an acceptable alternative to CABG for patients with LMD with a low or intermediate risk SS1 score. While the prognostic value of the SS1 has been studied and substantiated in LM PCI patients, some limitations have been pointed out, namely the absence of clinical variables, lack of a personalized approach to decision-making and absence of predictive ability in the CABG subset.^{1,5,6}

The SS2 emerged to overcome some of the limitations, by incorporating prognostically important clinical variables (such as age, gender, left ventricular ejection fraction (LVEF), creatinine clearance (CrCl), presence or absence of chronic obstructive airway disease (COPD) and peripheral artery disease (PAD)) and by giving an individualized estimate of mortality risk associated with each revascularization strategy⁸. By applying the SS2 in the all-comers population of the SYNTAX trial it was shown that subset of patients existed in all the tertiles of SS1 for which both CABG (SS2 CABG group) and PCI (SS2 PCI group) would confer mortality benefit.

2. Objectives

1. To find out the long-term outcomes in terms of mortality and major cardiac events (MACE) i.e. (death, myocardial infarction, target vessel revascularization rates (TLR) and stroke) following LM bifurcation stenting in Indian patients.
2. To validate the predictive power of SYNTAX scores (SS1 and SS2 PCI) in LMD who undergo bifurcation PCI.

3. Methods

This was a single-center, retrospective, observational study of patients who underwent LM PCI between March 2009 and December 2012 with at least one stent implanted in the LM bifurcation. Both single/provisional and planned two stent strategy patients were included in the study. The interventional strategy was left to the discretion of the treating operator. Acceptance of the patient for LM stenting required the consensus of the Heart Team involved in the decision-making. All data concerning demographic, clinical, angiographic and procedural characteristics were collected from the institutional cath lab-based dedicated database. Patients with 4-year follow up data were studied. All angiograms were retrospectively analyzed, by two operators blinded for clinical outcomes, for assessment of the angiographic variables necessary for the calculation of the SS1. The SS1 was calculated using the online calculator (<http://www.syntaxscore.com/calculator/start.htm>). The SS2 was estimated manually in each patient for both revascularization strategies (SS2 for PCI and SS2 for CABG) by matching the sum of points of both clinical (age, sex, COPD, CrCl, LVEF, PAD) and angiographic variables (SS1 and left main disease) with the corresponding prediction, using the published nomogram (<http://www.syntaxscore.com/calculator/start.htm>) SS2 PCI score alone was considered for this study analysis, as CABG was not part of the study. The follow up of patients was done by clinical visits every 3 months and telephonic conversation for those who lived far away (more than 100 km) from the center. Check angiograms were performed in patients who reported symptoms of angina or angina equivalent and/or positive non-invasive stress test (treadmill/stress perfusion imaging). This was according to the existing protocol. Routine follow up angiogram was not performed as part

of the study and re intervention was driven by clinical decisions. Use of fractional flow reserve was left to the operator's decision and performed in intermediate re-stenotic lesions (30–70%) before planning re-intervention.

3.1. Statistical methods

The distribution of categorical variables such as gender, use of intravascular ultrasound (IVUS), re intervention rates and mortality were expressed in terms of frequency and percentage. The distribution of continuous variables such as age, LVEF, SS1 and SS2 PCI were expressed in terms of mean with standard deviation. The association of TLR with gender, PAD, COPD, and mortality status was carried out by using Chi-square test. The comparison of age and LVEF in relation to other categorical variables was carried out by using independent Student's *t*-test. The Receiver Operator Characteristics Curve (ROC) along with area under curve (AUC) was used to assess the predictive power of SS1 and SS 2 for TLR and mortality. All statistical analysis was carried out at 5% level of significance with *p*-value < 0.05 was considered as statistically significant. The performance of the risk models was analyzed focusing on discriminative power and calibration. Discrimination indicates the extent to which the model distinguishes between patients who will or will not have MACE. It was evaluated by constructing ROC for each model. Calibration refers to the agreement between predicted outcomes and observed outcomes. The statistical analysis was carried out using IBM PASW statistics (SPSS) – Version 19.0.

4. Definitions

The LM stem was defined as unprotected if there was no patent bypass graft to the left anterior descending artery or the circumflex artery. Acute myocardial infarction during follow-up was defined according to the 2012 Universal definition of myocardial infarction.¹⁵ Target vessel revascularization (TLR) and target lesion revascularization were defined as any revascularization procedure of the target vessel or target lesion (from 5 mm distal to the stent up to 5 mm proximal to the stent), respectively. Cardiovascular death was defined as death due to a demonstrable cardiovascular cause or any unexplained death. Stroke was defined as new neurological defect adjudicated by a neurologist based on clinical and imaging features. The primary endpoint (MACE) was defined as the composite outcome of death, nonfatal myocardial infarction, TLR and stroke. These composite end points were assessed and compared with respect to SS1 and SS2 PCI scores.

5. Results

Out of the total 132 patients who underwent LM PCI during the study period, complete 4-year follow-up data was available for 103 patients. Among these 84 (81.5%) were males, the mean age of the patients participated in the study was 54.86 (± 11.43) years (Table 1). The mean age of male patients was 54.58 + 11.28 years and among female it was 56.11 (± 12.32). The mean LVEF among male patients was 52.2 (± 11.66) and it was marginally lower (*P* = 0.053) in females 58.2 (± 13.74). The mean SS1 score among the patients participated in the study was 27.9 (± 3.98) and the mean SS2 PCI score was 29.43 (± 9.005). The total MACE rates (TLR, death, MI and stroke) were 17 (16.5%). The TLR rate was 11 (10.7%) with 19 females 3 (15.8%) and 8 (9.5%) males (*p* = 0.425). There were 4 (3.9%) deaths in the group and 2 patients had myocardial infarction. No strokes were reported. Procedural characteristics are given in Table 2.

The mean age and LVEF were found to be lower among the patients having TLR, however the difference was not found to be

Table 1
Baseline characteristics (N = 103).

Age (mean ± SD)	54.86 ± 11.43
Male sex(%)	84(81.5%)
Creatinine clearance (ml/min) (mean ± SD)	78.82 ± 21.5
Pulmonary chronic obstructive disease (%)	12(11.6%)
Peripheral artery disease (%)	9(8.7%)
Ejection fraction (mean ± SD)	53.32 ± 10.17
Diabetes(%)	56(53%)
Dyslipidemia or statin treatment (%)	97(94.1%)
Hypertension on drug therapy(%)	49(47.5%)
Family history of cardiovascular disease (%)	7(6.7%)
Smoking (current)(%)	29(28.1%)
Stable CAD (%)	59(57.2%)
Acute coronary syndrome (%)	44(42.7%)
Non-ST elevation myocardial infarction (%)	5(4.85%)
ST-elevation myocardial infarction (%)	39(37.8%)
Cardiogenic shock (%)	1(0.9%)
Multi-vessel CAD (%)	53(51.4%)

Table 2
Procedural characteristics (N = 103).

Medina Class	
1,1,1	56(54.3%)
1,1,0	34(33.5%)
1,0,1	13(12.2%)
Drug eluting stent (%)	103(100%)
Promus Element (Everolimus)	73(70.8%)
Xience V (Everolimus)	10(9.7%)
Endeavour (Zotarolimus)	20(19.4%)
Intravascular ultrasound use (%)	56(54%)
Single stent strategy (%)	66(64%)
Double stent strategy (%)	37(36%)
Crush technique	21(58.3%)
TAP technique	15(40.54%)
SKS	1(2.70%)
Other vessel PCI	46(44.6%)
IABP use	21(20.3%)
Glycoprotein IIb/IIIa inhibitors	4(3.8%)
Choice of second antiplatelet drug	
Clopidogrel/Prasugrel/Ticagrelor in %	76%/13%/11%

statistically significant ($p = 0.088, 0.103$). The mean scores of SS 1 and SS 2 PCI were found to be marginally higher among the patients with TLR ($p = 0.681, 0.723$) (Table 3). None of the clinical variables in SS2 except LVEF were significantly related to TLR rates. There were no strokes reported.

The comparison of different variables in relation to mortality was given in Table 4. The mean age was found to be lower among the mortality cases, however the difference was not found to be statistically significant ($p = 0.910$). The mean LVEF was found to be significantly lower ($p = 0.001$) among the mortality cases. The mean scores of SS1 and SS2 PCI were found to be marginally higher

Table 3
The comparison of different variables in relation to target lesion revascularization (TLR).

Variables	TLR	N	Mean	SD	Statistical significance
Age in years	No	92	55.24	11.812	$p = 0.088$
	Yes	11	51.73	7.115	
LV EF%	No	92	53.83	11.907	$p = 0.103$
	Yes	11	49.09	14.536	
SYNTAX 1	No	92	27.83	4.102	$p = 0.681$
	Yes	11	28.45	2.806	
SYNTAX 2 PCI	No	92	29.143	9.2575	$p = 0.723$
	Yes	11	31.782	6.3491	

Table 4
The comparison of different variables in relation to Mortality.

Variables	N	Mean	SD	Statistical significance
Age in years	No Mortality	99	55.01	$p = 0.910$
	Mortality	4	51.25	
LVEF%	No Mortality	99	53.81	$p = 0.001$
	Mortality	4	41.25	
SYNTAX 1	No Mortality	99	27.81	$p = 0.817$
	Mortality	4	30.00	
SYNTAX 2 PCI	No Mortality	99	29.087	$p = 0.321$
	Mortality	4	37.800	

*Among the different variables in SS2 score, only Left ventricular ejection fraction (LVEF) was shown to be significantly different.

among mortality cases, but it was not found to be statistically significant ($p = 0.817, 0.321$). Among the 103 patients participated in the study, 4(3.9%) patients were expired. Mortality rate was marginally higher ($p = 0.203$) among females (10.5%) against 2.4% males.

The predictive power of SS1 and SS2PCI for the TLR and mortality was carried out by using Receiver Operating Curve (ROC). The area under curve for SS1 for predicting the TLR was 0.560 (54.5% sensitivity and 56.5% specificity with the cut off value of 28.5). The area under the curve for SS2PCI for predicting the TLR was 0.625 (Fig. 1) (63.6% sensitivity and 53.3% specificity with the cutoff value of 28.65) (Table 5)

The area under the curve for SS1 for predicting the mortality was 0.674, which yields 75% sensitivity and 66.7% specificity with the cutoff value of 29.5 (Table 6). The area under curve for SS2PCI for predicting the mortality was 0.833, which yields 100% sensitivity and 87.8% specificity with the cut off value of 34.35 (Fig. 2). The calibration analysis with Hosmer-Lemeshow goodness-of-fit test showed acceptable fit for both the models in terms of predicting TLR as well as mortality. All patients who died had decreased LVEF. It was observed that the mortality was not associated with other variables of SS2 (Age, renal function, gender, COPD and PAD) (Table 7).

There were a total of 4 deaths in the left main bifurcation PCI cohort of 132 patients during the study period. One death occurred immediately after stent placement. This patient with post MI LV dysfunction developed bradycardia and widening of QRS worsening to cardiac asystole and could not be revived. Two deaths occurred in the first month of PCI and the patients died suddenly following chest pain and the cause of death is presumed to be sub

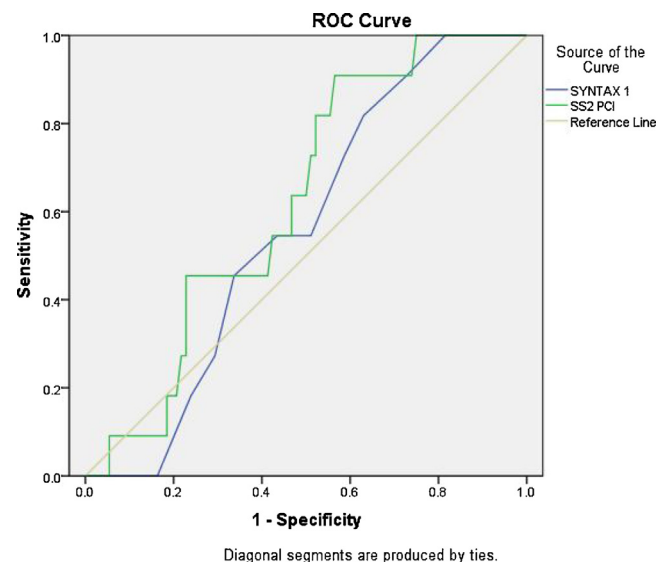
**Fig. 1.** ROC curve analysis of syntax I and syntax II PCI scores in predicting TLR.

Table 5

Predictive power of SYNTAX 1 (SS1) and SYNTAX 2 (SS2)PCI for predicting target vessel revascularization (ROC analysis).

Test Variable	Area	Cutoff Value	Sensitivity	Specificity
SS 1	0.560	28.5	54.5%	56.5%
SS2 PCI	0.625	28.65	63.6%	53.3%

Table 6

Predictive power of SYNTAX 1 and SS2PCI for predicting mortality (ROC analysis).

Test Variable	Area	Cutoff Value	Sensitivity	Specificity
SS 1	0.674	29.5	75%	66.7%
SS2 PCI	0.833	34.35	100%	34.35%

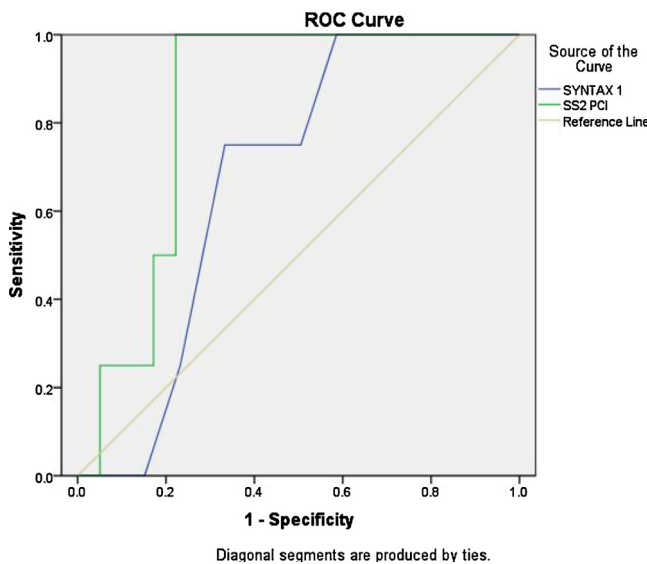


Fig. 2. ROC curve analysis of syntax I and syntax II PCI scores in predicting mortality.

acute stent thrombosis. The fourth patient collapsed 48 h after procedure with no h/o chest pain reported. The cause was thought to be arrhythmic in origin. There was one death in the cohort after 4.5 years following PCI, which was not included in the final analysis as the study looked at 4-year outcomes.

Table 7

Association of mortality with gender, COPD, PAD and Renal function.

Variables	Mortality		Significance Value
	Yes	No	
<i>Gender</i>			
Male	3	81	0.662
Female	2	17	
<i>COPD</i>			
Yes	0	8	0.662
No	5	90	
<i>PAD</i>			
Yes	0	8	0.229
No	5	90	
<i>Creatinine clearance ml/min (mean ± SD)</i>	74 ± 7.314	77.11 ± 13.78	0.618

NB: COPD = chronic obstructive airway disease; PAD = peripheral arterial disease.

6. Discussion

We studied the long term outcomes following LM PCI based on two risk prediction models namely SSI and SS2 PCI. The study group had an over all MACE rate of 16.5% at the end of four years with 3.8% mortality. The mean SS1 and SS2 PCI scores were marginally higher in the MACE group. The notable findings of our study were: 1) both scoring systems had a modest performance in predicting the TLR; 2) The SS2 PCI improved the performance of the purely anatomic SS1 score in mortality prediction following LM PCI; 3) Among the clinical variables in SS2, the LVEF was the single most important factor associated with mortality.

The findings are in line with the previous studies assessing the association between the SS1 and clinical outcomes, at different time points.^{1,12,16,17,18,24} In our study, the AUC of the SS1 for 4-year MACE was 0.67, which is comparable to that shown in other cohorts of LMD PCI with shorter follow-up (AUCs for SS1 between 0.53 and 0.64).^{19–23} As in our dataset, others have also shown a poorer discrimination by SS1 for overall composite MACE than for cardiac mortality in patients undergoing PCI.

Scarce data exists on the additional value of the SS2. It has been externally validated for long-term mortality in the *Drug Eluting stent of left main coronary artery disease (DELTA)* registry^{12,25} and in a large single-center registry by Xu et al that included 1528 patients with LMD subjected for PCI.²¹ In these cohorts, the SS2 PCI showed an AUC for 4-year mortality of 0.72 and 0.69, respectively, similar to that shown in the original SYNTAX trial population (AUC of 0.73), clearly outperforming the SS1 (AUCs of 0.57, 0.61 and 0.59, in the SYNTAX, DELTA and Xu populations, respectively). The results on mortality showed the AUC for SS1 for predicting the 4-year mortality being 0.67 and for the SS2-PCI 0.83 (which is higher than to the DELTA registry). We believe that these small differences occurred due to the smaller sample size and differences in the rate of the primary endpoint. Recently, the SS2 was prospectively applied to patients included in the Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial. It indicated equipoise for long-term mortality between CABG and PCI in subjects with LMD and intermediate anatomical complexity, and strengthened the notion that both clinical and anatomical features influence mortality predictions.

The calibration analysis showed goodness of fit for both the models and validated the same. For practical and clinical purposes, the SS2 seems to have a more predictable behavior. Furthermore one variable of SS2 PCI, the LVEF, shown to predict events independently and therefore we believe SS2 PCI model should be

better suitable for decision-making. Albeit in a small number of patients, these risk scores may be applicable to an unselected Indian patient cohort – with results that are broadly comparable to those from larger European and US registries/trials.^{17,18,24}

The risk factor models involving clinical variables should provide more information on long-term outcomes in a cohort of LMD PCI. In a recent publication by Janella et al from Brazil,²⁶ involving retrospective analysis of 349 patients with 6 risk score models (viz. SS1, SS2, ACEF (age, creatinine clearance, ejection fraction score) residual syntax score, syntax revascularization index, and clinical syntax score), the SS2 risk model provided the most precise predictive performance on mortality. This study had patients with multivessel disease and left main disease and mortality at 4 years was the primary endpoint. In comparison, our study involved lesser patients studied in a prospective manner. However the AUC for SS2 PCI is comparable in both the studies. We found SS2 PCI to be predictive for TLR as well.

7. Limitations of the study

Some important limitations should be pointed out in our study. First, the inherent limitations of a single-center retrospective study. Second, the small number of patients and low death events has limited the power of the statistical analysis and the ability to find statistical significance for many of the comparisons. The survival curve analysis was not informative as described earlier. Data on all cause mortality were unavailable for analysis. Our analysis did not include the different stenting techniques for bifurcation lesions. Not only that there were variations in the stenting strategies (with and without imaging guidance like IVUS) throughout the study period, but these could also play a role in defining the complexity and success of the procedure and outcomes. The SS2 score was analyzed in PCI alone. There was no control CABG arm.

8. Conclusions

Although small in number, the study validates the Syntax risk prediction models (SS1 and SS2 PCI) in predicting outcomes after LM PCI in the Indian population. The four year mortality following LM stenting was in our series was 3.8%. The SS2 score was a better predictor for mortality and TLR. Of the various clinical variables in SS2, the LVEF was the only predictor of death and TLR after LM PCI.

Conflicts on interests

None.

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