Late Coronary Stent Thrombosis

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Introduction

>20 years ago, coronary artery stents have improved the safety and particularly the efficacy of percutaneous coronary interventions (PCIs). Abrupt vessel closure, complicating 6% to 8% of balloon angioplasty procedures, was associated with a 5% mortality, 40% rate of myocardial infarction (MI), and 40% rate of emergency coronary bypass grafting. Stents significantly reduced these adverse events (Figure 1). The reduction of restenosis afforded by bare metal stents (BMS) was modest (30% to 40%). Repeat revascularization still occurred in 15% to 20% of cases. Drug-eluting stents (DES) with antiproliferative drugs attached via polymers on the stent surface to minimize smooth muscle proliferation have reduced restenosis and rates of target lesion revascularization by 50% to 70% compared with BMS across nearly all lesion and patient subsets. Initially and again more recently, safety concerns were raised about DES, particularly about late stent thrombosis (ST).

Historical Perspective

ST was a bane of stent implantation from the beginning. The initial experience with Wallstents in the late 1980s was overshadowed by ST rates approaching 24%. Subsequent series with Palmaz-Schatz and Gianturco-Roubin stents (still predominantly bailout stenting) observed ST in 6% to 12% of cases. The postprocedural antithrombotic regimen at the time consisted of aspirin, often in conjunction with oral anticoagulation. Dual antiplatelet therapy of aspirin and the thienopyridine ticlopidine in conjunction with a shift from bailout to elective stenting resulted in a significant reduction of ST to <2%. Earlier oral antiplatelet drug loading and glycoprotein IIb/IIIa antagonists further diminished ST. Although it has been suggested that the composite of definite and probable ST represents a good balance of specificity and sensitivity, reporting of definite and overall rates with careful adjudication of late unexplained deaths has been encouraged.

The second classification principle is based on the time of the adverse event relative to the index procedure (Figure 2). Early ST refers to the first 30 days after stent implantation and is further stratified into acute (<24 hours) and subacute (24 hours to 30 days). Late ST defines the time interval between 1 month and 1 year after stent implantation; very late ST includes any event beyond 30 days until the end of follow-up. Probable ST and possible ST have been added to the definition of ST because they provide higher sensitivity in detecting safety signals. Conversely, they are less specific and therefore critically dependent on detailed data collection about the cause of death or MI to avoid overreporting of ST.

An additional level of information is provided by reporting whether ST occurred in the context of an intercurrent target lesion revascularization. Thus, censoring of adverse events once intercurrent revascularization procedures occurred may disadvantage devices with lower (ie, DES) compared with devices with higher (ie, BMS) re-intervention rates. To avoid...
this form of selective reporting, it is recommended that both primary ST rates (without intercurrent target lesion revascularization) and secondary ST rates (with intercurrent target lesion revascularization) be provided. Primary ST rates identify safety signals related to the originally implanted device, whereas secondary ST rates provide information on the overall treatment strategy, taking into account the impact of frequency of repeat revascularization procedures.

### Frequency and Time of ST

Early ST (0 to 30 days) is encountered with a similar or even somewhat lower frequency after DES compared with BMS. A 30-day definite ST rate of 1.2% with BMS (506 patients), 1.0% with sirolimus-eluting stents (SES; 1017 patients), and 1.0% with paclitaxel-eluting stents (PES; 989 patients) was found in a sequential cohort comparison. A meta-analysis of 6 studies comparing BMS with SES in 2963 patients reported

### Table 1. Coronary ST

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Stent Type</th>
<th>Total Population, n</th>
<th>ST, n (%)</th>
<th>Definition of ST</th>
<th>Thienopyridine (%)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Karrillon et al</td>
<td>1996</td>
<td>BMS</td>
<td>2900</td>
<td>51 (1.8)</td>
<td>Definite and probable</td>
<td>Ticlopidine</td>
<td>Early</td>
</tr>
<tr>
<td>Moussa et al</td>
<td>1997</td>
<td>BMS</td>
<td>1001</td>
<td>19 (1.9)</td>
<td>Definite and probable</td>
<td>None (25)</td>
<td>Early</td>
</tr>
<tr>
<td>Schülen et al</td>
<td>1998</td>
<td>BMS</td>
<td>2833</td>
<td>65 (2.3)</td>
<td>Definite</td>
<td>Ticlopidine (80)</td>
<td>Early</td>
</tr>
<tr>
<td>De Servi et al</td>
<td>1999</td>
<td>BMS</td>
<td>939</td>
<td>14 (1.5)</td>
<td>Definite</td>
<td>Ticlopidine (75)</td>
<td>Early</td>
</tr>
<tr>
<td>Cutlip et al</td>
<td>2001</td>
<td>BMS</td>
<td>6186</td>
<td>53 (0.9)</td>
<td>Definite and probable</td>
<td>Ticlopidine</td>
<td>Early</td>
</tr>
<tr>
<td>Serruys et al</td>
<td>2001</td>
<td>BMS</td>
<td>600</td>
<td>17 (2.8)</td>
<td>Definite</td>
<td>Ticlopidine</td>
<td>Early</td>
</tr>
<tr>
<td>Heller et al</td>
<td>2001</td>
<td>BMS</td>
<td>1855</td>
<td>34 (1.8)</td>
<td>Definite</td>
<td>Ticlopidine</td>
<td>Early and late</td>
</tr>
<tr>
<td>Orford et al</td>
<td>2002</td>
<td>BMS</td>
<td>4509</td>
<td>23 (0.5)</td>
<td>Definite and probable</td>
<td>Ticlopidine, clopidogrel</td>
<td>Early</td>
</tr>
<tr>
<td>Wang et al</td>
<td>2002</td>
<td>BMS</td>
<td>1191</td>
<td>20 (1.7)</td>
<td>Definite</td>
<td>Ticlopidine</td>
<td>Early and late</td>
</tr>
<tr>
<td>Wenaweser et al</td>
<td>2005</td>
<td>BMS</td>
<td>6058</td>
<td>95 (1.6)</td>
<td>Definite</td>
<td>Ticlopidine, clopidogrel</td>
<td>Early and late</td>
</tr>
<tr>
<td>Lee et al</td>
<td>2005</td>
<td>BMS</td>
<td>1597</td>
<td>9 (0.5)</td>
<td>Definite</td>
<td>Clopidogrel</td>
<td>Early</td>
</tr>
<tr>
<td>Lee et al</td>
<td>2005</td>
<td>BMS</td>
<td>1415</td>
<td>1 (0.1)</td>
<td>Definite</td>
<td>Clopidogrel and cilostazol</td>
<td>Early</td>
</tr>
<tr>
<td>DES</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Serruys et al</td>
<td>1998</td>
<td>Hepacoat</td>
<td>414</td>
<td>1 (0.2)</td>
<td>Definite</td>
<td>Ticlopidine</td>
<td>Early</td>
</tr>
<tr>
<td>Mehran et al</td>
<td>2003</td>
<td>Hepacoat</td>
<td>200</td>
<td>2 (1)</td>
<td>Definite and probable</td>
<td>None</td>
<td>Early</td>
</tr>
<tr>
<td>Ong et al</td>
<td>2005</td>
<td>SES, PES</td>
<td>2006</td>
<td>20 (1.0)</td>
<td>Definite</td>
<td>Clopidogrel</td>
<td>Early</td>
</tr>
<tr>
<td>Iakovou et al</td>
<td>2005</td>
<td>SES, PES</td>
<td>2229</td>
<td>29 (1.3)</td>
<td>Definite, probable, and possible</td>
<td>Clopidogrel, ticlopidine</td>
<td>Early and late</td>
</tr>
<tr>
<td>Kuchulakanti et al</td>
<td>2006</td>
<td>SES, PES</td>
<td>2974</td>
<td>38 (1.3)</td>
<td>Definite</td>
<td>Clopidogrel</td>
<td>Early and late</td>
</tr>
<tr>
<td>Rodriguez et al</td>
<td>2006</td>
<td>SES, PES</td>
<td>225</td>
<td>5 (2.2)</td>
<td>Definite</td>
<td>Clopidogrel</td>
<td>Early, late, and very late</td>
</tr>
<tr>
<td>Urban et al</td>
<td>2006</td>
<td>SES</td>
<td>15157</td>
<td>126 (0.9)</td>
<td>Definite and probable</td>
<td>Clopidogrel</td>
<td>Early and late</td>
</tr>
<tr>
<td>Park et al</td>
<td>2006</td>
<td>SES, PES</td>
<td>1911</td>
<td>15 (0.8)</td>
<td>Definite, probable, and possible</td>
<td>Clopidogrel</td>
<td>Early, late, and very late</td>
</tr>
<tr>
<td>Daemen et al</td>
<td>2007</td>
<td>SES, PES</td>
<td>8146</td>
<td>152 (1.9)</td>
<td>Definite</td>
<td>Clopidogrel</td>
<td>Early, late, and very late</td>
</tr>
</tbody>
</table>

![Figure 1. Outcome of 112 patients with abrupt vessel closure in the present balloon angioplasty experience of a registry (1985 to 1986; total, 1801 patients) and 339 patients with abrupt vessel closure during balloon angioplasty treated with BMS (Palmaz-Schatz) (total, 4596 patients). CABG indicates coronary artery bypass grafting.](http://circ.ahajournals.org/Downloadedfrom)
Table 2. Definition of ST as Proposed by the Academic Research Consortium\textsuperscript{39}

<table>
<thead>
<tr>
<th>Definite ST</th>
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</thead>
<tbody>
<tr>
<td>Definite stent thrombosis is diagnosed when either angiographic or pathological confirmation is present</td>
<td></td>
</tr>
<tr>
<td>Angiographic confirmation of ST*</td>
<td></td>
</tr>
<tr>
<td>The presence of a thrombus originating in the stent or in the segment 5 mm proximal or distal to the stented region and at least one of the following criteria within a 48-h time window:</td>
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<tr>
<td>Acute onset of ischemic symptoms at rest (typical chest pain &gt;20 min)</td>
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<tr>
<td>New ischemic ECG changes suggestive of acute ischemia</td>
<td></td>
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<tr>
<td>Typical rise and fall in cardiac biomarkers</td>
<td></td>
</tr>
<tr>
<td>Pathological confirmation of stent thrombosis</td>
<td></td>
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<tr>
<td>Evidence of recent thrombus within the stent determined at autopsy</td>
<td></td>
</tr>
<tr>
<td>Probable ST</td>
<td></td>
</tr>
<tr>
<td>Clinical definition of probable ST is diagnosed after intracoronary stenting in the following cases</td>
<td></td>
</tr>
<tr>
<td>Any unexplained death within the first 30 d</td>
<td></td>
</tr>
<tr>
<td>Regardless of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause</td>
<td></td>
</tr>
<tr>
<td>Possible ST</td>
<td></td>
</tr>
<tr>
<td>Clinical definition of possible ST is diagnosed with any unexplained death from 30 d after intracoronary stenting until the end of trial follow-up</td>
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</tr>
</tbody>
</table>

\*The incident angiographic documentation of stent occlusion in the absence of clinical signs or symptoms (silent occlusion) is (for this purpose) not considered a confirmed stent thrombosis.

ST rates at 30 days of 0.5% with SES and 0.6% with BMS, respectively (relative risk [RR], 0.76; 95% confidence interval [CI], 0.30 to 1.88; \( P=0.55 \)).\textsuperscript{40} A pooled analysis of 5 trials using PES in 3513 patients showed early ST rates of 0.5% with PES compared with 0.6% with BMS (RR, 0.74; 95% CI, 0.31 to 1.80; \( P=0.51 \)).\textsuperscript{41} Finally, a recent analysis of various definitions of ST observed no difference between SES, PES, and BMS in the propensity for early ST.\textsuperscript{16}

Although late ST (>1 month to <1 year) had already been observed during the BMS era, it was largely ignored. Four registries comprising 9465 BMS patients reported rates of late ST ranging from 0% to 1% (average, 0.5%) and representing nearly one third of overall ST events (average, 1.6%) (Figure 3).\textsuperscript{26,28,29,42} Confirmation of this observation came from necropsy findings in a series of 13 patients succumbing to late ST after BMS implantation.\textsuperscript{43} Stenting across ostia, plaque disruption in the persistent region, extensive plaque prolapse caused by very lipid rich plaque, and in-stent restenosis were pathological correlates of late ST. In a meta-analysis, no differences existed in the overall (0.6% versus 0.5%; odds ratio, 1.05; 95% CI, 0.51 to 2.15; \( P=1.00 \)) and late (0.2% versus 0.3%; odds ratio, 99; 95% CI, 0.35 to 2.84; \( P=1.00 \)) incidence of ST between DES (2602 patients) and BMS (2428 patients).\textsuperscript{44} Similarly, no significant differences existed in the incidence of late ST between SES, PES, and BMS according to various definitions as proposed by the academic research consortium.\textsuperscript{16} Whether the 2 US Food and Drug Administration–approved DES differ with respect to early and late ST has been scrutinized in several randomized trials directly comparing SES and PES and in a meta-analysis.\textsuperscript{45} No significant differences were detected for up to 1 year of follow-up (Figure 4). Taken together, BMS and DES (SES or PES) show similar rates of ST for up to 1 year after the index procedure. ST occurred within the expected range in a broad spectrum of patients and lesions, but average dual antiplatelet therapy was longer after DES than BMS.

Case reports, observational studies, extended follow-up of trials comparing DES with BMS, and meta-analyses of randomized trials have corroborated that very late ST (>1 year) is more common with DES than BMS. The predisposition to ST of DES >1 year after implantation has been anticipated as design inherent.\textsuperscript{8} It was first documented in 4 patients who discontinued antiplatelet therapy or underwent a surgical procedure.\textsuperscript{46} Follow-up results in 826 patients assigned on a random daily basis to treatment with either BMS (n=281) or DES (n=546) indicated an increased risk of cardiac death (1.2% versus 0%; \( P=0.09 \)) and MI (4.1% versus 1.3%; \( P=0.04 \)) with DES during the time period of 7 to 18 months (a time when clopidogrel treatment had been discontinued),\textsuperscript{10} although overall rates of cardiac death (2.8% versus 2.5%; \( P=NS \)) and MI (6.1% versus 5.3%; \( P=NS \)) were similar at 18 months. The frequency and timing of definite ST encountered with first-generation DES have been examined in 8146 patients treated at 2 academic centers that...
adopter default DES use in routine clinical practice in 2002.11
Whereas the incidence of early ST (1.1%) was similar to
previous reports, the incidence of late ST continued at a
steady rate of 0.6% per year for up to 3 years of follow-up
(Figure 5). Pooled analysis of 4 randomized trials (1748
patients) comparing SES and of 5 randomized trials (3513
patients) comparing PES with BMS revealed similar rates of
protocol-defined ST up to 1 year but significantly more very
late ST (SES versus BMS: 0.6% versus 0%, \( P=0.03 \); PES
versus BMS: 0.7% versus 0.2%, \( P=0.03 \)).12 After readjudi-
cication of all ST events in these trials according to each of the
newly proposed academic research consortium categories,
differences in the incidence of very late ST diminished but
were still apparent.16 Another systematic review of 14 trials
comparing SES with PES revealed no difference in the
overall incidence of protocol-defined ST (SES, 1.5% versus
BMS, 1.3%; \( P=0.75 \)), but very late ST was more frequent
with SES (0.3% versus 0.04%; \( P=0.02 \)).14 Finally, a meta-
analysis of 6675 patients with follow-up ranging from 8 to 48
months reported no difference in the overall incidence of ST
between BMS and DES (0.10% versus 0.07%; RR, 1.03; 95%
CI, 1.29 to 19.52; \( P=0.02 \)).9 Accordingly, very late ST
is a distinct clinical entity complicating the use of first-
generation DES while being exceedingly rare after BMS. It
remains to be determined whether the yearly rate of 0.2% to
0.6% persists beyond 3 years, whether DES in off-label
settings is associated with higher rates of very late DES, and
whether newer-generation DES have a more favorable risk
profile.

**Clinical Sequelae of ST**

ST results in abrupt closure of the stented artery with the
associated risk of MI and death.24 The impact of ST is
influenced by the myocardial area at risk, its viability, the
degree of instantly recruitable collaterals, and rapid reperfu-
sion therapy. Moreover, ST may be responsible for late
complications of MI, including heart failure, arrhythmias, or
mechanical complications.

Mortality after ST is high. A pooled analysis of multicenter
BMS trials24 and a single-center registry of 6058 BMS
patients59 both observed a mortality of 7% at 30 days after
definite ST. Mortality at 30 days after definite ST in DES
amounted to 9% in a registry of 8146 patients41 and to 19%
in a series of 2974 patients.35 A recent report of definite or

![Figure 3. Overall and late ST in 4 observational
studies with BMS investigating ST beyond 30
days.26,28,29,42](image-url)

![Figure 4. Risk of ST in 9 trials directly comparing SES and PES with follow-up to 1 year. Updated from Reference 45.](image-url)
probable ST in randomized clinical trials of DES versus BMS revealed similar rates of mortality for both stent types (SES versus BMS, 31% versus 33%; PES versus BMS, 32% versus 28%).\textsuperscript{16} Case fatality rates may vary across studies, depending on the definition of ST (Figure 6). Thus, rates of MI are quite similar in series of definite only and definite/possible/probable ST, whereas mortality ranges between 11% (definite ST) and 45% (definite, probable, and possible ST) at 6 to 9 months of follow-up.\textsuperscript{11,34,35} The difference in case fatality of ST is related to the broader and therefore less specific inclusion of probable and possible as opposed to only definite ST cases.

Most ST patients develop MI (66% to 100% with DES\textsuperscript{11,16,35} and 60% to 87% with BMS) with no differences between DES and BMS.\textsuperscript{16,24,29} The consequences of ST may be grave in patients in whom multiple stents in different vessels occlude simultaneously, as has been observed in 7 of 152 patients (5%) with DES ST.\textsuperscript{11} Patients with suspected ST may show a thrombus without flow impairment resulting from spontaneous or drug-facilitated lysis and may suffer minimal or no myocardial injury. Patients suffering from ST are at significant risk of recurrent thrombotic stent occlusion; 11 of 95 patients (12%) with BMS ST and 3 of 152 patients (2%) with DES ST had recurrent ST after a first event.\textsuperscript{11,29} Impaired collateral flow after implantation of DES compared with BMS (collateral flow index, 0.15\pm0.10 versus 0.22\pm0.14; P<0.01) during 6 months of follow-up was suggested,\textsuperscript{47} but the clinical significance of this observation in patients with ST remains unclear. Definite early or late ST after DES implantation in 152 patients had comparable rates of death (13.2% versus 8.2%; P=0.24) and major adverse cardiac events (77% versus 75%; P=0.99).\textsuperscript{11}

The US Food and Drug Administration convened a meeting of its Circulatory System Devices Advisory Panel on December 7 and 8, 2006, to address the concern of whether the slight excess of very late ST with DES compared with BMS might be associated with increased rates of death or MI.
during long-term follow-up. The clinical outcomes of randomized clinical trials comparing SES and PES with BMS were analyzed in several systematic reviews and revealed no significant differences relative to death (PES, 6.1% versus BMS, 6.6%; hazard ratio [HR], 0.94; 95% CI, 0.70 to 1.26; \( P = 0.68^{12} \); SES, 6.0% versus BMS, 5.9%; HR, 1.03; 95% CI, 0.80 to 1.30\(^{14} \)) or MI (PES, 7.0% versus BMS, 6.3%; HR, 1.06; 95% CI, 0.81 to 1.39; \( P = 0.66^{12} \); SES, 9.7% versus BMS, 10.2%; HR, 0.97; 95% CI, 0.81 to 1.16\(^{14} \)) during long-term follow-up to 4 to 5 years.\(^{13} \) It was hypothesized that the small increase in very late ST with DES was balanced by a somewhat smaller early ST rate, less frequent need for repeat revascularization procedures, and fewer associated complications compared with BMS. This notion is supported by the observation of a higher rate of late and very late ST after readjudication of previously censored ST cases in patients allocated to treatment with BMS after intercurrent revascularization procedures.\(^{16} \) Yet a large-scale registry of 6033 DES and 13 738 BMS patients in Sweden reported similar rates of mortality (propensity score–adjusted Cox regression analysis: RR, 0.94; 95% CI, 0.83 to 1.06) and MI (RR, 0.94; 95% CI, 0.77 to 1.03) for up to 6 months, followed by an excess risk of death (RR, 1.20; 95% CI, 1.05 to 1.37) and MI (RR, 1.12; 95% CI, 0.95 to 1.32), using landmark analyses during follow-up to 3 years.\(^{15} \) Although groups of DES and BMS differed widely with respect to cardiovascular risk factors such as diabetes (DES, 24% versus BMS, 16%), number of stents, stent diameter, stent length, and target lesion location, limiting the value of adjustments made by propensity score analysis, concerns persist that the use of DES in more complex patient and lesion subsets not represented in the randomized clinical trials may be associated with higher adverse event rates.

### Risk Factors of ST

ST is a multifactorial problem related to patient, lesion, and procedural factors and to the coagulation system and response to antiplatelet therapy (Table 3). Early ST has been viewed as a problem originating from the procedure itself. Schühlen et al.,\(^{22} \) using a classification and regression tree, identified residual dissections, followed by length of the stented segment, as the most important predictors of ST within 30 days with BMS. The importance of residual dissections in the DES era has been reiterated when observing an increased risk of death (RR, 1.20; 95% CI, 1.05 to 1.37) and MI (RR, 1.12; 95% CI, 0.95 to 1.32), using landmark analyses during follow-up to 3 years.\(^{15} \) Although groups of DES and BMS differed widely with respect to cardiovascular risk factors such as diabetes (DES, 24% versus BMS, 16%), number of stents, stent diameter, stent length, and target lesion location, limiting the value of adjustments made by propensity score analysis, concerns persist that the use of DES in more complex patient and lesion subsets not represented in the randomized clinical trials may be associated with higher adverse event rates.\(^{48} \)

### Table 3. Multifactorial Origin of ST

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Drug response/interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness and robustness of neointimal stent coverage</td>
<td>Inhibition of platelet aggregation</td>
</tr>
<tr>
<td>Drug response/interactions</td>
<td>Coagulation activity</td>
</tr>
<tr>
<td>Gene polymorphism</td>
<td>Antithrombotic and anticoagulation therapy</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>Coagulation activity</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>Inhibition of platelet aggregation</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Discontinuation of antiplatelet therapy</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Incomplete stent apposition</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>Dissection</td>
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<tr>
<td></td>
<td>Device factors</td>
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<td></td>
<td>Stent surface</td>
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<td></td>
<td>Drugs</td>
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<tr>
<td></td>
<td>Polymer</td>
</tr>
</tbody>
</table>

Discontinuation of antiplatelet therapy has emerged as one of the most important predictors of ST. Aspirin withdrawal was responsible for admission with an acute coronary syndrome in 51 of 1236 patients (4%) with a mean delay between aspirin cessation and hospitalization of 10 ± 2 days.\(^{52} \) Notably, 10 of 51 patients (19%) presented with late and very late ST at a mean of 16 ± 7 months after BMS implantation. Discontinuation of antiplatelet therapy was related in descending order to patient noncompliance, dental procedures, surgical procedures, and bleeding. Predictors of the composite of definite, probable, and possible ST up to 9 months after DES implantation were identified in a cohort study of 2229 patients.\(^{34} \) The strongest predictor of early (HR, 161; 95% CI, 26 to 998; \( P < 0.001 \)), late (HR, 57; 95% CI, 15 to 220; \( P < 0.001 \)), and overall ST (HR, 90; 95% CI, 30 to 270; \( P < 0.001 \)) was premature discontinuation of antiplatelet therapy: both aspirin and thienopyridine in 4 patients and thienopyridine alone in 1 patient. Similarly, discontinuation of thienopyridines was more prevalent in patients suffering from ST after DES implantation compared with control subjects (37% versus 11%; \( P < 0.0001 \)) and emerged as an independent predictor of overall ST in a population of 2974 patients.\(^{35} \) It is noteworthy that most of these data are based on only a few events, that compliance with antiplatelet therapy is difficult to assess, and that even continued dual antiplatelet therapy provides but an imperfect safety net.\(^{53} \) Patients may still develop early and late ST despite adherence to the prescribed antiplatelet regimen. Dual antiplatelet therapy was
taken by 14 of 61 patients (23%) suffering from late ST after DES implantation, whereas only 16 (26%) were off antiplatelet therapy at the time of late ST (Figure 7).11 ST occurred late in 31 patients while on aspirin monotherapy, and most of them (30 of 31; 97%) experienced the event well after the recommended period of clopidogrel. Taken together, these data indicate that dual antiplatelet therapy is important but is no panacea for the prevention of ST with both BMS and DES, that discontinuation of either aspirin or clopidogrel should be avoided (particularly during the first 6 to 12 months after the index procedure), and that cessation of antiplatelet therapy is related mostly to noncompliance and surgical procedures.54,55

Similar to previous experience with BMS, ST complicating DES implantation is influenced by several additional patient, lesion, and procedural factors. In a series of 15 157 patients treated with SES and followed up prospectively for 1 year, ST occurred in 126 patients (0.9%: early, 0.7%; late, 0.2%), and multivariate analysis identified impaired postprocedural flow impairment, insulin-dependent diabetes, calcification, total occlusions, acute coronary syndrome, and number of treated lesions as predictors of overall ST.37 Renal failure, bifurcation lesions, total stent length, and diminished left ventricular function were additional clinical predictors of ST with DES in subsequent reports.34,35 Intravascular ultrasound in 15 patients with ST compared with 45 control subjects revealed smaller minimal stent area (4.3±1.6 versus 6.2±1.9 mm²; P<0.001), reduced stent expansion (65±18% versus 85±14%; P<0.001), and residual edge stenosis (67% versus 9%; P<0.001) to be more common in the ST patients than the control subjects.56

**Pathogenesis of ST**

Virmani and colleagues57 first described a case of local hypersensitivity reaction with extensive vasculitis of intima, media, and adventitia consisting predominantly of lymphocytes and eosinophils in a patient suffering very late DES thrombosis. Histopathological analysis revealed aneurysmal dilatation of the vessel wall within the stented segment with evidence of stent malapposition and thick fibrin thrombus between the stent and the arterial wall. Clinical evidence of hypersensitivity reactions stems from a registry,58 with 17 of 5783 patients reporting hypersensitivity symptoms probably or certainly related to DES.

In a recent necropsy comparison of 23 DES cases with 25 BMS cases (>30 days after the index procedure), delayed healing manifested by persistent fibrin deposition and incomplete reendothelialization emerged as an important discriminator between BMS and DES.59 Endothelialization (27±26% versus 66±25% versus 90±21%) was reduced whereas fibrin scores (3.0±0.9 versus 1.9±1.1 versus 0.9±0.8) were increased in DES patients with late ST compared with patients with both patent DES and BMS. Endothelialization was nearly complete in BMS specimens examined beyond 6 months, whereas incomplete endothelialization in DES specimens persisted beyond 40 months (Figure 8). Fourteen of 21 DES patients suffered late ST, which was related to delayed healing in all patients; in addition, the following pathological mechanisms were identified: chronic inflammation/hypersensitivity reaction, stenting over major side branches or bifurcation stenting using the crush technique, malapposition related to positive arterial remodeling or incomplete stent expansion, in-stent restenosis with superimposed thrombus, and penetration of necrotic core through stent struts. The results of this analysis are confounded by selection bias because patients with late DES thrombosis were more likely to undergo autopsy for suspected late thrombosis, whereas patients with BMS were more likely to be referred for other reasons.
Several clinical investigations support the notion of reduced or dysfunctional endothelialization after DES implantation. Kotani et al. compared stent strut coverage between BMS (n=22) and SES (n=15) 3 to 6 months after the procedure using intracoronary angioscopy. Struts of SES were not (grade 0, 20%) or were minimally (grade 1, 67%) covered, whereas BMS showed complete coverage in all cases (grade 2, 13%; grade 3, 87%). Although angioscopy is unable to provide histological evidence of endothelialization, it is not farfetched to conclude that both neointimal regrowth and reendothelialization were impaired by DES. Physiological evidence of dysfunctional endothelium comes from studies assessing vasomotion 6 months after DES implantation. Through the use of bicycle exercise during coronary angiography, the segment proximal and distal to DES showed paradoxical vasoconstriction, whereas BMS demonstrated normal vasodilatation (Figure 9), suggesting that DES either prevent reendothelialization or induce vascular damage with subsequent endothelial dysfunction and reduced nitric oxide availability. Using pharmacological evaluation of endothelial function 6 months after the index procedure, another study corroborated paradoxical vasoconstriction distal to the stent with a maximal decrease in the mean coronary diameter by 32% compared with baseline in SES-treated patients with an insignificant decrease in the BMS control group (2%; P=0.03).

A pooled analysis of intravascular ultrasound studies after SES (8.5% versus 0%; P<0.05) and PES (8.4% versus 3.5%; P<0.05) implantation revealed a higher incidence of incomplete stent apposition with DES compared with BMS that was not associated with any major adverse cardiac events at the 1-year follow-up. In contrast, a study of 13 DES patients undergoing intravascular ultrasound before emergency PCI at the time of very late ST showed a higher incidence and larger area of incomplete stent apposition compared with a control group of 144 event-free DES patients (frequency, 77% versus 12%; P<0.001; maximum area, 8.3±7.5 versus 4.0±3.8 mm²; P=0.03). Although vessel cross-sectional area was comparable for the reference segment, it was significantly larger for the in-stent segment in patients with very late ST compared with DES control subjects, suggesting positive arterial remodeling as a potential pathogenetic mechanism of very late ST. A similar observation was reported describing 2 cases of very late ST after DES implantation with late acquired incomplete stent apposition and pronounced positive arterial remodeling within the stented segment. Finally, drugs released from the drug-polymer combination may exert a thrombogenic effect on their own. Paclitaxel and sirolimus have been reported to enhance endothelial tissue factor expression, a cell surface receptor for coagulation factor VII, the principal activator of the coagulation cascade that activates factors IX and X.

In summary, delayed healing and impaired endothelialization are common features of most cases of late and very late ST, which either alone or in combination with chronic inflammation and hypersensitivity reactions, incomplete stent apposition resulting from positive arterial remodeling or stent
underexpansion, and penetration of the stent into a necrotic core leads to this adverse event. In contradistinction to the thick layer of neointima after balloon angioplasty or BMS implantation, the surface coverage on a DES may be thin and brittle or even absent and thus prone to rupture, not unlike a vulnerable plaque. It remains to be explained why SES are not more susceptible to this problem than PES in light of their attested thinner neointimal coverage. Inhomogeneity of neo-intimal hyperplasia with PES (thin on struts, thicker between struts) may account for this.

**Treatment of ST**

ST constitutes an emergency, be it early, late, or very late, just like any acute MI. Primary PCI is the therapy of choice, the goal being to mechanically recanalize the thrombosed stent. Procedural success in >90% of patients has been reported. Most thrombotic stent occlusions can be treated with balloon angioplasty alone, perhaps aided by thrombus aspiration. Additional stent implantation should be limited to significant residual dissections. Glycoprotein IIb/IIIa antagonists may be administered to improve microvascular reperfusion and to overcome increased platelet aggregation. Systemic fibrinolysis should be considered in the presence of ongoing significant ischemia and unavailability of prompt PCI. If platelet aggregation studies reveal insufficient (<50%) inhibition of platelet aggregation with standard dual antiplatelet therapy, the sustained administration of 150 mg/d clopidogrel should be considered.

**Prevention of ST**

Several preventive strategies may help to limit the risk of ST in patients treated with DES.
Antiplatelet Therapy

The importance of compliance with dual antiplatelet therapy has been underscored in a registry of 500 patients with acute MI treated with DES. Among discharged patients, 68 (14%) discontinued thienopyridine therapy within 30 days. Predictors of premature thienopyridine discontinuation were older age, lower socioeconomic status, preexisting cardiovascular disease, and lack of discharge instructions or cardiac rehabilitation referral. Mortality (7.5% versus 0.7%; HR, 9.0; 95% CI, 1.3 to 61; \( P = 0.02 \)) and rehospitalization (23% versus 14%; HR, 1.5; 95% CI, 0.78 to 3.0; \( P = 0.08 \)) were higher in patients without than with thienopyridine therapy. The study highlights the importance of simple measures to improve compliance such as careful counseling, patient cards with information on the duration and purpose of dual antiplatelet therapy, cardiac rehabilitation programs, attention to economic issues, and the avoidance of DES in noncompliant patients.

The optimal duration of dual antiplatelet therapy after DES implantation is not well established. Prolonged use of thienopyridines (9 to 12 months) has already been shown to be beneficial in reducing ischemic cardiovascular events in patients undergoing PCI with BMS and in patients with acute coronary syndromes and has been advocated as a class I indication in patients undergoing PCI not at increased risk of bleeding in American Heart Association/American College of Cardiology guidelines. The impact of thienopyridine treatment on long-term outcome after DES implantation has been examined in a single-center observational study of 4666 patients (3165 BMS patients, 1501 DES patients). Using landmark analyses of patients event free at 6 and 12 months, the investigators assessed the risk of death, MI, and the composite of death or MI at 2 years of follow-up stratified to stent type and self-reported thienopyridine intake at that point in time. Although thienopyridine use inferred no advantage in the 2-year risk of death (3.7% versus 4.5%; \( P = 0.50 \)) and death or MI (5.5% versus 6.0%; \( P = 0.70 \)) among BMS patients event free at 6 months, it significantly predicted lower adjusted rates of death (2.0% versus 5.3%; \( P = 0.03 \)) and death or MI (3.1% versus 7.2%; \( P = 0.02 \)) in DES patients. This pattern was maintained for patients who were event free and on or off thienopyridine at 12 months, suggesting an important prognostic benefit of clopidogrel treatment up to 1 year after DES implantation. Importantly, the risk of death or MI was lower in DES compared with BMS patients with thienopyridine use and was similar in DES compared with BMS patients without thienopyridine use at 6 and 12 months, confirming the absence of a negative effect of DES on overall prognosis. Therefore, it appears reasonable to maintain patients treated with (first-generation) DES for \( \geq 1 \) year on dual antiplatelet therapy if they tolerate it and are at low risk of bleeding. Whether prolonged dual antiplatelet therapy prevents late and very late ST after DES implantation, is associated with a lower rate of ischemic cardiovascular events, and has a favorable net clinical benefit requires confirmation in randomized, prospective trials. This appears particularly important because of the small but increased risk of bleeding observed with prolonged administration of dual antiplatelet therapy.

Adherence to a 12-month regimen of dual antiplatelet therapy after DES implantation has been endorsed by a recent science advisory report and by a clinical alert issued by the Society of Cardiac Angiography and Interventions. The former document also recommends deferring elective surgical procedures with significant risk of bleeding by at least 12 months after DES implantation, and surgeons are advised not to automatically discontinue antiplatelet therapy but rather to consult with the patient’s cardiologist.

Patient and Lesion Selection

Selection of patients suitable for DES implantation is another measure to reduce the risk of ST. Patients at increased risk of bleeding, those scheduled for elective surgery, patients with gastrointestinal disorders preventing absorption of thienopyridines, those requiring oral anticoagulation, patients with unexplained thrombocytopenia or established allergy to thienopyridines, and all those in whom compliance with extended dual antiplatelet therapy cannot be ensured should not receive DES and perhaps not be stented at all if an acceptable balloon angioplasty result is attained.

The need for surgical procedures may arise after recent DES implantation. Surgery poses a risk to patients with coronary artery disease in general but particularly to those who underwent stent implantation as a result of antiplatelet therapy withdrawal, increased platelet aggregation, and decreased fibrinolysis in the perioperative period. In a study of 103 stent patients undergoing noncardiac surgery, an alarming 5% mortality rate and 45% complication rate were noted. It should be determined whether the surgical procedure can be postponed beyond 12 months after stenting or whether dual antiplatelet therapy can be maintained throughout the perioperative period. If the risk of bleeding is judged to be unacceptably high, clopidogrel should be discontinued for \( \leq 5 \) days before the procedure and should be resumed within 48 hours with no interruption in aspirin (81 to 100 mg/d). No evidence exists that the addition of heparin or glycoprotein IIb/IIIa inhibitors is useful for preventing ischemic events in the perioperative period.

The risk-to-benefit ratio of PCI depends on the each individual patient. The benefit of DES is related largely to the more powerful inhibition of neointimal hyperplasia, which is of particular importance in smaller vessels less able to accommodate neointimal in-growth. A small randomized trial (500 patients) comparing SES with thin-strut BMS showed similar rates of binary restenosis (SES, 10% versus BMS, 13%; \( P = 0.52 \)) in vessels with a reference vessel diameter \( \geq 2.8 \) mm (mean reference vessel diameter, 3.1 mm). Similarly, a stratified subgroup analysis of a trial suggested a benefit of DES in terms of cardiac death, MI, and repeat revascularization in small vessels (stent diameter <3.0 mm) but the potential of harm in larger vessels. Accordingly, BMS remain a valuable alternative to DES in large vessels with discrete lesions. A step further, balloon angioplasty remains a valid option in selected patients. A meta-analysis comparing BMS with balloon angioplasty has shown similar outcomes in terms of death or MI (odds ratio, 0.90; 95% CI, 0.72 to 1.11), and the benefit in reducing repeat revascularization in favor of BMS from 16% to 4% was all but
exhausted with provisional stenting in 20% to 40% of cases.\(^6\) After balloon angioplasty, late thrombosis is not an issue, and thus thienopyridine therapy is of less importance; therefore, balloon angioplasty with provisional stenting should be the strategy of choice in patients requiring surgery in the near future or who are at high risk of bleeding.

**Technique**

Attention to technical details also may improve results when PCI is performed with DES. Because both the number of stents\(^27\) and stent length enhance the risk of ST, refraining from excessive overall stent length and from stent overlap is judicious. Moreover, proper deployment of the DES with care taken to fully expand it over its entire length, particularly in calcified lesions, should be ensured, and residual dissections should be avoided. For example, because using the multistent crush technique to treat bifurcations results in considerable stent overlap and has been associated with an excess risk of ST,\(^83\) provisional side-branch stenting appears preferable.\(^83\) Although DES compared with BMS have shown no excess risk when implanted in the setting of acute MI,\(^84,85\) the benefit of DES in this setting requires further study. The observation period is limited to 1 year so far; affected vessels are on average larger than in patients with stable coronary artery disease; and the viability of the underlying myocardium is reduced. This curtails the therapeutic potential of DES or BMS in patients with acute MI but also reduces the risk in case of ST.

**Future Developments**

The problem of very late ST may not apply less to second- or later-generation DES.\(^86\) Limited follow-up duration in low-risk patients precludes firm conclusions at this time. Because durable polymers used in first-generation DES are suspected to be responsible for some of the observed pathological changes, efforts concentrate on drug release via biodegradable polymers with reduced surface area through the use of reservoirs or coating of the abluminal surface only\(^87,88\) and on polymer-free drug release.\(^89\) However, the fact that early ST appears slightly lower in DES compared with BMS in randomized trials using identical patient management for both may be a hint that polymers protect from thrombosis during the phase when all stents are fully exposed to blood. Another approach banks on drugs with improved healing properties such as antibodies capturing CD34-positive endothelial progenitor cells\(^90\) or antithrombotic substances\(^32\) applied to the stent surface. Fully biodegradable stents based on polyactic acid or magnesium compounds are in clinical evaluation. Finally, stent coatings with improved biocompatibility such as titanium–nitride oxide have been shown to be more effective than conventional BMS in reducing restenosis and repeat revascularization, with in-stent late luminal loss (0.55±0.63 mm) comparable to that of zotarolimus-eluting stents (0.61±0.46 mm).\(^91\)

**Conclusions**

ST is a serious adverse event after PCI, resulting in abrupt closure with risk of MI and death. Although early ST and late ST occur with similar frequency after BMS or DES and outnumber very late ST by far, very late ST has emerged as a distinct clinical entity more germane to (at least the first-generation) DES than BMS. Delayed healing and impaired endothelialization induced by the drug-polymer combination are the prevailing mechanisms of late and very late ST. Immediate reperfusion, preferably by primary PCI, is the therapy of choice. Preventive measures such as careful attention to implantation details, uninterrupted dual antiplatelet therapy for ≥12 months, and alternative revascularization strategies in selected patients may curb this adverse event.

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