Treatment of bifurcation lesions with a thin-strut drug eluting stent with bioresorbable polymer: three-year clinical outcomes of the CENTURY II trial

G. Stankovic, MD, PhD
CENTURY II study and Bifurcation substudy
background and aim

• To demonstrate the safety and efficacy of the Ultimaster, a new sirolimus eluting stent with abluminally, gradient, coated bioresorbable polymer by comparing it with Xience everolimus-eluting stent with circumferentially coated durable polymer with respect to the freedom from Target Lesion Failure at 9 months

• Bifurcation substudy compared mid and long-term outcomes in patients with bifurcation lesions treated with bioresorbable polymer DES
Bifurcation stenting—background

- Optimal management of lesions involving main vessel and side branch in a coronary bifurcation remains controversial;

- Contemporary DES appear to reduce restenosis compared with BMS and yield better outcomes;

- Stent design appears to play an important role in bifurcation stenting;

- Clinical evidence for each individual DES is essential to enable informed choice in daily practice
## CENTURY II – Study devices

<table>
<thead>
<tr>
<th>Platform</th>
<th>Ultimaster DES</th>
<th>Xience DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin-strut (80µm) Co-Cr</td>
<td>Thin-strut (81µm) Co-Cr</td>
<td></td>
</tr>
<tr>
<td>Open cell design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDLLA-PCL copolymer</td>
<td>PVDF-HFP non-erodable fluorinated</td>
<td></td>
</tr>
<tr>
<td>resorbed within 3-4m</td>
<td>copolymer</td>
<td></td>
</tr>
<tr>
<td>Abluminal gradient</td>
<td>Circumferential coating</td>
<td></td>
</tr>
<tr>
<td>coating technology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>sirolimus 70 µg/cm²</td>
<td>everolimus 100 µg/cm²</td>
</tr>
</tbody>
</table>

**PDLLA-PCL** refers to the copolymer with primary polymer being polylactide (PDLLA) and the other being polycaprolactone (PCL). The **PVDF-HFP** refers to a fluorinated polyvinylidene fluoride-hexafluoropropylene copolymer, which is non-erodable. **Abluminal gradient coating technology** typically means a coating that is applied to the inner surface of the stent, while **Circumferential coating** refers to a coating applied along the entire circumference of the stent.
CENTURY II - Patient eligibility

**Inclusion criteria**
- Age $\geq 18$ years ($\geq 20$ years Japan)
- Suitable for treatment with DES
- RVD matching stents 2.5-4.0 mm
- Diameter stenosis $>50$
- Eligible for DAPT

**Main exclusion criteria - general**
- EF $<25$
- Renal failure
- Cardiogenic shock
- Planned staged procedure

**Additional exclusion criteria - Japan**
- AMI $<48$h
- Target lesion located in left-main trunk
- Ostial lesions
- Lesion in venous or arterial graft
- Previous ($<1$month) PCI with stenting
- Previous stenting in target lesion
CENTURY II – primary endpoint

TLF Kaplan-Meier curves – 9 months

Xience
5.27%
[3.69%; 7.50%]

Ultimaster
4.36%
[2.94%; 6.43%]

Number at Risk:
Ultimaster 551 539 539 538 536 536 533 531 530 527 527 527
Xience 550 537 537 536 534 534 532 531 527 525 521
Log-rank: p=0.9873
CENTURY II study Bifurcation lesions

Total population
N=1119

Randomization
1:1

Ultimaster
N=562

Xience
N=557

Bifurcation lesions
N=189

Ultimaster
N=92
Lesions=135

Xience
N=97
Lesions=131

Clinical Follow-up

Primary End-point – TLF at 9m

3 years FU rate 97.9%
## CENTURY II Bifurcation lesions
### Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ultimaster (N=92)</th>
<th>Xience (N=97)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, N</strong></td>
<td>65 ± 10</td>
<td>63 ± 10</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Gender, Males (%)</strong></td>
<td>79.4</td>
<td>83.5</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>30.4</td>
<td>30.9</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>73.9</td>
<td>73.2</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Dyslipidemia (%)</strong></td>
<td>77.2</td>
<td>72.9</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>History of CAD (%)</strong></td>
<td>31.8</td>
<td>24.4</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Current smoker (%)</strong></td>
<td>16.3</td>
<td>22.1</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Previous PCI (%)</strong></td>
<td>37.0</td>
<td>31.3</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Previous CABG (%)</strong></td>
<td>3.3</td>
<td>5.2</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Previous MI (%)</strong></td>
<td>31.5</td>
<td>29.9</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Renal Insufficiency (%)</strong></td>
<td>1.09</td>
<td>1.03</td>
<td>0.97</td>
</tr>
</tbody>
</table>
# CENTURY II Bifurcation lesions

Clinical syndrome at admission

<table>
<thead>
<tr>
<th></th>
<th>Ultimaster (N=92 pts)</th>
<th>Xience (N=97 pts)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent Ischemia (%)</td>
<td>17.4</td>
<td>26.8</td>
<td>0.12</td>
</tr>
<tr>
<td>Stable angina (%)</td>
<td>57.6</td>
<td>45.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>9.8</td>
<td>10.3</td>
<td>0.90</td>
</tr>
<tr>
<td>NSTEMI (%)</td>
<td>10.9</td>
<td>15.5</td>
<td>0.35</td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>4.4</td>
<td>2.1</td>
<td>0.37</td>
</tr>
<tr>
<td>CENTURY II Bifurcation lesions</td>
<td>Baseline procedural characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ultimaster</strong> (N=92 pts)</td>
<td><strong>Xience</strong> (N=97 pts)</td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>56.5</td>
<td>43.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Multivessel treatment (%)</td>
<td>33.7</td>
<td>19.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Vessels diseased location:</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>- RCA (%)</td>
<td>13.3</td>
<td>21.4</td>
<td>.</td>
</tr>
<tr>
<td>- LAD (%)</td>
<td>51.1</td>
<td>46.6</td>
<td>.</td>
</tr>
<tr>
<td>- Cx (%)</td>
<td>30.4</td>
<td>26.7</td>
<td>.</td>
</tr>
<tr>
<td>- LM (%)</td>
<td>5.2</td>
<td>5.3</td>
<td>.</td>
</tr>
<tr>
<td>Syntax Score, mean±SD</td>
<td>12.7±7.3</td>
<td>12.1±7.0</td>
<td>0.44</td>
</tr>
</tbody>
</table>
### CENTURY II Bifurcation lesions
#### Baseline procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ultimaster (N=92 pts) (Nlesions=133)</th>
<th>Xience (N=97 pts) (Nlesions=124)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Nr of lesions treated per pt. (mean±SD)</td>
<td>1.47±0.65</td>
<td>1.35±0.60</td>
<td>0.17</td>
</tr>
<tr>
<td>Nr of stents per lesion (mean±SD)</td>
<td>1.17±0.42</td>
<td>1.26±0.51</td>
<td>0.09</td>
</tr>
<tr>
<td>Nr stents per patient (mean±SD)</td>
<td>1.72±0.80</td>
<td>1.68±0.97</td>
<td>0.33</td>
</tr>
<tr>
<td>Total implanted stent length/pt (mm)</td>
<td>35.3±16.7</td>
<td>33.1±22.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Radial access (%)</td>
<td>69.57</td>
<td>68.04</td>
<td>0.62</td>
</tr>
<tr>
<td>RVD (mm), mean+SD</td>
<td>2.6 ± 0.5</td>
<td>2.6 ± 0.4</td>
<td>0.81</td>
</tr>
<tr>
<td>MLD (mm), mean+SD</td>
<td>0.9±0.4</td>
<td>0.8 ± 0.4</td>
<td>0.84</td>
</tr>
<tr>
<td>Pre-procedure Lesion length (mm), mean+SD</td>
<td>17.0±8.6</td>
<td>15.8±8.1</td>
<td>0.22</td>
</tr>
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</table>
## CENTURY II Bifurcation lesions
### Medina classification

<table>
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<th>1,0,1</th>
<th>0,1,1</th>
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</thead>
<tbody>
<tr>
<td>Ultimaster (%)</td>
<td>23.5</td>
<td>4.1</td>
<td>13.3</td>
</tr>
<tr>
<td>Xience</td>
<td>19.4</td>
<td>11.7</td>
<td>6.8</td>
</tr>
</tbody>
</table>

P = 0.89

<table>
<thead>
<tr>
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<th>0,1,0</th>
<th>0,0,1</th>
<th>1,0,0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultimaster (%)</td>
<td>30.6</td>
<td>15.3</td>
<td>3.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Xience</td>
<td>30.1</td>
<td>15.5</td>
<td>1.9</td>
<td>14.6</td>
</tr>
</tbody>
</table>
## CENTURY II Bifurcation lesions
### Bifurcation treatment

<table>
<thead>
<tr>
<th>Technique</th>
<th>Ultimaster (N\textsubscript{lesions}=135)</th>
<th>Xience (N\textsubscript{lesions}=131)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-stent technique, %</td>
<td>6.8</td>
<td>7.6</td>
<td>1.00</td>
</tr>
<tr>
<td>T-Stenting</td>
<td>1.0</td>
<td>2.8</td>
<td>0.62</td>
</tr>
<tr>
<td>V-Stenting</td>
<td>1.0</td>
<td>0.0</td>
<td>0.49</td>
</tr>
<tr>
<td>TAP</td>
<td>2.0</td>
<td>1.0</td>
<td>0.61</td>
</tr>
<tr>
<td>Crush</td>
<td>2.0</td>
<td>1.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Culottes</td>
<td>1.0</td>
<td>1.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Stent in MB, balloon in SB, %</td>
<td>45.0</td>
<td>48.6</td>
<td>0.68</td>
</tr>
<tr>
<td>Only MB stenting, %</td>
<td>48.0</td>
<td>43.8</td>
<td>0.58</td>
</tr>
<tr>
<td>Kissing Balloon post-stent, %</td>
<td>50.0</td>
<td>50.5</td>
<td>0.94</td>
</tr>
</tbody>
</table>
## CENTURY II – Bifurcation lesions – Clinical outcomes at 3 years

<table>
<thead>
<tr>
<th></th>
<th>Ultimaster (N=92 pts)</th>
<th>Xience (N=97 pts)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina, %</td>
<td>5.7</td>
<td>4.5</td>
<td>0.72</td>
</tr>
<tr>
<td>DAPT, %</td>
<td>17.1</td>
<td>23.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Bleeding, any %</td>
<td>9.8</td>
<td>8.3</td>
<td>0.71</td>
</tr>
</tbody>
</table>
CENTURY II Bifurcation lesions
Target Lesion Failure at 36 months

CENTURY-II - Kaplan-Meier survival curves - Cumulative Events
Target Lesion Failure Composite (TLF)

Xience 10.31% [5.68%; 18.31%]
Ultimaster 7.61% [3.70%; 15.30%]

Number at Risk
BP-SES  92  91  90  90  89  87  87  87  87  87  86  86  85
PP-EES  97  93  93  90  89  89  89  89  88  88  88  87  87

Log-rank p=0.4946
CENTURY II Bifurcation lesions
Clinical outcomes at 36 months

- Any death: 2.2, 6.2
- Cardiac Death: 0.0, 4.1
- Any MI: 3.3, 3.1
- TV related MI: 1.1, 2.1
- TLR (CD): 6.5, 7.2
- TVR-non TLR (CD): 1.1, 1.0
- ST: 1.1, 2.1

CD=Clinically Driven  ST=Definite and probable stent
CENTURY II Bifurcation lesions
Target Vessel Failure – 36 months FU

CENTURY-II - Kaplan-Meier survival curves - Cumulative Events
Target Vessel Failure Composite (TVF)

Cumulative incidence of events (%)

Number at Risk:
BP-SES  92  91  90  90  89  87  87  87  87  86  86  85
PP-EES  97  93  93  90  89  88  88  88  87  87  86  86  86

Log-rank p=0.2686

Xience
11.34%
[6.45% ; 19.54%]

Ultimaster
7.61%
[3.70% ; 15.30%]
CENTURY II Bifurcation lesions
Cardiac Death & MI – 36 months FU

CENTURY-II - Kaplan-Meier survival curves - Cumulative Events
Cardiac Death or MI

Number at Risk
BP-SES 92 90 90 90 90 89 89 89 89 89 89 89 89
PP-EES 97 93 93 92 91 91 91 91 90 90 90 90 90

Log-rank p=0.2288
Limitations

- The CENTURY II trial was designed to demonstrate non-inferiority of the Ultimaster DES compared with Xience DES treatment in every day clinical practice;
- The analysis of bifurcation stenting was a post-hoc analysis;
- The possibility for selection bias of simple bifurcation stenting procedures should be bared in mind as a desire to perform more simple and uncomplicated procedures;
- The number of patients does not allow definite conclusion about performance of the investigated DES’s and is hypothesis generating.
CENTURY II Bifurcation lesions
Conclusions

- The Ultimaster DES with bioresorbable polymer (in comparison to Xience DES and in absolute terms) is proven to be **safe and effective** in treating bifurcation lesions;
- The most widely used technique for bifurcation lesions in the CENTURY II trial was **provisional “cross over” stenting** using a single DES, reflecting contemporary simplified approach;
- Favorable 36 months clinical outcomes, with **low rate of TVF and ST following bifurcation stenting**, assure the safe use of Ultimaster DES in daily practice.
Thank You
Ultimaster:
the ULTImate design for
MASTERing complexity
Summary of key features

- Stent deliverability
- Vascular repair
- Challenging cases

No drug coating on parts of the stent that experience the most physical stress, preventing cracking and delamination.

Drug delivered specifically where needed: the abluminal side.

- 80 µm CoCr struts
- Sirolimus 3.9 µg/mm stent

PDLLA-PCL polymer, resorption time 3–4 months

Drug release kinetics match the biological response.

Data on file at Terumo Corporation (Doc nr. Des08-T).
Summary of key features

- Stent deliverability
- Vascular repair
- Challenging cases

Bifurcation

- 2-link design for excellent side-branch access
- Uniform scaffolding
- Allows overexpansion

A solution for any lesion

Diameters from 2.25 mm to 4.00 mm

Lengths from 9 mm to 38 mm

Data on file at Terumo Corporation (Doc nr. Des08-T).
Designed to facilitate treatment of the most challenging lesions

Facilitates bifurcation treatment

Excellent side-branch access

Uniform scaffolding

Radial strength

Allows overexpansion

Polymer integrity

Open-cell, 2-link design for excellent side-branch access

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.25–3.0</td>
<td>9.62</td>
</tr>
<tr>
<td>3.5–4.0</td>
<td>14.5</td>
</tr>
</tbody>
</table>

NC balloon catheter
Φ4.0 mm, NP
Area: 9.62 mm²

NC balloon catheter
Φ5.0 mm, NP
Area: 14.5 mm²

Test method: expand a cell with a balloon at nominal pressure. Φ, diameter.
Tests performed by and data on file at Terumo Corporation (Doc nr. SideBr03-T).
Facilitates bifurcation treatment

- Excellent side-branch access
- Uniform scaffolding
- Radial strength
- Allows overexpansion
- Polymer integrity

Uniform scaffolding for optimal coverage of bifurcation anatomy

Tests performed by and data on file at Terumo Corporation (Doc nr. SideBr03-T).
Facilitates bifurcation treatment

Excellent side-branch access

Uniform scaffolding

Radial strength

Allows overexpansion

Polymer integrity

Bench-tests highlight the high radial force achieved with Ultimaster

<table>
<thead>
<tr>
<th>Stent</th>
<th>Radial Force (N/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultimaster CoCr 80 µm</td>
<td>2.1</td>
</tr>
<tr>
<td>Synergy PtCr 74 µm</td>
<td>1.3</td>
</tr>
<tr>
<td>Resolute Integrity CoNi 91 µm</td>
<td>2.5</td>
</tr>
<tr>
<td>Xience Xpedition CoCr 81 µm</td>
<td>1.9</td>
</tr>
</tbody>
</table>

All stents: Φ3.0 mm

Tests performed by and data on file at Terumo Corporation (Doc nr. RadStr04-T).
Designed to facilitate treatment of the most challenging lesions

Facilitates bifurcation treatment

- Excellent side-branch access
- Uniform scaffolding
- Radial strength
- Allows overexpansion
- Polymer integrity

Over-expansion does not compromise structure and function of the stent

Tests performed by and data on file at Terumo Corporation (Doc nr. OverXp05-T).
Expansion capacity up to 5.8 mm
Result of independently initiated study

Samples of different stent sizes/models were deployed in vitro at nominal pressure (NP). Subsequently, over-expansion results for each design was tested with successive post-dilations using, used first a 5.0 × 12 non-compliant balloon followed by a 6.0 × 15 mm semi-compliant balloon with a pressure of 14ATM for largest designs.
Designed to facilitate treatment of the most challenging lesions

Facilitates bifurcation treatment

- Excellent side-branch access
- Uniform scaffolding
- Radial strength
- Allows overexpansion

Gradient coating ensures polymer integrity for reduced risk of delamination, even when overexpanded
Abluminal gradient coating demonstrates evidence of rapid vascular repair.

Both coatings were applied to the Kaname BMS platform.

Saito N et al. Medical Devices: Evidence and Research 2016:9 33-43