Drug Filled Stent

Optical Coherence Tomography Results from RevElution Trial

Stent Strut Coverage and Stent Apposition

Prof Martin Rothman
on behalf of
Dr. Stephen G. Worthley
Alexandre Abizaid, Ajay J Kirtane, Daniel Simon, Stephan Windecker, Gregg W Stone

Institution(s):
The University of Adelaide, Adelaide, Australia, Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil, Columbia University / Cardiovascular Research Foundation, New York, NY, Case Western Reserve University School of Medicine, Cleveland, United States, Bern University Hospital, Bern, Switzerland, Columbia University Medical Center and the Cardiovascular Research Foundation, New York, NY
Drug Filled Stent

Background

- Most drug-eluting stents (DES) use a polymer to control elution of an antiproliferative drug to reduce neointimal hyperplasia.

- Alternatives to durable polymer DES have shortcomings:
  - Bioabsorbable polymer technologies raise biocompatibility and inflammation concerns during the polymer degradation phase (3-24 months).
  - Polymer-free nanotechnologies may struggle to control and sustain drug elution.

- The drug-filled stent (DFS, Medtronic, Santa Rosa, CA) is designed to achieve controlled and sustained drug elution without a polymer.
  - A BMS surface avoids adverse effects of polymer degradation and could potentially allow for a shorter DAPT duration.
  - Drug Filled Stent with reversion to ‘BMS’ might allow for short DAPT.
Drug Filled Stent
Concept

- DFS is a novel polymer-free drug-eluting stent
- DFS is made from a tri-layer wire:
  - *Outer cobalt alloy layer for strength*
  - *Middle tantalum layer for radiopacity*
  - *Inner layer core material is removed and becomes a lumen that is continuously coated with drug*
- Drug (sirolimus) is protected and contained inside the stent
- Drug releases through multiple laser-drilled holes on the abluminal side of the stent
- Drug elution is controlled and sustained through natural diffusion via direct interaction with the vessel wall. Elution profile is similar to durable polymer DES
Drug Filled Stent
Preclinical Results

INFLAMMATION
Low inflammation similar to BMS

<table>
<thead>
<tr>
<th>Peri-strut Inflammation score</th>
<th>28 Days</th>
<th>90 Days</th>
<th>180 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>BMS</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>P-value</td>
<td>&gt; 0.99</td>
<td>&gt; 0.99</td>
<td>&gt; 0.99</td>
</tr>
</tbody>
</table>

Drug ELUTION
Sustained elution similar to existing DES

Representative histopathological image of DFS at 28 days

Porcine model

Drug Filled Stent
Preclinical Results

DFS demonstrated improved radial strength

Stent Radial Stiffness
(3.0 mm stent, n=3)

Radial strength was tested by measuring the force required to radially compress the DFS stent (diameter 3.0 mm) in a standard iris test and compared with the Resolute Onyx™ DES and Integrity BMS.

Results presented as average ± standard deviation.
Drug Filled Stent
Preclinical Results
In-vitro Assessment

DFS and Resolute Onyx demonstrated greater radiopacity compared to Integrity

In-vitro radiodensity assessment
(Micro focused X-ray)

Results presented as average of 6 measures ± SD
Under fluoroscopy, DFS demonstrated greater radiopacity than the Integrity stent™, and similar radiopacity as the Resolute Onyx and Omega™ stents.
In this study the *in vivo* release kinetics were measured for 3 prototype DFS builds that had different base hole diameters (15, 20, 25 μm).

In conclusion the results indicated that:

- DFS eluted drug in a sustained and titratable manner:  
  ↑ hole size → ↑ pool of readily soluble drug & ↓ sustained elution half-life

- As a result, DFS hole-size titrated peak tissue content and subsequent decline to a plateau representing high affinity bound drug:  
  ↑ hole size → ↑ peak drug content in tissue & ↓ post peak tissue clearance

- Tissue delivery by prototype DFS with different holes sizes was bioequivalent as the dependence on elution rate diminished over time

- Drug elution from DFS is controlled by diffusion and dissolution. Further investigations on dissolution-based drug elution are ongoing.
RevElution Clinical Trial

**Trial Design**

**De Novo Native Coronary Lesions**
- Vessel Diameter: 2.25 mm – 3.5mm
- Lesion Length ≤ 27 mm

**Medtronic Polymer-Free Drug-Eluting Coronary Stent** (N = 100)

- 10-15 sites in Australia, Brazil, Singapore

**Clinical**
- 30d
- 6mo
- 9mo
- 12mo
- 2yr
- 3yr
- 4yr
- 5yr

**Angio/OCT Angio/IVUS**
- 30d
- 2mo
- 3mo
- 6mo
- 9mo
- 2yr

**Primary Endpoint:** Late Lumen Loss (LL) at 9 months post-procedure as measured by quantitative coronary angiography (QCA)

**Key Secondary Endpoints:** Major Adverse Cardiac Events (MACE), Cardiac Death (CD), Target Vessel MI (TVMI), Target Vessel Failure (TVF), Target Lesion Failure (TLF), Stent Thrombosis (ST), Acute Success (device, lesion, procedure)

**Angiographic/IVUS:** Binary Angiographic Restenosis (BAR) rate (defined as ≥ 50% diameter stenosis (DS)); Percent Diameter Stenosis (%DS), Minimal luminal diameter, In-segment late lumen loss, Late loss index, Neointimal hyperplasia volume and percent volume obstruction (%VO), as measured by IVUS

**OCT Endpoints:** Stent Strut Tissue Coverage, Stent Apposition, Neointimal tissue thickness, Volume obstruction, Tissue Type

**Pharmacokinetic parameters:** 12 PK timepoints up to 30 days will be assessed
RevElution Clinical Trial
Inclusion & Exclusion Criteria

Key Inclusion Criteria

Evidence of ischemic coronary disease
• Unstable angina, stable angina, silent ischemia and/or positive functional study

Lesion characteristics
• Single or dual *de novo* lesions in two separate native target vessels
• RVD 2.25 – 3.5 mm
• Lesion length ≤ 27 mm
• TIMI flow ≥ 2
• Diameter stenosis ≥ 50% and < 100%

Key Exclusion Criteria

• Acute MI < 72h (unless cardiac enzymes have returned to normal)
• Previous PCI of target vessel < 9 months
• Planned PCI of any vessel < 30 days or of target vessel < 12 months
• Unprotected left main, aorto-ostial, bypass graft, bifurcation, heavily calcified lesions
• Target vessel that is excessively tortuous, has thrombus or requires use of other non-PTCA devices (such as cutting balloon, etc.)
• Hx stroke or TIA < 6 months
• PUD or UGIB < 6 months
• LVEF < 30%
RevElution Clinical Trial

Trial Design

100 Subjects

- 9 Month Cohort
  - 50 subjects
  - OCT Sub-Group
    - 30 subjects
    - 1M OCT Sub-Group
      - 15 subjects
      - 9M Angio/IVUS 20 subjects
    - 3M OCT Sub-Group
      - 15 subjects
      - 9M Angio/IVUS/OCT 30 subjects
  - 20 subjects

- 24 Month Cohort
  - 50 subjects
  - OCT Sub-Group
    - 30 subjects
    - 2M OCT Sub-Group
      - 15 subjects
      - 24M Angio/IVUS/OCT 30 subjects
    - 6M OCT Sub-Group
      - 15 subjects
      - 24M Angio/IVUS 20 subjects
  - 20 subjects
RevElution Clinical Trial
Trial Design

OCT Imaging Cohort
[N = 60]

9-Month OCT Subgroup
[N = 30]

24-Month OCT Subgroup
[N = 30]

1 Month
[N = 15]
Group 1

3 Months
[N = 15]
Group 3

2 Months
[N = 15]
Group 2

6 Months
[N = 15]
Group 4

1. Magnitude of neointimal hyperplasia formation
   • NIH area / volume
   • NIH thickness
   • Volume obstruction

2. Strut-level assessment
   • Coverage
   • Apposition

3. Tissue type characterization
   • Normal NIH
   • PLIA
   • Neoatherosclerosis

OCT Endpoints

Early
Mid-term
Very Late

Group 1
Group 2
Group 3
Group 4
No. Pts
60 15 15 15
15 30
30

0 M 1 M 2 M 3 M 6 M 9 M 24M
## RevElution Clinical Trial
### OCT Results – Cross Section Level

<table>
<thead>
<tr>
<th></th>
<th>1 Month Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 6 patients</td>
</tr>
<tr>
<td></td>
<td>N = 7 lesions</td>
</tr>
<tr>
<td></td>
<td>N = 8 stents</td>
</tr>
<tr>
<td>Analyzed Stent Length, mm</td>
<td>21.66 ± 9.41</td>
</tr>
<tr>
<td>Total number of analyzed cross-sections</td>
<td>258</td>
</tr>
<tr>
<td>Cross-Sections Analyzed Per Scaffold</td>
<td>36.86 ± 16.12</td>
</tr>
<tr>
<td>Mean reference lumen area, mm$^2$</td>
<td>7.43 ± 1.69</td>
</tr>
<tr>
<td>Mean reference lumen diameter, mm</td>
<td>3.24 ± 0.44</td>
</tr>
</tbody>
</table>

Daniel Chamié, MD Interventional Cardiologist, Institute Dante Pazzanese of Cardiology Director, OCT Core Laboratory, Cardiovascular Research Center Sao Paulo, Brazil
# RevElution Clinical Trial
## OCT Results – Strut level

<table>
<thead>
<tr>
<th></th>
<th>Post-Procedural</th>
<th>1 Month Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 5) patients</td>
<td>(N = 6) patients</td>
</tr>
<tr>
<td></td>
<td>(N = 6) lesions</td>
<td>(N = 7) lesions</td>
</tr>
<tr>
<td></td>
<td>(N = 7) stents</td>
<td>(N = 8) stents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>(2,891)</th>
<th>(3,099)</th>
<th>(89.84 \pm 5.06)</th>
<th>(2.03 \pm 2.73)</th>
<th>(0.002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of analyzed struts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of covered struts per lesion, %</td>
<td>---</td>
<td>(89.84 \pm 5.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of malapposed struts per lesion, %</td>
<td>(4.85 \pm 2.99)</td>
<td>(2.03 \pm 2.73)</td>
<td></td>
<td></td>
<td>(0.002)</td>
</tr>
<tr>
<td>Mean NIH thickness over covered struts, mm</td>
<td>---</td>
<td>(0.06 \pm 0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Daniel Chamié, MD Interventional Cardiologist, Institute Dante Pazzanese of Cardiology Director, OCT Core Laboratory, Cardiovascular Research Center Sao Paulo, Brazil
RevElution Clinical Trial

OCT Results – 1 Month Follow Up

Strut coverage

- Covered struts: 89.8%
- Malapposed struts: 2.0%

NIH thickness

- 0.06 mm

Daniel Chamié, MD Interventional Cardiologist, Institute Dante Pazzanese of Cardiology Director, OCT Core Laboratory, Cardiovascular Research Center Sao Paulo, Brazil
**RevElution Clinical Trial**

**Frequency of Covered Struts Per Lesion**

A univariable logistic GEE model of occurrence of thrombus in a stent section versus RUTSS shows that there is a considerable elevation of risk of thrombus as the RUTSS increases.¹

\[ \text{(RUTSS) = variable ratio of uncovered to total struts per section} \]

In a stent with 30% uncovered struts (70% covered), the odds ratio for thrombus is 9.0 (95% CI, 3.5 to 22.0) compared with a stent with complete coverage.¹

Daniel Chamié, MD Interventional Cardiologist, Institute Dante Pazzanese of Cardiology Director, OCT Core Laboratory, Cardiovascular Research Center Sao Paulo, Brazil

¹*Circulation.* 2007;115:2435-2441
- **Case 20001-002**

### Post-Procedure

- Age (n): 65
- Gender (M/F): M
- Diabetes (Y/N): Y
- Hypertension (Y/N): Y
- Diameter stenosis (%): 75
- RVD (mm): 3.5
- Lesion Length (mm): 10
- Pre-Dilatation Performed (Y/N): Y
- Stents Implanted (n): 1

### 1-Month Follow-up

- Smooth circular NIH

---

Daniel Chamié, MD Interventional Cardiologist, Institute Dante Pazzanese of Cardiology Director, OCT Core Laboratory, Cardiovascular Research Center Sao Paulo, Brazil
• **Case 20013-002**

<table>
<thead>
<tr>
<th>Post-Procedure</th>
<th>1-Month Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (n)</td>
<td>60</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>F</td>
</tr>
<tr>
<td>Diabetes (Y/N)</td>
<td>Y (ID)</td>
</tr>
<tr>
<td>Hypertension (Y/N)</td>
<td>Y</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>90</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>3.0</td>
</tr>
<tr>
<td>Lesion Length (mm)</td>
<td>16</td>
</tr>
<tr>
<td>Pre-Dilatation Performed (Y/N)</td>
<td>Y</td>
</tr>
<tr>
<td>Stents Implanted (n)</td>
<td>2</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>0.6, 14, 17, 17.8, 42.2</td>
</tr>
</tbody>
</table>

Daniel Chamié, MD Interventional Cardiologist, Institute Dante Pazzanese of Cardiology Director, OCT Core Laboratory, Cardiovascular Research Center Sao Paulo, Brazil
Case 20013-002

Early (1M) Healing of Overlapping Struts

Daniel Chamié, MD Interventional Cardiologist, Institute Dante Pazzanese of Cardiology Director, OCT Core Laboratory, Cardiovascular Research Center Sao Paulo, Brazil
RevElution Clinical Trial
Conclusions

- The 1M OCT data from the RevElution Clinical Trial (N = 6 patients; 8 stents) demonstrates an early healing profile with high rates of strut coverage of approx. 90% at 1 month.

- Additionally, the data also show a high efficacy profile as attested by low NIH formation.
  - The low malapposition seen post-procedure was effectively halved within 1 month giving evidence to rapid healing
  - At 1 M the NIH area was 0.49 mm$^2$, percent obstruction 5.82% and NIH thickness: 0.06mm

- Additional datasets at later timepoints will provide valuable information to further confirm these early results.