Cardiovascular Revascularization Medicine 20 (2019) 254–260

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

True double bifurcation lesions: new application of the self-expandable Axxess stent and review of literature with dedicated bifurcation devices

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ARTICLE INFO

Article history:
Received 3 November 2017
Received in revised form 3 April 2018
Accepted 9 April 2018

Keywords:
Bifurcation lesions
Axxess
PCI
Acute coronary syndrome

ABSTRACT

Complex coronary artery bifurcation lesions occurred in hard clinical scenarios, such as acute coronary syndromes, may represent a challenge for interventional cardiologists, with not-defined general consensus on treatment. Even if provisional stenting is the most common option used to restore rapidly the coronary branches flow, improvements in industrial technologies and design of new dedicated bifurcation devices might open new modalities of treatment in these complex cases. The Axxess stent (Biosensors Europe SA, Morges, Switzerland) is a self-expanding biolimus-eluting conical V-shape stent, specifically designed to treat "easily" coronary artery bifurcation lesions, with reported favorable long-term clinical results in stable patients compared to a provisional technique. We report for the first time the feasibility to use this device in a case of "true double coronary bifurcation lesion" occurred in the context of acute coronary syndrome. Moreover, we reviewed studies with bifurcation dedicated devices and available cases of "true double bifurcation lesions", underlying advantages/disadvantages of using one device over the others during acute coronary syndrome.

Contents

1. Introduction

The prevalence of coronary artery bifurcation lesions is reported to be between 15% and 20% of all performed coronary angiograms and despite progressive development of coronary percutaneous techniques, still those lesions represent a challenge for interventional cardiologists, especially in patients with Acute Coronary Syndromes (ACS) [1,2]. Thus, different strategies have been developed with the aim to redesign bifurcation anatomy and its carina, to ensure secondary branch access and to provide the optimal adaptation of the stent struts to the bifurcation angle [3–5]. However, despite these efforts, the gold-standard technique, especially during ACS, has not been yet defined and there is no general consensus on how to restore coronary branches flow due to presence of complex double coronary bifurcations lesions occurred during ACS. In those complex cases, probably most operators would opt for fast coronary flow restoration in the main vessel with provisional stenting, treating the close major branches only if required by limited flow or residual significant disease after this first provisional strategy. However, the availability of dedicated bifurcation devices easy-to-use also in the setting of ACS with proven good clinical evidences might give to operators new treatment options in those complex challenging bifurcations.

The Axxess stent (Biosensors Europe SA, Morges, Switzerland) is a self-expanding biolimus-A9 eluting stent designed to treat easily the complex anatomy of bifurcation lesions, with a rapid exchange-catheter running over a single wire. With a conical V shape, the device is positioned at the level of the bifurcation carina with no need of stent recrossing, allowing the treatment of both distal branches with

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https://doi.org/10.1016/j.carrev.2018.04.011
1553-8389/

minimum carina strut coverage. Moreover, the device is designed with one proximal marker and three distal markers that guarantee its correct placement into the carina and guide the distal branches stenting (if required) with minimum strut overlapping and risk of deformation of the device structure (Fig. 1). After the first cases [6], intravascular imaging and clinical results following Axxess implantation in bifurcation lesions are now encouraging for its wide use in different bifurcation types [7,8].

We reported for the first time the feasibility to treat a "true double bifurcation lesion" occurred during acute coronary syndrome by implantation of a single Axxess-stent. Moreover we reviewed studies available with bifurcation dedicated devices and cases of "true double bifurcation lesions" successfully treated with single dedicated bifurcation devices, underlying advantages/disadvantages of using one device over the others in ACS.

2. Case description

A-67-year old man with hypertension and hypercholesterolemia was admitted at our ICU center presenting chest pain, and clear ECG signs of anterior ischemia. Upstream treatment before the coronary angiography included ASA 250 mg i.v. and Ticagrelor 180 mg per os. Thus, he was transferred to the Cath-Lab to perform urgent coronary angiography, that showed severe and diffuse disease of the left anterior descending coronary artery (LAD) from proximal to mid segment, with high thrombus burden, determining a distal slow flow. Moreover, the significant disease of two large diagonal side branches (DSB), determining a double bifurcation lesion (Medina 0.1.1 and 1.1.1) was appreciable. Left circumflex and right coronary arteries were atherosclerotic in absence of significant coronary disease (Fig. 2A and B). Thus, we decided to approach the double bifurcations by using the Axxess dedicated stent. During the procedure, sodium heparin was administered to maintain an ACT at over 200 s. The LM was engaged with a 7 Fr EBU 4.0 guiding catheter (Medtronic, Inc) via femoral access. Two Balance Middle Weight angioplasty guidewires (BMW, Abbott Vascular) were advanced to the LAD and to the distal DSB. The distal DSB lesion was predilated with a 2.5 × 10 mm semi-compliant Pantera balloon (Biotronik) at 12 atm, and a 3.0 × 15 mm Pantera balloon was used to dilate mid LAD. Axxess 3.0 × 11 mm stent was implanted in the mid LAD between proximal and distal DSB, taking care to place the three distal markers correctly into the distal bifurcation (Fig. 2C, white arrow) as recommended by manufacturer. Then, a Biomatrix stent 3.0x14mm was implanted in the mid LAD in overlapping with Axxess to complete treatment of distal bifurcation. Of note, the proximal marker of the Axxess stent pointed through the ostium of the first DSB and was used as reference to place a third wire (Fig. 2D, white arrow) through the proximal struts of the Axxess self-expanded stent into the first DSB. Then, the ostium of the DSB and the proximal struts of Axxess were dilated by a 2.5 × 15 mm balloon to finally implant a Biomatrix stent 3.0 × 14mm into the first DSB, performing therefore a "modified" provisional T-stent. The treatment of this proximal bifurcation was completed by kissing balloon and the procedure was ended by implanting proximally a third Biomatrix stent 3.5x14mm in overlapping to the Axxess obtaining an excellent final result of the double bifurcation lesion (Fig. F). In summary, both first and second DSB of the double bifurcation lesion were treated: 1) the distal bifurcation lesion by the implantation of a single Axxess stent with elongation stenting of LAD, 2) the proximal bifurcation lesion by predilatation of the same Axxess struts and by stenting of the DSB (modified provisional stenting) using this time its proximal marker as reference. The patient was discharged the day after the procedure with 180 mg/day ticagrelor and 100 mg/day aspirin and he remained asymptomatic after the intervention with negative stress-test at 6 and 12 months. Coronary angiography will be performed during later follow-up only for new-onset clinical reasons, according our hospital policy.

3. Discussion

The optimal percutaneous treatment strategy for coronary bifurcation lesions is still a matter of debate. The interventional preferred strategy for bifurcations in which the critical stenosis is limited to the main vessel is the provisional stenting technique [2,3]. On the contrary, when a medium–large side-branch is involved, two stents technique or bifurcation dedicated stents might be a reasonable alternative. However, several randomized trials failed to show any clinical advantage of double stent techniques as compared to provisional one stent technique. In fact, a double stent strategy using balloon expandable stents gave controversial results with higher rates of short-term major adverse cardiovascular event (MACE) rates and increased risk of long-term late stent thrombosis (ST) and myocardial infarction (MI) as compared to a single stent strategy [1,9,10]. Moreover, two recent meta-analysis have shown that the double-stent versus single-stent approach to treat bifurcations was associated with an increased risk of developing MI and stent thrombosis, while there were no differences found in TLR (risk ratio 1.09, $p = 0.67$) [10,11]. Finally, a very recent report from the COBIS II registry has suggested that, since provisional stenting is the simplest and cheapest approach, this technique should be the first preference

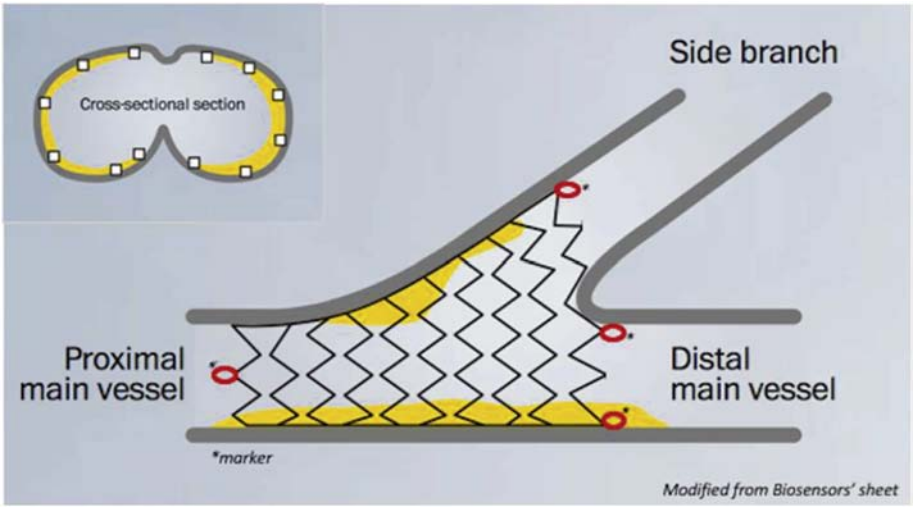

Fig. 1. Axxess stent design into a bifurcation carina: the device is a BA9-eluting dedicated bifurcation stent, with an abluminal biodegradable polymer, on a self-expandable platform. Once the stent and its two distal markers are correctly placed in the bifurcation, the carina is not covered (as shown in the cross-sectional section, upper left square).

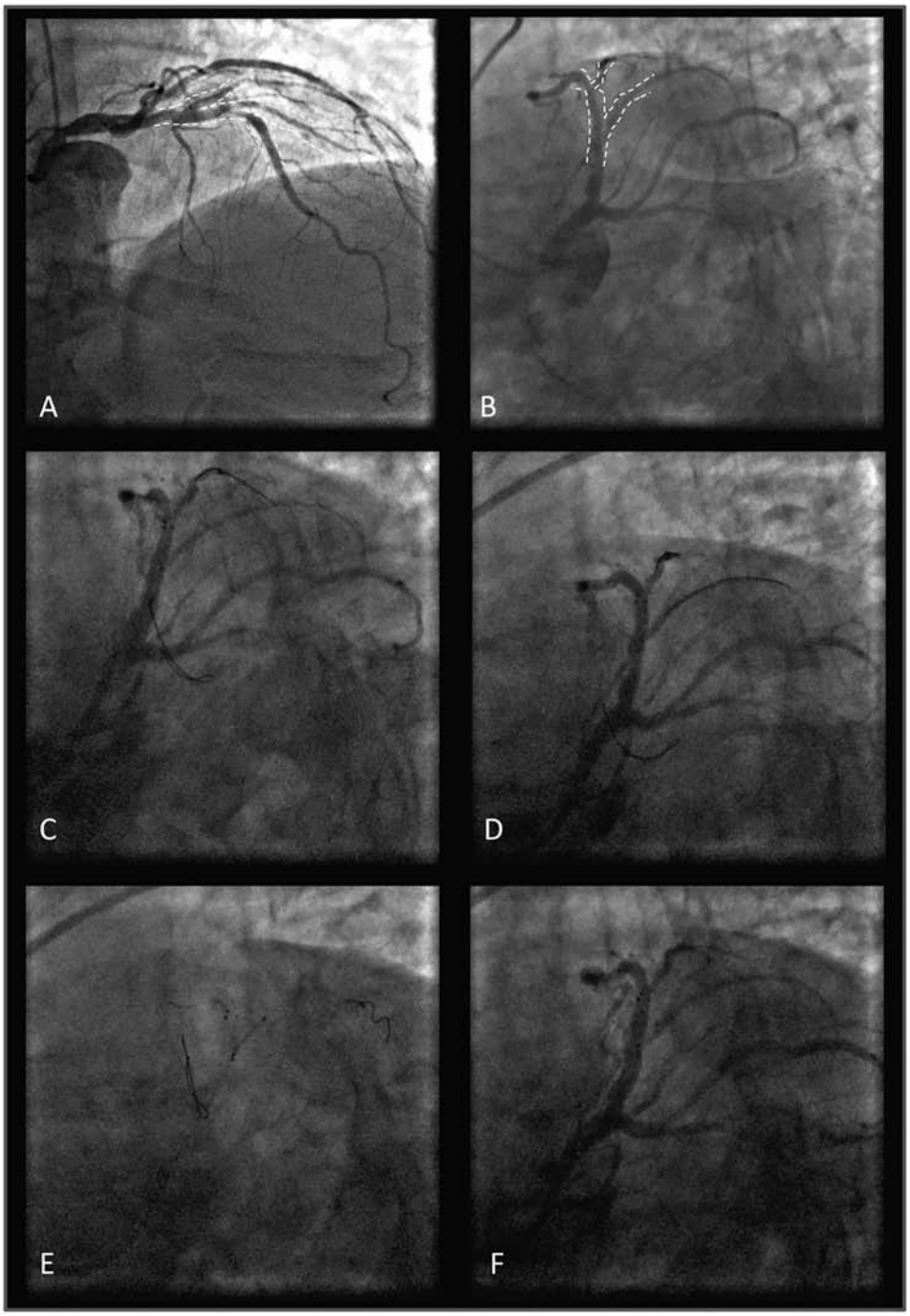

Fig. 2. Coronary angiography showing severe and diffuse LAD coronary artery disease with a double bifurcation lesion involving two large DSB (Figs. A–B). After pre-dilatation of the distal bifurcation lesion and mid LAD, Axxess 3.0 × 11 mm stent was implanted between the proximal and distal DSB, taking care to place the three distal markers correctly into the distal bifurcation (Fig. C, arrow). By using the proximal marker of the Axxess stent as reference pointing the ostium of the proximal SDB, a third wire was placed through the proximal struts of the Axxess self-expanded stent into the first DSB (Fig. D, arrow). After pre-dilatation, a Biomatrix stent 3.0x14mm was passed through these proximal struts of the implanted Axxess stent (Fig. E) and implanted into the proximal DSB performing therefore a "modified" provisional T-stent. After kissing balloon, final angiographic result of the double bifurcation lesion was excellent (Fig. F).

as the initial approach to treat coronary bifurcations occurred both in ACS both in stable patients [12], and the side branch should be treated with a stent only when its flow is compromised or when the balloon results are unsatisfactory. Nevertheless, we need to consider that in many true bifurcation lesions, there is an unacceptable pre-treatment risk of side-branch suboptimal result after the simple provisional stenting, especially in long lesions with two large side-branches, and "shifting" to a double-stent technique after the suboptimal result might complicate and prolong the procedure specially in an acute coronary syndrome scenario. In these cases, stenting the side branch after the main vessel stent placement requires high operator skills and performing a subsequent culotte or crush technique might provide major procedural difficulties - i.e. rewiring the side-branch, main vessel stent distortion, suboptimal carina strut coverage, difficulties in tracking a new stent to the side-branch into the implanted main vessel scaffold - with related high risk of target vessel/lesion failure at some point. Therefore, treating complex double bifurcation lesions occurred during ACS by new dedicated bifurcation devices might represent a useful and challenging

Table 1
Bifurcation dedicated devices: design, major clinical data available and advantages/disadvantages if used in true bifurcation lesions during acute coronary syndrome.

Bifurcation device	Design	Clinical data (ACS data available in bold)	Advantages in ACS	Disadvantages in ACS
NileR™(Minvasys, France)	Balloon-expandable device; Paclitaxel eluting stent; complex delivery system with two separate monorail catheters for main and side branch.	Prospective non-randomised BIPax trial showed favourable early 30-day results in 101 pts. treated with the paclitaxel-NileR stent. **No data in ACS available.**	–	Complex delivery system; Risk of wire twist; Require to maintain SB access during MV implantation
Multi-Link Frontier™ (Abbott Vascular, CA, USA)	Balloon-expandable device; mounted on a specialized dual balloon–dual guidewire delivery system;7Fr- compatible; SB port in its midportion to allow contemporary kissing balloon;	Lefèvre et al. reported a multicenter series with 105 patients, successful implantantion in 91% with a 17.1% MACEs rate at 6 months, SB restenosis rate of 29.9%. **No data in ACS available.**	–	7-French introducer required. Developed for SB stenting at first; self-alignment often incomplete; High SB restenosis.
BiOSS LIM (Balton, Poland)	Balloon-expandable paclitaxel eluting stent; new-available Sirolimus-stent; biodegradable polymer, similar to Tryton but designed for main-branch stenting at first step; central thin part connecting the proximal and distal device structure;	In the POLBOS II randomised trial, the sirolimus eluting device showed similar MACE (11.8%vs15%) and TLR (9.8%vs9%) rate at 12 months compared to DES implantation**, included stable and NSTE-ACS pts.; One international registry reported the safety and feasibility in 74 patients with left-main stenosis including 20% NSTE-ACS patients.**	Developed for MV stenting at first	Complex structure; Requires SB rewiring; risk of wire twist; Suboptimal SB ostium coverage; requires SB stenting for optimal treatment
Taxus Petal™ (Boston, MA, USA)	Balloon-expandable paclitaxel eluting stent; mounted on a dual guidewire–balloon delivery system; 8-Fr compatible.	In the FIM study, the Taxus Petal stent was successfully implanted in 89.3% patients, with a success rate of 73.5% (25/34) per device attempt. Additional stent in the SB required in 25%. Late loss at 6 months was 0.47 mm in proximal main vessel, 0.18 mm in side-branch. TVR at 1 year was 11.1%. **No data in ACS.**	Provisional stenting not precluded.	Low implantation success rate reported; not easy-to-use device with wire trapping risk; self-alignment often incomplete; requires 8-French sheet. High restenosis rate in MV stable segments.
Tryton™ (Tryton Medical, Inc., NC, USA)	Balloon-expandable stent; cobalt-chromium thin strut; designed for culotte technique and side- branch stenting at first step. Radio-opaque markers.	Despite excellent FIM study results, (6 months late loss 0.17 mm, TVR rate 3%), randomized Tryton Privotal Study failed to show non inferiority results vs provisional stenting with mandatory SB dilatation (TVF was 17.4% in Tryton group vs 12.8% in the provisional group; IVUS substudy showed favourable results with no differences in MV and SB luminal area at 9 months between two groups. **One long-term single-centre experience enrolling 91 pts. with 42% ACS, reported high TVR rate at 1 and 2 year follow-up.**	6-French introducer required; Radio-opaque markers.	Developed for side-branch stenting at first; balloon expandable not adapting to carena; precludes the use of a provisional strategy as by design the Tryton requires a double stenting technique with DES in the MV.
Sideguard™ (Cappella Medical Devices Ltd., Ireland)	Self expandable nitinol stent, funnel shaped flared proximal end, designed for side branch stenting at first step and a DES is than implanted in MV;	Sideguard I and II trials, enrolled 83 pts. in 9 centres, technical failure rate 11%, MACE rate 10.8% and TVR 3.6% at 6 months. Late loss 0.58 mm in the SB. No data in ACS. **No data in ACS.**	–	Developed for SB stenting at first; Requires rewiring and final kissing balloon; provisional stenting precluded.
Axxess™ (Devax Inc., CA, USA)	Self expandable stent; conical shape; biolimus A9-eluting stent; designed for MV stenting ending into the carena-proximal SB; Radio-opaque markers.	Studied in 302 pts. with de novo bifurcation stable lesions in the DIVERGE trial; SB was stented with DES Cypher in 64.7% pts.; restenosis rate at 9 months was 6.4% and late loss 0.17 $\pm$ 0.34 mm in the SB. MACE rate was 7.7% including 4.4% TLR at 9 months. **The Carinax registry** evaluated the safety and efficacy of the Axxess stent in **163 pts. with de novo bifurcation lesions including 25% ACS**, with angiographic success in all patients, **but no data are reported regarding the ACS patients treated in this registry.**	Developed for MV stenting at first; fast deployment; adapts its conical shape to carena; rapid exchange catheter over a single wire; SB recrossing and kissing balloon not required; proximal and distal radio-opaque markers; provisional stenting not precluded	7-French introducer required
Stentys ™ (Stentys SAS, Paris, Frances)	Self expandable syrolimus eluting stent; designed for MV stenting; The design allows for strut disconnection after balloon redilatation, requires SB rewiring	OPEN I trial enrolled 40 pts. with de novo stable coronary artery lesions, MACE rate at 30 days was 5.1%. OPEN II study in >200 patients confirmed excellent 4-year clnical data.	Developed for MV stenting at first; provisional stenting not precluded. Favourable results in STEMI patients compared to Resolute stent.	Requires SB rewiring;

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Table 1 (*continued*)

Bifurcation device	Design	Clinical data (ACS data available in bold)	Advantages in ACS	Disadvantages in ACS
		Apposition IV trial comparing Stentys SES with DES Resolute in STEMI patients showed favourable results, with minimum late loss 0.24 mm and excellent stent apposition at 9 months evaluated by OCT.		

option for interventional cardiologists, especially if we consider the criticism that "the optimal bifurcation device" which has to be used in the most of "bifurcation types" is still undefined.

In fact, the interest of interventional cardiologists for dedicated bifurcation devices has been hampered during the years by the practical difficulty to use them. Most of these devices have complex and asymmetrical design, implicating a more difficult placement that require high operator-skill, some have been specifically designed for side-branch treatment at first step, include balloon and self-expandable devices, require different-size introducers and have different torsion and rigidity properties, implicating a limited use specially for treatment of bifurcations occurred during acute coronary syndrome. Bifurcation dedicated devices characteristics, summary of their available clinical data and potential advantages/disadvantages of using each device for treating coronary lesions occurred during acute coronary syndrome are reported in Table 1.

The NileR (Minvasys, Gennevilliers, France) paclitaxel eluting stent and the Advanced Bifurcation Systems (ABS, Los Angeles, CA, USA) devices had a similar delivery system, balloon expandable stent with two independent monorail balloon catheters, one for stent deployment in the main branch and the other for opening the stent towards the side branch [13–15]. Despite these two stents were designed to overcome the problem of side branch rewiring after main branch stenting, other technical problems such the wire twisting, incomplete stent alignment and lacking of randomized clinical results also in setting of stable lesions justified the blunted interest of cardiologists for both these stents. For both, there are no previous reported experiences regarding their use for treatment of complex bifurcations during acute coronary syndrome.

The Tryton bifurcation device (Tryton Medical, Inc., Durham, North Carolina) was a bare-metal stent designed with different proximal and distal diameters designed for a "culotte technique" and first side-branch stenting. After preliminary satisfactory safety results from registries [16,17], the randomized Tryton Pivotal Trial comparing the device vs provisional stenting/side branch balloon strategy failed to show its non-inferiority in stable lesions, mainly related to higher periprocedural myocardial infarction rate (13.6% vs. 10.1%, $p = 0.19$) in the Tryton stent group [18]. However, its post hoc analysis restricted to lesions involving side-branch stenting with a reference vessel diameter ≥ 2.25 mm [19] supported the efficacy of the Tryton stent for treatment of stable bifurcation lesions involving large side-branches. Data on the use of Tryton stent in coronary artery bifurcation lesions occurred during ACS mainly have to be extrapolated from few international non-randomized experiences. A single-centre registry from the Academic Medical Center in Amsterdam reported one and two-year clinical follow-up data after Tryton stent implantation in 91 patients, of which almost a half (42%) had an acute coronary syndrome, but even in this experience the reported target-vessel failure rates were high (14.5% at one year and 20.3% at two year) [20]. Based on data available, Tryton stent may be considered in complex bifurcation anatomies with extensive disease in large side branches, but specific data are necessary in acute coronary syndrome patients specially when the device will be further improved by a drug-coating.

The sirolimus-eluting BIOSSR LIMR stent (Balton, Warsaw, Poland) has a structure similar to the Tryton but it is designed to treat the main branch first; the device consists of two parts, the proximal larger than distal, joined with two connecting struts at the middle zone. In the randomized open-label multicenter POLBOS II trial, when compared with standard bifurcation treatment with DES, the BIOSSR LIMR stent showed a similar cumulative MACE incidence (11.8% vs. 15%), and TLR rate (9.8% vs. 9%) at 12 months [21] in stable and NSTE-ACS coronary lesions; moreover, from an international registry its use resulted safety and feasible also in 74 patients with left-main stenosis including 20% NSTE-ACS patients [22]. However, due to its design the BIOSS LIMR often requires side-branch rewiring and leaves the side-branch ostium uncovered, with absolute need of a second side-branch stenting which may represent a further difficulty in ACS setting.

The Axxess stent is a self-expanding biolimus-A9 eluting stent specifically designed to treat easily the complex anatomy of bifurcation lesions, with a rapid exchange catheter running over a single wire. This stent meet the fashion idea to have available one dedicated bifurcation device that "might fit" all or almost all bifurcation lesions. It can be used for many bifurcation types, with the only limitation being a bifurcation angle of 70° or less. After the early safety and intravascular imaging results [23,24], the 3-year clinical results reported from the Diverge trial were encouraging [25]. The MACE rate was 9.3% at one year, 14.0% at two years and 16.1% at three years. Individual events at three years were 10.1% for ischemia-driven TLR, 2.0% for cardiac death, and 7.4% for MI. ST rate was low, with 2.0% definite ST and 0.7% probable ST. Verheye et al. reported the five-year clinical impact of side branch stenting with a drug-eluting stent following Axxess stent implantation in 400 pooled patients treated with the Axxess stent. There were no significant differences in terms of MACE and its individual components of death, MI and ischemia-driven TLR at five-year follow-up between patients treated with side branch stenting following Axxess stent implantation and patients treated with a provisional strategy without stent, with reported adjusted HR1.37(95% CI: 0.88–2.13) respectively. Moreover, there were no differences in definite ST after side branch stenting, with adjusted HR 1.0 (95% CI: 0.32–3.1) for Axxess plus side branch stent compared to Axxess only.

In the italian Carinax registry [26], a two-center study designed to evaluate the safety and efficacy of the Axxess stent in de novo bifurcation lesions compared to a propensity-matched population, 163 patients were enrolled, including 25% ACS, with angiographic success in all patients and no differences in intra-hospital and 12-month MACE between groups. IVUS analysis performed in only 21 patients showed inaccurate Axxess position in moderate-to-severe calcified lesions and in more distal lesions, suggesting to avoid its use in those cases. No data are reported regarding the ACS patients treated in this registry. Also, the recent published randomized COBRA trial was designed to investigate the healing response of stable true coronary bifurcations after Axxess implantation and it did not include ACS lesions: limited from small simple size, it compared $n = 20$ patients receiving Axxess in the main vessel/Biomatrix stent in the side-branch vs $n = 20$ patients receiving conventional culotte technique, reporting no differences in malapposition or uncovered segments between the two strategies at 9-months OCT evaluation [27].

Therefore, most of experience with dedicated bifurcation devices embraces elective patients with stable coronary artery disease. The APPOSITION IV trial [28] supports the use of the self-expandable sirolimus-eluting STENTYS for treatment of bifurcations in STEMI

patients. Compared with the balloon-expandable zotarolimus-eluting stent, STENTYS resulted in significantly less malapposition and uncovered struts at four months after implantation with similar rates of apposition and coverage segments between groups at nine months, as assessed by OCT. Luminal dimensions were significantly larger in the STENTYS group, with late loss being equivalent between groups, both at four and at nine months. Whether the use of the STENTYS can improve clinical outcomes in STEMI patients undergoing primary PCI compared to balloon-expandable stents needs to be proven.

In our case we show that Axxess stent implantation is feasible and possible for the treatment of complex bifurcation lesions occurred in the scenario of acute coronary syndrome, in which the "must" is to obtain restoration of coronary flow. Moreover for the first time we treated a "true double bifurcation lesion" by using a single Axxess stent as main scaffold for treatment of both proximal and distal bifurcation. Stent design permitted to approach the distal bifurcation as reported by manufacturer, successively stent struts at its proximal edge were easily recrossed to perform a provisional T stenting in the proximal diagonal side branch. Thus, the complex anatomy of this coronary tree was satisfactory preserved.

Previously, only two cases of "true double bifurcation lesion" were reported, treated differently. Jim MH et al. [5] reported the case of a double-bifurcation lesion treated by balloon-expandable sirolimus-eluting stents and the sleeve technique to reconstruct the vessel and its 2 bifurcations. The sleeve technique is a modified version of the crush technique. It involves stent placement in the side branch ostium, balloon-crush of the proximal protruding stent segment against the main vessel wall, and reconstruction of the side branch ostium by kissing balloon inflation, followed by stenting of the main vessel and reconstruction of the bifurcation again by a second kissing balloon inflation. However, in our opinion, this technique has the limit to "overcoverage" the bifurcation with stent struts deforming the natural carina and exposing the patient to high-risk of stent thrombosis. Compared to this technique, the advantage using the Axxess stent in difficult bifurcation lesions is also its self-expandable property which guarantees optimal and progressive strut coverage at carina site. In a second case report, Unzue L. et al. [29] used two Tryton Sidebranch Stent implanted in two side branches - close each other- and successively a single long DES was implanted into mid LAD between them and covering the two Tryton stent. Compared to this latter strategy, our case launches the "idea" to treat two close side-branches by implantation of a single self-expandable Axxess-stent and using its distal and proximal markers to guide the treatment of the two close diagonal side branches guaranteeing a minimum strut overlapping.

In conclusion, treatment of complex coronary bifurcations such as "true bifurcation lesions" still represents a challenging not-standardized procedure for interventional cardiologists, especially when occurred during ACS. In some cases, their treatment by bifurcation dedicated devices might be a fascinating option for "easy and fast" coronary flow restoration preserving the complex bifurcation anatomy, but further studies are necessary to test specifically these devices in ACS.

Conflict of Interest

The authors declare that they have no conflict of interest.

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