PCI σε επαναστενωτικές βλάβες

Τσαγάλου Ελευθερία
Επιμελήτρια
Θεραπευτική Κλινική Πανεπιστημίου Αθηνών
DES-ISR by Stent Generation

![Graph showing number of ISR by DES generation after initial stent implanting. The graph displays two categories: First and Second DES generation.](image)

*(Washington Hospital Center)*

Incidence 3-20% *(Dangas et al. JACC 2010;56:1897-907)*
Clinical Presentation and Outcomes of Coronary In-Stent Restenosis Across 3-Stent Generations

Marco A. Magalhaes, MD; Sa’ar Minha, MD; Fang Chen, PhD; Rebecca Torguson, MPH;


909 patients (1077 ISR lesions)
ISR is not benign...

**Graph Description:**
- **Logrank p = .0001**
- **De Novo** line
- **ISR** line
- **HR 2.03 (95% CI 1.62-2.55)**

**Table Description:**
- **Days:** 0, 200, 400, 600, 800, 1000
- **De Novo:** 1423, 1251, 1170, 1118, 1063, 1033
- **ISR:** 397, 327, 266, 251, 230, 216

After matching patients for cardiovascular risk factors, the overall MACE at 3 years was worse for group presenting with ISR compared to the group presenting with de novo coronary artery stenosis (*adjusted HR for clinical presentation of MI).*
Mechanisms of ISR

- **Biological factors**
  - Drug resistance
  - Hypersensitivity

- **Mechanical factors**
  - Non uniform stent strut distribution
  - Stent fractures
  - Polymer peeling
  - Non uniform drug deposition

- **Technical factors**
  - Incomplete stent expansion
  - Stent gaps or “misses” (uncovered lesion segments)
  - Barotrauma to unstented segments
DES IN-STENT RESTENOSIS:

Focal
- DES Fracture
- DES Gap
- Geographic Miss
- Uneven/Undelivered Drug
  - Non-uniform Strut Distribution
  - DES Damage
- DES Underexpansion (***)
- Hypersensitivity
- Drug Resistance

Mechanical Factors

Diffuse

Biological Factors

IVUS / OCT
- **Neointimal Proliferation**
  

  - Predominant Mechanism
  - Neointimal hyperplasia (SMC)

- **Neoatherosclerosis**

  Nakazawa G, Virmani R. J Am Coll Cardiol 2011;57:1314–22

  - Fibroatheroma. Lipid-laden Macrophages, calcium (Necrotic Core)
  - DES 30%, Earlier than BMS
  - Young, Unstable, Time, DES
**Difference of Tissue Characteristics Between Early and Late Restenosis After Second-Generation Drug-Eluting Stents Implantation**

— An Optical Coherence Tomography Study —

Hiroaki Iijima, MD; Shichiti Kuratsu, MD; Tomohiro Shinohara; Yusuke Toroi, MD;

<table>
<thead>
<tr>
<th></th>
<th>Early-ISR (n=30)</th>
<th>Late-ISR (n=23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMEN AREA, MM²</td>
<td>1.5±1.0</td>
<td>1.3±0.7</td>
<td>0.65</td>
</tr>
<tr>
<td>NIH AREA, MM²</td>
<td>4.2±2.1</td>
<td>4.1±1.7</td>
<td>0.89</td>
</tr>
<tr>
<td>HOMOGENEOUS INTIMA</td>
<td>8(26.7)</td>
<td>1(4.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>LIPID-LADEN</td>
<td>9(30.0)</td>
<td>16(69.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NEOATHEROSCLEROSIS</td>
<td>9(30.0)</td>
<td>17(73.9)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
### 2014 ESC Guidelines on Myocardial Revascularization

#### IVUS/OCT in ESC guideline 2014

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVUS or OCT to assess mechanisms of stent failure</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>
TREATMENT STRATEGIES

Balloon angioplasty

Focal restenosis
Stent underexpansion

Adjunctive Therapy
Rotational atherectomy
Cutting Balloon
Laser atherectomy
Drug Eluting balloons

1. IN.PACT Admiral is coated with a matrix of paclitaxel and an excipient, urea.

2. The coating comes into contact with water in the bloodstream upon inflation, hydrating the urea, which facilitates the release of paclitaxel at the target lesion.

3. Paclitaxel penetrates the vessel wall, where it remains at a therapeutic dose for over 180 days, addressing the causes of the restenosis.
RIBS V
A Randomized Comparison of Drug-Eluting Balloon vs Everolimus-Eluting Stent in Patients with Bare-Metal Stent-In-Stent Restenosis

- Inclusion Criteria
  - Informed Consent

- Randomization
  - 189 Pts BMS ISR

- 95 Pts DEB
  - 3 Died
  - 1 Thrombosis
  - 7 Refused
  - Mean: 271 days

- 94 Pts EES
  - 86 Pts Angio FU
  - Mean: 270 days

- Rx Centralized Stratification:
  - ISR Length & Edge

- 100% Angiographic Success

- Angiographic FU

- QCA Primary Endpoint

(170 Pts: 92% of Eligible)
✓ Superior angiographic results in the EES arm
✓ Similar rate of MACE
RIBS IV
(January 2010 – August 2013)

Inclusion Criteria
Informed Consent

309 Pts DES-ISR Randomization

Rx Centralized Stratification:
ISR Length & Edge

Xience Prime
(Abbott Vascular)

155 Pts EES
4 Died
18 Refused
1 Thrombosis

133 Pts Angio FU

155 Pts Clinical FU

154 Pts DEB

3 Died
12 Refused

SeQuent Please
(B. Braun)

154 Pts DEB

139 Pts Angio FU

QCA Primary End-point (90%)

3-Year Clinical FU (100%)

155 Pts Clinical FU

100% Angiographic Success

150 Pts DES-ISR Randomization
RIBS IV

3-Year Clinical Follow-up: Freedom From Death, MI, TLR

Breslow, p = 0.030
Log Rank, p = 0.036

3 Year FU 309 P (100%); FU Time 1057±163 days
Events at Final FU (3 Years)
3 Year FU 309 P (100%); FU Time 1057±163 days

TLR (35)
- EES: 11 (7%)
- DEB: 24 (14%)

TVR (49)
- EES: 17 (11%)
- DEB: 32 (21%)

Intention to Treat
**DEB for BMS-ISR or DES-ISR (I A)**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>LoE</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat PCI is recommended, if technically feasible.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>DES are recommended for the treatment of in-stent re-stenosis (within BMS or DES)</td>
<td>I</td>
<td>A</td>
<td>501, 502, 508, 511, 524</td>
</tr>
<tr>
<td>Drug-coated balloons are recommended for the treatment of in-stent restenosis (within BMS or DES).</td>
<td>I</td>
<td>A</td>
<td>501, 511, 524</td>
</tr>
<tr>
<td>IVUS and/or OCT should be considered to detect stent-related mechanical problems.</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

**A “class effect” of DEB has not been demonstrated**

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Additive and substance class</th>
<th>Dose [µg/mm²]</th>
<th>Approval</th>
<th>Vessel territory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxi™</td>
<td>Lutonix, USA</td>
<td>Polysorbate + sorbitol</td>
<td>2</td>
<td>CE certified, FDA approval</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Agent™</td>
<td>Boston Scientific, USA</td>
<td>Acetyl tributyl citrate</td>
<td>2</td>
<td>CE certified</td>
<td>Coronary</td>
</tr>
<tr>
<td>Ranger™</td>
<td>Boston Scientific, USA</td>
<td>Acetyl tributyl citrate</td>
<td>2</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>SteLLarex™</td>
<td>Spectranetics, USA</td>
<td>Polymethylene glycol</td>
<td>2</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Elutax SV™</td>
<td>Aachen Resonance, Germany</td>
<td>None</td>
<td>2.2</td>
<td>CE certified</td>
<td>Coronary/Peripheral</td>
</tr>
<tr>
<td>DanuBio™</td>
<td>Minvasys, France</td>
<td>n-Butyltri-n-hexyl citrate</td>
<td>2.5</td>
<td>CE certified</td>
<td>Coronary</td>
</tr>
<tr>
<td><strong>Regular dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orchid™</td>
<td>Acotec, China</td>
<td>Magnesium stearate</td>
<td>3</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>SeQuent™ Please</td>
<td>B. Braun, Germany</td>
<td>Iopromide</td>
<td>3</td>
<td>CE certified</td>
<td>Coronary</td>
</tr>
<tr>
<td>SeQuent™ Please OTW</td>
<td>B. Braun, Germany</td>
<td>Resveratrol</td>
<td>3</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Pantera Lux™</td>
<td>Biotronik, Germany</td>
<td>n-Butyltri-n-hexyl citrate</td>
<td>3</td>
<td>CE certified</td>
<td>Coronary</td>
</tr>
<tr>
<td>Passeo Lux™</td>
<td>Biotronik, Germany</td>
<td>n-Butyltri-n-hexyl citrate</td>
<td>3</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>LEGFLOW™</td>
<td>Cardionovum, Germany</td>
<td>Shellac</td>
<td>3</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>RESTORE™</td>
<td>Cardionovum, Germany</td>
<td>Shellac</td>
<td>3</td>
<td>CE certified</td>
<td>Coronary</td>
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<tr>
<td>AngloSculptX™</td>
<td>Spectranetics, USA</td>
<td>Nordihydroguaiaretic acid</td>
<td>3</td>
<td>CE certified</td>
<td>Coronary</td>
</tr>
<tr>
<td>Chocolate Touch™</td>
<td>QT Vascular, Singapore</td>
<td>undisclosed</td>
<td>3</td>
<td>CE certified, FDA approval</td>
<td>Coronary/Peripheral</td>
</tr>
<tr>
<td>Advance PTX™</td>
<td>Cook Medical, USA</td>
<td>none</td>
<td>3</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Dior™ II, BioStream™</td>
<td>Eurocor, Germany</td>
<td>Shellac</td>
<td>3</td>
<td>CE certified</td>
<td>Coronary</td>
</tr>
<tr>
<td>FREeway™</td>
<td>Biosensors, Switzerland</td>
<td>Shellac</td>
<td>3</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>essential™</td>
<td>iVascular, Spain</td>
<td>undisclosed</td>
<td>3</td>
<td>CE certified</td>
<td>Coronary</td>
</tr>
<tr>
<td>luminor™</td>
<td>iVascular, Spain</td>
<td>undisclosed</td>
<td>3</td>
<td>CE certified</td>
<td>Peripheral</td>
</tr>
<tr>
<td>iN.PACT™ (Admiral, Pacific, Falcon)</td>
<td>Medtronic Vascular, USA</td>
<td>Urea</td>
<td>3.5</td>
<td>CE certified, FDA approval (Admiral)</td>
<td>Coronary/Peripheral</td>
</tr>
</tbody>
</table>
Sirolimus Eluting Balloons

VIRTUE Sirolimus Eluting Balloon

DEVOIR Sirolimus Eluting Balloon
VIRTUE™ Sirolimus Eluting Balloon

**Virtue solves DEB Limus delivery challenge of tissue uptake and long-term elution**

Sirolimus tissue concentrations > 300-fold higher in coronary artery treatment site and target concentration maintained for 28 days

---

**Graph Details**

- **Axes:**
  - **Y-axis:** Tissue sirolimus concentration (ng/mg)
  - **X-axis:** Survival (days)

- **Legend:**
  - Coronary
  - Distal Myocardium
  - Kidney
  - Liver
  - Lung

- **Therapeutic concentration:** 1 ng/mg @ 28 days

- **Note:** Lung, liver and kidney below level of detection at 7 days

---

# SABRE: Clinical Safety Outcomes 24 Months Follow Up

## Intent to Treat Analysis (ITT)

<table>
<thead>
<tr>
<th>Event</th>
<th>In Hospital</th>
<th>30 Days*</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Death</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td><strong>TLR</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>6 (12.2%)</td>
<td>7 (14.6%)</td>
</tr>
<tr>
<td><strong>TLF</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>6 (12.2%)</td>
<td>7 (14.6%)</td>
</tr>
</tbody>
</table>

## Per Protocol Analysis (PP)

<table>
<thead>
<tr>
<th>Event</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Death</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>TLR</strong></td>
<td>1 (2.8%)</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td><strong>TLF</strong></td>
<td>1 (2.8%)</td>
<td>2 (5.7%)</td>
</tr>
</tbody>
</table>

*Adjudicated through May 2016*

Values are reported as n (%)

* Primary safety endpoint is 30 day TLF

* J Am Coll Cardiol Intv 2017*
Bioresorbable Vascular Scaffolds for Patients With In-Stent Restenosis

The RIBS VI Study

Breslow, $p = 0.02$

Log Rank, $p = 0.03$

Freedom from MACE (Cardiac Death, MI, TLR)

1 Year FU (FU Time 361±29 days)

J Am Coll Cardiol Intv 2017
Conclusions

• Incidence of ISR-DES ranges from 3 to 20% and can occur even 10 years after stent deployment

• It is important to understand the mechanism and phenotype of ISR (use of IVUS, OCT are helpful)

• The efficacy of Drug Eluting Modalities has significantly reduced the utilization of other therapeutic options such as BA, BMS, debulking devices and VBT

• DCB and DES are as effective for BMS-ISR while DES are the preferred strategy for most DES-ISR

• DES and DCB are associated with nearly 10-20% recurrence rate

• Next generation DCB and BVS should be evaluated in randomised trials
Σας ευχαριστώ
Treatment algorithm

FFR (IVUS/OCT) (-) Medical Rx
Asymptomatic Severity?

IVUS / OCT Underlying Mechanism

Focal
Gap Fracture Edge Body
DES DES DES DES

Diffuse
Underexpansion?
Avoid Geo Miss ↑ Pressure NC BA Cutting/Scoring
Optimization

Preferred DES: Hetero & 2nd G DES
Favor DEB: Multiple ST layers, major SB good acute result, short DAT, 1st ISR (?)

2nd G DES / DEB