ORIGINAL ARTICLE

The impact of coronary artery disease severity on long-term outcomes in unprotected left main coronary artery revascularization

Korunmasız sol ana koroner arter revaskülarizasyonunun uzun dönem sonuçları üzerine koroner arter hastalığı yaygınlığının etkisi

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ABSTRACT

Objective: The optimal treatment modality for left main coronary artery (LMCA) disease is still controversial. The aim of this study was to investigate long-term prognostic determinants of percutaneous coronary intervention (PCI) for LMCA disease and the role of coronary artery disease (CAD) severity in this population.

Methods: A total of 60 consecutive patients who underwent LMCA PCI were enrolled in this study. Baseline demographic and clinical variables were recorded, as well as the SYNTAX score (SS), SS II, and residual SS (rSS). The primary endpoints of the study were all-cause death, non-procedural myocardial infarction (MI), and stroke. The patients were then divided into 2 groups: patients without a composite endpoint (Group 1) and those with a composite endpoint (Group 2).

Results: Of the 60 patients, 15 (25%) were female and the mean age was 59.8±14.7 years. The median follow-up time was 25 months (range: 12–33 months). A primary composite endpoint was observed in 16 patients (26.7%): mortality occurred in 10 patients (16.7%), 4 (6.6%) experienced MI, and stroke was seen in 2 patients (3.3%). Target vessel revascularization was performed in 3 patients (5%). The mean SYNTAX score (Group 1: 19.9±9.8; Group 2: 26.8±12.2; p=0.029), SS II PCI (Group 1: 27.7 [range: 17.7–36.8]; Group 2: 34.2 [range: 27.9–55.2]; p=0.030) and rSS (Group 1: 0 [range: 0–5]; Group 2: 12.5 [range: 3.5–22.5]; p=0.001) were higher in patients with a composite endpoint. Additionally, creatinine (odds ratio [OR]:13.098; 95% confidence interval [CI]: 1.471–116.620; p=0.021), non-postdilatation (OR: 8.340; 95% CI: 1.230–56.570; p=0.030), and rSS (OR: 1.157; 95% CI: 1.024–1.307; p=0.019) were independent predictors of a primary composite endpoint.

Conclusion: CAD severity has prognostic value for mortality, MI, and stroke in patients who undergo unprotected LMCA PCI. An increased initial SS and post-procedural rSS were related to adverse cardiovascular outcomes. The rSS was also an independent predictor of major adverse cardiac and cerebrovascular events and mortality.

ÖZET

Amaç: Sol ana koroner arter hastalığının optimal tedavisi halen tartışmalıdır. Çalışmamızdaki amacımız sol ana koroner arter hastalığına perkütan koroner girişim (PKG) uygulanan hastalardaki uzun dönem prognostik belirteçleri ve bu popülasyondaki koroner arter hastalığı (KAH) yaygınlığının rolünü incelemektir.

Yöntemler: Toplam 60 adet ardışık sol ana koroner artere PKG uygulanan hasta çalışmamıza dahil edildi. SYNTAX skoru (SS), SS II ve rezidüel SS (rSS) yanı sıra bazal demografik ve klinik değişkenler kayıt edildi. Çalışmamızın birincil sonlanım noktaları tüm nedenlere bağlı ölüm, işleme bağlı olmayan miyokart enfarktüsü (ME) ve inmedir. Hastalar daha sonra 2 gruba ayrıldı: Kompozit sonlanım noktası olmayan hastalar (Grup 1) ve kompozit sonlanım noktasına sahip olanlar (Grup 2).

Bulgular: Altmış hastanın 15'i (%25) kadın olup ortalama yaş 59.8±14.7 idi. Ortanca takip süresi 25 (dağılım, 12–33 ay) aydı. Birincil kompozit sonlanım kriterleri 16 hastada (%26.7) görülmüş olup 10 hastada (%16.7) hastada mortaliteyi, 4 hastada (%6.6) ME'yi ve 2 hastada (%3.3) inmeyi içermektedir. Hedef damar revaskülarizasyonu 3 hastada (%5) uygulanmıştır. Ortanca SYNTAX skoru (Grup 1: 19.9±9.8; Grup 2: 26.8±12.2, p=0.029), SYNTAX II PKG skoru [Grup 1: 27.7 (dağılım, 17.7–36.8); Grup 2: 34.2 (dağılım, 27.9–55.2), p=0.030] ve rSS [Grup 1: 0 (dağılım, 0–5); Grup 2: 12.5 (dağılım, 3.5–22.5), p=0.001] birleşik sonlanımları olan hastalarda daha yüksektir. Ayrıca kreatinin (odds oranı [OR]=13.098; %95 güven aralığı [GA]=1.471–116.620; p=0.021), postdilatation yapılmaması (OR=8.340; %95 GA=1.230–56.570; p=0.030) ve rSS (OR=1.157; %95 GA=1.024–1.307; p=0.019) birincil birleşik sonlanımlar için bağımsız ön gördürücüler olarak saptandı.

Sonuç: KAH yaygınlığının sol ana koroner artere PKG uygulanan hastalarda mortalite, ME ve inme üzerine prognostik değeri vardır. Artmış başlangıç SS ve işlem sonrası rezidüel SS'leri olumsuz kardiyovasküler sonlanımlar ile ilişkilidir. rSS ayrıca MACCE ve mortalitenin bağımsız öngördürücüsüdür.

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The efficacy and safety of percutaneous coronary intervention (PCI) for left main coronary artery (LMCA) disease has been evaluated in several clinical studies and observational registry analyses. In recent years, PCI has been accepted as an alternative treatment modality to coronary artery bypass grafting (CABG) in patients with unprotected LMCA disease and low-to-intermediate coronary artery disease (CAD) severity as a result of improved PCI strategies and more effective medical therapy. The SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score (SS) was developed to determine the complexity and severity of coronary atherosclerosis and is used as a risk determinant and to decide upon a revascularization modality in patients with complex coronary anatomy.[1] In previous large-scale, randomized clinical trials, it has been demonstrated that PCI was non-inferior to CABG for unprotected LMCA revascularization in patients with a low-to-moderate SS. In the SYNTAX trial, the rate of a major adverse cardiac and cerebral event (MACCE) was similar between PCI and CABG groups in patients with low or moderate SS, while it was higher in patients with a high SS (≥33), mainly due to the greater need for repeat revascularization in the PCI group.[2] Similarly, the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial showed that there was no significant difference between PCI and CABG in patients with low-to-intermediate SS (≤32).[3] In contrast, the NOBLE (Nordic-Baltic-British Left Main Revascularization Study) research revealed more adverse cardiovascular and clinical outcomes with PCI than CABG due to higher revascularization rates, especially in patients with a high SS (>32).[4] These data suggest that an increased coronary atherosclerotic burden may be associated with impaired clinical outcomes in patients with unprotected LMCA disease after PCI. It may be related to increased residual CAD severity after revascularization of the LMCA. The objective of this study was to investigate long-term prognostic determinants of percutaneous intervention for unprotected LMCA disease and the role of CAD severity in this population.

METHODS

Study population

A total of 60 consecutive patients who underwent unprotected LMCA PCI were enrolled in this retrospective, observational study. The study was conducted at a single high-volume, tertiary center from 2010 to 2018. Patients with stable CAD, unstable CAD, or acute coronary syndrome and both provisional (single) or 2-stent planned strategy were included in the study. At least 1 stent implantation was performed for each patient. Intravascular ultrasound imaging was not used in any of the study cases. Patients who underwent CABG or were followed up with medical therapy alone, and patients with moderate-to-severe valvular heart disease, a mechanical complication of myocardial ischemia, malignancy, or a life expectancy <1 year were excluded from the study. The study was approved by the local ethics committe at Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital on October 9, 2018 (no: 2018-39).

Abbreviations:

AUC	*Area under the curve*
CABG	*Coronary artery bypass grafting*
CAD	*Coronary artery disease*
CI	*Confidence interval*
CXA	*Circumflex artery*
DES	*Drug-eluting stent*
LAD	*Left anterior descending*
LMCA	*Left main coronary artery*
MACCE	*Major adverse cardiac and cerebrovascular event*
MI	*Myocardial infarction*
NSTEMI	*Non-ST-segment elevation*
OR	*Odds ratio*
PCI	*Percutaneous coronary intervention*
POT	*Proximal optimization technique*
RCA	*Right coronary artery*
ROC	*Receiver operating characteristic*
rSS	*Residual SS*
SS	*SYNTAX score*
STEMI	*ST-segment elevation MI*
SYNTAX	*Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery*
TVR	*Target vessel revascularization*

Coronary angiographic evaluation

Coronary angiography was performed via femoral or radial access for each patient with a 6-F or 7-F guiding catheter. Intravenous heparin administration was performed in all cases according to recent guidelines. Balloon predilatation with non-compliant or compliant coronary balloons, as well as post-dilatation with kissing balloon dilatation and/or proximal optimization were performed as appropriate. Dual antiplatelet therapy with acetylsalicylic acid and clopidogrel, prasugrel, or ticagrelor were prescribed for 6 to 12 months, and for at least 12 months for patients with acute coronary syndrome. Two independent, experienced cardiologists evaluated coronary angiographic images individually to calculate the SS, SS II, and residual SS (rSS). The anatomical-based SS was calculated using coronary arteries with ≥50% luminal

stenosis and ≥1.5 mm diameter. Coronary arteries were divided into 16 segments. Each segment had a pre-specified corresponding weighing factor, as well as other determinant factors such as calcification and lesion length that were assessed and taken into account in the SS. Clinical variables such as age, gender, creatinine clearance, left ventricular ejection fraction, and characteristics of peripheral vascular disease or chronic obstructive pulmonary disease were recorded and used to calculate SS II. Finally, the rSS was calculated based on the remaining obstructive CAD after performing PCI for LMCA disease. The SYNTAX score calculator (www.SYNTAXscore.com) was used to obtain each score.

Clinical evaluation and follow-up

Baseline clinical and demographic variables of patients were recorded using the hospital database information. After the index procedure, patient's follow-up visits took place at the hospital or by telephone. Peri-procedural, post-procedural clinical evaluation, and death details were recorded. The primary endpoints of the study were non-procedural myocardial infarction (MI), stroke, and the composite of all-cause death and mortality. The patients were then divided into 2 groups: patients without a composite endpoint (Group 1) and those with a composite endpoint (Group 2).

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Data was expressed as n (%) for categorical variables, median (25^{th} and 75^{th} percentiles) for variables without a normal distribution and mean±SD for variables with normal distribution. The Pearson chi-squared, continuity-corrected chi-squared, and Fisher exact tests were used for categorical variables. After fitness to normal distribution was analyzed with the Kolmogorov-Smirnov test, Student's t-test was used to compare quantitative variables with normal distribution, and the Mann-Whitney U test was used to compare quantitative variables without a normal distribution. Univariate and multivariate logistic regression analyses were used to determine the independent predictors of the primary study composite endpoints. Receiver operating characteristic (ROC) analysis was conducted to determine the optimal SS, SS II, and rSS values to indicate both mortality and endpoints in terms of both sensitivity and specificity. The survival curve during long-term follow-up for these scores was analyzed using the Kaplan-Meier method, and a statistical assessment was performed using the log-rank test. A p value of <0.05 was considered statistically significant.

RESULTS

Sixty patients who underwent unprotected LMCA PCI were included in this study. Of these 60 patients, 15 (25%) were female and the mean age was 59.8±14.7 years. The primary endpoints of the study were MI, stroke, and all-cause death and mortality. The median length of follow-up was 25 months (12–33 months), and the longest period of follow-up was 60 months without a composite endpoint. Unprotected LMCA PCI was performed in 5 patients due to iatrogenic dissection of the LMCA during PCI of the left coronary artery system. Ten patients (16.7%) had osteal/proximal or mid LMCA disease, while 50 patients (83.3%) had a distal LMCA lesion. Of the 50 patients, 16 (26.7%) had a true bifurcation lesion. The median LMCA lesion percentage was 80% (25^{th}-75^{th} percentile: 70–90%). Provisional stenting was performed in 49 patients (81.7%) and a double-stent strategy was applied in 11 patients (18.3%). In addition, 39 patients (65%) had a left anterior descending (LAD) artery lesion, 30 patients (50%) had a circumflex artery (CXA) lesion, and 18 patients (30%) had a right coronary artery (RCA) lesion.

A primary composite endpoint was observed in 16 patients (26.7%): mortality occurred in 10 patients (16.7%), 4 (6.6%) experienced an MI (3 [5%] presented with ST-segment elevation MI [STEMI] and 1 [1.6%] with non-STEMI [NSTEMI]), and 2 patients (3.3%) suffered a stroke. Target vessel revascularization (TVR) was performed in 3 patients (5%). One presented with MI 7 months after the index procedure and was included in Group 2. TVR was performed in 2 patients with stable CAD during the follow-up period (Table 1).

Baseline demographic and clinical characteristics of the entire study population are demonstrated in Table 2. There were no statistically significant differences in age; gender; history of diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral arterial

Table 1. Clinical outcomes of the study population

Endpoint	Number of patients	
	n	%
Primary composite endpoint		
All-cause death	10	16.7
Myocardial infarction	4	6.6
NSTEMI	1	1.6
STEMI	3	5
Stroke	2	3.3
Repeat revascularization		
TVR	3	5
Acute ischemia driven	1	1.6
Clinically driven	2	3.3

NSTEMI: Non-ST-segment myocardial infarction; STEMI: ST segment elevation myocardial infarction; TVR: Target vessel revascularization.

disease, coronary artery disease, or atrial fibrillation; smoking status; level of leukocytes, thrombocytes, cholesterol, and triglycerides; medication usage, such as clopidogrel, prasugrel, oral anticoagulation, or calcium channel blockers; clinical presentation; and shock status between the groups. The rate of previous heart failure was higher in Group 2 (n=5, 31.3%) than in Group 1 (n=4, 9.1%; p=0.048), however the use of acetylsalicylic acid (Group 1: n=41, 93.2%; Group 2: n=9, 56.3%; p=0.002), ticagrelor (Group 1: n=13, 29.5%; Group 2: n=0, 0%; p=0.010), beta-blocker (Group 1: n=41, 93.2%; Group 2: n=11, 68.8%; p=0.026), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (Group 1: n=34,77.3%; Group 2: n=7, 43.8%; p=0.031) and a statin (Group 1: n=40, 90.9%; Group 2: n=9, 56.3%; p=0.005) was lower in Group 2. The mean hemoglobin level (Group 1: 13.0±2.1; Group 2: 11.6±2.7 g/dL; p=0.042) and ejection fraction was lower in Group 2 (Group 1: 50% [range: 43–60%]; Group 2: 41% [range: 35–50%]; p=0.044), though the creatinine level was higher (Group 1: 0.95±0.35 mg/dL; Group 2: 1.33±0.64 mg/dL; p=0.036).

The angiographic evaluation of the study patients is demonstrated in Table 3. There were no significant differences in the LMCA lesion percentage, lesion side, percentage of true bifurcation lesion, double-stent technique, predilatation, or use of kissing balloon between groups. The additional CXA lesion percentage (Group 1: n=18, 40.9%; Group 2: n=12, 75.0%; p=0.041) and intra-aortic balloon pump usage (Group 1: n=0, 0%; Group 2: n=3, 18.8%; p=0.016) were higher in Group 2 patients. Use of the proximal optimization technique (POT) was lower in Group 2 (Group 1: n=39, 88.6%; Group 2: n=10, 62.5%; p=0.030). CAD severity was also higher in patients with a composite endpoint. The mean SYNTAX score (Group 1: 19.9±9.8; Group 2: 26.8±12.2; p=0.029), SS II PCI (Group 1: 27.7 [range: 17.7–36.8]; Group 2: 34.2 [range: 27.9–55.2]; p=0.030) and rSS (Group 1: 0 [range: 0–5]; Group 2: 12.5 [range: 3.5–22.5]; p=0.001) were higher in Group 2 (Fig. 1a, b, and c-line 1). The mean SYNTAX score (Group 1: 20.1±10.0; Group 2: 30.0±11.4; p=0.007), SS II PCI (Group 1: 28.3 [range: 17.8–37.8]; Group 2: 37.2 [range: 32.1–51.0]; p=0.020) and rSS (Group 1: 0 [range: 0–5]; Group 2: 15.3 [range: 5.0–23.0]; p=0.001) were higher in the patients with mortality (Fig. 1a, b and c-line 2).

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal SS, SS II, and rSS values to indicate composite endpoints. The highest combined sensitivity and specificity values of SS crossed the curve at 28.5 (sensitivity: 56.3%; specificity: 79.5%). The area under the curve (AUC) was 0.669 (95% confidence interval [CI]: 0.504–0.834; p=0.047). The highest combined sensitivity and specificity values of SS II PCI crossed the curve at 25.45 (sensitivity: 87.5%; specificity: 45.5%). The AUC was 0.684 (95% CI: 0.531–0.837; p=0.030). The highest combined sensitivity and specificity values of rSS crossed the curve at 10 (sensitivity: 62.5%; specificity: 90.9%). The AUC was 0.773 (95% CI: 0.626–0.921; p=0.001) (Fig. 2a). ROC analysis was also conducted to determine the optimal SS, SS II, and rSS values to indicate mortality. The highest combined sensitivity and specificity values of SS crossed the curve at 28.5 (sensitivity: 70%; specificity: 78%). The AUC was 0.744 (95% CI: 0.579–0.909; p=0.016). The highest combined sensitivity and specificity values of SS II PCI crossed the curve at 25.45 (sensitivity: 100%; specificity: 44%). The AUC was 0.734 (95% CI: 0.592–0.876; p=0.020). The highest combined sensitivity and specificity values of rSS crossed the curve at 4.5 (sensitivity: 90%; specificity: 70%). The AUC was 0.827 (95% CI: 0.680–0.974; p=0.001) (Fig. 2b). Next, the whole study group was divided into 2 groups according to these values and long-term survival analyses were performed using Kaplan-Meier analysis. The results revealed that the long-term

Table 2. Baseline demographic and clinical characteristics

	All patients (n=60)	Patients without composite endpoint (n=44)	Patients with composite endpoint (n=16)	*p*
Age (years)	59.8±14.7	59±15	63±15	0.396
Gender (female), n (%)	15 (25)	11 (25)	4 (25)	0.640
Diabetes mellitus, n (%)	28 (46.7)	20 (45.5)	8 (50.0)	0.984
Hypertension, n (%)	40 (66.7)	30 (68.2)	10 (62.5)	0.918
Hyperlipidemia, n (%)	16 (26.7)	10 (22.7)	6 (37.5)	0.206
COPD, n (%)	2 (3.3)	2 (4.5)	0 (0)	0.534
Previous CVA, n (%)	1 (1.7)	0 (0)	1 (6.3)	0.267
Peripheral arterial disease, n (%)	2 (3.3)	1 (2.3)	1 (6.3)	0.466
Smoking, n (%)	41 (68.3)	27 (61.4)	14 (87.5)	0.054
Atrial fibrillation, n (%)	8 (13.3)	5 (11.4)	3 (18.8)	0.360
Chronic heart failure, n (%)	9 (15.0)	4 (9.1)	5 (31.3)	0.048
Previous CAD, n (%)	10 (16.7)	7 (15.9)	3 (18.8)	0.535
Hemoglobin (g/dL)	12.6±2.3	13.0±2.1	11.6±2.7	0.042
Leukocyte × 10^3/mm^3	9.9±4.3	9.7±4.0	10.5±5.1	0.529
Thrombocyte × 10^3/mm^3	259 (212.75–304)	264 (218–316)	247 (195–295)	0.266
Creatinine (mg/dL)	1.04±0.47	0.95±0.35	1.33±0.64	0.036
Total cholesterol (mg/dL)	151.5 (121.5–241.5)	151 (121–237)	163 (137–249)	0.520
LDL cholesterol (mg/dL)	75.5 (58.2–174.7)	62 (58–151.5)	118 (60.5–188)	0.126
HDL cholesterol (mg/dL)	41 (34–46)	41 (35–49)	41 (31–46)	0.509
Triglyceride (mg/dL)	111.5 (81.5–191.7)	103 (80–190)	141 (98–217)	0.103
Medication usage, n (%)				
ASA	50 (83.3)	41 (93.2)	9 (56.3)	0.002
Clopidogrel	30 (50.0)	23 (52.3)	7 (43.8)	0.770
Prasugrel	8 (13.3)	5 (11.4)	3 (18.8)	0.360
Ticagrelor	13 (21.7)	13 (29.5)	0 (0)	0.010
Warfarin	4 (6.7)	3 (6.8)	1 (6.3)	0.713
DOAC	5 (8.3)	4 (9.1)	1 (6.3)	0.597
Beta blocker	52 (86.7)	41 (93.2)	11 (68.8)	0.026
ACEI or ARB	41 (68.3)	34 (77.3)	7 (43.8)	0.031
Statin	49 (81.7)	40 (90.9)	9 (56.3)	0.005
Calcium channel blocker	4 (6.7)	2 (4.5)	2 (12.5)	0.287
Clinical presentation, n (%)				
Stable	18 (30.0)	13 (29.5)	5 (31.3)	0.463
USAP/NSTEMI	28 (46.7)	19 (43.2)	9 (56.3)	
STEMI	14 (23.3)	12 (27.3)	2 (12.5)	
Shock, n (%)	3 (5.0)	2 (4.5)	1 (6.3)	0.613
Ejection fraction (%)	50 (35.75–59.75)	50 (43–60)	41 (35–50)	0.044

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ASA: Acetylsalicylic acid; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular accident; DOAC: Direct oral anticoagulation; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; USAP: Unstable angina pectoris.

Table 3. Angiographic variables of the study group

	All patients (n=60)	Patients with composite endpoint (n=44)	Patients with composite endpoint (n=16)	*p*
Lesion side, n (%)				
Proximal/mid LMCA	10 (16.7)	7 (15.9)	3 (18.8)	0.535
Distal LMCA	50 (83.3)	37 (84.1)	13 (81.3)	
Additional vessel, n (%)				
LAD	39 (65.0)	28 (63.3)	11 (68.8)	0.951
CXA	30 (50.0)	18 (40.9)	12 (75.0)	0.041
RCA	18 (30.0)	11 (25.0)	7 (43.8)	0.140
SYNTAX score	21.7±10.82	19.9±9.8	26.8±12.2	0.029
Low-moderate SYNTAX, n (%)				
0–22	35 (58.3)	28 (63.6)	7 (43.8)	0.113
23–32	11 (18.3)	8 (18.2)	3 (18.8)	
High SYNTAX, n (%)				
≥33	14 (23.3)	8 (18.2)	6 (37.5)	
SYNTAX II PCI score	29.8 (18.9–40.5)	27.7 (17.7–36.8)	34.2 (27.9–55.2)	0.030
SYNTAX II CABG score	25.3±14.4	23.9±13.8	29.4±15.8	0.202
Residual SYNTAX score	2.0 (0–9.0)	0 (0–5)	12.5 (3.5–22.5)	0.001
Residual Syntax score, n (%)				
Low (8≥)	44 (73.3)	38 (86.4)	6 (37.5)	<0.001
High (8<)	16 (26.7)	6 (13.6)	10 (62.5)	
Medina classification, n (%)				
True bifurcation	16 (26.7)	10 (22.7)	6 (37.5)	0.206
1.1.1	10 (16.7)	6 (13.6)	4 (25.0)	
1.0.1	4 (6.7)	4 (9.1)	0 (0)	
0.1.1	2 (3.3)	0 (0)	2 (12.5)	
Others	44 (73.3)	34 (77.3)	10 (62.5)	
1.1.0	11 (18.3)	9 (20.5)	2 (12.5)	
1.0.0	15 (25.0)	10 (22.7)	5 (31.3)	
0.1.0	12 (20.0)	10 (22.7)	2 (12.5)	
0.0.1	6 (10.0)	5 (11.4)	1 (1.7)	
Guiding catheter, n (%)				
6 mm	3 (5.0)	1 (2.3)	2 (12.5)	0.171
7 mm	57 (95.0)	43 (97.7)	14 (87.5)	
IABP, n (%)	3 (5.0)	0 (0)	3 (18.8)	0.016
Stenting technique, n (%)				
Provisional/single stent	49 (81.7)	36 (81.8)	13 (81.3)	0.614
Double stent	11 (18.3)	8 (18.2)	3 (18.8)	
Simultaneous kissing	3 (5.0)	1 (2.3)	2 (12.5)	
TAP	4 (6.7)	3 (6.8)	1 (6.3)	
Culotte	2 (3.3)	2 (4.5)	0 (0)	
Crush	2 (3.3)	2 (4.5)	0 (0)	

Table 3. Angiographic variables of the whole study group *(continue)*

	All patients (n=60)	Patients with composite endpoint (n=44)	Patients with composite endpoint (n=16)	*p*
Stenting, n (%)				
Only LMCA	7 (11.7)	6 (13.6)	1 (6.3)	0.392
LMCA-LAD	41 (68.3)	30 (68.2)	11 (68.8)	0.967
LMCA-CXA	22 (36.7)	16 (36.4)	6 (37.5)	0.936
Stent type, n (%)				
BMS	0 (0)	0 (0)	0 (0)	
DES	60 (100)	60 (100)	60 (100)	
Stent diameter (mm)	3.5 (3.0–3.5)	3.5 (3.0–3.5)	3.5 (3.0–3.5)	0.821
Stent length (mm)	23 (16–24)	23.5 (16.0–25.0)	23.0 (16.0–24.0)	0.874
Second stent diameter (mm)	3.0 (2.8–3.3)	3.0 (2.88–3.25)	3.0 (2.88–3.25)	1.000
Second stent length (mm)	17 (16–23.75)	17 (16–23)	20 (16–27)	0.461
Predilatation, n (%)	34 (56.7)	25 (56.8)	9 (56.3)	0.969
Predilatation balloon diameter (mm)	2.5 (2.0–3.0)	2.5 (2.0–3.0)	3.0 (2.5–3.0)	0.163
Predilatation balloon length (mm)	15 (12–15)	15 (12–15)	15 (15–20)	0.111
Proximal optimization technique, n (%)	49 (81.7)	39 (88.6)	10 (62.5)	0.030
Postdilatation balloon diameter (mm)	4.03±0.57	4.1±0.6	3.9±0.3	0.424
Postdilatation balloon length (mm)	11.6±3.8	11.5±3.7	12.4±4.2	0.517
Kissing balloon, n (%)	9 (15.0)	8 (18.2)	1 (6.3)	0.240
Pre-TIMI score, n (%)				
0 or 1	14 (23.3)	10 (22.7)	4 (25.0)	0.552
2 or 3	46 (76.7)	34 (77.3)	12 (75.0)	
Post-TIMI score, n (%)				
0 or 1	2 (3.3)	0 (0)	2 (12.5)	0.068
2 or 3	58 (96.7)	44 (100)	14 (87.5)	

BMS: Bare-metal stent; CABG: Coronary artery bypass grafting; CXA: Circumflex artery; DES: Drug-eluting stent; IABP: Intra aortic balloon pump; LAD: Left anterior descending; LMCA: Left main coronary artery; PCI: Percutaneous coronary intervention; RCA: Right coronary artery; TAP: T and small protrusion; TIMI: Thrombolysis in myocardial infarction.

absence of a composite endpoint was significantly lower in patients with a higher SS (log-rank p=0.010), higher SS II PCI (log-rank p=0.019), and a higher rSS (log-rank p<0.001) (Fig. 3a-c respectively) and long-term survival was also found to be significantly lower in patients with a higher SS (log-rank p=0.003), higher SS II PCI (log-rank p=0.009), and a higher rSS (log-rank p<0.001) (Fig. 3d-f respectively).

Logistic regression was conducted and significant variables found in the univariate analysis were used in multiple logistic regression (Table 4). Multivariate logistic regression analysis revealed that the creatinine level (OR: 13.098; 95% CI: 1.471–116.620; p=0.021), non-POT (OR: 8.340; 95% CI: 1.230–56.570; p=0.030), and rSS (OR: 1.157; 95% CI: 1.024–1.307; p=0.019) were independent predictors of a primary composite endpoint.

Clinical variables of patients with stable CAD and acute coronary syndrome are demonstrated in Table 5. A higher SYNTAX score (Group 1: 21±9; Group 2: 29±13.3; p=0.033), SS II PCI (Group 1: 27.3 [range: 17.8–35.9]; Group 2: 41 [range: 29.6–59.8]; p=0.020) and rSS (Group 1: 2 [range: 0–5]; Group 2: 14 [range: 2–24]; p=0.015) were more distinct in acute coronary syndrome patients. Additionally, in the patients with acute coronary syndrome, the usage of acetylsalicylic acid (Group 1: 30, 96.8%; Group 2: 8, 72.7%;

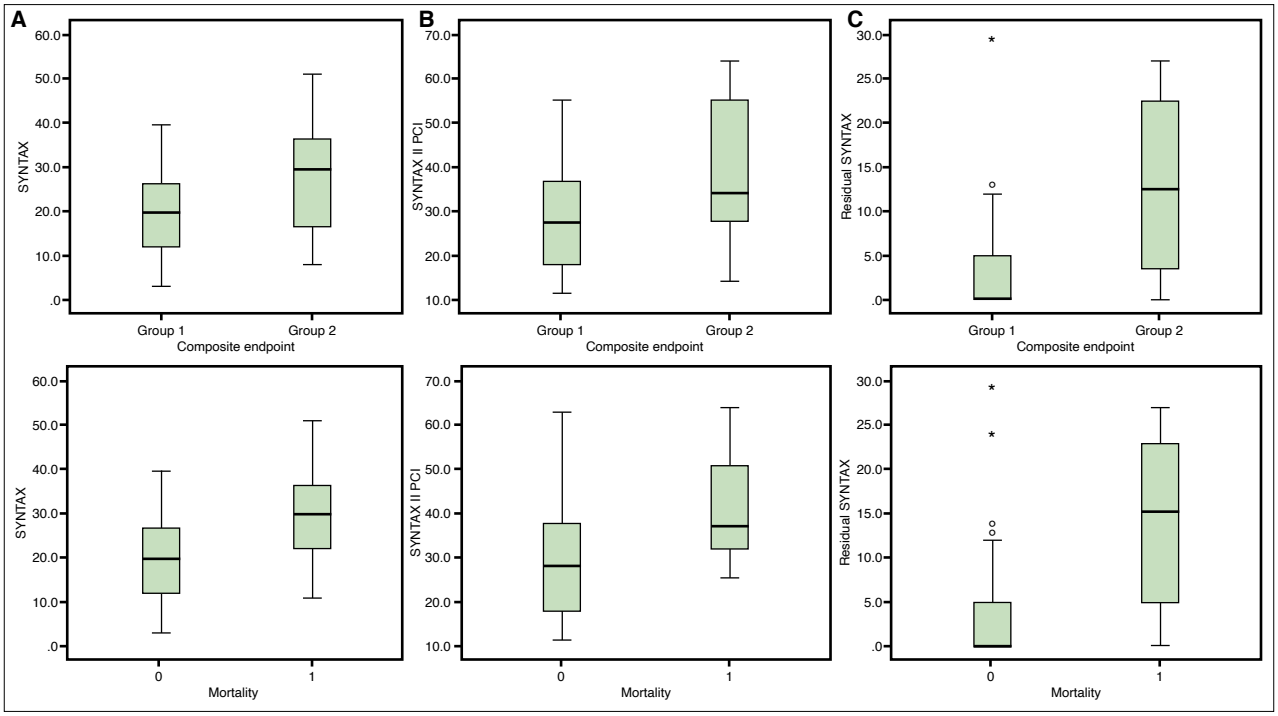

Figure 1. Comparison of **(A)** SYNTAX score, **(B)**, SYNTAX score II, and **(C)** residual SYNTAX score values of patients with and without composite endpoint (line 1) and mortality (line 2).

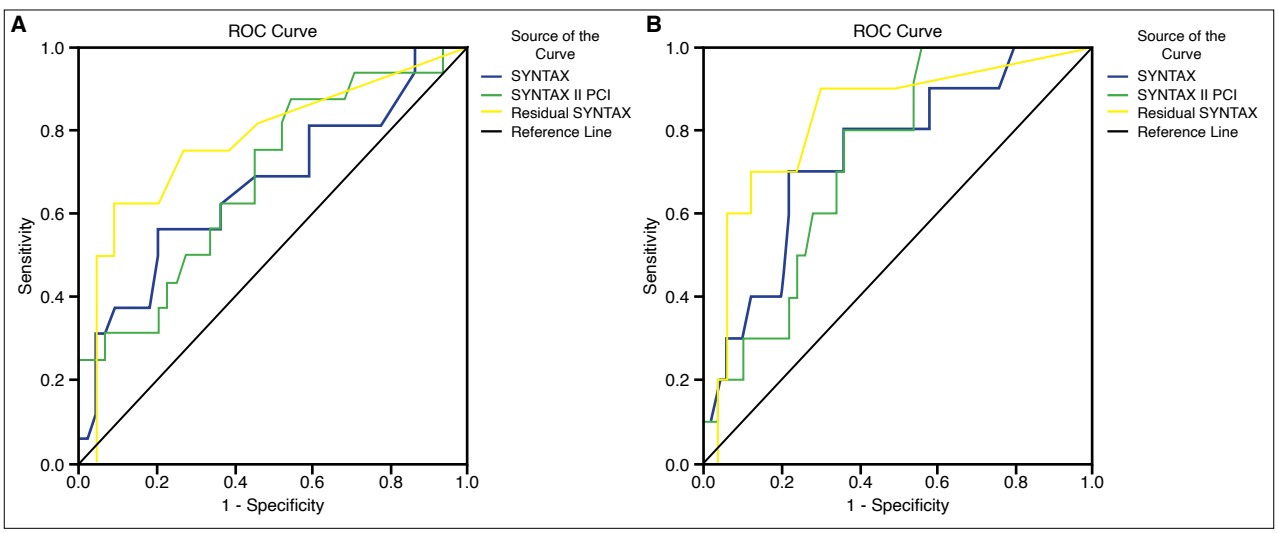

Figure 2. Receiver-operating characteristic (ROC) curves indicating the discriminative ability of the SYNTAX score, SYNTAX score II, and residual SYNTAX score for **(A)** composite endpoint and **(B)** and mortality.

p=0.049) and ticagrelor (Group 1: 11, 35.5%; Group 2: 0, 0%; p=0.020) was lower in patients with composite endpoints.

DISCUSSION

This study was an evaluation of long-term mortality and composite endpoints in patients with unprotected LMCA who underwent PCI. The CAD severity calculation according to SS, SS II, and rSS was strongly associated with adverse clinical outcomes and mortality. Additionally, incomplete revascularization was an independent predictor of death, MI, and stroke.

LMCA disease is observed in approximately 5% to 7% of patients who undergo invasive coro-

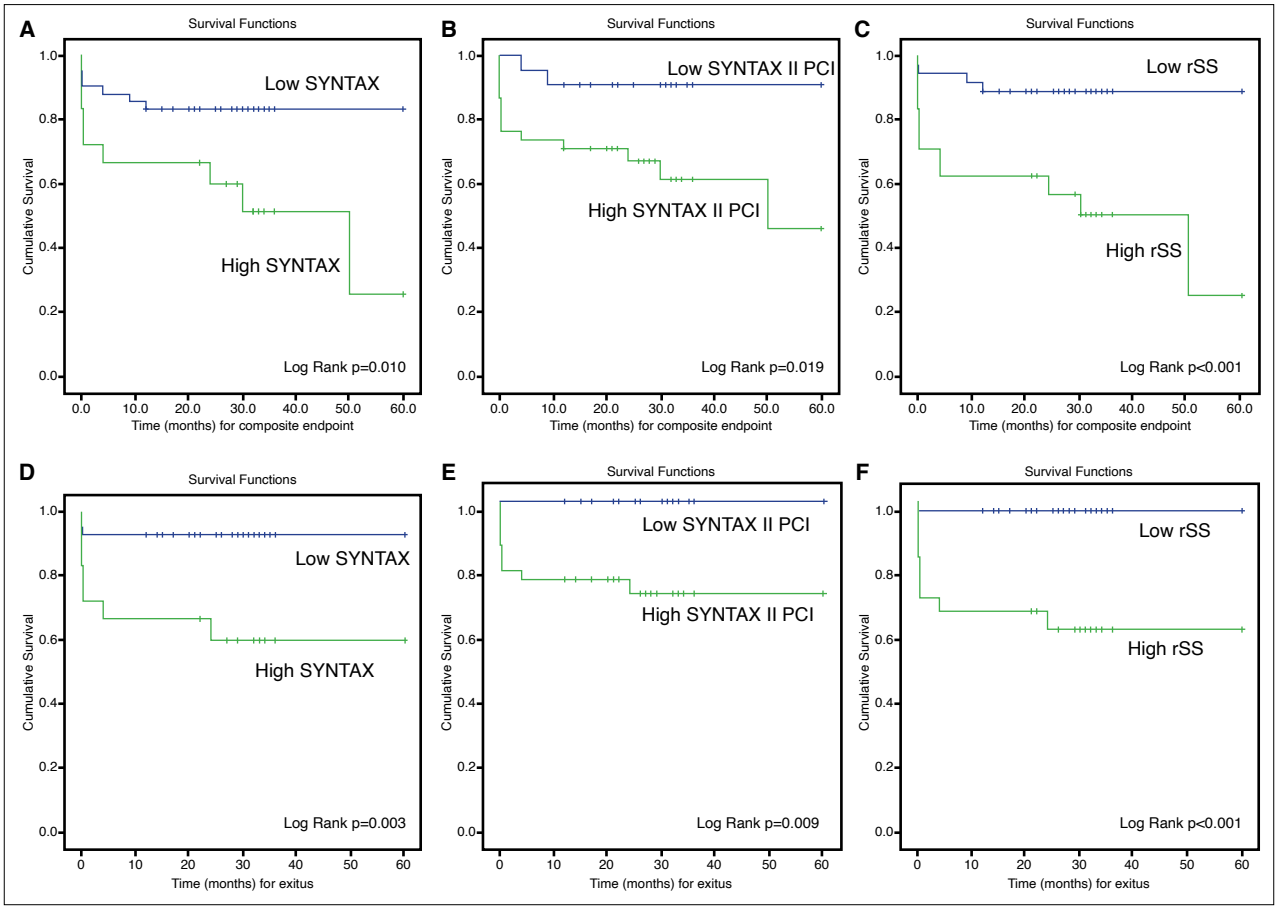

Figure 3. Kaplan-Meier survival curves of low and high **(A)** SYNTAX score, **(B)** SYNTAX score II, and **(C)** and residual SYNTAX score (rSS) groups for composite endpoint and low and high **(D)** SYNTAX score, **(E)** SYNTAX score II, and **(F)** rSS groups for mortality.

nary angiography.[5–7] The clinical importance originates from a mortality rate of up to 50% at 3 years in patients under medical therapy alone.[8] Several randomized clinical trials have evaluated optimal treatment modalities for unprotected LMCA disease. CABG had been accepted as the preferred treatment for significant unprotected LMCA disease due to the large area of jeopardized myocardium and

Table 4. Univariate and multivariate logistic regression analyses providing independent predictors of composite endpoints

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI (Lower-Upper)	*p*	Odds ratio	95% CI (Lower-Upper)	*p*
Creatinine	5.385	1.345–21.554	0.017	13.098	1.471–116.620	0.021
EF	0.944	0.894–0.998	0.041	0.948	0.854–1.052	0.318
CHF	4.545	1.041–19.857	0.044	1.292	0.118–14.085	0.834
SYNTAX score	1.063	1.004–1.126	0.036	1.009	0.898–1.133	0.884
SYNTAX score II PCI	1.055	1.010–1.103	0.017	0.933	0.838–1.039	0.208
rSS	1.126	1.044–1.214	0.002	1.157	1.024–1.307	0.019
non-POT	4.680	1.183–18.513	0.028	8.340	1.230–56.570	0.030

CHF: Chronic heart failure; EF: Ejection fraction; PCI: Percutaneous coronary intervention; POT: Proximal optimization technique; rSS: Residual SYNTAX score.

Table 5. Clinical variables of stable and ACS patients

	Stable patients (n=18)			ACS patients (n=42)		
	Patients without composite endpoint (n=13)	Patients with composite endpoint (n=5)	*p*	Patients without composite endpoint (n=31)	Patients with composite endpoint (n=11)	*p*
LMCA lesion side, n (%)						
Proximal/mid	3 (23.1)	2 (40)	0.433	4 (12.9)	1 (9.1)	0.607
Distal	10 (76.9)	3 (60)		27 (87.1)	10 (90.9)	
SYNTAX score	17.2±11.5	21.8±8.4	0.429	21±9	29±13.3	0.033
Low-moderate SYNTAX, n (%)						
0–22	10 (76.9)	3 (60)	0.350	18 (58.1)	4 (36.4)	0.021
23–32	0 (0)	2 (40)		8 (25.8)	1 (9.1)	
High SYNTAX, n (%)						
≥33	3 (23.1)	0 (0)		5 (16.1)	6 (54.5)	
SYNTAX II PCI score	28 (17–39.1)	26.7 (25.6–35.9)	0.924	27.3 (17.8–35.9)	41 (29.6–59.8)	0.020
SYNTAX II CABG score	26.4±14.2	21.7±13.5	0.537	22.9±13.8	32.8±16.1	0.057
Residual SYNTAX score	0 (0-0)	11 (5-22)	0.046	2 (0-5)	14 (2-24)	0.015
Residual Syntax score, n (%)						
Low (8≥)	12 (92.3)	2 (40)	0.044	26 (83.9)	4 (36.4)	0.006
High (8<)	1 (7.7)	3 (60)		5 (16.1)	7 (63.6)	
Medina classification, n (%)						
True bifurcation	0 (0)	2 (40)	0.065	10 (32.3)	4 (36.4)	0.541
1.1.1	0 (0)	1 (20)		6 (19.4)	3 (27.3)	
1.0.1	0 (0)	1 (20)		0 (0)	1 (9.1)	
0.1.1	0 (0)	0 (0)		4 (12.9)	0 (0)	
Others	13 (100)	3 (60)		21 (67.7)	7 (63.6)	
1.1.0	5 (38.5)	0 (0)		4 (12.9)	2 (18.2)	
1.0.0	4 (30.8)	2 (40)		6 (19.4)	3 (27.3)	
0.1.0	3 (23.1)	0 (0)		7 (22.6)	2 (18.2)	
0.0.1	1 (7.7)	1 (20)		4 (12.9)	0 (0)	
Stenting technique, n (%)						
Provisional/single stent	10 (76.9)	4 (80)	0.701	26 (83.9)	9 (81.8)	0.602
Double stent	3 (23.1)	1 (20)		5 (16.1)	2 (18.2)	
Simultaneous kissing	1 (7.7)	0 (0)		0 (0)	2 (18.2)	
TAP	0 (0)	1 (20)		3 (9.7)	0 (0)	
Culotte	1 (7.7)	0 (0)		1 (3.2)	0 (0)	
Crush	1 (7.7)	0 (0)		1 (3.2)	0 (0)	
Stenting, n (%)						
Only LMCA	3 (23.1)	1 (20)	0.701	3 (9.7)	0 (0)	0.392
LMCA-LAD	9 (69.2)	2 (40)	0.272	21 (67.7)	9 (81.8)	0.318
LMCA-CXA	4 (30.8)	2 (40)	0.561	12 (38.7)	4 (36.4)	0.593
Predilatation, n (%)	4 (30.8)	3 (60)	0.272	21 (67.7)	6 (54.5)	0.333
Proximal optimization technique, n (%)	11 (84.6)	3 (60)	0.299	28 (90.3)	7 (63.3)	0.063
Kissing balloon, n (%)	3 (23.1)	1 (20.0)	0.701	5 (16.1)	0 (0)	0.200
Antiplatelet usage, n (%)						
ASA	11 (84.6)	1 (20)	0.022	30 (96.8)	8 (72.7)	0.049
Clopidogrel	6 (46.2)	0 (0)	0.092	17 (54.8)	7 (63.6)	0.443
Prasugrel	2 (15.4)	1 (20)	0.650	3 (9.7)	2 (18.2)	0.393
Ticagrelor	2 (15.4)	0 (0)	0.510	11 (35.5)	0 (0)	0.020

ACS: Acute coronary syndrome; ASA: Acetylsalicylic acid; CABG: Coronary artery bypass grafting; CXA: Circumflex artery; LAD: Left anterior descending; LMCA: Left main coronary artery; PCI: Percutaneous coronary intervention; RCA: Right coronary artery; TAP: T and small protrusion.

combined highest ischemic risk. In recent decades, significant improvement in the outcomes of percutaneous interventions in unprotected LMCA disease patients has been seen as a result of advances in percutaneous techniques and stent devices, as well as more effective combined antiplatelet and anti-ischemic agents. Studies have confirmed that percutaneous intervention can be an effective and alternative treatment option to CABG in LMCA disease.[2-4,9,10] In the SYNTAX and PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) studies, CABG was compared to PCI with a first-generation drug-eluting stent (DES). In the SYNTAX trial, the incidence of a composite safety endpoint of MI, stroke, or death was 19% at 5 years in the PCI group.[2] The incidence of all-cause death, cardiac death, and MI (12.8%, 8.6%, and 8.2%, respectively) in the PCI group was not significantly different from that of the CABG group, while the stroke rate was lower in the PCI group, with an incidence of 1.5%. However, repeat revascularization was significantly greater in PCI patients, with an incidence of 26.7%.[2] In the PRECOMBAT study, the primary endpoint of MACCE (all-cause death, MI, stroke, or ischemia-driven TVR) between PCI and CABG patients was not significantly different at 5 years of follow-up, with a cumulative incidence of 17.5% in the PCI patients.[10] The incidence of death from any cause was 5.7% (cardiac and non-cardiac deaths were 3.8% and 2.0%, respectively). The rate of MI and stroke was 2.0% and 0.7%, and was not significantly different from that of the CABG patients. Ischemia-driven TVR occurred more frequently in the PCI group, with an incidence rate of 11.4%.[10] The EXCEL and NOBLE trials were 2 other prospective, clinical randomized studies comparing CABG and PCI with second-generation DESs. In the EXCEL trial, the primary composite endpoint of death, stroke, or MI at 3 years did not differ significantly between groups (15.4% of the patients in the PCI group).[3] Ischemia-driven revascularization was more frequent in the PCI patients (12.6%), however, the difference was more distinct in non-target revascularization. In contrast to other trials, in the NOBLE study, the rate of MACCEs was higher in the PCI patients (28%). While total the mortality rate was not significantly different, the incidence of MI and revascularization was significantly higher in the PCI group.[4] Similarly, the incidence rate of MACCE in our unprotected LMCA PCI patients was 16.7%. The rate of non-procedural MI was 6.6% in the same population (NSTEMI: 1.6%; STEMI: 5%). However, the stroke rate of 3.3% was higher than that of earlier trials.

In the subgroup analyses of the SYNTAX and EXCEL studies, CAD severity was found to be related to adverse clinical outcomes. In the SYNTAX trial, the participants were categorized according to a low (≤22), intermediate (23–32), or high (≥33) SS. The MACCE rate was not significantly different between the PCI and CABG patients with a low SS (PCI: 15.0%; CABG: 15.3%), while it was significantly higher in high SS patients (PCI: 20.6%; CABG: 16.8%). The rate of a MACCE after PCI was also greater in patients with an intermediate SS (PCI: 19.9%; CABG: 17.9%). Thus, PCI can be an acceptable alternative treatment modality for patients with intermediate SS.[11] In the EXCEL trial, patients with an SS of >33 were excluded from the study. The SS was low (≤22) in 60.5% of the patients and intermediate (23–32) in 39.5% of the patients. The rate of death, stroke, or myocardial infarction at 30 days was lower in PCI patients compared with CABG patients (PCI: 4.9%; CABG: 7.9%). At 3 years, the MACCE rate was not significantly different between groups (PCI: 23.1%; CABG: 19.1%).[3] This would appear to indicate that PCI is as effective as CABG in LMCA disease patients with low-to-intermediate SS. On the other hand, in the NOBLE study, the rate of MACCE was significantly higher in the PCI arm (29%) compared with the CABG (19%) arm at 5 years. Although the death rate was similar (PCI: 36%; CABG: 33%), non-procedural MI (PCI: 7%; CABG: 2%), and revascularization (PCI: 16%; CABG: 10%) were higher in the PCI group.[4] Unexpectedly, the stroke rate at 5 years tended to be higher in PCI patients, though it was lower at 30 days.[4] In contrast to the EXCEL trial, the NOBLE study included LMCA disease patients with a high SS. Increased CAD severity seems to be related to poorer prognosis and impaired cardiovascular outcomes in patients with LMCA disease who undergo PCI. PCI is recommended as class I indication for patients with LMCA disease and low SS in recent guidelines and it should also be considered in patients with intermediate SS.[12] Our results also showed an association between adverse clinical outcomes and a higher

SS. Previous studies have demonstrated that the SS II had a prognostic value for LMCA disease. He et al.[13] found that SS II was an independent predictor of long-term mortality in stable CAD patients who underwent LMCA PCI. In the DELTA (Drug-Eluting Stent of Left Main Coronary Artery Disease) registry and in a study that observed 1528 LMCA disease patients treated with PCI, the SS II had a similar prognostic value to that of the SS in the prediction of 4-year mortality.[14,15] We also found that patients with a primary composite endpoint had a higher SS II value, which had a discriminative ability to predict a poorer prognosis. It is also well known that increased CAD severity is related to a higher mortality rate in ischemic heart disease and it has been reported that the rSS was an independent predictor of mortality and ischemic events at 1 year in patients with NSTEMI[16] and patients with multivessel disease who underwent PCI.[17] Malkin et al.[18] demonstrated that incomplete revascularization predicted increased mortality in patients with LMCA PCI. We also found that the rSS was an independent predictor of death, MI, and stroke. Additionally, the rSS had a higher prognostic value compared with the baseline SS and SS II to predict mortality in our study. Finally, our results demonstrated that a higher rSS was related with a decreased survival rate and increased composite endpoints of mortality, stroke, and MI. However, the difference was more distinct in other endpoints compared to mortality, especially in the early stages of follow-up. This likely occurred due to the increased MI rate in patients with a higher rSS. Unsurprisingly, it is well known that a higher rSS is associated with adverse coronary events. Thus, we surmise that incomplete revascularization at the index procedure could be the underlying mechanism of increased MI rates. In previous studies, it has been demonstrated that an increased coronary atherosclerotic burden was associated with adverse cardiovascular outcomes in patients with LMCA disease. However, the baseline anatomic SYNTAX score was used to predict high-risk patients in all of the studies we examined. To the best of our knowledge, ours is the first to examine the rSS, which demonstrates CAD severity after PCI, in this population. We also observed that the rSS was a more effective scoring tool to predict high-risk patients than the baseline SYNTAX score. As a result, the baseline and post-procedural CAD severity seem to be the most important determinant factors to select a revascularization strategy in patients with unprotected LMCA disease. However, large-scale studies are needed for additional investigation.

Dual antiplatelet therapy is recommended for patients with acute coronary syndrome and/or those who will undergo a complex PCI, such as LMCA stenting, according to recent guidelines.[19] LMCA stenting was performed in all of our study patients, 70% of whom were admitted with acute coronary syndrome. Dual antiplatelet therapy was recommended for at least 1 year in all cases; however, some patients elected to discontinue treatment. As a result, composite endpoints were more common in this group.

Provisional stenting and a double-stent strategy for bifurcation lesions have been evaluated in several studies. Chen et al.[20] reported that of 482 patients with distal, true LMCA bifurcation lesions evaluated and followed up for over a year, 242 patients were treated with provisional stenting while 240 were treated with double-kissing crush stenting. Double-kissing crush stenting resulted in lower rates of target lesion revascularization, target vessel MI, and stent thrombosis compared with provisional stenting. According to recent guidelines, in true bifurcation lesions of the LMCA, double-kissing crush stenting may be preferred to a provisional stenting technique.[12] Additionally, intravascular imaging should be recommended for percutaneous left main revascularization.[21] In our study population, the incidence of a distal, true bifurcation lesion of LMCA was 26.7%, and 70% of the patients had acute coronary syndrome. Thus, a double-stent strategy was performed only in 18.3%, while proximal optimization was performed in over 80%. Maybe this result stems from the desire to be safe and fast in cases of acute coronary syndrome. Finally, proximal optimization appears to have reduced adverse cardiovascular outcomes.

Conclusion

CAD severity appears to have a prognostic value on mortality, MI, and stroke in patients with unprotected LMCA who undergo PCI. An increased initial SS and post-procedural rSS were related to adverse cardiovascular outcomes. rSS was also an independent predictor of MACCE and mortality.

Limitations

The small sample size is the main limitation of our study, as well as the lack of a control group. Additionally, the etiology of death, that is, a result of cardiac on non-cardiac causes, was uncertain, due to the retrospective nature of the study. Thus, our composite endpoint results were higher than they might have been.

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Keywords: Left main coronary artery disease; percutaneous coronary intervention; prognosis; residual SYNTAX score; SYNTAX score.

Anahtar sözcükler: Sol ana koroner arter; perkütan koroner girişim; prognoz; rezidüel SYNTAX skoru; SYNTAX skoru.