Atherosclerosis: Main cause of stent thrombosis/restenosis?

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Conflicts of interest:

None
MACE Cumulative Incidence

PES → SES

Paclitaxel
Sirolimus

Patients at risk (MACE):
Paclitaxel: 1033, 922, 850, 812, 771, 724, 681, 647, 617, 583, 547
Sirolimus: 1065, 954, 908, 861, 815, 775, 734, 696, 659, 609, 565

Log-rank P = .60

Paclitaxel-eluting stent → Sirolimus-eluting stent
Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease

Drug-eluting or bare-metal stents for percutaneous coronary intervention

Comparison of clinical outcomes at 10 years in patients treated with new-generation BP-SES versus new-generation PP-EES versus early generation SES

TLR

Coronary stenting: mechanical relief of obstructed arteries by restoring flow without addressing the complex underlying atherosclerotic disease process.

Rates of ISR and ST are substantially higher among patients with

- **complex lesions:** acute coronary syndromes, bifurcations, chronic total occlusions, longer lesions
- coexisting **conditions known to accelerate atherosclerosis:** diabetes, renal failure

suggesting that atherosclerosis progression and complications might play a pivotal role in stent failure
**In-stent restenosis (ISR):** - incompletely characterized cause of stent failure
- widely diverse clinical presentations

<table>
<thead>
<tr>
<th></th>
<th>Neointimal hyperplasia</th>
<th>Neoatherosclerosis</th>
<th>Stent underexpansion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representative OCT cross-section</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Characteristic features</td>
<td>Homogenous, bright, uniform layer</td>
<td>Heterogenous composition with in-stent necrotic core with thin fibrous cap, lipid or calcification and foamy macrophage accumulation</td>
<td>Stent area significantly smaller than vessel area</td>
</tr>
</tbody>
</table>
Stent thrombosis (ST): - due to a combination of patient, lesion, and procedural factors
- pathobiology remains unclear
What hampers the elucidation of stent failure mechanisms?

**Intravascular imaging:** signal interference from metal stent struts
inadequate histological validation of findings, among other factors

- Optical coherence tomography (OCT):
  - high-definition visualization and improved characterization of in-stent tissue
  - limited depth resolution and signal attenuation due to superficial thrombus or lipid-laden neointima

- Relative infrequency of stent thrombotic events
- Lack of serial imaging

**Histopathological examination of vessels from deceased patients:** inherent limitation of a retrospective analysis in a highly-selected population (those who died) at a single timepoint (end of life) and technical challenges of examining stented coronary arteries.

**Findings from preclinical models:** experimental atherosclerosis in animals may bear limited relation to the complex human atherosclerotic lesion that develops over decades.
Lack of correlation between OCT image patterns and distinct histological tissue characteristics

<table>
<thead>
<tr>
<th>OCT/OFDI Imaging Pattern</th>
<th>Histological Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogeneous pattern</td>
<td>Smooth muscle cell-rich neointimal tissue 39% (18/46 frames)</td>
</tr>
<tr>
<td>(n = 46 coregistered frames)</td>
<td>Collagen-rich tissue with rare smooth muscle cells 39% (18/46 frames)</td>
</tr>
<tr>
<td>Layered neointimal pattern</td>
<td>Healed neointimal rupture/erosion 59% (10/17 frames)</td>
</tr>
<tr>
<td>(n = 17 coregistered frames)</td>
<td>Accumulation of superficial elastic fibers 10% (2/17 frames)</td>
</tr>
<tr>
<td>High-intensity and high-attenuation pattern</td>
<td>Superficial macrophage accumulation 70% (14/20 frames)</td>
</tr>
<tr>
<td>(n = 20 coregistered frames)</td>
<td>Peristrit low-intensity pattern</td>
</tr>
<tr>
<td>Tissue coverage with irregular surface or intraluminal protruding mass</td>
<td>Organized thrombus 63% (5/8 frames)</td>
</tr>
<tr>
<td>(n = 8 coregistered frames)</td>
<td>Peristrit low-intensity pattern</td>
</tr>
<tr>
<td>Peristrit low-intensity pattern</td>
<td>Stent-induced hypersensitivity vasculitis 86% (6/7 frames)</td>
</tr>
<tr>
<td>(n = 10 coregistered frames)</td>
<td>Honeycomb (lotus root) pattern</td>
</tr>
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<td>(n = 7 coregistered frames)</td>
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In-stent atherosclerosis

The concept of atherosclerosis development inside an implanted stent as a primary substrate of stent failure has only gained prominence during the last decade.

In-stent atherosclerosis may demonstrate features associated with plaque instability (as those seen in de-novo coronary lesions), such as large lipid core, thin fibrous cap, and neovascularization.

**Neoatherosclerosis** is defined as the presence of neointimal lipid, calcification or both with or without necrotic core, **without communication with the underlying plaque**

In-stent atherosclerosis may reflect
• the development of de novo atherosclerosis within the neointima, termed **neoatherosclerosis** (i.e., infiltration of lipoproteins and leukocytes into the neointima mainly due to endothelial dysfunction) or the progression of pre-existing underlying native atherosclerosis, termed **paleoatherosclerosis**.

As **paleoatherosclerosis** is also considered any atherosclerotic process occurring behind the stent struts.

These processes may be enhanced by the effects of stent **metal/polymer-induced inflammation**.
In-Stent Neointimal Proliferation Correlates With the Amount of Residual Plaque Burden Outside the Stent
An Intravascular Ultrasound Study

Francesco Prati, MD; Carlo Di Mario, MD; Issam Moussa, MD; Bernhard Reimers, MD; Maria Teresa Mallus, MD; Antonio Parma, MD; Ernesto Lioy, MD; Antonio Colombo, MD

Conclusions—Late in-stent neointimal proliferation has a direct correlation with the amount of residual plaque burden after coronary stent implantation, supporting the hypothesis that plaque removal before stent implantation may reduce restenosis. (Circulation. 1999;99:1011-1014.)
(i) Plaque behind the stent (PBS) significantly decreases after BMS implantation, whereas it increases after DES implantation irrespective of underlying lesion type and location;

(ii) The changes in PBS are associated with parallel constrictive peri-stent remodeling in BMS and expansive remodeling in DES.

(iii) The decrease in PBS area is significantly associated with the extent of neointimal area at follow-up after BMS and DES implantation.

- This continuum suggests a unified mass effect and communication within the lesion where cells and tissue elements shift between the stent struts.

- Luminal dimensions after coronary stenting are determined by the combined effects of PBS, neointimal hyperplasia, and remodeling forces.
It should be noted that new atherosclerotic changes occurred in healed neointimal tissue inside an implanted stent at long-term follow-up.
Atherosclerotic and Thrombogenic Neointima Formed Over Sirolimus Drug-Eluting Stent
An Angioscopic Study

Tomoaki Higo, MD, Yasunori Ueda, MD, PhD, Jota Oyabu, MD, Katsuki Okada, MD, Mayu Nishio, MD, PhD, Akio Hirata, MD, PhD, Kazunori Kashiwase, MD, PhD, Nobuyuki Ogawara, MD, Shinichi Hirota, MD, PhD, Kazuhisa Kodama, MD, PhD

EDITORIAL COMMENT

One Step Forward and Two Steps Back With Drug-Eluting-Stents
From Preventing Restenosis to Causing Late Thrombosis and Nouveau Atherosclerosis*

Gaku Nakazawa, MD,† Marc Vorpahl, MD,† Aloke V. Finn, MD,‡ Jagat Narula, MD, PhD,§ Renu Virmani, MD†
Potential mechanisms of in-stent atherosclerosis development
Potential mechanisms of in-stent atherosclerosis development

1. Absent or dysfunctional endothelium due to endothelial denudation post-stenting, eluted drug-induced inhibition of reendothelialization, and disturbed flow-induced upregulation of pro-inflammatory genes might favor a greater lipid diffusion and inflammatory cell migration into (neo)intima in a similar, but potentially accelerated manner as the one depicted in panel A promoting neoatherosclerosis development.

2. Chronic foreign body inflammatory reaction to metal/polymer of stent struts with subsequent neovascularization and macrophage recruitment might enhance neoatherosclerosis development.

3. The underlying native atherosclerotic plaque might contribute to in-stent atherosclerotic lesion either directly via expansion through stent struts or indirectly via release of growth factors and chemoattractants.
Distinction between neo- and paleo-atherosclerosis may have potential important

- prognostic implications (e.g., the predisposition to adverse events may be heightened in cases of paleoatherosclerosis progression)

- therapeutic implications (e.g., pertaining to stent design or antithrombotic/antiatherosclerotic management)
OCT study: **direct communication** of the calcific neointimal tissue with the underlying atherosclerotic plaque in 60% of the in-stent calcific atherosclerotic lesions


OCT study: significant **post-stenting tissue protrusion** is an independent predictor of target lesion revascularization.
- In 96% of the cases immediately post-stenting, the stent struts appeared embedded within the disrupted atherosclerotic plaque leaving the stented segment with protruding thrombotic and plaque particles.
- An example case of this study demonstrated that the location of intrastent tissue protrusion at post intervention well matched that of neointima at follow-up


Histopathology study: **direct communication** of in-stent atherosclerotic plaque (composed of cholesterol crystals, macrophage foam cells, and necrotic debris) with the underlying native necrotic core


Histopathology study: late/very late ST may be attributed to **neointimal erosion** with or without in-stent atherosclerosis

The immune and inflammatory responses involve all layers of arteries
Poststent OCT findings

- Smooth protrusion
- Irregular protrusion
- Thrombus
- Disrupted fibrous tissue protrusion

Post-mortem ex vivo
(A) intravascular ultrasound
(B) optical frequency domain imaging
(C) coronary angioscopy of an in-stent mass after biodegradable polymer-coated sirolimus-eluting stent implantation.

(B) The polypoid mass contains cholesterol clefts (arrows), macrophages and degenerated debris (arrowheads)

(D) Continuity of native necrotic core (asterisk) to the polypoid mass
The association between in-stent neoatherosclerosis and native coronary artery disease progression: a long-term angiographic and optical coherence tomography cohort study

Masanori Taniwaki¹, Stephan Windecker¹, Serge Zaugg², Giulio G. Stefanini¹, Sandro Baumgartner¹, Thomas Zanchin¹, Peter Wenaweser¹, Bernhard Meier¹, Peter Jüni³, and Lorenz Räber¹*
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<tbody>
<tr>
<td>Patients</td>
<td>61</td>
<td>67</td>
<td>90</td>
<td>98</td>
<td>134</td>
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<tr>
<td>Stent Type</td>
<td>DES: 42; BMS: 19</td>
<td>Early-generation DES: 38; New-generation DES: 20</td>
<td>BMS: 34; DES: 56</td>
<td>Early-generation DES: 71; New-generation DES: 27</td>
<td>BMS: 47; Early-generation DES: 26; New-generation DES: 56; Unknown: 5</td>
</tr>
<tr>
<td>Time from Index Stenting to VLST, yrs Analysis</td>
<td>4.7 (3.1–7.5)</td>
<td>4.4 ± 0.4</td>
<td>4.6 (2.9–6.2)</td>
<td>4.9 (1.9–8.1)</td>
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<tr>
<td>Strut Malapposition, %</td>
<td>62.3</td>
<td>34.5</td>
<td>30</td>
<td>33.7</td>
<td>14.2</td>
</tr>
<tr>
<td>Neoatherosclerosis, %</td>
<td>49.2</td>
<td>27.6</td>
<td>29</td>
<td>34.7</td>
<td>31.3</td>
</tr>
<tr>
<td>Uncovered Stents, %</td>
<td>70.5</td>
<td>12.1</td>
<td>10</td>
<td>24.5</td>
<td>20.2</td>
</tr>
<tr>
<td>Stent Underexpansion, %</td>
<td>42.4</td>
<td>6.9</td>
<td>7</td>
<td>18.4 (concurrently with other findings)</td>
<td>4.5</td>
</tr>
<tr>
<td>Coronary Evagination, %</td>
<td>8.2</td>
<td>5.1</td>
<td>11</td>
<td>3.1</td>
<td>NR</td>
</tr>
<tr>
<td>Bifurcation Stenting, %</td>
<td>8.2</td>
<td>6.9</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Edge-Related Disease Progression, %</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Neointimal Hyperplasia, %</td>
<td>4.9</td>
<td>1.7</td>
<td>4</td>
<td>4.1</td>
<td>11.9</td>
</tr>
</tbody>
</table>

BMS = bare-metal stents; DES = drug-eluting stents; NR = not reported; VLST = very late stent thrombosis.
I can't see the FOREST with all these damn TREES in the way
Findings associated with strut protrusion in the lumen 
(*malapposed or uncovered struts, stent underexpansion, and evaginations*): 
2/3 of very late ST cases and the vast majority of early and late ST cases

- A cause-and-effect relationship has never been established to date

- Favorable thrombogenic profile of contemporary stents: *uncovered struts and stent malapposition are relatively common imaging findings without subsequent adverse events*

- **Paleoatherosclerotic plaque remains exposed to systemic risk factors** + locally disturbed blood flow

- Uncovered struts could be a *marker of delayed endothelial regeneration* \(\rightarrow\) superficial erosion

- Positive remodeling: further *mechanical stress on the plaque* \(\rightarrow\) neointimal cap disruption

- Uncovered or malapposed struts may have previously been covered by neointima: *pure epiphenomena at the time of thrombotic events* due to neointimal rupture and subsequent exposure of the underlying stent struts.

Uncovered and malapposed stent struts might actually constitute: *innocent bystanders, contributory factors, or a consequence of paleoatherosclerotic plaque complications* rather than causative factors per se of ST.
• The composition of thrombus aspirates retrieved from patients with early versus late ST as well as in BMS versus DES, is broadly similar, suggesting common pathophysiological mechanisms and questioning the currently proposed multifactorial etiology of ST.

• Leucocytes (neutrophils and eosinophils) and neutrophil extracellular traps constitute basic components of thrombus aspirates, as is the case in native vessel atherothrombosis.


Leukocyte accumulation in stent thrombus specimens
Histopathological studies in humans have demonstrated that neutrophils and NETs are abundantly present in disrupted atherosclerotic plaques, while they are nearly absent in intact plaques.
in-stent atherosclerosis contributing to ISR

neointimal rupture as a cause of ST

recurrent cycles of neointimal rupture and healing as a cause of ISR
neoatherosclerosis versus paleoatherosclerosis contribution in stent failure

neointimal erosion

paleoatherosclerosis complications behind the stent
In-scaffold neoatherosclerosis

- Bioresorbable Scaffold
  - After Implantation
  - ↓ Radial Support (>6–12 months)

- In-Scaffold Restenosis
  - Scaffold Thrombosis (Rupture)
  - Scaffold Thrombosis (Erosion)

- Fibrous Tissue
- Paleoatherosclerosis
- Lumen
- Neointimal Tissue
- Scaffold Strut
- Resorbed Scaffold Strut
- Thrombus
- Neoatherosclerosis
The Effect of Stent Artefact on Quantification of Plaque Features Using Optical Coherence Tomography (OCT): A Feasibility and Clinical Utility Study

Kamran Majeed, MBBS a, Eline Hartman, MD c, Trevor A. Mori, PhD b, Richard Alcock, MBBS, MD b, Jon Spiro, MBChB, MD c, Jurgen Ligthart, BSc d, Karen Witberg, RN c, Graham Hillis, MBChB, PhD a,b, Gijs van Soest, PhD e, Carl Schultz, MBChB, PhD a,b

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bMedical School, University of Western Australia, Perth, WA, Australia
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dOptical and Biomedical Engineering Laboratory, School of Electrical Engineering, University of Western Australia, Perth, WA, Australia
In-stent restenosis

Intracoronary imaging (IVUS/OCT) to identify number of stent layers and mechanism

Type I Mechanical
- Underexpansion
- Stent fracture
  - High pressure balloon +/- ELCA, RA, IVL
  - BA + DES
  - BA +/- scoring balloon
    - DCB, DES, VBT
    - BA +/- ELCA, IVL, RA
- Neoatherosclerosis without calcification
- Neoatherosclerosis with calcification
- DES
- VBT
- DCB, DES, VBT
- DCB

Type II Biologic
- Neoatherosclerosis without calcification
- Neoatherosclerosis with calcification
- Mixed mechanical and biologic
- Treatment individualized to lesion type
- High pressure balloon
- VBT
- DCB

Type III Mixed
- PCI
- CABG
- DCB, DES, VBT
- If PCI unsuccessful: CABG, OMT

Type IV >2 layers of DES ISR
- PCI
- CABG
- DCB, DES, VBT
- If PCI unsuccessful: CABG, OMT

Type V CTO
- PCI
- CABG
- DCB, DES, VBT
- If PCI unsuccessful: CABG, OMT
# Waksman In-Stent Restenosis Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mechanical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Underexpansion (Type I A)</td>
<td>High-pressure balloon</td>
</tr>
<tr>
<td></td>
<td>Stent fracture (Type I B)</td>
<td>DES</td>
</tr>
<tr>
<td>II</td>
<td>Biologic</td>
<td></td>
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<tr>
<td></td>
<td>Intimal hyperplasia (Type II A)</td>
<td>Balloon, DCB, DES, and VBT</td>
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<tr>
<td></td>
<td>Neoatherosclerosis, noncalcified (Type II B)</td>
<td>DCB and DES</td>
</tr>
<tr>
<td></td>
<td>Neoatherosclerosis, calcified (Type II C)</td>
<td>Scoring balloon, ELCA, and RA</td>
</tr>
<tr>
<td>III</td>
<td>Mixed pattern: Combined mechanical and biologic etiology</td>
<td>High-pressure balloon with DCB, DES, or VBT</td>
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<tr>
<td>IV</td>
<td>Chronic total occlusion</td>
<td>DCB or DES, VBT for multiple layers, CABG as needed</td>
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<tr>
<td>V</td>
<td>&gt;2 layers of stent</td>
<td>Balloon, DCB, VBT, and CABG</td>
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<tr>
<td>Early findings</td>
<td>Late findings</td>
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| Incomplete vessel expansion | Early findings:  
  - Ratio of minimum in-stent area/reference vessel area < 80%  
  - Minimum stent area < 5.5 mm² by IVUS  
  - Minimum stent area < 4.5 mm² by OCT  
  - Residual diameter stenosis > 20%  
  - For DES, aim at ~10% oversizing in vessels < 2.75 mm²  
  - Prevention: use of imaging to detect calcific lesions; aggressive lesion preparation including use of debulking devices  
  - Correction: high-pressure postdilatation (aneurysmal evidence with excimer laser and rotational)  
  
  Late findings:  
  - Dissection  
    - Flow-limiting  
    - > 200 μm at distal stent edge  
    - Angle of the dissection > 60°  
    - Dissection reaching the media  
    - Longitudinal length > 3 mm  
    - Prevention and diagnosis: intracoronary imaging  
    - Correction: DES and lipid-lowering therapy  
  
  - Geographical miss  
    - Minimum lumen area < 4.5 mm² and plaque burden > 50%  
  
  - Neootherosclerosis  
    - No formal cut-off (haemodynamic relevance)  
  
  - Dismantling  
    - Always pathological  
  
  - Malapposition  
    - Strut–vessel wall distance > 300 μm  
    - > 1 mm in length  
    - Prevention: accurate sizing (including procedural use of imaging)  
    - Correction: postdilatation to correct size and prolongation of DAPT  
  
  - Evaginations  
    - Major when extending ≥ 3 mm with a depth ≤ 10% of the stent diameter  
  
  - Uncovered struts  
    - Number ≥ 6%  
    - Uncovered length > 3 mm  
    - Diagnosis: intravascular imaging  
    - Correction: prolongation of DAPT |
Conclusions

- Accumulating histopathological and intravascular imaging studies during the last decade have unequivocally demonstrated the pivotal role of atherosclerosis progression and complications in stent failure.

- ISR and ST might be viewed as the consequence of a range of recurrent atherosclerosis complications occurring inside or behind the stent—with the exception of early restenosis resulting from excessive neointimal growth or mechanical/technical complications.

- Other stent type-related, procedural, and patient-related factors may play a modulatory or contributory role in atherosclerotic complications; however, they may not be essential to stent failure.

- Framework of thought - Numerous new lines of inquiry, which may either validate or refute this prediction

- Future prospective studies and further refinement of intravascular imaging technology to explore this concept and assess whether therapeutic strategies that target atherosclerosis locally (e.g., local delivery of pharmaceutical agents, miRNA-based strategies, closed-cell or mesh-covered stents with elution of potent antiatherosclerotic agents) or systemically (e.g., statins, immunosuppressive/anti-inflammatory compounds) could mitigate the risk of stent failure.
Thin-cap fibroatheroma (TCFA) neointima (arrowhead) were observed in mid part, whereas there were malapposed struts (white arrow) in the distal and proximal part.

TCFA (arrowhead) neointima and thrombus (asterisk) above the lipid neointima was observed.
acute/subacute stent thrombosis

late/very late stent thrombosis

Stent malapposition

Uncovered struts without stent malapposition

Coronary evagination

Ruptured neoatherosclerosis

Erosive neointima without neoatherosclerosis
Acute stent thrombosis: Edge dissection
Sub-acute stent thrombosis: Stent major malapposition
Late stent thrombosis: Isolated uncovered struts
Neoatherosclerosis lesion

Ruptured neoatherosclerotic lesion
Coronary evaginations

Stent underexpansion

SA = 1.6mm²

LA = 6.8mm²
Mechanisms of underlying very late scaffold thrombosis

A Scaffold discontinuity
42.1%

B Malapposition
18.4%

C Neoatherosclerosis

D Underexpansion
10.5%

E Uncoverage
5.3%

F Edge related progression
2.6%
Case 1: Myocardial bridge - ISR

metallic markers of the implanted scaffold

scaffold struts of the previously implanted Absorb BVS located inside the metal stent
c, d: Neointimal rupture site with a large burden of mural thrombus protruding into the lumen (c; d. plus signs) with highly attenuating area.
Case 3

paleoatherosclerosis complications behind the stent

ruptured plaque observed under the stent struts
Very late stent thrombosis due to probable plaque erosion and not plaque rupture

Case 4