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Swan, D., Loughran, N., Makris, M. orcid.org/0000-0001-7622-7939 et al. (1 more author) (2020) Management of bleeding and procedures in patients on antiplatelet therapy. Blood Reviews, 39. 100619. ISSN 0268-960X

https://doi.org/10.1016/j.blre.2019.100619

Management of Bleeding and Procedures in Patients on Antiplatelet Therapy

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Keywords: Aspirin; Anaesthesia; Bleeding; Clopidogrel; Antiplatelet; Ticagrelor; Prasugrel; Surgery

Abstract

Antiplatelet medications have long been the mainstay for secondary prevention in cardiovascular disorders. More recently, with the advent of coronary stents, there has been an increased use of more potent antiplatelet agents to prevent stent occlusion. Since these drugs are antithrombotic, it is not unusual for them to be associated with serious bleeding, particularly intracranial and gastrointestinal haemorrhage. There are no robust guidelines on how to manage these clinical situations, although there have been some important studies published recently in this area. Similarly, there is very limited evidence on how to manage urgent surgery in patients receiving these medications. In this review, we provide updated guidance on the management of bleeding and surgery on antiplatelet drugs while stressing the need for further studies to provide evidence-based guidelines.

Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality worldwide although mortality in the Western world is falling. A 68% decline in mortality in the UK observed from 1980 to 2013, has been largely attributed to public health measures and risk factor control, alongside a seven-fold increase in rates of percutaneous coronary intervention (PCI) from 1993 to 2013 (1). Since the widespread uptake of PCI, more and more patients are treated with single or dual anti-platelet therapy (APT) to prevent stent thrombosis. Use of drugs which prevent platelet aggregation, is associated with an increased risk of bleeding, which range from serious such as intracranial haemorrhage or gastrointestinal bleeding to minor skin bruising. Also, the subgroup of patients who require APT, due to their increased age and presence of comorbidities, also have an increased need for surgical interventions. It has been estimated that 4-8% of patients who have had a coronary stent inserted will require major surgery within one year of stent placement (2). Herein a dilemma arises regarding appropriate peri-operative management of their APT. On one hand, evidence has shown that continuation of APT peri-operatively can increase the frequency of procedural bleeding (3) whilst discontinuation can increase the risk of cardiovascular events (4, 5). This review aims to examine the risks associated with APT and the management of patients who are bleeding or who require emergency or elective surgery.

The anti-platelet agents and their mechanism of action

The most frequently encountered anti-platelet therapies are aspirin, the ADP-inhibitors clopidogrel, prasugrel and ticagrelor, and occasionally the GP IIb/IIIa inhibitors (summary in Table 1).

Aspirin

Aspirin irreversibly inhibits cyclo-oxygenase (COX)-1 and -2 (6-8), preventing production of thromboxane A2 (TXA2) from arachidonic acid and thereby blocking TXA2-induced platelet aggregation and stimulation of further TXA2 release.

ADP inhibitors (Thienopyridines)

ADP (adenosine diphosphate) binding to the P2Y12 and P2Y1 receptors is necessary for the subsequent exposure of GP IIb/IIIa and fibrinogen-mediated platelet-platelet interactions (9). There are three P2Y12 inhibitors currently in routine use; clopidogrel, prasugrel and ticagrelor. Clopidogrel and prasugrel must be metabolised to become active whilst ticagrelor is already in its active state. Clopidogrel and prasugrel inhibit the P2Y12 receptor irreversibly whereas ticagrelor binds reversibly (10). Cangrelor is an intravenous, direct-acting, reversible ATP (adenosine triphosphate) analogue with a high affinity for the P2Y12 receptor.

GPIIb/IIIa inhibitors

GPIIb/IIIa is critical for fibrinogen-mediated platelet binding to allow formation of the platelet aggregate. The available GP IIb/IIIa inhibitors are abciximab, eptifibatide and tirofiban, which are all administered via

intravenous infusion, due to their short half-lives. Abciximab is a chimeric (mouse/human) monoclonal antibody that binds to platelets, whereas tirofiban and eptifbatide are small molecule inhibitors (11). Abciximab is associated with a transient mild thrombocytopenia in 2-3% of patients which is of no clinical significance, but may also cause a severe thrombocytopenia in <2% due to the presence of preformed antibodies against murine IgG (12). It should be noted however, that abciximab (ReoPro, Janssen) was withdrawn from the market in 2019 due to interrupted production at a third-party manufacturing site. Eptifibatide and tirofiban, unlike abciximab, block the RGD (arginine-glycine-aspartate) sequence within GPIIb/IIIa, preventing the crucial association between fibrinogen and von Willebrand factor (13).

PAR antagonists

Protease activated receptor-1 and -4 (PAR-1 and PAR-4) are the two thrombin receptors expressed on the platelet surface. One PAR-1 antagonist, vorapaxar, has been approved by the FDA for secondary prevention in patients with prior myocardial infarction or peripheral arterial disease, but has not gained European approval and is not available for clinical use in the European Union (14).

Managing intracranial haemorrhage in patients on anti-platelet therapies

Incidence

Spontaneous ICH accounts for approximately 6-20% of all strokes (15), and at thirty days carries a mortality of over 40%. Size of haematoma and expansion of the bleed are strongly associated with worse outcomes (16). Whether concurrent APT has a significant impact on the overall morbidity and mortality is controversial, with conflicting results in spontaneous ICH and traumatic brain injury (17). Observational studies have identified an association between aspirin use and development of cerebral microbleeds, which are known to increase the risk of spontaneous ICH. Recently, Qiu *et al.* reviewed nearly 21,000 cases of cerebral microbleeds from 37 studies. They found that aspirin use was associated with an increased occurrence of lobar microbleeds, and that ICH rate was higher amongst those with cerebral microbleeds than without (18). Lobar bleeds have a higher recurrence rate, worse outcome, and are more commonly seen in anticoagulated patients, than bleeds affecting deep cortical structures (19). In patients anticoagulated with a vitamin K antagonist or direct oral antagonist following thromboembolic stroke, the recent CROMIS-2 study has shown that presence of cerebral microbleeds correlated far better with subsequent risk of ICH than the HAS-BLED scoring system, with rate of symptomatic ICH reported at 9.8/1000 patient years for those with cerebral microbleeds versus 2.6/1000 patients years in those without (20). The ongoing ASPREE-NEURO study, a prospective placebo-controlled cohort study in which patients are randomized to low-dose aspirin or placebo, and followed up by MRI to identify development of cerebral microbleeds and subsequent stroke, may provide more information for patients on aspirin (21). Most of the current data on ICH relates to aspirin and clopidogrel use. The TRITON-TIMI 38 trial of prasugrel with aspirin versus clopidogrel with aspirin reported an increase in life-threatening bleeding from 0.9% to 1.4% in the prasugrel arm, associated predominantly with prior cerebrovascular disease (22). The PLATO trial compared ticagrelor with clopidogrel. Major bleeding rates were unchanged but ICH was more common in ticagrelor-treated patients, hence previous ICH is a recommended

contraindication to ticagrelor administration (23). The GP IIb/IIIa inhibitors provide very potent platelet inhibition but have short half-lives and in the majority of cases of bleeding may be managed by simply stopping drug administration (17). At the other end of the spectrum, the PAR-1 inhibitor vorapaxar has such a long half-life (5-13 days) (14) that platelet transfusion would be futile, and hence is contraindicated in patients at high risk of ICH.

Surgically managed

Given the lack of agreement as to the importance of antiplatelet agents in spontaneous and traumatic ICH, it is unsurprising that optimal management of these patients is also unclear. For patients who require surgical management of bleeds, the general consensus is to provide supportive platelet transfusion (17). This recommendation is based primarily upon the results of a single randomized controlled trial of 780 patients undergoing craniotomy and haematoma evacuation. Patients who had recently taken aspirin and had evidence of platelet inhibition on platelet aggregometry were randomised to no platelets, one pool pre-surgery, or one pool pre- and one after 24 hours. The transfused arms had significantly reduced rates of ICH recurrence (14% versus 35%) and mortality (15.5% versus 34.2%) with improved six-month disability scores. Those patients with evidence of aspirin-resistance were not transfused, and had outcomes similar to aspirin-naïve individuals (24).

Non-surgically managed

The available evidence is even more conflicting for spontaneous bleeds and traumatic ICH not planned for surgical intervention. One small prospective study reviewed 45 patients with acute ICH, reduced platelet activity on presentation (using the VerifyNow system) and subsequent platelet transfusion. They found that transfusion within 12 hours was associated with a smaller haemorrhage size on follow-up and improved functional outcomes at three months (25). However, the PATCH study, a larger randomised controlled trial of 190 adults taking anti-platelet agents with spontaneous ICH found platelet transfusions were inferior to standard care, with a higher number of adverse events in patients in the platelet transfusion group (26). A more recent report of patients with traumatic ICH reviewed the effect of timing of transfusion. Patients taking pre-injury aspirin received one pool of platelets, and those on clopidogrel received two. Progression of haematoma was significantly associated with subdural bleeds and reduced conscious level on presentation, with no significant difference as to whether platelets were transfused within four hours of presentation. This finding could be explained by the presence of active drug metabolites in the circulation in the earlier time-frame, as investigators were unable to obtain the exact time of the last APT consumption. However, the degree of benefit provided by the platelet transfusions themselves could not be ascertained due to lack of a control non-transfused arm (27).

Role of drug therapies

The role of DDAVP in the setting of ICH has been examined in a handful of small, uncontrolled studies. There is some suggestion, but no robust evidence that DDAVP may temporarily improve platelet function providing some additional benefit (28, 29), and its use may be considered in this setting. There are rare reports of cerebrovascular or cardiac thrombotic events associated with DDAVP use however, so a judicious review of

comorbidities is recommended prior to administration (30, 31). DDAVP has been associated with hyponatraemia secondary to water retention. This risk is minimized by adherence to recommendations regarding fluid intake during treatment (32). Intracranial haemorrhage, particularly subarachnoid haemorrhage may also cause hyponatraemia, either due to SIADH (syndrome of inappropriate antidiuretic hormone) or cerebral salt wasting. In certain cases, vasopressin antagonists have been used to treat this condition (33). Evidence of hyponatraemia (serum sodium <135 mmol/l) should therefore warrant caution prior to DDAVP administration, but there are no formal recommendations to guide this practice. Recombinant factor VIIa increases thrombin generation at the platelet surface improving haemostasis. Its use has been reported in acute ICH but extreme caution is advocated, as the prothrombotic nature of rFVIIa may lead to adverse events in patients with pre-existing hypercoagulable states which required the antiplatelet medications (34).

Reintroduction of antiplatelet agents

There is very little data regarding whether to restart antiplatelet medications in patients who have suffered an ICH, and even less that addresses the issue of timing. The RESTART trial followed 537 patients post-ICH, half of whom restarted antiplatelet medications and the other half did not. At a median two years follow-up, 4% of the anti-platelet group had a recurrence of ICH versus 9% of the no anti-platelet group, and there was also no significant difference in rates of vascular adverse events (35). Effect of site of haemorrhage, surgical or non-surgical management, thrombotic risk factors and indication for anti-platelet agents on risk of recurrence and adverse cardiovascular events is not known, nor can we glean any information regarding the time at which antiplatelet medications should be restarted from this study. Reintroduction of antiplatelet agents at least seems likely to be safe in selected patients, but further information is required before formal recommendations can be made.

Summary

It is likely, although not fully established, that concomitant APT use may worsen outcomes in spontaneous and traumatic ICH. Platelet transfusion is recommended in patients planned for neurosurgical intervention, although the optimal time of delivery and dose required is uncertain. Evidence for platelet transfusion in the non-surgical setting in patients taking APT is less convincing with notable reports of worsened outcomes post platelet transfusion (26), and platelet transfusion is therefore not routinely recommended in these patients. The value of adjunctive therapies such as DDAVP and rFVIIa is unproven and associated with considerable risks requiring careful patient selection.

Managing gastrointestinal haemorrhage in patients on anti-platelet therapies

Gastrointestinal haemorrhage (GIH) is a common clinical presentation with or without concomitant antiplatelet medications (36). The UK incidence is around 50-190/10,000 patients per year (37, 38). A meta-analysis of 14 trials reported that low-dose aspirin (75-300mg) was associated with a relative risk of major GIH of approximately 2, with a modest annual absolute increased rate of 0.12%/year, which was slightly less for

single-agent clopidogrel (39). In terms of dual APT, aspirin plus clopidogrel confer reported rates of 1.3%-4.6% per year (40-42), whereas the newer P2Y12 inhibitors, prasugrel and ticagrelor, are associated with increased rates of GI bleeding compared to clopidogrel (major bleeding in 2.4% vs 1.8% prasugrel vs clopidogrel, non-coronary artery bypass graft-related major bleeding 4.5% vs 3.8% ticagrelor vs clopidogrel) (22, 23). GI haemorrhage is associated with increased risk of further ischaemic events and mortality (43) which may be related to premature cessation of antiplatelet medications alongside a prothrombotic state induced by bleeding (44).

Early endoscopic control of bleeding can prevent surgical intervention, reduce inpatient stay, and is recommended for patients suspected to have upper GI haemorrhage (45). Proton pump inhibition (PPI) is recommended in all patients unless contraindicated, as it has been shown to improve outcomes in both the acute bleed (46) and prevention of re-bleeds in patients continuing both single-agent and dual-agent antiplatelet therapy (47, 48). Choice of PPI should take the degree of inhibition of CYP2C19 into consideration, particularly for patients taking clopidogrel, which requires metabolism by this enzyme amongst others into its active form. Meta-analyses have reported an excess of adverse cardiovascular outcomes in patients receiving DAPT alongside PPIs (49). Omeprazole has been shown to reduce platelet reactivity *ex vivo* in the Omeprazole CLopidogrel Aspirin (OCLA) study (50), however in patients receiving omeprazole alongside clopidogrel in the COGENT trial (Clopidogrel and the Optimisation of Gastrointestinal Events Trial), there was no significant increase in cardiovascular events noted at a median duration of follow-up of 110 days (51). Pantoprazole and esomeprazole were not shown to affect platelet reactivity in patients undergoing PCI (52). Lansoprazole was shown to have no effect on platelet inhibition in healthy subjects receiving prasugrel, with some impairment of inhibition in those taking clopidogrel identified (53). There is therefore no definitive evidence of superiority of one PPI over another. Omeprazole certainly affects platelet inhibition, however this has not been clearly demonstrated to alter outcomes. Pantoprazole and esomeprazole also appear to be safe choices from the available evidence.

Discontinuation and reintroduction of the patient's antiplatelet agents has been discussed in a recent review by Scott *et al.* (36). For cases where endoscopic control has been achieved and recurrent bleeding risk is low, antiplatelet agents may be safely continued throughout. For patients on single-agent therapy with a high-risk of rebleeding, the antiplatelet therapy may be held for 3-7 days. For patients on dual APT, particularly following recent cardiac stent insertion, it is recommended to continue aspirin and discuss reintroduction of a second agent with a cardiologist.

In terms of platelet transfusions for acute GIH the limited evidence, is largely unfavourable. A retrospective review of approximately 400 patients with antiplatelet-associated GI bleeding found increased rates of cardiovascular events (23% versus 13%) and a significantly increased mortality rate (7% versus 1%) amongst platelet transfused patients compared to controls. However, the transfused patients had more severe presentations but platelet transfusions have not been shown to provide significant benefit (54). Based on these results, the 2018 Asian Pacific Gastroenterology guidelines do not recommend platelet transfusions (55),

whereas the American Society of Gastroenterology Guidelines include transfusion as an option in severe cases (56).

Summary

APT lead to a small but significantly increased risk of GIH. Acute management is with endoscopic intervention alongside supportive care with PPIs, and *H. pylori* eradication where appropriate. Antiplatelet drugs may require temporary cessation, but platelet transfusion is unlikely to be beneficial in most cases.

Managing anti-platelet therapies prior to elective surgery

The peri-operative management of APT is complex, and several factors must be considered before a management plan is formulated. The key factors are the indication for APT use and the type of surgery with its associated bleeding risk (57). Assessment of thrombotic risk should include the severity, elapsed time since the ischaemic event(s) and the type of stent inserted (58). In terms of bleeding risk, in addition to likelihood of bleeding from specific procedures, other relevant factors characteristic to the individual should also be taken into account (Table 2).

A simiplified perioperative algorithm for elective, emergency and neuraxial anaaesthesia is provided in Figure 1.

Aspirin

It was common practice to withhold aspirin for 5-7 days prior to major surgery but this is no longer recommended for most cases. A comprehensive systematic review by Burger et al. found that continuation of aspirin increased the rate of bleeding complications by 1.5-fold but did not increase the severity of bleeding complications (59). Similarly, a case study by Dacey et al. concluded that there was no increase in the amount of bleeding requiring transfusion when aspirin was continued throughout surgery (60). With regards to cardiac surgery, aspirin continuation increased post-operative bleeding and transfusion requirements with no effect on mortality, re-exploration rate or peri-operative myocardial infarction (61). The value of aspirin in reduction of thrombotic events has however been questioned by some recent studies. The POISE-2 trial randomised over 10,000 patients requiring non-cardiac surgery who were at risk of vascular complications between aspirin at 100mg or placebo. There was no difference in the primary outcome of death or non-fatal MI at 30 days, but increased bleeding in the aspirin group (major bleeding in 4.6% versus 3.8% of patients) was seen (62). The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial also compared administration of 100mg aspirin versus placebo on the day of surgery in coronary artery bypass grafting patients (CABG). No difference in thrombotic or bleeding complications was seen between the groups. From these studies, it seems likely that discontinuation of aspirin in high bleeding risk patients is safe, however it should be noted that the patients in the ATACAS trial were either not taking aspirin originally, or had stopped 4 days prior to surgery, so results do not truly reflect discontinuation vs. continuation of aspirin (63). In comparison, bleeding fatalities were reported following intracranial and prostatectomy surgery in patients receiving aspirin (59). If aspirin does

require discontinuation, no longer than 8-10 days was suggested by a meta-analysis in which the average time from cessation of aspirin to the development of adverse thrombotic events, particularly ACS, was 10.7 days (4). Adequate recovery of platelet function for haemostasis usually occurs within approximately 3 to 5 days (64-66), and may be faster in patients with high platelet turnover rates, so discontinuation for more than 5 days is not warranted in any case (67).

Current recommendations for patients taking aspirin as secondary prophylaxis are:

- In patients who require elective non-cardiac, or cardiac surgery- aspirin should be continued (57) (68).
- For surgeries with much higher bleeding risks such as neurosurgery, aspirin should be discontinued 5 days pre-operatively as per the French working group on perioperative haemostasis (GIHP) in collaboration with the French Society of Anaesthesia and Intensive Care Medicine (SFAR) Guidelines (67).

P2Y12 inhibitors

Careful consideration is required for higher-risk patients on these drugs, including those who require dual anti-platelet therapy (DAPT) for secondary prevention following ACS or pre- and post-PCI with stent insertion.

The peri-operative period poses a particular challenge to patients receiving DAPT, as the proinflammatory and prothrombotic state induced by surgery increase the thrombosis risk alongside the procedure-related bleeding risk (69). DAPT is critical in the prevention of stent thrombosis and many studies have found that premature discontinuation of DAPT before complete endothelialisation of the stent can result in major adverse coronary events (MACE) (70, 71). Concerns have been raised regarding a possible hypercoagulable state following discontinuation of anti-platelet agents, particularly clopidogrel (72), however the randomised controlled Platelet Activity after Clopidogrel Termination (PACT) study found no evidence of increased platelet activity following clopidogrel cessation, measured by several different techniques (73). Studies comparing bare-metal stents (BMS) with first generation drug-eluting stents (DES) (paclitaxel or sirolimus) identified a higher risk of in-stent thrombosis in DES-managed patients. The newer second generation DES (zotarolimus, ridaforolimus and everolimus) confer a lesser risk, whereas bioresorbable stents have a higher incidence of in-stent thrombosis reported, particularly during the first 30 days (68, 74). The particular stent in each patient therefore requires consideration, but in recent times, the majority of stents inserted are second generation DES.

A number of registries have reported that the non-cardiac surgery-related thrombosis risk in DES-PCI-treated patients plateaus after 3-6 months (68). A North American registry paired two cohorts of stented patients, one undergoing non-cardiac surgery within 24 months of stent placement, and one not. Risk of adverse cardiac events was increased in the first 30 post-operative days, irrespective of stent type. The incremental risk for MI decreased from 5% immediately after stent insertion to 2% at 1 year (75). Whilst stent type did not have a significant impact on risk, major cardiac events were more common in patients who were stented for MI (7.5%) versus unstable angina (2.7%) and elective revascularisation not associated with acute coronary syndrome (ACS) (2.6%). In the MI patients, the risk was significantly increased within the first 3 months following stent insertion (76). A Danish registry compared patients with DES-PCI-treated coronary artery disease (CAD)

undergoing a surgical procedure within 12 months of stent-placement with a control group undergoing the same procedure without a diagnosis of CAD. They found that risk of MI and cardiac-death was increased in the PCI group, but only for the 1st month post-PCI (77).

When discontinuing DAPT, the time at which it is safe to discontinue the available P2Y12 inhibitors is variable. With respect to cardiac surgery, in patients undergoing CABG within the CURE trial, discontinuation of clopidogrel from DAPT ≥5 days pre-operatively was not associated with increased bleeding complications (78). Platelet inhibition takes longer to resolve following discontinuation of prasugrel than clopidogrel (approximately 7-10 days compared with 7 for clopidogrel) (79)). This fact coupled with the increased rates of bleeding seen with prasugrel in the TRITON-TIMI trial (22) have led to recommendation of a longer time interval of 7 days pre-operatively by both the ESC and GIHP guidelines (67, 68). Ticagrelor was initially recommended for discontinuation 5 days pre-operatively, however this has been reduced to 3 days within the latest ESC guidelines (68), but remains at 5 days in the GIHP guidelines (67). A Swedish Nationwide study assessed CABG-related bleeding episodes in relation to timing of P2Y12 inhibitor discontinuation. They found no significant difference in bleeding rates between ticagrelor-treated patients in whom the drug was discontinued either >120 hours pre-operatively or between 72-120 hours, with increased bleeding at <72 hours. Whereas the clopidogrel-treated patients had more bleeding episodes if clopidogrel was discontinued between 72-120 hours compared with >120 hours pre-operatively (80). Another study compared patients undergoing CABG treated with DAPT with aspirin and ticagrelor with those receiving aspirin only. Discontinuation of ticagrelor >2 days pre-operatively was associated with increased rates of platelet transfusion (12.4% versus 3.6%) but not increased bleeding (81).

Longer discontinuation may be necessary for the P2Y12 inhibitors in surgeries with unacceptably high bleeding risks such as neurosurgical procedures, and transurethral resection of the prostate (58, 82, 83). For patients at both high thrombotic and high haemorrhagic risk, bridging may be considered (84-87), whereby the patient's oral ADP receptor antagonist is held 5-7 days pre-operatively, and an intravenous infusion of either a P2Y12 inhibitor or GP IIb/IIIa antagonist is administered until a few hours before surgery. The BRIDGE trial has shown promising results for the P2Y12 inhibitor cangrelor in this context. Patients receiving thienopyridines prior to coronary artery bypass surgery (CABG) stopped the thienopyridine 48 hours pre-operatively and were randomised to cangrelor or placebo until 6 hours prior to surgery. Cangrelor was shown to effectively maintain platelet inhibition without an associated significant increase in bleeding, although it is not presently FDA- or EMA-approved for this indication (88). GPIIb/IIIa inhibition has also been tested in a small phase 2 study of 30 patients with a DES inserted within the past 12 months, at high risk for in-stent thrombosis, who required eye or major surgery. Cloipidogrel was discontinued 5 days pre-operatively, with tirofiban commenced after 24 hours and stopped 4 hours before surgery. There were no thrombotic complications and one case of thrombolysis in myocardial infarction (TIMI) minor and 1 TIMI major bleeding episode reported (89).

Taking the above information into consideration, current recommendations are that for patients taking who require elective cardiac surgery (57, 58, 67, 68):

- Aspirin should be continued around the time of surgery.

- Ticagrelor should be discontinued 3 days before surgery.
- Clopidogrel should be discontinued 5 days before surgery.
- Prasugrel should be discontinued 7 days before surgery.

For patients with a history of recent MI, or who have undergone PCI and stent insertion requiring non-cardiac surgery (67, 68):

- Where possible, surgery should be postponed until at least 6 weeks after a medically managed MI (90).
- Non-cardiac elective procedures should be postponed until completion of DAPT if possible.
- Non-cardiac elective procedures should be postponed for at least 1 month post-stent insertion irrespective of type of stent or indication.
- Non-cardiac elective procedures should be postponed for up to 6 months in patients at high ischaemic risk eg. Who presented with MI, have bifurcating lesions, multiple or overlapping stents, impaired left ventricular ejection fraction, renal impairment or diabetes mellitus (91).
- Patients requiring surgery within 1 month of stent placement may be considered for bridging therapy

Restarting anti-platelets post-operatively

Two meta-analysis have shown improved outcomes in patients who restart DAPT after CABG compared to aspirin alone, without significantly higher rates of major bleeding (92, 93). Rates of thrombosis are high post-operatively, with significantly more MACE occurring in patients not taking anti-platelet agents (94). The ESC has recommended reinstation of DAPT from 24-96 hours post-CABG, and within 48 hours following non-cardiac surgery (68).

Early resumption of anti-platelets is likely to be more important in patients with more risk factors for ischaemia. A risk score such as the DAPT score (see Table 3.) can be used to identify patients at higher risk of thrombotic events (95). However, this score was designed to identify patients who may benefit from extended duration DAPT treatment, and not for use as a decision aid in when to restart DAPT. Consideration of the patient's bleeding risk is also required in conjunction. Two such bleeding risk scores have been generated from the PARIS study, a prospective observational study of patients on DAPT undergoing PCI. Reasons for cessation of DAPT included physician-recommended discontinuation, interruption for surgery and disruption due to non-compliance or bleeding (96). Of note, recent analysis has shown that patients ≥75 years are more likely to have DAPT held than younger patients, but that this is not associated with increased MACE (defined as a composite of cardiac death, probable or definite in-stent thrombosis, spontaneous MI or clinically indicated target lesion revascularization), whereas disruption of DAPT is associated with increased MACE in patients <75 years (97). Younger age has been identified as a risk factor in the DAPT score, and these results also suggest that disruption of DAPT may be better tolerated in older patients, highlighting the need for management to be tailored to the individual patient.

Current recommendations for restarting DAPT post-operatively are (68):

- Clopidogrel, prasugrel or ticagrelor should be recommenced after 24-96 hours post-operatively and ideally at <48 hours in those with recent (<6 weeks) PCI or who presented with ACS.

Managing anti-platelet therapies prior to neuraxial anaesthesia

Spinal haematoma is a rare but potentially devastating complication of neuraxial procedures with a reported incidence of anywhere between 1/1300-1/200,000 procedures (98). Risk factors for spinal haematoma include female gender, advanced age, wider gauge needles/catheters (incidence is higher for epidural than spinal anaesthesia), a history of excessive bleeding or bruising, multiple needle passes, and pre-existing bone disease such as osteoporosis (99, 100). Aspirin is generally considered safe to use during neuraxial procedures. A prospective study in nearly 1000 orthopaedic patients undergoing spinal or epidural anaesthesia, of whom approximately one fifth were taking pre-procedure aspirin, reported no increase in blood present at the time of needle/catheter placement or withdrawal in the group taking aspirin (100). Similarly, a randomized controlled trial of the role of low-dose aspirin for pre-eclampsia found no increase in bleeding events post-epidural in the intervention arm (101). Evidence pertaining to the ADP-receptor antagonists in neuraxial anaesthesia is sparse, and consequently, most guidelines have historically recommended that these drugs be withdrawn approximately a week pre-procedure (57, 102-104). The most recent GIHP recommendations are that regional anaesthesia is contraindicated in patients on P2Y12 inhibitors unless discontinued 5 days pre-procedurally for clopidogrel and ticagrelor and 7 days for prasugrel (67), in line with their recommendations for withdrawal pre-elective surgery, and the latest ESC guidelines do not specifically discuss this topic. The American Society of Anaesthesia and Regional Pain Medicine have also recommended a 5 day discontinuation period in their 2018 updated guideline (105). They have recommended that patients may restart clopidogrel with the neuraxial catheter still *in situ* for 1-2 days, provided a loading dose has not been administered. Ticagrelor and prasugrel have a faster onset of action, so catheter removal prior to reintroduction of these agents is mandated. Without a loading dose, ticagrelor and prasugrel may be given immediately post-catheter removal or needle placement, or after a 6 hour window if a loading dose is required (105).

Recommendations:

- If on aspirin monotherapy, this may be continued without interruption.
- If on dual-antiplatelet therapy, neuraxial anaesthesia should be postponed if possible in line with the recommendations for elective surgery.
- If neuraxial anaesthesia is required, clopidogrel and ticagrelor should be discontinued 5 days pre-procedure and prasugrel 7 days pre-procedure.
- For patients taking DAPT, platelet transfusion can be considered in emergency cases and tranexamic acid may be used as a haemostatic adjunct.
- Following removal of neuraxial catheter or needle placement, clopidogrel, prasugrel and ticagrelor may be restarted immediately.
- Clopidogrel may be restarted with the neuraxial catheter remaining *in situ* for 1-2 days.

Managing anti-platelet therapies prior to emergency surgery

When patients on APT need urgent surgical intervention the healthcare team are faced with the dilemma of reversing or counteracting the effects of these agents. One strategy is platelet transfusion. *In vitro* studies have found that in platelets treated with clopidogrel and aspirin, normalisation of platelet function is observed after the addition of two to three pools of treatment-naïve platelet concentrate (106). However, there are uncertainties within this that need to be addressed:

(i) The optimal platelet transfusion quantity needed to overcome the antiplatelet effects

(ii) The optimal timing of platelet transfusion relative to the last dose of the anti-platelet agents.

Quantity of platelets transfused

A unit of 0.7 x 10^{11} platelets produces an increment of 5000-10,000/μl in an average sized adult. Administration of 0.7 x 10^{11}/10kg of body weight has been recommended to produce a rise in platelet count of approximately 40,000/μl (107). The average size of a pool of platelets varies between institutions and countries. In the UK it is 3 x 10^{11} (108). Currently there is no definitive guidance on the ideal number of donor platelet units required to reverse the anti-platelet effects. Li *et al.* reported that the reversal of the inhibitory effects of aspirin on arachidonic acid (AA)-induced platelet aggregation was much more rapid than the reversal of the inhibition of ADP-induced aggregation by clopidogrel (64). This was demonstrated as reversal of aspirin's anti-platelet effect was achieved when mixed samples of aspirin-treated and treatment-naïve platelets contained 30% treatment-naïve platelets, compared to 90% required to reverse clopidogrel's anti-platelet effect.

Of the ADP-receptor antagonists, available evidence suggests that platelet transfusion can ameliorate the effects of clopidogrel more than prasugrel, and that ticagrelor-treated patients gain the least benefit from platelet transfusion. For example, transfusion of two pools of platelets to patients taking aspirin and clopidogrel restored ADP-induced platelet function determined by the VASP assay (vasodilator-stimulated phosphoprotein phosphorylation assay) (109). However, in patients recently administered loading doses of prasugrel and ticagrelor post-ACS, a ratio of 60% non-inhibited platelets to patient platelets was required to achieve platelet aggregation >40% measured by light transmission aggregometry in those receiving prasugrel, whereas platelets from ticagrelor-treated patients remained inhibited at all patient:donor platelet ratios (110). In keeping with these studies, the APTITUDE-ACS and APTITUDE-CAGB trials analysed platelet function deficits for patients with ACS requiring PCI, or undergoing cardiac surgery, respectively, receiving clopidogrel, prasugrel or ticagrelor. Overall, transfusion of platelets improved platelet-dysfunction in clopidogrel-treated patients to a greater degree than for prasugrel, which is likely to require a larger dose of platelets for reversal to be effective, or ticagrelor, which cannot be effectively reversed by platelet transfusion at all (111). One normal donor pool of platelets (apheresis or pooled) should provide more than 50 x 10^9/l uninhibited platelets, although the proportion of these that remain functional will depend on the antiplatelet agent administered, and when the last dose was received. One suggestion has been that for patients with evidence of platelet dysfunction, one pool

should be adequate for most surgical indications, with two advised for individuals requiring urgent neurosurgery or eye surgery (13).

Another factor that requires consideration is the pro-thrombotic risk of platelet transfusion in these already high-risk patients. The risk of thrombotic events rises early after withdrawal of DAPT in high-risk patients and further increases after surgery; the infusion of too many donor platelets may contribute to this pro-thrombotic state (86). Currently there is very little information regarding the risk of excessive platelet transfusions provoking adverse thrombotic events.

The timing of platelet transfusion

With regards to the timing of the platelet transfusion, in order for it to be effective there needs to be an absence of active anti-platelet metabolites in the patient's circulation, otherwise the transfused platelets will also be inhibited. Aspirin has a short half-life of 15-20 minutes and can be sufficiently cleared after two hours. Clopidogrel also has a short half-life of around 30 minutes but clearance of its active metabolites can take 6-8 hours after ingestion due to variations in absorption and metabolism between individuals (112). Prasugrel and ticagrelor also have similar half-lives, and *in vitro* studies investigating the effect of donor platelet transfusions on prasugrel and ticagrelor reversal found that functional platelet recovery was minimal when donor platelets were added to blood samples obtained two hours after dosing of prasugrel (113) or ticagrelor (114), in addition to aspirin. Zafar *et al.* therefore concluded that donor platelets should be transfused at least six hours after a dose of prasugrel (113). It has been recommended that platelets should ideally be transfused once 3-5 half-lives have elapsed, however this will clearly not always be possible (17). A more recent study by the same group tested the effect of platelet transfusion on patients who had received loading doses of ticagrelor and aspirin followed by maintenance for 5-7 days after drug discontinuation. Platelet aggregation (tested by the Multiplate and VerfyNow systems) following transfusion reached 59-79% of baseline levels at 24 hours and 100% at 48 hours, showing the utility of platelet supplementation in ticagrelor-treated patients 1 day post drug cessation despite this having essentially no effect during drug-treatment (115).

A pilot study carried out by Thiele *et al.* in 14 patients adopted a standardised management plan whereby surgery was delayed for 12-24 hours (if possible) after the last dose of aspirin and clopidogrel, then two platelet concentrates were transfused 1-2 hours prior to surgery. No observed increases in major bleeding or thrombotic complications were reported (112). This approach may therefore be appropriate for patients receiving clopidogrel or ticagrelor, but would not be considered safe in prasugrel-treated patients. Results of a larger retrospective cohort study in patients on single or dual antiplatelet agents (aspirin and/or clopidogrel only) undergoing urgent non-cardiac surgery were recently published in abstract form. All of these patients received two pools of platelets pre-operatively with resumption of antiplatelet therapy after 24-48 hours. In 181 patients, rates of adverse cardiac events (MI, heart failure or rise in troponin T) occurred in 5.5%, with surgery-related bleeding in 12% (116). Randomised trials have been recommended (116) to further evaluate this approach, which could be considered in patients with higher risks of thrombotic episodes in whom prolonged discontinuation of therapy is not desirable.

Non-transfusion strategies

Other strategies to help minimise bleeding and transfusion requirements exist. Tranexamic acid has been shown to improve the platelet function of those exposed to APT, resulting in a reduction in bleeding and transfusion (117). The same has been shown with aprotinin in patients undergoing a coronary artery bypass graft. However, there is limited clinical availability of aprotinin and concerns remain about its association with increased risk of myocardial infarction and development of renal failure (118). The British Society of Haematology guidelines recommend consideration of tranexamic acid to counteract the effect of anti-platelet agents after undertaking a risk-benefit assessment, and state that platelet transfusions can be used as an additional measure for critical bleeding but should not be used prophylactically (119). Off-label recombinant factor VIIa may limit bleeding by reversing the effects of anti-platelet therapy on thrombin generation (120), however is a controversial option due to its potential to increase the risk of arterial thromboembolic events, and should be considered only as a last resort (121).

Platelet transfusions do not reverse the effects of ticagrelor. A monoclonal antibody fragment (PB2452) is in early clinical development. A phase 1 trial in heathy donors reported reversal of ticagrelor's antiplatelet effect, measured by light transmission aggregometry, a POC $P2Y_{12}$ test and VASP assay, within 5 minutes, sustained for over 20 hours. Future studies are awaited (122).

Summary

Suggestions for the management of patients on APT requiring emergency high bleeding-risk surgery are:

- If on aspirin monotherapy, this can be continued in the majority of cases without further intervention.
- If on dual anti-platelet therapy:
    - Consider the use of pre-operative intravenous tranexamic acid as a haemostatic adjunct after undertaking risk-benefit analysis.
    - If the bleeding risk is thought to be very high, consider platelet transfusions.
    - Do not use platelet transfusions pre-operatively if anti-platelet therapy has not been discontinued due to active metabolites still remaining in the circulation. For patients on clopidogrel or prasugrel wait at least 6-8 hours after the last dose. Platelet transfusion should be considered in ticagrelor-treated patients especially if the last dose was >24 hours prior.

Ultimately there is no clear guidance on the appropriate dose of platelets required to reverse the effects of antiplatelet agents, with risks of excessive transfusion and under transfusion remaining. A possible strategy is to rapidly assess a patients bleeding risk and to overcome the transfusion dilemma by the adoption of a strict transfusion algorithm incorporating point-of-care testing.

Can point-of-care testing assist in this scenario?

There is large heterogeneity in response to APT that is not apparent on routine laboratory tests. Several rapid, point-of-care (POC) devices have been developed, which may provide a more reliable predictor of an individual's perioperative bleeding-risk, including their degree of platelet inhibition, and at least in theory their transfusion-need. POC tests exist which look specifically at platelet function, and inhibition by the various

antiplatelet agents. Generally, they are limited in that only one aspect of platelet function is assessed *in vitro*, which cannot fully replicate complex platelet physiology, and direct comparison of different devices is not possible due to fundamental differences in the principles of the assays utilised (123). The strengths and weaknesses of the various POC tests specific to antiplatelet agents are given in Table 4.

Various trials have incorporated tests of platelet function in order to assess prediction of future ischaemic or bleeding events in various settings in patients taking P2Y12 inhibitors. High levels of platelet reactivity to ADP have been shown to correlate well with increased risk of thrombotic events, however the relationship between platelet function and bleeding has been less clear (124). The ADAPT-DES study in nearly 9000 individuals reported that patients with high platelet reactivity scores despite DAPT with aspirin and clopidogrel were significantly more likely to suffer adverse ischaemic events, and less likely to have haemorrhagic complications (125). Incorporation of pre-operative ADP-induced platelet aggregometry identified all but one patient with severe coagulopathy requiring multiple transfusions during coronary artery bypass grafting with recent clopidogrel exposure (126), and use of TEG-PM (thromboelastography with platelet mapping) had similar benefit in the randomised prospective TARGET-CAGB trial, which used pre-operative assessment of ADP-inhibition in patients prior to CABG. Time-to-surgery was stratified according to TEG-PM results with a delay of 1 day, 3-5 days, and >5 days in patients with a maximum amplitude (MA) of >50 mm, 35-50 mm, and <35 mm respectively. Bleeding rates were similar in the various groups and waiting time was significantly reduced using this strategy (127).

A number of groups have incorporated tests of platelet function into ICH management pathways. There are concerns however, that platelet transfusion may not reliably affect these results in all cases, whether this has clinical relevance for the patient, and indeed, how relevant the results from these tests are in the setting of the altered haemostasis seen in patients with brain injury. Several studies have shown improvement in platelet reactivity testing following platelet administration *in vivo* (128-130), whereas others have found the opposite (131). Analysis of TEG-PM in 9 patients transfused for antiplatelet-ICH reported good sensitivity but extremely poor specificity for identifying the antiplatelet effect of aspirin or clopidogrel, and no significant effect was noted following platelet transfusion (132). This may reflect underlying the coagulopathy seen in patients with traumatic brain injury (TBI), which has some similarities to the phenomenon of trauma-induced coagulopathy (TIC). Patients not taking an ADP antagonist may display significant levels of ADP inhibition, which correlate with severity of the insult; the average ADP inhibition reported in TBI with a Glasgow coma scale (GCS) <8 is around 90%, compared with 45% if GCS >8, and 15% in healthy controls (133, 134). Transfusion of allogeneic platelets may be insufficient to correct this deficit.

Another recent study used platelet reactivity testing to identify COX-2 or ADP-inhibition in patients with traumatic ICH suspected to take an antiplatelet agent. Those with evidence of platelet inhibition were transfused platelets until the platelet reactivity testing normalised and given a single dose of desmopressin (DDAVP). 29% of the cohort had no evidence of inhibition, 92% of which avoided transfusion. Progression of haemorrhage occurred in 7%, irrespective of platelet-inhibition or transfusion status. The authors concluded that utilizing platelet reactivity testing was a safe means of reducing transfusion rates amongst individuals with

traumatic ICH, however, the benefit conferred by platelet transfusion in platelet-inhibited patients cannot be deduced from these results (135).

Based on these results, assessment of platelet function pre-operatively using POC tests can aid determination of safe timing of urgent or elective procedures, providing reassurance to surgeons that the patient has adequate platelet function to proceed, reducing waiting time and length of hospital stay (136), or be used to assess whether platelet transfusions are warranted pre-urgent procedures (13). Use in the elective setting has good supportive data and numerous groups are also routinely using POC tests to aid management of haemorrhagic complications, although issues regarding interpretation of results have been raised, particularly with respect to patients with ICH (132). Further evaluation of these algorithms is required, but with refinement and standardisation they could be incorporated into the everyday management of patients requiring emergency surgery when taking anti-platelet therapy.

Conclusion

In summary, APT is associated with an increased risk of intracranial and gastrointestinal bleeding. In those who develop ICH while on APT, platelet transfusion may be appropriate for planned neurosurgical intervention, although the timing and dosing is unclear. In all other scenarios, platelet transfusion may have a detrimental effect. APT is associated with GI haemorrhage but platelet transfusion is unlikely to be beneficial, whilst specific GI measures are likely to be more effective.

In patients requiring elective surgery, APT may be discontinued for a specified period if safe to do so, but cardiology advice should be sought in those with recently placed coronary stents. Urgent surgery on APT is an area that requires more research as no definitive guidance is possible at this stage. Similarly, use of POC methods to determine platelet function requires further validation when used as a perioperative tool.

Finally, the recent STOPDAPT-2 randomised study, in which patients undergoing PCI using an everolimus second generation DES were randomised between one month of DAPT with aspirin and clopidogrel followed by clopidogrel monotherapy and 12 months of DAPT, reported a significant reduction in the primary outcome of a composite of cardiovascular death, MI, ischaemic or haemorrhagic stroke, definite stent thrombosis, or major or minor bleeding at 12 months, in favour of the short duration DAPT arm. Such results could lead to future changes in practice, which may significantly reduce the complexity of peri-operative management of these patients (137).

Practice points

- Patients with intracranial haemorrhage taking APT (antiplatelet therapy) should be transfused platelets if planned for neurosurgical intervention but not if receiving medical management only

- Patients with upper gastrointestinal haemorrhage on APT do not benefit from platelet transfusions but need urgent endoscopic control of bleeding and proton pump inhibition with eradication of *H. pylori* infection if present
- For elective surgeries on those who are on APT, aspirin may be continued other than for high bleeding risk procedures while clopidogrel, prasugrel and ticagrelor should be discontinued several days pre-operatively

  For emergency surgeries on those who are on APT, transfusion of platelets may be considered in patients taking aspirin, clopidogrel or prasugrel if bleeding risk is considered high. Platelet transfusion does not reverse the effects of ticagrelor.

Research agenda

- Role of point of care testing of platelet function in in the peri-operative management of patients receiving APT who require emergency surgery, neuraxial anaesthesia or who present with ICH or GIH (gastrointestinal haemorrhage) requires further exploration.
- The optimal dose of platelets required and the timing of transfusion to maximise the benefit in patients on APT who develop ICH requiring neurosurgical intervention is yet to be clarified.
- Development of effective and safe reversal agents for APT is an area of unmet need.

Future considerations

Antiplatelet drugs have transformed the care of cardiovascular disease. However, with the benefit of reducing ischaemic complications comes the risk of bleeding, which may either be spontaneous, or worsened procedure-related bleeding. Evidence-based management strategies are required to minimise this risk. Future considerations may include i) improved selection of the patients who should receive single and dual APT ii) ongoing review of when it is safe to discontinue APT in different patient populations iii) establishing robust techniques which can determine adequacy of inhibition of platelet aggregation iv) the role of non-transfusion strategies in minimising the bleeding risk of APT and v) confirming the role of specific APT reversal agents in clinical practice.

DS and NL conducted the literature review and wrote the first draft. DS made edits for the final version. JT conceived the review and critically reviewed the manuscript. MM critically reviewed the manuscript. All authors approved the final version.

Conflicts of interest

JT has received honoraria from BMS-Pfizer, Boehringer, Bayer and Daichii-Sankyo. MM has participated in NovoNordisk advisory panels. He is the project lead of the EUHASS adverse event reporting scheme which receives funding from Bayer, NovoNordisk and Pfizer among others.

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