PERI-OPERATIVE MANAGEMENT OF ANTICOAGULATION AND ANTIPLATELET THERAPY

A British Society for Haematology Guideline

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Methodology

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified in the BCSH guidance pack (http://www.bcshguidances.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html) and the GRADE working group website http://www.gradeworkinggroup.org

Literature review details

Details of the literature review are in appendix 1

Review of manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Haemostasis and Thrombosis Task Force, BSH Guidelines Executive Committee and by the Haemostasis and Thrombosis sounding board of the BSH. The latter comprises 50 or more members of the BSH who have commented on the content and applicability in the UK setting. It has also been sent to the following organisations for review: The Royal College of Surgeons; The Royal College of Anaesthetists; Thrombosis UK, a patient-centred charity dedicated to promoting awareness, research & care of thrombosis; the British Dental Association; IntraHealth (who operate NHS GP and community pharmacies); and the British Cardiovascular Society; these organisations do not necessarily approve or endorse the contents.

Introduction

A BSH guideline on warfarin (Keeling*, et al* 2011) addressed the issue of perioperative management and is updated in this article to include the issue of perioperative management of patients on direct oral anticoagulants (DOACs) and antiplatelet agents which are becoming frequent clinical queries. This guideline will consider whether and when anticoagulants and antiplatelet agents should be stopped before elective surgery and invasive procedures, when agents can be restarted and how to manage patients on these drugs who require emergency surgery. If an anticoagulant or antiplatelet effect persists haemostasis may be improved by the use of pre-operative parenteral tranexamic acid which has been shown to reduce blood loss and transfusion requirements in both cardiac and trauma surgery, without increasing thrombotic complications (McIlroy*, et al* 2009, Shakur*, et al* 2010)

For agents with a slow offset and onset of action bridging therapy with an alternative drug at a full treatment dose can be considered in patients deemed to be at high risk of thrombosis; this mainly concerns whether treatment dose low molecular weight heparin (LMWH) or unfractionated heparin (UFH) should be given when warfarin is temporarily discontinued. Thromboprophylaxis with low dose LMWH is not regarded as “bridging”.

For some invasive procedures such as dentistry (Perry*, et al* 2007) (see also http://www.sdcep.org.uk/published-guidance/anticoagulants-and-antiplatelets/), joint injections (Ahmed and Gertner 2011), cataracts (Jamula*, et al* 2009), pacemaker insertion (Ahmed*, et al* 2010, Airaksinen*, et al* 2013) and certain endoscopic

procedures (Veitch*, et al* 2016) anticoagulation may not need to be stopped. Procedures that require anticoagulation to be stopped will vary in their bleeding risk and importantly the consequences of bleeding will depend on the site of surgery and local anatomy. Although some have grouped procedures into lower or higher risk (Baron*, et al* 2013, Spyropoulos and Douketis 2012) we think the operating surgeon, dentist, or interventional radiologist has to assess the risk of bleeding for the individual patient and discuss this and the plan for peri-operative anticoagulation with them. The plan must be recorded clearly in the notes including a plan for when the patient is discharged.

Warfarin and other vitamin K antagonists

Warfarin has a half-life of approximately 36 hours and as its effect subsides γ-carboxylated vitamin K dependent procoagulant factors need to be synthesised. Warfarin therefore needs to be stopped 5 days before elective surgery to ensure haemostasis has returned to normal. This is likely to differ for other vitamin K antagonists with different half-lives (acenocoumarol 10 hours, phenindione 8 hours, fluindione 3 days, phenprocoumon 5 days). If possible the INR should be determined the day before surgery to allow the administration of phytomenadione if the INR is ≥ 1.5 so reducing the risk of cancellation. The INR should be checked on the day of surgery. Stopping warfarin for a shorter time and attempting to reverse its effect with oral phytomenadione on the day before surgery did not prove a satisfactory alternative (Steib*, et al* 2010). Due to its slow onset of action warfarin can be resumed, at the normal maintenance dose (Douketis*, et al* 2012), or with two initial

days of double maintenance dose (Schulman*, et al* 2014), the evening of surgery (or the next day) if there is adequate haemostasis.

There have been many reviews and attempts to estimate the risk of peri-operative thrombosis (Dentali*, et al* 2012, Douketis*, et al* 2012, Dunn*, et al* 2007, Dunn and Turpie 2003, Siegal*, et al* 2012, Spyropoulos and Douketis 2012). The main question has been whether the risk of thrombosis is sufficiently high, in patients who have temporarily discontinued a coumarin, to use treatment dose LMWH or UFH pre-operatively and/or post operatively when haemostasis is secure. This is predicated on the assumption that bridging will reduce the thrombotic risk. It is noteworthy that in their meta-analysis Siegal and colleagues (Siegal*, et al* 2012) found no difference in the risk of thromboembolic events in eight studies comparing bridged and nonbridged groups of patients (odds ratio, 0.80; 95% CI, 0.42-1.54). Bridging was associated however with an increased risk of major bleeding in five studies (odds ratio, 3.60; 95% CI, 1.52-8.50). A further systematic review also concluded “while the antithrombotic efficacy of perioperative bridging with LMWH has not been demonstrated, increased bleeding risk is observed in different types of surgery” (Eijgenraam*, et al* 2013).

Patients taking warfarin for the treatment and secondary prevention of venous thromboembolism (VTE), for stroke prevention in atrial fibrillation (AF) or for mechanical heart valves (MHV), need separate consideration. For patients with acute VTE the risk of recurrence without anticoagulation is very high in the first three months (Kearon and Hirsh 1997) and surgery will increase the risk further. When a patient is more than three months from an acute event the risk of recurrence is much

lower, the treatment phase is over, and patients are remaining on an anticoagulant for secondary prevention (Kearon and Akl 2014). Prophylactic dose LMWH can substitute for warfarin after the acute treatment period hence patients with VTE more than 3 months prior can usually simply be given post-operative prophylactic dose LMWH (or a suitable alternative) rather than receive full dose bridging therapy while anticoagulation with a coumarin is re-established. Bridging might be considered for those thought to be at very high risk, such as patients with a previous VTE occurring whilst on therapeutic anticoagulation who now have a target INR of 3.5.

For patients with a MHV the risk varies with type of valve (bileaflet less than caged ball and tilting disc), position of valve (aortic less than mitral) and with patient risk factors (such as previous stroke or transient ischaemic attack (TIA), AF and reduced left ventricular ejection fraction). We have previously recommended bridging therapy for patients with MHVs other than those with a bileaflet aortic valve and no other risk factors (Keeling*, et al* 2011) and there is no strong evidence to change this recommendation.

For patients with atrial fibrillation the $CHADS_2$ score or more recently the CHA_2DS_2VASc score has been used to predict stroke risk. The $CHADS_2$ score may also predict risk of post operative stroke (Kaatz*, et al* 2011) and guidelines have suggested the $CHADS_2$ score is used to select patients for bridging (Douketis*, et al* 2012) whilst the previous BCSH guideline suggested bridging in only those with a previous stroke or TIA or multiple other risk factors (Keeling*, et al* 2011). There is now a randomized, double-blind, placebo-controlled trial of bridging in AF patients (Douketis*, et al* 2015). Patients were randomised to dalteparin (100 IU/kg bd) or

placebo from three days before until 24 hours before the procedure and then for five to ten days after the procedure. 1884 patients were enrolled, with 950 assigned to receive no bridging therapy and 934 assigned to receive bridging therapy. The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (risk difference, 0.1 percentage points; 95% confidence interval [CI] -0.6 to 0.8; P=0.01 for noninferiority). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (relative risk, 0.41; 95% CI 0.20 to 0.78; P=0.005 for superiority). The authors concluded forgoing bridging was noninferior to bridging for the prevention of arterial thromboembolism and decreased the risk of major bleeding. 38% of patients had a $CHADS_2$ score of ≥3, though only 3.1% had a score ≥5 (which requires a previous stroke or TIA plus at least three of four other risk factors), 9.4% had a previous stroke and 8.3% a previous TIA. Patients with a stroke or TIA within the previous 12 weeks were excluded. Our updated advice is in the table 1. When we say consider bridging we do not mean automatically give it but consider whether to or not in discussion with the patient.
In patients who are receiving pre-operative bridging with LMWH the last dose should be at least 24 h before surgery and some recommend if on a once a day regimen the last dose is halved for high risk surgery (Douketis*, et al* 2012). We recommend that post-operative bridging (i.e. full dose anticoagulation) is not started until at least 48 hours after high bleeding risk surgery although thromboprophylaxis should be given if indicated.

Emergency Surgery in patients on warfarin

If surgery can wait for 6–8 h then 5 mg of intravenous phytomenadione can restore coagulation factors, if not anticoagulation can be reversed with 25–50 u/kg of four-

factor prothrombin complex concentrate (Goldstein*, et al* 2015, Refaai*, et al* 2013),we would give at the lower end of this range and check the INR.

Post-operative management should follow the same strategy as for elective surgery.

Recommendations

- **Warfarin should be stopped for five days before an elective procedure if anticoagulation needs to be discontinued (1C).**
- **Patients with VTE more than 3 months earlier can usually be given post-operative prophylactic dose LMWH (or a suitable alternative) rather than bridging therapy (2C).**
- **Patients at very high risk of recurrent VTE, such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3.5, and patients who have had VTE less than three months previously should be considered for bridging (2D)**
- **Patients with AF who have a $CHADS_2$ score of ≤ 4 and who have not had a stroke or TIA in last three months should not receive bridging (1A)**
- **Patients with a bileaflet aortic MHV with no other risk factors do not require bridging whilst it should be considered in all other MHV patients (2C).**
- **We recommend that post-operative bridging is not started until at least 48 hours after high bleeding risk surgery (1C).**

Direct oral anticoagulants (DOACs)

The approach to the peri-operative management of patients on DOACs is based on an approximate calculation of the half-life of the drug and so its persistence in the

circulation, taking into account renal function. This is combined with consideration of the bleeding risk of the proposed procedure and a clinical evaluation of the patient's individual risk factors for thrombosis and bleeding. Current strategies for elective surgery do not routinely include measurement of either non-specific or specific coagulation parameters to assist in quantification of DOAC levels. For each of the drugs there are data on periods of discontinuation during the studies to evaluate the drug against coumarin therapy. In addition there is a single moderate sized, prospective study evaluating the outcomes of a set protocol for the peri-procedural management of patients on dabigatran (Schulman*, et al* 2015).

Dabigatran

During the RE-LY study treatments were transiently discontinued in 4591 subjects (Healey*, et al* 2012) that is around 25% of the study population. A range of procedures were performed – mostly cardiac catheterisation, dental extraction and colonoscopy but also more major surgery. The incidence of major bleeding was 3.8%, 5.1% and 4.6% respectively for dabigatran 110mg, dabigatran 150mg and warfarin and the rate of stroke and systemic embolism was 0.5% in each group for the 30 day period around the discontinuation. Significant bleeding and thrombosis were more common after emergency and major procedures.

A multicentre prospective study which included 324 standard risk and 217 high risk procedures and which broadly followed the protocol in table 2 reported low rates of major bleeding, 1.8% (0.7% - 3%) and thromboembolism, 0.2% (0-0.5%) in the 30 day period around the procedure (Schulman*, et al* 2015). Dabigatran was restarted post operatively only when haemostasis had been secured. After minor procedures it

recommenced at 75mg on the evening of the procedure escalating to 110mg or 150mg BD the following day. For major procedures the re-introduction was again guided by haemostasis with most patients restarting at normal full dose 48-72 hours post procedure. Bridging with LMWH or UFH was used in 1.7% of cases post-procedure but not at all pre-procedure. In this study 40% of the procedures had a high bleeding risk and of the 10 patients who had major bleeding, eight had undergone a high bleeding risk procedure.

Rivaroxaban

Data from the Rocket-AF study show that in 2130 patients undergoing 2980 procedures, periods of discontinuation of rivaroxaban for ≥3 days to allow surgery or an invasive procedure result in no significant difference in any of, major haemorrhage, clinically relevant non-major haemorrhage, stroke and systemic embolism, MI and death when compared to discontinuation of warfarin (Sherwood*, et al* 2014). There are no published data that report on a fixed protocol for peri-procedural discontinuation of rivaroxaban but several groups have proposed schedules for this (Heidbuchel*, et al* 2015, Lai*, et al* 2014). The manufacturer's advice is to discontinue rivaroxaban for over 24 hours and 48 hours respectively for low bleeding risk and high bleeding risk procedures.

Apixaban

Data from the Aristotle trial also describe 9260 procedures where anticoagulation may be interrupted (Garcia*, et al* 2014). The vast majority of the events were low risk procedures, and apixaban was discontinued for around 60% of these. Again the major outcomes were similar in patients taking warfarin and apixaban irrespective of

whether, or not, anticoagulation was discontinued. Of note in this observational study, when apixaban was discontinued it was for 2-5 days. There are no published data that report on a fixed protocol for peri-procedural discontinuation of apixaban. The manufacturer's advice is to discontinue apixaban for over 24 hours and 48 hours respectively for low bleeding risk and high bleeding risk procedures. Published schedules on the discontinuation of apixaban give different advice. Lai et al and Heidbuchal et al (Heidbuchel*, et al* 2015, Lai*, et al* 2014) take renal function into consideration and suggest minimum periods of discontinuation for those with CrCl of 15-30 mL/min undergoing high risk procedures of over 48 hours while Ward et al did not consider renal function but recommend discontinuation for high bleeding risk procedures for at least 60 hours (Ward*, et al* 2013).

In making recommendations we have considered the practicalities of instructing patients around periods of discontinuation. While Lai et al and the EHRA guideline (Heidbuchel*, et al* 2015, Lai*, et al* 2014) suggest a period of discontinuation for 36 hours in patients with CrCl of 15-30 mL/min undergoing low risk procedures this is not really practical for patients taking a once daily preparation like rivaroxaban and so we have chosen to recommend a 48 hour period of discontinuation for this group when using either apixaban or rivaroxaban.

Edoxaban

The most recent oral Xa inhibitor to be licenced in the UK is edoxaban. 50% of the drug is renally excreted and the half-life is 10-14 hours. The SPC suggests that for surgical or other procedures it should be discontinued preferably at least 24 hours before the procedure.

Emergency surgery in patients on DOACs

There are few data on the management of emergency surgery in patients receiving DOACs. The ability to make predictions regarding haemostasis at surgery in these patients is limited firstly by uncertainty in the concentration of each drug that is associated with haemostatic safety. Secondly, a UK NEQAS supplementary exercise undertaken in October 2014 found high coefficients of variation for the Haemoclot assay and for the chromogenic anti-Xa assays when assaying plasma levels of DOACs (personal communication, Dr Steve Kitchen, UKNEQAS, Sheffield). The greatest variation was seen in the measurement of low concentrations of drug, and worryingly in samples where there was no drug present drug was reported as being present. If an anticoagulant effect cannot be excluded neuroaxial anaesthesia should be avoided.

When possible, surgery should be delayed to allow the plasma level of the drug to fall. The concentration of drug can be estimated from the dose of the drug, time of last dose and the patients' renal function. Other factors such as patient sex, weight and the use of interacting drugs will also have less significant effects. The approximate half-life of the drugs according to renal function is given in table 2 above.

Coagulation tests

Examination of routine coagulation tests such as the PT, APTT and TT may allow an approximate estimate of the levels of drug present in the circulation (Kitchen*, et al* 2014). A normal TT effectively excludes the presence of dabigatran in a sample but

normal APTT and PT do not exclude the presence of significant concentrations of rivaroxaban, apixaban or edoxaban in a sample. Guidance would then suggest that advanced or non-routine assays can be applied to the situation but with caution given to the interpretation of results given the caveats mentioned above (Kitchen*, et al* 2014).

Prohaemostatic agents

It has been suggested that use of several pro-haemostatic agents might reduce the risk of peri-surgical bleeding in patients on DOACs who require emergency surgery. Most of the evidence cited in this regard relates to animal experiments and to the observation of changes in in-vitro tests of haemostasis. The usual view of clinicians is that treatment with a prothrombin complex concentrate (PCC) might improve outcomes but this doesn't take into account the potential for adverse thrombotic outcomes which are often overlooked. There are few data that strongly support the use of PCC and activated PCC in the management of emergency surgery (Makris 2014) and so a pragmatic approach might be to proceed with surgery considering PCC only in the event of diffuse coagulopathic bleeding. Tranexamic acid is likely to reduce bleeding and should be given.

Other strategies

Other general management strategies include avoiding further intake of anticoagulants and avoiding the use of any additional therapies such as NSAID and colloids (dextrans and starches) that might further compromise haemostasis. Dabigatran is minimally protein bound and so can be removed by dialysis if a procedure can be delayed for long enough for this to take place, but this is rarely

practical. Significant amounts of dabigatran can be removed by a single dialysis session although rebound increases in concentration have been observed on cessation of dialysis (Chai-Adisaksopha*, et al* 2015, Chang*, et al* 2013). This strategy is not applicable to rivaroxaban, apixaban and edoxaban which are all highly protein bound.

Specific reversal agents

Idarucizumab

In a prospective study of the administration of a standard dose of 5g of idarucizumab to 36 patients who were receiving dabigatran prior to undergoing an invasive or surgical procedure, normal intraoperative haemostasis was reported in 33, and mildly or moderately abnormal haemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab. In the same study major reversal of dabigatran effect on coagulation tests was observed in patients given idarucizumab in 88-98% of patients (Pollack*, et al* 2015).

Andexanet

There are no data on the use of andexanet in patients undergoing surgery but there are now promising data on the reversal of anticoagulation in healthy volunteers. In a study of apixaban and rivaroxaban treated volunteers who received a bolus dose of andexanet significant reductions in anticoagulant activity were seen in both groups. In apixaban-treated individuals, anti–factor Xa activity was reduced by 94% compared with 21% among those who received placebo and unbound apixaban concentration fell by 9.3 mcg/L compared with 1.9 mcg/L. Thrombin generation was fully restored in 100% of andexanet recipients and 11% of placebo recipients. In

rivaroxaban treated volunteers, anti–factor Xa activity was reduced by 92% compared with 18% among those who received placebo, and unbound rivaroxaban concentration fell by 23.4 mcg/L compared with 4.2 mcg/L. Thrombin generation was fully restored in 96% of andexanet and 7% of placebo recipients. These effects were sustained when andexanet was administered as a bolus plus an infusion. No serious adverse or thrombotic events were witnessed. Although these data cannot be directly interpreted as being able to secure haemostasis during surgery the findings are promising (Siegal*, et al* 2015).

Recommendations

- **Patients with normal renal function undergoing planned low risk procedures should not take a dose of a DOAC for 24 hours before the procedure (2B)**
- **Patients with normal renal function undergoing planned higher risk procedures should not take a dose of a DOAC for 48 hours before the procedure (2B)**
- **For patients with renal impairment see table 2 (2D).**
- **Following minor or low risk procedures in patients with low bleeding risk, anticoagulation can be recommenced 6-12 hours post procedure if haemostasis has been fully secured (2C)**
- **Following high risk procedures and in patients with an increased bleeding risk or in any situation where any increased risk of bleeding is unacceptable DOACs should not be re-introduced at full dose until at least 48 hours post procedure (2C)**

- **In patients with high thrombosis risk it is appropriate to consider prophylactic doses of anticoagulation before re-introducing full therapeutic dose DOAC (2D)**
- **Measurements of the DOACs by indirect methods using dilute thrombin time, ecarin clotting time and calibrated anti-Xa assays should currently be interpreted with caution in the management of patients receiving a DOAC who require emergency surgery (2B)**
- **A normal thrombin time can be interpreted as indicating that there is a minimal circulating concentration of dabigatran. Normal PT and APTT do not exclude significant concentrations of dabigatran, rivaroxaban or apixaban (1A)**
- **If an anticoagulant effect cannot be excluded neuroaxial anaesthesia should be avoided (1C).**
- **Prothrombin Complex Concentrates should not be routinely used in patients on DOACs prior to emergency surgery (2D)**
- **Tranexamic acid is likely to reduce bleeding in patient who have a residual anticoagulant effect (1C).**
- **Drugs and colloids that impair the haemostatic mechanism should be avoided in the peri-surgical management of patients receiving DOACs (2D)**
- **Idarucizumab should be used to reverse dabigatran therapy prior to emergency invasive procedures and surgery where the bleeding risk is considered significant (1C)**

- **Andexanet, when available, should be used to reverse apixaban, rivaroxaban or edoxaban prior to emergency invasive procedures and surgery where the bleeding risk is considered significant (2C)**

Antiplatelet therapy

Antiplatelet therapy is a key pharmacological intervention in the secondary prevention of cardiovascular disease. This pertains particularly to clopidogrel following ischaemic cerebrovascular disease and dual antiplatelet therapy (DAPT) following acute coronary syndromes (ACS) when a combination of aspirin and an ADP receptor (P2Y12) antagonist is indicated especially after coronary artery stenting. In these situations the small day-to-day increase in bleeding risk associated with aspirin, and more so with DAPT (Sorensen*, et al* 2009), is outweighed by their clinical benefit. However, the continuation of antiplatelet agents in the surgical setting is associated with an increase in bleeding risk. In a meta-analysis of 41 studies Burger et al (Burger*, et al* 2005) demonstrated that aspirin therapy was associated with a 1.5-fold increase in post-op bleeding events, but no increase in the severity of bleeds – concluding that low dose aspirin could be continued through most surgical procedures except neurosurgery and prostatectomy. A recent meta-analysis has shown that patients on clopidogrel who have a hip fracture can be managed by normal protocols with early surgery (Soo*, et al* 2016). However, the same may not be true for DAPT which is associated with significantly more surgery-related bleeding (14.7%) compared to aspirin (4.1%) (Singla*, et al* 2012). This bleeding risk has to be balanced against the considerable increased thrombotic risk associated with

premature termination or interruption of anti-platelet monotherapy (Biondi-Zoccai*, et al* 2006) or DAPT (Mehran*, et al* 2013, Rossini*, et al* 2015), which may be required to facilitate a surgical or other invasive procedure.

Non-cardiac surgical procedures

Three randomized controlled trials in high-risk elective surgery have compared temporary peri-operative interruption or continuation of aspirin in patients with stable cardiovascular disease, very few participants had experienced recent (<30 days) ACS or had undergone a stenting procedure (Devereaux*, et al* 2014, Mantz*, et al* 2011, Oscarsson*, et al* 2010). Two of the studies were terminated early with small numbers recruited and were therefore underpowered to assess differences in bleeding events (Mantz*, et al* 2011, Oscarsson*, et al* 2010). Omitting aspirin from 10 days prior to surgery until morning of surgery resulted in no increase in thrombotic events or decrease in bleeding events (Mantz*, et al* 2011) . In contrast, omitting aspirin from 7 days prior to surgery until 3 days post-op resulted in a significantly higher 30-day rate of Major Adverse Cardiac Events (MACE) [9% v 1.8%, p=0.02] but no difference in peri-operative blood loss (Oscarsson*, et al* 2010). Consensus views in guidelines have generally recommend continuation of aspirin monotherapy unless surgery is perceived to have a particularly high bleeding risk or is in a confined space such as brain, posterior eye chamber or medullary canal (Korte*, et al* 2011). More recently a larger RCT including 4382 patients already on an antiplatelet agent demonstrated no difference in the composite endpoint of death or non-fatal myocardial infarction (HR 1.00 (0.81-1.23)) nor in major bleeding (HR 1.11 (0.84-1.48) if aspirin was continued as opposed to being withheld from 1 day pre-op until 7 days post-op (Devereaux*, et al* 2014). In a separate group not on aspirin but

randomized to start it major bleeding was increased (HR 1.34 (1.03-1.74). There is very limited and less reliable data on bleeding risks and cardiovascular benefits of continuing single agent clopidogrel peri-operatively (Luckie*, et al* 2009). While some guidelines propose continuing clopiodgrel monotherapy in the same situations as with aspirin monotherapy (Ferraris*, et al* 2012), we do not believe there is sufficient evidence to make a recommendation.

More challenging is the management of DAPT around invasive procedures. This is an increasingly common scenario as more patients undergo percutaneous intervention (PCI) with stent insertion following ACS, when DAPT is recommended for at least 4 weeks following bare metal stent and 12 months following drug-eluting stent (although shorter duration DAPT is required with the newer bioabsorbable polymer drug-eluting stents). Between 4% and 8% of PCI patients will require surgery within 1 year of stenting. The risk of peri-operative MACE is greatest within the first month after PCI with gradually lessening risk at 2-6 months, 6-12 months and >1 year (Nuttall*, et al* 2008, Savonitto*, et al* 2011). Other recognized markers for post-op MACE include interruption of antiplatelet therapy, recent ACS, urgent or high cardiac-risk surgery and chronic kidney disease (Albaladejo*, et al* 2011, Rossini*, et al* 2015). There are no RCTs on which to base advice in this setting, hence most guidelines adopt a pragmatic expert consensus view, using a matrix assessing the patient's thrombotic risk and the bleeding risk associated with the type of invasive procedure being undertaken (Korte*, et al* 2011, Rossini*, et al* 2014).

In summary very low bleeding-risk procedures can be undertaken without stopping DAPT, whereas low risk procedures in patients with low thrombotic risk may be

undertaken on aspirin with temporary cessation of the ADP receptor antagonist. Ideally elective surgery in patients deemed to be at high thrombotic risk should be deferred until they are lower risk. If surgery cannot be deferred then it should generally proceed on aspirin with temporary discontinuation of the ADP receptor antagonist. In high thrombotic risk patients requiring high bleeding-risk surgery which cannot be deferred, consideration can be given to bridging with a parenteral short-acting glycoprotein IIb/IIIa inhibitor such as tirofiban or eptifibatide during the period of ADP receptor antagonist withdrawal (Savonitto*, et al* 2011).

Cardiovascular Surgery

The cardiovascular benefit of aspirin following coronary artery bypass graft (CABG) surgery is well established. In a meta-analysis of 13 studies the pre-op use of aspirin was associated with a significant reduction in ischaemic events (OR 0.56, 0.33 – 0.96) but with small increases in post-op bleeding and transfusion requirements and a 1.85-fold increased risk of re-exploration surgery (Hastings*, et al* 2015). In contrast in a recent randomized trial the administration of preoperative aspirin to patients undergoing coronary artery surgery did not result in a lower risk of death or thrombotic complications nor in a higher risk of bleeding as compared to placebo (Myles*, et al* 2016). Continuing clopidogrel pre-CABG was also shown, in a meta-analysis of 11 cohort studies, to increase post-op chest tube drainage and the requirement for blood products as well as 2-5 fold increase in re-exploration rates (Kunadian*, et al* 2006) . In both these meta-analyses the study groups were heterogeneous and poorly controlled. Indeed, in the clopidogrel analyses it is understood that many of the cases were also on aspirin. Furthermore, many of the included studies were pre-2000 when use of tranexamic acid, which has been shown

to reduce blood loss in both aspirin and clopidogrel treated patients (McIlroy*, et al* 2009, Shi*, et al* 2013) was less prevalent. Hence most recent cardiac guidelines recommend continuing aspirin pre-CABG unless there is a very high bleeding risk, a very low thrombosis risk or the patient would decline transfusion (Ferraris*, et al* 2012, Sousa-Uva*, et al* 2014).

Cardiac surgery under combined aspirin and clopidogrel is complicated by a further increase in bleeding, compared to aspirin alone. Compared to aspirin and clopidogrel DAPT, aspirin and ticagrelor DAPT had similar CABG-related bleeding rates while aspirin and prasugrel DAPT was associated with higher bleeding and surgical re-exploration rates (Held*, et al* 2011, Smith*, et al* 2012). Therefore, based on observational data on bleeding and drug metabolite half lives, it is recommended that clopidogrel and ticagrelor are discontinued 5 days pre-op and prasugrel 7 days pre-op while aspirin is continued throughout (Capodanno and Angiolillo 2013, Ferraris*, et al* 2012, Sousa-Uva*, et al* 2014). In particularly high thrombotic risk patients bridging, protocols with a short-acting parenteral antiplatelet agent during withdrawal of the oral ADP receptor antagonist have been proposed (Capodanno and Angiolillo 2013, Savonitto*, et al* 2011) . The parenteral glycoprotein IIb/IIIa inhibitor is usually commenced on day -3 and stopped 4-6 hours pre-op, and commenced 4-6 hours post-op until the ADP receptor antagonist can be restarted (within 7 days, when all bleeding has been controlled), and in the case of clopidogrel an initial loading dose is recommended (Sousa-Uva*, et al* 2014).

Emergency surgery in patients on antiplatelet therapy

When urgent high haemorrhage-risk surgery is indicated, and time does not permit cessation of one or both antiplatelet agents, there is evidence from both small in vitro (Li*, et al* 2012, Vilahur*, et al* 2007) and in vivo (Thiele*, et al* 2012) studies that transfusion of donor platelets may improve haemostasis. Platelets should be transfused at least 2 hours after the last dose of aspirin and 12-24 hours after the last dose of clopidogrel to avoid being inhibited by circulating drug or active metabolite. Reversal of aspirin requires fewer donor platelets and is more complete because aspirin inactivated platelets can be recruited by thromboxane generated in transfused platelets, so whilst 2 pools of platelets reverse the effect of aspirin, the effect of even higher doses of platelets when on ADP antagonists is less certain (Godier*, et al* 2015, Hansson*, et al* 2014, Li*, et al* 2012, Vilahur*, et al* 2007). A single dose of platelets in patients with an intracranial haemorrhage on aspirin did not improve outcome (Baharoglu*, et al* 2016) .

Inter-individual variation in sensitivity to ADP receptor antagonists, particularly clopidogrel, may allow some patients to have a shorter period of discontinuation pre-operatively (e.g. 3 days for clopidogrel or ticagrelor and 5 days for prasugrel). This is particularly relevant in urgent surgery situations when assessment of platelet function may help identify patients in which early surgery may be safer. Corredor et al (Corredor*, et al* 2015) have reviewed the utility of pre-op platelet function testing. A great variety of devices are available, however the most robust clinical evidence appears to be with thromboelastography platelet mapping or multiple electrode aggregometry. With the latter, a normal pre-op platelet aggregation response to ADP was associated with low post-op bleeding *(Ranucci, et al 2011)*. Using thromboelastography platelet mapping, platelet receptor inhibition (PRI) of >76% was associated with an 11-fold higher risk of transfusion while a PRI <34% had a

negative predictive value of 90% for requiring at least 2 units red cell transfusion (Kasivisvanathan*, et al* 2014, Kwak*, et al* 2010).

Neuroaxial anaesthesia

Horlocker et al (Horlocker*, et al* 2010), on behalf of the American Society of Regional Anesthesia reviewed several large studies of neuro-axial anaesthesia in a variety of surgical and obstetric settings. Although spinal haematoma has been reported following spinal or epidural anaesthesia, such events are rare – estimated incidence <1 in 150,000 epidural and <1 in 220,000 spinal anaesthetics. In a series of 61 cases of spinal haematoma, antiplatelet therapy was only implicated in three and furthermore no cases of spinal haematoma were reported in combined series of >6000 patients having central neural blockade while on antiplatelet therapy. Hence the guideline recommends spinal and epidural anaesthesia can be undertaken without cessation of NSAID or aspirin (Horlocker*, et al* 2010). In a review of practice this was done for low risk (e.g. peripheral nerve blocks) but not for high risk pain management procedures (Narouze*, et al* 2015). Limited evidence is currently available in relation to the safety of neuro-axial anaesthesia in patients receiving ADP-receptor antagonists, and therefore it is recommended that all such agents be discontinued 7 days prior to the procedure (Horlocker*, et al* 2010, Narouze*, et al* 2015).

Recommendations

- **When being used for secondary prevention of cardiovascular disease aspirin monotherapy can be continued for most invasive non-cardiac**

procedures (including neuroaxial anaesthesia) but, if the perceived bleeding risk is high, aspirin can be omitted from day -3 to day +7 with no net detriment (2C)

- **Aspirin can be continued both before and after coronary artery bypass surgery (1B)**
- **Hip fracture surgery can take place early in patients on clopidogrel (1B)**
- **For urgent low bleeding risk surgery in patients on antiplatelet agents routine platelet transfusion should not be given (2C)**
- **For urgent high-bleeding risk surgery in patients on antiplatelet agents**
    - **Given the uncertain net benefit of platelet transfusion, consider the use of intravenous tranexamic acid pre-operatively (2C)**
    - **If despite tranexamic acid there is excessive peri- or post-op bleeding, or if the bleeding risk is perceived to be very high, consider infusion of 2 pools of donor platelets. This may improve haemostasis if given at least two hours after the last dose of aspirin though even higher doses of donor platelets 12-24 hours after the last dose of clopidogrel may have a lesser effect (2C)**
- **In patients with a recent acute coronary syndrome or coronary artery stent on dual antiplatelet therapy low bleeding risk procedures should proceed without interruption of antiplatelet therapy (1C)**
- **In patients with a recent acute coronary syndrome or coronary artery stent on dual antiplatelet therapy elective high bleeding risk procedures should, if possible, be postponed in patients still requiring dual antiplatelet therapy (1C), and if surgery cannot be deferred aspirin**

should be continued and clopidogrel or ticagrelor interrupted from 5 days pre-op or prasugrel from 7 days pre-op (1C).

	Consider **bridging with treatment dose heparin in**
VTE	Patients with a VTE within previous 3 months. Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3.5.
AF	Patients with a previous stroke/TIA in last three months. Patients with a previous stroke/TIA and three or more of the following risk factors: • Congestive cardiac failure • Hypertension (> 140/90 mmHg or on medication) • Age >75 years • Diabetes mellitus
MHV	MHV patients other than those with a bileaflet aortic valve and no other risk factors

Table 1 Consider bridging with treatment dose heparin in patients who stop warfarin if thrombotic risk is especially high

Renal Function CrCl ml/min	Estimated half-life (hours)	Low bleeding risk	High bleeding risk
Dabigatran			
>80	13	24 hours	48 hours
>50 to <80	15	24-48 hours	48-72 hours
>30 to <50	18	48-72 hours	96 hours
Rivaroxaban			
>30	9	24 hours	48 hours
<30		48 hours	72 hours
Apixaban			
>30	8	24 hours	48 hours
<30		48 hours	72 hours
Edoxaban			
>30	10-14	24 hours	48 hours
<30		48 hours	72 hours

*All decisions need to consider state of haemostasis and new acquired risk factors for bleeding

Table 2 Stopping DOACs before surgery or invasive procedures for which anticoagulation needs to be stopped

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Review Process
Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website.

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Audit Tool
See http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html for template

Appendix 1
Search overview for perioperative management of anticoagulation and antiplatelet therapy

MEDLINE

1. exp Platelet Aggregation Inhibitors/
2. (antiplatelet therapy or Aspirin or Dipyridamole or Ticlopidine or Clopidogrel or Prasugrel or Ticagrelor).tw.
3. (platelet* adj1 (antagonist* or inhibitor* or antiaggregant*)).tw.
4. (antiplatelet adj1 (drug* or agent*)).tw.
5. exp Anticoagulants/
6. (anticoagula* or 4-hydroxycoumarins or Acenocoumarol or Dicumarol or Heparin or Heparin, low-molecular-weight or Phenindione or Phenprocoumon or Warfarin or Dabigatran or Rivaroxaban or Apixaban or Edoxaban).tw.
7. (thrombin* adj2 inhibitor*).tw.
8. or/1-7
9. exp Perioperative Care/
10. (perioperative or periprocedural).tw.
11. (pre-operative or intra-operative or post-operative or pre operative or intra operative or post operative).tw.
12. or/9-11
13. 8 and 12
14. (surgery or operation* or procedure* or intervention* or treatment*).tw.
15. exp specialties, surgical/
16. 14 or 15
17. 13 and 16
18. (animals not (humans and animals)).sh.
19. 17 not 18
20. limit 19 to english language

EMBASE

1. exp antithrombocytic agent/
2. (antiplatelet therapy or Aspirin or Dipyridamole or Ticlopidine or Clopidogrel or Prasugrel or Ticagrelor).tw.
3. (platelet* adj1 (antagonist* or inhibitor* or antiaggregant*)).tw.
4. (antiplatelet adj1 (drug* or agent*)).tw.
5. exp anticoagulant agent/
6. (anticoagula* or 4-hydroxycoumarins or Acenocoumarol or Dicumarol or Heparin or Heparin, low-molecular-weight or Phenindione or Phenprocoumon or Warfarin or Dabigatran or Rivaroxaban or Apixaban or Edoxaban).tw.
7. (thrombin* adj2 inhibitor*).tw.
8. or/1-7
9. exp perioperative period/
10. (perioperative or periprocedural).tw.
11. (pre-operative or intra-operative or post-operative or pre operative or intra operative or post operative).tw.
12. or/9-11
13. 8 and 12
14. (surgery or operation* or procedure* or intervention* or treatment*).tw.
15. exp specialties, surgical/
16. 14 or 15

17. 13 and 16
18. (animal/ or nonhuman/) not human/
19. 17 not 18
20. limit 19 to english language
21. limit 20 to embase

Records generated

Database searched	**Date searched**	**Results**
MEDLINE (OVID) 1946	16/4/15	4349
EMBASE (OVID)1974 to 2015 March 31	16/4/15	9145
Total		**13494**
After de-duplication		**11084**
Further duplicates removed during review (136)		**10948**
Exclusions (9693) Non-English (1) Non-human (15) Paediatric (5) Not relevant to clinical question (9580) Too few cases (92)		**1255**

Breakdown of remaining results

Articles included Antiplatelet only (380) NOAC only (69) VKA only (271) Both NOAC and VKA (63) Mixed antiplatelet and anticoagulant (220)	**1003**
Possible articles Possibly relevant based on title only (159) Surveys of practice (77) Relating to service or costs (16)	**252**

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