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## **An Update on Drug-Eluting Stent Thrombosis**

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### Executive Summary

**W**ith their introduction in 2003, drug-eluting stents revolutionized interventional cardiology and were quickly adopted into practice. Within a short period of time they were the stent of choice in over 90% of percutaneous coronary interventions. However, this past September, concerns were raised at the World Cardiology Congress in Barcelona about the risk of late stent thrombosis with drug-eluting stents. Since then, a flurry of research has occurred in an attempt to define the risk of late stent thrombosis in drug-eluting stents compared with bare-metal stents, as well as to determine the pathophysiology and predictors of late stent thrombosis. Longer use of dual antiplatelet therapy has been advocated and interventional cardiologists are modifying their practices in hopes of tipping the risk-benefit ratio in favor of optimizing patient outcomes.

## Introduction

Coronary stents are used in the majority of percutaneous coronary interventions (PCI). Currently, two major classes of stents are approved by the United States Food and Drug Administration (FDA) for human use: bare metal stents (BMS) and drug-eluting stents (DES). While the safety profile of DES is similar to BMS in the short term, concern has arisen about the potential for late stent thrombosis in those receiving DES (Figure 1). *Late stent thrombosis* is typically defined as occurring between 30 days to one year post-PCI, while *very late stent thrombosis* is that which occurs beyond one year following the index procedure. Some researchers have alternatively defined late stent thrombosis as occurring after 30 days and very late stent thrombosis as occurring after 180 days because it corresponds to the period beyond the protocol-mandated duration of clopidogrel use. Stent thrombosis is a rare but potentially devastating complication that can result in ST segment elevation myocardial infarction or death<sup>(1)</sup>. This has led to more careful use of DES worldwide<sup>(2)</sup>. Careful management that involves the cardiologist is warranted in patients who receive DES, as premature cessation of dual antiplatelet therapy with aspirin and clopidogrel is a potent predictor of late stent thrombosis.

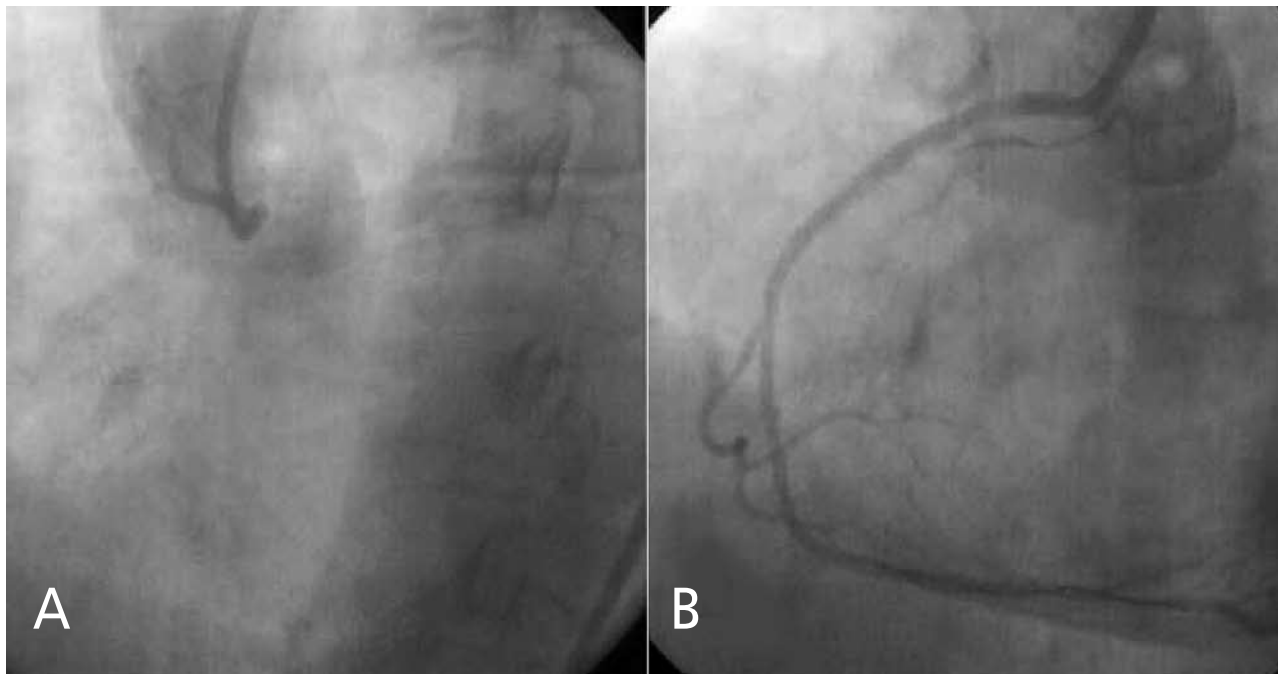
## Background of Drug-Eluting Stents

The introduction and use of DES in clinical practice revolutionized interventional cardiology. The initial pivotal trials that used DES for elective PCI in low to medium risk patients found decreased rates of target lesion revascularization and restenosis compared with bare metal stents<sup>(3-4)</sup>. Thereafter, widespread use of DES became routine practice for patients undergoing PCI, and to date, millions of DES have been implanted worldwide<sup>(2)</sup>.

Recently, however, several reports of late stent thrombosis with DES have raised concern<sup>(5,6)</sup>, leading to a decrease in overall use<sup>(2)</sup>. Previously, late events were seen in more than 5% of patients after brachytherapy and were rare with bare metal stents. DES are now also recognized as a risk factor for late thrombosis<sup>(6)</sup>.

## Incidence of Stent Thrombosis

Multiple studies have attempted to identify the incidence of late drug-eluting stent thrombosis. At 6 to 12 months, meta-analyses comparing DES to BMS reported no difference in the incidence of stent thrombosis<sup>(7-9)</sup>. The overall incidence of late stent thrombosis remained below 1% for both DES and BMS in these studies. More recently, studies suggest that DES may increase the risk of very late stent thrombosis. A



**Figure 1 Drug-eluting stent thrombosis** Panel A: Coronary angiogram showing thrombosis of a drug-eluting stent in the proximal RCA with TIMI 0 flow. Panel B: Coronary angiogram showing successful PTCA of proximal and mid right coronary artery with restoration of TIMI III flow after a drug-eluting stent thrombosis.

meta-analysis of 14 clinical trials with longer follow-up found that the incidence of very late drug-eluting stent thrombosis (>1 year post-implantation) was 0.5% with no events reported in bare metal stent patients (risk ratio [RR] = 5.02, 95% confidence interval [CI], 1.29 to 19.52,  $P = .02$ )<sup>(6)</sup>. The median time to thrombosis with DES was 15.5 to 18 months after PCI, while the median time to thrombosis with BMS was 3.5 to 4 months after PCI. Similarly, an analysis of the four principal paclitaxel randomized trials identified a 0.5% increase in the incidence of late stent thrombosis (6 months to 2 years) with the paclitaxel-eluting stents compared to bare metal stents<sup>(10)</sup>. Importantly, this did not translate into a cumulative increase in death or myocardial infarction in the DES population. This suggests that although drug-eluting stents increase the risk of late stent thrombosis, this may be offset by the concomitant decrease in revascularization procedures from bare metal stent restenosis and acute coronary syndromes<sup>(11)</sup>. However, there is currently no direct evidence to support this hypothesis.

While the randomized trials in these meta-analyses generally included low to medium risk patients (short de novo lesions in coronary arteries measuring 2.5 mm to 3.75 mm in diameter), patients in clinical practice receive DES for a wide variety of anatomic and clinical situations, such as overlapping stents, lesions in coronary artery bypass grafts, in the setting of an acute myocardial infarction, or bifurcation stenting. In addition, the number of patients on whom there exists long-term follow-up data is limited and the risk of stent thrombosis with dual antiplatelet therapy prolonged beyond 3 to 6 months is unknown. Consequently, the reported incidence of late drug-eluting stent thrombosis from the original trials may be an underestimate of their “real world” incidence (Table 1). An analysis of the REAL (REgistro AngiopLastiche dell’Emilia Romagna) Multicenter Registry did report a slightly higher rate of angiographically documented stent thrombosis with DES up to 2 years (1.0%), but this was not significantly different from the rate of stent thrombosis in the BMS group (0.6%,  $p=0.09$ )<sup>(12)</sup>. Similarly, a sex-based evaluation of the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry reported slightly higher overall rates of stent thrombosis at 1 year in patients receiving DES, but no difference in rates between women and men (1.3% vs. 1.2%,  $p=0.85$ )<sup>(13)</sup>.

**Table 1**  
Clinical events for studies investigating drug-eluting stents in ST-segment elevation myocardial infarction

Study	Mortality (%)		MI (%)		TVR (%)		MACE (%)		Total ST (%)		Early ST, <30 days (%)		Late ST, >30 days (%)	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
<b>Sirolimus</b>														
Spaulding, et al. 2006	2.3	2.2	1.1	1.4	5.6	13.4	7.3	14.3	3.4	3.6	3.1	3.1	0.3	0.6
Valgimigli, et al. 2005	8.0	9.1	6.9	9.1	6.9	20.5	18.4	31.8	0	2.3	0	2.3	0	0
Menichelli, et al. 2006*	0.6	3.1			5.0	13.1	6.9	16.9	3.1	3.8	3.1	3.8		
Jukema, et al. 2006*	1.3	2.5	5.7	9.5	5.1	13.3			1.3	1.9				
Lemos, et al. 2004	8.1	8.2			1.1	8.2	9.1	16.9	0	1.6	0	1.6		
Daemen, et al. 2006*					7.0	12.6	17.7	26.8						
Newell, et al. 2006	1.9	10.0	0.6	4.0	1.3	8.0	3.2	16.0	0	4.0				
Cheneau, et al. 2005	6.8	10.9	1.0	2.0	1.0	10.3	8.7	24.0	0	0.6	0	0.6	0	0
Percoco, et al. 2006	6.3	12.8	4.9	3.1	3.4	5.1	14.1	20.3	1.0	1.5	0.5	1.1	0.5	0.4
<b>Paclitaxel</b>														
Laarman, et al. 2006	4.5	6.5	1.6	1.9	5.2	8.1	8.7	12.6	1.0	1.0	0.6	1.0	0.3	0
Tierala, et al. 2006*	9.8	4.9	1.2	4.9	3.7	11.0	13.4	17.1						
Schwalm, et al. 2006	3.3	10.9	1.7	7.3			6.7	19.7	0	2.9	0	2.9		

\*Studies with results published in abstract form

## ***Pathophysiology and Predictors for Late Stent Thrombosis***

Our understanding of the pathophysiology of late stent thrombosis is currently evolving, however this phenomenon appears to be multifactorial in nature. Discontinuation of dual antiplatelet therapy is a well-known predictor of late stent thrombosis. Left ventricular dysfunction has also been cited<sup>(1)</sup>. Virmani and colleagues noted an association between localized hypersensitivity vasculitis and drug-eluting stent thrombosis<sup>(14)</sup>. In a recent study, 40 consecutive autopsies were performed on patients who died following drug-eluting stent implantation<sup>(15)</sup>. Even at 40 months after stent implantation, persistence of fibrin and incomplete endothelialization remained a potent thrombogenic stimulus for the development of late stent thrombosis in drug-eluting stents. In addition, these researchers found that a longer stent length with DES was associated with late stent thrombosis, as was stenting bifurcation lesions, plaque disruption near the stented segment, and penetration of a necrotic lipid-rich core with extensive plaque prolapse. Incomplete stent apposition has also been suggested as a possible risk factor for very late drug-eluting stent thrombosis<sup>(16)</sup>. Finally, resistance to antiplatelet therapy and heightened platelet reactivity may increase the risk of late DES thrombosis<sup>(17)</sup>.

## ***When is a Drug-Eluting Stent Warranted?***

The use of DES should be determined based on several factors, including the patient's risk of restenosis, the risk of bleeding, and the risk of late stent thrombosis prior to implantation of a drug-eluting stent<sup>(18)</sup>. Patients in whom a bare metal stent should be considered include patients with a pre-existing bleeding condition, patients who require PCI before undergoing a surgical procedure (particularly those individuals who necessitate premature discontinuation of dual antiplatelet therapy), and patients at markedly increased risk for late drug-eluting stent thrombosis. In selecting patients who would be expected to have a favorable outcome from a BMS, one can consider that the 9 month need for repeat revascularization with BMS implantation is 4-10% in native vessels of non-diabetic patients with de novo lesions that are non-ostial in nature and have a reference diameter of at least 3.5mm and a lesion length of less than 5 mm<sup>(19)</sup>.

As mentioned, those individuals with multiple risk factors for late drug-eluting stent thrombosis might be considered for bare metal stent implantation<sup>(1,9,15)</sup>. Unfortunately, many of the predictors of late stent thrombosis also increase the risk for restenosis<sup>(20)</sup>, therefore coronary artery bypass grafting may be an appropriate option for some patients.

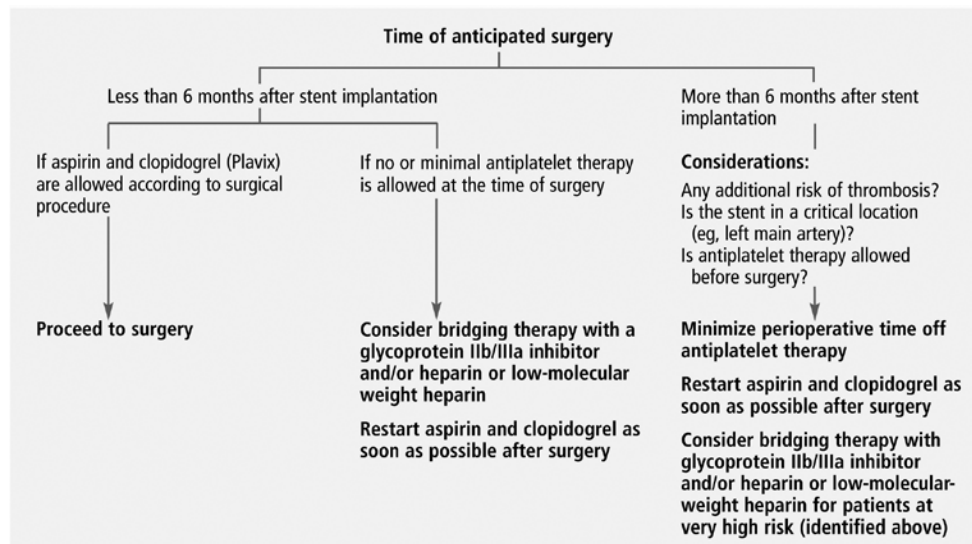
## ***Prevention of Late Stent Thrombosis***

Dual antiplatelet therapy with aspirin and clopidogrel following stent implantation is recommended by the stent manufacturers for at least four weeks to prevent stent thrombosis with BMS and three to six months to prevent late stent thrombosis with the sirolimus and paclitaxel-eluting stents, respectively. This treatment duration is based on the clinical trials that studied DES (3-4). However, on the basis of clinical trial data with BMS and brachytherapy, and advocated by the United States FDA advisory meeting in December 2006, many clinicians routinely recommend a duration of at least 12 months of dual antiplatelet therapy to prevent late drug-eluting stent thrombosis<sup>(21-22)</sup>.

Premature termination of dual antiplatelet therapy is clearly harmful and has been associated with a more than 50-fold increased hazard for stent thrombosis<sup>(1,23)</sup>. A prospective study found that one out of eight patients prematurely discontinued their clopidogrel within 30 days of drug-eluting stent implantation<sup>(24)</sup>. These patients had a significant increase in mortality during the next 11 months (7.5% vs. 0.7%,  $P < 0.0001$ ). Thorough patient education regarding the importance of dual antiplatelet therapy in preventing late stent thrombosis is imperative.

Many surgeons request complete termination of antiplatelet therapy prior to a scheduled procedure, but many operations may be safely performed on aspirin therapy<sup>(25)</sup>. Consequently, managing antiplatelet therapy around surgical procedures involves weighing the risk of precipitating stent thrombosis or native coronary thrombosis from the termination of antiplatelet therapy versus the risk of surgical bleeding from remaining on antiplatelet therapy. In order to balance these risks, there should be communication between the surgeon and cardiologist in the pre-operative period. If premature termination of dual anti-platelet therapy is needed prior to surgical intervention, a bridging strategy with a glycoprotein IIb/IIIa inhibitor and/or heparin or low-molecular weight heparin might be considered<sup>(18)</sup>. While this has been proposed, there is no data to support or refute this strategy (Figure 2).

Debate has arisen regarding the proper duration of dual antiplatelet therapy that is required beyond 6-12 months. Multiple cases of stent thrombosis have been reported following late cessation of antiplatelet therapy<sup>(26)</sup>. McFadden and colleagues reported four angiographically-confirmed cases of late drug-eluting stent thrombosis. The range of late stent thrombosis was 335 to 442 days post-implantation. In response to the recent concern regarding late drug-eluting stent thrombosis, the United States FDA spearheaded an open meeting of its Circulatory System Devices Panel on December 7 and 8, 2006<sup>(27)</sup>. On the first day, the panel concluded that in low to medium risk patients undergoing elec-



**Figure 2** Proposed algorithm for assessing the need for in-hospital or outpatient bridging therapy in patients with drug-eluting stents when dual anti-platelet therapy will need to be interrupted before surgery.\*

\*From Rabbat MG, Bavry AA, Bhatt DL, Ellis SG. Understanding and minimizing late thrombosis of drug-eluting stents. *Cleve Clin J Med* 2007;74:129-136

tive PCI for “on-label” indications, the use of DES as opposed to BMS increases the risk of very late stent thrombosis (>1 year post-implantation), but that this increased risk of stent thrombosis is not associated with an increased risk of death or myocardial infarction. The increased risk of stent thrombosis seemed to be offset by the increased risk of bare metal stent restenosis and repeat revascularization. However, since more than 60% of current DES use is “off-label”, with more complex patients and coronary lesions compared to the initial marketing approval, the FDA added that with more complex patients and lesion subsets, there is an expected increased risk in adverse cardiac events. The final recommendations were that consideration for longer dual antiplatelet therapy be given and that additional studies are needed for patients undergoing DES implantation for off-label indications.

Recently, two prospective registries confirmed that off-label use of drug-eluting stents was associated with higher rates of adverse outcomes up to 1 year post-implantation compared to on-label use (28-29). It should be noted that clopidogrel duration was not universally recorded, long-term outcomes were not identified past 1 year, and there was no control bare metal stent or coronary artery bypass graft group.

## Conclusion

Thrombotic events remain a rare but significant cause of death and myocardial infarction after PCI. Drug-eluting stents appear to increase the risk of late stent thrombosis compared to bare metal stents. Careful management that involves the cardiologist is warranted in patients who receive drug-eluting stents, as cessation of dual antiplatelet therapy can result in late stent thrombosis. Multiple predictors of late drug-eluting stent thrombosis have been identified and these should be considered when placing a DES and when determining a patient’s risk for late thrombosis. Bare metal stents may be preferable in patients who cannot afford clopidogrel, have a bleeding propensity, do not take medication reliably, or may require a surgical procedure in the near future. The elimination of potential restenosis with drug-eluting stents must be weighed against the possible need for lifetime dual antiplatelet therapy. The recommended duration of dual antiplatelet therapy has been extended and the upper limit has not yet been determined. There may be a point where the benefit of continued therapy is outweighed by the increased bleeding risk and cost. Next generation drug-eluting stents and the development of bioabsorbable stents, which remain in place only long enough to prevent the process of restenosis, are on the horizon.

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