Bioresorbable Vascular Scaffolds: Current Advances and Future Perspectives

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Disclosure Statement of Financial Interest

None whatsoever…
Interventional Cardiology:
The Beginning, the 1st Revolution, the 2nd Revolution and the Future

1977
Balloon (PTCA): Andreas Gruntzig performs the first PTCA in Zurich, Switzerland

1988
Bare Metal Stent (BMS):
Julio Palmaz and Richard Schatz develop a stainless steel stent for coronary applications

2002 - 2003
Drug-eluting stents (DES): introduced to the European and U.S.
Compensatory Expansive Remodeling of EEM > Lumen Reduction

Benign NIH Neo-Atheroma > Stent Thrombosis?

In-Stent Restenosis
Delayed Healing > Stent Thrombosis?
Late Acquired Malapposition > Stent Thrombosis?

Metallic Stent: a caged lumen doomed to get reduced, or a cage doomed to get malapposed
The Pathology of Neoatherosclerosis in Human Coronary Implants

PES 14 Months

SES 23 Months

BMS 96 Months

Nakazawa G. et al.
The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents.
J Am Coll Cardiol. 2011 Mar 15;57(11):1314-22
What is the Minimum Duration of Radial Scaffolding?

Quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months

n = 342 patients (n = 93 at 30-day F/U; n = 79 at 60-day F/U; n = 82 at 90-day F/U; n = 88 at 120-day F/U)

The lumen appears to stabilize approximately three months after PTCA

Serruys PW et al.
Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon.
A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months.
Circulation 1988 Feb;77(2):361-71
Bioabsorbable/resorbable Vascular Scaffolds: the disappearing "stents"
<table>
<thead>
<tr>
<th>Company</th>
<th>Stent</th>
<th>Development</th>
<th>Pre clinical</th>
<th>Clinical trials</th>
<th>Post market</th>
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<td>Biotronik</td>
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<td>Xenogenics</td>
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<td>Zorion Medical</td>
<td>Zorion BRS</td>
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</tbody>
</table>
Hydrolytic Degradation of PLA family of polymers

Onuma Y. Biodegradable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization? Circulation. 2011 Feb 22;123(7):779-97
Polylactic acid

*Polymer: a large molecule (macromolecule) composed of repeating structural units.

Lactic Acid ($C_3H_6O_3$)

Krebs Cycle

$CO_2$ & $H_2O$

Poly-lactic acid
- Poly-L-LA (PLLA).
- Poly-D,L-LA (PDLLA).
- etc.

Philp A et al.
Lactate: a signal coordinating cell and systemic function.
J Exp Biol. 2005 Dec; 208(Pt 24):4561-75
Relation between PLA Molecular Weight and Mass Loss and Loss in support

Onuma Y. Biodegradable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization? Circulation. 2011 Feb 22;123(7):779-97


What is Required of a Fully Bioresorbable Scaffold to Fulfill the Desire for "Vascular Restoration Therapy"?


Revascularization Resorption: How Fast can we/should we make it?

- Insufficient Support
- Inflammation Risk

? Sufficient Support
- Inflammation Risk

+ Sufficient Support
+ Inflammation Risk

Short resorption time (fast degradation) = insufficient support and/or risk for inflammation
Resorption of the Bioabsorbable Everolimus Eluting Vascular Scaffold

- 28 days
- 2 years
- 3 years
- 4 years

Onuma Y. Bioresorbable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization? Circulation. 2011 Feb 22;123(7):779-97
Pioneering Work: The Igaki Tamai

Bioresorbable Scaffolds: Rationale and Goals

- **Rationale**: Vessel scaffolding is only needed transiently.
- **Goal**: Revascularize the vessel like a metallic DES, then resorb naturally into the body.
- **Potential benefits**:
  - Restoration of natural physiologic vasomotor function in some patients
  - Enable vascular remodeling and tissue adaptation
  - Elimination of chronic sources of vessel irritation and sources for chronic inflammation
  - Possibly avoid current challenges with leaving a metal implant behind
  - Potentially reduce the need for lifelong DAPT
  - No permanent implant to complicate future interventions and reinterventions, particularly in younger patients
  - Non-invasive imaging with CCTA or MRA without ‘blooming artifact’

Serruys PW., Garcia-Garcia HM., Onuma Y.
From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade?
Eur Heart J. 2012 Jan;33(1):16-25b
ABSORB Cohort A
Clinical Study Overall Population

30 patients

Intent to treat

30 patients
clinical

6-month follow-up

Per treatment

29 patients
clinical

n = 1 missed F/U visits*

n = 4 excluded in Per Treatment Population
(3 received non-BVS stent, 1 device failure)

26 patients
QCA

19 patients
QCA/IVUS

n = 1 missed F/U visits*
n = 1 non-cardiac death**
n = 5 refused angiography

2 & 3-year follow-up

2-year follow-up

*One patient missed the 9, 12, 18 month and 2 year visits

**Two patients died of non-cardiac causes at 706 and 888 days

Serruys PW. AHA 2009
Is Non-Invasive Evaluation of the Treated Vessel Feasible?


Does Plaque Deformability Remain Scaffolded at F.U?


Bioresorbable scaffolds

The PCR-EAPCI Textbook – Percutaneous interventional cardiovascular medicine
Why We Do It: Palpography

Assessment of vascular compliance by elastography:
Pre, Post, 6 and 24 months after bioresorbable scaffolding

A bioabsorbable everolimus-eluting coronary stent system (ABSORB):
2-year outcomes and results from multiple imaging methods.
Lancet.2009 Mar 14;373(9667):897-910
Mechanotransduction:
or else…the translation of mechanical forces into chemical signals by cells


Does bioabsorption occur?

Serruys PW et al.
A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009 Mar 14;373(9667):897-910
Lessons Learnt from IVUS: Adaptive Constrictive Remodeling

absence of remodeling
late enlargement of the lumen
reduction of plaque media

Serruys PW.
Asian PCR 2013
How We Do It: OCT

Unlike Metallic stents, PLLA scaffolds allow the light to go through the struts.

With shadowing

Without shadowing

Metallic stent

Polymeric scaffold
Why We Do It: OCT

almost “histological” quantification of neointima between and inside of struts

Flow Area = Lumen Area – Strut Core Area

Neointimal Area = Scaffold Area – Lumen Area – Strut Core Area

Onuma Y. et al.


JACC Cardiovasc Interv. 2014 Dec;7(12):1400-11
What Did We Learn from Optical Coherence Tomography?

Serruys PW et al.

A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods.
Lancet. 2009 Mar 14;373(9667):897-910

Ormiston JA. et al.

First serial assessment at 6 months and 2 years of the second generation of absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study.
Is vasomotion restored?

Serruys PW et al.
A bioabsorbable everolimus-eluting coronary stent system (ABSORB):
2-year outcomes and results from multiple imaging methods.
Lancet.2009 Mar 14;373(9667):897-910
Absorb Cohort B1
Results of nitrate induced vasomotor function
5-years, n=23

Absorb Cohort B1 5 Year Results: B. de Bruyne TCT 2014
Is vasomotion restored?

MLD 2.45 mm
Mean LD 2.72 mm

MLD 1.58 mm
Mean LD 2.12 mm
Δ -0.6 mm (-22%)

MLD 2.32 mm
Mean LD 2.67 mm
Δ +0.55 mm (+26%)

Late Loss: -0.01 mm

Serruys PW. ACC 2011
Staying in shape: Comformability

Serruys PW., Garcia-Garcia HM., Onuma Y.
# ABSORB COHORT A: 5 YEAR F.U (THORAX CENTER)

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>6 months</th>
<th>2 years</th>
<th>5 years</th>
<th>P value 2yr. vs 5yr.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QCA</strong></td>
<td>N=8</td>
<td>N=8</td>
<td>N=7</td>
<td>N=8</td>
<td></td>
</tr>
<tr>
<td>MLD (mm²)</td>
<td>2.36</td>
<td>2.1</td>
<td>1.95</td>
<td>2.2 ↑</td>
<td>0.002</td>
</tr>
<tr>
<td>In - scaffold late loss(mm)</td>
<td></td>
<td>0.26</td>
<td>0.39</td>
<td>0.16↓↓</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>GS IVUS</strong></td>
<td>N=8</td>
<td>N=8</td>
<td>N=7</td>
<td>N=7</td>
<td></td>
</tr>
<tr>
<td>Minimal lumen area (mm²)</td>
<td>5.81</td>
<td>4.67</td>
<td>4.96</td>
<td>5.59↑</td>
<td>0.046</td>
</tr>
<tr>
<td>Mean lumen area (mm²)</td>
<td>6.95</td>
<td>6.17</td>
<td>6.56</td>
<td>8.09↑</td>
<td>0.03</td>
</tr>
<tr>
<td>Plaque area (mm²)</td>
<td>8.78</td>
<td>9.17</td>
<td>7.54</td>
<td>7.07↓</td>
<td>0.25</td>
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<tr>
<td>Vessel area (mm²)</td>
<td>15.72</td>
<td>15.34</td>
<td>14.09</td>
<td>13.76↓</td>
<td>0.35</td>
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<tr>
<td><strong>OCT</strong></td>
<td>N=6</td>
<td>N=7</td>
<td>N=7</td>
<td>N=8</td>
<td></td>
</tr>
<tr>
<td>Minimal lumen area (mm²)</td>
<td>4.43</td>
<td>2.70</td>
<td>2.93</td>
<td>4.62↑</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean lumen area (mm²)</td>
<td>6.56</td>
<td>4.71</td>
<td>4.99</td>
<td>6.51↑</td>
<td>0.02</td>
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## ABSORB COHORT A : 5 YEAR CLINICAL RESULTS

<table>
<thead>
<tr>
<th>Hierarchical</th>
<th>6 months 30 patients</th>
<th>12 months 29 patients*</th>
<th>3 years 29 patients*</th>
<th>5 years 29 patients*</th>
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</thead>
<tbody>
<tr>
<td>Ischemia driven MACE, % (n)</td>
<td>3.3%(1)*</td>
<td>3.4%(1)*</td>
<td>3.4%(1)*</td>
<td>3.4%(1)*</td>
</tr>
<tr>
<td>Cardiac death %</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>MI, % (n)</td>
<td></td>
<td></td>
<td></td>
<td>0.0%</td>
</tr>
<tr>
<td>Non Q MI</td>
<td>3.3%(1)**</td>
<td>3.4%(1)**</td>
<td>3.4%(1)**</td>
<td>3.4%(1)**</td>
</tr>
<tr>
<td>Ischemia driven TLR, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>by PCI</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>by CABG</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

* one patient withdrew consent after 6 months but vital status and absence of cardiac events is known through referring physician

** this patient also underwent a TLR, not qualified as ID-TLR (DS=42%) followed by post procedural troponin qualified as a non Q MI and died from his Hodgkin's disease at 888 days post procedure

No new MACE events between 6 months and 5 years

No ST up to 5 years (all patients off clopidogrel)
**ABSORB cohort B**

**Group B1**  \( (n = 45) \)

- QCA, IVUS, OCT, IVUS VH

**Group B2**  \( (n = 56) \)

- QCA, IVUS, OCT, IVUS VH

**Baseline**

- 6 Months
- 12 Months
- 18 Months
- 24 Months
- 36 Months

**Technical Details**

- **Sponsor/ Funding:** Abbott Vascular
- **Primary Investigators:**
  - PW Serruys MD, PhD
  - J Ormiston MD
- **DSMB:**
  - J Tijssen PhD, MD, PhD, P Urban MD
- **CEC:**
  - C Hanet MD, R Tölg MD, V Umans MD
- **Corelaboratory:**
  - Cardialysis
- **Prospective, open label, FIM**
- **Device Specifications:**
  - 3.0 x 18mm devices to treat up to 2 lesions ≤ 14mm in length

**Study Details**

- **12 sites Europe, Australia, New Zealand**
- **B de Bruyne, MD, PhD**
- **D Dudek, MD**
- **E Christiansen, MD**
- **P Smits, MD, PhD**
- **B Chevalier, MD**
- **D McClean, MD**
- **J Koolen, MD, PhD**
- **S Windecker, MD**
- **R Whitbourn, MD**
- **I Meredith, MD, PhD**

**Patient Enrollment**

- 101 patients enrolled between 19 March and 6 November 2009
**ABSORB COHORT B : 3 YEAR CLINICAL RESULTS**

<table>
<thead>
<tr>
<th></th>
<th>30 days N=101</th>
<th>6 months N=101</th>
<th>12 months N=101</th>
<th>2 years N=100*</th>
<th>3 years N=100*</th>
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<tbody>
<tr>
<td><strong>Cardiac death%</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Myocardial infarction% (n)</strong></td>
<td>2.0 (2)</td>
<td>3.0 (3)</td>
<td>3.0 (3)</td>
<td>3.0 (3)</td>
<td>3.0 (3)</td>
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<tr>
<td>Q wave MI</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Non Q wave MI</td>
<td>2.0 (2)</td>
<td>3.0 (3)</td>
<td>3.0 (3)</td>
<td>3.0 (3)</td>
<td>3.0 (3)</td>
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<tr>
<td><strong>Ischemia driven TLR% (n)</strong></td>
<td>0</td>
<td>2.0 (2)</td>
<td>4.0 (4)</td>
<td>6.0 (6)</td>
<td>7.0 (7)</td>
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<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>PCI</td>
<td>0</td>
<td>2.0 (2)</td>
<td>4.0 (4)</td>
<td>6.0 (6)</td>
<td>7.0 (7)</td>
</tr>
<tr>
<td><strong>Hierarchical MACE% (n)</strong></td>
<td>2.0 (2)</td>
<td>5.0 (5)</td>
<td>6.9 (7)</td>
<td>9.0 (9)</td>
<td>10.0 (10)</td>
</tr>
<tr>
<td><strong>Hierarchical TVF% (n)</strong></td>
<td>2.0 (2)</td>
<td>5.0 (5)</td>
<td>6.9 (7)</td>
<td>11.0 (11)</td>
<td>13.0 (13)</td>
</tr>
</tbody>
</table>

MACE: Cardiac death, MI, ischemia-driven TLR
TVF: Cardiac death, MI, ischemia-driven TLR, ischemia-driven TVR
*one patient missed his 2 year f.u

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**No scaffold thrombosis by ARC or protocol**

Only 3 additional TLR events between 1 and 3 years

Serruys PW. ACC 2013
Insight on evolution of late luminal loss over times

**ABSORB 1Y (including TLR) vs. ABSORB 3Y (including TLR)**

12M BVS (Cohort B): 0.27 ± 0.32 mm (N=56)
Insight on evolution of late luminal loss over times

**ABSORB 1Y (including TLR) vs. ABSORB 3Y (including TLR)**

12M BVS (Cohort B): 0.27 ± 0.32 mm (N=56)

36M BVS (Cohort B): 0.29 ± 0.43 mm (N=51)
Insight on evolution of late luminal loss over times

ABSORB 3Y (Including TLRs) vs. Xience 2Y

BVS (Cohort B): 0.29 ± 0.43 mm (N=51)

24M EES (SPIRIT II): 0.33 ± 0.37 mm (N=96)
Absorb Cohort B

Summary of Late Loss at 5-years

- IVUS revealed profound changes:
  - vessel increased in volume
  - scaffold increased in volume
  - while there was increase in IH the lumen increased in size due to scaffold and vessel size increase and accommodation
  - positive remodeling

Absorb Cohort B 5 Year Results; B de Bruyne, TCT 2014
Study Objective: Continued Access trial. FPI*: Jan 11, 2010

Endpoints: No hypothesis-testing, typical PCI clinical endpoints

Treatment: Up to 2 *de novo* lesions in different epicardial vessels
Planned overlapping allowed in lesions >22 and ≤ 28 mm

Device Sizes:
- Scaffold diameters: 2.5, 3.0, 3.5 mm
- Scaffold lengths: 12*, 18, 28 mm

* sizes to be introduced into the trial once available

FPI: First Patient In
Angina Status: EXTEND* vs. SPIRIT IV**
Propensity matched cohorts

Potential paradigm shift: Late Lumen Gain offers the potential for late post PCI Angina Reduction
**ABSORB EXTEND REGISTRY (n=512)**

**Acute/Subacute/Late Scaffold Thrombosis**

<table>
<thead>
<tr>
<th>Event</th>
<th>30 days N=512</th>
<th>180 days N=512</th>
<th>1 year N=512</th>
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<tbody>
<tr>
<td>Non-hierarchical events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death (%)</td>
<td>0.0</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>2.1</td>
<td>2.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Q-wave (%)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-Q-wave (%)</td>
<td>1.6</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Acute scaffold Thrombosis: 0/512 (0%)**

**Subacute Scaffold Thrombosis: 2/512 (0.4%)**

**Late Scaffold Thrombosis: 2/512 (0.4%)**

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EuroIntervention 2014; 9-online publish-ahead-of-print April
Kočka V. et al.
Bioresorbable vascular scaffolds in acute ST-segment elevation myocardial infarction: a prospective multicentre study 'Prague 19'.
Vessel preparation, size selection, gradual deployment, post-dilation & a ‘slow-food’ attitude!
some final thoughts…or else a glimpse into the future

2 years later: ESS has normalized over the scaffold, and a 210 um layer of neointima has developed.

Prophylactic Revascularization of Vulnerable Plaque to Prevent MI and Death: A Dream?

“Biodegradable Stents: They Do Their Job and Disappear”
Ron Waksman