Why do LM bifurcations need a different approach?

Eulogio García
Introduction

• The most important inch-long structure:

  • Supply for 75% of the myocardium
  • 9% patients undergoing coronary angiogram
  • Conservative management: dire prognosis (50% 10-year mortality).
  • 70-80% of LMCA lesions are bifurcations.

• Attractive target for PCI:

  • Short, proximal located, easily crossable with a wire or balloon.
  • Large vessel diameters
  • Rare stent thrombosis.
History

• 1912: James Herrick. First description of LM disease.

• 1978: Andreas Grüentzig. First LM balloon dilatation.

• 1980s: Geoffrey Hartzler. 9.4% of procedural death. 64% mortality at 3 years after LMCA balloon angioplasty.

• 1990s: BMS era. ULTIMA registry. Favorable results in low-risk patients (<65 years, LVEF>30% and no shock). High ISR rate.

• 2000s: DES. Erglis et al: 103 patients. BMS vs PES. Reduction in ISR with PES (22% vs 5.7%). LM bifurcation lesions penalized.

• Future: Dedicated stents?
LM disease: Histopathology

- **LM ostium:**
  - Adventitia lack.
  - Rare TICFA.
  - High muscle and elastic fibers.

- **LM bifurcation:**
  - Preference site for TICFA.
  - Bifurcation with higher diameter discrepancy.
CORPAL registry 2002-2008
LM bifurcation involvement (78%)

- 29%: 1,1,1 (n=174)
- 25%: 1,1,0 (n=150)
- 7%: 1,0,1 (n=42)
- 7%: 0,1,1 (n=42)
- 14%: 1,0,0 (n=84)
- 16%: 0,1,0 (n=96)
- 2%: 0,0,1 (n=12)
Why a Left Main Stent is Needed?

- Diameter mismatch LM /LAD/LCX
- High vessel angulation
- Prevent strut occlusion (jailing) of LAD/LCX
- Allow access to distal vessels in the event future
- Reduce the possibility of stent thrombosis
- Control neointimal proliferation
The AXXENT stent

- Material: Nitinol
- Vessel Range: 3.75-4.75 mm
- Length: 12 & 10 mm
- Drug: Biolimus A9
- Polymer: PLA (Biodegradable)

8, 10 & 12 mm flare diameter for wide angles

<table>
<thead>
<tr>
<th>Reference vessel diameter (±0.25 mm)</th>
<th>Stent length</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 mm</td>
<td>AXBF-3011</td>
</tr>
<tr>
<td>11 mm</td>
<td>AXBF-3014</td>
</tr>
<tr>
<td>3.5 mm</td>
<td>AXBF-3511</td>
</tr>
<tr>
<td>14 mm</td>
<td>AXBF-3514</td>
</tr>
</tbody>
</table>
Axxess™ 4.0x9mm

- The Axxess™ 4.0x9mm has been designed to suit larger vessel diameters (up to 4.75) and wider distinct bifurcation angles (flare-end diameters of 8, 10 and 12 mm).

Main modifications compared to the AXXENT stent:
- Shorter length to fit larger vessel diameters
- Shorter strut length
- Redesigned link pattern to optimize strut apposition

Material: Nitinol
Vessel Range: 3.75-4.25 mm
Length: 9 mm
Drug: Biolimus A9
Polymer: PLA (Biodegradable)
## Axxess™ Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Details</th>
</tr>
</thead>
</table>
| AXXESS      | France and Germany            | - Pilot study using bare metal stent Axxess Platform  
               |                               | - In-segment restenosis at 6 months  
               |                               | - 6 month follow-up completed, study completed |
| AXXESS PLUS | Europe, Brazil and New Zealand| - FIM Safety and performance evaluation of Axxess DES  
               |                               | - In-stent late loss at 6 months  
               |                               | - 5 year follow-up completed, study completed |
| DIVERGE     | Europe, Australia and New Zealand | - Evaluated best practices from AXXESS PLUS  
               |                               | - MACE\(^1\) at 9 months  
               |                               | - **5 year follow-up available**, study completed |
| AXXENT      | Europe                        | - Pilot study for Axxess LM DES\(^2\)  
               |                               | - MACE\(^3\) at 6 months  
               |                               | - 12 month follow-up available, study completed |
| COBRA       | Europe                        | - Randomized multicenter trial to compare Axxess DES along with BioMatrix™ with Cullotte technique using Xience V\(^\circ\)  
               |                               | - Stent strut coverage assessed by OCT at 9 months  
               |                               | - Enrolling |

1. MACE: Composite of death, MI and ischemia-driven TLR  
2. LM stent is not CE approved and not available.  
3. MACE: composite of death, MI, or TLR by surgery or percutaneous intervention
Axxent LMCA Trial

- **Design:** Multi center pilot study to evaluate the AXXENT stent (LM Bifurcated Coronary Stent System)

- **Objective:** To evaluate the feasibility and safety of LMCA stenting with AXXENT stent

- **Principal investigator:** Eberhard Grube, MD
  Helios Heart Center, Siegburg, Germany

33 patients enrolled in 4 clinical sites in Europe

- Clinical FU at 6 months in 100% (N=33)
- Angiographic FU at 6 months in 93.9% (N=31)
- IVUS FU at 6 months in 84.8% (N=28)

- Clinical FU at 12 months in 93.9% (N=31)
# Axxent LMCA Trial: Procedure Outcomes

<table>
<thead>
<tr>
<th>N procedures</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>AXXENT stent device success</td>
<td>30 (90%)*</td>
</tr>
<tr>
<td>Lesion Success</td>
<td>32 (97%)</td>
</tr>
<tr>
<td>Procedure Success</td>
<td>31 (94%)</td>
</tr>
</tbody>
</table>

### Stent Distribution Pattern (N, %)

- AXXENT stent only: 2 (6.1%)
- AXXENT stent in LM+ Cypher in Cx: 0 (0%)
- AXXENT stent in LM+ Cypher in LAD: 3 (9.1%)
- AXXENT stent in LM+ Cypher in both Cx & LAD: 27 (82%)

*All three deployment failures occurred in 12 mm model—stent too long for vessel*
Axxent LMCA Trial: Stent Distribution Patterns

LM only 6.1% (2/33)

LM + LCX: 0%

LM + LAD: 9.1% (3/33)

LM + LCX + LAD: 82% (27/33)
# Axxent LMCA trial

## 6 Months Angiographic Outcomes

<table>
<thead>
<tr>
<th>N=31 Patients</th>
<th>Left Main</th>
<th>LAD</th>
<th>LCX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD- mm</td>
<td>3.63 ± 0.37</td>
<td>2.65 ± 0.41</td>
<td>2.47 ± 0.41</td>
</tr>
<tr>
<td>%DS</td>
<td>9.6 ± 5.3</td>
<td>13.1 ± 6.7</td>
<td>14.6 ± 6.6</td>
</tr>
<tr>
<td>Acute Gain- mm</td>
<td>1.80 ± 0.84</td>
<td>0.82 ± 0.71</td>
<td>0.96 ± 0.58</td>
</tr>
<tr>
<td>6 mo FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD- mm</td>
<td>3.59 ± 0.46</td>
<td>2.41 ± 0.62</td>
<td>2.03 ± 0.64</td>
</tr>
<tr>
<td>%DS</td>
<td>9.66 ± 8.6</td>
<td>20.6 ± 18.1</td>
<td>28.4 ± 21.5</td>
</tr>
<tr>
<td>LL- mm</td>
<td>0.03 ± 0.30</td>
<td>0.24 ± 0.60</td>
<td>0.46 ± 0.69</td>
</tr>
</tbody>
</table>

Binary Restenosis:

- Left Main: 0/30 (0%)
- LAD: 2/29 (6.9%)
- LCX: 5/31 (16.1%)

No restenosis in the AXXENT stent.

## 1 Year Clinical Outcomes

![Graph showing clinical outcomes]
Lessons from the Axxent LMCA trial

• No restenosis and or late loss in AXXENT stent.

• Restenosis and late loss in LCX elevated compared to LAD, possibly related to underdeployed stents and vessel angulation.

• No late stent thrombosis observed through 12 months FU
73 year-old man, with hypertension, hypercholesterolemia and tabaquism.
Chest pain with positive stress test and inferior ischemia.
TTE: normal systolic function.
• EBU 3,5 7 French guiding catheter (radial access)

• 2 BMW® guidewires (Abbott Vascular Devices, Redwood, CA, USA) LAD and Cx

• Predilatation 3.5x10 NC Hiryu® (Terumo, Tokyo, Japan) at 12 atm

• 3.5x11 mm Axxess stent ® advanced to LM.
E. García, L. Unzué, FJ Rodríguez
Placement of a single Axxess stent as new treatment strategy for Medina 1,0,0 left main stem bifurcation lesion.
2013, IC-13-00488. Journal of Invasive Cardiology
• Final Kissing balloon (3.5x10 mm Hiryu at 10 atmospheres at the LM-LAD and semicompliant Sprinter 3x15 mm balloon at 10 atmospheres at the ramus)
CONCLUSIONS

• The Axxess stent is a safe and effective device suitable for complex as well as simple bifurcation treatment strategies.

• The use of Axxess stent in LM bifurcation lesions may be considered in selected cases, achieving good lesion coverage with minimal metal amount at the bifurcation.

• This Axxess stent is especially useful in bifurcations with major affectation of the main vessel (Medina 1,0,0) where the lesion can be attempted with the implantation of this unique stent, eventually avoiding the use of additional stents.
73-year-old man, smoker. Anterior MI in 2012 with primary angioplasty to proximal LAD.
- Residual LVSF 30%.
- Admitted with congestive heart failure (first episode).
• JL 4 7 French guiding catheter (femoral access)
• 2 BMW® guidewires (*Abbott Vascular Devices, Redwood, CA, USA*) LAD and Cx
• Predilatation with 3x12 mm Emerge balloon at 6 atm.
• 3.5x14 mm Axxess
• Final Kissing balloon (4x9 mm NC Sprinter at 16 atm. 4.5x8 mm NC Quantum Apex at 14 atm)
Axxess™ Advantages

- Treats parent vessel lesion without compromising the side branch
- Allows provisional treatment of side branch
- Allows optimal size selection and placement of additional stents as required
- Reduces restenosis in side branch
- Reduces adverse clinical event rates
- Reduces procedural complication rates
DIVERGE Trial Design

Prospective, single-arm, multi-center trial

Any bifurcation with: significant SB's ≥ 2.25 mm;
PV-SB angulation < 70°

PI: S. Verheye

Clinical FU

1 mo  6 mo  9 mo  12 mo  2 yrs  3 yrs  4 yrs  5 yrs

Angio / IVUS FU

1° Endpoint:  MACE* at 9 months

Key 2° Endpoints:  MACE* at 30 days, 6, 9 and 12 months and 2, 3, 4 and 5 years
Angiographic: In-stent restenosis and late loss at 9 months

*MACE = composite of all death, MI and ischemia-driven TLR

DAPT recommended:  12 months

302 patients
14 clinical sites
Europe, Australia and NZ

302 patients
14 clinical sites
Europe, Australia and NZ
DIVERGE Trial: Follow-up

**Enrollment**
- N=302

**6 Months Check up (N=302)**

**9 Months**
- N=301 (99.7% FU)

**12 Months**
- N=300 (99.3% FU)

**2 Years**
- N=300 (99.3% FU)

**3 Years**
- N=298 (99.3% FU)

**4 Years**
- N=297 (98.3% FU)

**5 Years**
- N=291 (96.3% FU)

**Lead in Cases**
- ≤ 3 per site

**Angiography**
- N=140 (94.0% FU)

**IVUS Evaluation**
- N=68 (91.0% FU)

*Verheye S., oral abstract presentation, EuroPCR 2013*
DIVERGE Trial: Medina Class

77.4% True Bifurcation*

DIVERGE Trial: 9-month Restenosis

Very low restenosis rate in bifurcation lesions

Location analysis:

- Proximal Edge: 2.8%
- Axxess: 0.7%
- Distal PV Cypher: 2.1%
- SB Cypher: 4.8%

Any in-segment bifurcation restenosis: 6.4% (9/140 at 9 months)

- Parent vessel RS: 3 pts
- Side branch RS: 4 pts
- Both: 2 pts

105 SB stents
DIVERGE Trial: 9-month Clinical Outcomes

Primary endpoint, its components, and cardiac events

N=301
99.7% FU
DIVERGE Trial: 5-year Clinical Outcomes

Primary endpoint, its components, and cardiac events

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>12 Months</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE*</td>
<td>9.3</td>
<td>14.0</td>
<td>16.1</td>
<td>18.2</td>
<td>21.3</td>
</tr>
<tr>
<td>All Death</td>
<td>2.3</td>
<td>3.0</td>
<td>5.1</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0.7</td>
<td>1.3</td>
<td>2.0</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>4.3</td>
<td>6.0</td>
<td>7.4</td>
<td>7.7</td>
<td>8.6</td>
</tr>
<tr>
<td>id-TLR</td>
<td>6.0</td>
<td>6.0</td>
<td>10.4</td>
<td>12.4</td>
<td>15.5</td>
</tr>
<tr>
<td>id-TVR</td>
<td>8.0</td>
<td>10.3</td>
<td>12.1</td>
<td>13.1</td>
<td></td>
</tr>
</tbody>
</table>

* MACE: Major Adverse Cardiovascular Events
DIVERGE Trial: MACE (All Death, MI, id-TLR) 5-year Outcomes

![Graph showing 5-year outcomes for different events: id-TLR, MI, and All Death. The graph indicates that the percent of events increases over time, with specific percentages at 5 years: id-TLR 11.8%, MI 8.4%, and All Death 6.5%.](image)
**DIVERGE Trial: Stent Thrombosis up to 5 years**

<table>
<thead>
<tr>
<th></th>
<th>DEFINITE</th>
<th>PROBABLE</th>
<th>POSSIBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE (in hospital)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>SUBACUTE (30 Days)</td>
<td>0.7% (2)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>LATE</td>
<td>0.3% (1)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>VERY LATE (1 YEAR – 5 Years)</td>
<td>1.7% (5)</td>
<td>0.7% (2)</td>
<td>2.1% (6)</td>
</tr>
</tbody>
</table>
DIVERGE Trial: VLST

- Only 5 definite VLST events in this complex patient population
- NO VLST resulted in death
- All are involving Cypher stents
- One attributed to whole bifurcation including Axxess
- One originated in distal Cypher, reaching into distal end of Axxess
The DIVERGE trial confirmed the safety and efficacy of the Axxess Biolimus A9-eluting stent up to 5 years.

The use of the Axxess stent for the treatment of complex bifurcation lesions resulted in low 5-year event rates:

- Cumulative MACE rate
  - At 9 month - 7.6%
  - At 5 years - 21.3%
- Ischemia-driven TLR
  - At 9 month - 4.3%
  - At 5 years - 12.4%
- Low very late definite stent thrombosis rate 1.7%

The increased death rate between year 4 and 5 was non-cardiac related.

Very few VLST events in this complex patient population with no event resulting into death.
The Axxess stent is the only dedicated self-expanding bifurcation DES offering a unique approach to fully reconstruct the bifurcation and sparing the carina.

The Axxess stent is the only dedicated bifurcation stent that has data out to 5 years in almost 500 patients.

Despite a complex patient population with 77% true bifurcations treated, the DIVERGE 5-year clinical outcomes are very comparable to results from trials looking at less complex treatment strategies.
**Axxess Plus: design**

**Lesion Location**

- 73% LAD/Diag
- 6% LCX/OM
- 4% RCA-PDA/PLSA
- 17% Left Main Stem

**Exclusion Criteria**

- MI within the previous 72h
- LVEF <30%
- Target vessel with intraluminal thrombus
- LM stenting excluded during the course of the study
# Axxent LMCA Trial: Baseline QCA

<table>
<thead>
<tr>
<th></th>
<th>Left Main</th>
<th>Left Anterior Descending</th>
<th>Left Circumflex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre Procedure QCA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion Length-mm</td>
<td>8.78 ± 2.93</td>
<td>8.81 ± 3.03</td>
<td>9.99 ± 5.46</td>
</tr>
<tr>
<td>RVD-mm</td>
<td>3.91 ± 0.31</td>
<td>2.99 ± 0.32</td>
<td>2.82 ± 0.31</td>
</tr>
<tr>
<td>MLD-mm</td>
<td>1.83 ± 1.01</td>
<td>1.83 ± 0.79</td>
<td>1.51 ± 0.55</td>
</tr>
<tr>
<td>%DS</td>
<td>53.8 ± 23.6</td>
<td>38.7 ± 24.8</td>
<td>45.8 ± 19.6</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcified</td>
<td>56%</td>
<td>58%</td>
<td>48%</td>
</tr>
<tr>
<td>MACC B2/C</td>
<td>65%</td>
<td>77%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Angulation LAD-LCX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>-</td>
<td></td>
<td>117° ± 23</td>
</tr>
<tr>
<td>91-150°</td>
<td>-</td>
<td></td>
<td>80.6%</td>
</tr>
</tbody>
</table>