



Challenges and innovations in coronary bifurcation stenting: the Tryton™ side-branch stent

Percutaneous coronary intervention (PCI) for bifurcation lesions is challenging despite the use of many different techniques and strategies, and is a predictor of procedural, early and late adverse outcomes, even in this drug-eluting stent era. The current limitations of PCI for bifurcation lesions are due, in part, to the use of stents designed and refined for the treatment of lesions in straight coronary segments. This has led several groups to develop novel dedicated stents specifically designed to treat bifurcation lesions. Among them, the TrytonTM side-branch stent has several innovative features that provide complete stent coverage and uniform strut apposition at the bifurcation site with full expansion of the side-branch ostium. This device is a balloon-expandable cobalt-chromium thin-strut bare-metal stent that is designed to integrate with 'workhorse' drug-eluting stents. Early clinical data are very encouraging, showing very low rates of neointimal proliferation (late loss at the branch site = 0.17 mm) and target lesion revascularization (1%). Dedicated bifurcation PCI, improving acute and long-term outcomes.

KEYWORDS: coronary bifurcation lesion – coronary stenting – dedicated bifurcation stent – percutaneous coronary intervention

Over the past three decades, percutaneous coronary intervention (PCI) has evolved to become a cornerstone for the treatment of coronary artery disease, with outcomes that are competitive with coronary artery bypass graft (CABG) surgery. Treatment of bifurcation lesions has evolved as well, with the strategy of deployment of a conventional drug-eluting stent (DES) in the main vessel (MV) and provisional stenting of the side branch (SB) if necessary having clinically acceptable results in selected lesions [1-3]. Despite these advances, recent studies consistently show bifurcation lesions to be more difficult to treat and associated with higher early and late complications [3,4]. Current practice is restricted by the limitations of stents to definitively address the pathoanatomic features unique to bifurcation disease, in other words, to achieve the same strut coverage and radial strength that has proven efficacious in lesions located in straight coronary segments. In this article, we review the significant challenges associated with PCI treatment of this lesion subset and analyze the technical characteristics and clinical results of stents specifically designed for bifurcation lesion treatment with a detailed description of a promising novel device, the TrytonTM SB stent (Tryton Medical, Inc., NC, USA).

The challenge of coronary bifurcation lesions

The epicardial coronary arteries ramify into branches similar to a tree, thereby providing blood-flow distribution throughout the myocardium via a stepwise adaptation of vascular diameter down to the capillary level, where oxygen and nutrient exchanges take place [5]. Constant exposure to turbulent flow and altered shear stress has been shown to promote atherosclerotic plaque formation at coronary bifurcations [6–10], mainly opposite the SB [11,12]. This may explain why bifurcation disease is frequently encountered and accounts for approximately 15–20% of PCIs that are performed [13,14].

Since the early days of coronary angioplasty, bifurcation lesions have been recognized to pose a number of technical challenges and to engender an increased risk of complications, suboptimal angiographic results and restenosis [15–17]. For these reasons, lesions located at a bifurcation have been considered high risk for balloon angioplasty and when located in the distal left main coronary artery or proximal left anterior descending-diagonal coronary arteries, they were deemed more appropriate for CABG [18]. In the early 1990s, new debulking techniques, such as rotational and directional atherectomy, appeared likely to facilitate the

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Future

treatment of bifurcation lesions. Despite initial enthusiasm, the results achieved with these devices were disappointing [19]. The parallel introduction of coronary stents, and more recently of DES, revitalized this field. By reducing elastic recoil and effectively treating dissections, stents eliminated the risk of abrupt vessel closure, which represented a major limitation of balloon angioplasty, resulting in more predictable results and higher success rates. Conversely, long-term outcomes with bare-metal stents (BMS) were hampered by excessive neointimal hyperplasia and high rates of restenosis and target lesion revascularization (TLR) [20-22], particularly when treating bifurcation lesions using stents in both branches [23,24].

The introduction of DES with their associated reduction in restenosis and repeat revascularization rates has led to improved outcomes in the treatment of bifurcation lesions, mainly due to reduction in MV restenosis. The restenosis rate in the SB, however, remains unsatisfactory [4,25]. Furthermore, MV stent implantation may enhance carina displacement and atheroma shift across the SB ostium, leading to SB ostium narrowing ('snow-plough' effect) [26,27]. This has been associated with an increased risk of transient or permanent branch closure, even when no lesion was present at the SB ostium prior to stenting [15,28-31]. Other mechanisms that are generally held responsible for SB compromise include ostium dissection and spasm, inadequate stent strut coverage of the ostium and thrombus formation. Moreover, the chance of SB loss, which is a common cause of procedural myocardial infarction [16,32,33], has been shown to be dependent on SB size, ostium disease, balloon:artery ratio, acute SB take-off angle and the presence of thrombus in acute coronary syndromes.

To overcome these challenges, interventional cardiologists have introduced an impressive number of creative techniques to approach bifurcation lesions with stents originally designed for treating lesions located in straight coronary segments. These are dubbed with a variety of fanciful appellations, including 'T' and its variations, 'V', simultaneous kissing stents, 'Y', skirt, culotte, crush, reverse crush, DK crush and minicrush [34,35]. The choice of technique depends on lesion morphology including SB take-off angle and disease burden. However, these double stenting strategies have not been found to be superior to the traditional 'provisional' strategy of MV stenting with balloon dilatation of the SB. In fact, several studies with DES suggest that there is no advantage on restenosis and repeat revascularization rates with the universal use of two stents compared with single stent deployment [1-4,36]. Moreover, the former strategy has been associated with longer procedure and fluoroscopy times, more contrast administration, increased rate of myocardial enzyme elevation and a trend suggesting a higher risk of stent thrombosis [2]. A common feature of the two-DES technique is the localization of restenosis mainly at the SB ostium (FIGURE 1) [4]. The usual explanation for this finding is insufficient SB stent expansion and scaffolding as well as incomplete SB ostium coverage and deficiencies in drug application, particularly when T-stenting is used in bifurcations with a less than 90° angle between the two branches. Thus, despite the lack of a firm agreement on the standard treatment of bifurcation lesions, provisional stenting of the SB is generally recommended in clinical practice, that is, the SB is treated with a stent only when its flow is compromised or when balloon results are unsatisfactory.

Nevertheless, there is a large proportion of bifurcation lesions with angiographically apparent disease in both MV and SB ('true' bifurcation lesions) in which the risk of SB closure is felt to be unacceptably high as to merit a two-stent strategy (Box 1). Moreover, a significant number of complex cases undergoing provisional stenting may 'crossover' to a second stent to obtain an acceptable angiographic result [3,4,37]. This entails the risk of failure to reaccess the SB after MV stent placement. Indeed, when the SB is compromised by dissection or plaque shift, subsequent reaccess may be difficult, if not impossible (FIGURE 2).

Among alternate solutions to provisional stenting, the culotte and crush techniques have been proposed to ensure complete stent coverage of bifurcation lesions, a result that is rarely achieved with other approaches. Both techniques require high operator skill and balance the advantage of full lesion coverage with the disadvantage of a double or triple layer of stent overlap. The benefits of the two different techniques were recently evaluated in the Nordic II, a multicenter trial in which 424 patients were randomized to culotte versus crush stenting using the sirolimus-eluting stent [38]. Both strategies had similar procedure and fluoroscopy times and contrast usage. The culotte cohort tended to have fewer procedurerelated releases of myocardial injury biomarkers (culotte 8.8 vs crush 15.5%; p = 0.08). At 6 months, there was no difference in target vessel revascularization (TVR) rates. Angiography

performed at 8 months in 88% of patients demonstrated a 57% reduction in MV and/or SB in-stent restenosis for the culotte cohort when compared with the crush cohort (4.5 vs 10.5%; p = 0.046). The benefit observed in the culotte cohort was primarily caused by a reduction of SB in-stent restenosis when compared with the crush cohort (3.8 vs 9.8%; p = 0.04). Although there was a benefit observed for in-segment restenosis of MV plus SB, this did not reach statistical significance (culotte 6.6 vs crush 12.1%; p = 0.10). The impact of multiple stent overlap is poorly understood but results in increased polymer contact and exposure to drug with delayed re-endothelization, which has been associated with a higher risk of stent thrombosis. Refined techniques using high-pressure two-step inflation with noncompliant and aggressively sized kissing balloons have demonstrated improved outcomes when the culotte and crush techniques are used [39-41]. The postdilation strategies were developed to ensure full expansion of the MV and SB stents allowing for subsequent SB access. Indeed, an intravascular ultrasound (IVUS) study assessing the crush stenting technique with one-step kissing balloon postdilation found stent underexpansion at the SB ostium in more than 60% of cases [42]. Interestingly, this finding was unnoticed on angiography. Moreover, the SB reaccess crossing a multiple-stent layer with a guidewire and a balloon is often technically challenging, time-consuming and may require use of specialized guidewires, increasing the risk of SB dissection. In cases of recrossing failure, the inability to place balloons for the final kissing inflation leads to MV and SB stent underexpansion and strut malapposition [41], which have been associated with a higher rate of major adverse cardiac events (MACEs). This risk has been shown to be significantly increased in highangle bifurcations (≥50°) [43], probably owing to flow disturbances created by the association of the high bifurcation angle and multiple layers of malapposed stent struts. Modifications of the crush technique, such as minicrush and balloon-crush, have been shown to improve SB access [44-46]. The success of these techniques is highly dependent upon SB reaccess and final kissing balloon inflations. Moreover, if the guidewire crosses the crushed SB stent not at the ostium but eccentrically at some distance distal to the ostium, the result after kissing balloon inflation will be displacement of the SB stent away from the ostium wall with the opposite side left with multiple layers of inadequately apposed stent struts [44].



Figure 1. Serial single frame coronary angiograms (left anterior oblique cranial projection) of a left anterior descending-first diagonal bifurcation lesion. (A) Acute result following implantation of a 3.5×28 mm sirolimus-eluting stent in the mid left anterior descending coronary artery and of a 2.5×8 -mm sirolimus-eluting stent in the first diagonal branch with T-stenting technique (arrow). (B) At 6-month angiographic follow-up, restenosis occurred at the side-branch ostium (arrow).

Dedicated bifurcation stents

The need for dedicated bifurcation stents (DBS) stems from the limitations of techniques used in the DES era, including failure to maintain SB access, difficult rewiring and balloon or stent tracking into the SB, distortion of the MV stent by SB stent dilation and inability to fully cover, scaffold and expand the SB ostium. The main need for a DBS is to provide interventional cardiologists with the ability to stent bifurcation lesions is a manner similar to lesions located in straight coronary segments, in other words, a straightforward technique with reliable deployment achieving complete lesion coverage and scaffolding. Compared with conventional stents, the first DBS were bulky with a larger crossing profile and lower flexibility, and were difficult to deliver, particularly in tortuous and calcified vessels [47-49]. Furthermore, precise positioning at the carina site was tricky and their use was limited because they did not have the ability to treat the entire range of bifurcation angles.

Box 1. Coronary bifurcation lesions most appropriate for a two-stent strategy as an intention-to-treat approach.

- 'True' bifurcation lesion: both main vessel and side branch have more than 50% stenosis with large plaque burden (Medina: 1-1-1, 1-0-1 and 0-1-1)
- Large side branch: large diameter side branch perfusing a substantial myocardial territory
- Important side branch: a side branch that you do not want to lose in the global context of a patient (branch responsible for symptoms of ischemia, location of ischemia, viability, collateralizing vessel and left ventricular function)
- Diffusely diseased side branch: side branch with diffuse disease or long lesion, which extend more than 3 mm distal to the ostium
- Bifurcation with a take-off angle that would be difficult to rewire



Figure 2. Serial single frame coronary angiograms (right anterior oblique cranial projection) obtained in a 'low-risk' bifurcation lesion involving the mid left anterior descending coronary artery and second diagonal branch (Medina 0-1-0). (A) Baseline preprocedure angiogram. Note the acute take-off angle of and the guidewire positioned in the branch vessel (arrows). (B) Acute occlusion of the diagonal branch after implantation of a 3.0×15 -mm everolimus-eluting stent in the mid left anterior descending coronary artery despite the presence of a jailed guidewire (1). Several attempts to recross the occluded branch ostium with a hydrophilic guidewire (2) failed and the patient developed acute myocardial infarction.

Finally, they were associated with restenosis rates similar to those observed with BMS when they were used in bifurcations. More recently, newer DBS have been developed in an attempt to simplify bifurcation lesion treatment and improve procedural results and, more importantly, longterm outcomes while maintaining optimal safety [50]. They can be broadly divided into two

Balloon-expandable stents	Self-expanding stents				
SB stents					
Tryton™ side-branch stent (Tryton Medical, Inc., NC, USA)	Sideguard™ (Cappella Medical Devices Ltd, Ireland)				
MV stents					
SideKick™ (Y-med Inc., CA, US)	Stentys™ (Stentys SAS, Paris, France)				
Multi-Link Frontier™ (Abbott Vascular, CA, USA)	Axxess Plus™ (Devax Inc., CA, USA)				
Twin-Rail™ (Invatec, Italy)					
Nile Croco™ (Minvasys, France)					
SLK-View™ (Advanced Stent Technologies, Inc., CA, USA)					
Antares™ side-branch adaptive stent (Trireme Medical, CA, USA)					
Petal™ (Boston Scientific MA USA)					
MV: Main vessel; SB: Side branch.					

 Table 1. Current dedicated stents for the treatment of coronary

 bifurcation lesions.

main types: first, MV stents that support the SB ostium, maintaining access to the SB after MV stenting and do not require recrossing of the MV stent struts; and second, SB stents that require another stent implanted in the MV to complete the procedure and require recrossing of the MV stent struts. They can be subdivided further according to the stent deployment characteristics (balloon-expandable or self-expanding stents). TABLE 1 shows the DBS that are currently available in Europe or are under clinical investigation. Although the currently available DBS cannot challenge the results of the provisional stenting strategy in the majority of bifurcation lesions, they are ultimately likely to prevail.

One of the earliest and best characterized first generation dedicated SB stents is the Multi-Link Frontier[™] (Abbott Vascular, CA, USA). The Frontier is an 18-mm slotted tube stainless steel (316L) stent with a construction that draws from the Multi-Link design. The Frontier has a SB portal in its midportion. Proximal to the portal, the stent has six crests, while distal to the portal the stent has five crests. The Frontier stent is mounted on a specialized dual balloon-dual guidewire delivery system. The delivery system, which is compatible with 7-Fr guide catheters, is designed to rotate the stent so that the portal is aligned with the SB ostium and allows for deployment using simultaneous kissing balloon inflations. Lefèvre et al. reported the results of a multicenter series with 105 patients demonstrating successful implantation in 91% with a 17.1% MACEs rate at 6 months [47]. Angiographic follow-up demonstrated a MV and SB restenosis rate of 25.3 and 29.9%, respectively, with an overall rate of 44.8%. It is important to note that this generation of the Frontier employed a BMS platform, which highlights the importance of using drug-eluting platforms with this type of dedicated bifurcation stent. A next-generation Frontier stent is currently undergoing development using the Xience VTM (Abbott Vascular, CA, USA) everolimus-eluting stent platform.

The first drug-eluting DBS to be developed is the AxxessTM (Devax, Inc., CA, USA), which is a nitinol self-expanding stent with a bioerodable polymeric system that delivers Biolomus A9 to the lumen wall. The Axxess stent is deployed in the MV with the distal end extending into the carina. A standard DES can be delivered through the deployed Axxess stent to treat SB and distal MV disease. This system was studied in 302 patients with *de novo* coronary bifurcation lesions [51]. Additional stenting of one branch was performed in 21.7% of patients, while both branches were stented in 64.7% of the cases. A follow-up at 9 months, performed in 93.3% of patients, demonstrated a restenosis rate of 6.4% (MV 3.6% and SB 4.3%) and late loss of 0.20 \pm 0.41 mm and 0.17 \pm 0.34 mm in the MV and SB, respectively.

The StentysTM (Stentys SAS, France) is a self-expanding tubular paclitaxel-eluting stent with a unique design, which allows for strut disconnection with balloon dilation. The Stentys stent is placed across the SB origin and the SB is reaccessed with a guidewire. A balloon is then tracked through the stent wall and inflated, disconnecting the struts. This creates an opening for the SB providing for ostial coverage. The Stentys first-in-man (FIM) Coronary Bifurcation Stent System for the Percutaneous Treatment of de novo Lesions in Native Bifurcated Coronary Arteries (OPEN) I trial is a multicenter consecutive series that enrolled 40 patients with de novo coronary bifurcation lesions [52]. Procedural success was achieved in 95.5% of patients. Interestingly, disconnection of the stent mesh overlying the SB ostium was achieved in 94.9% of the cases and a third of the patients were treated with an additional stent placed in the SB using the T-stent approach. The MACEs rate at 30 days was 5.1% (one postprocedural non-Q-wave myocardial infarction and one ischemia-driven repeat PCI 6 days after the index procedure). These results indicate device feasibility, and longer follow-up data and randomized studies are currently planned to demonstrate long-term safety and efficacy.

The Cappella Sideguard[™] (Cappella Inc., MA, USA) is a nitinol self-expanding stent with a funnel-shaped flared proximal end. The Cappella stent is mounted on a sheathed balloon delivery system for precise delivery. After lesion preparation, the stent is positioned and deployed in the SB with the proximal end at the ostium. Precise deployment is facilitated by a uniquely designed sheathed balloon system and radio-opaque markers delineating the proximal stent edge. Following deployment, the sheathed delivery balloon and guidewire are removed. A 'workhorse' DES is then tracked in the MV across the stented SB origin and deployed. The SB is reaccessed and simultaneous kissing balloon inflations are then performed. The initial results using the Cappella stent were captured in the Sideguard I and II trials, which included 83 patients at nine European centers. Technical failures were reported in ten (11%) patients with MACE rates of 4.8 and 10.8% at 30 days and 6 months, respectively. At 6 months, ischemia-driven TVR was 3.6%.



Figure 3. Tryton[™] side-branch stent showing the three zones: distal (side-branch) zone, central (transition) zone and proximal (main-vessel) **zone.** When positioned correctly within the coronary bifurcation area, the side-branch zone resides in the side branch, the transition zone at the side-branch origin and the main-vessel zone in the main vessel proximal to the side-branch ostium.

Angiographic follow-up, performed in 73 (88%) patients demonstrated a late loss of 0.21 and 0.58 mm in the MV and SB, respectively [GRUBE E, TRANSCATHETER CARDIOVASCULAR THERAPEUTICS MEETING, CA, USA, SEPTEMBER 2009, PERS. COMM.].

The Taxus PetalTM is a DBS developed by Boston Scientific Corporation (MA, USA) using the Taxus paclitaxel-eluting stent platform made of platinum chromium. The main design feature is the SB 'petal element' that upon deployment provides circumferential ostium coverage extending 2 mm into the SB. The Taxus Petal stent is mounted on a specialized dual guidewire–balloon delivery system which is 8-Fr guide catheter compatible. The dual guidewire system is designed to maintain SB guidewire access and align the petal with the SB origin. In addition to a standard



Figure 4. Two Tryton[™] side-branch stent delivery systems. A straight balloon and a stepped balloon.

Box 2. Key features of the Tryton[™] side-branch stent.

- Deliverability equivalent to state-of-the-art 'workhorse' drug-eluting stent
- Balloon-expandable stent thin-strut cobalt–chromium slotted-tube stent
- Generous (4-mm) landing zone (positioning tolerance at the carina site) allowing easy positioning
- Single-wire tracking, no need for rotational orientation and no risk of wire wrapping
- No bifurcation angle limitation
- Not contingent on anatomic variations and lesion complexity
- Maintenance of side-branch access during the procedure without risk of side branch closure
- side-branch closure

straight balloon, the delivery system features a second 'gumdrop-shaped' balloon positioned under the petal portion of the stent. When deployed, the gumdrop-shaped balloon outwardly deploys the petal portion of the stent. In the FIM study, the Taxus Petal stent was successfully implanted in 25 out of 28 (89.3%) patients, reflecting a success rate of 73.5% (25/34) per device attempt [53]. The main reasons for failure to achieve correct rotational alignment were both guidewire wrap and bias and the oval cross-sectional shape of the device. At 6-month angiographic follow-up (n = 21), in-segment late loss was 0.47 ± 0.45 mm (proximal MV), 0.41 ± 0.57 mm (distal MV) and 0.18 ± 0.39 mm (SB). Through 1 year, TVR was 11.1%, TLR 7.4% and there were no deaths, Q-wave myocardial infarctions or stent thromboses.

Tryton[™] side-branch stent ■ Stent design

The Tryton side-branch stent is a slotted-tube balloon-expandable cobalt-chromium BMS designed specifically to treat bifurcation lesions [54]. This device has a modular design characterized by three zones (Figure 3):

- A distal SB zone;
- A central transition zone;
- A proximal MV zone.

The distal SB zone has the design characteristics of a standard slotted-tube 'workhorse' stent, while the central transition zone has a specific geometry composed of three panels, each of which can be deformed in an independent fashion. The design of the central transition zone provides complete coverage and scaffolding of the SB ostium and can accommodate the full spectrum of the pathoanatomical morphologies of commonly encountered bifurcating coronary vessels. Finally, the proximal MV zone is composed of three fronds that are



Figure 5. Procedural steps for Tryton[™] side-branch stent use in conjunction with a 'workhorse' stent for the main vessel. MV: Main vessel; SB: Side branch. connected distally to the transition zone panels and terminate proximally in a circumferential band. The Tryton side-branch stent is provided on two different stent delivery systems: a straight balloon and a stepped balloon (FIGURE 4). The straight balloon is of a standard tubular design, and when inflated to 8 atm reaches a diameter of 2.5 mm. Conversely, the stepped balloon when inflated has a tapered geometry that corresponds to the proximal MV zone and distal SB zone. At nominal inflation pressure, the diameter of the proximal MV zone is 3.5 mm, while that of the distal SB zone is 2.5 mm. Both stent delivery balloons have a total of four radio-opaque markers. In addition to standard end markers delineating the proximal and distal ends of the stent, two central markers identify the proximal and distal extent of the transition zone. The central markers are used during the procedure to position the stent transition zone (4 mm in length) at the SB origin. Compared with other DBS, the design of the Tryton side-branch stent has several advantages that are summarized in Box 2. Clearly, the Tryton side-branch stent commits the operator to stenting both branches, precluding the use of a provisional strategy.

Delivery protocol

An inverted culotte technique (i.e., the SB is treated first) is used for the deployment of the Tryton side-branch stent. After choosing the angiographic view in which the foreshortening of the three bifurcation segments is minimal, the MV and SB lesions are predilated, leaving the guidewires in place. Based on MV and SB diameters, the appropriate Tryton side-branch stent is selected, advanced over the guidewire into the SB and positioned with the central transition zone markers straddling the SB origin and the proximal zone extending proximally into the MV. After deployment, the stent delivery system is removed and the guidewire initially placed in the SB is withdrawn into the proximal MV zone and advanced through the stent fronds into the distal MV. A standard DES is tracked through the MV zone of the Tryton side-branch stent with the proximal edge extending a few millimeters proximally to the Tryton side-branch stent and the distal edge positioned into the distal MV. The DES is then deployed, 'jailing' the stented SB, after which the MV stent-delivery balloon is removed. Finally, the SB is reaccessed with a guidewire after which a simultaneous kissing balloon postdilatation is performed (FIGURES 5 & 6). The entire procedure can be performed through a 6-Fr guide catheter.



Figure 6. Serial single frame coronary angiograms obtained in the right anterior oblique cranial projection. (A) Baseline angiogram demonstrating a 'true' bifurcation lesion (arrow) involving the left anterior descending coronary artery and first diagonal branch (Medina 1-1-1) (arrow). (B) Predilation of the first diagonal ostium. Note that both left anterior descending coronary artery (main vessel) and first diagonal (side branch) are wired. (C) Main vessel predilation. (D) The Tryton[™] side-branch stent is positioned with the central transition-zone markers (arrows) straddling the side-branch origin and the proximal zone extending proximally into the main vessel. (E) The Tryton side-branch stent is deployed with inflation of the stepped balloon. Arrows indicate transition-zone markers. (F) The guidewire initially placed in the side branch is being withdrawn proximally. (G) A 3.0 × 28-mm everolimus-eluting stent (Xience V[™]) is tracked through the main-vessel zone of the Tryton side-branch stent with the proximal edge extending a few millimeters proximally to the Tryton side-branch stent and the distal edge positioned into the distal main vessel. (H) After main vessel stenting, the side branch is reaccessed with a wire after which a simultaneous kissing balloon postdilatation is performed. (I) Final angiographic result.

Clinical trials

The Tryton I FIM study is a multicenter, prospective, single-arm study designed to assess the safety and feasibility of the Tryton side-branch stent when used in conjunction with standard DES to treat bifurcated *de novo* lesions within the native coronary arteries [55,56]. Patients were enrolled at three participating centers if they had stable angina, unstable angina or silent myocardial ischemia with coronary angiography showing a *de novo* bifurcation lesion involving a major epicardial vessel (left main bifurcation lesions were excluded) with a MV reference diameter of 2.5–5.0 mm and a SB reference diameter of 2.25–2.75 mm by visual estimate. The primary

Table 2. Baseline demographics of the Tryton I study.					
Variables	Values				
Patients (n)	30				
Female gender (%)	37				
Age (mean \pm SD in years)	66 ± 11.2				
Risk factors (%)					
Overweight	27.6				
Diabetes mellitus – Type 1 – Type 2	18.5 3.7 14.8				
Smoking status (%) – Nonsmoker – Current smoker	48.2 37				

– Current smoker	40.2 37			
– Previous smoker	14.8			
Hypercholesterolemia	70.4			
Hypertensive	70.5			
Family history of CAD	33.3			
Cardiac history (%)				
Previous MI	29.6			
Q-wave	14.8			
Non-Q-wave	14.8			
Previous CABG	3.7			
Prior PCI	33.3			
Anginal status (%)				
No angina	6.6			
Stable angina	56			
Unstable angina	36.7			
CABG: Coronary bypass graft; CAD: Coronary artery disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; SD: Standard deviation.				

study end point was procedural success, defined as angiographic success with no in-hospital MACEs (cardiac death, myocardial infarction, CABG or TLR). Clinical follow-up was planned at 30 days and 6 months, while angiographic follow-up was scheduled at 6 months.

The baseline clinical characteristics of the 30 patients enrolled in this study are presented in TABLE 2. Medina classification by visual estimation was available in all patients: five (17%) patients

had disease in all segments corresponding to a classification of 1-1-1; ten (33%) patients had disease in either the proximal or distal MV as well as disease in the SB (Medina 1-0-1 or 0-1-1); 14 (47%) patients had MV disease with no disease evident within the SB (Medina 1-1-0, 1-0-0 or 0-1-0) and one (3%) patient had disease limited to the SB (Medina 0-0-1). In total, 15 (50%) patients had disease in both the MV and SB (1-1-1, 0-1-1 or 1-0-1). The Tryton side-branch stent was implanted with angiographic success in 29 (96.7%) patients who also received a total of 39 DES (Cypher[™] [Cordis Corp., NJ, USA]: n = 30; TaxusTM [Boston Scientific, MA, USA]: n = 9) to complete the treatment of 29 bifurcation lesions. Kissing balloon was performed in all cases. In-hospital MACEs occurred in two patients. The first MACE occurred after a failed attempt to deliver the Tryton side-branch stent without predilation to a calcified left anterior descending-diagonal bifurcation lesion. The patient underwent simultaneous kissing balloon inflations resulting in vessel perforation, which was stabilized with implantation of a covered stent, resulting in SB occlusion. The patient was discharged from the catheterization laboratory in a stable condition but then arrested and died. The second MACE was caused by an abrupt occlusion of an intermediate ramus unrelated to the index procedure, which was successfully managed with stenting resulting in cardiac enzyme elevation meeting study criteria for acute myocardial infarction. This occurred after successful completion of a left anterior descending-diagonal bifurcation lesion treatment with the Tryton side-branch stent.

At 6-month clinical follow-up, performed in all patients, TLR and TVR were 1 and 3%, respectively (TABLE 3). In one patient, TLR was performed for a MV restenosis proximal to the DES, probably due to a geographic miss during the index procedure, while the second patient underwent TVR owing to progression of a MV

Table 3. Long-term clinical follow-up of the Tryton I study.

-	o-month tonow-up	9-month follow-up
	1	1
	1	
	0	0
	1	1
	3†	3 ⁺
	3	3
		1 1 0 1 3 [†] 3

[†]All three TVRs were not Tryton™ side-branch stent-related.

First TVR – performed in a patient who did not receive a Tryton stent and died after coronary perforation.

Second TVR – for the treatment of proximal edge restenosis of the main vessel drug-eluting stent. Third TVR – for the treatment of a main vessel de novo lesion that progressed not at the bifurcation site.

TVR: Target vessel revascularization.

untreated lesion located more than 10 mm distal to the DES. The qualitative comparative analysis of the 23 (78%) patients who underwent 6-month angiographic follow-up is shown in TABLE 4. The late lumen loss of the proximal and distal MV was 0.25 ± 0.43 mm and $0.00 \pm$ 0.31 mm, respectively, while that of the SB was 0.17 ± 0.35 mm. As a result of the very low late lumen loss values, no in-stent binary restenosis and only one (4.3%) in-segment binary restenosis were observed (FIGURE 7).

In conclusion, the first clinical experience indicates that, when used in conjunction with a DES, the Tryton side-branch stent is safe and associated with low late loss and low binary in-stent restenosis rates (target lesion restenosis: 3%; SB restenosis: 0%). These results are significantly better that those reported in registries and randomized studies employing different bifurcation techniques with one or two DES [2-4,25,40]. The most remarkable finding was the 0.17-mm SB late loss, a value that is not only significantly lower than those reported in BMS studies, but also inferior to those found using DES [4,37-40,57,58]. The low late loss and restenosis rate observed in the Tryton I FIM study were somewhat surprising for a BMS. Two distinct, albeit speculative, mechanisms might provide an explanation for these results: first, radial diffusion of the lipophilic antiproliferative drug from the DES implanted in the MV that may reduce neointimal proliferation of the distal SB zone; and second, complete coverage and better expansion of the SB ostium. While the first mechanism remains speculative, the second could be investigated by an IVUS study. For this reason, we designed the Intravascular Ultrasound Evaluation of Tryton Stent (IUVANT) study to evaluate with IVUS imaging the postprocedural and follow-up results of the Tryton side-branch stent implanted in *de novo* coronary bifurcation lesions. The study, performed at the Centro Cardiologico Monzino in Milan, Italy, has completed the enrollment with follow-up still ongoing. Preliminary results of this study were presented at the Transcatheter Cardiovascular Therapeutics Meeting, September 2009 [59]. In all cases, the Tryton side-branch stent was successfully implanted in 37 bifurcation lesions of 35 patients, and all DES (Xience V) were

Table 4. Angiographic parameters of patients undergoing angiographic follow-up (n = 23).

follow-up (n = 23).					
Parameter	Pre-PCI	Post-PCI	Follow-up	p-value	
PMV					
MLD (mm)	1.31 ± 0.36	2.58 ± 0.29	2.34 ± 0.47	0.01	
RVD (mm)	2.46 ± 1.20	3.15 ± 0.29	2.98 ± 0.24	0.11	
%DS	42.0 ± 42.3	17.3 ± 17.3	20.8 ± 21.0	0.67	
DMV					
MLD (mm)	1.40 ± 0.53	1.97 ± 0.45	1.97 ± 0.41	0.84	
RVD (mm)	2.01 ± 0.63	2.50 ± 0.36	2.41 ± 0.35	0.33	
%DS	33.9 ± 19.7	22.1 ± 13.3	20.5 ± 10.2	0.36	
SB					
MLD (mm)	1.22 ± 0.36	1.72 ± 0.36	1.55 ± 0.28	0.08	
RVD (mm)	1.88 ± 0.38	2.11 ± 0.25	1.89 ± 0.26	0.002	
%DS	34.4 ± 16.9	19.2 ± 10.7	18.4 ± 9.8	0.36	
Bifurcation angles (°) ⁺		45.8 ± 14.2	44.7 ± 17.4	0.09	
PMV LLL (mm)			0.25 ± 0.43		
DMV LLL (mm)			0.00 ± 0.31		
SB LLL (mm)			0.17 ± 0.35		
In-stent binary restenosis [‡]			0 (0)		
In-segment binary restenosis§			1 (4.3)		
p-value is given in paired comparison between post-PCI and follow-up. Values are n (%) or mean ± standard deviation. [†] Between DMV and SB. [†] Including all stented segments in the bifurcation.					

[§]Including stented and peristent segments (segment 5 mm proximal and 5 mm distal to the stent in the main vessel and side branch).

%DS: Percentage diameter stenosis; DMV: Distal main vessel; LLL: Late lumen loss; MLD: Minimal lumen diameter;

PCI: Percutaneous coronary intervention; PMV: Proximal main vessel; RVD: Reference vessel diameter; SB: Side branch.



Figure 7. Case example from a patient enrolled in the first-in-man Tryton I study; serial single frame angiograms obtained in the left anterior oblique cranial projection. (A) Baseline angiography showing a bifurcation lesion (Medina 1-1-1) involving the left anterior descending coronary artery and first diagonal branch (arrow). Note the large dimension of the side branch supplying a substantial area of myocardium (1). (B) Final angiographic result after Tryton™ side-branch stent implantation in conjunction with a drug-eluting stent. (C) 6-month angiographic follow-up.

Angiograms kindly provided by Eberhard Grube and Ralf Müller, Helios Heart Centrum, Siegburg, Germany.

properly placed in the MV with 100% angiographic and procedural success. Kissing balloon postdilation was performed in all cases and final IVUS imaging was successfully obtained in all SB and in all but one MV. Preliminary analysis of IVUS results demonstrated complete coverage of SB ostium with full stent expansion,

Figure 8. Case example from a patient enrolled in the Intravascular Ultrasound Evaluation of Tryton[™] Stent (IUVANT) study; serial single frame angiograms obtained in the right anterior oblique cranial projection. (A) Baseline angiography showing a bifurcation lesion (Medina 0-1-1) involving the left anterior descending coronary artery and first diagonal branch (arrow). (B) Final angiographic result after Tryton side-branch stent implantation. (C) Final intravascular ultrasound evaluation showing complete stent apposition, large final area and stent symmetry at the carina site.

D1: First diagonal branch; LAD: Left anterior descending coronary artery.

high symmetry and large final area at the carina site (FIGURE 8). Interestingly, the 26 patients who already underwent IVUS follow-up showed minimal in-stent neointimal growth, confirming the findings of the FIM study.

Future perspective

The initial data from the FIM study demonstrated feasibility of the Tryton side-branch stent to address a wide spectrum of high-risk bifurcation lesions as well as excellent long-term results (6-month late loss: 0.17 mm; TLR: 1%; TVR: 3%; and no SB failures). However, the early evidence comes from a small number of patients and this DBS has not been compared with other more traditional techniques using either a one-stent or two-stent approach. Thus, this work is being followed-up by a number of studies designed to build on these excellent results. At the forefront of this effort is the IUVANT study, which, as previously outlined, is focused on providing a better understanding of the impact of the Tryton side-branch stent on the pathoanatomy of bifurcation lesions by obtaining acute and comparison 6-month IVUS data. The IUVANT will also provide understanding of how the Tryton side-branch stent performs specifically in conjunction with an everolimus-eluting stent (Xience V/Xience PrimeTM).

In addition, there are a number of clinical registries that will broaden the understanding of the Tryton side-branch stent. These include the electronic Tryton 150 registry as well as the Rotterdam/ Poznañ registry. The former is a multicenter prospective consecutive study designed to characterize the 6-month procedural and clinical outcomes at ten leading centers in eight European countries. Using a standardized electronic clinical research form, data will be obtained at the time of the index procedure as well as at 6-month telephone follow-up. The recruitment phase is now complete, with follow-up ongoing. It is anticipated that the results of this study will be presented in the fall of 2010. The Rotterdam/Poznañ registry is a two-center prospective consecutive series studying the initial 100 lesions treated at the ThoraxCenter, Rotterdam, The Netherlands and the University Hospital of Lord's Transfiguration, Poznań, Poland. This study was designed to characterize the real-world experience with the Tryton side-branch stent providing procedural and 6-month outcomes. Patient enrollment and follow-up are now complete and were presented at the EuroPCR meeting in May 2010 [LESIAK M, A 'REAL-WORLD' EVALUATION OF THE TRYTON SIDE-BRANCH STENT. e-Tryton Study. EuroPCR Meeting, Paris, France, May 2010, Pers. Comm.].

Finally, Tryton Medical is in the planning stages of a large multicenter randomized controlled trial focused on the treatment of 'true' bifurcation lesions comparing the Tryton side-branch stent plus an approved DES (Tryton arm) with angioplasty plus an approved DES (provisional arm). This trial is central to Tryton Medical's efforts to obtain approval for the Tryton side-branch stent by the US FDA. Until final approval from the FDA is obtained, the details of this trial will not be available. However, it is our understanding that the trial will include more than 500 patients, with angiographic and IVUS substudies having the statistical power to test clinically driven hypotheses.

Financial & competing interests disclosure

Aaron V Kaplan is Founder and Director of Tryton Medical, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Executive summary

The challenge of bifurcation lesion treatment

- Coronary bifurcation disease is frequently encountered and approximately 15–20% of percutaneous coronary interventions are performed to treat stenoses at a bifurcation.
- Bifurcation lesion treatment continues to evolve but still poses a number of technical challenges.
- In the drug-eluting stent era, several studies have compared a dedicated two-stent strategy to a single 'provisional' strategy. No significant difference in target lesion revascularization has been observed.
- There are, however, a sizable number of 'true' bifurcation lesions that merit a two-stent strategy as an 'intention-to-treat' approach because of anatomical characteristics.

Stenting techniques for bifurcation lesions

- Among alternate strategies to provisional stenting, the culotte and crush techniques may achieve better results in terms of complete stent coverage of all bifurcation lesion segments compared with other two-stent techniques.
- Dedicated bifurcation stents have been developed to overcome the limitation of previous bifurcation stenting techniques, thereby providing safe and easy treatment of 'true' bifurcation lesions and ensuring full stent expansion, complete carina coverage, no stent distortion and preservation of side-branch access.

The Tryton™ side-branch stent

- The Tryton[™] side-branch stent (Tryton Medical, Inc., NC, USA) is a balloon-expandable cobalt–chromium bare-metal stent with a distal zone that scaffolds the side branch, a transition zone designed to accommodate the complete range of side-branch ostium anatomy and a proximal zone designed to accommodate a standard stent.
- The Tryton side-branch stent is positioned and deployed with the transition zone at the side branch origin, the distal end in the side branch and the proximal zone extending into the main vessel. After deployment in the side branch, any stent can be advanced in the main branch across the Tryton side-branch stent proximal zone to complete the bifurcation architecture.

Clinical studies with the Tryton side-branch stent

- The Tryton I first-in-man study demonstrated feasibility and safety of the Tryton side-branch stent when used in conjunction with a drugeluting stent in the treatment of complex bifurcation lesions with excellent long-term results (6-month late loss = 0.17 mm, TLR = 1%, TVR = 3% and no side-branch failures).
- Preliminary results of an ongoing intravascular ultrasound study demonstrate complete coverage of side-branch ostium with full stent expansion, high symmetry and large final area at the carina site after Tryton side-branch stent implantation. Moreover, minimal in-stent neointimal growth was observed at follow-up.

Future perspective

- Available clinical experiences indicate that the Tryton side-branch stent may provide the ability to more easily and definitely treat bifurcation lesions, fulfilling a large unmet need in percutaneous coronary intervention.
- A number of ongoing clinical registries and a planned large multicenter randomized controlled trial will broaden our understanding of the Tryton side-branch stent for the treatment of 'true' bifurcation lesions.

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