

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

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## Abstract

We describe a case of very late stent thrombosis (ST) in a patient presenting with hematemesis while taking aspirin and oral anticoagulation therapy (OAC). This case shows that the management of patients with an indication for OAC who undergo percutaneous coronary intervention with drug-eluting stent (DES) implantation is challenging because of the need to balance the risk of bleeding against the ongoing risk of ST. The use of DES should be discouraged in those patients because of the available treatment modalities in which major bleeding can occur. Close management between the gastroenterologist and cardiologist is advocated in patients with previous DES implantation and major gastrointestinal bleeding.

## Keywords

Very late stent thrombosis; drug-eluting stent; gastrointestinal bleeding; antiplatelet therapy; anticoagulation therapy.

## 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, DAT is recommended for at least 1 year after drug-eluting stent (DES) implantation<sup>[1]</sup>. Together with the increasing use of DES during PCI, a growing number of patients are taking oral anticoagulation (OAC)<sup>[2]</sup>. The combined use of antiplatelet and anticoagulation agents seems to be effective for prevention of ST and thromboembolism<sup>[3]</sup>. However, triple therapy (TT) of OAC, aspirin and clopidogrel is associated with an increased risk

for bleeding, especially gastrointestinal bleeding<sup>[4]</sup>. 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 in a patient presenting with hematemesis, while taking the combination of aspirin and OAC therapy.

## 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. Computed tomography of the head showed multiple old infarctions in both hemispheres suggestive of 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 (3.0 × 16 mm). After a consultation with a neurologist, OAC therapy was stopped and substituted by DAT 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 pump 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 to our clinic with severe hematemesis and a drop in hemoglobin 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 86 bpm, but he had no anginal complaints. He was treated with prothrombin complex concentrate (Cofact<sup>®</sup>) and 5 units of platelets followed by emergency esophago-gastric-duodenoscopy, which showed a Mallory-Weiss tear at the distal esophagus treated with band ligation. The patient then developed severe angina complaints. A 12-lead electrocardiogram showed ST-segment elevation in the precordial leads and reciprocal inferior ST-segment depression 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.

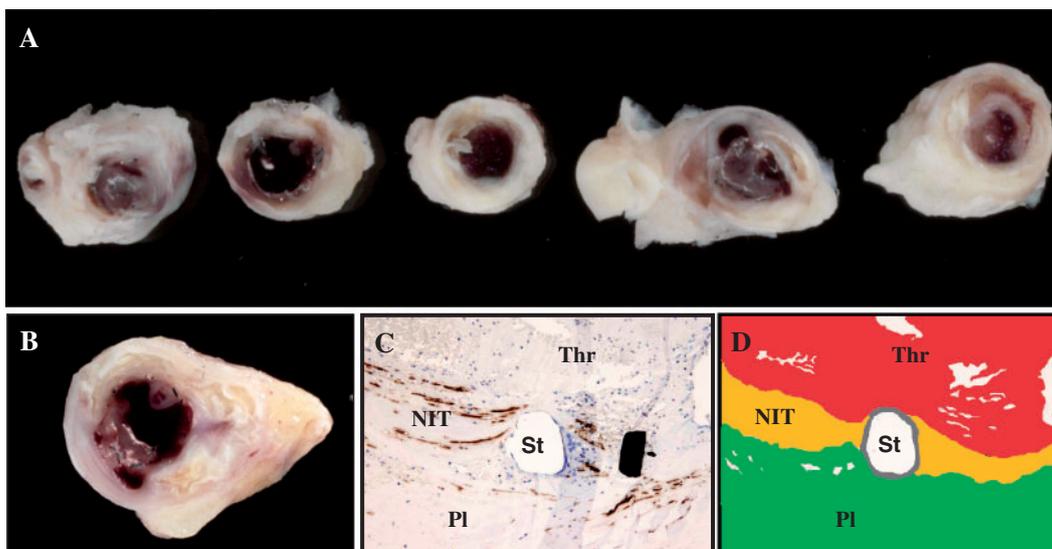
Autopsy of the heart was performed. The heart showed marked hypertrophy and dilatation of the left ventricle (heart weight 570 g). The largest part of the anterior wall of the left ventricle was replaced by scar tissue, consistent with old myocardial infarction, leading to attenuation of the wall and aneurysmatic dilatation. Macro-enzyme staining with nitroblue tetrazolium revealed an acute transmural myocardial infarction in the 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, total occlusion of the left anterior descending artery, and total occlusion of the stent in the first marginal branch of the circumflex (Fig. 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 (Fig. 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.

## Discussion

PCI procedures are performed increasingly in complex patients with multiple comorbidities, including patients treated with long-term OAC. OAC is the most effective treatment for the prevention of thrombotic events in conditions such as atrial fibrillation, prosthetic heart valves,



**Fig. 1.** Postmortem angiographic image showing the thrombotic material occluding the paclitaxel-eluting stent in the marginal branch of the circumflex (arrows). In addition, the postmortem angiography shows three-vessel disease with occlusion of the right coronary artery and left anterior descending coronary artery.



**Fig. 2.** Macroscopic images of the occlusive luminal thrombus within the paclitaxel-eluting stent (A,B). (C) A high power image of the result of staining with anti smooth muscle actin shows that the luminal surface of the stent is only sparsely embedded in neointimal tissue (magnification  $\times 200$ ). (D) A diagram of (C). Thr, thrombus; Pl, plaque; St, stent strut; NIT, neointimal tissue.

and recurrent ischemic stroke, however, DAT is superior to OAC alone or OAC combined with aspirin in preventing major adverse cardiovascular events after PCI<sup>[5]</sup>. Recently, TT of OAC, aspirin and clopidogrel has been recommended as the optimal antithrombotic treatment in patients on long-term OAC with moderate to 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<sup>[6]</sup>. Although TT can be considered as the most effective antithrombotic treatment in patients treated with long-term OAC, this is associated with a 3-5-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 using a proton pump inhibitor is recommended in all patients who receive TT and in patients with

risk factors for gastrointestinal bleeding treated with DAT<sup>[7]</sup>. 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 with OAC alone (3.9% vs 2.3% per year)<sup>[4,7]</sup>.

One third of bleeding events in patients taking 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 the 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<sup>[8,9]</sup>. The interruption of one or both antiplatelet agents has been demonstrated as a major factor responsible for ST in DES. Thus, the treatment for gastrointestinal bleeding, although sometimes necessary, may pose a substantial risk of (late) ST, especially in the era of DES<sup>[10]</sup>.

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.<sup>[11]</sup> found less endothelial coverage of DES struts compared with BMS struts, regardless of implant duration. In addition, Finn et al.<sup>[12]</sup> 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 showed only very limited incorporation in fibrocellular tissue and endothelial coverage was incomplete. In high-risk situations such as cessation of antithrombotic therapy, 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.

Patients with gastrointestinal bleeding after stent implantation are at high risk of morbidity and mortality both from the bleeding itself and the consequences of achieving hemostasis with the resultant risk of ST. To keep the risk of ST as low as possible, the chronic use of OAC poses a (relative) contraindication for DES implantation. 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 bare-metal stent<sup>[13]</sup>.

## Teaching points

- 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 in which major bleeding can occur.
- In particular, treatment of significant gastrointestinal bleeding requires a balance 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 major gastrointestinal bleeding.

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