ANTICOAGULANTS, ANTIPLATELETS AND FIBRINOLYTICS

ANTICOAGULANTS:

WARFARIN:

- CLINICAL PHARMACOLOGY:
  - Warfarin is readily absorbed form the gut, reaches peak blood concentration in 90 minutes and has a half-life of 36-42 hours
  - Blocks activation of vitamin K and thereby interferes with hepatic carboxylation of coagulation factors II, VII, IX and X
    - Without these, the EXTRINSIC coagulation pathway is blocked
  - Also blocks antithrombotic proteins (C and S)
    - Early procoagulant effect, but during maintenance the overwhelming effect is one of anticoagulation
  - Many drugs interfere with warfarin absorption, binding to albumin or hepatic metabolism ➔ profound effects on warfarin activity

Table 234-2 Warfarin Interactions

Consideration	Effect on Prothrombin Time or International Normalized Ratio*
Major	
Vitamin K malabsorption or dietary deficiency	↑
Excess vitamin K	↓
Reduced gut bacteria (antibiotics)	↑
Decreased warfarin absorption	↓
Altered warfarin metabolism (cytochrome P-450)	↑ or ↓
Drug effects	↑ or ↓
Other	
Decreased clotting factor production (liver disease)	↑
Increased metabolism of clotting factors (fever)	↑
Confounding technical or laboratory factors (e.g., phlebotomy, handling in transport, thromboplastin reagents)	↑ or ↓

  - There is also a prothrombotic rebound during warfarin withdrawal, as factors VII and IX increase more rapidly than proteins C and S
- COMPLICATIONS AND MANAGEMENT:
  - Two major complications ➔ bleeding and skin necrosis. BLEEDING IS THE MOST IMPORTANT COMPLICATION AND THE MOST IMPORTANT FACTOR INFLUENCING THE RISK OF BLEEDING IS THE INTESITY OF ANTICOAGULANT THERAPY
    - The risk of clinically significant bleeding is increased when the INR is in the range 3-4.5 and an exponential increase in bleeding events occurs when the INR is >5.0
  - Skin necrosis occurs primarily (although not exclusively) in patients with protein C deficiency and is caused by thrombosis of small cutaneous vessels ➔ stop warfarin and administer a parenteral anticoagulant

Determinants of bleeding

The following are major determinants of bleeding during warfarin therapy.

Intensity of anticoagulant effect. Both the target and the achieved INR determine the risk of bleeding, which increases significantly when the target INR is greater than 3 and the achieved INR is greater than 5.

Duration of anticoagulant therapy. The risk of bleeding is highest during the first few months of anticoagulant therapy, then falls somewhat, but it always remains above baseline. As the risk remains elevated throughout therapy, duration of treatment determines bleeding rates.

Patient characteristics. Factors that increase the risk of bleeding during warfarin therapy include:

- increased age (especially more than 75 years)
- diabetes mellitus
- presence of malignancy
- hypertension
- liver disease or acute or chronic alcoholism
- elevated creatinine or severe chronic kidney disease
- poor drug adherence or clinic attendance
- prior stroke or intracerebral haemorrhage
- presence of bleeding lesions (eg gastrointestinal blood loss)
- bleeding disorder (coagulation defects, thrombocytopenia with platelet count less than 75 x 10^9/L)
- previous severe haemorrhage during treatment with warfarin when INR was in the therapeutic range.

Concomitant therapy with drugs that affect haemostasis. Antiplatelet drugs (including aspirin, clopidogrel, prasugrel and ticagrelor) increase the risk of bleeding during warfarin therapy without an increase in the INR. Nonsteroidal anti-inflammatory drugs increase the risk of gastrointestinal bleeding during warfarin treatment.

Elevated INR but no clinical evidence of bleeding

For patients with elevated INR but no clinical evidence of bleeding, always carefully reassess the need for warfarin therapy and remove precipitating factor(s) if possible. The bleeding risk increases exponentially from INR 5 to 9. Closely monitor any patient with an INR higher than 6.

The onset of the effect of vitamin K on the INR can be expected within 6 to 12 hours.

If the **INR is higher than the therapeutic range but less than 5**:

Lower the dose or omit the next dose of warfarin. Resume therapy at a lower dose when the INR approaches the therapeutic range.

If the INR is only minimally above the therapeutic range (up to 10%), dose reduction may not be necessary.

If the **INR is 5 to 9**:

Cease warfarin therapy; consider reasons for elevated INR and patient-specific factors.

Give vitamin K:

phytomenadione 1 to 2 mg orally
or phytomenadione 0.5 to 1 mg IV [Note 1].

Measure the INR within 24 hours.

If the **INR is 9 or higher**:

Where there is a low risk of bleeding (see Determinants of bleeding), cease warfarin therapy and give vitamin K:

phytomenadione 2.5 to 5 mg orally
or phytomenadione 1 mg IV [Note 1].

Measure the INR in 6 to 12 hours and resume warfarin therapy at a reduced dose once the INR is less than 5.

Where there is high risk of bleeding (see Determinants of bleeding), cease warfarin therapy and give vitamin K:

phytomenadione 1 mg IV [Note 1].

Also consider:

Prothrombinex-VF 25 to 50 units/kg IV [Note 2]

PLUS

fresh frozen plasma 150 to 300 mL.

Measure the INR in 6 to 12 hours and resume warfarin therapy at a reduced dose once the INR is less than 5.

Any clinically significant bleeding where warfarin-induced coagulopathy is considered a contributory factor

Cease warfarin therapy, and use:

phytomenadione 5 to 10 mg IV [Note 1]

PLUS

Prothrombinex-VF 25 to 50 units/kg IV [Note 2]

PLUS, if available

fresh frozen plasma 150 to 300 mL.

Assess the patient continuously until the INR is less than 5 and the bleeding stops.

If Prothrombinex-VF is unavailable, cease warfarin therapy and use:

phytomenadione 5 to 10 mg IV [Note 1]

PLUS

fresh frozen plasma 10 to 15 mL/kg.

Assess the patient continuously until the INR is less than 5 and the bleeding stops.

RIVAROXABAN:

- An orally absorbed direct factor Xa inhibitor with a long duration of action
- High plasma protein binding, thus not expected to be dialyzable, no reversal.

DABIGATRAN:

Introduction

Dabigatran is an orally active direct thrombin inhibitor. Dabigatran is associated with nausea in some cases, although this rarely limits its use. Dabigatran is significantly renally excreted and should not be used in patients with severe renal impairment (eGFR less than 30 mL/min).

Clinical utility

Dabigatran has proven benefit in:

- prevention of venous thromboembolism following hip or knee replacement
- stroke prevention in some patients with atrial fibrillation.

Monitoring

There are no current laboratory tests that guide therapy with dabigatran. Measurement of the activated partial thromboplastin time (APTT) will help determine whether there is any effect of dabigatran present, but not the extent of haemostatic impairment.

Determinants of bleeding

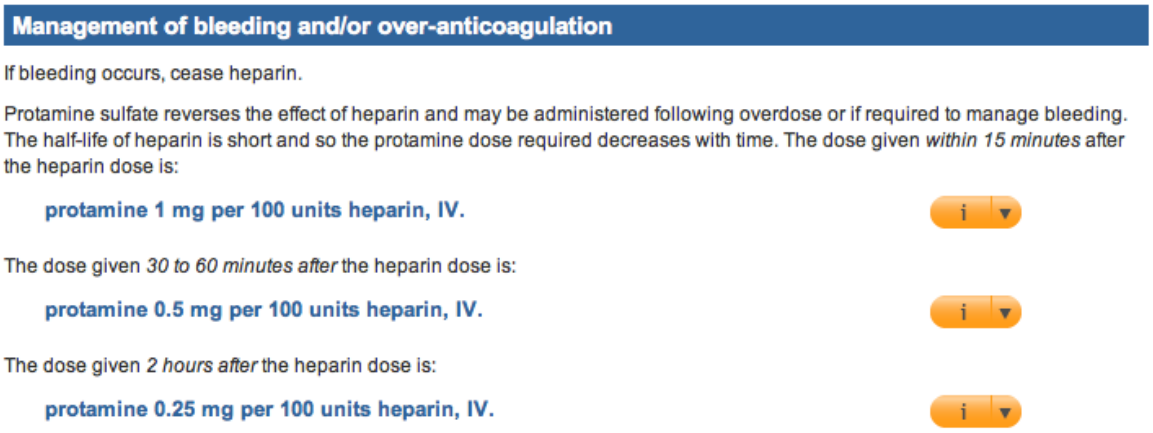
The risk of bleeding during therapy with dabigatran is increased by advanced age (75 years or more), low body weight (less than 50 kg) and renal impairment (eGFR 30 to 50 mL/min) [Note 1]. Clinical trials studying dabigatran excluded patients with risk factors for bleeding with other anticoagulants, such as recent surgery or trauma, kidney failure, bleeding diathesis, prior major bleeding or the use of concomitant drugs that affect haemostasis. Dabigatran should be used with extreme caution in these patients.

Management of bleeding and/or over-anticoagulation

There is no specific antidote for dabigatran. Supportive measures should be instituted. Establishing a diuresis may be of benefit. As dabigatran is renally excreted, consider high efficiency dialysis in extreme situations. Product information advises considering transfusion of fresh frozen plasma but this will not reverse the anticoagulant effect. Seek specialist advice.

UNFRACTIONATED HEPARIN:

- Mixture of polysaccharides
- The anticoagulant effect of UFH requires binding to ANTITHROMBIN, resulting in magnification of its inhibition of thrombin and factor Xa
- Subcutaneous administration has unpredictable bioavailability, but iseffective in reducing risk for DVT/PE by 60-70%
- Weight-based protocols exist for administration
- Heparin bleeding is increased with recent surgery or trauma, renal failure, alcohoism, malignancy, liver failure, GI bleeding and concurrent use of warfarin, fibrinolytics, steroids or antiplatelets
    - There is a 2-6% incidence of major bleeding overall
    - Bleeding is treated according to clinical severity and not APTT



- The adverse effects of protamine are significant, the predominant issue being ANAPHYLAXIS with a significant mortality rate.
    - Also, protamine has a short half-life (7 minutes), hence risk for heparin rebound
- For discussion of HIT, please see earlier chapter

LOW-MOLECULAR WEIGHT HEPARIN:

- Identical site of action, i.e. potentiation of activity of antithrombin
- LMWH has shorted polysaccharide chain that reduces its ability to inactivate thrombin and enhances the affinity for inactivity factor X-a
- Risk of HIT ten-fold LESS

Table 234-3 Advantages of Low-Molecular-Weight Heparin over Unfractionated Heparin	
Pharmacologic Effects	**Clinical Benefit**
Quick and predictable SC absorption	More reliable level of anticoagulation
More stable dose response	Eliminates need for monitoring
Resistance to inhibition by plateletfactor 4	Decreased incidence of thrombocytopenia
Decreased antiheparin antibody production	Greater antithrombotic effects
Greater anti-Factor Xa activity	Potential for reduced bleeding
Less anti-Factor IIa activity	Absence of "rebound"
Ease of administration	Outpatient therapy

- It is cleared by the kidneys and bleeding complications due to accumulation of the agent can occur in patients with significant renal impairment
    - Appropriate dosing in renal failure is unclear, but with creatinine clearance < 30, give half dose
- In obese patients up to 190kg, LMWH dosing based on total body weight did not lead to ANY EXCESS BLEEDING

Monitoring

LMWH are predictable and there is no need for monitoring in most situations. Anti-Xa level measurement has been used to guide dosing in renal impairment, pregnancy and morbid obesity. Therapeutic ranges vary and local laboratory ranges should be sought.

Determinants of bleeding

The determinants of bleeding during LMWH therapy are the same as those for UFH. Impaired kidney function is a much more important risk for bleeding with LMWH than with UFH.

Management of bleeding and/or over-anticoagulation

Protamine sulfate has less effect in reversing the anticoagulant effect of LMWH than of UFH but may be used, in addition to supportive measures, in critical clinical situations.

FONDAPARINUX:

- A synthetic pentasaccharide that binds to antithrombin and enhances its affinity for factor Xa, but not thrombin

HIRUDINS:

- CLINICAL PHARMACOLOGY:
    - DIRECT THROMBIN INHIBITIORS
        - CAPABLE OF INHIBITING BOTH CIRCULATING AND CLOT-BOUND THROMBIN
        - Do not inhibit other coagulation enzymes
        - Do not require antithrombin as a cofactor
        - Do not interact with platelet factor-4 or plasma proteins
        - MORE PREDICTABLE ANTICOAGULANT EFFECT
    - Examples include BIVALIRUDIN, LEPIRUDIN
- COMPLICATIONS AND MANAGEMENT:
    - BLEEDING, majority occurring at invasive sites

- Because half-life is short and an antidote IS NOT CURRENTLY AVAILABLE, management of haemorrhage may require only stopping the IV infusion
- Support the patient with coagulation factor replacement (FFP or PCC) if bleeding persists

ANTIPLATELET AGENTS:

Table 234-5 Oral Antiplatelet Agents

	Class	Mechanism of Action	Half-Life	Duration of Antiplatelet Effect	Typical Use	Typical Dose
Aspirin	Nonselective cyclooxygenase inhibitor	Irreversible inactivation	3–4 h	Up to 7 d	Treatment and prevention of ACS	162–325 milligrams PO once per day
Clopidogrel	Adenosine diphosphate receptor inhibitor	Irreversible inactivation	7–8 h	Up to 7 d	Treatment and prevention of ACS	300 milligrams PO loading dose (consider 600 milligrams if PCI is planned) followed by 75 milligrams PO once a day
Cilostazol	Selective phosphodiesterase inhibitor	Reversible inhibition	11–13 h	1 d	Peripheral artery disease	100 milligrams PO twice a day
Dipyridamole	Miscellaneous	Reversible inhibition	Biphasic: 40 min and 10 h	1 d	Secondary ischemic stroke prevention	200 milligrams extended-release PO twice a day (usually combined with low-dose aspirin)

- **ASPIRIN:**
  - CLINICAL PHARMACOLOGY:
    - IRREVERSIBLE BLOCKADE OF CYCLOOXYGENASE → an enzyme that in the platelet catalyses conversion of arachidonic acid to thromboxane A2 and in the blood vessel promotes protacyclin synthesis
    - Effect lasts for the life-span of the platelet
    - Side effects are GI and mainly dose-related
  - Used for primary and secondary prevention of cardiovascular disease
    - Overall effect is beneficial ➔ decreased risk of MI, ischaemic stroke and sudden cardiac death with increased risk of major bleeding (GI and ICH)
  - COMPLICATIONS AND MANAGEMENT:

        - Upper GI irritation is most common (life-threatening GI haemorrhage is uncommon)
        - Uraemia and combination of alcohol and aspirin greatly increase sensitivity to bleeding in response to aspirin
        - TREATMENT OF HAEMORRHAGE ➔ transfuse enough platelets to raise the count by 50. The haemostatic compromise might last for up to 7 days after aspirin has been discontinued.
- **CLOPIDOGREL AND TICLODIPINE:**
    - CLINICAL PHARMACOLOGY:
        - Selective inhibition of platelet activation by ADENOSINE DIPHOSPHATE → irreversibly inhibit the ADP receptor, hence the fibrinogen receptor is rendered ineffective
        - Clopidogrel is orally absorbed rapidly (600mg) results in full antiplatelet effect by two hours and is maintained for 48 hours
            - Omeprazole decreases the antiplatelet effect of clopidogrel by inhibiting CYP2C19
        - Ticlodipine is no longer marketed as it is has a significant risk for haematological problems (neutropenia and TTP)
    - COMPLICATIONS AND MANAGEMENT:
        - Bleeding should be treated with supportive care and platelet transfusion

Clopidogrel, prasugrel and ticagrelor

Introduction

Clopidogrel, prasugrel and ticagrelor inhibit platelet aggregation by blocking the platelet $P2Y_{12}$ receptor. Ticagrelor also has a potentiating effect on adenosine; the significance of this for its efficacy and adverse effects is not clear.

Clopidogrel and prasugrel lead to irreversible platelet inhibition and are given once daily. Ticagrelor is reversible and requires twice-daily dosing. As its antiplatelet action is of shorter duration than either clopidogrel or prasugrel, the duration of the risk of increased bleeding following ticagrelor's discontinuation is also shorter and it may be used in closer proximity to surgery. Some patients appear to have resistance to the antiplatelet effect of clopidogrel but, at the time of writing, there is no well-validated method of identifying these patients.

Clinical utility

Clopidogrel has proven benefit in:

- prevention of vascular ischaemic events in patients with symptomatic atherosclerosis (recent ischaemic stroke, recent myocardial infarction, or peripheral arterial disease with intermittent claudication).

Clopidogrel, co-administered with aspirin, has proven benefit in:

- acute coronary syndromes
- prevention of thrombosis after percutaneous coronary intervention.

Prasugrel, co-administered with aspirin, has proven benefit in:

- prevention of atherothrombotic events in patients with acute coronary syndromes (unstable angina, non–ST elevation myocardial infarction, ST elevation myocardial infarction) who are to undergo percutaneous coronary intervention.

Ticagrelor, co-administered with aspirin, has proven benefit in:

- prevention of atherothrombotic events in patients with acute coronary syndromes (unstable angina, non–ST elevation myocardial infarction, ST elevation myocardial infarction) who are to be medically managed or are to undergo percutaneous coronary intervention or coronary artery bypass grafting.

Monitoring

Only clinical monitoring is required for the antithrombotic or adverse effects of clopidogrel, prasugrel and ticagrelor.

Determinants of bleeding

The commonest adverse outcome of clopidogrel, prasugrel and ticagrelor is bleeding. The risk of bleeding increases markedly when they are combined with other drugs that effect haemostasis, such as other antiplatelet drugs, anticoagulants and nonsteroidal anti-inflammatory drugs (NSAIDs). Although selective cyclo-oxygenase-2 (COX-2) inhibitors (eg celecoxib) have a lower risk of causing bleeding than nonselective NSAIDs, this must be weighed against a possible increase in risk of thromboembolism.

A higher risk of bleeding may be seen when prasugrel is used for patients weighing less than 60 kg or aged 75 years or more. It should be avoided or used with extreme caution in these patients.

Ticagrelor should be avoided or used with extreme caution in patients at high risk of bleeding, such as those with low body weight (less than 60 kg), reduced kidney function and of older age (65 years or more).

Management of bleeding and/or over-anticoagulation

If bleeding occurs in a patient taking clopidogrel, prasugrel or ticagrelor, it should be managed supportively as there is no specific antidote. In life-threatening bleeding, platelet transfusion should be administered.

ABCIXIMAB, EPTIFIBATIDE AND TIROFIBAN:

- CLINICAL PHARMACOLOGY:
    - During platelet aggregation, fibrinogen binds to the glycoprotein platelet surface IIb-IIIa receptor
        - Thus, fibrinogen attached to GP IIb/IIIa receptors connecting adjacents platelets represents the final common pathway for platelet aggregation

Table 234-6 IV Antiplatelet Agents							
	Class	**Type**	**Mechanism of Action**	**Half-Life**	**Duration of Antiplatelet Effect**	**Loading Dose**	**Continuous Infusion**
Abciximab	GP IIb/IIIa receptor inhibitor	Monoclonal antibody	Noncompetitive inhibition	10 min	24–48 h	0.25 milligram/kg IV bolus	0.125 microgram/kg/min (maximum, 10 micrograms) IV
Eptifibatide	GP IIb/IIIa receptor inhibitor	Cyclic heptapeptide	Competitive inhibition	2.5 h	3–5 h	180 micrograms/kg IV bolus over 1–2 min	2 micrograms/kg/min IV
Tirofiban	GP IIb/IIIa receptor inhibitor	Nonpeptide	Competitive inhibition	2 h	3–5 h	0.4 microgram/kg/min IV for 30 min	0.1 microgram/kg/min IV

    - The above mentioned agents are the three that are commercially available at present
        - Used in the treatment of unstable angina, NSTEMI and high-risk ACS
        - Functional platelet recovery is usually seen 3-5 hours after stopping either eptifibatide or tirofiban infusion
    - These agents produce greatest benefit in patients undergoing PCI ➔ can be given at the time of PCI, rather than in ED
- COMPLICATIONS AND MANAGEMENT:
    - Increased risk for bleeding complications but no increased risk of ICH
    - Treatment involves red cell and platelet transfusion

<u>FIBRINOLYTICS:</u>

- Each fibrinolytic agent eventually converts PLASMINOGEN TO PLASMIN, which then enzymatically breaks apart the fibrin component of thrombi

STEPTOKINASE (FIRST GENERATION):

- Derived from β-haemolytic streptococci, binds to and activates circulating plasminogen ➔ eventually leads to thrombus dissolution
- Fibrinolytic effect persists for 24 hours, even though its half life is only 23 minutes, HENCE NO HEPARIN AFTERWARDS INITIALLY
- Streptokinase is ANTIGENIC → allergic reactions occur in ~6% of patients
    - Antibodies persist for 6 months after use ➔ unwise to use again in this window

ALTEPLASE (TISSUE PLASMINOGEN ACTIVATOR, SECOND GENERATION):

- A NATURALLY OCCURRING ENZYME IN VASCULAR ENDOTHELIAL CELLS THAT DIRECTLY CLEAVES A SPECIFIC PEPTIDE BOND IN PLASMINOGEN
- Alteplase has binding sites for fibrin ➔ would presume this would lead to less systemic fibrinolysis, but side effect profile is comparable to other fibrinolytics

- Half-life <5 minutes ➔ need to give as a weight-based infusion over 60-90 minutes

RETEPLASE AND TENECTEPLASE (THIRD GENERATION):

- Derived form modifications of ALTEPLASE, with the intent of improving efficacy and safety
    - RETEPLASE → prolonged half life to 18 minutes, allowing bolus administration
    - TENECTEPLASE ➔ prolonged half life, higher level of fibrin specificity and extended duration. Single weight-tiered bolus dosing over 5-10 minutes. 14 fold greater fibrin specificity and reduced systemic plasmin generation. Also has plasminogen activator inhibitor resistance 80x greater than alteplase, allowing for longer association of tenecteplase with fibrin-rich clot
- Despite this, neither reteplase nor tenecteplase demonstrate an absolute mortality or safety benefit in the treatment of STEMI

CONTRAINDICATIONS TO FIBRINOLYTIC THERAPY:

Table 234-7 General Contraindications to Fibrinolytic Therapy
Absolute
Active or recent (<14 d) internal bleeding
Ischemic stroke within the past 2–6 mo
Any prior hemorrhagic stroke
Intracranial or intraspinal surgery or trauma within the past 2 mo
Intracranial or intraspinal neoplasm, aneurysm, or arteriovenous malformation
Known severe bleeding diathesis
Current anticoagulant treatment (e.g., warfarin with INR >1.7 or heparin with increased aPTT)
Uncontrolled hypertension (i.e., blood pressure >185/100 mm Hg)
Suspected aortic dissection or pericarditis
Pregnancy
Relative*
Active peptic ulcer disease
Cardiopulmonary resuscitation for longer than 10 min
Hemorrhagic ophthalmic conditions
Puncture of noncompressible vessel within the past 10 d
Advanced age >75 y old
Significant trauma or major surgery within the past 2 wk to 2 mo
Advanced renal or hepatic disease

COMPLICATIONS AND MANAGEMENT OF FIBRINOLYTICS:

- HAEMORRHAGE ➔ most catastrophic being ICH
- Monitor Hb regularly ➔ a fall of >20g/L should prompt search for bleeding
    - Most occur at vascular puncture sites (70%)
    - Can occur at intracranial, intrathoracic, retroperitoneal, GI, GU or soft tissue site

- Significant bleeding mandates discontinuation of the fibrinolytic agents, antiplatelets and heparin
    - Volume resuscitation with blood products and fluids
    - Massive bleeding with haemodynamic compromise necessitates coagulation factor replacement with cryprecipitates (rich in fibrinogen) and/or FFP
    - Fibrinolytic associated ICH mandates aggressive approach:
        - Protamine if heparin used
        - Cryoprecipitate
        - FFP
        - Platelets
        - Antifibrinolytic agent