“Treatment of In-Stent Restenosis”

J. Eduardo Sousa, MD, PhD, FACC
Instituto Dante Pazzanese de Cardiologia
Hospital do Coração
Sao Paulo, Brazil
Treatment of In-Stent Restenosis

J. Eduardo Sousa, MD, PhD, FACC

No relationship to disclose.
Treatment of In-stent Restenosis

- ISR after Bare Metal Stent
- ISR after Drug-eluting Stent

The Real Question:

- Is ISR still a problem?
DES for ISR: Clinical Studies

- **Sirolimus-Eluting Stent**
  - FIM ISR (Sousa, Serruys)
  - RESEARCH (Saia, Serruys)
  - TROPICAL (Neuman)
  - ISAR-DESIRE (Kastrati)
  - SECURE (Teirstein, Costa)
  - e-Cypher (Sousa)

- **Paclitaxel-Eluting Stent**
  - TAXUS III (Grube, Serruys)

- **Randomized Trials**
  - SISR (USA, D. Holmes)
  - TAXUS V - ISR (USA, Stone, Ellis)
Sirolimus-Eluting Stent for the Treatment of In-Stent Restenosis
A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Study

J. Eduardo Sousa, MD, PhD; Marco A. Costa, MD, PhD; Alexandre Abizaid, MD, PhD; Amanda G.M.R. Sousa, MD, PhD; Fausto Feres, MD, PhD; Luiz A. Mattos, MD, PhD; Martina Centenero, MD; Gaio Maldonado, MD; Andrea S. Abizaid, MD; Ibraim Pinto, MD; Robert Falotico, PhD; Judith Jaeger, BA; Jeffrey J. Poppma, MD; Patrick W. Serruys, MD, PhD

Background—We have previously reported the safety and efficacy of sirolimus-eluting drug eluting stents (Synergy®) in patients with de novo coronary lesions. The present investigation evaluated the DES for ISR.

Methods and Results—Twenty-five patients with ISR at one or two sites underwent sirolimus-eluting drug eluting stenting. Eight patients were treated with a single site stenting and 17 with multiple sites stenting. All lesions were treated with the Synergy® stent. Intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) were performed before and at 9 months after stenting. The mean lesion length was 24.9 mm. The mean stent length was 32.7 mm. The mean stent diameter was 3.2 mm. The mean stent expansion was 11.0 mm. The mean stent coverage was 99.4%. The mean lesion gain was 2.6 mm. The mean minimal lumen diameter gain was 0.9 mm.

Conclusions—Sirolimus-eluting stent implantation is safe and effective in treating ISR, with a high rate of angiographic and intravascular ultrasound restenosis.

Sirolimus-Eluting Stent for Treatment of Complex In-Stent Restenosis
The First Clinical Experience

Muzaffer Degertekin, MD,* Evelyn Regar, MD,* Kengo Tanabe, MD,* Pieter C. Smits, MD, PhD,* Willem J. van der Giessen, MD, PhD, FACC,* Stephan G. Carrlton, MD, PhD,* Pin de Feyter, MD, PhD, FACC, FSCAI, Jeroen Vos, MD, PhD,* David P. Foley, MD, PhD, FACC,* Jurgen M. R. Ligterink, MS,* Jeffrey J. Poppma, MD, FACC, Patrick W. Serruys, MD, PhD, FACC* Rotterdam, The Netherlands; and Boston, Massachusetts

OBJECTIVES

In this study, we assessed the value of sirolimus-eluting stenting in patients with in-stent restenosis (ISR).

METHODS

Sirolimus-eluting stents were implanted in patients with ISR (n = 25). Intravascular ultrasound (IVUS) was performed before and after stenting. The results were analyzed at 9 months.

RESULTS

The mean lesion length was 25.6 mm. The mean stent length was 32.7 mm. The mean stent diameter was 3.2 mm. The mean stent expansion was 11.0 mm. The mean stent coverage was 99.4%. The mean lesion gain was 2.6 mm. The mean minimal lumen diameter gain was 0.9 mm.

CONCLUSIONS

Sirolimus-eluting stent implantation is safe and effective in treating ISR, with a high rate of angiographic and intravascular ultrasound restenosis.

TAXUS III Trial
In-Stent Restenosis Treated With Stent-Based Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation

Kengo Tanabe, MD; Patrick W. Serruys, MD, PhD; Elzbeth Cardone, MD; Pieter C. Smits, MD, PhD; Willem J. van der Giessen, MD, PhD; Maynard Stavros, MD; Pin de Feyter, MD, PhD; Ralf Muller, MD; Evelyn Regar, MD; Muzaffer Degertekin, MD; Jurgen M.R. Ligterink, MSc; Clemens D'Amico, MSc; Bianca Backx, PhD; Mary E. Russell, MD

Background—The first clinical study of paclitaxel-eluting stents for de novo lesions showed promising results. We performed the TAXUS III trial to evaluate the feasibility and safety of paclitaxel-eluting stent treatment for the treatment of de novo lesions (ISR).

Methods and Results—The TAXUS III trial was a single-arm, multicenter study that enrolled 20 patients with ISR. The criteria for lesion length were 5.0 mm, 5.0 mm, and 5.0 mm. The mean procedural time was 90 minutes. The mean total stent length was 32.7 mm. The mean stent diameter was 3.2 mm. The mean lesion gain was 2.6 mm. The mean minimal lumen diameter gain was 0.9 mm.

Conclusions—Paclitaxel-eluting stent implantation is considered safe and potentially efficacious in the treatment of ISR. The study results support the continued use of paclitaxel-eluting stents for the treatment of ISR.
Sirolimus-Eluting Stent for the Treatment of In-Stent Restenosis
A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Study

J. Eduardo Sousa, MD, PhD, Marco A. Costa, MD, PhD, Alexandre Abizaid, MD, PhD, Amanda G.M.R. Sousa, MD, PhD, Fausto Feres, MD, PhD, Luiz A. Mattos, MD, PhD, Marinella Centemero, MD, Galo Maldonado, MD, Andrea S. Abizaid, MD, Ibraim Pinto, MD; Robert Falotico, PhD, Judith Jaeger, BA; Jeffrey J. Popma, MD, Patrick W. Serruys, MD, PhD
Changes in % DS and MLD In-stent Sirolimus Eluting Stent: ISR (Sao Paulo)

<table>
<thead>
<tr>
<th>Time</th>
<th>%DS</th>
<th>MLD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>66.0</td>
<td>2.35</td>
</tr>
<tr>
<td>Post</td>
<td>0.9</td>
<td>2.64</td>
</tr>
<tr>
<td>4mo</td>
<td>2.71</td>
<td>2.38</td>
</tr>
<tr>
<td>1 y</td>
<td>7.15</td>
<td>1.81</td>
</tr>
<tr>
<td>3 y</td>
<td>16.7</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Late Loss: 0.33 mm (3 years)

J. Popma. Angiographic Core Lab, Boston
<table>
<thead>
<tr>
<th></th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
<th>48 Months</th>
<th>60 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>Q-wave MI</strong></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Non-Q-wave MI</strong></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>TVR (Non-TLR)</strong></td>
<td>0%</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
<td>8 (32%)</td>
</tr>
</tbody>
</table>

**SES for the Treatment of ISR**

Cumulative Clinical Outcome
ISR Study: 6-Year Follow-Up

Event Free Survival: MACE

Event Free Survival: TLR

Patients without Events (%)

Time (Months)
TROPICAL

Clinical Outcome at 180 Days

Non-Hierarchical Event Rate (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>TROPICAL</th>
<th>GAMMA I/II</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>3.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Death</td>
<td>18.8%</td>
<td>2.0%</td>
</tr>
<tr>
<td>MI</td>
<td>9.4%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Clinically driven TLR</td>
<td>2.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>3.9%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

P-values:
- MACE: P<0.001
- Death: P=0.490
- MI: P=0.004
- Clinically driven TLR: P<0.001
- Stent thrombosis: P=0.080

n= 162 SES
262 VBT

Franz-Joseph Neumann and Walter Desmet, PCR 2004

AHA 2004, New Orleans
The e–Cypher Registry

Real World Use of Sirolimus-Eluting Stents for the Treatment of In-Stent Restenosis


On behalf of the e-Cypher investigators

AHA 2004, New Orleans
 Participating Centers

282 Sites

LATIN AMERICA 97
Argentina 14
Brazil 17
Chile 8
Colombia 9
Costa Rica 2
Dominican Republic 2
Guatemala 1
Mexico 31
Panama 3
Uruguay 3
Venezuela 7

EUROPE 127
Austria 7
Belgium 4
France 30
Germany 1
Italy 10
Latvia 1
Luxembourg 1
Morocco 5
Netherlands 1
Portugal 9
Russian Federation 4
UK 4
Spain 36
Switzerland 9

MIDDLE EAST 15
Bahrain 1
Israel 11
Lebanon 2
Saudi Arabia 1

ASIA PACIFIC 43
Australia 11
India 18
Malaysia 3
Pakistan 2
Thailand 3
Vietnam 3
New Zealand 2
Philippines 1
Singapore

AHA 2004, New Orleans
Patient Enrolment

- Enrolled: 15524
- Analysable*: 15157
- FU at 1 month: 14298
- FU at 6 months: 13970
- FU at 12 months: 13069

* at least 1 SES in a CASS-defined coronary segment at a given index date
360 days follow-up: MACE

- de novo (n=11824)
- ISR (n=1395)

CEC-adjudicated events

<table>
<thead>
<tr>
<th>Event</th>
<th>de novo (%)</th>
<th>ISR (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>1.5</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>Other death</td>
<td>0.69</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>1.25</td>
<td>1.08</td>
<td></td>
</tr>
<tr>
<td>TLR PCI*</td>
<td>2.11</td>
<td>4.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TLR CABG*</td>
<td>0.3</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>7.17</td>
<td>5.53</td>
<td>0.0145</td>
</tr>
</tbody>
</table>

*Cypher stent related Patients treated at index with ISR and de novo lesion are not included.
All cases with reported death, MI, TLR or stent thrombosis were reviewed and adjudicated by CEC: ST was considered “definite” if angiographic documentation was available at any time, and “likely” (up to 30 days) for cardiac death and MI without angiography.

*Cypher stent related Patients treated at index with ISR and de novo lesion are not included
The ISR sub-population represents one of the important current indications for SES (1,751 patients, 12.2% of the WW registry population).

The overall stent thrombosis rate was low and similar in both in the ISR (0.95%) and the non-ISR group (0.87%).

With very low MACE rates at 1 year (7.1%), the subgroup of ISR patients did exceptionally well in terms of safety, contrary to expectations based on some of the previously available data from some other series.

Further target lesion revascularization at 1 year was more often done for ISR (4.0%) than for de novo patients (2.1%).
Treatment of In-stent Restenosis

- ISR after Bare Metal Stent
- ISR after Drug-eluting Stent

- The Real Question:
  - Is ISR still a problem?
Why do DES failure?

Causes of DES ISR:

- Stent under-expansion
- Asymmetric strut distribution
- Stent fracture
- Polymer disruption
- Peri-stent vessel wall injury
- Drug failure or resistance
- Polymer (or drug) hypersensitivity
20 pts with IVUS of both branches after “crush” DES showed frequent stent underexpansion at the side branch ostium.

- **Main vessel**
  - MSA <5mm² in 20%
  - MSA <4mm² in 10%

- **Side branch**
  - MSA <5mm² in 90%
  - MSA <4mm² in 55%
  - Ostium is the site of MSA in 65%

Costa et al. J Am Coll Cardiol (in press)
Bifurcation stenosis treated with 2 Cypher stents

7-month Follow-up
Why do DES failure?

Causes of DES ISR:
- Stent under-expansion
- Asymmetric strut distribution
- Stent fracture
- Polymer disruption
- Peri-stent vessel wall injury
- Drug failure or resistance
- Polymer (or drug) hypersensitivity
Pre Post

Stent cypher 3.0x33.0mm

Stent Fracture

FU 8m
Treatment: Another Cypher

Stent cypher 3.0x18.0mm
Why do DES failure?

Causes of DES ISR:

- Stent under-expansion
- Asymmetric strut distribution
- Stent fracture
- Polymer disruption
- Peri-stent vessel wall injury
- Drug failure or resistance
- Polymer (or drug) hypersensitivity
Cypher side-branch ostium after crush and repeated 20 atmos post-dilatation
Main branch ostium after Taxus stent crush and Repeated high pressure kissing post-dilatation
How to Treat DES ISR

- Balloon PCI
- Athero-ablative modalities (RA, DCA, or ELCA)
- Scoring devices (cutting balloon, Fx minirail, or Angiosculpt)
- Bare metal stent
- Drug-eluting stent
- Vascular brachytherapy
DES ISR treated with another DES

6 months TAXUS

Cypher 3.5/18mm

Post Cypher

6 months

6 months
The SISR Trial: 12 Month Outcomes of Sirolimus-eluting Stents for the Treatment of In-Stent Restenosis

David R. Holmes, Jr., Mayo Clinic; Jeffrey Popma, Brigham & Women’s Hospital; Richard Kuntz, Harvard Clinical Research Institute; Peter J. Fitzgerald, Stanford University Medical Center; Paul S. Teirstein, Scripps Clinic; Lowell Satler, Washington Hospital Center; Michael Sketch, Duke University Medical Center; Sidney A. Cohen, Cordis Corporation, Johnson & Johnson
Study Design

Patients with in-stent restenosis with native coronary artery lesions ≥ 15 mm and ≤ 40 mm in length and ≥ 2.5 mm to ≤ 3.5 mm in diameter (n=384)

Randomized 2:1

CYPHER® Sirolimus-eluting stent

259 Patients

Intravascular Brachytherapy Beta or Gamma

125 Patients

Primary endpoint – Target Vessel Failure (TVF): Cardiac death, MI, or TVR at 9 months post-procedure
SISR: Angiographic Outcomes @ 6 mos

- **Acute Gain (mm)**: SES 1.27, Brachytherapy 1.02, p<0.001
- **Late Loss (mm)**: SES 0.27, Brachytherapy 0.33, p=0.330
- **Loss Index (mm)**: SES 0.50, Brachytherapy 0.31, p=0.691
- **Net Gain (mm)**: SES 1.00, Brachytherapy 0.68, p<0.001
- **Restenosis (% of Patients)**: SES 19.8, Brachytherapy 29.5, p=0.067
SISR: Clinical Outcomes @ 9 mos

- **SES**
- **Brachytherapy**

<table>
<thead>
<tr>
<th>Event</th>
<th>SES</th>
<th>Brachytherapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.0</td>
<td>0.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Q-Wave MI</td>
<td>0.4</td>
<td>0.0</td>
<td>0.183</td>
</tr>
<tr>
<td>NQMI</td>
<td>2.3</td>
<td>0.0</td>
<td>0.004</td>
</tr>
<tr>
<td>TLR</td>
<td>8.5</td>
<td>19.2</td>
<td>0.008</td>
</tr>
<tr>
<td>TVR</td>
<td>10.8</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>TVF Primary Endpoint</td>
<td>12.4</td>
<td>21.6</td>
<td>0.023</td>
</tr>
</tbody>
</table>
SISR: FREEDOM from TLR @ 12 mos

[Graph showing time after initial procedure (days) vs. FREEDOM from TLR, with data points at 89.7% and 78.1% at certain time points. The graph includes a label for CYPHER® Brachytherapy Control.]
### Stent Thrombosis

<table>
<thead>
<tr>
<th></th>
<th>CYPHER</th>
<th>Brachytherapy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent Thrombosis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through 30 days</td>
<td>0 / 259 (0%)</td>
<td>0 / 125 (0%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Late Thrombosis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 31 through 360 days</td>
<td>3 / 259 (1.2%)</td>
<td>0 / 125 (0%)</td>
<td>0.554</td>
</tr>
</tbody>
</table>
A Prospective, Multicenter, Randomized Trial Evaluating the TAXUS Paclitaxel-Eluting Coronary Stent versus Vascular Brachytherapy for the Treatment of Bare Metal Stent In-Stent Restenosis

The TAXUS-V In-Stent Restenosis Trial

Gregg W. Stone, MD


Stone GW et al. JAMA 2006;295:1253-63
9 Month Ischemic and Non-Ischemic TLR

**Ischemic TLR**
- Brachytherapy (n=194): 13.9%
- TAXUS (n=191): 6.3%

**Non-Ischemic TLR**
- Brachytherapy (n=194): 6.7%
- TAXUS (n=191): 1.6%

**Any TLR**
- Brachytherapy (n=194): 20.1%
- TAXUS (n=191): 7.9%

*p* = 0.01 for Ischemic TLR, *p* = 0.01 for Non-Ischemic TLR, *p* < 0.001 for Any TLR

Stone GW et al. JAMA 2006;295:1253-63
Cumulative MACE to 9 Months

Stone GW et al. JAMA 2006;295:1253-63

- Brachytherapy (n=201)
- TAXUS (n=195)

Log Rank P=0.02

Cumulative MACE Rate

Days Since Index Procedure

0% 5% 10% 15% 20% 25%
0 30 60 90 120 150 180 210 240 270 300

19.9% 11.5%
*All 3 cases were stent thrombosis*

Stone GW et al. JAMA 2006;295:1253-63
Conclusion

CIPHER® and TAXUS® stents result in superior clinical and angiographic outcomes compared with vascular brachytherapy for the treatment of restenosis within a bare-metal stent.
Even in unfavorable subgroups
Study Overview
- Prospective, randomized 1:1, open-label trial
- Pts with bare metal in-stent restenosis randomized to:
  - TAXUS Express\textsuperscript{2} slow-release paclitaxel-eluting stent
  - VBT with and FDA-approved beta-source
- Clinical FU at 1, 4 and 9 months, and then yearly for 5 yrs
- Angiographic FU at 9 months planned in all patients
- IVUS FU at 9 months planned in 250 patients

Primary Endpoint: 9-month ischemic TVR
- Powered for sequential non-inferiority and superiority
With 438 patients having 9 month F/U (219 per group)

**Non-Inferiority Testing**

<table>
<thead>
<tr>
<th>Brachytherapy</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated TVR: 20%</td>
<td>Anticipated TVR: 20%</td>
</tr>
<tr>
<td>Delta 10%, 1-sided alpha 0.05 → 83% power</td>
<td></td>
</tr>
</tbody>
</table>

**Superiority Testing**

<table>
<thead>
<tr>
<th>Brachytherapy</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated TVR: 20%</td>
<td>Anticipated TVR: 10%</td>
</tr>
<tr>
<td>2-sided alpha 0.05 → 80% power</td>
<td></td>
</tr>
</tbody>
</table>

Allowing for 10% attrition, up to 488 patients could be enrolled
9 Month Analysis Segment Results
Paired Angiographic Analysis

Brachytherapy (n=170)  TAXUS (n=172)

- Baseline MLD: 0.83, 0.80 (0.61-1.02, 0.55-1.04) vs. 1.00, 1.00 (0.71-1.25)
- Acute Gain: 1.62, 1.38-1.94 vs. 2.08, 1.56-2.13
- Post-Proc. MLD: 1.84, 1.56-2.13 vs. 2.08, 1.83-2.48
- Late Loss: 0.22, -0.02-0.71 vs. 0.13, 0.05-0.42
- 9 month MLD: 1.55, 1.05-1.91 vs. 1.99, 1.03-2.25

p=0.51  p<0.001  p<0.001  p=0.08  p<0.001

Stone GW et al. JAMA 2006;295:1253-63
In-stent Restenosis Registry (ISR)

N = 41 patients
Vessel size: 2.5–3.5mm
18mm Cypher stent (1 or 2)

- 2 sites: Sao Paulo (Brazil) and Rotterdam
- São Paulo: Patients similar to those usually treated with brachytherapy
- Rotterdam: Including brachytherapy failures (4 pts), total occlusions (3 cases) and one heart transplant patient
- ASA + Clopidogrel (60 days)
- Primary end-point: 4, 12 and 48-mo MACE
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>100%</td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
</tr>
<tr>
<td>MI</td>
<td>0%</td>
</tr>
<tr>
<td>Emergent CABG</td>
<td>0%</td>
</tr>
<tr>
<td>Sub-acute Thrombosis</td>
<td>0%</td>
</tr>
</tbody>
</table>

30 Days Follow-up MACE (n=13,138)

CEC-adjudicated events

<table>
<thead>
<tr>
<th>Event</th>
<th>Non-ISR (n=11,514)</th>
<th>ISR (n=1,624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>1.34</td>
<td>0.99</td>
</tr>
<tr>
<td>Death</td>
<td>0.56</td>
<td>0.49</td>
</tr>
<tr>
<td>QMI</td>
<td>0.26</td>
<td>0.06</td>
</tr>
<tr>
<td>NQ MI</td>
<td>0.36</td>
<td>0.31</td>
</tr>
<tr>
<td>TLR</td>
<td>0.4</td>
<td>0.31</td>
</tr>
<tr>
<td>TVR</td>
<td>0.12</td>
<td>0.12</td>
</tr>
</tbody>
</table>

AHA 2004, New Orleans
6 Months Follow-up MACE (n= 11,920)

CEC-adjudicated events

- **MACE**
  - Non-ISR (n=10,442): 3%
  - ISR (n=1,478): 3.8%

- **Death**
  - Non-ISR (n=10,442): 1.39%
  - ISR (n=1,478): 1.42%

- **QMI**
  - Non-ISR (n=10,442): 0.35%
  - ISR (n=1,478): 0.14%

- **Non QMI**
  - Non-ISR (n=10,442): 0.58%
  - ISR (n=1,478): 0.54%

- **TLR**
  - Non-ISR (n=10,442): 0.35%
  - ISR (n=1,478): 0.58%
  - Total: 1.19%

- **TVR**
  - Non-ISR (n=10,442): 0.14%
  - ISR (n=1,478): 0.4%
  - Total: 0.88%

AHA 2004, New Orleans
Stent Thrombosis

Overall ST at 6 months:
non-ISR 0.87% vs. ISR 0.95% (ns)

CEC - adjudicated events: all cases with death, MI, TLR or reported stent thrombosis were reviewed

AHA 2004, New Orleans
Survival Free from Major Cardiac Adverse Event (MACE)

- Treatment Group
- Other
- ISR

6 Months MACE-Free Survival

Freedom from MACE (%) vs. Time After the Initial Procedure (Days)

- Log Rank Test: p = 0.0005
- Wilcoxon Test: p = 0.0045
- -2 Log (LR) Test: p = 0.0005

- 97.0% survival at 6 months for Treatment Group
- 96.2% survival at 6 months for ISR Group
- 97.0% survival at 6 months for Other Group
6 Month TLR-free Survival

Survival Free from Target Lesion Revascularization (TLR)

- Treatment Group
- Other
- ISR

Log Rank Test: p < .0001
Williamson Isozon Test: p < .0001
-2 Log (LR) Test: p < .0001

98.9%
97.9%

AHA 2004, New Orleans
Changes in % DS and MLD In-stent Sirolimus Eluting Stent: ISR (Sao Paulo)

<table>
<thead>
<tr>
<th></th>
<th>%DS</th>
<th>MLD(mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>66.0</td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>2.71</td>
<td>2.35</td>
</tr>
<tr>
<td>4mo</td>
<td>2.64</td>
<td>2.38</td>
</tr>
<tr>
<td>1y</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>3y</td>
<td>18.1</td>
<td></td>
</tr>
</tbody>
</table>

In-stent Late Loss: 0.33 mm (3 years)

J. Popma. Angiographic Core Lab, Boston
Diffuse In-Stent Restenosis

Pre-Intervention | Post 2 Sirolimus-Eluting Stents
ISR: Sirolimus-Eluting Stent

- 4 Months
- 1 Year
- 3 Years
ISR Study: 4-Year Follow-Up

Patients without Events (%)

Event Free Survival: TLR

Event Free Survival: MACE

Time (Months)
Back of ostium.
Cypher and Taxus Trials: TLR

SIRIUS, C-SIRIUS, E-SIRIUS, RAVEL, DIRECT, SVELT, TAXUS II, IV, and VI

**CYPHER** (6 months)  **TAXUS** (12 months)

- **DES Control**
  - \( P < 0.0001 \)
  - N=1204   n=870
  - 80% ↓
  - 3.5% (3.5%)

- **CYPHER TAXUS**
  - \( P < 0.0001 \)
  - N=1141   n=1148
  - 70% ↓
  - 4.9% (4.9%)
Recommended Strategy to Treat DES ISR

IVUS is recommended to identify mechanical problems

- Focal
  - POBA, scoring balloons, Another DES
  - Focal at edges
    - Another DES

- Diffuse
  - Another DES
ISR after Bare Metal Stents

In-Stent Restenosis = Intimal Hyperplasia
Sirolimus-Eluting Stent for the Treatment of ISR Patterns of In-stent Restenosis

Several mechanisms may explain DES ISR (stent under-expansion, fracture, polymer disruption, geographic miss, drug resistance and hypersensitivity)

The frequency of ISR after DES is low (< 5%).

The pattern of ISR after DES, in contra-distinction to bare metal stents, is predominantly focal (~80%).

ISR after DES is usually easily treated and 2rd success rates appear excellent.

Another DES seems to be the most reasonable approach to treat DES in-stent restenosis
Conclusions and Clinical Implications

- Compared to PCI with VBT, treatment of BMS ISR with the paclitaxel-eluting TAXUS stent:
  - Is safe
    - Comparable rates of target vessel thrombosis, MI, and death
  - Provides superior efficacy
    - Significant reduction in clinical and angiographic restenosis
- For pts in whom BMS are implanted, should restenosis occur, the availability of the TAXUS stent represents a simple, safe therapy resulting in a high rate of 9 month event-free survival, a reassuring option for an otherwise difficult to treat cohort of pts.