Coronary stent thrombosis: incidence, predictors and triggering mechanisms

Annually, millions of patients with obstructive coronary artery disease are treated worldwide with a coronary stent. As a result, coronary stent-related complications, even when occurring at a relatively low rate, have a major impact on total mortality and hospital stay. The most dreadful complication after coronary stenting is the abrupt thrombotic closure of the implanted stent: stent thrombosis (ST). Although several studies have already identified clinical, angiographic and procedural determinants of ST, a considerable group of patients develop ST in the absence or paucity of these risk factors. The pathophysiology of ST is generally considered as a culmination of several distinct, but often overlapping candidate pathological pathways including alterations involved in endothelial function, inflammation, platelet function and the hemostatic system. This review covers recent advances in this field of research and discusses the incidence, prognosis, correlates and triggering mechanisms of coronary ST.

**Incidence of coronary ST**

Despite being a relatively infrequent problem, ST has a major clinical impact because it results in life-endangering conditions such as myocardial infarction (in approximately 80%) and cardiac death (in up to 40% of cases) [10]. It is important to note that the risk of ST is directly related to the clinical presentation of the patient preceding stenting (the index PCI). For example, patients presenting with a STEMI have a fourfold increased risk for ST compared with patients undergoing coronary stent implantation for stable angina symptoms [6,18].

At present, it is fairly impossible to establish the true incidence of ST since an angiographic or pathologic confirmation is necessary to fulfill the ARC-criteria of definite ST. Nonetheless, large ‘real world’ and all-comer registries provide at least some insights into incidence rates of ST.

**Coronary ST: definitions**

The true impact and incidence of ST has been unknown for at least three decades because its definition varied widely among randomized clinical trials and observational registries. Therefore, to allow consistency and a fair comparison across studies and registries, a new uniform definition of ST was proposed by the Academic Research Consortium (ARC) in 2007 [17].

In the ARC criteria, ST is classified according to 1) the elapsed time between index PCI and the ST and 2) the likelihood for its presence. Timing is categorized in four categories (Table 1). In parallel, the level of evidence is divided into three categories relating to varying degrees of certainty: possible, probable and definite ST.

**KEYWORDS:** coronary stent thrombosis, risk factors, triggering mechanisms, high on-treatment platelet reactivity
ST. In the large all-comer cohort of the Dutch Stent Thrombosis Registry (n = 21,009), the reported incidence of ST was 2.1% (number of cases: n = 437) after a median follow-up of 30.9 months [6,18,19]. Similarly, in the Spanish ESTROFA registry (n = 23,500), the reported incidence of ST was 2% (number of cases: n = 301) after a median follow-up of 22 months [13].

In the Bern-Rotterdam registry, definite ST occurred in 192 of 8146 patients (treated with either a sirolimus-eluting stent [n = 3823] or a paclitaxel-eluting stent [n = 4323]) with an incidence density of 1/100 patient-years and a cumulative incidence of 3.3% at 4 years [20].

Multiple studies and registries have shown that the incidence rates of early ST are quite similar between bare-metal stents and drug-eluting stents [21]. For late and very late ST, however, the incidence appears to be slightly higher for DES as compared with BMS. And more importantly, the phenomenon of late and very late ST may be less frequent in second-generation DES and tends to be more frequent with paclitaxel-eluting stents than with sirolimus-eluting stents [22–25].

The observational SCAAR registry reported the incidence of ST in patients treated with multiple types of stents. A total of 73,798 stents from 47,197 procedures and 42,150 patients were included [22]. During a follow-up period of 3 years, the risk of ST was lower in DES as compared with BMS with an adjusted risk ratio of 0.79; (99% CI: 0.63–0.99). However, after 6 months of follow-up, the risk for ST was higher in DES compared with BMS with an adjusted risk ratio of 2.02 (99% CI: 1.30–3.14). Likewise, the Western Denmark Heart Registry confirmed this SCAAR ‘real world’ observation that very late definite STs were significantly increased in DES patients, in particular with paclitaxel-eluting stents [23].

The reported incidence of late and very late ST in second-generation DES, such as zotarolimus-eluting (Endeavor®) and everolimus-eluting stents (Xience V®) is very low, although ‘real world’ all-comer registries with a follow-up beyond a 2 year timeframe are limited [24–26].
Table 2. Incidence and predictions of stent thrombosis reported in large ‘real world’ cohorts.

<table>
<thead>
<tr>
<th>Study/registry name</th>
<th>Stent type</th>
<th>Patient no.</th>
<th>Follow-up</th>
<th>ST incidence (%) [n]</th>
<th>Early ST (%)</th>
<th>Late ST (%)</th>
<th>Very late ST (%)</th>
<th>Identified risk factors for early ST</th>
<th>Identified risk factors for late ST</th>
<th>Identified risk factors for entire group of ST</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESTROFA</td>
<td>100% DES (PES 63% and SES 37%)</td>
<td>23,500</td>
<td>22 months</td>
<td>2.0 (301)</td>
<td>49.5</td>
<td>30.0</td>
<td>20.5</td>
<td>ACS, STEMI, renal insufficiency, DM, long stent length, LAD artery stenting</td>
<td>STEMI, long stent length, early clopidogrel discontinuation</td>
<td>NA</td>
<td>[13]</td>
</tr>
<tr>
<td>Dutch Stent Thrombosis Registry</td>
<td>BMS 64% and DES 36%</td>
<td>21,009</td>
<td>30.9 months</td>
<td>2.1 (437)</td>
<td>73.2</td>
<td>13.3</td>
<td>13.5</td>
<td>Early clopidogrel discontinuation, undersizing, dissection, TIMI-flow &lt;3, CAD &gt;50% proximal of culprit, malignancy, no ASA, LVEF &lt;30%, bifurcation, CAD &gt;50% distal of culprit, any DES, total number of stents, no GP IIb/IIIa therapy</td>
<td>Early clopidogrel discontinuation, undersizing, malignancy, CAD &gt;50% proximal of culprit, TIMI flow post-PCI &lt;3, dissection, bifurcation stenting, LVEF &lt;30%, PAD, CAD &gt;50% distal of culprit, no ASA, any DES, DM, young age</td>
<td>Early clopidogrel discontinuation, malignancy, CAD &gt;50% proximal of culprit, TIMI flow post-PCI &lt;3, dissection, bifurcation stenting, LVEF &lt;30%, PAD, CAD &gt;50% distal of culprit, no ASA, any DES, DM, young age</td>
<td>[6]</td>
</tr>
<tr>
<td>Bern-Rotterdam cohort</td>
<td>100% DES (PES 53% and SES 47%)</td>
<td>8146</td>
<td>3 years</td>
<td>2.9 (152)</td>
<td>59</td>
<td>17</td>
<td>24</td>
<td>Hypertension, ACS, bifurcation stenting</td>
<td>Family history of CAD</td>
<td>ACS, diabetes</td>
<td>[9]</td>
</tr>
<tr>
<td>Kuchulakanti et al.</td>
<td>100% DES (SES 72% and PES 28%)</td>
<td>2974</td>
<td>6 months</td>
<td>1.3 (38)</td>
<td>79</td>
<td>21</td>
<td>NA</td>
<td>Early clopidogrel discontinuation, renal insufficiency, bifurcation stenting, in-stent restenosis</td>
<td>Early clopidogrel discontinuation, renal insufficiency, bifurcation stenting, in-stent restenosis</td>
<td>Early clopidogrel discontinuation, renal insufficiency, bifurcation stenting, in-stent restenosis</td>
<td>[11]</td>
</tr>
<tr>
<td>Iakovou et al.</td>
<td>100% DES (SES 48% and PES 52%)</td>
<td>2229</td>
<td>9 months</td>
<td>1.3 (29)</td>
<td>48</td>
<td>52</td>
<td>NA</td>
<td>Early clopidogrel discontinuation, renal insufficiency, bifurcation stenting, DM, reduced LVEF, long stent length</td>
<td>Early clopidogrel discontinuation, bifurcation stenting, reduced LVEF</td>
<td>Early clopidogrel discontinuation, renal insufficiency, bifurcation stenting, DM, reduced LVEF</td>
<td>[10]</td>
</tr>
<tr>
<td>Airoldi et al.</td>
<td>100% DES (SES 53%, PES 47%)</td>
<td>3021</td>
<td>18 months</td>
<td>1.9 (58)</td>
<td>47</td>
<td>37</td>
<td>11</td>
<td>Early clopidogrel discontinuation, renal insufficiency, bifurcation stenting, DM, reduced LVEF, long stent length</td>
<td>Early clopidogrel discontinuation with First 6 months, prior brachytherapy, LVEF &lt;30%, long stent length, small diameter stents</td>
<td>Early clopidogrel discontinuation with First 6 months, prior brachytherapy, LVEF &lt;30%, long stent length, small diameter stents</td>
<td>[55]</td>
</tr>
<tr>
<td>Park et al.</td>
<td>100% DES (SES 81%, PES 19%)</td>
<td>1911</td>
<td>19.4 months</td>
<td>0.8 (15)</td>
<td>25</td>
<td>75</td>
<td>NA</td>
<td>STEMI</td>
<td>Early clopidogrel discontinuation, renal insufficiency</td>
<td>Early clopidogrel discontinuation, STEMI, long stent length</td>
<td>Early clopidogrel discontinuation, STEMI, long stent length</td>
</tr>
</tbody>
</table>

ACS: Acute coronary syndrome; ASA: Acetyl salicylic acid; BMS: Bare-metal stent; CAD: Coronary artery disease; DES: Drug-eluting stent; DM: Diabetes mellitus; LAD: left anterior descending; LVEF: Left ventricular ejection fraction; PAD: Peripheral artery disease; PCI: Percutaneous coronary intervention; PES: Paclitaxel-eluting stent; SES: Serolimus-eluting stent; ST: ST-elevation myocardial infarction; TIMI: Thrombolysis in myocardial infarction.
Box 1. Commonly recognized risk factors for coronary stent thrombosis.

**Clinical factors**
- Young age
- Diabetes mellitus
- Renal failure
- Malignancy
- Cocaine use
- Low ejection fraction (<30%)
- Prior brachytherapy
- Black race
- Elevated C-reactive protein levels
- Acute coronary syndrome at presentation
- Absence of glycoprotein IIb/IIIa inhibitor treatment
- Premature discontinuation of antiplatelet therapy
- CYP2C19 slow and poor metabolizers
- High on-treatment platelet reactivity despite dual antiplatelet therapy with aspirin and clopidogrel

**Angiographic factors**
- Multivessel disease
- Small caliber of the coronary arteries
- High thrombotic burden

**Procedural factors**
- Undersizing of the stent or improper opposition of the stent
- Slow intracoronary flow post-PCI
- Bifurcation stenting
- Overlapping stents
- Polymer materials of first-generation DES
- Use of selfexpanding or coil stents
- Long total stent length
- Restenotic lesion
- Bypass lesion grafts
- Lack of intravascular ultrasound guidance
- Nonionic contrast medium
- Dissection
- CAD >50% proximal of culprit lesion

**Early versus late coronary ST**
Although early and (very) late ST share several common risk factors, the impact of these factors vary substantially. In particular, the pre-dominance of mechanical and anatomic factors underlying early ST has been commonly recognized for decades. Furthermore, a very important nonmechanical cause of ST occurring within the first 6 months after the index PCI is premature cessation of clopidogrel therapy, which is associated with hazard ratios up to 90 [6,10–13].

However, ST can also occur with appropriate use of dual antiplatelet therapy. A recent novel observation is the strong relationship between a high on-treatment platelet reactivity status and the occurrence of early ST [28–32].

Late ST might be less strongly related to mechanical factors, although acquired malapposition has been reported. Moreover, the influence of clopidogrel cessation on late and very late ST is less clear. The exact pathophysiological mechanisms underlying late ST are not completely understood, but the following morphologic substrates have been identified and associated with late and very late ST [34–40]:
- Incomplete and delayed re-endothelialization with persistent fibrin deposition due to the cytotoxic or cytostatic drugs used in DES;
- Sirolimus- and paclitaxel-induced expression of endothelial tissue factor;
- Delayed-hypersensitivity reactions to the durable polymer of DES;
- Diffuse in-stent restenosis with thrombosis;
- Late malapposition due to a chronic inflammatory process and vascular remodeling;
- Stent fracture;
- In-stent neoatherosclerosis with plaque rupture.

Although these observations might be biased by the fact that they are derived from anecdotal case reports and autopsy studies, recent studies using intravascular imaging technologies (such as intravascular ultrasound and optical coherence tomography studies) and histopathologic findings from thrombi obtained with aspiration catheters point in the same direction [40].

**Importance of adequate concomitant antithrombotic therapy**
The occurrence of ST after DES implantation has focused attention on the adequacy of the current dual antiplatelet regimen of aspirin and clopidogrel. Multiple antithrombotic strategies have been evaluated for their ability to minimize the incidence ST without increasing the risk for bleeding complications. At present, current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend the use of dual-antiplatelet therapy (aspirin and a thienopyridine) for all patients undergoing coronary stenting, although the optimal duration of this therapy, in particular after DES implantation, remains unclear. In view of this, a recently published analysis did not demonstrate any significant benefit associated with prolonged continuation of dual antiplatelet therapy as compared with the guideline-recommended clopidogrel duration of 12 months, although its sample size had limited power to detect a possible difference [41]. The cumulative
incidence of definite ST at 24 months after DES implantation was similar between the two groups (0.4 vs 0.4%; p = 0.76). Ongoing trials such as the Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy (ARCTIC, NCT00827411), the Dual Antiplatelet Therapy Trial (DAFT, NCT00977938) and the Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE, NCT00661206), are adequately powered to assess the optimal duration of dual-antiplatelet therapy after DES implantation.

It is also important to note that novel P2Y12 inhibitors with a stronger and more predictable pharmacodynamic response (such as prasugrel and ticagrelor) have been shown to reduce the incidence of early ST drastically as compared with clopidogrel [42,43].

High on-treatment platelet reactivity

In recent years, it has become clear that the standard ‘one-size-fits-all’ dosing regimen of dual-antiplatelet therapy is not adequate in a substantial group of patients. Consistent findings across multiple investigations have shown heterogeneity in individual patient responses to antiplatelet therapy resulting in hyper-responsiveness at one end of the spectrum with a subsequent increase in bleeding complications, and hyporesponsiveness at the other end of the spectrum with a subsequent increase in atherothrombotic events [44,45]. As of yet, multiple observational studies using various techniques, different platelet agonists and definitions have demonstrated the predictive value of platelet function testing prior to coronary stenting to identify individuals who exhibit a ‘high on-treatment platelet reactivity state’, and these individuals are at increased risk for coronary ST.

The mechanisms leading to a heightened on-treatment platelet reactivity status are not fully understood and are likely multifactorial. Accelerated platelet turnover, unpredictable active metabolite generation, up- and down-regulation of the platelet-receptor pathways, genetic polymorphisms, increased baseline platelet reactivity, poor compliance and drug–drug interactions, are among the multiple factors that have shown a significant effect [46]. A recent consensus document reports that several platelet function tests including the Multiplate® system (Dynabyte), the VerifyNow® system (Accumetrics), the flowcytometric vasodilator-stimulated-phosphoprotein assay (Biocytex, Marseille, France) and ‘classical’ light transmittance aggregometry, are capable of identifying patients at risk [45]. Of even more importance, the results of these tests have shown a clear relationship with the occurrence of atherothrombotic events, including ST.

Thus, high on-treatment platelet reactivity has emerged as an important risk factor for ST, in particular early ST. The possible role of high on-treatment platelet reactivity in the pathophysiology of late and very late ST needs to be explored in sufficiently powered studies.

Triggering mechanisms of coronary ST

Despite the long list of ‘chronic’ risk factors for ST, the mechanisms underlying the actual moment of onset of ST are less well-established. An individual’s susceptibility to coronary ST is complex with many interrelations among endothelium, the naked stent struts, the blood (rheology, platelet reactivity, clotting factors and inflammatory cells), the myocardium and various endogenous triggering processes that can change from minute to minute. Unlike the ‘chronic’ risk factors of ST, acute risk factors – or triggering factors – act within a short time frame and are often a consequence of a disturbance in the balance of the autonomic nervous system (sympathic versus parasympathic). A sympathetic trigger pattern (as a result of exertion or emotional stress) is characterized by increased blood and pulse pressures, a higher vascular tone (that can promote vasoconstrictive forces) and a relative prothrombotic state (increased platelet aggregability and decreased fibrinolysis) [47].

Recognition of the circadian variation in acute atherothrombotic events with a peak incidence between 6:00 am and noon has set the stage for the whole concept of triggering factors. The physiological changes early in the day produce a surge of typical sympathetic triggering patterns and cause a well-documented excess of approximately 30% of morning myocardial infarctions [48].

In the last two decades, several triggering factors have been identified in the setting of myocardial infarction, including heavy physical activity, emotional stress, eating, exposure to severe weather conditions, sexual intercourse, coffee and alcohol consumption and cocaine or marijuana use, and it is now accepted
that triggering factors precede nearly half of myocardial infarction onsets [49,50].

Given the similarities in several pathophysiological pathways between ST and myocardial infarction, it could be expected that at least some of the reported triggering mechanisms preceding myocardial infarction might also account for coronary ST.

Thus far, three observational studies have examined whether the onset of ST varies in a circadian manner and all studies confirm the similar pattern as seen in acute myocardial infarction: coronary ST occurs more often in the early morning hours between 06:00 am and noon [51–53].

Only one observational study has identified the triggering role of vigorous physical exercise, emotional stress and infection preceding coronary ST [54]. In this substudy of the Dutch Stent Thrombosis Registry, all patients who suffered a ST were intensively interviewed using standardized questionnaires about the conditions and activities in the time frame preceding the ST. Patients were asked whether they had performed any physical activity in the 2 h preceding the ST or had suffered a life event (emotional stress) in the 2 weeks preceding the ST. The degree of physical activity intensity was quantified by the Compendium of Physical Activities, a coding scheme that classifies physical activity by rate of energy expenditure. To objectify the impact of emotional stress, the Social Readjustment Rating Scale by Holmes and Rahe was used. To search for the presence of an infection, all medical records were checked and laboratory charts were screened for parameters indicative for an infection, including positive cultures, antibiotics use, C-reactive protein, blood sedimentation rate, leukocyte count and leukocyte differentiation.

A surprisingly high percentage (vigorous physical exercise 5%; emotional stress 11%; infection 10.5%) of interviewed patients reported a trigger. Moreover, analysis of the categories of ST revealed a higher prevalence of triggers with an increasing time interval between index PCI and ST. Interestingly, the prevalence of the studied triggering mechanisms was the highest (42%) in the group of patients presenting with a very late ST.

**Conclusion**

Coronary ST is a serious and potential life-threatening complication after coronary stenting. Therefore, every possible effort should be directed to identify those patients at highest risk for ST. Risk factors associated with ST can be categorized as clinical-, angiographic- and procedural-related. Moreover, noncompliance and nonresponsiveness to the prescribed dual antiplatelet therapy are factors that also play a major role. Understanding of these important risk factors may aid in better prevention.

**Future perspective**

At present, approximately 3 million PCI procedures per year are performed worldwide and it is expected that this number will be doubled by the year 2020.

Given these huge numbers of PCI-procedures, any reduction in complication rates will have a tremendous clinical impact, in particular when such a complication results in substantial morbidity, mortality and prolonged hospital stay, as is the case for coronary ST.

In the last few years, improvements in interventional techniques and adjuvant-combined antithrombotic therapy have further reduced the incidence of ST, and given the wealth in the pipelines of both the pharmaceutical and device companies, it is hoped and expected that the ST rate will decline further. However, despite these remarkable steps of progress, specific issues require study in greater detail. First, the role of triggering mechanisms preceding ST are insufficiently studied and great efforts should be directed to this novel field of research, preferably in parallel with information on platelet inhibition status, coagulation status and other ‘chronic’ risk factors. Second, no matter what level of evidence is required, it will be necessary to develop simple clinical algorithms to aid physicians in their interpretation and use of platelet function testing in the cathlab. The issue of personalized antiplatelet therapy on the basis of platelet function testing is important and worthy of effort and further study, and the cardiology community eagerly awaits the results of ongoing clinical trials.

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**Executive summary**

- Coronary stent thrombosis (ST) is the most dreadful complication after coronary stenting impact because it results in life-endangering conditions such as myocardial infarction (in approximately 80%) and cardiac death (in up to 40% of cases).
- Incidence varies between 1 and 5%, dependent on clinical presentation of the patient preceding stenting (the index percutaneous coronary interventions).
- ST is classified according to the elapsed time between index percutaneous coronary interventions, the occurrence of ST (acute/subacute/late and very late) and the level of evidence for its presence (definite, probable and possible).
- Risk factors associated with ST can be categorized as clinical-, angiographic- and procedural-related.
- Noncompliance to antiplatelet drugs is the strongest predictor.
- A high on-treatment platelet reactivity status is also associated with ST.
- The onset of ST varies in a circadian manner with peak incidence between 06:00 am and noon.
- Triggering mechanisms such as vigorous exercise, emotional stress and infection are likely to play a superimposing role.

**Bibliography**

Papers of special note have been highlighted as:

- of interest
- of considerable interest

Case–control study demonstrating a relatively high prevalence of high on-treatment platelet reactivity in patients with a history of coronary stent thrombosis.


