PHARMACOLOGY OF ORAL ANTICOAGULANTS

A Comprehensive Lecture Note for Final-Year MBBS Students

Course: Clinical Pharmacology and Therapeutics
Topic: Oral Anticoagulants

LEARNING OBJECTIVES

At the end of this lecture, students should be able to:

1. Define anticoagulants and explain their roles in the prevention and treatment of thromboembolic disorders.
2. Describe the physiological mechanisms of blood coagulation and identify the principal targets of oral anticoagulants.
3. Classify oral anticoagulants into their major pharmacological groups.
4. Explain the mechanisms of action, pharmacokinetics, pharmacodynamics, therapeutic indications, adverse effects, contraindications and drug interactions of individual oral anticoagulants.
5. Compare vitamin K antagonists with direct oral anticoagulants (DOACs).
6. Explain the principles of anticoagulation monitoring and dose adjustment.
7. Describe the management of anticoagulant-associated bleeding and the use of reversal agents.
8. Discuss the clinical use of oral anticoagulants in common medical conditions.
9. Apply pharmacological principles to clinical scenarios involving anticoagulant therapy.
10. Answer examination questions on oral anticoagulants using appropriate clinical reasoning.

1. INTRODUCTION

Anticoagulants are drugs that inhibit the coagulation process and reduce the formation or extension of blood clots within the vascular system.

They are important in modern clinical practice because thromboembolic disorders are major causes of morbidity and mortality.

Examples include:

- Deep vein thrombosis (DVT).
- Pulmonary embolism (PE).
- Ischaemic stroke associated with atrial fibrillation.
- Systemic embolism.
- Thromboembolism associated with mechanical heart valves.
- Venous thromboembolism associated with cancer, surgery or prolonged immobilisation.

Anticoagulants do not directly dissolve established thrombi. Instead, they interfere with the coagulation cascade, thereby preventing new clot formation and limiting the extension of existing thrombi. The body's endogenous fibrinolytic system is responsible for the gradual breakdown of fibrin, while selected patients may require additional treatment, such as thrombolytic therapy or thrombectomy.

1.1 Anticoagulants versus antiplatelet drugs versus thrombolytics

These three classes of drugs act on different aspects of haemostasis.

Feature	Anticoagulants	Antiplatelet drugs	Thrombolytics
Primary target	Coagulation factors	Platelet activation and aggregation	Cross-linked fibrin in established clots
Principal effect	Inhibit fibrin formation	Reduce platelet plug formation	Promote clot breakdown
Examples	Warfarin, apixaban, dabigatran	Aspirin, clopidogrel	Alteplase, tenecteplase
Major clinical applications	DVT, PE, cardioembolic stroke prevention	Acute coronary syndromes, atherosclerotic disease	Selected cases of acute ischaemic stroke, massive PE and STEMI
Major adverse effect	Bleeding	Bleeding	Major bleeding, including intracranial haemorrhage

Clinical principle: Anticoagulants are particularly important in fibrin-rich venous thromboembolism and cardioembolic disease, whereas antiplatelet drugs are central to many platelet-rich arterial thrombotic disorders. These are broad distinctions, and some patients require both classes.

2. PHYSIOLOGY OF HAEMOSTASIS

A sound understanding of haemostasis is necessary to understand the pharmacology of anticoagulants.

Haemostasis is the physiological process by which bleeding is arrested following vascular injury while blood remains fluid within intact vessels.

It involves four closely related processes:

1. Vasoconstriction.
2. Primary haemostasis.
3. Secondary haemostasis.
4. Fibrinolysis.

2.1 Primary haemostasis

Primary haemostasis involves the formation of a platelet plug at the site of vascular injury.

Following damage to the vascular endothelium:

1. Subendothelial collagen becomes exposed.
2. Von Willebrand factor binds to the exposed collagen.
3. Platelets adhere through glycoprotein Ib receptors interacting with von Willebrand factor.
4. Platelets become activated and release mediators, including ADP and thromboxane A_2.
5. Additional platelets are recruited and activated.
6. Platelets aggregate through glycoprotein IIb/IIIa receptors, which bind fibrinogen.

The result is a primary platelet plug.

Antiplatelet drugs such as aspirin and clopidogrel interfere with this process.

2.2 Secondary haemostasis

Secondary haemostasis involves activation of the coagulation system, culminating in the production of fibrin.

Fibrin reinforces the platelet plug and makes the clot more stable.

The coagulation system is traditionally described using three pathways:

- Intrinsic pathway.
- Extrinsic pathway.
- Common pathway.

Although this classification remains useful for understanding laboratory coagulation tests, the physiological coagulation system is more accurately understood as a coordinated, cell-based process involving tissue factor, platelets and activated coagulation factors.

A. Extrinsic pathway

The extrinsic pathway begins when tissue factor is exposed following tissue injury.

Tissue factor binds activated factor VII (VIIa), forming a complex that activates factors X and IX.

The tissue factor–VIIa complex is an important initiator of coagulation.

B. Intrinsic pathway

The traditional intrinsic pathway involves factors XII, XI, IX and VIII.

Activated factor IX combines with activated factor VIII on a phospholipid surface in the presence of calcium to form the intrinsic tenase complex.

This complex activates factor X.

C. Common pathway

The common pathway begins with the activation of factor X.

Activated factor X (Xa) combines with factor Va, phospholipid and calcium to form the prothrombinase complex.

This complex converts prothrombin (factor II) into thrombin (factor IIa).

Thrombin performs several important functions:

- Converts fibrinogen into fibrin.
- Activates factor XIII, which cross-links fibrin.
- Activates platelets.
- Amplifies coagulation by activating factors V, VIII and XI.

Cross-linked fibrin stabilises the clot.

2.3 Simplified coagulation cascade

```
Tissue injury
     |
     v
Tissue factor + Factor VIIa
     |
     v
Activation of Factor X
     |
     v
Factor Xa + Factor Va
     |
     v
Prothrombin (Factor II)
     |
     v
Thrombin (Factor IIa)
     |
     v
Fibrinogen
     |
     v
Fibrin
```

```
     |
     v
Factor XIII-mediated cross-linking
     |
     v
Stable fibrin clot
```

The intrinsic pathway also activates factor X through the factor IXa–VIIIa complex.

Major pharmacological targets

The principal targets of modern oral anticoagulants are:

1. Vitamin K recycling, which is necessary for the synthesis of functional coagulation factors.
2. Activated factor Xa.
3. Thrombin (factor IIa).

Understanding these three targets provides the foundation for the classification of oral anticoagulants.

3. CLASSIFICATION OF ORAL ANTICOAGULANTS

Oral anticoagulants can be divided into two major groups.

3.1 Vitamin K antagonists

Prototype: Warfarin.

Warfarin inhibits the vitamin K cycle, reducing the functional synthesis of vitamin K-dependent coagulation factors.

Other vitamin K antagonists, such as acenocoumarol and phenindione, have been used in some countries, but warfarin is the principal example for this lecture.

3.2 Direct oral anticoagulants

These are commonly abbreviated as DOACs.

They act directly on specific activated coagulation factors.

They are subdivided into:

A. Direct thrombin inhibitor

- Dabigatran etexilate.

B. Direct factor Xa inhibitors

- Apixaban.
- Rivaroxaban.
- Edoxaban.

The availability and licensed indications of individual drugs vary between countries.

Summary classification

Class	Drug	Primary pharmacological target
Vitamin K antagonist	Warfarin	Vitamin K epoxide reductase complex 1
Direct thrombin inhibitor	Dabigatran	Thrombin, factor IIa
Direct factor Xa inhibitor	Apixaban	Factor Xa
Direct factor Xa inhibitor	Rivaroxaban	Factor Xa
Direct factor Xa inhibitor	Edoxaban	Factor Xa

Important distinction: Unfractionated heparin and low-molecular-weight heparins are anticoagulants, but they are administered parenterally and are not oral anticoagulants.

4. WARFARIN

4.1 Introduction

Warfarin is an oral vitamin K antagonist that has been used for decades in the prevention and treatment of thromboembolic disorders.

It is particularly important in patients with mechanical prosthetic heart valves and in selected patients who cannot appropriately receive a direct oral anticoagulant.

Warfarin has a narrow therapeutic range, numerous drug and food interactions, and a delayed onset of full anticoagulant action. Consequently, treatment requires careful dose adjustment and laboratory monitoring.

4.2 Mechanism of action

Warfarin inhibits the enzyme **vitamin K epoxide reductase complex 1 (VKORC1)**.

This enzyme is responsible for regenerating reduced vitamin K from vitamin K epoxide during the vitamin K cycle.

Reduced vitamin K is required for the gamma-carboxylation of specific glutamate residues on several proteins involved in haemostasis.

This post-translational modification enables these proteins to bind calcium and interact appropriately with phospholipid surfaces.

Warfarin therefore reduces the functional synthesis of:

- Coagulation factor II (prothrombin).
- Coagulation factor VII.
- Coagulation factor IX.
- Coagulation factor X.
- Protein C.
- Protein S.

The first four are procoagulant factors. Proteins C and S are natural anticoagulants.

Warfarin consequently reduces the production of functional procoagulant factors but also decreases endogenous anticoagulant activity.

Mechanism summarised

```
Warfarin
   |
   v
Inhibition of VKORC1
   |
   v
Reduced regeneration of reduced vitamin K
   |
   v
Reduced gamma-carboxylation
   |
   v
Reduced functional activity of factors II, VII, IX and X
and proteins C and S
   |
   v
Reduced coagulation and thrombus formation
```

Why does warfarin have a delayed onset of action?

Warfarin does not directly inactivate coagulation factors already circulating in the blood.

Instead, it reduces the production of functional replacement factors.

The existing factors must undergo their normal clearance before the full anticoagulant effect develops.

Factor VII has a relatively short half-life, while factor II has a much longer half-life. Consequently, the anticoagulant effect develops gradually, with the full effect commonly taking several days.

The anticoagulant effect may persist for several days after warfarin is discontinued.

4.3 Why can warfarin initially increase thrombosis risk?

Protein C is a vitamin K-dependent natural anticoagulant with a relatively short plasma half-life.

Following warfarin initiation, functional protein C levels can fall relatively quickly, while procoagulant factors, particularly prothrombin, remain active for longer.

This transient imbalance may produce a temporary prothrombotic state.

In susceptible patients, warfarin initiation can be associated with:

- Warfarin-induced skin necrosis.
- Transiently increased thrombotic risk.

This is one reason why patients requiring immediate therapeutic anticoagulation may need an appropriate parenteral anticoagulant while warfarin takes effect.

However, **bridging is not required for every patient starting warfarin**. Its use depends on the clinical indication, the urgency of anticoagulation and the patient's thrombotic and bleeding risks.

4.4 Pharmacokinetics

Absorption

Warfarin is administered orally and is well absorbed from the gastrointestinal tract.

Distribution

It is highly bound to plasma proteins, particularly albumin.

Consequently, changes in protein binding and the effects of interacting drugs can influence its anticoagulant response, although changes in binding alone do not reliably predict the net clinical effect.

Metabolism

Warfarin undergoes hepatic metabolism.

The more potent S-enantiomer is metabolised predominantly by CYP2C9, whereas the R-enantiomer is metabolised through several pathways, including CYP1A2 and CYP3A4.

Genetic variation in CYP2C9 and VKORC1 can influence dose requirements.

Elimination

Warfarin is eliminated mainly after hepatic metabolism, with metabolites excreted through the kidneys.

Renal impairment can still complicate anticoagulation management through changes in bleeding risk, comorbidities and treatment response.

4.5 Therapeutic indications

Warfarin is used in:

1. Prevention of thromboembolism in patients with mechanical prosthetic heart valves.
2. Prevention of stroke and systemic embolism in selected patients with atrial fibrillation.
3. Treatment of deep vein thrombosis.
4. Treatment of pulmonary embolism.
5. Secondary prevention of venous thromboembolism.
6. Selected patients with antiphospholipid syndrome, particularly those with high-risk thrombotic disease.
7. Other selected thromboembolic conditions where a vitamin K antagonist is indicated.

Clinical pearl

Warfarin remains a standard oral anticoagulant for mechanical prosthetic heart valves.

DOACs should not be substituted for warfarin in patients with mechanical heart valves.

Warfarin is also generally preferred for patients with thrombotic antiphospholipid syndrome at high risk of recurrent events, particularly triple-positive patients.

4.6 Administration and dosage principles

Warfarin is administered orally, usually once daily.

There is no single universally appropriate starting or maintenance dose.

The dose is individualised according to:

- The clinical indication.

- Baseline INR.
- Age and body size.
- Liver function.
- Nutritional status.
- Concomitant medication.
- Bleeding risk.
- Genetic factors, where relevant.
- Subsequent INR measurements.

For many indications, the usual target INR is **2.0–3.0**.

For certain mechanical valves, a higher target may be required, depending on the valve type, position and patient-specific risk factors.

The correct target must be determined from the relevant valve-specific or indication-specific guideline.

A loading dose should not be used indiscriminately because rapid anticoagulation may increase the risk of complications without providing an appropriate clinical benefit.

4.7 Monitoring: Prothrombin time and INR

Warfarin is monitored using the prothrombin time (PT), expressed as the international normalised ratio (INR).

The INR standardises PT results to facilitate comparison between laboratories.

The INR is calculated using the patient's PT relative to a normal reference PT, adjusted for the international sensitivity index of the thromboplastin reagent.

Typical INR targets

Clinical indication	Common target INR
Atrial fibrillation	2.0–3.0
Treatment of DVT	2.0–3.0
Treatment of PE	2.0–3.0
Many mechanical aortic valves	2.0–3.0 or a valve-specific target
Some mechanical mitral valves	Commonly 2.5–3.5

These are teaching examples rather than universal prescriptions. Valve type, position and individual thrombotic risk can change the required target.

Interpretation

- **INR below target:** Anticoagulation may be insufficient, increasing thromboembolic risk.

- **INR within target:** Anticoagulation is generally within the intended therapeutic range.
- **INR above target:** Bleeding risk increases, especially as the INR rises substantially.

An elevated INR does not automatically mean that clinically significant bleeding is occurring.

Frequency of monitoring

Monitoring is more frequent during initiation, after dose changes, during acute illness and when interacting drugs are started or stopped.

Once stable, the interval may be extended according to the patient's circumstances and the local anticoagulation protocol.

A practical monitoring resource is the NHS Specialist Pharmacy Service warfarin monitoring guidance.

4.8 Adverse effects

A. Haemorrhage

Bleeding is the most important adverse effect.

It may present as:

- Epistaxis.
- Gingival bleeding.
- Haematuria.
- Gastrointestinal bleeding.
- Extensive bruising.
- Intracranial haemorrhage.
- Retroperitoneal haemorrhage.
- Heavy menstrual bleeding.

The risk is increased by excessive anticoagulation, interacting medications, uncontrolled hypertension and certain comorbidities.

B. Warfarin-induced skin necrosis

This uncommon but important complication typically occurs during the early days of treatment.

It is associated with a transient prothrombotic state, often related to rapid depletion of protein C.

It may present with painful erythematous or purpuric lesions that progress to skin necrosis.

C. Purple toe syndrome

This uncommon complication may occur after warfarin initiation and is thought to involve cholesterol microembolisation in affected patients.

It should be distinguished from other causes of digital ischaemia.

D. Teratogenicity

Warfarin crosses the placenta and can cause fetal harm.

Exposure during pregnancy may cause:

- Warfarin embryopathy.
- Fetal bleeding.
- Pregnancy loss.
- Other fetal complications.

Warfarin is generally avoided during pregnancy, although patients with mechanical heart valves present a particularly complex situation because both maternal thrombosis and fetal harm must be considered.

Pregnancy management requires specialist input rather than automatic substitution without assessing maternal risk.

E. Other adverse effects

Other possible adverse effects include gastrointestinal symptoms, rash and, rarely, hepatic injury.

4.9 Drug interactions

Warfarin has numerous clinically significant interactions.

These interactions may increase or decrease the INR and may also alter bleeding risk independently of the INR.

Drugs that may increase the INR

Examples include:

- Metronidazole.
- Trimethoprim–sulfamethoxazole.
- Fluconazole and selected other azole antifungals.
- Amiodarone.
- Some macrolide antibiotics.
- Some other antibiotics, depending on the drug and clinical circumstances.

Mechanisms include inhibition of warfarin metabolism, reduced vitamin K availability and changes associated with acute illness.

Drugs that may decrease the INR

Examples include:

- Rifampicin.
- Carbamazepine.
- Phenytoin, which has complex and sometimes biphasic effects.
- Other enzyme-inducing drugs.

These drugs may increase warfarin metabolism or otherwise alter the anticoagulant response.

Drugs that increase bleeding without necessarily increasing the INR

Examples include:

- Aspirin.
- Clopidogrel.
- Non-steroidal anti-inflammatory drugs (NSAIDs).

These agents may impair platelet function or damage the gastrointestinal mucosa, thereby increasing bleeding risk.

Combining warfarin with antiplatelet therapy should therefore be based on a clear clinical indication.

Food interactions

Vitamin K-rich foods include:

- Spinach.
- Kale.
- Broccoli.
- Other green leafy vegetables.

Patients do not usually need to avoid these foods completely. Instead, they should maintain a reasonably consistent dietary vitamin K intake.

Abrupt dietary changes can alter the INR.

Excessive alcohol consumption, acute illness and changes in nutritional status can also affect anticoagulation.

4.10 Contraindications and precautions

Warfarin should generally be avoided or used only under carefully controlled specialist supervision in patients with:

- Active major bleeding.
- Severe uncontrolled bleeding risk.
- Pregnancy, except in selected specialist-managed circumstances.
- Recent intracranial haemorrhage or certain high-risk intracranial conditions.
- Severe uncontrolled hypertension.
- Significant hepatic disease associated with coagulopathy.
- Inability to obtain necessary monitoring.
- Major drug interactions that cannot be managed safely.

The presence of a contraindication must be assessed in the context of the indication and the availability of alternative treatments.

4.11 Management of excessive anticoagulation

Management depends on the INR, the presence or absence of bleeding, the severity of bleeding and the underlying thrombotic risk.

A. Elevated INR without significant bleeding

Possible measures include:

- Withholding or adjusting warfarin temporarily.
- Rechecking the INR.
- Identifying and correcting interacting drugs or other causes.
- Administering oral vitamin K when indicated by the degree of INR elevation and clinical circumstances.

Not every elevated INR requires vitamin K.

B. Major or life-threatening bleeding

Management generally involves:

1. Stopping warfarin.
2. Immediate assessment and resuscitation.
3. Identifying and controlling the bleeding source.
4. Administering intravenous vitamin K when indicated.
5. Giving four-factor prothrombin complex concentrate (4F-PCC) for rapid replacement of vitamin K-dependent coagulation factors.

Fresh frozen plasma may be used when PCC is unavailable or unsuitable, depending on the clinical situation and local protocols.

Why combine PCC with vitamin K?

PCC supplies functional coagulation factors rapidly, whereas vitamin K enables the liver to synthesise functional factors subsequently.

PCC acts quickly, but its effect is temporary. Vitamin K helps sustain reversal.

5. DIRECT ORAL ANTICOAGULANTS (DOACs)

5.1 Introduction

Direct oral anticoagulants inhibit individual activated coagulation factors directly.

The principal agents are:

- Dabigatran.
- Apixaban.
- Rivaroxaban.
- Edoxaban.

DOACs are increasingly used for prevention and treatment of thromboembolic disorders.

Compared with warfarin, they generally have:

- More predictable pharmacokinetics.
- More rapid onset of action.
- Shorter half-lives.
- Fewer dietary interactions.
- Fewer clinically significant drug interactions overall.
- No requirement for routine INR monitoring.

However, they still require appropriate prescribing, assessment of renal and hepatic function, review of drug interactions and periodic clinical monitoring.

The following sections discuss each drug individually.

6. DABIGATRAN

6.1 Classification

Dabigatran is an oral, direct thrombin inhibitor.

It is administered as the prodrug dabigatran etexilate.

The prodrug is converted to active dabigatran after absorption.

6.2 Mechanism of action

Dabigatran directly inhibits thrombin, also known as factor IIa.

Thrombin is essential for the conversion of fibrinogen into fibrin.

By inhibiting thrombin, dabigatran:

1. Reduces conversion of fibrinogen to fibrin.
2. Reduces thrombin-mediated activation of coagulation factors.
3. Inhibits thrombin-mediated platelet activation.
4. Reduces the formation and propagation of fibrin-rich thrombi.

Unlike warfarin, dabigatran does not inhibit the synthesis of coagulation factors.

It inhibits the activity of an already formed coagulation enzyme.

6.3 Pharmacokinetics

Absorption

Dabigatran etexilate is administered orally.

Its bioavailability is low, approximately 3–7%.

Absorption is influenced by the formulation and gastrointestinal conditions.

Distribution

Dabigatran has relatively low plasma protein binding compared with warfarin.

Metabolism

The prodrug is converted to active dabigatran by esterases.

Dabigatran is not dependent on CYP3A4 metabolism to the same extent as apixaban or rivaroxaban.

Elimination

Dabigatran is predominantly eliminated by the kidneys.

Consequently, renal impairment can markedly increase exposure and bleeding risk.

6.4 Therapeutic indications

Depending on local approval and the specific formulation, dabigatran is used for:

- Prevention of stroke and systemic embolism in eligible patients with non-valvular atrial fibrillation.
- Treatment of DVT and PE.
- Prevention of recurrent DVT and PE after initial treatment.
- Prevention of venous thromboembolism after selected orthopaedic procedures.

For acute DVT or PE, dabigatran generally requires an initial course of parenteral anticoagulation before it is started.

This differs from apixaban and rivaroxaban, which can be initiated using oral regimens specifically designed for acute VTE treatment.

6.5 Adverse effects

The important adverse effects include:

- Bleeding.
- Dyspepsia.
- Gastrointestinal discomfort.
- Gastrointestinal haemorrhage.
- Anaemia.

Dyspepsia is a characteristic adverse effect of dabigatran.

6.6 Contraindications and precautions

Important considerations include:

- Active clinically significant bleeding.
- Severe renal impairment, according to the relevant indication and product information.
- Significant drug interactions.
- Certain mechanical prosthetic heart valves.
- Pregnancy and breastfeeding, where treatment requires specific assessment.

The appropriateness of dabigatran depends on renal function, indication, dose and local product information.

6.7 Drug interactions

Dabigatran is a substrate of P-glycoprotein (P-gp).

P-gp affects the absorption and disposition of dabigatran.

P-gp inhibitors can increase dabigatran exposure, whereas P-gp inducers can reduce its exposure.

Examples of relevant interacting drugs include:

- Dronedarone.
- Ketoconazole.
- Rifampicin.
- Certain other P-gp inhibitors or inducers.

The magnitude and clinical significance of each interaction depend on the drug combination, renal function and indication.

6.8 Reversal agent: Idarucizumab

Idarucizumab is a specific reversal agent for dabigatran.

It is a monoclonal antibody fragment that binds dabigatran with very high affinity, neutralising its anticoagulant activity.

It is used in selected patients who require urgent reversal because of:

- Life-threatening or uncontrolled bleeding.
- Emergency surgery or an urgent procedure when clinically significant dabigatran activity is present.

The standard adult reversal regimen is **5 g intravenously**, administered as two 2.5 g doses.

The possibility of recurrent anticoagulant activity should be considered in selected patients, particularly those with impaired renal function or substantial circulating dabigatran concentrations.

7. APIXABAN

7.1 Classification

Apixaban is a direct factor Xa inhibitor.

7.2 Mechanism of action

Apixaban selectively and reversibly inhibits activated factor X.

Factor Xa is responsible for converting prothrombin to thrombin as part of the prothrombinase complex.

Inhibiting factor Xa reduces thrombin generation.

This reduces fibrin formation and thrombus propagation.

Mechanism

```
Apixaban
    |
    v
Inhibition of Factor Xa
    |
    v
Reduced conversion of prothrombin to thrombin
    |
    v
Reduced fibrin formation
    |
    v
Reduced thrombus formation
```

Apixaban acts directly on factor Xa rather than inhibiting vitamin K recycling.

7.3 Pharmacokinetics

Absorption

Apixaban is administered orally and has an oral bioavailability of approximately 50%.

Distribution

It has substantial plasma protein binding.

Metabolism

Metabolism involves several pathways, including CYP3A4.

Apixaban is also a P-gp substrate.

Elimination

Apixaban is eliminated through multiple routes, including renal and non-renal pathways.

Renal impairment still requires careful consideration when selecting patients and determining the dose.

7.4 Therapeutic indications

Apixaban is used for:

1. Prevention of stroke and systemic embolism in eligible patients with non-valvular atrial fibrillation.
2. Treatment of DVT.
3. Treatment of PE.
4. Prevention of recurrent DVT and PE.
5. Prevention of venous thromboembolism after selected hip or knee replacement procedures.

The approved indications may differ between countries.

7.5 Dosage principles

Apixaban dosing depends on the indication.

For example, in adults with non-valvular atrial fibrillation, the commonly used dose is 5 mg twice daily.

A reduced dose of 2.5 mg twice daily is indicated in patients meeting the relevant product-specific criteria. In the commonly used US label, reduction is indicated when at least two of the following are present:

- Age 80 years or older.
- Body weight 60 kg or less.
- Serum creatinine 1.5 mg/dL or greater.

These criteria should not be applied indiscriminately to other indications, and local prescribing information should be followed.

Treatment of acute DVT or PE uses a different regimen from stroke prevention in atrial fibrillation.

Examination point: Always state the indication when discussing the dose of a DOAC.

7.6 Adverse effects

The principal adverse effect is bleeding.

Other possible adverse effects include:

- Anaemia.
- Nausea.
- Bruising.
- Gastrointestinal bleeding.

Serious bleeding may involve the gastrointestinal tract, intracranial compartment or other critical sites.

7.7 Drug interactions

Apixaban is affected by P-gp and CYP3A4.

Strong combined inhibitors may increase apixaban exposure and bleeding risk.

Strong combined inducers may reduce exposure and increase thromboembolic risk.

Examples include selected azole antifungals, rifampicin and certain anticonvulsants.

Concurrent NSAIDs or antiplatelet drugs may increase bleeding risk.

7.8 Reversal

Andexanet alfa is a specific reversal agent for apixaban in jurisdictions where it is approved and available for the relevant indication.

Four-factor PCC may be used as an alternative haemostatic strategy in selected major bleeding situations according to local protocols.

The precise choice depends on the severity of bleeding, time since the last dose, renal function, drug availability and local guidance.

8. RIVAROXABAN

8.1 Classification

Rivaroxaban is an oral direct factor Xa inhibitor.

8.2 Mechanism of action

Rivaroxaban selectively inhibits factor Xa.

This reduces the conversion of prothrombin to thrombin and consequently reduces fibrin formation.

Unlike dabigatran, rivaroxaban does not directly inhibit thrombin.

Unlike warfarin, it does not inhibit vitamin K recycling.

8.3 Pharmacokinetics

Absorption

Rivaroxaban is administered orally.

Food increases the absorption of certain doses. The 15 mg and 20 mg tablets used in common adult VTE and atrial fibrillation regimens must be taken with food.

Distribution

Rivaroxaban is highly protein-bound.

Metabolism

Its metabolism involves CYP3A4, CYP2J2 and non-CYP pathways.

It is also a P-gp substrate.

Elimination

Rivaroxaban undergoes renal and faecal elimination, including renal excretion of unchanged drug.

Renal function must therefore be assessed before prescribing.

8.4 Therapeutic indications

Rivaroxaban is used for:

- Prevention of stroke and systemic embolism in eligible patients with non-valvular atrial fibrillation.
- Treatment of DVT.
- Treatment of PE.
- Prevention of recurrent VTE.
- Prevention of VTE after selected hip or knee replacement procedures.
- Selected other thrombotic indications, including specific vascular regimens in combination with antiplatelet therapy.

Not every indication uses the same dose.

8.5 Adverse effects

The main adverse effect is bleeding.

Other possible adverse effects include:

- Anaemia.
- Gastrointestinal symptoms.
- Bruising.
- Gastrointestinal haemorrhage.

8.6 Drug interactions

Rivaroxaban is affected by both CYP3A4 and P-gp.

Important interacting drugs include:

- Strong CYP3A4/P-gp inhibitors.
- Strong CYP3A4/P-gp inducers.
- Other anticoagulants.
- Antiplatelet drugs.
- NSAIDs.

Drug interactions should be reviewed before treatment and whenever a new medication is introduced.

8.7 Reversal

Andexanet alfa has been used as a specific reversal agent for rivaroxaban in jurisdictions where it is approved and available.

Four-factor PCC may be considered for selected patients with major bleeding when specific reversal is unavailable or unsuitable.

The management of life-threatening bleeding should follow the relevant emergency protocol.

9. EDOXABAN

9.1 Classification

Edoxaban is an oral direct factor Xa inhibitor.

9.2 Mechanism of action

Edoxaban directly inhibits factor Xa.

This reduces thrombin generation and the subsequent conversion of fibrinogen into fibrin.

9.3 Pharmacokinetics

Edoxaban is absorbed orally and has a relatively predictable pharmacokinetic profile.

It is a P-gp substrate.

A substantial proportion of its elimination occurs through the kidneys, so renal function is important in dose selection.

9.4 Therapeutic indications

Depending on local approval, edoxaban is used for:

- Prevention of stroke and systemic embolism in eligible patients with non-valvular atrial fibrillation.
- Treatment of DVT and PE.
- Prevention of recurrent VTE.

For acute VTE treatment, an initial course of parenteral anticoagulation is generally required before edoxaban is started.

9.5 Adverse effects

The most important adverse effect is bleeding.

Other possible adverse effects include anaemia and gastrointestinal haemorrhage.

9.6 Dose considerations

Dose selection depends on the indication, renal function, body weight and relevant interacting medications.

Edoxaban has an important indication-specific renal function consideration: in non-valvular atrial fibrillation, some product labels advise against its use when creatinine clearance is very high, such as above 95 mL/min in the United States, because of reduced efficacy relative to warfarin in that population.

This restriction is not universal across all jurisdictions or indications.

9.7 Reversal

There is no single universally available reversal strategy for every jurisdiction.

Four-factor PCC may be considered for selected major bleeding situations under local protocols.

The choice of reversal treatment should be guided by the drug-specific product information and local emergency recommendations.

10. COMPARISON OF WARFARIN AND DOACs

This comparison is particularly important for final MBBS examinations.

Feature	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Drug class	Vitamin K antagonist	Direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Primary target	VKORC1	Thrombin, IIa	Factor Xa	Factor Xa	Factor Xa
Onset of action	Delayed	Rapid	Rapid	Rapid	Rapid
Half-life	Long and variable; commonly around 36–48 h	Approximately 12–17 h, depending on patient factors	Approximately 12 h	Approximately 5–13 h, depending on age and patient factors	Approximately 10–14 h
Renal elimination	No substantial unchanged renal elimination	Predominantly renal	Partial renal elimination	Partial renal elimination	Substantial renal elimination
Routine monitoring	INR required	No routine coagulation monitoring	No routine coagulation monitoring	No routine coagulation monitoring	No routine coagulation monitoring
Major interactions	Numerous drug and dietary interactions	Mainly P-gp interactions	P-gp and CYP3A4 interactions	P-gp and CYP3A4 interactions	P-gp interactions
Specific reversal	Vitamin K plus PCC when indicated	Idarucizumab	Andexanet alfa where approved and available; PCC may be used in selected cases	Andexanet alfa where approved and available; PCC may be used in selected cases	PCC may be considered in selected cases
Mechanical heart valves	Used when indicated	Not recommended	Not recommended	Not recommended	Not recommended

The pharmacokinetic values are approximate. They vary with age, renal function, hepatic function and other patient-specific factors. (American Heart Association Journals)

10.1 Advantages of DOACs over warfarin

DOACs generally offer:

1. Rapid onset of anticoagulant action.
2. Predictable pharmacokinetics.
3. Fixed dosing regimens for specific indications.
4. Fewer food interactions.
5. Fewer drug interactions overall.
6. No requirement for routine INR monitoring.
7. Lower risk of intracranial haemorrhage than warfarin in many studied populations.

Some DOACs are associated with increased gastrointestinal bleeding compared with warfarin in certain populations and regimens.

The comparative bleeding profile varies by drug, dose, patient population and indication.

10.2 Disadvantages of DOACs

These include:

1. Dependence on adherence because anticoagulant activity falls relatively quickly after missed doses.
2. Important renal function restrictions.
3. Drug interactions involving P-gp and, for selected agents, CYP3A4.
4. Potentially high acquisition costs.
5. Limited suitability in certain special populations.
6. The need to assess the last dose and residual anticoagulant activity during emergency procedures or major bleeding.
7. Limited availability of specialised assays and reversal agents in some settings.

10.3 Advantages of warfarin

Warfarin remains useful because:

- Its anticoagulant effect can be monitored through the INR.
- It is established for mechanical heart valves.
- It is often suitable for thrombotic antiphospholipid syndrome.
- Vitamin K and PCC can reverse its effect.
- It may be more affordable than DOACs in some healthcare settings.

10.4 Disadvantages of warfarin

These include:

- Delayed onset.

- Numerous drug interactions.
- Dietary interactions.
- Regular INR monitoring.
- A narrow therapeutic range.
- Variable dose requirements.
- Important pregnancy-related risks.

Clinical conclusion: DOACs are preferred over warfarin for many eligible patients with non-valvular atrial fibrillation or VTE, but warfarin remains essential in selected clinical situations. Treatment should be individualised rather than based on the assumption that one drug is always superior.

11. CLINICAL INDICATIONS FOR ORAL ANTICOAGULANTS

11.1 Atrial fibrillation

Atrial fibrillation produces disorganised atrial electrical activity and ineffective atrial contraction.

Blood stasis, particularly in the left atrial appendage, promotes thrombus formation.

A thrombus may embolise to the cerebral circulation and cause ischaemic stroke.

Oral anticoagulation reduces this risk.

Drug selection

In eligible patients with non-valvular atrial fibrillation, DOACs are commonly preferred over warfarin.

Warfarin remains indicated for patients with mechanical heart valves and is preferred in selected patients with high-risk antiphospholipid syndrome.

The decision to anticoagulate should take account of the patient's stroke risk, bleeding risk, comorbidities and preferences.

Bleeding risk scores should be used to identify modifiable risk factors and guide follow-up, not as the sole reason to withhold anticoagulation.

11.2 Deep vein thrombosis

DVT usually involves thrombus formation in the deep veins, particularly those of the lower limbs.

Risk factors include:

- Prolonged immobilisation.
- Surgery.
- Malignancy.
- Pregnancy and the postpartum period.
- Oestrogen-containing medication.
- Previous VTE.
- Inherited or acquired thrombophilia.

Oral anticoagulants prevent thrombus extension, pulmonary embolisation and recurrent VTE.

Apixaban and rivaroxaban can be initiated using their approved acute VTE regimens.

Dabigatran and edoxaban generally require initial parenteral anticoagulation before oral treatment.

Warfarin also requires an appropriate initial anticoagulant strategy when immediate anticoagulation is needed.

11.3 Pulmonary embolism

Pulmonary embolism usually results from embolisation of thrombi originating in the deep veins.

Anticoagulation is the principal treatment for most haemodynamically stable patients with confirmed PE.

Patients with haemodynamic instability may require advanced interventions, including systemic thrombolysis, catheter-directed treatment or surgical embolectomy, depending on the clinical circumstances.

Oral anticoagulants are used for continued treatment and prevention of recurrence once clinically appropriate.

11.4 Mechanical prosthetic heart valves

Patients with mechanical heart valves require long-term anticoagulation because the prosthetic surface and altered blood flow promote thrombosis.

Warfarin is the standard oral anticoagulant.

DOACs should not be used as substitutes for warfarin in patients with mechanical prosthetic valves.

11.5 Venous thromboembolism associated with cancer

Cancer increases the risk of venous thromboembolism through several mechanisms, including tumour-associated procoagulant activity, inflammation and treatment-related factors.

Selected DOACs may be appropriate for cancer-associated VTE.

However, drug selection must account for:

- Gastrointestinal or genitourinary bleeding risk.
- Tumour location.
- Renal and hepatic function.
- Drug interactions with anticancer therapy.
- Absorption problems.
- The patient's clinical status and preferences.

Low-molecular-weight heparin remains an important option in selected patients.

12. CONTRAINDICATIONS AND SPECIAL POPULATIONS

The decision to prescribe an oral anticoagulant requires assessment of both thromboembolic risk and bleeding risk.

12.1 Active bleeding

Active major bleeding is a contraindication to initiating routine anticoagulation until the situation has been assessed and managed.

The underlying cause of bleeding should be identified and treated.

12.2 Renal impairment

Renal function is especially important when prescribing dabigatran because most of the drug is eliminated through the kidneys.

Apixaban, rivaroxaban and edoxaban also require renal assessment.

Dose reduction or avoidance depends on the drug, indication, degree of impairment and relevant product information.

For DOAC dosing, creatinine clearance calculated using the Cockcroft–Gault equation is commonly used because this was the method employed in pivotal clinical studies and is specified in many product labels.

Estimated glomerular filtration rate and creatinine clearance should not automatically be treated as interchangeable for drug dosing.

12.3 Hepatic impairment

Severe hepatic disease may alter coagulation, drug metabolism and bleeding risk.

Warfarin dosing can be difficult to manage in significant hepatic dysfunction because the liver synthesises coagulation factors.

Some DOACs are contraindicated or not recommended in hepatic disease associated with coagulopathy and clinically significant bleeding risk.

The individual product information should be consulted.

12.4 Pregnancy

Warfarin crosses the placenta and can cause fetal harm.

DOACs are generally avoided during pregnancy because safety data are inadequate and their use is not routinely recommended.

Low-molecular-weight heparin is commonly used when anticoagulation is required during pregnancy because it does not cross the placenta.

Patients with mechanical heart valves require specialist management because maternal valve thrombosis and fetal risks must both be considered.

12.5 Breastfeeding

Warfarin is generally considered compatible with breastfeeding.

DOAC use during breastfeeding is usually avoided or approached cautiously according to the relevant product information and specialist advice because evidence is limited.

12.6 Older adults

Older adults have increased risks of both thromboembolism and bleeding.

Assessment should include:

- Renal function.
- Body weight.
- History of falls.
- Anaemia.
- Previous bleeding.
- Concomitant medication.
- Frailty.
- Cognitive function and ability to adhere to treatment.

Age alone is not a sufficient reason to withhold anticoagulation when there is a clear indication.

12.7 Patients undergoing surgery

The perioperative management of anticoagulants depends on:

- The anticoagulant being used.
- Renal function.
- The time of the last dose.
- The bleeding risk of the procedure.
- The patient's thromboembolic risk.
- The urgency of surgery.

For many patients taking DOACs, temporary interruption is sufficient, and routine heparin bridging is not necessary.

Patients taking warfarin may also be managed without bridging in many situations, but selected high-thrombotic-risk patients may require a different approach.

The decision should follow an appropriate perioperative anticoagulation protocol.

13. MONITORING OF ORAL ANTICOAGULANTS

13.1 Warfarin monitoring

Warfarin requires INR monitoring.

The INR guides dose adjustment and helps identify excessive or inadequate anticoagulation.

Monitoring is especially important during:

- Initiation.
- Dose changes.
- Acute illness.
- Introduction or discontinuation of interacting drugs.
- Major dietary changes.
- Suspected bleeding.
- Suspected recurrent thrombosis.

13.2 DOAC monitoring

Routine INR monitoring is not required for DOACs.

However, this does not mean that laboratory or clinical monitoring is unnecessary.

Before treatment, assessment generally includes:

- Full blood count.
- Renal function.
- Liver function.
- Body weight.
- Medication review.
- Assessment for active bleeding.
- Baseline coagulation testing where clinically appropriate.

Follow-up should assess adherence, bleeding, anaemia, renal function, hepatic function and changes in concomitant medication.

Stable patients generally require periodic review, commonly at least annually, with more frequent monitoring when renal impairment, frailty, advanced age or intercurrent illness increases risk. (SPS - Specialist Pharmacy Service)

13.3 Can PT and aPTT monitor DOACs?

Standard coagulation tests have important limitations.

Drug	Potential laboratory effect	Important limitation
Dabigatran	May prolong aPTT and thrombin time	aPTT is not a reliable quantitative measure; a normal aPTT does not exclude every clinically relevant concentration
Apixaban	May prolong PT variably	PT is insensitive and reagent-dependent
Rivaroxaban	May prolong PT	PT sensitivity varies by reagent and cannot reliably quantify the drug effect
Edoxaban	May prolong PT	Standard PT is not a reliable quantitative assay

When urgent assessment of anticoagulant activity is necessary, specialised drug-calibrated assays may be used where available.

Examples include:

- Diluted thrombin time or ecarin-based assays for dabigatran.
- Drug-calibrated anti-factor Xa assays for factor Xa inhibitors.

Results must be interpreted in the context of the drug, dose and time of the last administration.

14. MANAGEMENT OF DOAC-ASSOCIATED BLEEDING

Bleeding is the most important complication of all oral anticoagulants.

Management depends on the severity of bleeding, the drug involved, the timing of the last dose and the patient's clinical condition.

14.1 Initial assessment

The first priorities are:

1. Assess airway, breathing and circulation.
2. Identify the site and severity of bleeding.
3. Determine which anticoagulant the patient is taking.
4. Establish the dose and time of the last administration.
5. Assess renal function.
6. Obtain a full blood count and relevant coagulation tests.
7. Identify concurrent antiplatelet drugs or other interacting medication.
8. Arrange urgent specialist management when major bleeding is suspected.

14.2 Minor bleeding

Examples include mild epistaxis or minor bruising.

Management may involve:

- Local measures to control bleeding.
- Reviewing the timing of the last dose.
- Checking renal function and interacting medications where appropriate.
- Assessing whether treatment interruption is necessary.

Patients should not independently stop anticoagulation without appropriate medical advice unless they are being directed to seek emergency care.

14.3 Major bleeding

Major bleeding may include:

- Intracranial haemorrhage.
- Retroperitoneal haemorrhage.
- Severe gastrointestinal bleeding.
- Bleeding causing haemodynamic instability.
- Bleeding associated with a substantial fall in haemoglobin or transfusion requirement.

Management generally includes:

- Withholding the anticoagulant.
- Resuscitation and supportive care.

- Source control.
- Blood products when clinically indicated.
- Appropriate reversal treatment when indicated.

14.4 Specific reversal strategies

Anticoagulant	Specific reversal agent or strategy
Warfarin	Vitamin K plus 4F-PCC when indicated
Dabigatran	Idarucizumab
Apixaban	Andexanet alfa where approved and available; PCC may be considered in selected cases
Rivaroxaban	Andexanet alfa where approved and available; PCC may be considered in selected cases
Edoxaban	PCC may be considered in selected cases, according to local protocols

The availability, approval status and recommended use of reversal agents vary by jurisdiction and may change over time.

The 2025 practical guidance on DOACs discusses drug-specific reversal, supportive care and the use of haemostatic agents in major bleeding. (PubMed Central (PMC))

Important teaching points

First: Reversal agents are not routinely administered for every episode of bleeding.

Second: Reversal may increase thrombotic risk. The benefits and risks must be assessed.

Third: Activated charcoal may be considered in selected patients presenting soon after ingestion, provided it is clinically appropriate and airway protection is adequate.

Fourth: Dabigatran is the DOAC most amenable to removal by haemodialysis because of its relatively low protein binding, although idarucizumab is generally preferred for urgent reversal when indicated and available.

15. DRUG INTERACTIONS: AN INTEGRATED REVIEW

Drug interactions are a major cause of preventable anticoagulant complications.

15.1 Warfarin interactions

Warfarin interactions can occur through:

- Inhibition or induction of hepatic metabolism.

- Changes in vitamin K availability.
- Changes in nutritional status.
- Alteration of protein binding.
- Effects on platelet function or gastrointestinal integrity.

Examples include:

Drug or drug group	Potential effect
Metronidazole	May increase INR
Trimethoprim–sulfamethoxazole	May increase INR
Rifampicin	May decrease INR
Carbamazepine	May decrease INR
Amiodarone	May increase INR
NSAIDs	Increase bleeding risk, sometimes without changing INR
Aspirin	Increases bleeding risk
Clopidogrel	Increases bleeding risk

The direction and magnitude of an interaction may vary, so INR monitoring should be adjusted when clinically important changes occur.

15.2 DOAC interactions

DOAC interactions primarily involve:

- P-glycoprotein.
- CYP3A4, especially for apixaban and rivaroxaban.
- Drugs that independently increase bleeding risk.

Strong P-gp or CYP3A4 inhibitors may increase anticoagulant exposure.

Strong inducers may reduce anticoagulant exposure and compromise efficacy.

Concurrent use of antiplatelet drugs, NSAIDs or other anticoagulants may increase bleeding risk.

Clinical rule: Before prescribing an oral anticoagulant, review all prescribed drugs, over-the-counter medicines and relevant herbal products.

16. SPECIAL CLINICAL CONSIDERATIONS

16.1 What happens when a patient misses a DOAC dose?

Because DOACs have relatively short half-lives, missed doses can lead to a rapid decline in anticoagulant activity.

The correct advice depends on the particular drug and dosing regimen.

Patients should follow the missed-dose instructions for their specific medicine and should not double doses indiscriminately.

16.2 Why are DOACs unsuitable for some patients with mechanical heart valves?

Mechanical valves are highly thrombogenic surfaces.

Clinical studies have shown that DOAC strategies do not provide an appropriate substitute for vitamin K antagonists in this population.

Warfarin remains the standard oral anticoagulant.

16.3 Why is dabigatran particularly affected by renal impairment?

Dabigatran is predominantly eliminated by the kidneys.

Reduced renal clearance increases its plasma concentration and prolongs anticoagulant activity.

This may increase bleeding risk and influence the choice of drug, dose and monitoring frequency.

16.4 Why is routine INR monitoring inappropriate for DOACs?

DOACs directly inhibit specific coagulation factors and have relatively predictable pharmacokinetics.

The INR was developed to standardise PT monitoring for vitamin K antagonists.

It is not calibrated to measure the anticoagulant effect of DOACs reliably.

Therefore, a normal INR does not establish that a patient taking a DOAC has no clinically significant anticoagulant activity.

16.5 Why must the last dose be established in a bleeding patient?

DOAC concentrations change relatively quickly over time.

Knowing the time of the last dose helps clinicians estimate the likelihood of residual anticoagulant activity, especially when interpreted alongside renal function and the clinical situation.

17. CLINICAL CASE DISCUSSIONS

The following cases illustrate the application of pharmacological principles.

Case 1: Atrial fibrillation

A 72-year-old man with hypertension is diagnosed with non-valvular atrial fibrillation. He has no mechanical heart valve, and his renal function is adequate.

Questions

1. Why is anticoagulation being considered?
2. Which oral anticoagulants are appropriate options?
3. What baseline investigations are needed?
4. Why might a DOAC be preferred over warfarin?
5. What factors could influence the final drug choice?

Discussion

Atrial fibrillation increases the risk of cardioembolic stroke because thrombi may form in the left atrium or left atrial appendage.

Oral anticoagulation reduces the risk of stroke and systemic embolism.

A DOAC such as apixaban, rivaroxaban, dabigatran or edoxaban may be appropriate, depending on the patient's characteristics and local guidance.

Warfarin remains an alternative when clinically indicated.

Baseline assessment should include renal function, liver function, full blood count, medication review and an assessment of thromboembolic and bleeding risks.

Factors influencing selection include renal function, bleeding history, concomitant medication, adherence, cost and patient preference.

Case 2: Mechanical heart valve

A 45-year-old woman with a mechanical mitral valve asks whether she can change from warfarin to apixaban because she finds INR monitoring inconvenient.

Question

Is apixaban an appropriate substitute?

Discussion

No.

Warfarin remains the standard oral anticoagulant for mechanical prosthetic heart valves.

DOACs should not be substituted for warfarin in this setting because they have not demonstrated appropriate efficacy and safety for mechanical valve anticoagulation.

The patient's concerns about monitoring should be addressed by improving access to anticoagulation services rather than changing to an unsuitable drug.

Case 3: Dabigatran and renal impairment

A 78-year-old man taking dabigatran develops acute kidney injury and presents with gastrointestinal bleeding.

Questions

1. Why is renal impairment important?
2. What information should be obtained immediately?
3. What specific reversal agent may be considered?

Discussion

Dabigatran is predominantly eliminated by the kidneys.

Acute kidney injury may increase drug exposure and prolong its anticoagulant effect.

The clinician should determine the dose, time of the last administration, severity of bleeding, renal function, haemoglobin concentration and relevant coagulation results.

Idarucizumab may be indicated for life-threatening or uncontrolled bleeding when dabigatran activity is clinically relevant.

Supportive care and control of the bleeding source remain essential.

Case 4: Warfarin and antibiotics

A 65-year-old patient taking warfarin is prescribed metronidazole for an infection. A few days later, the INR is substantially above the therapeutic range.

Questions

1. What is the likely pharmacological explanation?
2. What complications are of concern?

3. How should the patient be managed?

Discussion

Metronidazole can inhibit warfarin metabolism and increase the INR.

The patient is at increased risk of bleeding.

Management depends on the INR, the presence of bleeding and the patient's thrombotic risk.

Warfarin dosing may need adjustment or temporary interruption, with repeat INR measurement. Vitamin K may be appropriate depending on the degree of INR elevation and the clinical circumstances.

Major bleeding requires emergency management and may require PCC and intravenous vitamin K.

Case 5: Acute deep vein thrombosis

A 56-year-old man presents with a confirmed proximal DVT. He is haemodynamically stable and has no contraindication to anticoagulation.

Questions

1. What is the therapeutic objective of anticoagulation?
2. Which oral agents can be initiated without a preceding course of parenteral anticoagulation?
3. Which DOACs generally require initial parenteral anticoagulation?
4. What baseline assessments are required?

Discussion

Anticoagulation reduces thrombus extension, pulmonary embolisation and recurrent VTE.

Apixaban and rivaroxaban have approved acute VTE regimens that can be initiated without preceding parenteral anticoagulation.

Dabigatran and edoxaban generally require an initial course of parenteral anticoagulation.

Warfarin also requires an appropriate initial anticoagulant strategy when immediate anticoagulation is needed.

Assessment should include renal function, liver function, full blood count, medication review, bleeding risk and the patient's clinical suitability for the proposed regimen.

18. EXAMINATION-FOCUSED SUMMARY

The following facts are particularly important for final MBBS examinations.

Warfarin

1. Warfarin is a vitamin K antagonist.
2. It inhibits VKORC1.
3. It reduces functional factors II, VII, IX and X.
4. It also reduces proteins C and S.
5. Its anticoagulant effect is delayed.
6. Its principal monitoring test is the INR.
7. Vitamin K and PCC are used in appropriate cases of excessive anticoagulation or major bleeding.
8. It is the standard oral anticoagulant for mechanical heart valves.
9. It crosses the placenta and can cause fetal harm.
10. It has numerous drug and dietary interactions.

Dabigatran

1. Dabigatran is a direct thrombin inhibitor.
2. It is administered as dabigatran etexilate.
3. It is predominantly eliminated by the kidneys.
4. Dyspepsia is a characteristic adverse effect.
5. Idarucizumab is its specific reversal agent.

Apixaban

1. Apixaban is a direct factor Xa inhibitor.
2. It is taken orally.
3. Its disposition involves P-gp and CYP3A4.
4. It is used in eligible patients with non-valvular AF and in VTE treatment and prevention.
5. Andexanet alfa is a specific reversal agent in jurisdictions where it is approved and available.

Rivaroxaban

1. Rivaroxaban is a direct factor Xa inhibitor.
2. It is administered orally.
3. It is affected by CYP3A4 and P-gp interactions.
4. Certain doses must be taken with food.
5. Andexanet alfa has been used for specific reversal where approved and available.

Edoxaban

1. Edoxaban is a direct factor Xa inhibitor.

2. Renal function is important in dose selection.
3. It generally requires initial parenteral anticoagulation for acute VTE treatment.
4. It has indication-specific prescribing restrictions.

General principles

1. All oral anticoagulants can cause bleeding.
2. DOACs do not require routine INR monitoring.
3. Lack of routine INR monitoring does not eliminate the need for clinical follow-up.
4. Renal function is important for DOAC selection and dosing.
5. Mechanical heart valves are an important indication for warfarin rather than a DOAC.
6. Anticoagulants prevent clot formation or extension; they do not directly dissolve established thrombi.
7. A patient's thrombotic and bleeding risks must both be assessed.

CONCLUSION

Oral anticoagulants are essential drugs in the prevention and treatment of thromboembolic disease.

Their clinical use requires an understanding of the coagulation cascade, the pharmacological targets of individual drugs, their pharmacokinetic properties and their potential for serious bleeding.

Warfarin inhibits vitamin K recycling and reduces the functional synthesis of several coagulation factors. Its use requires INR monitoring and careful management of drug and dietary interactions.

DOACs act directly on thrombin or factor Xa. They offer more predictable anticoagulant effects and generally do not require routine coagulation monitoring, but renal function, drug interactions, adherence and bleeding risk remain important considerations.

The central principle for medical students is that anticoagulant selection must be individualised. The best agent depends on the clinical indication, renal and hepatic function, pregnancy status, interacting drugs, bleeding risk, cost, availability and the patient's ability to adhere to treatment and monitoring.

A sound understanding of these principles will support safe prescribing, effective prevention of thromboembolic complications and appropriate management of anticoagulant-associated bleeding.