Original Article

Impact of the SYNTAX Score in the Prognosis of Patients with Multivessel Disease Treated by Percutaneous Coronary Intervention

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ABSTRACT

Background: The SYNTAX score stratifies the angiographic complexity of coronary artery disease and establishes the prognosis of patients with triple vessel and/or left main coronary artery disease, being an important tool to decide the best revascularization strategy. We assessed the impact of the SYNTAX score in the prognosis of a daily practice population with multivessel coronary artery disease treated by percutaneous coronary intervention with drug-eluting stents. **Methods:** We identified in the SAFIRA Registry elective patients with multivessel coronary artery disease treated with drug-eluting stents. Patients were grouped in SYNTAX score ≤ 8; SYNTAX score > 8 and ≤ 16, and SYNTAX score > 16, and clinical outcomes in terms of major adverse cardiac events were stratified according to the SYNTAX score groups. **Results:** Between 2009 and 2014, we identified 244 patients that met the study inclusion criteria. Patients were distributed in those with SYNTAX score ≤ 8 (n = 61; 25%), > 8 and ≤ 16 (n = 116; 47.5%), and > 16 (n = 67; 27.5%). Mean age was 64.6 ± 11.5 years and 73% were male. The SYNTAX score ranged between 1 and 39, with an average of 13.4 ± 6.8. In the follow-up period of 3.6 ± 2.1 years, there were higher rates of major adverse cardiac events in group > 16 (4.9% vs. 6.9% vs. 11.9%; $p < 0.01$) due to a higher incidence of target vessel revascularization (1.6% vs. 2.6% vs. 7.5%; $p = 0.08$). Four cases of definitive or probable stent thrombosis were detected (zero vs. 1.7% vs. 3.0%; $p = 0.41$). **Conclusions:** The SYNTAX score is able to stratify the risk of a daily practice population with coronary multivessel disease treated by percutaneous coronary intervention with drug-eluting stents.

DESCRIPTORS: Coronary artery disease. Percutaneous coronary intervention. Drug-eluting stents. Prognosis.

RESUMO

Impacto do Escore SYNTAX no Prognóstico de Pacientes com Doença Multiarterial Tratados por Intervenção Coronária Percutânea

Introdução: O escore SYNTAX estratifica a complexidade angiográfica e estabelece o prognóstico de portadores de doença triarterial e/ou com lesão de tronco, sendo uma importante ferramenta para decidir a melhor estratégia de revascularização. Avaliamos o impacto do escore SYNTAX no prognóstico de pacientes com doença arterial coronariana multiarterial da prática clínica tratados por intervenção coronária percutânea. **Métodos**: Identificamos no Registro SAFIRA pacientes com acometimento multiarterial tratados eletivamente com stents farmacológicos. Os pacientes foram agrupados em escore SYNTAX ≤ 8; escore SYNTAX > 8 e ≤ 16; e escore SYNTAX >16, e comparados quanto aos eventos cardíacos adversos maiores. **Resultados**: No período de 2009 a 2014, identificamos 244 pacientes, que preencheram os critérios de inclusão para o estudo. Foram distribuídos em escore SYNTAX ≤ 8 (n = 61; 25%), > 8 e ≤ 16 (n = 116; 47,5%), e > 16 (n = 67; 27,5%). A média de idade foi de 64,6 ± 11,5 anos e 73% eram do sexo masculino. O escore SYNTAX variou de 1 a 39, com média de 13,4 ± 6,8. No período de 3,6 ± 2,1 anos, observaram-se maiores taxas de eventos cardíacos adversos maiores no grupo > 16 (4,9% vs. 6,9% vs. 11,9%; $p < 0,01$), às custas de maior revascularização do vaso-alvo (1,6% vs. 2,6% vs. 7,5%; $p = 0,08$). Quatro casos de trombose do stent definitiva ou provável foram detectados (zero vs. 1,7% vs. 3,0%; $p = 0,41$). **Conclusões**: O escore SYNTAX é capaz de estratificar o risco em uma população com doença coronária multiarterial da prática clínica submetida à revascularização percutânea com implante de stents farmacológicos.

DESCRITORES: Doença da artéria coronariana. Intervenção coronária percutânea. Stents farmacológicos. Prognóstico.

The optimal revascularization strategy in patients with multivessel coronary artery disease (CAD) is still an important topic of debate among interventional cardiologists and cardiac surgeons.

The SYNTAX[1] score stratifies patients regarding the angiographic complexity of coronary injuries, allowing for the establishment of prognosis of patients with three-vessel CAD and/or trunk injury, and represents an important tool for the best revascularization-strategy decision, whether surgical or percutaneous.[2]

Higher SYNTAX scores are indicative of a more complex CAD, representing a major therapeutic challenge for percutaneous coronary intervention (PCI) and a worse long-term prognosis. The SYNTAX study demonstrated clearly that the surgical strategy results in greater benefits for these patients.[3,4]

Although the stratification by SYNTAX score is significantly contributing to clinical decision making in the treatment of patients with CAD, it is found that in populations of all-comer patients undergoing PCI, most have low-to-moderate anatomic complexity when measured by this score.[5-7]

This study assessed the impact of the SYNTAX score on the prognosis in everyday clinical practice for patients with multivessel CAD treated with PCI.

METHODS

Study design and population

This was a prospective cohort study conducted in a single center from July 2009 to April 2014 at the Complexo Hospitalar da Real e Benemérita Sociedade Portuguesa de Beneficência, Hospitais São Joaquim e São José, using the database from SAFIRA Registry (*SegurançA e eFIcácia dos Stents Farmacológicos em uma População do Mundo ReAl*/Safety and Efficacy of Drug-Eluting Stents in a Real-World Population). Patients with multivessel CAD with indication of elective PCI or in the setting of acute coronary syndrome (ACS) without ST-segment elevation with first- or second-generation drug-eluting stents (DES) were included. Patients with previous surgical coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) and patients with acute myocardial infarction with ST-segment elevation were excluded.

Patients underwent implantation of one or more drug-eluting stents and were pooled in three groups: SYNTAX score ≤ 8; SYNTAX score > 8 and ≤ 16; and SYNTAX score > 16, according to tertiles of the SYNTAX score obtained from an all-comers' population from the Limus eluted from A Durable versus ERodable Stent coating (LEADERS)[5] study. The SYNTAX score was calculated by an electronic calculator available at www.syntaxscore.com.

Data were collected through a specific staff form and stored in a database dedicated to the SAFIRA Registry. Clinical follow-up was conducted through periodic consultations at the institution, or by phone call by the cardiologist in charge.

Technical performance of the procedure

After obtaining the access, unfractionated heparin was administered at a dose of 100 U/kg. When glycoprotein IIb/IIIa inhibitors were used, the initial dose was 70 U/kg, seeking to keep the activated clotting time at 200-250 seconds.

Pre- and post-procedural serial angiographic analyses were performed, including qualitative assessments of coronary injuries. The angiograms acquisition occurred after intra-arterial administration of isosorbide mononitrate 10 mg (unless when clinically contraindicated) and included two orthogonal projections, separated by at least 30°, seeking to avoid overlapping of the arteries and optimizing visualization of the target lesion. The scans were recorded at a speed of 15 frames per second in DICOM® digital format and filed in CDR-type media.

Antiplatelet therapy

The protocol included a combination of two antiplatelet agents, acetylsalicylic acid (ASA) and clopidogrel, in loading doses of 200 and 300 mg, respectively, administered 24 hours before the procedure in elective cases. In cases of ACS, in those patients who had not been pre-medicated, ASA was chewed at a dose of 300 mg; as for clopidogrel, a loading dose of 600 mg was used. After ticagrelor and prasugrel were made available, these medications were incorporated for use in ACS, or in elective cases of greater complexity when angiographic PCI was performed *ad hoc*, in loading doses of 180 mg and 60 mg, respectively.

After the procedure, ASA was maintained indefinitely at a dose of 100 mg/day. P2Y12 inhibitors clopidogrel (75 mg daily), ticagrelor (90 mg twice daily), or prasugrel (10 mg daily) were recommended for a minimum of 1 year.

Definitions and study endpoints

Deaths were considered to be from cardiac origin, unless a non-cardiac cause could be unequivocally established. Acute myocardial infarction was defined as an increase in creatine kinase-MB fraction (CK-MB) above three times the upper limit of normal, with or without the appearance of new Q waves. Ischemia-guided target vessel revascularization consisted of the revascularization of the treated vessel during PCI index, either by a new PCI or by CABG, in the presence of symptoms or of ischemia in a noninvasive stratification.

The primary endpoint was major adverse cardiac events (MACE), a combination of cardiac death, nonfatal acute myocardial infarction, or ischemia-driven revascularization. Secondary endpoints included the assessment

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of individual components of the primary endpoint, and stent thrombosis, as defined by the Academic Research Consortium (ARC).[8]

Statistical analysis

Categorical variables were expressed as frequencies and percentages, and compared with the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were presented as means and standard deviations and were compared by analysis of variance (ANOVA). Curves of event-free survival were constructed using the Kaplan-Meier method. The odds of survival were compared by the log-rank test. Analyses were performed by STATA® statistical software (Stata Corp Company, College Station, Texas, United States), version 12. P-values < 0.05 were considered significant.

RESULTS

Between July 2009 and April 2014, 244 patients met the inclusion criteria for the study. Such patients were divided into three groups: SYNTAX ≤ 8 (low) group, which included 61 patients (25%); SYNTAX > 8 and ≤ 16 (intermediate) group, with 116 patients (47.5%); and SYNTAX > 16 (high) group, with 67 patients (27.5%).

The mean age was 64.6 ± 11.5 years, and 73% were male. Patients showed a similar clinical and demographic profile, with the exception of dyslipidemia and diabetes (19.6% vs. 18.9% vs. 35.8%; $p = 0.03$), more frequent in the group with high SYNTAX score. There was a predominance of stable clinical pictures (83.6%) and with respect to left ventricular function, a mild or moderate dysfunction was noted in most patients (Table 1).

The SYNTAX score ranged from 1 to 39, with a mean of 13.4 ± 6.8. The mean SYNTAX score was 6.3 ± 1.7 in the low SYNTAX score group; 12.6 ± 2.3 in the intermediate SYNTAX score group; and 22.3 ± 5.2 in the high SYNTAX score group (Figure 1).

Treatment comprised 452 vessels with 508 stents, with 2.1 ± 0.1 stents per patient and 1.1 ± 0.2 stents per vessel. The high SYNTAX score group showed higher prevalence of patients with three-artery involvement and left-main-coronary-artery injuries, but there was no difference between the numbers of vessels treated and the implanted stents among groups. The procedure time and the time to obtain final Thrombolysis In Myocardial Infarction (TIMI) 3 flow were similar (Table 2).

In the clinical-follow-up period of 3.6 ± 2.1 years, higher rates of MACE were found in the group with high SYNTAX score (4.9% vs. 6.9% vs. 11.9%; $p < 0.01$). Cardiovascular death occurred in zero vs. 0.9% vs. 1.6% ($p = 0.35$); myocardial infarction in zero vs. zero vs. 1.6% ($p = 0.28$); and ischemia-driven revascularization

TABLE 1
Clinical characteristics

Variables	SYNTAX ≤ 8 (n = 61)	SYNTAX > 8 and ≤ 16 (n = 116)	SYNTAX > 16 (n = 67)	p-value
Age, years	62.9 ± 11.2	65.3 ± 11.0	65.3 ± 12.5	0.62
Males, n (%)	47 (77.0)	77 (66.4)	54 (80.6)	0.08
Diabetes mellitus, n (%)	12 (19.6)	18 (18.9)	24 (35.8)	0.03
Dyslipidemia, n (%)	16 (26.2)	42 (36.2)	39 (58.2)	0.02
Hypertension, n (%)	46 (83.6)	95 (81.9)	56 (90.3)	0.54
Current smoking, n (%)	16 (26.2)	23 (19.8)	10 (14.9)	0.62
Previous AMI, n (%)	16 (26.2)	32 (27.6)	19 (28.4)	0.96
CRF, n (%)	8 (13.1)	16 (13.8)	9 (13.4)	0.89
Clinical presentation, n (%)				0,08
Asymptomatic	22 (36.1)	34 (29.3)	18 (26.9)	
Angina, stable	33 (54.1)	67 (57.8)	30 (44.8)	
ACS, low risk	0	2 (1.7)	5 (7.5)	
ACS, moderate risk	1 (1.6)	5 (4.3)	4 (6.0)	
ACS, high risk	5 (8.2)	8 (6.9)	10 (14.9)	
LV dysfunction, n (%)				0.71
Mild	21 (52.5)	38 (52.7)	16 (37.2)	
Moderate	12 (30.0)	23 (31.9)	19 (45.2)	
Severe	7 (17.5)	11 (15.3)	8 (18.6)	

AMI: acute myocardial infarction; CRF: chronic renal failure; ACS: acute coronary syndrome; LV: left ventricle.
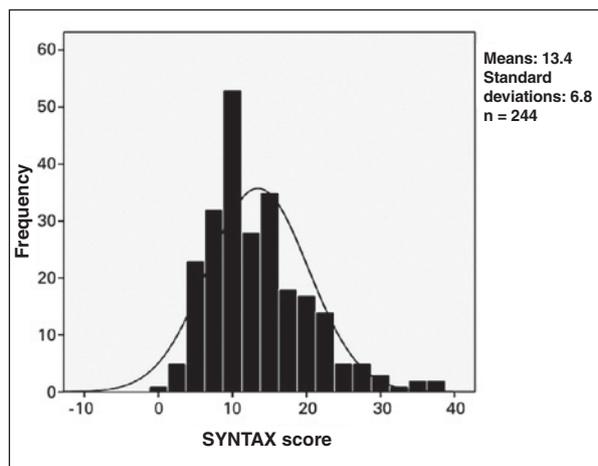
Figure 1 – Distribution of the SYNTAX score.

in 1.6% vs. 2.6% vs. 7.5% ($p = 0.08$). Four cases of defined or probable stent thrombosis were detected (zero vs. 1.7% vs. 3.0%; $p = 0.41$).

The Kaplan-Meier curve was used to calculate the estimated MACE-free survival at five years for all three groups. MACE-free survival was 95.1% in patients in the

group with score $\leq$ 8; 93.1% in the group with score > 8 and $\leq$ 16; and 88.1% in the group with score > 16 ($p < 0.01$) (Figure 2).

DISCUSSION

This study showed that the SYNTAX score has a discriminatory power for risk assessment in everyday clinical practice in multivessel disease patients undergoing PCI showing lower complexity than those in the SYNTAX trial population.

The LEADERS trial was the first to report the utility of the SYNTAX score as a predictor of MACE in an all-comers' population, including patients with ACS. The SYNTAX scores were prospectively collected in 1,397 of 1,707 patients, and a *post hoc* analysis was performed by stratifying one-year follow-up clinical results, according to one of the three tertiles. These tertiles ($\leq$ 8; > 8 and $\leq$ 16; > 16), which were also employed for the analysis of the current patients, were shown to be lower than those of the SYNTAX trial population. At the 1-year-follow-up, a lower MACE-free survival in the highest tertile was demonstrated (92.2%, 91.1%, and 84.6%; $p < 0.001$).[5]

TABLE 2
Angiographic and procedure characteristics

Variables	SYNTAX $\leq$ 8 (n = 61)	SYNTAX > 8 and $\leq$ 16 (n = 116)	SYNTAX > 16 (n = 67)	*p*-value
Number of affected vessels, n (%)				< 0.01
2	60 (98.4)	104 (89.7)	52 (77.6)	
3	1 (1.6)	12 (10.3)	15 (22.4)	
LMCA lesion, n (%)	1 (1.6)	1 (0.9)	7 (10.4)	< 0.01
Number of vessels treated	91	271	90	0.37
Number of stents implanted	104	306	98	0.31
Treated vessels, n (%)				0.80
LMCA	2 (2.2)	3 (1.1)	1 (1.1)	
AD	35 (38.5)	90 (33.2)	36 (40)	
CX	26 (28.6)	87 (32.1)	22 (24.4)	
RC	28 (30.8)	91 (33.6)	31 (34.4)	
Injury type, n (%)				0.21
A	8 (8.8)	35 (12.9)	5 (5.6)	
B1	27 (29.7)	78 (28.8)	37 (41.1)	
B2	19 (20.9)	52 (19.2)	13 (14.4)	
C	47 (40.7)	106 (39.1)	35 (38.9)	
Procedure time, minutes	55.8 ± 21	55.2 ± 28	56.0 ± 30	0.08
Final TIMI flow, n (%)				0.32
0	0	0	2 (2.2)	
1	1(1.1)	1 (1.1)	2 (2.2)	
2	0	2 (0.7)	3 (3.3)	
3	90 (98.9)	268 (98.9)	85 (94.4)	

LMCA: left main coronary artery; AD: Anterior descending artery; CX: Circumflex artery; RC: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction.
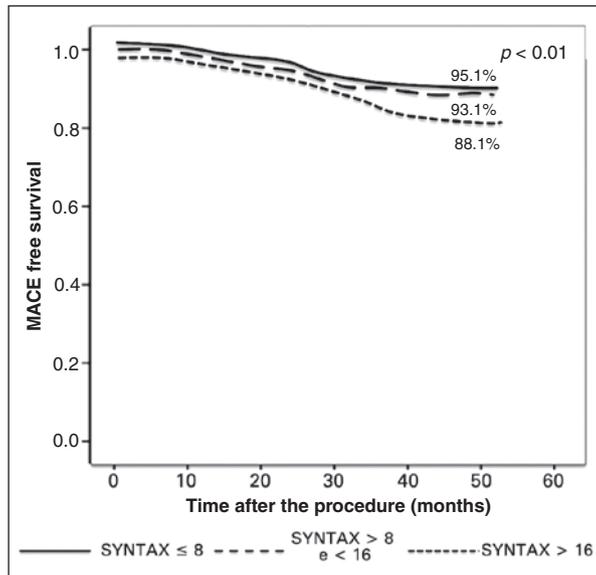
Figure 2 – Kaplan-Meier curves for the primary endpoint according to the SYNTAX score. MACE: major adverse cardiac events.

In the RESOLUTE III All Comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention), the SYNTAX scores were prospectively collected in 2,033 of 2,292 patients treated with second generation drug-eluting stents, and the clinical outcome was stratified according to tertiles (≤ 9, > 9 and ≤ 17, and > 17). After a 12-month follow-up, rates of MACE (8.5% vs. 11.2% vs. 20.0%; $p < 0.0001$), myocardial infarction (8.0% vs. 12.1% vs. 18.2%; $p < 0.0001$), need for repeat revascularization (5.0% vs. 7.7% vs. 13.7%; $p < 0.0001$), and target-vessel failure (5.2% vs. 5.9% vs. 11.7%; $p < 0.0001$) were significantly higher in patients in the highest tertile. After a multivariate adjustment, the SYNTAX score was identified as an independent predictor of MACE, myocardial infarction, repeat revascularization, and target vessel failure (all, $p < 0.05$).[6]

Even in patients with acute myocardial infarction with ST-segment elevation undergoing primary PCI excluded from the SYNTAX study, the SYNTAX score was able to predict clinical events after 1 year. The SYNTAX score was calculated retrospectively in 807 patients from the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab with Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction) studies, who were stratified according to the tertiles ≤ 9, > 9 and ≤ 16, and > 16. At 1-year follow-up, all clinical endpoints, including death, death/reinfarction, MACE, and stent thrombosis were significantly higher

in patients in the highest tertile. The SYNTAX score was identified as an independent predictor of death, MACE, and stent thrombosis at one-year follow-up.[7]

Study limitations

The SYNTAX score has several limitations, including intra- and inter-observer variability, and the absence of specific algorithms for patients with previous percutaneous coronary intervention or CABG. Another limitation of the SYNTAX score is that it does not incorporate the clinical characteristics of patients.

CONCLUSIONS

The SYNTAX score was able to stratify the risk in a population with multivessel coronary disease in everyday clinical practice undergoing percutaneous coronary intervention with drug-eluting-stent implantation. A SYNTAX score > 16 identified patients at higher risk of major adverse cardiovascular events that can possibly benefit from optimized stent implantation techniques.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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None.

REFERENCES

1. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Coronary artery by-pass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised-clinical SYNTAX-trial. Lancet. 2013;381(9867):629-38.

2. King SB 3rd, Lembo NJ, Weintraub WS, Kosinski AS, Barnhart HX, Kutner MH, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). N Engl J Med. 1994;331(16):1044-50.

3. Pocock SJ, Henderson RA, Rickards AF, Hampton JR, King SB 3rd, Hamm CW, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. Lancet. 1995;346(8984):1184-9.

4. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. J Am Coll Cardiol. 2003;41(8):1293-304.

5. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, et al. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. J Am Coll Cardiol. 2010;56(4):272-7.

6. Garg S, Serruys PW, Silber S, Wykrzykowska J, van Geuns RJ, Richardt G, et al. The prognostic utility of the SYNTAX score on 1-year outcomes after revascularization with zotarolimusand everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial. JACC Cardiovasc Interv. 2011;4(4):432-41.

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2014;22(3):258-63

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7. Garg S, Sarno G, Serruys PW, Rodriguez AE, Bolognese L, Anselmi M, et al. Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a substudy of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) trials. JACC Cardiovasc Interv. 2011;4(1):66-75.

8. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med. 2007;356(10):1020-9.