Very Late Stent Thrombosis After Discontinuation of Antiplatelet Agents During Anticoagulation Therapy in a Patient with Peri-stent Contrast Staining After Implantation of a Second-generation Drug-eluting Stent

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Abstract:
A 54-year-old man was admitted to our hospital due to intermittent chest pain. He had a history of acute myocardial infarction, and peri-stent contrast staining had been observed at the stent implantation site. The patient previously underwent anticoagulation therapy for left ventricular thrombus and antiplatelet therapy to prevent stent thrombosis. More than one year after implantation of a drug-eluting stent, antiplatelet drugs were discontinued, and anticoagulant alone was prescribed according to the guidelines, which resulted in very late stent thrombosis. The risks of both bleeding and thrombosis must be fully considered when deciding whether or not to discontinue antiplatelet therapy during anticoagulation therapy.

Key words: very late stent thrombosis, peri-stent contrast staining, antiplatelet therapy, anticoagulation therapy

Introduction
The advent of drug-eluting stents (DESs) has dramatically reduced the incidence of restenosis after stent implantation (1). However, it has also caused a new problem in very late stent thrombosis (VLST) (2). Adequate antithrombotic therapy is essential to prevent VLST; however, the more antithrombotic drugs used, the higher the risk of bleeding. Recently, the concept of a high bleeding risk has been considered increasingly important (3), and accordingly, guidelines have recommended the aggressive reduction of antithrombotic agents (4, 5). However, in some patients, antiplatelet drugs should never be discontinued.

We herein report a case of coronary artery peri-stent contrast staining (PSS) following second-generation DES implantation complicated by acute myocardial infarction (AMI) due to VLST after the discontinuation of antiplatelet agents despite being on anticoagulation therapy.

Case Report
A 54-year-old man presented to the emergency department of our hospital with episodes of intermittent chest pain at rest for 1 h. He had a history of ST-segment elevation AMI two years previously, and emergent coronary stenting (Xience Alpine 3.0×33 mm; Abbott, Santa Clara, CA, USA) for the proximal left anterior descending artery had been performed (Fig. 1A). During hospitalization for AMI, a left ventricular thrombus was discovered. Subsequently, anticoagulation therapy with warfarin was initiated, and he was treated with triple antithrombotic therapy (aspirin 100 mg/day, clopidogrel 75 mg/day, and warfarin 3.5 mg/day).

At the time of discharge, liver dysfunction caused by clopidogrel was suspected. In addition, a risk of bleeding was also considered; accordingly, clopidogrel was discontinued, and the patient was followed at his local community hospital. One year after stenting, routine follow-up coronary angiography (CAG) was performed in our hospital. No in-
stent restenosis was observed; however, mono-focal PSS was observed at the site where the Xience stent was placed (Fig. 1B). At the time of follow-up CAG, the left ventricular thrombus had disappeared, and the left ventricular wall motion exhibited tendency toward improvement. Therefore, it was recommended that his family physician stop anticoagulation therapy and continue only single antiplatelet therapy (SAPT) consisting of aspirin.

Six months after discontinuing anticoagulation therapy, recurrence of left ventricular thrombus was found on routine follow-up echocardiography at his local community hospital. Anticoagulation therapy with warfarin was restarted, and aspirin was discontinued instead. Other risk factors for atherosclerotic cardiovascular disease included a history of smoking and very well-controlled hypercholesterolemia, which was treated with statins and proprotein convertase subtilisin kexin type 9 inhibitor.

One month after the discontinuation of antiplatelet therapy with aspirin, the present attack of chest pain occurred. His height and weight were 171 cm and 56 kg, respectively. A physical examination revealed a pulse rate of 78 beats/min, a blood pressure of 94/62 mmHg, a respiratory rate of 15 breaths/min, a peripheral capillary oxygen saturation of 94% on room air, and a body temperature of 35.6 °C. There was no heart murmur, and no other abnormal findings were observed on the physical examination. The cardiothoracic ratio was 45%, and chest radiography revealed no lung congestion. Electrocardiography revealed obvious ST-segment elevation in leads V1-4, with a heart rate of 75 beats/min and sinus rhythm (Fig. 2). Echocardiography revealed an apical aneurysm without thrombus, with a left ventricular ejection fraction of 44%.

Laboratory examinations revealed normal troponin I (0.01 ng/mL) and creatine kinase (51 U/L) levels. His white blood cell count was 7,120/μL, with a hemoglobin level of 13.8 g/dL and platelet count of 217,000/μL. The prothrombin time-international normalized ratio (1.9) was well controlled. After loading doses of aspirin (200 mg) and clopidogrel (300 mg) were administered, emergent CAG was performed, which revealed severe stenosis with translucency at the site where the Xience stent had been placed (Fig. 1C). Furthermore, PSS was observed at the stent site, similar to the find-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Coronary angiography. Immediately after stent implantation at the proximal left anterior descending artery at the time of the first myocardial infarction (A). Peri-stent contrast staining at the implanted stent site (arrow) at the time of routine follow-up coronary angiography (B). Very late stent thrombosis at the peri-stent contrast staining site (arrow) (C).
Figure 2. An electrocardiogram on admission.

Figure 3. Intracoronary imaging at the peri-stent contrast staining site. Optical frequency domain imaging clearly demonstrated a thrombus attached to the exposed stent struts (arrow) (A). Intravascular ultrasound demonstrated incomplete stent apposition due to marked abnormal positive remodeling of the vessel wall (arrows) (B).

ings on follow-up CAG.

After performing the first aspiration thrombectomy, optical frequency domain imaging clearly depicted a thrombus attached to the exposed stent struts (Fig. 3A), and an intravascular ultrasound examination revealed incomplete stent apposition due to marked abnormal positive remodeling of the vessel wall (Fig. 3B). The cause of acute coronary syndrome (ACS) was diagnosed as VLST due to abnormal vessel enlargement caused by a second-generation DES.

Subsequently, an additional aspiration thrombectomy was performed. As a result, coronary flow of thrombolysis in myocardial infarction grade 3 was achieved, and the procedure was completed. The postoperative maximal troponin I and creatine kinase levels increased to 1.42 ng/mL and 83 U/L, respectively. Maintenance doses of aspirin 100 mg/day and anticoagulation therapy with warfarin were continued. Clopidogrel 75 mg/day was discontinued at discharge. The patient was discharged on day 7 without any complications. Subsequently, there was no occurrence of stent thrombosis, recurrence of left ventricular thrombus or hemorrhagic com-
Stent thrombosis is a rare complication that occurs in 0.5% of all patients who undergo stent implantation and has been reduced with the use of second-generation DESs compared to first-generation DESs and even bare-metal stents (6, 7). PSS is characterized as contrast staining outside the stent extending to ≥20% of the stent diameter on CAG (8). Pathophysiologically, PSS is believed to reflect an abnormal response of the vessel wall to a DES (9). PSS is reported as a potential cause of late stent thrombosis (8, 10). However, PSS associated with implantation of an everolimus-eluting stent (EES), a second-generation DES, is rare compared to that in a first-generation DES (0.9% and 4%, respectively) (11). Furthermore, it is even rarer for patients with PSS caused by EES implantation to develop VLST (0% to 5.3% of PSS lesions) (10-12). Therefore, there is no consensus regarding the use of antithrombotic therapy for PSS. It has been suggested that dual antiplatelet therapy (DAPT) should be continued to prevent stent thrombosis in patients with PSS (8, 12). However, if anticoagulation is required, then long-term triple therapy with DAPT is considered to be harmful according to the guidelines because the risk of bleeding is too high (4).

In our patient, the DAPT score was calculated to be 1 point at the time of follow-up CAG, which was considered to denote a low ischemic risk. More than one year after the implantation of the second-generation DES, antiplatelet drugs were discontinued, and anticoagulant alone was prescribed in accordance with the relevant guidelines, which resulted in ACS due to VLST. To our knowledge, this is the first report to describe a patient with PSS who developed VLST despite being on anticoagulation therapy. A previous study reported that the incidence of definite stent thrombosis was 8.2% at 3 years in patients with PSS after first-generation DES implantation, and a representative case of VLST, when all antiplatelet drugs were discontinued at the time of non-cardiac surgery, was described (8). In another study, antiplatelet drugs were discontinued in all patients who developed VLST, despite PSS being observed after EES implantation (13).

Although whether or not DAPT should be mandatory in all patients with PSS is unclear, SAPT appears to be essential even under anticoagulation therapy. The Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial showed that the efficacy of anticoagulant monotherapy with rivaroxaban was non-inferior and superior to combination antithrombotic therapy with rivaroxaban plus an antiplatelet drug with regard to safety in patients with atrial fibrillation and stable coronary artery disease at one year after revascularization (14). However, the incidence of AMI was numerically higher, although not significant, in the anticoagulant monotherapy group than in the combination therapy group (13/1,108 and 8/1,107 cases, respectively).

It is possible that antiplatelet agents should not be discontinued in some high-risk patients, such as those with first-generation DESs and those with PSS. In contrast, in our case, VLST did not occur without anticoagulation when SAPT alone was administered, suggesting that anticoagulation may have a limited effect in preventing VLST in patients with PSS. A large-scale, multicenter, prospective randomized trial reported that there was no significant difference between rivaroxaban and warfarin with regard to the prevention of myocardial infarction in patients with non-valvular atrial fibrillation (0.9% and 1.1% per year, respectively) (15). It was also reported that the rate of stent thrombosis was not significantly different between patients with atrial fibrillation receiving apixaban and those receiving warfarin (0.74% and 0.97% at 6 months, respectively) (16). There seems to be no significant difference between direct oral anticoagulants and warfarin with regard to the prevention of VLST.

The guidelines recommend that patients who require continuous anticoagulation therapy discontinue antiplatelet drugs and continue anticoagulation therapy alone after one year of stenting, considering the risk of bleeding (4, 5). However, in patients who appear to be at a high risk of developing VLST, including those with PSS, there may be a greater benefit to continuing SAPT in addition to anticoagulation beyond one year after stenting. In such cases, both the risk of bleeding and the risk of VLST must be fully considered when deciding whether or not to discontinue SAPT. Since the spring of 2020, routine follow-up CAG has been rarely performed, due to the fact that the guidelines described them as non-beneficial (4) and because this procedure was considered non-essential and non-urgent during the coronavirus disease 2019 pandemic. However, there will always be some coronary artery lesions, such as PSS, that are very dangerous if antiplatelet drugs are discontinued. In patients who require permanent anticoagulation, especially those with left main trunk or proximal left anterior descending artery stenting, cardiac computed tomography before discontinuing antiplatelet therapy may be useful according to the guidelines at one year after stent implantation. If PSS is found, continued antiplatelet therapy in combination with anticoagulation therapy may be useful for preventing VLST. In addition, it is important to inform the patient’s family physician of the danger of discontinuing all antiplatelet drugs, even if the patient is undergoing anticoagulation therapy.

The authors state that they have no Conflict of Interest (COI).

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