Drug Eluting Stents

Post Market Surveillance

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OVERVIEW

Post Market (PM) Surveillance

- Background on PM Surveillance of Currently Approved DES
- Strengths/Weaknesses of Approved DES
  PM Monitoring
- Medtronic Endeavor PM Surveillance Issues
- Specific Recommendations for PM Surveillance for Medtronic Endeavor
Cordis’ CYPHER 04/24/03
Boston Scientific’s TAXUS 03/04/04

FDA Approval Letters
Accessed at www.fda.gov
Cordis’ CYpher 04/24/03
Boston Scientific’s TAXUS 03/04/04

• Long-term outcome (beyond 12 M) “unknown at this time”
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• 5 year outcomes on original randomized pt cohorts

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- 5 year outcomes on original randomized pt cohorts
- 2000 US patient registry to evaluate “for the potential for less frequent adverse events”

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- Long-term outcome (beyond 12 M) “unknown at this time”
- 5 year outcomes on original randomized pt cohorts
- 2000 US patient registry to evaluate “for the potential for less frequent adverse events”
- Reports 3M, 6M, 12M, 18M and annually thereafter
### 6 CYPHER® Stent Registries

<table>
<thead>
<tr>
<th>Study Type</th>
<th>OUS e-CYPHER</th>
<th>US e-CYPHER*</th>
<th>D.E.S. COVER</th>
<th>S.T.L.L.R.</th>
<th>Japan- PMS</th>
<th>J-CYPHER</th>
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<tbody>
<tr>
<td>Enrollment</td>
<td>Open Enrollment Registry</td>
<td>Open Enrollment Registry</td>
<td>Open Enrollment Registry</td>
<td>Angio eval: stent deployment on TVR</td>
<td>Open Enrollment Registry</td>
<td>Open Enrollment Registry</td>
</tr>
<tr>
<td># of Sites</td>
<td>15,157</td>
<td>2,067</td>
<td>4,235</td>
<td>1,554</td>
<td>2,032</td>
<td>14,087</td>
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<tr>
<td>Location</td>
<td>279</td>
<td>38</td>
<td>140</td>
<td>41</td>
<td>50</td>
<td>41</td>
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<td></td>
<td>41 Countries</td>
<td>United States</td>
<td>United States</td>
<td>United States</td>
<td>Japan</td>
<td>Japan</td>
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<tr>
<td>Independent CEC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Independent Data Mgmt</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Monitoring</td>
<td>3%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>3%</td>
</tr>
<tr>
<td>Anti-platelet Medications</td>
<td>ASA, Ticlopidine, Clopidogrel</td>
<td>ASA, Ticlopidine</td>
<td>ASA, Ticlopidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Follow-up</td>
<td>1, 6, and 12 months</td>
<td>Also yearly f/u to 5-years</td>
<td>* FDA mandated PMS</td>
<td></td>
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</table>
1 Year Registry F/U Published
3 Years Post Approval

Interventional Cardiology

Safety of Coronary Sirolimus-Eluting Stents in Daily Clinical Practice
One-Year Follow-Up of the e-Cypher Registry

Philip Urban, MD, FESC; Anthony H. Gershlick, MD; Giulio Guagliumi, MD, FESC; Philippe Guyon, MD; Chaim Lotan, MD; Joachim Schofer, MD; Ashok Seth, MD, MBBS, DSc; J. Eduardo Sousa, MD, PhD; William Wijns, MD, PhD, FESC; Claude Berge, MSc; Monika Deme, MD; Hans-Peter Stoll, MD; on behalf of the e-Cypher Investigators

“This analysis of 1-year data...suggests a high degree of safety of SES, with a rate of ST similar to that observed in clinical trials”

Circulation 2006; 113: 1434-41
**DES – Circa 2006**

6 million implants - ? late stent thrombosis

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**March 2006**

**BASKET-LATE**

**ACC**

**September 2006**

**ESC Annual Meeting**

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### Meta-analysis, DES RCT

<table>
<thead>
<tr>
<th>Death or Q wave MI</th>
<th>BMS (%)</th>
<th>DES (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>sirolimus</td>
<td>3.9%</td>
<td>6.3%</td>
<td>0.03</td>
</tr>
<tr>
<td>paclitaxel</td>
<td>2.6%</td>
<td>2.3%</td>
<td>0.68</td>
</tr>
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</table>

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<table>
<thead>
<tr>
<th>Outcome</th>
<th>BMS (%)</th>
<th>DES (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>0</td>
<td>1.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.3</td>
<td>4.1</td>
<td>0.04</td>
</tr>
<tr>
<td>CV death/nonfatal MI</td>
<td>1.3</td>
<td>4.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Restenosis-related TVR</td>
<td>6.7</td>
<td>4.5</td>
<td>0.21</td>
</tr>
<tr>
<td>MACE</td>
<td>7.9</td>
<td>9.3</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Two-year data suggest different rates of blood clots and heart attacks between the Cypher sirolimus-eluting coronary stent and the Taxus stent.

Cardiologists question the risks in using drug-coated stents.
DES Information Management
2006-2007

N=84
Industry Press Releases
- Positive
- Equivocal
- Negative

N=3
FDA Press Releases/
Patient Updates
- Positive
- Equivocal
- Negative

N=50
Medical Journal Articles (JACC)
- Positive
- Equivocal
- Negative
Swedish Coronary Angiography and Angioplasty Registry

Swedish Coronary Angiography and Angioplasty Registry

DES Patients More Often Had:
- Diabetes
- HTN
- Previous PCI
- Previous CABG
- Previous MI
- Previous HF
- Previous Renal Failure
- Multivessel Disease
- Received Multiple Stents

Not Randomized
Subject to Physician Bias
Swedish Coronary Angiography and Angioplasty Registry

DES Patients More Often Had:
- Diabetes
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Not Randomized
Subject to Physician Bias

New Swedish Registry Results Show No Overall Increased Deaths With DES

ESC Press Release
September 2, 2007
What Has DES History Taught Us?

• Original PM surveillance plan for approved DES was reasonable but would have benefited from:
  – Longer Mandated F/U
  – Better Understanding of Physician Stent Choices
  – Better and More Timely Public Reporting
Post-Approval Study Sponsor Proposal

Medtronic Endeavor

- Prospective, Multi-center, Non-Randomized
- Single Arm, 5-year follow-up
- CEC
- ST = ARC Definite and Probable

- Proposed Sample Size 5300
  - 3300 OUS PROTECT; 2000 US Registry
  - Expected Yield 1941 On-Label Patients
  - Assumed ST rate 0.5% at 1 year
Post-Approval Study Sponsor Proposal

Medtronic Endeavor

Choice of Control Group – US Study

Sponsor: Compare to Control Group (BMS) from RCT
ARRIVE Simple v. TAXUS Overall

\[ N = 3,964 \]

### All Death

RD = +1.2% [-0.4%, 2.8%]

- **TAXUS (N=1400)**
  - Cumulative Event Rate
  - Years Since Index Procedure
  - 1 Year: 3.4% (46)
  - 2 Years: 4.6% (68)

- **ARRIVE (N=2564)**
  - Cumulative Event Rate
  - Years Since Index Procedure
  - 1 Year: 0.9% (12)
  - 2 Years: 0.6% (7)

### Q Wave MI

RD = -0.3% [-1.0%, 0.4%]

- **TAXUS (N=1400)**
  - Cumulative Event Rate
  - Years Since Index Procedure
  - 1 Year: 0.9% (12)
  - 2 Years: 0.6% (7)

- **ARRIVE (N=2564)**
  - Cumulative Event Rate
  - Years Since Index Procedure
  - 1 Year: 0.9% (12)
  - 2 Years: 0.6% (7)

### ARC Primary ST Definite/Probable

RD = +0.2% [-0.8%, 1.2%]

- **TAXUS (N=1400)**
  - Cumulative Event Rate
  - Years Since Index Procedure
  - 1 Year: 1.4% (18)
  - 2 Years: 2.9% (42)

- **ARRIVE (N=2564)**
  - Cumulative Event Rate
  - Years Since Index Procedure
  - 1 Year: 0.9% (12)
  - 2 Years: 0.9% (12)

### TVR

RD = -6.2% [-8.6%, -3.8%]

- **TAXUS (N=1400)**
  - Cumulative Event Rate
  - Years Since Index Procedure
  - 1 Year: 13.4% (183)

- **ARRIVE (N=2564)**
  - Cumulative Event Rate
  - Years Since Index Procedure
  - 1 Year: 7.2% (98)
Post-Approval Study Sponsor Proposal

Medtronic Endeavor

Choice of Control Group – US Study

Sponsor: Compare to Control Group (BMS) from RCT

Better Control Would Be Concurrent Registry of Non-Endeavor Stent Patients

Must Ask About MD Reasons For Stent Selection
Post-Approval Study Sponsor Proposal
Medtronic Endeavor

“Acceptable” Very Late ST Rates Too High

• Major Objective of Upper 95% CI for VLST < 1% for each 12 month period beginning at 12 M
• This would accept a 4% VLST rate at 5 years
Implications of Small Increased Risk

Assumes: 6 million Stent Implants
Excess 0.5% Risk in DES Group

<table>
<thead>
<tr>
<th>Market Share</th>
<th>Number of Stents</th>
<th>Excess Stent Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>900,000</td>
<td>4500</td>
</tr>
<tr>
<td>18%</td>
<td>1.08 million</td>
<td>5400</td>
</tr>
<tr>
<td>20%</td>
<td>1.2 million</td>
<td>6000</td>
</tr>
<tr>
<td>25%</td>
<td>1.5 million</td>
<td>7500</td>
</tr>
<tr>
<td>30%</td>
<td>1.8 million</td>
<td>9000</td>
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</table>
### Power Calculation

**On-Label Comparison**

\[ \alpha = 0.05 \quad \beta = 0.80 \]

<table>
<thead>
<tr>
<th></th>
<th>Very Late Stent Thrombosis (%)</th>
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<tbody>
<tr>
<td></td>
<td>BMS</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
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## Power Calculation

### On-Label Comparison

α = 0.05  β = 0.80

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<td>BMS</td>
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<td>0</td>
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<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
</tr>
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**TAXUS Registries > 7000; Cordis Registries > 20,000**
Delay in Public Reporting of Study Findings

• “Blinding” results for 3 years is unnecessary and needlessly delays public access to data.

• Annual reports should be made public at time of submission to FDA.
Recommendations

- Registry of ~10,000 PCI Patients (BMS and DES)
- Reason for MD Stent Choice
- Blinded Endpoint Adjudication
- > 3 Year Follow-up
- Public Release of Data Upon Submission to FDA
Conclusion

- Impossible to Identify All Safety Issues With a Device Prior to Device Approval
- We Can Do Better:  
  - Larger Studies  
  - Longer Studies  
  - Better Understanding of Physician Choices  
  - More Timely Public Reporting
Drug Eluting Stents

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