Percutaneous Coronary Intervention (PCI)

1977: Andreas Gruentzig performs the first successful percutaneous transluminal coronary angioplasty (PTCA). However, widespread use is limited by two major complications - acute vessel closure during or immediately after procedure, and restenosis of the vessel due to elastic recoil, smooth muscle proliferation and neointimal hyperplasia.1

1980 to 1990: Incidence of abrupt vessel occlusion post-PTCA remains at 4-8%, with more than 20% of patients requiring emergency coronary artery bypass graft surgery (CABG). Restenosis rates vary from 30-50%.2

1993: Food and Drug Administration (FDA) approves bare metal stents (BMS) for elective use in the United States. BMS effectively eliminate acute vessel closure, but initial trials report acute (24 hrs) and subacute (24 hrs-30 days) stent thrombosis of 16-24%. Dual antiplatelet therapy reduces the incidence of BMS thrombosis to the current rate of 1.2%. Incidence of late restenosis remains high though (20-25%). Restenosis occurs as a side-effect of the normal healing process. Scar tissue grows around the stent mesh in a process called neointimal hyperplasia. The incidence peaks at three months and reaches a plateau at three to six months.

2002: Drug-eluting stents (DES) approved for use in Europe. These stents are impregnated with a drug (sirolimus or paclitaxel) that retards the neointimal proliferation that leads to restenosis. Alas, DES also delay re-endothelialisation, thereby increasing the risk of stent thrombosis.

2003-2004: FDA approve DES.

2005: Eighty-five percent of all stents implanted in Europe and United States are DES.2 DES reduce restenosis by 74% at four years compared with BMS.3, 4 Instead, late stent thrombosis (LST) at 30 days to one year, and even very late stent thrombosis (> 1 yr) with DES, turn out to be significant concerns. The angiographic incidence of LST is reported in the literature between 0.5-3.1%. The actual clinical incidence may be higher.5

2005: European Society of Cardiology and AHA/ACC/SCAI extend the recommended duration of therapy to 12 months (from three to six months), in patients at low risk of bleeding.

2007: Scientific Advisory published by AHA/ACC/SCAI/ADA. The advisory stresses the importance of 12 months of dual antiplatelet treatment after DES and recommends postponing elective surgery for one year after placement. Aspirin should be continued perioperatively if surgery cannot be delayed.6

2009: FDA approves new antiplatelet drug. Prasugrel is an oral thienopyridine with a greater antithrombotic activity than clopidogrel.

2010: Guidelines on myocardial revascularisation published by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. Remarkably, the report recommends that single-vessel disease or two-vessel disease in a nonproximal left anterior descending (LAD) coronary artery is the only scenario for which PCI is the preferred intervention in a stable patient. For all other disease subsets, surgery is favoured.7


Antiplatelet Therapy

Thienopyridines

Clopidogrel (Plavix®) is an adenosine diphosphate (ADP) receptor antagonist. It is a prodrug, which is oxidised to an active metabolite via the hepatic cytochrome P450-dependent CYP3A4 pathway. It...
Refresher Course: Rather anaesthetise a patient with CABG than a stent

permanently inactivates the mechanisms that are essential for platelet aggregation. Normalisation of coagulation relies on the release of new platelets into the circulation. The half-life is short (four hours) but full recovery from the drug is long (seven days) due to irreversible platelet inhibition. Dose - loading dose: 300-600 mg, daily dose: 75 mg.

Aspirin
Aspirin inhibits the arachidonate thromboxane A\(_2\) (TxA\(_2\)) pathway. A single dose of 150 mg completely eliminates platelet TxA\(_2\) production. The ability of platelets to aggregate is partially restored within four to five days of stopping aspirin.

GP IIb/IIIa Antagonists
Platelet GPIIb/IIIa receptor antagonists are used for the prevention of immediate thrombosis of coronary stents. They are prescribed as infusions for 24-48 hrs after PCI.
- Abciximab (ReoPro\(^{\text{®}}\)): High affinity receptor binding. After discontinuation of infusion, receptor occupancy decreases to 70% in 12 hrs. Effective platelet aggregability is restored in 48 hrs, but residual receptor blockade can be seen up to seven days later.
- Tirofiban (Aggrastat\(^{\text{®}}\)): Plasma half-life of two hours. At four hours after stopping the infusion, the platelet aggregability is 50%.
- Eptifibatide (Integrilin\(^{\text{®}}\)): Plasma half-life of 2.5 hrs. Within six hours after stopping the infusion, platelet function recovers to more than 50%.

Treatment regimes in patients with stents
- BMS: Aspirin 75-325 mg daily plus clopidogrel 75 mg daily for four to six weeks. Aspirin is continued for life.
- DES: Aspirin 75-325 mg daily plus clopidogrel 75 mg daily for at least one year. Aspirin is continued for life. Clopidogrel > 1 yr if at risk patients.

Non-responders to treatment and platelet resistance
Twelve to twenty per cent of patients do not respond to aspirin, especially women and patients with diabetes, and 6-24% of patients do not respond to clopidogrel. This may be as a result of genetic polymorphism, drug interactions and compliance.

The perioperative dilemma
PCI is currently the preferred therapeutic option for coronary artery disease. More than two million people undergo PCI annually. More than 90% will receive one or more intracoronary stents. Approximately 5% of these patients will undergo non-cardiac surgery within the first year after stenting and an increasing number will continue to present for surgery thereafter.

All involved - surgeon, cardiologist and anaesthetist must ensure appropriate perioperative management to avoid a high incidence of postoperative cardiac morbidity and mortality in these patients.

Premature cessation of antiplatelet therapy has been shown to be the most powerful predictor of stent thrombosis. A large multi-center trial showed a 90-fold higher rate of DES thrombosis in patients who prematurely discontinued dual antiplatelet therapy. Other risk factors include renal failure, diabetes mellitus, poor ejection fraction, stents involving bifurcation lesions and multiple stents. In the surgical setting, the risk is further increased by the postoperative phase of platelet hyperaggregability and decreased fibrinolysis.

Until adequately covered by a layer of endothelial cells, the exposed stent struts are a potent nidus for the formation of thrombus. Unfortunately, there are currently no clinical tests available to identify which patients have endothelialised their stents and which have not. (See Figure 1)

Stent thrombosis is a catastrophic complication and results in myocardial infarction in 40-60% and death in 15-45% of cases! As opposed to in-stent restenosis, or for that matter an acute coronary syndrome (ACS), secondary to atheromatous plaque rupture, in-stent thrombosis abruptly severs the coronary blood flow and does not allow time for the coronary circulation to compensate via collateral blood flow.

Timing is everything
Delay elective non-cardiac surgery for a minimum of 45-90 days after BMS implantation and one year after DES implantation. However, some risk does extend beyond these time frames. Notably
for patients with DES, the risk of major adverse cardiac events post-non-cardiac surgery are not significantly associated with time from stenting to surgery. In fact, a growing body of evidence suggests that there is no “safe” interval for patients with DES undergoing non-cardiac surgery.

### Dual antiplatelet therapy is everything

Fear of excessive bleeding frequently prompts the withdrawal of antiplatelet agents seven to ten days before a surgical procedure. However, cessation of antiplatelet drugs leads to a prothrombotic rebound effect. Simultaneously, the systemic inflammatory response and the acute phase reaction to surgery increase platelet adhesiveness and decreases fibrinolysis. The perioperative cardiac death rate in some reports is five to 10 times increased in patients whose antiplatelet therapy has been withdrawn.

Aspirin is for life and should almost never be discontinued. Don’t stop statins perioperatively.

### The risk of bleeding

A meta-analysis of 4,002 patients undergoing cardiac surgery showed significant increase in bleeding, transfusion requirements, ventilation requirements, length of hospital stay and surgical re-exploration in those on clopidogrel. The evidence for increased surgical bleeding in non-cardiac surgery is less clear. Chassot analyses the data as follows.

Increase in surgical blood loss with aspirin alone is 2.5-20%. Increase in surgical blood loss with combination of aspirin and clopidogrel is 30-50% and average increased transfusion requirement of 30% without concomitant increased morbidity and mortality except in intracranial surgery.

### Management plan

Various recommendations for perioperative management have been published. No definitive standard of care has been presented. Management needs to be individualised. Generally, the risk of withdrawing seems higher than the risk of bleeding. (See proposed algorithm by Chassot et al: Table I and Figure 2.)

A “bridging therapy” with short-acting intravenous antiplatelet agents (GPIIb/IIIa Antagonists) has been described for those cases where the risk of stent thrombosis and the risk of surgical bleeding is high. However, bridging therapy requires hospitalisation of the patient and is costly. Furthermore, patients are still at risk of stent thrombosis during the window of normal platelet function. More data are required to elucidate the risk-benefit ratio.

### Catheterisation facilities

For patients identified as high risk for stent thrombosis, surgery should be planned in a hospital with cardiac catheterisation facilities. PCI is the treatment of choice for perioperative stent thrombosis.

### Conclusion

Given the choice and taking into account the above, I would much rather anaesthetise a patient for non-cardiac surgery post-CABG than post-coronary artery stenting. But we generally don’t have the choice. As anaesthetists we have to be aware of the developments in the field of interventional cardiology and its implications to us and to our patients in the perioperative period.

### References:

Refresher Course: Rather anaesthetise a patient with CABG than a stent

Table I: Proposed scheme for management of patients taking antiplatelet therapy and requiring surgery. MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MS, bare metal stent; DES, drug eluting stent; EF, ejection fraction.

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6 months after MI, PCI, BMS, CABG, stroke &gt;12 months if complications</td>
<td>6–24 weeks after MI, PCI+BMS, CABG, or stroke (0 complication); &gt;12 months after DES; high-risk stents (long, proximal, multiple, overlapping, small vessels, bifurcation); low EF, diabetes</td>
<td>&lt;6 weeks after MI, PCI, BMS, CABG; &lt;6 months after same if complications; &lt;12 months after high-risk DES; &lt;2 weeks after stroke</td>
</tr>
<tr>
<td>Low risk</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Transfusion normally not required;</td>
<td>Elective surgery: OK; maintain aspirin</td>
<td>Elective surgery: postpone; vital or emergency</td>
</tr>
<tr>
<td>peripheral, plastic, and general surgery,</td>
<td></td>
<td>surgery: OK; maintain aspirin and clopidogrel</td>
</tr>
<tr>
<td>biopsies; minor orthopaedic, ENT, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>general surgery; endoscopy; eye anterior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chamber; dental extraction and surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion frequently required; visceral</td>
<td>Elective surgery: OK; maintain aspirin</td>
<td>Elective surgery: postpone; surgery absolutely</td>
</tr>
<tr>
<td>surgery; cardiovascular surgery; major</td>
<td></td>
<td>required: OK; maintain aspirin, clopidogrel (if</td>
</tr>
<tr>
<td>orthopaedic, ENT, reconstructive surgery;</td>
<td></td>
<td>prescribed)</td>
</tr>
<tr>
<td>endoscopic urology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible bleeding in a closed space;</td>
<td>Elective surgery: OK; maintain aspirin; withdraw</td>
<td>Elective surgery: postpone; surgery absolutely</td>
</tr>
<tr>
<td>intracranial neurosurgery; spinal canal</td>
<td>aspirin (maximum 7 days)</td>
<td>required: OK; maintain aspirin, or replace aspirin by</td>
</tr>
<tr>
<td>surgery; eye posterior chamber surgery</td>
<td></td>
<td>aspirin and clopidogrel</td>
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Figure 2: Algorithm for preoperative management of patients under antiplatelet therapy. MI, myocardial infarction; ACS, acute coronary syndrome; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; BMS, bare metal stent; DES, drug eluting stent. *High-risk stents: long (0.36 mm), proximal, overlapping, or multiple stents implantation, stents in chronic total occlusions, stents in small vessels or bifurcated lesions. **Examples of low-risk situations: three months after BMS, stroke, uncomplicated MI, PCI without stenting. ***Risk of bleeding in closed space: intracranial neurosurgery, intra-medullary canal surgery, posterior eye chamber ophthalmic surgery. In these situations, the risk/benefit ratio of upholding vs. withdrawing aspirin must be evaluated for each case individually; in case of aspirin upholding, early postoperative re-institution is important. (Reprinted from Chassot et al.)