PATIENTS WITH CORONARY ARTERY BIFURCATION LESIONS TREATED BY AXXESS STENT IMPLANTATION

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SUMMARY

***Objectives**: To compare the result and safety of the Axxess biolimus-eluting stent with the second-generation drug-eluting stent (DES) in the treatment of bifurcation lesions. **Subjects and methods**: Between May 2014 and December 2017, 141 patients with de novo bifurcation lesions were treated with the Axxess stent (Axxess group: 51 patients) and without the Axxess stent (Control group: 90 patients treated with DES). The primary objectives were (1) the device, the angiographic, and the procedural success rate; and (2) the trouble in side branch (SB) access and the procedural complication rate (including SB occlusion). **Results**: Device success was obtained in all patients in both groups. Angiographic success was obtained in 50 patients (98.04%) in the Axxess group and in 80 patients (88.89%) in the control group (p = 0.057). Procedural success was obtained in 50 patients (98.04%) in the Axxess group and in 80 patients (88.89%) in the control group (p = 0.057). Trouble in SB access did not occur in the Axxess group but in 19 patients (21.11%) in the control group (p < 0.001). Procedural complications occurred in 1 patient (1.96%) in the Axxess group and in 10 patients (11.11%) in the control group (p = 0.057). **Conclusion**: The result and safety of the Axxess biolimus-eluting stent were better than DES in treating bifurcation lesions. The present study suggests that the Axxess stent may represent a valid alternative approach for treating bifurcation lesions.*

** Keywords: Coronary bifurcation lesions; Axxess stent.*

INTRODUCTION

The main vessel (MV) stenting and provisional side branch (SB) stenting technique is the preferred approach for the treatment of bifurcation lesions [1]. This strategy, however, has two major limitations: (1) the risk for SB occlusion [2, 3] and (2) the technical issues in the cross-over to complex-2 stent approach. The Axxess Biolimus A9 Eluting Coronary Bifurcation Stent System (AXXESS System; Biosensors, International, Morges, Switzerland; Fig. 1) is a dedicated bifurcation stent designed to cover the lesion at the level of the carina [4, 5, 6]. The present study is a prospective, two-center one designed to *assess the result and the safety of the Axxess stent compared to second generation balloon-expandable drug-eluting stent (DES) for the treatment of bifurcation lesions in a real-world population.*

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Date received: 08/6/2021

Date accepted: 22/6/2021

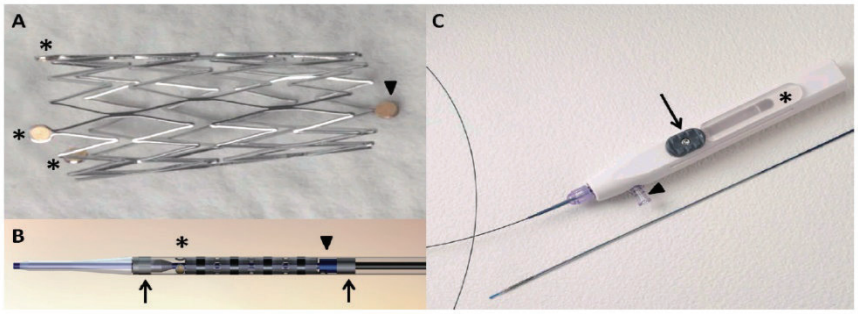

Figure 1: The Axxess Biolimus A9 Eluting Coronary Bifurcation Stent System.

SUBJECTS AND METHODS

1. Subjects

Between May 2014 and December 2017, all consecutive patients with de novo bifurcation lesions treated at Vietnam National Heart Institute, Bach Mai Hospital, and Ha Noi Medical University Hospital were screened for the study.

** Inclusion criteria:*

- Age ≥18 years;

- Acute coronary artery syndrome (ACS, including STEMI, NSTEMI and Unstable Angina);

- Bifurcation *de novo* lesions (Coronary artery narrowing occurring adjacent to, and/or involving the origin of a significant side branch [7]);

- Main vessel reference diameter ≥ 2.75 mm ≤ 4.75 mm (by visual estimate);

- Side branch reference diameter ≥ 2.5 mm (by visual estimate);

- Bifurcation angle < 70° with Axxess group (by visual estimate).

** Exclusion criteria:*

- Women who are pregnant;

- Cardiogenic shock (Acute systolic blood pressure < 80 mm Hg despite correction of hypovolemia and inotropic drugs);

- Left main disease (Stenosis > 50%);

- Contraindications to prolonged dual-antiplatelet therapy

- Known sensitivity to "litmus" compounds, stainless steel, titanium, or nickel

- Life expectancy < 1 year.

Patients treated with the Axxess DES (Axxess group) were compared with patients treated with second-generation balloon expandable DES in the same period (control group). The local Vietnam National Heart Institute Committees approved the study protocol, and all patients gave written informed consent.

2. Methods

** Percutaneous coronary intervention:*

In the control group, the bifurcation lesion was treated according to the "gold standard" technique, MV stenting with provisional SB stenting [1]. The technique for the 2-stent approach was left to operator's choice [8]. A patient was considered for Axxess stent implantation based on (a) satisfaction of the angiographic criteria; (b) proximal MV lesion length < 14 mm (suitable for treatment with the longest Axxess stent); (c) bifurcation angle < 70° and (d) operator's preference. In the Axxess group, the following four approaches have

been reported: (1) Axxess stent alone; (2) Axxess stent plus additional DES in the distal MV; (3) Axxessstent plus additional DES in the SB; and (4) Axxess stent plus additional DES in the distal MV and in the SB [4]. All patients received unfractionated heparin before starting the procedure. All patients were on dual anti-platelet therapy. Patients continued to receive daily lifelong aspirin (100 mg/day) and a thienopyridine for at least 12 months.

** Quantitative Coronary Angiography (QCA):*

QCA was performed using the single-vessel QCA. Bifurcation lesions were classified according to Medina et al. [9]. Stent malapposition was defined as space behind stent struts not overlying SB. Lumen symmetry was calculated as minimum lumen diameter divided by maximum lumen diameter. Evaluation of stent struts jailing the SB orifice was based on the extent of isolated struts found in this region using images obtained from the MB pullback. Isolated struts were defined as one or more stent struts across the SB ostium.

** Study objectives:*

The study's primary objectives were (1) the device success, defined as successful deployment of the stent into the target lesion, without system failure or device-related complication. In the Axxess group, accurate stent deployment was considered if ≥ 1 of the 3 distal markers of the stent was clearly placed in each of the MV and SB, or if at least 2 markers were in the triangle formed by the carina and the ostia of the branch vessels [4, 5, 6]; (2) angiographic success, defined as a < 20% residual stenosis in MV with final TIMI 3 flow in both (MV and SB) vessels without flow-limiting dissection or angiographic thrombus [10]; (3) procedural success, defined as lesion success without any in-hospital major adverse cardiovascular events (MACE), including death, both spontaneous and peri-procedural myocardial infarction (MI), and repeat (both surgical or percutaneous) target lesion (TLR) or vessel revascularization [10]; (4) procedural complication rate, including SB occlusion, defined as intraprocedural TIMI flow grade < 3 immediately after MV stenting in the control group and after Axxess stent implantation in the Axxess group [2]; (5) trouble in SB access, defined as failure to recross in the SB through the MV stent cell; (6) stent deformation, defined as a distortion of the proximal end or distal end of the stent as a consequence of forward pressure on an angioplasty balloon or guide catheter [11]; and (7) assessment of resources utilization, including the total number of stents, the contrast media volume and the procedural time. All deaths were considered cardiac unless attributable to a specific noncardiac cause. MI was defined according to the third universal definition [12]. In particular, peri-procedural MI was defined as creatine-kinase mass concentration > 3 times upper-limit-of normal increase plus either evidence of prolonged ischemia (> 20 min) as demonstrated by prolonged chest pain, or ischemic stent thrombosis (ST) changes or new pathological Q waves, or angiographic evidence of a flow limiting complication [12]. Medical records, discharge summaries, and coronary angiography were systematically reviewed by two expert interventional cardiologists.

** Statistical analysis:*

The sample size was selected expecting a >10% procedural complications rate in the Control group [2], 14] and a <3% rate in the Axxess group. Therefore, a total of at least 47 patients provides the study 80% power (using a one-sided Chi-square test with a significance level of 0.05) and 95% confidence interval (CI) to prove the above hypothesis. All analyses were conducted according to the intention-to-treat principle. Continuous data were reported as mean ± standard deviation. Categorical data are presented as absolute numbers and percentages. Continuous variables were compared using an unpaired Student's T-test and categorical data using the X2 test or Fisher exact test, as appropriate. Patients in the Control group were selected from patients with de novo bifurcation lesions treated in our centers in the same study period (nonrandomized nature). A propensity score was calculated by performing a multiparsimonious multivariable logistic regression with stent type as the dependent variable. Variables included in the logistic regression model were (a) vessel type; (b) bifurcation site; (c) bifurcation type according to Medina's classification; (d) reference vessel size, minimal lumen diameter, and lesion length in both the MV and SB, (e) bifurcation angle; (f) SYNTAX score; (g) age, sex, and diabetes mellitus. P values of < 0.05 were considered statistically significant. Statistical analyses were performed using Stata 11.2 for Windows (Stata Corp. LP).

RESULTS

1. Patients population

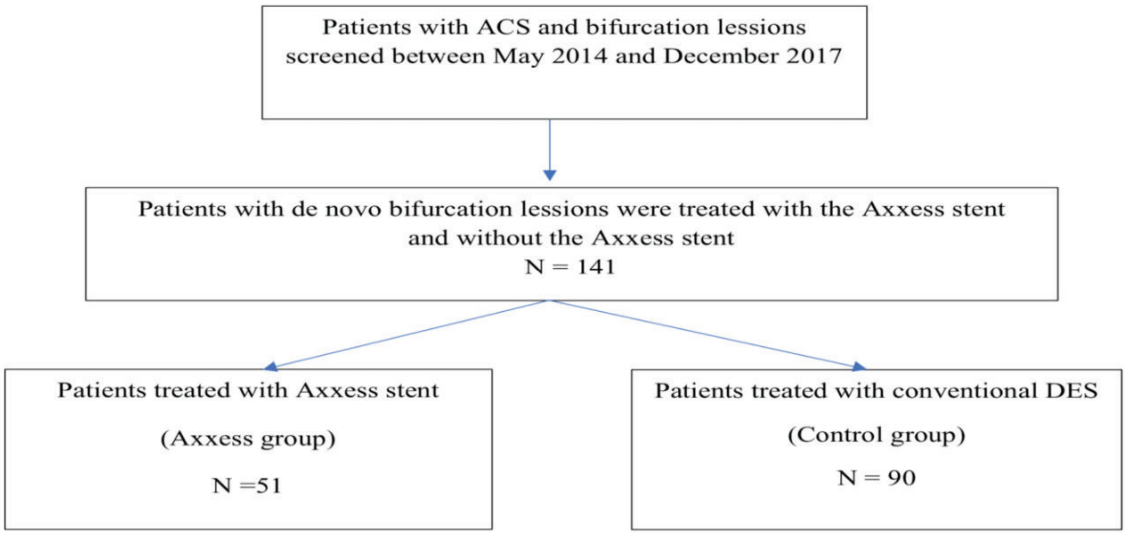

Figure 2: Flow-chat of the study.

Table 1: Baseline clinical characteristics.

Variable	Axxess group n = 51	Control group n = 90	p-value
Demographics			
Age (years)	64 ± 7	67 ± 10	0.047
Male sex	40 (78.43)	63 (70)	0,278
Physical measurements			
Body mass index (kg/m^2)	22.22 ± 2.91	21.96 ± 2.38	0.572
Heart rate (b.p.m)	77 ± 7	82 ± 13	0.017
Systolic blood pressure (mmHg)	128 ± 17	131 ± 21	0.300
Diastolic blood pressure (mmHg)	77 ± 8	78 ± 12	0.679
Risk factors			
Hypertension	38 (74.5)	73 (81.1)	0.357
Diabetes mellitus	13 (25.5)	29 (32.2)	> 0.05
Previous myocardial infarction	9 (17.7)	3 (3.3)	0.009
Prior PCI	20 (39.2)	12 (13.3)	< 0.001
Current smoking	11 (21.6)	23 (25.6)	0.595
Presentation at admission			
Unstable angina	45 (88.24)	46 (51.11)	< 0.001
NSTEMI	1 (1.96)	10 (11.11)	
STEMI	5 (9.8)	34 (37.78)	
Left ventricular ejection fraction (%)	61.3 ± 10.6	55.3 ± 14.6	0.011
EF < 40%	2 (3.9)	13 (14.8)	
EF ≥ 40%	49 (96.1)	75 (85.2)	< 0.05
Laboratory measurements			
Creatinin (µmol/L)	93.3 ± 16.3	95.4 ± 26.2	0.613
White blood cell count (G/L)	8.61 ± 2.19	9.48 ± 3.91	0.153
Haemoglobin (mg/dL)	139.7 ± 10.8	135.8 ± 16.2	0.131
Platelet count (G/L)	242.35 ± 61.74	254.78 ± 73.34	0.317

(Value are n (%) or mean ± SD)

Table 2: Lesions characteristics

Variable		Axxess group n = 51	Control group n = 90	p-value
SYNTAX score		16.6 ± 4.3	18.8 ± 7.1	0.040
SYNTAX score ≤ 22	n (%)	49 (96.08)	65 (72.22)	
23 ≤ SYNTAX score ≤ 32	n (%)	2 (3.92)	22 (24.44)	
SYNTAX score > 32	n (%)	0 (0.0)	3 (3.33)	0.001
Target vessel	n (%)			
Left anterior descending/diagonal		47 (92.16)	65 (72.22)	0.007
Circumflex/obtuse marginal		3 (5.88)	9 (10.0)	
Right/posterior descending		1 (1.96)	16 (17.78)	
Medina classification	n (%)			
Medina 1.1.1		33 (64.71)	35 (38.89)	
Medina 1.1.0		7 (13.73)	36 (40.0)	
Medina 1.0.1		2 (3.92)	4 (4.44)	0.005
Medina 0.1.1		5 (9.80)	5 (5.56)	
Medina 1.0.0		3 (5.88)	3 (3.33)	
Medina 0.1.0		1 (1.96)	7 (7.78)	
Medina 0.0.1		0 (0.0)	0 (0.0)	
Bifurcation angle < 70°		51 (100)	61 (67.78)	< 0.001

Fifty-one patients were included in the Axxess groups and ninety patients were included in the control groups (*figure 2*). There were some clinical differences between the two groups. The higher rate of STEMI, heart rate, SYNTAX score, and EF < 40% were in the control group. But the higher rate of true bifurcation (including Medina 1.1.1, Medina 1.0.1 and Medina 0.1.1) was in the Axxess group (*Table 1, 2*).

Table 3: Procedural characteristics.

Variable		Axxess group n = 51	Control group n = 90	p-value
Transradial approach	n (%)	0 (0.0)	80 (88.89)	< 0.001
Pre-dilation	n (%)			
Main vessel		51 (100)	90 (100)	1.00
Side branch		46 (90.2)	20 (22.22)	< 0.001
Stent implantation	n (%)			
Main vessel only		14 (27.45)	86 (95.56)	< 0.010
Main vessel + Side branch		37 (72.55)	4 (4.44)	

Variable	Axxess group n = 51	Control group n = 90	p-value
Device success n (%)	51 (100)	90 (100)	1.000
Number of stents implanted (including Axxess) n (%)			
1 stent	3 (5.88)	61 (67.78)	
2 stents	13 (25.49)	23 (25.56)	< 0.001
3 stents	33 (64.71)	5 (5.56)	
4 stents	2 (3.92)	1 (1.11)	
Failure to recross in the SB n (%)	0 (0.0)	19 (21.11)	< 0.001
Post-dilation n (%)			
Main vessel only	0 (0.0)	81 (90)	< 0.001
Final kissing balloon inflation	51 (100)	8 (8.89)	
Postprocedure n (%)			
Residual stenosis < 20% in MV	51 (100)	90 (100)	1.00
Residual stenosis < 50% in SB	51 (100)	69 (76.67)	< 0.001
TIMI grade flow < 3 in MV	0 (0.0)	2 (2.22)	0,535
TIMI grade flow < 3 in SB	0 (0.0)	10 (11.11)	0.088
Perforation due to stent deformation n (%)	1 (1.96)	0 (0.0)	0.362
Angiographic success n (%)	50 (98.04)	80 (88.89)	0.057
Procedural time (min)	66.4 ± 19.0	47.8 ± 22.7	< 0.001
Contrast volume (mL)	222.2 ± 66.9	181.7 ± 50.6	< 0.001

* *Device success:* was obtained in all patients in both groups.

* *Procedural characteristics and angiographic success:*

Predilation in SB was performed in 90.2% of cases in the Axxess group and in 22.22% of cases in the control group (p < 0.001). Complex bifurcation stenting approach (that is, both MV and SB stenting) was more frequent in the Axxess group (37/51 [72.55%] vs. 4/90 [4.44%]; p < 0.01).

Angiographic success was obtained in 50 patients (98.04%) in the Axxess group and in 80 patients (88.89%) in the control group (p = 0.057). The final diameter stenosis in the SB was significantly lower in the Axxess group.

* *Procedural complications:*

Procedural complications occurred in 1 patient (1.96%) in the Axxess group and in 10 patients (11.11%) in the control group (p = 0.057). In particular, type I coronary perforation was caused by stent deformation that occurred in one case of the Axxess group due to the forward pressure on an angioplasty balloon, and SB occlusion occurred in 10 patients (11.11%) in the control group.

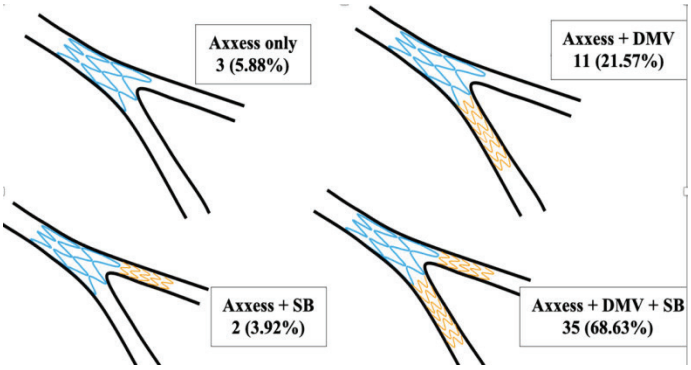

Figure 3: Stent distribution patterns in the Axxess group.

Table 4: Intra-procedural complications in true bifurcation.

Variable	Axxess group n = 40	Control group n = 44	p-value
Slow flow (TIMI < 3) in SB; n (%)	0 (0.0)	9 (20.45)	0.007
Failure to recross in the SB; n (%)	0 (0.0)	17 (38.64)	< 0.001

The number of stents implanted was higher in the Axxess group (*table 3*). Trouble in SB access did not occur in any Axxess group patient but in 19 patients (21.11%) in the control group ($p < 0.001$). Residual stenosis < 50% in SB was obtained in all patients in the Axxess group and in 69 patients (76.67%) in the control group ($p < 0.001$). TIMI grade flow 3 in SB was obtained in all patients in the Axxess group and in 80 patients (88.89%) in the control group ($p = 0.088$). Trouble in SB access and slow flow in SB occurred in true bifurcation lesions (that is, 1.1.1 or 1.0.1 or 0.1.1 according to Medina classification) (*table 4*). Axxess stent deformation occurred in one case of the Axxess group due to the forward pressure on an angioplasty balloon (*table 4*). In the Axxess group, the contrast media volume was higher (222.2 ± 66.9 mL vs. 181.7 ± 50.6 mL; $p < 0.001$) and the procedural time was longer (66.4 ± 19 vs. 47.8 ± 22.7; $p < 0.001$).

Table 5: In-hospital complication.

Variable	Axxess group n = 51	Control group n = 90	p-value
Death n (%)	0 (0.0)	1 (1.11)	1.00
Bleeding n (%)	1 (0.71)	0 (0.0)	1.00

** Procedural success and in-hospital outcome:*

Procedural success was obtained in 50 patients (98.04%) in the Axxess group and in 80 patients (88.89%) in the control group ($p = 0.057$).

In-hospital major adverse cardiovascular events (MACE), did not occur in any Axxess group patient, but cardiac death occurred in one case (1.11%) in the control group.

DISCUSSION

The main results of this study comparing Axxess stent versus conventional DES are: (1) device success is similar in the two approaches; (2) angiographic and procedural successes are higher with the Axxess stent; and (3) trouble in SB access rate and procedural complications rate (including SB occlusion) are lower with the Axxess stent.

1. Advantages of Axxess stent

The provisional SB stenting technique is the preferred approach for the treatment of bifurcation lesions [1]. However, this approach encompasses two major issues: (1) the risk for SB occlusion and (2) the technical aspects of rewiring the SB through the MV stent cells. Intraprocedural SB occlusion with the provisional SB stenting approach has been reported in 7 - 20% of cases, and it is associated with an increased risk of MI [2]. Although one can argue that flow may be restored in the majority of cases (both spontaneously or by intervention), SB may still remain occluded in up to 30% of patients even if adopting the strategy of "jailed wire" [2].

In this study, we observed that both these procedural complications (i.e., SB occlusion) and trouble in SB access after MV stenting are lower with the Axxess stent than with conventional DES. However, there are some problems, these results have been reached at the price of a higher number of stents, higher contrast media volume, and prolonged procedural time. Our finding, therefore, supports the concept that the Axxess stent implantation represents a valid alternative for the treatment of bifurcation lesions. Although deemed ideal for the Medina 1.1.0 bifurcation lesions, the Axxess stent has been used in the majority of cases to treat true bifurcation lesions [4, 5, 6]. We should highlight that almost procedural complications (SB occlusion) and/or trouble in SB access occurred in true bifurcation lesions. Therefore, implantation of the Axxess stent seems ideal for all bifurcation lesions with SB ostial disease at baseline.

2. Disadvantages of Axxess stent

The disadvantages of AxxessTM stent implantation are the higher number of stents implanted in the MV.

In the Axxess group, 2 stents in the MV (the Axxess in the proximal MV and a DES in the distal MV) were needed in 90.20% of cases (*figure 3*). So, this may be a limitation due to the increase in procedural costs. However, this approach may represent an opportunity for an optimal bifurcation reconstruction. Different 2-stent techniques using conventional balloon-expandable DES have been proposed. Each technique has advantages and disadvantages, making the selection rather difficult and mostly dependent on the operator's preference [1]. Drawbacks in complex bifurcation stenting are not uncommon and include distortion or rupture of MV stent struts following SB balloon dilation [1]; and suboptimal final ostial SB lumen. Thanks to its properties and design, the Axxess stent may solve these issues at the price of 1 additional stent implanted in the distal or

proximal MV. We should highlight, indeed, the limitations of the Axxess stent, those are (1) the relatively short (11 or 14 mm) length that limits the treatment of long lesion in the proximal MV and (2) the need for additional DES to treat proximal and/or distal MV lesion or dissection occurring during the procedure.

3. In-hospital outcome

The in-hospital MACE rate was similar in the two groups. However, this study was not powered to test clinical differences between one approach versus the other. Therefore, this result must be treated with caution.

CONCLUSION

The present study suggests that using the Axxess stent represents a valid alternative for the treatment of most bifurcation lesions. Randomized studies comparing Axxess stent versus balloon-expandable DES are needed to clarify whether the observed technical advantages will actually translate into a better clinical outcome.

STUDY LIMITATIONS

Limitations of the study are (1) the nonrandomized design, (2) the lack of clinical follow-up, (3) the lack of quantitative coronary angiography for the evaluation of bifurcation lesions. Furthermore, this study was not powered to test the clinical superiority of one approach versus the other. Therefore, any conclusion on clinical outcome should be drawn with caution.

Disclosure: none.

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