Very Late Stent Thrombosis after Implantation of Drug Eluting Stent

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Abstract
A case of late stent occlusion of a Sirolimus eluting Cypher™ stent (Cordis, Johnson and Johnson) presenting as acute ST elevation myocardial infarction 22 months after deployment is reported. The possible mechanisms are discussed.

INTRODUCTION
There has been a growing concern among cardiologists regarding the increasing number of case reports of very late stent thrombosis after Drug Eluting Stent (DES) implantation. The incidence of subacute and late stent thrombosis within the first 30 days in patients randomized to sirolimus eluting Cypher™ (Cordis, Johnson and Johnson) stents in clinical trials is reported to be no different from that with control bare metal stents.1 Stent thrombosis as late as 17 months2 and more recently as late as 26 months after Sirolimus Eluting Stent (SES) has been reported.3

The discontinuation of antiplatelet medication has been strongly associated with DES thrombosis and is usually seen within two weeks after cessation of treatment2 but now cases of stent thrombosis several months after antiplatelet discontinuation (especially clopidogrel and while the patient was still on aspirin) are being reported2,4 leading to a debate on how long should one continue dual antiplatelet drug therapy after DES implantation.

We report a case of very late stent thrombosis 22 months after SES implantation and 19 months after clopidogrel discontinuation despite aspirin continuation.

CASE REPORT
A 45 years old hypertensive, nonsmoker, nondiabetic, dyslipidemic male with no significant family history of premature coronary artery disease presented with acute coronary syndrome in October 2003. On coronary angiography he had double vessel disease and underwent stent implantation to mid left anterior descending (LAD) and mid left circumflex (LCx) in October 2003 using a 3.0 x 33 mm Cypher™ and 2.5 x 24 mm Taxus™ (Boston Scientific) stent respectively with good result. He was subsequently discharged on aspirin 150 mg/day, clopidogrel 75 mg/day, atorvastatin 10mg/day and atenolol 10 mg/day. He discontinued Clopidogrel 4 months later. Subsequently patient had been asymptomatic and a recent Treadmill test done 4 days prior to the present admission was negative for exercise inducible reversible ischemia at moderate workload. He was admitted to our center with severe substernal chest pain and diaphoresis of 1 hour duration in July 2005. His resting ECG showed 3 mm ST elevation with tall T waves in Anterior chest leads suggestive of Hyperacute anterior wall myocardial infarction.

He was given a loading dose of 600 mg of Clopidogrel and shifted to the Catheterization Laboratory. Angiogram revealed abrupt complete occlusion of the LAD at the proximal end of the Cypher stent (Fig. 1). The Taxus stent in LCx was patent with evidence of TIMI-3 flow and right coronary artery was normal. A 0.014 x 190 cms Whisper wire™ (Guidant Corporation) was used to cross the occluded segment in the LAD. Weight adjusted abciximab bolus followed by infusion was started. Serial balloon dilatations within the stent were made. There was evidence of a 30 – 40% lesion at the distal end of the stent, which persisted even after serial balloon dilatation. This area was covered with a 2.5 x 13 mm Cypher stent. Post dilatation with a 3 mm balloon was done in the distal portion of the stent including the area of overlap; a brisk TIMI-3 flow without any residual stenosis was achieved (Fig. 2). The patient is doing well on follow up.

DISCUSSION
Although DES have helped overcome the limitation of instent restenosis a new problem that seems to be associated with the use of DES is one of very late stent thrombosis. Very late stent thrombosis after SES and
Paclitaxel eluting stent (PES) has been reported up to 780^3 and 442^4 days, respectively, after the procedure. Stent thrombosis usually occurs within a few days after discontinuation of Aspirin therapy and days to months after Clopidogrel discontinuation, and appears more closely related to discontinuation of aspirin. ^2 Nevertheless there are reports of cases that have occurred several months after discontinuation of clopidogrel even though the patient continued to be on aspirin, as in this particular case. Ong et al^3 reported the incidence of late stent thrombosis to be 0.35% in a cohort of 2006 patients who received DES and were followed up for a period of 1.5 years. They reported eight angiographically proved events of late stent thrombosis in seven patients. Three cases were related to complete cessation of antiplatelet therapy, two cases occurred within a month of stopping clopidogrel while the patients were still on aspirin, and three cases occurred several months (2 – 23 months) after clopidogrel discontinuation at a time when patients were apparently clinically stable on aspirin monotherapy. None of the patient reported with very late stent thrombosis in literature were on dual antiplatelet therapy. This has raised the pertinent question as to whether clopidogrel should be continued life long after DES implantation as put forward by Liistro and Colombo. ^5

The mechanism seems to be related to delay in the healing process and also may be contributed to late hypersensitivity reaction and consequent inflammatory changes predisposing to stent thrombosis even years after initial deployment^6 as in the present case.

These hypotheses are based upon histological characterization of tissue responses in animal studies revealing arrest of healing process and presence of inflammatory cells as a part of this delayed healing. In addition to this phenomenon, hypersensitivity reaction to the polymer and localized hypersensitivity vasculitis within the stented segment could have contributed to the adverse outcome. Late stent malapposition was seen in 21% of Cypher implants in the RAVEL study compared to only 4% in the control arm can also potentially be a contributing cause. ^6

A recent report has highlighted the issue of endothelial dysfunction 6 months after sirolimus eluting stent placement. While the subgroup which received bare metal stents demonstrated normal exercise induced vasodilatation the DES group demonstrated paradoxical vasoconstriction in the persisting region as well as the vessel portion well away from the distal stent margin. The authors proposed that this may be contributed towards increase rates of delayed stent thrombosis. ^7

In conclusion this report highlights an important issue and argues in favor of a very long-term continuation of dual antiplatelet therapy after drug eluting stent implantation.

REFERENCES