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Peri-operative Anticoagulation Guideline

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CONTENTS LIST:

1. Introduction

The purpose of this guideline is to provide a framework for the peri-operative management of anticoagulant or antiplatelet agents in patients having elective surgery at Jersey General Hospital. The guideline is applicable to all surgical specialities and is intended to encompass all routine elective surgical procedures undertaken.

During the peri-operative period the thromboembolic risks of stopping anticoagulant/antiplatelet medication must be carefully balanced against the additional bleeding risk presented by continued use of such medication. In some cases, oral anticoagulant medication will need to be stopped and temporarily replaced with shorter acting alternatives. This is commonly known as “Bridging Anticoagulation”.

Peri-operative management of anticoagulant/antiplatelet therapy in non-elective cases is not considered within this guideline. Such emergency management should be discussed by the surgical team, oncall anaesthetist and if necessary haematologist.

2. Pre-operative Assessment

The assessment of elective surgical patients should be done by the pre-operative assessment team, in advance of the planned operative date.

Risk of peri-operative thromboembolic adverse events will be assessed and classified as detailed in this guideline. The bleeding risk of the surgical procedure will also be considered and a risk based management strategy implemented. This may involve discussion between the peri-operative multi-disciplinary team including anaesthetist, surgeon, haematologist and sub-specialty medical team.

If a patient is taking anticoagulant medication then a full blood count must be taken. Patients requiring bridging therapy (*see Appendix 1: A flowchart for the Pre-operative Management of the Elective Surgical Patient on Anticoagulants and/or Antiplatelet agents, & Appendix 2: Bridging Anticoagulation Timeline.*) and those taking Dabigitran must also have an eGFR within 8 weeks of the surgical date. If the eGFR is <30ml/min and bridging anticoagulation required then the patient should be managed with Unfractionated Heparin (UFH) and not Low Molecular Weight Heparin (LMWH). The Pre-operative Assessment team should arrange admission 1 day prior to the operation date for administration of UFH. Patients will have an accurate weight recorded for appropriate prescription of LMWH or UFH if bridging anticoagulation is required.

Patients will be advised to stop anticoagulant medication and/or antiplatelet agents as detailed in this guideline. If temporary cessation of these medications is required it will be with reference to the timeline specified. (*Appendix 3:Timeframe for the cessation of oral anticoagulants and antiplatelet agents for elective surgery)*

Clear instructions must be delivered to the patient and specific written instructions (*Appendix 4: Patient information letter*) given to the patient. Patients or carers will

need to be trained to administer enoxaparin if required. Where required arrangements will be made for patients to have appropriately timed INR or coagulation tests taken.

Decisions relating to the peri-operative alteration of anticoagulation should be recorded in the pre-operative assessment document. This should include any discussions between the peri-operative multi-disciplinary team.

3 Risk Assessment

Peri-procedural management is based on the assessment of competing risks. Formation of a patient specific plan will involve coordination and good communication between care providers.[1]

3.1 Thromboembolic Risk Assessment

The risk of thrombosis when anticoagulation is stopped depends upon the condition for which the drug was commenced. For example, in patients with non valvular atrial fibrillation, the CHADS2 or CHA2DS2-VASc score can be used to estimate risk of stroke or arterial thromboembolism.[1]

Thrombosis risk can be classified into low, moderate and high. (*Table 1*[1])

Table 1 – Thrombosis risk assessment

Thrombosis risk level	Estimated annual thrombosis risk (without anticoagulation)	Indication for vitamin K antagonist therapy		
		Atrial fibrillation	Venous thromboembolism	Mechanical heart valve
HIGH	>10%	• CHADS2 score of 5 or 6 • Rheumatic valvular heart disease • Recent (within 3 months) stroke or TIA	• Recent (within 3 months) VTE event • Severe thrombophilia	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 months) stroke or TIA
MODERATE	5-10%	CHADS2 score of 3 or 4	• VTE within the past 3-12 months • Recurrent VTE • Non-severe thrombophilia • Active cancer (treated within 6 months or palliative)	Bileaflet aortic valve prosthesis and 1 or more additional risk factor for stroke: • Atrial fibrillation • Previous stroke or TIA • Hypertension • Diabetes mellitus • Congestive heart failure • Age over 75 years
LOW	<5%	Non-valvular AF with CHADS2 score 0-2 and no previous stroke or TIA	• VTE >12 months previous and no other risk factors	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke

Fig 5 | Suggested risk stratification for perioperative thromboembolism. Adapted, with permission, from Douketis and colleagues.[21] Severe thrombophilia includes protein C, protein S, or antithrombin deficiency; antiphospholipid antibodies, or multiple abnormalities. Non-severe thrombophilia includes heterozygosity for factor V Leiden or prothrombin G20210A mutation. High risk patients also include those with a previous stroke or transient ischemic attack more than three months before the planned surgery and a CHADS2 score less than 5, those with previous thromboembolism during temporary interruption of vitamin K antagonists, and those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (such as cardiac valve replacement, carotid endarterectomy, major vascular surgery). AF=atrial fibrillation; CHADS2 score=one point for each of the following: congestive heart failure, hypertension, age 75 years or more, and diabetes mellitus, and two points for a history of stroke or transient ischemic attack; MHV=mechanical heart valve; TIA=transient ischemic attack; VTE=venous thromboembolism

3.1.1 Atrial Fibrillation

The annual risk of stroke in atrial fibrillation can be estimated using the CHADS2 *(table 2, table 3)* or CHA2DS2-VASc score. The CHADS2 score is used in the American College of Chest Physicians (ACCP) guidelines for peri-procedural management of Warfarin.[2]

CHA2DS2-VASc score is a modified version of the CHADS2 score in which age over 75 is given 2 points and the presence of vascular disease, age 65-74 years and female sex are given one point. No studies evaluating this method of risk assessment in the peri-procedural setting have been published.[1]

However, other Jersey General Hospital guidelines, use CHA2DS2-VASC in protocolised risk assessment. The ACCP guidelines classify high thromboembolic risk patients as those with a CHADS2 score of 5 or 6. The comparable annualized stroke risk using CHA2DS2-VASC would have a score of 8 or 9. For continuity of risk assessment this guideline will therefore classify high risk as a CHA2DS2-VASC score of greater than 8.

Table 2 - CHADS2 risk assessment score[3]

		Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age over 75 years	1
D	Diabetes Mellitus	1
S2	Previous Stroke, TIA or Thromboembolism	2

Table 3 - CHADS2 annual stroke risk[3]

CHADS2 Score	Stroke Risk %	95% CI
0	1.9	1.2-3.0
1	2.8	2.0-3.8
2	4.0	3.1-5.1
3	5.9	4.6-7.3
4	8.5	6.3-11.1
5	12.5	8.2-17.5
6	18.2	10.5-27.4

3.1.2 DVT/PE

In patients taking oral anticoagulants for venous thromboembolism (VTE) recurrence is associated with multiple factors including thrombophilia, immobility and cancer. Time from last VTE is important and the risk is highest in the first 6 months.[1]

3.1.3 Mechanical Heart Valves

Arterial thromboembolism and prosthetic valve thrombosis are complications seen with mechanical heart valves. Risk is higher with mitral position and caged ball type valves when compared to aortic position and tilting disc or bileaflet. Mechanical valves with previous thromboembolism, known atrial thrombus, left atrial enlargement, atrial fibrillation and reduced left ventricular systolic function also elevate risk.[1]

The American Heart Association (AHA)/American College of Cardiology(ACC)[4] guidelines suggest bridging therapy is not required for those with one bileaflet aortic mechanical valve with no other risk factors for thrombosis.

In patients with mechanical prosthetic valves there is more evidence for the use of UFH and some centres admit patients for treatment with UFH until 4 hours pre-operatively with resumption of UFH post-operatively.[5] However, the AHA/ACC[4] recommend bridging with either UFH or LMWH during the time the INR is sub therapeutic in patients undergoing invasive procedures with either:

1) mechanical aortic valve replacement and any thromboembolic risk factor.
2) Older generation aortic valve replacement
3) Mechanical mitral valve replacement

3.1.4 Percutaneous Coronary Intervention

Percutaneous Coronary Intervention (PCI) and non-cardiac surgery requires special consideration because of the risks of ischaemic events including stent thrombosis, particularly if anti-platelet therapy is stopped peri-operatively. The consequences of stent thrombosis will depend on stent position but for a left main stem stent it is in most cases fatal.[5] The risk of stent thrombosis in the peri-operative period is highest in the first 4 to 6 weeks after stent insertion. After this time the risk is low but varies from study to study. There is some data to suggest the risk is stabilized after the first 6 months and non-cardiac surgery may be possible without increased risk.[6]

AHA/ACC guidance[6] recommends elective non-cardiac surgery should be:

- Delayed 14 days after balloon angioplasty.
- Delayed 30 days after bare metal stent (BMS) implantation
- Delayed 365 days after drug-eluting stent (DES) implantation.

However, elective non cardiac surgery after DES maybe considered after 180 days if the risk of further delay is greater than the expected risks of ischaemia and stent thrombosis. These recommendations are broadly similar to the European Society od Cardiology (ESC). The ESC[5] add that with new-generation DES, unless high risk ACS, dual antiplatelet therapy (DAPT) beyond 6 months is no longer recommended.

The value of continuing Aspirin or DAPT to prevent stent thrombosis is uncertain due to the lack of prospective trials. However, the AHA/ACC recommend, in patients whom DAPT will need to be discontinued, elective non cardiac surgery should not be performed within:

- 30 days after BMS implantation (ideally 3 months[5])
- 365 days after DES implantation
- 14 days of balloon angioplasty (if aspirin will need to be discontinued peri-operatively)

If patients do require urgent non cardiac surgery during the first 4 to 6 weeks after BMS or DES, DAPT should be continued unless the relative risk of bleeding outweighs the benefit of the prevention of stent thrombosis. This decision should be individualized after discussion between treating clinicians. There is no evidence to suggest that warfarin, antithrombotics, or glycoprotein IIb/IIIa agents will reduce risk after discontinuing oral antiplatelet agents[6] but the ESC suggest they should be considered.[5]

In patients who receive coronary stents and must undergo surgical procedures that mandate discontinuation of $P2Y_{12}$ platelet receptor inhibitor therapy it is recommended aspirin be continued and the $P2Y_{12}$ platelet receptor inhibitor therapy restarted as soon as possible.[6, 5]

If non cardiac surgery is required a consensus decision among treating clinicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful. Due to the lack of availability of percutaneous intervention in Jersey consideration should be given to referring patients who require elective surgery within these time limits to another centre. As such all cases should be discussed with a cardiologist.

If during routine pre-operative assessment it is discovered a patient may require coronary intervention prior to surgery then the surgical and cardiology teams should reach a consensus decision about the timing of procedures and types of stent used. If the elective non cardiac surgery is likely to occur within 1 to 12 months of percutaneous intervention then the strategy of a BMS with 4-6 weeks DAPT and continuation of aspirin peri-operatively maybe an option. With more urgent non cardiac surgery, if coronary revascularization is absolutely necessary then coronary artery bypass grafting can be considered.[8]

3.2 Bleeding Risk Assessment

Bleeding risk is the competing risk to thromboembolism when considering a peri-operative anticoagulation strategy. The bleeding risk of the invasive procedure needs to be assessed pre-operatively. In some simple procedures with a low risk of bleeding it maybe possible for patients to safely continue their oral anticoagulants throughout the peri-procedural period. Communication within the peri-operative team is vital to accurately make an assessment.

The HAS-BLED score is widely used in patients taking warfarin for atrial fibrillation.

Risk factors include hypertension, abnormal renal and liver function, stroke, older age, Non Steroidal Anti-inflammatory drugs and use of anti platelets agents.[1] However, it's use in the peri-operative setting is limited and no peri-procedural bleeding risk assessment models exist.

Procedures can be stratified by expected blood loss. Patient and operator factors will have influence on individual risk. Quantifying blood loss is not the only important factor. Bleeding in certain anatomical sites will have more importance than others.

The ACCP have stratified procedures to bleeding risk to aid decision making.[1]

Table 4 - Procedural Bleeding Risk[1]

High Bleeding Risk (2 day risk of major bleed 2-4%)	Low Bleeding Risk (2 day risk of major bleed 0-2%)
Heart valve replacement	Cholecystectomy
Coronary artery bypass	Abdominal hysterectomy
Abdominal aortic aneurysm repair	Gastrointestinal endoscopy with or without biopsy, enteroscopy, biliary or pancreatic stent without sphincterotomy, endosonography without fine needle aspiration
Neurosurgical, urologic, head and neck, abdominal, or breast cancer surgery	Insertion of a pacemaker or cardiac defibrillator and electrophysiologic testing
Bilateral knee replacement	Simple dental extractions
Laminectomy	Carpal tunnel repair
Transurethral prostate resection	Knee or hip replacement and shoulder, foot, or hand surgery
Kidney biopsy	Arthroscopy
Polypectomy, variceal treatment, biliary sphincterotomy, pneumatic dilatation	Dilatation and curettage
Multiple tooth extractions	Skin cancer excision
Vascular and general surgery	Abdominal hernia repair
Any major operation (duration >45 minutes)	Hemorrhoidal surgery
	Axillary node dissection

	Hydrocele repair
	Cataract and non-cataract eye surgery
	Non-coronary angiography
	Bronchoscopy with or without biopsy
	Skin, bladder, prostate, thyroid, breast, and lymph node biopsies

4. Specific Procedures

4.1 Carotid Endarterectomy

Patients undergoing carotid endarterectomy are usually at moderate or high risk of thromboembolism and as such are usually prescribed anticoagulants or oral antiplatelet agents. However, it is a high bleeding risk procedure. The ACCP[2] suggest that in patients with moderate risk of thrombosis, no bridging therapy, maybe considered. In Jersey all cases should be discussed with the operating consultant surgeon and anaesthetist.

4.2 Dental/Cataract Surgery

The British Committee for Standards in Haematology and SIGN advise that the risk of bleeding from routine outpatient dental surgery is low if the INR is <4 and in most patients undergoing routine outpatient dental surgery, including extraction, warfarin need not be interrupted.[7,] 8 Minor dental procedures include tooth extractions and root canal procedures. Different approaches include continuing vitamin K antagonists with an oral antifibrinolytic drug, partial VKA interruption (2-3 days) and complete VKA interruption. Multiple extractions may be considered higher risk. ACCP guidelines also recommend continuing vitamin K antagonists for minor dental procedures with co-administration of an oral prohemostatic agent or stopping vitamin K antagonists 2 to 3 days before the procedure.[2]

Cataract extraction is largely an avascular procedure and prospective cohort studies report an incidence of clinically important bleeding of <3%. Meta-analysis of patients continuing vitamin K antagonists had an overall incidence of bleeding of 10% but almost all were self limiting. ACCP guidelines recommend warfarin can be continued in patients who require cataract surgery.[14] However, an important consideration is the safety of peri and retrobulbar anaesthesia in such cases.

4.3 Neuroaxial blockade

An abnormality of coagulation is a relative contra-indication to the use of a regional anaesthetic technique.[9] The increased risk of haemorrhagic complications in patients is unquantifiable and exists as a spectrum of absolute risk. The type of neuraxial and peripheral nerve block is an important factor. Epidural with catheter techniques have the highest risk of haemorrhagic complications followed by single-shot epidural/ spinal/ paravertebral/ deep blocks/ superficial perivascular/ fascial/ superficial techniques in order of reducing risk.[9]

AAGBI have published recommendations relating to drugs which modify coagulation.[9] *(table 5)*

Table 5

Table 1 Recommendations related to drugs used to modify coagulation. Recommended minimum times are based in most circumstances on time to peak drug effect + (elimination half-life × 2), after which time < ¼ of the peak drug level will be present. For those drugs whose actions are unrelated to plasma levels, this calculation is not relevant. Data used to populate this Table are derived from ASRA and ESRA guidelines [1, 2] and information provided by drug manufacturers. These recommendations relate primarily to neuraxial blocks and to patients with normal renal function except where indicated.

Drug	Time to peak effect	Elimination half-life	Acceptable time after drug for block performance	Administration of drug while spinal or epidural catheter in place[1]	Acceptable time after block performance or catheter removal for next drug dose
Heparins					
UFH sc prophylaxis	< 30 min	1–2 h	4 h or normal APTTR	Caution[2]	1 h
UFH iv treatment	< 5 min	1–2 h	4 h or normal APTTR	Caution[2]	4 h
LMWH sc prophylaxis	3–4 h	3–7 h	12 h	Caution[3]	4 h[3]
LMWH sc treatment	3–4 h	3–7 h	24 h	Not recommended	4 h[4]
Heparin alternatives					
Danaparoid prophylaxis	4–5 h	24 h	Avoid (consider anti-Xa levels)	Not recommended	6 h
Danaparoid treatment	4–5 h	24 h	Avoid (consider anti-Xa levels)	Not recommended	6 h
Bivalirudin	5 min	25 min	10 h or normal APTTR	Not recommended	6 h
Argatroban	< 30 min	30–35 min	4 h or normal APTTR	Not recommended	6 h
Fondaparinux prophylaxis[5]	1–2 h	17–20 h	36–42 h (consider anti-Xa levels)	Not recommended	6–12 h
Fondaparinux treatment[5]	1–2 h	17–20 h	Avoid (consider anti-Xa levels)	Not recommended	12 h
Antiplatelet drugs					
NSAIDs	1–12 h	1–12 h	No additional precautions	No additional precautions	No additional precautions
Aspirin	12–24 h	Not relevant; irreversible effect	No additional precautions	No additional precautions	No additional precautions
Clopidogrel	12–24 h		7 days	Not recommended	6 h
Prasugrel	15–30 min		7 days	Not recommended	6 h
Ticagrelor	2 h	8–12 h	5 days	Not recommended	6 h
Tirofiban	< 5 min	4–8 h[6]	8 h	Not recommended	6 h
Eptifibatide	< 5 min	4–8 h[6]	8 h	Not recommended	6 h
Abciximab	< 5 min	24–48 h[6]	48 h	Not recommended	6 h
Dipyridamole	75 min	10 h	No additional precautions	No additional precautions	6 h
Oral anticoagulants					
Warfarin	3–5 days	4–5 days	INR ≤ 1.4	Not recommended	After catheter removal

Table 1. *(Continued)*

Drug	Time to peak effect	Elimination half-life	Acceptable time after drug for block performance	Administration of drug while spinal or epidural catheter in place	Acceptable time after block performance or catheter removal for next drug dose
Rivaroxaban prophylaxis[5] (CrCl > 30 ml.min^{-1})	3 h	7–9 h	18 h	Not recommended	6 h
Rivaroxaban treatment[5] (CrCl > 30 ml.min^{-1})	3 h	7–11 h	48 h	Not recommended	6 h
Dabigatran prophylaxis or treatment[7]					
(CrCl > 80 ml.min^{-1})	0.5–2.0 h	12–17 h	48 h	Not recommended	6 h
(CrCl 50–80 ml.min^{-1})	0.5–2.0 h	15 h	72 h	Not recommended	6 h
(CrCl 30–50 ml.min^{-1})	0.5–2.0 h	18 h	96 h	Not recommended	6 h
Apixaban prophylaxis	3–4 h	12 h	24–48 h	Not recommended	6 h
Thrombolytic drugs					
Alteplase, anistreplase, reteplase, streptokinase	< 5 min	4–24 min	10 days	Not recommended	10 days

UFH, unfractionated heparin; sc, subcutaneous; APTTR, activated partial thromboplastin time ratio; iv, intravenous; LMWH, low molecular weight heparin, NSAIDs, non-steroidal anti-inflammatory drugs; INR, international normalised ratio; CrCl, creatinine clearance.

Notes to accompany Table 1

1 The dangers associated with the administration of any drug that affects coagulation while a spinal or epidural catheter is in place should be considered carefully. There are limited data on the safety of the use of the newer drugs in this Table, and they are therefore not recommended until further data become available. The administration of those drugs whose entry in this column is marked as 'caution' may be acceptable, but the decision must be based on an evaluation of the risks and benefits of administration. If these drugs are given, the times identified in the column to the left ('Acceptable time after drug for block performance') should be used as a guide to the minimum time that should be allowed between drug administration and catheter removal.

2 It is common for intravenous unfractionated heparin to be given a short time after spinal blockade or insertion of an epidural catheter during vascular and cardiac surgery. Local clinical governance guidelines should be followed and a high index of suspicion should be maintained if any signs attributable to vertebral canal haematoma develop.

3 Low molecular weight heparins are commonly given in prophylactic doses twice daily after surgery, but many clinicians recommend that only one dose be given in the first 24 h after neuraxial blockade has been performed.

4 Consider increasing to 24 h if block performance is traumatic.

5 Manufacturer recommends caution with use of neuraxial catheters.

6 Time to normal platelet function rather than elimination half-life.

7 Manufacturer recommends that neuraxial catheters are not used.

5. Bridging Therapy

In cases where it is necessary to stop oral anticoagulants for an invasive procedure it is sometimes replaced with low molecular weight heparin. This process is termed “Bridging Therapy”

Bridging therapy is used to minimize time without anticoagulation when warfarin is interrupted for invasive procedures but validated strategies based on high quality data are lacking. Existing data suggest that the use of bridging therapy may increase the risk of bleeding for some patients without reducing the risk of thrombosis.[1]

Additionally, shorter half lives and the time to anticoagulant activity of newer oral anticoagulant agents make bridging therapy unnecessary with these agents.[1]

There are multiple observational studies including bridging therapy. Meta analysis suggests bridging therapy does not reduce thromboembolic risk in patients having an invasive procedure but bleeding risk complications may be increased.[1]

To date the only published prospective double blind randomised controlled trial in this setting is the BRIDGE[10] trial, although the PERIOP-2 study remains ongoing. The BRIDGE study randomised patients taking warfarin for atrial fibrillation to receive low molecular weight heparin (Dalteparin 100 Units/Kg) (934 patients) or placebo (950 patients) administered subcutaneously twice daily from 3 days before the procedure until 24 hours before and then from 5 to 10 days after the procedure. Warfarin was stopped 5 days before the procedure and resumed 24 hours after. Mean $CHADS_2$ score was 2.3 and 2.4 in the no bridging and bridging groups respectively. The incidence of arterial thromboembolism was 0.4% in the no bridging group and 0.3% in the bridging group (risk difference 0.1%; 95%CI -0.6 to 0.8; p=0.01). 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)

Further evidence suggests in patients with active cancer bridging therapy increases bleeding risk without affecting the risk of thromboembolism. Other studies have identified association between peri-operative bridging therapy and increased bleeding risk.[1]

Multiple bridging therapy guidelines are published including the ACCP, BCSH, AHA/ACC and ESC. The most detailed guideline by the ACCP were published before the publication of the BRIDGE study. The suggested approach classifies patients as low, moderate or high risk of thrombosis (see table 1) and bridging therapy is then based on bleeding risk. (table 6)

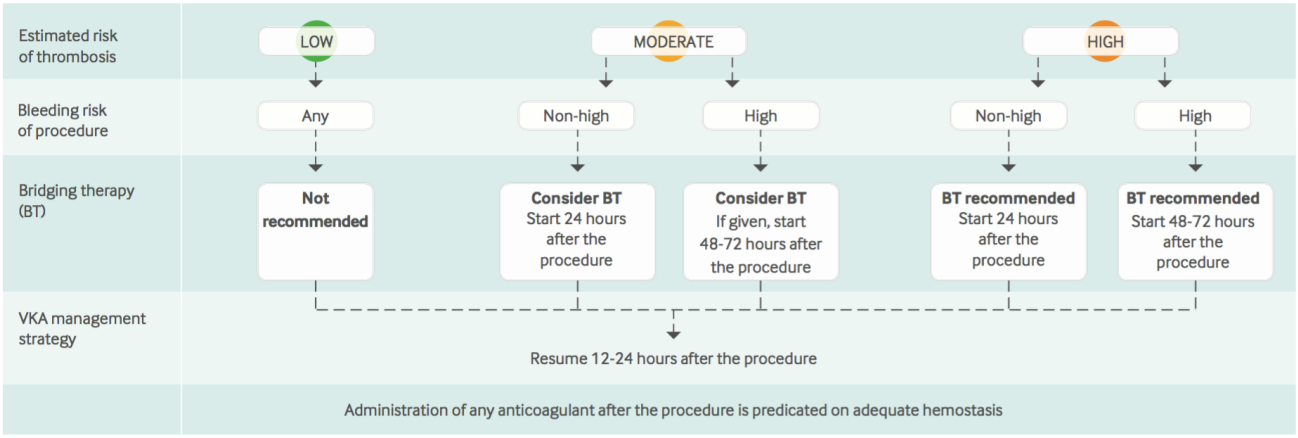


Fig 7 | American College of Chest Physicians' suggested approach to elective post-procedure management of vitamin K antagonists (VKAs)[21]

During the pre-operative assessment consideration should be made to the competing risks of bleeding and thromboembolism. This may involve the peri-operative multidisciplinary team including listing surgeon, anaesthetic team and haematologist. If the balance of risk is in favour of bridging anticoagulation therapy then consideration should also be given to converting the patient to the newer direct thrombin inhibitors/factor Xa inhibitors due to the advantageous pharmacokinetics.

In general there is better evidence for the efficacy and safety of LMWH in comparison to UFH in bridging.[5]

If bridging therapy is required then patients or carers should be given a calendar based timeline for intervention. The pre-operative assessment staff must deliver training to patients or carers to ensure correct technique for out of hospital administration of Enoxaparin. If it is not possible to educated patients or carers then arrangements must be made with the patient's community nurse.

Bridging anticoagulation should be arranged at the pre-operative assessment clinic as follows:

Discontinue Warfarin treatment 5 days before the procedure.

1. If eGFR >30ml/min commence Enoxaparin 1.5mg/kg subcutaneously (s/c) daily 3 days before the procedure. This Enoxaparin dose should be rounded to the nearest whole syringe size.
2. Stop Enoxaparin 1.5mg/kg s/c 24 hours before the procedure
3. Measure INR and FBC 1 day before procedure.
4. If INR greater than 1.8 give oral Phytomenadione (vitamin K_1) 2mg and recheck INR on day of surgery.
5. Restart Warfarin on the evening or day after surgery at patients usual dose.
6. Restart Enoxaparin 1.5mg/kg s/c 12 to 24 hours post operative with low

bleeding risk and 48 to 72 hours post operatively with high bleeding risk. In high bleeding risk cases consider prophylactic dose Enoxaparin for the first 48 hours.

7. Check INR on post operative day 3.
8. Continue Enoxaparin 1.5mg/kg s/c until INR within target range.

A full blood count (FBC) should be taken with the pre-operative INR. If the patient is thrombocytopenic then consideration of Heparin Induced Thrombocytopenia must be made by the peri-operative team.

If eGFR >30ml/min and bridging is required then consideration should be made to use IV UFH to achieve an aPTT of 60-85 seconds. Therapeutic dose IV unfractionated heparin should be stopped 4-6 hours before surgery.[2] Such cases should be discussed with the peri-operative team and haematologist.

If the patient is discharged before the INR is within target range, the patient, should be given a supply of Enoxaparin to continue until they are advised to stop at anticoagulation follow up. A minimum of 10 days supply should usually be prescribed.

For patients whose routine anticoagulation is managed by the Nurse Led Dosing Advice Service, an anticoagulation nurse appointment should be arranged via the haematology secretary. (442597) The yellow A4 Ward Discharge Re-referral Form should be completed and sent to pathology. Alternatively, if the patients routine anticoagulation is managed by their General Practitioner (GP), a follow up appointment with the GP should be arranged and a supply of Enoxaparin prescribed until that date.

6. Specific Medication

6.1 Warfarin

Warfarin is a highly bioavailable vitamin K antagonist, (VKA) readily absorbed from the gastrointestinal tract and metabolized primarily through the CYP2C9 enzyme. VKAs act by depleting the active (reduced) form of vitamin K. Reduced vitamin K is a co-factor in the production of clotting factors II, VII, IX, and X. After being oxidized, Vitamin K must be reduced for further carboxylation reactions. VKAs inhibit vitamin K epoxide reductase which catalyses this reduction. Thus the anticoagulant effect of warfarin is a result of a decrease in factors II, VII, IX, and X.

Variable dietary vitamin K and drug interactions can result in fluctuations in effect. Warfarin has a half life of 36-42 hours so it usually takes several days for it's effects to develop or abate.[1] Fluctuations in effect can lead to increased risks of bleeding or thrombosis. Discontinuing warfarin can result in a temporary hypercoagulable state although clinical relevance in this setting is unknown.

If it is decided to stop Warfarin this should be done 5 days before the procedure and restarted at the pre existing dose on day one post procedure unless bleeding risk is high.

6.2 Unfractionated Heparin

Unfractionated heparin is a naturally occurring glycosaminoglycan (porcine or bovine) with a variable molecular weight. (5000-35000 Daltons) It has multiple mechanisms of action within the coagulation cascade including potentiation of antithrombin, inhibiting factor Xa at low doses and with increasing heparin concentrations progressive inhibition of factors IXa, Xia, and XIIa. It is metabolized by the reticuloendothelial system. When given intravenously it has immediate effect with a plasma half time of 30 minutes- 2 hours. With subcutaneous injection onset is delayed up to 2 hours with a more prolonged effect. (10 hours)[7]

Anticoagulant effects can be monitored with APTT testing and platelet count should be observed for the immune mediated Heparin Induced Thrombocytopenia. Low dose molecular weight heparin has superseded unfractionated heparin for most indications.

6.3 Low molecular weight heparins (LMWH)

Low molecular weight heparins (LMWH) have an average molecular weight of <8000 Daltons. In contrast to UFH the anti-Xa effect predominates and have better availability when given subcutaneously. The APTT is relatively insensitive to LMWH. An anti-Xa level can be used to monitor LMWH but it's predictive value against thrombosis and bleeding is not high.[7]

LMWH is principally excreted by the kidneys and there is an association between major bleeding and a creatinine clearance of <30ml/min.[7] The ACCP recommend UFH instead of LMWH in patients with a creatinine clearance <25ml/min.

6.4 Aspirin and other NSAIDs

Aspirin (acetyl salicylic acid) inhibits the cyclo-oxygenase enzyme. At low dose this is selective to platelet cyclo-oxygenase. The acetylation of cyclo-oxygenase results in permanent inhibition of platelet thromboxane A_2 production and thus inhibits platelet aggregation for the lifespan of the platelet.

Meta-analysis has suggested Aspirin may increase the risk of bleeding complications peri-operatively by 50%, but, in patients at risk of ischaemic heart disease withdrawal increased cardiac events.[11]

The POISE-2 trial[9], a 2 by 2 factorial trial randomly assigned 10,010 patients at risk of vascular complications preparing to undergo non-cardiac surgery to receive aspirin or placebo and clonidine or placebo. Patients started taking 200mg aspirin or placebo and continued 100mg aspirin daily for 30 days post operatively in the initiation stratum or for 7 days followed by their usual dose in the continuation stratum. There was no significant difference in the primary outcome composite of death or non fatal myocardial infarction at 30 days. Major bleeding was more common in the aspirin group. (hazard ratio 1.23 95% CI 1.01-1.49). Outcomes were similar in both aspirin strata. Carotid endarterectomy surgery and patients within 6 weeks of BMS and 1 year of DES were excluded. Only 23% of the study

population had known coronary artery disease(CAD).

The AHA/ACC guideline recommendation is that in patients who have not had previous coronary stenting it may be reasonable to continue aspirin when the risk of potential increased cardiac events outweighs the risk of increased bleeding.[6] The ESC guidelines suggest the POISE-2 trial does not support the routine use of aspirin in patients undergoing non-cardiac surgery but it is uncertain if patients with a low bleeding risk and high thromboembolic risk could benefit from low dose aspirin. For spinal surgery, certain neurosurgical or ophthalmological operations it should be stopped for 7 days. They conclude it should be an individualised decision.[5]

The POISE 2 investigators suggest haemostasis is unimpaired if at least 20% of platelets have normal COX-1 activity. As platelets are replaced 12% every 24 hours, stopping aspirin 72 hours or more before surgery may be adequate to minimize bleeding risk.[12]

6.5 Dipyridamole

Dipyridamole inhibits cellular reuptake of adenosine and inhibits platelet phosphodiesterase resulting in reduced platelet adhesion and aggregation. There is little data on bleeding risk from dipyridamole in invasive procedure. SIGN guidelines suggest discontinuation is not generally required but risk should be assessed individually.[7] AAGBI guidelines for regional anaesthesia similarly suggest it can be continued.[3]

6.6 Clopidogrel/Ticagrelor

Clopidogrel is a thienopyridine derivative which reduces platelet aggregation through inhibition of the adenosine diphosphate $P2Y_{12}$ receptor preventing the glycoprotein IIb/IIIa receptor from transforming into its active form. It is a prodrug which is metabolized in the liver to the active metabolite. It is effective after 2 hours but full inhibition is only apparent after 3-7 days unless a loading dose is given. The inhibition is irreversible and permanent for the duration of the platelets lifespan. (7-10 days) Genetic variations in the CYP2C19 enzyme result in variable metabolism to the active metabolite and thus there is a subset of poor responders. Guidelines suggest discontinuing Clopidogrel 7 days prior to invasive procedures if the risk of bleeding is deemed to exceed the risk of thrombosis.[9, 7, 13]

Ticagrelor is an oral reversible $P2Y_{12}$ ADP receptor antagonist which inhibits ADP induced signaling but does not inhibit ADP binding. It is metabolized rapidly by the CYP3A4 enzyme to the active metabolite. The terminal half life of the drug is 7 hours and 9 hours for the active metabolite. Despite this the AAGBI recommend stopping ticagrelor for 5 days before neuroaxial blockade.[9]

6.7 Direct Thrombin/Xa inhibitors

The limitations of VKAs have lead to the development of alternative oral anticoagulants given as fixed doses without the requirement for routine monitoring

of effect. Currently available are the direct thrombin inhibitors and factor Xa inhibitors.[1]

Dabigatran is a direct thrombin inhibitor administered as the prodrug dabigatran etexilate. It promotes anticoagulation by binding to the active site of thrombin, competitively inhibiting the conversion of fibrinogen to fibrin. Peak plasma concentration is reached within 1.5 hours and about 80% of the drug is excreted through the kidneys. The half life ranges from 8-14 hours.[1]

RE-LY trial compared two dosing regimes of Dabigatran with Warfarin and data was collected on interruption for procedures. Initially it was recommended to stop Dabigatran 24 hours before the procedure. Later this was changed to 24 hours before low bleeding risk procedures and 2-5 days before for high bleeding risk procedures depending on renal function. The incidence of bleeding and thromboembolism did not differ significantly between the three groups. For patients receiving Dabigatran there was no difference in major bleeding complications before or after the change in pre-procedure stopping time. [14]

Oral factor Xa inhibitors target the prothrombin binding site on factor Xa. They include Rivaroxaban, Apixaban and Edoxaban.

Rivaroxaban reaches peak plasma concentration in 2-4 hours and it's half life is 7-11 hours. Bioavailability is 66% but absorption can be improved if taken with food. Only 33% is renally excreted.

Investigators from the ROCKET AF trial[15] assessed temporary interruption of rivaroxaban and warfarin. Bridging therapy was used at their discretion. Oral anticoagulation was stopped 3 or more days before with no significant difference in major bleed complications or thromboembolism between rivaroxaban and warfarin or bridging therapy and no bridging therapy.

Apixaban reaches peak plasma concentration in 3 hours and has a half life of 8-15 hours. Only 25% of the drug is excreted renally with most metabolized by the liver. The ARISTOTLE trial[16] reported outcomes of peri-procedural management of patients taking Apixiban and Warfarin. Bridging therapy was at the discretion of local investigators. The Apixiban was stopped in most patients 2-5 days before the procedure. Again there was no significant difference between groups.

The Dresden NOAC registry records data on the interruption of the New Oral Anticoagulants with similar findings. There was no difference in cardiovascular events when comparing bridging therapy to no bridging therapy but the odds ratio for major bleeding was 5.0 (1.2-20.4).

These initial reports of outcomes from interruption of target specific oral anticoagulants seem to support a no bridging approach which is consistent with the known pharmacokinetics of these agents.[1]

The manufacturers of Rivaroxaban and Apixaban suggest restarting the drug when adequate haemostasis has been achieved. There is no explicit instruction for

Dabigatran but the principle should be the same. The time to peak concentration with all target specific oral anticoagulants is rapid so haemostasis is vital to prevent post procedural bleeding.[1]

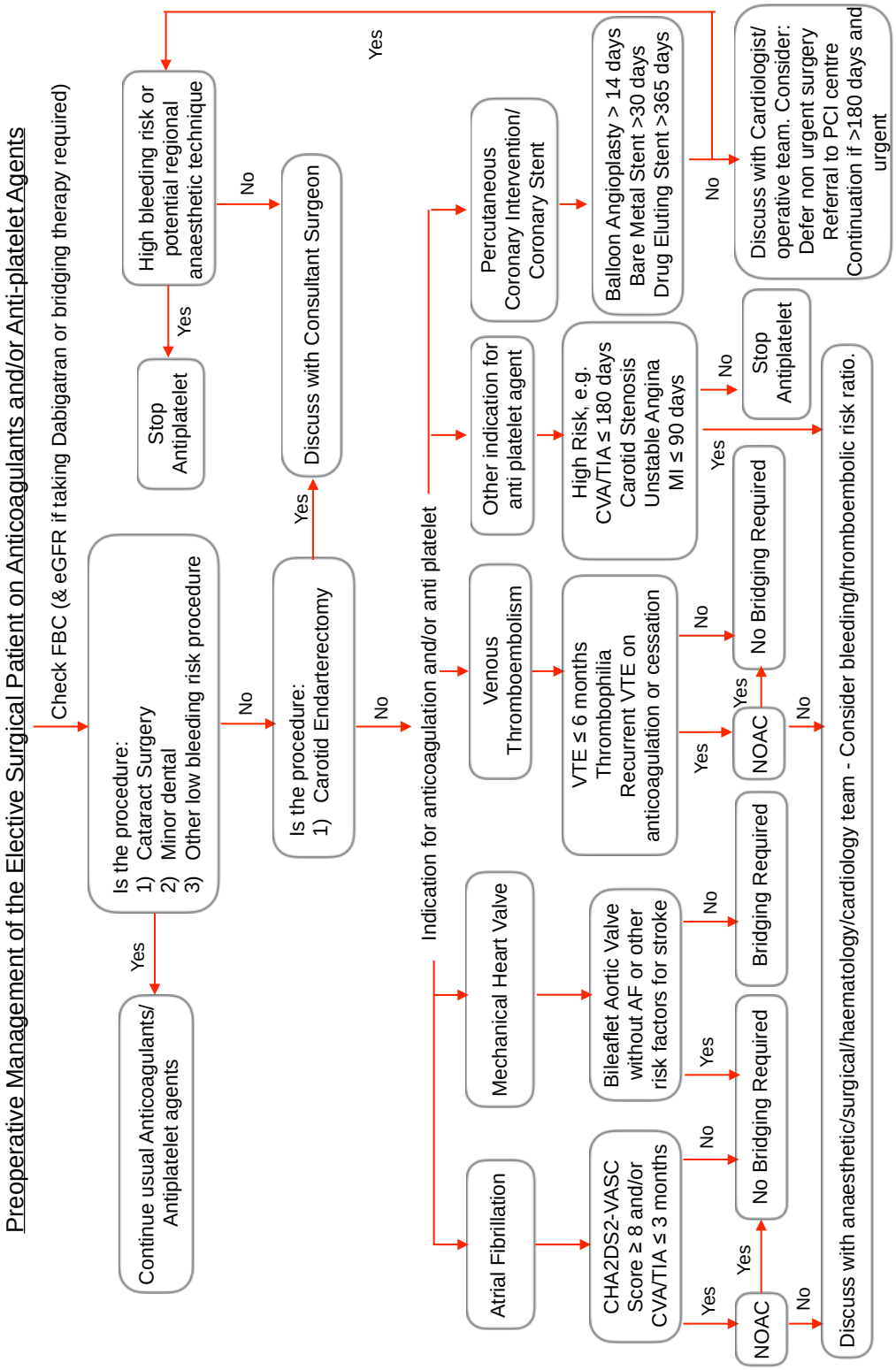
7. Restarting oral anticoagulants/antiplatelet agents

The decision to restart oral anticoagulants or antiplatelet agents will depend on balancing the competing risks of thromboembolism and bleeding. The bleeding risk can most accurately be assessed post-operatively.

In patients with a low bleeding risk oral anticoagulants or antiplatelet agents can be restarted 12-24 hours post operatively. If the bleeding risk is considered higher then 48-72 hours may be safer. In such cases prophylactic dose Enoxaparin should be considered for the first 48 hours.

8. Appendix

8.1. A flowchart for the Pre-operative Management of the Elective Surgical Patient on Anticoagulants



8.2. Bridging Anticoagulation Timeline

Bridging Anticoagulation Timeline

Is Bridging Therapy Required?

(refer to "Pre-operative management of the Elective Surgical Patient on Anticoagulants and/or Antiplatelet Agents")

At Pre-operative Assessment Visit

- *Check FBC and eGFR*
- *Inform patient of Bridging Therapy Timeline*
- *Give Patient Calendar based information letter*
- *Ensure Patient or Carer has been trained in the administration of Enoxaparin or community nurse has been arranged*
- *Ensure Enoxaparin has been prescribed if eGFR >30ml/min*
- *If eGFR ≤30ml/min discuss with anaesthetist*

5 days before the Procedure

- *Discontinue Warfarin*

3 days before the Procedure

- *Commence Enoxaparin 1.5mg/kg s/c once daily*

24 Hours before the Procedure

- *Stop Enoxaparin*
- *Measure INR & FBC*
- *If INR ≥1.8 give 2mg Phytomenadione (Vitamin K) orally*
- *If the patient is thrombocytopenic then consideration of Heparin Induced Thrombocytopenia must be made by the peri-operative team.*

On the day of the Procedure

- *Measure INR again if ≥1.5 24 hours before the procedure*

1 day after the Procedure

- *Restart Warfarin at patients usual dose*
- *Restart Enoxaparin 1.5mg/kg s/c 12-24 hours post operative with low bleeding risk*
- *Consider prophylactic Enoxaparin in high bleeding risk patients*

2-3 days after the Procedure

- *Restart Enoxaparin 1.5mg/kg s/c 48-72 hours post operative with high bleeding risk*
- *Check INR on post-operative day 3*
- *Continue Enoxaparin 1.5mg/kg once daily until INR within target range*

8.3. Timeframe for the cessation of oral anticoagulants and antiplatelet agents for elective surgery

Adapted from AAGBI Guidelines[3]

Drug	Recommended Minimum Time Prior to Procedure
Heparins	
UFH sc prophylaxis	**4 hours or normal APTT**
UFH iv treatment	**4 hours or normal APTT**
LMWH sc prophylaxis	**12 hours**
LMWH sc treatment	**24 hours**
Heparin Alternatives	
Danaparoid prophylaxis	**Avoid – consider Xa levels**
Danaparoid treatment	**Avoid – consider Xa levels**
Fondaparinux prophylaxis	**36-42 hours - consider Xa levels**
Fondaparinux treatment	**Avoid – consider Xa levels**
Antiplatelet Agents	
NSAIDS	**Usually continue** **2 days in high bleeding risk procedures** **Np additional precautions for neuroaxial blockade**
Aspirin	**7 days.** **Np additional precautions for neuroaxial blockade**
Clopidogrel	**7 days**
Prasugrel	**7 days**
Ticagrelor	**5 days**
Dipyridamole	**Usually continue** **1-2 days in high bleeding risk procedures** **Np additional precautions for neuroaxial blockade**
Oral Anticoagulants	
Warfarin	**5 days. INR ≤1.4**
Rivaroxaban prophylaxis (CrCl >30ml/min)	**18 hours**
Rivaroxaban treatment (CrCl >30ml/min)	**48 hours**
Dabigatran prophylaxis or treatment	
(CrCl >80ml/min)	**48 hours**
(CrCl 50-80ml/min)	**72 hours**
(CrCl 30-50ml/min)	**96 hours**
Apixaban prophylaxis	**48 hours**
Apixaban treatment	**≥48 hours. No AAGBI recommendation for neuroaxial blockade.**

8.4. Patient information letter

Health and Social Services
Department of Anaesthesia
General Hospital, Gloucester Street
St Helier, Jersey, JE1 3QS

States of Jersey
The States of Jersey Department for
Health & Social Services

Pre-Operative Assessment Service

Date: ____/_____/_____

Dear

Stick Addressograph Here
MRN: _____
Patient Name: _____
DOB: _____/_____/_____

As part of your pre-operative preparation it is necessary to replace your usual Warfarin anticoagulant medication with a shorter acting alternative. This is called bridging therapy. Your pre-operative assessment nurse will have discussed this process with you. Your pre-operative assessment nurse will also have arranged for you, or your carer or a district nurse to administer injections of Enoxaparin instead. This is a timeline of when you should stop your warfarin tablets and when you should have injections of Enoxaparin.

Medication Timeline

Date	Day	Warfarin	Enoxaparin	INR
___/___/____	-6	Last Dose of Warfarin	No Enoxaparin	
___/___/____	-5	Stop Warfarin	No Enoxaparin	
___/___/____	-4	No Warfarin	No Enoxaparin	
___/___/____	-3	No Warfarin	Enoxaparin 1.5mg/kg	
___/___/____	-2	No Warfarin	Enoxaparin 1.5mg/kg	
___/___/____	-1	No Warfarin	Enoxaparin 1.5mg/kg	✓
___/___/____	0 (Day of Procedure)	No Warfarin	No Enoxaparin	
___/___/____	1	Restart Warfarin	Enoxaparin	
___/___/____	2	Continue Warfarin	*Dose decided by Surgical team*	
___/___/____	3	Continue Warfarin		✓

Pre-operative Assessment Service
Jersey General Hospital

Contact numbers:
For Main Theatre/Day Surgery: 442156
Private Patients: 444299

PRE-OPERATIVE ASSESSMENT

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10. DEVELOPMENT AND CONSULTATION PROCESS

10.1 Consultation Schedule

Name and Title of Individual	Date Consulted
Pre-operative Assessment Nurses	21/11/2016
Andrew Mitchell	30/11/2016
Chris Mattock	21/11/2016
All Consultant Anaesthetists	21/11/2016
All Consultant Surgeons	21/11/2016
Sebastian McNeilly/Pharmacy	23/01/2017

Name of Committee/Group	Date of Committee/Group meeting
Clinical Directors	24/03/2017