Mechanisms and Predictors of Early, Late, and Very Late Stent Thrombosis

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Potential conflicts of interest

Speaker's name: Lisette Okkels Jensen

☑️ I have the following potential conflicts of interest to report:

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Overview

- Drug-eluting stents (DES) markedly reduce clinical and angiographic restenosis compared to bare metal stents.
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Late and very late ST are rare but potentially lethal complications.
Overview

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- However, stent implantation may be followed by a measureable but relatively small number of stent thrombosis (ST).

- Late and very late ST are rare but potentially lethal complications.

- It has been suggested that stent malapposition plays an important role in patients who develop very late ST after DES implantation.
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However, stent implantation may be followed by a measureable but relatively small number of stent thrombosis (ST).

Late and very late ST are rare but potentially lethal complications.

It has been suggested that stent malapposition plays an important role in patients who develop very late ST after DES implantation.

Other mechanisms may be involved in patients presenting with early ST.
A total of 12,374 patients were treated with PES (1,304), SES (2,212) and BMS (8,858).

Jensen LO. EuroIntervention 2010;5:898-905
A total of 12,374 patients were treated with PES (1,304), SES (2,212) and BMS (8,858).
Prognostic influence of ST and ISR
Prognostic influence of ST and ISR

ST vs. non-TLR: Relative Risk: 2.71 (95%CI: 1.72-4.27) p<0.001
IRS vs. non-TLR: Relative Risk: 1.17 (95%CI: 0.79-1.75); p=NS
Predictors of Stent Thrombosis

- Patient Factors
- Lesion Factors
- Procedural & Medical RX Factors
## Predictors of Stent Thrombosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lesion</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Long segment disease</td>
<td>Stent underexpansion</td>
</tr>
<tr>
<td>Acute presentation</td>
<td>Small vessel diameter</td>
<td>Stent malapposition</td>
</tr>
<tr>
<td>Cancer</td>
<td>Saphenous venous graft</td>
<td>Strut fracture</td>
</tr>
<tr>
<td>DAPT non-responsiveness</td>
<td>Chronic total occlusion</td>
<td>Edge dissection</td>
</tr>
<tr>
<td>Premature cessation of DAPT</td>
<td>Bifurcation lesion</td>
<td>Multiple stents</td>
</tr>
<tr>
<td>Hypersensitivity to polymer or drug</td>
<td></td>
<td>Stent overlap</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Geographic miss and residual stenosis</td>
</tr>
</tbody>
</table>
Early Stent Thrombosis

Twelve patients with baseline IVUS who had early ST 30 days after enrollment were compared with 389 patients without early ST.
Early Stent Thrombosis  IVUS findings

- Minimum lumen area < 5 mm²
- Significant residual stenosis
- Stent edge dissection
- Tissue protusion

Horizons Choi SY et al. Circulation Cardiovasc Interv 2011
Malapposition Definition

- **Malapposition** (Incomplete stent apposition) is a lack of contact between stent struts and the underlying vessel wall not overlying a side branch.

- **Acute malapposition** is mostly technique dependent and can occur after implantation of any stent type.

- **Late malapposition**, detected at follow-up, can be late and acquired (occurring between implantation and follow-up) or acute and persistent.
Late Malapposition

♂ 62 years old – ANGIO FU 222 days after PCI

DES 3.0 x 16 mm
Incidens of late Malapposition

Late acquired malapposition

- **Taxus pooled**: Steinberg et al. JACC Cardiovasc Interv. 2010
- **SIRIUS**: Ako et al. J Am Coll Cardiol. 2005
- **Endeavor II**: Fajadet et al. Circulation. 2006
- **MISSION**: van der Hoeven BL et al J Am Coll Cardiol. 2008
- **Horizons**: Maehara A et al. Circulation 2009
Malapposition Mechanism

ISA due to positive remodeling

Increase in vessel dimensions with an equal amount of persistent plaque growth

Increase in vessel dimensions without an equal amount of persistent plaque growth
Malapposition Mechanism

ISA due to “thrombus jailing”

Apparent successful implantation of stent during ACS with jailing from thrombus between the vessel wall and the stent struts

Apparition from incomplete stent apposition after dissolution of thrombotic material
Malapposition and stent thrombosis

Incomplete Stent Apposition and Very Late Stent Thrombosis After Drug-Eluting Stent Implantation

Stéphane Cook, MD; Peter Wenaweser, MD; Mario Togni, MD; Michael Billinger, MD; Cyrill Morger, MD; Christian Seiler, MD; Rolf Vogel, MD, PhD; Otto Hess, MD; Bernhard Meier, MD; Stephan Windecker, MD

Background—Stent thrombosis may occur late after drug-eluting stent (DES) implantation, and its cause remains unknown. The present study investigated differences of the stented segment between patients with and without very late stent thrombosis with the use of intravascular ultrasound.

Methods and Results—Since January 2004, patients presenting with very late stent thrombosis (>1 year) after DES implantation underwent intravascular ultrasound. Findings in patients with very late stent thrombosis were compared with intravascular ultrasound routinely obtained 8 months after DES implantation in 144 control patients, who did not experience stent thrombosis for ≥2 years. Very late stent thrombosis was encountered in 13 patients at a mean of 630±166 days after DES implantation. Compared with DES controls, patients with very late stent thrombosis had longer lesions (23.9±16.0 versus 13.3±7.9 mm; \( P<0.001 \)) and stents (34.6±22.4 versus 18.6±9.5 mm; \( P<0.001 \)), more stents per lesion (1.6±0.9 versus 1.1±0.4; \( P<0.001 \)), and stent overlap (39% versus 8%; \( P<0.001 \)). Vessel cross-sectional area was similar for the reference segment (cross-sectional area of the external elastic membrane: 18.9±6.9 versus 20.4±7.2 mm²; \( P=0.46 \)) but significantly larger for the in-stent segment (28.6±11.9 versus 20.1±6.7 mm²; \( P=0.03 \)) in very late stent thrombosis patients compared with DES controls. Incomplete stent apposition was more frequent (77% versus 12%; \( P<0.001 \)) and maximal incomplete stent apposition area was larger (8.3±7.5 versus 4.0±3.8 mm²; \( P=0.03 \)) in patients with very late stent thrombosis compared with controls.

Conclusions—Incomplete stent apposition is highly prevalent in patients with very late stent thrombosis after DES implantation, suggesting a role in the pathogenesis of this adverse event. (Circulation. 2007;115:2426-2434.)

Patients presenting with very late stent thrombosis (1 year) after DES n=13
Controls (IVUS obtained 8 months after DES implantation in 144 control patients)
Malapposition and stent thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Very Late ST</th>
<th>DES Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of segments</td>
<td>13</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Reference segment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM CSA, mm²</td>
<td>18.9±6.9</td>
<td>20.4±7.2</td>
<td>0.46</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>10.6±3.2</td>
<td>8.5±3.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Stent segment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM CSA, mm²</td>
<td>28.6±11.9</td>
<td>20.1±6.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Stent CSA, mm²</td>
<td>7.7±2.0</td>
<td>7.5±2.0</td>
<td>0.83</td>
</tr>
<tr>
<td>Minimal stent CSA, mm²</td>
<td>6.6±2.0</td>
<td>6.6±1.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Minimal stent CSA &lt; 4 mm², n (%)</td>
<td>2 (15%)</td>
<td>9 (5%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Stent expansion</td>
<td>0.68±0.19</td>
<td>0.81±0.18</td>
<td>0.04</td>
</tr>
<tr>
<td>Overlapping stents</td>
<td>0.61±0.23</td>
<td>0.67±0.18</td>
<td>0.66</td>
</tr>
<tr>
<td>Nonoverlapping stents</td>
<td>0.72±0.21</td>
<td>0.81±0.18</td>
<td>0.23</td>
</tr>
<tr>
<td>In-stent lumen CSA, mm²</td>
<td>6.7±1.5</td>
<td>6.9±1.9</td>
<td>0.65</td>
</tr>
<tr>
<td>Neointimal hyperplasia, mm²</td>
<td>0.7±0.5</td>
<td>0.6±0.5</td>
<td>0.72</td>
</tr>
<tr>
<td>ISA, n (%)</td>
<td>10 (77)</td>
<td>21 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal ISA CSA, mm²</td>
<td>8.3±7.5</td>
<td>4.0±3.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Maximal ISA length, mm</td>
<td>6.3±6.3</td>
<td>1.5±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal ISA depth, mm</td>
<td>1.8±2.5</td>
<td>0.8±0.5</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Cook S. CIRCULATION 2007
Malapposition and stent thrombosis

Expansion was assessed at follow-up. “Underexpansion” probably represented an increase in reference vessel size (positive remodeling) rather than true underexpansion.
Intravascular ultrasound assessed incomplete stent apposition and stent fracture in stent thrombosis after bare metal versus drug-eluting stent treatment the Nordic Intravascular Ultrasound Study (NIVUS)☆☆☆

Petteri Kosonen a,b, Sails Vikman a,*, Lisette Okkels Jensen c, Jens Flensted Lassen d, Jan Harnek e, Göran K. Olivecrona e, Andrejs Erglis f, Eigil Fossum g, Matti Niemelä h, Kari Kervinen h, Antti Ylitalo i, Mikko Pietilä j, Jens Aaroe k, Thomas Kellerth l, Kari Saunamäki m, Per Thayssen c, Lars Hellsten n, Leif Thuesen d, Kari Niemelä a
### Nordic IVUS Study

Stent Thrombosis and malapposition

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Early</th>
<th>Late</th>
<th>Very late</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMS, n (%)</strong></td>
<td>0 (0)</td>
<td>7 (58)</td>
<td>0 (0)</td>
<td>3 (16)#</td>
<td>10 (27)</td>
</tr>
<tr>
<td><strong>DES, n (%)</strong></td>
<td>2 (29)</td>
<td>4 (31)</td>
<td>1 (17)</td>
<td>32 (52)#</td>
<td>39 (45)</td>
</tr>
<tr>
<td><strong>-PES, n (%)</strong></td>
<td>2 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>12 (36)</td>
<td>14 (37) *</td>
</tr>
<tr>
<td><strong>-SES, n (%)</strong></td>
<td>0 (0)</td>
<td>2 (50)</td>
<td>0 (0)</td>
<td>19 (70)</td>
<td>21 (58) *</td>
</tr>
<tr>
<td><strong>-other DES, n (%)</strong></td>
<td>0 (0)</td>
<td>2 (29)</td>
<td>1 (25)</td>
<td>1 (100)</td>
<td>4 (31)</td>
</tr>
</tbody>
</table>

124 patients with definite stent thrombosis assessed by IVUS

- # $p=0.005$ DES vs BMS
- * $p=0.02$ PES vs SES
Complete fracture

Partial fracture
Absence of strut > 180°

50 years old - ST 1272 days after primary PCI

BMS 4.5 x 30 mm

The Nordic Intravascular Ultrasound Study (NIVUS)

Nordic IVUS Study
Stent Thrombosis
In 124 patients with ST, a stent fracture was seen in 23 stents

- 17 were total and 6 partial

- In the DES group, there were 14 (16%) patients with fractures and in the BMS group 9 (24%) (p=0.28)
17 studies with 4648 patients
- 2453 BMS and 2195 DES
- 4 SES, 4 PES, 1 EES, 2 ZES, 3 DES vs DES, and 3 BMS only

LSM more common in DES than BMS
- OR=2.5, p=0.02 when both RCT and observational studies were included
- OR=4.4, p=0.002 when only RCT were included
- SES > PES > ZES > EES
Meta-Analysis of Very Late ST in LSM

- 5 studies with 2080 patients
  - 228 LSM and 1852 no LSM
  - 3 Late ST (<12 mos), none in LSM
  - 6 Very late ST (>12 mos), 4 in LSM

- Risk of very late ST was higher in LSM patients (OR=6.5 95% CI 1.34-34.91, p=0.02).
Pooled Analysis of **Very Late ST in LSM**

6 TAXUS studies with 1580 patients
IVUS substudies of TAXUS IV, V, VI and TAXUS-ATLAS WH, LL, and DS trials

- At 9-month follow-up: 36 cases of late-acquired ISA

  7 (2.7%) BMS patients

  17 (3.1%) patients with TAXUS slow-release (TAXUS Express or TAXUS Liberté)

  12 (15.4%) patients receiving TAXUS moderate-release

Steinberg DH J Am Coll Cardiol Intv 2010
Pooled Analysis of Very Late ST in LSM

6 TAXUS studies with 1580 patients
IVUS substudies of TAXUS IV, V, VI and TAXUS-ATLAS WH, LL, and DS trials

• Over 2 ensuing years, major adverse cardiovascular events were similar in patients with late-acquired ISA versus control subjects with no ISA
  BMS (14.3% vs. 7.9%, p = 0.54),
  TAXUS (overall, 8.3% vs. 8.1% p = 0.87)
  TAXUS slow-release formulation (0% vs. 7.9%, p=0.28)

• There was no impact of late-acquired ISA on stent thrombosis.

Steinberg DH J Am Coll Cardiol Intv 2010
Coronary Aneurysm Formation

- Coronary aneurysms developed in 15/1,197 (1.25%) consecutive pts with late angiographic follow-up after DES implantation.
  - Coronary aneurysms were more frequently implanted during acute myocardial infarction and use of longer stents.
  - On IVUS, LSM area measured 12.1 ± 8.6mm².
  - Two patients presented with acute myocardial infarction secondary to DES thrombosis, and 4 additional patients presented with unstable angina and underwent repeat PCI with a significant reduction in LSM area (11.6 ± 3mm² to 5.5 ± 0.6mm², p<0.05).
  - Dual antiplatelet therapy was recommended in the remaining 9 patients who were asymptomatic at CAN diagnosis.

- After a mean follow-up of 399±347 days, the 1-year event-free survival was 49±14% and was related to aneurysm size on IVUS. In 2 pts aneurysms disappeared and IVUS showed abluminal thrombosis.

Stent Thrombosis

65 years old – very late ST 1129 days after PCI

DES 3.0 x 24 mm
Stent Thrombosis

♂ 55 years old - ST 2174 days after PCI

LM shaft  LM distal  Bifurcation  LAD prox

Stent fracture site

Proximal  Cypher 3.5 x 18 mm  Distal
Stent thrombosis

♂ 59 years old - ST 543 days after PCI
Stent Thrombosis

♂ 59 years old - ST 543 days after PCI
OCT stent undersized
51 year old male admitted with NSTEMI

Known with IHD

Risk faktors: Hypercholesterolemia and family history

PCI of proximal and distal Cx (2 stents covering a 41 mm segment) and RM1 in 2010 (all Cypher)

PCI of RM1 three months earlier due to in-stent restenosis (Xience)
Very Late Stent Thrombosis

Cx stent thrombosis
Very Late Stent Thrombosis

Proximal stent in Cx

Cypher stent in proximal Cx unrelated to occlusion. Fully covered and with evaginations

Hougaard M. Eurointervention 2015
Very Late Stent Thrombosis

- Plaque rupture
- Intimal hyperplasia
- White thrombus in relation to rupture site
- Red thrombus proximal to rupture site
- Malapposed but covered stent struts

Neoartherosclerosis (most pronounced distally) – plaque rupture distally

Hougaard M. Eurointervention 2015
Very Late Stent Thrombosis

Final results after Xience stent 3.0 x 28 mm

Hougaard M. Eurointervention 2015
NIR Spectroscopy

NIR IVUS Provides Both Chemical Data and Structural Image

- The TVC Imaging System utilizes a single catheter that emits both a near infrared laser beam and a high frequency of ultrasound beam.
- Determining vessel composition with Near Infrared Spectroscopy

Schulz et al. J Am Coll Cardiol 2009
The proximal end of the stent that thrombosed is located in a lipid-core plaque.

Recurrent pain eight hours post stenting

Data courtesy of Dr. I.K. Jang
Massachusetts General Hospital
Conclusion

- A combination of factors may be involved in early ST, including:
  - Procedure related factors
  - Patient/lesion characteristics
  - Antiplatelet therapy
  - Impaired endothelialization

- Mechanical problems:
  - Smaller lumen CSA within the stent (underexpansion / tissue protrusion)
  - Residual disease outside the stent, edge dissection

- Malapposition are more important in very late ST

- A minimum stent area of 5.0 mm² has shown to be a consistent predictor of DES failure
The frequency of late malapposition appears to be greater after DES implantation.

Late and very late stent thromboses are rare – and very rare in stents with late malapposition.

There is more to very late stent thromboses than late stent malapposition: delayed healing, inflammation and hypersensitivity may also play an important role.

Causes of very late stent thrombosis are multifactorial. Late malapposition may be contributory in some patients whereas in other patients there are other causes.