REVIEW ARTICLE

Re-occurrence of Stent Thrombosis Post Angioplasty- A Comprehensive Review

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Abstract

Coronary diseases are caused by to inability of arteries to carry sufficient oxygenated blood to the heart muscles. Mostly, obstruction to the blood flow occurs due to the formation of a clot in the blood vessels. Thrombosis leads to the narrowing of blood vessels and to correct narrowed blood vessels, a specialized medical device- stents are placed inside the vessels via angioplasty. Even after successful placement of stents and correction of blood vessel narrowing problem occurs. Stent thrombosis is a common problem that occurs after percutaneous coronary intervention. It occurs due to the formation of blood clots within or around the stent, blocking the vessel partially or entirely leading to heart attack and other health issues. This review article focuses on establishing a basic understanding of stent thrombosis along with a few case histories of re-occurrences of stent thrombosis where patients suffered stent thrombosis. Various online scientific and medical databases like MedScape, Medline, Science Direct, SciLit, Scopus, Web of Science, Research Gate, and Google Scholar were browsed to collect the literature on 'Stent thrombosis' and 'Recurrences of Stent Thrombosis' for compilation of this review article. This study revealed that modern scientifically evolved and tested and medicated stents along with blood thinners, can be a standard method for prevention of 'stent thrombosis'.

Keywords: Stent thrombosis, Angioplasty, Recuurrence, Percutaneous Coronary Intervention, Myocardial infarction.
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Introduction

Stent thrombosis (ST) can be described as a serious complication that can occur after percutaneous coronary intervention (PCI) in which a stent is implanted to widen narrowed or blocked blood vessels in the heart.[1] It occurs by the formation of a blood clot within or around the stent, which may cause an artery to entirely or partially block, a heart attack, or sudden death. ST continues to be an important management concern for patients having PCI, and recurrent ST is especially concerning despite considerable advancements in stent technology and the use of antiplatelet medication.[2]

For the treatment of obstructive coronary artery disease, most of the patients having percutaneous coronary intervention (PCI) use coronary artery stents, mostly drug-eluting stents. They reduce the need for repeat revascularization compared to balloon angioplasty alone (formerly known as percutaneous transluminal coronary angioplasty) and prevent the stented artery from abruptly closing down right after the procedure.[3] A rare but dangerous adverse drug reaction of PCI with stenting is stent thrombosis. When patients first appear with symptoms, they typically have an acute coronary syndrome with ST-segment elevation on the ECG.[4,5] Total or partial thrombotic blockage of a coronary artery by a thrombus that arises in or near an intracoronary stent is what causes it. This result is observed when performing coronary angiography, which is essentially required to confirm the diagnosis. Stent thrombosis can result in death and myocardial infarctions often.[6]

By widening coronary artery stenosis, mechanical coronary revascularization restores coronary flow. Catheter-based techniques also result in severe endothelial damage and cause stress to the artery wall.[7] Therefore, opening the coronary artery and preventing or minimizing the effects of iatrogenic tissue injury should be considered as part of a successful and safe percutaneous coronary intervention (PCI).

PCI is now a successful (less restenosis), secure (treatment of emergency artery closure during balloon angioplasty), and useful (stents were designed for lesions of convoluted architecture and difficult conditions) revascularization technique thanks to the use of stents. Therefore, coronary stenting is considered the first-line treatment due to these advantages.[8] However, apart from these advantages this life-saving device carries the risk of a life-threatening complication known as stent thrombosis. The rate of stent thrombosis-associated serious events continues to be high; 26% of patients with stent thrombosis die and 63% suffer myocardial infarction.[9,10]

Etiology of Stent Thrombosis

Large randomized trials and registries have identified patient/lesion, procedural, or stent factors related to stent thrombosis.[11,12] The Champion-Phoenix study found angiographic thrombus load, total stent length, and non-ST-elevation myocardial infarction (NSTEMI) and

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ST-elevation myocardial infarction (STEMI) at presentation as independent predictors of acute stent thrombosis.[13] Through different cohort studies, it was identified that there are many independent risk variables for early stent thrombosis, including diabetes mellitus, renal insufficiency, Duke danger score, final stent minimum luminal diameter, preprocedural thienopyridine medication, baseline hemoglobin, and the severity of coronary artery disease. The small cross-sectional area of less than 5 mm, malposition of stent struts, plaque prolapse or protrusion, edge dissection, and residual stenosis played significant roles in predicting early stent thrombosis in an intravascular ultrasound (IVUS) sub-study of the Horizon AMI (acute myocardial infarction) trial.[14] The main cause of stenosis was bifurcation stenting; it has widely contributed to thrombosis in stents. In spite of using a variety of stents, patients with STEMI had a greater risk of stent thrombosis, as demonstrated by the Triton TIMI 38 study, which also demonstrated a 50% reduction in risk with more effective antiplatelet medication like prasugrel.[15]

Factors Associated With Stent Thrombosis

Several factors are responsible for the development of recurrent ST, including incomplete stent apposition, malapposition, stent under expansion, stent fracture, and neoatherosclerosis. Incomplete stent apposition occurs when the stent is not completely in contact with the vessel wall, which leaves a gap between the stent and the wall where blood can pool and clot. Malapposition occurs due to the incorrect positioning of the stent within the vessel, resulting in uneven expansion and gaps between the stent and vessel wall. Stent under expansion can occur if the stent is not inflated enough, resulting in a smaller-than-intended diameter and an increased risk of ST. Stent fracture can occur if the stent is subjected to excessive pressure or stress, forming cracks or breaks in the stent struts. Finally, neoatherosclerosis is the development of new atherosclerotic lesions within or around the stent, which can promote clot formation.[16]

Patient-related factors

Patient-related factors include sub-acute stent thrombosis risk, such as clinical presentation (stable angina vs. acute coronary syndrome) and hemodynamics Stability (coronary perfusion pressure and flow). In these different subsets of patients, there may be the varied potential of thrombogenicity and resultant sub acute stent thrombosis.[17]

Stent-related factors

The length and number of stents placed in a lesion as well as the stent geometry, were considered to affect the incidence of sub-acute stent thrombosis. Similarly, stent-specific features such as anticoagulant coatings and stent material may influence the rate of stent thrombosis.[18] Stent used in the treatment should have undergone basic studies before implanting it.

Procedural-Related Factors

Non-optimal procedural success (stent under expansion, stent malapposition, inflow/outflow disease, dissection) has been clarified as a significant independent predictor of early stent thrombosis by autopsy and IVUS investigations.[19, 20] A method that increases the risk of thrombotic occlusion is the stenting of bifurcation lesions using stent struts that are not opposed to the artery wall, which causes damage to the arterial wall and causes stenosis.[21]

Antiplatelet Therapy-Related Factors

Premature withdrawal of antiplatelet medications or their ineffectiveness is the main reason for stenosis. According to the Dutch stent thrombosis registry analysis, drugs such as clopidogrel cessation were a significant independent predictor of stent thrombosis.[22,23] Clopidogrel therapy interruption during the first 30 days following PCI increased the hazard ratio for stent thrombosis to 36.5 (95% CI 8.0–167.8), and it was also associated with a significantly higher risk of stent thrombosis between 30 days and six months (hazard ratio 4.6, 95% CI 1.4 to 15.3).[24] Similarly, stent thrombosis was independently correlated with the lack of aspirin medication.[25] Antiplatelet drugs used for the treatment should be used for a specific period of time.

Stent Thrombosis—Histopathology and Intravascular Ultrasound (IVUS)

The studies of stenosis showed that thrombus formation and acute inflammation happen first, then neointimal growth after the coronary stent implantation. Platelet and fibrin deposition, as well as neutrophil infiltration, are associated with the struts of the stent within the first 24 hours after stenting in humans.[26,27] The inflammation in the arterial wall is caused by the interaction between the stent and the artery wall; more inflammation is associated with tunica media damage and stent strut penetration of the lipid core.

There are connections between inflammation and the development of neointimal as well. A neointimal, including smooth muscle cells, was discovered two weeks after stenting. Restenosis may occur in stents left in place for more than 30 days due to excessive neointimal growth connected to arterial repair. The neointimal thickness at stent strut positions is greater when the tunica media has been harmed and when the struts are in contact with plaque.[26] Although the exact time it takes for people to fully endothelialize stents is unknown, at least three months are probably needed.[30] Histopathological evidence of inflammation and IVUS evidence of vascular remodeling are linked to very late DES thrombosis. Eosinophilic infiltrates are more prevalent in thrombi extracted from very late DES thrombosis, especially in SES, compared to other MI causes, and they correlate with the degree of stent malapposition.[27]

Classification of Stent Thrombosis

Stent thrombosis is categorized in the definition based on the date and degree of evidence. A diagnosis of stent thrombosis must meet the following criteria:

- *Definite or verified incident* (angiographic or pathologic evidence of stent thrombosis and symptoms indicative

of acute coronary syndrome).

- *Probable event:* target vascular myocardial infarction without angiographic proof of stent thrombosis or sudden undetermined death within 30 days.
- *Potential event*: any unsolved death that occurs after 30 days.[28]

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).[29]

Early stent thrombosis is further subdivided into acute (<24 hours) and sub-acute (1–30 days).

Early Thrombosis

The animal model for stent thrombosis showed rapid thrombus formation, cyclic variations in blood flow, and acute obstruction. The animal model for stent thrombosis showed abrupt thrombus formation, cyclic variations in blood flow and acute obstruction.[30] According to human conclusions, a platelet-rich thrombus is the primary factor inducing early stent blockage.[29] According to certain theories, early stent thrombosis has been attributed to the procedure itself. The primary symptoms of early stent thrombosis was shown to be poor post-procedural outcomes in individuals with acute stent thrombosis by IVUS examinations.[31,32]

Late Stent Thrombosis

Late stent thrombosis was associated with the following morphological substrates.[33]

- Stenting across significant arterial side branches results in increased blood flow turbulence and low-flow foci at the stent's edges because the struts of the stent are not opposed to the artery wall. Local fibrin and platelet deposition are increased in these regions of low flow velocity.
- Disruption of plaque in the artery segments adjacent to stents
- Stenting of necrotic lipid-rich plaques with plaque prolapse; in severely necrotic plaques, stent struts deeply penetrate the lipid core and are not in contact with the arterial wall. The absence of migrating and proliferating smooth muscle cells in close proximity to the stent may have prevented the establishment of a compact endothelialized neointimal in an artery with a substantial lipid core.
- Diffuse in-stent restenosis with thrombosis.

Very Late Stent Thrombosis After Des Implementation

Very late stent thrombosis is a distinct entity complicating the use of first-generation (sirolimus and paclitaxel) drug-eluting stents.

- Cytotoxic drugs used in DESs to reduce smooth muscle cell growth after coronary intervention also inhibit endothelialization. Delayed healing manifested by persistent fibrin deposition and incomplete re-endothelialization emerged as the prevailing mechanism of DES thrombosis in necropsy studies.[34,35]
- Drugs released from the drug-polymer combination might be thrombogenic on their own. Sirolimus and paclitaxel induce expression of endothelial tissue factor that is, the principal activator of the coagulation cascade.[36,37]
- Autopsy studies of patients with very late stent thrombosis showed extensive intima, media, and adventitia vacuoles.[38] A recently published study[39] correlated the Histopathological findings from aspirated thrombus specimens with intracoronary ultrasound structural changes of the arterial wall. The pathogenic mechanisms of late and very late stent thrombosis is depicted in Figure 1. The study demonstrated that very late stent thrombosis is associated with histopathological and serological signs of inflammation. Eosinophilic infiltrates were associated with evidence of vessel remodeling leading to secondary stent malapposition. These findings suggest eosinophilic coronary arteritis due to delayed hypersensitivity reactions as one of the causes of very late DES thrombosis.

Case Studies Report On Re-Occurrence of Stent Thrombosis

Coronary Stent Infection Presented as Recurrent Stent Thrombosis

- *Case Summary*

It is a case of a 69-year-old man who was admitted to the hospital for transurethral resection of the prostate (TURP) for benign prostatic hyperplasia along with prophylactic antibiotics and intravenous cefazolin. The patient had a history of hypertension, type 2 diabetes mellitus, and ischemic heart failure (ejection fraction: 32%). Heart failure symptoms

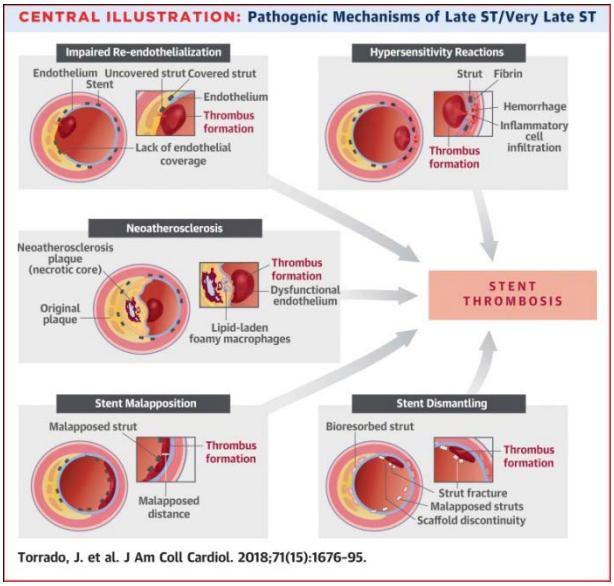

Figure 1: Mechanism of late ST/very late ST

were absent prior to surgery, and a chest radiograph showed no signs of pulmonary congestion or edema. Intubation was performed because non-ST elevation myocardial infarction, acute pulmonary edema, and respiratory failure resulted after TURP. The electrocardiogram demonstrated sinus rhythm with an early ventricular beat and left ventricle hypertrophy, and the echocardiography revealed hypokinesia in the inferior and anterior wall along with significant left ventricle systolic dysfunction (ejection fraction: 36%). Drugs such as Diuretic medications were provided for heart failure, aspirin and clopidogrel were given for myocardial infarction and a suitable antibiotic (Piperacillin-tazobactam) was given for concurrent pneumonia. After these treatments, the patient had no fever and the C-reactive protein level appeared to have dropped, suggesting that the infection had been controlled. However, the pulmonary edema continued to respond poorly to the medication.

When coronary angiography was performed two weeks later due to the patient's acute cardiac dysfunction and difficulty weaning off the ventilator, and it demonstrated triple artery disease, primarily with distal left main (LM) stenosis and chronic complete blockage of the distal right coronary artery (RCA). The patient declined coronary bypass surgery (CABG) due to the high surgical death rate. Thus, sequentially, PTCA was planned in place of it. Two drug-eluting stents (DES) were placed in the distal RCA (Everolimus-eluting stents: Promus element 2.538 mm and Promus element 3.038 mm, Boston Scientific, Natick, MA, USA). One week later, the left side received PTCA. One bare metal stent (Liberate 2.520 mm, Boston Scientific), one DES (Promus element 2.7532 mm, Boston Scientific), and another DES (Promus element 3.520 mm, Boston Scientific) were placed in the middle left anterior coronary artery (LAD) and the LM to the proximal LAD, respectively. The patient's health improved after the PTCA, and he was successfully weaned off the ventilator while continuing to take aspirin and clopidogrel, which are both dual antiplatelet drugs. But four days later, a fever started to appear. Chest discomfort and a sudden ST-elevation myocardial infarction appeared one week after the operation. Emergent angiography identified pseudo aneurysm development and sub-acute stent thrombosis at the distal LM stent. Some pus-like material was discovered during manual thrombus aspiration. Furthermore, the debris underwent bacterial culture. Following the PTCA, the flow was restored, and heparin (350 U/hour) and tirofiban hydrochloride, an intravenous glycoprotein IIb/IIIa inhibitor, were also administered. However, concurrent fever and prolonged bacteremia were also reported. The urgent PTCA was performed a day after chest discomfort and a repeat ST elevation myocardial infarction returned. Repeated angiography showed progression of the LM pseudo aneurysm and recurrent stent thrombosis. Figure 2. shows various images of replaced stent and materials aspirated from thrombosized stents.

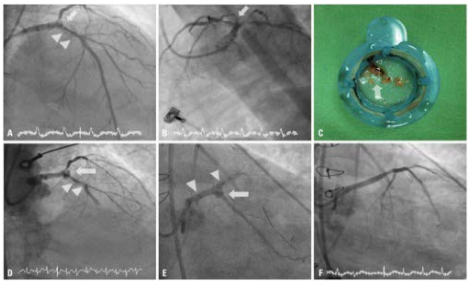

Figure 2: A and B are emergent angioplasty for first-time stent thrombosis. C Material from manual thrombus aspirator reveals thrombi with pus-like material. D is emergent angioplasty for the second time. E and F are Graft stents being inserted from LM to proximal LAD (stent margin marked as arrowheads) to cover coronary pseudo aneurysm

Despite all of this strong medication, the patient's intermittent fever stayed, and ten days later, he passed away from acute sepsis and multiple organ failure.

The conclusion from the Case study

The combined efforts of medical and surgical therapy have been reported to have a 38.9% fatality rate.[40] As a result of this, infections with an implanted stent are extremely uncommon but have a very bad outcome. Even though stent infection is uncommon, its potential must nevertheless be closely monitored. The widespread use of DES has led to an increase in reports of stent infection. The inhibition of neointimal formation could result in the metallic stent being uncovered intraluminally, creating a nidus for bacterial adherence, especially in cases of late stent infection. In addition to patient- and stent-related risk factors, it is generally accepted that procedural risk factors, such as uneven sterility during the surgery, protracted indwelling catheter use, and frequent wire changes, also play a significant role in early stent infection.[41]

A case report of an unusual occurrence of stent thrombosis

- *Case Summary*

This case study is of an elderly patient who reported to a hospital three days after an elective percutaneous intervention to the right coronary artery. A 70-year-old man arrived at a hospital with stent thrombosis caused by non-absorption of antiplatelet drugs. Due to previous colorectal cancer, the patient underwent a laparoscopic high anterior resection and discovered that pills were flowing entirely into his colostomy bag. The patient underwent further crushed antiplatelet treatment as well as balloon angioplasty and stenting procedures.

Conclusion from the Case Study

When a significant part of the gut is removed, drug absorption from the gastrointestinal tract is changed. The length of the residual small intestine and drug absorption are related.[42] Drug bioavailability may be decreased in people with short bowel due to altered intestinal luminal transit time and inadequate contact time with intestinal mucosa. There is not much research in this field, and in-stent thrombosis can readily occur due to difficulties with antiplatelet drug

absorption that are easily missed in routine practice. Using intravascular imaging methods like OCT or IVUS, the cause of stent thrombosis can be determined.

Platelet function tests after stenting should be taken into consideration when treating patients with short bowel lengths or malabsorption syndromes. Different formulations or doses of antiplatelet therapy might be trailed when there is insufficient platelet inhibition, and the effectiveness of the treatment should be observed. We advise speaking with a chemist or a medicines information service in these situations. It may also be necessary to enlist the assistance of a qualified gastroenterologist, preferably in the multidisciplinary setting of an intestinal rehabilitation center.[43]

Long-Term Clinical Outcome After a First Angiographically Confirmed Coronary Stent Thrombosis An Analysis of 431 Cases

Study Design and Patient Population

A multicenter research called the Dutch Stent Thrombosis Registry was conducted successfully in three major centers nationwide. From January 2004 to February 2007, all patients who presented with a stent thrombosis that was angiographically confirmed were taken into account. The research was done in accordance with the principles of the Helsinki Declaration. Patients provided informed consent for the registry's data to be included. Detailed information was obtained regarding the patient's characteristics, the index PCI surgery and the emergency PCI procedure for the initial stent thrombosis and two experienced interventional cardiologists independently assessed the coronary angiograms from the index procedure and the stent thrombosis. An agreement emerged between the two reviewers in cases of disagreement, or a third interventional cardiologist was consulted.

An appropriate pretreatment with a 300-mg clopidogrel loading dosage was given to patients with stable angina pectoris who underwent a scheduled PCI surgery at least 48 hours prior. Patients who required an urgent PCI due to acute coronary syndrome received a 600-mg loading dose of clopidogrel at the time of the intervention. At the time of the stent thrombosis, all patients were given clopidogrel 600 mg loading dose. The interventional cardiologist decided whether to administer glycoprotein IIb/IIIa treatment during index PCI and at the time of the stent thrombosis.

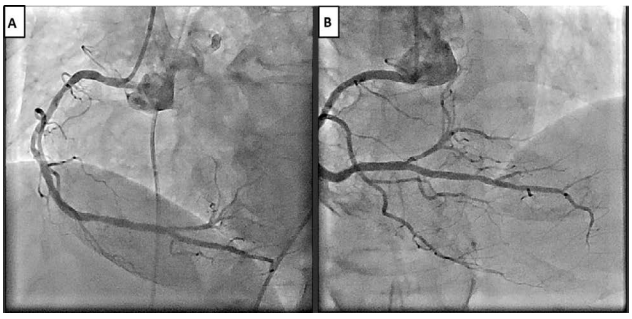

Figure 3: An uncommon case of stent thrombosis

Clinical Follow-Up

Clinical follow-up data was gathered through pharmacy and hospital records and telephone interviews with patients, their families, and general practitioners. Information was gathered regarding the occurrence of severe adverse cardiac events, which were predefined as death, recurring stent thrombosis, any myocardial infarction, and any coronary revascularization (either PCI or coronary artery bypass grafting [CABG]).

Result

About 437 people with definite stent thrombosis were enrolled during the study. Six of those people were not included in the analysis because they had already experienced stent thrombosis before the inclusion period began. Despite the fact that case reports, registries, and meta-analyses have discovered a number of correlates linked to an elevated risk for stent thrombosis,[44-46] there is currently not much known about the long-term clinical outcome following a first definite stent thrombosis in the context of mixed BMS and DES use.[47] The current multicenter observational analysis indicates that the clinical outcome includes the biggest cohort of patients with stent thrombosis to date.

Thrombosis is unfavorable in individuals who have their first identifiable stent embolism. The high incidence rate of recurrent stent thrombosis is notable despite the reduced mortality rates revealed than those reported by others.[48,49] Almost one in Five individuals who had previously undergone a confirmed stent thrombosis also experienced a definite recurrent thrombosis. In addition, it was frequent for stent thrombosis to reoccur more than once in the population under study. Patients who received further coronary stent therapy after the initial stent thrombosis fared less well. Randomized trials are essential in determining the best approach to managing stent thrombosis patients. With a high mortality rate and a significant chance of stent thrombosis recurrence, the long-term clinical result following a first definitive stent thrombosis is unfavorable. Glucose intolerance, left ventricular, long stent length, complicated coronary lesions, post-procedural TIMI flow below grade 3, the insertion of an extra coronary stent during emergency PCI for stent thrombosis, and an ejection fraction of 45% were all linked to a poor result. Figure 3. shows rare cases of stent thrombosis.

Treatment And Management

During angiography, a prompt aspiration thrombectomy or angioplasty should be performed to restore the patency of the thrombosed vessel. Compliance and drug resistance should be evaluated. More potent antiplatelet therapy, for example, prasugrel or ticagrelor, should be considered.[50] The current recommendation is to continue the dual antiplatelet drug therapy for one year after drug-eluting stent placement and at least one month following the bare-metal stent. The stent should be assessed with either intravascular ultrasound (IVUS) or optical coherence tomography (OCT)

to determine stent apposition, expansion, and the presence of edge dissections. Optimization of stent deployment with appropriate postulation and treatment of edge dissections with additional stents are imperative to prevent repeat stent thrombosis. Additional stent implantation should be avoided if possible because each millimeter of the stent increases the probability of stent thrombosis. Whether it is early, late, or extremely late, ST is an emergency, just like any acute MI. Primary PCI is the preferred treatment with the intention of mechanically recanalizing the thrombosed stent. It has been claimed that >90% of patients had successful procedures. Balloon angioplasty is usually sufficient to treat most thrombotic stent occlusions, maybe with the use of thrombus aspiration. Only large residual dissections that require further stent placement should be performed. Glycoprotein IIb/IIIa antagonists may be given to treat excessive platelet aggregation and enhance microvascular reperfusion. In the event of prolonged severe ischemia and the absence of early PCI, systemic fibrinolysis should be taken into account. The prolonged dose of 150 mg/d of clopidogrel should be taken into consideration if platelet aggregation assays show insufficient (50%) suppression of platelet aggregation with normal dual antiplatelet treatment.

Conclusion

PCI with stent insertion is the first line of therapy for coronary revascularization. Stenosis is the main cause of death in patients who underwent PCI. Although early ST and late ST occur with similar frequency after BMS or DES and outnumber very late ST by far, very late ST has emerged as a distinct clinical entity more germane to (at least the first-generation) DES than BMS. Delayed healing and impaired endothelialization induced by the drug-polymer combination are the prevailing mechanisms of late and very late ST. The preferred treatment is immediate reperfusion, ideally by primary PCI. This adverse event may be avoided by taking measures, such as paying special attention to the details of the implantation, continuing dual antiplatelet treatment for at least 12 months, and adopting alternative revascularization procedures in some patients. Since stents are being used more quickly across various regions of the world, more patients are currently at risk for this harmful outcome. By comprehending the underlying pathophysiological mechanisms, risk factors for stent thrombosis may be defined more precisely. Identification of risk factors is necessary to prevent this possibly deadly outcome. Successful drug-eluting stent implantation was followed by nine months of "real-world" patients, but the cumulative incidence of stent thrombosis in these patients was much higher than that observed in clinical studies. Predictive factors for thrombotic events were found to contain bifurcation lesions, renal failure, diabetes, poor ejection fraction, and the early discontinuation of antiplatelet medications. Despite enormous developments in antiplatelet medication, thrombotic events continue to be the primary cause of death after percutaneous coronary interventions. It has been shown that polymer-based paclitaxel-eluting stents and sirolimus-eluting stents can reduce restenosis risk and neointimal hyperplasia without increasing the risk of stent thrombosis. Most surgeons prefer drug-eluting stents for various clinical and anatomical disorders, many of which have not been thoroughly researched in randomized trials. The observational cohort research during the time period of nine months shows the proportion of a population who have the risk factors of stent thrombosis, and it also shows the clinical outcome of stent thrombosis.

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