Oral Anticoagulants

The oral anticoagulants available in the UK are warfarin, acenocoumarol, phenindione, dabigatran etexilate, rivaroxaban and apixaban.\(^1\)

- Warfarin continues to be the most widely used oral anticoagulant but the use of the newer oral anticoagulants (dabigatran etexilate, rivaroxaban and apixaban) is increasing.
- Warfarin antagonises vitamin K (needed for the synthesis of clotting factors) and takes 2-3 days to exert its full effect.
- In some situations heparin needs to be given for immediate anticoagulation, whilst waiting for the INR to get into the required range.
- Dabigatran etexilate, rivaroxaban and apixaban are relatively newer oral anticoagulants. Dabigatran etexilate is a direct thrombin inhibitor, whilst rivaroxaban and apixaban inhibit activated factor Xa.
- Dabigatran etexilate, rivaroxaban and apixaban do not require monitoring of the INR.

### Indications and targets

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<th>Anticoagulation recommendations(^2, 3, 4, 5, 6, 7, 8, 9, 10)</th>
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<td>Prophylaxis of venous thromboembolism</td>
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<td>Calf DVT.</td>
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<td>Recurrence of DVT (whilst on warfarin).</td>
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<td>Mitral stenosis or regurgitation - for those who have any of the following: atrial fibrillation, history of systemic embolism, left atrial thrombus, an enlarged left atrium.</td>
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<td>Inherited thrombophilia (symptomatic), antiphospholipid</td>
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Paroxysmal nocturnal haemoglobinuria (PNH).

| Anticoagulation recommendations | Paroxysmal nocturnal haemoglobinuria (PNH). | Long-term. | Anticoagulation may be appropriate for patients with lower indices if additional risk factors are present. |

Atrial fibrillation.

| Anticoagulation recommendations | Atrial fibrillation. | Long-term. | Warfarin - 2.5 for patients with a high proportion of PNH clones (greater than 50%) and a platelet count greater than 100 x 10^9/L. |

Cardioversion.

| Anticoagulation recommendations | Cardioversion. | Three weeks before and four weeks after cardioversion. | Warfarin - 2.5 (cardioversion is generally cancelled if INR is <2 on the day, so to minimise this it may be appropriate to use 3 as a target before the procedure). |

Mural thrombus.


Dilated cardiomyopathy.


Arterial grafts (if needed).

| Anticoagulation recommendations | Arterial grafts (if needed). | Long-term. | Antiplatelet drugs are first-line. If additional anticoagulation with warfarin is considered necessary, target INR should be 2.5. |

Coronary thrombosis.


Artificial valves.

| Anticoagulation recommendations | Artificial valves. | Long-term. | Warfarin: Bileaflet aortic 3.0. Bileaflet mitral 3.5. Tilting disk (any site) 3.0. Caged ball/disk (any site) 3.5. If type not known, aim for 3.0 (aortic) or 3.5 (mitral). |

Coronary artery grafts.

| Anticoagulation recommendations | Coronary artery grafts. | Not indicated. | Not indicated. |

Coronary angioplasty and stents.

| Anticoagulation recommendations | Coronary angioplasty and stents. | Not indicated. | Not indicated. |

NB: the use of warfarin to treat thromboses has more evidence base than the use of heparin.

When to use aspirin plus warfarin

The following are recommended:[11]:

- Patients on an antiplatelet agent for primary prevention of cardiovascular disease (CVD) or peripheral arterial disease or previous ischaemic stroke should have this stopped if they develop an indication for warfarin.
- Patients on aspirin or clopidogrel for secondary prevention of CVD with stable coronary heart disease (one definition being symptom-free for >12 months following acute myocardial infarction) should also have this stopped if they develop an indication for warfarin.
- For patients who have had an acute coronary syndrome (ACS) within the previous year:
  - Those on a single antiplatelet agent should continue this even if they have to start oral anticoagulation. The antiplatelet agent should be stopped 12 months post-ACS.
  - Those on dual antiplatelets following ACS or insertion of drug-eluting stents, who then need to start oral anticoagulants, should be assessed with cardiological and haematological specialists and an attempt made to determine the risk versus benefits of triple therapy.
- If a patient on warfarin develops the need for a coronary artery stent then bare metal stents are preferred, as triple therapy will only be needed for four weeks, following which clopidogrel can be stopped (and aspirin can be stopped at 12 months provided the patient remains cardiovascularly stable).
- There is evidence that in patients undergoing heart valve replacement, aspirin should be continued when warfarin is commencement[12].

Dabigatran etexilate, rivaroxaban and apixaban

- Treatment of DVT and pulmonary embolism:[3, 4, 5]:
  - Dabigatran etexilate is recommended as an option for treating recurrent DVT and pulmonary embolism in adults.
  - Rivaroxaban is an option for the treatment of DVT and pulmonary embolism.
• Prevention of venous thromboembolism\[^{3, 4, 5, 8, 13}\]:
  - Dabigatran etexilate, rivaroxaban and apixaban are licensed for use in adults after total hip replacement or total knee replacement surgery.
  - Dabigatran etexilate is recommended as an option for preventing recurrent DVT and pulmonary embolism in adults.
  - Rivaroxaban is an option for the prevention of recurrent DVT and pulmonary embolism in adults.

• Atrial fibrillation\[^{9, 10}\]:
  - Dabigatran etexilate, rivaroxaban and apixaban are now recommended as alternatives to warfarin, in the prevention of stroke and systemic embolism in patients with atrial fibrillation.
  - They are as effective as warfarin in the reduction of the relative risk of stroke and systemic embolisation in patients with atrial fibrillation. Their use is limited to non-valvular atrial fibrillation with one or more of the following risk factors:
    - **For dabigatran etexilate:**
      - Previous stroke.
      - Previous transient ischaemic attack.
      - Previous systemic embolism.
      - Left ventricular ejection fraction below 40%.
      - Symptomatic heart failure of New York Heart Association (NYHA) class 2 or above.
      - Age 75 years or older.
      - Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.
    - **For rivaroxaban and apixaban:**
      - Congestive heart failure.
      - Hypertension.
      - Age 75 years or older.
      - Diabetes mellitus.
      - Prior stroke or transient ischaemic attack.
  - The decision about whether to start treatment with dabigatran etexilate, rivaroxaban or apixaban should follow a discussion between the clinician and patient regarding the risks and benefits compared with warfarin.
  - NICE recommends two dose options for dabigatran etexilate - a regular dose and a lower dose for those patients at high risk of bleeding.
  - Dabigatran etexilate, rivaroxaban and apixaban have all been associated with lower rates of intracranial haemorrhage but also a possible increase in gastrointestinal bleeding.

**Editor's Note**

November 2017 - Dr Hayley Willacy has recently read a study comparing the safety of direct oral anticoagulants (DOACs) and warfarin in the treatment of venous thromboembolism\[^{14}\]. The study identified 59,525 adults (12,489 DOAC users and 47,036 warfarin users) with a new diagnosis of venous thromboembolism and a prescription for a DOAC or warfarin within 30 days of diagnosis. Of the 59,525 participants, 1,967 (3.3%) had a major bleed and 1,029 (1.7%) died during the follow-up period. The risk of major bleeding was similar for DOACs compared with warfarin use. Bleeding rates at 30 days ranged between 0.2% and 2.9% for DOACs and 0.2% and 2.9% for warfarin. Bleeding rates at 60 days ranged between 0.4% and 4.3% for DOACs and 0.4% and 4.3% for warfarin. No difference was found in the risk of death for DOACs compared with warfarin use. Results remained unchanged after further analyses, including when a longer period of follow-up (180 days) was used.

**Warfarin**

**Contra-indications**\[^{15}\]

The Medicines and Healthcare products Regulatory Agency (MHRA) revised its list of contra-indications in 2009 as a result of Yellow Card reports received over the years. The current list is as follows:

- Known hypersensitivity to warfarin or to any of the excipients.
- Haemorrhagic stroke.
- Clinically significant bleeding.
- Within 72 hours of major surgery with risk of severe bleeding.
- Within 48 hours postpartum.
- Pregnancy (first and third trimesters, can cause congenital malformations and fetal death).
- Drugs where interactions may lead to a significantly increased risk of bleeding - eg, antiplatelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), venlafaxine or duloxetine.
- Uncorrected major bleeding disorder (eg, haemophilia, chronic kidney disease).
- Potential bleeding lesions - eg, active peptic ulcer, oesophageal varices.
- Uncontrolled severe hypertension.
- An unco-operative or unreliable patient.
- A patient at risk of repeated falls.

\[^{NB}:\] treatment with warfarin is not contra-indicated when breast-feeding.
Initiation[2, 11]

Ideally, the baseline prothrombin time should be used to assess dosage but if the clinical situation requires it, initiation should not be delayed. Guidance for acute venous thromboembolism recommends that parenteral anticoagulation continue for at least five days and until the INR is ≥2 (whichever is the longer)[11]. If rapid anticoagulation is required, a loading dose of 5-10 mg should be given on the first day. The subsequent dosage regime depends on the prothrombin time expressed as the INR.

Computer-assisted dosing is superior to manual dosing but not widely available at present[11]. When initiating an oral anticoagulant, consider the existence of comorbidity or therapy likely to increase the risk of bleeding - for example:

- Hypertension.
- Renal impairment.
- Abnormal LFTs.
- Cardiac failure.
- Low body weight.
- Parenteral feeding.
- Acute illness.
- Vitamin K deficiency.
- Drugs likely to potentiate the effect of anticoagulation.
- Advanced age.

If any condition is present which is likely to potentiate the effect of warfarin, or if the baseline prothrombin time is prolonged, consider reducing the first loading dose.

Aim for an INR within 0.5 units of the target.

In atrial fibrillation there is no need to increase warfarin rapidly. An initial dose of 2-3 mg a day achieves therapeutic coagulation in most people in 3-4 weeks.

Thrombophilia

Patients with protein C deficiency are at risk of developing skin necrosis with warfarin. The loading dose should therefore be omitted at initiation. A similar cautious approach should be instigated in patients with protein S deficiency.

Monitoring[15]

People on oral anticoagulants need regular monitoring of INR. INR is checked daily until in the therapeutic range, twice a week for 1-2 weeks, weekly until stable, then every 6-12 weeks.

Change in a patient's condition - eg, liver disease, intercurrent illness, a new drug started - necessitates more frequent testing.

Enhancement of warfarin effect can occur in:

- Loss of weight.
- Acute illness.
- Cessation of smoking.

Reduction of warfarin effect can occur in:

- Weight gain.
- Diarrhoea.
- Vomiting.

In patients with unstable INRs, supplementation of the diet with 100-150 micrograms of vitamin K may improve anticoagulant control[11].

Near-patient testing (NPT) and patient self-management (PSM)[11]

INR monitoring is normally managed by local anticoagulant clinics but, with appropriate training, self-management using a portable coagulation monitor (eg, CoaguChek® S system) can be safe and reliable and much more convenient for many patients. A worrying trend is for patients to buy monitors directly from the manufacturer and use them without proper training. It is hoped that the manufacturers can be engaged to encourage patients to discuss the options with their GP prior to purchase. A recent study found that PSM was as clinically effective as conventional care[16]. It is not deemed cost-effective in the UK compared with usual care, due to the increased frequency of testing but it is recognised that it may improve quality of life in highly motivated individuals who do not have time to attend clinics.

- Patients should conduct NPT, with or without PSM, within a managed anticoagulation clinic programme[11].
- The programme should aim for the same standards of care as a hospital clinic.
- Patients should be assessed for capability - only patients able to follow the same total quality management procedures as hospitals should undertake NPT ± PSM.
- Patients should be audited regularly for comparison with laboratory results, proportion of INRs in range and adverse events.
Patient advice

Patients should be advised to:

- Take the prescribed dose at the same time, daily.
- Report any bruising or bleeding immediately.
- Attend for blood tests as advised.
- Avoid pregnancy - ensure adequate contraception.
- Avoid aspirin - use paracetamol for pain.
- Avoid contact sports and activities carrying a risk of head injury.
- Remind medical and dental carers of anticoagulant use
- Avoid non-steroidal anti-inflammatory drugs (NSAIDS) - diclofenac, meloxicam can be used with care.
- Keep the primary care organisation booklet up to date.

Complications and reasons to discontinue warfarin[15]

The main adverse effect of warfarin is haemorrhage. Risk factors for haemorrhage in patients taking warfarin include:

- High intensity of anticoagulation (INR >4.0).
- Age ≥65 years.
- Highly variable INRs.
- History of gastrointestinal bleeding.
- Uncontrolled hypertension.
- Cerebrovascular disease.
- Serious heart disease.
- Risk of falling.
- Anaemia.
- Malignancy.
- Trauma.
- Renal insufficiency.
- Concomitant drugs.

Other adverse effects include hypersensitivity, rash, alopecia and diarrhoea. See monograph for full list.

Managing haemorrhage and/or a high INR[1, 2]

If the patient has life-threatening bleeding (eg, intracranial or gastrointestinal haemorrhage), hospital admission is indicated. Hospital management involves giving phytoenadione (vitamin K1) 5-10 mg by slow intravenous injection, together with dried prothrombin complex (factors II, VII, IX and X) 30-50 units/kg. Fresh frozen plasma 15 mg/kg should be used if dried prothrombin complex cannot be obtained but is suboptimal[11]. In other cases, manage as below:

- INR above 8 without bleeding or with only a minor bleed (eg, haematuria or epistaxis) - stop warfarin, administer vitamin K1, using the intravenous solution orally (unlicensed use) 2.5-5 mg by mouth, or 0.5-1 mg by intravenous injection slowly. Check INR again 24 hours later; if more than 0.5 above target value, give another dose of vitamin K1. Restart warfarin when INR <5.0.
- INR of 5-8, no bleeding - stop warfarin. If minor bleed, administer vitamin K1 1-2.5 mg by mouth, using intravenous preparation orally. In either case, warfarin can be started again when INR <5.0.

A high INR is often due to a drug interaction (see monograph for a full list)[17]. If possible, prescribe drugs that do not interact with warfarin. Note that considerable variation exists between drugs in the same class (eg, antibiotics).

If the haemorrhage occurred when the warfarin level was in the therapeutic range, consider an underlying cause such as unsuspected renal or gastrointestinal tract pathology.

Managing a low INR

- Ask the patient if they have missed any doses.
- Consider increasing the dose temporarily and adding a booster dose if necessary. Measure the INR again 2-3 days later.

Stopping warfarin[11]

There was initial concern that stopping anticoagulation abruptly would cause a rebound hypercoagulable state. This has not been confirmed by prospective trials and it is now known that warfarin can be stopped without any associated clinical risk, once therapy has been completed[11].

Interactions[18]

- Warfarin is enhanced by alcohol, allopurinol, paracetamol, SSRIs, lipid-regulating drugs, cranberry juice, influenza vaccine and many other drugs and is reduced by oral contraceptives and St John's wort. The effect of other herbal and complementary remedies should not be forgotten[19].
- Advise people on warfarin to check with their pharmacist that any new medicine they are prescribed or buy is OK to take with warfarin.
- Reassess the need for warfarin regularly; a person's cardiovascular risk and the risk of bleeding will change over time.
Managing unavoidable interactions

- If an interacting drug will be used for less than five days, often no dosage change is necessary. Omission of one full warfarin dosage may be prudent with known potentiating drugs.
- If an interacting drug will be used for more than five days, check the INR one week after starting therapy and adjust the warfarin dose accordingly. The INR should also be monitored when an interacting drug is stopped.
- During amiodarone loading, reduce warfarin by half and check INR weekly.
- Major changes in diet (especially involving salads and vegetables) consumption may affect warfarin control.

Special clinical scenarios\cite{15}

- **Ischaemic stroke in atrial fibrillation patients**: the risk of early recurrent embolism of haemorrhagic stroke is small, so a break in treatment is justified in order to minimise the risk of secondary haemorrhage. The break should be for 2-14 days depending on the size of the infarct and the blood pressure.
- **Intravenous drug users**: thrombosis of the iliofemoral vein is common in this patient group. The use of low molecular weight heparin should be considered as an alternative to oral warfarin, particularly if monitoring is difficult because of the patient's lifestyle or there is difficulty in accessing veins.\cite{20}
- **Cancer patients with venous thromboembolism**: low molecular weight heparin gives a better risk/benefit profile (recurrent thromboembolism versus bleeding) than warfarin and should be considered first-line in these patients.\cite{21}
- **Patients with peptic ulcers**: patients with active peptic ulcers are at increased risk of bleeding when on warfarin, so should be reviewed regularly, advised how to recognise bleeding and informed what to do should bleeding occur.
- **Head injuries**: patients on warfarin are at an increased risk of intracranial bleed following a head injury and a low threshold to perform a CT head scan is needed. If there is a high suspicion of an intracranial bleed then the INR should be reversed without delay. There is also a risk of delayed intracranial bleed even if the initial CT scan was normal. Therefore, it is recommended that the INR be kept close to 2.0 for the first four weeks following a significant head injury.\cite{11}

**Managing anticoagulation prior to surgery**

- For surgery where there is no risk of severe bleeding, surgery can be performed with an INR of <2.5, unless there is a risk of life-threatening thromboembolism.
- Where there is a risk of severe bleeding, warfarin should be stopped three days before surgery. If anticoagulation is deemed necessary, INR should be reduced to <2.5 and heparin started. If warfarin cannot be stopped beforehand, low-dose vitamin K should be used to reverse anticoagulation.
- For dental surgery, anticoagulants can be continued, providing the INR is in the therapeutic range (<3).\cite{22}

Improving compliance\cite{18}

Compliance can be improved by:

- Prescribing the smallest number of tablets each day.
- Use of daily dosing rather than alternate day dosing if possible.
- Avoiding using half tablets, as patients may find it difficult to break tablets exactly in half.

Dabigatran etexilate, rivaroxaban and apixaban\cite{23, 24, 25}

Rivaroxaban, apixaban or dabigatran etexilate may be options for patients who are unable to tolerate or comply with warfarin and its therapeutic drug monitoring.

Cautions and/or contra-indications

- Rivaroxaban, apixaban and dabigatran etexilate are contra-indicated in severe renal impairment and also any clinical scenario associated with enhanced coagulopathy as for warfarin – eg, hepatic disease.
- They are also contra-indicated in paediatric populations (ie under the age of 18 years), pregnancy and lactation, due to inadequate evidence of safety and efficacy.
- Rivaroxaban and apixaban interact with medications which inhibit or induce both CYP3A4 and/or P-gp – eg, ketoconazole.
- In comparison, dabigatran etexilate is not affected by the cytochrome P450 medications but does interact with drugs that effect P-gp. For example, amiodarone, verapamil and clarithromycin are P-gp inhibitors, which would lead to increased dabigatran levels. The converse is true of P-gp inducers – eg, rifampicin, carbamazepine and phenytoin. Close clinical surveillance is necessary when these drugs are co-administered, especially if mild-to-moderate renal impairment is also present.
- SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) also lead to increased leading risk with dabigatran etexilate.
- Care should also be taken when either drug is co-administered with NSAIDs and platelet aggregator inhibitors.

Both drugs do not require formal therapeutic drug monitoring but by their nature they can lead to increased bleeding and thus monitoring Hb may be advised. Despite this, with dabigatran etexilate the measurement of activated partial thromboplastin time may help in certain scenarios.
Adverse effects
Rivaroxaban and apixaban

- Bleeding and anaemia can occur.
- Dizzy spells, headache and syncope have been reported so there may be a mild effect on the ability to drive and the use of machines.
- Nausea and gastrointestinal upset.
- Peripheral oedema and fever have also been reported.
- Abnormal renal tests and LFTs.

Dabigatran etexilate

- Epistaxis.
- Anaemia.
- Nausea and gastrointestinal discomfort, including diarrhoea.
- Abnormal LFTs.

NB: Idarucizumab (Praxbind) was released in January 2016. This rapidly reverses the anticoagulant effect of dabigatran.

Further reading & references

- Measurement of non-Coumarin anticoagulants and their effects on tests of Haemostasis; Guidance from the British Committee for Standards in Haematology (2014)
- Antithrombotics: indications and management; Scottish Intercollegiate Guidelines Network - SIGN (updated Jun 2013)
- Rivaroxaban for the treatment of deep vein thrombosis and preventing recurrent venous thromboembolism; NICE Technology Appraisal Guidance, June 2013
- Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism; NICE Technology Appraisal Guidance, July 2012
- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism; NICE Technology Appraisal Guidance, December 2014
- Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults; NICE Technology Appraisal Guidance, January 2012
- Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation; NICE Technology Appraisal Guidance, February 2013
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults; NICE Technology Appraisal Guidance, April 2009
- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation; NICE Technology Appraisal Guidance, March 2012
- Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation; NICE Technology Appraisal Guidance, May 2012
- Guidelines on oral anticoagulation with warfarin, British Committee for Standards in Haematology (2011)
- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults; NICE Technology Appraisal Guidance, September 2008
- Warfarin: changes to safety information; Medicines and Healthcare products Regulatory Agency, 2009 (archived content)
- Anticoagulation; NICE CKS, February 2015 (UK access only)
- Summary of Product Characteristic (SPC); Apixaban - Eliquis®, Bristol-Myers Squibb-Pfizer, electronic Medicines Compendium, Jul 2014
- Summary of Product Characteristic (SPC); Dabigatran etexilate®, Boehringer Ingelheim Limited, electronic Medicines Compendium, Dec 2014
- Summary of Product Characteristic (SPC); Rivaroxaban®, Bayer plc, electronic Medicines Compendium, Dec 2014

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