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Predicted and Observed Mortality at 10 Years in Patients With Bifurcation Lesions in the SYNTAX Trial

Kai Ninomiya, MD,[a,*] Patrick W. Serruys, MD, PhD,[a,b,*] Scot Garg, MD, PhD,[c] Chao Gao, MD,[d,e] Shinichiro Masuda, MD,[a] Mattia Lunardi, MD, MSc,[a] Jens F. Lassen, MD, PhD,[f] Adrian P. Banning, MD,[g] Antonio Colombo, MD,[h,i] Francesco Burzotta, MD, PhD,[j] Marie-Claude Morice, MD,[k] Michael J. Mack, MD, PhD,[l] David R. Holmes, MD,[m] Piroze M. Davierwala, MD,[n,o,p] Daniel J.F.M. Thuijs, MD, PhD,[q] David van Klaveren, PhD,[r] Yoshinobu Onuma, MD, PhD,[a] on behalf of the SYNTAX Extended Survival Investigators

ABSTRACT

BACKGROUND Percutaneous coronary intervention (PCI) of bifurcation lesions is associated with higher rates of adverse events, and currently it is unclear whether PCI or coronary artery bypass grafting (CABG) is the safer treatment for these patients at very long-term follow-up.

OBJECTIVES The aim of this study was to investigate the impact of bifurcation lesions on individual predicted and observed all-cause 10-year mortality in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial.

METHODS In the SYNTAXES (SYNTAX Extended Survival) study, 10-year observed and individual predicted mortality derived from the SYNTAX score 2020 (SS-2020) was compared between patients with ≥1 bifurcation (n = 1,300) and those with no bifurcations (n = 487).

RESULTS Among patients treated with PCI, patients with >1 bifurcation lesion compared with those without bifurcation lesions had a significantly higher risk for all-cause death (19.8% vs 30.1%; HR: 1.55; 95% CI: 1.12-2.14; $P = 0.007$), whereas following CABG, mortality was similar in patients with and those without bifurcation lesions (23.3% vs 23.0%; HR: 0.81; 95% CI: 0.59-1.12; $P = 0.207$; $P_{interaction} = 0.006$). In PCI patients, a 2-stent vs a 1-stent technique was associated with higher mortality (33.3% vs 25.9%; HR: 1.51; 95% CI: 1.06-2.14; $P = 0.021$). According to the SS-2020, among those with ≥1 bifurcation, there was equipoise for all-cause mortality between PCI and CABG in 2 quartiles of the population, whereas CABG was superior to PCI in the 2 remaining quartiles.

CONCLUSIONS Bifurcation lesions require special attention from the heart team, considering the higher 10-year all-cause mortality associated with PCI. Careful evaluation of bifurcation lesion complexity and calculation of individualized 10-year prognosis using the SS-2020 may therefore be helpful in decision making. (Synergy Between PCI With TAXUS and Cardiac Surgery: SYNTAX Extended Survival [SYNTAXES], NCT03417050; Taxus Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries [SYNTAX], NCT00114972) (J Am Coll Cardiol Intv 2022;15:1231–1242) © 2022 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

From the [a]Department of Cardiology, National University of Ireland, Galway, Galway, Ireland; [b]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [c]Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom; [d]Department of Cardiology, Xijing Hospital, Xi'an, China; [e]Department of Cardiology, Radboud University, Nijmegen, the Netherlands; [f]Department of Cardiology, Odense University Hospital, Odense, Denmark; [g]Department of Cardiology, John Radcliffe Hospital, Oxford University Hospitals, Oxford, United Kingdom; [h]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele-Milan, Italy; [i]Humanitas Clinical and Research Center IRCCS, Rozzano-Milan, Italy; [j]Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; [k]Département of Cardiologie, Hôpital Privé Jacques Cartier, Générale de Santé Massy, France; [l]Department of Cardiothoracic Surgery, Baylor University Medical Center, Dallas, Texas, USA; [m]Department of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA; [n]University Department of Cardiac Surgery, Heart Centre Leipzig, Leipzig, Germany; [o]Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; [p]Department of Surgery, University of Toronto, Toronto, Ontario, Canada; [q]Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Rotterdam, the Netherlands; and the [r]Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands. *Drs Ninomiya and Serruys contributed equally to this work.

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ABBREVIATIONS AND ACRONYMS

3VD = 3-vessel disease

ARD = absolute risk difference

CABG = coronary artery bypass grafting

DES = drug-eluting stent(s)

LMCAD = left main coronary artery disease

MI = myocardial infarction

PCI = percutaneous coronary intervention

SS-2020 = SYNTAX score 2020

At least one-fifth of percutaneous coronary interventions (PCIs) involve treatment of a bifurcation lesion, with greater numbers in patients with multivessel disease.[1,2] In patients with 3-vessel disease (3VD) and/or left main coronary artery disease (LMCAD), PCI of bifurcation lesions is associated with higher adverse event rates compared with PCI in patients without them.[3] Coronary artery bypass grafting (CABG), which circumvents bifurcation lesions, conceivably provides better long-term outcomes; however, data pertaining to the very long term mortality of these patients treated by CABG or PCI are scarce.[2-4] Furthermore, whether the presence of a diseased bifurcation detected at the time of diagnostic angiography should be a deterrent to PCI and favors CABG as a safer modality of revascularization remains to be elucidated.

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The SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score 2020 (SS-2020) can be used to individualize the prediction of all-cause mortality at 10 years after CABG or PCI[5]; however, whether the presence of a bifurcation lesion is a dominant factor in decision making remains to be demonstrated. The aim of this prespecified subgroup analysis of the SYNTAXES (SYNTAX Extended Survival) study[6] was to investigate the impact of bifurcation lesions on individual predicted and observed all-cause 10-year mortality in patients with 3VD and/or LMCAD undergoing PCI or CABG.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The present study was a post hoc subgroup analysis of the SYNTAXES study (NCT03417050), an investigator-driven extended 10-year follow-up of the SYNTAX trial (NCT00114972).[6] The SYNTAX trial was a multicenter, randomized controlled trial conducted at 85 hospitals across 18 North American and European countries, which adopted an "all-comers" design with minimum exclusion criteria. A total of 1,800 patients with de novo 3VD and/or LMCAD, deemed eligible for both PCI and CABG on the basis of the consensus of a heart team, were randomized in a 1:1 fashion to undergo either PCI with the default use of paclitaxel-eluting stents (Taxus Express, Boston Scientific) or CABG. Patients deemed ineligible for either PCI or CABG were entered into nested CABG or PCI registries.

The main result of the SYNTAXES study in terms of vital status up to 10 years has been reported.[6] The median duration of follow-up was 11.2 years (IQR: 7.7-12.1 years) overall and 11.9 years in survivors. The SYNTAX and SYNTAXES trials were approved by the ethics committees at each investigating center, and all patients provided written informed consent before participation in the SYNTAX trial. Follow-up was performed in accordance with local law and regulations of each participating institution and complied with the Declaration of Helsinki.

BIFURCATION SUBGROUP. Patients were categorized into 4 groups: 1) presence of ≥1 bifurcation lesion and treatment with PCI; 2) no bifurcation lesion and treatment with PCI; 3) presence of ≥1 bifurcation lesion and treatment with CABG; and 4) no bifurcation lesion and treatment with CABG. A bifurcation was defined as a ≥50% diameter stenosis adjacent (within 3 mm) to a significant division of a major epicardial coronary artery according to the definition of the anatomical SYNTAX score.[7] The Medina classification was used to categorize the lesion, and the main vessel and branches were required to be ≥1.5 mm in diameter to be accounted for in the analyses. The presence and complexity of bifurcations was assessed by an independent core laboratory blinded to treatment assignment.

OUTCOMES. The primary endpoint was all-cause mortality at 10 years. All analyses were performed according to the intention-to-treat principle. Vital status was confirmed by (electronic) health care record review and national death registries. Patients with missing vital status were included in the analysis and censored at the last date of contact or observation. Major adverse cardiac and cerebrovascular events at 5 years (a composite of all-cause death, myocardial infarction [MI], stroke, and any repeat revascularization) were adjudicated by an independent clinical events committee.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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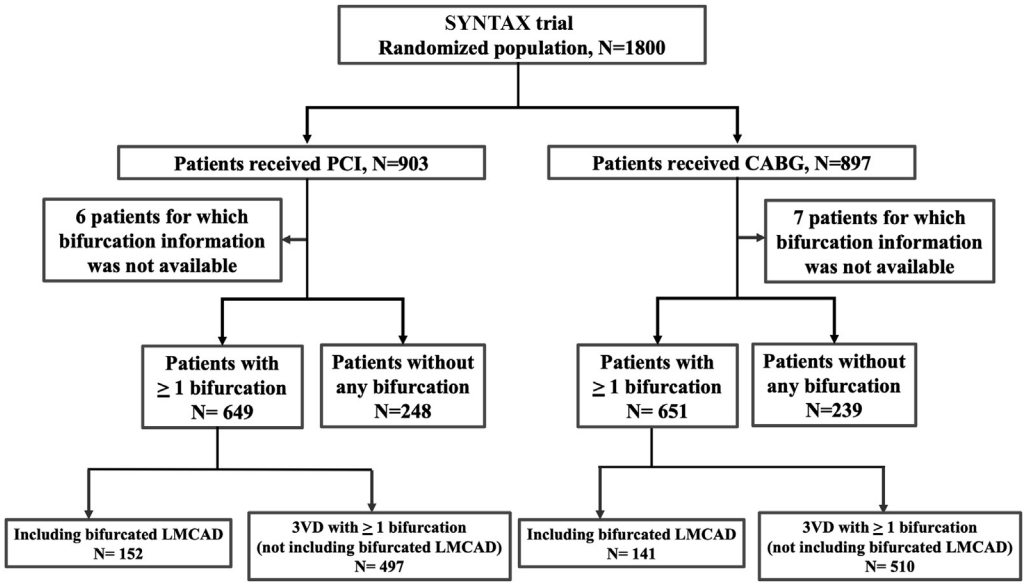
FIGURE 1 Flowchart of the Present Study



3VD = 3-vessel disease; CABG = coronary artery bypass grafting; LMCAD = left main coronary artery disease; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

STATISTICAL ANALYSIS. Continuous variables with normal distribution are expressed as mean ± SD and were compared using independent-samples Student's *t*-tests or are described as median (IQR) and were compared using the Wilcoxon rank sum test if not normally distributed. Categorical variables are presented as counts and percentages and were compared using chi-square or Fisher exact tests as appropriate. The Kaplan-Meier method was used to estimate the cumulative incidence of events over time, and the log-rank test was performed to examine the differences among groups. HRs with 95% CIs were evaluated by using Cox proportional regression models. The risk difference between PCI and CABG was also assessed in adjusted Cox proportional hazards models stratified by patients with at least 1 bifurcation and without any bifurcation, with an evaluation of the treatment-by-subgroup interaction. The confounders used for adjustment of the HR calculations were age, sex, body mass index, current smoking, hypertension, medically treated diabetes, dyslipidemia, previous MI, and previous cerebrovascular disease. Predicted mortality at 10 years after either PCI or CABG was computed with the probabilistic formulas of the SS-2020.[5] Calibration plots were generated to evaluate the agreement between predicted and observed rates of 10-year mortality in each treatment arm, with smooth calibration curves on the basis of a Cox model that fitted a restricted cubic spline of the mortality predictions (on the log-hazard scale) to the observed mortality outcomes.

The predicted individual absolute risk differences (ARDs) in all-cause mortality between CABG and PCI for each patient were ranked in descending order of magnitude according to the predicted PCI mortality minus predicted CABG mortality and shown as scatterplots. The dots in the scatterplots were connected with the use of locally estimated scatterplot smoothing curves. The observed mortality of treatments for each individual was calculated by the mortality of the nearest 10% population (after ranking) and then fitted by the locally estimated scatterplot smoothing curve. The external validation of the SS-2020 in the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) registry showed that individual predicted ARDs in all-cause death at 5 years of <4.5% and ≥4.5% offer sensible cutoffs for "equipoise of PCI and CABG" and "CABG better," respectively.[8] We applied this criterion to the present study population to identify in a heterogeneous population with bifurcation lesion(s) who would benefit or be harmed following PCI or CABG.

Statistical significance was defined as a 2-sided *P* value <0.05. All statistical analyses were

TABLE 1 Baseline Characteristics According to the Presence of Bifurcation and Revascularization Strategies

	PCI			CABG		
	Patients Without Any Bifurcation (n = 248)	Patients With at Least 1 Bifurcation (n = 649)	*P* Value	Patients Without Any Bifurcation (n = 239)	Patients With at Least 1 Bifurcation (n = 651)	*P* Value
Age, y	63.5 ± 10.0	65.9 ± 9.5	<0.001	63.7 ± 9.8	65.3 ± 9.8	0.030
Male	71.4 (177/248)	78.4 (509/649)	0.028	74.5 (178/239)	80.6 (525/651)	0.051
Body mass index, kg/m^2	28.1 ± 4.8	28.1 ± 4.8	0.961	28.1 ± 4.9	27.9 ± 4.4	0.606
Diabetes	23.4 (58/248)	26.3 (171/649)	0.392	25.5 (61/239)	24.4 (159/651)	0.727
On insulin	8.9 (22/248)	10.0 (65/649)	0.705	10.0 (24/239)	10.6 (69/651)	0.902
Metabolic syndrome	41.6 (87/209)	47.8 (250/523)	0.138	50.8 (93/183)	44.0 (224/509)	0.252
Hypertension	66.1 (164/248)	69.8 (453/649)	0.296	66.9 (160/239)	63.1 (411/651)	0.306
Dyslipidemia	77.6 (191/246)	79.0 (509/644)	0.648	74.0 (174/235)	78.7 (509/647)	0.146
Current smoking	20.6 (51/248)	17.6 (114/649)	0.335	23.6 (56/237)	21.5 (139/647)	0.522
Previous MI	29.7 (73/246)	33.1 (212/641)	0.377	29.1 (69/237)	35.6 (229/643)	0.077
Previous cerebrovascular disease	11.7 (29/248)	13.9 (90/647)	0.442	15.7 (37/236)	15.0 (97/647)	0.832
Previous stroke	5.6 (14/248)	3.3 (21/645)	0.122	4.2 (10/236)	5.1 (33/647)	0.725
Previous transient ischemic attack	4.4 (11/248)	4.3 (28/647)	1.000	4.7 (11/239)	5.3 (34/646)	0.863
Previous carotid artery disease	4.8 (12/248)	9.4 (61/649)	0.028	8.8 (21/239)	8.3 (54/651)	0.787
Peripheral vascular disease	8.1 (20/248)	9.4 (61/649)	0.603	9.6 (23/239)	11.1 (72/651)	0.624
Chronic obstructive pulmonary disease	7.3 (18/248)	5.9 (53/649)	0.782	7.5 (18/239)	9.8 (64/651)	0.36
Chronic kidney disease	17.5 (41/234)	20.3 (124/612)	0.667	17.9 (38/212)	19.2 (109/568)	0.777
Creatinine clearance, mL/min	89.1 ± 37.9	85.1 ± 34.0	0.132	86.9 ± 31.2	84.6 ± 28.5	0.304
LVEF, %	59.2 ± 12.4	58.5 ± 13.2	0.447	59.1 ± 12.5	57.7 ± 13.1	0.164
Congestive heart failure	4.9 (12/247)	3.7 (24/645)	0.449	4.3 (10/235)	5.8 (37/638)	0.499
Clinical presentation		0.688			0.873	
Silent ischemia	14.1 (35/248)	14.2 (92/649)		13.8 (33/239)	15.2 (99/651)	
Stable angina	54.8 (136/248)	57.6 (374/649)		57.7 (138/239)	56.8 (370/651)	
Unstable angina	31.0 (77/248)	28.2 (183/649)		28.5 (68/239)	28.0 (182/651)	
EuroSCORE	3.4 ± 2.5	3.9 ± 2.6	0.018	3.5 ± 2.5	3.9 ± 2.8	0.060
Parsonnet score	8.0 ± 6.2	8.75 ± 7.2	0.146	7.8 ± 6.2	8.6 ± 7.0	0.092
Disease type			0.093			0.162
3VD	56.0 (139/248)	62.2 (404/649)		57.3 (137/239)	62.7 (408/651)	
LMCAD	44.0 (109/248)	37.8 (245/649)		42.7 (102/239)	37.3 (243/651)	
Disease type			<0.001			<0.001
LMCAD only	9.3 (23/248)	2.9 (19/649)		13.0 (31/239)	2.8 (18/651)	
LMCAD + 1VD	12.1 (30/248)	5.7 (37/649)		10.0 (24/239)	6.8 (44/651)	
LMCAD + 2VD	12.5 (31/248)	12.2 (79/649)		9.2 (22/239)	12.9 (84/651)	
LMCAD + 3VD	10.1 (25/248)	16.9 (110/649)		10.5 (25/239)	14.9 (97/651)	
2VD (no LMCAD)	2.8 (7/248)	1.4 (9/649)		1.3 (3/239)	2.5 (16/651)	
3VD (no LMCAD)	53.2 (132/248)	60.9 (395/649)		56.1 (134/239)	60.2 (392/651)	
Number of lesions	3.5 ± 1.5	4.7 ± 1.8	<0.001	3.6 ± 1.7	4.7 ± 1.7	<0.001
SYNTAX score	21.7 ± 9.0	31.1 ± 11.1	<0.001	21.3 ± 9.6	32.0 ± 10.6	<0.001
SYNTAX score tercile						
Low	58.1 (144/248)	23.6 (153/649)	<0.001	61.9 (148/239)	19.5 (127/651)	<0.001
Intermediate	31.5 (78/248)	35.7 (232/649)	0.24	24.7 (59/239)	37.0 (241/651)	<0.001
High	10.5 (26/248)	40.7 (264/649)	<0.001	13.4 (32/239)	43.5 (283/651)	<0.001
Predicted 10-y mortality rates by SYNTAX score 2020, %	22.7 ± 17.0	28.9 ± 18.3	0.173	21.6 ± 15.7	23.6 ± 16.7	0.266
Any total occlusion	25.8 (64/248)	23.6 (153/649)	0.487	19.7 (47/239)	23.2 (151/651)	0.276
Number of stents	4.0 ± 2.3	4.9 ± 2.2	<0.001			
Total stent length per patient, mm	76.3 ± 51.3	90.4 ± 46.1	<0.001			
Number of conduits	–	–	–	2.7 ± 0.7	2.8 ± 0.7	0.06

Continued on the next page

TABLE 1 Continued

	PCI			CABG		
	Patients Without Any Bifurcation (n = 248)	Patients With at Least 1 Bifurcation (n = 649)	*P* Value	Patients Without Any Bifurcation (n = 239)	Patients With at Least 1 Bifurcation (n = 651)	*P* Value
Grafts used						
LIMA	–	–	–	87.2 (198/227)	85.5 (532/622)	0.529
RIMA	–	–	–	31.3 (71/227)	27.0 (168/622)	0.221
LIMA or RIMA	–	–	–	91.2 (207/227)	91.8 (571/622)	0.776
BIMA (both LIMA and RIMA)	–	–	–	27.3 (62/227)	20.7 (129/622)	0.042
Radial artery	–	–	–	14.1 (32/227)	14.1 (88/622)	0.985
Venous	–	–	–	74.9 (170/227)	83.1 (517/622)	0.007
Off-pump CABG		19.8 (45/227)	13.0 (81/621)	0.016		

Values are mean ± SD or % (n/N).

2VD = 2-vessel disease; 3VD = 3-vessel disease; BIMA = bilateral internal mammary artery; CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LIMA = left internal mammary artery; LMCAD = left main coronary artery disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RIMA = right internal mammary artery; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

performed with SPSS version 26.0 (IBM) and R version 3.5.1 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. Of 1,800 randomized patients in the SYNTAX trial, 1,787 patients (99.3%) were included in the present study, with 13 exclusions because of missing information on bifurcation lesions. Among the remaining 1,787 patients, 1,300 (72.7%) had ≥1 bifurcation lesion, and 487 patients had no bifurcation lesions (Figure 1).

Baseline characteristics of patients with or without bifurcation lesions are summarized in Table 1. Compared with patients without bifurcation lesions, those with bifurcation lesions were older and had a greater number of lesions and higher anatomical SYNTAX scores in both arms. Furthermore, the ratio of 3VD to LMCAD was higher in patients with ≥1 bifurcation vs those without bifurcations. In the PCI group, patients with bifurcation lesions were more frequently male and had higher European System for Cardiac Operative Risk Evaluation scores compared with those without bifurcation lesions.

CLINICAL OUTCOMES OF PATIENTS WITH AND WITHOUT BIFURCATION LESIONS AND AVERAGE TREATMENT EFFECT OF PCI VS CABG. The presence of a bifurcation lesion was associated with numerically higher rates of death, stroke, or MI at 5 years following PCI (21.9% vs 17.3%; HR: 1.20; 95% CI: 0.85-1.70; $P = 0.294$) and CABG (17.2% vs 13.0%; HR: 1.20; 95% CI: 0.80-1.79; $P = 0.389$) (Table 2). In the PCI arm, the risk for repeat revascularization at 5 years was significantly higher among patients with bifurcations than without (26.7% vs 19.4%; HR: 1.50; 95% CI: 1.08-2.08; $P = 0.016$), whereas there was no significant difference following CABG (11.5% vs 14.6%; HR: 0.81; 95% CI: 0.54-1.22; $P = 0.322$; $P_{interaction} = 0.016$) (Table 2).

All-cause death at 5 years was numerically higher in patients with vs without a bifurcation lesion following treatment with PCI (15.6% vs 9.7%; HR: 1.51; 95% CI: 0.96-2.39; $P = 0.071$), whereas there was no significant difference following CABG (12.3% vs 10.0%; HR: 0.97; 95% CI: 0.61-1.55; $P = 0.911$). There was no significant interaction between the presence of a bifurcation lesion and the treatment effect on all-cause mortality at 5 years following PCI or CABG ($P_{interaction} = 0.237$).

At 10 years, the presence of ≥1 bifurcation lesion was an independent predictor of all-cause death with PCI (30.1% vs 19.8%; HR: 1.55; 95% CI: 1.12-2.14; $P = 0.007$), whereas mortality following CABG was similar between patients with and without bifurcation lesions (23.3% vs 23.0%; HR: 0.81; 95% CI: 0.59-1.12; $P = 0.207$; $P_{interaction} = 0.006$) (Table 2). Of note, a landmark analysis in patients with bifurcation lesions treated with PCI shows a continuous and significant divergence of cumulative mortality beyond 5 years (Figure 2).

CLINICAL OUTCOMES OF PATIENTS WITH 3VD AND BIFURCATION LESIONS VS DISTAL LMCAD: "AVERAGE TREATMENT EFFECT". In patients with bifurcation lesions, the adjusted risk for death, stroke, or MI at 5 years was significantly higher after PCI than CABG among those with 3VD (23.1% vs 16.1%; HR: 0.70; 95% CI: 0.52-0.93; $P = 0.015$), whereas it was similar in those with distal LMCAD (17.8% vs 21.3%, HR: 1.19; 95% CI: 0.69-2.06; $P = 0.527$). At 5 years the risk for repeat

TABLE 2 Unadjusted and Adjusted HRs of Bifurcation vs Nonbifurcation on Long-Term Clinical Outcomes According to Revascularization Strategies

		Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	$P_{interaction}$
Death or stroke or MI at 5 y						0.992
PCI group	Bifurcation vs no bifurcation	1.31 (0.93-1.84)	0.124	1.20 (0.85-1.70)	0.294	
CABG group	Bifurcation vs no bifurcation	1.38 (0.93-2.06)	0.111	1.20 (0.80-1.79)	0.389	
Revascularization at 5 y						0.016
PCI group	Bifurcation vs no bifurcation	1.48 (1.07-2.03)	0.017	1.50 (1.08-2.08)	0.016	
CABG group	Bifurcation vs no bifurcation	0.80 (0.53-1.19)	0.268	0.81 (0.54-1.22)	0.322	
All-cause death at 5 y						0.237
PCI group	Bifurcation vs no bifurcation	1.65 (1.06-2.58)	0.027	1.51 (0.96-2.39)	0.071	
CABG group	Bifurcation vs no bifurcation	1.24 (0.78-1.95)	0.365	0.97 (0.61-1.55)	0.911	
All-cause death at 10 y						0.006
PCI group	Bifurcation vs no bifurcation	1.67 (1.22-2.28)	0.001	1.55 (1.12-2.14)	0.007	
CABG group	Bifurcation vs no bifurcation	1.01 (0.74-1.37)	0.970	0.81 (0.59-1.12)	0.207	

The covariables in the adjusted models include age, sex, body mass index, current smoking, hypertension, medically treated diabetes, dyslipidemia, previous myocardial infarction, and previous cerebrovascular disease.

Abbreviations as in Table 1.

revascularization was significantly lower with CABG compared with PCI among those with bifurcations and 3VD (11.4% vs 27.4%; HR: 0.40; 95% CI: 0.30-0.55; $P < 0.001$) or distal LMCAD (12.1% vs 24.3%; HR: 0.51; 95% CI: 0.28-0.91; $P = 0.022$).

In patients with 3VD and ≥1 bifurcation, CABG had an average beneficial effect on survival at 10 years compared with PCI (21.0% vs 31.0%; HR: 0.61; 95% CI: 0.47-0.79; $P < 0.001$), whereas in patients with distal LMCAD, the risk for all-cause mortality was comparable (31.9% vs 28.3%; HR: 0.95; 95% CI: 0.61-1.48; $P = 0.827$; $P_{interaction} = 0.052$) (Table 3).

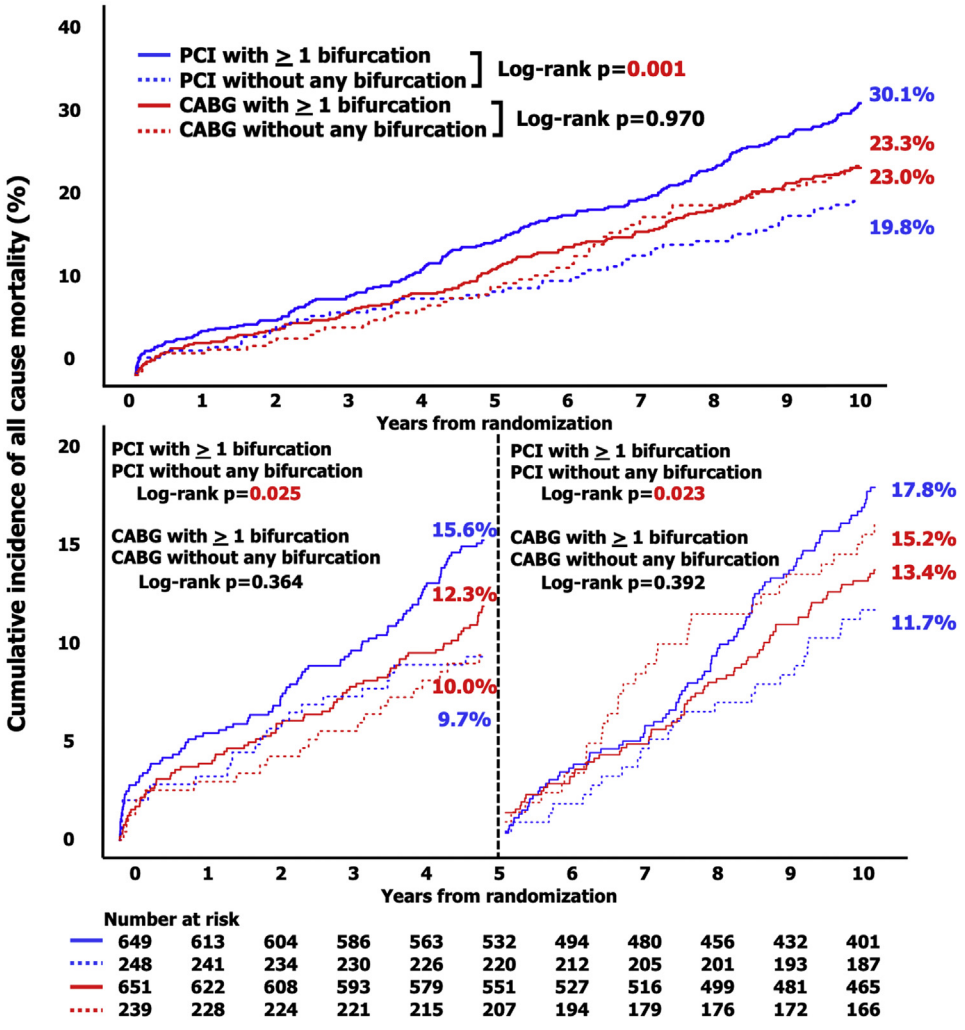
IMPACT OF NUMBER OF BIFURCATIONS AND MEDINA CLASSIFICATION ON OUTCOME. In PCI patients, beyond the significant and overall discrimination in all-cause mortality between patients with and those without bifurcations, there was no further discrimination when these patients were stratified according to the number of bifurcations and Medina classification (Supplemental Table 1).

IMPACT OF BIFURCATION STENTING TECHNIQUE (1 STENT VS 2 STENTS). Among the 820 bifurcation lesions, 512 patients (699 lesions) were stented (85.2%): 359 patients (70.1%) were treated with a 1-stent technique, and 153 patients (29.9%) were treated with at least one 2-stent technique (Supplemental Figure 1A). The detailed distribution of bifurcation stenting techniques is shown in Supplemental Figure 1B. The risk for repeat revascularization at 5 years was significantly higher among patients receiving a 2-stent compared with a 1-stent technique (33.3% vs 23.7%; HR: 1.60; 95% CI: 1.12-2.28; $P = 0.010$). At 5 years, all-cause death was similar between patients treated with a 2-stent compared with a 1-stent technique (15.0% vs 13.4%; HR: 1.13; 95% CI: 0.68-1.88; $P = 0.642$), whereas at 10 years, use of a 2-stent technique was an independent predictor of all-cause death after adjustment (33.3% vs 25.9%; HR: 1.51; 95% CI: 1.06-2.14; $P = 0.021$) (Table 4). A landmark analysis after the first 5 years of follow-up showed a significant divergence of the Kaplan-Meier curves over the last 5 years (Figure 3).

PREDICTED AND OBSERVED INDIVIDUAL TREATMENT BENEFIT IN SURVIVAL ACCORDING TO THE SS-2020. Supplemental Figure 2 shows the calibration plots of the SS-2020 for 10-year mortality in patients with and those without bifurcation lesions undergoing CABG or PCI. The SS-2020 showed helpful discrimination (C index = 0.70-0.75) and good calibration performance (intercept and slope) in the PCI (Supplemental Figures 2A and 2C) and CABG (Supplemental Figures 2B and 2D) arms, irrespective of the presence (Supplemental Figures 2A and 2B) or absence (Supplemental Figures 2C and 2D) of a bifurcation lesion. The predicted and observed treatment benefits for survival with CABG over PCI (ARD in mortality) in patients with ≥1 bifurcation were reasonably calibrated (Supplemental Figures 2E and 2F). However, in the absence of a bifurcation, in 3 of the 4 quartiles, no treatment benefit (or difference in mortality) was observed with one modality of revascularization over the other, and hence no valuable prediction was expected (Supplemental Figure 2F).

Supplemental Figures 2G and 2H display the Kaplan-Meier curves for all-cause mortality in each quarter of the population following CABG or PCI according to the presence (Supplemental Figure 2G)

FIGURE 2 The Impact of Bifurcation Lesions on All-Cause Death Up to 10 Years



In the PCI arm, the incidence of all-cause death at 10 years was significantly higher in patients with ≥1 bifurcation, whereas the mortality in the CABG arm was similar. The landmark analysis shows that in patients with bifurcation lesions treated with PCI, there was a continuous and significant divergence in the cumulative incidence of mortality beyond 5 years. Abbreviations as in Figure 1.

or absence (Supplemental Figure 2H) of a bifurcation lesion. Among those with ≥1 bifurcation, there was equipoise for all-cause mortality between PCI and CABG in the first 2 quartiles, whereas CABG was superior to PCI in the third and fourth quartiles (log-rank $P = 0.017$ and log-rank $P < 0.001$, respectively) according to the treatment benefit predicted by the SS-2020. In patients without bifurcations, there was no consistency in the prediction of mortality in all quartiles and no difference in observed mortality.

The **Central Illustration** shows scatterplots of individual predicted mortalities after PCI or CABG according to the SS-2020 and the actual observed mortality at 10 years in those individuals with bifurcation lesions. The individual scatterplots of predicted and observed mortality are interconnected by locally weighted scatterplot smoothing curves. If we aim at a predicted ARD of 0% in mortality between CABG and PCI for patients with bifurcations, then only 22.7% of patients in the SYNTAX trial would have been eligible for PCI. If the CREDO-Kyoto cutoff criterion (a maximal but acceptable predicted ARD in mortality of <4.5%) is used, then 48.1% of the population with ≥1 bifurcation could have legitimately been treated with PCI.

TABLE 3 Unadjusted and Adjusted HRs of Coronary Artery Bypass Grafting vs Percutaneous Coronary Intervention on Long-Term Clinical Outcomes Among Patients With 3-Vessel Disease With Bifurcation or Distal Left Main Coronary Artery Disease

		Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	$P_{interaction}$
Death or stroke or MI at 5 y						0.079
3VD with bifurcation	CABG vs PCI	0.71 (0.53-0.94)	0.018	0.70 (0.52-0.93)	0.015	
Distal LMCAD	CABG vs PCI	1.25 (0.75-2.11)	0.395	1.19 (0.69-2.06)	0.527	
Revascularization at 5 y						0.458
3VD with bifurcation	CABG vs PCI	0.39 (0.29-0.53)	<0.001	0.40 (0.30-0.55)	<0.001	
Distal LMCAD	CABG vs PCI	0.48 (0.27-0.86)	0.013	0.51 (0.28-0.91)	0.022	
All-cause death at 5 y						0.062
3VD with bifurcation	CABG vs PCI	0.66 (0.47-0.93)	0.016	0.61 (0.43-0.87)	0.007	
Distal LMCAD	CABG vs PCI	1.35 (0.73-2.47)	0.337	1.22 (0.64-2.34)	0.552	
All-cause death at 10 y						0.052
3VD with bifurcation	CABG vs PCI	0.63 (0.49-0.81)	<0.001	0.61 (0.47-0.79)	<0.001	
Distal LMCAD	CABG vs PCI	1.15 (0.76-1.75)	0.508	0.95 (0.61-1.48)	0.827	

The covariables in the adjusted models include age, sex, body mass index, current smoking, hypertension, medically treated diabetes, dyslipidemia, previous myocardial infarction, and previous cerebrovascular disease.
Abbreviations as in Table 1.

DISCUSSIONS

FINDING OF THE PRESENT STUDY. The results of the present study can be summarized as follows. First, the significantly higher risk for repeat revascularization at 5 years in patients with ≥1 bifurcation compared with those without any bifurcations is seen following PCI but not CABG.

Second, the presence of ≥1 bifurcation was an independent predictor of 10-year all-cause mortality after covariate adjustment in patients treated with PCI, whereas it had no impact on mortality after CABG. There was a significant interaction between the presence of bifurcation lesions and the modality of revascularization on 10-year all-cause mortality.

Third, the PCI technique used to treat the bifurcation may have an impact on long-term clinical outcomes; at 5 years there was no significant difference in mortality between 1- and 2-stent techniques, whereas at 10 years, a 2-stent technique was an independent predictor of all-cause death.

Fourth, among patients with ≥1 bifurcation and according to the treatment benefit predicted by the SS-2020, there was equipoise for all-cause mortality between PCI and CABG in 2 quartiles of the whole population, whereas CABG was superior to PCI in the 2 remaining quartiles. Among patients without any bifurcations, there was no significant treatment benefit of CABG over PCI in any quartile and thus no individual preferred treatment.

TABLE 4 Unadjusted and Adjusted HRs of 2- vs 1-Stent Technique on Long-Term Clinical Outcomes

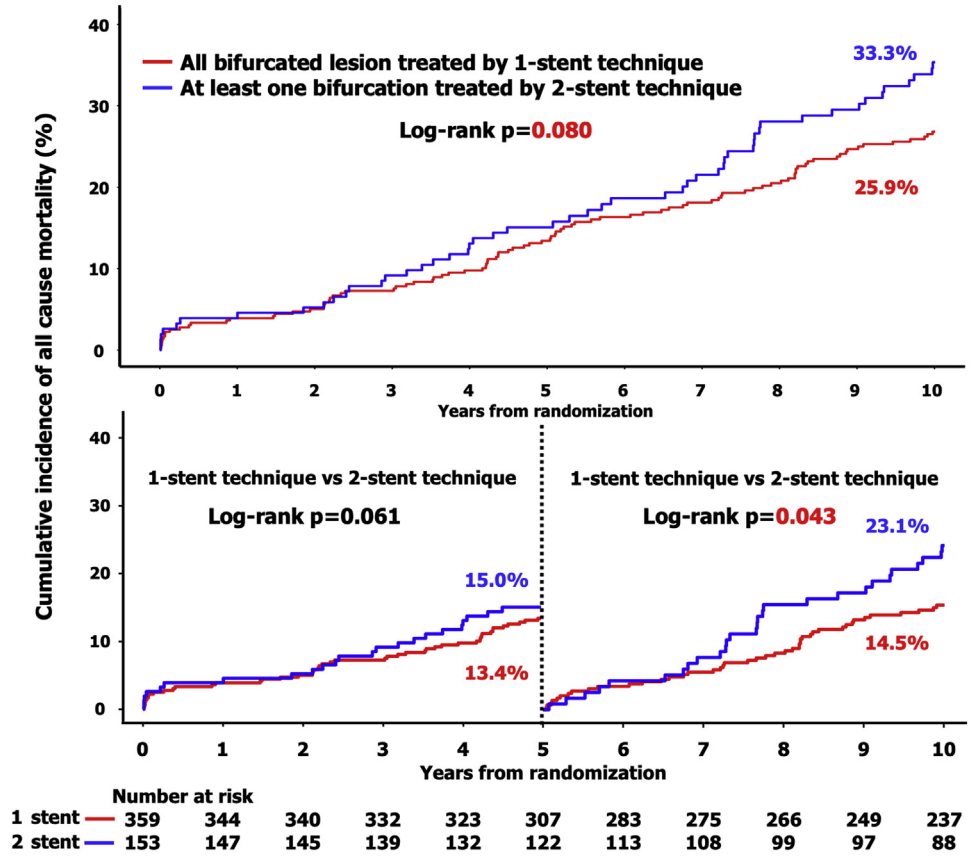
		Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Death or stroke or MI at 5 y					
PCI group	2-stent vs 1-stent	1.29 (0.86-1.94)	0.214	1.33 (0.88-2.02)	0.171
Revascularization at 5 y					
PCI group	2-stent vs 1-stent	1.52 (1.07-2.15)	0.018	1.60 (1.12-2.28)	0.010
All-cause death at 5 y					
PCI group	2-stent vs 1-stent	1.14 (0.69-1.87)	0.606	1.13 (0.68-1.88)	0.642
All-cause death at 10 y					
PCI group	2-stent vs 1-stent	1.36 (0.96-1.91)	0.081	1.51 (1.06-2.14)	0.021

The covariables in the adjusted models include age, sex, body mass index, current smoking, hypertension, medically treated diabetes, dyslipidemia, previous myocardial infarction, and previous cerebrovascular disease.
Abbreviations as in Table 1.

IMPACT OF BIFURCATION LESIONS ON ALL-CAUSE MORTALITY AFTER CABG OR PCI. In the present study, the presence of ≥1 bifurcation was associated with an increased risk for 10-year mortality among patients with 3VD or LMCAD following PCI, whereas no significant difference was seen following CABG. This difference in mortality is expected on the basis of the revascularization modality: PCI deals mainly with the lesion and its complexity, in contrast to CABG, which bypasses the bifurcation, needing only a quality distal landing zone for the graft anastomosis.

Current guidelines recommend calculating the anatomical SYNTAX score if left main or multivessel revascularization is considered.[9] Bifurcation lesions are a component of the anatomical SYNTAX score and require special attention from the heart team, considering their higher 10-year all-cause mortality observed after PCI. In contrast, patients who underwent PCI without bifurcation lesions had the best life expectancy at 10 years compared with the other

FIGURE 3 The Impact of the 2 Different Stent Techniques on Long-Term Clinical Outcomes



Up to 5 years, there was no significant difference in all-cause death between patients treated with a 2-stent technique vs a 1-stent technique, whereas beyond 5 years, Kaplan-Meier curves in a landmark analysis show significant divergence between a 2-stent technique and a 1-stent technique.

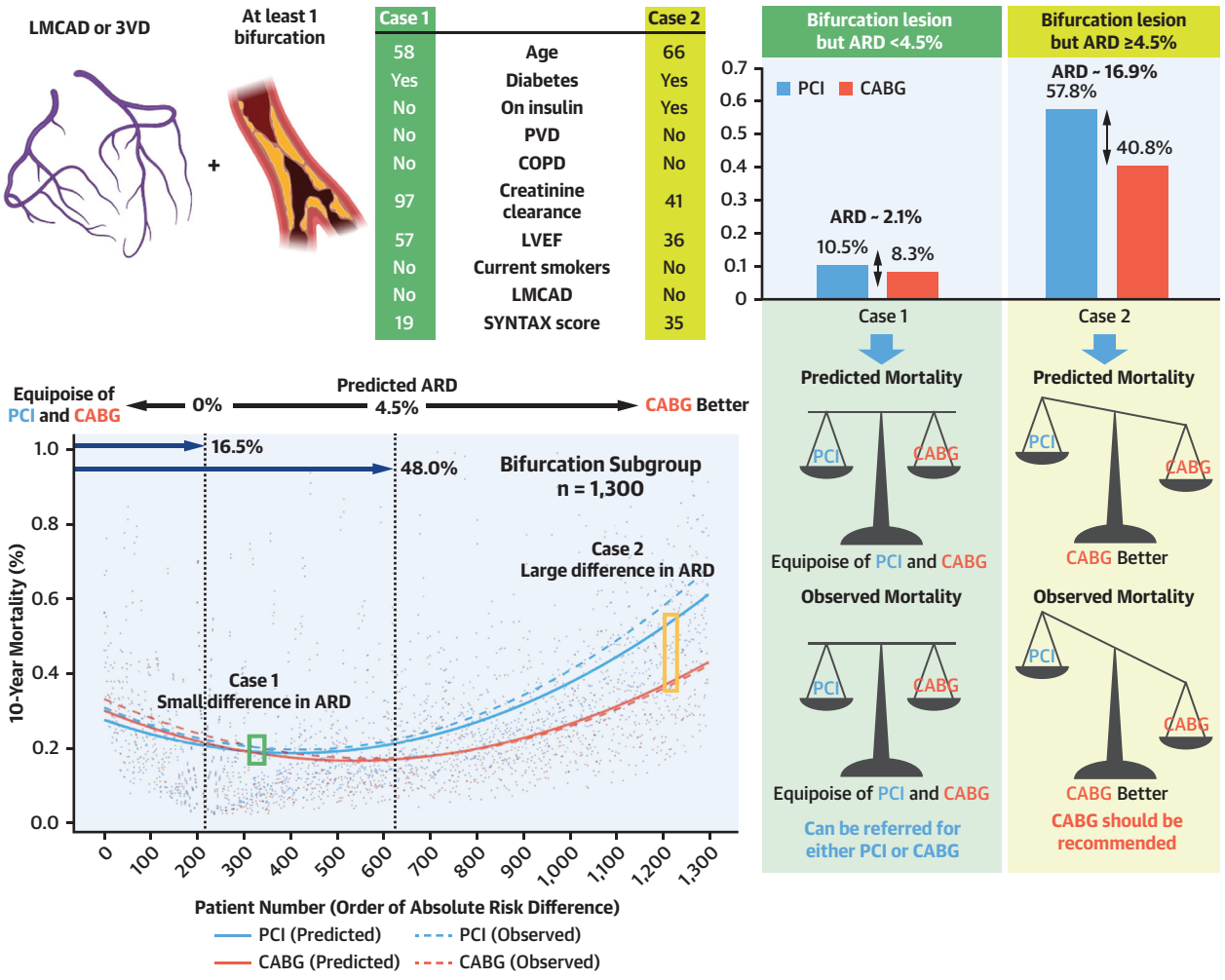
groups. This shows that in the absence of bifurcation lesions, even first-generation drug-eluting stents (DES) can have a better long-term prognosis compared with CABG.

RECENT PROGRESS IN BIFURCATION TREATMENT. **Distal left main disease.** The most important bifurcation lesion is the one involving the distal left main coronary artery, and data reporting outcomes for this specific lesion are somewhat contradictory. In the 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions coronary revascularization guidelines, CABG has a Class 1 recommendation for managing LMCAD, while PCI has a Class 2a recommendation, provided it can offer equivalent revascularization to that possible with CABG, whereas in Europe, the Class 1 recommendation for PCI persists irrespective of the location of the left main disease, provided the total SYNTAX score remains <23.[9,10]

In the present study patients with distal LMCAD had a comparable risk for all-cause mortality at 5 and 10 years with PCI or CABG. However, in the EXCEL trial, overall mortality at 5 years was higher in patients undergoing PCI than those undergoing CABG (13.0 vs 9.9%; OR: 1.38; 95% CI: 1.03-1.85).[11] In contrast, a recent meta-analysis of 4 large, randomized trials showed that among patients with LMCAD who had low to intermediate coronary anatomical complexity, there was no statistically significant difference in long-term mortality between PCI and CABG.[12] A heart team approach and individual prediction using the SS-2020 may therefore be helpful to select the modality of revascularization.

3VD with bifurcation lesion. Randomized trials have shown significantly higher mortality and higher incidence of death, MI, and stroke with PCI using DES compared with CABG in patients with multivessel

CENTRAL ILLUSTRATION **Treatment Recommendation According to the Predicted Absolute Risk Difference for 10-Year Mortality in Patients With Bifurcation Lesions**



Ninomiya K, et al. J Am Coll Cardiol Intv. 2022;15(12):1231–1242.

In case 1, the patient's predicted 10-year mortality rate is 10.5% after percutaneous coronary intervention (PCI) and 8.3% after coronary artery bypass grafting (CABG), giving a predicted absolute risk difference (ARD) of ~2.1% (<4.5%); therefore, the patient can be referred for either PCI or CABG. In case 2, the patient's predicted 10-year mortality rate is 57.8% after PCI and 40.8% after CABG, giving a predicted ARD of ~16.9% (≥4.5%); therefore, CABG should be recommended. Scatterplots show the individual predicted mortalities after PCI or CABG according to SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score 2020, and the actual observed mortality at 10 years in those individuals with bifurcation lesions. 3VD = 3-vessel disease; COPD = chronic obstructive pulmonary disease; LMCAD = left main coronary artery disease; LVEF = left ventricular ejection fraction; PVD = peripheral vascular disease.

coronary artery disease and intermediate to high anatomical complexity.[6,13] At 2 years, in a subanalysis of the SYNTAX II trial, a single-arm trial using contemporary devices and practice, treatment of a bifurcation lesion, albeit in a limited sample size, was nevertheless associated with a trend toward a higher incidence of target lesion failure compared with nonbifurcation lesions.[2] In the present study, in patients with 3VD and >1 bifurcation, CABG had a significant average beneficial effect on survival at 10 years compared with PCI. This fact enhances the benefit of CABG for patients with 3VD with complex anatomy and reminds us that bifurcation lesions require additional special attention in the heart team

discussion, as bifurcation disease substantially affects PCI technique and aggressiveness, whereas CABG is performed in a similar fashion irrespective of bifurcation disease.

Device and technique. A recent meta-analysis showed that there was no difference in the risk for MACE up to 3 years between 1- and 2-stent approaches for PCI of bifurcation lesions.[14] During the past decade of bifurcation PCI treatment, patient and lesion characteristics, devices, PCI techniques, and patient prognosis have all changed significantly, and despite increased patient and lesion complexity, clinical outcomes after bifurcation PCI have improved.[4] Lee et al[15] also reported that a 2-stent technique was a significant independent predictor of adverse 3-year clinical outcomes when using first-generation DES, but not with second-generation DES. Our results showed similar trends, and the unfavorable outcomes encountered in the SYNTAX trial may be mitigated by PCI using new-generation DES. Furthermore, the current extensive assessment of bifurcation anatomy with noninvasive and intravascular imaging and the strictly codified 2-stent technique used may have in the meantime considerably improved outcomes.

However, data pertaining to very long term mortality in patients with bifurcation lesions treated with different PCI techniques are limited. In our study, there was no significant difference up to 5 years, whereas at 10 years, the 2-stent technique was an independent predictor of all-cause death, suggesting that very long term follow-up may be needed to assess the superiority of one technique over another.

"AVERAGE TREATMENT EFFECT" VS "PERSONALIZED TREATMENT BENEFIT" IN PATIENTS WITH OR WITHOUT BIFURCATION LESIONS. The selection by practitioners of a preferred therapy, when 2 treatment options are available, relies predominantly on an "average treatment benefit," traditionally provided by an ARD (or treatment benefit) derived from Kaplan-Meier estimates in randomized trials. However, the goal is to identify who in a heterogeneous population, subjected to a novel treatment, will benefit or be harmed by a new therapy and who will have an equipoise outcome.[5]

The methodological foundation of this approach lies in the accuracy of outcome predictions for each modality of treatment, allowing personalized and individual predictions of the benefit of one treatment over another.[5,8] In the present study, the SS-2020 formally identified a cohort composed of 22.7% of patients in the randomized population who had bifurcation lesions and had a risk difference of <0 (ARD $\leq$ 0%) in mortality between PCI and CABG (**Central Illustration**).

However, today, the use of an individual predicted ARD of 0% with the SS-2020, derived from the original SYNTAX trial using outdated technology and techniques of implantation, seems to be too restrictive, as it leads to the recommendation of CABG in the majority of patients with 3VD without LMCAD. In the SYNTAX II trial, there was a significant reduction in 5-year all-cause mortality compared with the SYNTAX I PCI cohort (8.1% vs 13.8%; $P = 0.013$).[16] Furthermore, all-cause mortality at 1 year was 2.8% lower in the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) 3 trial (fractional flow reserve-guided PCI) than in the SYNTAX trial (4.4% vs 1.6%).[17] This is probably the reason why the threshold of equipoise in mortality at 5 years moved from an ARD of 0% to an ARD of 4.5% in the external validation of the CREDO-Kyoto cohort.[8]

STUDY LIMITATIONS. First, the extended follow-up of the SYNTAXES trial up to 10 years was only for survival status, and data on other clinical endpoints with independent adjudication were limited to 5 years. Second, the SYNTAX trial was conducted between 2005 and 2007 with unrestricted use of first-generation paclitaxel DES for treatment with PCI. The technological improvements of PCI devices and surgical techniques, as well as adjunctive optimal pharmacologic therapies including the state-of-the-art therapies such as proprotein convertase subtilisin/kexin type 9 and sodium-glucose cotransporter 2 inhibitors, limit the generalizability of our findings to current practice.

However, it is unavoidable that the findings from long-term follow-up data are based on outdated technology, while evidence for contemporary technology can be derived only from short-term follow-up studies. The calculation of individualized 10-year prognosis using the SS-2020 may therefore be helpful in decision making even in different eras.

CONCLUSIONS

Bifurcation lesions require special attention from the heart team, considering the higher 10-year all-cause mortality seen following PCI, especially in patients with 3VD. Careful evaluation of bifurcation lesion complexity and calculation of individualized 10-year prognosis using the SS-2020 may therefore be helpful in decision making.

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ADDRESS FOR CORRESPONDENCE: Dr Patrick W. Serruys, National University of Ireland-Galway, University Road, Galway H91 TK33, Ireland. E-mail: patrick.serruys@nuigalway.ie.

PERSPECTIVES

WHAT IS KNOWN? PCI of bifurcation lesions is associated with higher rates of adverse events, but whether PCI or CABG is the safer modality of revascularization for these lesions long-term remains to be elucidated.

WHAT IS NEW? The presence of at least 1 bifurcation was an independent predictor of 10-year all-cause mortality in patients receiving PCI, whereas it had no impact on mortality after CABG. There was a significant interaction between the presence of bifurcation lesions and the modality of revascularization on 10-year all-cause mortality.

WHAT IS NEXT? Further research using the SS-2020 and its derivatives could enhance the individual prediction of long-term mortality and support clinical decisions regarding the modality of revascularization in patients with bifurcation lesions.

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KEY WORDS bifurcation lesion, CABG, long-term clinical outcomes, PCI, SYNTAX

APPENDIX For supplemental figures and tables, please see the online version of this paper.