REVIEW

Stent thrombosis in 2008: Definition, predictors, prognosis and treatment

La thrombose de stent en 2008 : définition, facteurs prédictifs, pronostic et traitement

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Summary
Stent thrombosis remains a major pitfall of stent implantation in contemporary percutaneous coronary intervention, leading to high rates of death and nonfatal myocardial infarction (MI). Recently, the emergence of drug-eluting stents (DES) has raised concerns regarding the occurrence of late and very late stent thrombosis. Last year, a standardized definition of stent thrombosis was established to provide consistency in the reporting of this complication and to enable accurate and reliable data to be described for both types of stents: bare metal and drug eluting. Subsequent to the publication of this new definition, many updated data have been reported in the literature. On the other hand, antiplatelet therapy response variability is a recent concept and its real place in the pathogenesis of stent thrombosis is yet to be determined. In this article, we review the definition of and predictors for stent thrombosis focusing on DES use and variability in response to antiplatelet therapy, prognosis and treatment.

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MOTS CLÉS
Thrombose de stent ; Angioplastie coronaire

Résumé
La thrombose de stent reste aujourd’hui l’une des principales complications dans le domaine de la cardiologie interventionnelle, conduisant à de nombreux décès et infarctus du myocarde non fatals. Récemment, l’émergence des stents actifs a été suivie d’une vive polémique sur un potentiel surrisque d’événements tardifs et très tardifs. L’année dernière, une définition standardisée de la thrombose de stent a été établie afin d’améliorer la description de
Stent implantation has been a great advance in percutaneous coronary intervention (PCI), decreasing the frequency of acute closure and restenosis. Stents are metallic, however, and their implantation in coronary arteries triggers platelet activation, which may lead to thrombus formation and subsequent stent thrombosis. Before the introduction of dual antiplatelet therapy, stent thrombosis was a frequent complication. The incidence of stent thrombosis after implantation of a bare-metal stent (BMS) at the beginning of the 1990s ranged from 10 to 15%[1,2]. Currently, with the new antiplatelet regimen associating aspirin and a thienopyridine, this incidence has fallen to around 1% over the first 12 months, as reported in the latest studies and meta-analyses of BMS versus drug-eluting stents (DES)[3–11]. Nevertheless, although not frequent, stent thrombosis remains a severe complication responsible for a high mortality rate (20–40%)[5,7,12–14] and morbidity, including nonfatal myocardial infarction (MI) in 70% of cases[5,7,12–14].

The emergence of DES has raised concerns regarding the occurrence of late and very late stent thrombosis related to delayed strut endothelialization and potential prothrombotic characteristics of the DES itself[15,16]. In this context, the Academic Research Consortium (ARC) definition of stent thrombosis[17] was published recently to enable consistent and reliable information to be used for both types of stents: BMS and DES. The aetiology of stent thrombosis is multifactorial and has been attributed to various clinical, biological and angiographic predictors, including low left ventricular ejection fraction (LVEF), acute coronary syndrome (ACS) and history of diabetes mellitus[18–23]. Recently, variability in responsiveness to antiplatelet therapy was identified as an important predictor in the pathogenesis of stent thrombosis. However, the ideal test to determine antiplatelet responsiveness and the value of optimal platelet inhibition has yet to be determined[24]. In addition, we are experiencing a wide variability in response with the currently approved antiplatelet therapy. The purpose of this review is to cover the definition of and predictors for stent thrombosis, focusing on DES use and variability in response to antiplatelet therapy, prognosis and treatment.

**ARC definition of stent thrombosis**

The lack of consensus on the definition of stent thrombosis among clinical trials has led to disparities in reports of stent thrombosis and, in particular, has prevented comparison of stent thrombosis rates between studies. To address this issue, the ARC definition of stent thrombosis was established[17] and stent thrombosis was categorized according to:

- the timing after initial PCI;
- the evidence of stent thrombosis.

**Timing of stent thrombosis**

Stent thrombosis is considered as acute when occurring between 0 and 24h after stent implantation, subacute between 24h and 30 days, late between 30 days and 1 year, and very late after 1 year. Acute or subacute stent thrombosis can also be replaced by the term early stent thrombosis.

**Definite stent thrombosis**

The presence of an angiographic confirmation of stent thrombosis (the presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent) is associated with the presence of at least one of the following criteria within a 48-hour window: acute onset of ischaemic symptoms at rest, new ischaemic electrocardiographic changes that suggest acute ischaemia or typical rise and fall in cardiac biomarkers; or in the presence of a pathological confirmation of stent thrombosis (evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy). The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

**Probable stent thrombosis**

Probable stent thrombosis is defined as the presence of any unexplained death within the first 30 days after stent implantation, or in the presence of any MI related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause, irrespective of the time after the index procedure.

**Possible stent thrombosis**

Possible stent thrombosis is defined as any unexplained death from 30 days after intracoronary stenting until the end of follow-up.
Incidence of stent thrombosis

Since September 2006 (European Society of Cardiology, World Congress of Cardiology in Barcelona) and the controversy about DES use and the risk of late events, much ink has flowed, yet no clear-cut conclusion can currently be drawn on the potential increased risk of very late stent thrombosis with DES. Indeed, if results for early stent thrombosis seem relatively clear and show no difference between DES and BMS, results for late and very late stent thrombosis are more debated. Moreover, we have to keep in mind that the time of dual antiplatelet therapy is usually longer for DES than for BMS.

Early stent thrombosis

Early definite stent thrombosis was a common complication following BMS implantation in the early 1990s and before the introduction of combined antiplatelet therapy—with an incidence ranging from 10—15% [1,2]. The advent of new antiplatelet regimens that combined aspirin and thienopyridine has greatly decreased the incidence of stent thrombosis to around 1% in the latest studies and meta-analyses [3—11]. To date, no difference has been found between DES and BMS in terms of early stent thrombosis [4,8,9,25,26]; and as for BMS, the rate of early stent thrombosis after DES implantation is approximately 1% (Fig. 1).

Late stent thrombosis

According to recent studies and meta-analyses, the incidence of late stent thrombosis seems to be similar for DES and BMS, at around 0.5% [4,8,11,25,26]. The cumulative event rates for both types of stents are consequently around 1.5% (Fig. 2). Nevertheless, the duration of use of dual antiplatelet therapy was usually longer for DES compared with BMS in these studies (3 or 6 months versus 1 month), thus making conclusions more difficult. At 1 year, Spaulding et al. [8]—in their meta-analysis of the four Cypher trials (RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS), including 1748 patients and using the ARC definition of stent thrombosis—reported a cumulative rate of stent thrombosis of 0.8% for BMS versus 1.8% for sirolimus-eluting stents (SES) (p = 0.53).

By using the perprotocol definition of stent thrombosis, Stone et al. [9] reported in their meta-analysis of nine trials (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS and TAXUS I-V), including 3513 patients, a cumulative rate of stent thrombosis of 0.6% for BMS versus 1.2% for SES (p = 0.2) and 0.9% for BMS versus 1.3% for paclitaxel-eluting stents (PES) (p = 0.3). By using the ARC definition of stent thrombosis, Mauri et al. [6], in their meta-analysis of the same nine trials, reported a cumulative rate of late stent thrombosis of 1.7% for BMS versus 1.5% for SES (p = 0.7) and 1.4% for BMS versus 1.8% for PES (p = 0.52). Jensen et al. [27], in their registry of 12,395 patients, reported a cumulative rate of stent thrombosis of 2% for BMS versus 1.6% for DES (p = 0.5) and 1.4% for BMS versus 1.8% for PES (p = 0.52). To finish, in their meta-analysis of 38 trials Stettler et al. found that stent type was not a predictor of late stent thrombosis [28]. Indeed, using the ARC definition, they reported an incidence of stent thrombosis of 1% for BMS, 1.1% for PES and 1.1% for SES (p = 0.62).

Very late stent thrombosis

The incidence of very late stent thrombosis is, today, still poorly described and authors disagree about the potential...
increased risk of very late stent thrombosis after DES implantation. Several authors have reported an incidence of very late stent thrombosis between 0.4 and 0.6% per year after DES implantation [8,11,29]. Few data are available on the rate of very late stent thrombosis after BMS implantation. Considering the results presented by Gruberg et al. at the Transcatheter Cardiovascular Therapeutics (TCT) congress in 2006, the incidence of very late stent thrombosis seems to be higher for DES than for BMS: 0.6% per year versus 0.2% per year, respectively. Moreover, Stettler et al. [28] reported in their meta-analysis of 38 trials including 18,023 patients that even if the rates of death are similar for BMS, SES and PES, the rate of very late stent thrombosis is significantly higher in the PES group. Consequently, according to these meta-analyses, it seems that DES increase moderately but significantly the risk of very late stent thrombosis.

Predictors of stent thrombosis

Predictors of stent thrombosis are usually classified into three groups:

- those related to the patient;
- those linked to the treated lesion;
- those associated with the PCI procedure (Fig. 3).

The occurrence of stent thrombosis is related usually to the association of multiple factors.

Clinical correlates of stent thrombosis

Many predictors have been identified for stent thrombosis such as ACS presentation [12,14,22,30–33], LVEF [14,19,22,33–35], diabetes mellitus [5,19,21,33,36], renal failure [19,22,33], discontinuation of antiplatelet therapy [5,19,22,37], lesion length and diameter [12,22,34,38], preprocedural minimal luminal diameter (MLD) and percentage stenosis [12,22,34,38], lesion severity (type C lesion) [14,39], bifurcation lesion [5,19], total stent length [12,19,22,33], maximum balloon diameter [14,30,35], postprocedural MLD and residual stenosis diameter [12,19,34–36,39], total number of stents implanted and number of stents per lesion [19,22,34,35], stent underexpansion and/or malapposition [18,23,38], postprocedural thrombolysis in myocardial infarction (TIMI) flow and residual thrombus [12,14,18,34,35], residual dissection [12,14,18,23,34,35] and use of brachytherapy [19].

Except for some mechanical factors, especially the presence of residual dissection and use of brachytherapy, predictors of early stent thrombosis and late stent thrombosis are quite similar (Table 1). As mentioned above, DES use (together with longer duration of dual antiplatelet therapy compared to that for BMS) does not increase the incidence of late stent thrombosis but seems to increase moderately the risk of very late stent thrombosis.

In order to estimate the hazard ratios (HR) and identify predictors of stent thrombosis with higher HR, we reviewed articles in the literature that reported HR values and their variances for predictors of stent thrombosis. Data sources were obtained by conducting a computerized literature search of the MEDLINE database using the words “stent thrombosis”. All HR were inversely proportionally weighted by the variance of the HR. Then a mean of all reported HR was conducted. Predictors of stent thrombosis with higher HR are shown on Fig. 4.
Table 1  Predictors for early stent thrombosis versus late stent thrombosis.

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<th>Predictors of early stent thrombosis</th>
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<td>Left ventricular ejection fraction</td>
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Discontinuation of antiplatelet therapy

Today the role of antiplatelet-therapy discontinuation in terms of early stent thrombosis is well recognized and not questioned [5,19,22,37]. It is the strongest predictor of early stent thrombosis; Iakovou et al. reported a relative risk of 161.17 in this situation [19]. The current European and North American guidelines, which highlight the need for dual antiplatelet therapy during the first 4 weeks after PCI, are derived directly from those results [40]. By contrast, the real place of antiplatelet therapy discontinuation in terms of late and very late stent thromboses remains to be determined. Results of several studies seem to have identified discontinuation of antiplatelet therapy as a predictor of late stent thrombosis in case of DES use, reporting a relative risk of stent thrombosis between 24.79 and 57.13 [19,22,25]. Yet other studies have reported contradictory results and have not found any link between discontinuation of antiplatelet therapy and incidence of late or very late stent thrombosis [41]. Currently no data are available in the case of BMS use.

Antiplatelet therapy low response: a new concept

Antiplatelet therapy resistance is a new concept and its definition remains unclear because of frequent confusion between biological resistance and clinical resistance, which are potentially connected. With regard to biological resistance (failed platelet inhibition), several studies have shown a large interindividual variability in biological response to antiplatelet therapy (either aspirin [24,42–44] or clopidogrel [42,45–48]). Many authors have consequently suggested an important role of antiplatelet therapy resistance in the incidence of cardiovascular events after PCI. Recent reviews have reported a rate of aspirin resistance between 5.5 and 43% [43,44] and a rate of clopidogrel resistance between 11 and 44% [48]. Moreover, some authors have shown recently that aspirin resistance and clopidogrel resistance are linked [42]. However, the definition of biological resistance is still confusing due to the many different biological tests used in the literature and the lack of consensus. For example, Lordkipanidze et al. [24] recently showed that the rate of aspirin resistance among patients with stable coronary artery disease (CAD) could vary between 2.8 and 59.3% according to the type of test used.

More importantly, recent studies have shown that patients with low response to antiplatelet therapy, and especially a low response to clopidogrel, were at higher risk of early cardiovascular events and suggested clinical resistance [47,49–52]. Indeed, Chen et al. [53,54] showed that aspirin resistance is associated with a higher incidence of myocardial infarction after nonurgent PCI. Matezky et al. [47] showed that clopidogrel resistance is associated with an increased risk of cardiovascular events at 6 months in patients with an acute MI; while Price et al. [55] demonstrated similar results in patients undergoing PCI with DES implantation. Several authors have already suggested the role of antiplatelet low response in terms of the incidence of stent thrombosis. Wenaweser et al. [56] showed that 52% of patients presenting with stent thrombosis have a combined resistance to aspirin and clopidogrel versus 38% of control patients with stable CAD. Barragan et al. [57] found similar results and reported that 63% of patients presenting with stent thrombosis have a resistance to clopidogrel versus 40% of control patients with stable CAD. Additionally, some authors have recently shown that patients with glycoprotein (GP) IIb/IIIa receptor polymorphism PlA2 are more frequently resistant to aspirin [32,46] and that this polymorphism is also a predictor for stent thrombosis (with a relative risk of 5.26) [58]. On the other hand, the recent TRITON TIMI-38 substudy
demonstrated that a greater platelet aggregation inhibition as obtained by prasugrel compared to clopidogrel standard therapy significantly decreases the rate of stent thrombosis [59].

Histopathological correlates of late stent thrombosis

Some authors have reported pathological findings for late stent thrombosis. In addition to the often evoked delayed strut endothelialization [15,16], Farb et al. [60] suggested other pathological mechanisms of late and very late stent thrombosis according to autopsy data. Among the aetiologies suggested are in-stent restenosis, chronic inflammation, and atherosclerosis progression proximal or distal to the stent. Regarding in-stent restenosis, the severe narrowing caused by neointima formation might be a leading cause for clot formation and late or very late stent thrombosis. Such findings were reported in several cases. In others, coronary angiograms showed intimal dissection in the nonstented arterial edges. Coronary atherosclerosis is a diffuse disease, and the number of vulnerable thin-cap atheromas increases with the number of coronary risk factors. A plaque rupture that occurs in close proximity to the stent can extend to the adjacent stented segment and present as late stent thrombosis. Finally, Farb et al. [60] suggested that stenting of highly necrotic and inflammatory plaques might also lead to late or very late stent thrombosis.

Outcome of stent thrombosis

Patients presenting with stent thrombosis have a poor prognosis. This complication therefore remains an important issue in the current interventional cardiology practice.

Clinical presentation

Ten to 30% of patients presenting with definite stent thrombosis will die in hospital [5,7,12—14,33]. Moreover, stent thrombosis can lead to unexplained sudden deaths. This was often not considered in the past (leading to an underestimation of the real rate of death), but is now included in the new ARC definition of stent thrombosis. According to the same reviews, nonfatal acute MI is the most frequent clinical presentation of stent thrombosis (70—80% of cases) [5,7,12—14].

Late outcome

Many authors have reported the poor short-term prognosis of stent thrombosis. Indeed, Cutlip et al. [12] reported a 1-month mortality rate of 20%, while Orford et al. [39] recently found a 6-month mortality rate of 48% after definite stent thrombosis. Furthermore, this rate does not include unexplained deaths, and underestimates the real overall mortality rate. As described in the literature, currently the only predictive factors of death after definite stent thrombosis are the presence of a residual dissection after stent thrombosis treatment, a TIMI flow grade 3 after treatment of stent thrombosis, and the presence of a residual stenosis above 50% after stent thrombosis treatment [10]. Furthermore, 15—39% of patients presenting with a stent thrombosis and who are successfully treated will experience a recurrent MI within the first month [5,10,61]. These recurrent MI are most often related to recurrent stent thrombosis.

Treatment of stent thrombosis

Preventive treatment

The basis of preventive treatment for stent thrombosis is, above all, to perform the best PCI possible, including good expansion and apposition of the stent. In this context the role of intravascular ultrasound must be highlighted. Indeed, to avoid all mechanical predictors for stent thrombosis as previously described, this technique that usually allows a better stent apposition is systematically recommended by some authors [62,63]. Regarding antiplatelet therapy, the preventive treatment for early stent thrombosis is relatively well codified. However, the situation is more confusing for late and very late stent thromboses.

Preventive treatment for early stent thrombosis is based on the well-known combined antiplatelet therapy of aspirin and thienopyridine (European and North American guidelines) [40,64]. Indeed, the introduction of a thienopyridine in addition to aspirin resulted in a sharp decrease in the occurrence of stent thrombosis at the end of the 1990s [65—69]. Many studies have demonstrated effectively the benefit of the dual antiplatelet therapy aspirin + ticlodipine to begin and aspirin + clopidogrel thereafter within the first 4 weeks after a BMS implantation [65—69]. The combination of aspirin and clopidogrel is used most often because it has fewer adverse events. Since the emergence of DES, initial study results suggest that this association must be pursued for 3—6 months [6,8,9]. Guidelines currently recommend 12-month dual antiplatelet therapy after DES implantation [40]. Some authors [19,22] suggest that this association must be pursued for more than 12 months but no strong data regarding the safety and the benefit of such a prescription are currently available. Consequently, for each patient the risk/benefit balance must be analysed with caution.

Several studies have shown an additional benefit of a clopidogrel loading dose [40,51,70—75]. Currently, authors and guidelines agree that this loading dose must be 600 mg in the case of a stent implantation in the setting of an ACS [40,51]. More recently, Montalescot et al. [72] suggested that a 900 mg clopidogrel loading dose can improve early platelet inhibition. Additional studies must be performed, however, to analyse the clinical benefit of such clopidogrel loading doses. The recent TRITON TIMI-38 substudy demonstrated that a greater platelet aggregation inhibition, as obtained by prasugrel compared to standard clopidogrel therapy, significantly decreases the rate of stent thrombosis [59]. Nevertheless, a higher rate of major bleeding is still the principal limit of a systematic prasugrel prescription; this treatment, consequently, is not currently recommended for routine practice.

Curative treatment

As described above, stent thrombosis presents in most cases as an acute MI. Thus the principal objective must
be to obtain early effective reperfusion. Nevertheless, we must highlight one important point: the thrombus quality in patients with a stent thrombosis differs from that in patients presenting with a usual acute MI. Indeed, experimental studies and data from human autopsy studies [76] have shown that in the case of stent thrombosis, the thrombus is almost totally composed of platelets and contains very little fibrin. This fact leads to important conclusions. Indeed, the low rate of fibrin may explain the poor efficacy of thrombolysis to obtain effective reperfusion in this setting. Thus many authors prefer emergency PCI for treatment of stent thrombosis [77,78].

Results concerning the impact of thrombus aspiration for stent thrombosis treatment are debated in the literature. If this technique seems feasible and safe, its impact in terms of short- and long-term patient outcomes is still unknown [61,79–81]. Indeed, only two small retrospective studies (<25 patients) [61,81] have shown that thrombus aspiration permits around 90% of reperfusion success but no data are currently available on short- and long-term outcomes. Nevertheless, in the presence of a large thrombus this technique could probably help to obtain effective reperfusion. Moreover, according to the results of the TAPAS study [82], use of thrombus aspiration before stenting of the infarcted artery improves the 1-year clinical outcome after usual ST-elevation MI compared to conventional PCI. As mentioned previously, thrombus quality seems to be a good rationale for use of GP IIb/IIIa inhibitors. Some authors [10,61,78] have shown the efficacy of this treatment, with a reperfusion success rate around 90% when associated with PCI. Moreover, Wenaweser et al. [10] reported that use of GP IIb/IIIa inhibitors is the only factor associated with a decrease in recurrent stent thrombosis after a first successfully treated stent thrombosis. Although no impact on mortality was found in these studies, GP IIb/IIIa inhibitor use is associated with increased reperfusion success and decreased recurrences in the case of stent thrombosis.

The most important point is to obtain an effective reperfusion, with TIMI flow grade 3, as quickly as possible. Primary PCI must be the first choice considering the low rate of reperfusion obtained with thrombolysis. One of the remaining questions is the choice between conventional balloon angioplasty and new stent implantation. No data are available in the literature and physician experience seems to be the most important factor in this decision. Indeed, this decision is most often directly influenced by the procedure result.

Conclusion

Although rare, stent thrombosis remains a severe complication in interventional cardiology, leading to high rates of death and nonfatal MI. Many predictors have today been identified in the literature; discontinuation of antiplatelet therapy seems to be one of the stronger predictors for stent thrombosis, at least during the first year. To date, the optimal duration of dual antiplatelet therapy remains unknown. In addition, the role of low response to antiplatelet therapy in the development of this complication remains unclear because of the lack of consensus on the biological definition in the literature. On the other hand, the emergence of DES has raised concerns regarding the occurrence of late stent thrombosis. If the rates of early and late stent thromboses are similar between BMS and DES, it seems that there is a small but significant increase in the rate of very late stent thrombosis after DES implantation compared to BMS. Nevertheless, according to the literature, DES use seems to not be associated with an increase in mortality. This discordance could be explained by a reduction in the rate of complications related to repeat revascularization. Indeed, it has been demonstrated clearly that DES use is associated with a decrease in the rate of repeat revascularization. Finally, a new generation of DES is currently available. However, today no data regarding the rate of very late stent thrombosis have been reported; thus pending results of larger studies, no conclusion can be drawn regarding their safety. In summary, regarding the treatment of stent thrombosis, the most important conclusion is to obtain an effective reperfusion as early as possible and physician experience in this context will most likely be determinant.

Conflict of interest

No conflict of interest exists.

References


