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ORIGINAL STUDIES

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Two years clinical outcomes with the state-of-the-art PCI for the treatment of bifurcation lesions: A sub-analysis of the SYNTAX II study

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Abstract

Background: Bifurcation PCI is associated with a lower rate of procedural success, especially in multivessel disease patients. We aimed to determine the impact of bifurcation treatment on 2-years clinical outcomes when a state-of-the-art PCI strategy (heart team decision-making using the SYNTAX score II, physiology guided coronary stenosis assessment, thin strut bioresorbable polymer drug-eluting stent, and intravascular ultrasound guidance) is followed.

Methods: Three-vessel disease patients enrolled in the SYNTAX II trial (n = 454) were categorized in patients with (a) ≥1 treated bifurcation (n = 126), and (b) without bifurcation (n = 281). The primary endpoint was the occurrence of major adverse cardio and cerebrovascular events (MACCE—a composite of all-cause death, stroke, any myocardial infarction, or any revascularization) at 2 years. Secondary endpoints were the occurrence of target lesion failure (TLF) defined as cardiac death, target-vessel myocardial infarction and ischemia-driven target lesion revascularization, and the individual components of the composite primary endpoint, as well as stent thrombosis.

Results: A total of 145 bifurcation were treated in 126 patients. At 2 years, MACCE occurred in 75/407 patients (20.7% for bifurcation versus 17.5% for nonbifurcation, hazard ratio [HR] of 1.28, CI95% 0.78–2.08, p = .32). TLF presented a trend toward higher occurrence in bifurcation (16.8% vs. 10.8%, HR 1.75, CI95% 0.99–3.09,

Abbreviations: CABG, coronary artery bypass graft; FFR, fractional flow reserve; GDMT, Guideline-directed medical therapy; IDR, ischemia-driven revascularization; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; MACCE, major adverse cardiovascular or cerebrovascular events; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; TLF, target lesion failure.

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p = .053). Definite stent thrombosis did not differ at 2-year between groups (0.8% for the bifurcation vs. 0.7% for the nonbifurcation, p = .92).

Conclusion: Bifurcation treatment in patients with three-vessel disease undergoing state-of-the-art PCI had similar event rate of MACCE but was associated with a trend toward higher incidence of TLF compared with nonbifurcation lesions.

KEYWORDS
bifurcation, drug eluting stents, percutaneous coronary intervention, three-vessel disease

1 | INTRODUCTION

Bifurcation lesions are involved in up to 20% of percutaneous coronary interventions (PCI),[1] and that number can be higher in multivessel diseased patients.[2] Bifurcation treatment poses great technical difficulties and a variety of strategies is offered to the interventional cardiologist. Historically, PCI of bifurcation lesions are known to be associated with poorer procedural success, thus with worse clinical outcomes when compared with PCI of nonbifurcation lesions.[3,4]

Extensive debate on the best approach for bifurcation percutaneous treatment is still ongoing.[3,5–8] Multiple trials have tested mostly the approach of a provisional stent techniques versus the upfront treatment with two stents. However, most trials do not use physiological assessment of the lesions and none of these trials combine the guidance by physiology with image guidance of the intervention (e.g., intravascular ultrasound, IVUS or optical coherence tomography, OCT).

SYNTAX II is a study on multivessel disease patients, without involvement of left main stem, with the use of the so-called state-of-the-art PCI (i.e., intervention guided by IVUS and instantaneous wave-free ratio—iFR, chronic total occlusions (CTOs), and bifurcation lesions performed preferably by specialists and using newer generation drug eluting stents). We sought to investigate the clinical outcomes of the state-of-the-art PCI for bifurcation lesions, compared with PCI for nonbifurcation lesions in three-vessel disease patients of the SYNTAX II study.

2 | METHODS

2.1 | Study population

This is a posthoc analysis of the SYNTAX II study. SYNTAX II is an all-comers, multicenter, open label, single-arm study which enrolled 454 patients with three-vessel coronary artery disease without left main involvement who were candidates for revascularization. The recruiting center's heart teams screened the patients who had to have a SYNTAX score II with an equipoise between CABG and PCI.[9] Details of the study are published elsewhere.[2]

For the purpose of this analysis patients were categorized in two groups: (a) those with the presence of at least one bifurcation lesion that was considered physiologically significant and was treated and (b) patients without any bifurcation lesion diagnosed with visual assessment of coronary angiography. Forty patients had bifurcation lesions but not treated after physiological assessment, thus these patients were not included in the analysis. Bifurcation lesion was defined as a stenosis that occurs at, or adjacent to a significant division of a major epicardial coronary artery. Main vessel and branch must be at least 1.5 mm of size to be accounted for in the analyses.[2,10]

2.2 | State-of-the-art PCI

The approach used in these patients combined physiologically guided intervention, a mandatory post-PCI intravascular ultrasound (IVUS) assessment of adequate stent expansion and apposition,[11] and the use of a novel thin strut (70 μm, with abluminal biodegradable polymer coating stent—SYNERGY, Boston Scientific). Also, bifurcation treatment followed the consensus of the European Bifurcation Club (EBC)[10] and CTO PCI was preferably performed by a dedicated CTO operator. Guideline-directed medical therapy (GDMT) and strict control of LDL-cholesterol were also advocated during the follow-up of the trial.

Physiology assessment of lesions intended to treat was performed with a hybrid coronary physiology approach using iFR and fractional flow reserve (FFR)—according to the flowchart in Figure 1. The lesion was treated if considered functionally significant (iFR <0.86 or iFR between 0.86 and 0.93 with an FFR <0.80). Decision regarding the strategy and technique for bifurcation intervention was left to the discretion of the operator with a protocoled recommendation derived from the EBC consensus. Since the patients had 3-vessel disease, the procedures could also be done in a staged fashion.

2.3 | Study endpoints and definitions

The primary endpoint for the present analysis is the composite of MACCE, or patient oriented composite endpoint: a composite of all-cause death, stroke, any myocardial infarction (MI), or any revascularization, at 2 years.[12] Secondary endpoints comprised the device oriented composite endpoint of target lesion failure (TLF), the individual nonhierarchical components of the primary endpoint, as well as definite stent thrombosis, at 2 years. TLF is defined as the composite of cardiac death, target vessel MI, and ischemia-driven

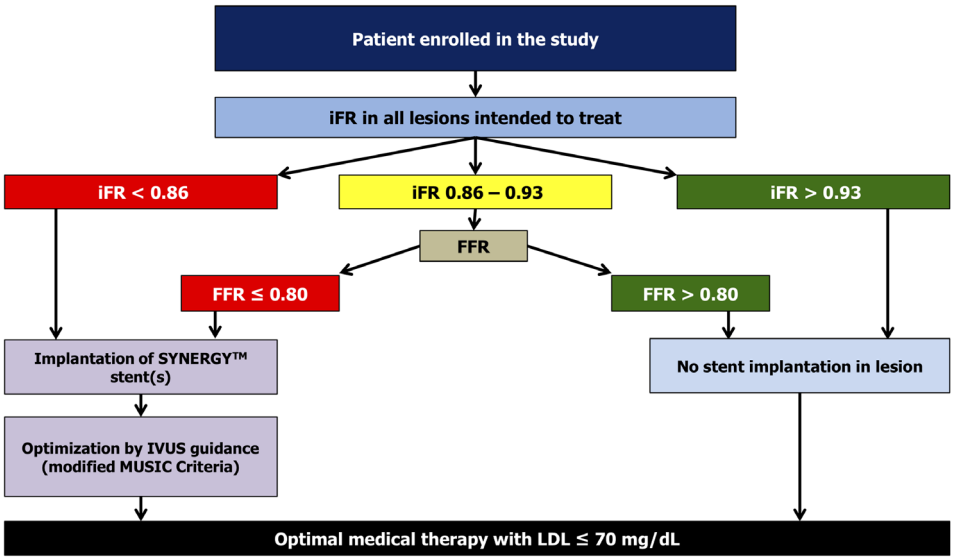

FIGURE 1 SYNTAX II flowchart for the physiological assessment of all lesions intended to be treated [Color figure can be viewed at wileyonlinelibrary.com]

revascularization. MI was defined according to the Society for Cardiovascular Angiography and Interventions (SCAI) consensus for periprocedural MI (when ≤48 hr) or to the Third Universal Definition for MI (if >48 hr after the index procedure).[13,14] Stent thrombosis was defined in accordance with the Academic Research Consortium.[15] All adverse events were adjudicated by an independent clinical event committee. All patients signed informed consent. Follow-up is ongoing through 5 years, and the present report is complete in all patients through 2 years. Quantitative coronary angiography (QCA) analysis for assessment of bifurcation lesions was performed in an independent angiographic core laboratory (Cardialysis, Rotterdam, the Netherlands).[16]

2.4 | Statistical analysis

Continuous data are presented as mean ± standard deviation of the mean or as median and interquartile range according to data distribution. Comparisons were performed using Student's *t*-test or Mann–Whitney *U* test whenever appropriate. Categorical data were compared with the Chi-square test or Fisher's exact test and are shown as absolute number and percentages. Event rates were based on Kaplan–Meier estimates, and plotted in time-to-first-event analyses and compared with Cox proportional hazards model. The confounders used for adjustment of the hazard ratio calculations were: age, sex, diabetes, smoking status, hyperlipidemia, and hypertension. Two-sided α error of .05 was considered to determine statistical significance. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Baseline and procedural characteristics

From the 454 patients included in the study, 447 had PCI performed. One hundred and twenty-six (126) patients had at least one bifurcation treated comprising a total of 145 treated bifurcations, and 281 patients had no bifurcation lesions diagnosed with visual assessment of the angiography (Figure 2). Baseline characteristics were balanced between the groups, except for the presence of hyperlipidemia, higher in the treated bifurcation group (Table 1).

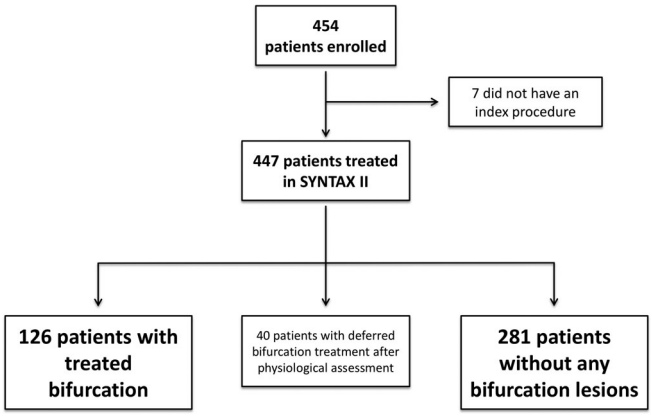

FIGURE 2 Patient flowchart

By angiographic core laboratory analysis, patients in the treated bifurcations group had greater anatomic complexity, as reflected by a higher anatomic SYNTAX score. On the other hand, SYNTAX score II along with its 4-year mortality prediction for PCI were comparable between the two groups. (Table 2). The number of lesions undergoing physiological assessment were the same between the groups, but a greater number of coronary segments were assessed and treated in the bifurcation group (Table 2). Overall, the number and length of stents were higher in the bifurcation group (Table 2). Intravascular ultrasound data showed that malaposition was low and comparable between groups (6.0% vs. 6.3%)—Table 2. Also, worthy of mentioning is that postdilatation performed based on IVUS findings was significantly higher in the patients with a treated bifurcation lesion (46% vs. 36.8%, p = .004, respectively). Visually assessed Medina 1,1,1 occurred in 54 of the 145 bifurcations (37.2%). Final kissing balloon

TABLE 1 Baseline characteristics of three-vessel disease patients treated for bifurcation lesions and without bifurcation lesions

Characteristic	Treated bifurcation (*n* = 126)	Nonbifurcation (*n* = 281)	Difference (95% CI)	*p*-value
Age (years)	66.2 ± 9.9 (126)	66.3 ± 9.7 (281)	−0.1 [−2.1, 2.0]	.93
Male	96.0% (121/126)	92.9% (261/281)	3.1% [−1.4%, 7.7%]	.22
Body mass index (kg/m^2)	29.4 ± 5.3 (126)	28.8 ± 4.4 (281)	0.7 [−0.3, 1.7]	.21
COPD	8.7% (11/126)	11.4% (32/281)	−2.7% [−8.8%, 3.5%]	.42
Peripheral vascular disease	7.1% (9/126)	7.1% (20/281)	0.0% [−5.4%, 5.4%]	.99
Creatinine clearance (mL/min)	83.6 ± 27.4 (126)	82.6 ± 27.4 (281)	1.0 [−4.8, 6.8]	.74
LVEF (%)	57.6 ± 7.2 (126)	58.3 ± 8.3 (281)	−0.6 [−2.3, 1.0]	.46
Current smoker	10.1% (12/119)	16.0% (44/275)	−5.9% [−12.8%, 1.0%]	.12
Diabetes mellitus Type I or II	27.2% (34/125)	29.7% (83/279)	−2.5% [−12.0%, 6.9%]	.60
Insulin dependent diabetes	10.4% (13/125)	7.2% (20/279)	3.2% [−2.9%, 9.4%]	.27
Oral mediation only	14.4% (18/125)	20.4% (57/279)	−6.0% [−13.8%, 1.7%]	.15
Diet only	2.4% (3/125)	1.8% (5/279)	0.6% [−2.5%, 3.7%]	.71
Hypertension (or on treatment for hypertension)	78.4% (98/125)	75.0% (210/280)	3.4% [−5.4%, 12.2%]	.46
Hyperlipidemia (or on treatment for hyperlipidemia)	83.9% (104/124)	73.5% (202/275)	10.4% [2.1%, 18.7%]	.023
Medical history				
Peripheral vascular disease	7.1% (9/126)	7.1% (20/281)	0.0% [−5.4%, 5.4%]	.99
Previous stroke	4.8% (6/126)	5.0% (14/281)	−0.2% [−4.7%, 4.3%]	.92
Previous MI	14.4% (18/125)	12.1% (34/280)	2.3% [−5.0%, 9.5%]	.53
Pulmonary hypertension (moderate/severe)	0.0% (0/113)	0.4% (1/255)	−0.4% [−1.2%, 0.4%]	1.00
Anginal status				.67
Silent ischemia	3.2% (4/126)	6.0% (17/281)		
Stable angina	72.2% (91/126)	69.0% (194/281)		
Unstable angina	24.6% (31/126)	24.6% (69/281)		
None of the above	0.0% (0/126)	0.4% (1/281)		

was performed in 41.7% of bifurcations. Two-stent techniques in at least one of the bifurcation lesions per patient were used in 63 patients (50%). The most common approaches for treating bifurcation according to the MADS classification were: MB stenting across SB 27.6%, PM stenting with or without KB 22.1% and Culotte 6.9% (Data S1—Table S1). Core laboratory QCA analysis of the bifurcation lesions are presented in Data S1—Table S2.

3.2 | Clinical outcomes

At 2 years the primary composite endpoint (MACCE) occurred in 75 patients (20.7% for treated bifurcation vs. 17.5%, hazard ratio [HR] of 1.28, CI95% 0.78–2.08, p = .32). Patients with treated bifurcation presented a trend toward higher occurrence of TLF at 2 years (16.8% vs. 10.8%, HR 1.75, CI95% 0.99–3.09, p = .053), compared with those without any bifurcation. With the exception of stroke (1.6% vs. 2.2%, HR 0.38, CI 95% 0.05–3.20, p = .37) and revascularization (8.2% vs. 10.9%, HR 0.86, CI 95% 0.41–1.78, p = .68); all cause death (5.6% vs. 1.8%, HR 2.78, CI 95% 0.83–9.37, p = .10), and MI (8.0% vs. 4.3%, HR 2.09, CI 95% 0.89–4.94, p = .09) contributed to increase MACCE in the treated bifurcation group compared with nonbifurcation, respectively (Figure 3). Definite stent thrombosis did not differ at 2-year between groups (0.8% for treated bifurcation vs. 0.7% for nonbifurcation, p = .92). Bifurcation treatment with two or more stents had comparable MACCE, TLF, and stent thrombosis to treatment with only one stent (Figure 4). A posthoc power calculation for the primary endpoint taken into account the event rates and two-sided alpha of .05 resulted in a low power of 9.97%. The sample size needed for reaching a difference in the primary endpoint with an 80% power would be of 5,630 three-vessel diseased patients.

4 | DISCUSSION

The main finding of this study is that in patients with three-vessel disease that are candidates for both percutaneous or surgical coronary revascularization, the presence of bifurcation lesions that were treated using the state-of-the-art PCI did not impact on the occurrence of the composite endpoint of death, MI, stroke, or any revascularization, compared with percutaneous treatment of nonbifurcation lesions. However, we showed that, in this population, there was a trend toward increasing TLF (device oriented composite endpoint) when treating bifurcation lesions.

TABLE 2 Anatomical and procedural characteristics of three-vessel disease patients treated for bifurcation lesions and patients without bifurcation lesions

Characteristic	Treated bifurcation (*n* = 126)	Nonbifurcation (*n* = 281)	Difference (95% CI)	*p*-value
Per patient information				
Anatomical SYNTAX score	21.5 ± 5.7 (126)	19.7 ± 6.5 (281)	1.9 [0.5, 3.2]	.006
Syntax score II (for treatment with PCI)	29.8 ± 8.2 (126)	29.7 ± 8.5 (281)	0.1 [−1.6, 1.9]	.88
4 year predicted mortality PCI (pct)	8.5 ± 7.6 (126)	8.5 ± 8.6 (281)	−0.1 [−1.8, 1.7]	.92
Number of assessed lesions (by iFR/FFR) (mean ± *SD*, *N*)	3.56 ± 0.93 (126)	3.43 ± 0.98 (281)	0.13 [−0.07, 0.33]	.21
Number of assessed segments (by iFR/FFR) (mean ± *SD*, *N*)	4.06 ± 1.06 (126)	3.44 ± 0.98 (281)	0.61 [0.40, 0.83]	<.001
Number of treated segments (mean ± *SD*, *N*)	3.22 ± 1.12 (126)	2.55 ± 1.13 (278)	0.68 [0.44, 0.91]	<.001
Chronic total occlusion	31.7% (40/126)	25.6% (72/281)	6.1% [−3.5%, 15.7%]	.20
Vessels treated:				
RCA	61.1% (77/126)	62.2% (173/278)	−1.1% [−11.4%, 9.1%]	.83
LAD	99.2% (125/126)	89.2% (248/278)	10.0% [6.0%, 14.0%]	<.001
LCX	76.2% (96/126)	63.7% (177/278)	12.5% [3.2%, 21.9%]	.013
3VD	43.7% (55/126)	35.6% (99/278)	8.0% [−2.3%, 18.4%]	.12
Stent information				
Per patient				
Total stent length (mean ± *SD*, *N*)	109.3 ± 54.54 (126)	87.26 ± 51.02 (277)	22.06 [11.05, 33.08]	<.001
Number of stents (mean ± *SD*, *N*)	4.33 ± 1.85 (126)	3.57 ± 1.91 (281)	0.77 [0.37, 1.17]	<.001
Per lesion				
Total stent length (mean ± *SD*, *N*)	38.80 ± 23.32 (355)	34.73 ± 22.45 (696)	4.07 [1.16, 6.98]	.006
Number of stents (mean ± *SD*, *N*)	1.54 ± 0.76 (355)	1.43 ± 0.75 (696)	0.10 [0.01, 0.20]	.035
Per segment				
Total stent length (mean ± *SD*, *N*)	35.41 ± 21.21 (389)	34.68 ± 22.39 (697)	0.73 [−2.00, 3.46]	.60
Number of stents (mean ± *SD*, *N*)	1.40 ± 0.66 (389)	1.43 ± 0.75 (697)	−0.03 [−0.12, 0.06]	.52
Per stent				
Mode of stenting				.001
Direct stenting	8.8% (48/546)	14.5% (145/998)	−5.7% [−9.0%, −2.5%]	
Predilatation	91.2% (498/546)	85.5% (853/998)	5.7% [2.5%, 9.0%]	
Stent length (mm; mean ± *SD*, *N*)	25.23 ± 9.28 (546)	24.22 ± 9.13 (998)	1.01 [0.05, 1.97]	.039
IVUS postprocedural information (per stent)				
Postdilation done based on IVUS findings	46.0% (154/335)	36.8% (269/731)	9.2% [2.8%, 15.6%]	.004
Malapposition present	6.0% (20/334)	6.3% (46/731)	−0.3% [−3.4%, 2.8%]	.85
Minimum stent area (mm^2; mean ± *SD*, *N*)	6.16 ± 2.33 (315)	6.21 ± 2.31 (680)	−0.05 [−0.36, 0.26]	.75
Medina type for treated bifurcations only (visual assessment)				
1,1,1	37.2% (54/145)	(0/0)		
1,1,0	20.0% (29/145)	(0/0)		
1,0,1	5.5% (8/145)	(0/0)		
0,1,1	9.0% (13/145)	(0/0)		
1,0,0	4.1% (6/145)	(0/0)		
0,1,0	14.5% (21/145)	(0/0)		
0,0,1	9.7% (14/145)	(0/0)		
Staged procedure	15% (19/126)	32% (89/281)		<.001

Treating bifurcation was historically prone to worst prognosis following PCI.[16] For instance, bifurcation lesion is one of the criteria that increases the anatomical SYNTAX score—a tool that shows the coronary complexity and that is recommended by Guidelines for decision making on the most appropriate treatment strategy (PCI or CABG).[17]

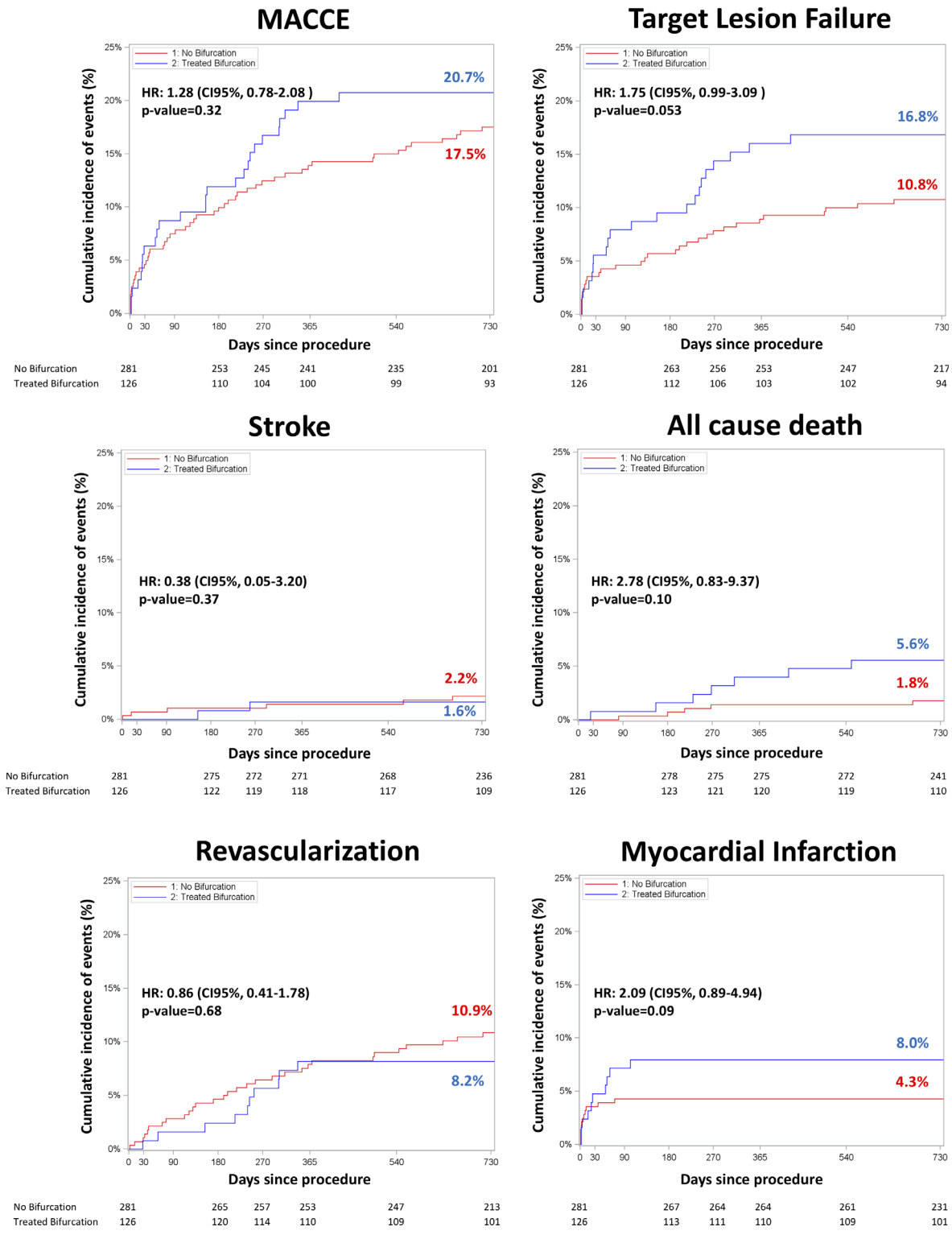

FIGURE 3 Time-to-first event curves for the primary composite endpoint of all-cause death, any stroke, any myocardial infarction or any revascularization (MACCE); target lesion failure, and the individual nonhierarchical components of the primary endpoint according to the treatment of bifurcation in the three-vessel disease patients of SYNTAX II [Color figure can be viewed at wileyonlinelibrary.com]

With the development and spread use of the second generation thin strut drug eluting stents, with better flexibility, conformability and deliverability, it is thought that PCI in complex scenarios, such as in bifurcation lesions and three-vessel disease, would have improved outcomes.[18] In addition, the use of intravascular imaging guidance, such as IVUS is proven to decrease long-term mortality and also stent thrombosis after bifurcation treatment with drug eluting stents.[19] Therefore, it would be reasonable to assume that the

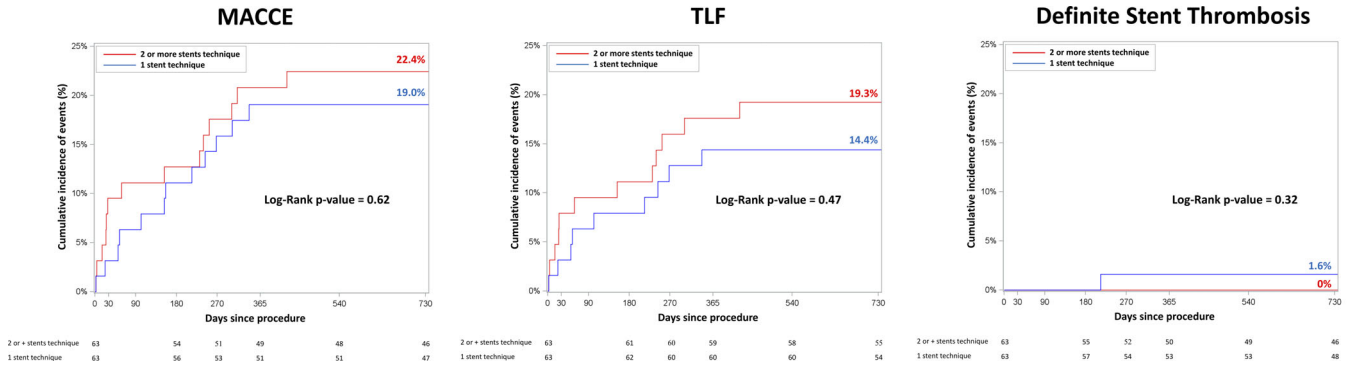

FIGURE 4 Time-to-first event curves for the composite endpoint of MACCE, target lesion failure and definite stent thrombosis according to the treatment strategy of bifurcation (two or more stents vs. one-stent technique) [Color figure can be viewed at wileyonlinelibrary.com]

combination of these techniques in complex three-vessel disease patients would result in better clinical outcomes following PCI for bifurcation.

The 5-years follow-up of the LEADERS all-comers randomized trial, showed a higher composite endpoint of cardiac death, MI, and clinically indicated target vessel revascularization in patients with at least one bifurcation lesion, compared with those without bifurcation.[16] In a sub-analysis of patients receiving both zotarolimus and everolimus eluting stents in the RESOLUTE all-comers trial,[20] comparing PCI for bifurcation lesions versus nonbifurcation lesions, the investigators found no difference between the groups with regards to cardiac death, TLF, major adverse cardiac events, TLR and definite or probable stent thrombosis. The results of this sub-analysis of the RESOLUTE trial are in keeping with our findings; however, even though the follow-up was the same as in SYNTAX II, some differences must be acknowledged. In SYNTAX II there was higher anatomical complexity represented by a numerically higher SYNTAX score (21.5 vs. 18.7) and also less patients treated with a one-stent technique for bifurcation lesions (50% vs. 79.1% in RESOLUTE).

An upfront two-stent technique usually is preferred when both the side branch and the distal main vessel are severely diseased or when the angulation between these vessels is high enough to compromise the future access to the side branch. Regarding the comparison of one- versus planned two-stent technique, it has been consistently shown that provisional stenting results in better prognosis,[21,22] despite some specific publication showing otherwise.[23] Although the 5-years outcomes of the DK-Crush II trial showed improvement in TLR with the two-stent technique, some differences from our report must be noted. First, SYNTAX II patients are three-vessel diseased, thus with higher risk; second, the two-stent technique in the present report comprised all the available techniques, not only one protocoled approach, like in DK-Crush. Also, follow-up in the present analysis is shorter—2 years. Our results show no statistical difference between one- versus two-stent technique with regards to MACCE, TLF, or definite stent thrombosis; despite some visual separation of the Kaplan–Meier curves in favor of one-stent technique. Nevertheless, one should bear in mind that this analysis is underpowered, not allowing a definitive conclusion.

4.1 | Limitations

Some limitations to our analysis must be acknowledged. First, this is a posthoc analysis, thus presenting inherent limitations. Decision on performing bifurcation treatment technique was left to the discretion of the operators following protocoled approach and were therefore not randomized; unmeasured confounders might have played a role on the outcomes. The relative small sample size might be considered a limitation; however, with the state-of-the-art approach in three-vessel disease patients, the number of patients involved is considerable. The results of the present analysis should thus be considered hypothesis-generating, and describe associations but not causality.

5 | CONCLUSION

In our substudy, bifurcation treatment in patients with three-vessel disease undergoing state-of-the-art PCI had similar event rates of MACCE but was associated with a trend toward higher incidence of TLF compared with nonbifurcation lesions. This is a substudy, thus not powered for the current analysis. The findings must be interpreted as exploratory and hypothesis generating.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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