Fatal very late stent thrombosis in a paclitaxel-eluting stent after treatment of a gastrointestinal bleeding: a case report

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Abstract

We describe a case of very late stent thrombosis (ST) in a patient presented with haematemesis, while taken aspirin and oral anticoagulation therapy (OAC). This case shows that the management of patients with indication for OAC who undergo percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation is challenging because the need to balance the risk of bleeding against the ongoing risk of ST. The use of DES might be discouraged in those patients, because of the available treatment modalities when a major bleeding occurs. A close management between gastroenterologist and cardiologist is advocated in patients with previous DES implantation and a major gastrointestinal bleeding.
**Introduction**

The use of dual antiplatelet therapy (DAT) with aspirin and a thienopyridine in the setting of percutaneous coronary intervention (PCI) with stent implantation is the standard care to prevent stent thrombosis (ST). Currently, after drug-eluting stent (DES) implantation DAT is recommended for at least 1 year. Together with the increasing use of DES during PCI, a growing number of patients is taking oral anticoagulation (OAC). The combined use of antiplatelet and anticoagulation agents appears as the most effective for prevention of ST and thromboembolism. However, triple therapy (TT) of OAC, aspirin and clopidogrel is associated with an increased risk for bleeding, especially the risk for gastrointestinal bleeding. Gastrointestinal bleeding after DES implantation presents a serious threat to patients due to the competing risks of gastrointestinal hemorrhage and ST. The optimum management of a patient with gastrointestinal bleeding with previous DES implantation is unclear. We report a case of very late ST (>1 year) in a patient presented with hematemesis, while taken the combination of aspirin and OAC.

**Case Report**

In October 2005, a 65-year-old male with a history of anterior myocardial infarction in 1982, was referred to our clinic for a non ST-elevation myocardial infarction. Cardiovascular risk factors included family history of coronary artery disease, hypertension, hypercholesterolemia, and smoking. General medical history reported recurrent transient ischemic attacks and an acute ischemic stroke, despite aspirin therapy. Further, CT of the head showed multiple old infarctions in both hemispheres suggestive for cardiogenic embolism and therefore, the patient was subsequently treated with OAC.

On presentation, chronic medication included statin, beta-blocker, nitrate, calcium-antagonist, and an angiotensin receptor blocker. Subsequent coronary angiography showed a dominant circumflex with a significant stenosis of the first marginal branch, an occluded left anterior descending coronary artery with retrograde filling, and an occluded right coronary artery. The patient was included in the SPIRIT II trial and the first marginal branch was treated with stent implantation with a TAXUS paclitaxel-eluting stent (3.0x16 mm). After consultation of a neurologist, oral anticoagulation therapy was stopped and substituted by dual antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (loading dose 300 mg, 75 mg/day), which was prescribed for 6 months. The patient was discharged without in-hospital complications.

At 6 months, the patient was asymptomatic and pre-specified follow-up coronary angiography showed a good angiographic stent result. In addition, intravascular ultrasound was performed and showed absence of in-stent-restenosis. Clopidogrel was stopped and replaced by OAC therapy again, while aspirin (100 mg/day) was continued and a proton pomp inhibitor was added to the patients’ chronic medication. At 1 year, the patient visited the outpatient clinic and was asymptomatic.
Two days after the 1 year follow-up visit, the patient was readmitted in our clinic with severe hematemesis and a hemoglobin drop of 2.6 g/dL (13.9 to 11.3 g/dL). On arrival, the patient was pale and diaphoretic, with blood pressure 105/70 mmHg and heart rate of 86 bpm, but he had no anginal complaints. He was treated with prothrombin complex concentrate (cofact®) and five units of platelets followed by emergency esophago-gastric-duodenoscopy, which showed a Mallory-Weis tear at the distal esophagus treated with band ligation. Hereafter, the patient developed severe angina complaints. A 12 lead ECG showed ST-segment elevation in the precordial leads and reciprocal ST-segment depressions inferior compatible with an anterolateral acute myocardial infarction. Within minutes, the patient experienced sudden profound hypotension, followed by cardiorespiratory arrest and pulseless electrical activity; resuscitation attempts were unsuccessful.

Autopsy of the heart was performed. The heart showed marked hypertrophy and dilatation of the left ventricle (heart weight 570 gram). Largest part of the anterior wall of the left ventricle was replaced by scar tissue, consistent with old myocardial infarction, leading to attenuation of the wall and aneurysmatic dilatation. Macro-enzyme staining with NBT (Nitroblue Tetrazolium) revealed an acute transmural myocardial infarction basal lateral region, which was in the perfusion territory of the stented artery. Postmortem angiography showed multiple severely stenosed lesions in all major epicardial coronary branches, a total occlusion of the left anterior descending artery, and total occlusion of the stent in the first marginal branch of the circumflex (Figure 1). The stented segment was excised and cross-sectioned using a diamond saw, which revealed an occlusive luminal thrombus. This was histologically confirmed in plastic embedded sections (Figure 2). Moreover, microscopy showed that the luminal surface of the stent was surrounded by fibrin-rich thrombus with only sparse embedding in neointimal tissue. There was no apparent inflammation.
Figure 1: Post-mortem angiographic image.
The image shows the thrombotic material occluding the paclitaxel-eluting stent in the marginal branch of the circumflex (arrows). In addition, the post-mortem angiography shows three-vessel disease with occlusion of the right coronary artery and left anterior descending coronary artery.

Figure 2: Thrombus within the paclitaxel-eluting stent.
Macroscopic images of the occlusive luminal thrombus within the paclitaxel-eluting stent (Panel A and B). Panel C is a high power image of the result of staining with anti smooth muscle actin and shows that the luminal surface of the stent is only sparsely embedded in neo-intimal tissue (magnification x200). Panel D is a drawn version of panel C. Thr = thrombus; Pl = plaque; St = stent strut; NIT = neointimal tissue.
Discussion

PCI-procedures are performed in increasingly complex patients with multiple comorbidities, including patients treated with long-term OAC. OAC is the most effective treatment in the prevention of thrombotic events in conditions such as atrial fibrillation, prosthetic heart valves, and recurrent ischemic stroke, however, DAT is superior to OAC alone or OAC combined with aspirin in preventing major adverse cardiovascular events following PCI. Recently, TT of OAC, aspirin and clopidogrel, has been recommended as the optimal antithrombotic treatment in patients on long-term OAC with moderate-high thromboembolic risk, owing to the favorable net clinical benefit. Short-term DAT without OAC is the optimal strategy in patients with low thromboembolic risk. Although, TT can be considered as the most effective antithrombotic treatment in patients treated with long-term OAC, it is associated with a 3- to 5-fold higher bleeding rate when compared with DAT. Owing to this inherent risk of major bleeding, patients should always be treated with TT for as short a time as possible. Furthermore, gastric protection by a proton pump inhibitor is recommended in all patients who receive TT and in patients with risk factors for gastrointestinal bleeding treated with DAT. Because of the high bleeding risk with TT, our patient was treated with DAT for 6 months followed by OAC and aspirin. The combined use of OAC plus aspirin is associated with an increase in major bleeding of 1.6% per year compared to OAC alone (3.9% versus 2.3%).

One third of bleeding events in patients with OAC plus aspirin originate from the gastrointestinal tract. If hemorrhage is significant, it can produce intravascular volume depletion, tachycardia, and an increase in myocardial demand, decreased perfusion and recurrent ischemia. Nowadays, it is unclear how to manage acute major life-threatening gastrointestinal bleeding in a patient who has undergone PCI with DES implantation. In the absence of specific guidelines, the current practice is based on treatment for gastrointestinal bleeding in general and frequently includes the prompt interruption of antithrombotic therapy, blood transfusions, and in case of OAC therapy, prothrombin complex concentrates for the reversal of OAC. The interruption of one or both antiplatelet agents has been demonstrated as a major responsible factor for ST in DES. Thus, treatment for gastrointestinal bleeding, although sometimes necessary may pose a substantial risk of (late) ST, especially in the era of DES.

Another important underlying substrate for very late ST in DES is impaired re-endothelialization resulting in a prothrombotic environment. In a morphological autopsy study comparing DES with bare-metal stents (BMS), Joner et al., found less endothelial coverage of DES struts compared to BMS struts, regardless of implant duration. In addition, Finn et al. reported incomplete neointimal coverage of stent struts as the most important morphometric predictor of ST. Similarly, in our patient, more than 1 year after implantation, the DES struts were only very limited incorporated in fibrocellular tissue and endothelial coverage was incomplete. In high-risk situations such as cessation of antithrombotic therapy, thrombosis
Drug-eluting stent thrombosis may develop on the uncovered/non-uniform healed stent struts. It is unknown whether re-endothelialization with DES is only delayed or persistently incomplete up to a later time point. Therefore, the window of vulnerability of DES for ST remains undefined. Our case report emphasizes the risk of hemorrhagic complications in a patient on long-term OAC after previous DES implantation. To the best of our knowledge this is the second report of ST after platelet transfusion for major gastrointestinal bleeding. However, in the 3 cases reported previously, early ST occurred in a BMS.13

Conclusion
In patients with life-long OAC and an indication for PCI the use of DES has to be avoided, because of the available treatment modalities when a major bleeding occurs. In particular, treatment of significant gastrointestinal bleeding requires balancing between the ongoing risk of ST in DES against further catastrophic bleeding. Close combined management between gastroenterologist and cardiologist is advocated to optimize patient outcomes in patients with previous DES implantation and a major gastrointestinal bleeding.
References


