How to Minimize Stent Thrombosis
Ajay J. Kirtane, MD, SM; Gregg W. Stone, MD

Case Presentation—A 58-year-old diabetic woman with stable angina pectoris (class II symptoms despite medical therapy) presented for elective cardiac catheterization after undergoing a stress test that demonstrated anterior wall ischemia at a low-moderate workload. Coronary angiography demonstrated single-vessel disease with a 90% lesion in the left anterior descending (LAD) coronary artery (Figure, A). Treatment with percutaneous coronary intervention (PCI) was selected as a revascularization strategy, and a drug-eluting stent (DES) was deployed in the LAD without complications (Figure, B). Before discharge, a treating physician concerned about the risk for stent thrombosis assessed the patient’s platelet reactivity using point-of-care testing, which demonstrated minimal platelet response to clopidogrel. This clinician update will discuss strategies for the prevention of stent thrombosis.

Stent Thrombosis Background
The most feared complication related to coronary stent placement is stent thrombosis, which, although fortunately rare ( occurring in \( \approx 0.5\% \) to \( 1\% \) of patients within 1 year), most commonly presents as an acute myocardial infarction (MI).\(^1\) Treatment for stent thrombosis almost always requires emergent repeat PCI, although optimal reperfusion is only achieved in two thirds of patients.\(^2\) As a result, stent thrombosis has been associated with 30-day mortality rates of 10% to 25%. Moreover, \( \approx 20\% \) of patients with a first stent thrombosis experience a recurrent stent thrombosis episode within 2 years.

The mechanisms underlying stent thrombosis are multifactorial (Table 1) and include patient-related factors, procedural factors (including stent choice), and postprocedural factors (including type and duration of antiplatelet therapy). Numerous strategies may be employed to reduce the occurrence of stent thrombosis (Table 2).

Role of Patient Selection
Stent thrombosis occurs more frequently in complex patients and lesions, especially in those with acute coronary syndromes, diabetes mellitus, chronic kidney disease and diffuse disease, small vessels, and bifurcation lesions requiring multiple stents.\(^1\)\(^3\) Additionally, premature discontinuation of dual-antiplatelet therapy within 6 months has been strongly associated with stent thrombosis, especially in the setting of trauma or performance of surgical procedures.\(^4\) These patient-related factors can be critical in clinical decision making relative to the overall revascularization strategy (whether to implant a bare metal stent [BMS] or DES, or to instead consider coronary artery bypass grafting). Understanding the risk of stent thrombosis according to these patient-related factors facilitates use of procedural strategies to minimize the risk of stent thrombosis, especially in high-risk patients (see Procedural Factors).

Procedural Factors
Procedural factors associated with stent thrombosis include the stent type selected (whether BMS or DES, and even the specific DES used), as well as whether the stent is adequately expanded and apposed to the vessel wall and is placed in a vessel with sufficient runoff to support adequate flow through the stent.

High-Pressure Stent Deployment and Adequate Expansion
Early in the stent experience, Colombo and colleagues demonstrated with intravascular ultrasound that stent under-expansion and/or malapposition occurred not infrequently after stent deployment and was associated with
stent thrombosis. On the basis of these and other observations, adequate stent sizing and high-pressure (>14 atmospheres) stent deployment and post dilation to ensure expansion are considered essential to minimize stent thrombosis. Although the use of adjunctive intravascular ultrasound to ensure appropriate sizing and expansion has not been proven in randomized trials to be essential, intravascular ultrasound can be useful to confirm stent apposition and expansion, which in observational studies has been linked to lower stent thrombosis at both 30 days and 1 year.

Bare Metal Stent Versus Drug-Eluting Stent and Stent-Related Factors

Stent thrombosis after BMS typically occurs within the first 30 days after implantation, although rarely can occur later. In contrast, stent thrombosis after DES can occur years afterward, with an annual incidence of 0.2% to 0.3% in patients with noncomplex coronary artery disease and 0.4% to 0.6% after unrestricted use. Thus, stent thrombosis rates arising from within the original stent are higher with DES than BMS, with the differences emerging predominantly beyond the first year after implantation. A variety of potential causes of late stent thrombosis occurring with DES have been implicated, including delayed or absent endothelialization of the stent struts, hypersensitivity/inflammatory and/or thrombotic reactions to the DES polymers, strut fractures, late malapposition/aneurysm formation, and the development of neoatherosclerosis within stents with new plaque rupture.

Despite concerns about late stent thrombosis with DES, long-term follow-up of randomized DES versus BMS studies has demonstrated that after taking into account stent thrombotic events after procedures for restenosis (so called “secondary” stent
Table 2. Strategies to Minimize the Occurrence of Stent Thrombosis

<table>
<thead>
<tr>
<th>Patient selection</th>
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</thead>
<tbody>
<tr>
<td>Screening for likely adherence to prescribed medical regimens (including ability to afford dual antiplatelet therapy)</td>
</tr>
<tr>
<td>Careful screening for bleeding risk (or ability to tolerate dual antiplatelet therapy)</td>
</tr>
<tr>
<td>Confirmation of no upcoming surgical procedures in the recent future (6 wk for BMS, 6–12 mo for DES)</td>
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<table>
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<tr>
<th>Stent selection and deployment</th>
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<tbody>
<tr>
<td>Consider use of stents with proven lower stent thrombosis rates</td>
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<tr>
<td>Appropriate vessel sizing</td>
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<tr>
<td>High-pressure stent deployment and post-dilation</td>
</tr>
<tr>
<td>Ensuring absence of edge dissections</td>
</tr>
<tr>
<td>Ensuring adequate inflow and outflow</td>
</tr>
<tr>
<td>Avoiding the use of 2 stents in bifurcation lesions (if possible)</td>
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<table>
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<tr>
<th>Peri- and post-procedure care</th>
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<tbody>
<tr>
<td>Use of more potent oral antiplatelet regimens (eg, prasugrel, ticagrelor) in appropriately indicated clinical scenarios such as acute coronary syndromes in patients with acceptable bleeding risk</td>
</tr>
<tr>
<td>Patient education and clinical follow-up emphasizing the importance of adherence to prescribed dual antiplatelet therapy</td>
</tr>
<tr>
<td>Continuation of dual antiplatelet therapy without interruption whenever possible if a dental, endoscopic, or surgical procedure is necessary (which is feasible for most surgeries other than neurovascular)</td>
</tr>
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BMS indicates bare metal stents; DES, drug-eluting stents.

thrombosis events, which occur more commonly after BMS than DES), the overall incidence of stent thrombosis (primary plus secondary) does not seem to be increased with DES compared to BMS,10 and the overall late rates of death and MI are similar with DES and BMS.11 Moreover, the benefits of DES in reducing restenosis and subsequent adverse events offset the small excess risk of very late primary stent thrombosis with DES,12 albeit by a slim margin.

Potential stent modifications to reduce stent thrombosis have included improving the biocompatibility of the stent and polymer, using bioabsorbable polymers, eliminating the polymer entirely, and/or using stent surface modifications to stimulate vascular endothelialization. Many of these designs are currently undergoing clinical evaluation. At present, data with second-generation DES including the Xience V/Promus everolimus-eluting stent and the Endeavor zotarolimus-eluting stent have demonstrated favorable rates of stent thrombosis compared to first-generation DES.13,14

Antiplatelet Regimens

Choice of Antiplatelet Therapy

Dual antiplatelet therapy with aspirin and a thienopyridine is currently recommended for PCI patients in whom stents are implanted on the basis of randomized trials showing reduced rates of stent thrombosis with aspirin plus ticlopidine compared to aspirin alone or aspirin plus warfarin.15 Clopidogrel compared to ticlopidine has comparable efficacy with an enhanced safety profile.16 Therefore, poststenst therapy with aspirin and clopidogrel is currently the standard of care for the majority of patients undergoing PCI with either BMS or DES worldwide. In patients with acute coronary syndromes, the rates of stent thrombosis have also been reduced by replacing clopidogrel with more potent antiplatelet agents such as prasugrel and ticagrelor, although this benefit is achieved at the cost of increased bleeding.17,18 Additionally, although some interventionalists have adopted a practice of routinely administering double-dose clopidogrel for either a week or longer after stent implantation in order to prevent stent thrombosis, this practice is largely empirically based rather than supported by clinical data, particularly among the elective PCI population.

Clopidogrel is a prodrug that requires the CYP2C19 enzyme to be converted into its active metabolite. The US Food and Drug Administration recently added a boxed warning to the label of clopidogrel about its reduced effectiveness in patients who are poor metabolizers of this drug.19 However, although polymorphisms in the gene encoding the CYP2C19 allele as well as high on-clopidogrel platelet reactivity have been associated with adverse clinical events in patients undergoing PCI,20,21 genetic testing is not widespread, its utility has not been prospectively validated, and what to do if a poor metabolizer is identified is uncertain. At present, no prospective randomized studies have demonstrated benefits of using a more potent alternative antiplatelet regimen (such as higher-dose clopidogrel, prasugrel, or ticagrelor) for stable PCI patients identified at increased risk for events on clopidogrel by either a polymorphism in CYP2C19 or high on-treatment residual platelet reactivity. In fact, the first such randomized trial to examine this hypothesis, Gauging Responsiveness With a VerifyNow Assay: Impact on Thrombosis and Safety (GRAVITAS) recently reported no benefit of a strategy of doubling the standard daily dose of clopidogrel (from 75 to 150 mg per day) after PCI in patients with high on-treatment platelet reactivity.22 Importantly, after successful DES implantation in this study cohort, the 6-month composite rate of cardiovascular death, MI, or stent thrombosis was low in both groups (2.3% at 6 months) despite higher on-treatment platelet reactivity with standard-dose clopidogrel.

Duration of Antiplatelet Therapy

Observational studies have uniformly documented that premature thienopyridine discontinuation within 6 months after DES placement is strongly associated with stent thrombosis.4 Whether prolonged dual antiplatelet therapy beyond this time will enhance freedom from stent thrombosis and/or death and MI is unknown, with some studies in support of this hypothesis and others against. Only 1 randomized trial addressing the issue of prolonged dual antiplatelet therapy for the prevention of stent thrombosis has been completed, with no significant differences in the primary composite end point of...
cardiac death/MI (or stent thrombosis) observed in patients treated with an additional 2 years of clopidogrel along with aspirin compared to aspirin alone. Several additional randomized trials are ongoing to address the relative safety and efficacy of prolonged dual antiplatelet therapy. In the absence of prospective randomized data on extended-duration dual antiplatelet therapy, current recommendations are for 12 months of dual antiplatelet therapy in most patients after DES and BMS. Among DES-treated patients who are at higher risk for bleeding, shorter durations of dual antiplatelet therapy (generally, minimum 6 months) can be considered on the basis of the early clinical trial experiences with predominantly first-generation DES; ongoing trials assessing earlier discontinuation regimens should shed further light on this issue. For BMS-treated patients, a minimum of 2 to 4 weeks of dual-antiplatelet therapy is currently recommended, but 12 months is still considered to be ideal, especially among patients with acute coronary syndromes.

Summary

Stent thrombosis is a devastating complication of stent implantation, and strict attention to patient risk factors and ability to adhere to prescribed medical regimens is necessary before proceeding with stent implantation. Assiduous care to technical detail is necessary to optimize stent implantation and deployment, particularly in complex disease, and novel stents are emerging with the potential to inherently lower the risk of stent thrombosis. Elective surgery within the first year after DES placement should be avoided or performed without discontinuation of either aspirin or clopidogrel if possible. Finally, data on the use of antiplatelet agents more potent than clopidogrel for high-risk patients are limited to those with acute coronary syndromes, for whom prasugrel and ticagrelor can be beneficial, albeit at a potentially greater risk of bleeding complications. It is thus essential to carefully consider the individual patient’s risk of stent thrombosis (and MI) compared to bleeding before using these agents.

Case Resolution

Despite the patient’s high on-treatment platelet reactivity with clopidogrel, given the excellent stent result achieved and absent randomized trial data demonstrating a favorable risk–benefit ratio of double-dose clopidogrel or prasugrel/ticagrelor in elective PCI for stable angina, the patient was discharged uneventfully from the hospital on aspirin plus standard-dose clopidogrel to continue for 1 year, with plans for routine clinical follow-up with her referring cardiologist. One year later, the patient was doing well, without stent thrombosis or recurrent symptoms, and clopidogrel was discontinued. The patient remains free of symptoms or events at 2 years. In the interim, the patient’s treating physicians have stopped routinely testing platelet reactivity for elective PCI patients while awaiting prospective clinical data demonstrating the benefit of treatment modifications based on these results.

Disclosures

Dr Stone has served on an advisory board for and received honoraria from Abbott Vascular and Boston Scientific. He has consulted for Volcano, Medtronic, BMS-Sanoﬁ, Merck, AstraZeneca, and Eli Lilly. Dr Kirtane reports no conﬂicts.

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