

# Very Late Stent Thrombosis Of A Cypher Stent And Review Of The Literature

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## Abstract

We discuss a case of a 67 year old woman presented to the Emergency Department of the Gold Coast Hospital (Queensland, Australia) in February 2008 with a one hour history of central heavy chest pain with radiation to her left arm.

## CASE REPORT

A 67 year old woman presented to the Emergency Department of the Gold Coast Hospital (Queensland, Australia) in February 2008 with a one hour history of central heavy chest pain with radiation to her left arm. She denied any other associated symptoms and her pain was relieved with sublingual glyceryl trinitrate in addition to intravenous morphine. She was also prescribed 300 milligrams of aspirin as per chest pain protocol. Initially her blood pressure was stable and recorded as 121/82. She was not tachycardiac and the remainder of her vital signs within normal limits. Her physical examination was unremarkable. During her stay in the emergency department her blood pressure dropped to 71/34 and an electrocardiogram (ECG) revealed an inferior ST segment elevation.

The patient's cardiac risk factors included a history of hypertension and a previous non-ST segment elevation myocardial infarction (NSTEMI) which required stenting to the right coronary artery (RCA) on the 18th of June 2003 with a Cypher® drug eluting stent (DES). The patient had been on clopidogrel antiplatelet therapy since her initial angiogram however had ceased this 6 days prior to presentation in line with surgical advice prior to an expected colonoscopy. It was unknown as to why she was continuing to receive clopidogrel therapy and why she was not on dual antiplatelet therapy.

Following the acquisition of the ECG the patient was subsequently transferred to the coronary catheter lab for primary percutaneous coronary intervention (PCI). Coronary catheterisation revealed a normal left main coronary artery (LMCA), some minor irregularities in the left anterior

descending (LAD), minor disease in the circumflex artery but of greatest importance was

Following acquisition of the ECG, the patient was transferred to the coronary catheter lab for primary PCI. This showed normal LMCA, minor irregularities in the LAD, minor disease in the circumflex but most importantly occlusion in a previously stented region in the RCA. The lesion was balloon-angioplastied without the requirement for further stenting. Angiographically a good result was obtained with no residual stenosis. The troponin I (cTnI) peaked at 3.4 micrograms per litre (normal range is less than 0.04 micrograms per litre). She had an uneventful recovery and a routine echocardiogram was performed following her angiography which showed preserved left ventricular systolic function. She was subsequently discharged on day 2 following her angioplasty.

## DISCUSSION

Late stent thrombosis is a well known complication of drug eluting stents (DES) following revascularisation during coronary angiography. A meta-analysis of over 6000 patients by Bavry et al., 2006, incorporating randomised controlled trials of paclitaxel stents versus bare metal stents (BMS) or sirolimus stents versus bare metal stents (BMS) indicated that the risk of late thrombosis is increased 4-5 fold in drug eluting stents after 6-12 months following revascularisation. In the analysis provided, the incidence of early thrombosis between DES and BMS was similar up to 1 month, beyond which there was a greater risk with DES<sup>1</sup>. The median time to thrombosis observed through the study for sirolimus and paclitaxel stents respectively were 15.5 and 18 months, 11 and 14 months longer than late BMS thrombosis<sup>1</sup>. What still

remains unclear is how long after revascularisation can thrombosis occur and currently there have been limited reports beyond 1 year of implantation.

The term very late stent thrombosis has been used loosely without adequate definition. The implications of such relate to the duration of anti-platelet therapy required and the time period over which this continues to be instituted. The time period of occurrence of very late stent thrombosis (VLST) is ill defined with 12 months post implantation as the current marker<sup>2</sup>. The number of reported very late stenoses is limited, likely due to the limited follow up of coronary stent patients. Currently the longest reported case is 834 days following implantation reported by Merkely et al., 2009. We present here a case of VLST occurring almost 6 years after insertion of a sirolimus drug eluting stent in a patient on clopidogrel.

As noted by many authors restenosis in a drug eluting stent beyond 1 year of implantation is a rare occurrence with reports from Henderson et al., 2006 and Luscher et al., 2007 suggesting the occurrence of VLST after implantation of a DES at 4 years (comparing pooled data) is 0.6% to 0.7%<sup>4,5</sup>. Lagerqvist et al., 2007 also reported an increased rate of death, as compared to bare-metal stents in a Swedish retrospective study. The trend indicated that the risk of death was 0.5 percentage points higher and composite death or MI was 0.5 to 1.0 percentage points higher per year after 6 months<sup>6</sup>. This brought into question the long term safety of drug-eluting stents and called for randomised trials to evaluate the risk. A follow on study by James et al., 2009 analysing patients from the same registry (Swedish Coronary Angiography and Angioplasty Registry) dispelled any suggestion of a significant difference in the combined outcome of death and MI in those receiving DES or BMS. This study also reinforced the risk of late events, with significantly higher rates of late events in those receiving DES as compared with those receiving BMS<sup>7</sup>.

A great area of controversy which still remains is the length of treatment for antiplatelet therapy. Current guidelines by the American College of Cardiologists (ACC) and American Heart Association (AHA) joint taskforce suggest that in patients who have undergone PCI, clopidogrel 75 milligrams daily should be given for at least 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding<sup>8</sup>. Furthermore following restenosis, the guidelines advise indefinite use of antiplatelet

therapy.

In the case presented the restenosis occurred 2110 days following the implantation of the stent, triggered 6 days after cessation of clopidogrel. Some suggestions for potential causes of late stent thrombosis include delayed healing which is consistent with reported high rates of death and myocardial infarction in patients with drug eluting stents after cessation of clopidogrel, from the Duke database. The study indicated that among patients who had a DES who were event free at 6 months, clopidogrel use was a statistical significant predictor of lower adjusted rates of death (2.0% with clopidogrel compared with 5.3% without) and death or MI (3.1% vs. 7.2%) at 24 months. Among patients with DES who were event-free at 12 months (252 with and 276 without clopidogrel), clopidogrel use continued to predict statistically significant lower rates of death (0% vs. 3.5% without clopidogrel use) and death or myocardial infarction (MI) (0% vs. 4.5% without) at 24 months<sup>9</sup>. The study concluded that indeed long term use of clopidogrel in patients with DES may be associated with a reduced risk for death and death or MI. The issue which still remains is what the appropriate duration of Clopidogrel therapy should be and what the temporal relationship between Clopidogrel cessation and VLST is.

A single centre observational study was conducted by Roy et al., 2009 which assessed compliance to dual antiplatelet therapy particularly clopidogrel following implantation of DES and subsequent angiographic or autopsy-proven stent occlusion. The investigators concluded that clopidogrel cessation was an independent predictor of cumulative stent thrombosis at 30 days and 6 months but not at 12 months<sup>10</sup>.

Often patient factors may contribute to increased risk of stenosis, such as diabetes or tortuous coronary anatomy as well as complex lesions, in which case DES are often indicated. In the case presented, no comorbidities were present and restenosis occurred some 5 years and 9 months following implantation indicating that there are no definitive factors which predict very long term outcomes of stent implantation. However of interest was the lack of dual antiplatelet therapy. Dean et al., 2009 found that prolonged dual antiplatelet therapy improves clinical outcomes in patients considered high risk who have had Sirolimus-eluting stents implanted. At 12 and 18 months followed, the investigators showed that those patients who had taken standard clopidogrel therapy with aspirin (i.e. 12 months) had an increased risk of VLST compared with those on prolonged clopidogrel therapy (18 months) and aspirin

(5.6% vs. 1.1%)<sup>11</sup>. The case we reported did not represent a high risk patient however, as she had no significant comorbidities. The mechanism of VLST is thus still uncertain. Some have postulated that poor endothelialisation with ongoing clopidogrel therapy may have a role in the mechanism. Could the stent thrombosis be related to the lack of aspirin management. What is clear from this case and any further VLST cases which may be reported, is that there may be a necessity to alter current guidelines for antiplatelet therapy. It is evident that although guidelines exist, this is what they are and that therapy should be tailored to each individual, and issues such as risk benefit need to be considered when contemplating duration of antiplatelet therapy. Ultimately there is need for large scale randomised clinical trials for the evaluation of duration of antiplatelet therapy.

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