Update in DES Technology

Adam Witkowski, MD, PhD, FESC
Dept. of Interventional Cardiology and Angiology
Institute of Cardiology, Warsaw, PL

Cairo, 26th Feb 2018

Disclosures

• Presenter: Adam Witkowski
• I have nothing to disclose
Design of 2nd generation DES

- Alloy: cobalt-chromium, platinium-chromium, thin struts (<80 mc)

- Polymer: durable or bioabsorbable vs non-polymeric, drug-coated stents, drug-filled stents

- Drug: paclitaxel, sirolimus or sirolimus derivatives (EES, ZES, BES)

- Fully bioresorbable DES (3rd generation DES or 1st generation BRS?)

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**CE-approved DES with primary clinical endpoint**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Material</th>
<th>Polymer</th>
<th>Drug</th>
<th>Approval Status</th>
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**CE-approved DES with angiographic efficacy data**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Material</th>
<th>Polymer</th>
<th>Drug</th>
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**CE-approved DCB**

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<th>Polymer</th>
<th>Drug</th>
<th>Approval Status</th>
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**Bioresorbable stents**

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<thead>
<tr>
<th>Brand</th>
<th>Material</th>
<th>Polymer</th>
<th>Drug</th>
<th>Approval Status</th>
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European Heart Journal
doi:10.1093/eurheartj/ehu278
DES: an update 2018

• Biodegradable polymer DES
• Drug-Filled Stents
• Bioresorbable DES

BIO-RESORT (TWENTE III):
A prospective, randomized, three-arm trial comparing two different biodegradable polymer-based drug-eluting stents and a durable polymer-based drug-eluting stent in all-comers with coronary artery disease

Clemens von Birgelen, MD PhD
Thoraxcentrum Twente, MST, Enschede, the Netherlands
on behalf of the BIO-RESORT Investigators

TCT 2016
### Primary Endpoint and Sample Size

- **Primary endpoint is Target Vessel Failure (TVF) at 1-year**, a composite of cardiac death, target-vessel MI, and clinically driven target-vessel revascularization.

- **Sample size was calculated**, assuming a TVF rate of 8.5% at 1-year (based on previous trials\(^1,2\) and further assumptions), with the non-inferiority margin set at 3.5%.

A sample size of 3,540 randomized subjects would yield a power of at least 85% to detect non-inferiority with a one-sided alpha level of 0.025 (from 0.05 adjusted for multiple testing to 0.025), allowing for 3% loss to follow-up.

Sample size calculation was performed with PASS software (NCSS, Kaysville, UT, USA).

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\(^1\) von Birgelen et al. J Am Coll Cardiol. 2012: TWENTE trial

Clemens von Birgelen @ TCT 2016
Study Flow Diagram

3,514 patients randomized and analyzed (study population, all-comers study)

1:1:1 randomization following stratification for diabetes mellitus

1,172 pts. allocated to SYNERGY
1,169 pts. allocated to ORSIRO
1,162 pts. completed 1-year follow-up**
1,165 pts. completed 1-year follow-up#
1,163 pts. completed 1-year follow-up§

- 1-year follow-up data were obtained from 99.3% of the study population, which represents 99.9% of the patients who still participated in the trial or had died.
- During the first year of follow-up, 21 patients (0.6%) withdrew consent, while only 3 / 3,514 patients (< 1‰) were actually “lost” (i.e., could not be contacted).

Primary Endpoint
Target Vessel Failure at 1-Year Follow-Up

Synergy vs. Resolute Integrity: $P_{\text{non-inferiority}} < 0.0001$
Orsiro vs. Resolute Integrity: $P_{\text{non-inferiority}} < 0.0001$

Vessel Failure is a composite of cardiac death, target vessel-related MI, or clinically driven target vessel revascularization.
Components of TVF at 1-Year Follow-Up

At 1-year follow-up, there was no statistically significant difference between stent groups in the components of Target Vessel Failure (TVF).

Carli Death
- Synergy
- Resolute
- Integrity

Logrank-P = 1.00, HR 1.00 (0.42-2.41)

TV-related MI
- Synergy
- Resolute
- Integrity

Logrank-P = 0.42, HR 0.81 (0.48-1.36)
Logrank-P = 0.51, HR 0.84 (0.50-1.42)

Clinically indicated TVR
- Synergy
- Resolute
- Integrity

Logrank-P = 0.34, HR 0.77 (0.45-1.32)
Logrank-P = 0.60, HR 0.87 (0.51-1.47)

Conclusion

- Use of all three drug-eluting stents for the treatment of a complex all-comers population resulted in favorable clinical outcomes.

- Very thin strut everolimus-eluting Synergy and sirolimus-eluting Orsiro stents, which have dissimilar biodegradable polymer coatings, were non-inferior to the thin strut durable polymer zotarolimus-eluting Resolute Integrity stent.

- The absence of a loss of 1-year safety and efficacy with the use of the novel stents is a prerequisite before assessing potential benefits at longer term follow-up.

Clemens von Birgelen @ TCT 2016
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 also have shortcomings:
  - Bioabsorbable polymer technologies may increase inflammation during the polymer degradation phase
  - Polymer-free technologies have challenges controlling and sustaining drug elution

- The drug-filled stent (DFS, Medtronic, Santa Rosa, CA) is designed to achieve controlled and sustained drug elution without a polymer
  - Zero polymer exposure avoids adverse effects of polymer-induced inflammation and could potentially allow for a shorter DAPT duration

Concept – I

- DFS is a novel polymer-free drug-eluting stent (81µm struts)

- DFS is made from a tri-layer wire:
  - Outer cobalt alloy layer for strength
  - Middle tantalum layer for radiopacity
  - Inner lumen continuously coated with drug

Stephen G. Worthley @ EuroPCR 2017
Drug-Filled Stent

**Concept – II**

- Drug (sirolimus) is protected and contained inside the stent
- Drug releases through abluminal laser-drilled holes
- Drug elution is controlled through natural diffusion via direct interaction with the vessel wall
- Elution profile is similar to durable polymer DES

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**RevElution Trial**

**Study Design**

**Drug-Filled Stent (N=100)**

- 15 sites in Australia, Brazil and Singapore

**Clinical follow-up (N=100)**

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

**OCT follow-up (N=60 (4x15))**

- 2mo
- 3mo
- 6mo
- 9mo
- 1yr
- 2yr
- 3yr
- 4yr
- 5yr

**Angio/IVUS follow-up (N=100 (2x50))**

**PRIMARY ENDPOINT:** In-stent late lumen loss at 9 months in 9M cohort (50 pts)

**Key 2nd Endpoints:**
- Major Adverse Cardiac Events (MACE), Target Lesion Failure (TLF) and components
- QCA / IVUS Endpoints: % diameter stenosis, in-segment late lumen loss, NIH volume and % volume obstruction
- Key OCT Endpoints: Stent strut tissue coverage, neointimal tissue thickness, stent (mal)apposition, % volume obstruction and NIH tissue characterization
- Pharmacokinetic Analysis: 12 PK timepoints up to 30 days will be assessed
- DAPT Regimen: ASA indefinitely and clopidogrel ≥ 6 months (12 months in pts not at high risk of bleeding)

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**Study sponsor:** Medtronic

**Study sponsor:** NCT02480348

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**RevElution Trial**

**Baseline Angiographic Characteristics**

<table>
<thead>
<tr>
<th>%</th>
<th>9 Month Cohort N=50 pts, 56 lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target vessel location</strong></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>52.0</td>
</tr>
<tr>
<td>LCX</td>
<td>32.0</td>
</tr>
<tr>
<td>RCA</td>
<td>26.0</td>
</tr>
<tr>
<td><strong>ACC/AHA lesion class</strong></td>
<td></td>
</tr>
<tr>
<td>– B2</td>
<td>50.0</td>
</tr>
<tr>
<td>– C</td>
<td>26.8</td>
</tr>
<tr>
<td><strong>TIMI 3 flow</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>98.2</td>
</tr>
<tr>
<td><strong>RVD (mm)</strong></td>
<td>2.70 ± 0.43</td>
</tr>
<tr>
<td><strong>MLD (mm)</strong></td>
<td>0.97 ± 0.28</td>
</tr>
<tr>
<td><strong>% Diameter stenosis</strong></td>
<td>63.8 ± 9.5</td>
</tr>
<tr>
<td><strong>Lesion length (mm)</strong></td>
<td>12.85 ± 5.21</td>
</tr>
<tr>
<td><strong>Lesions treated per patient</strong></td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td><strong>Radial approach</strong></td>
<td>86.0</td>
</tr>
<tr>
<td><strong>Lesion success</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Device success</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Procedure success</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>100.0</td>
</tr>
</tbody>
</table>

1. The attainment of <50% residual stenosis of the target lesion using any percutaneous method.
2. The attainment of <50% residual stenosis of the target lesion using only the DFS.
3. The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.

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**RevElution Trial – Primary Endpoint**

**Late Loss Cumulative Frequency Distribution at 9 Months**

![Graph showing late loss cumulative frequency distribution at 9 months for DFS and Resolute ZES historical control.](graph.png)

- **DFS** (n=49 lesions): 0.26 ± 0.28
- **Resolute ZES historical control** (n=93 lesions): 0.36 ± 0.52

\[ \Delta = 0.10 \text{ mm} \]

95% CI (upper one-sided)<sup>*</sup> = 0.05 mm

\[ P_{\text{non-inferiority}} < 0.001 \]

<sup>*</sup>The CI is based on a prespecified propensity score-based adjusted comparison, accounting for lesion length, baseline RVD, age, sex, diabetes, history of MI and worst CCS Angina Class as independent variables.

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**RevElution Trial**

**OCT Results at 1, 3 and 9 Months**

**Covered Struts**

<table>
<thead>
<tr>
<th></th>
<th>1M OCT Cohort</th>
<th>3M OCT Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covered struts per lesion (%)</td>
<td>91.4</td>
<td>99.0</td>
</tr>
</tbody>
</table>

**Malapposed Struts**

<table>
<thead>
<tr>
<th></th>
<th>1M OCT Cohort</th>
<th>3M OCT Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malapposed struts per lesion (median, %)</td>
<td>0.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

1M: n=14 patients, 17 lesions, 19 stents, 605 cross-sections and 7403 struts analyzed
3M: n=15 patients, 17 lesions, 19 stents, 651 cross-sections and 7451 struts analyzed
9M: n=25 patients, 29 lesions, 32 stents, 1102 cross-sections and 12819 struts analyzed


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**RevElution Trial**

**Clinical Results at 12 Months (DFS first 50 pts)**

<table>
<thead>
<tr>
<th>% (n)</th>
<th>30 Days (n=50 pts)</th>
<th>12 Months (n=50 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Target vessel MI</td>
<td>0</td>
<td>4.0 (2)</td>
</tr>
<tr>
<td>Q-wave</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-Q-wave</td>
<td>0</td>
<td>4.0 (2)</td>
</tr>
<tr>
<td>Cardiac death or target vessel MI</td>
<td>0</td>
<td>4.0 (2)</td>
</tr>
<tr>
<td>ARC definite/probable ST</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Early (0-30 days)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Late (31-360 days)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clinically-driven TLR</td>
<td>0</td>
<td>2.0 (1)</td>
</tr>
<tr>
<td>Clinically-driven TVR</td>
<td>0</td>
<td>2.0 (1)</td>
</tr>
<tr>
<td>TLF (cardiac death, TV-MI, TLR)</td>
<td>0</td>
<td>4.0 (2)</td>
</tr>
<tr>
<td>TVF (cardiac death, TV-MI, TVR)</td>
<td>0</td>
<td>4.0 (2)</td>
</tr>
<tr>
<td>MACE (death, MI, TLR, emCABG)</td>
<td>0</td>
<td>4.0 (2)</td>
</tr>
</tbody>
</table>
Which material selection criteria are important for a BRS?

**Biocompatibility profile**: Material should not produce any negative local or systemic side effects

**Resorption parameters**: Need to be carefully controlled to ensure material resorption in a timely manner without causing tissue damage or inflammation. At the same time it also ensures vascular support during healing process. Ideally, resorption should occur within 1 year

**Mechanical characteristics**: Material & Design have to be adapted (e.g. yield strength, tensile strength, elongation) to achieve optimal scaffold performance (e.g. prevent for strut breakage with high flexibility while expansion)


Which materials can be used for BRS?

Current BRS technologies are

**Polymeric materials**

**Natural metallic elements**
AIDA: Bioresorbable Scaffolds versus Metallic Stents in Routine PCI

- Randomised: EES vs BVS
- 924 vs 921 pts
- No significant difference in the rate of TVF between the patients who received a bioresorbable scaffold and the patients who received a metallic stent
- The bioresorbable scaffold was associated with a higher incidence of device thrombosis than the metallic stent through 2 years of follow-up

JJ Wyrzykowska et al. NEJM 2017

Stent Thrombosis With Drug-Eluting Stents and Bioresorbable Scaffolds
Evidence From a Network Meta-Analysis of 147 Trials (n=126,526 patients)

- Contemporary DES, including biocompatible DP-DES, BP-DES, and polymer-free DES, showed a low risk of definite or probable stent thrombosis at 1 year
- BVS had an increased risk of device thrombosis compared with CoCr-EES, PtCr-EES, and H-SES
- Data from extended follow-up are warranted to confirm the long-term safety of contemporary coronary devices.

Si-Hyuck Kang et al, J Am Coll Cardiol Intv 2016
Magmaris components

A combination of proven Orsiro elements and the benefits of a resorbable Magnesium Scaffold

- **Backbone**
  - Mg alloy
  - Tantalum markers

- **Coating**
  - PLLA

- **Drug**
  - Limus

- **Delivery system**
  - RX, 0.014”
  - 6F compatible

- **6-crown & 2-link design**

- **150µm strut thickness**

- **Proven resorption profile**
  - Proven technology identical to Orsiro coating

- **Proven technology**
  - same as for Orsiro

- **Release kinetics**
  - comparable to Orsiro

- **Adapted from Orsiro system**

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Magmaris resorption process over time

<table>
<thead>
<tr>
<th>0m</th>
<th>3m</th>
<th>6m</th>
<th>12m</th>
<th>24m</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Implantation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg backbone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug <strong>BIOlute</strong> coating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double eye radiopaque markers</td>
<td></td>
<td></td>
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Magmaris resorption in OCT imaging

Immediately after implantation, struts are well apposed to the vessel wall. While the Magnesium resorption process continues, endothelialization progresses. At 12 months after implantation, the Magnesium resorption is almost completed.

Clinical Results
TLF rate at 6-month

<table>
<thead>
<tr>
<th>Event</th>
<th>n=120</th>
<th>%</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>TLF¹</td>
<td>4</td>
<td>3.3</td>
<td>1.3-8.3</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>1²</td>
<td>0.8</td>
<td>0.0-4.6</td>
</tr>
<tr>
<td>Target Vessel MI</td>
<td>1</td>
<td>0.8</td>
<td>0.0-4.6</td>
</tr>
<tr>
<td>Clinically driven TLR</td>
<td>2</td>
<td>1.7</td>
<td>0.2-5.9</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0.0</td>
<td>0.0-3.1</td>
</tr>
<tr>
<td><strong>Scaffold Thrombosis</strong></td>
<td><strong>0</strong></td>
<td><strong>0.0</strong></td>
<td><strong>0.0-3.1</strong></td>
</tr>
</tbody>
</table>

1. Composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization and CABG
2. 58 old smoker, CV RF: hypertension and hyperlipidemia, stable angina CCS Class II, treated with a DREAMS 2G 3.0x20mm in the distal RCA. Patient experienced an unwitnessed death 134 days post procedure. Since a cardiac cause could not be ruled out, patient was adjudicated as cardiac death by the Clinical Event Committee
Comparison of in-segment LLL in PROGRESS, BIOSOLVE-I and BIOSOLVE-II

Late Lumen Loss (mm)

Cumulative Frequency (%)

0.27±0.37
0.52±0.48
0.63±0.51

PROGRESS vs BIOSOLVE-II: p <0.0001
BIOSOLVE-I vs BIOSOLVE-II: p =0.0010

BIOSOLVE-I (6-month)
BIOSOLVE-II (6-month)
PROGRESS (4-month)

Clinical study
Device generation

PROGRESS
AMS
BIOSOLVE-I
DREAMS 1G
BIOSOLVE-II
Magmaris (DREAMS 2G)


Comparison of in-segment LLL in PROGRESS, BIOSOLVE I and BIOSOLVE II

Study Name
Device generation

BIOSOLVE-I
Kozlen NL
FIM Registry
46/50 subjects

BIOSOLVE-II
Haude DE
FIM Registry
123/121 subjects

BIOSOLVE-IV
Hsu TD
FIM Registry
0/363 subjects

BIOSOLVE-IV
TBD
RCT
2:1 Dreams vs BVS/DES
TBD


Status / Comment
Completed – 1st LLL 6m
Published in Lancet, 2013
3 year FUP publication submitted to Euroint.
12m FUP completed
Data evaluation ongoing
12m results to be presented at EUROPCR, 2015.
Enrollment
Startup, preparation phase
Endpoint analysis every 200 subjects possible

31
32
CONCLUSIONS

• Biodegradable polymer DES and drug-filled stents shows similar efficacy and safety as second generation durable biocompatible polymer DES

• DAPT with 2\textsuperscript{nd} generation DES may be shorter (1 month) in patients with high risk of bleeding

• Bioabsorbable DES – promising, but currently still under investigation. More randomised trials vs 2\textsuperscript{nd} generation DES are needed.