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Perioperative Management of Patients with DES

Introduction: A review of the evolution of interventional cardiology and percutaneous coronary intervention (PCI) begins with percutaneous transluminal coronary angioplasty (PTCA). Charles Dotter, a vascular radiologist at the University of Oregon in Portland, introduced transluminal angioplasty in 1964. His innovation moved traditional radiology beyond the realm of diagnostic imaging toward non-surgical intervention to treat vascular disease. Resistance, especially from the surgical community, difficulties reproducing his techniques and occurrence of complications resulted in angioplasty being rejected and ignored in the U.S. for nearly 15 years. Dotter's techniques were embraced and expanded by investigators in Europe (notably Dr. Eberhart Zeitler in Germany) who introduced Dr. Andreas Gruentzig to the procedure. Via a complicated and interesting story Dr Gruentzig ended up at Emory University in Atlanta, Georgia; where he became the '*American Pioneer*' of this non-surgical intervention.

However, PTCA results were plagued by vascular recoil and restenosis. The development of the bare metal stent (BMS) resolved this issue by preventing elastic recoil. Subsequently, a new problem developed— neointimal hyperplasia. This growth of tissue into the stent restricted the vessel lumen causing restenosis. To answer this problem, drug eluting stents (DES) which prevented neointimal hyperplasia were developed. Clinical trials have shown that the use of DESs for PCI are associated with significant reductions in the risks of early restenosis and the need for target-lesion revascularization, as compared with use of BMSs. Based on this data, DESs are used in more than 50% of PCI procedures in clinical practice reducing the need for repeat PCI. Longer term studies have shown that along with these benefits comes a cost. There is an increased rate of late stent thrombosis (ST), a potentially catastrophic event which is usually manifest as a myocardial infarction, malignant arrhythmia or sudden cardiac death. It is felt that delayed arterial healing and endotheliazation in DES compared to BMS after implantation leads to the increased risk of late ST.

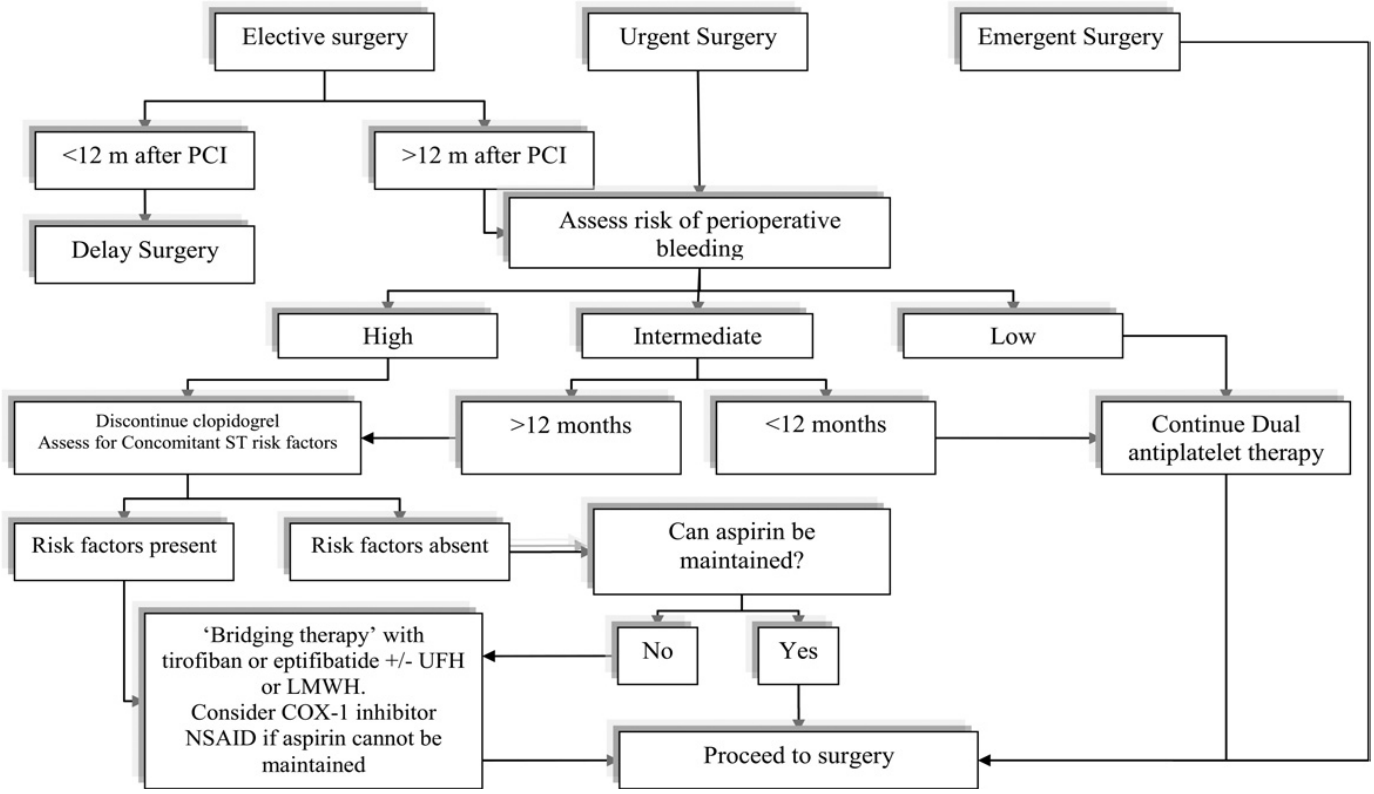
Dual antiplatelet therapy, (aspirin and clopidogrel), have been shown to decrease the risk of late ST in DES. Current PCI guidelines recommend that clopidogrel 75 mg daily, along with aspirin (325mg for the first 6 months and 81mg thereafter), should be given for *at least* 12 months after implantation of DESs if patients are not at high risk for bleeding. The optimal duration of dual antiplatelet therapy and the risk–benefit ratio for long-term dual antiplatelet therapy remains unknown. Because of the risk associated with discontinuation most physicians are now treating most patients indefinitely…leading us to the topic of this *Heartbeat*.

The following is a summary of the most important points taken from a *state-of-the art paper* reviewing perioperative management of patients with drug-eluting stents.

- The risk of perioperative stent thrombosis (ST) after drug eluting stents (DES) has been well-established in patients undergoing noncardiac surgery early after percutaneous coronary intervention (PCI). This increased thrombogenic risk is secondary to catecholamine release, increased platelet aggregability, and decreased fibrinolysis occurring during surgery leading to a hypercoagulable state. In addition, acute withdrawal of antiplatelet therapy might trigger a rebound effect significantly increasing the risk of ST and a potentially catastrophic complication with mortality ranging from 9% to 45%.

- Antiplatelet agents are crucial to the prevention of ST, which is a platelet-mediated process by inhibiting various steps of the thrombus formation process. Dual antiplatelet therapy—presently aspirin and clopidogrel—is recommended for up to a year for all patients receiving DES unless there is a high risk of bleeding. The guidelines also add that in patients with clinical features associated with a higher risk of ST (i.e., renal insufficiency, diabetes, or procedural characteristics, such as multiple stents or treatment of a bifurcation lesion), extending dual antiplatelet therapy beyond 1 year is reasonable. Many physicians treat all patients post PCI indefinitely with dual antiplatelet therapy (no data). ***The single most important predictor of ST is the cessation of antiplatelet therapy but this has to be balanced against the perioperative risk of bleeding*** **(Figure 1).**

Figure1. Algorithm of Perioperative Management of Patients with DES



COX _ cyclooxygenase; DES _ drug-eluting stent(s); LMWH _ low molecular weight heparin; NSAID _ nonsteroidal anti-inflammatory drug; PCI _ percutaneous coronary intervention; ST _ stent thrombosis; UFH _ unfractionated heparin.

- Bleeding risk is based on a 3-4 fold increase in bleeding time in healthy volunteers. However it should be remembered that in several studies, even when there was an increase in surgical bleeding in patients on dual anti-platelet therapy and an increase in transfusion requirements, there was no change in mortality or surgical outcome.

- All elective surgical procedures should be delayed for at least 6 months and ideally 12 months after a DES PCI. If *early* surgery (before one year) cannot be delayed due to urgency, maintaining dual antiplatelet therapy with aspirin and clopidogrel is extremely important because the risk of ST is significantly increased. This applies to most surgical procedures, except those in areas where bleeding is in a closed space and might be catastrophic, such as intracranial, spinal medullary, and posterior chamber ophthalmic surgeries. Transurethral prostate resection would also fall into this category unless using potassium-titanyl-phosphate laser which is considered safe. In cases of '*high hemorrhagic risk' early* surgery, "bridging therapy" could be considered.

- For cardiac surgery, the data (low dose aspirin is associated with low and combination therapy is associated with high excessive bleeding risk), support the ACC/AHA guidelines which recommend that, in patients taking aspirin/clopidogrel for whom coronary artery bypass grafting (CABG) is planned, aspirin should be continued and clopidogrel should be withheld for at least 5 days unless the urgency for revascularization outweighs the risks of excess bleeding. However, when considering the bleeding risk with CABG on clopidogrel and ASA in patients who underwent surgery when clopidogrel was held for less than 5 days, the increase in excess bleeding was only 1%.

- For non-cardiac surgery the data is not as clear-cut and sometimes conflicting. Decisions have to be made on a case-by-case basis by determining the estimated risk of ST weighed against the risk of bleeding (Table 1).

Table 1. Hemorrhagic Risk in Non-cardiac Surgery

Surgical Hemorrhagic Risk	Transfusion Required	Type of surgery
Low	Usually not required	Peripheral, plastic, and general surgery, biopsies; minor orthopedic, otolaryngology and general surgery; endoscopy; eye anterior chamber, dental extraction and surgery
Intermediate	Frequently required	Visceral surgery; cardiovascular surgery; major orthopedic, otolaryngology, and urologic reconstructive surgery
High	Possible bleeding in a closed space	Intracranial neurosurgery; spinal canal surgery; eye posterior chamber surgery & Surgical TURP*

*Surgical TURP fits here because of the high-risk of bleeding (Laser TURP is the exception)

- Patients undergoing surgical procedures 12 months after PCI are at a lower risk of perioperative ST and major adverse cardiac events (MACE) compared with earlier surgery. But because of significant delays in re-endothelialization with DES, the ST risk is still significant. Maintenance of dual antiplatelet therapy is recommended, whenever possible, unless bleeding risk is unacceptable.

- In contrast, if ST risk factors are absent and the hemorrhagic risk is significant, stopping clopidogrel five days before surgery and continuing aspirin is appropriate. Antiplatelet therapy should be reintroduced as soon as possible post-operatively. Because ST usually occurs quite soon post-operatively, clopidogrel should be restarted once the risk of bleeding has diminished (ideally within the first 24 h) with a loading dose of 300 mg to 600 mg. Maintaining single antiplatelet therapy with aspirin applies to patients without concomitant risk factors of ST undergoing surgery more than 12 months after PCI (*later surgery*).

- Just as in the case of *early surgery* with high hemorrhagic risk, *later surgery* in the presence of ST risk factors (renal insufficiency, diabetes, or procedural characteristics, such as multiple stents or treatment of a bifurcation lesion)—when dual antiplatelet therapy is too risky, "bridging therapy" with a GP IIb/IIIa inhibitor (specifically eptifibatide or tirofiban not abcixmab) with or without heparin should be considered (this is not evidence-based). Aspirin and clopidogrel should be discontinued 5 days before surgery. Intensive perioperative monitoring and prompt PCI are very important should ST occur because of the high-risk. Dual antiplatelet therapy should be restarted as soon as possible postoperatively.

Conclusions:

Perioperative management of patients with DES is a critical issue. Maintenance of dual antiplatelet therapy remains the mainstay of ST prevention for at least one year—but most continue indefinitely. In high-risk surgical hemorrhage cases, maintaining short-term single antiplatelet therapy with aspirin is associated with low risk of ST. If aspirin must be discontinued, "Bridging therapy" should be considered but there is minimal evidence-based data to support such therapy.

Additional studies addressing the long-term use of dual antiplatelet therapy after implantation of DES are ongoing. Until then, physicians' (and patients') preferences and responses to uncertainty are driving practice more than the data are.

Abualsand AO, Eisenberg EJ. **STATE-OF-THE-ART PAPER**. Perioperative management of patients with drug eluting stents. *J Am Coll Cardiol Intv*, February 2010; 3: 131-142

Jeffery E VanHook DO, Cardiology Fellow UMDNJSOM

Mario L Maiese DO, FACC, FACOI
Clinical Associate Professor of Medicine, UMDNJSOM Email: **maiese1@comcast.net**

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