The Devax Bifurcation Experience Review of the DEVAX Clinical Program and Trial Results

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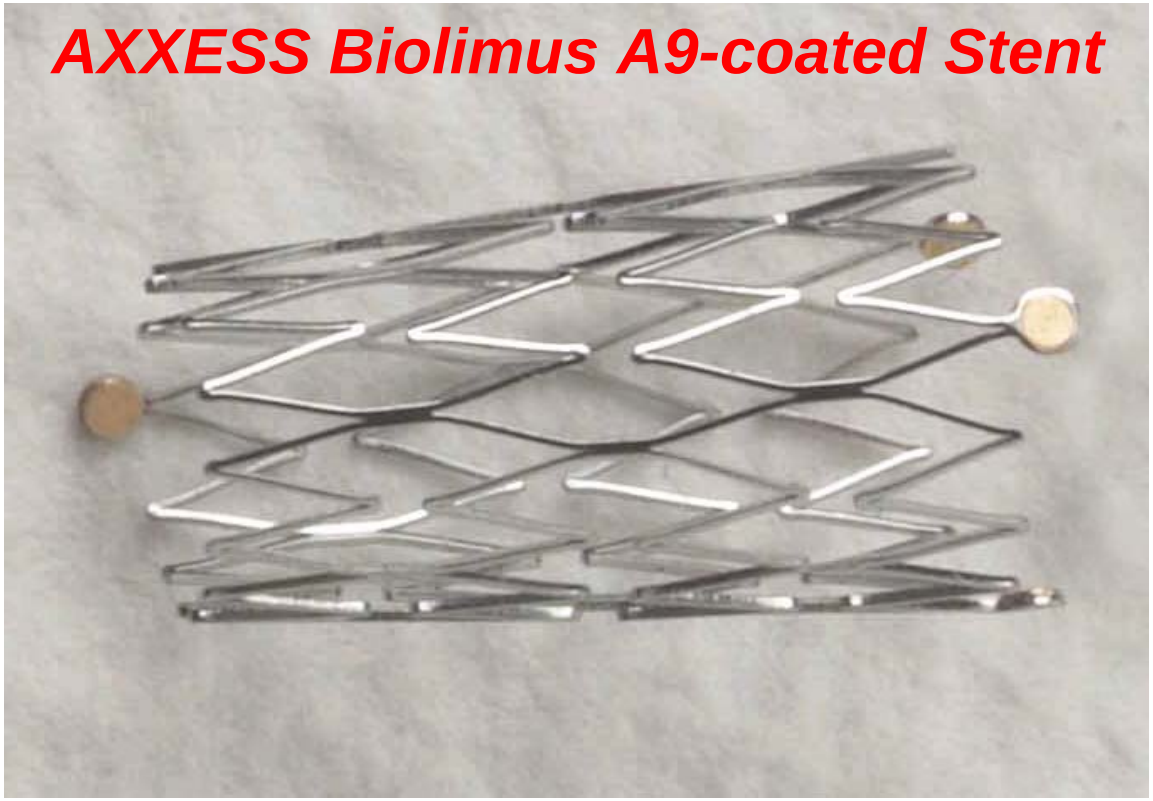
DEVICE DESCRIPTION

AXXESS Biolimus A9-coated Stent



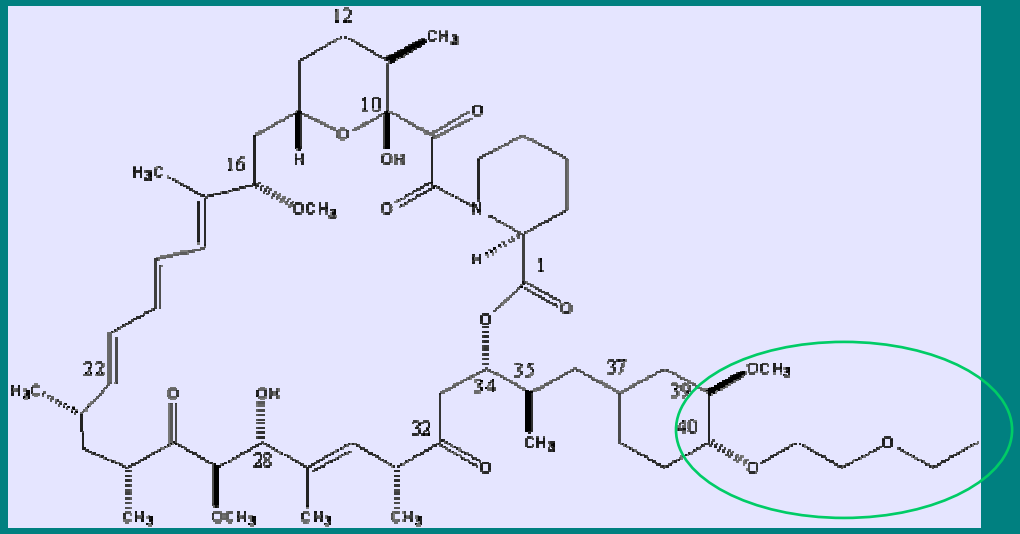
Self expanding nickel-titanium (Nitinol) alloy
Conical shape
Available in 2.5, 3.0, or 3.5mm in diameter and in 10, 14, or 20mm in length

Biolimus A9® coated onto the stent platform with a bioabsorbable polymer matrix (PLA) in a dose of 22µg per mm of stent length

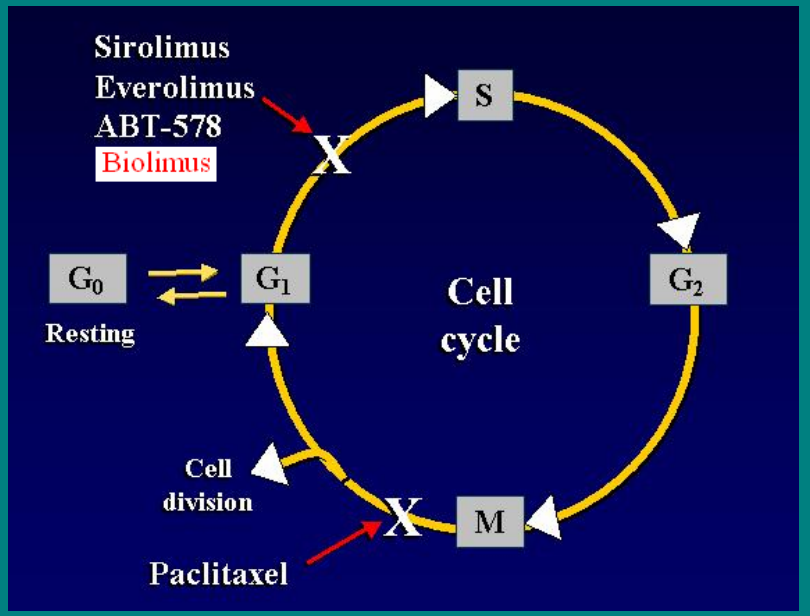
BIOLIMUS A9®

New Molecular Entity

- Sirolimus analog
- Same macrocyclic “limus” family
- $C_{55}H_{87}NO_{14}$
- More lipophilic than Sirolimus/Everolimus
- Potent immunosuppressant



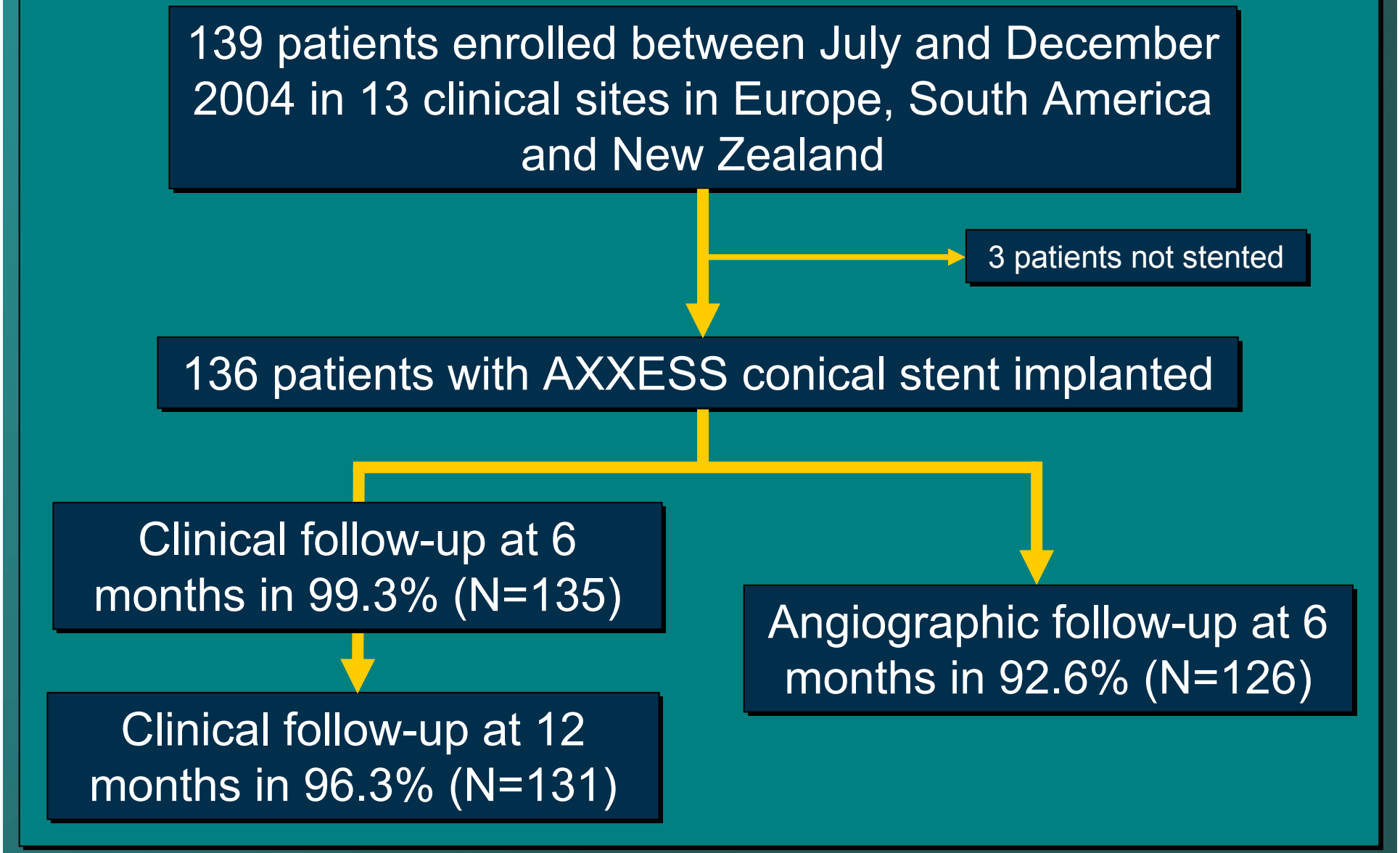
40-O-(2-ethoxyethyl) Modification,
Most preferred position for stent-based applications, as it doesn’t affect FKBP binding properties



Mechanism of Action

- Anti-proliferative agent
- Binds to FKBP-12
- Inhibits mTOR activity
- Inhibits G1 phase of the cell cycle

AXXESS PLUS TRIAL FLOWCHART



KEY INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

- *De novo* bifurcation lesion in a native coronary vessel
- Vessel size:
  - 2.5-4.0mm in the PV
  - >2.25mm in the SB
- Lesion length:
  - <30mm in PV
  - <15mm in SB

EXCLUSION CRITERIA

- AMI <72 hours
- LVEF < 30%
- More than 1 lesion in the target vessel
- Presence of thrombus in the target lesion or severe calcium

ENDPOINTS

Primary Endpoint

- Late lumen loss at 6 months FU in the AXXESS stent (compared to historical control with the *non-coated AXXESS* stent)

Safety Endpoint

- MACE at 6 months FU

Secondary Endpoints

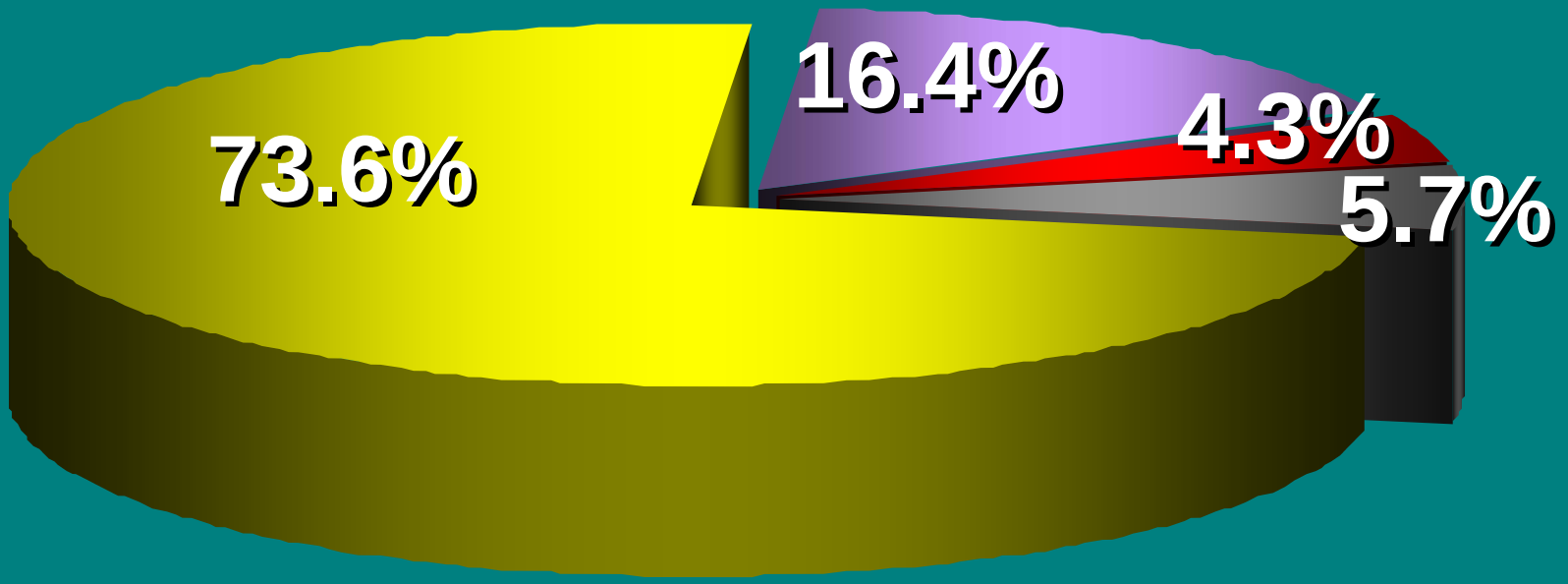
- Binary restenosis (≥50% DS at FU) in the PV and SB; MACE at 12 months

BASELINE DEMOGRAPHICS

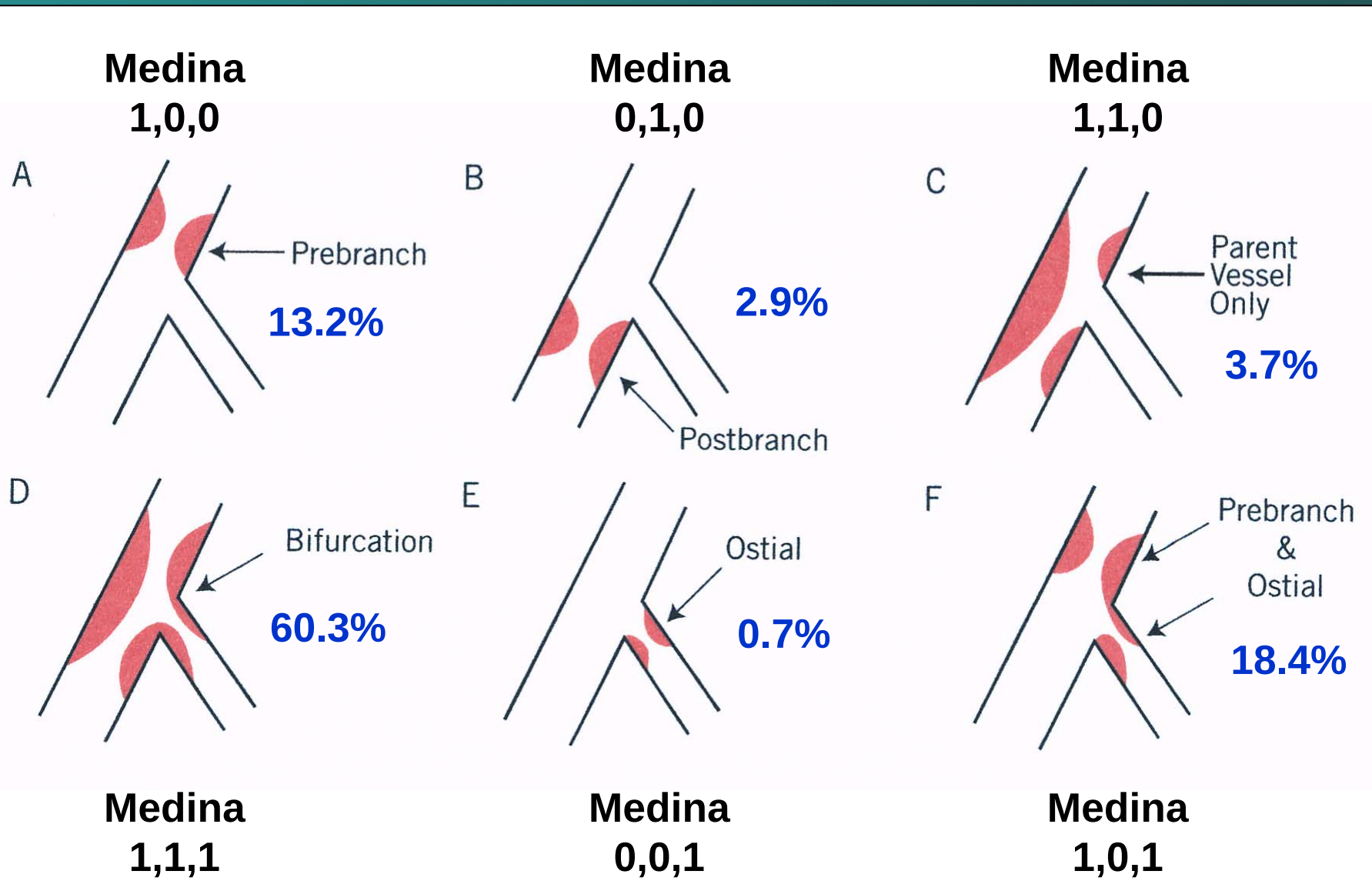
Variable	N=139
Age, years	64.5
Female	26.4%
Diabetes	16.4%
Hypertension	72.9%
Hyperlipidemia	78.6%
Smoking	51.5%
Previous MI	31.4%
Previous PCI	30%
Previous CABG	4.3%
Congestive heart failure	1.4%
Left ventricule EF, %	65.5±13.2

LESION LOCATION

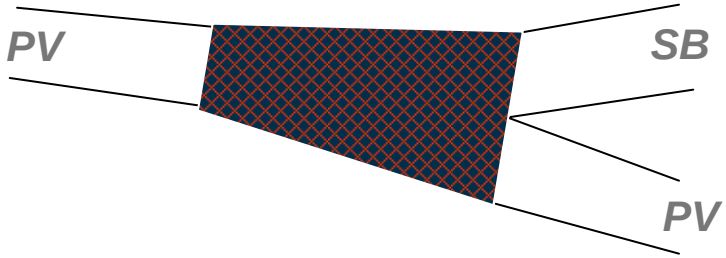
N=139



Bifurcation Classification (DUKE)

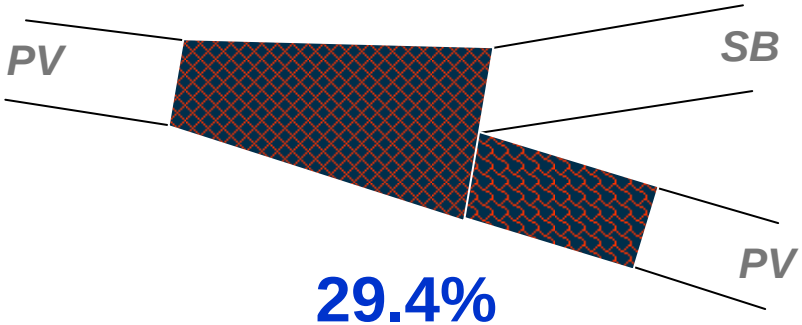


TREATMENT CONFIGURATIONS



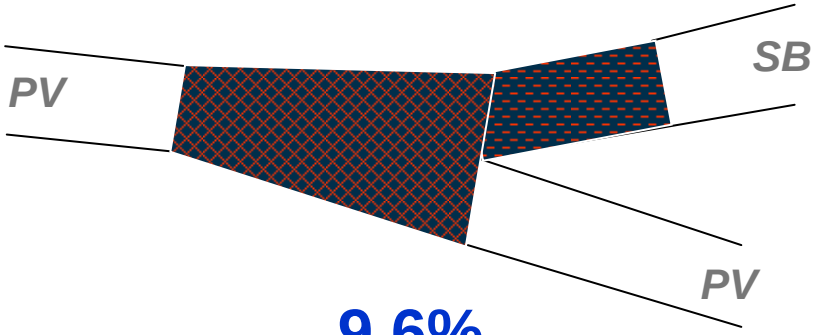
19.1%

AXXESS Stent Only



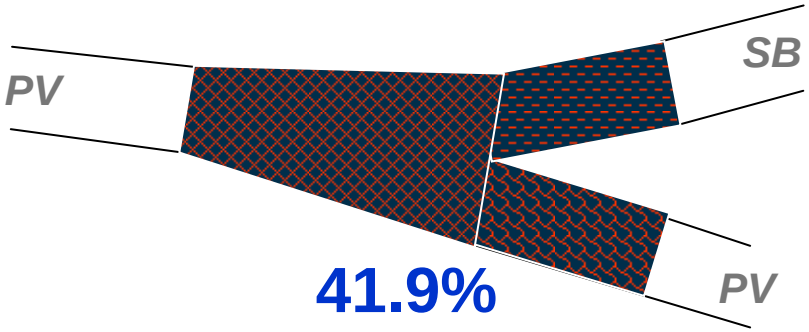
29.4%

AXXESS Stent + Distal PV Stent



9.6%

AXXESS Stent + SB Stent



41.9%

AXXESS Stent + Distal PV and SB Stents

PRE- AND FINAL QCA

Variable	PV	SB
BASELINE		
Lesion length, mm	16.28	7.43*
RD, mm	2.86	2.34*
MLD, mm	0.78	0.88*
% DS	72.9	62.2*
FINAL†		
MLD, mm	2.27	1.89*
% DS	23.8	22.3
Acute gain, mm	1.49	1.01*

**p<0.05 versus PV; †in-segment analysis*

PARENT VESSEL QCA AT FOLLOW-UP

Variable	N=126
LATE LUMEN LOSS	
AXXESS conical stent, mm	0.09
In-stent, mm	0.21
In-segment, mm	0.26
RESTENOSIS	
AXXESS stent, mm	4%
In-stent, mm	5.6%
In-segment, mm	10.5%
PRIMARY ENDPOINT	***BA9 BMS***
AXXESS late loss, mm	0.11 vs. 0.46 (p<0.001)

SIDE BRANCH QCA BY TREATMENT MODALITY

Variable	No Rx (N=26)	PTCA (N=40)	Stent (N=70)
BASELINE			
Lesion length, mm	4.84	5.90	9.29*
RD, mm	2.31	2.24	2.41†
MLD, mm	1.24	0.89	0.74*
% DS	46.3	60.2	69.3*

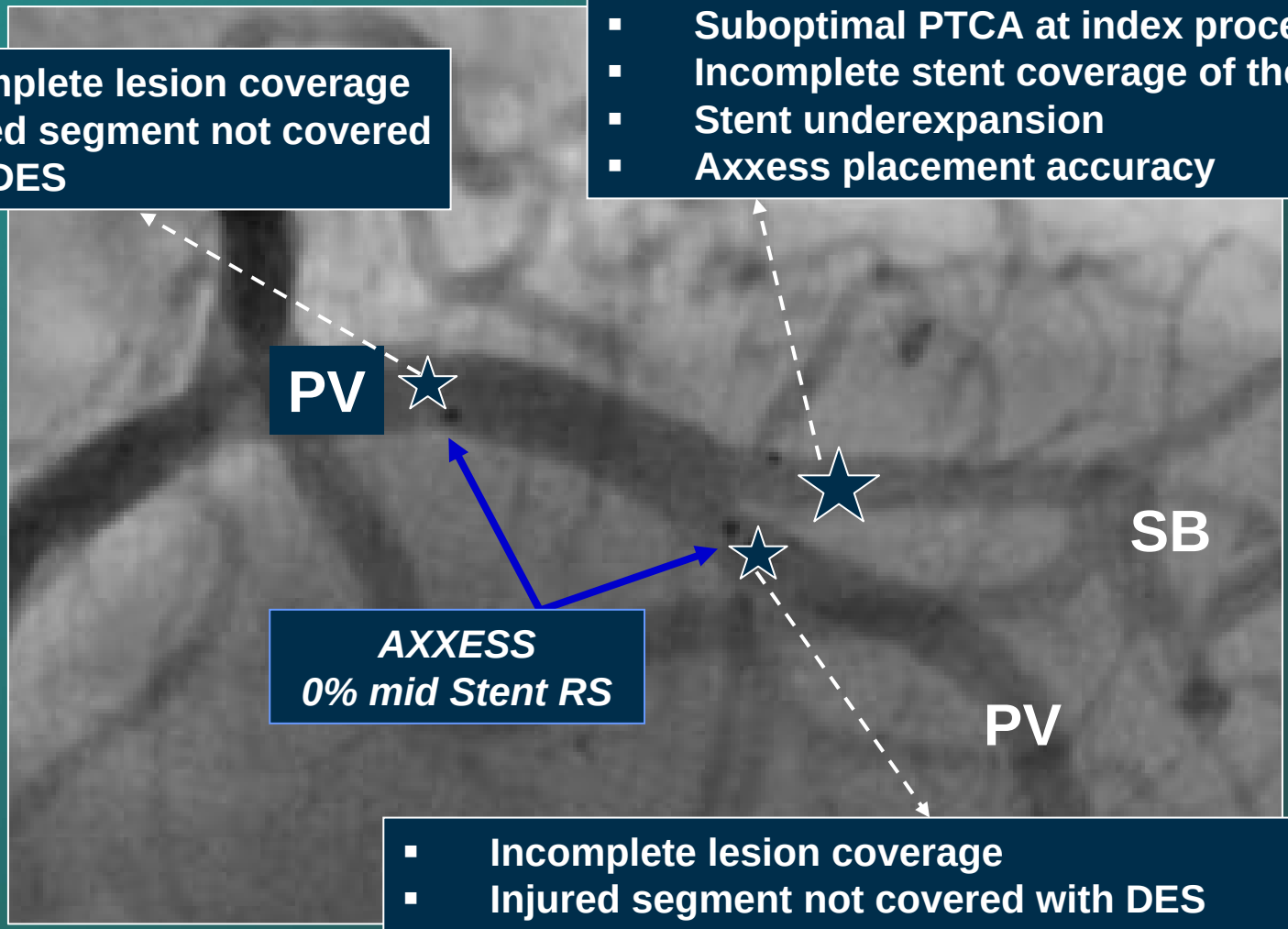
*p<0.0001 vs. PTCA vs. NT; p=0.02 vs. PTCA vs. NT

SB Follow-up QCA

FOLLOW-UP	No treatment (N=26)	PTCA (N=40)	Stent (N=70)
In-segment			
MLD, mm	1.59	1.49	1.82*
%DS	31.0	33.1	25.4†
Late lumen loss, mm	0.24	0.19	0.21
Restenosis, %	12.0	25.0	7.9
5mm ostium			
MLD, mm	1.65	1.54	2.15‡
%DS	28.2	30.7	11.5§
Late lumen loss, mm	0.20	0.18	0.28
Outcomes for SB with lesion success at index procedure			
Restenosis, %	8.3	13.8	8.2

**p=0.04 vs. NT, and p=0.01 vs. PTCA; †p=0.05 vs. PTCA; ‡ p<0.0001 vs. NT and vs. PTCA; §p=0.0005 vs. NT, and p<0.0001 vs. PTCA*

Location and Causes of RS



- Incomplete lesion coverage
- Injured segment not covered with DES

- Suboptimal PTCA at index procedure
- Incomplete stent coverage of the SB ostium
- Stent underexpansion
- Axxess placement accuracy

AXXESS
0% mid Stent RS

- Incomplete lesion coverage
- Injured segment not covered with DES
- "Gap" between AXXESS stent and additional DES
- Distal dissection

IN-HOSPITAL MAJOR EVENTS

Outcome	N=139
MACE*	5% (7)
Death	0% (0)
MI	5% (7)
Q wave	0.7% (1)
Non-Q wave	4.3% (6)
TLR	0% (0)
Acute/subacute thrombosis	0% (0)

**Defined as death, MI and TLR*
MI=myocardial infarction
TLR=target lesion revascularization

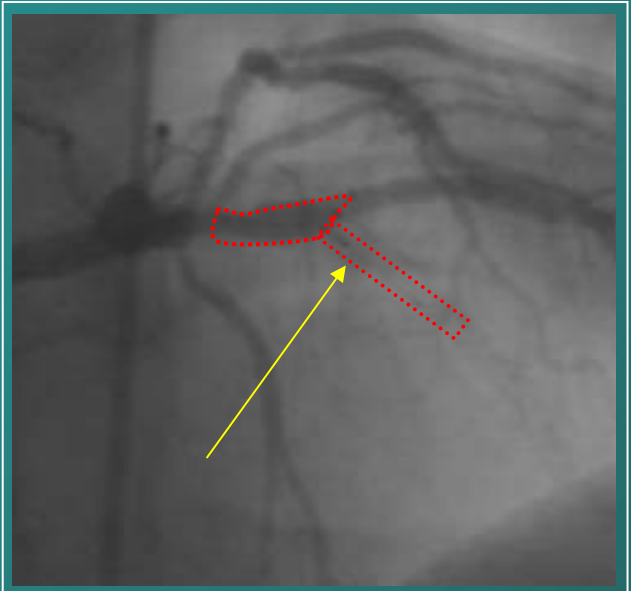
CUMULATIVE CLINICAL OUTCOMES

12 Months Follow-up	N=131
Death	
Cardiac	0.8% (1)
Non-cardiac	0.8% (1)
MI	
Q wave	1.5% (2)
Non-Q wave	5.3% (7)
TLR	
PCI	9.2% (12)
CABG	0.8% (1)

STENT THROMBOSIS: N=3 (2.3%)

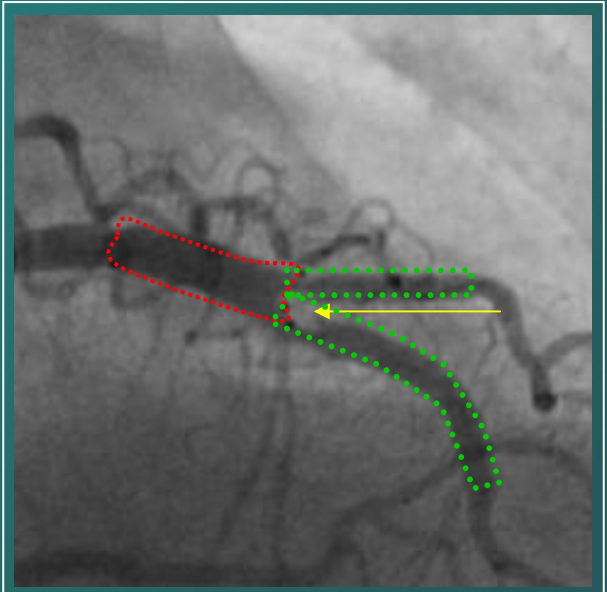
SES

AXXESS Stent



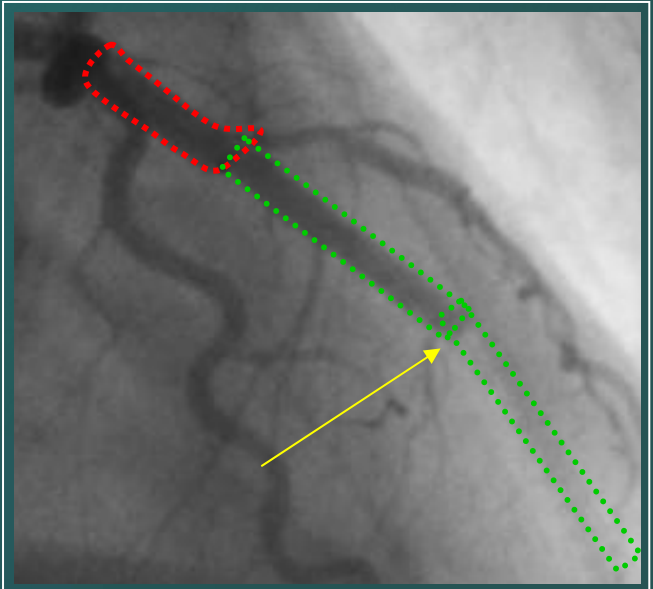
61 days of FU

Patient taken off clopi-dogrel post prostate sur-gery 51 days post- pro-cedure due to haema-turia. Presented with MI, underwent revasc



98 days of FU

Patient off clopidogrel after 1 month. Globular thrombus just distal to Axxess stent (not TO). Angiography at 6 mo. with excellent outcome



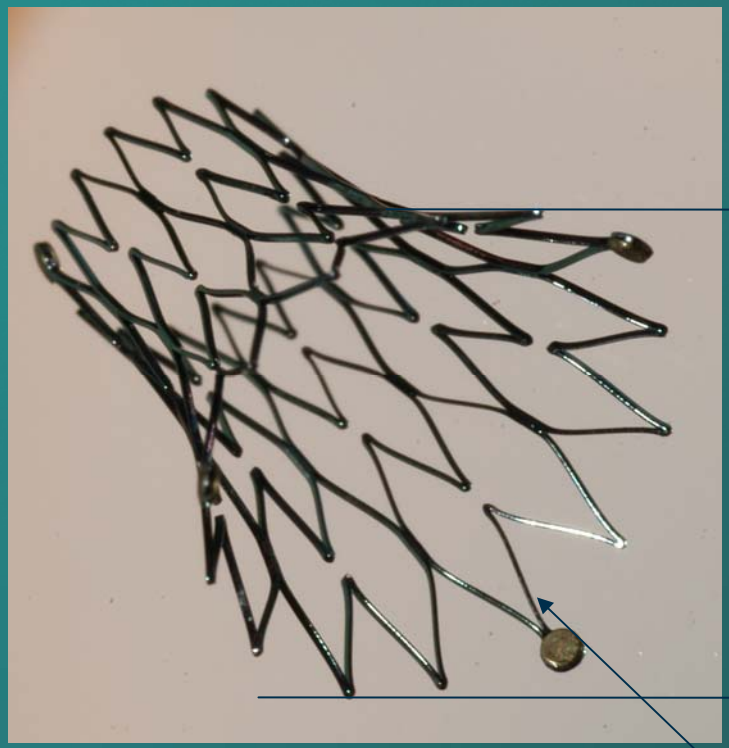
182 days of FU

3 SES placed in the PV distal to the Axxess stent to cover a procedural spiral dissection. Occlu-sion in the SES. Patient was asymptomatic

CONCLUSIONS

- In the Axxess Plus trial, the AXXESS Biolimus A9-coated stent was effective in reducing in-stent late loss compared to the historical Axxess non-coated control group (0.11 vs. 0.46mm, *p<0.001*)
- As a bifurcation strategy with the combination of AXXESS +/- distal Cypher stent use (80% of cases used additional DES)
  - Overall TLR at 12 months was 10%,
  - Restenosis in the PV was 10%
  - Restenosis in the SB was 10% (where historic controls are usually >20%) and results appeared superior with DES rather than PTCA or no treatment (more treatment failure)
- Stent thrombosis occurred in 3 patients due to plavix discontinuation

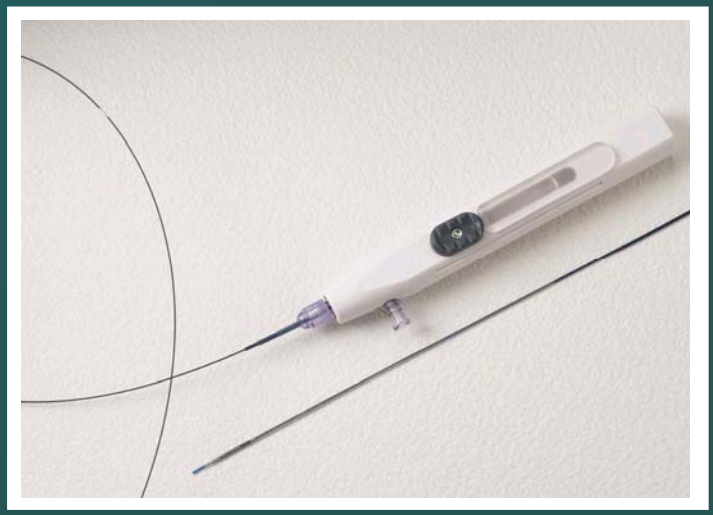
AXXENT™ Left Main Stent

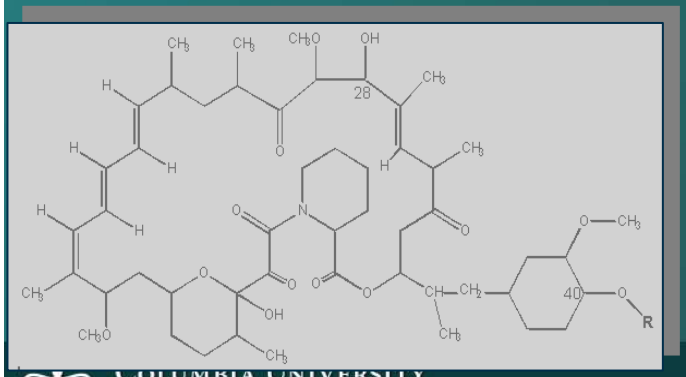


8, 10 & 12 mm
flare diameter

Material:	**Nitinol**
Vessel Range:	**3.75-4.75 mm**
Length:	**12 & 10 mm**

4.8F Rx Delivery System



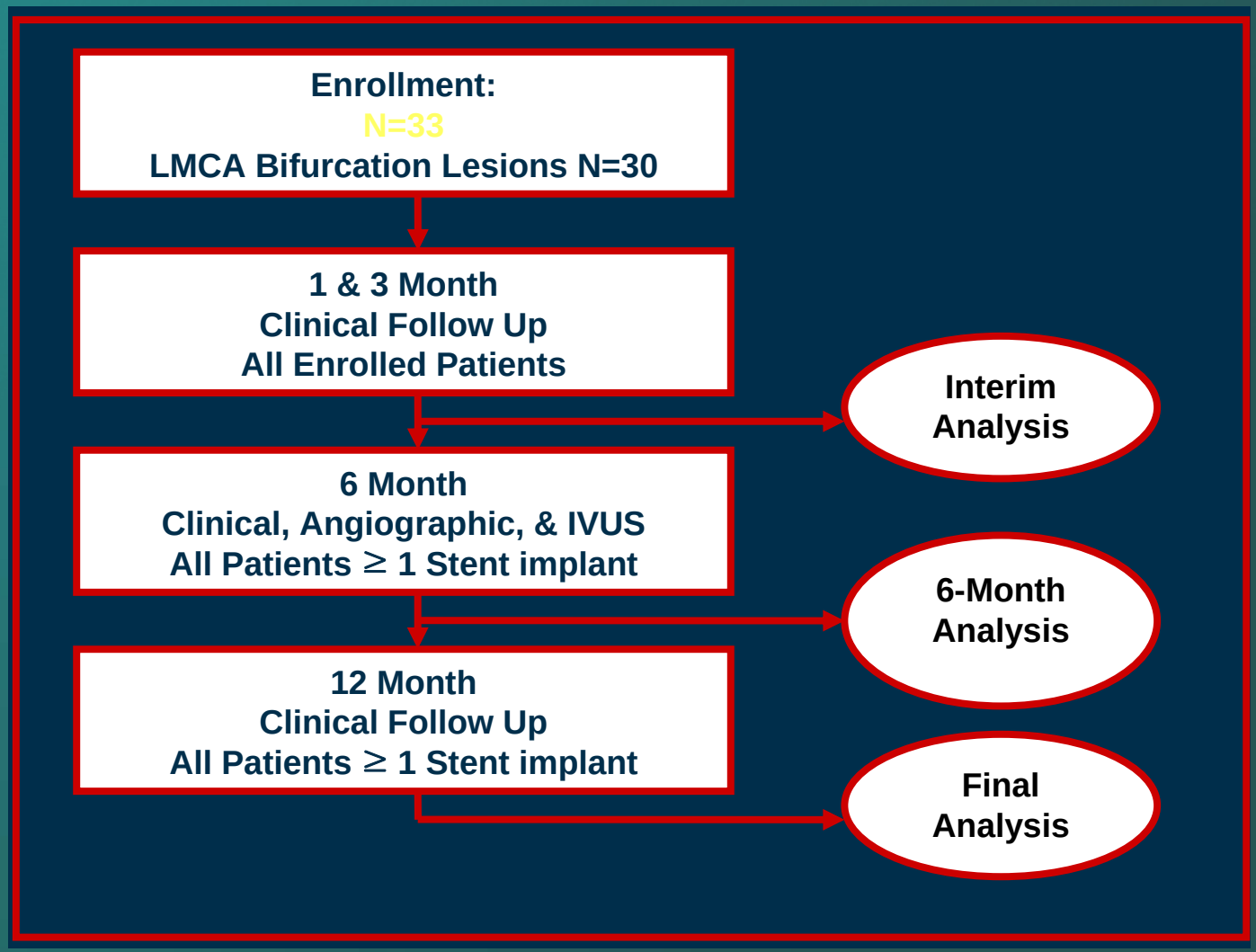


Biolimus A9® coating

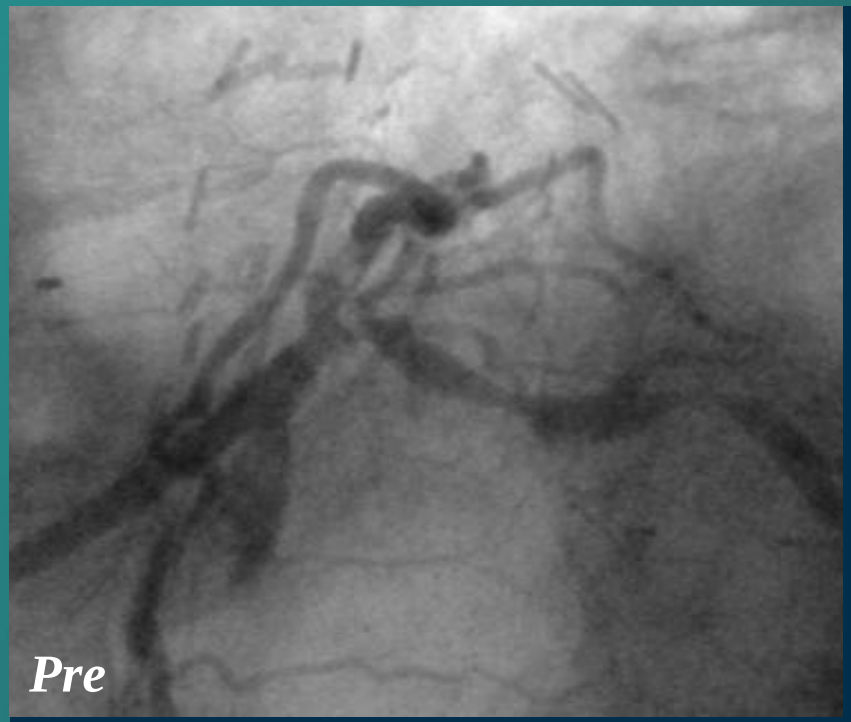
AXXENT Pilot Study

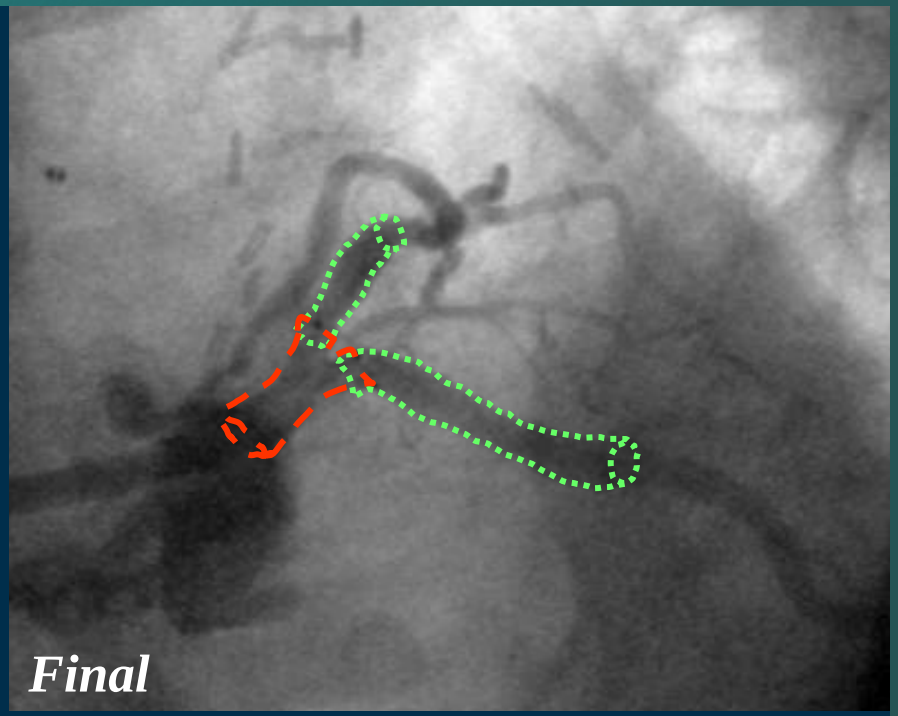
- **Study Objectives**
  - Evaluate the feasibility of the AXXENT stent in *de-novo* LMCA bifurcation lesions (protected and unprotected)
- **Study Design**
  - Multi-center single arm pilot study
  - N=30
  - ASA and Plavix for 12 months
- **Primary Endpoint**
  - MACE at 6 and 12 months
- **Secondary Endpoints**
  - Restenosis & Late Loss in the LMCA, LAD, and LCX at 6 months
  - Tissue volume in the AXXENT stent by IVUS

AXXENT Study Schema



Therapeutic Approach





- Implant AXXENT stent to cover the LMCA and carina
- Implant Cypher stents in the LAD and LCX “end to end” with the AXXENT stent

Principal Inclusion/Exclusion

Inclusion

- 18-80 years symptomatic patient with CCS ≥ 1 or positive functional study
- Protected or unprotected *de novo* LMCA bifurcation lesion
- RVD 3.75-4.75 mm for the LMCA
- Lesion length up to 15 mm in the LAD & LCX

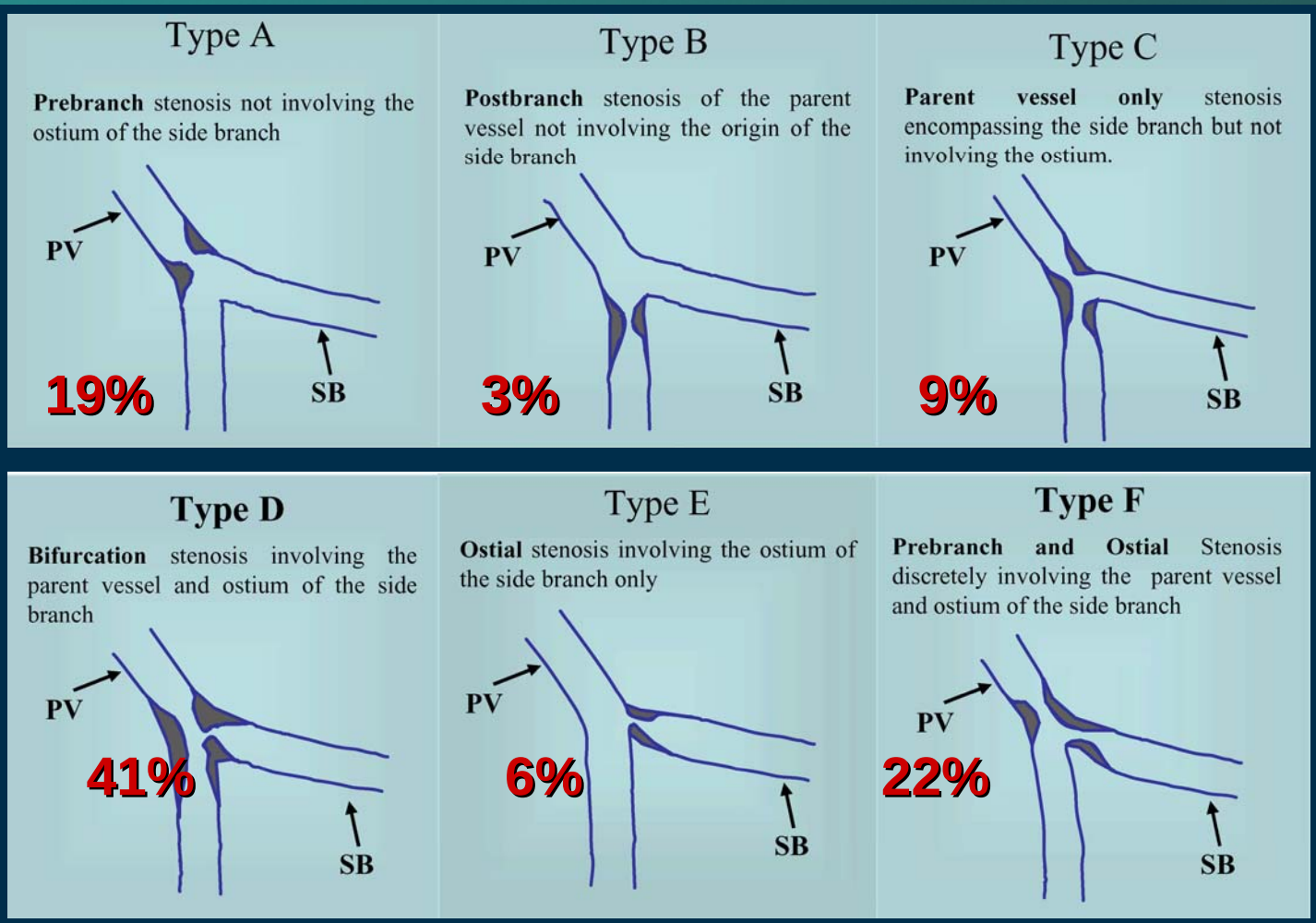
Exclusion

- Known allergy to Plavix, aspirin, the stent/drug or polymer materials, or other required medications
- Major co-morbidity
- MI within 72 hours of the procedure
- LVEF < 40%
- Presence of thrombus in the TL or severe calcification.
- Distal lesion in any of the branch vessels

Patient Demographics

Age	**65.5** ± 11.4 years
Male	**75.8%**
Diabetic	**24.2%**
Insulin Dependent	**3.0%**
Current or history of smoking	**63.7%**
Hypercholesterolemia	**81.8%**
Hypertension	**66.7%**
Previous MI	**24.2%**
Previous PCI	**42.4%**
Previous CABG/Protected LMCA	**18.2%**
CCS III or IV	**27.2%**
Mean Ejection Fraction	**73.3 ± 10.7%**

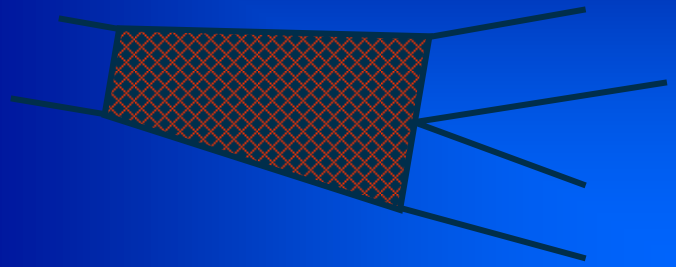
Lesion and Bifurcation Type



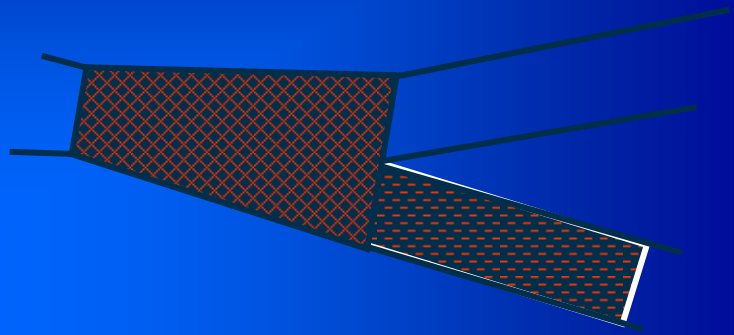
LCX= Side Branch; 19% proximal (ostial, shaft, ostial and shaft), 81% distal Bifurcation

Stent Implant Distribution

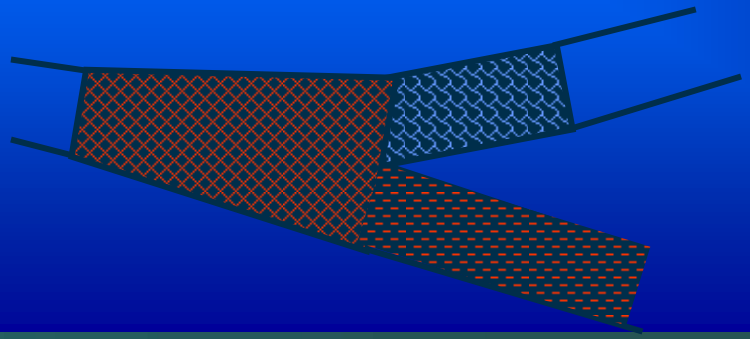
1 Stent: 2 (6%)



2 Stents: 6 (18%)



3 Stents: 23 (75%)



Procedure Outcomes

N procedures	33
AXXENT Device Success	30 (90%)*
AXXENT Stent Flare Diameter	
8mm	17
10mm	8
12mm	6
Lesion Success	32 (97%)
Procedure Success	30 (90%)
Stent Distribution by Vessel (N, %)	
AXXENT in LMCA	31 (100%)
Cypher in LAD	27 (88%)
Cypher in LCX	23 (74%)

*All deployment failures occurred in 12 mm model- stent too long for vessel

Baseline QCA

N=33 Patients	LM	LAD	LCx
Length-mm	8.78 ± 2.93	8.81 ± 3.03	9.99 ± 5.96
RVD- mm	3.91 ± 0.31	2.99 ± 0.32	2.82 ± 0.31
MLD- mm	1.83 ± 1.01	1.83 ± 0.79	1.51 ± 0.55
%DS	53.8 ± 23.6	38.7 ± 24.8	45.8 ± 19.6
Morphology			
Calcified	56%	58%	48%
MACC B2/C	65%	77%	65%

Clinical Outcomes

Follow Up	Hospital	Discharge-30 Days	Discharge-180 Days
Death	0	0	0
MI			
QW	0	0	1 (3.0%) §
NQW	2 (6.1%)	0	0
TLR			
PCI	0	0	3 (9.1%) *
CABG	1 (3%)	0	0
Any MACE	2 (6.1%)	0	4 (12.1%)
Stent Thrombosis	0	0	0

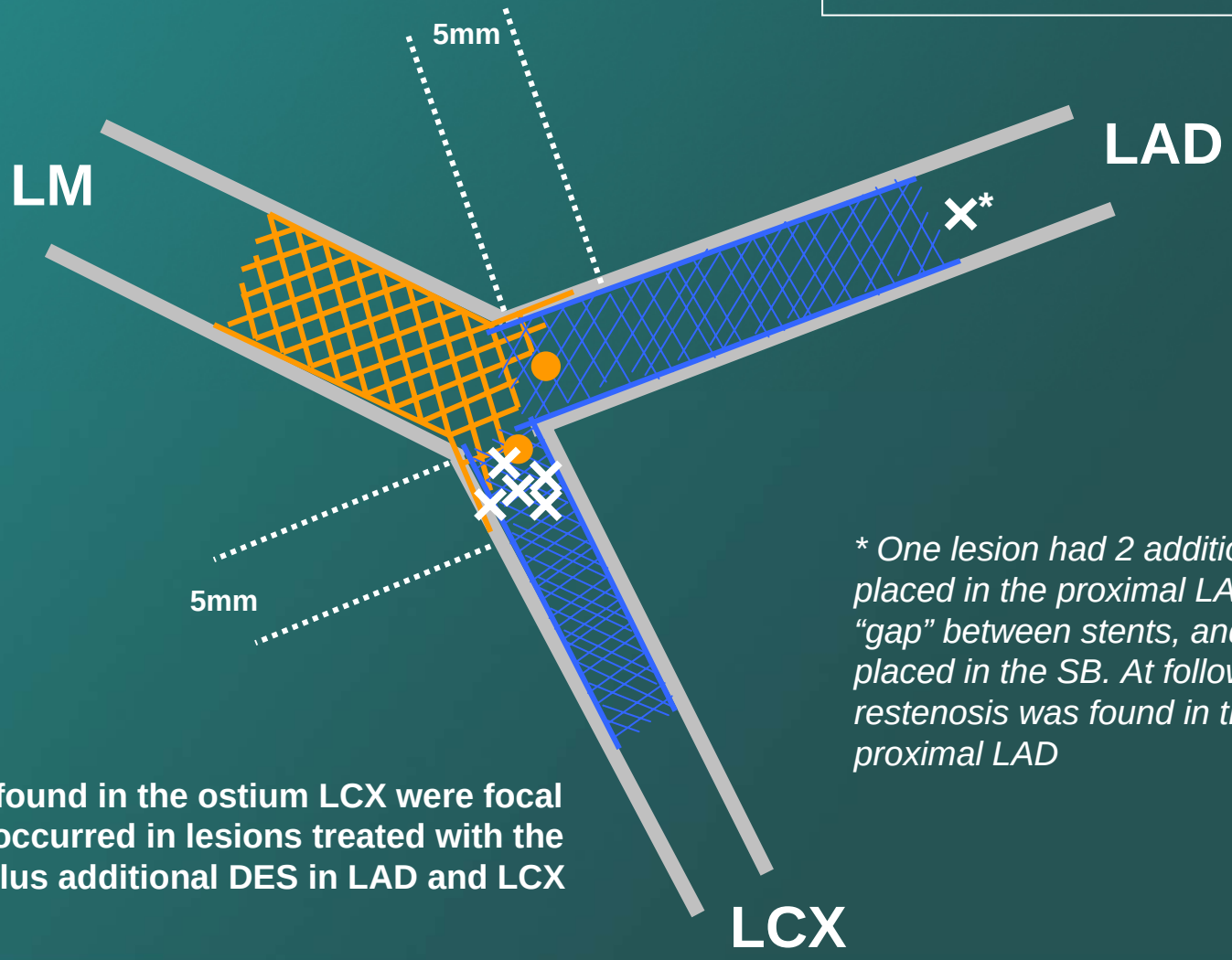
*All TLR was in LCX

§180 day QWMI due to RCA occlusion

Follow Up QCA

N=31 Patients with AFU (94%)	LM	LAD	LCX
Post Procedure			
MLD- mm	3.63 ± 0.37	2.65 ± 0.41	2.47 ± 0.41
%DS	9.6 ± 5.3	13.7 ± 6.7	14.6 ± 6.6
Acute Gain- mm	1.80 ± 0.84	0.82 ± 0.71	0.96 ± 0.58
6 Month Follow Up			
MLD- mm	3.59 ± 0.46	2.41 ± 0.62	2.03 ± 0.64
%DS	9.66 ± 8.5	20.6 ± 18.1	28.4 ± 21.5
Late Loss- mm	0.03 ± 0.30	0.24 ± 0.26	0.46 ± 0.69
Binary Restenosis	0%	2 (6.9%)	5 (16.1%)

AXXENT Trial
Restenosis Location



** One lesion had 2 additional stents placed in the proximal LAD with a "gap" between stents, and no stent placed in the SB. At follow-up, restenosis was found in the "gap" in proximal LAD*

All restenosis found in the ostium LCX were focal (<10mm), and occurred in lesions treated with the DEVAX stent plus additional DES in LAD and LCX

Summary

- Procedure is feasible with 10mm version of the device
- No restenosis and or late loss in the LM AXXENT stent
- Restenosis and late loss in LCX elevated compared to LAD, possibly related to underdeployed Cypher stents and vessel angulation
- No late stent thrombosis observed upto 6 months
- Further studies are planned with modified devices and techniques to evaluate this promising alternative to bypass surgery.

Next steps…DIVERGE

N= 600 patients (250 currently enrolled)

Angiographic Cohort = 300 patients

IVUS Cohort = 150 patients

- Primary Endpoint: 9M MACE
- Key Secondary Endpoints:
  - 30 day MACE
  - QCA Analysis 9M
  - IVUS Analysis 9M
  - Stent thrombosis throughout 5 year follow up.

DES in BIFURCATIONS

Study	*Colombo et al.* (randomized)		*Pan et al.* (randomized)		*Tanabe et al.*	*Moussa et al.*	*Hoye et al.*	Axxess Plus
Clinical sites	5		2		1	1	3	13
N	22*	63	50*	41	58	120	231	136
DES	SES	SES	SES	SES	SES	SES	SES/ PES	AXXESS BA9
Technique	Prov.	M. T- (63.5%) T- (31.7%) V- (3.2%) Y- (1.6%)	Prov.	T- (?)	T- (63%) Crush (26%) Culotte (8%) Kissing (3%)	Crush (100%)	Crush (100%)	AXXESS + DES in PV/SB (40%)
Lesion length, mm								
PV	12.2	10.8	-	-	-	18.6	15.4	16.1
SB	5.1	5.5	-	-	-	12.4	9.0	7.4
RVD, mm								
PV	2.6	2.6	3.0	2.9	2.6	2.9	2.7	2.9
SB	2.1	2.1	2.5	2.5	2.0	2.4	2.4	2.3
Angiographic FU, %	95.5	87.3	87	89	67.7	NO	77.2	92.7
Restenosis, %								
PV	4.8	5.7	2	5	6.8	-	9.1	10.5
SB	14.2	21.8	10	15	13.6	-	25.3	7.9
TLR, %	4.5	9.5	2	5	8.6	11.3	9.7	7.4

PRE-, FINAL AND FU ANGIOGRAPHY