Canberra Health Services

**Procedure**

**Anticoagulation Therapeutic Management (Adults only)**

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| Purpose |

To provide guidance to Medical Officers within Canberra Health Services on the appropriate use of anticoagulants; to identify patients in need of anticoagulation; prescribing and the initiation, monitoring and management of anticoagulation.

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| Alerts |

* Anticoagulant medicines as a group, are identified as high-risk medicines. This means that a small error in prescribing, dispensing, administering, or monitoring these medicines, can result in catastrophic patient harm.
* Anticoagulant medications have been repeatedly implicated in causing serious complications. Although some incidents are expected due to the nature of these medications predisposing to bleeding, failure to follow appropriate prescribing and monitoring procedures can lead to serious bleeding or thrombotic incidents. Special consideration should be given to those patients, on anticoagulant medications, that have an epidural in place or are at risk of a fall.
* There are currently **NO** available strategies for immediate reversal of apixaban or rivaroxaban (Direct Acting Oral Xa inhibitors).

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| Scope |

This procedure applies to all adult patients admitted to the Canberra Hospital. The procedure is to be followed by all Medical Officers involved in the therapeutic management of anticoagulation medications for both perioperative and bleeding patients.

For information on the identification of patients in need of Venous Thromboembolism (VTE) Prevention, and the appropriate use of prophylactic measures, follow the *Venous Thromboembolism (VTE) Prevention Procedure* located on the CHS Policy and Guidance Documents Register.

Exclusions:

* Patients admitted to the University of Canberra Hospital are out of scope for this procedure.
* Patients under 16 years of age are out of scope for this procedure.

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| Section 1 – Anticoagulation Decisions |

When deciding to use anticoagulation medications for a patient, the Medical Officer is responsible for determining the indication, evaluating the risk of treatment and documenting both in the clinical record. The decision to prescribe should be based on a risk assessment of the patient’s risk of clotting versus bleeding. The use of risk stratification tools in atrial fibrillation (AF), such as the Congestive heart failure, Hypertension Age (CHA2DS2-VASc[1](#_ENREF_1),[2](#_ENREF_2)) and Hypertension Abnormal renal and liver function (HAS-BLED) 15 score, are strongly encouraged.

Decisions regarding anticoagulation should be made in conjunction with the patient, being mindful of patient preferences in addition to the medical indications and contraindications. Where there is a strong indication for anticoagulation (e.g. acute VTE, high risk AF) but a decision is made to withhold anticoagulation, this should also be adequately documented in the patient’s clinical record, and the inpatient medication chart (or Electronic Medicines Management system (EMM) if applicable).

**Table 1** **Anticoagulation Choices** (below) may be used to guide anticoagulation choices. Further information is available under specific parts of this document and within prescribing information.

| **Drug** | **Mechanism of action** | **Reversibility** | **Main indications** | **Contraindications** | **Monitoring** |
| --- | --- | --- | --- | --- | --- |
| Heparin | Indirect inhibitor of factor Xa (FXa) and thrombin via antithrombin | Yes.  Short half-life.  Ceasing infusion usually adequate. Protamine may be used. | Short term anticoagulation where there is a need for the ability to cease quickly (high bleeding risk/perioperative)  Extracorporeal and procedural anticoagulation  VTE prophylaxis | Heparin induced thrombocytopenia (HIT) | Activated partial thromboplastin time (APTT) |
| Low molecular weight heparin | Indirect inhibitor of FXa via antithrombin | Partially reversible with Protamine. | Initiation of therapeutic anticoagulation  VTE prophylaxis  VTE treatment in patients with active malignancy  VTE prophylaxis and treatment in pregnancy | HIT  Not recommended in severe renal failure  Dose reduction required in moderate renal impairment | Usually not required.  Consider specific anti-Xa levels in renal impairment and extremes of body weight |
| Danaparoid | Indirect inhibitor of FXa via antithrombin | Cease infusion (elimination half-life 10 hours) | HIT | Caution in renal impairment due to prolonged half-life – 24 hours | Anti-Xa levels |
| Warfarin | Inhibition of production of vitamin K dependent clotting factors prothrombin, FVII, FIX, FX | Phytomenadione (Vitamin K), prothrombin complex concentrate | Long term anticoagulation is preferred where there is renal impairment or issues with compliance. | Pregnancy | INR |
| Rivaroxaban | Direct inhibition of FXa | No | Treatment and prevention of VTE  Stroke prophylaxis in non-valvular AF | Pregnancy  Renal impairment (Creatinine Clearance (CrCl) estimated by Cockcroft Gault equation <15mL/min)  Liver disease (Childs-Pugh >B) | Usually not required  Specific anti-Xa levels available |
| Apixaban | Direct inhibition of FXa | No | Treatment and prevention of VTE  Stroke prophylaxis in non-valvular AF | Pregnancy  Renal impairment (CrCl estimated by Cockcroft Gault equation <25mL/min)  Liver disease (Childs-Pugh >B) | Usually not required.  Specific anti-Xa levels available. |
| Dabigatran | Direct inhibition of thrombin | Idarucizumab (approval from haematologist mandatory) | Treatment and prevention of VTE  Stroke prophylaxis in non-valvular AF | Pregnancy  Renal impairment (CrCl estimated by Cockcroft Gault equation <30mL/min)  Liver disease with coagulopathy | Usually not required.  Dilute thrombin time available.  Consider in renal impairment with CrCl estimated 30-40mL/min |

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| Section 2 – Initiation and Management of Heparin |

1. **Indication**

* Due to the short half-life of heparin, it is useful for providing therapeutic anticoagulation in a patient where there is a concern regarding potential for bleeding.
* Treatment of acute VTE in the medically unstable patient or in those patients for whom surgery is imminent.
* Prevention of arterial thromboembolism in medically unstable patients with cardiac arrhythmias and/or presumed embolic stroke.
* Perioperative anticoagulation in patients with prosthetic heart valves.

1. **Contraindications**

* Not be administered via the intramuscular route.
* Known hypersensitivity to heparin, including heparin induced thrombotic thrombocytopenia.
* Severe thrombocytopenia.
* Patients for whom suitable blood coagulation tests cannot be performed at appropriate intervals.
* Patients who are in an uncontrollable active bleeding state.

1. **Precautions**

* Gastric or duodenal ulcers, continuous tube drainage of the stomach or small intestine.
* Subacute bacterial endocarditis.
* Severe hypertension.
* During and immediately after spinal tap, anaesthesia or major surgery especially eye, brain or spinal cord.
* Increased bleeding tendency e.g. haemophilia.
* Liver disease, renal disease (potential causes of acquired coagulopathy or uraemic platelet dysfunction).

1. **Presentation**

* Heparin pre-mix bag: Heparin 25,000 units in 250mL sodium chloride 0.9% (concentration = 100 units/mL).

1. **Location Stored**

* Imprest locations and main Pharmacy.

1. **Prescribing**

* It is the responsibility of the prescriber to check the patient’s baseline Activated Partial thromboplastin time (APTT) and full blood count (FBC) and to seek senior advice if abnormal.
* Assess each patient for risk factors associated with bleeding complications from anticoagulant therapy. Table 3 outlines some risk factors for bleeding complications. Seek guidance if unsure.
* The patient’s weight must be ascertained either by physically weighing them, or if not possible, by accurate estimation.
* The prescriber must fill in the Heparin Infusion Baseline Information box (which includes patient weight, the indication for treatment, baseline platelets and APTT and target APTT ratio and range (seconds)) on the Heparin Intravenous Infusion Order and Administration Chart – Adult
* All intravenous heparin prescriptions (including loading doses, rate changes based on APTT results, additional bolus doses and pausing infusions) must be prescribed on the Heparin Intravenous Infusion Order and Administration Chart – Adult in the Heparin Ordering Section

1. **Preparation**

* Standard pre-mix bags must be used for all intravenous heparin infusions. Premix bags are available as: 25,000 units in 250mL sodium chloride 0.9% (concentration = 100 units/mL).
* Pre-mix bag changes are recorded by two nurses on the Heparin Intravenous Infusion Order and Administration Chart – Adult pre-mix bag set up section.

1. **Line Requirements**

* Patients will require a dedicated line for heparin infusions.
* The infusion must not be stopped or interrupted for other medications.
* APTT blood samples should be drawn from the contra-lateral arm if possible, or if a double-lumen line, from the lumen that does not have heparin running.
* If no other peripheral or arterial line assay draw site is available, collecting the APTT sample from a double-lumen line may be performed using the following procedure:
  + Stop heparin
  + Flush both lumens with 20ml 0.9% NaCl each
  + Wait 5 minutes
  + Aspirate and discard 10ml of blood from lumen (not infusing heparin)
  + Collect specimen (from lumen not infusing heparin)
  + Flush lumen with 20ml 0.9% NaCl (in lumen not infusing heparin)
  + Restart heparin in lumen that was infusing heparin

1. **Administration**

* Administration of heparin infusion must be co-signed by two nurses on the Heparin Intravenous Infusion Order and Administration Chart – Adult in the Heparin Administration section. This includes co-signing for administration of loading doses, rate changes based on APTT results, additional bolus doses and pausing infusions.
* A loading dose is administered from the standard bag using the bolus function in the Braun infusion pump. Refer to Table 2 – Heparin Administration for further information on how to do this.
* Pre-mix bag changes are also recorded by two nurses on the Heparin Intravenous Infusion Order and Administration Chart – Adult pre-mix bag set up section.

**Table 2 – Heparin Administration** – also refer to the Heparin Intravenous Infusion Order and Administration Chart.

|  |  |  |
| --- | --- | --- |
|  | **Loading Dose** | **Continuous Infusion** |
| **Dose** | \*The loading dose may be omitted in patients considered at increased risk for bleeding.    60 to 80kg: 5000 units    <60kg or >80kg: 80units/kg  (= 0.8mL/kg)  **Maximum loading dose 8000 units** | **60 to 80kg:**  After loading dose, initial infusion rate is 1250 units/hr = 12.5 mL/hr’  **<60kg or >80kg:** Commence infusion at a rate  of 18units/kg/hr  (equivalent to 0.18mL/kg/hr)    **Adjust dose according to APTT nomogram** |
| **Preparation** | Use standard heparin pre-mix bag:  25,000 units in 250mL sodium chloride 0.9% = 100 units/mL | Use standard heparin pre-mixbag:  25,000 units in 250mL sodium chloride 0.9% = 100 units/mL |
| **Infusion Pump**  **Settings** | First set B Braun pump to administer heparin as a continuous infusion and press start. (i.e. the VTBI is 250mL)  Once infusion is running use the bolus setting (yellow ‘BOL’ button) to enter the correct number of units to be administered as the loading dose – 5000 units is the default | 60 to 80kg:  The infusion rate in the B Braun pump library defaults to deliver heparin 1250 units/hr = 12.5mL/hr      <60kg or >80kg:  The infusion rate in the B Braun pump library defaults to deliver heparin 1250 units/hr = 12.5mL/hr. Adjust this rate according to prescribed continuous infusion dose. |
| **Administration**  **Time** | 3 to 5 minutes administered via B Braun pump using drug library | Continuous Infusion administered via B Braun pump using drug library |

1. **Titration Required**

The prescriber adjusts the dose and infusion rate of the heparin infusion according to APTT result referring to nomogram provided by Pathology with Coagulation Profile. Subsequent changes to infusion rate are to be prescribed on the Heparin Ordering section of the Heparin Intravenous Infusion Order and Administration Chart – Adult and administered by two nurses in the Heparin Administration section.

**Note:**

Results will differ according to the reagent used by Pathology. Ranges and nomogram may be varied if reagents change.

1. **Incompatibilities**

* Complex: refer to the Australian Injectable Drugs Handbook for a complete up-to-date list or contact the ward pharmacist.

1. **Therapeutic Drug Monitoring**

* Check APTT six hours after commencing infusion, and then as recommended by nomogram, according to APTT.
* Adjust the dose according to APTT referring to nomogram provided with the coagulation profile Pathology report.
* Once in the therapeutic range, APTT should be checked daily as the clinical effect may change depending on antithrombin target and protein binding.
* If APTT ratio is not in the therapeutic range after three consecutive measurements seek Haematology consult.
* Check platelet count three times weekly. If there is an abrupt decrease in platelet count (e.g. 50%), consider Heparin Induced Thrombocytopenia (HIT) (see section 8) and arrange immediate Haematology consult.
* In certain clinical circumstances an APTT may be inaccurate, such as in the presence of a lupus anticoagulant. An alternative is an anti Xa assay.
* A Haematology consult is recommended if APTT prior to anticoagulation is prolonged or if there are any concerns.

1. **Adverse Effects**

* Bleeding - the major adverse event potentially related to standard heparin infusion is bleeding. If a patient on heparin develops bleeding, cease heparin infusion and seek urgent Haematology consult.
* Heparin induced thrombocytopenia (HIT).
* Local irritation.
* Hypersensitivity reactions.

1. **Changing Therapy to or from Therapeutic Enoxaparin**
   1. **Heparin Infusion to therapeutic Enoxaparin:**

If the patient is to be changed from a heparin infusion to therapeutic enoxaparin, the calculated dose of enoxaparin should be administered as soon as the heparin infusion is ceased, assuming the patient is not over-anticoagulated on heparin at the time.

* 1. **Therapeutic Enoxaparin to Heparin Infusion:**
* If the patient is to be changed from therapeutic enoxaparin to a heparin infusion, the heparin infusion should be commenced when the next dose of enoxaparin is due, assuming the patient is not over-anticoagulated at the time. A loading dose of heparin is not generally required when transitioning from therapeutic enoxaparin to therapeutic unfractionated heparin. A loading dose of heparin is generally required when starting therapeutic anticoagulation with unfractionated heparin in an individual previously on prophylactic doses of anticoagulation with enoxaparin.
* If there is uncertainty as to the patient’s coagulation status and/or the patient is over-anticoagulated, Haematology should be consulted before the change occurs.
* Care should be taken to ensure that it is clear which anticoagulant is being ceased, and that the plan for changing from one anticoagulant to the other is communicated to clinical staff to avoid duplication of anticoagulant therapy.

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| Section 3 – Initiation and Management of Warfarin |

Warfarin should be prescribed in the designated area of the National Standard Inpatient Medication Chart or the EMM.

1. **Prior to Commencing Warfarin Therapy**

Ensure the baseline International Normalised Ratio (INR), platelets and liver function tests are within normal range. If abnormalities are detected, seek senior/specialist advice.

1. **Risk Factors for Bleeding Complications of Anticoagulation Therapy**

Assess each patient for risk factors associated with bleeding complications from anticoagulant therapy. Table 3 outlines some risk factors for bleeding complications. Seek guidance if unsure.

**Table 3 - Risk Factors for Bleeding Complications of Anticoagulation Therapy**[**3**](#_ENREF_3)

| **Risk Factor** | **Details** |
| --- | --- |
| Age | >65 years |
| Cardiac | Uncontrolled hypertension |
| Gastrointestinal | History of gastrointestinal haemorrhage, active peptic ulcer, significant liver dysfunction or liver failure |
| Haematologic/Oncologic | Thrombocytopenia (Platelet count < 50x109/L), platelet  dysfunction, coagulation defect, underlying malignancy |
| Neurologic | History of stroke, cognitive or psychological impairment |
| Renal | Renal insufficiency |
| Trauma | Recent trauma, history of falls, major surgery less than 14 days ago |
| Alcohol/impaired nutritional status | Excessive alcohol intake, hypoalbuminaemia |
| Medications | Refer to potential interactions |

1. **Determining the INR Range**

Determine and document on the EMM or the National Standard Inpatient Medication Chart the target INR range for the patient. Table 4 (below) can be used as a guide for standard indications.

**Table 4 - Target INRs for Common Warfarin Indications**[**4**](#_ENREF_4)

| **Target INR** | **Indication for warfarin** |
| --- | --- |
| 2 to 3 | * Prevention of deep vein thrombosis (DVT) * Therapy for DVT or pulmonary embolism (PE) * Prevention of systemic embolism (AF, valvular heart disease, after AMI, tissue heart valves - first three months) |
| 2.5 to 3.5 | Bi-leaflet mechanical heart valve (aortic) |
| 3 to 4.5 | Mechanical prosthetic heart valve (high risk), and high-risk conditions such as Antiphospholipid Syndrome. |

1. **Initiating Warfarin Therapy** 
   1. **Acute DVT or PE:**

Treatment with low molecular weight heparin (LMWH) or unfractionated heparin should overlap with warfarin. Commence warfarin on the same day as the unfractionated heparin or LMWH. The unfractionated heparin or LMWH should be given for a minimum of five days ensuring the INR is in the therapeutic range for at least 48 hours before the heparin is ceased and warfarin continues as monotherapy

* 1. **Post-operative patients:**

Restart with ‘normal’ pre-operative maintenance dose of warfarin. Some patients may require overlap with heparin therapy as outlined above. This will need to be assessed for each individual. Seek specialist advice if unsure.

**Table 5 - Typical Daily Dose of warfarin to Maintain INR 2 - 3**

|  |  |
| --- | --- |
| **Age (years)** | **Warfarin daily dose** |
| < 50 | 6 to 8 milligrams (mg) |
| 50 – 69 | 4 to 6mg |
| >70 | 3mg |

**Note:**

The practice of giving warfarin 10mg on days 1 and 2 (i.e. loading doses) is not recommended. This does not result in more rapid anticoagulation and is more likely to result in poor control of INR. Seek early specialist advice and follow the Warfarin Medication Standing Order.

1. **Adjustment of Warfarin Doses**

Table 6 (below) can be used to *guide* dose adjustment.

**Table 6 – Warfarin Dose Adjustment Guide for Target INR 2 - 3**[**5**](#_ENREF_5)

|  |  |
| --- | --- |
| **INR** | **Recommended Action for Warfarin management** |
| < 1.5 | Increase dose by 30 to 40% (usually 2mg)  Repeat INR 24 to 48 hours |
| 1.6 to 1.9 | Consider increasing warfarin dose by 20 to 25% (usually about 1mg/day) if two consecutive INRs are low |
| 2 to 3 | No change |
| 3.1 to 4.5 | Seek advice from senior medical officer  Repeat INR in 24 hours |
| 4.6 to 5 | Omit warfarin for one night  Repeat INR in 24 hours |
| > 5 | Refer to the section ‘Management of an elevated INR’ in this  document |

1. **INR Monitoring**

* During the induction/initiation phase monitor the INR daily if on therapeutic heparin.
* Note that the full effect of a dose change is not reflected in the INR for two to three days.
* Maintenance therapy: Once the INR is stable and in the therapeutic range, INRs can be measured weekly. The interval can then be gradually increased at the prescriber’s discretion up to every four weeks.

More frequent INR monitoring will be required if there are significant diet changes, inter-current illness or other medication changes have been made.

1. **Medication Interactions**

* Many medicines interact with warfarin. The effects can be unpredictable. Any change in medications suspected to interact with warfarin will require close monitoring of the patient’s INR.
* There are a number of tools available to assist with checking for potential interactions, including [Lexicomp](http://www.uptodate.com/crlsql/interact/frameset.jsp) available through the ACT Health Library. If uncertain phone the Medicines Information Service at the Canberra Hospital (5124 3333) or contact the Pharmacy (5124 2121) for advice.

1. **Patient Education**

All staff involved with patient care should discuss the therapy with the patient or other care providers where possible and these interactions should be documented in the clinical record. This should include but is not limited to; reason for prescribing, importance of INR monitoring, target INR range, side effects and the importance of adhering to dose recommendations. There are patient information booklets available as a separate resource that is routinely provided to patients. Please contact the pharmacy for hard copies of these resources.

1. **Management of Bleeding or an Excessively Elevated INR**

* For non-bleeding patients, specific reversal is often not required, but may be indicated in patients at high risk of bleeding.
* For bleeding patients, general measures should be undertaken as outlined in Section 7.
* Warfarin may be reversed with immediate infusion of prothrombin complex concentrate (PCC) available from the transfusion laboratory. This is a three-factor product (containing prothrombin, FIX and FX). Although it contains no FVII, observational studies report superiority over reversal with fresh frozen plasma (FFP) alone. FVII has a short half-life and there are limited amounts of clotting factors within each unit of FFP. National Guidelines recommend the addition of FFP to Prothrombinex (Prothrombinex-VF) only for life threatening haemorrhage.
* In all cases where warfarin reversal is required, phytomenadione (vitamin K), should be administered to restore the production of coagulation factors. Phytomenadione is available on Imprest in most patient areas.

Table 7 (below) provides *guidance* on warfarin reversal in these circumstances. (Adapted from Tran et al, 2013[4](#_ENREF_4))

**Table 7 - Guidelines for Warfarin Reversal**

| **Clinical Scenario** | **INR** | **Phytomenadione dose** | **FFP/**  **Cryosupernatant** | **Prothrombinex** | **Other Action** | **Next INR** |
| --- | --- | --- | --- | --- | --- | --- |
| No bleeding, recent or urgent surgery | <4.5 | None | None | None | Consider withholding or reducing the dose of Warfarin | As per prescribing Medical Officer request |
| 4.5 to10 | 0.5mg to 1mg IV or 1mg to 2mg PO if high risk of bleeding | None | None | Withhold Warfarin | Within 24 hours |
| >10 | 3mg to 5mg PO or IV | None | 15 to 30units/kg if bleeding risk is high or urgent surgery is required | Withhold Warfarin | 12-24 hours |
| Clinically significant bleeding where warfarin induced coagulopathy is considered a significant contributor | >1.5 with critical organ (life-threatening) bleeding | 5 to 10mg IV | 1 to 2 units | 15 to 50units/kg | Withhold Warfarin. Assess continuously until INR<5 and bleeding stops | 15 minutes after correction |
| >2, with not life-threatening bleeding | 5 to 10mg IV | None | 15 to 50units/kg | Withhold Warfarin | 15 minutes after correction |

1. **Discharge Planning and Ongoing Care**

* Warfarin dosing information will be required for handover on discharge. On discharge, the patient’s General Practitioner (GP) will need to receive copies of INR results and all relevant details of treatment during the initiation phase. It is recommended that a patient’s GP be personally contacted if warfarin has been commenced during hospital admission. If this is not possible, seek assistance from the hospital GP Liaison Office on 5124 4183 and Clinical Support Nurse 5124 7760. Patients may also contact the Discharge Liaison Nurse via switch.
* Prescribers are responsible for ensuring that INR monitoring can be performed one to two days following discharge and/or patients will have an appointment with their GP in the next one to two days if discharging a patient who has not yet established a therapeutic INR range.
* If the patient requires a referral to Community Nursing or Hospital in the Home (HITH), information on INR results during the admission as well as instructions regarding warfarin dosing and management details will be required. If the patient is not self-medicating, medication orders will be required.
* Prescribers providing Rule 3 Exemption Pathology Forms for multiple INRs must personally take on the responsibility for responding to all INRs resulting from that form.

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| Section 4 – Initiation and Management of Low Molecular Weight Heparin (LMWH) |

1. **Prior to Initiation of LMWH**

* Check baseline creatinine clearance, APTT, PT and platelet count.
* Consider the risk of bleeding. The risk of bleeding needs to be weighed against the risk of thromboembolic events. Table 3 may be used as a guide.
* Check the patient’s weight. This should be measured, although an estimate may need to be used in the acute situation if weighing is not practical. If an estimate is used, it should be clearly documented that the dose is based on an estimate, and a weight should be obtained as soon as feasible.

1. **Initiating LMWH**

* Enoxaparin is the preferred LMWH on the CHS Formulary.
* Determine the dose and dosing schedule. For adults, Table 8 summarises standard dosing.
* Chart LMWH on the EMM, preferably in the VTE prophylaxis section of the chart.
* LMWH should be administered prior to Warfarin, when they are being commenced concurrently.

**Table 8 - Enoxaparin Dosing**

| **Dosing Intention** | **Normal dose** | **Severe renal impairment (CrCl<30mL/min)** | **Extreme weight ranges**  **(<50kg or >120kg, or BMI> 40kg/m2)** |
| --- | --- | --- | --- |
| Prophylaxis | 40mg subcutaneously (subcut) once daily | 20mg subcut once daily | Consider 0.5mg/kg subcut twice daily or 0.6mg/kg/day |
| Therapeutic dosing | 1mg/kg subcut twice a day  or  1.5mg/kg subcut once daily | 1mg/kg subcut once daily | 1mg/kg subcut twice daily  or  1.5mg/kg subcut once daily.  For high BMI, dose reduction may be required based on measured anti-Xa levels, aiming for a 4-hour post dose level of 0.5 to 1unit/mL (twice daily dosing) or 0.5 to 1.5units/mL for once daily dosing. |

For use in haemodialysis and other extracorporeal procedures, see specific procedural policies and Medication Standing Order CHS19/128.

**There is no consensus for dose adjustment at the extremes of weight.** LMWH levels are higher in low weight individuals treated with fixed dose prophylaxis regimens. In morbidly obese patients fixed dosing may lead to lower levels. However, in this group weight-based treatment dosing may lead to higher concentrations due to relatively reduced volumes of distribution.

1. **Monitoring**

* There is no need for routine monitoring of LMWH levels in the majority of patients.
* Monitoring may be required in renal impairment, or patients who are obese (BMI ≥30).
* If performing anti-Xa levels to monitor it is essential that the specific anticoagulant and the time of last dose be specified on the Pathology form. Ask Pathology exactly what needs to be specified on the form as levels are unusable when not taken on time, because it is not considered to be clinically urgent.
* HIT is rare with LMWH, however may occur, particularly if there has been recent exposure to unfractionated heparin. A platelet count 7 to 10 days after initiation of therapy is recommended.
* Patient education and training on self-administration must be provided when patients are to remain on therapy beyond the duration of the current admission/attendance.
* While no specific LMWH monitoring is required by patients’ GPs, handover to the GP must include the indication for therapy, expected duration of treatment and any specific follow up arrangements for anticoagulation.

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| Section 5 – Initiation and Management of Direct Acting Oral Anticoagulant (DOAC) |

Direct Acting Oral Anticoagulants (DOACs) are a group of small molecule drugs that directly inhibit enzymatic activity of coagulation factors.

**Prior to Commencing DOACs**

* Baseline Full Blood Count (FBC), Renal function or urea and electrolytes (EUC), liver function test (LFT), prothrombin time (PT) and APTT should be performed and investigated if abnormal.
* A pregnancy test is recommended in women of childbearing age as Direct Acting Oral Anticoagulants are contraindicated in pregnancy
* Patient age and weight should be determined
* Creatinine clearance should be calculated using the COCKCROFT-GAULT equation. (refer to AMH or online calculators such as <https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc>):
  + Mass/weight should be the lowest of the patient’s actual or ideal body weight
* Assess patient’s indication and suitability, including bleeding risk and concurrent medications for potential drug interactions. Table 3 may be used as a guide to assess the risk of bleeding.

1. **Doses and Duration of Treatment**

Table 9 summarises the doses and duration of treatment with DOACs .

**Table 9 - Doses and Duration of Treatment with Direct Acting Oral Anticoagulants**

| **Indication** | **Dabigatran (Pradaxa)** | **Rivaroxaban (Xarelto)** | **Apixaban**  **(Eliquis)** |
| --- | --- | --- | --- |
| Stroke prevention in non-valvular AF with ≥ 1 risk factor | 150mg twice daily indefinitely  110mg twice daily for:   * ages ≥ 75years, * CrCl 30-50mL/min * high bleeding risk | 20mg once daily indefinitely  15mg daily if:   * CrCl 30-50mL/min * and/or   in combination with dual antiplatelet therapy (DAPT)  Rivaroxaban (Xarelto PI has been updated to use in patients with severe renal impairment (CrCl 15-29mL/min) where previously contraindicated below CrCl 30 mL/min). | 5mg twice daily indefinitely  2.5mg twice daily if two of these risk factors:   * age ≥ 80 years * weight ≤ 60kg * creatinine ≥ 133 micromol/L |
| Treatment of DVT | 150mg twice daily for 3 months (with parenteral anticoagulant for at least 5 days prior to starting dabigatran)  110mg twice daily for:   * ages ≥ 75years, * CrCl 30-50mL/min * high bleeding risk | 15mg twice daily for 3 weeks then 20mg once daily.  After 6 months (if extended treatment is needed), 10 or 20 mg once daily. (AMH) | 10mg twice daily for 7 days, then 5mg twice daily.  May reduce dose after 6 months to 2.5 mg twice daily if extended treatment is needed (AMH) |
| Long-term prevention of recurrent DVT and / or PE | 150mg twice daily  110mg twice daily for:   * ages ≥ 75years, * CrCl 30-50mL/min, * high bleeding risk | 10, or20mg once daily | 5mg twice daily  May reduce dose after 6 months to 2.5 mg twice daily if extended treatment is needed. (AMH) |

1. **Special Considerations**

**Table 10 - Special Considerations for use of Direct Acting Oral Anticoagulants**

| **Consideration** | **Dabigatran**  **(Pradaxa)** | **Rivaroxaban (Xarelto)** | **Apixaban (Eliquis)** |
| --- | --- | --- | --- |
| Renal Impairment | Contraindicated if CrCl ≤ 30mL/min.  Use with caution if CrCl 30 to 50mL/min as area under the curve (AUC) plasma drug concentration increased 2.7-fold. Consider therapeutic drug levels within this range. | Contraindicated if CrCl < 15mL/min. (  Administration in renal impairment may be considered in selected patients with careful monitoring.  Dose adjustment to 15mg daily for stroke prevention in AF may be considered if CrCl 30-49mL/min.  No evidence for dose adjustment in VTE treatment in the first six months.  Haematological or renal medicine advice is required. | Contraindicated if CrCl ≤ 25mL/min  Administration in renal impairment may be considered in selected patients with careful monitoring. Haematological or renal medicine advice is strongly recommended. Refer to *Apixaban Use in Adults with Severe Kidney Disease Guideline*. |
| Hepatic Impairment | Child- Pugh A or B – use with caution.  Contraindicated in Child-Pugh C cirrhosis. | Child- Pugh A or B – use with caution.  Contraindicated in Child-Pugh C cirrhosis. | Child- Pugh A or B – use with caution.  Contraindicated in Child-Pugh C cirrhosis. |
| Weight | ≤ 50kg or ≥ 120kg, less than 25% change in plasma drug concentration, no dose adjustment although clinical data on safety and efficacy is lacking – consider non- DOACs). | ≤ 50kg or ≥ 120kg, or BMI over 40kg/m2, less than 25% change in plasma drug concentration, no dose adjustment although clinical data on safety and efficacy is lacking – consider non-DOACs | ≤ 50kg or ≥ 120kg, or BMI over 40kg/m2, less than 25% change in plasma drug concentration, no dose adjustment although clinical data on safety and efficacy is lacking – consider non-DOACs |
| Age | AUC for plasma drug concentration up to 2-fold higher after 65 years, use 110mg twice a day dose after 75 years (recom­mendation based on Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) data - see Reference 5, [Reilly et al 2014](https://www.ncbi.nlm.nih.gov/pubmed/24076487/)) | No dose adjustment for age alone. | No dose adjustment, unless age ≥80 years, **indication AF**, and any or both of weight ≤60kg, or serum creatinine ≥133micromol/L |
| Potential Interactions (common examples only) To check interactions consider an on-line tool (e.g. [Lexicomp](http://www.uptodate.com/crlsql/interact/frameset.jsp)) | P-glycoprotein inhibitors or inducers:  Inhibitors of P-glycoprotein include (but are not limited to) ciclosporin, clarithromycin, erythromycin, itraconazole, ritonavir, ketoconazole, amiodarone, verapamil, and ticagrelor.  Inducers of P-glycoprotein include (but are not limited to) rifampicin and St John’s wort.  The manufacturer contradicts use with glecaprevir with pibrentasvir, and discourages use with tacrolimus (AMH). | P-glycoprotein inhibitors or inducers:  Inhibitors of P-glycoprotein include (but are not limited to) clarithromycin, erythromycin, ritonavir, ketoconazole, amiodarone, verapamil, and ticagrelor.  Inducers of P-glycoprotein include (but are not limited to) rifampicin and St John’s wort.  Medicines that are potent CYP3A4 inhibitors include (but are not limited to) clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, and verapamil.  Medicines that are potent CYP3A4 inducers include (but are not limited to) phenobarbital, phenytoin and rifampicin. | P-glycoprotein inhibitors or inducers:  Inhibitors of P-glycoprotein include (but are not limited to) clarithromycin, erythromycin, ritonavir, ketoconazole, amiodarone, verapamil, and ticagrelor.  Medicines that are potent CYP3A4 inhibitors include (but are not limited to) clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, and verapamil  Medicines that are potent CYP3A4 inducers include (but are not limited to) phenobarbital, phenytoin and rifampicin. |

1. **Monitoring**

* Routine monitoring when using Direct Acting Oral Anticoagulants as either thromboprophylaxis or therapeutic anticoagulants is not required. There may be some circumstances where measurement of the anticoagulant effect may be desirable, such as in emergency surgical planning, especially in renal impairment, and actively bleeding patients. If performing anti-Xa levels to monitor it is essential that the specific anticoagulant and the time of last dose be specified on the Pathology form.
* For patients with a creatinine clearance of 30 to 50mL/min on dabigatran, studies have shown that some patients may have higher plasma concentrations. This may be associated with an increased risk of bleeding without a concurrent reduction in thrombotic risk. These patients may be considered for a lower dose or alternative agent. Measurement of therapeutic levels may be used to guide dosing in this group of patients.

When measurement is considered necessary, haematological advice is recommended. The following assays are recommended:

* Dabigatran – Thrombin time (TT) is sensitive to even small concentrations. Normal results indicate the absence of dabigatran. When there is a need to determine therapeutic levels, a dilute thrombin time (HEMOCLOT ™) is recommended.
* Rivaroxaban and apixaban – Specific anti-Xa assays are used to determine therapeutic levels. The name of the Xa inhibitor taken by the patient must be specified on the Pathology request form as different assays are performed.
* The recommendations for monitoring DOACs are summarised in Table 11.

**Table 11 - Summary of Laboratory Tests and Patterns for Direct Acting Oral Anticoagulants**

|  |  |  |  |
| --- | --- | --- | --- |
| **Test** | **Dabigatran** | **Rivaroxaban** | **Apixaban** |
| Significant anticoagulant effect unlikely | TT and APTT normal | PT normal | Normal PT does not exclude presence of therapeutic apixaban |
| Anticoagulant effect present | TT prolonged  APTT prolonged | PT prolonged or normal | PT prolonged or normal |
| Specific assays to quantify drug presence | Dilute thrombin clotting time assay (HEMOCLOT™ assay) | Modified anti Xa specific for rivaroxaban | Modified anti Xa specific for apixaban |

Direct Acting Oral Anticoagulants may interfere with specialised coagulation assays, including factor levels, natural anticoagulant levels (protein C, S and antithrombin) and lupus anticoagulant.

1. **Bleeding Risk**

All anticoagulants are associated with a risk of bleeding. There are some differences between oral anticoagulants and bleeding risk which may be considered when the decision to prescribe an anticoagulant is made. These are summarised in Table 12.

**Table 12 - Comparison of Bleeding Risk between Warfarin and Direct acting Oral Anticoagulants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Warfarin** | **Dabigatran** | **Rivaroxaban** | **Apixaban** |
| Bleeding Risk | Risk highest in the first 3 months of starting treatment | Compared with warfarin:  Slightly lower risk of bleeding in the brain  Slightly higher risk of bleeding in the gut | Compared with warfarin:  Slightly lower risk of bleeding in the brain  Slightly higher risk of bleeding in the gut | Compared with warfarin:  Slightly lower risk of bleeding in the brain  No difference in bleeding risk in the gut |

1. **Transitioning Between Anticoagulants**

Transition between anticoagulants should be done by a senior medical officer or in consultation with a Haematologist. The requirement for a loading/induction dose (for the treatment of VTE) needs to be assessed individually based on risk versus benefit if the patient is being transitioned from a heparin-based anticoagulation strategy to a Direct Acting Oral Anticoagulant, within the first three weeks of treatment.

* 1. **Conversion between Direct Acting Parenteral Anticoagulants and Parenteral Anticoagulants**

Table 13 (below) summarises the Conversion with Parenteral Anticoagulants.

**Table 13 - Conversion between Parenteral Anticoagulants**

|  |  |
| --- | --- |
| **Clinical scenario** | **Recommended procedure** |
| From continuous IV heparin infusion to DOACs | Commence Direct Acting Oral Anticoagulants immediately when infusion is ceased |
| From LMWH to DOACs | Commence Direct Acting Oral Anticoagulants when the next LMWH dose would have been due (12-24 hours after the final LMWH dose) |
| From rivaroxaban or apixaban to unfractionated heparin (UFH) or LMWH | Start UFH or LMWH 12 hours after the last dose (if previously on a twice daily dosing regimen) or 24 hours after the last dose (if previously on a once daily regimen).  No loading dose of UFH is required when starting infusion, commence directly with maintenance rate. |
| From dabigatran to UFH or LMWH | CrCl ≥ 30mL/min: wait 12 hours (for AF, VTE) or 24 hours (for VTE prophylaxis post THR or TKR) |

* 1. **Conversion from Warfarin to Direct Acting Oral Anticoagulants**

**Warfarin to DOACs**

Direct Acting Oral Anticoagulants may be preferred by patients as routine blood tests are not required and there are less interactions with other medicines and food. However patients who are anticoagulated with warfarin do not necessarily need to change treatment, especially if their anticoagulation has been stable. If patients choose to transition to a Direct Acting Oral Anticoagulant, the following steps can be followed:

* discontinue warfarin.
* Measure INR.
* If the INR is ≤2.5, commence Direct Acting Oral Anticoagulant.
* If the INR is >2.5, then measure INR in 1 to 2 days and commence Direct Acting Oral Anticoagulant when INR≤2.5.

**Conversion from Direct Acting Oral Anticoagulants to Warfarin**

When switching from a Direct Acting Oral Anticoagulant to warfarin, it is necessary to consider the (see Table 14 below):

* elimination half-life of the Direct Acting Oral Anticoagulant which will be influenced by the patient’s renal function
* delay in onset of action of warfarin
* INR reading which is affected by both Direct Acting Oral Anticoagulant and warfarin. If maintaining anticoagulation is critical, switching from Direct Acting Oral Anticoagulant to enoxaparin before starting warfarin may be preferable.

**Table 14 - Suggested Conversion Strategies from DOAC to Warfarin**

|  |  |  |
| --- | --- | --- |
| **Creatinine Clearance** | **Rivaroxaban or Apixaban** | **Dabigatran** |
| Greater than 50mL/min | Stop rivaroxaban or apixaban 4 days after starting warfarin | Stop dabigatran 3 days after starting warfarin |
| 31 to 50mL/min | Stop rivaroxaban or apixaban 3 days after starting warfarin | Stop dabigatran 2 days after stating warfarin |
| 15 to 30mL/min | Stop rivaroxaban or apixaban 2 days after starting warfarin | Stop dabigatran 1 day after starting warfarin |

* Start with a warfarin dose of 5mg or less.
* The first INR should be measured on day 3 after warfarin initiation, with the aim to identify high levels thereby maintaining caution with ongoing warfarin dosing.
* Point of Care INR should not be used to assess the INR during transition period as Direct Acting Oral Anticoagulants may impact INR estimation more unpredictably.
* Stop the Direct Acting Oral Anticoagulant once INR is ≥ 2 on 2 consecutive days considering the effect of Direct Acting Oral Anticoagulant on INR.

1. **Managing Bleeding on Direct Acting Oral Anticoagulants**

The general principles for managing bleeding are described in Figure 1 (below), and include:

* Drug discontinuation – Anticoagulants should be ceased in anyone presenting with significant bleeding. The timing of recommencement will depend on the severity of bleeding, ongoing risk factors (e.g. poor renal function, anatomical lesions), and the initial indication for anticoagulation.
* Baseline laboratory assessment – Baseline assessment of haemoglobin should be done to assess severity of bleeding. Coagulation studies including PT, APTT and TT and where available specific drug levels should be performed to assess effect of drug on the coagulation system and to guide the need for intervention should be done. Assessment of renal function as calculated by Creatinine Clearance will help predict drug clearance.
* General supportive measures – Surgical, endoscopic and radiological procedures to identify source and limit bleeding should be performed considering procedure related bleeding risk in an anticoagulated patient. Adequate hydration to enhance clearance of rivaroxaban and dabigatran should be maintained. Platelet transfusion may be considered in actively bleeding patients on concurrent anti-platelet therapy or if platelets are ≤ 50 x 109.
* Activated charcoal – This should be considered in patients with moderate to severe bleeding who present within two hours of last Direct Oral Anticoagulant dose.
* Administration of haemostatic agents – Current evidence on the use of pro-haemostatic agents in patients with dabigatran or rivaroxaban is limited. There is no published data on apixaban reversal currently. The risk and benefit of administration of haemostatic agents should be assessed in each individual patient. Until further information is available it is reasonable to consider their use in patients with life- or limb-threatening bleeding. The activated prothrombin complex concentrate Factor Eight Inhibitor Bypassing Activity (FEIBA™) and prothrombin complex concentrates (PCC) have been shown to reduce bleeding in animal models with variable effect on coagulation parameters in animals and healthy volunteers. Results with Recombinant factor VIIa (rFVIIa) are less consistent. Note that while PCC is stocked in the transfusion laboratory, FEIBA may not be available. Consultation with a haematologist is required.
* For patients on dabigatran presenting with severe, life threatening bleeding, or requiring surgery for a life-threatening problem, specific reversal with idarucizumab should be considered. It is essential that bloods are taken for PT, APTT, TCT and dilute thrombin time prior to administration of idarucizumab, however if there is life threatening bleeding and the last dose is likely to have been within a time frame where significant drug activity is still likely to be present, the dose does not need to be delayed waiting for results. Approval by a haematologist is mandatory and early consultation is advised. Idarucizumab is stored in main Pharmacy and in the transfusion laboratory who can be contacted through the main switchboard . The usual dose is 5g (2 x 2.5g vials) intravenously over 5-10 minutes (as a bolus or two consecutive infusions). Further dosing (beyond 5g) is not usually required, however repeat coagulation testing following the dose is recommended to evaluate coagulopathy.

**Note**:

There are currently **NO** available strategies for immediate reversal of apixaban or rivaroxaban (Direct Acting Oral Xa inhibitors).

**Figure 1: Management of Direct Acting Oral Anticoagulant Associated Bleeding**



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| Section 6 – Management of Bleeding in Anticoagulated Patients |

As bleeding in anticoagulated patients can be excessive, specific measures to arrest bleeding (surgical, angiographic or endoscopic) should be undertaken as soon as possible.

1. **Consider Reversal of Anticoagulants Where Possible:**

* Warfarin reversal should be managed as per Section 3 with phytomenadione (vitamin K) and prothrombin complex concentrates (PCC). PCC is available from the transfusion laboratory.
* Heparin has a short half-life and, in most cases, ceasing heparin infusion will enable rapid reversal (over approximately four hours). If more immediate heparin reversal is required, protamine may be given at a dose of 1mg for every 100 units of heparin to be neutralised over 10 minutes. Protamine must be given with caution. Sudden hypotension and anaphylaxis may be seen. The maximum is 50mg per dose. Excessive dosing may exert an anticoagulant effect.
* LMWH are not fully reversible. In the event of bleeding after a recent dose of LMWH, partial reversal of LMWH with protamine may be indicated. A dose of protamine 1mg for every 1mg of enoxaparin (if given in the previous eight hours) should be given.
* Patients on dabigatran with severe or life-threatening bleeding may benefit from reversal with idarucizumab. There is no specific reversal agent for oral Xa inhibitors. Specific advice for bleeding patients on Direct Acting Oral anticoagulants is found in Section 5.
* Anticoagulation and their reversal agents are currently under various phases of development and clinical evaluation. This is a rapidly evolving area and specific antidotes for oral Xa inhibitors may be available in the near future. Consult with Haematology for current advice if clinically relevant. Andexanet alfa, which is a universal anti-Xa inhibitor reversal agent, received US FDA accelerated approval in May 2018.

1. **Over-Anticoagulation with Warfarin**

Where over-anticoagulation is contributing to bleeding (for example, INR>6), the risk of thromboembolism is high, and the bleeding is not life threatening, partial reversal may be considered. In all other cases, complete warfarin reversal is recommended, recommencing anticoagulation once haemostasis has been obtained. See table 7 for advice on warfarin reversal.

1. **Supportive Care**

General supportive care, including fluid resuscitation, blood transfusion and inotropic support should be provided.

1. **Coagulation Support**

Coagulation support with FFP and platelet transfusion may need to be considered, especially in the event of massive transfusion or concurrent use of antiplatelet agents. While the administration of FFP and cryoprecipitate is usually directed by the results of coagulation studies, these may be prolonged, and not reversible, with the use of DOACs. Haematology advice should be sought.

1. **Maintaining Haemostasis**

Consider activation of the *Critical Bleeding Massive Transfusion - Adults Procedure* if haemostasis cannot be adequately maintained.

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| Section 7 – Perioperative Management of Anticoagulation |

In the perioperative setting it is important to establish the risks of bleeding and thromboembolism as well as weigh the risk versus benefit of ceasing anticoagulation.

Assessment of all patients on anticoagulation with planned surgery should occur in the preadmission clinic, or for inpatients as soon as the need for surgery becomes apparent. Assessment should occur using the following process, documented in the patients’ medical record. Please see Attachment 1, Perioperative Anticoagulation Guidelines:

1. Determine if anticoagulant needs to be stopped. Many minor procedures may be performed in patients on anticoagulation.
2. Consider delaying surgery. For patients with recent thromboembolic events or on short courses of anticoagulation, there may be value in delaying surgery to minimise the risk.
3. Assess the surgical bleeding risk.
4. Determine the time to cease anticoagulation, if required.
5. Determine whether bridging anticoagulation is required.
6. Determine the type and dose of bridging anticoagulation, if required.
7. Recommence anticoagulation post operatively.

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| Section 8 – Diagnosis and Management of Heparin Induced Thrombocytopenia (HIT) |

1. **Consider Heparin Induced Thrombocytopenia**

HIT should be considered if the platelet count begins to drop 5 to 10 days after exposure to heparin. Note it can occur more rapidly (24 hours) in someone exposed to heparin in the preceding 100 days. LMWH can cause HIT, however this is very rare. Other potential causes of thrombocytopenia need to be considered. The “4Ts” score is a useful pre-test probability scoring system to estimate the likelihood of HIT (see Table 14).

**Table 14 - The “4Ts” Score**

| **Points** | **0** | **1** | **2** |
| --- | --- | --- | --- |
| Timing of platelet count fall | Platelet count fall < 5 days without recent heparin exposure | Consistent with fall at 5 to 10 days but not clear (missing platelet count) or onset > day 10 or fall ≤ to 1 day with prior heparin exposure within past 30 to 100 days | Clear onset at days 5 to 10, or ≤ 1 day if prior heparin exposure within 30 days |
| Thrombocytopenia | Platelet count fall  < 30%  or nadir < 10 x 109/L | Platelet count fall 30 to 50% or  nadir 10 to 19 x 109/L | Platelet count fall  > 50% and nadir > 20 x 109/L |
| Thrombosis or other sequelae | None | Suspected thrombosis, but not proven, or non-necrotising skin lesions | Confirmed new thrombosis, skin necrosis, or acute systemic reaction following administration of IV unfractionated heparin bolus |
| Other causes of Thrombocytopenia present | Definite | Possible | None apparent |
| Pre-test probability score: | | 6-8: High probability of HIT  4-5: Intermediate probability  0-3: Low probability | |

1. **Laboratory Diagnosis**

If HIT is suspected the Haematology Service should be contacted. HIT screening tests should be ordered by the Medical Officer. False positive HIT screening tests can occur in a variety of clinical situations. The diagnosis of HIT requires interpretation of both clinical and laboratory results. Specialised assays may not be readily available, and patients may need to be pre-emptively treated for HIT prior to results being available.

1. **Management**

* Cease all heparin products, including LMWH and heparinised saline used to flush venous catheters and locks for line patency.
* Consult a haematologist for assistance with performing a 4Ts score. If the 4Ts score results in a low probability, heparin products may be resumed cautiously with careful monitoring of FBC daily, and clinical review for thrombosis. If the 4Ts score results in an intermediate or high probability of HIT, then discuss with haematology regarding alternative anticoagulants while awaiting results of screening tests. If screening tests are positive, then confirmatory functional testing will usually be recommended.
* Anticoagulation with danaparoid, fondaparinux, argatroban (Food and Drug Administration (FDA) listed, bivalirudin (FDA listed), or Direct Acting Oral Anticoagulants **must** be commenced due to the significantly increased risk of life and limb-threatening thrombosis. Anticoagulant therapy can be switched to warfarin after the initial phase of platelet activation has resolved, as often determined by resolution of thrombocytopenia.
* Submit Adverse Drug Reaction Report. This ensures that the patient’s file includes an adverse drug reaction alert regarding the reaction to prevent further exposure to heparin.

1. **Danaparoid Use in Patients with HIT**[**6**](#_ENREF_6)

Presentation

Danaparoid solution for injection is presented as 750 units of anti-factor Xa activity/0.6mL ampoules.

* 1. Therapeutic Anticoagulation is achieved with a loading dose of danaparoid followed by an ongoing IV danaparoid infusion.

Patients with renal failure receiving dialysis are to be prescribed intermittent IV boluses instead of a continuous IV infusion as set out below.

* + 1. Bolus dose for patients with adequate renal function. Draw up required loading dose according to patient’s weight and give as an intravenous bolus.

Table 15 gives dose adjustment for danaparoid IV bolus according to body weight.

**Table 15 – Danaparoid IV Bolus Loading Dose According to Body Weight**

|  |  |
| --- | --- |
| **Body Weight** | **Danaparoid Dose (rounded to nearest full ampoule danaparoid 750 units/0.6mL)** |
| < 60kg | 1500 units |
| 60 to less than 75kg | 2250 units |
| 75 to 90kg | 3000 units |
| > 90 kg | 3750 units |

* + 1. Continuous IV infusion

Draw up 3 ampoules of 750 units/0.6mL (2250 units) and add to 250mL of 5% glucose (final concentration 9 units/mL)

The bolus loading dose of danaparoid should be followed by a danaparoid infusion of 400units/hour (44.4mL/hour) for four hours, then 300units/hour (33.3mL/hour) for four hours, and then 200units/hour (22.2mL/hour).

As the plasma half-life of danaparoid is prolonged (approximately 25 hours), the first anti-Xa level should be taken approximately 24 hours after initial commencement of danaparoid, and then subsequently daily.

Subsequent danaparoid dose adjustments should be made to keep anti-Xa activity therapeutic between 0.5 to 0.8 units/mL.

Suggested algorithm for adjustment of IV infusion:

|  |  |  |  |
| --- | --- | --- | --- |
| Anti-Xa level (units/mL) | Dose adjustment | Calculation | Action |
| <0.5 | Increase infusion rate by 20% | New rate x 1.2 | Monitor anti-Xa every 24 hours |
| 0.5-0.8 | No change | No change | Monitor anti-Xa every 24 hours |
| 0.8-1.0 | Decrease infusion rate by 20% | New rate x 0.8 | Monitor anti-Xa every 24 hours |
| >1.0 | Decrease infusion rate by 50% | New rate x 0.5 | Monitor anti-Xa every 24 hours |

In some treatment settings, it may be advisable to aim for a lower anti-Xa level (e.g. 0.3 units/mL) for a patient with a high risk of bleeding. A higher anti-Xa level may be sought (e.g. 0.8-1.0 units/mL) for a patient with life or limb threatening venous or arterial thrombosis, or extra corporeal circulation clotting during continuous renal replacement therapy (CRRT), provided that bleeding is not a problem.

Consider alternative anticoagulant if CrCl< 30mL/min, especially if there is an increased bleeding risk. The elimination half life is significantly prolonged and the drug will accumulate. Monitoring of anti Xa level and suitable dose reduction is required. Consider reduction of the loading dose and maintenance dose by approximately one third in a patient with CrCl <30mL/min if there is a risk of bleeding and the patient does not have acute thrombosis.

* 1. Maintenance phase of therapeutic anticoagulation

After initial full anticoagulation with IV danaparoid, and evidence of successful treatment of HIT with a normal platelet count, falling/normal d-dimers and no clinical evidence of new thrombosis, de-escalation to a subcutaneous danaparoid can be considered after 4 to 5 days particularly if the patient is well enough for discharge. Once there is clinical stability with no evidence of thrombosis or bleeding, oral alternatives could be considered including DOAC and warfarin. If selecting warfarin, overlap with parenteral anticoagulation is generally advised for at least 5 days, and until the INR is therapeutic. Avoid high loading doses of warfarin > 5mg.

**Table 16 – Danaparoid Maintenance Dose According to Body Weight**

|  |  |
| --- | --- |
| **Body Weight** | **Danaparoid Dose** |
| < 55kg | 1500 units SUBCUT twice daily |
| 55 – 90kg | 2250 units SUBCUT twice daily |
| > 90kg | 1500 units SUBCUT three times daily |

* 1. Prophylactic anticoagulation with danaparoid

Prophylactic anticoagulation is sometimes necessary for patients after their initial treatment for HIT, but will be required for subsequent prolonged hospitalisation and/or immobility as they should not be exposed to heparin again. If patients may require urgent surgery, the treating team may elect to avoid warfarin and to continue prophylaxis with danaparoid 750 units SUBCUT twice daily

The total daily dose of danaparoid should be reduced by 25 to 50% in patients with severe renal impairment i.e. CrCl <30 mL/minute.

1. **Therapeutic Anticoagulation with danaparoid in Renal Replacement Therapy** 
   1. Dialysis every other day or less frequently
      * + Danaparoid 3750 units intravenous bolus before first two occasions of haemodialysis **then** dosing varies according to pre-dialysis plasma anti-factor Xa activity
        + Danaparoid 3000 units IV bolus (if pre-dialysis plasma anti-factor Xa levels <0.3 units/mL)
        + **or** danaparoid 2500 units IV bolus (if pre-dialysis plasma anti-factor Xa levels 0.3-0.35 units/mL)
        + **or** danaparoid 2000 units IV bolus (If pre-dialysis plasma anti-factor Xa levels 0.35-0.4 units/mL).

*If patient < 55kg:*

* + - Danaparoid 2500 units IV bolus before first two occasions of haemodialysis **then** dosing varies according to pre-dialysis plasma anti-factor Xa activity
* danaparoid 2000 units IV bolus (if pre-dialysis plasma anti-factor Xa levels <0.3 units/mL)
  + - **or** danaparoid 1500 units IV bolus (if pre-dialysis plasma anti-factor Xa levels 0.3-0.35 units/mL)
    - **or** danaparoid1500 units IV bolus (If pre-dialysis plasma anti-factor Xa levels 0.35-0.4 unit/mL).
  1. For Daily Dialysis:
* Danaparoid 3,750 units IV bolus before first dialysis then
* Danaparoid 2,500 units before the second dialysis.

*If patient < 55kg*

* Danaparoid 2,500 units IV bolus before first dialysis then
* Danaparoid 2,000 units before the second dialysis.
* Aim for plasma anti-Xa level of < 0.3 units/mL **pre-dialysis** and 0.5 – 0.8 units/mL **during dialysis**.

1. **Locking parenteral lines in patients with HIT**

Sodium chloride 0.9% or citrate 4%.

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| Section 9 – Anticoagulation in Pregnancy |

Warfarin is a known teratogen, especially during the first trimester. The use of direct acting oral anticoagulants is contraindicated during pregnancy. The management of anticoagulation in pregnancy will need to be individualised for each woman, based on their willingness to accept risk and inconvenience, given the paucity of data in this setting.

1. **Prior to Pregnancy**

* The need for anticoagulation should be reviewed prior to pregnancy.
* Women on long term anticoagulation should have a plan for anticoagulation developed in consultation with their treating specialist (cardiologist/haematologist, etc.) and/or foetal medicine specialist.
* Women attempting pregnancy should be advised to have frequent pregnancy tests and switch from warfarin as soon as pregnancy is confirmed. This approach is safe, provided warfarin is ceased in early pregnancy (within six weeks of last menstrual period).
* For women who have a desire to avoid warfarin at all in pregnancy, and who are willing to accept the inconvenience of subcutaneous injections, switching to LMWH while attempting pregnancy may be considered. Given the paucity of data with LMWH in high risk heart valves, warfarin therapy may still be preferred for these women.
* For women on long term direct acting oral anticoagulants, the potential for harm to the foetus in early gestation remains unknown. Consideration should be given to pre-emptive conversion to LMWH when attempting to conceive. Frequent pregnancy testing and switching to LMWH may also be considered.

1. **During Pregnancy**

* Thromboprophylaxis is indicated during pregnancy in women with:
* Antiphospholipid Syndrome, including recurrent miscarriages, unexplained foetal death (after 10 weeks gestation), with prophylactic LMWH and aspirin
* prior idiopathic or oestrogen-associated (pregnancy, oral contraceptive pill associated) VTE
* high risk thrombophilia (homozygous FV Leiden, antithrombin deficiency, multiple thrombophilia) with a family history of thrombosis. Some guidelines recommend therapeutic anticoagulation in women with AT deficiency and a positive family history.
* Women with a prior history of a single VTE associated with a transient risk factor (other than hormonal, for example, surgery) do not require VTE prophylaxis during pregnancy, but should be vigilant for symptoms of VTE.
* VTE during pregnancy should be initially treated with therapeutic LMWH during pregnancy, and for at least six weeks post-partum, for a total duration of therapy of at least three months.
* For women requiring long term anticoagulation, LMWH in a therapeutic dose should be continued throughout pregnancy, using a once daily or twice daily regimen. Increasing weight and increased renal clearance may affect therapeutic enoxaparin levels and dosing adjustments may be considered if subtherapeutic anti-Xa levels are confirmed – these levels should be taken four hours post dose (follow standard reference range supplied by ACT Pathology).
* Mechanical heart valves require anticoagulation to be maintained throughout pregnancy. This is a complex issue and early haematology and obstetric consultation should be sought. Ideally, pre-pregnancy planning should occur for all women with mechanical heart valves.
* Consultation with a specialist for further advice is recommended in women requiring continuous anticoagulation during pregnancy.

1. **Peri partum**

* All women requiring anticoagulation during pregnancy require a plan to manage delivery.
* In general, it is preferable to induce delivery electively if receiving doses of enoxaparin greater than 40mg SC daily so that an anticoagulation management can be planned.
* Women on warfarin in the second and third trimesters for mechanical heart valves will need bridging anticoagulation. Women using LMWH can have it simply withheld the night before induction or planned delivery to enable delivery with minimal anticoagulant effect. For guidance on withholding or bridging anticoagulation see Section 6 on perioperative anticoagulation.
* Women requiring prophylactic or therapeutic anticoagulation during pregnancy should have anticoagulation recommenced once bleeding is controlled. Dosing should adapt to the changing weight of the patient throughout pregnancy, and if concerned, anti-Xa levels can be performed four hours post dose.

1. **Postpartum**

* The postpartum period carries a higher risk of VTE.
* Prophylactic anticoagulation should be considered in women at high risk of VTE. Follow the *Venous Thromboembolism (VTE) Prevention Procedure*. Risks include:
* prolonged bed rest in the ante partum period.
* excessive blood loss (>1000mL) with surgery.
* blood transfusion.
* concurrent medical conditions including Systematic Lupus Erythematosus SLE, heart disease, sickle cell disease.
* postpartum infection.
* high risk thrombophilia (antithrombin deficiency, homozygous FV Leiden or prothrombin mutations, combined thrombophilic conditions).
* Prophylaxis should also be considered in women who have any two of the following:
* BMI>30kg/m2.
* post-partum haemorrhage >1000mL.
* smoking.
* any thrombophilia.
* pre-eclampsia.
* foetal growth restriction
* Extended prophylaxis for 6 weeks is advised in all women requiring prophylaxis during pregnancy and may be considered for selected women with multiple risk factors.
* Women on long term warfarin therapy may have this reintroduced after delivery. Breast feeding is not a contraindication to warfarin.

Direct acting oral anticoagulants should not be commenced or recommenced in breast feeding women.

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| Evaluation |

**Outcome**

Patients requiring anticoagulation therapy are managed as per this procedure.

**Measures**

Monitoring and reporting will include annual anticoagulation audit including:

* Major bleeding and clinically relevant non-major bleeding events in patients receiving therapeutic anticoagulation
* Proportion of results that are in therapeutic range in patients receiving warfarin

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| Related Policies, Procedures, Guidelines and Legislation |

**Policies**

* Informed Consent- Clinical
* Medication Handling

**Procedures**

* Venous Thromboembolism (VTE) Prevention
* Critical Bleeding Massive Transfusion - Adults
* Fresh Blood Product Administration Adults, Paediatrics and Neonates
* Infection Prevention Control
* Haemodialysis for Adults
* Patient Identification and Procedure Matching

**Guidelines**

* Access for Renal Replacement Therapy
* Antepartum Haemorrhage APH
* Apixaban Use in Adults with Severe Kidney Disease

**Legislation**

* *Health Records (Privacy and Access) Act* 1997
* *Human Rights Act* 2004
* *Work Health and Safety Act* 2011

**Other**

* Australian Charter of Healthcare Rights

**Medication Standing Orders**

* Warfarin

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| Definition of Terms |

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| **Abbreviation** | **Terminology** |
| APTT | Activated partial thromboplastin time |
| INR | International normalised ratio |
| VTE | Venous thromboembolism |
| DOAC | Direct Acting Oral Anticoagulant |
| LMWH | Low molecular weight heparin |
| PT | Prothrombin time |
| FBC | Full Blood Count |
| HIT | Heparin Induced Thrombocytopenia |
| AF | Atrial Fibrillation |
| TT | Thrombin time (also called Thrombin clotting time) |
| PCC | prothrombin complex concentrates |
| BMI | Body Mass Index |
| HITTS | Heparin induced thrombosis-thrombocytopenia syndrome |
| non-valvular AF | Non-valvular atrial fibrillation (Patients with atrial fibrillation without valvular heart disease or a prosthetic heart valve. |

Definition of clinician within the VTE Prevention Clinical Standard -

<https://www.safetyandquality.gov.au/sites/default/files/2020-01/venous_thromboembolism_prevention_clinical_care_standard_-_jan_2020_2.pdf>

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| Search Terms |

Venous Thrombosis, Pulmonary embolism, Venous thromboembolism, Anticoagulation, Heparin, Warfarin, Rivaroxaban, Apixaban, Dabigatran, Danaparoid

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| Attachments |

Attachment 1: Perioperative Anticoagulation Guidelines

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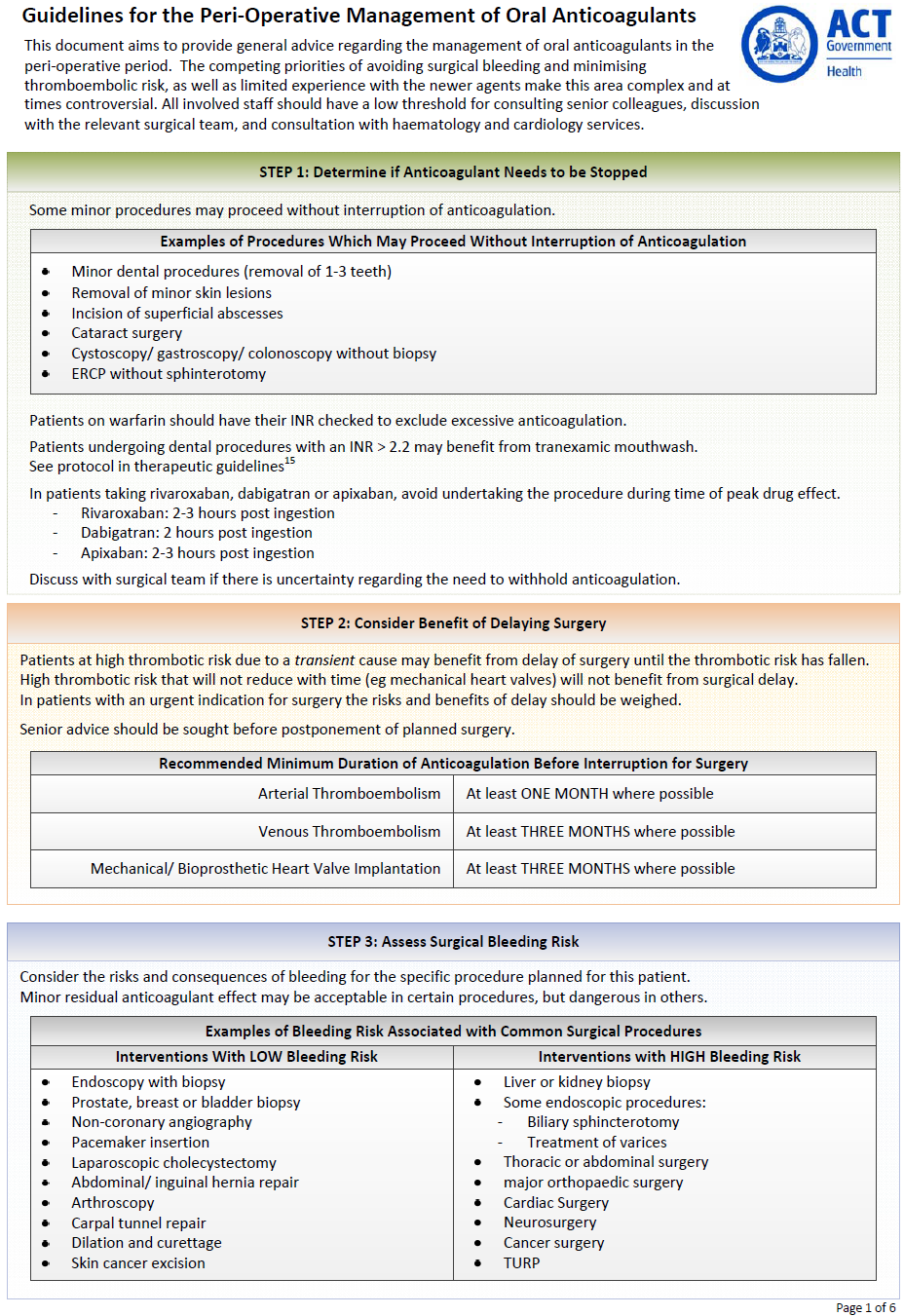
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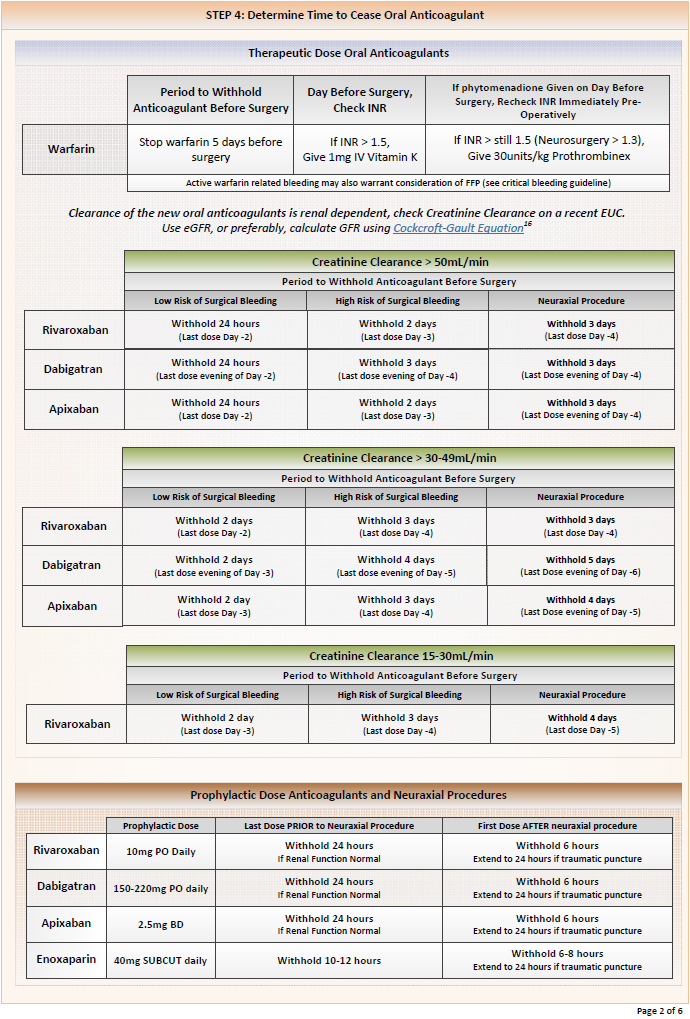
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| *26 June 2022* | *Complete Review* | *Melissa O’Brien, A/g ED-CAS* | *CHS Policy Committee* |
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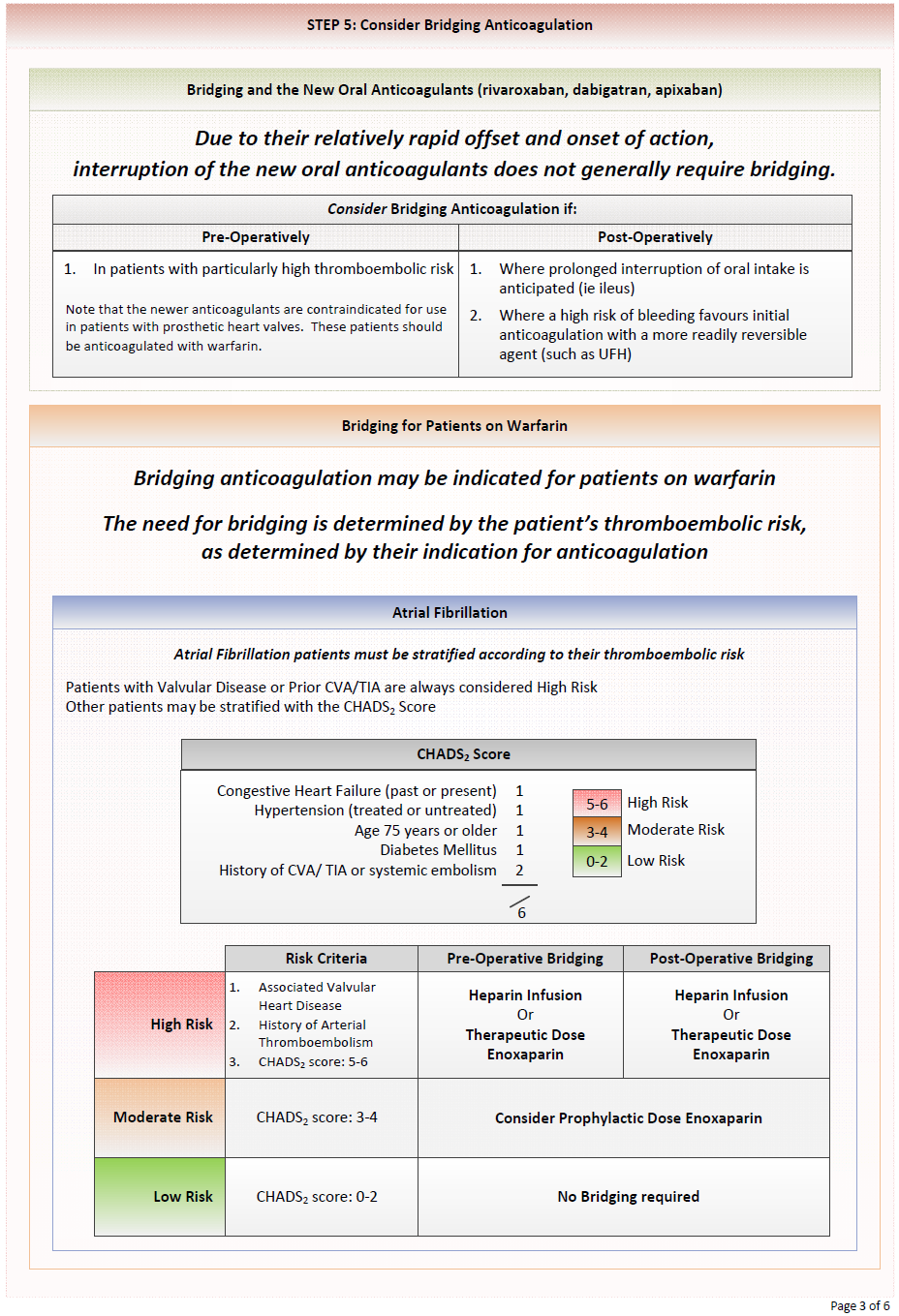
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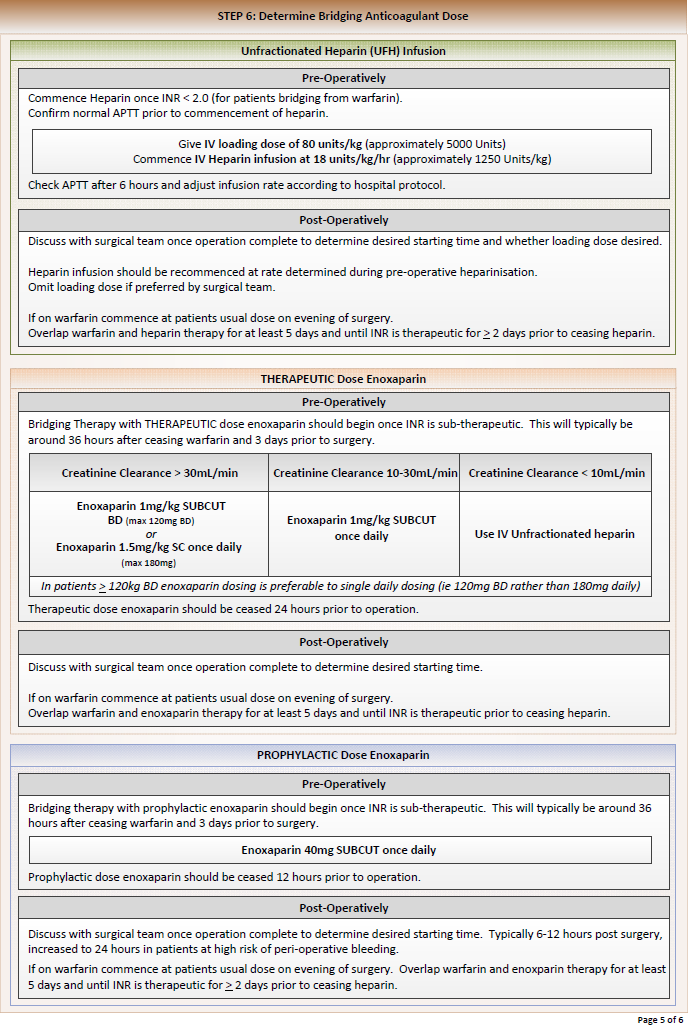
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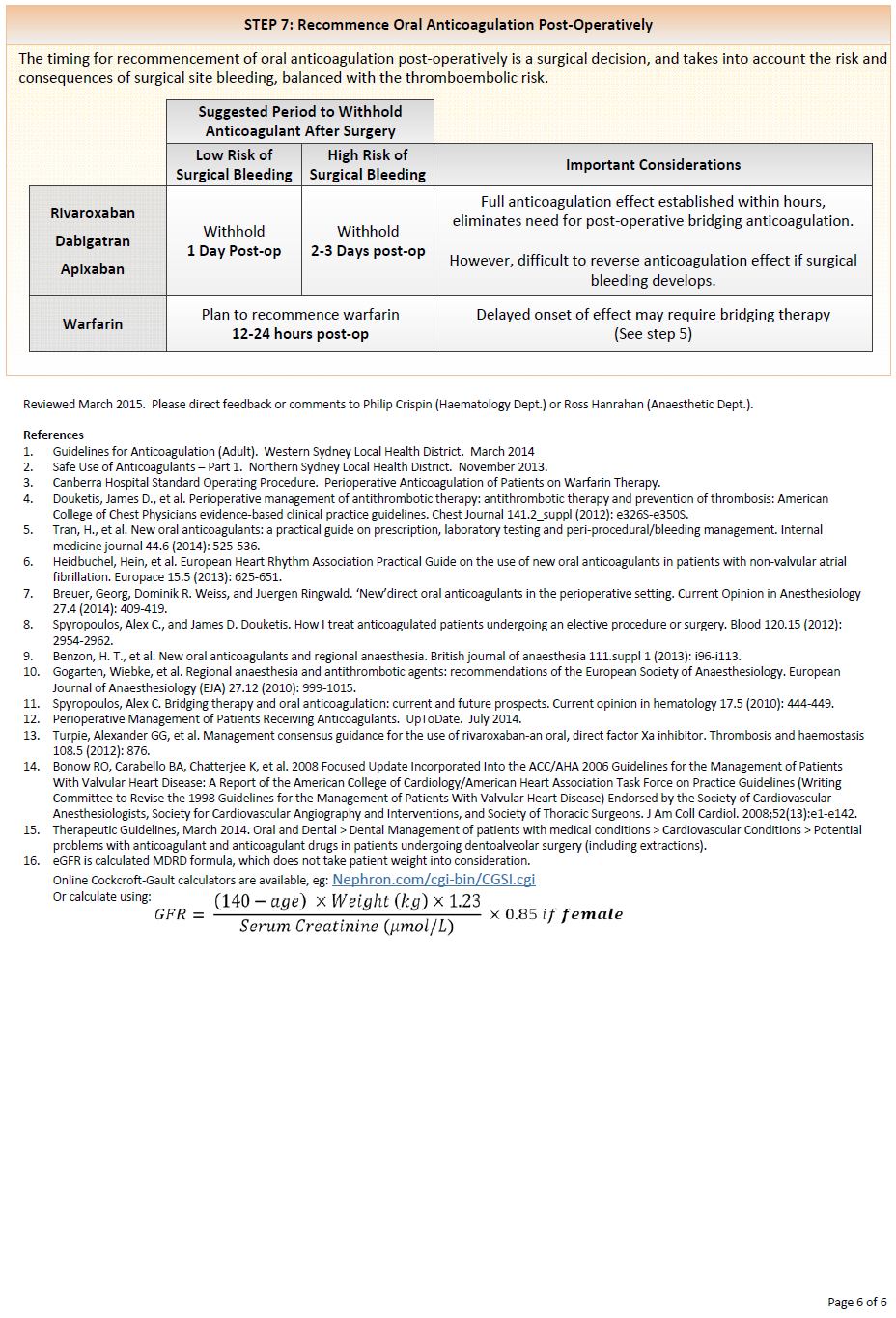
Attachment 1 – Perioperative Anticoagulation Guidelines



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