Stent Thrombosis and Drug Eluting Stents

Update - What do we know; what is still unclear

Tony Gershlick, University Hospitals of Leicester, UK
Is there an excess (clinical risk) w DES?

What is the magnitude of the problem?

Which patients are at risk?

Which factors influence stent thrombosis?

What is the logic to current APT regimen for DES?

Upcoming Trials – will they provide insight?

How should we manage patients in the meantime?


Stent thrombosis ~20%!
Stent Thrombosis (Bare Metal Stents)

1.7%
Bare metal stents

One week

Two – six weeks
Drug-eluting stents: a meta-analysis of randomised controlled trials

Cécile Roiron, Paola Sanchez, Anissa Bouzamondo, Philippe Lechat and Gilles Montalescot

Heart published online 10 Oct 2005;
doi:10.1136/hrt.2005.061622

SUBACUTE THROMBOSIS

<table>
<thead>
<tr>
<th></th>
<th>DES Better</th>
<th>BMS Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL</td>
<td>0.320</td>
<td>0.118</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>2.533</td>
<td>4.525</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>2.173</td>
<td>0.177</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>1.70</td>
<td>1.50</td>
</tr>
<tr>
<td>SES-SMART</td>
<td>1.129</td>
<td>4.128</td>
</tr>
<tr>
<td>SCANDENT STENT</td>
<td>1.163</td>
<td>5.159</td>
</tr>
<tr>
<td>ENDEAVOR II</td>
<td>3.846</td>
<td>7.560</td>
</tr>
</tbody>
</table>

SIROLIMUS: p=0.01

<table>
<thead>
<tr>
<th></th>
<th>DES</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORES</td>
<td>13/128</td>
<td>1/138</td>
</tr>
<tr>
<td>TAXUS II</td>
<td>0.141</td>
<td>0.150</td>
</tr>
<tr>
<td>ASPECT</td>
<td>4/118</td>
<td>0.499</td>
</tr>
<tr>
<td>TAXUS III</td>
<td>5/266</td>
<td>0.259</td>
</tr>
<tr>
<td>TAXUS IV</td>
<td>4/662</td>
<td>5/652</td>
</tr>
<tr>
<td>ELUTES</td>
<td>1/152</td>
<td>1/155</td>
</tr>
<tr>
<td>DELIVER</td>
<td>2/517</td>
<td>2/512</td>
</tr>
<tr>
<td>PATENCY</td>
<td>0/24</td>
<td>0/24</td>
</tr>
<tr>
<td>TAXUS VI</td>
<td>1/219</td>
<td>3/227</td>
</tr>
<tr>
<td>TAXUS V</td>
<td>4/560</td>
<td>4/567</td>
</tr>
</tbody>
</table>

PACLITAXEL: p=0.55

Heterogeneity p=0.27 Total 0.37, p=0.44 44:4445 37:4275

Odds Ratio 6 1.10 60
Sirolimus Eluting Stent vs. Bare Metal Stent

BMS 24 months after deployment

Cypher 16 months after deployment

Delayed re-endothelialisation is likely

Circulation 2003;107:1340–1341
Stent Under-expansion and Stent Thrombosis (SES)

- Plaque Burden (%): 62 vs. 46
  - p<0.001

- Significant Residual Stenosis (%): 10 vs. 4
  - p<0.001

- Stent Area (mm²): 4.3 vs. 6.2
  - p<0.001

- Stent Expansion: 0.65 vs. 0.85
  - p<0.001

JACC 2005;45:995–998
38 yr old female with known CAD; Smoker... 
...died suddenly 6 months following stent implantation

One TAXUS stent in the proximal LAD with excellent angiographic results

No healing observed after 6 months
Table 2. World Health Organization Causation Assessment Categories for Associated Hypersensitivity Identified in the MAUDE Database

<table>
<thead>
<tr>
<th>Putative Causative Agent</th>
<th>Certain</th>
<th>Probable</th>
<th>Possible</th>
<th>Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>2 (1%)</td>
<td>0</td>
<td>221 (84%)</td>
<td>39 (15%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>0</td>
<td>240 (92%)</td>
<td>22 (8%)</td>
</tr>
<tr>
<td>Agents administered during</td>
<td>0</td>
<td>3 (1%)</td>
<td>13 (5%)</td>
<td>246 (93%)</td>
</tr>
<tr>
<td>implantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYFHER stent</td>
<td>1 (&lt;1%)</td>
<td>7 (3%)</td>
<td>230 (92%)</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>TAXUS stent</td>
<td>0</td>
<td>2 (18%)</td>
<td>9 (82%)</td>
<td>0</td>
</tr>
</tbody>
</table>

For percent values, each agent is denominated by the number of cases in which the agent was used.

Potential causes of hypersensitivity. The polymer coating can fragment and expose metal struts (14), raising concern that nickel and molybdenum in the stainless steel may cause hypersensitivity (6). However, bare-metal stents have not been demonstrated to cause hypercosinophilic, IgE-mediated reactions in a human autopsy series of over 400 stents (14). The deficiencies in the DES are evident with the use of the...
Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluting Stents

Premature discontinuation clopidogrel HR 161
Limitations of Clopidogrel

• Variable response – “Resistance”
• Time of onset of action
• Irreversible

Maximal aggregation versus time since loading dose of clopidogrel

$y = 35.28 + 29.09 \times e^{-1.072 \times x}$
$r^2 = 0.101$
Most covered by extension of APT

Some idiosyncratic responses

Most patient not taking DUAPT @ 1 year

Patients stopping due to non-cardiac procedures
Dr. A. Gershlick,  
Consultant in Cardiology and Respiratory Medicine,  
Glenfield Hospital.

Dear Dr. Gershlick,

This gentleman is under your care - he has Marfan's syndrome and has had aortic valve surgery and coronary artery stenting.

He presents to us with a pilonidal sinus, which requires surgery. However, he is on Clopidogrel at the moment.

I would be grateful if you could let us know if we can stop the Clopidogrel, and for how long it would be safe to do this, around the time of his surgery.

Kind regards,

Yours sincerely,

[handwritten note: *No-cannot stop Clopidogrel*]
Coronary artery stents and non-cardiac surgery

G. M. Howard-Alpe1,+,†, J. de Bono2, L. Hudsmith2, W. P. Orr3, P. Foex1 and J. W. Sear1

1 Nuffield Department of Anaesthetics and
2 Department of Cardiovascular Medicine, University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK
3 Department of Cardiology, Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK
Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

Eugène P McFadden, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pickard, Lowell F Satler, Ron Waksman, Patrick W Serruys

Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concerns about delayed endothelialisation of the stent struts that occurred late after elective implantation of polymer-based paclitaxel-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

Metallic coronary stents are implanted in more than 1·5 million patients per year. Polymer-based coronary stents eluting sirolimus or paclitaxel substantially reduce the need for repeat percutaneous intervention compared with bare-metal stents, and drug-eluting stents are rapidly replacing bare-metal stents. A meta-analysis\(^1\) of 11 randomised trials (5013 patients) showed no evidence of benefit from using drug-eluting stents. Angiography showed an isolated proximal lesion of the left anterior descending artery (figure 1A). Electrophysiological investigations were negative. The patient underwent percutaneous intervention with one paclitaxel-eluting stent (3·5 mm diameter, 16 mm long; Taxus Express 2), in April, 2003 (figure 1B and 1C) and was subsequently asymptomatic. In June, 2004, aspirin...
## DES Stent Thrombosis

<table>
<thead>
<tr>
<th>Day</th>
<th>Stent</th>
<th>Vessel</th>
<th>CK</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>343</strong> Taxus 3 x 16mm</td>
<td>LAD</td>
<td>6500</td>
<td>Stopped 5 days prior (bladder polyps)</td>
</tr>
<tr>
<td>2</td>
<td><strong>442</strong> Taxus 3.5 x 16mm</td>
<td>LAD</td>
<td>3500</td>
<td>Stopped 7 days prior (colon)</td>
</tr>
<tr>
<td>3</td>
<td><strong>375</strong> Cypher* 3.0 x 33mm</td>
<td>Cx OM₂</td>
<td>--</td>
<td>Stopped 14 days prior</td>
</tr>
<tr>
<td>4</td>
<td><strong>335</strong> Cypher* 3.0 x 18mm</td>
<td>LAD</td>
<td>--</td>
<td>Stopped 14 days prior (colonoscopy)</td>
</tr>
</tbody>
</table>

*Patent BMS

*Lancet 2004;364:1519–1521*
DES and ST - what was the data?

Was there a problem and when

Pre

ESC

Post
Incidence of Serious Adverse Events (Death or MI)

All randomized studies up to latest available follow-up

- **Control (BMS)**
  - 3.9%
  - 6.3%
  - $\Delta + 2.4\%$
  - $p = 0.03$
  - n=870

- **DES**
  - 2.3%
  - 2.6%
  - $\Delta + 0.3\%$
  - $p = 0.68$
  - n=1675
  - n=1685

Gaemzind E. ESC 2006. Oral Presentation #992
Freedom From (Protocol) Stent Thrombosis

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

- 99.4% (5)
- 98.8% (10)

P=0.20

TAXUS I, II, IV, V, VI
(n=3,506)

- 99.1% (14)
- 98.7% (20)

P=0.29

Independent CRF patient-level meta-analysis
Freedom From Death or Myocardial Infarction

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

TAXUS I, II, IV, V, VI
(n=3,506)

89.7% (88) P=0.39
88.4% (100)

88.2% (182) P=0.77
87.6% (186)

Bare metal stent (n=878)
Bare metal stent (n=1,757)

CYPHER stent (n=870)

TAXUS stent (n=1,749)

Time after Initial Procedure (years)
Freedom From (Protocol) Stent Thrombosis

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

TAXUS I, II, IV, V, VI (n=3,506)

Variation in Definitions

5 vs. 0, P=0.025

9 vs. 2, P=0.033

Bare metal stent (n=878)

CYPHER stent (n=870)

TAXUS stent (n=1,749)

Time after Initial Procedure (years)

Independent CRF patient-level meta-analysis
Stent Thrombosis
Proposed Standard Definitions (ARC)

- **Definite/Confirmed**
  - Acute coronary syndrome AND
  - [Angiographic confirmation of thrombus or occlusion OR
  - Pathologic confirmation of acute thrombosis]

- **Probable**
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion

- **Possible**
  - Unexplained death after 30 days

**Timing of Event**
- Acute (24 hours)
- Subacute (1-30 days)
- Late (30 days – 1 year)
- Very Late (> 1 year)
Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents

Laura Mauri, M.D., Wen-huss Hsieh, Ph.D., Joseph M. Massaro, Ph.D., Kalon K.L. Ho, M.D., Ralph D'Agostino, Ph.D., and Donald E. Cutlip, M.D.

B  Paclitaxel Stent (Protocol)

D  Paclitaxel Stent (ARC)
cause of death was carcinoma of the lung with metastases. An autopsy was not done and the death certificate is not available.

Cardiac Death 229 days post-procedure
The patient was a 52 year-old man with a history of dyslipidemia and current smoking who presented with CCS Class IV angina and a positive functional ischemia study. On 12/4/2003 he underwent the index procedure pre-treatment balloon angioplasty and delivery of one assigned stent in the mid RCA. A second assigned stent was placed distal to and overlapping the first assigned stent as treatment for a site reported grade A distal dissection. The Angiographic Core Lab reported a 28% final residual in-lesion stenosis with no dissection and TIMI 3 flow. The post-procedure course was uncomplicated and the patient was discharged on 12/5/2003 on ASA and clopidogrel. On 7/20/2004 the patient died. The site reported a "sudden death: unknown cause." An autopsy was not performed. A narrative reported that the patient's private physician was not involved in the patient's care at the time of death. No further information will be forthcoming.
Reanalysis of trial data out to 4 years
- there is an incidence of very late ST
- not clinically important
- but not off label use / all comers

⚠️ what about off label / when and why?
Broader DES Use: At least 60% of current DES use is outside of the label

- Lesion subsets
  - Multivessel disease
  - Left main
  - Bifurcation lesions
    - Dedicated bifurcation DES systems
  - CTO
  - ISR
  - Small vessels/stents, large vessels/stents
  - SVG’s

- High risk patient subsets
  - Diabetics
  - Renal dysfunction
3. INDICATIONS FOR USE:

The TAXUS Liberté Stent System is indicated for treatment of de novo and restenotic lesions or total occlusions in patients with coronary artery disease – angina; silent ischemia; acute myocardial infarction – to improve luminal diameter and reduce restenosis within the stent and at the stent edges in native coronary arteries.

The TAXUS Liberté Stent System is also indicated for treatment of abrupt or threatened closure in patients with failed interventional therapy. The treated lesion length should be less than the nominal stent length (8 mm, 12 mm, 16 mm, 20 mm, 24 mm, 28 mm or 32 mm) with reference vessel diameters from 2.25 to 5.00 mm.

- Stenting of Saphenous Vein Grafts.
- Unprotected left main coronary artery.
- Heavily calcified lesions.
- Lesions involving arterial segments with highly tortuous anatomy.
- Lesions involving a bifurcation.
- Left ventricular ejection fraction < 30%.
- Cardiogenic shock.
- Presence of definite or probable intraluminal thrombus.
- Any patients judged to have a lesion which may prevent proper stent deployment.
- Direct Stenting of total occlusions.
II. **Indications for use covered by the CE Mark² ('On-label')**

The TAXUS Liberté Stent System is indicated for treatment of de novo and restenotic lesions or total occlusions in patients with coronary artery disease – angina, silent ischemia, acute myocardial infarction – to improve luminal diameter and reduce restenosis within the stent and at the stent edges in native coronary arteries.

The TAXUS Liberté Stent System is also indicated for treatment of abrupt or threatened closure in patients with failed interventional therapy.

<table>
<thead>
<tr>
<th>Indication / Sub-group</th>
<th>EUROPE ‘On-Label’</th>
<th>US ‘On-label’</th>
<th>Material Reported to NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Vessel</td>
<td>YES</td>
<td>YES</td>
<td>BSC Submission (July 2005)</td>
</tr>
<tr>
<td>Long Lesions</td>
<td>YES</td>
<td>YES</td>
<td>BSC Submission (July 2005)</td>
</tr>
<tr>
<td>Diabetics</td>
<td>YES</td>
<td>NO</td>
<td>BSC Submission (July 2005) Update Letter (January 2007)</td>
</tr>
<tr>
<td>In Stent Restenosis</td>
<td>YES</td>
<td>NO</td>
<td>Update Letter (May 2006)</td>
</tr>
<tr>
<td>Chronic Total Occlusions</td>
<td>YES</td>
<td>NO</td>
<td>Update Letter (May 2006)</td>
</tr>
<tr>
<td>AMI</td>
<td>YES</td>
<td>NO</td>
<td>Update Letter (May 2006)</td>
</tr>
<tr>
<td>Cypher ‘on label’</td>
<td>Cypher ‘off label’</td>
<td>Not explicitly included or excluded</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Single de novo lesions ≤ 30mm length</td>
<td>Unresolved thrombus at lesion site</td>
<td>Direct stenting</td>
<td></td>
</tr>
<tr>
<td>Vessel diameter 2.25mm to 4.0mm</td>
<td>Vessel diameter &lt;2.25mm</td>
<td>Bifurcations</td>
<td></td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>Unprotected left main</td>
<td>Multivessel</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Tortuous vessels that may impair stent placement in region of obstruction or proximal to lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AMI – dossier currently under review</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic total occlusion</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Saphenous vein graft</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Brachytherapy of target lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesions &gt;30mm length</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transplant patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The TAXUS ARRIVE 1 Peri-Approval Registry of 2585 Patients

Stent thrombosis rates through 12 months in selected complex patient/lesion subsets

<table>
<thead>
<tr>
<th></th>
<th>Long Lesions (&gt; 20 mm)</th>
<th>Patients with Multiple TAXUS Stents</th>
<th>Lesions with Multiple TAXUS Stents</th>
<th>Multi-vessel Stenting</th>
<th>Bifurcations</th>
<th>Acute MI</th>
<th>Diabetic</th>
<th>Insulin-Requiring Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent Thrombosis</td>
<td>3.7% (23/624)</td>
<td>3.4% (34/1009)</td>
<td>4.1% (14/340)</td>
<td>3.8% (16/421)</td>
<td>3.5% (7/198)</td>
<td>2.9% (7/242)</td>
<td>3.1% (23/750)</td>
<td>6.3% (15/238)</td>
</tr>
</tbody>
</table>

Off label higher within the year time frame
FDA > CDRH > News > FDA Statement on Coronary Drug-Eluting Stents

FDA Statement on Coronary Drug-Eluting Stents

FDA is providing the following information in response to inquiries asking for the agency’s position on adverse events related to coronary drug-eluting stents (DES). This information describes our position at this time and does not represent new agency policy.

FDA has been closely monitoring DES since they came to the United States market in 2003 and 2004 – and will continue to monitor the devices. We are aware of recent data that show an increase in the rate of death and myocardial infarction (heart attack) possibly due to stent thrombosis (a blood clot in the stent) in patients treated with DES. The specific studies that have prompted recent media inquiries are the BASKET-LATE study (presented at the March 2006 American College of Cardiology Scientific Sessions in Atlanta, Georgia) and the September 2006 European Society of Cardiology Annual Meeting World Congress of Cardiology Meeting in Barcelona, Spain). The small but significant increase in the rate of death and myocardial infarction observed in these studies was noted in patients followed 18 months to 3 years after stent implantation.

While the studies presented at the Atlanta and Barcelona meetings have raised important questions, the data we currently have do not allow us to fully characterize the mechanism, risks, and incidence of DES thrombosis. A more formal evaluation of the data in these studies is necessary, and any conclusions are dependent upon a thorough peer review. FDA intends to more formally evaluate the studies presented in Atlanta and Barcelona.
Off-label/Real-world DES thrombosis

1. Washington Hospital Data

- 12 month outcome
- ‘on-label’ (n=1773, 55%) vs ‘off-label’ (n=1365, 45%) DES use
- Off-label = >33mm, ISR, SVG, AMI, LMS, CTO
2. Rotterdam/Bern Registry

- 8,146 consecutive (ALL) DES cases in Bern/Rotterdam 2002 - 2005
- Angiographically proven ST
- 90% of all DES patients complete clinical follow-up
- In-hospital mortality 7%, non-fatal MI 72%
3. Prairie Registry

- 5280 consecutive DES patients 2003-2006
- 89% complete clinical follow-up. Mean 18/12
- Angiographically proven ST
4. BASKET-LATE

- 746 patients; 1133 lesions
- Randomised 2:1 DES:BMS in BASKET trial
- Event-free patients at 6/12 followed up for 18/12
- ‘Real-world’ population
  - 84% of all PCIs included
  - 67% MVD; 58% STEMI/UA
  - 27% ≤2.5mm; 2 stents/pt

- Increased late death/MI, though not all due to ST
- Overall death/MI equivalent
- TVR benefit small
5. Swedish PCI Registry

- 13,738 BMS + 6033 DES implanted in 2003-2004
- Complete long-term f/up from National registry of MI, CABG, and death
- DES use in Sweden 62% → 26% from Jan 06 to Oct 06
6. Duke Registry

- Median follow-up 3.1 years

6-Month Landmark Analysis
Adjusted Cumulative Rates of Death or Nonfatal MI

E Eisenstein, et al. JAMA 2007;297:159-168
Relationship between thrombosis and antiplatelet therapy discontinuation

3021 pts
Complete F/U for 18 months
58 thrombosis

- 9 with clopidogrel
- 42 before 6 mo
- 16 after 6 mo
- 7 without clopidogrel

Thienopyridine therapy assumption
Thienopyridine therapy discontinuation
Thrombotic Event
Patients with double antiplatelet therapy %

Thrombosis rate %

- Thrombosis rate without thienopyridine
- Thrombosis rate with thienopyridine

- No thieno* (0 - 6) HR=11.7; 95%CI, 3.47-39.24, p<0.0001
- No thieno* (6 - 18) HR=1.01; 95%CI, 0.30-3.46, p=0.98

Legend:
- Yellow: Thrombosis rate without thienopyridine
- Red: Thrombosis rate with thienopyridine
Cumulative incidence of ST = 58/3021 pts (1.9%)

ST within 6 month: 42 pts (1.4%)
ST after 6 month: 16 pts (0.5%)

Patients without thienopyridine

Patients with thienopyridine

No. of Patients

Discontinued thienopyridine
262 259 2438 1861 1293 921 314 700

On thienopyridine
263 439 583 1161 1215 1728 2100 2377 2321
EARLY
APT 6 months
Discontinuation (op)
Poorly apposed stent

DELAYED - re-endothelialisation
Idiosyncrasy (polymer)

LATE
➢ Recent discontinuation APT
➢ Period after discontinuation
➢ On APT
LAD & diagonal stent 14 months prior
Stopped clopidogrel 3 weeks earlier
Presented as NSTEMI
EARLY
- APT 6 months
- Discontinuation = SAT
- Trial & Registry
- D-re-endothelialisation
- Idiosyncrasy

LATE
- Recent discontinuation APT
- Period after discontinuation
- On APT
Stent malapposition in SIRIUS

Baseline

Follow-up

Normal wall bias
## Stent malapposition in SIRIUS

<table>
<thead>
<tr>
<th></th>
<th>Cypher Stent (n=80)</th>
<th>Bare Stent (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline malapposition</td>
<td>13 (16.3%)</td>
<td>9 (14.7%)</td>
</tr>
<tr>
<td>Resolved</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Persistent</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>New late malapposition</td>
<td>7 (8.7%)*</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Need for

1. Long term adequately powered trial
2. Handle on whether any one stent presents less of a risk

3. The PROTECT Randomized Trial

8,000 patient global randomized trial of the Endeavor vs. the Cypher stent. Primary endpoint = stent thrombosis
PI: W. Wijns; Sponsor: Medtronic Corp.

None are RCT DES versus BMS in all-comers “off-label” study
PRIMARY OBJECTIVE

- Comparison of overall stent thrombosis rate of the Endeavor® versus Cypher® Coronary Stent in a "real world" patient population

SECONDARY OBJECTIVE

- Comparison of composite endpoint of total death and non-fatal myocardial infarctions (intention-to-treat population)
- Assessment of safety and efficacy in patient subgroups with:
  - Specific clinical indications and/or
  - Vessel characteristics
  - Lesion characteristics
Drug-Eluting Stents in the Coronary Artery: issues that may affect the non-cardiologist

A.H. Gershlick, G. Richardson
University Hospitals of Leicester UK LE3 9QP

We would therefore recommend:
1. All patients carry an information/warning card indicating the required period of APT (12).
2. All LaST be reported.
3. Patients should not have their APT discontinued without thought or discussion.
4. If the patient develops a rash thought due to clopidogrel then it must not be simply discontinued, as alternatives such as ticlopidine may be considered (12).
5. There is no place for swopping to an unproven, “cheaper” anti-platelet agent such as dipyridamol.
6. If the non-cardiac procedure can be undertaken on APT without excess bleeding risk then it should be.
7. If not then contact with the interventional cardiologist is mandatory. Review of the lesion, procedural timing, the angiographic result and assessment of other demographics may allow a stent thrombosis risk to be balanced against a surgical bleeding risk.
Watch this space
The consequences of a rare adverse event

~3 million stents implanted 65% DES

1.5% stent thrombosis rate

~ 30,000 patients w ST

50% AMI/death
What do we know

- Delayed re-endothelialisation
- Trial data to 4 years suggests no significant clinical difference
- But an excess of very late ST
- Off label registries suggests excess very late > 1 year
- Current on going clinical trials all comers (label?) not BMS

- APT – one year knee jerk
- Most events occur within 6 months
- Events occur on APT - late

- Who and why n.b. very late on or off DAPT
- New APA - ? Impact on late and very late / cost efficacy
Stent thrombosis and

APT

the pathology

the natural history

the timing

the drugs

APT - What, for how long,
why and what to do about drug failure
Activation of platelets: stenting vs PTCA

- % of CD62 positive platelets
- Day after intervention
- Stent vs PTCA
MACE in patients treated with antiplatelet vs anti-coagulants

<table>
<thead>
<tr>
<th>Study</th>
<th>ISAR (n=517)</th>
<th>FANTASTIC (n=485)</th>
<th>STARS (n=1653)</th>
<th>MATTIS (n=350)</th>
<th>CLASSICS (n=1020)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin+ASA</td>
<td>6.2</td>
<td>8.6</td>
<td>2.7</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td>ASA</td>
<td>1.6</td>
<td>5.7</td>
<td>0.5</td>
<td>5.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Ticlopidine+ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel+ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pre-treatment

Effect of Timing of Loading Dose on MACE at 30d

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Clopidogrel pre</th>
<th>No-pre</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre*</td>
<td>No-pre*</td>
<td>893</td>
</tr>
<tr>
<td>3 to &lt; 6 hrs</td>
<td>7.9</td>
<td>7.0</td>
<td>893</td>
</tr>
<tr>
<td>6 to 24 hr</td>
<td>6.8</td>
<td>9.4</td>
<td>881</td>
</tr>
</tbody>
</table>

RRR: -13.4
P: NS

Overall CREDO Results

Hazard ratio (95% CI)

0.4 0.6 0.8 1.0 1.2

Pre-loading
where is the evidence?
Optimal Clopidogrel Loading (ISAR-CHOICE)

ADP (20 μmol/l)-induced Aggregation (%)

- 300mg: 85.1
- 600mg: 69.8
- 900mg: 64.8

p = 0.004 for 300mg vs 600mg
p = 0.39 for 600mg vs 900mg

Circulation 2005;112:2946–2950
Inhibition of platelet aggregation with 600 mg clopidogrel

Maximal aggregation versus time since loading dose of clopidogrel

Variable patient response
Unpredictable
Variable clinical practice

Maximal aggregation
5 μmol/L ADP (%)

Time of sample taken at PCI
**HUMAN METABOLISM**

- Independent of renal or hepatic function
  - Mechanism of inactivation
    - sequential dephosphorylation to the nucleoside
    - major circulating metabolite 10,000-fold less active than parent

SC-831-9017 and SC-100199
HUMAN PHARMACOKINETICS

- Plasma t0.5 = 3.3 minutes

Graph showing:
- Stepped infusion 0.1 – 4 μg/kg/min
- Steady-state infusion 4 μg/kg/min
- Infusion discontinued
Plasma levels of cangrelor during and after infusion in patients with NSTE ACS

APT in the longer term & Stent thrombosis

?? Mechanism, timing, cause ??
Stent Thrombosis (Bare Metal Stents)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Era</th>
<th>Thrombosis Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karillon</td>
<td>2900</td>
<td>'92–95</td>
<td>1.8</td>
</tr>
<tr>
<td>De Servi</td>
<td>939</td>
<td>'95–96</td>
<td>1.5</td>
</tr>
<tr>
<td>Schuller</td>
<td>2833</td>
<td>'92–97</td>
<td>2.3</td>
</tr>
<tr>
<td>Cutlip</td>
<td>6186</td>
<td>'95–99</td>
<td>0.9</td>
</tr>
<tr>
<td>Moussa</td>
<td>1001</td>
<td>'93–95</td>
<td>1.9</td>
</tr>
<tr>
<td>Werner</td>
<td>215</td>
<td>'95–96</td>
<td>1.9</td>
</tr>
<tr>
<td>Cheneau</td>
<td>7484</td>
<td>'93–02</td>
<td>0.4</td>
</tr>
<tr>
<td>ARTS I</td>
<td>1205</td>
<td>'93–02</td>
<td>2.8</td>
</tr>
<tr>
<td>Wenaweser</td>
<td>605.8</td>
<td>'95–03</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Within the first 6 months (until re-endothelialisation)
DES – inadequate re-endothelialisation – need to maintain DAPT
Polymer damaged by expansion in air at room temperature
360 days FU: stent thrombosis
Drug-Eluting Stents Versus Bare Metal Stents in Percutaneous Coronary Interventions (A Meta-Analysis)

Ciro Indolfi, MD, Maria Pavia, MD, MPH, and Italo F. Angelillo, DDS, MPH

(Am J Cardiol 2005;95:1146–1152)
Drug-eluting stents: a meta-analysis of randomised controlled trials

Cécile Routon, Paola Sanchez, Anissa Bouzamondo, Philippe Lechat and Gilles Montalescot

Heart published online 10 Oct 2005; doi:10.1136/hrt.2005.061622
Predictors of DES Thrombosis

35 Autopsy Examinations Following Stent Placement
(N=32 DES, 7 BMS)

- SAT 8/39 stents, LST 11/39 stents
- All BMS with complete endothelialization
- Predictors
  - Stent across ostia of major sidebranch
  - Strut penetration of necrotic core
  - Stent malapposition
  - Increasing stent length
  - Focal delayed no healing (absence of intima)
  - Hypersensitivity

Joner, Virmani et al. Circulation 2005;112:3210
We would therefore recommend:

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2. All LaST be reported.
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7. If not then contact with the interventional cardiologist is mandatory. Review of the lesion, procedural timing, the angiographic result and assessment of other demographics may allow a stent thrombosis risk to be balanced against a surgical bleeding risk.
Incidence of Late stent Thrombosis: >30 days

- DES: 5.0 events per 1000 pts, P = 0.22
- BMS: 2.8 events per 1000 pts
- SES: 3.5 events per 1000 pts, P = 0.61
- BMS: 4.9 events per 1000 pts
- PES: 6.3 events per 1000 pts, P = 0.034, RR = 3.6

Am J of Medicine 2006;119, 1056-1061
Something appears to be happening late (very late)
Off label/registry

> one year

➢ BUT :-
Drug-Eluting Stents & Stent thrombosis

When thinking about APT:

- how common compared to BMS
- especially so-called "off-label"
- when does it occur
- why
“I don’t know about you, but I still take 75 mg Plavix daily whether I need it or not”
In assessing the risk of stent thrombosis, we remain keenly interested in the long-term follow-up of patients enrolled in the original pivotal DES randomized trials as well as those in the more complex patient and lesion subsets (for example, patients with diabetes; acute myocardial infarction or multiple vessel disease; or lesions involving arterial bifurcations, the left main coronary artery, and long arterial segments) who are currently being treated in “real world” randomized and registry studies.

FDA also continues to closely evaluate information related to the duration of treatment with clopidogrel (Plavix), a drug used in combination with aspirin to reduce/prevent clotting in DES patients. Although the duration of clopidogrel appeared to be adequate for the selected patients in the original clinical trials conducted to support FDA approval, the agency recognizes that the optimal duration of clopidogrel in more complex patients has not been defined. The recommended duration of clopidogrel administration and patient compliance with the prescribed regimen are likely interrelated with patient and anatomical factors that are associated with DES thrombosis. Additional clinical data are likely needed to reach conclusions regarding the optimal antiplatelet therapy regimen for DES patients.

FDA will convene a public meeting of the Circulatory System Devices Advisory Panel by the end of the year in an effort to improve our knowledge regarding the incidence and timing of stent thrombosis as well as the appropriate duration of clopidogrel use in patients who receive DES. This Panel of outside experts will assist the agency in the review and analysis of the available scientific data and provide recommendations for appropriate actions to address this issue, such as possible changes to device labeling or the need for additional clinical studies. An announcement of this meeting will appear on FDA’s web site, www.fda.gov/cdrh.
Inhibition of platelet aggregation with 600 mg clopidogrel

Maximal aggregation versus time since loading dose of clopidogrel

Variable patient response
Unpredictable
Variable clinical practice

TIME OF SAMPLE TAKEN AT PCI

Note: PJS et al. Circulation 2005;111
Limitations of Clopidogrel

- Variable response – “Resistance”
- Time of onset of action
- Irreversible

**Prasugrel** (CS-747, LY640315), a novel potent thienopyridine P2Y12 receptor antagonist, has the potential to achieve higher levels of inhibition of ADP-induced platelet aggregation than currently approved doses of clopidogrel.

**Prasugrel** (Lilly/Sankyo)
- Rapid onset
- Higher and more consistent level of platelet inhibition

**TRITON – TIMI 38 trial (Prasugrel vs Clopidogrel PCI in ACS)**
Platelet inhibition with prasugrel (CS-747) compared with clopidogrel in patients undergoing coronary stenting: the subset from the JUMBO study

V L Serebruany, M G Midei, H Meilman, A I Malinin and D R Lowry

Postgrad. Med. J. 2006;82;404-410
doi:10.1136/pgmj.2006.047696

Background: Based on the preclinical and phase 1 studies, prasugrel, a novel platelet ADP P2Y12 receptor blocker, may be a more potent platelet inhibitor than clopidogrel. This study compared the antiplatelet properties of prasugrel in a small subset of patients enrolled in the JUMBO trial, and compared with historic clopidogrel treated controls.

We conclude that for the higher loading and maintenance dosing regimens chosen in the JUMBO trial, prasugrel is a more potent antiplatelet agent than clopidogrel. Two episodes of profound platelet inhibition, which are not seen with clopidogrel, raise concerns with regard to higher bleeding risks, especially during long term prasugrel use. Whether stronger platelet inhibition will yield better clinical outcomes remains to be determined in the ongoing phase 3 superiority trial (TRITON).

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**Figure 1** Graph illustrates changes of the 5 μM ADP induced platelet aggregation after loading with 40 mg and 60 mg prasugrel and 300 mg clopidogrel during coronary stenting. Higher degree of platelet inhibition, and lack of rebound at 24 hours after intervention distinguish prasugrel from clopidogrel.
Champion Platform TMC-CAN-05-03

Clopidogrel Metabolism

Clopidogrel

- hepatic metabolism and hydrolysis
- Prodrug conversion
- Active agent forms disulfide bridge with cysteine of P2Y12 receptor
- Irreversible binding

Portal circulation

P2Y12 receptor

Platelet
Plasma levels of cangrelor during and after infusion in patients with NSTE ACS

Effect of cangrelor on ADP-induced platelet aggregation in patients with NSTE ACS

Whole blood impedance aggregometry

![Graph showing the effect of cangrelor on ADP-induced platelet aggregation. The x-axis represents time after onset of infusion in hours (0.5, 1.5, 2.5, 3.5, 5, 24, 20 m post, 1 h post). The y-axis represents mean % inhibition of platelet aggregation. The graph shows an increase in inhibition with increasing infusion doses (0.05, 0.2, 0.5, 2 μg/kg/min). The data is from Storey RF et al. Thromb Haemost. 2001; 85:401-7.]
300 & 600mg Clopidogrel: Time to and maximum response

- 300 mg loading dose/ 1 x 75mg
- 600 mg loading dose/ 2 x 75mg

ADP 20 μmol/L - induced aggregation [%]

Time intervals from administration [hours]
Limitation of Thienopyridines: clopidogrel & ticlopidine

- Ticlopidine: Toxicity
- Clopidogrel: Resistance,
  » Variability in response
  » Time to onset
  » Relatively modest anti-platelet effect (~40%)
  » Oral drug not ideal for the acute care PCI setting
  » Irreversible leading to delaying surgery for 5-7 days for platelet regeneration
HUMAN METABOLISM

- Independent of renal or hepatic function
  - Mechanism of inactivation
    - sequential dephosphorylation to the nucleoside
    - major circulating metabolite 10,000-fold less active than parent

SC-931-9017 and SC-100199

cangrelor

dephosphorylated major metabolite
HUMAN PHARMACOKINETICS

- Plasma $t_{0.5} = 3.3$ minutes

Graph showing:
- Stepped infusion: 0.1 – 4 $\mu$g/kg/min
- Steady-state infusion: 4 $\mu$g/kg/min
- Infusion discontinued

Plasma concentration (ng/mL) vs. Time (h)
Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin.

Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G.

Department of Medicine and Cardiology, Aarhus University Hospital, Denmark. steen.husted@as.aaa.dk

AIMS: This double-blind, parallel-group study assessed the pharmacodynamics, pharmacokinetics, and safety of AZD6140, a highly selective P2Y12 receptor antagonist. METHODS AND RESULTS: A total of 150 patients were randomized to receive AZD6140 50, 100, or 200 mg, or clopidogrel 75 mg qd for 28 days. All groups showed comparable decreases in platelet aggregation after initial dosing (day 1) and at steady state (day 28). Maximal inhibition of platelet aggregation (IPA) was observed 2-3 hours post-dose at steady state, the three higher doses of AZD6140 completely inhibited platelet aggregation (mean IPA > 90%) whereas the 200 mg bid dose of clopidogrel (approximately 60%). Clinical adverse events, except one in a patient receiving 400 mg bid aspirin, were relatively mild and of low severity. CONCLUSION: AZD6140 100 and 200 mg bid were associated with significantly greater inhibition of platelet aggregation compared to AZD6140 50 mg bid and clopidogrel 75 mg qd (14 mg/kg) in patients with stable coronary artery disease (CAD) and a history of myocardial infarction (MI) or stroke. Further studies are warranted in patients with acute coronary syndrome.
Platelet P2 receptors: old and new targets for antithrombotic drugs.

Cattaneo M.

Università degli Studi di Milano, Unità di Ematologia e Trombosi-Ospedale San Paolo, Via di Rudini 020142 Milano, Italy, marco.cattaneo@unimi.it

Platelets possess three P2 receptors for adenine nucleotides: P2Y1 and P2Y12, which interact with ADP, and P2X1, which interacts with ATP. The interaction of adenine nucleotides with their platelet receptors plays an important role in thrombogenesis. Thienopyridines such as ticlopidine, an antagonist of the platelet P2Y12 ADP receptor, reduces the incidence of vascular events in patients at risk, but it also has some important drawbacks: a relatively high incidence of toxic effects; delayed onset of action; high inter-individual variability in response. Another thienopyridine, clopidogrel, has superseded ticlopidine, because it is an efficacious antithrombotic drug and is less toxic than ticlopidine. However, the high inter-patient variability in response still remains an important issue. These drawbacks justify the continuing search for agents that can further improve the clinical outcome of patients with atherosclerosis through greater efficacy and/or safety. A new thienopyridyl compound, prasugrel, which is characterized by higher potency and faster onset of action compared with clopidogrel, is currently under clinical evaluation. Two direct and reversible P2Y12 antagonists, cangrelor and AZD6140, have very rapid onset and reversal of platelet inhibition, which make them attractive alternatives to thienopyridines, especially when rapid inhibition of platelet aggregation or its quick reversal are required. Along with new P2Y12 antagonists, inhibitors of the other platelet receptor for ADP, P2Y1, and of the receptor for ATP, P2X1, are under development and may prove to be effective antithrombotic agents.
• In the modern era, stent thrombosis is the most serious safety endpoint occurring after PCI.

• Reductions in restenosis can not be traded for increased risk of subacute (within 30 days) or late stent thrombosis (>30 days).

• Overall stent thrombosis risk can not exceed the risk of similarly severe adverse events after CABG (death, large MI) or POBA (subacute closure, emergent CABG, large MI).
A “Rare” Adverse Event Could Have Major Consequences

- 2.5 million stents implanted
- 1.2% stent thrombosis rate
- ~30,000 people affected
- 45% of ST leads to death
- 60% of ST leads to MI
Final 1 year FU results of the e-Cypher OUS PMS Registry

for the e-Cypher investigators

Relationship of MACE and ST

Cardiac Death
N=205
53 ST (26%)

Stent Thrombosis
N=126

Myocardial Infarction
N=168
55 ST (33%)

13437 patients with FU up and/or AE to 360 days
BMS restenosis carries an acute risk

N = 1186

Hospitalized: ACS/AMI
36% (425/1186)

AMI = 9.5%
(112/1186)

Death = 0.7%
(8/1186)

Chen Am Heart J 2006;151:1260-1264
Stent Thrombosis
Proposed Standard Definitions (ARC)

- **Definite/Confirmed**
  - Acute coronary syndrome AND
  - [Angiographic confirmation of thrombus or occlusion OR
  - Pathologic confirmation of acute thrombosis]
- **Probable**
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
- **Possible**
  - Unexplained death after 30 days

**Timing of Event**
- Acute (24 hours)
- Subacute (1-30 days) ➔ “Early”
- Late (30 days – 1 year)
- Very Late (> 1 year)
Definite or Probable: **Cypher versus Velocity**
- Sirolimus-Eluting (Dublin-Def+ Prob)
- Bx VELOCITY (Dublin-Def+ Prob)

1.5 vs 1.7%, p=0.70

Definite or Probable: **Endeavor versus Driver**
- Endeavor (Definite/Probable ST)
- Driver (Definite/Probable ST)

0.5 vs 1.4%, p=0.06