Introduction

Anticoagulation therapy is most commonly indicated in the presence of atrial fibrillation (AF), deep venous thrombosis (DVT), pulmonary embolism (PE), and after placement of prosthetic heart valves.

Vitamin K Antagonists (Warfarin)

The most recognized and widely used drug of this group is warfarin, which has been available for more than 50 years.
The half-life of warfarin is 36 to 42 hours

warfarin is a drug of difficult titration due to the high number of pharmacological interactions and genetic variations that can affect its metabolism

Direct Inhibitors of Factor Xa (Rivaroxaban, Apixaban)

The common mechanism of action these drugs, also known as direct oral anticoagulants (DOACs), is to bind to the active site of factor Xa, thus inactivating it. Factor Xa is considered the rate-limiting step for the progression of the coagulation cascade, thrombin activation, and ultimately clot formation

Some advantages of prescribing DOACs are their short half-life and rapid onset of action, allowing for an easier interruption and re-initiation of anticoagulation therapy after surgery.

Furthermore, it seems that the direct inhibitors of factor Xa have a lower bleeding risk compared to vitamin K antagonists, making the use of routine coagulation tests unnecessary

However, the pharmacokinetic properties of each DOAC can vary according to the renal and liver function of the patient

Direct Inhibitors of Thrombin

Dabigatran is the only medication in this group. Its mechanism of action is the direct inhibition of thrombin, preventing the conversion of fibrinogen to fibrin and thus clot formation. Dabigatran has a quick onset of action (0.5 to 2 hours) and the plasma half-life is around 12 hours; however, the half-life of this drug is affected by renal function, as its excretion is 80% by the kidneys and less than 10% by the liver.

It is recommended to avoid dabigatran use with creatinine clearance (CrCl) less than 30ml/min, due to the potential for drug accumulation and adverse effect of bleeding

Heparins

The binding of the heparin molecule to the antithrombin receptor enhances its potency to inactivate factors II and Xa. This drug has been widely used for years, with multiple indications and dosages. One of the most concerning adverse effects of this pharmacological group is the possibility of heparin-induced thrombocytopenia. Fortunately, this complication is infrequent, though it is dependent on the dose, route of administration, and type of heparin.

In patients with renal failure and a CrCl < 30 ml/min, low molecular weight heparin (LMWH) should be avoided or adjusted to renal function

Heparin can be administered as a therapeutic dose for the patient with high thromboembolic risk
As a generalized consideration, patients with a high risk of bleeding will benefit from anticoagulation interruption However, those patients with high thromboembolic risk might benefit from bridging therapy and the shortest period of anticoagulation withdrawal as possible.

Scenarios:

An elective surgical procedure should be deferred up to 3 months after an episode of VTE, if possible.

For patients with a recent **acute ischemic stroke** undergoing elective surgical procedures, the risk of having a major cardiovascular event after surgery is high, especially within the first 3 months. It is best to defer the surgery up to 9 months when the risk of cardiac events has plateaued after a stroke

Another common scenario is the patient with **coronary stents**, most of which are on dual anti-aggregation. Approximately 5% of these patients will require surgery during the next year after coronary stent implantation.

Bridging anticoagulation consists of the substitution of a long-acting anticoagulant (usually with warfarin) for a shorter-acting anticoagulant (usually LMWH) to limit the time of sub therapeutic anticoagulation levels and minimize thromboembolic risk

Clinical scenarios that may benefit from bridging therapy are those involving patients with high thromboembolic risk.

The patient with a mechanical heart valve: Mitral valve replacement, aortic valve replacement with additional risk factors (stroke, TIA, cardio embolic event, or intracardiac thrombus), more than 2 mechanical valves.

Patients with stroke, episode of systemic emboli, or VTE during the last 3 months. Patients presenting with a thromboembolic event after interruption of chronic anticoagulation therapy or those presenting with VTE while on therapeutic anticoagulation.

Treatment / Management

How to bridge?

During the preoperative period

Discontinue warfarin five days before surgery.

Three days before surgery, start subcutaneous LMWH or unfractionated heparin (UFH), depending on the renal function of the patient at therapeutic doses.

Two days before surgery assess INR, if greater than 1.5 vitamin K can be administered at a dose of 1 to 2 mg. Discontinue LMWH 24 hours before surgery or 4 to 6 hours before surgery if UFH.

Patients who opt for or require tinzaparin should be given a prescription/supply and instructions for administration. They should also be given a follow up appointment in the unstable clinic following the procedure.

Remember to adjust dose of tinzaparin for patients with renal impairment **GFR <20ml/min**

The last dose of warfarin should be taken on the evening of **day -6.**

LMWH is started on the morning of day -3 and is continued until day -1 (ie 24 hours before surgery). If the surgery poses a high risk of bleeding, this final dose of LMWH on day -1 may only be half the dose of anticoagulant

It is usual to have the INR checked on the day before the procedure to allow for correction if Vitamin K (phytomenadione) if the **INR ≥ 1.5.**

During the postoperative period:

If the patient is tolerating oral intake, and there are no unexpected surgical issues that would increase bleeding risk, restart warfarin 12 to 24 hours after surgery.
If the patient received preoperative bridging therapy (high thromboembolic risk) and underwent a minor surgical procedure, resume LMWH or UFH 24 hours after surgery. If the patient underwent a major surgical procedure, resume LMWH or UFH 48 to 72 hours after surgery.
Always assess the bleeding risk and adequacy of homeostasis before the resumption of LMWH

How to manage patients on DOAC anticoagulation therapy undergoing elective surgery?

It is important to note that bridging therapy is not indicated in patients on DOACs. The predictable pharmacological effect of DOACs allows a properly timed interruption of anticoagulation therapy before surgery. The appropriate timing interruption for patients on DOAC anticoagulation is based on the invasiveness and bleeding risk of the procedure, pharmacokinetic profile of the DOAC, and clinical characteristics of the patient

As a common recommendation among guidelines, DOACs should be held **3 half-life times** before low-risk procedures and **5 half-life times** before high-risk procedures. Nevertheless, there are some procedures considered less than low bleeding risk, such as a colonoscopy without biopsy, where DOAC therapy may be continued

For **high bleeding risk procedures**, rivaroxaban, apixaban, and dabigatran should be suspended **48 hours before surgery** in patients with CrCl >50 ml/min. If the renal function was compromised (CrCl< 50ml/min), these drugs should be interrupted for **four days before surgery**.

For **low bleeding risk procedures**, rivaroxaban, apixaban, and dabigatran should be suspended **24 hours before surgery** in patients with CrCl>50ml/min. If the renal function is compromised (CrCl <50 ml/min),these drugs should be suspended **two days before the procedure**.

Regardless of renal function, all drugs should be reinitiated **at 48 hours** for high bleeding risk surgical procedures and **24 h**ours for low bleeding risk procedures.

How to manage antithrombotic therapy in patients undergoing elective surgery?

For patients treated with intravenous UFH, the infusion should be interrupted 4-6 hours before puncture or catheter removal/manipulation. However, if the patient is receiving UFH subcutaneously, the drug should be interrupted 8-12 hours before puncture or catheter removal/manipulation. Independent of the route of UFH administration, the drug can be restarted 1 hour after puncture or catheter removal/manipulation.

For patients receiving a prophylactic dose of **LMWH**, the drug should be interrupted for **12 hours before puncture** or catheter removal/manipulation and **24 hours** if the dose is therapeutic. Independent of LMWH dose, the drug may be restarted 4 hours after puncture or catheter removal/manipulation.

For patients **receiving DOACs**, the time of interruption will vary according to the specific drug. Patients on rivaroxaban at a prophylactic dose (less than 10 mg/day) should have the drug interrupted 22 to 26 hours before a spinal or epidural approach.

If the patient is on apixaban at a prophylactic dose, it should be discontinued **26 to 30 hours** before a spinal or epidural puncture or catheter placement. Both of these drugs may be restarted 4 to 6hours after the puncture or catheter removal/manipulation.

If the patient is on Warfarin anticoagulation, the **INR should be less than 1.4** before any spinal or epidural approach.

An urgent procedure is defined as one that can be delayed up to 24 hours, giving time to the physician to conduct anticoagulation reversal based on repeated coagulation tests.

Reversal of warfarin:

For non-significant bleeding with alterations of the INR, conservative strategies such as interruption of the drug and oral vitamin K are suitable options. In the emergent scenario, the reversal of warfarin anticoagulation is based on prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP) administration as follows:

INR 2-4: PCC 25 IU/kg IV
INR ≥4-6: PCC 35 IU/kg IV
INR >6: PCC 50 IU/kg IV

Vitamin K: 10 mg IV administered slowly
FFP: 10 to 20 ml/kg

Trauma patients:

1 gm of tranexamic acid can be used at arrival and repeat dose of 1 gm in 8 hours
PCC is commercially available as prothrombin complex concentrate both contain heparin and are thus contraindicated in patients with a past medical history of heparin-induced thrombocytopenia

Reversal of DOACs:

The FDA recently approved andexanet alfa for the reversal of the anticoagulative effects of apixaban and rivaroxaban. DOAC anticoagulation represents a problem for the clinician. What is known is that the cost of the specific new reversal drugs is still high, limiting their use and widespread availability.

Complications

There are two major complications of poor management of perioperative anticoagulation. The first is bleeding, which occurs if the provider fails to interrupt anticoagulation therapy in an appropriate timeframe. On the other hand, however, patients who have their anticoagulation interrupted too early in the perioperative period are at high risk of thromboembolic events, as surgical procedures themselves induce a hypercoagulable state. Thus, appropriate interruption of anticoagulation in the perioperative period is a delicate balancing act between the potentially severe complications of bleeding and thrombosis

Administration of Tinzaparin subcutaneous injection

Tinzaparin is a low –molecular weight heparin used to ensure effective anticoagulation when oral anticoagulants are either not indicated or are producing a sub-therapeutic INR.

Patients who are being initiated onto warfarin following a DVT or PE.

1. Patients requiring LMWH for bridging when starting warfarin

When initiating warfarin therapy Tinzaparin should usually be administered for 5 days concurrent with warfarin therapy and continued until the INR is above 2.0 for two consecutive INRs. If the INR subsequently drops below 2.0 within the first 2 weeks following DVT/PE Tinzaparin should be given until INR is back within the therapeutic range as the risk of re-thrombosis is at its highest during this time. If the INR is 2.0 or above when the target INR is 2.5 a warfarin dose increase without LMWH should be adequate in most cases.

For INRs falling below 1.5 in weeks 3-4 following an acute DVT/PE tinzaparin should be restarted until the INR returns to therapeutic range. INRs above 1.5 should normally respond to dosage adjustment to return to therapeutic range.

Patients who have sub therapeutic anticoagulation and have a high thrombosis risk

	Usual range	Tinzaparin below INR	Procedure
VTE			
VTE within 2 weeks of episode	2.0 -3.0	2.0 Initial treatment requires two INRs over 2.0 and 5 concurrent days with warfarin before discontinuation	Try to avoid until treatment episode is over Discuss with surgeon/ endoscopy if long-term
VTE within 4 weeks of episode	2.0 -3.0	1.5	
VTE high risk	3.0- 4.0	2.0	Requires bridging
MCV			
Bileaflet aortic valve No other risk factors	2.0- 3.0	Not required	Discussion with surgeon/ endoscopy

Bileaflet aortic valve With risk factors	2.0- 3.0	2.0	Discussion with surgeon/ endoscopy
MCV ON-X	2.5-3.5 for 3 months then 1.5-1.5	2.0 for first 3 months then not required	Discussion with surgeon/ endoscopy
MCV	2.5 -3.5	2.0	Requires bridging
MCV	3.0- 4.0	2.0	Requires bridging
AF			
AF with no other risk factors	2.0- 3.0	Not required	Usually not required
AF with risk factors	2.0 -3.0 or 2.5- 3.5	Not required	Discussion with surgeon/ endoscopy

This table has been compiled from available guidelines. Please be aware that this only a suggested guideline, a clinical decision may be made which may override these guidelines.

Patients found to have a sub therapeutic INR in clinic

1. Counsel patient regarding need for tinzaparin. Check whether they have had tinzaparin in the past, whether they self-inject or have a supply at home. Check weight of patient

2. For those in 1 above who have their own supply and self– inject, if weight has not changed. Give booster dose of warfarin, ask patient to self-inject tinzaparin as early as possible. Give patient an appointment for next unstable clinic (tomorrow) or arrange INR with Ambulatory care clinic(ACC) if a Friday.

3. For those with no supply, firstly ask duty GP to provide a prescription. Give patient an appointment for next unstable clinic (tomorrow) or arrange INR with Ambulatory care clinic (ACC) if a Friday. Give booster dose of warfarin.

4. Patients for who it is not possible to obtain a prescription send patient to Ambulatory care clinic (ACC)

5. Remember in all cases to call ambulatory care to inform them of patient's arrival ext 3482

2. Method of administration

Staff administering tinzaparin must have valid BLS and anaphylaxis training and be trained to give LMWH. (PGD 088).(PGD013) Those clinic operators who do not fall in this category will need to make arrangements to have tinzaparin administered either by sending the patient to a hospital clinic or Ambulatory Care Centre as appropriate.

- Ensure that the patient falls into the relevant category.
- It is recommended that male pharmacists should have a female chaperone with them when injecting female patients.
- If the dose of tinzaparin is not known (ie from previous, recent documentation) the patient should be weighed and the dose calculated from the product literature.
- Ensure that the patient understands the procedure.

- For full syringe dosages of tinzaparin ie 0.5ml, 0.7ml or 0.9ml there is no need to expel the air from the syringe as this acts as a 'pocket' beneath the skin.

- For doses less than a full syringe all the air should be expelled along with the excess volume of solution leaving the volume required in the syringe. There is no need to reintroduce the air bubble into the syringe.

- The injection should be injected subcutaneously into the abdomen since this is the body's thickest subcutaneous pad, which reduces the risk of puncturing the underlying muscle. (For abdominal surgery or post pregnancy patients the upper arm should be used for injections)

- Pinch the abdominal skin and insert the needle into the skin at a 90° angle with the bevel of the needle uppermost.

- Let go of the skin and withdraw the syringe plunger. Ensure that no blood enters the syringe. If there is discard syringe and restart procedure

- If no blood is present re-pinch skin and inject tinzaparin. Leave needle in skin for 1-2 secs then withdraw. Do not massage the injection site as this will cause bruising.

- Complete all necessary documentation

- Ensure that patients wait for 10minutes post injection before leaving the clinic in case of anaphylaxis.

3. Documentation

3.1. The dose of tinzaparin administered should be recorded on DAWN-AC along with the name of the operator.

3.2. On Fridays the communication sheet (Appendix 1) should be completed and taken to ACC to ensure that the nurse practitioners are aware of care needed over the weekend.

3.3. Stocks of tinzaparin should be booked out to ACS from the pharmacy store as per procedure SOP AC5

Appendix 1

Pharmacy Department Queen Elizabeth Hospital

Anticoagulant Clinic / Nurse Practitioner Communication Sheet

Patients Name	D.O.B/Unit	Dosing information and comment s	Next appt v us
		Dose of tin Tinzaparin FBC neede Warfarin d Notes/ DA	
		Dose of tin Tinzaparin FBC neede Warfarin d Notes/ DA	
		Dose of tin Tinzaparin FBC neede Warfarin d Notes/ DA	
		Dose of tin Tinzaparin FBC neede Warfarin d Notes/ DA	

Pharmacist _____ Date_____

Any queries please contact the above on ext 2317