How do scaffold and stent design maximize safety

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Scaffold thrombosis in ABSORB BVS

Recent studies show increased thrombosis tendency in BVS vs DES. Thrombosis in general however has multifactorial causes, thick strut design being one of them.

<table>
<thead>
<tr>
<th>ABSORB II – 3-year data¹</th>
<th>ABSORB III – 2-year data²</th>
<th>AIDA – 2-year data³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite/Probable Scaffold Thrombosis (in %)</strong></td>
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</tr>
<tr>
<td>Absorb</td>
<td>Xience</td>
<td>Absorb</td>
</tr>
<tr>
<td>2,8%</td>
<td>0,0%</td>
<td>1,9%</td>
</tr>
</tbody>
</table>

P=0.03 | P=NS | P<0.001

1) Adapted from Serruys P. et al., The Lancet 2016; 388(10059):2479-2491
2) Adapted from Ellis S.G.oral abstract presentation at ACC 2017
3) Adapted from Wykrzykowska J.J. et al., New England Journal of Medicine 2017, published online ahead of print
Scaffold thrombosis in Magmaris

BIOSOLVE-I data from Haude M. et al., EuroIntervention 2016;12:e160-e166
BIOSOLVE-II data from Haude M., oral abstract presentation, EuroPCR 2017
BIOSOLVE-III data from Haude M., oral abstract presentation, EuroPCR 2017
Pathology of Scaffold Failure

Early scaffold failure (within 30 days)

Late/Very late scaffold failure (beyond 30 days)

Alfonso et al., JACC Cardiovasc Int, Volume 10, Issue 1, January 2017
Evaluation of acute thrombogenicity in a well established porcine arteriovenous shunt model

Stent geometry, coating and backbone composition impact on acute thrombogenicity

Thicker stent struts show greater thrombus deposition as compared with thinner stent struts
Evaluation of acute thrombogenicity in Magmaris vs. Absorb vs. Orsiro

- **Shunt study 1**: Comparison of acute thrombogenicity of **Absorb vs Magmaris vs. Orsiro**
  - Detection of platelets and inflammatory cells by immunofluorescence
  - Estimation of thrombus deposition by SEM

**Shunt model**
- AV-shunt with a sylgard tube (inner diameter 2.70mm)
- 1h blood flow or until >50% reduction of blood flow
- Target blood activated clotting times (ACT) were kept between 150-190s by i.v. Administration of heparin (low heparin model)
- No antiplatelet agents (e.g. Aspirin, clopidogrel) were used

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Waksman R. et al., Circ Cardiovasc Interv 2017;10:e004762
Results Shunt Study 1: Magmaris vs. Absorb vs. Orsiro

- **Shunt study 1**: Comparison of acute thrombogenicity of *Absorb* vs *Orsiro* and *Magmaris*
  - Detection of platelets and inflammatory cells by immunofluorescence
  - Estimation of thrombus deposition by SEM

Photos and images showing the comparison of Absorb, Orsiro, and Magmaris.
Results Shunt Study 1:
Magmaris vs. Absorb vs. Orsiro
Immunofluorescence

- Significantly less platelet coverage in Magmaris and Orsiro compared to Absorb

Magmaris

Orsiro

Absorb

Waksman R. et al., Circ Cardiovasc Interv 2017;10:e004762
1- Absorb is a registered trademark of Abbott Laboratories
Evaluation of acute thrombogenicity in Magmaris vs. 316L-Equivalent

- **Shunt study 2**: Effect of magnesium backbone on acute thrombogenicity of Magmaris vs Magmaris scaffold design in stainless steel (316L-equivalent):
  - Detection of platelets and inflammatory cells by immunofluorescence
  - Estimation of thrombus deposition by SEM

**Shunt model**
- AV-shunt with a sylgard tube (inner diameter 2.70mm)
- 1h blood flow or until >50% reduction of blood flow
- Target blood activated clotting times (ACT) were kept between 150-190s by i.v. Administration of heparin (low heparin model)
- No antiplatelet agents (e.g. Aspirin, clopidogrel) were used
Results Shunt Study 2: Magmaris vs. 316L-Equivalent

**Shunt study 2:** Effect of magnesium backbone on acute thrombogenicity of *Magmaris* vs *316L-Equivalent*:
- Detection of platelets and inflammatory cells by immunofluorescence
- Estimation of thrombus deposition by SEM
Results Shunt Study 2:
Magmaris vs. 316L-Equivalent Immunofluorescence

- Significantly less platelet coverage in Magmaris compared to 316-L equivalent Magmaris

P = 0.012
Conclusions

- Geometric design of Magmaris impacts favorably on acute thrombogenicity relative to Absorb and Orsiro.
- Decreased inflammatory cell attachment in Magmaris relative to Absorb and Orsiro is observed 1 hour following AV shunt flow.
- The BIOlute coating showed reproducible hemocompatibility on various designs.
- The backbone Magnesium material seems to have a beneficial effect on acute thrombosis risk.
Pathology of Scaffold Failure

Early scaffold failure (within 30 days)

Late/Very late scaffold failure (beyond 30 days)

Alfonso et al., JACC Cardiovasc Int, Volume 10, Issue 1, January 2017

Early ScT Late/Very late ScT
Background on Neoatherosclerosis

- **Autopsy studies** reported a prevalence of neoatherosclerosis of **35%** in SES, **19%** in PES and **29%** in EES at a median duration of approximately 1 year\(^1\)

- **Clinical studies** reported a prevalence of neoatherosclerosis in patients receiving 1\(^{st}\) gen DES and >50% luminal narrowing of **13%** and **16%** in 2\(^{nd}\) gen DES at 1 year\(^3\)

- **Clinical registries** reported a prevalence of neoatherosclerosis as the underlying cause of VLST in **31%** of patients (PRESTIGE)\(^2\)

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\(^1\)Otsuka and Joner et al., Eur Heart J. 2015 Aug 21;36(32):2147-59

\(^2\)Guagliumi and Joner et al., TCT 2015, manuscript in preparation

\(^3\)Seung-Yul Lee et al. Circ Cardiovasc Interv. 2015;8:e001878
Hypothesis and aims

**Hypothesis**
- Vascular restoration therapy using RMS and reduction of overall plaque burden by statins will independently result in decreased neoatherosclerosis progression.

**Aims**
- To investigate the impact of bioresorbable stent implantation on progression of neoatherosclerosis in a novel animal model relative to conventional metallic drug eluting stents.
- To investigate the impact of systemic high-dose statin treatment (3mg/kg/d) on progression of neoatherosclerosis in a novel animal model in both bioresorbable and metallic drug eluting stents.
- To investigate whether incomplete endothelial coverage results in neoatherosclerosis formation (RMS vs DES).
Animal study design
Differential progression of neoatherosclerosis

- 33 New Zealand rabbits
- 1% cholesterol diet for Day 7, 28, 35, 61, 91, and 161
- 0.025% cholesterol diet for Day 7, 28, 35, 61, 91, and 161
- Magmaris implantation for Day 7
- 316-L equivalent DES implantation for Day 7
- Scanning Electron Microscopy analysis for Day 28
- Scanning Electron Microscopy analysis for Day 28
- Denudation for Day 35
- Denudation for Day 35
- OCT imaging and baseline histology for 11 rabbits (5 Magmaris and 6 316-L equivalent DES) for Day 61
- OCT imaging and histopathology for 11 rabbits with Magmaris for Day 91
- OCT imaging and histopathology for 11 rabbits with 316-L equivalent DES for Day 91
- Statins or No Statins for Day 91

Start

Day 7
- Magmaris implantation
- Scanning Electron Microscopy analysis
- Denudation
- OCT imaging and baseline histology for 11 rabbits (5 Magmaris and 6 316-L equivalent DES)
- OCT imaging and histopathology

Day 28
- Scanning Electron Microscopy analysis
- Denudation
- OCT imaging and histopathology

Day 35
- OCT imaging and histopathology

Day 61
- OCT imaging and histopathology

Day 91
- OCT imaging and histopathology

Day 161

Formation of neo-atherosclerosis irrespective of RMS or DES
Device technical overview
Magmaris vs 316L-equivalent

### Specifications

<table>
<thead>
<tr>
<th></th>
<th>Magmaris</th>
<th>316L-equivalent</th>
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<tbody>
<tr>
<td>Backbone material</td>
<td>Proprietary Mg alloy</td>
<td>Stainless steel (316L)</td>
</tr>
<tr>
<td>Coating/drug</td>
<td>BIOlute – resorbable PLLA eluting a limus drug</td>
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</tr>
<tr>
<td>Strut thickness/width</td>
<td>150/150 µm</td>
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</tbody>
</table>

*Customized only for this study
Applied methodology in a rabbit model

**OCT**
In-vivo diagnostic

**SEM**
Endothelialization

**HE**
Overview – Primary endpoint

**RAM-11**
Macrophages quantification

**OCT**
Analysis of vessel and stent morphometry, scoring of neoatherosclerosis by means of foam cell infiltration

**SEM**
Detection of endothelial integrity

**HE**
Standard histology assessment, including inflammatory response and foam cell infiltration

**RAM-11**
Quantitative analysis of foamy macrophages in the neointima

**RMS**
Analysis of vessel and stent morphometry, scoring of neoatherosclerosis by means of foam cell infiltration

**DES**
Standard histology assessment, including inflammatory response and foam cell infiltration

**RMS**
Quantitative analysis of foamy macrophages in the neointima

**DES**
Quantitative analysis of foamy macrophages in the neointima
Histology – Neoatherosclerosis scoring results – Primary endpoint

<table>
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<tr>
<th>Neoatherosclerosis score – Quadrant based analysis</th>
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<tbody>
<tr>
<td><strong>Minimal</strong></td>
</tr>
<tr>
<td><strong>Mild</strong></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td><strong>Massive</strong></td>
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**Magmaris vs. DES**  
$p < 0.0001; B: -0.391$

RMS  
Magmaris

**DES**  
316L-equivalent

**Statin vs. Placebo**  
$p = 0.001; B: -0.286$
OCT – Neoatherosclerosis scoring

**Definition of Neoatherosclerosis**

- Signal rich band with attenuation or low signal intensity area followed by signal rich band with attenuation

**RMS**
Magmaris

**DES**
316L-equivalent

**OCT score**
[vessel circumference]

- **Score 0**: No macrophage infiltration
- **Score 1**: Infiltration in <25%
- **Score 2**: Infiltration in 25%
- **Score 3**: Infiltration in 25-50%
- **Score 4**: Infiltration in 50-75%
- **Score 5**: Infiltration in >75%
OCT – Neoatherosclerosis results

**Significant** reduction in foamy macrophages in BRS compared to DES on frame level and on animal level!

**Magmaris vs. DES**
- \( p < 0.0001; \) B: -0.606

**Statin vs. Placebo**
- \( p = 0.873; \) B: -0.070

Generalized Estimating Equations

OCT NA-score (estimated means with lower/upper 95% CI)
Reduction of RAM 11-positive superficial foamy macrophages as a sign of Neoatherosclerosis in BRS compared to DES after 161 days.
Little neointimal coverage in the DES compared with positive remodelling with enhanced neointimal coverage in the BRS.
SEM

RMS
Magmaris

DES
316L-equivalent

![SEM images of RMS and DES](image)

![Box plot showing mean area endothelialized %](image)

\[ p < 0.001 \]
Increased leakiness of EC junctions in DES
Conclusions

- Neointimal macrophages were frequently observed in the current study and tend to form within the superficial neointima.

- Magnesium based scaffolds (Magmaris) reduce neointimal macrophages as a sign of early neoatherosclerosis compared to 316L-equivalent DES.

- Statin treatment as applied in the current study does significantly reduce formation of neointimal macrophages in both BRS and DES.

- Magnesium based scaffolds show larger neointima burden as compared to 316L-equivalent DES.

- Magnesium based scaffolds exhibit greater endothelial integrity as compared to 316L-equivalent DES.

- Outlook: Future clinical studies will need to confirm these results