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Dedicated Bifurcation Stents

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Abstract

Bifurcations still remain one of the most challenging lesions to be treated in the modern PCI era. They are associated with lower procedural success rates, higher rates of periprocedural complications, and complicated long-term outcomes. Their incidence is assessed to be approximately 15–20%. There is still debate on how should they be treated—one-stent versus two-stent techniques, whether there is a need for obligatory proximal optimization or kissing balloons. Multiple clinical trials have tested different PCI strategies. We will cover theoretical basics of treating bifurcations and describe different types of dedicated bifurcation stents—Nile PAX, Nile SIR, BiOSS Expert, BiOSS LIM, Stentys, Tryton, and Axxess Plus. We will discuss the data from studies comparing these bifurcation devices and will show our own experience and results working with these devices. There will be a discussion, tips, and tricks treating bifurcation lesions with dedicated devices—most common pitfalls and how to deal with them.

Keywords: bifurcation, left main, new devices

1. Introduction

Bifurcations still remain one of the most challenging lesions to be treated in the modern PCI era. They are associated with lower procedural success rates, higher rates of periprocedural complications, and complicated long-term outcomes. Their incidence is assessed to be approximately 15–20%. There is still debate on how should they be treated—one-stent versus two-stent techniques, whether there is a need for obligatory proximal optimization or kissing balloons. Multiple clinical trials have tested different PCI strategies.

The conventional stents are not designed for bifurcations as there is huge variation in vessel anatomy, mostly discrepancy in proximal and distal diameter of the treated vessel and a need

for free access in the side branch. One major problem in bifurcation PCI is the high rate of SB ostium restenosis. There are also several procedural difficulties such as maintaining access to the side branch, irregular overlapping, and uneven distribution of struts at the carina. The final result and long-term success rates are highly variable and are operator dependent.

Closure of side branch bigger than 1 mm often is associated with 14% incidence of periprocedural myocardial infarction [1].

The dedicated bifurcation stents are produced to tackle most of these problems.

Dedicated bifurcation stents give hope for technically straightforward and fast success rate; they aim to protect the SB and allow permanent SB access as well as optimal MB and SB scaffolding and coverage. They also tend to limit multiple layering of stent struts, limit gaps in support, and prevent restenosis reducing SB risk, optimizing immediate and long-term outcomes.

2. Anatomy, physiology, and conventional stent treatment

Coronary bifurcation lesions should be viewed as three major parts—proximal main branch, distal main branch, and a side branch. Significant side branch is defined on the subjective judgment of the operator, which warrants its diameter, length, size of myocardial mass supplied, its viability, and left ventricular function.

Treating a bifurcation comes with the risk of losing SB patency; thus, the operator should thoroughly review the plaque burden at the carina, its angle, and diameter of MB and SB.

The MADS classification presents various techniques used in bifurcation stenting. There is one-stent (provisional) or two-stent strategy. Provisional stent strategy is done in majority of cases; it is recommended by the European Bifurcation Club as KISSS principle (Keep It Simple, Swift and Safe). At first, the MV is stented, the stent diameter is 1:1 according to distal MB diameter, and then operator should perform POT (proximal optimization technique) and eventually kissing balloon inflation. POT presents short oversized balloon dilation at proximal part of the stent (from proximal edge of the stent to proximal carina edge). This technique apposes stent struts to the proximal MV and enhances scaffolding at the SB ostium. After this, if operator decides based on SB ostium stenosis and flow, kissing balloon inflation could be done. Kissing inflation involves rewiring of the SB from the distal strut at SB ostium, and getting a balloon through the stent struts could be the most challenging part of bifurcation treatment. After rewiring, two NC balloons are simultaneously inflated in MB and SB.

After POT and kissing, if there is a need for SB stenting because of low flow or SB dissection, there are basically few strategies—T stenting, TAP (T stenting and protrusion), culotte, and crush techniques. In all two-stent techniques, kissing balloon dilation is mandatory to achieve full stent expansion at both ostia; sometimes, final POT should be considered.

T-stenting strategy is chosen when there is scaffolding at the SB ostium from the POT and when SB angulation is nearly 90°. If SB is not covered by POT technique and the angle is acute, crush (minicrush), culotte, and TAP should be considered as they all cover SB ostium with struts. In crush (minicrush), the stent in SB is placed overlapping the MB and is crushed with oversized

balloon; finally, kissing balloons should be inflated. In culotte, SB stent also covers some of the MB and this part in MB is overexpanded with POT, leaving double strut layer at the proximal MB; final kissing is a must. More modern minicrush and miniculotte use shorter stent overlapping, thus decreasing strut burden. In Tap, the SB stent is left to protrude a bit proximal to carina, while leaving a balloon in MB for simultaneous kissing, thus making a neostrut carina.

Sometimes, if there is a large and diseased SB prone to ischemia and deterioration in LV function (mostly in left main), a two-stent strategy is chosen instead of provisional stent. It is operator's decision which part MB or SB to be stented first and which of two-stent strategies to choose.

Bioresorbable stents, besides their potential advantage to dissolve with time, have a lot of limitations—they are thicker (some techniques require multiple struts layers and you cannot always go with provisional one-stent strategy) and have limited expansion property and increased rates of thrombosis. Absorb BRS (Abbott Vascular USA) is already taken down from market. DESolve BRS (Elixir Medical USA) and Magmaris (BIOTRONIK Germany) could be a choice, but still there are a few data.

There are several devices dedicated to bifurcation treatment.

3. Tryton and Tryton SHORT stents

One of them is the dedicated bifurcational stents, Tryton and Tryton SHORT stents.

The delivery system of the stent is based on rapid-exchange catheter with single-wire tracking (no risk of wire wrap or bias); there is no need for rotational orientation. The stent has low profile and is 5-Fr guide compatible with two central markers delineating central transition zone used to precisely position the stent (**Figures 1–3**).

The deployment sequence of the stent consists of wiring the side branch and predilatation. Then, Tryton is positioned and is deployed from main branch to the side branch, after which the main branch is wired and a DES is positioned 1 mm proximal to the Tryton proximal edge. After deploying the stent in the main branch, rewiring of side branch and kissing is performed.

There are several drawbacks of Tryton system. It is a bare metal stent with consistently <5% TLR in all clinical studies in over 1,800 pts. It requires adequate proximal landing zone and accurate positioning, but the learning curve is short. It is not indicated for <2.25 mm vessels and is tied to two-stent strategy as intention to treat.

There are several randomized studies as far as this stent is concerned.

TRYTON randomized 704 patients with bifurcation coronary lesions at 58 centers (30 from Europe and 28 from the United States). At 9 months, TVF was 4.6% higher in the bifurcation stent group compared with the provisional group ($p = 0.11$). TVF was mainly presented by higher rates of periprocedural myocardial infarction rate (13.6 vs. 10.1%). The SB in-segment diameter stenosis was lower in the bifurcation stent group compared with the provisional group (31.6 vs. 38.6%), with no difference in binary restenosis rates (diameter stenosis $\geq 50\%$) at 9 months follow-up (22.6 vs. 26.8%) [2].

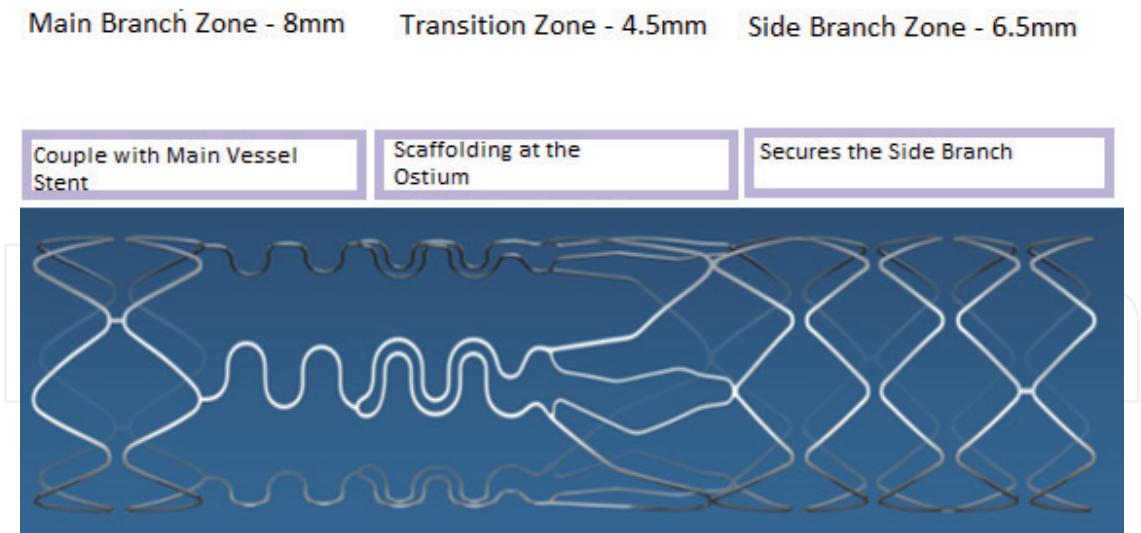


Figure 1. Tryton structure. It is cobalt-chromium balloon expandable stent. The strut thickness is 85 mkm and the total length of the stent is 19 mm. The transition zone can flare and rotate in order to accommodate the atomic variations of the side branch ostium and scaffolds like a main vessel stent at the ostium.

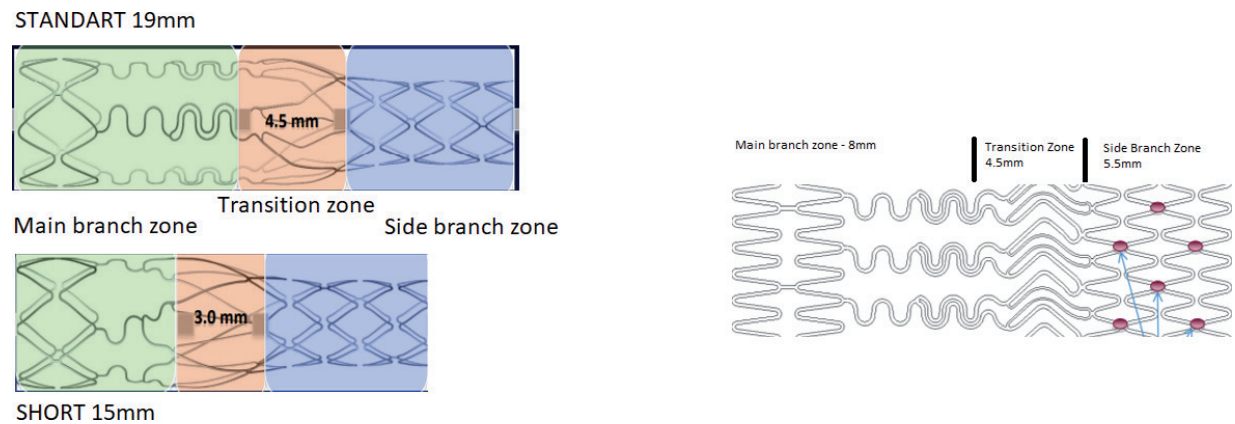


Figure 2. Tryton and Tryton SHORT stents. The proximal part of the main branch zone was designed to accommodate larger expansion, and the side branch zone is with additional links in order to increase radial force of the stent. The SHORT stent has 3 mm shorter landing zone, and the position of central markers is optimized for large vessels and has improved delivery system.

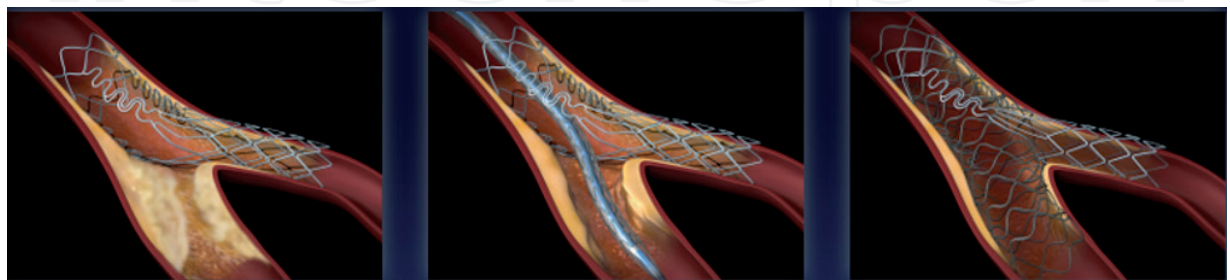


Figure 3. Tryton deployment scheme. The stent is positioned and deployed after predilatation (secures and protects side branch). The next pictures show treatment of main vessel with approved DES through main vessel portion of Tryton. The final step is kissing balloon postdilatation to ensure complete lesion and ostium coverage. Source: Genereux [3].

After TRYTON study, a subanalysis of it examines the benefit of the Tryton compared with provisional stenting in treatment of complex bifurcation lesions involving large SB. Among the 704 patients enrolled in the TRYTON trial, 289 patients (143 provisional and 146 Tryton stent)

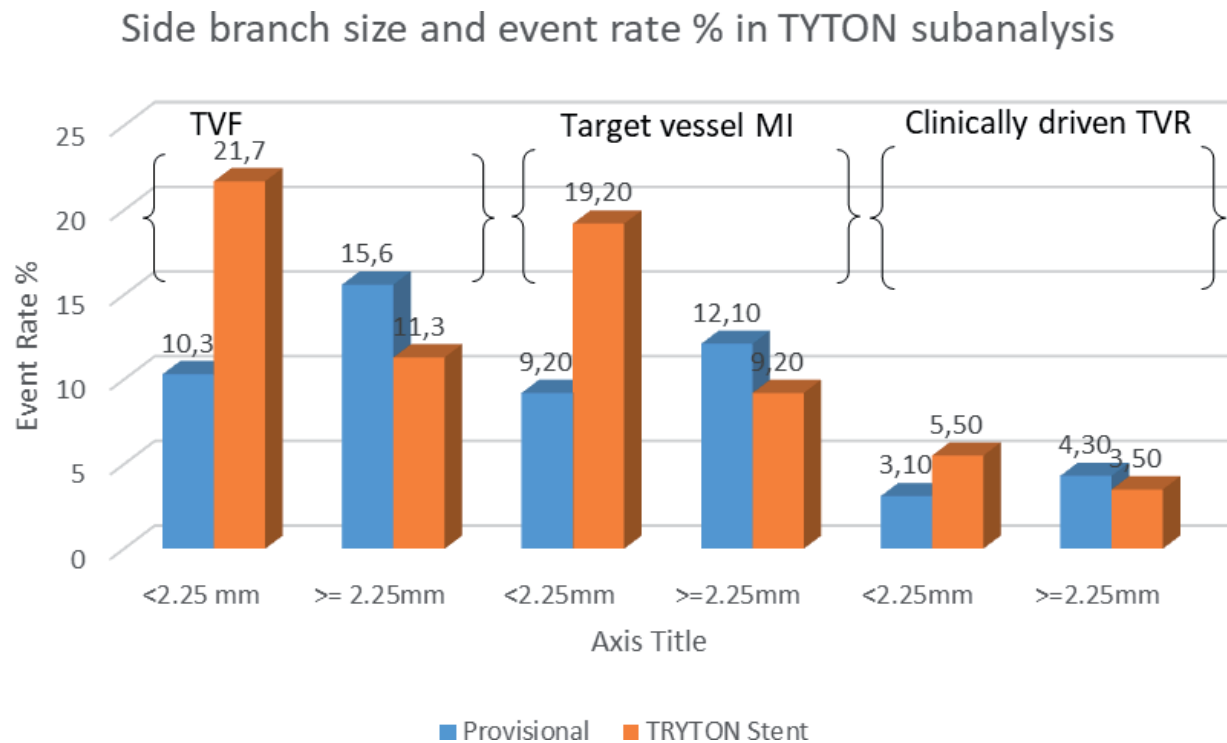


Figure 4. TRYTON subanalysis results.

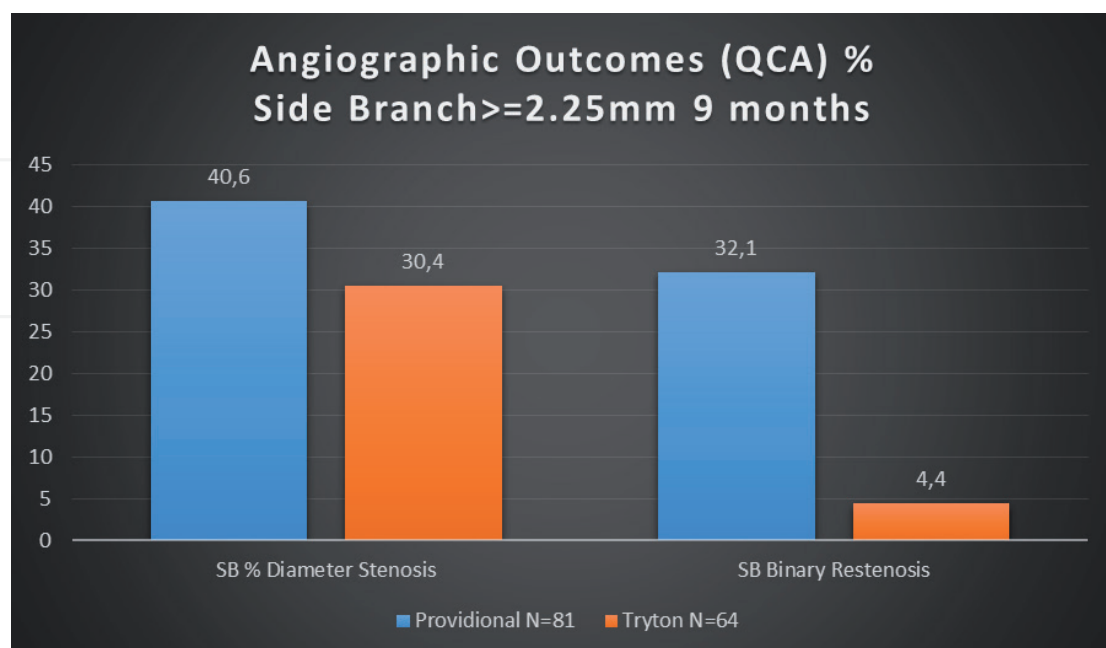


Figure 5. QCA outcomes in TRYTON subanalysis (Genereux et al. Catheter Cardiovasc Interv. 2015).

Confirmatory study	Randomized trial > = 2.25mm		
Endpoints %	TRYTON N = 133	TRYTON N = 146	Provisional N = 143
Death			
Procedural	0% (0.0)	0% (0.0)	0% (0.0)
30-day	0% (0.0)	0% (0.0)	0% (0.0)
Myocardial infarction			
Procedural (3xCKMB)	10.5% (14/133)	9.2% (13/141)	12.1% (17/141)
Procedural (5x CKMB)	4.5% (7/133)	3.4% (4/118)	6.8% (7/103)
30-day	10.8% (14/130)	8.2% (12/146)	11.9% (17/143)
Stent thrombosis	0% (0.0)	0.7% (1/146)	0.0% (0/143)

Table 1. Procedural and 30-day follow-up.

had an SB ≥ 2.25 mm. The primary endpoint of TVF was numerically lower in the Tryton group compared with the provisional group (11.3% vs. 15.6%, $P = 0.38$). No difference among the rates of clinically driven target vessel revascularization or cardiac death was seen. In-segment percent diameter stenosis of the SB was significantly lower (10.2%) in the Tryton group compared with the provisional group. In conclusion, 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 [4] (**Figures 4 and 5**).

TRYTON confirmatory study rationale was to prospectively confirm the safety (periprocedural MI) of the Tryton dedicated bifurcation stent in the treatment of true bifurcation lesions involving large side branches (>2.25 mm by QCA analysis). The angiographic inclusion criteria were the same. The study included 28 investigational centers with 12-month enrolment. Procedural and 30-day follow-up are given in **Table 1**.

4. AXXESS stent

Another bifurcation stent is AXXESS.

Axxess is self-expanding nickel-titanium alloy; it has conical shape and proximal and distal gold markers, facilitating implantation. The device is Biolimus A9 coated using a bioabsorbable polymer matrix in a dose of 22 mg/mm of stent length. The strut thickness is 0.15 mm and the drug release rate is 70% in 30 days, remaining 30% released in <6 months with polymer absorption 6–9 months.

There are three models of the stent—11 and 14 mm in length with reference diameter 2.75–3.25 mm. The maximal proximal and distal stent diameters are 3.75 and 6 mm, respectively. For reference diameter 3.25–3.75, the maximal proximal and distal stent diameters are 4.25 and 6.5 mm. The delivery system is covered sheath, that is, rapid-exchange delivery catheter. It is 5 Fr of higher compatible.

The goal of stent placement is to cover the proximal lesion segment as well as the ostium of the side branch and distal patent vessel without compromising access to the side branch. It is accomplished if two markers - in 1 branch and 1 is in the other. Axxess provides convenient placement marker for additional distal stents (**Figure 6**).

Stent implantation—the AXXESS stent is advanced so it is astride the carina and is pushed further forward as far as it will go. Implantation steps: a wire is placed in each branch; the stent is advanced to the most angulated branch, and the distal stent markers are aligned with the carina; the self-expanding distal struts partially expand as the sheath is partially withdrawn after which the partially expanded stent in the main branch is advanced to cover the bifurcation (**Figure 7**).

4.1. Clinical studies

There is a growing body of literature that supports the use of the AXXESS system in the treatment of coronary bifurcation lesions. The first-in-man AXXESS Plus trial reported results at 6 months in 139 patients who underwent implantation across 13 centers, with low rates of TLR (7.5%) and late-lumen loss (0.09 mm). There was a low rate of periprocedural complications (MACE rate 5% (n = 7), non-Q wave MI 4.3% (n = 6)), with a late-stent thrombosis rate of 2.1% (three patients, two of whom associated with premature cessation of antiplatelet therapy) [6].

The following DIVERGE Trial was a prospective, single-arm, multicenter trial. Any type of bifurcation lesion was included with significant SB larger than 2.25 mm and PV-SB angulation <70° (**Figure 8**).

About 302 patients in 16 clinical sites in Europe, Australia, and New Zealand were included. Clinical follow-up at the first, sixth, ninth month, and after that yearly up to fifth year was completed.

First endpoint was MACE at 9 months, with secondary end points and 12 months and 2-, 3-, 4- and 5-year death, cardiac death, MI-Q and non-Q, TLR, TVR, stent thrombosis at 30 days, 6,

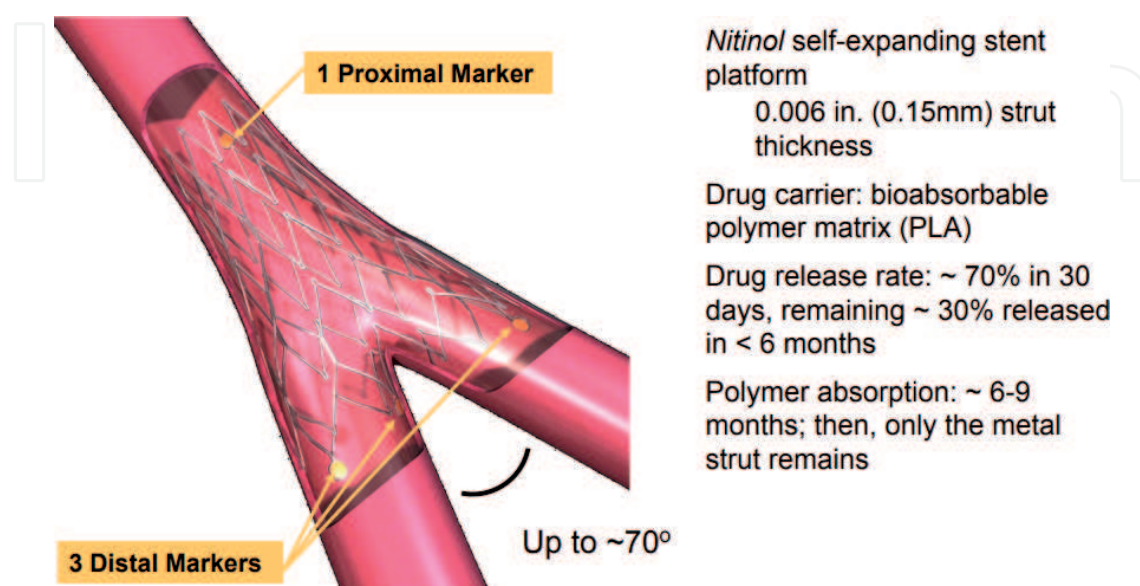


Figure 6. Axxess structure. Source: Rizik et al. [5].

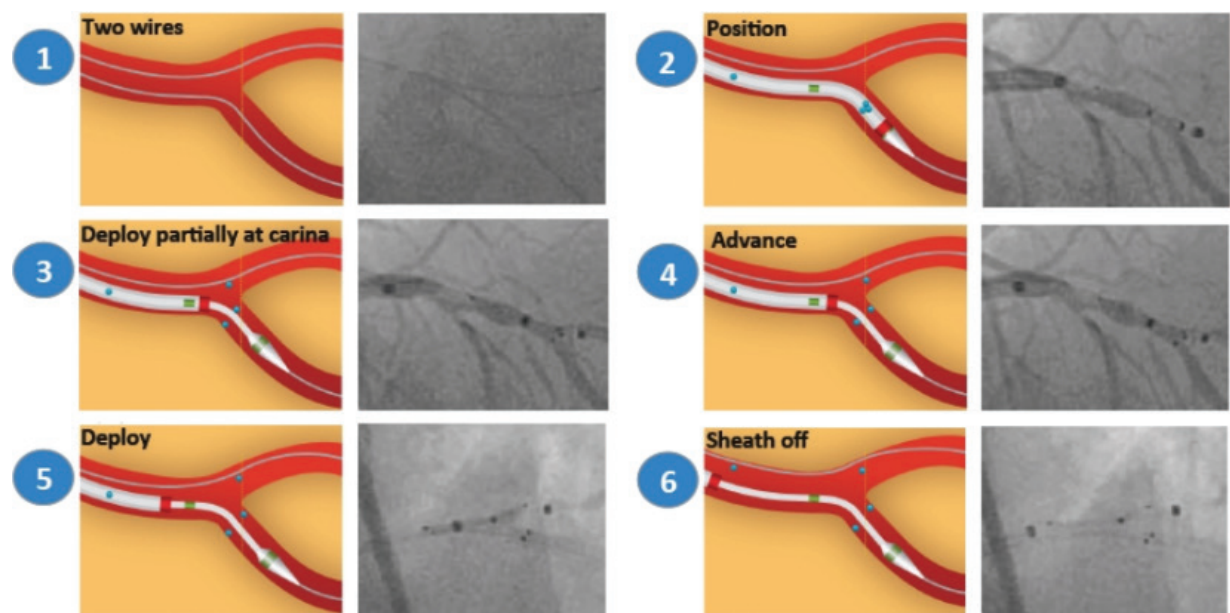


Figure 7. Axxess deployment sequence.

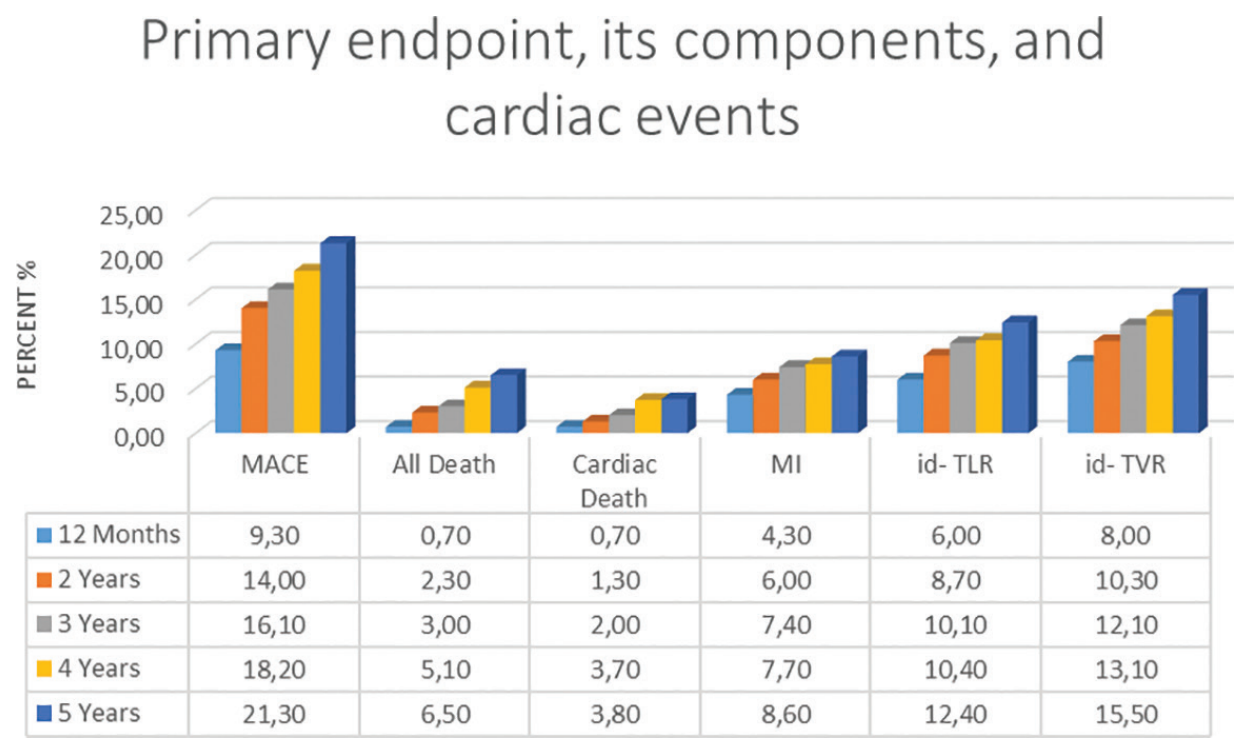


Figure 8. DIVERGE trial: 5-year outcomes.

9, and 12 months and 2, 3, 4, and 5 years. The angiographic secondary end points were in-stent restenosis and late loss at 9 months. DAPT for 12 months was recommended. About 77.4% of all patients were with true bifurcations with predominating Medina 1:1:1.

Axxess only was used in 12.3%; Axxess with PV stenting in 17.7%, Axxess with SB stenting in 4%, and stenting of the two branches was present in 64.7%. In general, side branch stent was used in 68.7%.

9 – month QCA results

At follow-up		Parent vessel N = 140	Side branch N = 140
Late loss (mm)	In-stent LL (Axxess only)	0.18 ± 0.49	-
	In-stent LL (all stents)	0.29 ± 0.50	0.29 ± 0.45
	In-lesion LL	0.20 ± 0.41	0.17 ± 0.34
Restenosis per vessel	In-stent LL (Axxess only)	0.7%	-
	In-stent (Cypher)	2.3%	4.8%
	In-lesion restenosis	3.6%	4.3%
	(all stents + edges)		
Overall bifurcation restenosis	In-stent PV+SB	5% (7/140)	
	In-stent or edges PV+SB	6.4% (9/140)	

Table 2. QCA results.

Nine-month QCA results are presented in **Table 2** [7, 8].

Another study evaluating Axxess in bifurcation treatment is COBRA [8]. It compares Axxess + DES versus culotte with EES. OCT stent and lumen area at ninth month are compared. The percentage of uncovered struts in each bifurcation segment at 9 months (primary endpoint) was similar between groups. Five-year clinical follow-up was available for all patients and included major adverse cardiac events [MACE; a composite of cardiac death, myocardial infarction (MI) and ischemia-driven target lesion revascularization (TLR)], target-vessel (TVR) and non-target-vessel revascularization (non-TVR), non-TLR, and stent thrombosis. At

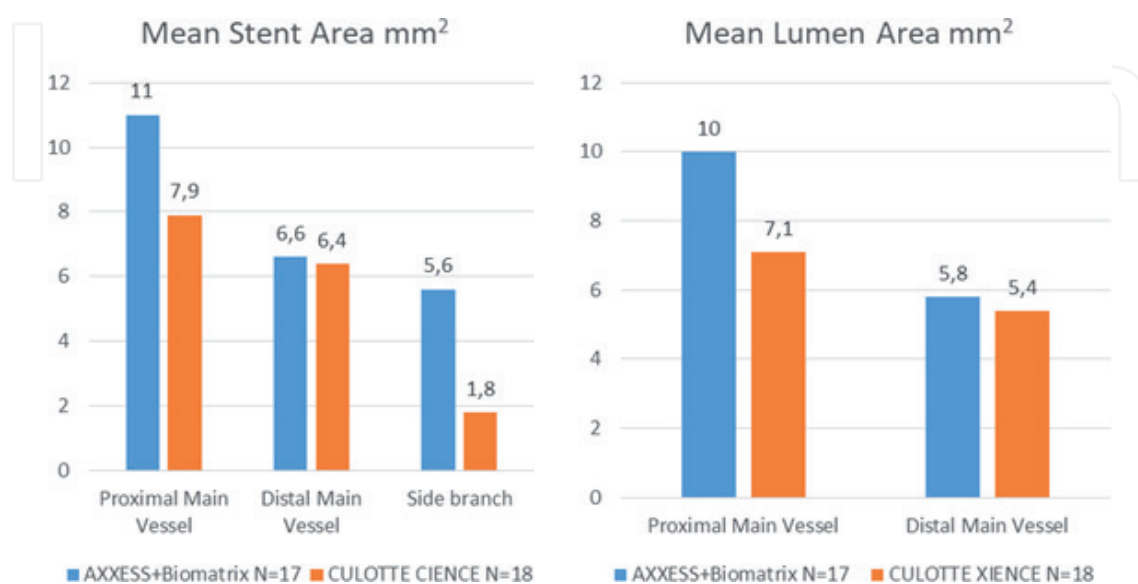


Figure 9. COBRA trial results at 9 months.

5 years, in the culotte group, one patient had undergone TLR and another suffered a clinical MI, resulting in 10% MACE versus none in the Axxess group. TVR (5 vs. 10%, $P = 0.54$) and non-TVR (5 vs. 20%, $P = 0.39$) rates were similar between the Axxess and culotte groups, respectively. There was no stent thrombosis (**Figure 9**).

In conclusion, Axxess is a self-expanding coated device with positive results in bifurcation lesions, including complex morphology. It has relatively high profile, and frequently multiple stents are used in cases of double stenting. There is some proof of larger luminal gain in the carina segment. Prospective data support its use in complex coronary bifurcations; however, its use has yet to be studied in a large-scale randomized controlled trial.

5. BiOSS stent

The BiOSS stent (Balton, Warsaw, Poland)—Bifurcation Optimisation Stent System was created and firstly used in 2008. It has three generations. At first, it started as bare metal BiOSS stent, then drug-eluting stents—BiOSS Expert in 2010; then in 2012, BiOSS LIM was introduced. Recently, in 2018, the last generation BiOSS LIM C was tested in man.

5.1. The stent design

All generations of BiOSS stent have the same primary design. As it is delivered by one 0.014 guidewire through rapid-exchange system with five French guiding catheter, it makes BiOSS no different than the other conventional stents. The difference comes with the strut and balloon design.

We know from the Murray's law (see **Figure 10**) of bifurcations that there is difference between main vessel and side branch diameters. In plain words, the bigger the side branch, the bigger the difference of proximal and distal part of the main vessel. When we plan to stent a bifurcation, we should choose a stent that has the diameter of the distal part of the main vessel, and after implantation, we do a proximal optimization—to dilate a bigger balloon at the proximal part (above carina) to keep the stent conformation as the natural anatomic structure.

In case we choose stent size 1:1 in diameter to the proximal part of the main vessel it will overstretch the distal part thus moving the carina and plaque to the orifice of the side branch and compromising the blood flow. Secondly, the conventional stents, even with open cell design, will have struts at the side branch orifice.

Main difference between those different generation of stents are the material (BiOSS Expert and LIM being the same design stainless steel 140- μ m struts and BiOSS LIM C made from cobalt-chromium alloy 70- μ m struts) and different drug (first-generation BiOSS Expert eluted paclitaxel and the next BiOSS LIM and LIM C eluted sirolimus). So there is huge difference between them as 140 μ m may provoke arterial wall injury and lead neointimal proliferation and thinner struts may facilitate endothelialization [8]. The other important difference is the

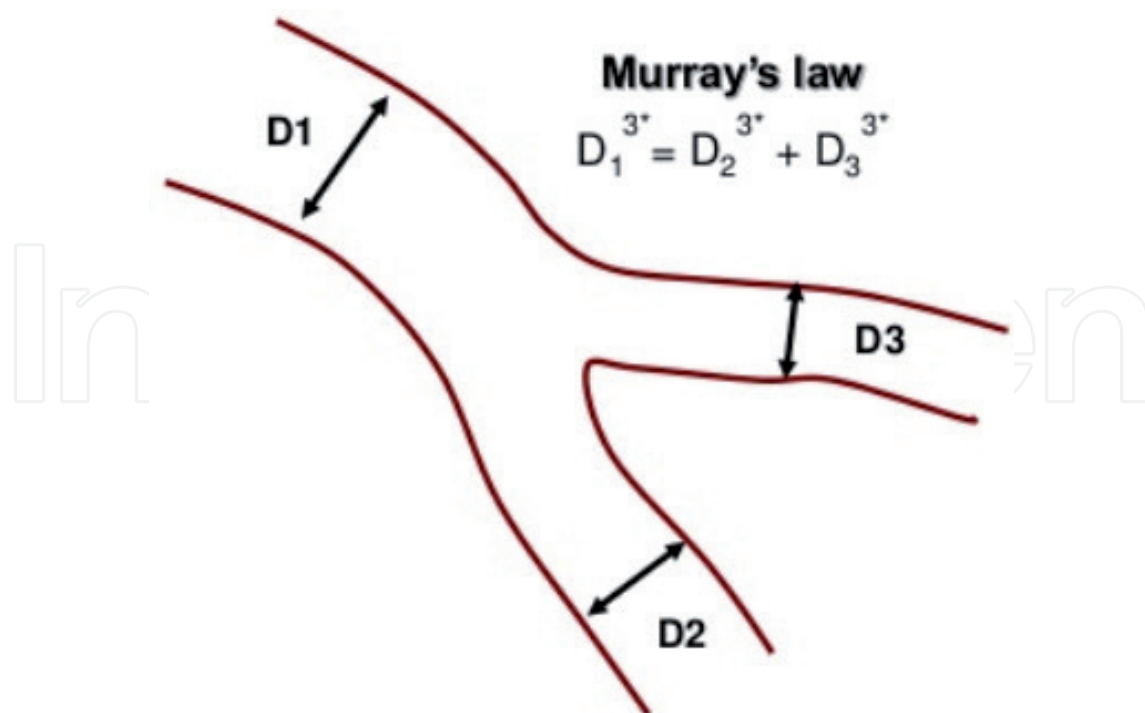


Figure 10. Visualization of Murray's law.

drug that is eluted paclitaxel in BiOSS Expert and sirolimus in LIM and LIM C as it was shown that sirolimus decreased the rates of MACE and TLR [9, 10].

5.2. How the stent design of BiOSS comes to tackle these problems?

The stent is made of two parts—proximal and distal with two small connecting struts at the middle zone (0.9–1.5 mm in length). The proximal part of the stent has a larger diameter than the distal one—the ratio is 1.15–1.3. Proximal diameters vary from 3.25 to 4.5 mm and the distal ones from 2.5 to 3.75; the stent length is 15, 18, and 23 mm. The proximal part is always a bit shorter than the distal one (average 1 mm). So, for instance, the smallest stent is 2.5 × 3.25 mm in diameter—distal and proximal part and the largest one is 3.75 × 4.5 mm, and there are four varieties between them with 0.5–0.75 difference in proximal and distal diameters (2.75 × 3.5 mm; 3.0 × 3.5 mm; 3 × 3.75 mm; 3.5 × 4.25 mm). So with three different lengths, it makes a total of 18 combinations. The stent is delivered on a bottle-shaped balloon (Bottle, Balton, Poland), allowing bigger proximal and smaller distal diameter when inflated. It is semicompliant balloon with nominal pressure of 10 atm and burst pressure of 18 atm (**Figures 11 and 12**).

The stent has three markers: two at both ends and one in the middle. The markers at both ends are like every other stent—they show proximal and distal ends of the device. The midmarker shows the proximal end of the distal (smaller) part of the stent—it should be positioned exactly at the carina as shown in **Figure 13**. So this placement helps to keep the natural anatomic proportions (bigger proximal part, smaller distal) and keep same carina confirmation—it has no carina displacement because the lateral force from proximal stretching counterbalances with the medial force from distal stretching. The other important design virtue is that there are no struts at the opening of the side branch.

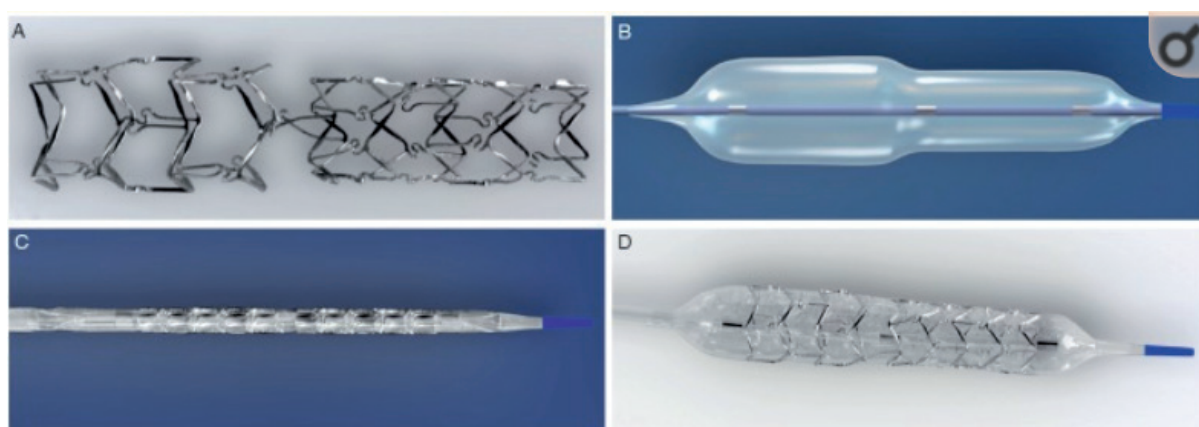


Figure 11. (A) Expanded stent; (B) stent balloon only; (C) stent system not expended; (D) expanded stent system. Source: Gil et al. [11].

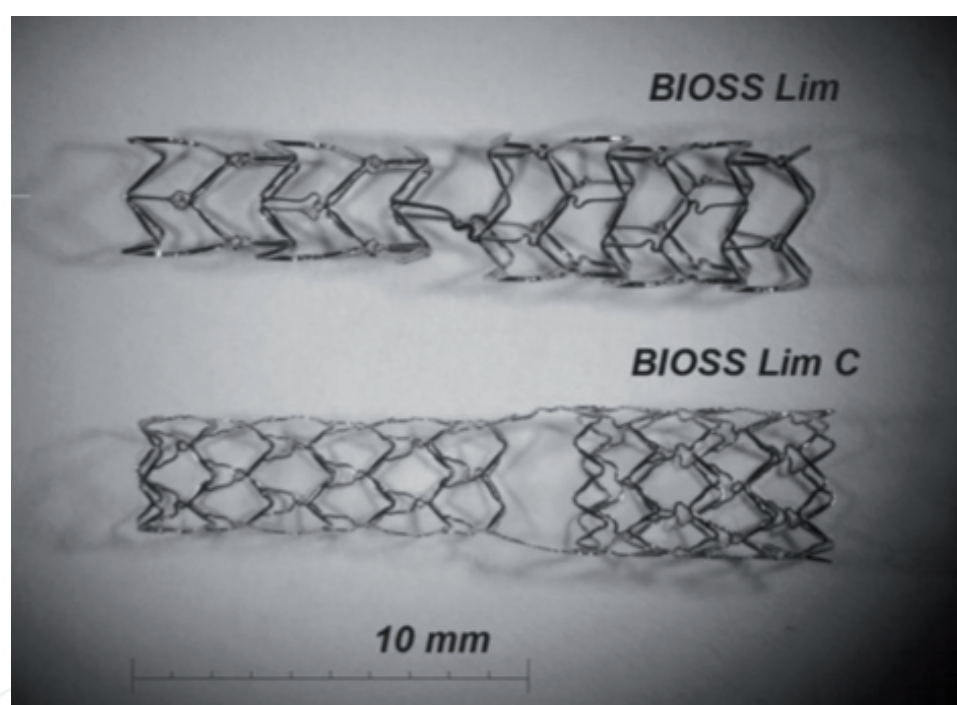


Figure 12. BIOSS Lim and BIOSS Lim C stents. Source: Gil et al. [12].

An IVUS study showed that BiOSS stent provides better access to the SB in comparison with the conventional drug-eluting stents. There was significantly bigger orifice length found in the BiOSS group—a parameter, which represents the access to the SB [13]. The analysis of the plaque, lumen, and vessel areas shows that BiOSS stent design spares the proximal optimization technique (POT), which is strongly recommended by the European Bifurcation Club [14]. But this imposes the question whether no struts at the carina could predispose to restenosis. This issue was addressed in the IVUS study and showed that the carina actually had the least neointimal burden during follow-up [15]. This study also showed that sirolimus was better than paclitaxel in rates of neointimal hyperplasia.

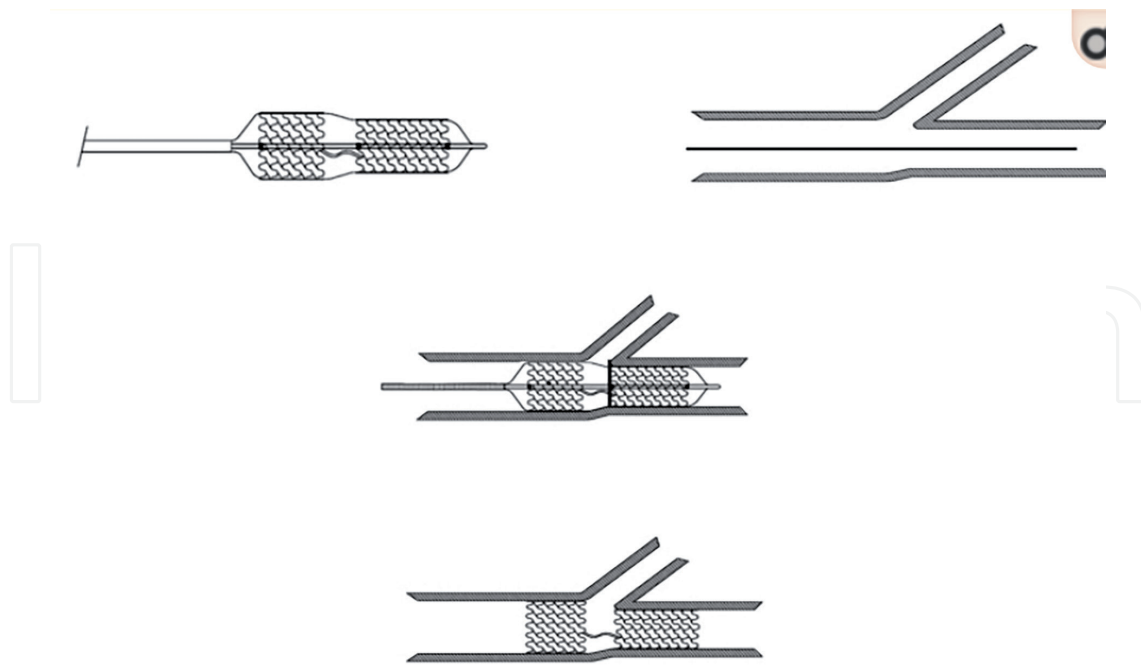


Figure 13. Visualization of stent positioning. Source: Gil et al. [12].

5.3. What are the results when comparing BiOSS stent versus conventional DES in treating bifurcation lesions?

Two randomized multicenter trials compared BiOSS Expert and LIM versus conventional drug-eluting stents—POLBOS I (2010–2013) and POLBOS II (2012–2013).

They have published results at 12 and 48 months of follow-up.

POLBOS I (n = 243) study compared BiOSS Expert (paclitaxel) stent versus conventional DES—paclitaxel, sirolimus, everolimus, zotarolimus, and tacrolimus stents (LucChopin2, Xience, Promus, Cypher, Prolim, Orsiro, Biomime, Biomatrix, Resolute Integrity, and Optima). POT balloons were advised but left to operator discretion. Kissing was left to operator discretion in BiOSS group, and in DES group, there was second randomization for kissing balloons.

At 12 months of follow up, the cumulative incidence of MACE was similar in both groups 13.3% in BiOSS vs. 12.2% in DES. There were also no significant differences in cardiac-related death (0 in BiOSS vs. 1.6% in DES), myocardial infarctions (1.6% in BiOSS vs. 3.2% in DES), and stent thrombosis (0.8% in BiOSS vs. 0 in DES). Target vessel revascularizations were significantly higher in BiOSS group 15.8% vs. 9.7% in DES group. Target lesion revascularizations were also significantly higher in BiOSS group 11.5% vs. 7.3% in DES group.

POLBOS II (n = 202) compared the next-generation BiOSS LIM (sirolimus) stent vs. regular DES (same as above). POT and kissing were left to operator discretion in BiOSS group and POT to operator discretion but kissing randomized in DES group. At 12 months, there were no significant differences in MACE (11.8% in BiOSS vs. 15% in DES), death (1% in BiOSS vs. 3% DES), MI (1.9 vs. 3%), TLR (9.8% in BiOSS vs. 9% in DES), and TVR (13.7% in BiOSS vs.

12% in DES). Final kissing was associated with significantly less TLR only in BiOSS group (5.9 vs. 11.8%, $p < 0.05$), but POT technique was associated with less TLR in both groups (in BiOSS 5.3% vs. 12.5% $p < 0.05$ and in DES group 2.9% vs. 25% $p < 0.01$).

When analyzed POLBOS I and II at 48 months, there were no statistical differences in terms of MACE (DES vs. BiOSS: 18.8 vs. 19.8%, $p = 0.64$), TLR (12.1 vs. 15.3%, $p = 0.34$), MI (4.5 vs. 2.1%, $p = 0.72$), or cardiac death (2.2 vs. 1.8%, $p = 0.81$) between DES and BiOSS groups.

5.4. Why one should use BiOSS stent if the long-term results are the same?

Implanting BiOSS stent will not spare you the proximal optimization or the kissing balloons if there is a need for such techniques. In theory, it will leave the SB ostium open, thus making it easier to reach with a wire and go through it with a balloon for a kissing. In case you need two-stent technique, there will be less struts at the carina and easier to go through with a second stent.

So in our opinion, BiOSS stent makes treating of bifurcation lesion simpler and sometimes cheaper (sparing a smaller balloon for opening the struts to the side branch in order to reach with a bigger one for kissing).

5.5. What are the pitfalls in implanting BiOSS stent?

In our opinion, there are two main issues when implanting BiOSS stent. The first is when you have long lesion that includes bifurcation. Consider that longest BiOSS is 23 mm in length with approximately 46/50% length in proximal and distal length, so having a longer than 12 mm proximal or distal lesions means that if you are planning to use BiOSS, you will need at least two stents, one regular DES and one BiOSS; in this case, implanting just one long regular DES and doing proximal optimization is more suitable.

The second is that when implanting BiOSS stent, it is of crucial matter to find very good projections where carina is seen, because you have to place the middle marker at the ostium of the main branch (**Figure 14**).

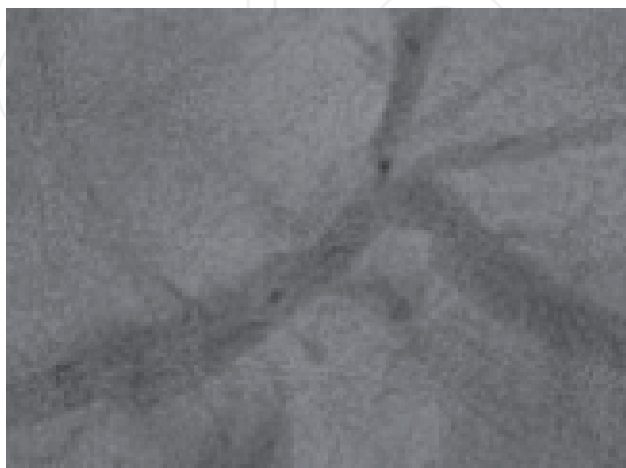


Figure 14. Correctly positioned stent (angio).

Implanting the stent beyond the carina will compromise the side branch ostium; in the other case, implanting the stent too much proximal to the carina will not have these adverse effects in the side branch but will leave struts at the carina.

In conclusion, BiOSS stent should be considered a good choice for treating bifurcation lesions, intended for one- or two-stent strategy.

6. Nile concept

Minvasys offers one of the current stent solutions for bifurcation stenting. First approved stent from Nile family is Nile CroCo, which takes CE brand in 2005. Nile CroCo presents the basic Minvasys concept of bifurcation stenting. Future generations of dedicated stents are based on Nile CroCo.

6.1. Nile CroCo

Nile CroCo stent is based on cobalt-chromium bare metal platform. The stent consists of three segments. Proximal segment includes 7–9 cells (depending on stent size), the medial segment includes 8–10 cells, and the distal segment includes 6–8 cells (**Figure 15**). This distribution ensures same metal to artery ratio (between 10.3 and 14.6%) [16] along entire bifurcation, which is important for optimal stent apposition. Stent thickness of Nile CroCo platform is 73 μm . Two stent length are offered—18 and 24 mm; three diameters for main branch balloon (2.5, 3.0, and 3.5 mm) and three diameters for side branch balloon (2.0, 2.5, and 3.0 mm) are offered. There are seven stents with different MB and SB diameters (as follows: 2.5–2.0, 3.0–2.0, 3.0–2.5, 3.5–2.5, 3.5–3.0, 2.5–2.5, and 3.0–3.0 mm), each of them proposed in two lengths (18 and 24 mm).

Stent delivery system integrates two monorail balloons: one for the side branch and one for the main branch. It requires 6.0F guiding catheter for stent delivery, and two 0.014-inch guide-wires, previously positioned in MB and SB. Both balloons have similar characteristics with nominal pressure 8 atm and rated burst pressure 14 atm (**Figure 16**).

Cobalt-chromium stent platform is mounted on main branch balloon. The system also contains side branch catheter tip. Side branch balloon is located proximally from the stent. Both balloon catheters are rapid exchange. In order to prevent entanglement of two balloon shafts, during system delivery, there is autorelease sheath. The system is equipped with five roentgen-positive markers—three of them located on MB balloon—proximal, distal, and medial. Medial marker is located exactly on the bifurcation. There are two additional markers, pointing proximal and distal parts of SB balloon.

Despite the fact that every dedicated bifurcation stent proposes a unique approach to bifurcation lesion, Nile system allows provisional T-stenting in the A category, according to MADS classification. Provisional stenting strategy is recommended as the first-line approach by many modern consensuses.

Stenting procedure (**Figure 17**). The stenting procedure begins with placement of two guidewires distally in the main branch and side branch (step 1). Predilatation of MB and SB (if stenosis seems to be significant) is crucial for seamlessly stent delivery. Optimal stent size must be selected according to distal diameters of MB and SB. The system must be introduced on the both rapid-exchange balloon catheters. After that, the system is pushed through the guiding catheter. During the advancement, autorelease sheath must be released. Two monorail balloon catheters are advanced until distal part of the stent crosses through stenosis in the main branch. When the midsegment of the stent is positioned on the carina, and the tip of SB balloon catheter is in the proximal part of the SB (step 2), the system will stop and the operator will feel resistance. At this moment, the middle roentgen positive marker must be exactly at the level of carina (shown with a narrow at step 2). In this way, the operator is maximally facilitated in optimal positioning the stent because it can use guidewires as well as the radiopaque marker and tactile sensation.

In about 40% of cases, twisting of guidewires may occur. This can be easily solved by retrieving the system in the guiding catheter and repositioning one of the guidewires.

After optimal stent positioning, the MB balloon is inflated, providing stent implantation in the main branch (step 3). After this step, the medium “strutless” part of the stent is positioned exactly at the level of bifurcation. Next step is advancement of the SB balloon catheter into SB ostium (step 4). This can be achieved easily, because of two facts. First of all, the SB guidewire is not jailed, so there is no need to recross wires. Furthermore, there is a “defect” in the struts, at the level of carina that allows balloon advancement. The next step (step 5) is kissing, using both balloons, integrated in the system. Because of the special SB balloon shape, overextension of the proximal segment of the bifurcation is avoided. After the removal of delivery system (step 6), both guidewires stay positioned into main branch and side branch. This made implantation of additional stent (only if necessary) very easy.

This concept of stent implantation is preserved in next two generations of Nile stents—Nile PAX and Nile SIR.

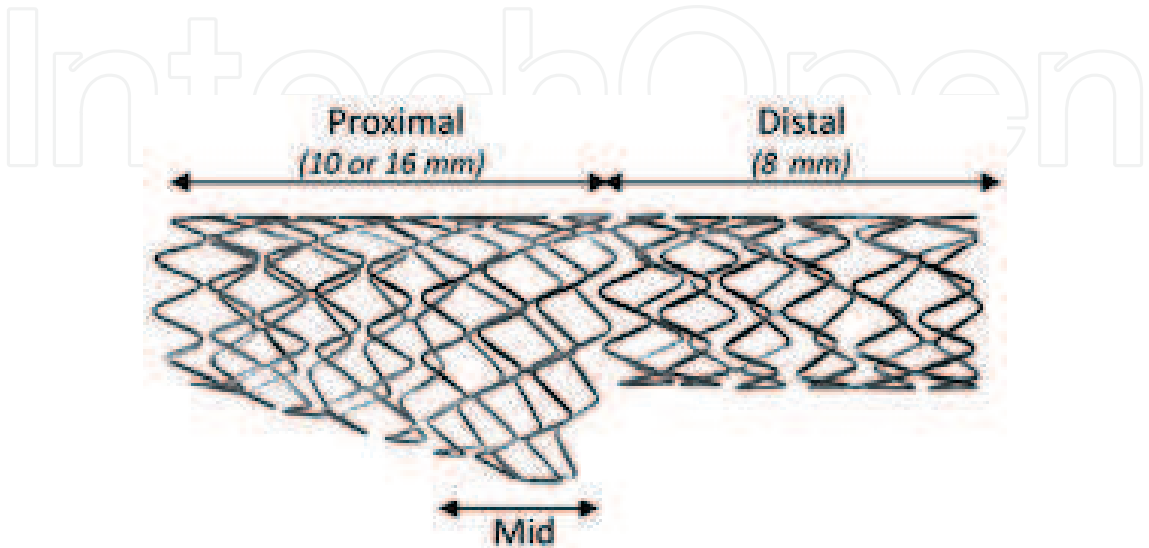


Figure 15. Nile CroCo structure. Source: [17].

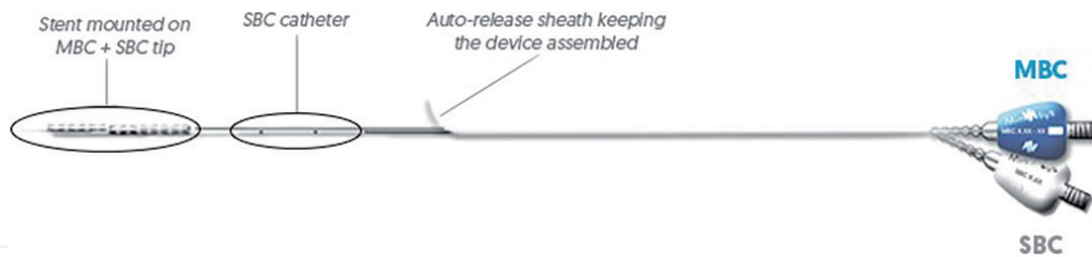


Figure 16. Scheme of delivery system. Source: [17].

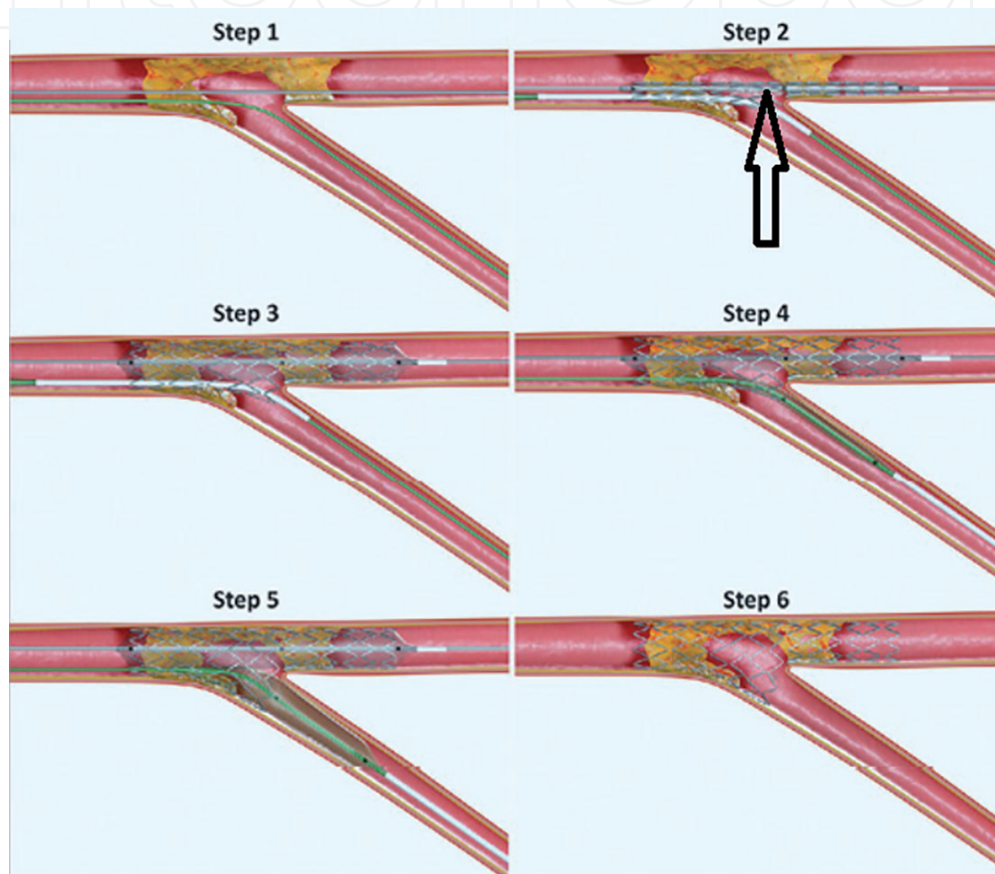


Figure 17. Stenting procedure step-by-step. Source: [17].

Bruno Garcia Del Blanco et al. reported the results of a series of 151 patients treated successfully by implantation of Nile CroCo stent [18]. Success in stent positioning and implantation was reported in 99% of patients. Radial approach was used in 75% of patients. In more than 80% of patients, 6F introducer and guiding catheter was enough. Significant lesion at the ostium of the SB was reported in 73% of patients. A kissing inflation with the system was performed in almost all (95%). In 19% of cases, additional stent was implanted in MB, while in 10% of cases, additional stent was implanted in SB. Among 138 patients with a complete follow-up at 6 months, the MACE rate was 14% and the TLR was 7.2%, despite the fact that the patient profile being relatively severe, including 55 patients with myocardial infarction <24 h. Guidewire twisting—as mentioned earlier—requiring repositioning was noted in 33% of cases.

6.2. Nile PAX

In 2009, next-generation (**Figure 18**) bifurcation stent gets CE brand approval. Stent structure, stent sizes, and delivery system are the same as in Nile CroCo. The stent was made by same cobalt-chromium alloy with similar metal to artery ratio (between 10 and 15%). Strut thickness is 73 μm , but in Nile PAX, there are additional 5- μm polymer-free coatings with paclitaxel only on the abluminal surface in crystallized form. Drug concentration is 2.5 $\mu\text{g}/\text{mm}^2$, and based on manufacturer's data, whole drug is released 45 days after stent implantation.

Stent delivery system and the steps of stent implantation are actually the same as described for Nile CroCo stents. Because of that, we will repeat the steps, using our real clinical case for visualization.

We present 68-year-old female with stable angina pectoris and bifurcation LM stenosis (Medina 0:1:1) (**Figure 19**).

We placed two 0.014 inch guidewires in MB and SB and made predilatation of MB with NC balloon 2.0/20 mm (please note that LCx is chosen for MB). Stent positioning with central marker at the level of carina is shown in **Figure 20**.

The balloon for the SB postdilatation may be seen in guiding catheter on this step. After angiographic verification of optimal stent apposition, MB balloon was inflated (**Figure 21**). Final kissing was made, using both balloons incorporated in system, and the final result is visualized in **Figure 22**.

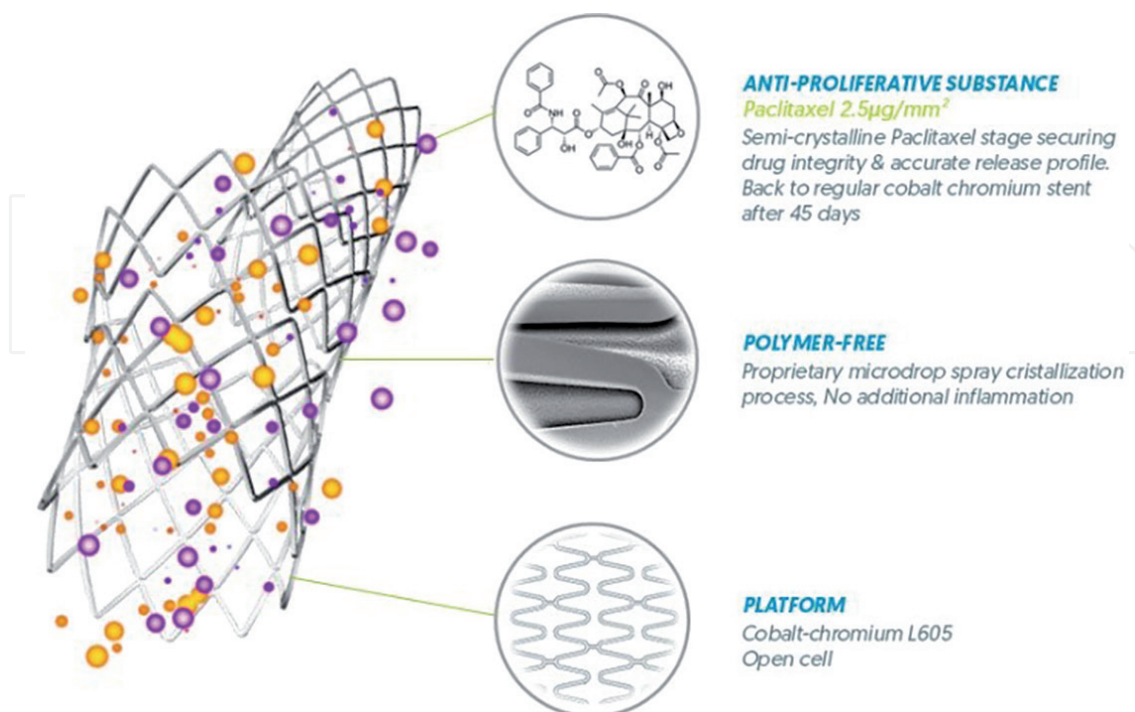


Figure 18. Nile PAX stent. Source: Owned by Acibadem City Clinic.

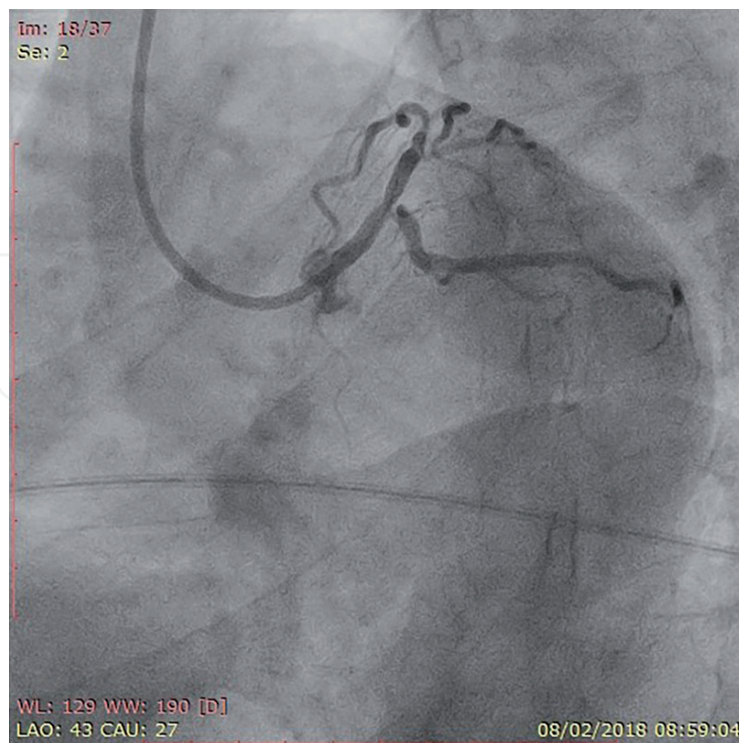


Figure 19. Stenosis before the beginning of the procedure. Source: Owned by Acibadem City Clinic.

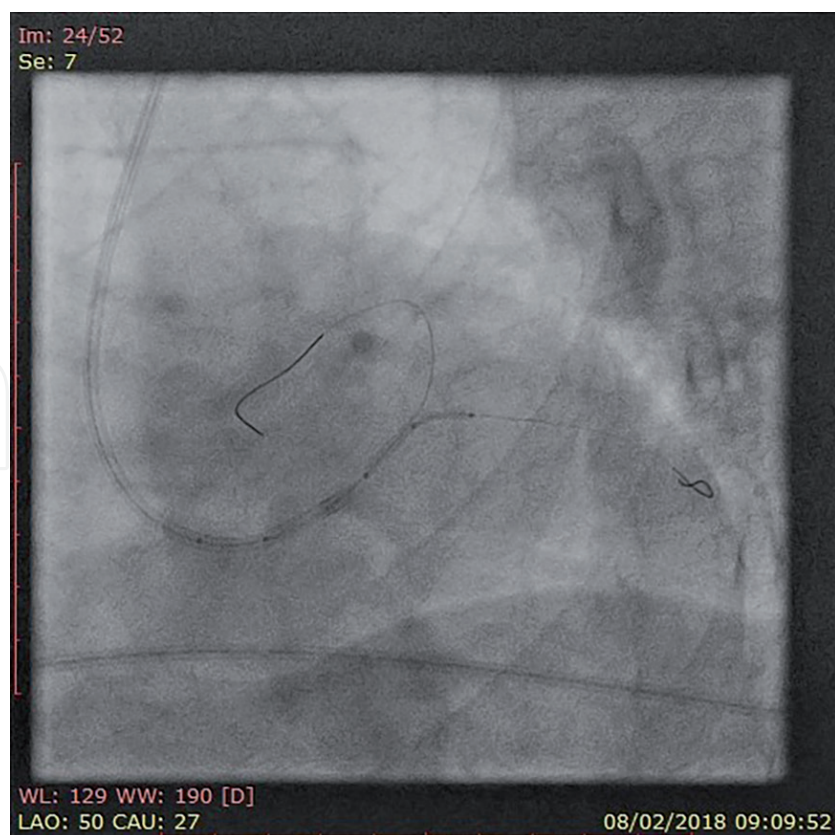


Figure 20. Stent positioning. Source: Owned by Acibadem City Clinic.

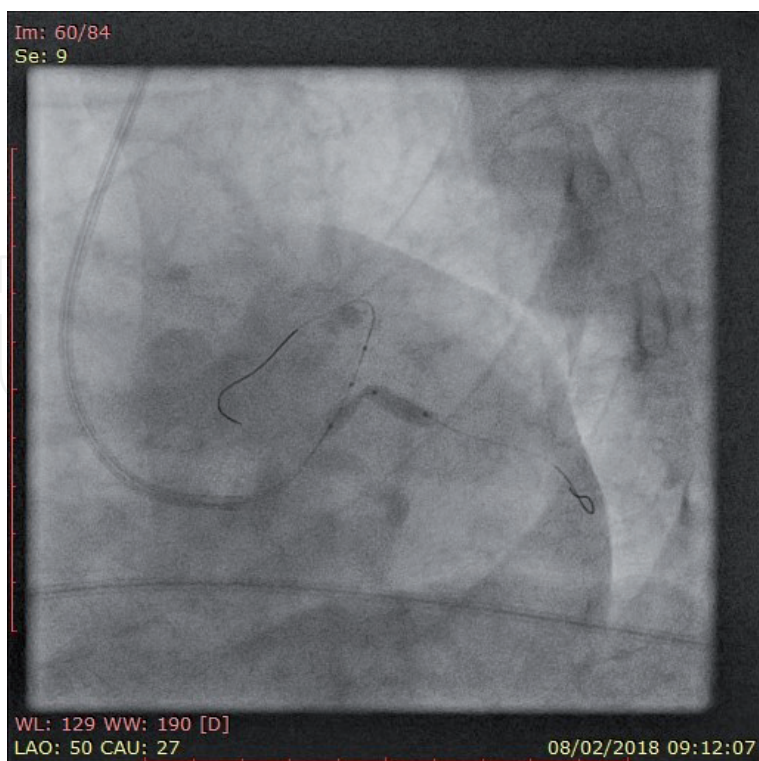


Figure 21. Inflation of MB balloon. Source: Owned by Acibadem City Clinic.

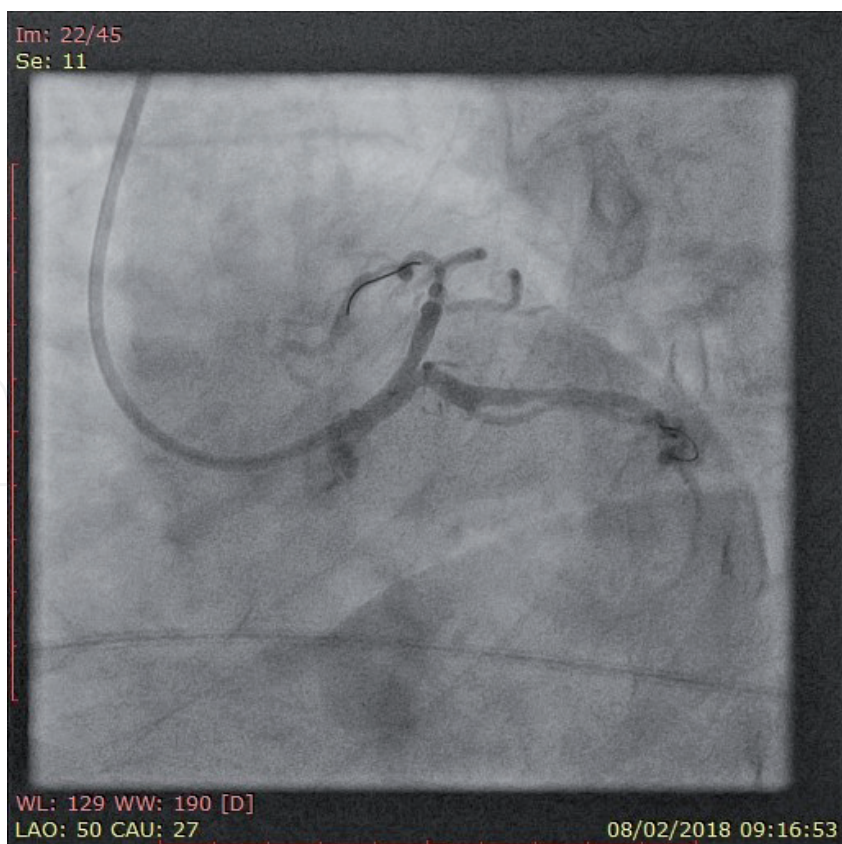


Figure 22. Final result. Source: [20].

In 2012, results from a big trial with Nile PAX stent were published [19]. The trial is multicenter, including 101 patients from Europe and Brazil. Our team is part of this study. Procedural success and 30-day follow-up data of the paclitaxel-eluting version (Nile PAX) were presented. In 80% of cases, the LAD-diagonal branch bifurcation was the target lesion with 62% also having an SB lesion. In total, 102 lesions were treated, of which 62% had a stenosis on each of the main or side branches. Procedural success was achieved in 97% of cases. An additional stent was implanted in the SB in 25% of cases. Longer-term (9-month) clinical follow-up data of this study were presented at EuroPCR 2011 (by Bruno Garcia). The rate of restenosis was 13.9% in the MB, 12.8% in the SB, and a total of 18.6% in the bifurcation, which led to a TLR of 12.6% with only one myocardial infarction reported.

In order to reduce the rate of SB restenosis (12.8%) found in the Nile PAX trial, a new Nile PAX study with systematic use of a paclitaxel-eluting balloon (Danubio; Minvasys) in the SB at the end of the procedure shows only 2% rate of restenosis.

6.3. Nile SIR

Last generation of Minvasys Nile family is Nile SIR dedicated bifurcation stent. It is based on the same conception as Nile CroCo and Nile PAX but covered by sirolimus as antiproliferative drug. Sirolimus is deposited with biodegradable polymer on abluminal stent surface with concentration $1.4 \mu\text{g}/\text{mm}^2$. About 85% of the drug is expected to be eluted within 48 days after implantation, and complete reversion to BMS is expected within 180 days.

The active drug is deposited on abluminal stent surface on two layers (**Figure 23**). First layer (A) contains sirolimus, poly-L lactic acid, poly(lactic-co-glycolic) acid, and polyvinylpyrrolidone. It is located between stent strut and layer B. Layer B is water soluble, contains polyvinylpyrrolidone, and had only protective function.

Between 2013 and 2014 in India, 37 patients with symptomatic bifurcation stenosis were treated by implantation of Nile SIR and followed up. Most of the patients had LAD-DIAGONAL stenosis (74%), and 26% had LCx-OM stenosis. Stable angina at admission was reported in 64.9%, and the rest was with unstable angina pectoris. There were no procedural complications or adverse cardiac events till discharge. In 27% of patients, there was additional stent implanted at the MB level,

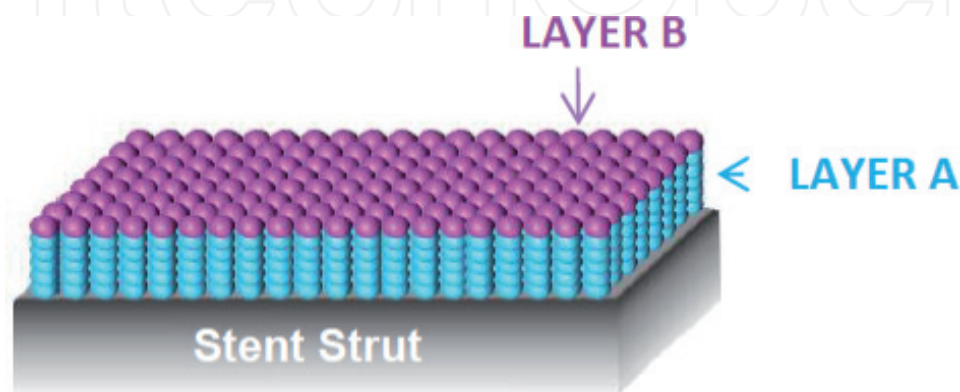


Figure 23. Drug deposal on the stent.

and 3% of patients had additional stent implanted in SB. During 6-month clinical follow-up, there was no MACE reported. Three of the patients were died from noncardiac reason. Angiographic follow-up was done in 15 of these patients. In-stent late-lumen loss was reported as follows: on the proximal MB level 0.15 ± 0.15 , on the distal MB level 0.16 ± 0.29 , and on the SB level 0.26 ± 0.41 .

In our center, 42 patients with bifurcation LM stenosis were treated in the past 2 years. About 52.94% of patients had stable angina and 47.06% with acute MI (including one patient with STEMI). Based on the Medina classification, bifurcation lesions were type 1:1:1 in 33.82%, type 1:0:1 in 20.59%, and type 0:1:1 in 11.76% patients. Procedural success was achieved in all patients. According to center protocol, clinical follow-up was done on the first month. Control angiography with intravascular ultrasound was done on the sixth month. Twenty-four (57.14%) patients were followed up angiographically. We observed two MACE (4.76%)—one patient died before FU and one in-stent restenosis at the SB level. The measures of the late-lumen loss were 0.22 ± 0.38 , 0.29 ± 0.34 , and 0.18 ± 0.31 mm for the main branch proximal, distal, and side branch, respectively.

Conflict of interest

There is no conflict of interest to declare.

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