Stent thrombosis:
patophysiology, predisposing factors, definition, classification, prevention and treatment
Definition of ST – ARC definition

**Definite Stent Thrombosis**
- Angiographic or pathologic confirmation of partial or total thrombotic occlusion within the peri-stent region
AND at least ONE of the following, additional criteria:
- Acute ischemic symptoms
- Ischemic ECG changes
- Elevated cardiac biomarkers

**Probable Stent Thrombosis**
- Any unexplained death within 30 days of stent implantation
- Any myocardial infarction, which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

**Possible Stent Thrombosis**
- Any unexplained death beyond 30 days

Time frame of ARC definition of ST

- **Acute** ≤ 1d
- **Subacute** >1d - ≤1mo
- **Early ≤ 1 mo**
- **Late > 1 mo ≤ 1 year**
- **Very Late > 1 year**

- **0 day to 1 day** Acute stent thrombosis
- **>1 day to 1 month** Subacute stent thrombosis
- **>1 month to 1 year** Late stent thrombosis
- **> 1 year** Very late stent thrombosis
Prevalence of ST with BMS in registries

Mean: 1.6%

<table>
<thead>
<tr>
<th>Name</th>
<th>N</th>
<th>1m</th>
<th>1m</th>
<th>1m</th>
<th>6m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karrillon</td>
<td>2,900</td>
<td>1,8</td>
<td>1,5</td>
<td>2,3</td>
<td>0,9</td>
</tr>
<tr>
<td>De Servi</td>
<td>939</td>
<td>1,5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Schühlen</td>
<td>2,833</td>
<td>2,3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cutlip</td>
<td>6,186</td>
<td>0,9</td>
<td></td>
<td></td>
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<tr>
<td>Moussa</td>
<td>1,001</td>
<td>1,9</td>
<td></td>
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<tr>
<td>Serrys</td>
<td>1,205</td>
<td>2,8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wenaweser</td>
<td>6,058</td>
<td>1,6</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

N=21,122
Prevalence of ST with DES (6 Cypher registries data)

25,156 patients 1 year follow up

Protocol definition

ARC definition

Early (< 30 days) Late (30 d – 1 year)
The importance of the issue
Outcome after ST

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sirolimus-Stent Trials</th>
<th>Paclitaxel-Stent Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sirolimus Stent (N=13)</td>
<td>Paclitaxel Stent (N=22)</td>
</tr>
<tr>
<td></td>
<td>Bare-Metal Stent (N=15)</td>
<td>Bare-Metal Stent (N=18)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (30.8)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td></td>
<td>5 (33.3)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>13 (100)</td>
<td>17 (77.3)</td>
</tr>
<tr>
<td></td>
<td>13 (86.7)</td>
<td>14 (77.8)</td>
</tr>
<tr>
<td>Fatal event</td>
<td>4 (30.8)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td></td>
<td>4 (26.7)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Q-wave</td>
<td>8 (61.5)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td></td>
<td>5 (33.3)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Non–Q-wave</td>
<td>5 (38.5)</td>
<td>10 (45.5)</td>
</tr>
<tr>
<td></td>
<td>9 (60.0)</td>
<td>10 (55.6)</td>
</tr>
</tbody>
</table>

SES: 878 patients – PES: 1400 patients – BMS 2267 patients

1.2 % ST 0.6 % ST

Factors of stent thrombosis

- Procedural factors
- Factors related to the patients and/or the lesion
- The effect of the stent mechanical features

Procedural factors of ST

- Malapposition and/or underexpansion
- Multiple stents
- Total length of the stent
- Persistent slow coronary blood flow
- Dissections
- Strut penetration into necrotic core

Patient / lesion factors of ST

- Premature discontinuation of dual antiplatelets
- Low EF
- Diabetes
- Renal insufficiency
- STEMI/ACS
- Ostial and/or bifurcation
- In-stent restenosis lesion
- Genetic variation

Stent design factors of ST

- Open cell vs closed cell
- Strut thickness
- Polymer type and thickness
- DES vs BMS ??

Question of reendothelization?

Percentage of endothelization

Duration (months)

BMS

DES

Joner et al. JACC 2006.
The length of the stent: Moreno’s metaanalysis

\[ Y = -1.455 + 0.121 X \]

95% CI for \( b \): 0.014 – 0.223

\( R = 0.716; P = 0.031 \)

Moreno et al. JACC 2005.
IVUS can help us: malapposition / underexpansion

- 2,575 patients were treated with 4,722 Cypher stents.
- 21 (0.8%) had stent thrombosis of whom 15 had IVUS.
- 12/15 SES thrombosis lesions had stent CSA <5.0mm² (vs 13/45 controls).

*Residual edge stenosis = edge lumen CSA <4.0mm² & plaque burden >70%.

Fuji et al. 2005. JACC
Independent predictors of post-procedural incomplete stent apposition (by IVUS of 339 lesions treated with DES)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2.36</td>
<td>1.09–5.11</td>
<td>0.03</td>
</tr>
<tr>
<td>Intracoronary thrombus</td>
<td>7.47</td>
<td>1.67–33.47</td>
<td>0.009</td>
</tr>
<tr>
<td>NSTE MI</td>
<td>2.73</td>
<td>1.09–6.83</td>
<td>0.03</td>
</tr>
<tr>
<td>Sirolimus-eluting stent</td>
<td>2.90</td>
<td>1.49–5.67</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Incidence of incomplete stent apposition: 13.9%
Is there role of intracoronary thrombus in ST?

Large thrombus burden (LTB) vs. small thrombus burden $p < 0.001$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10-yr increase)</td>
<td>0.95</td>
<td>0.37-0.82</td>
<td>0.003</td>
</tr>
<tr>
<td>Stent thrombosis at presentation</td>
<td>6.24</td>
<td>2.06-18.92</td>
<td>0.001</td>
</tr>
<tr>
<td>Bifurcation stenting</td>
<td>6.46</td>
<td>1.64-10.02</td>
<td>0.002</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>0.11</td>
<td>0.01-0.81</td>
<td>0.03</td>
</tr>
<tr>
<td>Large thrombus burden</td>
<td>8.73</td>
<td>3.39-22.47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Independent predictors of IRA ST

Sianos J Am Coll Cardiol 2007;50:573–83
ST with endothelial progenitor cell capture stent (EPCC). How it can be?

**Cause:** undersized stent deployment

**Solution:** IVUS estimation of the vessel size

TYPHOON 4 yr FOLLOW UP

Definite/probable stent Thrombosis (%)

BMS (n=250)
- Early (0 to 30 days): 9 (3.6%)
- Very Late (> 1yr): 3 (1.2%)

CYPHER (n=251)
- Early (0 to 30 days): 6 (2.4%)
- Very Late (> 1yr): 5 (2.0%)

P = 0.83

The ST in the real world: 2.1% (BMS + DES)

Werkum et al. JACC 2009.
Stent thrombosis: Answer in the genes?

Odds ratio for stent thrombosis with the 2C19*2 vs. 2C19*1 genetic variant (n= 4975)

Answer in the genes?

Odds ratio for stent thrombosis with the 2C19*2 vs. 2C19*1 genetic variant (n= 4975)

Next generation ADP receptor antagonist?

**DM**

HR 0.52 (0.33-0.84), P = 0.007

Clopidogrel 3.6

Prasugrel 2.0

**No DM**

HR 0.45 (0.31-0.65), P < 0.001

Clopidogrel 2.0

Prasugrel 0.9

P_{interaction} = 0.63

Definite or probable stent thrombosis.

TIMI 38.
IVUS guidance against ST

p = 0.013
MISSION! - IVUS substudy

New enemy: late malapposition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SES (n = 115)</th>
<th>BMS (n = 93)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number evaluated</td>
<td>104</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Any site‡</td>
<td>39 (37.5)</td>
<td>10 (12.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Persistent</td>
<td>19 (18.3)</td>
<td>9 (11.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Acquired</td>
<td>26 (25.0)</td>
<td>4 (5.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Proximal stent edge</td>
<td>17 (16.3)</td>
<td>7 (8.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Persistent</td>
<td>14 (13.5)</td>
<td>7 (8.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Acquired</td>
<td>3 (2.9)</td>
<td>0 (0.0)</td>
<td>0.26*</td>
</tr>
<tr>
<td>Stent body</td>
<td>27 (26.0)</td>
<td>2 (2.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Persistent</td>
<td>6 (5.8)</td>
<td>1 (1.3)</td>
<td>0.14*</td>
</tr>
<tr>
<td>Acquired</td>
<td>21 (20.2)</td>
<td>1 (1.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Distal stent edge</td>
<td>13 (12.5)</td>
<td>4 (5.0)</td>
<td>0.08*</td>
</tr>
<tr>
<td>Persistent</td>
<td>6 (5.8)</td>
<td>2 (2.5)</td>
<td>0.47*</td>
</tr>
<tr>
<td>Acquired</td>
<td>7 (6.7)</td>
<td>2 (2.5)</td>
<td>0.30*</td>
</tr>
</tbody>
</table>

*J Am Coll Cardiol 2008;51:618-26
Very late stent thrombosis on dual antiplatelet therapy

STEMI + PCI
8 month later
834 days after PCI

Triggered by NSAID despite dual antiplatelet therapy

What type of DES
COMPARE-AMI study

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>PROMUS® (XIENCE V®) Stent (n = 241)</th>
<th>TAXUS® Liberté® Stent (n = 213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>5,3%</td>
<td>6,1%</td>
</tr>
<tr>
<td>TVR</td>
<td>1,2%</td>
<td>2,3%</td>
</tr>
<tr>
<td>Death</td>
<td>1,6%</td>
<td>2,8%</td>
</tr>
<tr>
<td>MI*</td>
<td>1,4%</td>
<td>2,9%</td>
</tr>
<tr>
<td>ST</td>
<td>0,0%</td>
<td>1,4%</td>
</tr>
</tbody>
</table>

Elvin Kedhi PCR 2009
ST with the 3rd generation DES: LEADERS study with biodegradable polymer

Questionable effect of hypersensibility?

Conclusion – What to do against ST?

• **Optimization of stent deployment** and **dual antiplatelet therapy** with aspirin and a thienopyridine (especially prasugrel) have achieved the currently accepted 30-day ST rate of 1%. Reports of late DES thrombosis, often in association with cessation of antiplatelet therapy, suggest that long-term combined antiplatelet therapy might be appropriate.

• With **IVUS guided PCI**, the decrease in procedural failure could make the PCI safer with less ST.

• Careful drug treatment of concomitant diseases (NSAIDs-ibuprofen).