The concept of stenting—intravascular mechanical support by transluminally placed endoprostheses—was first proposed by Charles Dotter 30 years ago. As an intrinsic property of the metallic endoprostheses, early thrombotic occlusion of freshly deployed stents has been a concern since their introduction to human coronary circulation in 1986. The unacceptably high rates (up to 24%) of thrombotic events seen in early clinical experience were first approached pharmacologically by aggressive anticoagulation with low-molecular-weight dextran, dipyridamole, and warfarin. Although this strategy helped reduce the incidence of stent thrombosis into a single-digit range, the benefit was obtained at a cost of significantly longer hospitalization and increased hemorrhagic/vascular complications. As intravascular ultrasound (IVUS) began to have widespread use in the clinical environment in the early 1990s, the importance of mechanical optimization at stent deployment for the prevention of stent thrombosis was underscored. The collaborative work of J.M. Tobis and A. Colombo demonstrated an unexpectedly high percentage of IVUS-detected stent deployment issues, including incomplete stent expansion, incomplete apposition, and asymmetric expansion, even after angiographically successful results. These observations led to the concept of high-pressure stent deployment with IVUS guidance, achieving lower rates of subacute thrombosis with antiplatelet therapy alone (aspirin and ticlopidine). The superiority of this antiplatelet therapy after “optimal” stent expansion with routine high pressure-post-dilatation was subsequently confirmed by several randomized trials when compared with other antithrombotic regimens.

Nevertheless, stent thrombosis has not been eliminated; in this modern stent era, the incidence is reported to be 1% overall and can be more frequent in high-risk patient/lesion subsets or multivessel procedures. Despite the reduced relative incidence, the absolute number of patients with stent thrombosis is increasing in parallel with the exponential increase in the use of stents in the broad spectrum of complex lesions. The clinical consequences for these patients are generally catastrophic, including short-term mortality rates of up to 20% to 25% and major myocardial infarction in 60% to 70% of cases. The economic impact of these events is also substantial; a recent retrospective study by Reynolds et al reported that median total hospital cost was $11,134 per patient, excluding costs due to delayed complications, outpatient costs, and other indirect costs related to stent thrombosis. Given that a total of 800,000 stents are implanted in the United States annually, a conservative stent thrombosis rate of 0.9% would result in an additional health care economic burden of more than $80 million per year even for direct hospital-based costs alone. These facts continue to demand the development of definitive strategies for the prevention of this serious complication.

Study Design and Methodological Considerations

Over the past several years, a number of clinical studies have investigated potential predictors of acute and subacute stent thrombosis, including the article by Cheneau et al in the present issue of Circulation. The goals of these studies were to provide a better understanding of the underlying mechanisms responsible for stent thrombosis and, ultimately, to establish an optimal strategy to eliminate this dreaded complication. This particular attempt, however, involves several methodological challenges, primarily resulting from the low incidence of stent thrombosis in contemporary patient series. Given the incidence of 0.4% to 2.0%, enough power to avoid statistical errors requires considerably large patient sample sizes. This leads to difficulty in collecting comprehensive data on clinical, procedural, and diagnostic variables for the entire sample, particularly when IVUS characteristics are included. For example, in the study of Cheneau et al, only 27 subacute closure cases were identified out of 7484 consecutive patients. This small patient group was actually compared with a “control” group of 69 patients without subacute closure—selected to be 3 times the size of the subacute closure group—matched by some basic clinical and procedural characteristics. In addition to potential type II errors, a certain risk may also exist as to whether these 69 lesions represent a reasonable control population. Indeed, the rates of incomplete stent apposition (3%), dissection (0%), and tissue protrusion (0%) in this “control” group were relatively low compared with those reported in other stent studies. On the other hand, these low incidences of morphological abnormalities might be due to the single-center study design performed at the institution experienced in IVUS-guided stenting. As pointed out in the limitation section, results can vary depending on whether IVUS is used in an interactive guidance or documentary fashion.
Another methodological issue derived from the low incidence of stent thrombosis is the difficulty in designing a prospective study with enough statistical power to confirm possible risk factors predisposing to subsequent thrombotic events. For this reason, most of the currently available data were based on retrospective analyses of the past cumulative patients. Given the requirement of large sample size, this generally requires patient enrollment over several years, often spanning the transition of stent designs and indications, deployment techniques, and pharmacological regimens as described above. In addition, a multiple logistic regression model is often necessary to circumvent potential bias related to retrospective analyses. Given a significantly low event rate, however, this approach may cause important correlations to drop out in the presence of real or accidental stronger relations. Most importantly, with retrospective analyses, it remains an open question whether altering identified risk factors would reduce stent thrombosis.

Finally, considering its low incidence, the definition of stent thrombosis can significantly influence the study results. Angiographically documented subacute closure of the stented segment, as used by Cheneau et al., is a scientifically reasonable definition but may result in dropout of thrombosis cases with no angiographic examination at the time of events. In contrast, the use of major adverse cardiac events as a clinical definition can avoid this limitation but may potentially overestimate the incidence of stent thrombosis. Similarly, the observation period for stent thrombosis varied among studies (within 1 week or 1 month, including or excluding the first 24 hours). This can theoretically affect the overall thrombosis rates as well as the predictors of stent thrombosis because the mechanisms for acute, subacute, and late thrombosis may be potentially different.

**Stent Thrombosis: A Multifactorial Process**

Although the exact pathophysiology has not been fully elucidated, multiple factors are apparently involved in the development of stent thrombosis (Figure). The first important category consists of device-related factors (or stent thrombogenicity), including stent material, design, surface coating, and the interaction with adjunctive therapy such as intracoronary brachytherapy. To date, among a number of commercially available bare-metal stents approved for clinical use, no specific stent type has been reported to be associated with increased angiographic or clinical stent thrombosis. However, a recent prospective, randomized pilot study by Gurbel et al. demonstrated that platelet activation was greater during the 30 days after implantation of an open-cell versus a closed-cell stent, which was potentially related to the different scaffolding properties of the stents. Other investigators also suggested stent length and the use of multiple stents per lesion, particularly with different stent designs, as significant risk factors, although these variables may be partly related to the underlying lesion factors requiring these procedures. While stent surface coating with heparin appears to reduce stent thrombosis, antiproliferative drug-eluting stents can be associated with delayed endothelialization and late persistence of dense fibrin as seen after intracoronary brachytherapy. These device-related factors may be successfully approached by further technical improvement of the stent itself.

The second category comprises patient- or lesion-specific factors, including vessel size, acute coronary syndrome/unstable angina, plaque characteristics, local platelet/coagulation activity, coronary blood flow, and left ventricular ejection fraction. For example, in the present IVUS study by Cheneau et al., subacute vessel closure was seen mainly in noncalcified lesions. Other studies suggested higher age and diabetes mellitus as important risk factors.
morphism of platelet glycoprotein IIIa gene ($P^T_{III}$) may also be associated with an increased risk of stent thrombosis. Because these risk factors are often difficult to modify immediately, patient/lesion triage for nonstent interventions or enhanced pharmacological therapy may provide alternative approaches. In addition, embolic protection devices might be useful in some high-risk patients to prevent the occurrence of slow coronary flow that can occasionally follow stenting.

The third category includes procedure-related factors. As summarized in the Table, among several risk factors that have been proposed, the most consistent variables are smaller final lumen dimensions (stent underexpansion) and residual dissections. These observations were replicated in the present study by Cheneau et al., suggesting that mechanical factors continue to contribute to stent thrombosis even in this modern stent era with optimized antiplatelet regimens. On the other hand, there is significant overlap in each risk factor between thrombosis and nonthrombosis cases, undoubtedly representing a multifactorial process of this phenomenon. It is highly unlikely that any randomized trial comparing IVUS with angiographic guidance will be large enough to show a statistically significant benefit for IVUS-guided optimization in further reducing stent thrombosis, given its low incidence. Nevertheless, the importance of procedural optimization cannot be overemphasized because these risk factors are the only variables that operators could alter in the catheterization laboratory.

**Clinical Implications in a Changing World**

The strongly positive results of the recent drug-eluting stent trials suggest that our approach to stenting may soon be undergoing a sweeping change. Driven by the higher performance expectations of this revolutionary technology, the scope of coronary interventions will be expanded from conventional, conservative indications to significantly higher-risk patients (poor left ventricular function, diabetes, acute myocardial infarction, etc), complex lesions (small vessels, bifurcation lesions, long or diffuse lesions, left main disease, etc), and multivessel procedures. Even granted that thrombosis rates of these new-generation stents are similar to those of conventional bare-metal stents, the expansive use of stents would theoretically result in a considerable increase in the absolute number of patients with this disastrous complication. Furthermore, the deployment of stents in these more complicated settings, particularly with strong antiproliferative drug-eluting stents, may lead to an increased risk of thrombotic events as a result of the augmented prevalence of the first- and second-category risk factors described above. As revisited by Cheneau et al., procedural optimization reducing the third-category risk factors will therefore be of particular importance in this situation. At present, IVUS is the only practical tool to directly visualize the stents deployed within coronary arteries in vivo, allowing reliable quantitative and qualitative assessment of the procedural results in clinical settings. Although the use of IVUS in all patients for the sole purpose of reducing thrombosis is not warranted from a cost standpoint, online IVUS guidance will have a continued role in the drug-eluting stent era by providing a level of optimization that will help deliver truly low rates of this complication, as operators are faced with continually more difficult anatomic and technical challenges.

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References


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