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The AXXESS™ Self-Expanding Biolimus A9™ Eluting Stent System for coronary bifurcation lesions

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Abbreviations

BMS	bare metal stent
DES	drug-eluting stent
IVUS	intravascular ultrasound
LMCA	left main coronary artery
MACE	major adverse cardiac events
MI	myocardial infarction
MV	main vessel
PCI	percutaneous coronary intervention
PLA	polylactic acid
SB	side branch
SES	sirolimus-eluting stent
TLR	target lesion revascularisation

Introduction

Procedural difficulties during and worse outcome after percutaneous coronary interventions (PCI) in bifurcated lesions are related to the mismatch between the cylindrical shape of balloon-expandable stents and the Y-shape of the bifurcation. Indeed, most available tools and techniques fail to optimally conform to this variable bifurcation anatomy and to restore ideal flow characteristics, making these lesions more prone to restenosis and stent thrombosis. The Biosensors AXXESS™ Biolimus A9™ Eluting Coronary Bifurcation Stent System (AXXESS System) intends to provide an adequate answer to these issues by combining conical shape with self-expanding and -apposing properties as well as limus-mediated antiproliferative effects.

Device description and implantation technique

The AXXESS System is a self-expanding, conically-shaped laser-cut stent from nitinol (nickel-titanium alloy) in the austenitic (i.e., superelastic) phase with a 0.006-inch (0.15 mm) strut thickness, specifically designed to conform to the anatomy at the level of the bifurcation carina (Figure 1). It has a rapid-exchange delivery system with hydrophilic coating, which allows controlled stent release upon withdrawal of a cover sheath using an actuator. Optimal deployment is guided by progressive flaring of three gold markers at the distal stent edge during unsheathing. Ideally, the stent can be positioned with these markers in both distal branches, allowing easy access for additional branch stenting whenever appropriate. The current version of the AXXESS System can accommodate vessels from 2.75 to 4.25 mm diameter, and is available in two different lengths (10 and 14 mm). The stent is designed to exert a stable amount of force again the vessel wall over its stated diameter. The distal flare can expand to as much as 8 mm in the largest diameter version. A special version of the AXXESS System has been designed for left main bifurcation lesions, allowing for larger diameters (up to 4.75 mm) and distinct bifurcation angles (flare-end diameters of 8, 10 and 12 mm).

The drug-eluting version (AXXESS Plus) is coated with Biolimus A9™, a highly lipophilic, semi-synthetic sirolimus analogue with an alkoxy-alkyl group replacing hydrogen at position 42-O (Biosensors International, Morges, Switzerland).[1] At a cellular level, biolimus forms a complex with intracellular FKBP-12, which binds to the mammalian target of rapamycin and reversibly inhibits cell-cycle

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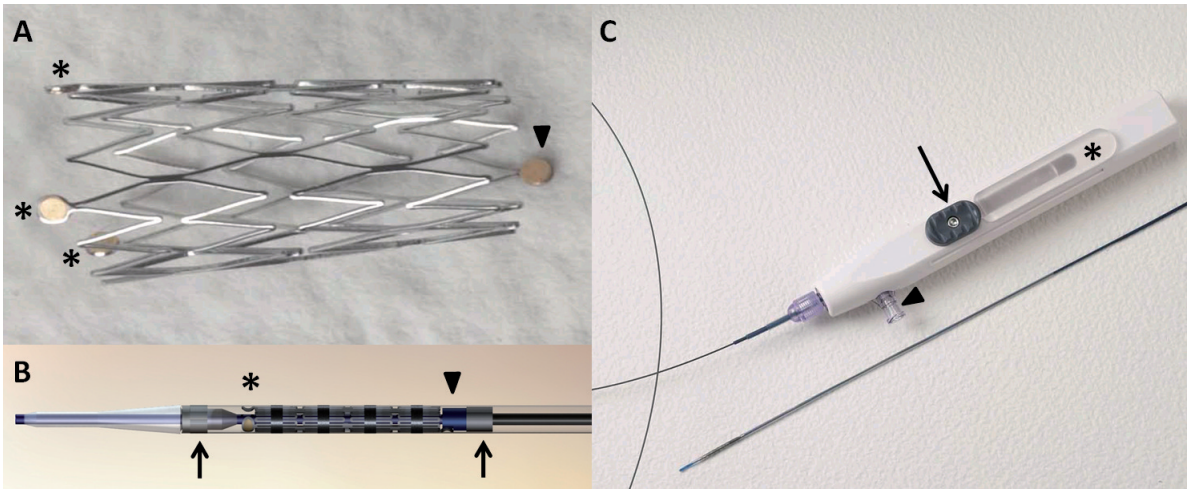

Figure 1. AXXESS stent and delivery system. The AXXESS System is a conically-shaped self-expanding nitinol stent, specifically designed for the treatment of coronary bifurcation lesions. It has three highly visible radio-opaque markers located at the tip of the stent to facilitate placement (Panel A, asterisks). These markers are also convenient for accurate placement of additional stents in the branch vessels. A fourth marker locates the proximal edge of the stent (Panel A, arrowhead). The crimped stent (Panel B) is contained in a cover sheath with radio-opaque edges (arrows), extending outside the distal and proximal markers of the stent (asterisks and arrowhead, respectively). Progressive stent deployment and expansion is controlled by an actuator on the delivery system (Panel C, arrow). (arrowhead: flush-port; asterisk: safety-lock).

transition of proliferating smooth muscle cells with a similar potency to sirolimus. The drug is immersed at a concentration of 22 µg per mm stent length into a biodegradable polymer, polylactic acid (PLA), which is applied solely to the abluminal surface of the AXXESS stent. On the basis of *in vivo* studies, PLA completely dissolves into carbon dioxide and water after a 6-9 months period (data on file at Biosensors). A similar combination of PLA and abluminal biolimus-elution has previously shown to represent a safe and effective alternative to a stent eluting sirolimus from a durable polymer in an all-comers population of patients with chronic stable coronary artery disease or acute coronary syndromes.[2]

The current version of the AXXESS stent necessitates a 7 Fr approach and fits most bifurcations up to an angle of 70° (or higher for the left main version with flare-end diameters up to 12 mm). Critical steps of the procedure are represented in Figure 2.[3] Predilatation of main vessel (MV) and side branch (SB) using a standard bifurcation two-wire technique is left at the discretion of the operator, but is highly recommended for tight lesions and heavily calcified vessel segments, in order to facilitate lesion crossing and optimal distal flaring at the carina site. The AXXESS System is then advanced on one of both wires, preferably towards the distal branch presenting the sharpest angle with the proximal mother vessel, hereby facilitating the stent flare into the opposite vessel. At the carina level, the stent is then progressively unsheathed, intending one or two distal stent markers to protrude into the opposite distal branch. As long as the cover sheath contains more than half the stent length, further adjustment of the stent position remains possible. Once an optimal position has been obtained, the delivery system is gently maintained at the carina level, while further unsheathing fully releases the stent. With optimal positioning, the stent spans both the MV and the SB, without obstructing access to either. Most often, a third wire is then easily advanced towards the opposite branch. It is recommended to test easy crossing towards this branch with a conventional balloon in order to exclude any resistance due to accidental strut crossing, after which the jailed wire can be retrieved. At this stage, the angiographic result can eventually be optimised using a kissing balloon inflation. Depending on initial lesion anatomy and actual procedural result, one or two additional, preferably drug-eluting stents (DES) can then be implanted in the distal MV and SB to complete lesion coverage, hereby respecting a 1 to 2 mm overlap with the distal AXXESS System markers. Final high-pressure and kissing balloon inflations of appropriate size are recommended in this overlap region, while avoiding vessel damage outside the stent edges.

From bench to bedside

The AXXESS System has been under development since 2003 by Devax, Inc., a development stage company with offices in Lake Forest, CA, USA. The company has recently been acquired by Biosensors International Group, which was already licensing the biodegradable polymer and proprietary Biolimus A9™ used in the AXXESS Plus.

The clinical implementation of the AXXESS stent has been preceded by intense bench development as well as preclinical *in vivo* testing.

First, optimal size and flaring capabilities as well as technical deployment steps have been evaluated in flow models in order to optimally conform to most bifurcation anatomies as well as to provide reproducible stent release at the target site (Figure 3).

Next, deployment strategy and periprocedural *in vivo* handling and visualisation have extensively been assessed in numerous porcine coronary bifurcations.

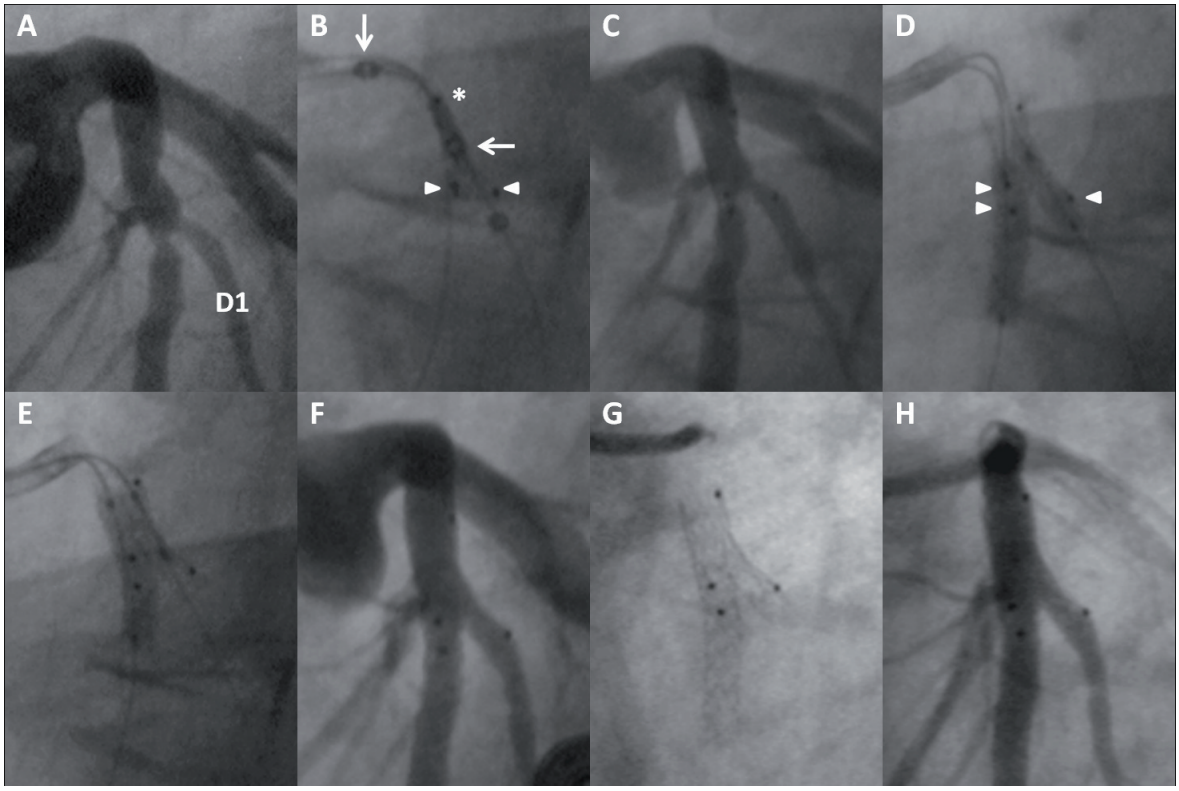

Figure 2. Key procedural steps. Panel A. Magnification of a LAO-cranial projection of a 0,1,1 lesion in the bifurcation of the left anterior descending artery (LAD) and first diagonal branch (D1). Panel B. After double wiring and predilatation of LAD and D1, the AXXESS System is advanced towards D1 and progressively unsheathed (arrows: sheath markers), aiming at positioning at least one distal stent marker (arrowheads) in the distal LAD. In this case two distal markers protrude into the LAD, while one remains deeply into the D1, confirming optimal position at the target site. (asterisk: proximal stent marker). Panel C. Immediate result after AXXESS deployment. Only the stent edge markers are now visible. Panel D. Procedural optimisation requires rewiring towards the LAD, followed by kissing balloon inflation. In this case we opted for additional stenting of the ostium of both distal branches, aiming at slight overlap with all three distal AXXESS markers (arrowheads). Panel E. Finally, stent expansion is optimised with more proximal high-pressure and kissing balloon inflation. Panel F. Final angiographic result. Panel G: Stent-boost image shows how the stent frames perfectly conform to native bifurcation anatomy. Panel H: Angiographic image nine months after AXXESS implantation.

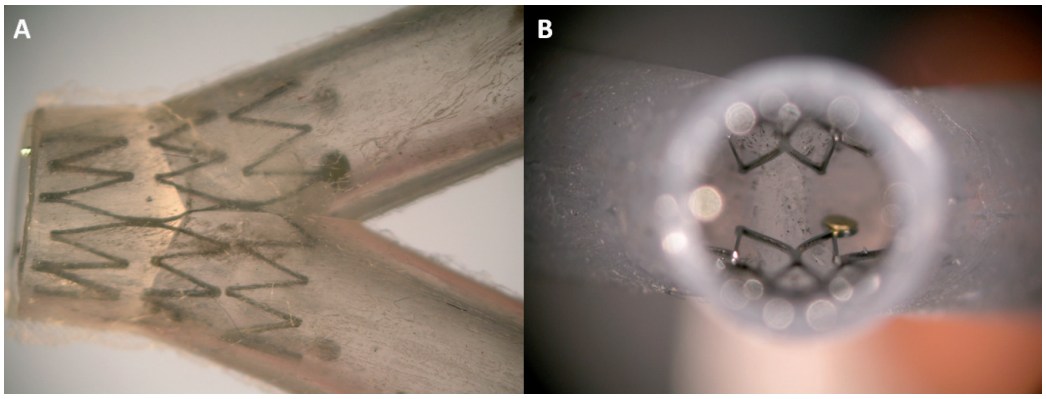

Figure 3. Bench model. Panel A. Optimal seating of the AXXESS stent after implantation in a flow model. The three distal stent markers nicely span the whole carina area, ensuring easy access to both distal branches. Panel B. Perpendicular view on the carina confirming partial coverage of the flow-divider and protrusion of struts in both distal branches.

Parallelly, the long-term effects of the AXXESS™ Biolimus A9™ Eluting System were evaluated in a porcine coronary model, and compared with those of a bare metal stent (BMS) and polymer only stent controls.[4] In this study, the AXXESS Plus stent favourably modulated neointimal formation at 28 and 90 days. Long-term inhibition of neointimal hyperplasia was not sustained, presumably because of delayed cellular proliferation and inflammation. However, a distinct species response to the antiproliferative and immunosuppressive effects of biolimus may in part account for the disparity between these early and late results.[5] Moreover, a different anatomic and cellular substrate of atherosclerotic versus normal porcine coronary arteries, as well as differences in physiologic

stimuli for neointimal formation, could equally play a role.[6] Although the AXXESS System is designed to minimise stent overlap and avoid stent distortion at the bifurcation site, a minimal overlap with additional branch stents has been proposed to avoid ostial branch restenosis due to improper lesion coverage. In a porcine study evaluating a BMS and two different types of DES overlapped with the AXXESS™ Biolimus A9™ Eluting System, a delay in the degree of vascular healing with DES was seen compared to BMS.[7] In this study, the specific type of DES that was overlapped with the biolimus-eluting stent did not affect the behaviour of the overlap zone in terms of most of the histomorphometric measures at 28 or 180 days.

Currently, 517 patients have been treated with the AXXESS System in well conducted multicentre single-arm studies with prospective enrolment and careful and independent monitoring of data acquisition and event reporting.

In a first safety and efficacy study, 43 patients successfully underwent implantation of the AXXESS BMS. This experience was soon followed by a larger (N=139) registry using the AXXESS Plus biolimus-eluting version, with or without adjunctive paclitaxel- or sirolimus-eluting stents (SES).[8] The primary endpoint of this study was in-stent angiographic late loss at 6-months follow-up, as measured by quantitative computerised angiographic analysis. A careful analysis was performed for each bifurcation segment taking into account the treatment modality in the SB (additional DES, balloon only, or no treatment). Overall in-stent late loss in the stented MV segment was 0.19 mm (0.9 mm in the AXXESS stent and 0.21 mm in the distal MV stent). A similar late loss was seen in the SB, but resulted in a significantly higher restenosis rate in the SB in patients undergoing SB balloon only angioplasty, as compared to SB stenting or no treatment (25% vs. 9.2% and 12%, respectively). The overall rate of major adverse cardiac events (MACE) at six months was 11.2%, including death (0.7%), any myocardial infarction (MI, 6%) and ischaemia-driven target lesion revascularisation (TLR, 7.5%). A limited number of patients in the AXXESS Plus trial underwent intravascular ultrasound (IVUS) interrogation at six months follow-up, confirming effective lesion coverage along with significant neointimal suppression.[9]

Based on these results, the pivotal DIVERGE trial was designed to expand these results in a broader population (N=302), keeping stricter protocol obligations for lesion treatment, such as the mandated use of SES as additional stents for the distal MV and SB if the residual diameter stenosis exceeded 30%.[10] In this large cohort with 77% of true bifurcation lesions, the AXXESS System was delivered successfully in 99% of cases, with optimal positioning in 93%. Most patients underwent additional implantation of SES (65% in both distal MV and SB; 18% in MV only; 4% in SB only). The primary endpoint in this trial was the rate of MACE at nine months after stent implantation, a composite of death, MI and TLR. The cumulative MACE rate for the total population was 7.7%, including 0.7% death, 4.3% MI and 4.3% TLR. There were two early and one late stent thromboses. The first 150 patients were included in a substudy with angiographic follow-up, and among these, a subgroup (N=76) equally was scheduled for IVUS analysis. In this cohort, in-bifurcation restenosis occurred in nine patients (6.4%), of whom only one (0.7%) in the AXXESS segment. IVUS analysis confirmed potent antiproliferative efficacy after biolimus elution with neointimal hyperplasia obstruction as low as 4% of stent volume. Moreover, a net increase in mean volume of stent and lumen from 7 mm^3/mm from procedure to over 9 mm^3/mm at nine months follow-up corroborated the expected progressive further expansion of a nitinol stent early after implantation.

Similar encouraging results have been obtained in the left main coronary artery (LMCA) bifurcation with an adapted AXXESS design with larger diameter and distal flare, conforming to typically wider angles between the left anterior descending artery and the circumflex artery. In the AXXENT trial, a small cohort of patients (N=33) underwent IVUS immediately after PCI of the LMCA and at six months follow-up.[11] The AXXESS System in the LMCA showed enlargement through follow-up as well as significant neointimal suppression. In wide angle bifurcations, however, greater neointimal formation and relatively inadequate stent expansion contributed to luminal narrowing in the circumflex ostium, underscoring the need for appropriate lesion selection and/or improved LMCA stent design.

Based on these results, CE-Mark for the Biosensors AXXESS™ Biolimus A9™ Eluting Coronary Bifurcation Stent System was obtained in July 2010.

The operator's perspective

Novel dedicated bifurcation stents have been developed to provide easier access to the SB, to scaffold more effectively its ostium, and to match more closely to the anatomy at the carina level. However, many of these devices are limited by the variation in bifurcation anatomy, with different angles and size mismatch between mother and daughter branches, and variable extent of atherosclerotic disease.

The AXXESS strategy therefore represents a stepwise bifurcation reconstruction, tailored to this variable vessel anatomy. The conical shape of the AXXESS System provides optimal coverage of the wider carina region, while separate balloon-expandable DES of different lengths can be selected according to branch vessel size and extent of disease. The self-expanding properties of the AXXESS allow for conformance of the device to the vessel contour without disruption of the stent or coating, and preserve the access to both branches by flaring of the distal stent portion at the carina level. Careful positioning of the device with distal stent markers in both branches is a learning process, but step-wise stent release and highly visible sheath and progressively flaring distal stent markers provide a predictable outcome and deployment at the target site in most cases, as evidenced by high percentages of perfect stent position in the DIVERGE trial. Moreover, the AXXESS System has adopted early in its development an antiproliferative polymer and drug combination designed to highly effectively and safely inhibit neointima formation, combining third generation DES principles: reduced polymer content, exclusively located on the abluminal stent face; fully biodegradable polymer; potent antiproliferative sirolimus analogue; and finally reduced drug dose with abluminal elution. The triple stent approach, as applied in most AXXESS procedures, represents both an opportunity (optimal bifurcation reconstruction) and a limitation (procedural cost). However, in PCI of complex bifurcation lesions such tailored approach could be preferred over current double

stenting techniques, such as culotte or crush, which typically recommend high pressure non-compliant kissing balloon dilatation to compress, distort or correct obstructing stent struts at the carina level. In contrast, the AXXESS technique allows for provisional branch stenting with balloon expandable stents, without distortion from their cylindrical shape. Because the AXXESS System covers the ostium of the branch vessels, distal stents are placed at or slightly distal to the carina, thus eliminating ostial stent strut obstruction and minimising stent strut overlap, providing undisturbed flow into the distal branch vessels. The combination of these characteristics with the self-expanding properties of the AXXESS System and the local drug delivery could be a mechanistic explanation of the very low MACE and stent thrombosis rate observed in the DIVERGE trial. This dedicated stenting technology is therefore particularly suited for PCI of true bifurcation lesions, especially in large coronary vessels, and could eventually provide a tailored and highly effective approach for treatment of the LMCA bifurcation.

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