Late stent Thrombosis; Neoatherosclerosis

Mohamed Abdelghany, MD
Professor of Cardiovascular medicine, Cairo University

Stent Thrombosis

• Infrequent but serious complication:
• Overall incidence: 0.6% to 5% in studies
• Substantial mortality associated with stent thrombosis
• Most cases of stent thrombosis occur within the first 30 days after placement, irrespective of stent type (Reported rates tend to be lower in clinical trials than in registries)
• More frequent after ACS
Stent Thrombosis: a Multifactorial Problem

Definition of Stent Thrombosis According to the Valve Academic Research Consortium

<table>
<thead>
<tr>
<th>Level of Certainty</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Angiographic or pathological confirmation of partial or total thrombotic occlusion within the peri-stent region AND at least 1 of the following additional criteria: Acute ischemic symptoms Ischemic electrocardiogram changes Elevated cardiac biomarkers</td>
<td>Acute (&lt; 24 h)</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td>Late</td>
</tr>
<tr>
<td>Any unexplained death &lt; 30 days of stent implantation Any myocardial infarction 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</td>
<td>31 days to 1 yr</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>Very Late</td>
</tr>
<tr>
<td>Any unexplained death beyond 30 days</td>
<td>&gt; 1 yr</td>
</tr>
</tbody>
</table>
Predictors of Stent Thrombosis
Early versus Late and very Late Stent Thrombosis

<table>
<thead>
<tr>
<th>Early Stent Thrombosis</th>
<th>(Very) Late Stent Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td>Malignancy, heart failure, peripheral artery disease, diabetes mellitus, acute coronary syndromes, nonadherence to dual-antiplatelet therapy, genetic polymorphisms, thrombocytosis</td>
</tr>
<tr>
<td><strong>Lesion</strong></td>
<td>Bifurcation lesion, LAD, vessel size, lesion length, thrombus, saphenous vein grafts</td>
</tr>
<tr>
<td><strong>Procedural</strong></td>
<td>Stent undersizing, stent underexpansion, stent malapposition, dissection, no pre-procedural thienopyridine administration, bivalirudin as antiplatelet in STEMI patients, stent length</td>
</tr>
<tr>
<td><strong>Post-procedural</strong></td>
<td>Discontinuation of antiplatelet therapy</td>
</tr>
</tbody>
</table>

Rates of Stent Thrombosis
After STEMI

Giovanna Sarno et al. JACC 2014;64:16-24

American College of Cardiology Foundation
**Early/late Stent Thrombosis After STEMI**

- **Lower risk of early/late ST** in the n-DES and old-DES groups compared with the BMS.

- **Higher risk of very late ST** was observed in the old-DES group compared with the BMS group.

---

**DES Versus BMS**

- Cumulative rate of stent thrombosis is similar for bare metal and the **first generation DES** (SES and PES) at up to five years.

- **Late stent thrombosis**: Slight predominance of BMS stent thrombosis.

- **Very late stent thrombosis**: Preponderance of **first generation DES**.

- The rate of very late stent thrombosis with DES between **one and four years** is approximately 0.6 percent.

- Current body of evidence from randomized trials suggests that long-term cumulative rates of stent thrombosis are **lower with EES than SES or PES**.
CONCLUSION:
Treatment with EES is associated with a lower risk of very late stent thrombosis compared with early-generation drug-eluting stents.

Circulation, 2012

lower incidence of MACE, MI, TVR, and stent thrombosis with second generation DES compared with BMS
Contemporary DES, including biocompatible DP-DES, BP-DES, and polymer-free DES, showed a low risk of definite or probable stent thrombosis at 1 year. **BVS had an increased risk of device thrombosis compared with** cobalt-chromium- everolimus-eluting stents, platinum-chromium-EES, and hybrid sirolimus-eluting stents.

**Mechanisms of Late And Very Late Stent Thrombosis**

It is multifactorial

1. Delayed endothelial coverage
   
   Re-endothelialization after stent implantation is significantly delayed in DES compared with BMS and is likely responsible for the higher rates of very late ST with first-generation DES

2. Persistent fibrin deposition
Mechanisms of Late And Very Late Stent Thrombosis

3. Ongoing vessel inflammation (inflammatory reaction to the durable polymer coatings used in early-generation DES)

4. Late stent malapposition (Late stent malapposition is typically the result of positive vessel wall remodeling (i.e., outward arterial wall expansion “away” from the stent struts that were well apposed at the time of implantation), appears more commonly in DES compared with BMS, and has been associated with (very) late ST

4. Neoathero- sclerotic plaques in the neointima within previously stented areas, which may rupture, causing ST

Optical Coherence Tomography Findings in Patients With Coronary Stent Thrombosis

A Report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort)

- Uncovered struts and underexpansion were most common in acute/subacute ST,
- Uncovered struts and neoatherosclerosis were most common in late/very late ST

Representative images of very late drug-eluting stent thrombosis, evaluated by optical coherence tomography (OCT). Arrows denote intracoronary thrombus and arrowheads indicate OCT findings: stent malapposition (A), uncovered struts without stent malapposition or evagination (B), coronary evagination (C), ruptured neoatherosclerosis (D), and erosive neointima without neoatherosclerosis (E).

Adriaenssens et al Circulation.2017
Neoatherosclerosis

Accumulation of lipid-laden foamy macrophages within the neointima with or without necrotic core formation and/or calcification

- Dysfunctional endothelial coverage following stent placement poorly formed cell-to-cell junctions → greater entry of lipoproteins into the sub-endothelial space
- Local blood flow disturbance following stent → adhesion and migration of monocytes into the sub-endothelial space → foamy macrophages in the subluminal or peri-strut regions
- Development of the necrotic core
- Thin-cap fibroatheroma, which may eventually lead to **in-stent plaque rupture**.
**DES Restenosis**

- **Neointimal Proliferation**
  - Due to trauma
  - Predominant mechanism
  - Neointimal hyperplasia (SMC)

- **Neoatherogenesis**
  - Due to stent
  - Fibroatheroma, lipid-laden macrophage, Ca, necrotic core
  - DES 30% earlier than BMS
  - Young, unstable, time, DES

- **Thrombus**

---

**Incidence and Timing of Neotherosclerosis**

Nakazawa et al. JACC 2009; JACC 2010

Nakazawa G, Virmani R. J Am Coll Cardiol 2011;57:1314–22

- DES
- BMS

Incidence of atherosclerosis

Total Case number examined

Duration (month)

Incidence of atherosclerosis

DES

BMS
2. DES Restenosis: New Roads, New Ruts

<table>
<thead>
<tr>
<th>Smooth muscle cellularity</th>
<th>Bare metal stent</th>
<th>Drug-eluting stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proteoglycan content</th>
<th>Bare metal stent</th>
<th>Drug-eluting stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Bare metal stent</th>
<th>Drug-eluting stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>Focal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time course</th>
<th>Bare metal stent</th>
<th>Drug-eluting stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak 6 months</td>
<td>Delayed onset</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neoatherosclerosis</th>
<th>Bare metal stent</th>
<th>Drug-eluting stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrequent, late</td>
<td>Frequent, early</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OCT appearance</th>
<th>Bare metal stent</th>
<th>Drug-eluting stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogeneous</td>
<td>Heterogenous/ Layered</td>
<td></td>
</tr>
</tbody>
</table>

DHZ Restenosis Registry

Utilization of stent type and incidence of restenosis

1st generation DES: 8/2002-12/2005
New generation DES: from 1/2006

10,004 patients with Angio FU

Cassese et al. *Heart* online first
Optical Coherence Tomography (OCT)

Use of OCT in ISR

Evaluation for mechanical causes
Assessment of underlying tissue type

DES Restenosis

“Layered” DES ISR
**DES Restenosis**

- OCT in 50 Pts with DES ISR
  - 58% Rupture, 52% TCFA, 58% Thrombus

Kang SJ, Mintz GS. Circulation. 2011;123:2954-2963

**DES Restenosis**

Ruptured Neoatherosclerosis

“The elusive link between very late ISR and ST”

Alfonso F. (PRESTIGE Study)
Neoatherosclerosis Causing Late ST DES Restenosis

Neoatherosclerosis in BMS
Yellow plaque is the cause of event

BMS, 3 years  BMS, 8 years

No yellow plaque  Disrupted yellow plaque
No event  Unstable angina
Comparison of DES
Healing and atherosclerosis progression

<table>
<thead>
<tr>
<th></th>
<th>Healing</th>
<th>Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>Good</td>
<td>Delayed by thick neointima</td>
</tr>
<tr>
<td>Cypher</td>
<td>Bad</td>
<td>Accelerated</td>
</tr>
<tr>
<td>Taxus</td>
<td>Bad</td>
<td>Accelerated/ natural course?</td>
</tr>
<tr>
<td>Endeavor</td>
<td>Good</td>
<td>Delayed by thick neointima</td>
</tr>
<tr>
<td>Nobori</td>
<td>Good</td>
<td>Accelerated/ natural course?</td>
</tr>
<tr>
<td>Xience V</td>
<td>Good</td>
<td>Accelerated/ natural course?</td>
</tr>
<tr>
<td>Resolute</td>
<td>Good</td>
<td>Accelerated/ natural course?</td>
</tr>
</tbody>
</table>
Mechanisms of DES Restenosis

- **Biological factors**
  - Drug resistance
  - Hypersensitivity
- **Mechanical factors**
  - Non uniform stent strut distribution
  - Stent fractures
  - Polymer peeling
  - Non uniform drug deposition
- **Technical factors**
  - Incomplete stent expansion
  - Stent gaps or “misses” (uncovered lesion segments)
  - Barotrauma to unstented segments

Hypersensitivity Reactions

CYPHER in LCX @ 4 months

- Rash, hives, dyspnea, persistence after stopping Plavix, eosinophilia, elevated IgE, skin biopsy consistent with drug reaction when no drugs administered, Gallium scan consistent with inflammation at the stent site or LV draining lymph nodes, and eosinophils attacking the stent at autopsy.

Taxus in LAD @ 130 days

Nebecker JR. et al. JACC 2006; 47: 175-181
Polymer Mishaps: Bonding and Webbing

Bonding = polymer sticks to itself forming a bridge when the stent is expanded

Webbing = polymer pulling away from the expanded stent due to sticking

Not a strut: polymer sticking to itself

Exposed strut

DES fractures

Post

Follow-up

Restenosis

Technical factors
Stent underexpansion

Medical Management (including oral antiproliferative agents)

Repeated PCI:
- Balloon angioplasty (BA)
- Non-compliant balloons
- Cutting /Scoring balloons (CB)
- Drug-Eluting Ballons (DEB)
- Brachytherapy (VBT)
- Rotational atherectomy / Laser
- Bare-Metal Stents (BMS)
- Drug-Eluting Stents (DES)
  - Homo-DES
  - Hetero-DES (Switch)

Coronary Surgery
Neoatherosclerosis

- May occur in months to years following stent placement, whereas atherosclerosis in native coronary arteries develops over decades
- Pathologic and clinical imaging studies have demonstrated that neoatherosclerosis occurs more frequently and at an earlier time point in DES when compared with bare metal stents (31% in 1st DES versus 16% with BMS)
- It increases with time in both types of stents
- Early development of neoatherosclerosis occur not only in first-generation DES but also in second-generation DES

Clinical Perspectives

Neoatherosclerosis

- Raises the concern that effective of secondary prevention measures has not yet been achieved.
- The factors that predispose individuals to neoatherosclerosis, and their overlap with risk factors for native atherosclerosis, remain poorly defined
- Effective treatment strategies to prevent this complication have yet to be established.
- Need studies to assess the impact of stent technology and risk factor modification on disease progression.
Thank You