Summary and Key Recommendations

• The risk for perioperative cardiac events is increasing as the prevalence of ischaemic heart disease and coronary stents rises in the surgical patient population.

• The presence of coronary artery stents makes the perioperative management of antiplatelet therapy essential.

• Preoperative discontinuation of aspirin taken for secondary prevention is associated with increased risk of adverse cardiac events. This risk is highest for patients with coronary stents.

• Most routine operations can be undertaken without interrupting aspirin unless there is a risk of bleeding into an enclosed space. This also applies to dipyridamole.

• When clopidogrel is used as monotherapy, and discontinuation considered essential, low-dose aspirin should be substituted (unless contra-indicated).

• In situations of high thrombotic risk, when the patient is on dual antiplatelet therapy, elective surgery should generally be delayed until clopidogrel can be safely stopped.

• When surgery cannot be delayed and thrombotic risk is high, the continuation of both aspirin and clopidogrel should be a discussion between surgeon, anesthetist, and cardiologist.

• At present there is a lack of evidence about the bleeding risks with newer antiplatelet agents (prasugel, ticagrelor, cangrelor).

• Recent advances in stent technology support a shorter period of DAPT (Dual Antiplatelet Therapy) coverage.
Introduction

Patients presenting for operations are commonly on antiplatelet medication. It is estimated that 4-10% of patients with coronary stents will present for non-cardiac surgery within the subsequent year. The higher overall morbidity of this elective surgical population increases the risk of perioperative myocardial events. There is evidence that the traditional approach of stopping these drugs before surgery puts these patients at a greater risk of perioperative ischaemic cardiovascular events, a point which is particularly true in patients with coronary stents. Conversely, there are suggestions that the increased intraoperative bleeding of patients on antiplatelet drugs is in most instances manageable [1,2]. This poses an important challenge: the need to balance the risk of intra-operative bleeding of patients on antiplatelet agents against the risk of adverse cardiovascular events when stopping these agents. An evidence-based approach is necessary for the optimal management of perioperative antiplatelet medication therapy, but given the lack of definitive trial based evidence, most literature is recommendation based on expert consensus opinion.

1. Antiplatelet agents

1.1 Acetylsalicylic acid (Aspirin)

Aspirin acetylates the enzyme cyclooxygenase 1 (COX-1) and to a smaller degree, COX-2. COX-1 is part of the arachidonic acid pathway towards the production of Thromboxane A₂ (TXA₂). The latter is mainly produced in platelets and leads to platelet aggregation as well as vasoconstriction, so the inhibition of COX-1 results in reduced levels of TXA₂ and consequently reduced platelet aggregation [3]. The blocking of COX-1 by aspirin is irreversible, and platelet function can only recover through synthesis of new platelets. Platelets have a lifespan of approximately 10 days but not 100% need to be functional for effective aggregation, so platelet function is partially restored 4 to 5 days after stopping the drug [4].

Aspirin at low doses has been shown to reduce the risk of myocardial infarction and death in patients with ischaemic heart disease [5,6], the risk of stroke in cerebrovascular disease [7] and the risk of stroke after carotid endarterectomy [8]. Its major side effects are increased bleeding and gastrointestinal complications. Although gastrointestinal effects are dose dependent, even at low doses aspirin increases the risk of gastrointestinal bleeding 2 to 3 fold [3].

It is worth noting the phenomenon of aspirin-‘resistance’, whereby platelets continue to exhibit high reactivity despite treatment. It is not fully understood but thought to be multifactorial, and estimates of its incidence vary depending on the laboratory assay used to quantify platelet function. A meta-analysis in 2007 reported a 27% incidence for clinical aspirin resistance, with these patients being at higher risk of cardiovascular complications [9].

**Indications:** Aspirin is the most commonly used antiplatelet drug. It is used for secondary prevention in coronary artery disease, after coronary stent implantation and after coronary artery bypass grafting. It is also used in secondary prevention of cerebro-vascular and peripheral vascular disease as well as after carotid endarterectomy or stenting [3,10]. Regular use of aspirin has been found to reduce the incidence of developing colorectal, oesophageal and breast cancer and also a reduced risk of metastasis from colorectal cancer.

1.2 Thienopyridines (Clopidogrel, Prasugrel)

Both are prodrugs that undergo metabolic activation by p450-dependent hepatic enzymes. The active metabolites inhibit the platelet P2Y₁₂-receptor, which in turn blocks ADP - mediated platelet aggregation (ADP: adenosinediphosphate). This process is irreversible, so despite the short half-life of
thienopyridines, the antiplatelet effect of these drugs disappears only when enough new platelets have been synthesized. In the case of clopidogrel, platelet function does not return to normal until 7 to 10 days after cessation of therapy [3].

Clopidogrel has been shown to reduce endpoints such as vascular death, myocardial infarction and ischaemic stroke in patients with recent ischaemic events when compared to aspirin [11]. While there is clear evidence of the added benefit of dual antiplatelet therapy with aspirin and clopidogrel in acute coronary syndromes, the situation is less clear in patients with stable angina or previous ischaemic stroke [3,12,13]. Current NICE guidelines recommend monotherapy with clopidogrel for ischaemic stroke and aspirin alone for stable angina. [58]

The main side effect of clopidogrel is bleeding. Dual antiplatelet treatment compared to monotherapy with aspirin increases the risk of minor bleeds in most of the studies mentioned above. A few trials report an increase in major bleeds, e.g. the CURE trial, with a 2.7% rise with aspirin monotherapy to 3.7% with combination therapy [12], whereas other trials show a remarkably good safety profile of dual therapy without excess major bleeds [13]. Analogous to aspirin there is the problem of clopidogrel ‘resistance’: about one-third of patients exhibit a degree of clopidogrel resistance with an associated higher risk for adverse cardiac and vascular events despite treatment [3].

Indications: Clopidogrel is the main thienopyridine in use. It is used on its own in cases of aspirin-contra-indications or intolerance and increasingly as preferred monotherapy after transient ischaemic attack (TIA) or cerebrovascular accident (CVA). More commonly, clopidogrel is used in combination with aspirin in higher risk cases, such as secondary prevention of high risk coronary artery disease, in acute coronary syndromes (ST-elevation and non-ST-elevation myocardial infarction) and after coronary stent implantation [10]. It is worth noting that aggressive antiplatelet therapy is necessary in the early stages after coronary stent implantation as there is a high risk of acute stent thrombosis prior to endothelial-ization of the stent.

Current recommendations for stable coronary disease treated with bare metal stents (BMS) is to continue antiplatelet treatment with acetylsalicylic acid and clopidogrel for one month and for 12 months in patients with acute coronary syndrome and then lifelong continuation with aspirin alone [14]. Drug eluting stents (DES) are designed to inhibit fibroblastic proliferation and reduce late in-stent re-stenosis. This also delays early stent endothelialisation so the risk for early stent thrombosis persists for longer when compared to bare metal stents and hence the recommendation is to continue dual antiplatelet therapy for 6 months in stable coronary artery disease and 12 months in acute coronary syndrome. [14] Improved stent technology and drug elution with the second and third generation DES stents do not necessitate antiplatelet therapy beyond 6 months (with some differences between American and European guidelines). [48, 59]

Prasugrel is a newer thienopyridine with more potent, more consistent and a quicker onset of platelet inhibition compared to clopidogrel [15]. Its pharmacodynamics are similar to clopidogrel, with irreversible platelet inhibition but it exhibits much less inter-patient variability and recovery of platelet function also takes much longer as compared to clopidogrel. It is currently used mainly in the acute setting as an adjunct to percutaneous coronary intervention but might well become more common in long-term antiplatelet therapy. Other indications include therapy in diabetic patients and also in patients who have had stent thrombosis while on clopidogrel. It is contraindicated in patients who have a high risk of bleeding (Elderly>75 yrs, Low BMI, Hepatic and renal impairment, GI bleed)

1.3 Ticagrelor

Ticagrelor is an agent of the new cyclopentyltriazolopyrimidine class that, like the thienopyridines, blocks the P2Y12-receptor, but in a reversible fashion and at a different binding site. Its anti-platelet
effect is more potent and faster in onset than clopidogrel. It displays a lower incidence of resistance hence the platelet inhibition is more consistent. Platelet inhibition is not discernible five days after discontinuation of the drug [10]. In a large study of secondary prevention in patients with acute coronary syndrome, ticagrelor was superior to clopidogrel in reducing death from vascular causes and myocardial infarction [16], but at present it is unclear whether ticagrelor causes more bleeding complications than clopidogrel. It is currently the drug of choice, along with aspirin, for patients post acute coronary symptoms and post PCI [59]

1.4 Dipyridamole

Dipyridamole increases intraplatelet concentrations of cyclic adenosine monophosphate (cyclic AMP), which in turn inhibits platelet aggregation and leads to vasodilation. There is evidence that the combination therapy of aspirin and dipyridamole is more effective than aspirin alone in secondary prevention of ischaemic stroke [17,18] but no benefit could be shown in coronary artery disease [18]. After stopping dipyridamole platelet aggregation recovers quickly, so when used alone it can be stopped one day prior to interventions.

**Indication:** Dipyridamole is recommended in combination with aspirin for the secondary prevention of ischaemic stroke [19]. Its use has been declining with the advent of the thienopyridines.

1.5 Cilostazol

Cilostazol is a phosphodiesterase type III inhibitor that suppresses platelet aggregation reversibly, with self-limiting effects based on its half-life of 10 hours [42]. It is a vasodilator indicated for the improvement of walking distances in patients with intermittent claudication for whom lifestyle modifications and other appropriate interventions have failed to improve their symptoms [45, 46]. However in the UK current recommendations are for clopidogrel rather than cilostazol.

1.6 Glycoprotein IIb/IIIa receptor antagonists (Tirofiban, Abciximab)

The final step of platelet aggregation is the activation of Glycoprotein IIb/IIIa receptors which bind substrates such as fibrinogen leading to the interlinking of adjacent platelets. Blocking Gp IIb/IIIa receptors is therefore a very powerful way of inhibiting platelet aggregation. After a bolus dose of abciximab platelet aggregation returns to at least 50% of baseline within 24 hours [3]. Tirofiban has a half-life of 2 hours, is therefore given as a bolus followed by an infusion and platelet function recovers to 50% of baseline within 4 hours of stopping [3]. These drugs require intravenous administration and need specialist supervision. Current indications are as an adjunct to PCI or after an acute MI while awaiting PCI and also have been used as bridging therapy in high risk patients undergoing urgent surgery soon after a cardiovascular intervention. [56].

Side effects of GP IIb/IIIa blockade are major bleeding (increase from 2.7% to 4.1% [20]) and thrombocytopenia (1-2% of cases of abciximab treatment [3]). As Glycoprotein IIb/IIIa receptor antagonists are used only in the acute context of acute coronary syndromes, they are not encountered in the perioperative setting of elective operations.

NICE guidelines on antiplatelet medication (Concise summary: last revised August 2020)

**Primary prevention**

Current NICE guidance does not recommend routine primary prevention for cardiovascular disease. Primary prevention with aspirin may be considered for patients with controlled hypertension who have a high cardiovascular risk (>20% in 10 yrs ) or who have diminished renal function.
Secondary prevention

Table 1: Summary of current NICE guidance regarding the use of antiplatelets (60)

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Device used</th>
<th>Bleeding risk</th>
<th>Duration of DAPT therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI for stable ischaemic heart disease</td>
<td>BMS/DES</td>
<td>High</td>
<td>1 month (can continue up to 3 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>6 months (can continue up to 12 months)</td>
</tr>
<tr>
<td>PCI for Acute coronary symptoms</td>
<td>BMS/DES</td>
<td>High</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>12 months (can continue &gt;12 months)</td>
</tr>
</tbody>
</table>

BMS - Bare metal stent  
DES - Drug eluting stent (2nd generation)  
DAPT - Dual antiplatelet therapy (Aspirin with clopidogrel/ticagrelor/prasugrel)  
Bleeding risk - specific to patient eg age, concomitant anticoagulant therapy, CKD, Diabetes
2. Risk of cardiovascular events

2.1 Cardiovascular events in the perioperative period

The risk of thromboembolic events is increased in the perioperative period due to several factors. Firstly, an acute phase response promotes increased platelet adhesiveness and decreased fibrinolysis, leading to a hyper-coagulant state. Secondly, the stress response of surgery leads to an increased sympathetic tone, vasospasm and higher shear stress on arterial plaques. Dehydration due to fasting raises blood viscosity, both increasing the risk of vascular ischaemic events. Thirdly, there is a rebound phenomenon after stopping antiplatelet drugs with increased platelet adhesiveness in the period of decreasing drug effect [21].

2.2 Discontinuation of antiplatelet therapy

The rebound phenomenon after discontinuation of antiplatelet agents has been mentioned above. To what extent this increases the risk for cardiovascular events depends on the agent used and the indication for antiplatelet therapy, so risk needs to be discussed in that context.

2.2.1 Aspirin for prevention of perioperative myocardial infarction

Two randomised, double-blinded, placebo-controlled trials investigated the risk of major perioperative cardiac events in patients on aspirin undergoing intermediate to high-risk non-cardiac surgery. One showed a relative risk reduction for such events of 80% with preoperative aspirin [22], while the other trial did not show any difference in the incidence of thrombotic events between groups taking or not taking aspirin in the preoperative period [23]. These results are contradictory but upon closer inspection both trials missed the recruitment target to fulfill their own power calculations and there were small but distinct differences in the management of the study drug. In the negative trial, aspirin was more likely to be recommenced earlier in the postoperative period and could have thus provided more cardio-protection, as the majority of adverse events happened within the first three postoperative days in both trials.

The POISE-2 trial was a large, multicenter, randomised controlled trial (RCT) that looked at the effects of aspirin and clonidine, both vs placebo on perioperative mortality and myocardial infarction in patients ‘at risk’. The trial found no difference in peri-operative cardiac outcomes but did find an increase in major bleeds between the aspirin group and the placebo (4.6% vs 3.8%). However only 23% of patients had known prior coronary artery disease and the trial excluded patients with stents who had not completed the full course of DAPT [25]. By contrast, when a subset of patients with previous PCI were analysed separately, aspirin was found to reduce the relative risk of death and non-fatal myocardial infarction with a hazard ratio of 0.5 (p=0.0360) [26].

The European Society of Cardiology guidelines from 2017 recommend continuing aspirin perioperatively if bleeding risk allows (class IB evidence) [48].

2.2.2 Aspirin / Clopidogrel in patients with coronary stents

Premature cessation of DAPT is one of the strongest predictors of stent thrombosis with catastrophic results [28] and this was highlighted in an early small observational study [29]. A total of 27 patients were operated on within three weeks of percutaneous coronary intervention. 6 out of 7 patients in
whom thienopyridine treatment was stopped died in the postoperative period, but there was only one death in the 20 patients in whom it was continued.

There are several reasons why the thrombotic risk is increased after coronary intervention: in the immediate aftermath any dilated coronary lesion is unstable because dilatation disrupts the plaque and its endothelial covering. Furthermore, any deployed stent represents a foreign surface with increased thrombogenicity prior to endothelization. With drug eluting stents (DES), this process is delayed, therefore the risk of stent thrombosis is higher and persists for longer. However, Compared with 1st generation DES, newer generation DES are associated with lower risk of stent thrombosis and require a shorter duration of DAPT [48].

The Danish registry study in 2016 [24] and a number of other recent studies have pointed to time since stent insertion and other comorbidities rather than interruption of antiplatelets per se as being the more important determinant of postoperative major cardiac and cerebral events (MACCE) [30,31,43,44]. Howell et al in a prospective observational study found no evidence of a protective effect of DAPT from perioperative MACE in patients with stents having noncardiac surgery [43]. Furthermore a study that looked at the effectiveness of platelet inhibition by platelet mapping assays perioperatively found that the incidence of cardiac events was high in spite of adequate antiplatelet cover and the authors postulated that time from PCI to surgery and supply-demand of blood flow in the immediate postoperative period was more relevant [44].

2.2.3 Antiplatelet therapy for other indications

In cerebrovascular disease, a small case-control study postulated more than a 3-fold risk for ischaemic events in aspirin withdrawal [32] and current guidelines support antiplatelet therapy for 3-6 months following a stroke or TIA and long term cover with DAPT after carotid endarterectomy and carotid or vertebral stenting.[51]. A meta-analysis on risks of perioperative aspirin discontinuation acknowledges the lack of prospective studies and is therefore careful with bold statements and risk estimates. An interesting observation is the mean time-interval between aspirin withdrawal and adverse events: it was shortest for acute coronary syndromes (mean of 8.5 days), followed by 14.3 days for acute cerebral events and 25.8 days for acute peripheral arterial syndromes [1]. This could be interpreted as confirming the notion that coronary ischemia is the most likely and most important adverse consequence of a short interruption of antiplatelet therapy in the perioperative phase.

Current NICE guidelines support monotherapy with clopidogrel or aspirin or modified release dipyridamole in patients with peripheral arterial disease along with risk reduction with exercise smoking cessation and statins. Secondary to interventions such as angioplasty / stents or surgical revascularization, monotherapy or DAPT is continued for 6-12 months [50]. No data are currently available for risk associated with dipyridamole or clopidogrel discontinuation in the above indications.

2.3 Cardiovascular risk stratification depending on morbidity and time intervals

Another approach to classifying thrombotic risk focuses on the exact type of cardiovascular morbidity and importantly also on the time delay since the occurrence of cardiovascular events [61].
3. Risk of intra-operative bleeding under antiplatelet therapy

3.1 Acetylsalicylic acid

Two randomized, controlled, prospective trials investigating perioperative bleeding and thrombotic risks in patients on aspirin or placebo undergoing non-cardiac surgery have been published [22,23]. Both were not powered to detect a difference in bleeding events, so their negative findings in that aspect have to be interpreted with caution. However, in light of the fact that all other available studies are either from cardiac surgery or represent retrospective or non-randomized data, their results should not be dismissed entirely. In the first trial, a total of 220 patients at risk of cardiovascular events were randomized to either aspirin or placebo with all bleeding outcomes (amount of bleeding, surgeon’s assessment of bleeding tendency, transfusion requirements) being non-significant between the groups [22].

The second trial investigated 291 patients assigned to either aspirin or placebo and found no significant difference in ‘major bleeding’ or ‘bleeding’ events [23]. All other studies in non-cardiac surgery are non-randomized, small and in part also of limited quality. A meta-analysis of available data arrived at an increase of bleeding rate by a factor of 1.5 in patients on aspirin [1]. This increase in bleeding, however, did not seem to cause higher morbidity or mortality, with a few notable exceptions.
Most surgery such as dental, minor general, vascular, ophthalmological and dermatological procedures, as well as biopsies and endoscopies seemed safe. The exceptions were in tonsillectomies, where the re-operation rate was significantly increased and in transurethral prostatectomies, where two fatalities were reported as well as a higher transfusion rate. Finally, aspirin increased the risk of intracerebral hematoma following neurosurgery, and it was implicated in bleeding-related fatalities [1]. In orthopaedic surgery the evidence is mixed. One large trial found an increase in local and gastrointestinal bleeding in patients undergoing hip arthroplasty that was not reproduced in other trials of major orthopaedic operations [34]. As mentioned already, continuation of aspirin was also found to increase the risk of major bleeding in the POISE-2 trial [25].

3.2 Clopidogrel / dual therapy

Almost all evidence regarding clopidogrel monotherapy has been generated in cardiac surgery. A meta-analysis of coronary artery bypass surgery trials showed that clopidogrel taken until the operation significantly increased blood loss, transfusions, surgical re-exploration and length of hospital stay while not significantly affecting mortality [35]. A small retrospective analysis of non-elective orthopedic surgery performed under clopidogrel found no serious complications or increased transfusion requirements compared to matched control [36].

In dual antiplatelet therapy, one study investigating various non-coronary surgical procedures after stent insertion found only a small increase of transfusion rates from 39% (no antiplatelet therapy) to 43% (dual therapy) [37]. In contrast, another study looking at a similar patient group found a much higher difference between single and dual antiplatelet therapy: the risk of severe bleeding increased from 4 to 21% [38]. Both studies were small reflecting the paucity of the evidence-base in non-cardiac surgery. A recent review estimated the increase of blood loss with aspirin to be 20% and with dual treatment 50% across non-cardiac surgery, but found no clear increase in mortality or morbidity except in neurosurgery [39]. More recently the investigators on the OBTAIN clinical trial showed an increased risk of bleeding with dual antiplatelet therapy with no evidence of a protective effect on perioperative MACE in patients who have undergone previous PCI [43].

A recent study found that dual therapy with aspirin and clopidogrel was not associated with an increase in bleeding complications or transfusion requirements in patients undergoing peripheral arterial surgery [49]. In addition a recent meta-analysis (2938 patients) has shown that patients on clopidogrel with hip fractures can be managed as per usual protocols (Early surgery and continuation of clopidogrel) [57].

There are insufficient data to draw any conclusions about perioperative bleeding risk with dipyridamole.

3.3 Risk stratification for intraoperative bleeding depending on type of surgery

Independent of antiplatelet medication, the risk of hemorrhage of surgery can be classified depending on the type and location of surgery [2]. It is important to note that both the risk of hemorrhage and the potential consequences determine the grading:
Table 3: Risk of hemorrhage during surgery

| High haemorrhagic risk: (including surgery in a closed space) | • open thoracic and thoracoabdominal surgery  
• nephrectomy  
• femur surgery  
• TURP, prostatectomy  
• Major pelvic surgery  
• Hepatic resection  
• Posterior chamber of eye  
• Intracranial surgery, spinal canal surgery |
|---------------------------------------------------------------|
| Intermediate haemorrhagic risk:  
  transfusion frequently required | • cardiac / vascular surgery  
• major general, orthopaedic, ENT or urologic surgery |
| Low haemorrhagic risk  
  transfusion normally not required | • minor general, orthopaedic, ENT or urologic surgery  
• peripheral and plastic surgery  
• eye surgery in anterior chamber  
• dental extraction and surgery  
• biopsies, endoscopy  
• breast surgery  
• Carotid endarterectomy, Endovascular aortic stents, peripheral endarterectomies, limb amputations |

4. Regional Anesthesia and anti-platelet drugs

Neuraxial anaesthesia is often considered in patients taking antiplatelet agents for coronary stent protection and the decision to use such a technique must be based on careful assessment of the overall balance of risk and benefit for each individual. Regarding the time frame between stopping antiplatelet agents and neuraxial blockade, the following guidelines have been published by the Association of Anaesthetists [62] and the American Society of Regional Anaesthetists.[47].

Table 4: Recommended time intervals for discontinuation and recommencement of anti-platelet agents before and after neuraxial puncture or catheter removal (based on ASRA and AAGBI guidelines)

<table>
<thead>
<tr>
<th></th>
<th>Time before puncture or catheter removal</th>
<th>Time after puncture or catheter removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>None</td>
<td>After catheter removal</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7 days</td>
<td>6 hrs after catheter removal</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>7-10 days</td>
<td>6 hrs after catheter removal</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>5 days</td>
<td>5 hrs after catheter removal</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>42 hours</td>
<td>After catheter removal</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>10 days</td>
<td></td>
</tr>
<tr>
<td>NSAIDS</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
5. Practical approach to perioperative antiplatelet treatment in non-cardiac surgery

The perioperative management of antiplatelet therapy must always balance the thrombotic risks of stopping with the bleeding risks of continuing the drugs. The basic questions prior to surgery that provide the necessary information for decision making are outlined below:

• what is the nature of the operation?
• how necessary / urgent is it?
• what is the indication for antiplatelet therapy?
• how high is the thrombotic risk?
• what is the risk for bleeding?
• what are the potential consequences of bleeding?
• if discontinued, when to recommence antiplatelet therapy?

Several US and European professional bodies have published guidelines [41,42,43,52,54, 56,59,60]. There is general consensus on the main principles of managing antiplatelet therapy perioperatively: a simplified approach that covers most straightforward cases is outlined in the algorithm in figure 1. It should be emphasized that these guidelines do not cover cardiac surgery. Borderline situations need further consideration, for instance of the precise bleeding risk of surgery as detailed in chapter 3.3, and of the precise thrombotic risk (see chapter 2.3).

In patients who have coronary stents, not only the type of stent (BMS versus DES) but the time since insertion and complexity of the stent needs to be considered in addition to patient co-morbidities such as systolic dysfunction, renal dysfunction and diabetes. [44]. As details of the stent per se may not be apparent at pre-assessment, a pragmatic policy would be to discuss each case individually between surgeon, cardiologist and anaesthetist for stents placed within the preceding year.

An overview of this decision-making process depending on thrombotic vs hemorrhagic risk is given in Table 5 below.

Transurethral prostate resection is an example of a practical dilemma: reports of two fatal hemorrhages associated with aspirin treatment [1], should lead to careful consideration of whether to continue or withhold aspirin therapy [42]. In practice however, surgeons are divided in their approach and local agreements are necessary to avoid unnecessary cancellations.

Elective surgery and patients with stents:
Elective surgery should be deferred in patients with drug eluting stents for at least 6 months and with bare metal stents for at least 1 month. After balloon angioplasty elective surgery should be deferred for at least 2 weeks. Aside from the timing of surgery relative to PCI , patient co-morbidities and indication for PCI (stable heart disease vs acute coronary symptom) are also important factors to take into consideration.

Recent stenting and urgent surgery
In patients presenting for surgery on dual antiplatelet therapy after recent coronary stenting, the key question is whether it is feasible to delay the operation. If these delays are not acceptable, operating under dual therapy is recommended [42]. If the bleeding risk is deemed high then an individualized risk-benefit analysis needs to be made, aspirin should be continued and such surgeries should be performed in centers that have access to cardiac catheterization facilities 24/7. Bridging therapy with IV antiplatelets (Tirofiban, cangrelor, eptifibatide) may be necessary. [55].

Unplanned / emergency surgery in patients on dual therapy:
Both aspirin and clopidogrel have short half-lives, and plasma levels of active drug are low only
hours after the last dose. However as stated earlier their effects on platelet function is irreversible. In the case of emergency surgery and significant bleeding risk consider use of tranexamic acid. If despite tranexamic acid there is excessive bleeding, consider transfusing 2 pools of platelets at least 2 hours after the last aspirin dose and 12 hours after clopidogrel [56]

**Elective surgery after recent stroke or vascular surgery**
Elective surgery should be deferred in patients who have had a recent ischaemic stroke for at least 6 months as the risk for recurrent stroke is highest if surgery takes place soon afterwards and then declines [61]. Patients who have had carotid endarterectomies, carotid / vertebral stents will usually be on long term antiplatelet therapy. Aspirin should be continued without interruption wherever possible and if other antiplatelets need to be stopped, risk needs to be discussed with the patient and advice sought from a neurologist.

Similar considerations apply to patients on antiplatelets after peripheral arterial interventions (angioplasty, stents, surgical revascularization)

**Table 5: Overview of decision-making process for perioperative management of DAPT**

<table>
<thead>
<tr>
<th>THROMBOTIC RISK</th>
<th>HEMORRHAGIC RISK</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Continue aspirin, discontinue clopidogrel and resume within 24-72 hours with a loading dose</td>
<td>Postpone elective surgery, if surgery cannot be deferred continue aspirin, stop clopidogrel, resume within 24-72 hours with a loading dose</td>
<td>Postpone elective surgery, if surgery cannot be deferred continue DAPT perioperatively</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Continue aspirin, discontinue clopidogrel and resume within 24-72 hours with a loading dose</td>
<td>Postpone elective surgery, if surgery cannot be deferred continue aspirin, stop clopidogrel, resume within 24-72 hours with a loading dose</td>
<td>Postpone elective surgery. If surgery cannot be deferred, continue aspirin, stop clopidogrel, resume within 24-72 hours with a loading dose, consider bridging with short acting IV antiplatelets</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Continue aspirin, discontinue clopidogrel and resume within 24-72 hours with a loading dose</td>
<td>Postpone elective surgery, if surgery cannot be deferred continue aspirin, stop clopidogrel, resume within 24-72 hours with a loading dose</td>
<td>Postpone elective surgery. If surgery cannot be deferred, continue aspirin, stop clopidogrel, resume within 24-72 hours with a loading dose, consider bridging with short acting IV antiplatelets</td>
<td></td>
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</tbody>
</table>
Stopping and restarting antiplatelet agents

If antiplatelet therapy is discontinued, it should be for the shortest time possible. Inter-individual variation in sensitivity to ADP receptor antagonism may allow some patients to have a shorter period of discontinuation. Assessment of platelet function may help identify such patients. Corredor et al have reviewed the utility of platelet function testing in cardiac surgery and found the most robust evidence was for thrombo-elastography to be incorporated into a blood management algorithm to reduce transfusion [53].

Post-operatively, early reinstitution is important after ensuring hemostasis. There is scant evidence to support bridging therapy during the period of antiplatelet withdrawal: heparin does not replace the antiplatelet effects and should not be used and there is minimal data regarding short-acting antiplatelet drugs such as Glycoprotein IIb/IIIa inhibitors (tirofiban, eptifibatide). However, such a strategy is likely to be associated with higher risk of bleeding [54].

In the case of clopidogrel, restarting with a loading dose should be considered (e.g. 300 mg given as soon as possible post-operatively) [52]. The second thienopyridine, prasugrel, although more potent than clopidogrel, displays similar pharmacodynamic properties and should be treated in the same way as clopidogrel. For the reversible P2Y12-inhibitor ticagrelor, similar considerations apply as for clopidogrel, bearing in mind the greater potency of the drug with regards to bleeding. Dipyrimadole has a reversible effect with a short half-life. It is usually given in combination with aspirin and similar principles to stopping aspirin would apply in combination therapy.

Finally, the current paucity of reliable, high quality evidence and the development of several new platelet inhibitors make this a situation in flux where alterations to current practice can be expected as new evidence becomes available.
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