



## Original Study

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# Usefulness of The Syntax Revascularization Index and The Concept of Reasonable Incomplete Revascularization In “All-Comer” Patients Undergoing Percutaneous Coronary Intervention

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## Abstract

**Objectives:** In particular settings, achieving complete coronary revascularization could be very challenging. The Syntax Revascularization Index (SRI) represents a useful tool to assess the degree of coronary revascularization in patients undergoing percutaneous coronary intervention (PCI). This study aimed to assess the prognostic usefulness of the SRI in an “all comer” cohort of patients undergoing PCI.

**Methods:** We performed a prospective observational single-center study, including 305 “all comers” patients, who underwent 327 PCI from January 1st to June 30th. According to the Syntax revascularization index (SRI), patients were subdivided into 4 subgroups: G1 (SRI < 50%), G2 (50% ≤ SRI < 70%), G3 (70% ≤ SRI < 100%) and G4 (SRI = 100%). One-year follow-up was performed in all patients. Major adverse cardiac events (MACE) were defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction and unplanned revascularization.

**Results:** The mean age was 62.3 ± 10.7 years, 80% were males. The distribution between SRI subgroups was as follows: G1 (n = 45, 14.8%); G2 (n = 30, 9.8%); G3 (n = 43, 14.1%), and complete revascularization (G4) (n = 187, 61.3%). In comparison with G4, 1-year survival free from MACE and cardiovascular death were lower in G1 [(94.6% vs. 86.7%; log-rank p = 0.048) and (96.8% vs. 88.9%; log-rank p = 0.022), respectively]. SRI satisfactorily predicted 1-year MACE and the optimal SRI cut-off was 75%. Reasonable incomplete revascularization (75% ≤ SRI < 100%) performed as well as complete revascularization in the settings of diabetes, elderly patients, left ventricular dysfunction and high-risk patients.

**Conclusion:** Our data showed the importance of complete revascularization in improving cardiovascular outcome. SRI ≥ 75% represented a reasonable target when complete revascularization is not achievable.

## Keywords

Incomplete revascularization, Percutaneous coronary intervention, Syntax score, Syntax revascularization index

## Introduction

Complete revascularization appears to be intuitively desirable in patients with coronary artery disease (CAD). Historically, coronary artery bypass grafting (CABG) surgery used to be the gold standard to reach complete revascularization [1,2]. Thanks to the advancements made in percutaneous revascularization techniques with the increased expertise of operators, percutaneous coronary intervention (PCI) has become the most widely used revascularization modality in patients with stable coronary artery disease (SCAD) and those with acute coronary syndromes (ACS) [3]. Although up to 50% of patients undergoing PCI for ACS have multivessel CAD [4,5], PCI has proven to be capable of obtaining high rates of complete revascularization [6].

However, achieving complete revascularization may be very challenging, particularly in patients with very complex CAD or in those at high risk due to severe comorbidities (elderly,

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diabetes, chronic kidney disease...). Furthermore, obstinately following "the dogma" of revascularization completeness might be harmful in some scenarios, increasing the risk for adverse events such as coronary perforations, stent thrombosis (ST) or lesion restenosis [7-9].

To overcome these difficulties, the concept of 'reasonable incomplete revascularization' using a derivative of the Syntax score (SS) called Syntax Revascularization Index (SRI) was developed [10]. SRI was demonstrated to predict major adverse cardiac events (MACE) after PCI with first-generation drug-eluting stents (DES) and an SRI  $\geq 70\%$  was considered as reasonable goal for patients with complex CAD [9]. More recently, Xu, et al. confirmed these findings using second generation DES, with an SRI cutoff of 85% [11].

In Tunisia, complete revascularization faces many difficulties such as the increasing prevalence of diabetes [12], the problematic percutaneous management of chronic total occlusions (CTO) and stent reimbursement issues. In addition, data regarding the impact of the degree of coronary revascularization on cardiovascular outcome are scarcely reported.

For all these reasons, we performed this prospective study aiming to evaluate the impact of the degree of coronary revascularization (as assessed by SRI) on mid-term cardiovascular outcome in a population of 'all comer' Tunisian CAD patients undergoing PCI.

## Material and Methods

### Study population

We performed a prospective observational single-center study, at the Cardiology Department of Abderrahmen Mami Hospital, Ariana, Tunisia. From January 1<sup>st</sup> to June 30<sup>th</sup> 2017, "all comer" patients undergoing coronary angiography and showing significant CAD were screened. Patients who underwent PCI were included into the study; while those in whom either medical therapy or surgical revascularization were indicated, were not included. The exclusion criteria were the following: i) Age < 18 years; ii) Pregnant or lactating women; and iii) Incomplete data at enrollment. SS was evaluated, and SRI calculated in all patients. According to the degree of coronary revascularization, as assessed by SRI, patients were subdivided into 4 subgroups: **G1** (SRI < 50%); **G2** (50%  $\leq$  SRI < 70%); **G3** (70%  $\leq$  SRI < 100%) and **G4** (SRI = 100%). The study was carried out according to the principles of Helsinki declaration, and an informed written consent was obtained in all patients.

### Percutaneous revascularization, medical therapy and score calculation

All PCI procedures were performed by 4 experienced operators according to current guideline recommendations [13]. Radial route was the preferred first-line access. Before PCI, patients received intra venous aspirin (250 mg), a loading dose (300-600 mg) of clopidogrel and a bolus of unfractionated heparin. The use of bare metal stents (BMS), DES or drug-eluting balloons (DEB) was dependent on the patient's insurance status, presence of diabetes, lesions' location and

length, and operator's discretion. Only DES of second and third generation were used.

In ACS patients with multivessel disease, staged PCI was generally indicated: PCI of the culprit artery was performed during the index procedure, while the remaining lesions in the non-culprit arteries were treated either during the same hospitalization or within 30 days from the Index PCI. Multivessel disease patients referred for SCAD generally underwent multivessel PCI (of the selected lesions to be treated) within the same procedure.

Coronary lesions located within a segment with a reference diameter of  $\geq 2.0$  mm, were assessed by visual estimation and quantitative coronary analysis (QCA). They were considered significant if there was more than 70% reduction in the lumen diameter  $\geq 50\%$  in case of stenosis of proximal left anterior descending or left main (LM)].

Each coronary lesion considered to be significant was scored to yield the overall SS, which was calculated with the SS online calculator (<http://www.syntaxscore.com/calculator/start.htm>) [14]. For each patient, all angiographic variables involved in the calculation of SS were computed by the consensus of two independent experienced interventional cardiologists blinded to clinical data. In case of discordance a third interventional cardiologist's opinion was requested.

The residual Syntax score (rSS) being a measure of the relative completeness of revascularization, was calculated based on the remaining obstructive CAD after treatment with PCI [15]. The Delta Syntax score (DSS), representative of the burden of disease removed by PCI, was calculated by subtracting the rSS from the baseline SS [10]. Then the SRI, representative of the degree of revascularization after PCI, was calculated by dividing the DSS by the baseline SS and multiplying the result by 100 [(SRI = (DSS/SS)  $\times$  100) [10]. To calculate the baseline Syntax score II (SS II), we used the SS II online calculator (<http://www.syntaxscore.com/calculator/start.htm>) [16]. Complete revascularization was defined as SRI = 100%; otherwise it was considered to be incomplete. Reasonable incomplete revascularization was defined as an incomplete revascularization with an SRI above the determined ideal cut-off. Subjects with SS II  $\geq 25$  (median) were considered as high-risk patients.

When PCI was indicated, lesions to be treated or to be left to medical therapy among those considered to be significant, were selected by the consensus of the interventional cardiologists' team. No intra-coronary imaging or invasive functional assessment modalities were available during the study period. Since neither ticagrelor nor prasugrel are available in Tunisia, clopidogrel was the only anti P2Y<sub>12</sub>-receptor inhibitor prescribed in our population. After undergoing PCI, patients were discharged with dual anti platelet therapy (DAPT): aspirin 100-160 mg and a maintenance dose of clopidogrel (75 mg), daily. All variables were prospectively collected by two research fellows.

### Follow-up

The follow up was performed by either clinical visit or phone call at 3, 6 and 12 months to document information

about the occurrence of MACE or any hospitalization. Clinicians involved in the follow-up were blinded to PCI data. If a patient was hospitalized in another structure, data about that hospitalization was requested from the attending physician after the patient's consent.

## Definitions and endpoints

The primary endpoint was the occurrence of MACE at 1-year follow-up. Secondary endpoints were components of the primary endpoint (cardiovascular death, non-fatal MI, unplanned revascularization, definite ST and hospitalization for cardiovascular reason at 1 year).

MACE were defined as the composite endpoint of cardiovascular death, non-fatal MI and unplanned revascularization. All deaths were considered of cardiovascular origin unless otherwise documented. MI was defined according to the consensus document on the third universal definition of MI [17]. Unplanned revascularization included any need for further revascularization during follow-up excluding PCI of non-culprit lesions scheduled within a staged revascularization strategy. Target lesion revascularization (TLR) was defined as a repeat revascularization (percutaneous or surgical) of the treated lesion. According to the Academic Research Consortium recommendations, definite ST was defined as the presence of a thrombus (at the angiogram) that originates in the stent or in the segment 5 mm proximal or distal to the stent [18]. ST was considered to be acute if occurring within the first 24 hours, subacute if > 24 hours to 30 days, and late if > 30 days to 1 year after stent implantation [19]. Hospitalization for cardiovascular reason was defined as the composite of hospitalization for coronary ischemic events, arrhythmia, heart failure and stroke.

## Statistical analysis

Continuous variables were presented as mean  $\pm$  SD and were compared using the Student unpaired t-test. Categorical variables were presented as counts and percentages and compared using the  $\chi^2$ -test when appropriate (expected frequency > 5); otherwise, the Fisher exact test was used.

The independent predictors of incomplete revascularization were identified using a stepwise logistic regression. At univariate analysis the following variables were tested: Age  $\geq$  75 years, male gender, current smoking, diabetes, hypertension, PAD, prior stroke, prior MI, prior PCI, prior CABG, CKD, ACS, LVEF  $\leq$  40%, multivessel disease, intra-stent restenosis, LM disease, CTO, SS > 22, SS II  $\geq$  25 (median) and medical insurance. Those with  $p < 0.1$  were included in a multivariate model.

Event-free survival during follow-up was evaluated according to the Kaplan-Maier method [20]. The difference between the different subgroups [(complete vs. incomplete revascularization) and (G1, G2 and G3 vs. G4)] was assessed by log-rank  $p$ .

Receiver Operating Characteristic (ROC) curve and area under the curve (AUC) were used to assess discrimination of SRI and to identify its ideal cut-off to predict MACE at 1 year [21].

Stepwise Cox regression was then performed to identify independent predictors of 1-year MACE. The parameters included in univariate analysis were the following: age  $\geq$  75 years, male gender, current smoking, diabetes, hypertension, PAD, prior stroke, prior MI, prior PCI, prior CABG, CKD, ACS, LVEF  $\leq$  40%, multivessel disease, intra-stent restenosis, LM disease, CTO, SS > 22, SS II  $\geq$  25 (median), exclusive use of DES, complete revascularization and SRI  $\geq$  ideal cut-off. Those with  $p < 0.1$  were included in a multivariate model.

Finally, univariate Cox regression was employed to compare reasonable incomplete revascularization (ideal SRI cut-off  $\leq$  SRI < 100%) vs. complete revascularization in the following specific subgroups: diabetics and non-diabetics patients; age  $\geq$  75 years and age < 75 years; LVEF  $\leq$  40% and LVEF > 40%; SSII  $\geq$  25 and SSII < 25.

In all cases  $p$  values < 0.05, were considered statistically significant. All data were processed using SPSS version 21.0 (SPSS, Chicago, Illinois).

## Results

From January 1<sup>st</sup> to June 30<sup>th</sup>, 311 "all comer" patients underwent 333 PCI at our centre. Six patients were excluded because of incomplete data. Then, a total of 305 patients, who underwent 327 PCI, were finally included into the study. Figure 1 illustrates the flow chart of the study population. According to the revascularization degree, the distribution between SRI subgroups was as follows: (G1, SRI < 50%) ( $n = 45$ , 14.8%); (G2, 50%  $\leq$  SRI < 70%) ( $n = 30$ , 9.8%); (G3, 70%  $\leq$  SRI < 100%) ( $n = 43$ , 14.1%), and complete revascularization (G4, SRI = 100%) was obtained in 187 patients (61.3%).

## Patients' characteristics and independent predictors of incomplete revascularization

Table 1 summarizes the clinical baseline characteristics of the study population. The mean age was  $62.3 \pm 10.7$  years, and 80% were males. Diabetes and hypertension were prevalent in 55.7% and 47.5% of cases, respectively while 37% and 35.7% of patients were current smokers and had dyslipidemia, respectively. There were significant differences between the rates of elderly patients, those with a history of MI or a history of CABG among different SRI groups (Table 1).

Table 2 summarizes the angiographic and procedural characteristics of the study population. The mean SS was  $10.5 \pm 7.2$  and 10.2% of patients had SS > 22. The mean SS II score was  $26.6 \pm 9.4$  (Figure 2). There were significant differences between the prevalence of multivessel disease, LM disease and CTOs between the different SRI groups (Table II). In incompletely revascularized patients, the SS was higher (particularly in G1 and G3) as well as SS II (particularly in G1 and G2), comparatively with complete revascularization subgroup (G4) (Figure 2).

The multivariate analysis identified SS > 22 [Odds ratio (OR): 2.64, 95% confidence interval (CI) 1.01-7.05;  $p = 0.048$ ] and multivessel disease (OR: 14.95, 95% CI 8.11-27.58;  $p < 0.001$ ) as the independent predictors of incomplete revascularization (Table 3).

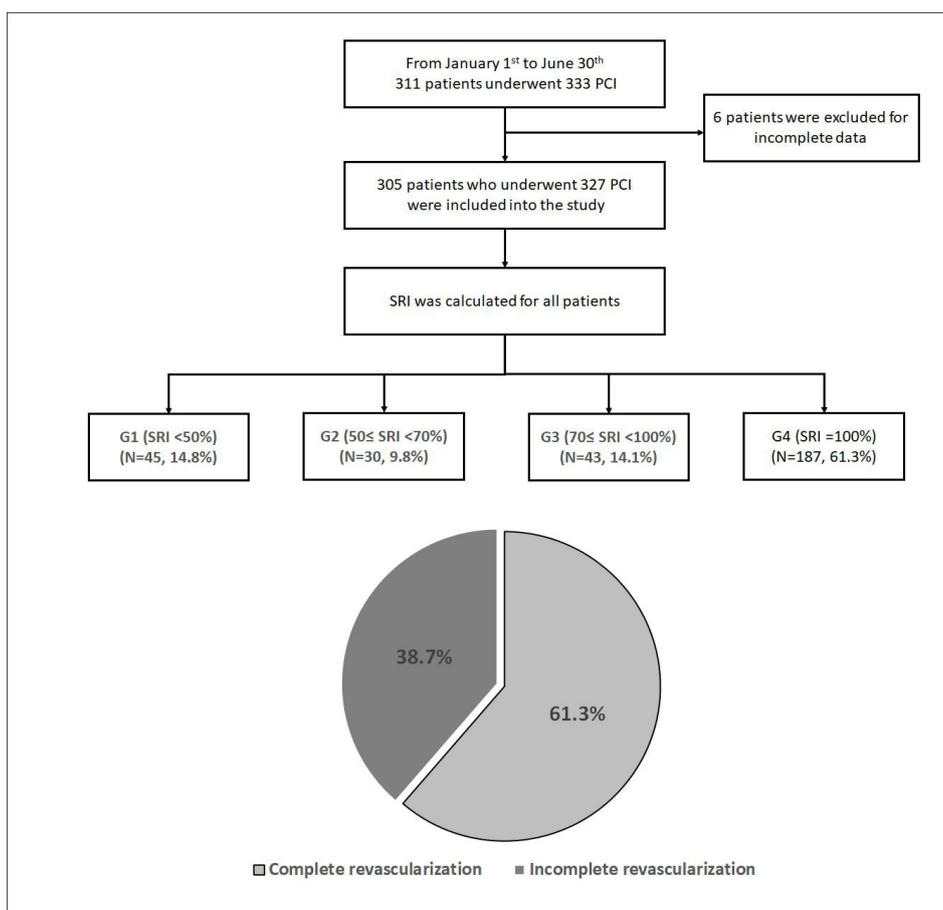


Figure 1: Flow chart of the study population.

Abbreviations: SRI = Syntax revascularization index; PCI = Percutaneous coronary intervention.

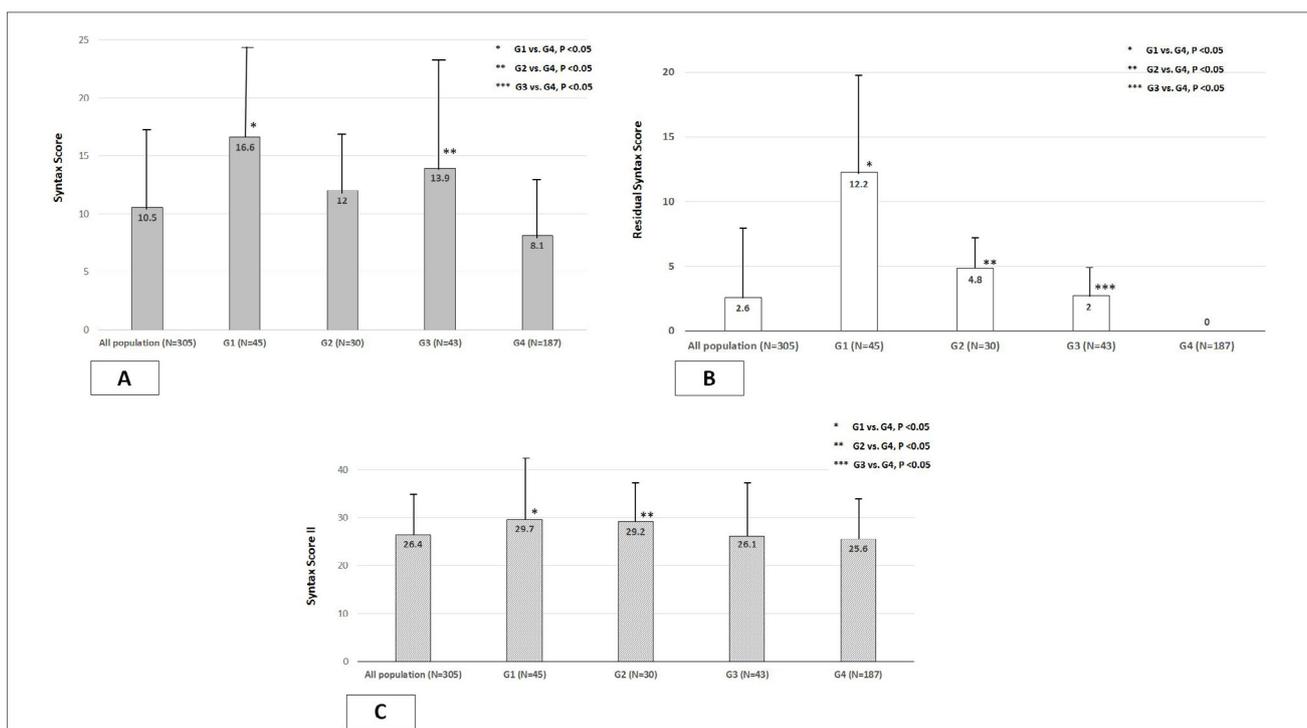


Figure 2: Baseline Syntax score (A), residual Syntax score (B) and Syntax score II (C) according to SRI subgroups.

**Table 1:** Baseline clinical characteristics according to SRI subgroups.

	All Patients (N = 305)	G1 (N = 45)	G2 (N = 30)	G3 (N = 43)	G4 (N = 187)
Age, years, mean ±SD	62.3 ± 10.7	64.5 ± 11.6	66.4 ± 8.3	62.2 ± 10	61.2 ± 10.8
Age ≥ 75 years, n (%)	41 (13.4)	11 (24.4) *	4 (13.3) **	6 (13.9) ***	20 (10.7)
Male gender, n (%)	244 (80)	36 (80)	25 (83)	38 (88)	145 (77.5)
Diabetes, n (%)	170 (55.7)	27 (60)	18 (60)	24 (55.8)	101 (54)
Currentsmoker, n (%)	113 (37)	17 (37.7)	12 (40)	16 (37)	68 (36.3)
Hypertension, n (%)	145 (47.5)	27 (60)	13 (43.3)	14 (32.5)	91 (48.6)
Hyperlipidemia, n (%)	109 (35.7)	13 (28.8)	12 (40)	15 (34.8)	69 (36.9)
BMI, mean ±SD	26.4 ± 2.8	26.5 ± 2.9	26.2 ± 2.7	26.1 ± 2.6	26.5 ± 2.9
Prior MI, n (%)	78 (25.6)	21 (46.6) *	4 (13.3)	8 (18.6)	45 (24)
Prior PCI, n (%)	92 (30.2)	13 (28.8)	6 (20)	12 (27.9)	61 (32.6)
Prior CABG, n (%)	16 (5.2)	6 (13.3) *	0	5 (11.6)	5 (26)
Prior stroke, n (%)	9 (3)	2 (4.4)	1 (3.3)	1 (2.3)	5 (2.6)
PAD, n (%)	18 (5.9)	3 (6.7)	0	3 (7)	12 (6.4)
CKD, n (%)	36 (11.8)	6 (13.3)	5 (16.6) **	7 (16.2) ***	18 (9.6)
LVEF, % ± SD	50.4 ± 8.4	48.9 ± 8.5	48.5 ± 10	49.9 ± 7.6	51.1 ± 8.3
LVEF ≤ 40%, n (%)	40 (13.1)	9 (20)	4 (13.3)	3 (7)	24 (12.8)
<b>ClinicalPresentation</b>					
SCAD, n (%)	102 (33.4)	20 (44.4)	11 (34.3)	7 (16.3)	64 (34.2)
STEMI, n (%)	91 (29.8)	11 (24.4)	10 (33.3)	19 (44.1)	51 (27.2)
NSTEMI, n (%)	81 (26.6)	10 (22.2)	6 (20)	12 (27.9)	53 (28.3)
Unstableangina, n (%)	31 (9.2)	4 (9)	3 (10)	5 (11.6)	19 (10.3)
<b>Medicalinsurance, n (%)</b>	266 (87.2)	39 (86.7)	27 (90)	36 (83.7)	164 (87.7)

Abbreviations: BMI = Body mass index; CABG = Coronary artery bypass grafting; CKD = Chronic kidney disease; LVEF = Left ventricular ejection fraction; MI = Myocardial infarction; NSTEMI = Non-ST elevation myocardial infarction; SCAD = Stable coronary artery disease; STEMI = ST elevation myocardial infarction; PAD = Peripheral artery disease; PCI = Percutaneous coronary intervention; SRI = Syntax revascularization index. \* G1 vs. G4, P < 0.05; \*\* G2 vs. G4, P < 0.05; \*\*\* G3 vs. G4, P < 0.05.

**Table 2:** Angiographic and procedural characteristics according to SRI subgroups.

	All Patients (N=305)	G1 (N=45)	G2 (N=30)	G3 (N=43)	G4 (N=187)
Coronarystatus, n (%)		*	**	***	
Single VD	159 (52.1)	5 (11.1)	4 (13.4)	9 (20.9)	141 (75.4)
2-VD	101 (33.1)	21 (46.6)	13 (43.3)	23 (53.4)	44 (23.5)
3-VD	45 (14.8)	19 (42.3)	13 (43.3)	11 (25.7)	2 (1.1)
ISR, n (%)	31 (10.2)	3 (6.7)	1 (3.3)	5 (11.6)	22 (11.8)
LM disease, n (%)	17 (5.6)	3 (6.6)	1 (3.3)	6 (13.9) ***	7 (2.3)
CTO, n (%)	29 (9.5)	12 (26.6) *	3 (10) **	4 (9)	10 (3)
Number of stents, mean ± SD	1.3 ± 0.9	1.2 ± 0.6	1.1 ± 0.33	1.4 ± 0.8	1.3 ± 1
Length of stents, mm, mean ± SD	31.2 ± 17.5	27.5 ± 18.3	31.7 ± 10.8	37.3 ± 16.8	30.5 ± 18
Type of PCI, n (%)					
DEB	31 (10.2)	5 (11.1)	2 (6.7)	2 (4.6)	22 (11.8)
Only BMS	40 (13.1)	8 (17.7)	1 (3.3)	7 (16.3)	24 (12.8)
BMS/DES	27 (8.8)	2 (4.4)	1 (3.3)	3 (7)	21 (11.2)
Only DES	207 (67.9)	30 (66.8)	26 (86.6)	31 (72.1)	120 (64.2)

Abbreviations: BMS = Bare metal stent; CTO = Chronic total occlusion; DEB = Drug eluting balloon; DES = Drug eluting stent; ISR = Intra-stent restenosis; LM = Left main; PCI = Percutaneous coronary intervention; VD = Vessel disease. \* G1 vs. G4, P < 0.05; \*\* G2 vs. G4, P < 0.05; \*\*\* G3 vs. G4, P < 0.05.

**Table 3:** Multivariate analysis for incomplete revascularization predictors.

Variables	OR (95%CI)	P
Age ≥ 75	1.424 (0.61-3.30)	0.410
Multivessel disease	<b>14.95 (8.11-27.58)</b>	<b>&lt; 0.001</b>
LM disease	0.631 (0.195-2.041)	0.442
CTO	1.537 (0.508-4.073)	0.387
SS > 22	<b>2.64 (1.01-7.05)</b>	<b>0.048</b>
SS II ≥ 25	1.011 (0.527-1.940)	0.973

Abbreviations: CI = Confidence interval; CTO = Chronic total occlusion; LM = Left main; OR = Odds ratio; SS = Syntax score.

## One-year clinical outcome and the predictive value of SRI

One-year clinical outcome was obtained in all patients. Overall, 25 patients (8.2%) experienced MACE at 1 year (Table 4). Patients with complete revascularization experienced less cardiovascular deaths (3.2% vs. 9.3%;  $p = 0.023$ ), ST (4.2% vs. 0.5%;  $p = 0.023$ ) and MACE (5.3% vs. 12.7%;  $p = 0.022$ ) in comparison with patients incompletely revascularized (Table 4). At 1-year follow up, survival free from MACE was significantly reduced (87.3% vs. 94.6%;  $p = 0.021$ ) as well as survival free from cardiovascular death (90.7% vs. 96.8%;  $p = 0.024$ ) and definite ST (99.5% vs. 95.7;  $p = 0.023$ ) in patients who underwent incomplete revascularization in comparison with whom completely revascularized (Figure 3). No difference was observed concerning hospitalization for cardiovascular reason (Figure 3).

Table 5 summarizes 1-year clinical outcome according to SRI subgroups. Significant differences were observed between different SRI subgroups in terms of cardiovascular deaths, definite ST and MACE (Table 5). KM analysis also showed significant differences among different SRI groups in terms of MACE, cardiovascular deaths and ST free survivals (Figure 4).

ROC curve analysis revealed that SRI predicted the occurrence of 1-year MACE (AUC: 0.627, 95%CI significantly

0.508-0.745;  $p = 0.036$ ) (Figure 5). The optimal SRI cut-off was 75% for a sensitivity of 0.721 and a specificity of 0.520.

Multivariable Cox regression identified prior stroke [Hazard ratio (HR): 6.78, 95% CI 1.30-35.4;  $p = 0.023$ ], ACS (HR: 4.60, 95% CI 1.41-15.02;  $p = 0.012$ ), LVEF  $\leq 40\%$  (HR: 2.93, 95% CI 1.04-8.26;  $p = 0.042$ ), SS II  $\geq 25$  (HR: 3.65, 95% CI 1.14-11.71;  $p = 0.029$ ) and SRI  $\geq 75\%$  (HR: 0.41, 95% CI 0.16-0.99;  $p = 0.048$ ) as independent predictors of MACE at 1-year follow up (Table 6).

## Complete vs. reasonable incomplete revascularization in particular subsets of patients

Reasonable incomplete revascularization ( $75 \leq \text{SRI} < 100\%$ ) was obtained in 35 patients (11.5%). Figures 6 illustrated the comparison between complete and reasonable incomplete revascularization in terms of MACE (Figure 6A), cardiovascular death (Figure 6B) and unplanned revascularization (Figure 6C) at 1 year, respectively. In diabetic and elderly patients, achieving complete revascularization had no benefit at 1 year in comparison with reasonable incomplete revascularization (all  $p$  NS). In patients with impaired LVEF, no difference in 1-year outcome was observed according to the degree of revascularization; while in patients with LVEF  $> 40\%$ , although no difference was observed in terms of overall MACE occurrence, complete revascularization protected against CV death at 1 year follow up (HR: 0.19 95% CI 0.04-

**Table 4:** One-year clinical outcome complete vs. incomplete revascularization.

	All Patients (N = 305)	Incomplete revascularization (N = 118)	Complete revascularization (N = 187)	P
MACE, n (%)	25 (8.2)	15 (60)	10 (40)	<b>0.022</b>
All cause death, n (%)	21 (6.9)	12 (10.2)	9 (4.8)	0.072
CV death, n (%)	17 (5.6)	11 (9.3)	6 (3.2)	<b>0.023</b>
Non-fatal MI, n (%)	9 (3)	4 (3.4)	5 (2.7)	0.719
Definite ST, n (%)	6 (2)	5 (4.2)	1 (0.5)	<b>0.023</b>
Unplanned revascularization, n (%)	15 (4.9)	8 (6.8)	7 (3.7)	0.232
TLR, n (%)	10 (3.3)	5 (4.2)	5 (2.7)	0.455
Non TLR, n (%)	9 (3)	6 (5.1)	3 (1.6)	0.080
Hospitalization for CV reason, n (%)	26 (8.5)	13 (11)	13 (7)	0.216

Abbreviations: CV = Cardiovascular; MACE = Major cardiac events; MI = Myocardial infarction; ST = Stent thrombosis; TLR = Target lesion revascularization.

**Table 5:** One-year clinical outcome according to SRI subgroups.

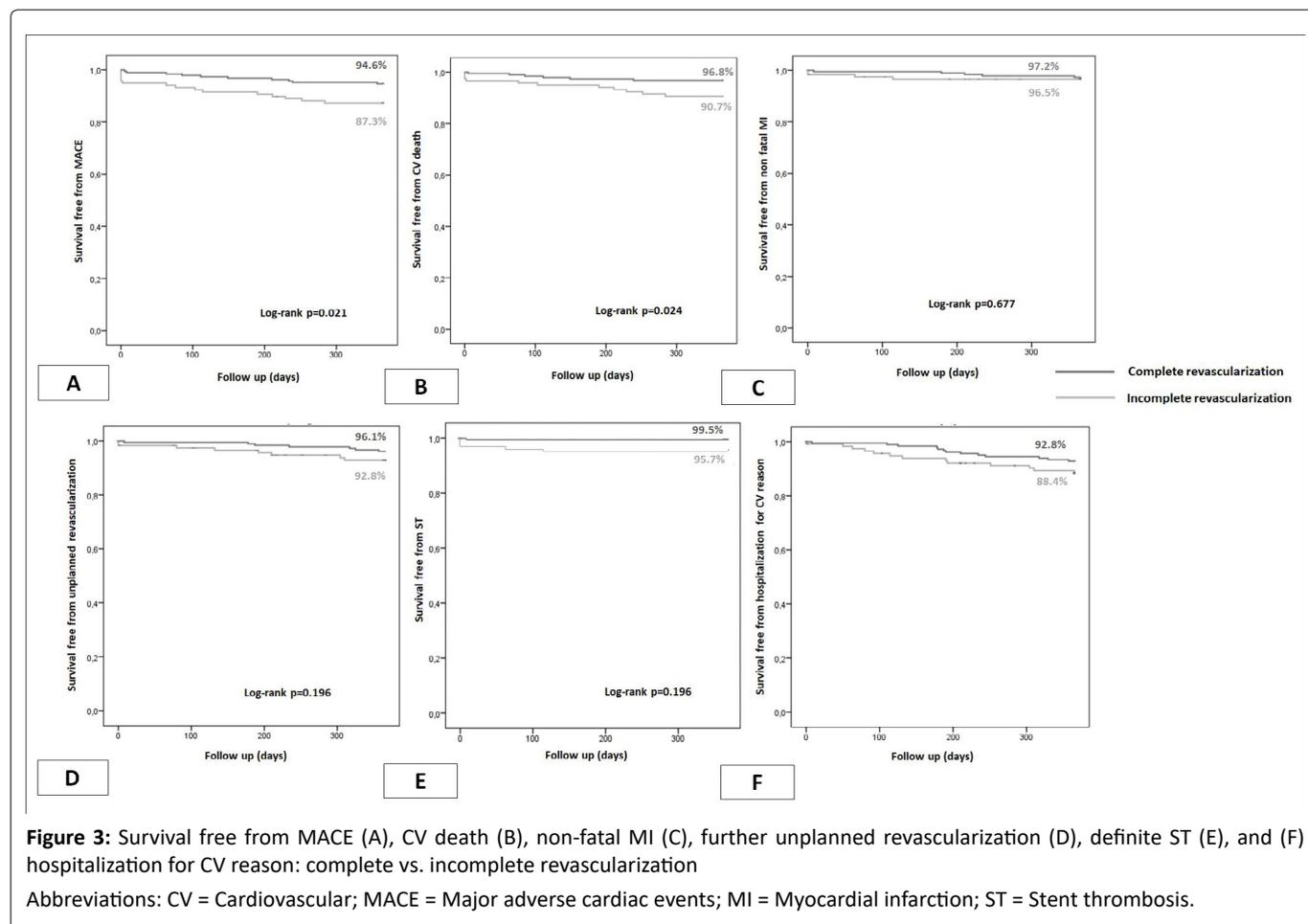
	G1 (N = 45)	G2 (N = 30)	G3 (N = 43)	G4 (N = 187)
MACE, n (%)	6 (13.3)	4 (13.3)	5 (11.6)	10 (5.3)
All-cause death, n (%)	5 (11.1)	4 (9.3)	9 (4.8)	21 (6.9)
CV death, n (%)	5 (11.1)*	2 (6.7)	4 (9.3)	6 (3.2)
Non-fatal MI, n (%)	1 (2.2)	2 (6.7)	1 (2.3)	5 (2.7)
DefiniteST, n (%)	2 (4.4)*	2 (6.7)**	1 (2.3)	1 (0.5)
Unplanned revasc., n (%)	2 (4.4)	2 (6.7)	4 (9.3)	7 (3.7)
TLR, n (%)	1 (2.2)	1 (3.3)	3 (7)	5 (2.7)
Non-TLR, n (%)	2 (4.4)	1 (3.3)	3 (7)***	3 (1.6)
Hospitalization for CV reason, n (%)	5 (11.1)	4 (13.3)	4 (9.3)	14 (7)

Abbreviations: CV = Cardiovascular; MACE = Major adverse cardiac events; MI = Myocardial infarction; revasc = Revascularization; ST = Stent thrombosis; SRI = Syntax revascularization index; TLR = Target lesion revascularization. \* G1 vs. G4,  $P < 0.05$ ; \*\* G2 vs. G4,  $P < 0.05$ ; \*\*\* G3 vs. G4,  $P < 0.05$ .

**Table 6:** Predictors of 1-year MACE occurrence. Multivariate analysis.

Variables	HR (95%CI)	P
Age ≥ 75 years	1.415 (0.43-4.66)	0.568
PAD	0.41 (0.10-1.67)	0.216
<b>Prior stroke</b>	<b>6.78 (1.30-35.4)</b>	<b>0.023</b>
<b>LVEF ≤ 40%</b>	<b>2.93 (1.04-8.26)</b>	<b>0.042</b>
<b>ACS</b>	<b>4.60 (1.41-15.02)</b>	<b>0.012</b>
SS > 22	1.73 (0.56-5.36)	0.343
<b>SS II ≥ 25</b>	<b>3.65 (1.14-11.71)</b>	<b>0.029</b>
Complete revascularisation	0.75 (0.17-3.31)	0.700
<b>SRI ≥ 75%</b>	<b>0.41 (0.16-0.99)</b>	<b>0.048</b>

Abbreviations: ACS = Acute coronary syndrome; CI = Confidence interval; HR = Hazard ratio; LVEF = Left ventricular ejection fraction; MACE = Major adverse cardiovascular events; PAD = Peripheral artery disease; SS = Syntax score; SRI = Syntax revascularization index.



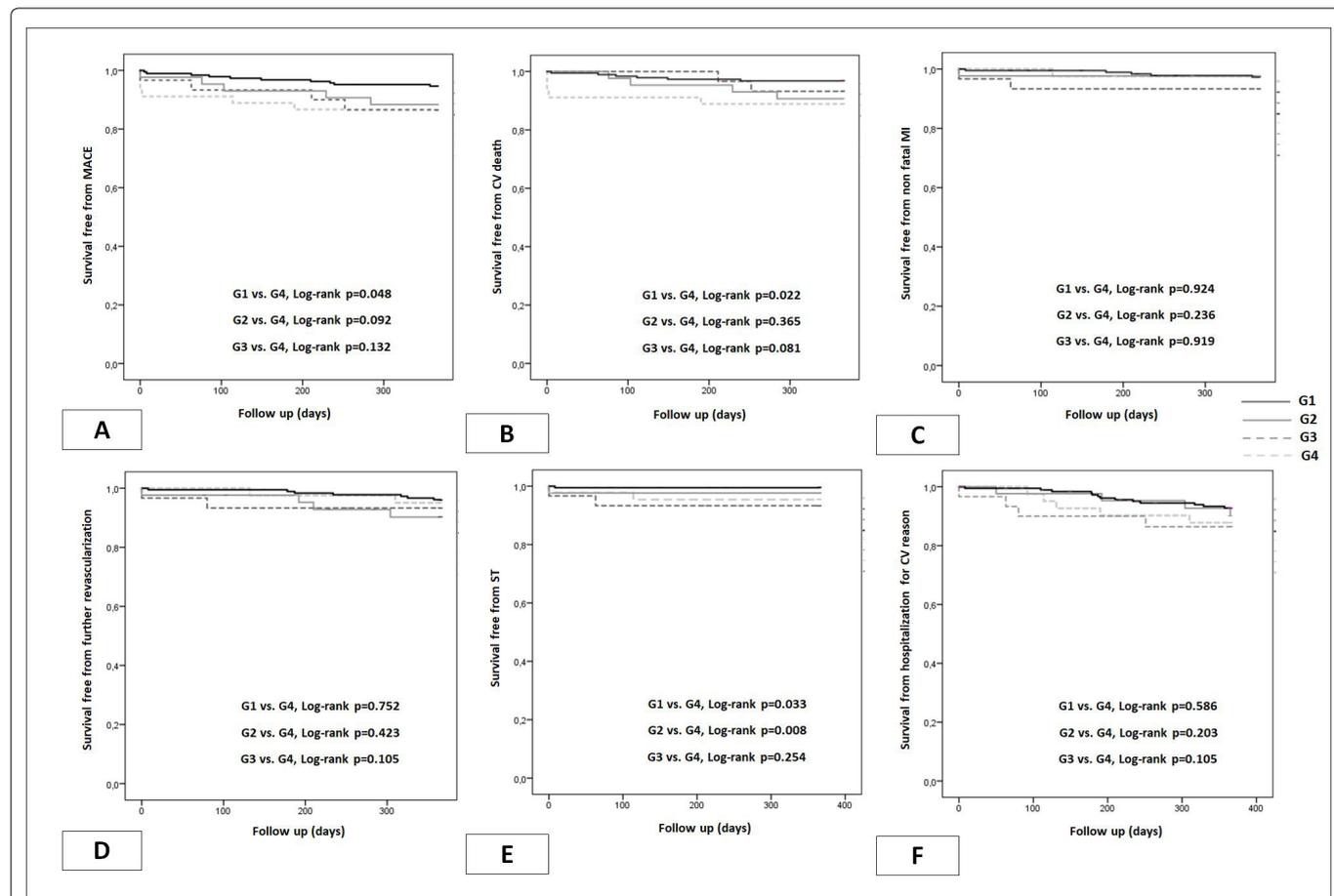
0.96;  $p = 0.044$ ), in comparison with reasonable incomplete revascularization (Figure 6B). In high risk patients ( $SS \geq 25$ ), achieving complete revascularization did not influence 1-year outcome (all  $p$  NS); whereas in lower risk patients ( $SS < 25$ ), complete revascularization was shown to reduce CV death in comparison with reasonable incomplete revascularization (HR: 0.09 95% CI 0.01-0.98;  $p = 0.048$ ) (Figure 6B).

## Discussion

In the current study, we assessed for the first time, the added value of SRI on mid-term clinical outcome in a prospective contemporary cohort of “real world” all comer patients undergoing PCI. The major findings can be

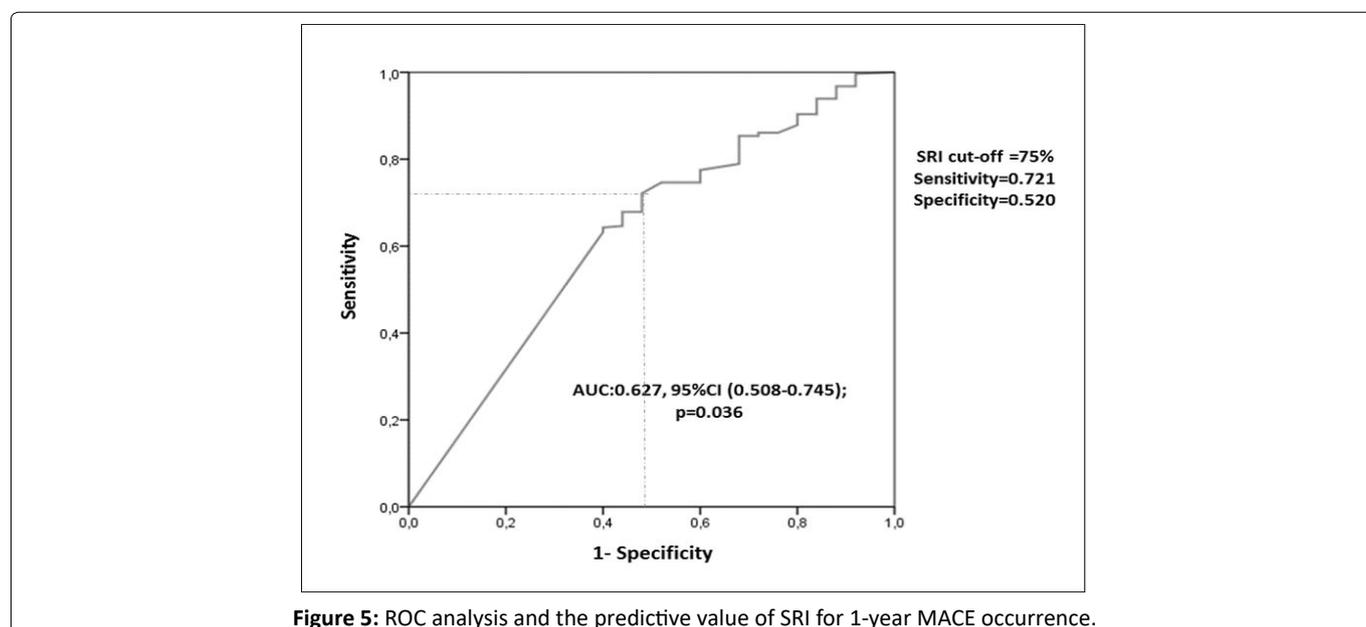
summarized as follows: a) Complete revascularization was obtained in 61.3% of patients, b) The independent predictors of incomplete revascularization were multivessel disease and  $SS > 22$ , c) SRI satisfactorily predicted mid-term outcome and  $SRI \geq 75\%$  protected against 1-year MACE, d) reasonable incomplete revascularization ( $75 \leq SRI < 100$ ) led to similar mid-term outcome than complete revascularization in elderly, diabetic and high-risk patients.

According to clinical characteristics, our study population showed a high cardiovascular risk profile. Indeed, diabetes was prevalent in more than half our patients (55.7%). This prevalence is much higher than that in other all comer PCI studies and largely above the Tunisian average (15.1%)

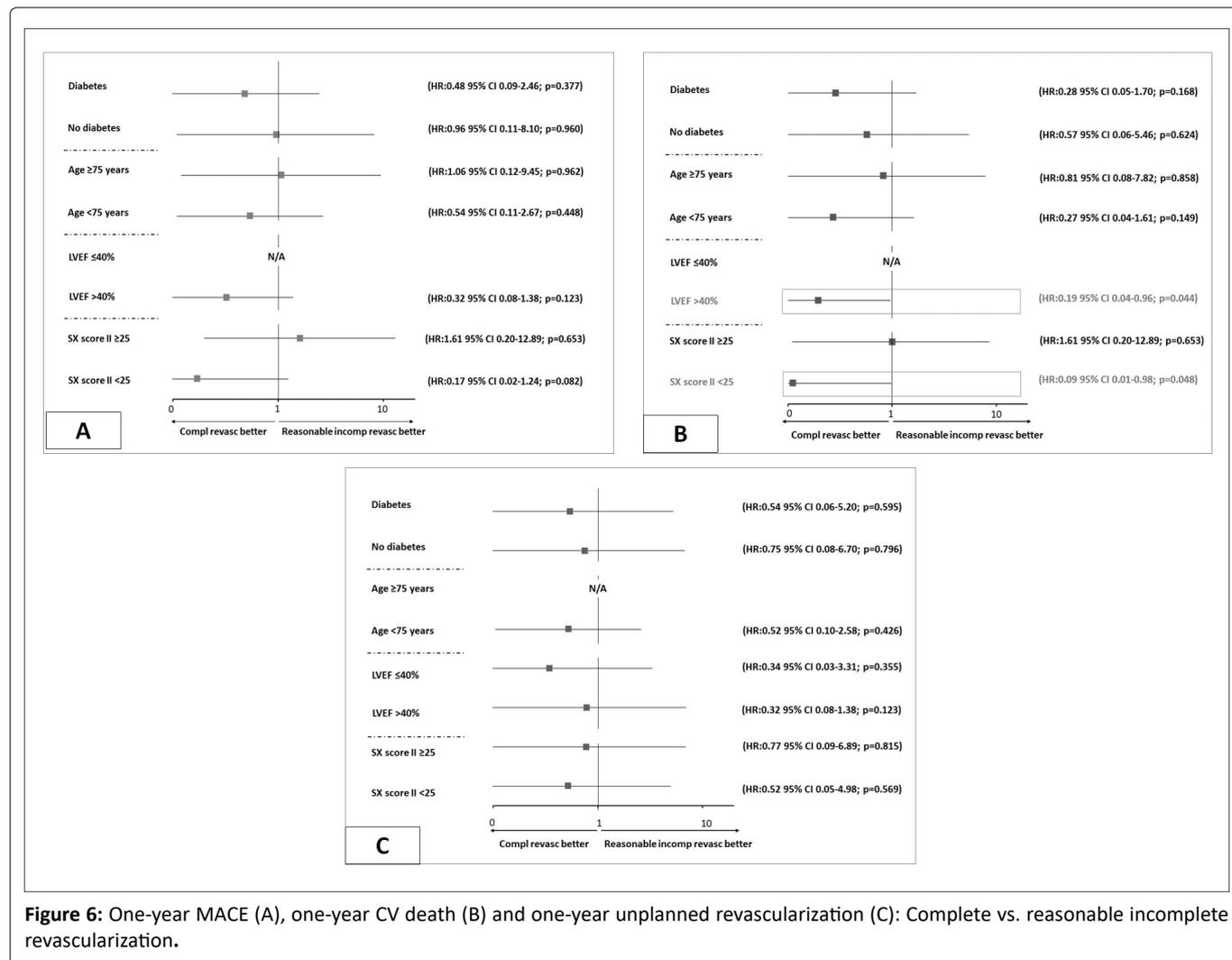


**Figure 4:** Survival free from MACE (A), CV death (B), non-fatal MI (C), further unplanned revascularization (D), definite ST (E), and (F) hospitalization for CV reason according to SRI subgroups.

- A)** At 1 year, survival free from MACE was 86.7% (G1), 86.5% (G2), 88.4% (G3), and 94.6% (G4).
  - B)** At 1 year, survival free from CV death: 88.9% (G1), 93.2% (G2), 90.7% (G3), and 96.8% (G4).
  - C)** At 1 year, survival free from non-fatal MI: 97.6% (G1), 93.3% (G2), 97.7% (G3), and 97.2% (G4).
  - D)** At 1 year, survival free from further unplanned revascularization: 95.1% (G1), 93.3% (G2), 90.2% (G3), and 96.1% (G4).
  - E)** At 1 year, survival free from definite ST was 95.4% (G1), 93.3% (G2), 97.7% (G3), and 99.5% (G4).
  - F)** At 1 year, survival free from hospitalization for CV reason was 87.8% (G1), 86.4% (G2), 90.1% (G3), and 92.8% (G4).
- Abbreviations: CV = Cardiovascular; MACE = Major adverse cardiac events; MI = Myocardial infarction; ST = Stent thrombosis.



**Figure 5:** ROC analysis and the predictive value of SRI for 1-year MACE occurrence.



[12,22]. Such differences might be due to the close relationship between diabetes and CAD and to the fact that diabetes is under diagnosed in the Tunisian population and can often be firstly diagnosed following a coronary event. The prevalence of other risk factors [smoking (37%), hypertension (47.5%), dyslipidemia (35.7%) and overweight (mean BMI  $26.4 \pm 2.8$ )] further confirm the high-risk profile of our population.

The mean age of our patients was  $62.3 \pm 10.7$ , while elderly (age  $\geq 75$ ) represented 13.4%. Interestingly, the elderly proportion in all incomplete revascularization SRI subgroups was higher than that in complete revascularization subgroup. Although it was not identified as an independent predictor at multivariate analysis, age  $\geq 75$  was associated with incomplete revascularization at univariate analysis. The reluctance of interventional cardiologists to perform long and cumbersome procedures in older patients, consequently decreasing the chances of achieving complete revascularization, could explain this latter finding.

There were also significantly more patients with CKD in the SRI subgroups G2 and G3, in comparison with G4. Patients with CKD are more likely to develop contrast induced nephropathy [13]. Therefore, interventionalists tend to reduce procedural time and contrast exposure in these patients. Achieving complete revascularization is consequently more challenging.

One of the originalities of our study is that we included both single and multivessel CAD in comparison with other registries focusing on the SRI concept which only included multivessel disease patients [4,10]. We believed this can better illustrate real life practice. Indeed, the presence of several lesions (proximal, mid and/or distal) within the same vessel or in significant side branches, in a single vessel disease patient could also challenge the completeness of revascularization. Multivessel disease was encountered in almost half of our patients (47.9%) and strongly predicted incomplete revascularization (OR 14.95; CI 8.11-27.58;  $p < 0.001$ ). The mean SS score was  $10.5 \pm 7.2$  and 1/10 (10.2%) of patients had a SS  $> 22$ . The fact that SS  $> 22$  independently predicted incomplete revascularization further highlights that the more complex and extensive is CAD the lower are the chances to obtain complete revascularization. CTO, a well-known predictor of incomplete revascularization in literature [23], was present in only 9.5% of patients. This low prevalence comparatively with other registries [24], might be explained by the fact that most CTO patients were either referred for surgical revascularization (particularly those with multivessel disease) or left on medical therapy, and then not included in our study. Furthermore, only 1/5 of CTO patients enrolled underwent a PCI attempt for their CTO. Although CTO was associated with incomplete revascularization in univariate analysis, it did not appear in the multivariate model.

In the ARTS-II trial, Sarno, et al. found no significant difference in 5-year survival without MACE between patients with complete and incomplete revascularization undergoing PCI (with first-generation sirolimus DES) or CABG [25]. Interestingly, in patients incompletely revascularized by PCI, the authors revealed a significantly lower MACE survival in the higher SS tertile compared with the low (HR 0.56, 95% CI 0.32-0.96,  $p = 0.04$ ) and intermediate (HR 0.50, 95% CI 0.28-0.91,  $p = 0.02$ ) tertiles, while survival between the low and intermediate SS tertiles was not significantly different.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial could be considered as the ultimate trial of incomplete revascularization in SCAD patients [26]. Although this trial failed to show a clinical benefit for routine PCI in these low risk patients, its nuclear substudy highlighted the prognostic impact of the residual ischemic burden [27]. Indeed,  $\geq 10\%$  reversible ischemia was associated with adverse 5-year mortality when left on medical therapy alone.

Nowadays in the era of second-and third-generation DES, MACE driven by TLR considerably decreased [13]. This tends to encourage interventional cardiologists to target more complete revascularization in their patients.

In our study, incomplete revascularization was associated with significantly lower survival free from MACE and cardiovascular death. These findings were in accordance with the results of a meta-analysis of 35 randomized and observational studies including 89,883 PCI and CABG patients [22]. Complete revascularization was associated with lower long-term mortality, MI and repeat coronary revascularization [22]. Interestingly, ST was more often experienced by our incompletely revascularized patients. Intuitively, complete revascularization tends to require more and longer stents. In our study, no difference was found between G4 and all incomplete revascularization subgroups in terms of stent numbers and length (all  $p$  NS). Hence, the higher rate of ST in patients with incomplete revascularization might be due to the higher complexity (length, calcifications, tortuosity) of their treated lesions preventing optimal stent apposition.

Initially applied using rSS [28], the concept of reasonable incomplete revascularization has been extended to the SRI. In patients with de novo 3-vessel CAD or unprotected LM disease, Génereux et al. found that 5-year outcomes were inversely proportional to the SRI [10]. The Youden index identified an SRI cut-off of  $< 70\%$  for prediction of 5-year all-cause mortality (HR: 4.13, 95% CI 2.79-6.11;  $p < 0.0001$ ). Hence, an SRI  $\geq 70\%$  was considered as a reasonable goal for patients with complex CAD in whom complete revascularization is not always possible.

In our study SRI was also found to satisfactorily predict 1-year cardiovascular outcome (AUC = 0.627;  $p = 0.036$ ). Our data showed that although no difference was observed in terms of MACE, MI, ST and hospitalization for cardiovascular reason, patients with  $70 \leq \text{SRI} < 100\%$  (G3) tend to have lower survival free from CV death ( $p = 0.081$ ) and significantly higher rate of non-TLR unplanned revascularization (7% vs. 1.6%;  $p = 0.046$ ). Hence, the cut-off of 70% (generated in a

complex CAD North-American and European cohort) could not be applicable to our Tunisian all-comer population.

In our cohort, ROC curve analysis identified 75% as the ideal SRI cutoff (sensitivity = 0.721; specificity = 0.520). Importantly, SRI  $\geq 75\%$  (i.e. complete and reasonable incomplete revascularization) protected against 1-year MACE (HR: 0.41, 95%CI 0.16-0.99;  $p = 0.048$ ), while complete revascularization (by itself) did not appear to independently predict 1-year MACE on multivariate Cox analysis. The other predictors of mid-outcome were prior stroke, LVEF  $\leq 40\%$ , ACS and SS II  $\geq 25$  as reported in previous studies [29-32].

In the Registry to Evaluate Safety and Effectiveness of Everolimus Drug Eluting Stent for Coronary Revascularization (SEEDS), Xu, et al. evaluated the impact of the revascularization degree on 2-year MACE in Asian complex CAD patients [11]. In accordance with our results, 2-year mortality and MACE were higher in lower SRI subgroup ( $< 50\%$ ) [11]. The SRI predicted mortality and MACE at 2 years and the optimal SRI cut-off in this latter population was as high as 85% [11]. This difference in SRI cut-offs came mainly from the fact that our population had considerably less complex and extensive CAD than the SEEDS population. Indeed, when restricted to patients with low SS, the optimal SRI cut-off of the SEEDS registry decreased to 70-75% [11].

In our study, reasonable incomplete revascularization ( $75 \leq \text{SRI} < 100$ ) was compared with complete revascularization in 4 different clinical scenarios: diabetes, elderly patients, impaired LVEF and high-risk patients (as assessed by SS II).

In our population, in both diabetic and non-diabetic patients, complete revascularization did not provide any clinical benefit at 1-year follow-up. A post hoc nonrandomized analysis of the completeness of revascularization included 751 patients treated by either CABG or PCI (264 and 487, respectively) [29]. No difference was observed in diabetic patients receiving reasonable incomplete revascularization vs. those completely revascularized (HR: 1.51, 95%CI 0.93-2.47,  $p$  NS) [29]. Hence, in diabetic patients treated by PCI, complete revascularization seemed to not have a clinical benefit in comparison with reasonable incomplete revascularization, allowing the assumption of leaving a "reasonable" ischemic burden on medical therapy alone, especially in case of extensive and diffuse CAD.

In a substudy of the SHINANO registry including elderly patients (mean age of 81 years), Harada et al. reported a 51.2% complete revascularization rate [30]. The investigators found that MACE incidence by survival analysis was significantly higher in the incomplete revascularization group (21.1% vs. 7.4%,  $p < 0.001$ ) at 1-year, concluding that complete revascularization appears to suppress midterm ischemic events in elderly patients. Differently, in 502 ACS patients aged  $\geq 75$  (with a complete revascularization rate of 40.4%), Chen, et al. [33] did not find significant differences in cumulative survival and event-free survival rates between incomplete and complete revascularization. The impact of reasonable incomplete revascularization was not assessed in the 2 latter studies. In our patients aged more than 75 years ( $n = 41$ ), we obtained complete revascularization in 48.7%

of cases. Reasonable incomplete revascularization showed the same performance than complete revascularization in terms of MACE and cardiovascular death at 1-year. Indeed, in elderly patients, treating all lesions can be challenging not only due to the complexity of CAD but also to the associated comorbidities. Furthermore, this subset of patients has generally a relatively decreased physical activity status. Thus, only targeting lesions with prognostic importance (subtending large myocardial territories) in a reasonable incomplete revascularization fashion, could represent a valuable approach to balance the benefit/risk ratio.

In our population, 40(13.1%) patients had a LVEF  $\leq$  40%. Complete revascularization was achieved in 60% of these cases. No difference in unplanned revascularization was observed between complete and reasonable incomplete revascularization (HR 0.34, 95%CI 0.03-3.31,  $p = 3.55$ ). Conversely, we showed that in the presence of mildly impaired or preserved LVEF ( $> 40\%$ ), complete revascularization should be targeted as it protected against cardiovascular death in comparison with reasonable incomplete revascularization. Similarly, when the risk was low (SSII  $< 25$ ), complete revascularization remains the most appropriate strategy to reduce mid-term cardiovascular mortality, while no benefit of complete revascularization was demonstrated in high risk patients, emphasizing the safety and efficiency of a reasonable incomplete revascularization approach in high risk patients (SS II  $\geq 25$ )

### Study limitations

Our study has some limitations. First, its single-center design and the relatively limited number of patients do not allow the generalization of the results. Nonetheless, it represents the first study in North Africa focusing on the impact of the degree of coronary revascularization. Second, in the absence of FFR assessment, only an anatomical definition was used to evaluate the revascularization completeness. Third, coronary lesions faced in our study were less complex than in other reports (as assessed by SS). However, it reflects a "real life" Tunisian CAD population treated in our everyday cathlab practice. Fourth, the impact of prescribed medical therapy as well as patient's compliance (particularly to DAPT), was not assessed. Fifth, assessing the effects of the revascularization degree on symptoms and quality of life was beyond the scope of the current study. Sixth, the low number of subjects in the evaluated subgroups makes difficult to generalize the results. Finally, longer outcome is required to better understand the real impact of coronary revascularization degree on cardiovascular outcome.

### Conclusion

Our results further confirm the importance of complete revascularization in CAD patients in insuring a better cardiovascular outcome. However, when such a target is not achievable, the concept of reasonable incomplete revascularization relying on SRI ( $\geq 75\%$ ) appears to be a valuable option, particularly in the setting of diabetes, age  $\geq 75$ , LVEF  $\leq 40\%$  and SS II  $\geq 25$ . Larger multicenter studies

with longer follow up are needed to better identify the impact of a reasonable incomplete coronary revascularization in particular subsets in whom complete revascularization can be challenging.

### Conflicts of Interest

None to declare.

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