DES Controversy
Stent Thrombosis, Not Time to Panic

Dual Anti-platelet Therapy, How Long?

Cheol Whan Lee, MD
University of Ulsan,
Asan Medical Center,
Seoul, Korea
Disclosure

Nothings
## RAVEL, ZERO Trial

You do 100 patients and 0 come back.

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus-stent (N=118)</th>
<th>Bare-stent (N=120)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion Length, mm</td>
<td>9.6</td>
<td>9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-MLD, mm</td>
<td>0.94</td>
<td>0.95</td>
<td>NS</td>
</tr>
<tr>
<td>Post-MLD, mm</td>
<td>2.43</td>
<td>2.41</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up MLD, mm</td>
<td>2.42</td>
<td>1.64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Late Loss, mm</td>
<td>-0.01±0.33</td>
<td>0.80±0.53</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Angiographic Restenosis, %</td>
<td>0</td>
<td>27</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1-Year TLR, %</td>
<td>0</td>
<td>23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Death, %</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>MACE- free survival, %</td>
<td>97</td>
<td>73</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*NEJM 2002;346:1773*
Dramatic reductions in odds ratio for restenosis were seen across all subgroups of patients in the SIRIUS trial.

A degree of efficacy rarely have been seen for any particular therapy in medicine history.
**DES Euphoria**
To Open or Not To Open

Restenosis, the Achilles heel of bare-metal stenting, had finally been cured.

Based on pivotal clinical trial evidence, the US FDA approved both CYPHER in 2003 as well as TAXUS in 2004.
Prevalence of DES Usage

DES for All Kinds of Patients

• On-label use of DES is estimated to account for <40% of DES use.

• More than 60% of the DES is currently used for off-label indications, such as more complex lesions or higher risk clinical setting.
A 73-year-old man received Taxus stent implantation 14 months ago. Aspirin was discontinued before resection of a newly diagnosed colon carcinoma. 1 week later, on the evening of surgery, he developed a big anterior AMI.
Incidence of All Death or MI in Pooled DES Data

All randomized studies up to latest available follow-up

Doubts were emerging.

Camenzind E, ESC 2006
Swedish Shock
DES euphoria cool down!

Safety Issues, swirling around the world.

After 6 months, the DES-group compared to the BMS group:
Mortality: 32% ↑, 0.5%/year ↑
Death/MI: 20% ↑, 0.5-1%/year ↑
No interval differences → Is it a permanent problem?

“Real-life experience, from an entire country”
An Epidemic of Violent Language

- Clot magnet
- Lethal gun
- Malignant disease
- Monster
- Time bomb
- Vulnerable strut

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Purpose of FDA Meeting
December 7 - 8, 2006
1st day: on-label, 2nd day: off-label

- Assess safety and efficacy of DES
- Assess objective data presented by FDA, industry, professional societies, academic physicians
  - stent thrombosis (BMS vs DES)
  - mortality risk (BMS vs DES)
  - on-label vs off-label usage of DES
  - length of continuation for dual antiplatelet therapy

A rare but life-threatening disease
1,748 patients in 4 RCT treated with SES or BMS
3,513 patients in 5 RCT treated with PES or BMS

Analyzed the major clinical end points of the trials

NEJM 2007;356:998-1008
There were no significant differences in the cumulative rates of death/MI at 4 years.

Stent thrombosis after 1 year was more common with both SES and PES than with BMS.
Analysis of 14 Trials Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

Adnan Kastrati, M.D., Julinda Mehilli, M.D., Jürgen Pache, M.D., Christoph Kaiser, M.D., Marco Valgimigli, M.D., Ph.D., Henning Kelbæk, M.D.,

4,985 patients in 14 RCTs comparing SES with BMS
Mean F/U interval ; 12.1 to 58.9 months
Primary End point: death from any cause
Other outcomes: death/MI, death/MI/reintervention

NEJM 2007;356:1030-9
The use of SES does not have a significant effect on overall long-term survival and survival free of MI, as compared with BMS.

There was a slight increase in the risk of ST associated with SES after the first year.
Late Stent Thrombosis
Real-World Data (n=8,146)

The incidence of late ST did not diminish but rather continued at a steady rate of 0.6% during the 1st 3 y. The true rate is underestimated since only angiographically proven ST were included.

ST accounted for 32% of MI, but for only 2% of deaths.

Serruys et al, Lancet 2007;369:667

“Window of vulnerability”
No Safe Period!

These data reflect higher stent-thrombosis rates than seen elsewhere, but they also reflect a higher-risk population.
An observational study examining consecutive patients receiving coronary stents at Duke Heart Center (BMS, n=3165; DES, n=1501).

Landmark analyses (6, 12, 24m): death/MI, death/MI/revascularization
A Greater Sense of Optimism
The overall risk of mortality & MI is probably OK

- Death, death/myocardial infarction: no difference in BMS group, big difference in DES group
- The extended use of clopidogrel in patients with DES may be associated with a reduced risk for death & death/MI.

HR=2.43, 95%CI 1.12-5.26, p=0.03

HR=1.93, 95%CI 1.05-3.56, p=0.04

JAMA 2007;297:159
Inadequate Data
FDA Panel Summary

Major conclusion _ neither here nor there

RCT data are insufficient to really make any concrete recommendations about either the appropriateness of off-label use of DES, or the most appropriate length of time to administer dual anti-platelet therapy.

Still hungry?
Visit at FDA website: open public hearing, Dec 7. 2006
http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4253oph1_index.htm
Urgent Need for More Data

• ZEST trial
  comparison of the efficacy of Endeavor vs Cypher vs Taxus stent for native coronary lesions in 2,640 real-world patients

“Window of Vulnerability” for ST

The safety and efficacy of FDA’s 1 year-recommendation should be formally tested.
**AMC Data, Incidence of ST (Any ARC)**

<table>
<thead>
<tr>
<th>Time after index procedure (days)</th>
<th>Cumulative Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DES (n=3,375)</td>
</tr>
<tr>
<td></td>
<td>BMS (n=4,777)</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0%</td>
</tr>
<tr>
<td>1.7</td>
<td>1.7%</td>
</tr>
<tr>
<td>2.3</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

**Overall P** ((loglog–rank)) = 0.061

**Very Late Stent thrombosis**

*Jan1997-Feb2006*

**VLST, small but real!**

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**Clopidogrel, How long?**

Dual anti-platelet therapy should be continued through at least 1 year in patients at low risk of bleeding.

Dual anti-platelet therapy for > 1 year may be needed for sicker patients (AMI, CRF, diabetes) & complex lesions.

The appropriate duration for clopidogrel administration can only be determined by a large-scale RCT.
The debate on DES will continue!

“DES world, the growing fear factor”

Based on available patient-level meta-analysis, the overall risk of mortality & MI is no different for DES & BMS, even if LST does appear to be more of a problem with DES.

The DES landscape has changed considerably in the past few months. LST certainly occurs more frequently with current DES than BMS.
Moving Forward
Future Is Bright!

Solution, upcoming soon!

Polymer is enemy, but drugs are OK. It is just a matter of how to use it!

The LST issue may ultimately be resolved by a safer smart DES.