Impact of Incomplete Revascularisation on 10-year All-cause Death in Patients with Three-vessel Disease or Left Main Coronary Artery Disease: Insights from the SYNTAX Extended Survival Study

Kuniaki Takahashi, Patrick W. Serruys, Daniel J.F.M. Thuijs, A. Pieter Kappetein, Marie-Claude Morice, Friedrich-Wilhelm Mohr, Michael J. Mack, Nick Curzen, Piroze Davierwala, Milan Milojevic, Rutao Wang, Hironori Hara, Faisal Sharif, Joanna J. Wykrzykowska, Robbert J. de Winter, Yoshinobu Onuma, Stuart J. Head, David R. Holmes Jr., On behalf of the SYNTAX Extended Survival Study Investigators

Submitted

ABSTRACT

Objectives

The goal of this study was to evaluate the effect of completeness of revascularisation on 10-year all-cause death in patients with percutaneous coronary intervention (PCI) versus those undergoing coronary artery bypass grafting (CABG).

Background

The impact of incomplete (IR) versus complete revascularisation (CR) on 10-year all-cause death has not been fully investigated in patients with three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD).

Methods

The SYNTAX Extended Survival Study evaluated the vital status up to 10 years of patients who were originally enrolled in the SYNTAX trial. In the present sub-study, outcomes of the CABG CR group were compared with the CABG IR, PCI CR, and PCI IR groups. In addition, in the PCI cohort, the residual SYNTAX score (rSS) was used to quantify the extent of IR and its prognostic impact. The rSS of 0 suggests CR, whereas a rSS>0 identifies IR of variable degree.

Results

IR was more frequently observed in patients with PCI vs. CABG (56.0% vs. 35.7%). IR was more common in patients with 3VD compared with LMCAD in both PCI (58.0% vs. 52.9%) and CABG arm (41.3% vs. 27.2%). Patients undergoing PCI with CR had a similar risk of 10-year all-cause death compared with those undergoing CABG (22.0% for PCI with CR vs. 23.8% for CABG with IR vs. 23.7% for CABG with CR). In contrast, those with PCI and IR had a significantly higher risk of all-cause death at 10 years compared with CABG and CR (33.9% vs. 23.7%; adjusted hazard ratio [aHR]:1.68; 95% confidence interval [CI]:1.22-2.30; p<0.001). When patients with PCI were stratified according to the rSS, those with a rSS≤8 had a comparable risk of all-cause death at 10 years as the other terciles (22.0% for rSS=0 vs. 24.0% for rSS>0-4 vs. 28.9% for rSS>4-8), whereas a rSS> 8 had a significantly higher risk of 10-year all-cause death as compared with those undergoing PCI with CR (53.0% vs. 22.0%; aHR:3.75; 95% CI:2.33-6.05; p<0.001).

Conclusion

Incomplete revascularisation is common after PCI; the degree of incompleteness has a major impact on 10-year mortality. Patients with a rSS ≤8 after PCI had a comparable risk of 10-year all-cause death compared with those after CABG, whereas

patients with a rSS>8 after PCI had a marked increase in 10-year mortality. Further studies are needed to optimize outcomes in this high-risk population.

Keywords

Coronary artery bypass grafting; Incomplete revascularisation; Left main coronary artery disease; Percutaneous coronary intervention; residual SYNTAX score; Three-vessel disease.

INTRODUCTION

The aim of myocardial revascularisation is to relieve ischemia of patients to improve clinical outcomes including mortality [1, 2]. The nuclear sub-study of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial has shown that patients on medical therapy with >10% of reversible ischemia had an excess of 5-year mortality. In contrast, in the revascularisation group also treated with medical therapy, a reduction of residual ischemia from >10% of the myocardium to ≤ 5% by revascularisation resulted in a lower risk of mortality and myocardial infarction (MI) [2]. Although numerous randomized clinical trials have tested the efficacy and safety of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) with drug-eluting stent (DES) in patients with severe coronary artery disease (CAD) [3], the selection of the most appropriate mode of revascularisation for a given patient remains a complex process [4, 5].

The 2018 European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgery (EACTS) guidelines on myocardial revascularisation suggest that (i) the use of surgical mortality scores of STS score (class IB) or EuroSCORE II (class IIb B) to estimate in-hospital mortality, (ii) calculation of the anatomical SYNTAX score (SS) (class IB) to assess the extent and complexity of coronary artery disease (CAD) and to predict long-term morbidities and mortality after revascularisation, and (iii) expected completeness of revascularisation (class IIa B) are of paramount importance for decision-making of revascularisation strategies between CABG and PCI [6, 7]. To date, there have been several comparative studies evaluating the impact of IR vs. CR on clinical outcomes in patients with complex CAD undergoing CABG or PCI [8-16]. Among them, only the MASS II (Second Medicine, Angioplasty, or Surgery Study) has evaluated outcomes beyond 5 years, although it was conducted in the era of bare-metal stent (BMS) with a limited number of patients [12].

More recently, the SYNTAX Extended Survival (SYNTAXES) study has assessed survival prognosis at 10 years in all-comers patients with *de novo* three-vessel disease (3VD) or left main coronary artery disease (LMCAD) randomized to PCI or CABG who were originally enrolled in the SYNTAX trial [17]. The present analysis evaluates outcomes according to completeness of revascularisation in patients who underwent percutaneous or surgical revascularisation in the SYNTAXES study.

METHODS

Study design and population

The study design and the primary and final 5-year results of the SYNTAX (NCT00114972) trial have been published previously [18-20]. In summary, the SYNTAX trial was a prospective, international, multicenter, randomized controlled trial conducted at 85 centers in Europe and the United States between March 2005 and April 2007. Based on clinical judgement and consensus of heart team consisting of a cardiothoracic surgeon and interventional cardiologist at each center, all-comers patients with *de novo* 3VD or LMCAD who were anticipated to achieve a clinical equipoise between CABG and PCI were enrolled and randomized in a 1:1 fashion to either CABG (n= 897) or PCI (n= 903) with TAXUS Express paclitaxel-drug eluting stents (PES) (Boston Scientific Corporation, Marlborough, MA, USA). The SYNTAX trial (NCT00114972) completed patient follow-up up to 5 years [20], and the SYNTAXES study (NCT03417050) has evaluated vital status up to 10 years [17]. These trials were approved by the ethics committees at each investigating center, and all patients provided their written informed consent prior to participation in the SYNTAX trial.

Completeness of revascularisation

In the SYNTAX CABG arm, due to the overall lack of protocol driven angiographic follow-up after surgery, we used the surgical investigator-reported classification of either CR or IR according to the anatomical SS; the surgeons had a surgical report on the location of their bypass grafts based on the anatomical SS established by the Heart Team and concluded to be CR or IR. The definition of CR was predefined by the trial protocol [19]; investigators documented a binary outcome as to whether any lesion with more than 50% diameter stenosis in vessels ≥1.5 mm as estimated on the diagnostic angiogram during the local Heart Team conference was actually treated by the revascularisation.

In the PCI arm, we previously quantified the extent of IR by an independent core laboratory unaware of and blind to patient outcome (i.e. residual SS [rSS]) [21], which was calculated as the sum of the individual scores of coronary lesions with ≥ 50% diameter stenosis in vessel ≥ 1.5 mm but left untreated [14, 21, 22]. The rSS of 0 indicates CR, whereas a rSS > 0 indicates IR with a higher rSS representing more coronary stenoses left untreated. The ΔSS, representing the burden of disease treated with PCI, was calculated by subtraction of the rSS from the baseline anatomical SS [14, 21, 22].

Study endpoint

The pre-specified primary endpoint of the SYNTAXES trial was all-cause death at 10 years. Vital status was confirmed by electronic healthcare record review and national death registry.

Statistical analyses

All the analyses are performed according to as-treated principle [16]. The cumulative incidence of clinical adverse events up to 10 years is assessed using the Kaplan-Meier method and compared using the log-rank test. Hazard ratio (HR) with 95% confidence interval (CI) is assessed by a Cox proportional regression model. To adjust for potential confounding factors, the following variables are entered into a multivariable Cox regression model: age, sex, body mass index (BMI), medically treated diabetes mellitus, hypertension, dyslipidemia, current smoking, previous MI, previous cerebrovascular disease, chronic kidney disease (defined as creatinine clearance < 60 mL/min), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), left ventricular ejection fraction (LVEF), clinical presentation (stable or unstable angina), disease type (LMCAD or 3VD), and anatomical SS. Multivariable Cox regression model is used to compare outcomes of the CABG CR group with the CABG IR, PCI CR, and PCI IR groups. Patients with missing vital status are included in the analysis and censored at the time of lost to follow-up or at 5 years if centers decided not to participate in the SYNTAXES study with 10-year extended follow-up (only 2 centers with a total of 5 patients declined participation) [17]. Continuous variables were reported as mean ± standard deviations (SD) or median and interquartile range (IQR), and are compared using Student's *t* tests or Mann-Whitney U test, respectively. Categorical variables are reported as percentages and numbers, and are compared using Chi-square or Fisher's exact test as appropriate. All tests are two-sided and a p-value of <0.05 is considered to be statistically significant. All analyses are performed using SPSS Statistics, version 25 (IBM Corp., Armonk, 281 N.Y., USA).

RESULTS

Study population

Among 1,800 patients enrolled in the SYNTAX trial, 34 (1.9 %) patients did not undergo PCI or CABG, of whom 8 (0.4%) patients were treated medically, and the rSS was not available in 26 (1.4%) patients who underwent PCI. As a result, 1,740 (96.7%) patients were included in the present analysis (CABG, n= 865; PCI, n=875) (**Figure 1**). Overall, 54.1% achieved CR, however, patients undergoing PCI resulted in a higher

rate of IR compared with CABG (56.0% for PCI vs. 35.7% for CABG) (**Figure 2A**). In both PCI and CABG arms, patients with 3VD were more likely to had IR, compared with those with LMCAD (**Figure 2B** and **2C**).

Baseline characteristics according to the completeness of revascularisation are presented in **Table 1**. Patients undergoing PCI with IR had a higher prevalence of co-morbidities (medically treated diabetes, on insulin, hypertension, and lower LVEF).

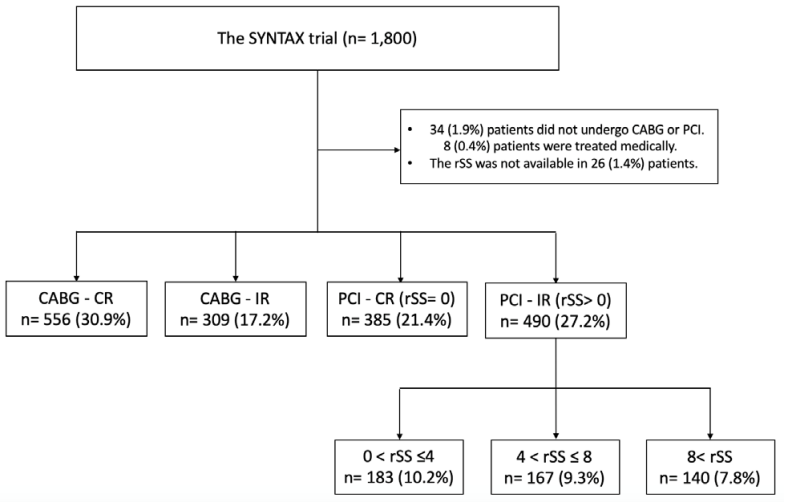

Figure 1. Patient flow diagram of the present study.
CABG: coronary artery bypass grafting; CR: complete revascularization; IR: incomplete revascularization; PCI: percutaneous coronary intervention; rSS: residual SYNTAX score.

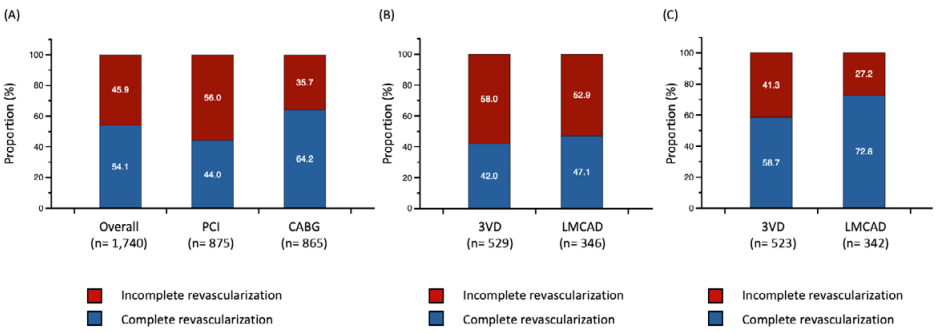

Figure 2. Proportion of completeness of revascularization in the overall population (A), PCI arm (B), and CABG arm (C).
For the PCI cohort, the completeness of revascularization was based on the Core Laboratory analysis, whereas for the CABG cohort, it was investigator-reported.
CABG: coronary artery bypass grafting; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; 3VD: three-vessel disease.

Table 1. Baseline characteristics according to completeness of revascularization.

	CABG			PCI			
	CR	IR	p-value	CR	IR	p-value	Overall p-value
Age (year)	64.6± 9.8	65.4± 9.8	0.243	64.7± 9.8	65.9± 9.5	0.060	0.115
Sex			0.755			0.026	0.048
Male	79.9 (444)	79.0 (244)		72.7 (280)	79.2 (388)		
Female	20.1 (112)	21.0 (65)		27.3 (105)	20.8 (102)		
Body mass index (kg/m^2)	28.0± 4.5	27.7± 4.2	0.317	28.1± 4.7	28.2± 4.9	0.748	0.482
Diabetes	22.7 (126)	25.2 (78)	0.392	20.5 (79)	29.8 (146)	0.002	0.008
Insulin	9.0 (50)	12.0 (37)	0.162	7.0 (27)	12.2 (60)	0.010	0.036
Metabolic syndrome	48.2 (212)	41.4 (104)	0.087	43.1 (137)	48.2 (191)	0.170	0.185
Hypertension	64 (356)	62.5 (193)	0.646	68.1 (262)	70.8 (347)	0.378	0.040
Dyslipidemia	77.5 (428)	77.3 (235)	0.938	77.9 (299)	79.6 (386)	0.537	0.836
Current smoker	23.9 (132)	19.5 (60)	0.144	20.3 (78)	16.7 (82)	0.181	0.040
Previous myocardial infarction	31 (170)	37.5 (115)	0.055	29.9 (114)	33.1 (160)	0.325	0.157
Previous cerebrovascular disease	14.2 (78)	16.2 (50)	0.412	12.3 (47)	14.3 (70)	0.386	0.528
Previous stroke	5.1 (28)	4.5 (14)	0.735	3.9 (15)	3.9 (19)	0.986	0.775
Previous transient ischemic attack	4.2 (23)	6.5 (20)	0.132	3.4 (13)	5.3 (26)	0.170	0.216
Previous carotid artery disease	7.4 (41)	10.0 (31)	0.175	7.3 (28)	9.0 (44)	0.362	0.443
Peripheral vascular disease	9.0 (50)	13.6 (42)	0.036	8.3 (32)	9.8 (48)	0.450	0.096
Chronic obstructive pulmonary disease	9.7 (54)	7.8 (24)	0.339	8.8 (34)	7.6 (37)	0.491	0.601
Chronic kidney disease	17.9 (90)	20.9 (58)	0.304	20.3 (75)	19.7 (91)	0.822	0.713
Creatinine clearance (ml/min)	86.6± 29.4	83.2± 29.3	0.128	87.2± 32.0	85.8± 38.3	0.566	0.446
Left ventricular ejection fraction	59.3± 13.5	56.7± 12.5	0.025	60.4± 12.1	58.0± 13.6	0.034	0.016
Congestive heart failure	5.1 (28)	5.6 (17)	0.777	4.2 (16)	3.7 (18)	0.726	0.553
Clinical presentation			0.062			0.216	0.181
Silent ischemia	13.5 (75)	15.5 (48)		13.8 (53)	13.9 (68)		
Stable angina	60.6 (337)	52.4 (162)		60.0 (231)	54.7 (268)		
Unstable angina	25.9 (144)	32.0 (99)		26.2 (101)	31.4 (154)		

Table 1. Baseline characteristics according to completeness of revascularization. (*continued*)

	CABG			PCI			
	CR	IR	p-value	CR	IR	p-value	Overall p-value
EuroSCORE	3.6± 2.5	4.0± 3.0	0.037	3.6± 2.7	3.9± 2.5	0.144	0.085
Parsonnet SCORE	8.1± 6.7	9.0± 7.2	0.065	8.2± 7.1	8.9± 6.8	0.133	0.101
Disease type			<0.001				<0.001
3VD	55.2 (307)	69.9 (216)		57.7 (222)	62.7 (307)		
LMCAD	44.8 (249)	30.1 (93)		42.3 (163)	37.3 (183)	0.134	
Disease type			<0.001			<0.001	<0.001
LMCAD only	7.4 (41)	1.0 (3)		8.1 (31)	1.8 (9)		
LMCAD+1VD	10.8 (60)	3.2 (10)		10.6 (41)	5.1 (25)		
LMCAD+2VD	15.1 (84)	7.5 (23)		14.0 (54)	11.2 (55)		
LMCAD+3VD	11.5 (64)	18.5 (57)		9.6 (37)	19.2 (94)		
2VD	1.4 (8)	2.9 (9)		2.9 (11)	1.0 (5)		
3VD	53.8 (299)	66.9 (206)		54.8 (211)	61.6 (302)		
SYNTAX score	27.9± 11.0	31.2± 11.6	<0.001	23.6± 10.0	32.2± 11.0	<0.001	<0.001
Low (0-22)	35.4 (196)	22.9 (70)	<0.001	50.4 (193)	19.5 (95)	<0.001	<0.001
Intermediate (23-32)	33.2 (184)	35.3 (108)	0.537	33.7 (129)	35.7 (174)	0.544	0.830
High (>32)	31.4 (174)	41.8 (128)	0.002	15.9 (61)	44.9 (219)	<0.001	<0.001
Optimal medical therapy at discharge	32.6 (181)	31.7 (98)	0.800	46.5 (179)	54.1 (265)	0.026	<0.001
Any antiplatelet therapy	92.4 (514)	90.0 (278)	0.209	99.2 (382)	98.6 (483)	0.370	<0.001
Aspirin	89.0 (495)	87.1 (269)	0.386	96.1 (370)	96.7 (474)	0.616	<0.001
Thienopyridine	16.9 (94)	20.4 (63)	0.203	98.7 (380)	96.7 (474)	0.059	<0.001
Statin	76.1 (423)	72.2 (223)	0.205	85.2 (328)	87.8 (430)	0.269	<0.001
Beta blocker	79.9 (444)	77.3 (239)	0.385	81.3 (313)	80.8 (396)	0.857	0.577
ACEi or ARB	48.6 (270)	53.4 (165)	0.173	63.4 (244)	70.2 (344)	0.033	<0.001

Data are presented as mean ± standard deviation or percentage (number).

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CABG: coronary artery bypass grafting; CAD: coronary artery disease; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; 3VD: three-vessel disease.

In terms of extent and complexity of CAD, patients with IR more commonly had 3VD and a higher anatomical SS. In patients undergoing PCI, those with IR more frequently had complex lesions (total occlusion [TO], bifurcation, diffuse or small vessel disease, heavy calcification, severe tortuosity, and long lesions [defined as lesions with > 20mm]), resulting in a higher rSS (2.1± 3.4 for CR vs. 7.0± 8.0 for IR) (**Table 2**).

In patients undergoing CABG, those with CR received more grafts for less complex CAD, as reflected by a lower anatomical SS (27.9± 11.0 for CR vs. 31.2± 11.6 for IR; p< 0.001), and fewer TO (19.5% for CR vs. 27.1% for IR; p= 0.010) (**Table 2**).

Table 2. Procedural characteristics according to completeness of revascularization.

	CABG			PCI			
	CR	IR	p-value	CR	IR	p-value	Overall p-value
Number of lesions	4.1± 1.7	4.9± 1.7	<0.001	3.7± 1.7	4.8± 1.7	<0.001	<0.001
Any TO	19.5 (108)	27.1 (83)	0.010	12.3 (47)	33.4 (163)	<0.001	<0.001
1TO	17.3 (96)	24.8 (76)		12.1 (46)	29.9 (146)		
2TO	2.2 (12)	2.3 (7)		0.3 (1)	3.5 (17)		
Any bifurcation	72.2 (400)	75.2 (230)	0.348	62.7 (239)	79.9 (390)	<0.001	<0.001
Diffuse or small vessel disease	-	-	-	18.4 (71)	25.3 (124)	0.015	
Any aorto-ostial lesion	-	-	-	17.1 (65)	13.1 (64)	0.105	
Any angiographically visible thrombus	-	-	-	2.6 (10)	2.5 (12)	0.877	
Any heavy calcification	-	-	-	42.8 (163)	54.1 (264)	<0.001	
Any severe tortuosity	-	-	-	55.9 (213)	74.2 (362)	<0.001	
Any lesion length > 20 mm	-	-	-	46.2 (176)	64.1 (313)	<0.001	
Left arterial dominance	-	-	-	16.9 (65)	19.0 (93)	<0.001	
Number of stents implanted	-	-	-	4.5± 2.4	4.7± 2.1	0.228	-
Total stent length per patient	-	-	-	86± 51.8	86.5± 44.6	0.900	-
Off pump CABG	14.9 (83)	15.3 (47)	0.896	-	-	-	
Use of LIMA graft	86.3 (480)	85.4 (264)	0.716	-	-	-	
Number of total conduits	2.8± 0.7	2.6± 0.7	<0.001	-	-	-	-
Number of arterial conduits	1.4± 0.7	1.4± 0.6	0.777	-	-	-	-
Number of venous conduits	1.5± 0.9	1.2± 0.9	<0.001	-	-	-	-

Data are presented as mean ± standard deviation or percentage (number).
CABG: coronary artery bypass grafting; CAD: coronary artery disease; LIMA: left internal mammary artery; PCI: percutaneous coronary intervention; TO: total occlusion.

In the SYNTAX trial enrolling patients from 2005 to 2007, approximately half of patients undergoing PCI received optimal medical therapy (OMT) [23], defined as the combination of at least one antiplatelet therapy, statin, βblocker, and angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker at discharge, and the rate of OMT was significantly higher in patients with PCI and IR vs. CR (54.1% vs.

46.5%; p= 0.026). In contrast, only one third of patients undergoing CABG received OMT at discharge, and a rate of OMT was similar between patients with IR and CR in the CABG cohort (31.7% vs. 32.6%; p= 0.800) (**Table 1**).

Outcomes according to completeness of revascularisation in patients undergoing PCI or CABG

The median duration of follow-up after randomization was 11.2 years (interquartile range 8.0 to 12.1 years). All-cause death occurred in 442 (25.4%) of patients at 10 years and 549 (31.6%) at maximum follow-up of 12.7 years. The crude rates of 10-year all-cause death was 23.7% in patients with CABG and CR, 23.8% with CABG and IR, 22.0% with PCI and CR, and 33.9% with PCI and IR (p< 0.001) (**Figure 3A** and **Table 3**). Notably, patients undergoing PCI who achieved CR had a similar risk of all-cause death at 10 years to those undergoing CABG (**Figure 3A** and **Table 3**). After adjustment for baseline characteristics, the risk of all-cause death remained significantly higher in patients undergoing PCI with IR, compared with those undergoing CABG with CR (adjusted HR: 1.68; 95% CI: 1.22 to 2.30; p< 0.001) (**Table 3**).

The stratified analysis according to disease type (3VD or LMCAD) yielded similar results in patients with 3VD (**Figure 3B** and **Table 3**). Specifically, the crude rates of 10-year all-cause death was 20.4% in patients with CABG and CR, 20.7% with CABG and IR, 24.3% with PCI and CR, and 33.1% with PCI and IR (p< 0.001). In contrast, patients with LMCAD who underwent PCI with CR had a lower adjusted risk of 10-year all-cause death as compared with CABG with CR (adjusted HR: 0.47; 95% CI: 0.26 to 0.86) (**Table 3**). This significant survival benefit at 10 years was no longer observed at a maximum follow-up (**Online Figure 1** and **Online Table 1**).

Outcomes stratified according to the rSS in patients undergoing PCI

Baseline characteristics according to the rSS are presented in **Table 4**. Patients with a higher rSS were older and more likely to be female. A higher rSS was associated with a progressive increase in co-existing comorbidities (medically treated diabetes, on insulin, PVD, CKD, and lower LVEF) and greater EuroSCORE or Parsonnet SCORE. Similarly, patients with a higher rSS had a greater anatomical SS at baseline and a higher prevalence of complex lesions (TO, diffuse or small vessel disease, heavy calcification, severe tortuosity, and lesion length). Although the number of lesions was greater in patients with a rSS of >8, the number of stents implanted and total stent length per patient were similar among the four rSS groups. Of note, a higher rSS was associated with a more frequent use of OMT at discharge (**Table 4**).

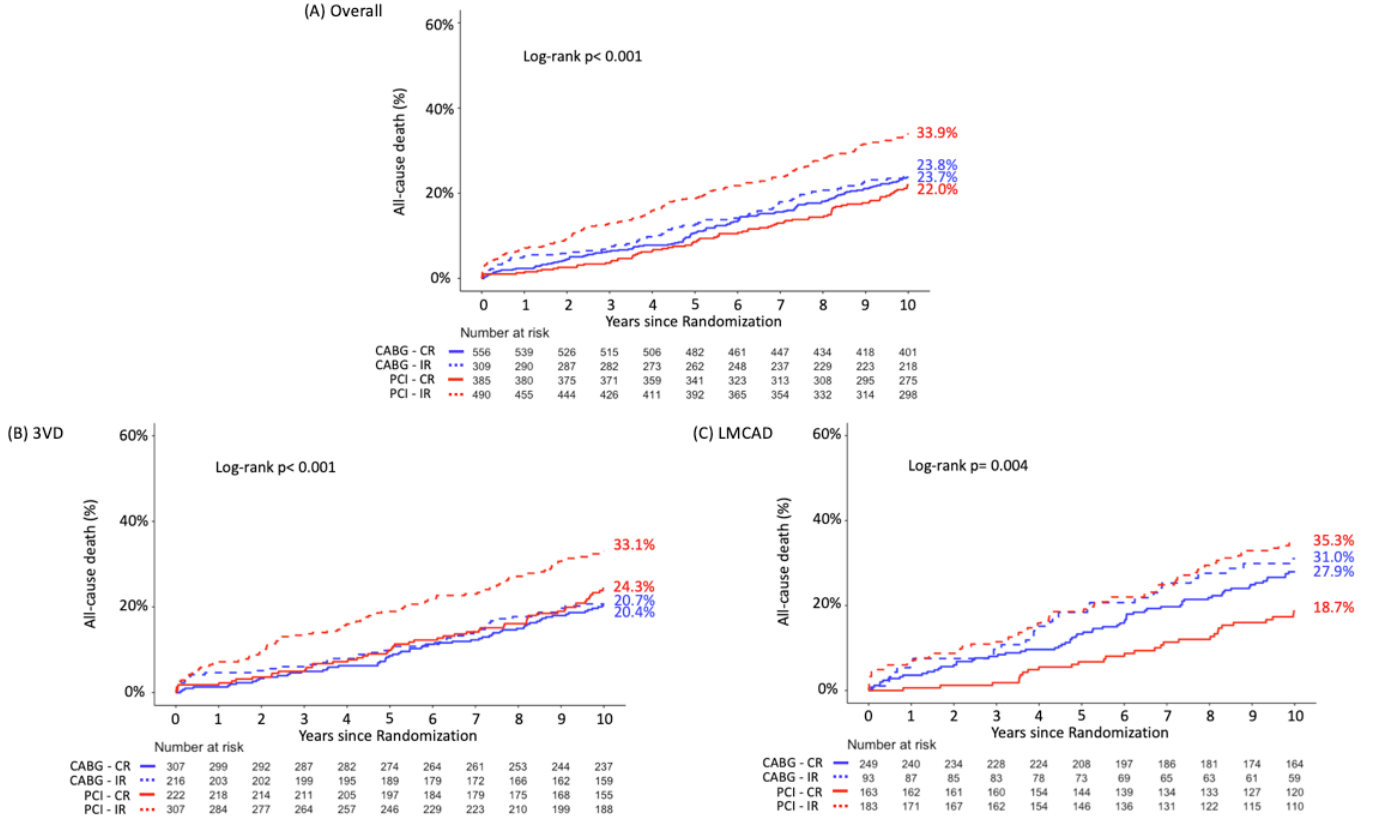

Figure 3. Kaplan-Meier curves for the primary endpoint of all-cause death up to 10 years according to randomized treatments of CABG (blue) or PCI (red) and completeness of revascularization. (A) overall population; (B) 3VD cohort; (C) LMCAD cohort.

CABG: coronary artery bypass grafting; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; 3VD: three-vessel disease, CR: complete revascularization, IR: incomplete revascularization..

Table 3. Crude and adjusted all-cause death at 10 years according to completeness of revascularization.

	Crude incidence					Adjusted HR (95% CI)				
	CABG – CR (n= 556)	CABG – IR (n= 309)	PCI – CR (n= 385)	PCI – IR (n= 490)	p-value	CABG - CR	CABG - IR	PCI - CR	PCI - IR	p-value
Overall	23.7 (128)	23.8 (71)	22.0 (81)	33.9 (162)	<0.001	1.00 (reference)	0.97 (0.66-1.42)	0.86 (0.59-1.26)	1.68 (1.22-2.30)	<0.001
3VD	20.4 (61)	20.7 (43)	24.3 (52)	33.1 (99)	<0.001	1.00 (reference)	0.99 (0.58-1.70)	1.50 (0.89-2.52)	1.92 (1.23-2.97)	0.010
LMCAD	27.9 (67)	31.0 (28)	18.7 (29)	35.3 (63)	0.004	1.00 (reference)	0.97 (0.55-1.73)	0.47 (0.26-0.86)	1.57 (0.97-2.55)	0.002

Data are presented as percentage (number of deaths).

CABG: coronary artery bypass grafting; CI: confidence interval; CR: complete revascularization; HR: hazard ratio; IR: incomplete revascularization; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Table 4. Baseline and procedural characteristics according to the residual SYNTAX score in patients treated with PCI.

	rSS= 0 (n= 385)	0 < rSS ≤ 4 (n= 183)	4 < rSS ≤ 8 (n= 167)	8< rSS (n= 140)	p-value
Age (year)	64.7± 9.8	64.8± 8.8	66.0± 9.8	67.3± 9.9	0.029
Sex					0.025
Male	72.7 (280)	81.4 (149)	82.0 (137)	72.9 (102)	
Female	27.3 (105)	18.6 (34)	18.0 (30)	27.1 (38)	
Body mass index (kg/m^2)	28.1± 4.7	28.4± 5.2	27.6± 4.6	28.6± 4.7	0.272
Diabetes	20.5 (79)	26.8 (49)	26.3 (44)	37.9 (53)	0.001
Insulin	7.0 (27)	10.9 (20)	7.2 (12)	20.0 (28)	<0.001
Metabolic syndrome	43.1 (137)	50.7 (74)	42.0 (58)	52.7 (59)	0.153
Hypertension	68.1 (262)	71.0 (130)	73.7 (123)	67.1 (94)	0.510
Dyslipidemia	77.9 (299)	75.7 (137)	80.7 (134)	83.3 (115)	0.345
Current smokers	20.3 (78)	15.3 (28)	16.2 (27)	19.3 (27)	0.442
Previous myocardial infarction	29.9 (114)	32.0 (58)	28.8 (47)	39.3 (55)	0.179
Previous cerebrovascular disease	12.3 (47)	16.9 (31)	10.8 (18)	15.0 (21)	0.296
Previous stroke	3.9 (15)	2.7 (5)	3.6 (6)	5.8 (8)	0.580
Previous transient ischemic attack	3.4 (13)	6.6 (12)	5.4 (9)	3.6 (5)	0.311
Prior carotid artery disease	7.3 (28)	10.4 (19)	7.2 (12)	9.3 (13)	0.565
Peripheral vascular disease	8.3 (32)	6.0 (11)	9.6 (16)	15.0 (21)	0.040
Chronic obstructive pulmonary disease	8.8 (34)	6.0 (11)	8.4 (14)	8.6 (12)	0.704
Chronic kidney disease	20.3 (75)	14.5 (25)	17.2 (27)	29.3 (39)	0.010
Creatinine clearance	87.2± 32.0	92.5± 48.3	83.6± 28.2	79.6± 32.4	0.011
Left ventricular ejection fraction	60.4± 12.1	59.8± 12.9	57.3± 13.9	56.4± 13.8	0.041
Congestive heart failure	4.2 (16)	2.2 (4)	4.2 (7)	5.0 (7)	0.586
Clinical presentation					0.547
Silent ischemia	13.8 (53)	12.6 (23)	15.0 (25)	14.3 (20)	
Stable angina	60.0 (231)	52.5 (96)	55.7 (93)	56.4 (79)	
Unstable angina	26.2 (101)	35.0 (64)	29.3 (49)	29.3 (41)	
EuroSCORE	3.6± 2.7	3.6± 2.4	3.8± 2.5	4.4± 2.6	0.020
Parsonnet SCORE	8.2± 7.1	7.8± 5.9	8.6± 6.8	10.8± 7.6	0.001
Disease extent					0.359
3VD	57.7 (222)	65.0 (119)	59.9 (100)	62.9 (88)	
LMCAD	42.3 (163)	35.0 (64)	40.1 (67)	37.1 (52)	
Disease extent					<0.001
LMCAD	8.1 (31)	2.2 (4)	3.0 (5)	0 (0)	
LMCAD+1VD	10.6 (41)	4.4 (8)	7.8 (13)	2.9 (4)	
LMCAD+2VD	14.0 (54)	10.9 (20)	10.8 (18)	12.1 (17)	
LMCAD+3VD	9.6 (37)	17.5 (32)	18.6 (31)	22.1 (31)	
2VD	2.9 (11)	2.2 (4)	0 (0)	0.7 (1)	
3VD	54.8 (211)	62.8 (115)	59.9 (100)	62.1 (87)	
Number of lesions	3.7± 1.7	4.7± 1.7	4.8± 1.7	5.0± 1.7	<0.001
SYNTAX score	23.6± 10.0	29.1± 10	31.7± 9.8	36.9± 11.9	<0.001
Low	50.4 (193)	27.9 (51)	17.5 (29)	10.8 (15)	<0.001
Intermediate	33.7 (129)	39.9 (73)	37.3 (62)	28.1 (39)	0.135
High	15.9 (61)	32.2 (59)	45.2 (75)	61.2 (85)	<0.001
Residual SYNTAX score	0± 0	3.0± 1.0	6.2± 1.1	15.0± 9.0	<0.001

Table 4. Baseline and procedural characteristics according to the residual SYNTAX score in patients treated with PCI. (*continued*)

	rSS= 0 (n= 385)	**0 < rSS ≤ 4 (n= 183)**	**4 < rSS ≤ 8 (n= 167)**	**8< rSS (n= 140)**	p-value
Δ SYNTAX score	1.5± 0.7	1.8± 0.8	2.0± 0.9	1.9± 0.9	<0.001
Number of stents	4.5± 2.4	4.9± 2.2	4.6± 2.0	4.6± 2.1	0.305
Total stent length per patient	86± 51.8	91.6± 47.8	83.9± 42.3	82.6± 42.4	0.289
Any TO	12.3 (47)	22.4 (41)	28.3 (47)	54.0 (75)	<0.001
1TO	12.1 (46)	22.4 (41)	25.3 (42)	45.3 (63)	
2TO	0.3 (1)	0 (0)	3.0 (5)	8.6 (12)	<0.001
Any bifurcation	62.7 (239)	77.6 (142)	77.7 (129)	85.6 (119)	<0.001
Diffuse or small vessel disease	18.4 (71)	26.2 (48)	20.4 (34)	30.0 (42)	0.018
Any aorto-ostial lesion	17.1 (65)	13.1 (24)	11.4 (19)	15.1 (21)	0.329
Any angiographically visible thrombus	2.6 (10)	2.2 (4)	2.4 (4)	2.9 (4)	0.981
Any heavy calcification	42.8 (163)	47.5 (87)	53 (88)	64 (89)	<0.001
Any severe tortuosity	55.9 (213)	74.9 (137)	74.7 (124)	72.7 (101)	<0.001
Left arterial dominance	16.9 (65)	19.7 (36)	19.8 (33)	17.1 (24)	0.780
Any lesion length > 20 mm	46.2 (176)	57.9 (106)	62.0 (103)	74.8 (104)	<0.001
Optimal medical therapy at discharge	46.5 (179)	50.3 (92)	52.1 (87)	61.4 (86)	0.025
Any antiplatelet therapy	99.2 (382)	100 (183)	98.8 (165)	96.4 (135)	0.020
Aspirin	96.1 (370)	98.4 (180)	95.8 (160)	95.7 (134)	0.473
Thienopyridine	98.7 (380)	100 (183)	97.6 (163)	91.4 (128)	<0.001
Statin	85.2 (328)	86.9 (159)	89.8 (150)	86.4 (121)	0.538
Beta blocker	81.3 (313)	82.0 (150)	79.6 (133)	80.7 (113)	0.952
ACEi or ARB	63.4 (244)	67.8 (124)	67.7 (113)	76.4 (107)	0.046

Data are presented as mean ± standard deviation or percentage (number).
CABG: coronary artery bypass grafting; CAD: coronary artery disease; LIMA: left internal mammary artery; LMCAD: left main coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; 3VD: three-vessel disease.

Ten-year all-cause death stratified according to the gradient of rSS are presented in **Figure 4** and **Table 5**. Compared with patients who achieved CR (i.e. rSS of 0), patients with a rSS of ≤ 8 had a comparable risk of all-cause death at 10 years (22.0% for rSS of 0 vs. 24.0% for 0< rSS≤ 4 vs. 28.9% for 4< rSS≤ 8), whereas patients with rSS of >8 had a more than 3.5-fold higher risk of 10-year all-cause death, compared with those with rSS of 0 (adjusted HR: 3.75; 95% CI: 2.33 to 6.05; p< 0.001) (**Figure 4A** and **Table 5**). These findings were largely consistent with subgroups of 3VD or LMCAD (**Figure 4B, 4C** and **Table 5**) and at maximum follow-up (**Online Figure 2** and **Online Table 2**).

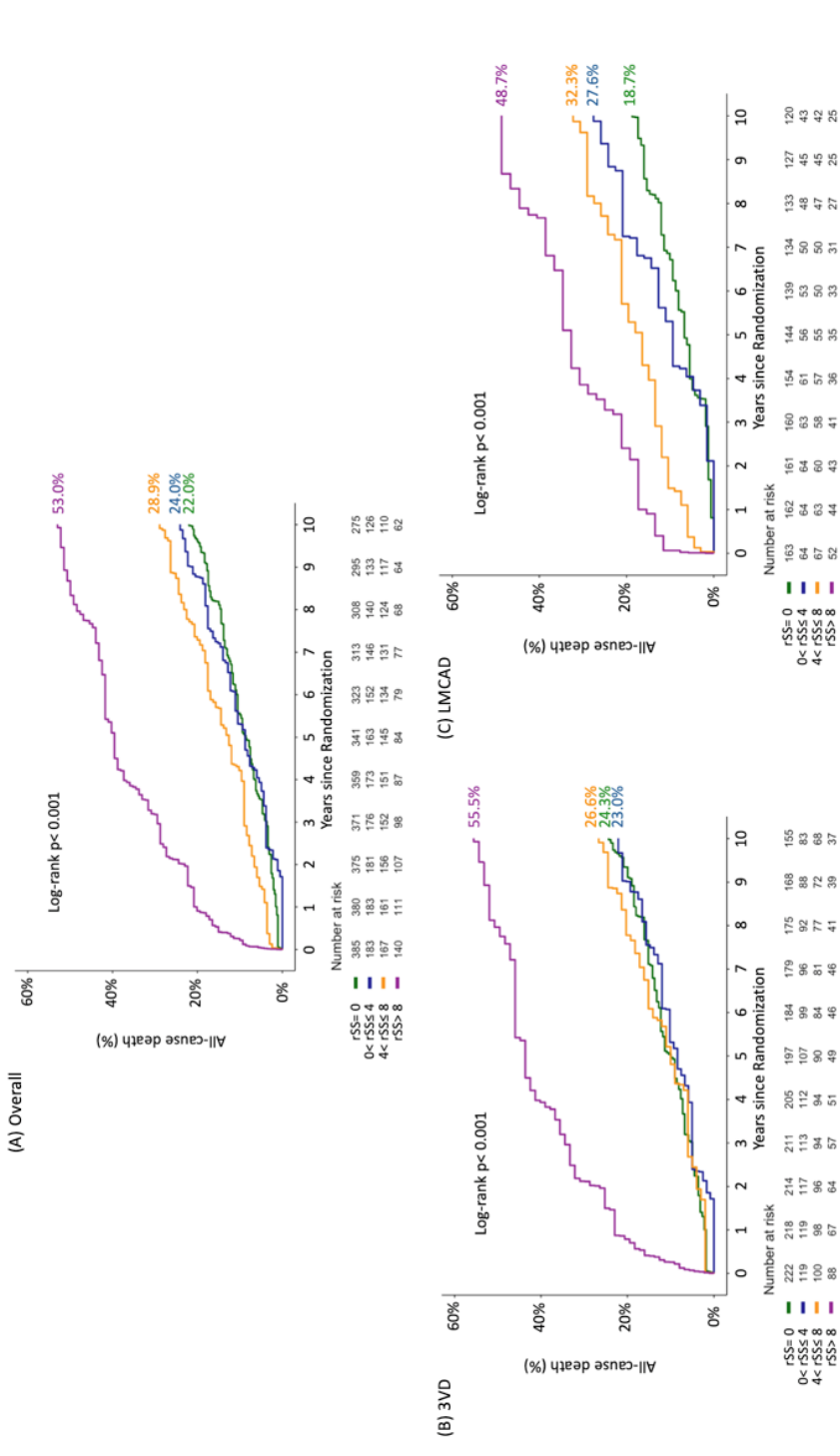

Figure 4. Kaplan-Meier curves for the primary endpoint of all-cause death up to 10 years according to the rSS in patients who underwent PCI. (A) overall population; (B) 3VD cohort; (C) LMCAD cohort.
Abbreviations are as in Figure 3.

Table 5. Crude and adjusted all-cause death at 10 years according to the rSS.

	Crude incidence					Adjusted HR (95% CI)				
	rSS= 0	0< rSS≤ 4	4< rSS≤ 8	8< rSS	p-value	rSS= 0	0< rSS≤ 4	4< rSS≤ 8	8< rSS	p-value
Overall	22.0 (81)	24.0 (42)	28.9 (47)	53.0 (73)	<0.001	1.00 (reference)	1.47 (0.89-2.41)	1.17 (0.69-2.00)	3.75 (2.33-6.05)	<0.001
3VD	23.0 (52)	24.3 (25)	26.6 (26)	55.5 (48)	<0.001	1.00 (reference)	0.92 (0.49-1.75)	0.61 (0.28-1.30)	3.19 (1.74-5.83)	<0.001
LMCAD	18.7 (29)	27.6 (17)	32.3 (21)	48.7 (25)	<0.001	1.00 (reference)	5.01 (2.12-11.82)	2.93 (1.26-6.82)	5.17 (2.14-12.48)	<0.001

Data are presented as percentage (number of deaths).

CI: confidence interval; HR: hazard ratio; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; rSS: residual SYNTAX score; 3VD: three-vessel disease.

DISCUSSION

The main findings of the present study can be summarized as follows.

1. IR was more frequently observed in patients with PCI when compared with CABG. Irrespective of the revascularisation strategy, patients with 3VD were more prone to have IR than those with LMCAD.
2. Patients undergoing PCI with CR had a similar risk of all-cause death at 10 years compared with those undergoing CABG. In contrast, PCI with IR resulted in a significantly higher risk of all-cause death at 10 years.
3. Although a rSS was associated with a progressive increase in clinical comorbidities and complex lesions among patients undergoing PCI, patients with a rSS of ≤ 8 had a similar risk of all-cause death compared with those with rSS of 0. However, patients with a rSS of >8 had a more than 3.5-fold higher risk of all-cause death at 10 years despite a higher rate of OMT at discharge.

Early studies in 1980s demonstrated a survival benefit of CR over IR in stable patients with multivessel disease who underwent CABG [24-26]. This clinical benefit of CR was somewhat mitigated when the internal mammary artery was grafted to the left anterior descending artery [11, 27, 28]. Nevertheless, a recent study-level meta-analysis from 28 studies between 2000 and 2013 including 83,695 patients with a median follow-up period of 4.7 years showed that CR resulted in a greater survival benefit over IR in patients with CABG (RR: 0.76; 95% CI: 0.63-0.90) [29]. Consistently, a previous analysis in the SYNTAX trial demonstrated that, CR with CABG had a lower risk of all-cause death at 4 years compared with IR (HR: 0.70; 95% CI: 0.49-0.98; p= 0.039) in all-comers 3VD or LMCAD patients consisting of randomized patients and nested registry [14]. Conversely, the present analysis confined to the randomized SYNTAX patients found that CR had a similar risk of 10-year all-cause death compared with IR. This discrepancy in the 4-year SYNTAX data [14] was likely attributable to the fact that the nested CABG registry included patients with a more complex anatomy (anatomical SS: nested CABG registry 37.8± 13.3 vs. randomized CABG 29.1±11.4, p< 0.001) and more clinical comorbidities, accounting for a significantly higher risk of all-cause death in patients undergoing CABG with IR vs. CR.

The similar advantage of CR vs. IR among PCI population has been reported during the past two decades [30-33]. A more recent study-level meta-analysis with 156,240 patients from 38 studies has shown that CR with PCI was associated with a significantly lower risk of all-cause death (OR: 0.69; 95% CI: 0.61-0.78; p< 0.001) compared with IR [34]. The present study supports those previous findings and further extended this timeframe up to 10 years, demonstrating that, IR, in contrast to CR, was associated

with a significantly increased risk of 10-year all-cause death in patients undergoing PCI (**Table 3**).

Among those studies, the completeness of revascularisation was classified as binary (i.e. complete vs. incomplete). As a result, the IR group pools together patients with any lesions left untreated regardless of its location, extent, and complexity, representing a vast heterogeneity of patients with IR. For a more accurate risk stratification, quantification of residual burden of coronary atherosclerosis after PCI, namely the rSS, was introduced in the context of moderate to high-risk acute coronary syndromes [22], showing a poorer 30-day and 1-year mortality in patients with a rSS> 8. Subsequently, the rSS was externally validated in the SYNTAX trial [21]. The present study further supports a graded spectrum of IR and identified patients with a rSS> 8 being a more than 3.5-fold higher risk of all-cause death at 10 years (**Table 5**). Incomplete revascularisation is a multifactorial phenomenon related to small vessel disease, highly calcified lesion, extreme tortuosity, extremely angulated bifurcation lesions among others, although the main identifiable reason for IR remained the presence of a TO not successfully recanalized [14]. Thus, a high residual SS post procedure is difficult to predict prior to the attempted treatment. The Japanese and European CTO score are the only established predictor of anticipated treatment failure that could be a strong and reliable deterrent for a percutaneous treatment and favor a surgical approach. Nevertheless, it remains difficult to predict a high rSS prior to the procedure prospectively, and only post procedure, is it feasible and realistic to quantify the rSS. However, if operators are unable to reduce the score below the threshold of 8, then they should be aware that their patients will be at high risk of a fatal late outcome. These patients with IR need definitely more intensive pharmacotherapy [23] and aggressive risk factor modification (e.g. smoking cessation [35]) for secondary prevention. Interestingly, the present analysis has found a progressively greater use of OMT according to the rSS, suggesting that investigators might perceive a higher risk of adverse events in patients with a higher rSS, although the rate of OMT was suboptimal with approximately two thirds of patients receiving OMT at discharge. In this regard, the recently proposed "aspirin-free strategy" may be helpful since it has shown to be associated with a significantly lower risk of bleeding events without a trade-off in ischemic risks, potentially resulting in a lower risk of mortality especially in high-risk patients [36-39].

The rSS is purely an angiographic (anatomic) index quantifying the residual burden of anatomic lesions left untreated, whereas Bech et al. first demonstrated in 1999 that "residual ischemia", defined as FFR≤ 0.89 after PCI, was associated with a higher risk of adverse events at two years [40]. Subsequently, several studies have confirmed

that observation. Nevertheless, functional assessment of rSS is rarely performed in daily practice. Recently, the ERIS (Evolving Routine Standards of FFR Use) study demonstrated that physiology-guided PCI was performed in 7% of the total PCI volume [41]. Interestingly, even if FFR value after coronary stent implantation was suboptimal (defined as post PCI FFR≤ 0.88), in 89% of these cases, no further intervention was performed. Reasons for a low prevalence of FFR use after PCI are multifactorial; (i) physiology optimization with FFR is performed only in cases in which FFR has been used for decision making prior to the PCI; (ii) the need to administer adenosine post procedure increases the procedure time and cost and exposes the patient a second time to the side effects of the drug; (iii) a standardized threshold to perform additional procedure based on randomized trials is lacking; (iv) the difficulty to interpret the manual FFR pullback and identify the underlying causes in case of suboptimal post-PCI FFR results with the possible need for intravascular imaging in order to identify the remediable mechanistic cause.

Against this background, another index integrating anatomical and physiological information after PCI, termed the residual functional SS (rFSS), which is calculated by the sum of the rSS in vessels with FFR≤ 0.80, has been recently introduced [42]; specifically, in a pre-specified sub-study of the 3V FFR-FRIENDS (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease) registry (n= 1,136), which performed FFR measurement in all major coronary arteries post-procedure [43], patients with functional IR, defined as a rFSS≥ 1, was associated with a significantly higher risk of MACE at two years as compared to those with functional CR (i.e. rFSS of 0) [42]. However, the results should be interpreted cautiously, because the study included a lower-risk population without TO with a relatively small sample size (n=385), resulting in only 24 MACE events, most of which were ischemia-driven revascularisation [42], a less objective endpoint with respect to death or MI [44]. Nevertheless, these findings with functional assessment at post-procedure are of great interest, and further investigations are warranted including cost-effectiveness of the prediction models.

Limitation

Our findings should be interpreted in light of the following limitations. First, as discussed previously, physiological assessment pre- and post-procedure was not mandatory in the SYNTAX trial. Nevertheless, the present study provided unique information after angiographically guided PCI regarding 10-year all-cause death, which is the most robust endpoint that is clinically relevant for both patients and physicians. In addition, it has to be emphasized that the use of FFR varies significantly across countries, centres, and operators ranging from 3% to 30% of the total volume of PCI

due to equipment, reimbursement, and operator choice. Even resting indices such as instantaneous wave-free ratio have not increased the usage of physiology-guided PCI significantly [41, 45, 46]. Second, although the SYNTAX trial collected baseline information that are related to mortality and the present analysis accounted for imbalances in multivariable models, the role of unmeasured confounders cannot be excluded. Third, the SYNTAX trial was conducted between 2005 and 2007 with a default use of the first-generation DES for treatment with PCI, as well as less concerted attention to multidrug OMT, which may limit generalizability of our findings to our current practice [47]. Nevertheless, the SYNTAXES study is the first randomized data that was meticulously conducted and achieved a high follow-up rate of 93.8% for 10-year vital status (1,689 out of 1,800 enrolled patients) [17].

CONCLUSION

CR was less frequently achieved in patients undergoing PCI when compared to CABG, especially in cases with 3VD. Patients undergoing PCI with CR had a comparable risk of all-cause death at 10 years compared with those undergoing CABG. In contrast, patients undergoing PCI with IR had a significantly higher risk of all-cause death at 10 years. Patients undergoing PCI with IR represented a population with great heterogeneity of clinical and anatomic comorbidities. Patients with a rSS of ≤ 8 had a similar risk of all-cause death compared with those with CR, whereas patients with a rSS of > 8 had a more than 3.5-fold higher risk of all-cause death at 10 years despite a higher rate of OMT at discharge.

Abbreviations List

CABG:	coronary artery bypass grafting
CAD:	coronary artery disease
LMCAD:	left main coronary artery disease
MI:	myocardial infarction
PCI:	percutaneous coronary intervention
3VD:	three-vessel disease

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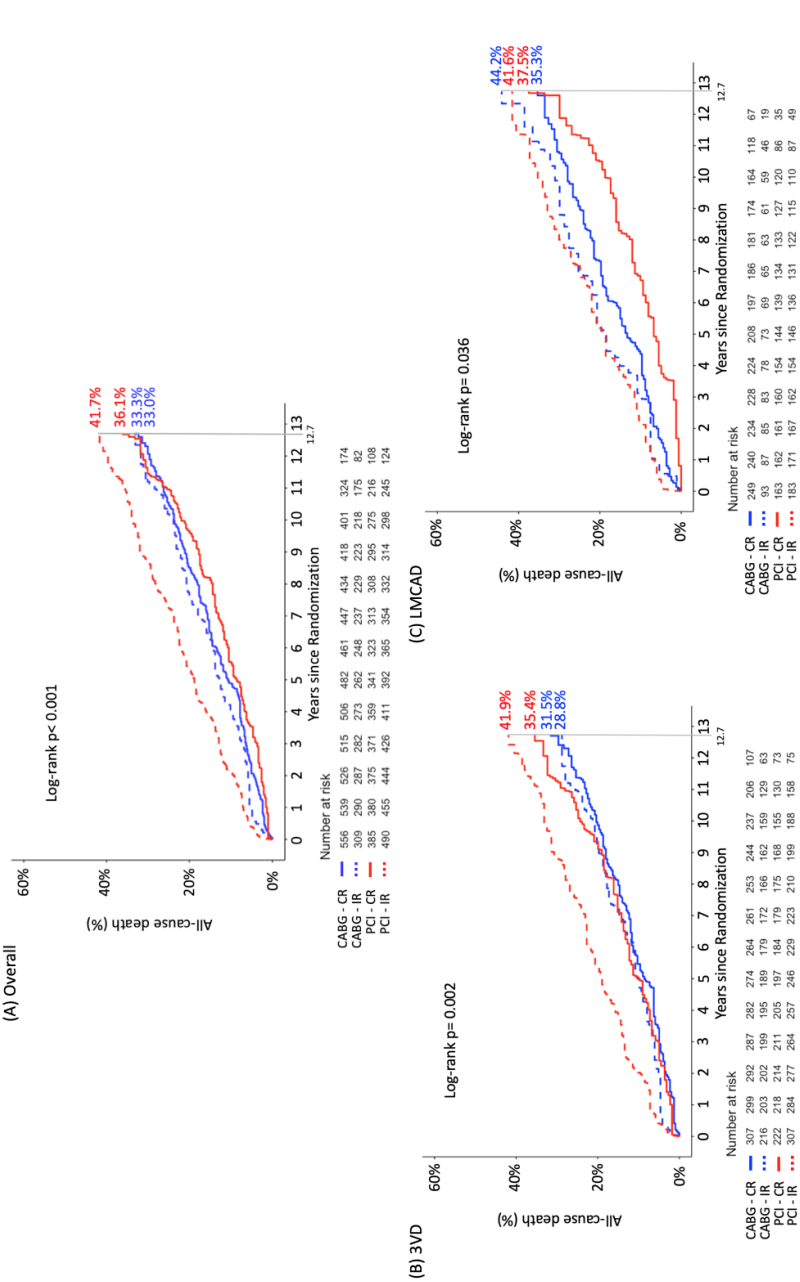
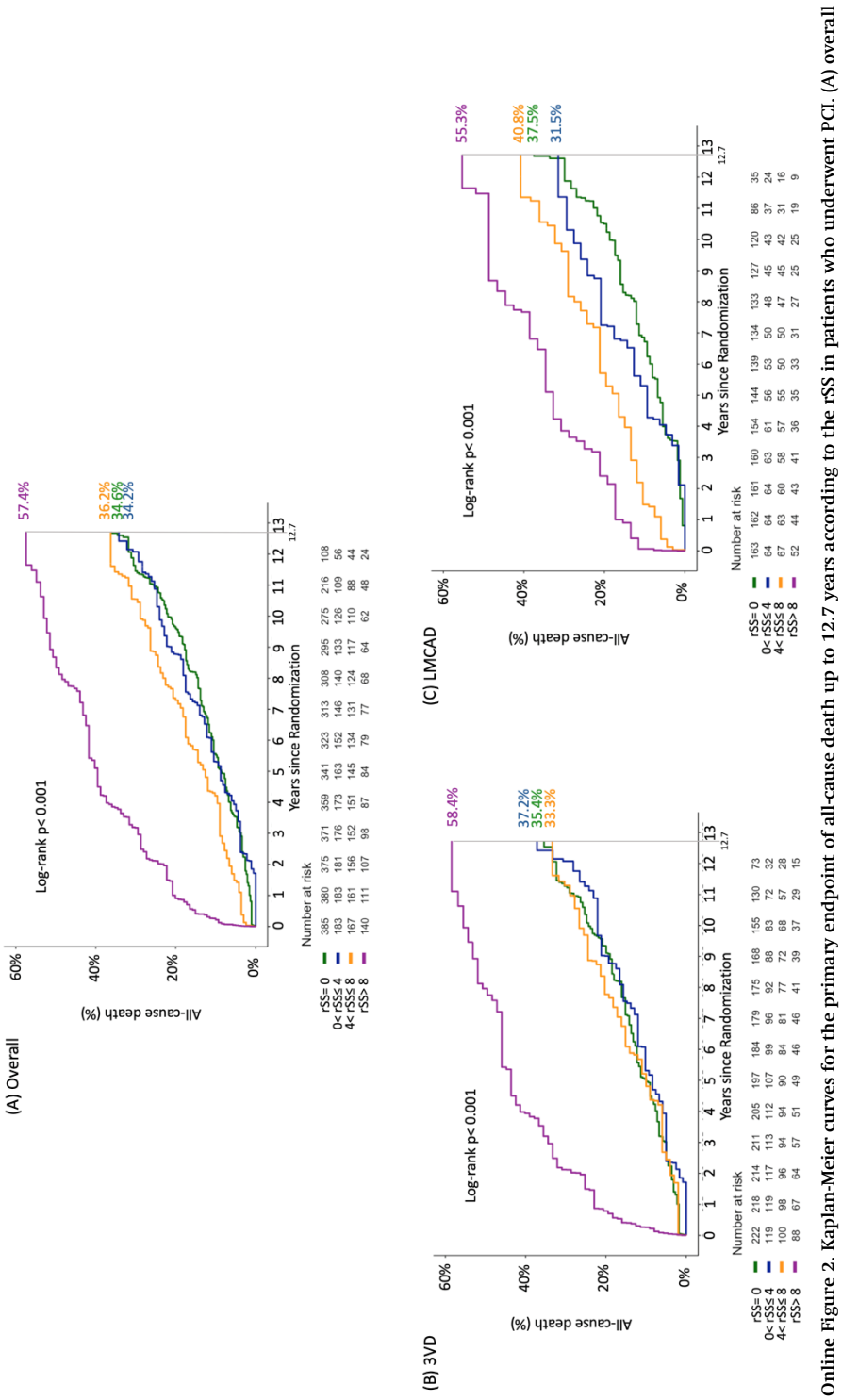
SUPPLEMENTAL MATERIAL



Online Figure 1. Kaplan-Meier curves for the primary endpoint of all-cause death up to 12.7 years according to randomized treatments of CABG (blue) or PCI (red) and completeness of revascularization. (A) overall population; (B) 3VD cohort; (C) LMCAD cohort.
CABG: coronary artery bypass grafting; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; 3VD: three-vessel disease, CR: complete revascularization, IR: incomplete revascularization.



Online Figure 2. Kaplan-Meier curves for the primary endpoint of all-cause death up to 12.7 years according to the rSS in patients who underwent PCI. (A) overall population; (B) 3VD cohort; (C) LMCAD cohort.
Abbreviations are as in Figure 2.

Online Table 1. Crude and adjusted all-cause death during a maximum follow-up according to completeness of revascularization.

	Crude incidence					Adjusted HR (95% CI)				
	CABG – CR	CABG – IR	PCI – CR	PCI – IR	p-value	CABG - CR	CABG - IR	PCI - CR	PCI - IR	p-value
Overall	33.3 (157)	33.0 (91)	36.1 (110)	41.7 (185)	<0.001	1.00 (reference)	1.05 (0.74-1.49)	1.02 (0.73-1.43)	1.52 (1.13-2.05)	0.018
3VD	31.5 (80)	28.8 (57)	35.4 (68)	41.9 (114)	0.002	1.00 (reference)	1.06 (0.65-1.71)	1.64 (1.04-2.60)	1.66 (1.10-2.50)	0.034
LMCAD	35.3 (77)	44.2 (34)	37.5 (42)	41.6 (71)	0.036	1.00 (reference)	1.11 (0.66-1.88)	0.62 (0.37-1.04)	1.49 (0.94-2.35)	0.019

Data are presented as percentage (number of deaths).
CABG: coronary artery bypass grafting; CI: confidence interval; CR: complete revascularization; HR: hazard ratio; IR: incomplete revascularization; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Online Table 2. Crude and adjusted all-cause death during a maximum follow-up according to the rSS.

	Crude incidence					Adjusted HR (95% CI)				
	rSS= 0	0< rSS≤ 4	4< rSS≤ 8	8< rSS	p-value	rSS= 0	0< rSS≤ 4	4< rSS≤ 8	8< rSS	p-value
Overall	34.6 (110)	34.2 (52)	36.2 (56)	57.4 (77)	<0.001	1.00 (reference)	1.12 (0.71-1.77)	0.92 (0.56-1.52)	2.84 (1.83-4.41)	<0.001
3VD	35.4 (68)	37.2 (33)	33.3 (31)	58.4 (50)	<0.001	1.00 (reference)	0.74 (0.41-1.34)	0.55 (0.27-1.09)	2.46 (1.40-4.30)	<0.001
LMCAD	37.5 (42)	31.5 (19)	40.8 (25)	55.3 (27)	<0.001	1.00 (reference)	3.44 (1.58-7.48)	1.90 (0.86-4.16)	3.92 (1.79-8.59)	0.002

Data are presented as percentage (number of deaths).
CI: confidence interval; HR: hazard ratio; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; rSS: residual SYNTAX score; 3VD: three-vessel disease.