Early Stent Thrombosis
Past, Present, and Future

Stéphane Cook, MD; Stephan Windecker, MD

For 2 decades, coronary artery stents were introduced into clinical practice with 2 objectives in mind: to attenuate restenosis on the one hand and to prevent or treat abrupt vessel closure on the other. The first elective coronary stent implantation was performed in March 1986 by Jacques Puel, MD, to treat restenosis after plain balloon angioplasty. The first bail-out stenting procedure was carried out only a few months later by Ulrich Sigwart, MD, who successfully sealed an occlusive dissection. Although both groundbreaking procedures were performed in very different clinical settings, neither cardiologist, fortunately, encountered significant problems during the periprocedural period; otherwise, coronary stenting would have been doomed to failure. It took only a few more cases until an unanticipated bane of coronary stenting became noticeable: stent thrombosis. Aggressive antithrombotic regimens were sought as unanticipated bane of coronary stenting became noticeable: stent thrombosis. Aggressive antithrombotic regimens were sought as remedies, and aspirin was given in conjunction with dipyridamole, sulfapyrazone, and oral anticoagulation (acenocoumarin) for up to 6 months. Despite these measures, the initial experience with the self-expanding Wallstent was overshadowed by unacceptably high rates of stent thrombosis, approaching 24%, as well as bleeding complications. Subsequent series with the Palmaz-Schatz and Gianturco-Roubin stent, still mainly in the setting of bailout stenting, continued to result in stent thrombosis in 6% to 12% of cases.

The advent of dual antiplatelet therapy with aspirin and the thienopyridine ticlopidine in concert with an expansion of the indication of coronary stenting from bailout procedures to elective cases resulted in a significant reduction of stent thrombosis, to <2%, as well as fewer bleeding complications. Moreover, recognition of the importance of stent implantation technique, appropriate pretreatment and loading with thienopyridines, and the use of glycoprotein IIb/IIIa antagonists in the setting of acute coronary syndromes led to a further decline in stent thrombosis.

The Present

At the end of the bare metal stent era, stent thrombosis nearly fell into oblivion because of the prevailing concern of restenosis. Nevertheless, stent thrombosis continued to be a serious complication, with rates of morbidity and mortality approaching those of spontaneous myocardial infarction.

Thirty-day mortality after bare metal stent thrombosis was in the range of 7% to 25%. The most important predictors of bare metal stent thrombosis were a poor postprocedural result such as inadequate stent expansion, residual dissections, and inappropriate inhibition of platelet aggregation.

Drug-eluting stents resulted in a drastic reduction of neointimal hyperplasia and therefore repeat revascularization procedures. Careful scrutiny of early safety data were unrevealing and showed similar or even lower rates of stent thrombosis with drug-eluting than with bare metal stents. However, longer-term follow-up in more complex patients and lesions led to the recognition of another nuisance, very late stent thrombosis. The insinuation of safety concerns with drug-eluting stents during the 2006 convention of the European Society of Cardiology in Barcelona, also known as the ESC firestorm, stimulated powerful research on the topic of stent thrombosis. The article by Aoki and colleagues published in this issue of Circulation was born out of these research efforts, but it focuses on an entity largely ignored since the ESC firestorm: early rather than late or very late stent thrombosis after drug-eluting stent implantation.

As previously reported, the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial randomly assigned 13 819 patients with moderate- to high-risk acute coronary syndromes to 1 of 3 antithrombotic regimens: heparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, or bivalirudin alone. The present analysis is based on the quantitative coronary angiography subgroup of 3405 patients (25%) included in the percutaneous coronary intervention (PCI) arm of ACUITY. Definite or probable stent thrombosis within 30 days was encountered in 48 of 3405 patients (1.4%) in the overall population, in 43 of 3043 patients (1.4%) treated with drug-eluting stents, and in 5 of 362 patients (1.4%) treated with bare metal stents. With nearly 90% of patients treated with drug-eluting stents, the present study addresses 3 unresolved issues:

1. What is the incidence of stent thrombosis with drug-eluting stents in patients with moderate- to high-risk acute coronary syndromes during the early period, encompassing the vast majority (60% to 80%) of stent thromboses?
2. What are the clinical and angiographic predictors of drug-eluting stent thrombosis in patients with acute coronary syndromes?
3. What is the efficacy of bivalirudin as compared with heparin plus glycoprotein IIb/IIIa inhibitors to prevent early stent thrombosis?

To date, none of the large independent registries or randomized controlled trials of patients undergoing PCI with drug-eluting stents has specifically addressed these questions.
The absolute rates of early definite (0.9%), and definite or probable stent thrombosis (1.4%) in the present study are clearly higher compared with the incidence of early stent thrombosis in stable patients undergoing PCI under elective conditions (0.3% to 0.4%). Yet the results correspond well to the 1.4% rate of early definite or probable stent thrombosis recently reported for the clopidogrel arm of patients included in another acute coronary syndrome trial, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38.14 The amplified risk of early stent thrombosis in patients with acute coronary syndromes results from the accumulation of several simultaneous prothrombotic conditions: local thrombus burden at the site of plaque rupture, impaired flow due to distal embolization with obstruction of the microcirculation, incomplete stent apposition related to dissolution of initially jailed material or stent mismatch (undersize or underexpansion), vulnerable plaque with necrotic components, plaque prolapse through stent struts into the lumen, impaired healing capacity, a procoagulable state, incomplete inhibition of platelet activation, and impaired left ventricular function. In analogy to the bare metal stent era, early stent thrombosis with drug-eluting stents represents a risk continuum largely determined by the clinical setting, ranging from low risk in patients with stable coronary artery disease, to intermediate risk in patients with acute coronary syndromes, and extending to high risk in patients with acute ST-segment elevation myocardial infarction (STEMI) (Table 1).

What do we learn from the clinical and angiographic predictors of early stent thrombosis in patients with acute coronary syndromes? First, it is reassuring that the incidence of early stent thrombosis is identical with respect to stent type (bare metal versus drug-eluting stent), which is in line with previous observations in patients treated for on- and off-label indications. Second, patient-related factors including insulin-dependent diabetes mellitus, extent of coronary artery disease, and renal failure confirm previous reports with both bare metal and drug-eluting stents but unfortunately are not modifiable. Third, angiographic predictors, notably lumen dimensions after stent implantation, highlight the importance of optimal stent implantation technique. In this context, the exceedingly low incidence of residual dissections, a predictor of early stent thrombosis in previous reports, points to the high quality of the interventional cardiologists involved in the present study. Yet some predictors of stent thrombosis went undetected in the present study. The impact of stent length on the risk of stent thrombosis (no stent=no risk of stent thrombosis!) was not explored; nor was the importance of stent overlap. Similarly, the bifurcation treatment technique was only superficially reported and therefore escaped a more detailed analysis, as did left ventricular ejection fraction because of incomplete data sampling.

Fourth, an important and modifiable independent risk factor of both definite, and definite and probable early stent thrombosis in patients with acute coronary syndromes was the lack of preprocedural thienopyridine administration. Of note, among patients who were not pretreated with thienopyridines in ACUITY, the composite of ischemic events (death, myocardial infarction, and revascularization for ischemia) was more frequent with bivalirudin monotherapy than with heparin plus a glycoprotein IIb/IIIa antagonist.15 Similarly, deferred selective as compared with routine use of glycoprotein IIb/IIIa inhibitors failed to show noninferiority because of a modest increase in the composite of ischemic events (7.9% versus 7.1%, risk difference 0.8%, 95% confidence interval [CI] 0.97 to 1.29) in the ACUITY Timing study, although this increase was offset by more bleeding events.16 These observations underscore the importance of timely and adequate inhibition of platelet aggregation in patients with acute coronary syndromes undergoing PCI and suggest that supplementary inhibition of platelet aggregation with glycoprotein IIb/IIIa inhibitors be strongly considered in the absence of thienopyridine treatment.

Finally, the manuscript addresses the effectiveness of direct thrombin inhibition in the prevention of early stent thrombosis in patients with acute coronary syndromes. This is important and appropriate! The majority of acute coronary syndromes are caused by rupture of a vulnerable plaque allowing direct contact between the highly thrombogenic necrotic core and circulating platelets, resulting in platelet recruitment, activation, and aggregation, as well as activation of the coagulation cascade with generation of thrombin.17 Thrombin not only converts fibrinogen to fibrin resulting in local thrombus formation, but also promotes thrombosis by activation of factor V, VIII, and XIII, inhibition of fibrinolysis, and platelet activation. As opposed to antiplatelet agents, as well as unfractionated and low–molecular weight heparin, direct thrombin inhibitors not only block soluble but also clot-bound thrombin. Accordingly, one would assume that the risk of early stent thrombosis was diminished in the vicinity of vulnerable lesions with more potent thrombin inhibition. Yet the results of ACUITY fail to fulfill this promise. The direct thrombin inhibitor bivalirudin had no additional protective effect when compared with heparin plus a glycoprotein IIb/IIIa inhibitor. The trend was actually the opposite. Thirty-five of the 2240 patients (1.6%) who received bivalirudin with or without glycoprotein IIb/IIIa inhibitor suffered early stent thrombosis compared with 13 of 1112 patients (1.1%) who received heparin plus a glycoprotein IIb/IIIa inhibitor. That the difference is marginal and statistically insignificant will not prevent us from giving bivalirudin to patients with acute coronary syndromes (especially in patients at increased bleeding risk). However, it is far from the pathophysiologically founded expectation even if it is not completely unexpected.

Whereas the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) study (4570 patients) showed similar rates of early stent thrombosis among low-risk patients with stable coronary artery disease (pretreated with thienopyridine) receiving bivalirudin (0.5%) and heparin (0.4%, $P=0.52$),18 a higher rate of acute stent thrombosis (within 24 hours) was observed among patients with STEMI who were treated with bivalirudin (1.3%) compared with those who were treated with heparin plus a
Table 2. Risk of Early Stent Thrombosis (Protocol or Definite) Across Bivalirudin Trials

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<thead>
<tr>
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<th>Stable Angina18</th>
<th>UA/NSTEMI10</th>
<th>STEMI15</th>
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<tbody>
<tr>
<td></td>
<td>(n = 4570)</td>
<td>(n = 3602)</td>
<td>(n = 3405)</td>
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<td>Heparin/LMWH (=HEP), %</td>
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<td>( P )</td>
<td>0.52</td>
<td>NS</td>
<td>0.30</td>
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UA indicates unstable angina; NSTEMI, Non-ST segment elevation myocardial infarction. Table 2: Risk of Early Stent Thrombosis (Protocol or Definite) Across Bivalirudin Trials.

The Future

The present study appropriately turns our attention to the somewhat neglected issue of early stent thrombosis. It underlines the persistent and elevated risk of early stent thrombosis in patients with moderate- to high-risk acute coronary syndromes irrespective of the implanted stent type. The study also identifies modifiable risk factors such as suboptimal postprocedural results and absence of thienopyridine pretreatment. This will reinforce our quest to strive for an optimal postprocedural result and appropriate inhibition of platelet aggregation at the time of PCI. To further improve on clinical outcome in the future, we will have to carefully weigh the ischemic risk of an individual patient, as defined by the clinical presentation, angiographic and clinical risk factors, and type of planned intervention, against the risk of bleeding. For example, major bleeding was associated with an even higher case fatality rate than acute stent thrombosis in HORIZON-AMI.15

The study touches on a moving target in light of new promising pharmacological agents. Prasugrel, a novel thienopyridine with more predictable inhibition of platelet aggregation, has been shown to reduce early stent thrombosis by 71% compared with clopidogrel (0.42% versus 1.44%, hazard ratio =0.29, 95% CI 0.15 to 0.56, \( P =0.0001 \)) in patients with acute coronary syndromes treated with either bare metal or drug-eluting stents.14 Moreover, the agent appears particularly beneficial in patients at increased risk of stent thrombosis, such as diabetic patients and those with STEMI, without a disproportionately increased risk of bleeding in these subgroups. Therefore, adequate, timely, and predictable inhibition of platelet activation in conjunction with an optimal postprocedural result hopefully will soon render early stent thrombosis an orphan disease.

Disclosures

Dr. Windecker is a consultant for Abbott, Biosensors, Biotronik, Boston Scientific, Medtronic, and Johnson and Johnson and receives lecture fees from Abbott, Biosensors, Biotronik, Boston Scientific, Medtronic, and Johnson and Johnson. Dr Cook reports no conflicts.

References


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