Review

Focused Clinical Review: Periprocedural Management of Antiplatelet Therapy in Patients with Coronary Stents

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Coronary stent implantation, particularly drug eluting stents, is now the major method of coronary revascularisation. Following drug-eluting stent implantation dual antiplatelet therapy with aspirin and thienopyridine is recommended for at least 12 months. Premature discontinuation, often at the time of noncardiac surgery, has been associated with stent thrombosis which has a significant risk of death and myocardial infarction. Late (>30 days) and very late (>365 days) stent thrombosis appears to more common with DES and poses the questions of when is it safe to stop antiplatelet therapy post coronary stenting and how to manage patients who need non-cardiac surgery. This article reviews the evidence for stent thrombosis and the peri-operative management of patients with coronary stents and provides an algorithm for patient management based on multidisciplinary assessment of bleeding risk, perioperative cardiac event and stent thrombosis risk.

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Introduction

Over 40,000 percutaneous coronary interventions (PCI) are performed in Australia and New Zealand each year with the majority of patients receiving drug eluting stents [1]. Drug eluting stents (DES) significantly reduce the incidence of instent restenosis which can present as both angina and acute coronary syndromes (ACS) [2]. However this early benefit has been soured by recent concerns of increased late stent thrombosis with drug eluting stents which is often associated with serious clinical consequences. It is estimated that 5% of patients will require non-cardiac surgery within the first year following stent implantation and that up to 40% of cases of reported stent thrombosis occur in the perioperative setting often when dual antiplatelet therapy (DAPT) is withheld [3]. An appreciation of stent thrombosis and the role of antiplatelet therapy are then critical to any specialist who treats patients with coronary stents especially when a surgical procedure is planned.

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Abbreviations: ACS, acute coronary syndrome; BA, balloon angioplasty; BMS, bare metal stent; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; DES, drug eluting stent; EES, everolimus eluting stent; MACE, major adverse cardiac event; MI, myocardial infarction; NSTEACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PES, paclitaxel eluting stent; SES, sirolimus eluting stent; STEACS, ST elevation acute coronary syndrome; ZES, zotarolimus eluting stents.

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Clinical Use of Dual Antiplatelet Therapy

Aspirin irreversibly inactivates cyclo-oxygenase enzyme reducing the levels of vasoactive compounds thromboxane A2 and prostacyclin with a resultant 25% reduction in myocardial infarction, stroke and vascular death when used as secondary prevention in high risk patients [4,5]. The thienopyridine derivative clopidogrel is a prodrug that when activated irreversibly binds to the platelet P2Y12 receptor and antagonises adenosine diphosphate [6]. Clopidogrel has been shown to be an effective alternative antiplatelet agent to aspirin and dual antiplatelet therapy with aspirin and clopidogrel improves outcomes in high risk patients with unstable angina, non-ST-elevation (NSTEACS) and ST elevation ACS (STEACS) [7–9]. Prasugrel, a more potent and rapidly acting oral thienopyridine is also now available as an alternative to clopidogrel. In the Triton-TIMI 38 trial prasugrel was compared with clopidogrel in patients with high risk acute coronary syndromes undergoing PCI. Prasugrel significantly reduced myocardial infarction, urgent target vessel revascularisation and stent thrombosis compared with clopidogrel but

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was associated with increased risk of major bleeding [10].

Dual antiplatelet therapy is critical as adjunctive therapy following implantation of coronary stents. The early use of bare metal stents was hindered by early vessel closure and stent thrombosis usually occurring in the first few weeks after stent implantation with reported rates of up to 20% [11]. Leon et al. demonstrated the efficacy of dual antiplatelet therapy in reducing early stent thrombosis with bare metal stents where the combination of aspirin and ticlodipine reduced early stent thrombosis to 0.5% which was significantly superior to warfarin and aspirin (2.7%) and aspirin alone (3.5%) [12].

Stent Thrombosis and Late Events with Drug Eluting Stents

Stent thrombosis is an infrequent but potentially catastrophic complication of both bare metal stent (BMS) and DES implantation. Stent thrombosis is defined angiographically as an occluded or subtotally occluded infarct related artery in a stented vessel in the presence of thrombus. This may underestimate the true occurrence of stent thrombosis. Clinically, stent thrombosis is defined as target vessel myocardial infarct (MI), urgent target vessel revascularisation or unexplained cardiac death which may overestimate its true incidence [13].

Acute (<24 h) and subacute (<30 days) stent thrombosis has been well described in both BMS and DES and occurs at an incidence of less than 1% at 30 day follow-up [14]. Risk factors for stent thrombosis include procedural related factors such as acute myocardial infarction, stent malapposition where the stent is not apposed to the arterial wall, stent underexpansion, small luminal diameter, complex anatomy such as bifurcation lesions in addition to patient factors such as low ejection fraction, diabetes, renal failure and clopidogrel resistance [15]. Acute stent thrombosis has significant morbidity and mortality with up to 64% incidence of death or MI at presentation and 21% six-month mortality rate [14].

Late (>30 days) and very late (>365 days) stent thrombosis is uncommon after BMS implantation but has been described. The cumulative incidence of stent thrombosis was 0.5% at 30 days, 0.8% at one year and 2% at 10 years in a retrospective review of over 4500 patients with BMS [16]. The rare occurrence of late events seems to be related to the fact that near-complete endothelialisation is thought to occur by three months following BMS implantation [17]. With DES, endothelialisation is delayed and incomplete and may form a substrate for late stent thrombosis particularly when exposed to other factors such as chronic inflammation and hypersensitivity to stent polymer, late stent malapposition, remodelling and aneurysm formation, penetration of necrotic core by stent struts, instent restenosis with thrombus formation and complex lesions [18]. Soon after the widespread uptake of DES, several case reports raised concerns regarding the increased incidence of late and very late thrombosis particularly in the setting of cessation of dual antiplatelet therapy which often occurred at times of noncardiac surgery [3].

Analysis of the pivotal DES trials found that the four-year rate of stent thrombosis was similar between first generation drug eluting and bare metal stents in these relatively simple lesions. However, after the first 12 months stent thrombosis occurred more commonly in the DES groups with a rate of 0.6% over the period from one to four years [19,20]. The use of DES in this population was not associated with any increase in death or MI and as expected there was a marked reduction in target-lesion revascularisation [19,20]. Similarly late stent thrombosis was reported to occur at an annual rate of 0.4–0.6% during four-year observational follow-up by Wenaweser et al. at two large European centres [21]. The higher event rate in practice is likely related to the frequent "off label" use of stents that is excluded in clinical trials [22]. Of note is that the overall contribution of stent thrombosis to overall mortality appears to be small [21].

Importance of Antiplatelet Therapy in Prevention of Stent Thrombosis

Although stent thrombosis is mulifactorial, premature discontinuation of dual antiplatelet therapy is a major risk factor. A prospective observational cohort by Iakovou et al. [23] of 2229 patients treated with DES with nine-month follow-up identified 17 cases of stent thrombosis, 50% of which were late events. Premature antiplatelet therapy discontinuation was associated with a 90-fold increase in the risk of stent thrombosis. Adverse outcomes related to premature cessation of dual antiplatelet therapy was also demonstrated in the PREMIER registry of 500 DES treated patients where one in seven patients prematurely stopped thienopyridine therapy and this was associated with a significant increased risk of death (7.5% versus 0.7%) [24].

How Long to Continue Dual Antiplatelet Therapy Following Drug Eluting Stent Implantation

Extended use of clopidogrel following DES seems to have a beneficial effect which may be in part due to reduction in stent thrombosis. In an extended observation of the BASKET-LATE trial [25], 746 patients with stented lesions surviving six months without major events were followed for a further one year. Following the discontinuation of clopidogrel at six months the combined rate of cardiac death and myocardial infarct (4.9% versus 1.3%) as well as late stent thrombosis (2.6% versus 1.3%) was significantly higher in the DES group compared to BMS. This study concluded that the use of DES prevented five major events per 100 patients in the first six months which was countered by an excess of three major events per 100 patients in months 7–18 possibly due to increased late stent thrombosis.

Unfortunately there is minimal randomised trial data to guide the ideal duration of dual antiplatelet therapy following DES. A recent observational study from the Duke Heart Centre suggests that prolonged therapy may be beneficial [26]. Over 4500 patients were assessed at six months and 12 months post BMS and DES implantation. Amongst patients with DES who were event free at six months, continued clopidogrel use was a significant pre-