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A Randomized Trial of a Dedicated Bifurcation Stent Versus Provisional Stenting in the Treatment of Coronary Bifurcation Lesions

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ABSTRACT

BACKGROUND Bifurcation lesions are frequent among patients with symptomatic coronary disease treated by percutaneous coronary intervention. Current evidence recommends a conservative (provisional) approach when treating the side branch (SB).

OBJECTIVES The TRYTON (Prospective, Single Blind, Randomized Controlled Study to Evaluate the Safety & Effectiveness of the Tryton Side Branch Stent Used With DES in Treatment of de Novo Bifurcation Lesions in the Main Branch & Side Branch in Native Coronaries) bifurcation trial sought to compare treatment of de novo true bifurcation lesions using a dedicated bifurcation stent or SB balloon angioplasty.

METHODS We randomly assigned patients with true bifurcation lesions to a main vessel stent plus provisional stenting or the bifurcation stent. The primary endpoint (powered for noninferiority) was target vessel failure (TVF) (cardiac death, target vessel myocardial infarction, and target vessel revascularization). The secondary angiographic endpoint (powered for superiority) was in-segment percent diameter stenosis of the SB at 9 months.

RESULTS We randomized 704 patients with bifurcation coronary lesions at 58 centers (30 from Europe and 28 from the United States). At 9 months, TVF was 17.4% in the bifurcation stent group compared with 12.8% in the provisional group ($p = 0.11$), mainly because of a higher periprocedural myocardial infarction rate (13.6% vs. 10.1%, $p = 0.19$). The TVF difference of +4.6% (2-sided 95% confidence interval: −1.0 to 10.3; upper limit of the 1-sided 95% confidence interval: 10.3) was not within the pre-specified noninferiority margin of 5.5% ($p = 0.42$ for noninferiority). The SB in-segment diameter stenosis among the angiographic cohort was lower in the bifurcation stent group compared with the provisional group (31.6% vs. 38.6%, $p = 0.002$ for superiority), with no difference in binary restenosis rates (diameter stenosis ≥50%) at 9 months follow-up (22.6% vs. 26.8%, $p = 0.44$).

CONCLUSIONS Provisional stenting should remain the preferred strategy for treatment of non-left main true coronary bifurcation lesions. (Prospective, Single Blind, Randomized Controlled Study to Evaluate the Safety & Effectiveness of the Tryton Side Branch Stent Used With DES in Treatment of de Novo Bifurcation Lesions in the Main Branch & Side Branch in Native Coronaries [TRYTON]; NCT01258972) (J Am Coll Cardiol 2015;65:533–43) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CK = creatine kinase

DES = drug-eluting stent(s)

MB = main branch

MI = myocardial infarction

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

SB = side branch

TVF = target vessel failure

TVR = target vessel revascularization

Bifurcation lesions are frequent among patients presenting with symptomatic coronary disease and undergoing percutaneous coronary intervention (PCI), accounting for approximately 15% to 20% of the lesions treated by PCI (1). Despite major advancements in stent technology, bifurcation lesions are still challenging for interventional cardiologists and treatment is associated with increased periprocedural myocardial infarction (MI), stent thrombosis, long-term restenosis, and cost (2,3). Although many techniques and strategies have been proposed (4–10), the conservative (provisional) approach, where the main branch (MB) is treated first and the side branch (SB) is only treated if required, remains the current standard of therapy (2,3,11–14). However, enrollment bias, small sample sizes, heterogeneous PCI techniques, and the lack of rigorous endpoints have complicated definitive conclusions in prior studies. Recently, several small nonrandomized studies showed initial favorable outcomes for a dedicated bifurcation stent, a bare-metal stent designed to secure and treat the bifurcation SB (15–19). The TRYTON (Prospective, Single Blind, Randomized Controlled Study to Evaluate the Safety & Effectiveness of the Tryton Side Branch Stent Used With DES in Treatment of de Novo Bifurcation Lesions in the Main Branch & Side Branch in Native Coronaries) bifurcation trial was a prospective, multicenter, single-blind, randomized, controlled study evaluating the bifurcation stent compared with SB balloon angioplasty, with drug-eluting stents (DES) in the main vessel for the treatment of de novo true bifurcation lesions.

SEE PAGE 544

METHODS

PATIENT SELECTION. The TRYTON study enrolled patients with symptoms or objective evidence of ischemia due to a significant (≥50% narrowing by visual assessment) true bifurcation lesion (Medina classification 1,1,1; 1,0,1; or 0,1,1) (20) located in a de novo native coronary artery with an SB from ≥2.5 mm to ≤3.5 mm in diameter and an MB from ≥2.5 mm to ≤4.0 mm in diameter. Lesion length was ≤28 mm in the MB (treatable with a single stent) and ≤5 mm in the SB. The MB and SB (when required) were treated with DES commercially available in the United States.

Important exclusion criteria were as follows: ST-segment elevation MI within 72 h or non-ST-segment elevation MI within 7 days preceding the index procedure; left ventricular ejection fraction <30%; impaired renal function (serum creatinine >2.5 mg/dl or 221 μmol/l) or on dialysis; left main coronary artery disease (protected and unprotected); trifurcation lesions; total occlusion of the target vessel; severely calcified lesion(s); the presence of excessive tortuosity; and angiographic evidence of thrombus. The complete list of inclusion and exclusion criteria is provided in Online Table 1.

STUDY DEVICE AND PROCEDURE. The Tryton Side Branch Stent (Tryton Medical Inc., Durham, North

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Carolina) is a dedicated SB non-DES composed of a cobalt chromium alloy with 3 zones: an SB zone (5.5 to 6.5 mm) deployed within the SB; a transition zone (4.5 mm) at the SB ostium; and an MB zone (8 mm) (Online Figure 1).

The implantation technique involves lesion preparation (pre-dilation of MB and SB), placement of the bifurcation stent into the SB, and placement of a commercially available DES within the MB. Simultaneous or sequential final kissing balloon inflation is then performed. Patients randomized to the provisional PCI strategy underwent PCI per standard operator technique, with final kissing balloon post-dilation. For both groups, implantation of an unplanned additional stent inside the SB was allowed only in cases of Thrombolysis In Myocardial Infarction flow grade <3, dissection type B or greater, or residual stenosis >80%. Pre-procedure and post-procedure dual antiplatelet therapy were recommended to conform to the American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions joint guidelines for PCI (13).

STUDY DESIGN AND OVERSIGHT. The TRYTON trial was a prospective, multicenter, randomized, single-blind, controlled clinical trial. The overall study design is shown in **Figure 1**. After completion of the diagnostic angiogram and confirmation of subject eligibility, patients were randomly assigned with the use of a computer-generated scheme, blocked separately at each participating site, and stratified by MB drug-eluting use and clinical site. The institutional review board at each participating site approved the TRYTON trial, and all patients provided written informed consent. The sponsor (Tryton Medical, Inc.) and the members of the executive committee designed the trial. The sponsor funded the study and participated in site selection and management. Data collection and monitoring were performed by an independent third-party contract research organization. The executive committee met regularly in person to monitor all aspects of the conduct of the trial.

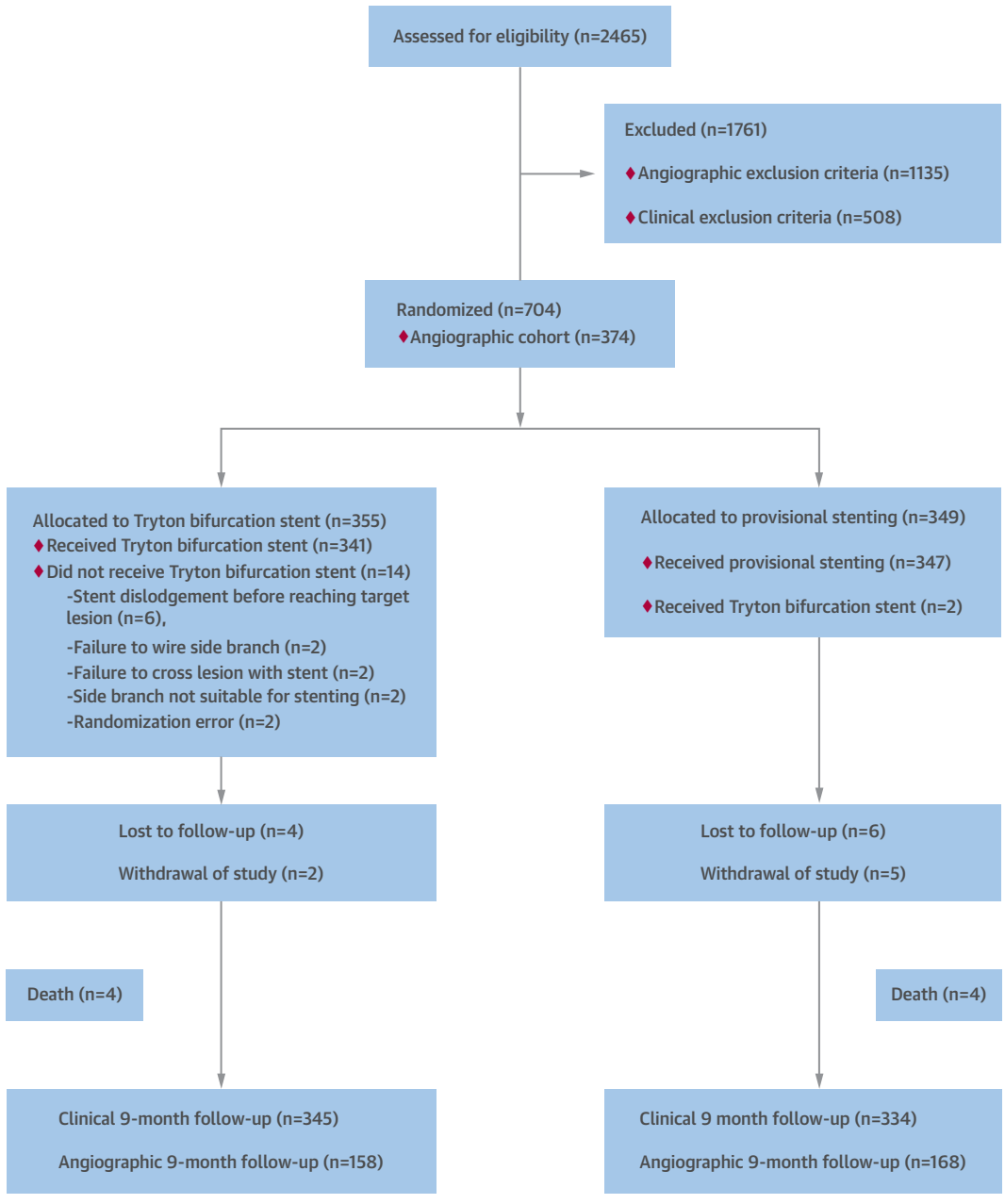
DATA MANAGEMENT. An independent clinical events committee adjudicated all serious adverse events (Harvard Cardiovascular Research Institute, Boston, Massachusetts). A data and safety monitoring board met frequently and had access to all study data and treatment assignments when requested. All data were sent for analysis to independent consulting biostatisticians. An independent angiographic core laboratory (Cardiovascular Research Foundation, New York, New York) analyzed all baseline, follow-up, and event angiograms. Online Table 2 lists the members of the committees, the institutions, and the research organizations participating in the TRYTON trial.

STUDY ENDPOINTS. The primary endpoint (powered for noninferiority) at 9-month follow-up was the rate of target vessel failure (TVF) defined as the composite of cardiac death, target vessel MI (Q-wave or non-Q-wave [3 × upper limit of normal creatine kinase {CK}-MB]), and clinically driven target vessel revascularization (TVR) in the MB or SB. The secondary angiographic endpoint (powered for superiority) was the SB in-segment percent diameter stenosis of the bifurcation stent compared with SB balloon angioplasty at the 9-month follow-up. Pre-specified additional clinical secondary endpoints included the following: the rates of device success (<30% residual stenosis within the SB), lesion success (<50% residual stenosis using any percutaneous method), and procedural success (lesion success without the occurrence of in-hospital major adverse cardiac events [death, MI, emergent coronary artery bypass graft, clinically driven target lesion revascularization]); the rate of all-cause and cardiac mortality; the rate of Academic Research Consortium-defined stent thrombosis (21); and the rate of target lesion revascularization. Important endpoints are specifically defined in Online Table 3. All patients were followed clinically during the index hospitalization, at 30 days, 6 months, 9 months, and then annually up to 5 years.

STATISTICAL ANALYSIS. For the primary endpoint, we estimated that with a sample of 664 patients, the study would have at least 81% power to show noninferiority of the bifurcation stent compared with the standard provisional approach, assuming the rate of TVF at 9 months would be 13% in the provisional group and 11% in the bifurcation stent group, with a margin for noninferiority of 5.5% and using a 1-sided binomial test of proportions with a significance level of $\alpha = 0.025$. The number was increased to 704 patients to account for an expected 6% loss to follow-up.

For the secondary angiographic endpoint, we estimated that with a sample of 318 patients, the study would have at least 90% power to show the superiority of the bifurcation stent compared with the standard provisional approach, assuming that 9-month in-segment SB percent diameter stenosis would be reduced by 8% (from 31% in the provisional treatment group to 23% in the bifurcation stent group), assuming an SD of 22% in both arms and using a 2-sided t test with a significance level of $\alpha = 0.05$. This number was increased to 374 patients (187 per arm) to account for an expected 15% loss to

FIGURE 1 Patient Flow Chart and Enrollment



Intention-to-treat population. Clinical follow-up at 9 months was 97%, and angiographic follow-up (pre-specified cohort) at 9 months was 87%.

angiographic follow-up. An exploratory post-hoc analysis was performed to evaluate the presence of a significant interaction between the primary endpoint and its components and the vessel diameter of the SB at baseline. Categoric variables were compared using the Fisher exact test. Continuous variables, which are presented as mean ± SD, were compared using the Student *t* test. All analyses were performed with data from the intention-to-treat population, which included all patients who underwent randomization regardless of the treatment actually received. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data using Kaplan-Meier estimates and compared using the log-rank test. A 2-sided alpha level of 0.05 was used for all superiority testing. All

statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

PATIENTS AND ENROLLMENT. Between December 17, 2010, and November 20, 2012, a total of 704 patients with angina and/or ischemia involving a true coronary bifurcation lesion were enrolled at 58 sites (30 in Europe and 28 in the United States) and were randomly assigned to the provisional strategy (n = 349) or the bifurcation stent strategy (n = 355). All patients were followed for at least 9 months (median follow-up period, 366 days; range 4 to 840 days). Clinical and angiographic (pre-specified angiographic cohort) follow-up was obtained in 97% and 87% of patients, respectively (**Figure 1**). The baseline characteristics of the patients in the 2 groups were generally well balanced (**Table 1**). True bifurcation lesions, which were visually assessed by site operators as ≥50% diameter stenosis in both the SB and either the proximal or distal MB (Medina classification 1,1,1; 1,0,1; and 0,1,1), were present in all but 3 patients (0.4%; 2 in the bifurcation stent group and 1 in the provisional group) (Online Figure 2A), with no difference between groups in the type of bifurcation.

When assessed by the angiographic core laboratory, true bifurcations at randomization were present in 88.1% of the entire cohort (bifurcation stent group: 89.9%, provisional group: 86.2%) (Online Figure 2B), with no difference between groups in the type of bifurcation. Among the entire cohort, bifurcation lesions involved the left descending artery and diagonal branches in 75.8% of cases; the left circumflex, marginal, or ramus branches in 18.2% of cases; and the right coronary artery in 6.0% of cases, with no difference between groups. On angiography, no major differences were seen in the MB lesions between both groups; however, lesions in the SB from the bifurcation stent group were, on average, slightly more severe (diameter stenosis 58.0% vs. 54.0%, $p < 0.001$) and longer (4.8 vs. 4.4 mm, $p < 0.001$) (**Table 2**).

PROCEDURAL OUTCOMES. Of the 355 patients assigned to the bifurcation stent group, 341 (96.1%) received the study stent in the SB. Reasons for the bifurcation stent not being implanted were the following: stent dislodgment of balloon before reaching target lesion (n = 6); failure of the coronary wire to cross the target lesion (n = 2); failure of the stent to cross the target lesion (n = 2); SB not suitable for stenting (occlusive dissection with wire and SB deemed too small for stenting) (n = 2); and randomization error (n = 2). No patients died during or within 30 days of the procedure in either group. Nontarget lesions (other than the index bifurcation lesion) were treated in 43 patients (12.1%) and 59 patients (16.9%) in the bifurcation stent and provisional groups, respectively. Additional stents in the SB for bailout situations (dissection type B or greater, Thrombolysis In Myocardial Infarction flow grade <3, or residual stenosis >80%) were more frequent in the provisional

TABLE 1 Baseline Clinical Characteristics of Randomized Patients

	Tryton Stent (N = 355)	Provisional (N = 349)	p Value
Age, yrs	64.5 ± 10.6	64.6 ± 9.4	0.92
Male	255/355 (71.8)	256/349 (73.4)	0.67
Smoking history			0.62
Current smoker	62/355 (17.5)	53/348 (15.2)	
Former smoker	123/355 (34.6)	125/348 (35.9)	
Never	170/355 (47.9)	170/348 (48.9)	
Diabetes mellitus	85/355 (23.9)	98/349 (28.1)	0.23
Hypertension	260/355 (73.2)	256/348 (73.6)	0.93
Hyperlipidemia	260/351 (74.1)	266/344 (77.3)	0.33
Family history of premature CAD	114/309 (36.9)	101/311 (32.5)	0.27
Prior MI	105/350 (30.0)	131/347 (37.8)	0.03
Prior PCI	135/355 (38.0)	146/349 (41.8)	0.32
Prior CABG	9/353 (2.5)	7/349 (2.0)	0.80
History of congestive heart failure	6/355 (1.7)	3/349 (0.9)	0.51
Prior stroke	8/350 (2.3)	13/343 (3.8)	0.28
Prior transient ischemic attack	10/351 (2.8)	8/346 (2.3)	0.81
Renal insufficiency on dialysis	0/355 (0.0)	1/348 (0.3%)	0.49
Atrial fibrillation	38/354 (10.7)	24/348 (6.9)	0.08
Mean left ventricular ejection fraction, %	57.7 ± 9.6	57.5 ± 9.9	0.81
Clinical presentation			0.94
Stable angina	262/355 (73.8)	261/349 (74.8)	
ACS-UA	71/355 (20.0)	69/349 (19.8)	
Silent ischemia	20/355 (5.6)	18/349 (5.2)	
No angina	2/355 (0.6)	1/349 (0.3)	
Functional test showing ischemia	126/201 (62.7)	117/185 (63.2)	0.92
Access site			0.60
Femoral	231/355 (65.1)	225/349 (64.5)	
Radial	123/355 (34.6)	124/349 (35.5)	
Other	1/355 (0.3)	0/349 (0.0)	
Number of vessels with ≥50% stenosis*			0.12
1-vessel disease	239/355 (67.3)	217/349 (62.2)	
2-vessel disease	98/355 (27.6)	105/349 (30.1)	
3-vessel disease	18/355 (5.1)	27/349 (7.7)	
Medina classification (site reported)*			0.51
1,1,1	260/355 (73.2)	239/348 (68.7)	
1,0,1	41/355 (11.5)	43/348 (12.4)	
0,1,1	52/355 (14.6)	65/348 (18.7)	
1,1,0 or 1,0,0 or 0,1,0 or 0,0,1†	2/355 (0.6)	1/348 (0.3)	
Antiplatelet therapy pre-loading before index procedure	298/355 (83.9)	299/349 (85.7)	0.53

Values are mean ± SD or n/N (%). *Site reported. †Not true bifurcation.

ACS-UA = acute coronary syndrome-unstable angina; CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 2 Quantitative and Qualitative Angiographic Findings at Baseline and After Procedure

	Tryton Stent (N = 355)	Provisional (N = 349)	p Value
Main branch			
Baseline			
Reference vessel diameter, mm	2.91 ± 0.36	2.91 ± 0.35	0.82
Minimal lumen diameter, mm	0.99 ± 0.37	1.01 ± 0.35	0.51
Diameter stenosis, %	66.16 ± 11.87	65.46 ± 11.10	0.42
Lesion length, mm	16.8 ± 7.3	16.0 ± 6.8	0.11
Thrombus	3/354 (0.8)	4/349 (1.1)	0.72
Tortuosity			0.007
Moderate	0/354 (0.0)	5/349 (1.4)	
Severe	0/354 (0.0)	2/349 (0.6)	
Calcification			0.04
Moderate	48/354 (13.6)	59/349 (16.9)	
Severe	10/354 (2.8)	19/349 (5.4)	
Post-procedure			
Reference vessel diameter, mm	2.99 ± 0.37	2.97 ± 0.36	0.70
In-segment minimal lumen diameter, mm	2.34 ± 0.37	2.36 ± 0.36	0.52
In-segment diameter stenosis, %	21.60 ± 7.82	20.61 ± 8.00	0.10
In-stent minimal lumen diameter, mm	2.71 ± 0.38	2.70 ± 0.34	0.79
In-stent diameter stenosis, %	9.33 ± 7.43	8.97 ± 7.54	0.53
In-segment acute gain, mm	1.41 ± 0.44	1.35 ± 0.45	0.27
In-stent acute gain, mm	1.76 ± 0.44	1.67 ± 0.39	0.058
Side branch			
Baseline			
Reference vessel diameter, mm	2.25 ± 0.30	2.21 ± 0.33	0.09
Minimal lumen diameter, mm	0.95 ± 0.34	1.02 ± 0.34	0.009
Diameter stenosis, %	58.00 ± 14.28	54.01 ± 14.46	<0.001
Lesion length, mm	4.8 ± 1.6	4.4 ± 1.1	<0.001
Thrombus	1/354 (0.3)	3/349 (0.9)	0.37
Tortuosity			0.15
Moderate	0/354 (0.0)	0/348 (0.0)	
Severe	0/354 (0.0)	2/348 (0.6)	
Calcification			0.81
Moderate	20/354 (5.6)	18/348 (5.0)	
Severe	4/354 (1.1)	7/348 (2.0)	
Angulation, °			0.009
0–45	293/354 (82.8)	258/348 (74.1)	
>45–90	44/354 (12.4)	74/348 (21.3)	
>90	17/354 (4.8)	16/348 (4.6)	
Post-procedure			
Reference vessel diameter, mm	2.31 ± 0.33	2.25 ± 0.33	0.008
In-segment minimal lumen diameter, mm	2.04 ± 0.37	1.56 ± 0.43	<0.001
In-segment diameter stenosis, %	11.98 ± 9.64	30.51 ± 17.19	<0.001
In-stent minimal lumen diameter, mm	2.36 ± 0.32	–	–
In-stent diameter stenosis, %	-2.21 ± 10.12	–	–
In-segment acute gain, mm	1.07 ± 0.42	0.57 ± 0.39	<0.001
In-stent acute gain, mm	1.38 ± 0.43	–	–

Values are mean ± SD or n/N (%).

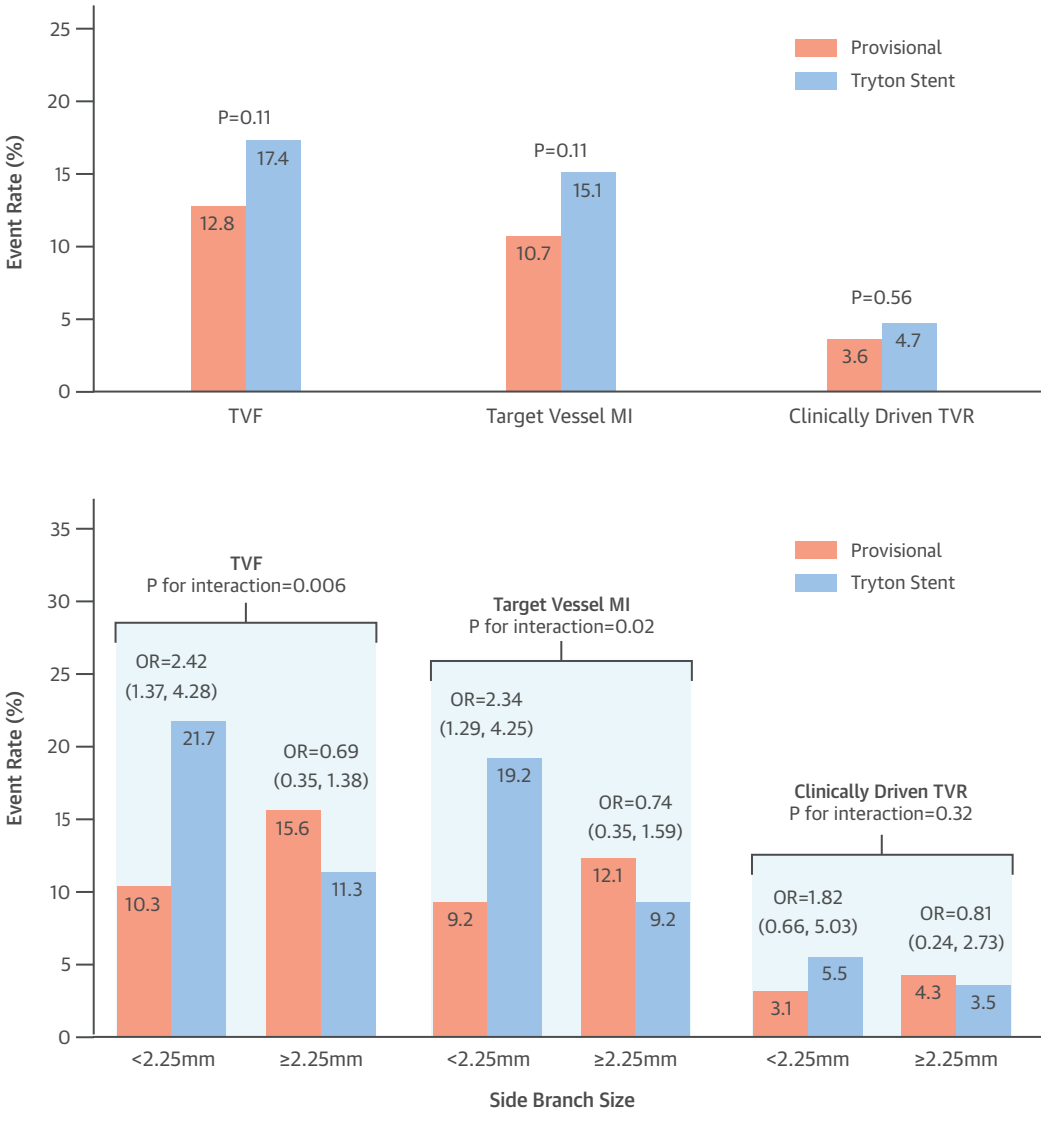
group (8.0%) than in the Tryton group (2.8%) (p = 0.02). There was no difference in final balloon post-dilation ("kissing") between both groups (bifurcation stent 86.2% vs. provisional 85.1%). On average, procedures were longer (70.5 ± 33.1 min vs. 56.9 ± 31.5 min; p < 0.001) and required more contrast (260.9 ± 105.5 ml vs. 223.3 ± 92.5 ml; p < 0.001) in the bifurcation stent group. No difference in acute renal failure was noticed between groups (bifurcation stent 0.6% vs. 0.3%). Online Table 4 shows other important procedural and devices characteristics.

No differences were seen between groups in the post-procedure angiographic results in the MB (Table 2). However, patients in the bifurcation stent group showed improved post-procedure angiographic results in the SB, with higher in-segment acute gain and in-segment minimal lumen diameter and lower residual stenosis compared with the provisional strategy. Lesion, procedure, and device success were achieved more frequently in the bifurcation stent group compared with the provisional group (100% vs. 88.1%, p < 0.001; 79.7% vs. 70.5%, p = 0.006; and 90.8% vs. 76.8%, p < 0.001, respectively).

CLINICAL OUTCOMES AT 9 MONTHS. At 9 months after randomization, TVF (the primary endpoint) was 17.4% in the Tryton group compared with 12.8% in the provisional group (p = 0.11). The difference of +4.6% (2-sided 95% confidence interval: −1.0 to 10.3; upper limit of the 1-sided 95% confidence interval: 10.3) was not within the pre-specified noninferiority margin of 5.5% (p = 0.42 for noninferiority). Rates of each component of the primary endpoint are shown in the Central Illustration. The difference in the primary endpoint was mainly due to a higher rate of periprocedural MIs (13.6% vs. 10.1%, p = 0.19) after bifurcation stent implantation. Among the 88 identified target vessel MIs, 81 (92%) were CK-MB elevation <10 × upper limit of normal. Rates of Academic Research Consortium-defined stent thrombosis (Tryton 0.6% vs. provisional 0.3%, p = 1.00 [all early stent thrombosis, between 1 and 30 days]) and death (Tryton 1.2% vs. provisional 1.2%, p = 1.00) were similar and low in both groups (Table 3). The occurrence of adverse events over the initial 9 months is shown in Online Figure 3. No significant interaction was detected in regard to the primary endpoint and whether the procedure was performed within or outside of the United States.

ANGIOGRAPHIC FINDINGS AT 9 MONTHS. At 9 months after randomization, the SB in-segment diameter stenosis (secondary powered endpoint) was lower in the bifurcation stent group compared with the provisional group (31.6% vs. 38.6%, p = 0.002 for superiority). No differences between groups were

CENTRAL ILLUSTRATION **Bifurcation Stent Compared With Provisional Stenting and the Impact of Side Branch Sizes on Clinical Outcomes**



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The primary endpoint (TVF) and its components (cardiac death [not shown because 0% in both groups], target vessel MI, and clinically driven TVR), stratified by SB sizes. A significant interaction was shown between treatment strategies and SB sizes (≥2.25 mm vs. <2.25 mm per QCA assessment) with respect to the occurrence of the primary endpoint of TVF (p for interaction = 0.006) and target vessel MI (p for interaction = 0.02). MI = myocardial infarction; OR = odds ratio; QCA = quantitative coronary angiography; SB = side branch; TVF = target vessel failure; TVR = target vessel revascularization.

seen in the rate of binary restenosis (diameter stenosis ≥50%) in the MB or SB at follow-up (Table 4).

SIDE BRANCH ANALYSIS. Table 5 and the Central Illustration show the rate of primary and secondary powered endpoints in patients with larger SBs (SB at baseline ≥2.25 mm by quantitative coronary angiography [QCA], equivalent to ~≥2.5 by visual estimate) compared with the patients with smaller SBs (<2.25 mm by QCA), a post-hoc non-pre-specified analysis. A significant interaction was shown between treatment strategies and SB sizes (≥2.25 mm vs. <2.25 mm) in the occurrence of TVF (p for

TABLE 3 Clinical Outcomes at 9 Months

	Tryton Stent (N = 355)	Provisional (N = 349)	p Value
TVF*	60/345 (17.4)	43/337 (12.8)	0.11
Death	4/347 (1.2)	4/337 (1.2)	1.00
Cardiac	0/343 (0.0)	0/333 (0.0)	–
Noncardiac	4/347 (1.2)	4/337 (1.2)	1.00
Target vessel MI	52/345 (15.1)	36/337 (10.7)	0.11
Q-wave	2/343 (0.6)	1/333 (0.3)	1.00
Non-Q-wave	50/345 (14.5)	34/337 (10.1)	0.08
Nontarget vessel MI	2/343 (0.6)	2/334 (0.6)	1.00
Q-wave	0/343 (0.0)	0/333 (0.0)	–
Non-Q-wave	2/343 (0.6)	2/334 (0.6)	1.00
Modified ARC MI	54/345 (15.7)	38/338 (11.2)	0.09
Periprocedural PCI	47/345 (13.6)	34/336 (10.1)	0.19
Peri-CABG	1/343 (0.3)	0/333 (0.0)	1.00
Spontaneous	7/343 (2.0)	5/335 (1.5)	0.77
Sudden death	0/343 (0.0)	0/333 (0.0)	–
Reinfarction	0/343 (0.0)	0/333 (0.0)	–
Q-wave MI†	2/343 (0.6)	1/333 (0.3)	1.00
Non-Q-wave MI†	52/345 (15.1)	36/338 (10.7)	0.09
TVR	19/344 (5.5)	13/335 (3.9)	0.37
Clinically driven TVR	16/343 (4.7)	12/334 (3.6)	0.56
Nonclinically driven TVR	4/344 (1.2)	2/334 (0.6)	0.69
MB	14/343 (4.1)	10/334 (3.0)	0.54
SB	9/343 (2.6)	5/334 (1.5)	0.42
Non-TVR	13/343 (3.8)	12/333 (3.6)	1.00
Target lesion revascularization	17/344 (4.9)	11/335 (3.3)	0.34
Clinically driven target lesion revascularization	14/343 (4.1)	10/334 (3.0)	0.54
Nonclinically driven target lesion revascularization	3/344 (0.9)	2/334 (0.6)	1.00
MB	12/343 (3.5)	8/334 (2.4)	0.50
SB	9/343 (2.6)	5/334 (1.5)	0.42
ARC-defined stent thrombosis (definite, probable)	2/343 (0.6)	1/334 (0.3)	1.00
MB	2/343 (0.6)	1/334 (0.3)	1.00
SB	2/343 (0.6)	0/333 (0.0)	0.50
MACE (death, MI, emergent CABG, clinically driven TLR)	65/349 (18.6)	45/340 (13.2)	0.06

Values are n/N (%). *Defined as cardiac death, target vessel MI, or clinically driven TVR. †Cumulative of target vessel, nontarget vessel, and undetermined vessel.

ARC = Academic Research Consortium; MACE = major adverse cardiac event(s); MB = main branch SB = side branch; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization; other abbreviations as in Table 1.

TABLE 4 Angiographic Follow-Up at 9 Months

	Tryton Stent (N = 158)	Provisional (N = 168)	p Value
Quantitative angiographic findings			
MB			
Reference vessel diameter, mm	2.95 ± 0.35	2.88 ± 0.32	0.05
In-segment minimal lumen diameter, mm	2.14 ± 0.56	2.13 ± 0.48	0.85
In-segment diameter stenosis, %	27.77 ± 15.87	26.02 ± 14.01	0.29
In-stent minimal lumen diameter, mm	2.47 ± 0.54	2.44 ± 0.43	0.58
In-stent diameter stenosis, %	16.47 ± 14.28	14.94 ± 12.75	0.31
SB			
Reference vessel diameter, mm	2.29 ± 0.29	2.24 ± 0.31	0.10
In-segment minimal lumen diameter, mm	1.56 ± 0.56	1.36 ± 0.38	<0.001
In-segment diameter stenosis, %	31.57 ± 22.91	38.63 ± 16.16	0.002
In-stent minimal lumen diameter, mm	1.67 ± 0.62	–	–
In-stent diameter stenosis, %	26.72 ± 25.44	–	–
Binary restenosis			
MB			
In-segment	16/158 (10.1)	15/168 (8.9)	0.85
In-stent	7/158 (4.4)	3/167 (1.8)	0.21
SB			
In-segment	35/155 (22.6)	45/168 (26.8)	0.44
In-stent	31/152 (20.4)	–	–
MB or SB			
In-segment	44/156 (28.2)	56/168 (33.3)	0.34
In-stent	33/153 (21.6)	–	–

Values are mean ± SD or n/N (%).

Abbreviations as in Table 3.

interaction = 0.006) and target vessel MI (p for interaction = 0.02).

DISCUSSION

The main results of the TRYTON trial can be summarized as follows. 1) A bifurcation 2-stent strategy in true bifurcations compared with the standard 1-stent provisional strategy did not meet the noninferiority TVF endpoint, mainly because of more frequent small periprocedural MIs. 2) Bifurcation stent use was associated with a reduced stenosis of the SB compared with the provisional approach at 9-month follow-up. 3) Both strategies were safe, with low rates of stent thrombosis, cardiac death, and clinically driven revascularization. 4) There was a disparity between angiographic restenosis and clinically driven TVR for both arms, indicating that SB angiographic restenosis is uncommonly expressed clinically. 5) A post-hoc analysis of SB size identified a strong interaction in the occurrence of the primary endpoint (TVF), showing lack of benefit of the bifurcation 2-stent strategy in smaller SBs and potential benefit in larger SBs.

The present study demonstrates and confirms the safety of the provisional approach as the primary strategy when facing complex bifurcation lesions. The need for additional stenting for bailout situations with the provisional approach was relatively infrequent (8% for the provisional group vs. 2.9% for the bifurcation stent group). The bifurcation stent approach was also safe, with a high implantation

success rate (>96%) and no safety concerns (cardiac death, stent thrombosis) compared with the provisional approach.

Despite lower SB diameter stenosis in the bifurcation stent group compared with the provisional group (31.6% vs. 38.6%) at 9-month follow-up, no differences were seen related to the binary restenosis rate (defined as diameter stenosis of ≥50%; 22.6% vs. 26.8%), illustrating that most of the SB lesions at follow-up were <50% stenosis. Moreover, an important discrepancy between the angiographic rate of binary restenosis and the need for subsequent clinically driven revascularization (~4% of the entire cohort) highlights the clinical impression that moderate lesions in the SB ostium, especially when short (~4 to 5 mm in the current study), are rarely clinically significant. Physiological assessment of the SB (via fractional-flow reserve performed post-procedure) rather than anatomic assessment (angiography) would have potentially reduced this discrepancy and increased the correlation with clinical outcomes (22–24).

Small periprocedural CK-MB elevations (~90% <10 × UNL CK-MB elevation) occurred more frequently with a 2-stent strategy and dominated the primary clinical endpoint (TVF). These findings are consistent with the results of 2 recent meta-analyses, including all current randomized trials comparing the provisional approach with a 2-stent technique, showing no differences in terms of death, need for revascularization, or stent thrombosis between the 2 strategies, but an increase in periprocedural MIs (2,3). More aggressive lesion preparation, increased coronary instrumentation, especially in smaller SBs, and longer procedural times may explain these results. However, this increase in periprocedural MIs did not result in clinically significant adverse events, such as cardiac death and the need for revascularization. Likewise, favorable angiographic results of the bifurcation stent strategy in SB diameter stenosis at 9-month follow-up also did not result in clinical benefit. These findings illustrate the well-known discrepancy between angiography (diameter stenosis severity) and biologic (CK-MB and troponin elevation) surrogate endpoints compared with hard clinical endpoints in coronary angioplasty clinical trials, if a certain threshold level of the surrogates is not reached (25–29).

STUDY LIMITATIONS. The TRYTON bifurcation study has several limitations that should be acknowledged. Only 41% of the study population met the entry criteria for SB diameter size (≥2.25 mm per QCA, equivalent to ~≥2.5 per visual estimate). Although providing meaningful insights into the clinical relevance of treating SBs with a dedicated SB stent, the inclusion of ~60% of patients not meeting the inclusion criteria for SB diameter reduced our capacity to demonstrate the value of a dedicated bifurcation stent strategy in true bifurcations with SBs of significant size. The large SB findings in the post-hoc analysis are intriguing and hypothesis generating, and will require further investigation. Only short lesions (≤5 mm) of the SB were included in the TRYTON trial. The benefit of the bifurcation stent in SB lesions >5 mm, potentially facilitating the delivery of a second DES (or bioresorbable scaffold) in the SB, remains to be established. The current version of the bifurcation stent is a non-DES; a drug-eluting platform may have led to different results (30–34). The protocol-mandated selection criteria excluded important lesion subsets, such as bifurcation lesions involving the left main artery, where the use of a dedicated bifurcation stent approach, given the larger jeopardized myocardial mass, could be of greater benefit. Because bifurcation stent implantation was a relatively new procedure (especially in the United States) and relatively few patients were treated per site (United States, mean of 6.3 patients per site; Europe, mean of 16 patients per site), learning curve issues must be considered. This is compounded by the realization that optimal implantation technique is mandatory to achieve the full advantage of the bifurcation stent. Finally, the quantitative angiographic analyses for bifurcation lesions in this manuscript represent conventional

TABLE 5 Primary and Secondary Endpoints at 9 Months Stratified by Side Branch Size

	Tryton Stent	Provisional	p Value
Side branches <2.25 mm	N = 208	N = 205	
TVF*	44/203 (21.7)	20/195 (10.3)	0.002
Cardiac death	0/201 (0.0)	0/194 (0.0)	—
Target vessel MI	39/203 (19.2)	18/195 (9.2)	0.006
Clinically driven TVR	11/201 (5.5)	6/195 (3.1)	0.32
In-segment SB % diameter stenosis†	32.35 ± 23.26	36.79 ± 14.99	0.13
Side branches ≥2.25 mm	N = 146	N = 143	
TVF*	16/141 (11.3)	22/141 (15.6)	0.38
Cardiac death	0/141 (0.0)	0/139 (0.0)	—
Target vessel MI	13/141 (9.2)	17/141 (12.1)	0.56
Clinically driven TVR	5/141 (3.5)	6/139 (4.3)	0.77
In-segment SB % diameter stenosis‡	30.43 ± 22.53	40.61 ± 17.20	0.004

Values are n/N (%) or mean ± SD. Nonhierarchical intention-to-treat population. *TVF is defined as cardiac death, target vessel MI, or clinically driven TVR. †From the angiographic cohort: n = 94 for Tryton group and n = 87 for provisional group. ‡From the angiographic cohort: n = 64 for Tryton group and n = 81 for provisional group.

Abbreviations as in Tables 1 and 3.

single-vessel methodology, and newer bifurcation algorithms showed somewhat different results (35) (Online Table 5).

CONCLUSIONS

On the basis of failure to achieve the noninferiority primary clinical endpoint, provisional stenting should remain the preferred strategy in the treatment of non-left main true coronary bifurcation lesions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Symptomatic coronary stenosis frequently involves arterial branch points, and percutaneous interventions on these bifurcation lesions are associated with a relatively high risk of adverse events.

TRANSLATIONAL OUTLOOK: Future studies comparing dedicated bifurcation devices with other novel stent technologies (e.g., bioresorbable scaffolds) will better define optimum approaches to management of patients with bifurcation lesions undergoing percutaneous revascularization.

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