Stent thrombosis: Rethinking of drug eluting stents
Rahman MT, Haque SA, Chowdhury AW, Aziz M

Introduction
Percutaneous transluminal coronary angioplasty has become the most frequently used method for myocardial revascularization. The use of uncoated coronary-artery stents during percutaneous intervention has decreased the incidence of acute complications and improved the outcome of patients, but restenosis within the stent compromises the long-term results. As a consequence, the prevention and treatment of in-stent restenosis have become priorities in interventional cardiology.

Drug-eluting stents, which markedly reduce in-stent restenosis, have relegated all other therapeutic approaches to the background. However, it is gradually emerging that rates of late restenosis after the use of drug-eluting stents are higher than initial experience suggested, particularly in patients who have complex lesions or are at high risk for complications (e.g. those with multivessel disease or diabetes). In such cases, rates of binary in-segment restenosis are 8.9 to 18.9%. Recently, the problem of late thrombosis (>1 month after the procedure) has further dampened initial enthusiasm and has reduced the indiscriminate use of first-generation drug-eluting stents. As a result, interventional cardiologists have tended to revert to more predictable devices (e.g. uncoated stents or ones that are coated with so-called inert compounds, such as silicon carbide and titanium-nitride-oxide), which are designed to decrease acute surface thrombogenicity. Thus, in-stent restenosis is likely to remain an important clinical issue.

Catheter-based drug delivery was originally developed by Harvey Wolinsky to prevent restenosis after balloon angioplasty. In the 1990s, extensive research was carried out to improve catheter-based, site-specific (or local) intra-arterial delivery of drugs. However, studies in animals and humans showed marked variability of site-specific uptake in the arterial wall and a quick washout of the compound that were being studied, so clinically convincing results could not be demonstrated. These difficulties favored the development of stent-based drug delivery.

For several years restenosis was the Achilles' heel of coronary artery stenting by limiting long-term efficacy. Introduction of drug eluting stents (DES) reduced this problem dramatically.

Recently, studies have indicated that this reduction in restenosis might have been obtained at the expense of a higher incidence of stent thrombosis, particularly late stent thrombosis. This supposition has reignited a debate about the mechanisms of stent thrombosis especially in relation to DES.

1. Dr. Md. Toufiqur Rahman, FCPS, MD, Assistant Professor, Cardiology
2. Dr. S Azizul Haque, FCPS, MD, FACC, FRCP, Professor, Department of Cardiology, SSMCH, Dhaka
3. Dr. A Wadud Chowdhury, FCPS, MD, Associate Professor, Department of Cardiology, NICVD
4. Dr. Mustafizul Aziz, MCPS, MD, Department of Cardiology, NICVD
Epidemiology
The incidence of stent thrombosis has been reported in a number of studies most of which have found an incidence of 0.5-2%, but despite being a quantitatively minor problem, stent thrombosis has a major clinical impact owing to high risk of myocardial infarction and death. Thus, mortality due to stent thrombosis has been reported to be as high as 45%.

Definition and classification
A new standard definition of stent thrombosis was recently proposed by an Academic Research Consortium (ARC) in order to make it possible to compare the true rates of stent thrombosis across different trials and registries. The ARC is composed of clinical investigators, industry representatives and regulators including the Food and Drug Administration, and the definition categorizes stent thrombosis according to the level of documentation and timing.

- Definite or confirmed event (symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis).
- Probable event (unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of stent thrombosis).
- Possible event (any unexplained death after 30 days).

Based on the elapsed time since stent implantation stent thrombosis can be classified as:

- Early (0-30 days post stent implantation)
- Late (>30 days)
- Very late (>12 months)

Often, early stent thrombosis is further subdivided into acute (<24 hours) and subacute (1-30 days) events.

Mechanisms: vascular response to stenting and the importance of platelets and coagulation
Both bare metal stents (BMS) and DES induce platelet adhesion, activation and thrombus formation and, therefore, effective anti-platelet therapy is mandatory for some time after stent implantation. Gradually, stents are covered with endothelial cells that do not induce thrombus formation, and the need for platelet inhibition decreases.

Cytotoxic drugs used in DES in order to reduce smooth muscle cell growth after coronary intervention also inhibit this endothelialisation.

Furthermore, sirolimus and paclitaxel induce expression of tissue factor in the stented lesion causing activation of the coagulation system.

The polymers used to load these drugs may cause inflammation in the coronary artery characterized by infiltration of eosinophilic cells in the vessel wall suggestive of hypersensitivity reaction and this might also contribute to a prothrombotic environment.

Mechanisms
Clinical factors:

- Procedure and lesion-related parameters:
  * Use of multiple stents
  * Small vessel diameter
  * Coronary dissection
  * Geographic miss
  * Slow flow
  * Long lesions
  * Stent malapposition
  * Underexpansion of the stent
  * Stent design (strut thickness and polymer type)
  * Bifurcation lesions

- Patient characteristics:
  * Diabetes
  * Acute Coronary Syndromes (especially STEMI)
  * Left ventricular dysfunction
  * Renal failure
* Advanced age
* High platelet reactivity

Anti-platelet therapy:
* Inadequate intensity of therapy (i.e. non-dual platelet inhibition or insufficient dose)
* Non-compliance
* Premature cessation of anti-platelet therapy

**Platelets and anti-thrombotic therapy**
Platelets have a pivotal role in thrombus formation including stent thrombosis and thus, an optimal anti-platelet therapy is of crucial importance in the prevention of stent thrombosis. High platelet reactivity is a risk factor for thrombotic events.

Relative low-responsiveness to anti-platelet therapy (often referred to as drug resistance) is associated with ischemic cardiovascular events such as unstable angina, myocardial infarction and cardiac death.

Furthermore, it has been shown that high post-interventional platelet reactivity and incomplete inhibition of the P2Y12 platelet receptors are risk factors for subacute stent thrombosis\(^{13,14}\). An impaired response to anti-platelet therapy with aspirin has been reported in patients suffering stent thrombosis\(^{15}\).

Thus, measuring the effect of anti-platelet therapy might prove valuable in determining the optimal treatment for the individual patient. However, currently no golden standard or guidelines on such measurements exist.

Dual anti-platelet therapy with aspirin and clopidogrel must be continued for a longer time period after implantation of DES than after BMS implantation and treatment for 12 months are usually recommended.

Aspirin should be continued life-long. Clinically, there is a temporal link between cessation of dual anti-platelet therapy and occurrence of stent thrombosis\(^{16}\), and recently presented registry data indicate that some patients might benefit from prolonged dual anti-platelet therapy\(^{17,18}\).

However, dual anti-platelet therapy for more than 12 months has not been tested in clinical trials and is, therefore, currently not recommended, because long-term dual anti-platelet therapy is associated with an increased risk of bleeding complications\(^{19}\). The challenge is to find the optimal balance in order to achieve the lowest possible risk of stent thrombosis without subjecting patients to an unnecessary risk of bleeding complications.

**Perspectives: Future prevention of stent thrombosis**

Tents coated with new cytotoxic drugs and polymers may have different properties in terms of affecting endothelialisation, vascular inflammation and indication of tissue factor activity.

Coating with NO-donors may decrease platelet adhesion and aggregation. Stents coated with CD34-antibodies may capture circulating endothelial progenitor cells and may be able to prevent thrombosis by increasing and accelerating endothelial coverage.

Furthermore, development of biodegradable stents also be a way to decrease the incidence of late and very late stent thrombosis.

Anti-thrombotic therapy is likely to be optimized with the development of new more efficient anticoagulants and anti-platelet drugs with a lower risk of bleeding complications. Patients and health personnel should be informed about the risk associated with premature cessation of therapy.

Development of new tests able to assess platelet inhibition may identify patients with a reduced benefit from aspirin or clopidogrel and may make it possible to further individualize and optimize anti-platelet therapy.
The risk of stent thrombosis has been a known complication after PCI for quite a long time and might be increased after implantation of DES. The issue of in-stent thrombus formation, therefore, has attracted great attention once again.

Though evidence remains inconclusive, some studies indicate that the incidence of late and very late stent thrombosis is increased after DES implantation.

Importantly, it is unknown whether very late stent thrombosis is a time limited phenomenon and thus, the problem might increase, if events continue to accrue over time.

As a consequence, large-scale clinical trials with long-term follow-up as well as mechanistic studies are highly warranted. Currently, it is not known whether very late stent thrombosis is prevented with an extended course of dual anti-platelet therapy.

Certainly, the issue of stent thrombosis emphasizes the importance of careful patient selection and individualized therapy, which, in future, might partly be based on measurement of the intensity of platelet inhibition.

References


