Stent Thrombosis in the Era of the Drug-Eluting Stent

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ABSTRACT

Coronary stent thrombosis (ST) has been regarded as a rare but catastrophic complication of bare-metal stent (BMS) implantation that normally occurs during the first few weeks after stenting. In the drug-eluting stent (DES) era, there has been increasing concern regarding higher rates of ST due to delayed endothelialization. However, a pooled meta-analysis of randomized clinical trials and registry studies showed rates of ST (0.4-1.5%) after DES to be similar to those of BMS. The rate of ST did not differ between sirolimus- and paclitaxel-eluting stents. Additionally, the rates of late ST were similar between DES and BMS. Remarkably, very late occurrence of ST, which develops up to 1-2 years after DES implantation, was significantly associated with complete cessation of antiplatelet therapy. Further large-scale studies are needed to determine the optimal combination and duration for antiplatelet therapy in order to prevent these serious thrombotic events. (Korean Circulation J 2005;35:791-794)

KEY WORDS: Thrombosis; Drug-eluting stent.

Considering the 6-months angiographic restenosis rate of 30-40% with balloon angioplasty and of 20-30% with bare-metal stents (BMS), restenosis after percutaneous coronary intervention (PCI) has been a major limitation of treatment. Recently, the advent of the drug-eluting stent (DES) dramatically reduced the restenosis rate to less than 10%. Since then, there has been an explosive rise in their use in clinical practice over a very short period. While the short- and medium-term safety and efficacy of DES have been well-demonstrated, several cases of late thrombotic events, occurring months or even years after DES implantation, have aroused the attention of patients and physicians in regards to the unexpected, adverse effects of DES.

Coronary stent thrombosis (ST) has been regarded as a rare but catastrophic event that occurs after stent implantation, and almost always causes acute myocardial infarction (AMI) or sudden cardiac death. Since bare-metal stents are known to be re-endothelialized within a few weeks after the procedure, dual antiplatelet therapy for approximately 2-4 weeks might be enough to prevent ST. Therefore, this rapid endothelialization of stents makes late thrombosis (>30 days after procedure) exceedingly rare and has mainly been confined to patients undergoing coronary brachytherapy. Although DES dramatically reduces in-stent restenosis, there may be increased concerns regarding higher rates of ST due to delayed endothelialization. Furthermore, recently reported data on late ST raise concerns about long-term safety and necessitate serious caution against extraordinarily late onset of ST.

Frequency and Timing of ST

During the early clinical period of the use of stents in human coronary arteries, unacceptably high rates (15-20%) of thrombotic occlusion due to stent thrombogenicity were major limitations. Although the incidence of this catastrophic event was decreased to a single-digit number by the use of aggressive anticoagulation therapy, this approach has been associated with longer periods of hospitalization and higher rates of hemorrhagic complications. Significant improvements in the prevention of ST have been achieved through the technical development of stent implantations and the use of potent antiplatelet agents. Application of high-pressure dilatation during stent deployment (under the guidance of intravascular ultra-sound) was used to ensure optimal stent expansion and to prevent stent malapposition. Dual antiplatelet therapy with aspirin plus a thienopyridine, along with the high-pressure technique, significantly reduced ST rates. Nevertheless, ST has not been completely eliminated, and several previous studies have reported ST in 0.5-2% of patients following BMS implantation.
In the DES era, a pooled meta-analysis of randomized clinical trials showed similar rates of ST (0.4-0.6%) after DES to those of BMS. The rate of ST did not differ between sirolimus- and paclitaxel-eluting stents. Prospective registry studies, which included more complex lesions and an “off-label” population, showed that the incidence of ST was approximately 1.0-1.5%; is the incidence was within the expected range of BMS, but was higher than rates of ST observed in randomized clinical trials. In hospital patients, a higher incidence of ST was found after paclitaxel-eluting stent implantation compared with sirolimus-eluting stent implantation (1.7% vs. 0.8%, p=0.09), although this difference did not reach statistical significance. Considering the fact that the duration of thienopyridine therapy tended to be longer with paclitaxel-eluting stents than with sirolimus-eluting stents in the clinical trials, the possibility of a higher thrombogenicity of paclitaxel might have been alleviated by a longer duration of dual antiplatelet therapy. However, it may be difficult to declare the inferiority of any type of DES due to the paucity of ST occurrences after DES implantation.

ST mostly occurs during the first few days after an implantation procedure. It seems reasonable to believe that late occurrence of ST would be extremely rare after endothelialization of BMS. Accordingly, late ST in the BMS era was regarded as a rare phenomenon, mainly limited to patients undergoing coronary brachytherapy. The ST rates in patients who underwent coronary brachytherapy are up to 5-7%, which is higher than that seen in control patients. The high incidence of ST after brachytherapy is thought to be caused mainly by impaired endothelialization, fibrin deposition, and platelet activation. Although coronary brachytherapy was the most important risk factor of late ST in the BMS era, late ST in the absence of prior coronary brachytherapy was also reported. Colombo et al. showed that 40% of stent thrombosis (0.6% of a total of 1.5%) occurred more than 2 months after stent implantation. Other studies demonstrated that late ST occurred at rates of 0.6-0.8% in non-brachytherapy patients and was almost as frequent as early ST. It is quite compelling that late ST is not confined to stented coronaries undergoing brachytherapy, but is actually a more generalized phenomenon that may be exaggerated in the irradiated artery.

Animal studies have raised concerns regarding the development of late ST after DES implantation due to delayed endothelialization. Some anecdotal reports regarding late angiographically-confirmed ST have been reported recently. In a single center experience with a large, consecutive, unselected population, the incidence of late angiographic stent thrombosis (LAST) after DES implantation was 0.35-0.72%. These events mainly occurred with a temporal relation to the discontinuation of antiplatelet therapy. Although it is difficult to compare the actual incidence of LAST between DES and BMS due to the paucity of reports, a recent meta-analysis of clinical trials showed that the rates of late ST were similar between DES and BMS (0.23% vs. 0.25%, respectively; OR 0.99, 95% CI 0.35-2.84, p=1.00). Further large-scale studies may be required to determine the differential pattern and risk factors of LAST in terms of the differences between DES and BMS, and to define whether longer-term pharmacological treatment may decrease or prevent this catastrophic complication.

Predictors of ST

Over the past several years, a number of studies have evaluated potential predictors of acute and subacute ST. Although the underlying pathophysiology has not been fully clarified, multiple risk factors related to the device, patients, lesions, and procedures have been suggested in the development of ST. Device-related factors such as stent material, design, surface coating, and adjunctive therapeutic agents, such as radiation or drugs, were suggested as risk factors. Additionally, total stent length and the use of multiple stents per lesion may be significant risk factors in association with lesion characteristics. Importantly, persistence of fibrin, platelet recruitment, and delayed endothelialization after coronary brachytherapy or antiproliferative drug-eluting stent implantation could be significantly associated with the development of ST. In terms of the patient- and lesion-related factors, several studies suggested that vessel size, lesion length, acute coronary syndrome, plaque characteristics, local platelet/coagulation activity, old age, diabetes, and left ventricular ejection fraction were important risk factors.

Procedure-related risk factors linked to the development of ST include deployed stent morphometric abnormalities (underexpansion and asymmetry), morphologic abnormalities (dissection, incomplete apposition, thrombus, and tissue protrusion), mechanical vessel injury, and anti-thrombotic therapy.

Although reports regarding the risk factors of ST after DES implantation are rare, it may be certain that the aforementioned device-, patient-, lesion-, and procedure-related risk factors may also be significantly related to the development of ST in the DES era. A meta-analysis of clinical DES trials showed that the risk of ST was related to the stent length and the number of stents per patient. Additionally, Iakovou et al. reported that premature discontinuation of antiplatelet therapy, renal failure, bifurcation lesions, diabetes, and low ejection fraction were identified as predictors of thrombotic events in consecutive “real-world” hospital patients. A recent study using intravascular ultrasound demonstrated that stent underexpansion and signifi-
can residual reference segment stenosis were associated with ST after successful sirolimus-eluting stent implantation.\textsuperscript{58}

**Relationship between Antiplatelet Therapy and Development of ST**

After DES implantation, premature discontinuation of antiplatelet therapy was the most important predictor of ST.\textsuperscript{4,7,10} These studies showed that thrombus occurred in 29% patients (OR 9.89, 95%CI 29.9-269) who prematurely discontinued dual antiplatelet therapy, and this event could develop approximately 1 year after uncomplicated stenting. Ong et al.\textsuperscript{7} also showed that LAST might develop when patients were stable on antiplatelet monotherapy. These reports raise the paramount significance of antiplatelet therapy for prevention of ST after DES implantation.

At this time, we should consider the potential clinical consequences of this phenomenon. Patients with coronary artery diseases may have significantly higher chances of undergoing surgical procedure than the normal population due to a higher prevalence of surgery-necessitating complications resulting from cardiovascular risk factors. If the patient needs a subsequent surgical procedure requiring the interruption of antiplatelet therapy, DES could not be pertinent treatment for coronary intervention. Patients may not be as compliant with prolonged antiplatelet therapy in real practice as they are in clinical trials; this may potentially lead to a higher risk of ST events. In these situations, we should seriously weigh the risk of ST against the risk of restenosis before DES implantation. Another important issue is how unplanned surgery should be dealt with after DES implantation. In a case of minor surgery, the surgical procedure may be done without interruption of antiplatelet therapy despite the increased risk of bleeding. If the patient is expected to receive major surgery, preoperative discontinuation of antiplatelet therapy for less than 4-5 days should be considered.

Most importantly, it should be emphasized that extremely late ST can develop up to 1-2 years after DES implantation. It is still unclear when antiplatelet therapy can be safely stopped, and how long dual antiplatelet therapy is needed to prevent late ST. To clarify these issues, further large-population registries and a prolonged post-marketing survey including unselected, real-world hospital patients should be conducted. Furthermore, considering the fact that ST also occurs when patients are stable on antiplatelet therapy, further studies are needed to investigate the relationship between ST and resistance to antiplatelet therapy, to screen vulnerable patients to ST, and to prescribe adequate antiplatelet regimens beyond standard dual antiplatelet therapy after DES implantation.

**Conclusions**

In randomized trials and registries, DES showed similar rates of ST compared to those of BMS. Several patient- and procedure-related risk factors of ST were identified, and complete discontinuation of ST therapy was the most important predictor of thrombotic events after DES implantation. Further large-scaled studies are needed to determine the optimal combination and duration for antiplatelet therapy that should be used to prevent these serious thrombotic events.

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