Next Generation Drug-eluting Stent: Will It Solve the Problem?

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Yonsei University Healthcare System
Commercially Available DES

**Cypher**
- Drug: Sirolimus
- Polymer: PEVA + PBMA blend
- Stent: BX Velocity

**TAXUS**
- Drug: Paclitaxel
- Polymer: Polyolefin derivative
- Stent: Express²

**Endeavor**
- Drug: Zotarolimus
- Polymer: PC Coating
- Stent: Driver Cobalt
Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year’s meeting.

“Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown,” said Yusuf. “I’ve a feeling the data we’re seeing today is only the tip of the iceberg. We need to encourage more

obtain this data from the manufacturers,” said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). “The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed,” he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

“There’s no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest
Technology “in part” Solves Issues

- Technology Adoption

- Time

- LST
- SAT
- DES
- BMS
- POBA

- Acute Closure
- Restenosis

The Changing balance between DES & BMS in USA:

91% >>>>> 71%

65% : 35%

DES : BMS

June, 2007
Pros & Cons

Long-Term Outcomes with DES vs. BMS in Sweden

CONCLUSIONS

Drug-eluting stents were associated with a reduced rate of death, as compared with bare-metal stents. This advantage was seen as early as after 6 months, when the risk of death was 0.5 percentage point higher with bare-metal stents and a composite of death or myocardial infarction

No. at Risk
Bare-metal stent 12,880 12,473 12,354 12,228 9298 5966 3199
Drug-eluting stent 5,770 5,605 5,541 5,471 3434 1777 626

LaST: Is There A Problem?

- 7 million X 0.6%/year: 42,000 pts
- 1 million new DES/year: 6,000/yr
- LaST: compared to what?
  - BMS?
  - DES?

Yes, there is a problem!!
Benefit / Risk Profile of DES vs BMS

Risk

Stent thrombosis

6,000/yr
>80% MI/Death

MI, Death

Benefit

Reduced restenosis

Reduced TLR

200,000/yr
<2% MI/Death
Contributors to Stent Thrombosis
Compounding Factors Beyond the Stent

Patient & Lesion Factors
- ACS, unstable angina
- Underlying coagulopathy, malignancy
- Diabetes, low ejection fraction or chronic renal failure
- Vessel size, lesion length, arterial structure
- Vulnerable plaque regions

Procedural Complexity
- Morphometric (asymmetry, under-expansion, poor apposition)
- Morphologic (dissection, thrombus, protrusion)
- Mechanical vessel injury
- Anti-thrombotic therapy

Stent Thrombogenicity
- Material
- Design
- Surface coating
- Local drug effect
- Incomplete endothelialization

Stent thrombosis is quite frequent in the first 6 months after stenting.

Most of the effort should concentrate there.

- Thienopyridine therapy continuation
- Thienopyridine therapy discontinuation
- Thrombotic event
### Procedural & In-Hospital Complication - Stent thrombosis vs No stent thrombosis

<table>
<thead>
<tr>
<th>Events</th>
<th>ST (n=38), n (%)</th>
<th>No ST (n=2936), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic success</td>
<td>31 (79)</td>
<td>2718 (98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abrupt closure</td>
<td>2 (6)</td>
<td>7 (0.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>No reflow</td>
<td>0</td>
<td>9 (0.6)</td>
<td>...</td>
</tr>
<tr>
<td>Intra-arterial balloon pump</td>
<td>3 (8)</td>
<td>80 (2.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5 (0.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q wave</td>
<td>4 (10)</td>
<td>11 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Q wave</td>
<td>12 (32)</td>
<td>318 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (3)</td>
<td>3 (0.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3 (8)</td>
<td>24 (3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (5)</td>
<td>58 (2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>2 (5)</td>
<td>85 (3)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Circulation. 2006;113:1108-1113*
M/70, Stable Angina
Cypher Stent at p-LAD on May 2006
Follow-Up Angiography
March 2007 (9 mo. After Stenting)
STEMI after Stopping Aspirin and Clopidogrel for 7 days
For EGD and Colonoscopy on September 2007
Prolonged DAP: *Protecting the Patient vs. Protecting the Vessel*

- Does DAP prevent LaST?

**6-Month Landmark Analysis**

*Adjusted Cumulative Mortality Rates*

<table>
<thead>
<tr>
<th></th>
<th>% (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES+C - DES-C</td>
<td>-3.3 (-6.3, -0.3)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Eisenstein et al. JAMA 2006

Duke University Medical Center
DES thrombosis
Morphologic Predictors

SAT 8/39, LST 11/39: Autopsy study

Predictors
1. Stent across ostia of major side branch
2. Strut penetration of necrotic core
3. Stent Malapposition
4. Increasing stent length
5. Delayed or absence of endothelialization
6. Hypersensitivity

Joner, Virmani et al. Circulation 2005;112:3210
Localized Hypersensitivity and Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent
Should We Be Cautious?

Late Stent Malapposition?

Drug-eluting stent group

Baseline

Follow-up

Struts may be potentially vulnerable

(4 - 16%)
Mechanisms Leading to DES Incomplete Stent Apposition

Positive Remodeling of an initially well apposed stent

A dissolution of jailed material in AMI due to thrombolysis

Localized initial underexpansion due to a site of calcification (fulcrom)

Cook S et al. Circulation. 2007;115:2426-34
Late Stent Malapposition After Drug-Eluting Stent Implantation
An Intravascular Ultrasound Analysis With Long-Term Follow-Up

• Late stent Malapposition in 12% after DES

Predictors
1. Total stent length
2. Primary stenting in AMI
3. Chronic total occlusion

• Late stent thrombosis: none

MK Hong et al 2006 Circulation
Incomplete Neointimal Coverage!
Delayed endothelialization

Subclinical Thrombus

33 %

P = 0.14

14 %

Kotani, et al. JACC 2006
Absence of Endothelialization – 9 months after cypher

Absence of Endothelialization may be linked with malapposition.
Heterogeneity of neointimal healing after DES

Relationship Between VLST and ISA in DES Patients

Very Late Stent Thrombosis (> 1 year) was more frequent in the presence of Incomplete Stent Apposition.

<table>
<thead>
<tr>
<th>ISA as evaluated by IVUS</th>
<th>DES Patients with VLST (n=13)</th>
<th>DES Control: Patients without VSLT (n=175)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Segments Evaluated</td>
<td>13</td>
<td>12/175 (12%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ISA (n, %)</td>
<td>10/13 (77%)</td>
<td>12/175 (12%)</td>
<td></td>
</tr>
<tr>
<td>Maximal ISA Area (mm²)</td>
<td>8.3±7.5</td>
<td>4.0±3.8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Cook S et al. Circulation. 2007;115:2426-34

Incomplete Stent Apposition and Very Late Stent Thrombosis After Drug-Eluting Stent Implantation,
Human Post-Mortem: Fibrin & Endothelialization

Comparison of Endothelialization between DES with LST (>30 d) and Patent Stents

From Renu Virmani

% Struts endothelialized

Thrombosis  No Thrombosis

p<0.03
 Nearly 100% of the drug elutes in the first 7 days and complete at 12 days.

**Endeavor (A1)**

Late Stent Thrombosis—Factors to Consider

Discontinuation of Anti-Platelet Therapy

Late Stent Thrombosis

- Baseline
- Follow-up
  - No Restenosis
  - Positive Restenosis

In a Taxus and Cypher study of patients with late incomplete apposition upon stopping antiplatelet discontinuation:

- 20% had stent thrombosis.

**Graph:**

- Uncoated stent
- PC-coated stent

- Patents Adhered x 10^6

- Time Point (Hours) 1.0 1.5
Endeavor

Clinical Events (%)

DES Arms from Combined Trials

9-Month Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>MI</th>
<th>TLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDEAVOR</td>
<td>0.8</td>
<td>2.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Combined Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EI, EII, EIICA, EIII (n=1296)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXUS</td>
<td>1.3</td>
<td>4.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Meta-Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXUS II, IV, V, VI (n=1718)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYPHER</td>
<td>1.0</td>
<td>2.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Integrated Trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRIUS, E-SIRIUS, DIRECT, SVELTE, RAVEL (n=1204)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source:
No Late Stent Thrombosis in Over 1,300 Patients
No Late Stent Thrombosis in 994 Patients > 2 yr f/u

Days Post Procedure
1 2 3 // 12 13 14 // 30 // 100 150 // 270 360 // 720 // 1080

EII
n=598
= 0.5%

EII CA
n=296
= 0.0%

EIII
n=323
= 0.0%

Overall Thrombosis = 0.3%

ENDEAVOR I-III Clopidogrel Therapy for ≥ 3 months
XIENCE V (A2)

MULTI-LINK VISION®
Stent

MULTI-LINK VISION®
Stent Delivery System

Everolimus

Fluoropolymer
### Consistent Power in Late Loss

<table>
<thead>
<tr>
<th>Comparator</th>
<th>SPIRIT First 30/30</th>
<th>SPIRIT II 225/75</th>
<th>Spirit III 669/333</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Loss in stent (mm)</td>
<td>.10</td>
<td>.11/0.37*</td>
<td>.16 / .31*</td>
</tr>
<tr>
<td>Late Loss in segment (mm)</td>
<td>.09</td>
<td>.07/0.15</td>
<td>.14/.28*</td>
</tr>
<tr>
<td>Binary ISR</td>
<td>0%</td>
<td>1.3%/3.5%</td>
<td>2.3%/5.7%</td>
</tr>
<tr>
<td>Binary Insegment restenosis</td>
<td>&lt;5%</td>
<td>3.4%/5.8%</td>
<td>4.7%/8.9%</td>
</tr>
<tr>
<td>MACE</td>
<td>7.7%</td>
<td>2.7%/6.5%</td>
<td>4.6%/8.1%*</td>
</tr>
<tr>
<td>Comparator</td>
<td>Xience V vs Vision</td>
<td>Xience V vs Taxus</td>
<td>Xience V vs Taxus</td>
</tr>
</tbody>
</table>

*Statistically Significant Difference  p<0.05
Minimal Injury
Minimizing Strut and Polymer Thickness

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Strut Thickness</th>
<th>Polymer Thickness</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYPHER®</td>
<td>140 um</td>
<td>12.6 um</td>
<td>152.6 um</td>
</tr>
<tr>
<td>TAXUS®</td>
<td>132 um</td>
<td>16 um</td>
<td>148 um</td>
</tr>
<tr>
<td>ENDEAVOR</td>
<td>91 um</td>
<td>5.3 um</td>
<td>96.3 um</td>
</tr>
<tr>
<td>XIENCE V</td>
<td>81 um</td>
<td>7.6 um</td>
<td>88.6 um</td>
</tr>
</tbody>
</table>

3.0 mm diameter stents, 500x magnification
Rapid Re-endothelialization  
14-Day Rabbit Iliac Study

Courtesy of Dr. R Virmani
New Polymer (A3)

BioLinx in “Endeavor Resolute”

- A C10 polymer (lipophilic/hydrophilic, stimulate a controlled drug release)
- A C19 polymer (hydrophilic, more biocompatible, and helpful in drug elution)
- A poly vinyl pyrrolidone (hydrophilic, initial drug burst)
**Biodegradable Polymer (A4)**

- **Stent:** S-Stent
- **Polymer:** Proprietary biodegradable PLA
- **Drug:** Biolimus A9®
- **Delivery System:** Tiger Rx balloon catheter
- **Sizes:**
  - 6-cell: 2.5-3.25mm / 8-28mm
  - 9-cell: 3.5-4.0mm / 8-28mm

*Not available for sale in the United States.*
Dual DES (A5)

- Zotarolimus + Dexamethasone
  ➞ Zodiac program

- Pimecrolimus/paclitaxel Vs Pimecorolimus
  ➞ GENESIS trial

- Sirolimus/Genistein
  cf) Genistein ....
  *potential isoflavone, dose-dependent antiplatelet and antiproliferative properties*
Vasculoprotective DES (A6)

Endothelial Progenitor Cells Coating the Stent Surface

Vasculoprotective Effect of EPC Capture

- Inhibits Inflammation
- Inhibits Proliferation
- Inhibits Migration
- Promote healing & re-endothelialization
Nano-porous TiO$_2$ coating (A7)

Anodic Oxidation Process

- Electro-polishing
- First anodizing
- Etching
- Second anodizing
- Pore widening

Nano-porous TiO$_2$ coating (A7)
Unique Microporous Stent Surface (On Site Coating)

Before     Coating     After
ISAR-TEST

Intracoronary Stenting and Angiographic Restenosis: Test Equivalence Between 2 Drug-Eluting Stents (Nanoporous Polymer Free coating)

450 Patients

- Polmyer-free Rapamycin stent
  - No. of patients: 225
  - ISAR I stent

- Polymer-based Paclitaxel stent
  - No. of patients: 225
  - Taxus
- **first fully absorbable DES, consist of**
  - **Bioabsorbable polymer**
  - **Everolimus**
  - **Bioabsorbable BVS polylactic acid stent platform**

BVS stent (A8)
REVA’s “slide & lock” stent

- A fully absorbable polymer stent with a “slide & lock” design ➔ negligible stent recoil
- Radiopaque tyrosine-derived polycarbonate backbone
- RESORB trials has been recently designed
The CardioMind™ .014” Wire Based Stent Delivery System

(NoX instead of Rx)

Head to Toe Solution...
Conclusion

- Currently, various innovative DES are emerging with the intention to avoid the current pitfalls.
- Abolition of neointimal hyperplasia is no longer the ultimate goal and has been replaced by the development of more thin, biocompatible and bioabsorbable stents that facilitate adequate endothelialization as well as normalization of arterial wall.
Thank you for your attention!