Thrombosis After Implantation of Drug-Eluting Stents

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Thrombosis is the sudden occlusion of a stented coronary artery due to thrombus formation. Despite major improvements in antiplatelet therapy, thrombotic events remain the primary cause of death after percutaneous coronary interventions.1,2 The clinical consequences of stent thrombosis are frequently catastrophic and include death in 20% to 48% of cases or major myocardial infarction in 60% to 70%. When bare metal stents (BMS) were first introduced, stent thrombosis was a common complication. Most episodes occurred within 2 weeks of stent implantation and often resulted in myocardial infarction and, not infrequently, death.3 Technical improvements, such as the use of adequately sized balloons and high-pressure deployment, helped to substantially decrease thrombosis rates.3,4 In addition, a regimen of dual antiplatelet therapy (aspirin plus a thienopyridine) was found to reduce the incidence of stent thrombosis even further.5 Dual antiplatelet therapy is prescribed for 2-4 weeks after BMS implantation, the time required for stent endothelialization to take place. Thrombosis that occurs more than 30 days after the implantation of a BMS is extremely rare. This complication first appeared when intracoronary radiation (brachytherapy) was introduced as a treatment for in-stent restenosis.5,6 Intracoronary radiation was found to delay re-endothelialization in animals, thus predisposing to late stent thrombosis. Prolonging the duration of dual antiplatelet therapy to 6-12 months largely resolved this problem.5,6 Similar to brachytherapy, drug-eluting stents (DES) have an antiproliferative effect that delays stent re-endothelialization. For this reason, DES trials have mandated dual antiplatelet therapy for 2-6 months, as well as the indefinite use of aspirin.

Drug-eluting stent thrombogenicity

Stent platforms, polymer coating, eluted drug (sirolimus or paclitaxel), and other factors might contribute to DES thrombogenicity.7 First, stent design might influence the degree of platelet activation after coronary stent deployment. In a randomized trial, an open-cell stent design (versus closed-cell design) was associated with a greater degree of platelet activation after coronary stent deployment. In a randomized trial, an open-cell stent design (versus closed-cell design) was associated with a greater degree of platelet activation at 24 hours and 30 days. Because the stent devices are similar, the observed differences must reflect the properties of the polymer. Furthermore, both the polymer coating and the medication with which it is impregnated might influence the propensity for thrombosis.7 It has been proposed that agents that use this pathway (such as atorvastatin) might interfere with hepatic conversion of clopidogrel (a prodrug) to its active moiety and thus might diminish clopidogrel-induced platelet inhibition. This type of
drug-drug interaction could be of greater significance to individuals with genetically determined diminished CYP 3A4 activity who manifest a reduced response to clopidogrel platelet inhibition. However, significant interactions were not reported in the big randomized studies and in a small registry that specifically tackled the issue.

What is the pathologic basis of DES thrombosis? Virmani et al proposed that a hypersensitivity reaction could contribute to the development of this event, reporting a case of fatal acute myocardial infarction and cardiac rupture as a result of late thrombosis of a Cypher stent deployed 18 months previously. This was the first case to be described of a localized hypersensitivity vasculitis in response to a Cypher coronary stent resulting in an acute myocardial infarction secondary to late in-stent thrombosis at 18 months. The hypersensitivity reaction could have been caused by the metallic stent, polymer, or sirolimus. Available pathological evidence, however, supports the hypothesis that hypersensitivity to the polymer was the most likely mechanism. Hypersensitivity to metals such as molybdenum, nickel, and chromium has been reported in 10% of patients undergoing stenting. Hypersensitivity to bare stainless steel stents has been associated with restenosis and not thrombosis, and a late eosinophil-rich infiltrate has not been reported in human stented arteries. There is a likely spectrum of allergic responses to DES in sensitive patients, varying from benign reactions to exsudative inflammation with medial destruction, stent malaposition, and aneurysm formation with late in-stent thrombosis.

**Classification of stent thrombosis**

Stent thrombosis can be categorized according to the timing of occurrence as early (≤30 days) or late (>30 days). Stent thrombosis can be further categorized as *intra-procedural* (during the procedure), or *subacute* (after the end of the procedure to 30 days). In another, more conventional, classification early stent thrombosis is categorized as *acute* (≤24 hours) or *subacute* (between 24 hours and 30 days).

**Intra-procedural stent thrombosis**

Intra-procedural stent thrombosis is a rare event (<0.01% in our experience with bare metal stents), with the exception of specific settings such as acute myocardial infarction, thrombus-containing lesions and dissections, and is relatively “benign” compared to post-procedural stent thrombosis (early and late). Chieffo et al reported the occurrence of intra-procedural stent thrombosis during elective implantation of sirolimus-eluting stents (SES, 670 patients) in the absence of acute myocardial infarction, thrombus-containing lesions, and residual peri-stent dissections. Intra-procedural stent thrombosis is less likely to be associated with early stent thrombosis, and it has been suggested that it might be related to the fact that it was not associated with acute myocardial infarction.
Intra-procedural stent thrombosis occurred in 5 patients (0.7%). None of the patients with intra-procedural stent thrombosis were pretreated with glycoprotein IIb/IIIa inhibitors. Only total stent length per vessel (exact OR: 1.03, 95% CI: 1.011 to 1.046, p=0.0028) was associated with the occurrence of intra-procedural stent thrombosis. It is worth noting that intra-procedural stent thrombosis did not occur in patients who were treated with elective glycoprotein IIb/IIIa inhibitors. This complication has not been reported in the core and pivotal DES trials. The lack of occurrence of this complication in any of the patients who were enrolled in randomized trials is reassuring but should be evaluated taking into account the average stent length in such trials (18.8 mm in the RAVEL trial, 21.5 mm in the SIRIUS trial, and 23 mm in the E-SIRIUS trial) and the greater use of glycoprotein IIb/IIIa inhibitors (60.4%) in the SIRIUS trial.

Incidence of post-procedural stent thrombosis (early and late) after DES implantation

Although both the definition and mechanism for detection vary between reported series, the recorded incidence of stent thrombosis in the modern era of stent deployment varies from a low 0.4% with intravascular ultrasound (IVUS) guidance to a high 2.8% after multi-vessel stenting. SES (Cypher™, Cordis/Johnson & Johnson, Warren, NJ) and polymer based paclitaxel-eluting stents (PES, Taxus™, Boston Scientific, Nat-ick, MA) have been shown to reduce neointimal hyperplasia and risk of restenosis without increasing the risk of stent thrombosis (0.4% at 1 year for SES and 0.6% at 9 months for PES) in the setting of randomized trials. A meta-analysis of 11 randomized trials (5013 patients) showed no evidence that the short-to-medium-term safety profiles of SES or PES differed from those of bare-metal stents. In another metaanalysis of 10 randomized studies (5030 patients) the risk of thrombosis after DES versus BMS was compared, and the relationship between the rate of DES thrombosis and stent length was evaluated. The authors found that DES do not increase the risk of stent thrombosis (either early or late), at least under appropriate anti-platelet therapy (Figure 2). In addition, they did not find any differences between SES and PES regarding the incidence of stent thrombosis (Figure 3). Furthermore, the risk of stent thrombosis after DES implantation is related to stent length (Figure 4). In another meta-analysis of eight trials (total of 13 study arms) in 3817 patients with coronary artery disease who were randomized to either PES or BMS, the authors reported that standard dose PES do not increase the hazard of stent thrombosis compared to BMS. However, these trials were not powered to detect or exclude an effect of DES on rare events such as stent thrombosis. In addition, the inclusion criteria for these trials were relatively restrictive and mostly excluded high-risk patients. Operators are now using DES for a wide variety of clinical and anatomic situations, many of which have not been investigated in the randomized studies.

In a small single center registry of 652 patients treated with SES, Jeremias et al reported a rate of approximately 1% at a median follow-up of 100 days. More recently, Ong et al reported the incidence of late angio-
graphic stent thrombosis events in an unselected DES population from a single center registry.\textsuperscript{19} Patient population consisted of 2006 patients treated with either SES (n=1017) or PES (n=989). All patients had at least 1 year of follow-up with a mean duration of 1.5 years. Angiographically proven late stent thrombosis occurred with an incidence of at least 0.35\% (95\% confidence limits 0.17\% to 0.72\%) in patients treated with DES. The authors highlighted the fact that late angiographic stent thrombosis may also occur when patients are stable on antiplatelet monotherapy. In a more recent study, Iakovou et al reported the results from a prospective registry including a total of 2229 consecutive patients who underwent successful SES (1062 patients) or PES (1167 patients) implantation.\textsuperscript{10} There were no significant differences between the 2 groups in procedural complications and in-hospital outcome. At 9-month follow-up 29 patients (1.3\%) had stent thrombosis (9 [0.8\%] with SES and 20 [1.7\%] with PES, p=0.09), which is a somewhat higher incidence than the one reported in the randomized studies. Fourteen patients had subacute thrombosis (0.6\%) and 15 patients had late thrombosis (0.7\%). Among these 29 patients, 13 died (case fatality rate, 45\%) (Figure 5).

\textbf{Are there any differences in stent thrombosis rates between SES and PES?}

With the exception of the REALITY study, none of the randomized studies or registries revealed a sta-
statistically significant difference between SES and PES regarding the incidence of stent thrombosis.

The REALITY study randomized 1386 patients from 90 centers in Europe, Asia, and Latin America to either SES or PES. Stent lengths up to 33 mm were used in the trial, which permitted inclusion of patients with small vessel diameters of 2.25 to 3.0 mm, no upper lesion length, and multiple vessel stenting. One third of the trial population was diabetic. The difference between the 2 stent groups was not statistically significant regarding the incidence of stent thrombosis in the intention to treat analysis. However, there was a difference in the population actually treated.

The SIRTAX and the TAXI studies were also head to head comparisons which did not reveal any significant difference regarding the rates of thrombotic events between the two stents.20,21 Other comparisons from registries have yielded the same results, demonstrating no superiority of one stent type over the other.19,22,23

Predictors of stent thrombosis after DES

In the study by Iakovou et al, patients who developed thrombotic events were older than those who did not (68 ± 11 vs. 62 ± 10 years, p= 0.001), more frequently had diabetes (59% vs. 26%, p= 0.0002), chronic renal failure (26% vs. 5.5%, p<0.0001) and treatment of bifurcational lesions (57% vs. 21%, p<0.0001), and had a lower ejection fraction (45 ± 9% vs. 54 ± 8%, p<0.0001).10 The incidence of stent thrombosis according to selected patient characteristics is shown in Figure 6. Although bifurcational treatment was accompanied by a higher than expected incidence of stent thrombosis, there were no significant differences be-
two cases seem to indicate that the risk of late thrombosis is specific to DES: in two patients in whom a DES py was impending non-cardiac surgery. Furthermore, risk of late stent thrombosis may reflect the fact that the DES implantation was not associated with an increased rate of late thrombosis in real-life situations is higher.10

The finding that in these trials and their meta-analyses of both early and late stent thrombosis were found to be similar in the DES and bare metal stent groups.10,11 Independently, predictors of stent thrombosis were premature discontinuation of antiplatelet therapy (hazard ratio [HR]: 89.78, 95% CI: 29.90-269.60, p<0.001), renal failure (HR: 6.49, 95% CI: 2.60-16.15, p<0.001), bifurcation lesions (HR: 6.42, 95% CI: 2.93-14.07, p<0.001), diabetes (HR: 3.71, 95% CI: 1.74-7.89, p=0.001), and a lower ejection fraction (HR: 1.09, 95% CI: 1.05-1.36, p<0.001 for each 10% decrease). Similarly, in the study by Jeremias et al discontinuation of dual antiplatelet therapy was accompanied by a 30-fold increase in the risk of thrombosis.18

In an IVUS study of 15 patients treated with DES, Fuji et al showed that stent underexpansion and residual reference segment stenosis are associated with stent thrombosis after successful SES implantation.26

With the accumulation of more IVUS data we can expect more useful IVUS insights into the pathogenesis of this event.

Stent thrombosis and antiplatelet therapy

In the randomized trials, DES have mandated dual antiplatelet therapy for 2-6 months, as well as the indefinite use of aspirin.12,13,15,16,27,28 In these trials, the rates of both early and late stent thrombosis were found to be similar in the DES and bare metal stent groups. The finding that in these trials and their meta-analyses DES implantation was not associated with an increased risk of late stent thrombosis may reflect the fact that the vast majority of patients continued aspirin indefinitely.

While clinical trials indicate that DES have a good overall safety profile, a recent registry suggests that the rate of late thrombosis in real-life situations is higher.10

In this registry, the most important predictor of late stent thrombosis was the cessation of antiplatelet therapy.10 Therefore, patients may not be as compliant with antiplatelet therapy in actual practice as they are in clinical trials, potentially leading to a higher number of events. The interruption of antiplatelet therapy was also reported to have preceded several cases of late thrombosis with DES.29,30 In these case reports, the most common reason for stopping antiplatelet therapy was impending non-cardiac surgery. Furthermore, two cases seem to indicate that the risk of late thrombosis is specific to DES: in two patients in whom a DES caused thrombosis, a bare metal stent that was implanted at the same time as the DES remained patent.9 Most noteworthy, however, is the very late occurrence of the stent thrombosis cases, ranging between 11 and 21 months after DES implantation.29,30 Thus, it is unclear when it is safe to stop antiplatelet therapy.

The delayed endothelialization associated with implantation of DES may extend the risk of thrombosis beyond 30 days, and for this reason the duration of the standard double antiplatelet therapy has to be prolonged up to 6 months and more. Angiographically documented late (>6 months) stent thrombosis is extremely rare with bare-metal stents except after intracoronary irradiation, which delays vascular healing. There is concern that DES might also be susceptible to late stent thrombosis related to delayed endothelialization of the stent struts. Studies in animals have generated concern that DES could also be prone to late stent thrombosis, although extrapolation of such findings to human beings might be unreliable. Evidence from animal models suggests that the SES do not impede endothelialization. In contrast, animal studies with PES clearly show delayed re-endothelialization. However, these studies were done with stents in which the polymer coating, design, and drug-release kinetics differed substantially from those of SES and PES. With the PES, about 10% of the paclitaxel is released by 10 days; the rest remains in the polymer indefinitely. With the SES, almost all the sirolimus has eluted by 6 weeks, leaving a polymer-coated bare-metal stent. It is unclear whether this difference is of any clinical importance in terms of the potential for long-term adverse events. It is worth noting that, based on the design of the pivotal clinical trials that led to approval of such stents, dual antiplatelet therapy is prescribed on an empirical basis, for 2-3 months after implantation of SES, and for 6 months after implantation of PES, with lifelong aspirin. However, many operators are now prescribing dual antiplatelet therapy for a longer period (6 months to more than 12 months).

Of course it must be noted that issues such as platelet and clopidogrel resistance, along with newly emerging concepts such as the high post-treatment platelet reactivity and incomplete P2Y12 receptor inhibition, must be taken into account when considering the impact of antiplatelet therapy on stent thrombosis.31-35 Recently, a number of reports, using various definitions, have dichotomized patients who are treated with clopidogrel into a minority of “non-responders” and a majority of “responders”. Such classifications imply that treatment leads to an all-or-none response, with potentially important clinical implications.
Serebruany et al evaluated the responses of patients to clopidogrel using ex vivo measures of platelet aggregation and activation in a large, heterogeneous patient population. They conducted secondary post-hoc analyses of a dataset consisting of volunteers (n=94) and patients after coronary stenting (n=405), with heart failure (n=25), and after stroke (n=20). The response of subjects to clopidogrel followed a normal, bell-shaped distribution, with a mean and standard deviation of 41.9 ± 20.8% when aggregation was induced by 5 μmol/l of adenosine diphosphate. When hypo-responsiveness and hyper-responsiveness to clopidogrel were taken as being two standard deviations away from the mean, their prevalence in these patients was 4.2% and 4.8%, respectively. Pretreatment platelet activity and clinical characteristics were not associated with responsiveness to clopidogrel. The authors concluded that individuals receiving clopidogrel exhibit a wide variability in response that follows a normal distribution. The clinical implications of this variability are unknown but are potentially important. Clinical trials are needed to define whether hypo-responders to clopidogrel are at increased risk for thrombotic events and whether hyper-responders are at increased risk for bleeding. If so, the individualization of antiplatelet therapy, including clopidogrel dosing, may be possible in the future but will require the ability to measure responsiveness easily and reproducibly, by a method that has been proven to be predictive of clinical events.

Comment

Early and late stent thrombosis following the implantation of DES is rare, but is associated with serious consequences; thus, it is important for physicians to recognize the risk of late stent thrombosis. Discontinuation of antiplatelet therapy is the most important predictor of late stent thrombosis with DES. Therefore, two factors to consider before implanting a DES are: 1) whether the patient will need to undergo surgery requiring the interruption of antiplatelet therapy; and 2) whether the patient is likely to be compliant with antiplatelet therapy. In situations that may lead to the interruption of antiplatelet therapy, the risk of restenosis (or need for DES) should be seriously weighed against the risk of late thrombosis. Once a DES is implanted, the patient needs to be clearly informed about the risk of developing thrombosis should they not be compliant with the therapy. Furthermore, if the patient is to undergo surgery, the option to delay interrupting aspirin preoperatively or to maintain it throughout the surgery should be considered. Maintaining the patient on aspirin, however, increases the risk of bleeding complications. Another option would be to postpone elective surgery for as long as possible, although it is still not clear when the risk of late stent thrombosis with DES abates. The use of DES is currently the optimal way to prevent restenosis; however, DES are associated with a rare risk of late stent thrombosis, with consequences such as myocardial infarction and death. It is necessary for physicians and patients to be aware, not only of the risk of thrombosis, but also of the most important contributing factor: interruption of antiplatelet therapy. For this reason, it is imperative to avoid stopping antiplatelet therapy. Physicians can do so by maintaining patients on antiplatelet therapy indefinitely and by stressing the importance of compliance.

References