What you need to know about warfarin

Patients on anticoagulants are eligible for both the new medicine service and targeted medicines use reviews. This article aims to refresh your knowledge on warfarin.

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Warfarin has been the main oral anticoagulant used for the prevention and treatment of venous thromboembolism (VTE) and embolic stroke for over 50 years. The expanded therapeutic role for anticoagulation and an ageing population has led to a rapid increase in patients prescribed warfarin and associated monitoring services over the past two decades. It is estimated that 840,000 people require long-term anticoagulant therapy in the UK.

Increased national focus on addressing under-diagnosis of atrial fibrillation (AF) and ensuring appropriate antithrombotic therapy as part of the stroke prevention agenda suggests that the number requiring oral anticoagulation is set to increase further. Regular international normalised ratio monitoring and appropriate warfarin dose adjustment coupled with patient adherence are important factors in achieving good anticoagulation control and preventing thrombotic and haemorrhagic events.

Pros and cons of warfarin

Studies have shown that warfarin significantly reduces the risk of primary and secondary VTE. For example, warfarin reduces the risk of ischaemic stroke by approximately 67 per cent in patients with AF. However, clinical and operational issues can make managing warfarin patients challenging. Panel 1 summarises the pros and cons of therapy.

Regular audit of the National Patient Safety Agency (NPSA) guidance on actions that make anticoagulants safer.

Pros
- Evidence base shows clear benefit
- Once daily administration (long half-life)
- Availability of a specific antidote to reverse over-anticoagulation
- Regular monitoring service supports patient adherence
- Low acquisition cost

Cons
- Wide inter- and intra-patient variability in pharmacokinetics and response. Factors affecting response include genetic polymorphisms, age, health status (eg, infection, liver function, thyroid function, stress), concomitant drugs, diet, alcohol consumption and adherence
- Narrow therapeutic window
- Numerous drug and food interactions
- Slow onset of action (delayed effect)
- Need for regular INR monitoring and associated costs

Warfarin initiation

Warfarin antagonises vitamin K, resulting in decreases in functional vitamin K dependent clotting factors. Initiating therapy is a fine balance between ensuring a therapeutic INR is reached in a timely manner to prevent thrombosis while avoiding excessive anticoagulation and haemorrhage. There is an increased risk of haemorrhage during the first four weeks of anticoagulation and such events can affect the subsequent acceptability of warfarin to both patients and clinicians.

An appreciation of the pharmacology, pharmacodynamics and pharmacokinetics of warfarin facilitates safe initiation. Warfarin has a long half-life of about 40 hours so it takes about eight days to reach steady state. To reduce the time taken, loading doses are frequently used. However, another key component to the onset of action of warfarin is the time taken for functional vitamin K dependent clotting factors to be depleted. The clearance of these clotting factors depends on their half-lives, which vary widely. At the start of warfarin therapy initial changes in INR are due to depletion of factor VII (shortest half-life, six hours). The actual antithrombotic effect of warfarin depends on the clearance of prothrombin, which has a half-life of between 50 and 72 hours. Therefore antithrombotic action is not typically present until day 5.

Warfarin has both a delayed onset of action and prolonged effect; the maximum effect of a dose occurs up to 48 hours after administration and the effect can last five days. After discontinuation of warfarin dose, INR typically takes five days to return to normal.

Loading protocols

A variety of warfarin loading protocols are in use. The optimal protocol has been the
subject of much debate over the past decade and two Cochrane reviews are currently under way to evaluate the most appropriate loading dose regimens in different indications. The two primary dosing strategies use either 10mg or 5mg as an initial dose. There is no evidence to suggest that a 10mg dose is superior to a 5mg initial dose, but consecutive high loading doses (eg, ≥10mg for two days or more) are associated with an increased risk of INR overshoot and haemorrhage.

Despite the range of protocols available there is general consensus as to when fast or slow initiation regimens would be most suitable. The British Committee for Standards in Haematology guidance recommends a slow regimen (eg, 2mg–5mg as initial dose) for outpatients who do not require rapid anticoagulation; therapeutic anticoagulation should be achieved within three or four weeks in most patients. For those requiring rapid anticoagulation because of high risk of imminent thrombosis (eg, acute pulmonary embolism), a faster regimen is more appropriate. In addition, co-prescribing a parenteral anticoagulant, such as a low molecular weight heparin (LMWH), is recommended to ensure an immediate anticoagulant effect is provided until the INR is stabilised. The parenteral anticoagulant should be continued for at least five days and until the INR is therapeutic for at least 24 hours, whichever is longer.

Data have shown merit in using age-adjusted initiation regimens to account for the increased sensitivity of elderly patients to warfarin. Other patient groups that may benefit from a reduced initial dose include those with low body weight, hepatic impairment or cardiac failure.

Blood tests and targets
The INR is an expression of the time it takes for a fibrin clot to form (prothrombin time) following the addition of thromboplastin (a tissue extract containing tissue factor and phospholipids required to activate clotting). The results are adjusted to allow for the sensitivity of the thromboplastin used, making the INR test reproducible across the world. Essentially it is a measure of anticoagulation. Because warfarin is dosed to INR effect, exhibits wide inter- and intra-patient variability and has a narrow therapeutic window, patients require frequent INR monitoring at the start of therapy. This enables timely assessment of the dose required to achieve and maintain a therapeutic INR.

The relative frequency of monitoring during initiation will depend on the indication and intensity of loading. Treatment for acute thrombosis often necessitates initial daily or alternate day monitoring, whereas for outpatients being slow loaded initial weekly monitoring may be appropriate. As consecutively stable INR readings are achieved intervals between monitoring appointments are gradually increased. The maximum recommended interval is 12 weeks. Most stable patients attend their clinic every eight to 12 weeks.

A growing evidence base over many years for the use of warfarin in a number of indications has led to widely accepted target INR ranges and durations of treatment to support appropriate management and dose adjustments. Examples are given in Panel 2.

Any decision to deviate from the usual target

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**PANEL 2: TARGET INR RANGES AND DURATIONS OF TREATMENT FOR DIFFERENT INDICATIONS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Target INR</th>
<th>INR range</th>
<th>Length of treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>2.5</td>
<td>2–3</td>
<td>At least three months (consider lifelong if severe or unprovoked)</td>
</tr>
<tr>
<td>Proximal vein thrombosis</td>
<td>2.5</td>
<td>2–3</td>
<td>At least three months (consider lifelong if severe or unprovoked)</td>
</tr>
<tr>
<td>Calf vein thrombosis</td>
<td>2.5</td>
<td>2–3</td>
<td>At least six weeks</td>
</tr>
<tr>
<td>Recurrent VTE when warfarin stopped</td>
<td>2.5</td>
<td>2–3</td>
<td>At least six months (consider lifelong)</td>
</tr>
<tr>
<td>Recurrent VTE while still on warfarin</td>
<td>3.5</td>
<td>3–4</td>
<td>At least six months (consider lifelong)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.5</td>
<td>2–3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>2.5</td>
<td>2–3</td>
<td>Three weeks before and four weeks after</td>
</tr>
<tr>
<td>Mural thrombosis</td>
<td>2.5</td>
<td>2–3</td>
<td>At least three months</td>
</tr>
<tr>
<td>Mechanical prosthetic valves</td>
<td>2.5</td>
<td>2–3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Bioprosthetic valves</td>
<td>2.5</td>
<td>2–3</td>
<td>Three to six months</td>
</tr>
</tbody>
</table>

* Review and consideration of stopping therapy or extending duration should be undertaken by haematologist. † Depends on type of valve, position and patient risk factors for thrombosis.

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**PANEL 3: PATIENT COUNSELLING AND EDUCATION POINTS**

- What warfarin is and how it works
- Why the patient has been asked to take it (including explanation of the patient’s condition and rationale for use of warfarin using risk scores and decision aids where appropriate)
- Different people respond to warfarin differently, so monitoring and dose adjustments are needed
- How warfarin is monitored (explanation of INR blood clotting test)
- That warfarin is dosed to reach a target INR, the target for the patient’s condition and the expected duration of treatment
- The frequency of monitoring and the patient’s responsibility to attend appointments, take doses and communicate changes (eg, in diet, health, etc) to the clinic in a timely manner
- The purpose of the yellow oral anticoagulation therapy pack (information booklet, record book and alert card) and to present the yellow record book (or other patient-held record) to healthcare professionals, including pharmacists
- The implications of having a high or low INR (reinforce necessity of monitoring)
- Main side effects*
- Explain the different strengths and colours of warfarin tablets, how to make up specified doses and that the medicine should be taken at the same time each day
- The importance of adherence, tips for remembering to take the tablet and what to do if a dose or doses are missed
- Interactions with other medicines (eg, avoid aspirin unless under direction of a doctor)*
- Interactions with food* and advice on alcohol consumption*
- That acute illness (eg, diarrhoea, vomiting) can affect INR and the clinic should be notified of changes to health that continue for more than three days
- Exercise (contact sports should be avoided because of increased risk of bleeding)
- What to do if admitted to hospital (notify the clinic of elective admission two weeks in advance and retrospectively of emergency admissions — doses may need to be altered or stopped)
- What to do if undergoing a dental procedure (doses may need to be altered or stopped depending on the procedure)
- Issues to consider when going on holiday* (the clinic should be notified in good time so monitoring can be scheduled appropriately and, where necessary, information about INR monitoring options overseas can be found. Patients taking long haul flights should keep mobile and well hydrated.
- Clinic times and contact details
- Specific advice for women of child-bearing age (periods will be heavier and contraception is needed) and women on hormone replacement therapy (a review may be needed)
- Specific advice for patients with deep vein thrombosis (eg, on stockings, keeping mobile and hydrated, worsening pain, leg swelling, discoloration or dyspnoea)

*Further details are given in an accompanying Prescribing & medicines management article (p255).
challenge to get the right balance between points of the patient journey: on initiation, on anticoagulant medicine is given at various factors associated with warfarin therapy. Due to the many clinical and operational counselling and patient education clinic. Some clinics are loaning POCT devices. They will usually be seen at least annually in adjusting their warfarin doses themselves. In addition, small numbers of patients have adjustments from their anticoagulation clinic. Some patients have purchased POCT devices for AF. These tools may add value to consultations, resulting in more satisfactory dialogue and promoting a partnership approach and adherence. Key points to cover in patient education are listed in Panel 3.

The nationally recognised yellow oral anticoagulation therapy pack includes a warfarin information booklet. Patients are encouraged to read this at the start of therapy and to keep it as a resource to remind themselves of key aspects of their warfarin therapy. The booklet is available in a variety of languages (www.npsa.nhs.uk/health/alerts).

**Patient-held records**

Anticoagulation services are expected to provide patients with an up-to-date record of their latest INR test results, dosage information and next clinic appointment. Although most clinics provide patients with a yellow oral anticoagulation therapy record book for this purpose, NPSA guidance is not prescriptive on the format of the patient-held record. 

### KEY POINTS

- Warfarin has a delayed onset of action (maximum effect occurs up to 48 hours after administration) and prolonged effect.
- Target INR ranges depend on indication. INRs less than 1.5 increase risk of thrombosis and over 3.5 increase risk of intracranial haemorrhage.
- Patient-held records should be reviewed before dispensing warfarin.

### Testing options

**Sampling**

Sampling can be venous or capillary. In venous sampling, blood is drawn from a vein into a sodium citrate collection tube. The quantity required depends on the brand of tube used but is in the order of 1.5–3ml in the laboratory the sample is centrifuged and platelet poor plasma removed.

Thromboplastin is added and the time taken for the sample to clot is measured optically.

In capillary sampling, a lancet is used to obtain about 10µl of whole blood. The blood is placed onto a disposable reagent strip within a coagulation point of care testing (POCT) device. INR results are typically available within 60 seconds. Although laboratory INR determination is still used by some anticoagulation clinics most now routinely use capillary sampling and POCT.

Some patients have purchased POCT devices (in the region of £400) and are self-monitoring INRs with advice for dose adjustments from their anticoagulation clinic. In addition, small numbers of patients have been supported to self-manage their anticoagulation; testing their INR and adjusting their warfarin doses themselves. They will usually be seen at least annually in clinic. Some clinics are loaning POCT devices to patients to explore self-monitoring or for use on holiday.

### Counselling and patient education

Due to the many clinical and operational factors associated with warfarin therapy, providing the patient with comprehensive verbal and written education is essential. The NPSA recommends that information about anticoagulant medicine is given at various points of the patient journey: on initiation, on discharge from hospital, at the first anticoagulation clinic appointment and at regular intervals throughout treatment.

At an initial consultation, it can be a challenge to get the right balance between ensuring patients’ questions and concerns are addressed and covering all relevant topics within an allotted time.

There is growing evidence that patients’ adherence is associated with their satisfaction with the information they have received about their medicines. Adherence is strongly linked to anticoagulation control; poor adherence will result in increased thrombotic and haemorrhagic events. Because the level of information that patients desire is likely to vary, information must be tailored appropriately to individuals. A variety of risk scores for thrombotic and haemorrhagic events as well as patient decision aids are available (eg, to consider the use of warfarin adjustment applied to 37mg. For normal fluctuations of INR (eg, ±0.5), weekly dose adjustments are usually in the order of 10–20 per cent, depending on the patient’s previous response. When a fluctuation in INR is due to a drug interaction, depending on the mechanism of interaction and the degree of the effect on the INR, dose adjustments of 25–50 per cent may be required. The average daily dose of warfarin to achieve stable therapeutic INR is between 3.5mg to 6.5mg. However some patients need as little as 0.5mg daily and, rarely, others may require over 20mg.

**Question missed appointments**

If a patient has missed a monitoring appointment it may not be safe to give a further supply of warfarin. Conversely, it may not be safe for the patient to stop treatment. Factors to consider include the patient’s general adherence to appointments and his or her level of anticoagulation control. For patients who have their warfarin regularly dispensed in the same pharmacy it is possible to check the date of the last supply of warfarin. Patients expected to have sufficient remainder should be advised to return to the clinic for a monitoring appointment before warfarin is dispensed. Decisions taken to dispense or not to dispense warfarin when monitoring appointments have been missed should be documented.

**Make a record**

The NPSA recommends that dispensing software allows the date of the last clinic appointment, the last INR test result and the current dose of warfarin to be recorded when this information is being checked before dispensing a repeat prescription. It would seem appropriate to record this information even when the software does not support this functionality.

### PANEL 4: HOW TO REVIEW PATIENT-HELD RECORDS

**Gather the key facts**

Before reviewing the specifics of the patient’s latest INR results, key facts that should be gathered are indication, target INR and duration of treatment. These details can be found on page four of the yellow record book or, alternatively from the GP or anticoagulation clinic. The next step is to check the latest INR result, warfarin dose and date of the next scheduled blood test.

Wherever possible, this should be done in the context of the history of the patient’s previous INRs and warfarin doses.

**What to look out for**

- **There are some general themes that a review of a patient’s yellow book should reveal.** Consecutively therapeutic INRs should result in gradual lengthening in appointment interval while out of range INRs will often result in a shortening in appointment interval. Where information is missing or dose adjustments and appointment intervals appear inappropriate the patient’s anticoagulation clinic or GP, or both, should be contacted.

- **Understand dose adjustments**

 INRs that are just outside of range (eg, ±0.2 of the upper and lower limits of the specified range) will often correct themselves without dose adjustment but the practitioner may occasionally decide to reduce the appointment interval to determine whether an upward or downward trend in INR is emerging. INRs that deviate further from the range will usually require dose adjustment and a potential reduction in the appointment interval.

 For patients established on warfarin, dose adjustments are based on the total weekly dose of warfarin. For example, a patient taking 5mg of warfarin Monday to Friday and 6mg on Saturday and Sunday, will have a dose for AF. These tools may add value to consultations, resulting in more satisfactory dialogue and promoting a partnership approach and adherence. Key points to cover in patient education are listed in Panel 3.

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Pharmacist not only needs to know they are pharmacy and it should be explained that the warfarin. Patients sometimes present their emergency, of identifying the patient is on with them at all times but, if this is not feasible them proactively to relevant healthcare reminded to keep their records and to present information on the latest INR result but also have the ability not only to provide into the yellow book. Most computer systems use computer-printed labels, which are stuck computer-generated print out. Some clinics with the specified information in the form of a written record book but to provide patients some clinics are opting not to use a hand-developed hand-written records which may result in the lack of specific antidotes for safety and effectiveness. Current concerns also exist around the lack of specific antidotes for anticoagulant services operate as well as specific tools used (eg, counselling checklists) or policies followed. This minimises the risk of giving advice that conflicts with the clinic. Patients sometimes present their alert card rather than their book to the pharmacy and it should be explained that the pharmacist not only needs to know they are on warfarin but also needs to be able to review their management to ensure that the supply of medicines is safe.

Warfarin patients recently discharged from hospital frequently experience changes to their warfarin dose requirements. Reasons for this may include acute illness, change in diet or change in their medicines regimen. Patients are required to take their discharge summaries to their anticoagulation clinic appointments to ensure the clinic can make well informed decisions about warfarin therapy. It should not be assumed that because a prescription has been written for warfarin that it is appropriate to dispense. Panel 4 describes how community pharmacists can review patient-held records.

New oral anticoagulant agents

Over the next few years a host of new oral anticoagulants will enter the UK market for use in stroke prevention in AF. Key characteristics of warfarin and some of the latest agents are outlined in Panel 5. In general, in the selected trial populations data suggest that the newer agents are either non-inferior or demonstrate modest benefit over warfarin. In addition, they offer a number of advantages, such as predictable pharmacokinetics, no requirement for monitoring of blood clotting time, fewer drug interactions and standardised dosing. However these advantages are expected to come with a considerable price tag. Furthermore, as with all new drugs, there are uncertainties with regards to their long-term safety and effectiveness. Current concerns also exist around the lack of specific antidotes for these newer agents and the impact of withdrawing the regular monitoring component of oral anticoagulation on patients’ adherence.

Initial reviews of the data for the newer oral anticoagulants together with consideration of the cost implications and uncertainties indicate that warfarin continues to be the first choice oral anticoagulant for AF. However a managed entry approach that identifies and prioritises patient groups considered to benefit most from the newer agents is appropriate. Community pharmacists are well placed to respond to queries about the newer agents providing unbiased information and reinforcing local decisions on prescribing of the newer agents.

References


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