Perspectives on Drug-eluting Stent Safety and Efficacy with Regulatory Recommendations

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Cardiovascular Research Foundation
Conflict of interest disclosure

• Consultant to and lecture fees: Boston Scientific, Abbott Vascular, BMS Imaging
• Equity: Devax, Xtent
• Board of directors: Devax
Overview

- Drug-eluting stents markedly reduce clinical and angiographic restenosis compared to BMS
  - ⇒ decreased recurrent ischemia requiring repeat hospitalization and revascularization procedures, (including CABG) and improved quality of life
- Safety concerns have arisen from reports of late stent thrombosis, and increased composite death and Q-wave MI rates
- Most studies have been inconclusive due to insufficient sample size, use of historical controls, limited follow-up duration or lack of access to original source data (requiring use of partial published data, abstracts and internet sources)
DES RCTs: Methodology

• Clinical trial databases (n=9) were obtained from Cordis and BSC by the Cardiovascular Research Foundation with permission for unrestricted academic analyses (Stone, Leon, Mehran, Kirtane and Pocock), performed by a CRF academic statistician (Martin Fahy)
  - RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, TAXUS I, II, IV, V, VI
• Pre-specified analysis plan prior to data review
  - Intention to treat – no patients censored at baseline
  - Variables
    - Safety: death (all, cardiac and non-cardiac), MI (all, Q-wave and non Q-wave), death and MI, cardiac death and MI, death and Q-wave MI, stent thrombosis (protocol defined)
    - Efficacy: TLR and TVR
    - Note – no MACE/TVF composites
  - Time intervals: Latest FU (4 years), 0 - 30 days, ≥30 days, 30 days - 1 year, and ≥1 year to 4 years
  - Kaplan-Meier analysis to maximally utilize all available FU information, with log-rank or exact log-rank analysis
9 Prospective, Double-Blind, Randomized Trials

Freedom From (Protocol) Stent Thrombosis

RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS
(n=1,748)

TAXUS I, II, IV, V, VI
(n=3,513)

99.4% (5) P=0.20
98.8% (10)

99.1% (14) P=0.30
98.7% (20)

Independent CRF patient-level meta-analysis
9 Prospective, Double-Blind, Randomized Trials

Freedom From (Protocol) Stent Thrombosis

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Independent CRF patient-level meta-analysis

- **RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS**
  - 99.4% (5) P=0.20
  - 98.8% (10) P=0.30
  - After 1 year
    - 5 vs. 0, P=0.025
    - 9 vs. 2, P=0.028

- **TAXUS I, II, IV, V, VI**
  - 99.1% (14) P=0.30
  - 98.7% (20) P=0.30
  - After 1 year
    - 5 vs. 0, P=0.025
    - 9 vs. 2, P=0.028

Bare metal stent (n=878)
CYPHER stent (n=870)
Bare metal stent (n=1,758)
TAXUS stent (n=1,755)
9 Prospective, Double-Blind, Randomized Trials

Freedom From All Cause Death

RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS
(n=1,748)

TAXUS I, II, IV, V, VI
(n=3,513)

Time after Initial Procedure (years)

P=0.23
94.7% (45)
93.3% (57)

P=0.68
93.9% (86)
93.4% (92)

Bare metal stent (n=878)
CYPHER stent (n=870)

Bare metal stent (n=1,758)
TAXUS stent (n=1,755)

Independent CRF patient-level meta-analysis
9 Prospective, Double-Blind, Randomized Trials
Freedom From Myocardial Infarction

RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS
(n=1,748)

TAXUS I, II, IV, V, VI
(n=3,513)

Prospective, Double-Blind, Randomized Trials
Freedom From Myocardial Infarction

**RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS**
(n=1,748)

- **CYPHER stent** (n=870)
- **Bare metal stent** (n=878)

93.8% (53)
P = 0.86

93.6% (55)

**TAXUS I, II, IV, V, VI**
(n=3,513)

- **TAXUS stent** (n=1,718)
- **Bare metal stent** (n=1,727)

93.7% (105)
P = 0.66

93.0% (115)

Independent CRF patient-level meta-analysis
9 Prospective, Double-Blind, Randomized Trials

Freedom From Ischemic TLR

RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS
(n=1,748)

TAXUS I, II, IV, V, VI
(n=3,513)

P<0.0001
92.2% (66)
76.4% (202)
P<0.0001
89.9% (166)
80.0% (338)

Bare metal stent (n=878)
CYPHER stent (n=870)

Bare metal stent (n=1,758)
TAXUS stent (n=1,755)

Independent CRF patient-level meta-analysis
## CYPHHER 4-Study RCT Meta-Analysis (N=1,748)

### All events: 0 – 4 Years (part 1)

<table>
<thead>
<tr>
<th></th>
<th>Cypher (N=870)</th>
<th>BMS (N=878)</th>
<th>RR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>6.7% (57)</td>
<td>5.3% (45)</td>
<td>1.27 [0.86,1.88]</td>
<td>0.23</td>
</tr>
<tr>
<td>- Cardiac</td>
<td>3.5% (29)</td>
<td>2.7% (23)</td>
<td>1.26 [0.73,2.18]</td>
<td>0.40</td>
</tr>
<tr>
<td>- Non cardiac</td>
<td>3.3% (28)</td>
<td>2.7% (22)</td>
<td>1.27 [0.73,2.23]</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>6.4% (55)</td>
<td>6.2% (53)</td>
<td>1.03 [0.71,1.51]</td>
<td>0.86</td>
</tr>
<tr>
<td>- Q-wave</td>
<td>2.1% (18)</td>
<td>1.3% (11)</td>
<td>1.64 [0.77,3.47]</td>
<td>0.19</td>
</tr>
<tr>
<td>- Non Q-wave</td>
<td>4.5% (38)</td>
<td>5.0% (43)</td>
<td>0.88 [0.57,1.36]</td>
<td>0.55</td>
</tr>
</tbody>
</table>

**Kaplan-Meier estimates**

**RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS**
<table>
<thead>
<tr>
<th>Event</th>
<th>Cypher (N=870)</th>
<th>BMS (N=878)</th>
<th>RR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI</td>
<td>11.6% (100)</td>
<td>10.4% (89)</td>
<td>1.12 [0.84, 1.49]</td>
<td>0.44</td>
</tr>
<tr>
<td>Death or Q-MI</td>
<td>8.2% (70)</td>
<td>6.4% (54)</td>
<td>1.30 [0.91, 1.86]</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td>8.8% (75)</td>
<td>8.2% (70)</td>
<td>1.07 [0.77, 1.48]</td>
<td>0.69</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.2% (10)</td>
<td>0.6% (5)</td>
<td>2.00 [0.68, 5.85]</td>
<td>0.20</td>
</tr>
<tr>
<td>Ischemic TLR</td>
<td>7.8% (66)</td>
<td>23.6% (202)</td>
<td>0.29 [0.22, 0.39]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic TVR</td>
<td>12.1% (102)</td>
<td>27.5% (235)</td>
<td>0.38 [0.30, 0.48]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

Kaplan-Meier estimates

Independent CRF patient-level meta-analysis
<table>
<thead>
<tr>
<th>Event</th>
<th>Taxus (N=1745)</th>
<th>BMS (N=1758)</th>
<th>RR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6.1% (86)</td>
<td>6.6% (92)</td>
<td>0.94 [0.70,1.26]</td>
<td>0.68</td>
</tr>
<tr>
<td>- Cardiac</td>
<td>2.4% (36)</td>
<td>3.0% (42)</td>
<td>0.86 [0.55,1.35]</td>
<td>0.51</td>
</tr>
<tr>
<td>- Non cardiac</td>
<td>3.8% (50)</td>
<td>3.7% (50)</td>
<td>1.01 [0.68,1.49]</td>
<td>0.98</td>
</tr>
<tr>
<td>MI</td>
<td>7.0% (111)</td>
<td>6.3% (105)</td>
<td>1.06 [0.81,1.39]</td>
<td>0.66</td>
</tr>
<tr>
<td>- Q-wave</td>
<td>1.4% (22)</td>
<td>1.1% (17)</td>
<td>1.30 [0.69,2.45]</td>
<td>0.42</td>
</tr>
<tr>
<td>- Non Q-wave</td>
<td>5.8% (91)</td>
<td>5.3% (90)</td>
<td>1.02 [0.76,1.36]</td>
<td>0.92</td>
</tr>
</tbody>
</table>

TAXUS I, TAXUS II, TAXUS IV, TAXUS V, TAXUS VI
Kaplan-Meier estimates
# TAXUS 5-Study RCT Meta-Analysis (N=3,513)

## All events: 0 – 4 Years (part 2)

<table>
<thead>
<tr>
<th>Event</th>
<th>Taxus (N=1745)</th>
<th>BMS (N=1758)</th>
<th>RR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI</td>
<td>12.4% (187)</td>
<td>11.8% (183)</td>
<td>1.03 [0.84,1.26]</td>
<td>0.79</td>
</tr>
<tr>
<td>Death or Q-MI</td>
<td>7.3% (105)</td>
<td>7.5% (107)</td>
<td>0.99 [0.76,1.29]</td>
<td>0.93</td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td>8.9% (139)</td>
<td>8.5% (136)</td>
<td>1.03 [0.81,1.30]</td>
<td>0.82</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.3% (20)</td>
<td>0.9% (14)</td>
<td>1.44 [0.73,2.84]</td>
<td>0.30</td>
</tr>
<tr>
<td>Ischemic TLR</td>
<td>10.1% (166)</td>
<td>20.0% (338)</td>
<td>0.46 [0.38,0.55]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic TVR</td>
<td>17.2% (272)</td>
<td>24.7% (409)</td>
<td>0.62 [0.53,0.73]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**TAXUS I, TAXUS II, TAXUS IV, TAXUS V, TAXUS VI**  
Kaplan-Meier estimates

Independent CRF patient-level meta-analysis
Death or Q-wave MI

All randomized studies up to latest available follow-up

<table>
<thead>
<tr>
<th>Rate of death or Q-MI (%)</th>
<th>Control (BMS)</th>
<th>DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ + 2.4% P=0.03</td>
<td>3.9 n=870</td>
<td>6.3 n=878</td>
</tr>
<tr>
<td>∆ + 0.3% P=0.68</td>
<td>2.3 n=1675</td>
<td>2.6 n=1685</td>
</tr>
<tr>
<td>∆ + 2.0% P=0.14</td>
<td>6.4 n=870</td>
<td>8.4 n=878</td>
</tr>
<tr>
<td>∆ - 0.2% P=0.93</td>
<td>7.5 n=1758</td>
<td>7.3 n=1755</td>
</tr>
</tbody>
</table>

Cypher trials

Camenzind E, ESC 2006

Taxus trials

CRF, TCT 2006
Why is there no increase in death/MI with DES despite an increase in late stent thrombosis?

### 3 Possibilities

1. **Causes of death and MI in pts with CAD undergoing stent implantation are multifactorial, and often remote from stent site**
   - Relatively small excess risk of late stent thrombosis leading to death or MI might be lost against this greater non-stent related background rate

2. **The excess in death and MI from late stent thrombosis with DES is offset by reduction of death and MI by preventing restenosis**

3. **The definition of stent thrombosis used in the pivotal trials censored thrombotic events after TLR, biasing against DES**
   - By ITT there are no differences in the rates of late stent thrombosis between DES and BMS
Is In-stent Restenosis a Benign Entity?

Presentation of BMS ISR as Acute MI

ISR presenting as MI (%)

<table>
<thead>
<tr>
<th></th>
<th>Bossi (n=234)</th>
<th>Chen (n=1186)</th>
<th>Nayak (n=212)</th>
<th>Walters (n=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISR</td>
<td>3.5</td>
<td>9.5</td>
<td>10.4</td>
<td>19.4</td>
</tr>
</tbody>
</table>

From 2006

Nayak AK et al. Circ J 2006;70:1026-29
Bossi I et al. JACC 2000;35:1569-76
Walters DL et al. AJC 2002;89:491-4
Chen MS et al. AHJ 2006,151:1260-1264
Is ISR a Benign Entity?

1186 cases of single lesion bare metal ISR at the Cleveland Clinic

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>64.1%</td>
<td>Effort Angina</td>
</tr>
<tr>
<td>26.4%</td>
<td>Unstable Angina</td>
</tr>
<tr>
<td>9.5%</td>
<td>Acute MI</td>
</tr>
<tr>
<td>-7.3%</td>
<td>NSTEMI</td>
</tr>
<tr>
<td>-2.2%</td>
<td>STEMI</td>
</tr>
</tbody>
</table>

Chen MS et al. *AHJ* 2006,151:1260-1264

8 (0.7%) procedural deaths

106 cases (8.9%) totally occluded
TAXUS II, IV, V, VI: Death and MI Within 7 Days of TLR and Stent Thrombosis

Total intent-to-treat population: 3445 patients

Control 1727
- Stent thrombosis: 14 pts
  - 12 patients with death or MI

TAXUS 1718
- Ischemia-driven TLR: 290 pts
  - 11 patients with death or MI
- Ischemia-driven TLR: 135 pts
  - 4 patients with death or MI
- Stent thrombosis: 20 pts
  - 19 patients with death or MI

Σ: 23 Pts with Death or MI
(4 Deaths + 21 MIs)

Σ: 23 Pts with Death or MI
(3 Deaths + 23 MIs)
CYPHER 4-Study RCT Meta-Analysis (N=1,748)

Stent Thrombosis: 0 – 4 Years

Protocol definition (primary ST only)
- Bare metal: 5
- Cypher: 10

ARC def/prob (primary ST only)
- Bare metal: 9
- Cypher: 13

ARC def/prob (primary and secondary ST)
- Bare metal: 15
- Cypher: 13

Primary = Thrombotic episodes before TLR
Secondary = Thrombotic episodes after TLR
Duke Database Death/MI Analysis

Adjusted death/MI rates at 24 months in patients without events at 6 months

- **Clopidogrel status at 6 months**
  - Overall P value = 0.07; $P_{\text{int}} = 0.12$

- **Clopidogrel status at 12 months**
  - Overall P value <0.001; $P_{\text{int}} = 0.003$

**Graphs**

- **On clopidogrel**
- **Off clopidogrel**

**Data**

- **DES**
  - N=637, 3.1% On, 7.2% Off
  - N=417, 5.5% On, 6.0% Off
  - N=252, 4.5% On, 3.6% Off

- **BMS**
  - N=579, 5.5% On, 6.0% Off
  - N=1976, 0.0% On, 4.7% Off
  - N=1644, 4.7% On, 3.6% Off

Eisenstein EL et al. JAMA 2007;297: on line
Milan Stent Thrombosis Experience

2,160 consecutive pts with DES implanted

Colombo A, TCT 2006
Safety of Long-Term Clopidogrel

3 Placebo Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Significant bleeding (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>3.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>ASA + Clopidogrel</td>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>ASA + Placebo</td>
<td>8.8%</td>
<td>0.07</td>
</tr>
<tr>
<td>CREDO</td>
<td>3.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA + Clopidogrel</td>
<td>6.7%</td>
<td></td>
</tr>
<tr>
<td>ASA + Placebo</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td>CHARISMA</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>ASA + Clopidogrel</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td>ASA + Placebo</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

**Study Details**

- **CURE**: N=12,563, 1 year FU, CURE major bleed. NEJM 2001;345;494-502
- **CREDO**: N=2,116, 1 year FU, TIMI major bleed. JAMA 2002;288:2411-20
- **CHARISMA**: N=15,603, 2.5 year FU, GUSTO major + moderate bleed. NEJM 2006;354:1706-17
U.S. Cost Implications of Long-term Clopidogrel

- At $4 per day, Clopidogrel costs ~$1500 per year
- As many as 1 million U.S. patients per year receive DES
  - One year of Clopidogrel would cost ~$1.5B
- For 4 million U.S. patients with DES implanted
  - One year of Clopidogrel would cost ~$6.0B
Frequency of In-stent Restenosis - CRF

October 24, 2002

282 pts with 311 ISR lesions

Bare Stents

April 24, 2003

39 pts with 44 ISR lesions

SES

October 24, 2003

one year FU

April 24, 2004

86% Reduction of ISR Cases!!

October 24, 2003

one year FU
Drug-Eluting Stents: Safety vs. Efficacy

- DES represent a remarkable advance - by preventing restenosis DES have reduced the need for repeat PCI and CABG and improved the quality of life for hundreds of thousands of patients.

- Like any medical advance, DES have side effects, the most concerning of which is an increased incidence of primary late stent thrombosis of ~2 per 1000 pts per year (~1 event per every 500 patient-years) compared to BMS, though this is offset by an excess rate of secondary thrombotic events from treatment of BMS restenosis.

- Moreover, the highest quality data to date suggest that with 4 years follow-up, DES when used on label do not increase overall death and MI rates, in part because of prevention of adverse events associated with restenosis.
Drug-Eluting Stents: Recommendations

• Given the similar (low frequency) rates of death, MI and total (primary + secondary) stent thrombosis with on label use of DES and BMS, current DES approval pathways are for the most part acceptable – to modify approval trials to be powered for safety or to require longer-term FU is unnecessary and would be excessively burdensome.

• More rigorous post market surveillance (with greater rates of monitoring required to ensure event rate accuracy) is appropriate, as is an FDA “Dear Doctor” letter reinforcing the need to carefully weigh the risks and benefits of DES on a per patient basis, especially when considering off-label use.
Long-term clopidogrel: Whether long-term clopidogrel would reduce late stent thrombosis, thus warranting the risks and cost, is completely unknown. In the U.S. we don’t change practice recommendations based on hope or need without firm evidence-based medicine. Therefore, pending the completion of an adequately powered randomized trial, the FDA-regulated “label” mandate (3 months for Cypher, 6 months for Taxus) shouldn’t change. The ACC/AHA guidelines currently recommend 1 year of clopidogrel for DES, which is sufficient.