Original Studies

Outcomes of a Dedicated Stent in Coronary Bifurcations with Large Side Branches: A Subanalysis of the Randomized TRYTON Bifurcation Study

Philippe Généreux,[1,2,3] MD, Annapoorna Kini,[4] MD, Maciej Lesiak,[5] MD, Indulis Kumsars,[6] MD, Géza Fontos,[7] MD, Ton Slagboom,[8] MD, Imre Ungi,[9] MD, PhD, D. Christopher Metzger,[10] MD, Joanna J. Wykrzykowska,[11] MD, PhD, Pieter R. Stella,[12] MD, PhD, Antonio L. Bartorelli,[13] MD, William F. Fearon,[14] MD, Thierry Lefèvre,[15] MD, Robert L. Feldman,[16] MD, Giuseppe Tarantini,[17] MD, PhD, Nicolas Bettinger,[1,2] MD, Girma Minalu Ayele,[2] PhD, Laura LaSalle,[2] MPH, Dominic P. Francese,[2] MPH, Yoshinobu Onuma,[18] MD, PhD, Maik J. Grundeken,[11] MD, Hector M. Garcia-Garcia,[18] MD, PhD, Linda L. Laak,[19] BSN, Donald E. Cutlip,[20] MD, Aaron V. Kaplan,[19,21] MD, Patrick W. Serruys,[18] MD, PhD, and Martin B. Leon,[1,2*] MD

Objectives: To examine the benefit of the Tryton dedicated side branch (SB) stent compared with provisional stenting in the treatment of complex bifurcation lesions involving large SBs. Background: The TRYTON Trial was designed to evaluate the utility of a dedicated SB stent to treat true bifurcation lesions involving large (≥2.5 mm by visual estimation) SBs. Patient enrolled in the trial had smaller SB diameters than intended (59% SB ≤2.25 mm by Core Lab QCA). The TRYTON Trial did not meet its primary endpoint due to an increased rate of peri-procedural myocardial infarctions (MIs). Methods: The TRYTON Trial randomized 704 patients to the Tryton SB stent with main vessel DES versus provisional SB treatment with main vessel DES. The rates of the primary end point of target vessel failure and the secondary powered end point of angiographic percent diameter stenosis in the SB at 9 months were assessed and compared between the two treatment strategies among patients with a SB ≥2.25 mm diameter at

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[1]Columbia University Medical Center/NewYork Presbyterian Hospital, New York, New York
[2]Cardiovascular Research Foundation, New York, New York
[3]Hôpital Du Sacré-Coeur De Montréal, Université De Montréal, Montréal, Québec, Canada
[4]Mount Sinai Medical Center, New York, New York
[5]1st Department of Cardiology, University of Medical Sciences, Poznan, Poland
[6]Latvian Center of Cardiology, Paul Stradins Clinical University Hospital, Riga, Latvia
[7]Gottsegen Hungarian Institute of Cardiology, Budapest, Hungary
[8]Department of Cardiology, OLVG, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[9]2nd Department of Medicine and Cardiology Center Medical Faculty, Albert Szent-Györgyi Clinical Center, University of Szeged- Department of Cardiology, Szeged, Hungary
[10]Wellmont CVA Heart Institute, Kingsport, Tennessee
[11]Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands
[12]Department of Interventional Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands
[13]Centro Cardiologico Monzino, University of Milan, Milan, Italy
[14]Division of Cardiovascular Medicine, Stanford University Medical Center, Stanford, California
[15]Institut Cardiovasculaire Paris Sud, Hôpital Privé Jacques Cartier, Massy, France
[16]MediQuest Research Group, Ocala, Florida
[17]Azienda Ospedaliera Di Padova, Padova, Italy
[18]Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands
[19]Tryton Medical Inc., Durham, North Carolina
[20]Harvard Clinical Research Institute, Beth Israel Deaconess Medical Center, Boston, Massachusetts
[21]Dartmouth-Hitchcock Medical Center, New Hampshire, Lebanon

baseline determined by Core Lab QCA. Results: Among the 704 patients enrolled in the TRYTON Trial, 289 patients (143 provisional and 146 Tryton stent; 41% of entire cohort) had a SB ≥2.25 mm. The primary end point of TVF was numerically lower in the Tryton group compared with the provisional group (11.3% vs. 15.6%, *P* = 0.38), and was within the non-inferiority margin. No difference among the rates of clinically driven target vessel revascularization (3.5% vs. 4.3% *P* = 0.77) or cardiac death (0% both groups) were seen. In-segment percent diameter stenosis of the SB was significantly lower in the Tryton group compared with the provisional group (30.4% vs. 40.6%, *P* = 0.004). Conclusions: Analysis of the TRYTON Trial cohort of SB ≥2.25 mm supports the safety and efficacy of the Tryton SB stent compared with a provisional stenting strategy in the treatment of bifurcation lesions involving large SBs.

Key words: coronary bifurcation; PCI; coronary stent

INTRODUCTION

Coronary artery bifurcation lesions are frequent, accounting for 15%–20% of the lesions treated by percutaneous coronary intervention (PCI), and associated with a worse prognosis compared with non-bifurcation lesions [1,2]. Recently, many techniques and strategies have been developed to simplify and improve the outcomes when treating these complex lesions [3–13]. The results of most randomized trials support the use of a provisional (1-stent) strategy over a 2-stent strategy in the treatment of bifurcation lesions. Some have questioned the applicability of these studies in the treatment of lesions involving large side branches (SB) [14]. The TRYTON Trial was the first large, randomized, controlled trial to compare the Tryton Side Branch Stent (Tryton Medical Inc., Durham, North Carolina), a dedicated bifurcation bare metal stent designed to secure and treat the bifurcation SB, to SB balloon angioplasty only (provisional stenting) for the treatment of *de novo* true bifurcation lesions [14]. Despite a lower post-procedural and 9-month follow-up percent diameter stenosis (%DS) of the SB, the Tryton Side Branch Stent failed to meet the non-inferiority margins for the primary end point of target vessel failure (TVF; composite of cardiac death, myocardial infarction [MI], and target vessel [main or SB] revascularization). This was due primarily to an excess of small (>3× CK-MB elevation) peri-procedural MIs. One of the reasons for these results might have been the enrollment of a large proportion (59%) of patients with SBs less

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*Correspondence to: Martin B. Leon, MD; Columbia University Medical Center, New York-Presbyterian Hospital, 161 Fort Washington Ave., 6th Floor, New York, NY 10032. E-mail: ml2398@columbia.edu

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than 2.25 mm by quantitative coronary angiography (QCA), which is equivalent to approximately 2.5 mm by visual assessment, and are inappropriately small for a stent mounted on a 2.5 mm or larger balloon catheter (SB region). Therefore, we sought to study the impact of SB vessel diameter on these results.

METHODS

Patient Selection

The TRYTON Trial has been previously described in detail [14]. In brief, the TRYTON trial was designed to enroll patients with symptoms or objective evidence of ischemia due to a significant (≥50% narrowing) true bifurcation lesion (Medina classification 1,1,1; 1,0,1; or 0,1,1) [15] located in a *de novo* native coronary artery with a SB from ≥2.5 to ≤3.5 mm in diameter and a main branch (MB) from ≥2.5 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. Lesion evaluation was based on visual estimates of the baseline angiography. Important exclusion criteria were ST-segment elevation MI within 72 hr or non-ST-segment elevation MI within 7 days preceding the index procedure, left ventricular ejection fraction less than 30%, impaired renal function (serum creatinine >2.5 mg/dL or >221 μmol/L) or on dialysis, left main coronary artery disease (protected or unprotected), trifurcation lesions, a total occlusion of the target vessel, severely calcified lesion(s), the presence of excessive tortuosity, and angiographic evidence of thrombus.

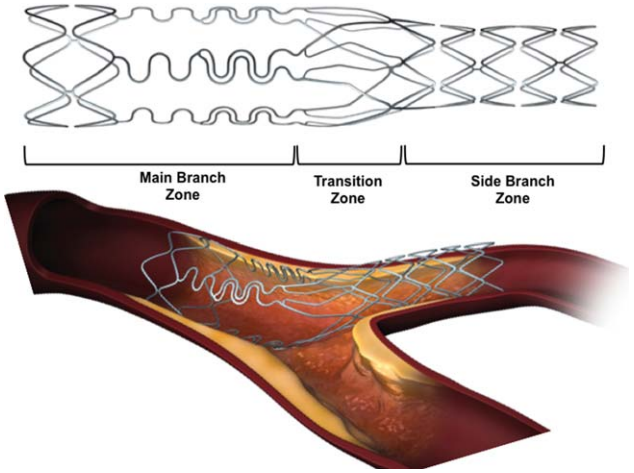

Fig. 1. Tryton side branch stent. The Tryton Side Branch Stent consists of a non drug-eluting stent made of three zones: (1) side branch zone, (2) transition zone, and (3) main branch zone. The side branch zone is a typical slotted tube design for insertion into the side branch, the transition zone is composed of undulating struts designed to provide adequate radial strength and coverage throughout the carina, and the main branch zone has a minimal metal-to-artery ratio intended as an open path for a main branch stent which will further lock the Tryton Side Branch Stent in place. Tryton stent sizing available at the time of the study were (main branch/side branch) 2.5/2.5 mm, 3.0/2.5 mm, 3.5/2.5 mm, 3.5/3.0 mm, and 4.0/3.5 mm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Study Device and Procedure

The Tryton Side Branch Stent is a dedicated SB bare metal stent composed of a cobalt chromium alloy with three zones: a SB zone (5.5 to 6.5 mm) deployed within the SB, a transition zone (4.5 mm) at the SB ostium, and a MB zone (8 mm) (Fig. 1).

The implantation technique involves lesion preparation (SB pre-dilatation mandated, MB pre-dilation optional), placement of the Tryton Side Branch Stent into the SB, and placement of a drug-eluting stent commercially available in the United States within the MB. Simultaneous final kissing balloon inflation is then performed. Patients randomized to the provisional PCI strategy underwent PCI per standard operator technique (pre-dilation in MB or SB, as indicated), with final kissing balloon post-dilation after MB placement of a DES. For both groups, implantation of an unplanned additional stent inside the SB was allowed in cases of Thrombolysis in Myocardial Infarction (TIMI) flow less than 3, dissection type B or worse, or residual stenosis more than 80%. Pre- and post-procedure dual antiplatelet therapy was recommended to conform to the American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions joint guidelines for PCI [16].

Study Design and Oversight

The TRYTON Trial was a prospective, multicenter, randomized, single-blind, controlled clinical trial. After completion of the diagnostic angiogram and confirmation of subject eligibility, patients were randomly assigned using a computer-generated scheme, blocked separately at each participating site, and stratified by MB drug-eluting stent usage and clinical site. The TRYTON trial was approved by the institutional review board at each participating site, and all patients provided written informed consent.

All serious adverse events were adjudicated by an independent clinical events committee (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 (ACL) (Cardiovascular Research Foundation, New York, New York) analyzed all baseline, follow-up, and event angiograms utilizing conventional single-vessel algorithm analysis.

Study End Points

The primary end point (powered for non-inferiority) at 9-month follow-up was the rate of TVF, defined as the composite of cardiac death, target vessel MI (Q-wave or non-Q-wave [creatine kinase-MB 3× the upper limit of normal]), and clinically-driven target vessel revascularization in the MB or SB. The secondary angiographic end point (powered for superiority) was SB in-segment %DS of the Tryton Side Branch Stent compared with SB balloon angioplasty at 9-month follow-up. Pre-specified additional clinical secondary end points included the success rate of the device (<30% residual stenosis within the SB), lesion (<50% residual stenosis using any percutaneous method), and procedure (lesion success without the occurrence of in-hospital major adverse cardiac events [death, MI, emergent coronary artery bypass grafting, clinically-driven target lesion revascularization]), the rate of all-cause and cardiac mortality, the rate of Academic Research Consortium-defined stent thrombosis [17], and the rate of target lesion revascularization. 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

Categorical variables were compared using the Fisher exact test. Continuous variables, which are presented as mean ± standard deviation, 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. 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, Cary, North Carolina).

RESULTS

Patients and Enrollment

Among the 704 patients enrolled in the TRYTON trial, 289 patients (41.1%; 143 provisional and 146 Tryton Side Branch Stent) had an SB ≥2.25 mm by ACL QCA assessment and represented the "intended" population. The baseline characteristics of the patients in the two groups are shown in Table I. True bifurcation lesions as assessed by operators as ≥50% DS 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 two patients (0.7%), with no difference between groups in the type of bifurcation.

When assessed by the ACL, true bifurcations at randomization were present in only 87.5% of the entire

TABLE I. Baseline Clinical Characteristics Among Patients with Large Side Branches

Variable	Tryton stent ($N = 146$)	Provisional ($N = 143$)	*P* value
Age (years)	64.5 ± 10.7	65.2 ± 9.2	0.56
Men	116/146 (79.5%)	117/143 (81.8%)	0.66
Smoking history			0.83
Current smoker	25/146 (17.1%)	22/142 (15.5%)	
Ex-smoker	52/146 (35.6%)	52/142 (36.6%)	
Never	69/146 (47.3%)	68/142 (47.9%)	
Diabetes mellitus	37/146 (25.3%)	41/143 (28.7%)	0.60
Hypertension	100/146 (68.5%)	109/142 (76.8%)	0.15
Hyperlipidemia	104/144 (72.2%)	107/139 (77.0%)	0.41
Family history of premature CAD	51/135 (37.8%)	37/128 (28.9%)	0.15
Prior myocardial infarction	43/145 (29.7%)	57/141 (40.4%)	0.06
Prior PCI	54/146 (37.0%)	62/143 (43.4%)	0.28
Prior CABG	5/145 (3.4%)	5/143 (3.5%)	1.00
History of congestive heart failure	2/146 (1.4%)	0/143 (0.0%)	0.50
Prior stroke	4/146 (2.7%)	4/140 (2.9%)	1.00
Prior transient ischemic attack	9/146 (6.2%)	4/141 (2.8%)	0.26
Renal insufficiency on dialysis	0/146 (0.0%)	0/142 (0.0%)	–
Atrial fibrillation	18/146 (12.3%)	12/143 (8.4%)	0.34
Mean Left ventricular ejection fraction	57.1 ± 9.4	56.8 ± 10.7	0.82
Clinical presentation			0.32
Stable angina	108/146 (74.0%)	98/143 (68.5%)	
ACS-UA	28/146 (19.2%)	34/143 (23.8%)	
Silent ischemia	81/146 (5.5%)	11/143 (7.7%)	
No angina	2/146 (1.4%)	0/143 (0.0%)	
Functional test showing ischemia	50/81 (61.7%)	46/72 (63.9%)	0.87
Access site			0.52
Femoral	94/146 (64.4%)	88/143 (61.5%)	
Radial	51/146 (34.9%)	55/143 (38.5%)	
Other	1/146 (0.7%)	1/143 (0.7%)	
Number of vessel with ≥50% stenosis[a]			0.86
1 vessel disease	91/146 (62.3%)	90/143 (62.9%)	
2 vessels disease	47/146 (32.2%)	39/143 (27.3%)	
3 vessels disease	8/146 (5.5%)	14/143 (9.8%)	
Medina classification[a]			0.88
1,1,1	95/146 (65.1%)	94/143 (65.7%)	
1,0,1	26/146 (17.8%)	21/143 (14.7%)	
0,1,1	24/146 (16.4%)	27/143 (18.9%)	
1,1,0 or 1,0,0 or 0,1,0 or 0,0,1[b]	1/146 (0.7%)	1/143 (0.7%)	
Antiplatelet therapy pre-loading before index procedure	127/146 (87.0%)	119/143 (83.2%)	0.41

Values are (*n*/*N*) % or mean ± standard deviation. CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACS-UA, acute coronary syndrome-unstable angina.
[a]Site reported.
[b]Not true bifurcation.

TABLE II. Quantitative and Qualitative Angiographic Findings at Baseline and After Procedure

Variable	Tryton stent ($N = 146$)	Provisional ($N = 143$)	P value
Main Branch			
Baseline			
Reference vessel diameter (mm)	3.09 ± 0.35	3.06 ± 0.34	0.51
Minimal lumen diameter (mm)	1.12 ± 0.39	1.05 ± 0.38	0.16
Diameter stenosis (%)	63.82 ± 11.96	65.62 ± 11.52	0.19
Lesion length (mm)	16.14 ± 6.84	16.05 ± 6.53	0.91
Thrombus	0/146 (0.0%)	2/143 (1.4%)	0.24
Tortuosity			0.02
Moderate	0/146 (0.0%)	3/143 (2.1%)	
Severe	0/146 (0.0%)	2/143 (1.4%)	
Calcification			0.23
Moderate	17/146 (11.6%)	22/143 (15.4%)	
Severe	3/146 (2.1%)	5/143 (3.5%)	
Post-procedure			
Reference vessel diameter (mm)	3.16 ± 0.36	3.11 ± 0.35	0.21
In-segment minimal lumen diameter (mm)	2.50 ± 0.35	2.49 ± 0.36	0.72
In-segment diameter stenosis (%)	20.62 ± 7.29	19.82 ± 7.59	0.36
In-stent minimal lumen diameter (mm)	2.89 ± 0.38	2.82 ± 0.34	0.14
In-stent diameter stenosis (%)	8.53 ± 7.15	8.91 ± 7.18	0.66
In-segment acute gain (mm)	1.4 ± 0.5	1.4 ± 0.4	0.25
In-stent acute gain (mm)	1.8 ± 0.5	1.8 ± 0.4	0.97
Side Branch			
Baseline			
Reference vessel diameter (mm)	2.53 ± 0.23	2.52 ± 0.22	0.76
Minimal lumen diameter (mm)	1.06 ± 0.34	1.15 ± 0.35	0.03
Diameter stenosis (%)	58.13 ± 12.74	54.11 ± 14.34	0.01
Lesion length (mm)	4.80 ± 1.24	4.60 ± 0.86	0.11
Thrombus	0/146 (0.0%)	0/143 (0.0%)	–
Tortuosity			0.15
Moderate	0/146 (0.0%)	0/143 (0.0%)	
Severe	0/146 (0.0%)	2/143 (1.4%)	
Calcification			0.96
Moderate	7/146 (4.8%)	6/143 (4.2%)	
Severe	1/146 (0.7%)	2/143 (1.4%)	
Angulation (degrees)			0.008
0–45	128/146 (87.7%)	108/143 (75.5%)	
>45–90	16/146 (11.0%)	32/143 (22.4%)	
>90	2/146 (1.4%)	3/143 (2.1%)	
Post-procedure			
Reference vessel diameter (mm)	2.61 ± 0.26	2.54 ± 0.27	0.02
In-segment minimal lumen diameter (mm)	2.33 ± 0.27	1.74 ± 0.48	<0.001
In-segment diameter stenosis (%)	10.71 ± 6.82	30.89 ± 18.78	<0.001
In-stent minimal lumen diameter (mm)	2.59 ± 0.27	–	–
In-stent diameter stenosis (%)	0.57 ± 8.24	–	–
In-segment acute gain (mm)	1.3 ± 0.4	0.6 ± 0.5	<0.0001
In-stent acute gain (mm)	1.5 ± 0.4	–	–

Values are (n/N) % or mean ± standard deviation.

cohort (Tryton 88.4%, provisional 86.7%), with no difference between groups in the type of bifurcation. Among the entire cohort, bifurcation lesions involved the left anterior descending coronary artery and diagonal branches in 68.5% of the cases, the left circumflex, marginal, or ramus branches in 22.5%, and the right coronary artery in 9.0%, with no difference between groups. Angiographically, no major differences were seen in the MB lesions between both groups except for the presence of moderate or severe tortuosity, which was slightly more frequent in the provisional group (Table II). Regarding the SB, lesions in the Tryton group were slightly more severe (%DS, 58.13 ± 12.74 vs. 54.11 ± 14.34, $P = 0.01$) but less angulated ($P = 0.008$) (Table II).

Procedural Outcomes

Of the 146 patients assigned to the Tryton group, 142 (97.3%) received the study stent in the SB. Reasons for the Tryton stent not being implanted include: stent

TABLE III. Procedural and Devices Characteristic

Variable	Tryton stent ($N = 146$)	Provisional ($N = 143$)	P value
Pre-dilatation of the main vessel performed	129/144 (89.6%)	114/142 (80.3%)	0.03
Pre-dilatation of the side branch performed	139/146 (95.2%)	86/138 (62.3%)	<0.001
Final kissing balloon technique			
Attempted	134/146 (91.8%)	128/143 (89.5%)	0.55
Not attempted	7/146 (4.8%)	11/143 (7.7%)	0.34
Unsuccessful	5/146 (3.4%)	4/143 (2.8%)	1
Tryton stent successfully delivered	142/146 (97.3%)	1/143 (0.7%)	<0.001
2.5/2.5 × 19 mm	81/142 (5.6%)	–	
3.0/2.5 × 19 mm	40/142 (28.2%)	–	
3.5/2.5 × 19 mm	51/142 (35.9%)	1/1 (100.0%)	
3.5/3.0 × 18 mm	40/142 (28.2%)	–	
4.0/3.5 × 18 mm	3/142 (2.1%)	–	
Additional stent in side branch (bail-out stenting)	1/146 (0.7%)	8/143 (5.6%)	0.02
Main vessel-study stent			
Drug-eluting stent successfully deployed	144/146 (98.6%)	142/143 (99.3%)	0.57
Drug-eluting stent type			0.25
XIENCE (everolimus-eluting)	85/144 (59.0%)	76/142 (53.5%)	
PROMUS (everolimus-eluting	37/144 (25.7%)	51/142 (35.9%)	
Resolute Integrity (zotarolimus-eluting)	7/144 (4.9%)	5/142 (3.5%)	
Endeavor (zotarolimus-eluting)	5/144 (3.5%)	4/142 (2.8%)	
Sirolimus-eluting	10/144 (6.9%)	6/142 (4.2%)	
Non-target lesion treated	21/146 (14.4%)	23/143 (16.1%)	0.74
Additional non-study stent implanted[a]			0.36
0	109/146 (74.7%)	100/143 (69.9%)	
1	29/146 (19.9%)	33/143 (23.1%)	
2	6/146 (4.1%)	7/143 (4.9%)	
≥3	2/146 (1.4%)	3/143 (2.1%)	
Bare metal stent	3/47 (6.4%)	0/56 (0.0%)	0.09
Drug-eluting stent	44/47 (93.6%)	56/56 (100.0%)	
Adjunctive devices	3/146 (2.1%)	1/143 (0.7%)	0.62
Rotational atherectomy	0/3 (0.0%)	1/1 (100.0%)	0.25
Cutting or AngioSculpt balloon	0/3 (0.0%)	0/1 (0.0%)	-
Other	3/3 (100.0%)	0/1 (0.0%)	0.25
Procedure time (min)	68.7 ± 30.1	55.9 ± 27.3	<0.0001
Fluoroscopic time (min)	24.0 ± 13.8	18.6 ± 11.6	<0.0001
Contrast volume (mL)[b]	269.2 ± 98.3	227.9 ± 88.7	0.0003

Values are (n/N) % or mean ± standard deviation.

[a]Defined as additional stents used during the procedure, including non-target lesion.

[b]Cumulative contrast used during the index procedure, including diagnostic and intervention.

dislodgment during stent delivery ($n = 1$), severe dissection after patient underwent pre-dilatation, with SB not suitable for stenting ($n = 1$), failure to cross SB with guidewire ($n = 1$), and randomization error ($n = 1$). The four failures to implant TRYTON stent occurred among patients where procedures were performed via femoral access and native (no prior CABG) coronary disease. No patients died during or within 30 days of the procedure in either group. Non-target lesions were treated in 21 (14.4%) and 23 (16.1%) patients in the Tryton and provisional group, respectively. Lesion pre-dilatation of the MB (89.6% vs. 80.3%, $P = 0.03$) and the SB (95.2% vs. 62.3%, $P < 0.001$) were more frequent in the Tryton group compared with the provisional group. There was no difference in type of DES used in the MB between the groups. Additional stents in the SB for bail-out situations (dissection type B or worse, TIMI flow <3, or residual stenosis >80%) were more frequent in the provisional group than in the Tryton group (8 [5.6%] vs. 1 [0.7%], $P = 0.02$). There was no difference in final balloon post-dilation ("kissing") between the groups (Tryton 91.8% vs. provisional 89.5%). On average, procedures were longer (68.7 ± 30.1 min vs. 55.9 ± 27.3 min, $P < 0.0001$) and required more contrast (269.2 ± 98.3 mL vs. 227.9 ± 88.7 mL, $P = 0.0003$) in the Tryton group. Table III shows other important procedural and devices characteristics.

No differences were seen between groups in the post-procedure angiographic results in the MB (Table III); however, Tryton stent patients showed improved post-procedure angiographic results in the SB, with significantly higher in-segment acute gain and in-segment

minimal lumen diameter and lower residual stenosis compared with the provisional strategy (Table II). Lesion, procedure, and device success were achieved more frequently in the Tryton stent group compared with the provisional group (100% vs. 84.5%, $P < 0.001$, 97.9% vs. 83.1%, $P < 0.001$, and 92.2% vs. 46.5%, $P < 0.001$, respectively).

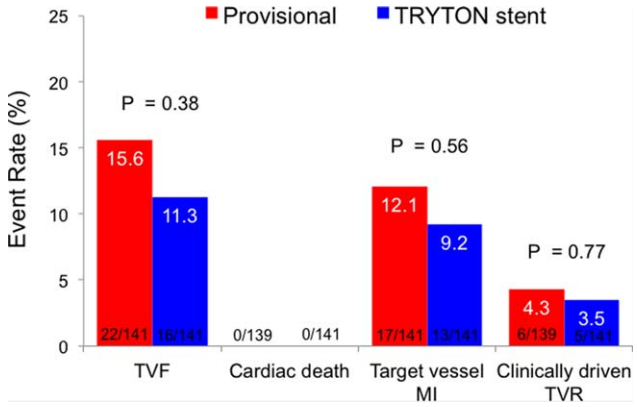

Fig. 2. Primary end point and its components. TVF, target vessel failure; TVR, target vessel revascularization; MI, myocardial infarction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Clinical Outcomes at 9 Months

At 9 months after randomization, TVF was 11.3% in the Tryton group compared with 15.6% in the provisional group ($P = 0.38$). The difference of −4.3% (2-sided 95% confidence interval [CI], −12.9 to 4.4; upper limit of the 1-sided 95% CI, 4.4%) was within the pre-specified non-inferiority margin of 6.5%, with a power of approximately 75% (see Supporting Information for further statistical information). Rates of each component of the primary end point are shown in Fig. 2. The numerically non-significant difference in the primary end point (TVF) seen in favor of the Tryton stent was mainly driven by numerically lower rates of target vessel MI (Tryton 9.2% vs. provisional 12.1%, $P = 0.56$), and to a lesser extent, clinically driven target vessel revascularization (Tryton 3.5% vs. provisional 4.3%, $P = 0.77$; Table IV and Fig. 2). There was no difference in rate of death (Tryton 1.4% vs. provisional 0.7%, $P = 1.00$), ARC-defined stent thrombosis (Tryton 0.7% vs. provisional 0.0%, $P = 1.00$) or clinically driven target lesion revascularization (Tryton 3.5% vs. provisional 2.9%, $P = 1.00$). Table V shows primary outcomes according to SBs diameter. Strong

TABLE IV. Clinical Outcomes at 9 Months

Variable	Tryton stent ($N = 146$)	Provisional ($N = 143$)	P value
Target vessel failure[a]	16/141 (11.3%)	22/141 (15.6%)	0.38
Death	2/143 (1.4%)	1/140 (0.7%)	1.00
Cardiac	0/141 (0.0%)	0/139 (0.0%)	–
Non-cardiac	2/143 (1.4%)	1/140 (0.7%)	1.00
Target vessel myocardial infarction	13/141 (9.2%)	17/141 (12.1%)	0.56
Q-wave	1/141 (0.7%)	0/139 (0.0%)	1.00
Non-Q-wave	12/141 (8.5%)	17/141 (12.1%)	0.43
Non-target-vessel myocardial infarction	0/141 (0.0%)	1/139 (0.7%)	0.50
Q-wave	0/141 (0.0%)	0/139 (0.0%)	–
Non-Q-wave	0/141 (0.0%)	1/139 (0.7%)	0.50
Modified ARC myocardial infarction	13/141 (9.2%)	18/141 (12.8%)	0.45
Peri-procedural percutaneous coronary intervention	12/141 (8.5%)	17/141 (12.1%)	0.43
Peri-CABG	1/141 (0.7%)	0/139 (0.0%)	1.00
Spontaneous	0/141 (0.0%)	1/139 (0.7%)	0.50
Sudden death	0/141 (0.0%)	0/139 (0.0%)	–
Re-infarction	0/141 (0.0%)	0/139 (0.0%)	–
Q-wave myocardial infarction[b]	1/141 (0.7%)	0/139 (0.3%)	1.00
Non-Q-wave myocardial infarction[b]	12/141 (8.5%)	18/141 (12.8%)	0.33
Clinically driven target vessel revascularization	5/141 (3.5%)	6/139 (4.3%)	0.77
Clinically driven target lesion revascularization	5/141 (3.5%)	4/139 (2.9%)	1.00
Main branch	4/141 (2.8%)	3/139 (2.2%)	1.00
Side branch	4/141 (2.8%)	2/139 (1.4%)	0.68
ARC-defined stent thrombosis (definite, probable)	1/146 (0.7%)	0/143 (0.0%)	1.00
Main branch	1/146 (0.7%)	0/143 (0.0%)	1.00
Side branch	1/146 (0.7%)	0/143 (0.0%)	1.00
MACE (death, MI, emergent CABG, clinically-driven TLR)	12/146 (8.2%)	17/143 (11.9%)	0.33

Values are (n/N) %. ARC, Academic Research Consortium; CABG, coronary artery bypass graft; MI, myocardial infarction; TLR, target lesion revascularization; MACE, major adverse cardiac events.

[a]Target vessel failure is defined as cardiac death, target vessel myocardial infarction, clinically driven target vessel revascularization.

[b]Cumulative of target vessel, non-target vessel, and undetermined vessel.

TABLE V. Clinical Primary End Points at 9 Months Stratified by Side Branch Size

Variable	Side branches <2.25 mm			Side branches ≥2.25 mm			
	Tryton stent ($N=208$)	Provisional ($N=205$)	P value	Tryton stent ($N=146$)	Provisional ($N=143$)	P value	P value interaction
Target vessel failure[a]	44/203 (21.7%)	20/195 (10.3%)	0.002	16/141 (11.3%)	22/141 (15.6%)	0.38	0.006
Cardiac death	0/201 (0.0%)	0/194 (0.0%)	–	0/141 (0.0%)	0/139 (0.0%)	–	–
Target vessel myocardial infarction	39/203 (19.2%)	18/195 (9.2%)	0.006	13/141 (9.2%)	17/141 (12.1%)	0.56	0.02
Clinically driven target vessel revascularization	11/201 (5.5%)	6/195 (3.1%)	0.32	5/141 (3.5%)	6/139 (4.3%)	0.77	0.32

Non-hierarchical intention to treat population.
Values are (n/N) %.
[a]Target vessel failure is defined as cardiac death, target vessel myocardial infarction, clinically-driven target vessel revascularization.

TABLE VI. Angiographic Follow-Up at 9 Months

Variable	Tryton stent ($N=146$)	Provisional ($N=143$)	P value
Quantitative angiographic findings			
Main branch			
Reference vessel diameter (mm)	3.13 ± 0.35	2.99 ± 0.32	0.01
In-segment minimal lumen diameter (mm)	2.32 ± 0.55	2.21 ± 0.50	0.20
In-segment diameter stenosis (%)	26.13 ± 14.24	26.28 ± 13.99	0.95
In-stent minimal lumen diameter (mm)	2.72 ± 0.43	2.53 ± 0.43	0.01
In-stent diameter stenosis (%)	13.09 ± 9.43	15.26 ± 12.22	0.23
Side branch			
Reference vessel diameter (mm)	2.51 ± 0.28	2.46 ± 0.27	0.31
In-segment minimal lumen diameter (mm)	1.74 ± 0.59	1.45 ± 0.42	0.001
In-segment diameter stenosis (%)	30.43 ± 22.53	40.61 ± 17.20	0.004
In-stent minimal lumen diameter (mm)	1.88 ± 0.65	–	–
In-stent diameter stenosis (%)	24.77 ± 24.91	–	–
Binary restenosis			
Main branch			
In-segment	6/64 (9.4%)	8/81 (9.9%)	1
In-stent	1/64 (1.6%)	2/81 (2.5%)	1
Side branch			
In-segment	14/63 (22.2%)	26/81 (32.1%)	0.26
In-stent	11/62 (17.7%)	–	–
Main branch or side branch			
In-segment	18/63 (28.6%)	31/81 (38.3%)	0.29
In-stent	11/62 (17.7%)	2/2 (100.0%)	0.04

Values are (n/N) % or mean ± standard deviation.

interactions were shown in regards of the occurrence of the primary end-point of TVF and peri-procedural MI.

Angiographic Findings at 9 Months

At 9 months after randomization, the SB in-segment DS% was lower in the Tryton group compared with the provisional group (30.4% vs. 40.6%, $P=0.004$), with no difference in rate of binary restenosis (22.2% vs. 32.1%, $P=0.26$). No differences between groups were seen in DS% and the rate of binary restenosis (DS ≥ 50%) in the MB at follow-up (Table VI).

DISCUSSION

The current report, drawn from the large pivotal TRYTON Trial, evaluated the safety and efficacy of the Tryton Side Branch Stent among patients undergoing PCI of bifurcation lesions involving a large SB (≥2.25 mm by ACL QCA assessment). The main findings of the current report are: (1) A Tryton 2-stent strategy in true bifurcation lesions compared with the standard 1-stent provisional strategy showed favorable results for the Tryton Side Branch Stent, with a numerically lower rate of TVF (primary end point), meeting the pre-specified non-inferiority margin in this

subgroup. (2) Tryton stent use was associated with reduced stenosis of the SB compared with the provisional approach at 9-month follow-up. (3) A Tryton strategy significantly reduced bail out stenting of the SB. (4) Both strategies were safe, with low rates of stent thrombosis and cardiac death. This post-hoc analysis supports the safety (non-inferiority) and efficacy of the Tryton Side Branch Stent among an appropriately selected population of patients with large SB bifurcation lesions.

The TRYTON Trial recently reported the failure of the Tryton Side Branch Stent to meet non-inferiority for the primary end point of TVF compared with provisional stenting [14]. This difference was mainly driven by an excess of small peri-procedural MIs, with no significant difference in cardiac death or clinically driven revascularization. More importantly, a strong interaction was demonstrated between SB size, PCI strategy, and the occurrence of TVF and MI (Table V) [14]. Indeed, the Tryton stent demonstrated favorable results among patients with a large SB and worse outcomes among patients with a small SB, leading to the conclusion that provisional stenting should be the strategy of choice for bifurcation lesions, when involving small SBs. The failure to enroll the intended population of large SBs ($\geq$2.5 mm by site operator visual assessment, equivalent to $\sim$2.25 mm by QCA) highlights the difficulty in conducting a rigorous large-scale randomized trial in coronary bifurcation disease. Moreover, the lower than expected SB size in the majority of patients precluded the demonstration of non-inferiority of the Tryton stent for the primary safety end point. The current report suggests that in the intended population, the Tryton Side Branch Stent would have met the non-inferiority end point compared with provisional stenting. On the basis of these findings, the TRYTON XA registry is currently enrolling an additional 133 patients with SB diameter $\geq$2.25 mm confirmed by ACL QCA (NCT01258972). This registry is intended to further validate the benefit of a dedicated bifurcation stent for true bifurcation lesions involving large SBs.

Notably, the rate of target vessel MI was numerically lower among the Tryton group compared with the provisional approach, which is the opposite of what was shown among the entire study population [14]. Indeed, among the entire cohort, and especially among the subgroup of patients with smaller SBs ($<$2.25 mm by QCA), the rate of MI (largely periprocedural MI) was higher in the Tryton group. This finding highlights the importance of selecting appropriately large SBs if peri-procedural complications are to be minimized. The inclusion of patients with SBs smaller than the prespecified reference vessel diameter was preferentially detrimental to the Tryton group. Patients assigned to the provisional arm with a SB reference vessel diameter less than 2.25 mm (by QCA) were treated with appropriately sized balloons (2.0 and 2.25 mm diameter). Patients assigned to the Tryton group with a SB reference vessel diameter less than 2.25 mm (by QCA) were treated with Tryton stent mounted on a 2.5 mm stent delivery balloon (SB region), which were inappropriately large for the SB treated. This led to increase overstretch in the Tryton group and may have contributed to the increase in peri-procedural creatine kinase-MB elevation and poorer long-term results. The Tryton SB stent was not provided on smaller balloons to avoid treatment of small SBs where bare metal stents are known to have higher rates of acute complications and poorer long-term outcomes. This finding may largely explain the interaction seen between SB size, PCI strategy, and the occurrence of MI (Table V), thereby driving the primary end point (TVF).

In the current cohort, the Tryton stent demonstrated a statistically significant lower SB %DS at 9 months compared with the provisional group (30.4% vs. 40.6%, $P = 0.004$), with no significant difference in the rate of binary restenosis (22.2% vs. 32.1%, $P = 0.26$). This finding is not surprising given the higher acute gain seen with the Tryton stent compared with the provisional approach (1.3 ± 0.4 mm vs. 0.6 ± 0.5 mm, $P < 0.0001$). Another reason for this finding may be that patients within the Tryton group underwent more aggressive lesion preparation (pre-dilation) of both the MB and the SB (Table III), potentially allowing for better stent expansion. That being said, no difference was seen in the rate of clinically driven revascularization (both target lesion and target vessel). Whether a drug-eluting version of the Tryton stent would result in lower restenosis compared with provisional stenting is unknown.

Importantly, the use of the Tryton stent in large SBs almost eliminated the need for additional SB "bail-out" stenting compared with the provisional approach (0.7% vs. 5.6%, $P = 0.02$). The reduction of bail out stenting has important implications in the treatment of bifurcation lesion involving large SB's, for example, LMCA-LCx, when a patient can become unstable with SB occlusion.

Notably, procedures were longer and required more contrast in the Tryton group compared with provisional stenting. This finding is not surprising since it compared a single stenting approach to a "2-stent technique" (Tryton) approach. While the aim of a dedicated bifurcation stent is to simplify bifurcation PCI and preserve SB patency, it would be interesting to compare the Tryton stent strategy to other complex 2-stent techniques such as crush, Double Kissing-crush, and standard culotte techniques.

This analysis of the TRYTON randomized trial has several limitations that should be acknowledged. First,

despite representing the initial intended population of the TRYTON trial, this sub-study was not specified in the statistical evaluation plan; therefore, it should be seen as hypothesis generating. This hypothesis will be further tested in the ongoing TRYTON XA registry (NCT01258972). Second, while it is widely accepted that visual assessment overestimates reference vessel diameter compared with QCA measurement, enrolling sites were not mandated to record their visual estimation of SB diameter at the time of PCI. This sub-analysis, therefore, represents a QCA extrapolation of what should be a visually assessed 2.5 mm SB. Third, only short lesions (<5 mm) with diameter stenosis more than 50% were allowed to be enrolled in the TRYTON trial, and whether these conclusions would remain valid with more diffuse or physiologically significant (fraction flow reserve-assessed) disease of the SB will require further investigation. Fourth, the quantitative angiographic analyses for bifurcation lesions in this manuscript represent conventional methodology using a single vessel analysis algorithm. The use of newer dedicated bifurcation algorithms, developed after the design and execution of the current trial, may yield somewhat different results regarding QCA findings [18,19]. Fifth, whether the use of dedicated bifurcation stents is cost-effective compared with the provisional approach or 2-stent strategies, especially in light of procedure time, contrast use, and other resource utilization remain to be seen. Finally, the current version of the Tryton stent is a bare metal stent; whether a drug-eluting version will increase the beneficial effect of the Tryton stent in large SBs remains to be demonstrated.

CONCLUSIONS

This analysis of the TRYTON Trial intended cohort supports the safety and efficacy of the Tryton SB stent compared with a provisional stenting strategy in treatment of bifurcation lesions involving significant SBs.

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