Section 5
Factors affecting warfarin

Objectives

On completion of this section you should be able to:

- analyse the wide range of factors that can affect warfarin therapy
- summarise the main factors that pharmacists and pharmacy technicians should be particularly aware of (eg, drug interactions, diet, lifestyle)
- predict drug and disease interactions with warfarin.

Several factors can affect an individual’s response to warfarin, including:

- drug interactions (including herbal remedies)
- disease states
- age
- pregnancy
- diet
- alcohol
- concordance.

5.1 Drug interactions

Almost any drug can interact with warfarin. Interactions involving warfarin can be divided into two main groups:

- pharmacokinetic
- pharmacodynamic.

Pharmacokinetic effects

A pharmacokinetic interaction is one that will alter the plasma concentration of warfarin and result in a change in the INR. These types of interactions are mainly due to an effect on the metabolism of warfarin, but some drugs also affect the absorption of warfarin, while others can cause displacement from protein binding sites.

Pharmacodynamic effects

A pharmacodynamic effect is one that increases the risk of bleeding without altering the plasma concentration of warfarin (eg, when paroxetine is taken with warfarin). The mechanism of this interaction is not fully understood. Any drug that affects platelet aggregation (eg, clopidogrel) will also increase the risk of bleeding without changing the INR.

Read any standard clinical pharmacy textbook for more details about the mechanism of drug interactions with warfarin.
Clinically significant drug interactions

The use of an interacting drug with warfarin is very difficult to avoid in patients with multiple disease states and consequent polypharmacy. These interactions may lead to a loss of anticoagulation (thereby increasing the risk of thrombosis) or they may cause over-anticoagulation (thereby leading to a risk of haemorrhage).

When a patient is stabilised on warfarin the INR must be closely monitored during the introduction, discontinuation or dosage adjustments of any interacting medication (eg, amiodarone).

The BCSH guidelines on oral anticoagulants state that:

- if a drug change lasts less than five days either no change, minor dose reduction or omit one complete dose of warfarin, if known potentiating drug given
- if the drug change lasts more than five days check the INR one week after commencing the new drug and adjust the warfarin dose on the basis of the result.

Practice point

Find out what arrangements are in place locally for additional INR blood checks when interacting drugs are co-prescribed for a patient already on warfarin. How do you ensure that these additional INR checks have been carried out?

It is important to understand the mechanism of any drug/drug interaction with warfarin and to know what advice to give to the patient about their warfarin when other medication is altered in any way.

Warfarin is metabolised by several P450 iso-enzymes in the liver. Any drug that affects the cytochrome P450 P2C9 enzyme system (which is the primary site of the metabolism of the S-isomer of warfarin, the more potent form of warfarin) has the potential to have a marked effect on anticoagulation, either by increasing or decreasing the INR. Both amiodarone and fluconazole affect this enzyme system and can potentiate the anticoagulant effect of warfarin.

There are other medicines which, if co-prescribed with warfarin, require additional counselling advice such as:

- any medicine with the potential to cause gastrointestinal ulceration and subsequent gastrointestinal bleeding (eg, alendronic acid or NSAIDs)
- any medicine that inhibits platelet function tends to increase the risk of bleeding (eg, NSAIDs, aspirin and clopidogrel). This effect on platelet function is not reflected in the INR and will not be detected by normal monitoring.

Patients and pharmacists should be particularly alert to the potential for interaction between warfarin and over-the-counter products (eg, cimetidine, miconazole and oral or topical NSAIDs).

In addition, pharmacists should also be aware of the potential interactions between herbal medicines and warfarin.
The co-administration of warfarin and NSAIDs is cited by the National Patient Safety Agency (NPSA) as the drug interaction most commonly associated with clinically significant adverse reactions. 18

If possible, NSAIDs should be avoided by patients taking warfarin, particularly by those at greater risk from drug interactions such as the elderly or patients with severe liver disease.

If an NSAID is required to treat a patient who is taking warfarin it should preferably be given at low dosages and introduced slowly, with close monitoring of the INR and the patient for signs of bleeding complications. Some centres also advise the use of a proton pump inhibitor.

Table 3 describes some drugs which are known to interact with warfarin, as described in the British national formulary. 3

### TABLE 3 Selected examples of drug interactions with warfarin

<table>
<thead>
<tr>
<th>Drugs which enhance the anticoagulant effect</th>
<th>Drugs which reduce the anticoagulant effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Oestrogens</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Phenytoin*</td>
</tr>
<tr>
<td>Azole antifungals (fluconazole, itraconazole, ketconazole, miconazole)</td>
<td>Primidone</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Progestogens</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Rifamycins</td>
</tr>
<tr>
<td>Entacapone</td>
<td>Vitamin K present in some enteral feeds</td>
</tr>
<tr>
<td>Fibrates</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>Thyroxine</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
</tr>
</tbody>
</table>

* The metabolism of coumarins is accelerated by phenytoin (there is a possibility of a reduced anticoagulant effect, but enhancement has also been reported).

Erythromycin and other macrolides interact with warfarin unpredictably and only affect certain individuals.

**Practice point**

*Have a look at appendix 1 (Interactions) in the current edition of the British national formulary and also look at the current edition of Stockley’s drug interactions. 19 Make a note of the clinically significant drug interactions with warfarin that you come across most often in your practice.*
Influenza vaccination

The concurrent use of warfarin and influenza vaccine is normally safe, but there have been some reports of serious bleeding in a few patients. (The mechanism of interaction is not understood but it may involve an alteration in the synthesis of blood clotting factors.)

It is worth noting that intramuscular injections should be given with care to patients suffering from coagulation disorders or who are on anticoagulant therapy because of the risk of localised bleeding.

Some centres advise giving a deep subcutaneous injection and keeping the target INR at the low end of the range prior to the injection. They also ask patients to have their INR checked one week after the vaccination and advise them about the risk of bleeding.

Practice point

What advice is given in your own local area/trust for administering influenza vaccine to patients on warfarin and checking the INR afterwards?

Herbal and other alternative medicines

Over the last 10 years the use of alternative medicines has increased substantially and therefore it is important to educate patients on the safety of these medicines while taking warfarin. A survey of 515 users of herbal medicines in the UK found that 26 percent would consult their GP for a serious adverse drug reaction associated with a conventional over-the-counter medicine, but not for a similar reaction to a herbal medicine.20

Some alternative medicines, including food supplements, may interact with warfarin. Many alternative health products have no regulations on the strength and quantities of active ingredients and therefore monitoring the addition of an alternative medicine to a patient stabilised on warfarin can be difficult.

Some widely used alternative medicines that can affect INR are:

- chondroitin
- ginger
- garlic
- ginseng
- ginkgo biloba
- glucosamine
- St John’s wort.
Practice point

Find out what advice your local anticoagulant clinic gives about use of herbal and complementary medicines with warfarin. What does the NPSA advise? Are there any differences in approach?

5.2 Disease states

Many disease states may alter the effects of warfarin, including:

- hypothyroidism
- hyperthyroidism and fever
- liver disease
- congestive heart failure.

Hypothyroidism

This medical condition results in a reduced metabolic rate, which means vitamin K-dependent clotting factors remain in the circulation longer. Thus, a patient with an underactive thyroid will require a higher dose of warfarin. However, when the patient takes levothyroxine and the thyroid function starts to normalise, the warfarin requirement will fall.

Hyperthyroidism and fever

Both hyperthyroidism and fever result in a hypermetabolic state, which may accelerate the clearance of vitamin K-dependent clotting factors. Thus the amount of warfarin required to produce an anticoagulant effect would decrease. This means when a patient starts to take carbimazole or propylthiouracil to correct their thyroid function, their warfarin requirement will increase as their thyroid function normalises.

Liver disease

The use of warfarin in patients with severe liver disease is contraindicated due to the unpredictable effects of liver disease on coagulation, such as:

- vitamin K deficiency due to intra- or extra-hepatic cholestasis
- reduced synthesis of coagulation factors due to severe hepatocellular damage
- functional abnormalities of platelets and fibrinogen found in many patients with liver failure.

Congestive heart failure

Heart failure can cause hepatic congestion of blood flow and inhibit the metabolism of warfarin leading to excessive anticoagulation with a risk of bleeding. This can be troublesome in patients with frequent exacerbations of heart failure (ie, worsening of heart failure, usually requiring hospitalisation).
5.3 Age

Many diseases associated with stroke and thromboembolism become more common with increasing age. Generally, elderly people have an increased sensitivity to the anticoagulant effect of warfarin and require a lower mean daily dose to achieve a given anticoagulant effect.

For example, patients over 75 years of age need less than half the daily warfarin dose of patients aged under 35 for an equivalent level of anticoagulation.

Polypharmacy, which increases the chance of drug interactions, and the decline in cognitive function in some elderly patients makes this a particularly challenging patient group in which to manage anticoagulant therapy safely and effectively.

Practice point

Talk to some of your elderly patients who are taking warfarin to find out how they manage their therapy. What did you learn that you can apply to your own practice?

5.4 Pregnancy

The BNF guidance regarding oral anticoagulants during pregnancy is as follows:

Oral anticoagulants are teratogenic and should not be given in the first trimester of pregnancy. Women of child-bearing age should be warned of this danger since stopping warfarin before the sixth week of gestation may largely avoid the risk of fetal abnormality.

Oral anticoagulants cross the placenta with risk of placental or fetal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, oral anticoagulants should be avoided in pregnancy especially in the first and third trimesters.

Organogenesis occurs during the sixth to the twelfth week of gestation and exposure to warfarin at this time may be associated with embryopathy. However, due to the immaturity of the fetal liver there is a continuing risk of fetal bleeding throughout pregnancy.

The possible need for alternative treatment with heparin in the first trimester – and for two to three weeks before delivery – should be explained. Avoiding oral anticoagulants reduces the risk of embryopathy, but heparin can cause maternal osteoporosis and thrombocytopenia.

Women may breast-feed their babies while they are taking warfarin.

Additional information is provided in the Royal College of Obstetricians and Gynaecologists’ guideline, Thromboembolic disease in pregnancy and the puerperium: acute management (28) February 2007, which can be downloaded from: http://www.rcog.org.uk/index.asp?Page ID=533

5.5 Diet

Patients who are taking warfarin should be encouraged to eat a sensible, well-balanced diet and not go on ‘crash’ diets or start ‘binge’ eating. If patients need to lose weight, encourage them to contact their doctor or practice nurse for advice.
An increase in dietary vitamin K sufficient to reduce the anticoagulant response to warfarin can occur in patients who are being treated with some enteral feeds and in those on weight-reduction diets that are rich in green vegetables.

A well-balanced ‘western’ diet provides about 300 micrograms of vitamin K a day. Vitamin K-rich foods include:

- green leafy vegetables (eg, spinach, Brussels sprouts, broccoli, lettuce)
- chick peas
- liver
- egg yolks
- cereals containing wheat bran and oats
- mature and blue cheeses
- avocado
- olive oil.

### 5.6 Alcohol

Alcohol can act both as an enzyme inhibitor and an enzyme inducer:

- binge drinking results in hepatic dysfunction and can potentiate the response to warfarin through impaired synthesis of coagulation factors, thus producing an increase in INR (alcohol in this situation acts as an enzyme inhibitor)
- a chronic alcoholic (heavy abuser) may show a diminished effect from warfarin, and in this case a decrease in INR is seen (alcohol in this situation acts as an enzyme inducer).

#### Practice point

*Find out what advice your local anticoagulant clinic gives about alcohol to patients taking warfarin. How does this compare with the advice you give? What, if anything, will you do differently as a result?*

### 5.7 Concordance

Poor concordance may be a reason for unexpected and marked variations in anticoagulant control, and the best way to avoid complications with oral therapy is to be certain that the risks of too much or too little anticoagulation are clearly understood by the patient. You should therefore ensure that patients and carers receive adequate verbal and written information about their warfarin treatment to make certain that it is used safely.

Information should be provided before the first dose of anticoagulant is given. It should be reinforced upon discharge from hospital, at the first anticoagulant clinic appointment, and whenever necessary throughout the course of treatment.
Patients should also be encouraged to document missed doses of warfarin in their anticoagulant record. This will aid dosing decisions when their INR is measured.

**Case studies**

Reflect on and complete the following case studies to help you prepare for similar or related cases in your practice.

**Umesh**

<table>
<thead>
<tr>
<th>Patient</th>
<th>72-year-old male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Target INR</td>
<td>2.5 (range 2.0-3.0)</td>
</tr>
<tr>
<td>Duration</td>
<td>Lifelong</td>
</tr>
<tr>
<td>History</td>
<td>Umesh had a heart attack in the past and now has heart failure. In May he was diagnosed with atrial fibrillation and was started on warfarin as an outpatient, using a low slow-start protocol (ie, 2 mg a day for two weeks with once-weekly monitoring). His maintenance dose is 2 mg a day.</td>
</tr>
</tbody>
</table>
| Patient medication record | Aspirin 75 mg daily  
Amlodipine 5 mg daily  
Enalapril 10 mg twice daily  
Furosemide 80 mg daily  
Digoxin 62.5 micrograms in the morning  
Simvastatin 20 mg at night  
Amiodarone 200 mg daily  
Warfarin 1 mg and 3 mg tablets |

1. Umesh attends the anticoagulant clinic in August. His amiodarone had been stopped by the cardiologist two weeks previously. What is likely to happen to his warfarin dose?

2. When should Umesh be asked to return to the clinic?
3. What other drugs in his patient medication record could possibly affect his INR if they were either discontinued or the dose was changed? Explain these effects.

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Bernie Patient 76-year-old male

History Bernie comes into the pharmacy to purchase garlic tablets. He is well known to you but you have not seen him for several months. He informs you that he has been staying with his daughter in Kent. He is taking amiodarone and warfarin.

1. On questioning Bernie you discover that his daughter has recommended that he should take garlic supplements to help his heart problems. He has now been taking them for four weeks. What would you advise?

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Turn to the end of the section for suggested answers.
George

Patient 52-year-old male
Indication Atrial fibrillation for cardioversion
Target INR 2.5 (range 2.0-3.0)
Duration Indefinite period
Patient medication record Warfarin 1 mg and 3 mg tablets
Levothyroxine 50 micrograms to be started on 12 April

An excerpt from his ‘yellow booklet’ (see Section 7.1 for more information about the ‘yellow booklet’):

<table>
<thead>
<tr>
<th>Date</th>
<th>INR</th>
<th>Recommended dose</th>
<th>Next appointment</th>
<th>Clinic record</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 January</td>
<td>3.2</td>
<td>3 mg</td>
<td>2 weeks</td>
<td></td>
</tr>
<tr>
<td>12 February</td>
<td>2.8</td>
<td>3 mg</td>
<td>3 weeks</td>
<td></td>
</tr>
<tr>
<td>5 March</td>
<td>2.6</td>
<td>3 mg</td>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>2 April</td>
<td>1.6</td>
<td>Boost 5 mg for 1 day then 3 mg</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>9 April</td>
<td>1.7</td>
<td>3 mg</td>
<td>1 week</td>
<td></td>
</tr>
</tbody>
</table>

1. What do you expect to happen to George’s INR and warfarin dose once he starts on levothyroxine on 12 April?

Turn to the end of the section for suggested answers.
Summary

- Optimal therapy with warfarin is achieving a fine balance between preventing a thromboembolic event, without increasing the risk of bleeding. Several factors can affect this balance.

- When a patient is stabilised on warfarin, the INR must be closely monitored during the introduction, discontinuation or dosage adjustments of any interacting medication (including St John’s wort, other herbal remedies and over-the-counter medicines) where there is the potential for an adverse effect on the INR.

- Pharmacists and technicians should be particularly aware of the effects of changes in thyroid hormones on warfarin therapy and of the added complications faced by elderly patients.

- Alcohol and foods with a high vitamin K content (eg, spinach) will affect INR levels.

- Poor concordance may be a common reason for unexpected marked variations in anticoagulant control (see Section 7 for further information).

Intended outcomes

By the end of this section you should be able to:

<table>
<thead>
<tr>
<th>Learning objective</th>
<th>Well can you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciate the large number of different factors that can affect warfarin therapy.</td>
<td></td>
</tr>
</tbody>
</table>
Reflective questions

1. Why are elderly patients on warfarin more of a challenge to manage?

2. Which foods have a high vitamin K content?

3. Is the effect of warfarin enhanced or inhibited by the following drugs or herbal remedies:
   - amiodarone?
   - carbamazepine?
   - cimetidine?
   - erythromycin?
   - St John’s wort?

Suggested answers

Case study 2: Umesh (page 36)

1. Umesh attends the anticoagulant clinic in August. His amiodarone had been stopped by the cardiologist two weeks previously. What is likely to happen to his warfarin dose?

   His warfarin dose will probably need to be increased but this need (reflected by a decrease in INR) may not be observed for several weeks or even months. This is because amiodarone can take months to be totally eliminated from the body.

2. When should Umesh be asked to return to the clinic?

   He should be asked to return to the clinic on a weekly basis until his INR is stable within the therapeutic range.

3. What other drugs in his patient medication record could possibly affect his INR if they were either discontinued or the dose was changed? Explain these effects.

   - The effect of aspirin on platelet aggregation increases the risk of bleeding from the gastrointestinal tract and other sites during concurrent warfarin therapy.
   - Simvastatin may alter the INR within four to seven days of starting, stopping or changing the dose. The mechanism is not fully understood.
   - Digoxin also has an effect on INR when doses are altered.
**Case study 3: Bernie (page 37)**

1. On questioning Bernie you discover that his daughter has recommended that he should take garlic supplements to help his heart problems. He has now been taking them for four weeks. What would you advise?

   Garlic taken in the amounts used in cooking does not interact with warfarin. However, at high doses (as found in garlic oil capsules and tablets) it may have an antiplatelet effect. While this should not result in the patient’s INR increasing, it may increase the risk of bleeding for this patient. You may wish to advise Bernie that:

   - It is unlikely that garlic has an important reaction with warfarin
   - Alternative, complementary and herbal medicines have not been studied to the same extent as prescription medicines, and therefore information about safety and interactions is much more anecdotal
   - He should keep taking his garlic capsules on a regular basis but watch out for signs of bleeding
   - He should inform the anticoagulant clinic if he decides to stop taking them.

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**Case study 4: George (page 38)**

1. What do you expect to happen to George’s INR and warfarin dose once he starts on levothyroxine on 12 April?

   George’s clinic results on 2 April and 9 April indicate that his requirements for warfarin have increased due to his underactive thyroid. Starting on levothyroxine would correct his underactive thyroid. This would result in an increase in INR and consequently a lower dose of warfarin would be required.
Section 6

Initiating, maintaining and stopping anticoagulant therapy

Objectives

On completion of this section you should be able to:

- describe how warfarin therapy is initiated
- illustrate the different types of induction regimen and the importance of INR monitoring throughout this process
- manage patients whose INR values are outside their target range.

The effectiveness and safety of warfarin is critically dependent upon maintaining the INR within the target range. In this section you will learn about the various types of induction regimes, when they should be used, and the frequency of monitoring INRs. An exemplar case study is used to illustrate the Fennerty induction regimen in a patient newly diagnosed with atrial fibrillation. You will also get an opportunity to see how patients who are outside their normal target INR range are typically managed.

6.1 Initiating treatment

Before initiating anticoagulant therapy an assessment of the patient’s coagulation status is necessary, including:

- a baseline INR
- indication for treatment
- appropriate INR target range
- proposed duration of treatment.

All these results should be recorded in the patient’s case records and oral anticoagulant therapy booklet (the ‘yellow booklet’ – see Section 7 for further information).

Following the administration of warfarin an observable anticoagulant effect is delayed. The delay may range from two to seven days because warfarin does not act directly on the inactive clotting factors already in circulation but on the rate of synthesis of new factors by the liver. Therefore when rapid anticoagulation is required in acute thromboembolism, heparin and warfarin are usually administered on day 1, with heparin being withdrawn once a stable target INR is reached. The BCSH guidelines state that patients should receive heparin therapy for at least five days and that it should not be discontinued until the INR has been in the therapeutic range for two consecutive days.

It is also usual to initiate warfarin therapy with loading doses in order to reach a stable target INR more quickly. There is a variety of induction regimens that are used to establish patients on warfarin. The more urgent the need for treatment, the more aggressive the induction regimen – the ‘Fennerty induction regimen’, for example, is a rapid induction regimen that starts with a loading dose of 10 mg of warfarin a day. (The BCSH 1998 guidelines contain detailed advice about this regimen in appendix II.)
For patients who require rapid induction of oral anticoagulation the BCSH updated guidelines advise that starting with 5 mg doses or a single 10 mg dose followed by 5 mg doses, may be preferable to regimens that start with repeated 10 mg doses (ie, the Fennerty regimen) in certain patient groups, eg:

- people over 60 years of age
- those with liver disease or cardiac failure
- those at high risk of bleeding.\(^{10}\)

For outpatients who do not require rapid initiation, a slow-loading regimen is safe and achieves therapeutic anticoagulation in the majority of patients within three to four weeks.

### Recommendation from the BCSH

For outpatients who do not require rapid anticoagulation a slow loading regimen* is safe and achieves therapeutic anticoagulation in the majority of patients within three to four weeks (grade B, level IIb). This appears to avoid over-anticoagulation and bleeding associated with rapid loading.

*The loading regimes studied were 2 mg, 3 mg and 5 mg daily.

For patients requiring rapid initiation of oral anticoagulation, regimens that start with 5 mg doses or a single 10 mg dose, followed by 5 mg doses may be preferable to regimens that start with repeated 10 mg doses in certain patient groups, eg, the elderly (over 60 years of age), those with liver disease or cardiac failure and those at high risk of bleeding (grade B, level IIb).\(^{10}\)

### Practice point

*Find out what induction regimes are used or preferred in your own area of practice for different patient groups.*

### Frequency of monitoring

During the induction and initial stabilisation of patients on warfarin, daily INR measurements are often necessary, particularly with the more aggressive induction regimes. After initial stabilisation the INR will, in most cases, dictate the frequency of monitoring.

Weekly monitoring is advised for four to six weeks after stabilisation, gradually changing to every one to two months if concordance and control are good. The BCSH guidelines state that extending the recall frequency to 12 weeks can be acceptable. The tinted panel overleaf describes starting warfarin in a patient with atrial fibrillation.
**Practice point**

*Speak to some of your patients who have been prescribed warfarin recently. Find out about their experiences of being initiated on this therapy.*

**Starting on warfarin: a patient’s journey**

Mr SL is a 58-year-old man who has had a pacemaker in place for many years. His present medication is co-dydramol taken regularly for knee pain. He has also received occasional courses of antibiotics. He is allergic to penicillin.

Recently, at a pacemaker clinic review, he was noted to have atrial fibrillation. He was asymptomatic – ie, he had none of the symptoms usually associated with atrial fibrillation such as irregular and rapid pulsations of the heart, shortness of breath, profuse sweating, chest pain and extreme fatigue. Mr SL was referred to the cardiology department at the local hospital where it was decided that in order to prevent a stroke he should be anticoagulated for life. A letter was sent to his GP asking him to prescribe warfarin 1 mg, 3 mg and 5 mg tablets and Mr SL was referred to the anticoagulant clinic to commence his warfarin therapy as an outpatient.

The clinic staff telephoned Mr SL to arrange an appointment, to obtain a summary of his other medication, and to check that he had obtained a prescription for warfarin from his GP. He was instructed to take 10 mg of warfarin at 6pm on Sunday evening (day 1) and to attend the clinic on Monday morning (day 2).

At his first appointment at the clinic Mr SL’s INR was measured by capillary blood sample (finger prick). He was seen by the pharmacist who educated him about his warfarin therapy and gave him a warfarin booklet. Mr SL was dosed using a Fennerty induction regimen, which meant that he had to return to the clinic every day for at least the first three days of treatment. In line with the BCSH guidelines, his target INR was 2.5 (range 2.0-3.0).

<table>
<thead>
<tr>
<th>Summary of Mr SL’s progress through the Fennerty induction regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INR</strong></td>
</tr>
<tr>
<td>Sunday Day 1</td>
</tr>
<tr>
<td>Monday Day 2</td>
</tr>
<tr>
<td>Tuesday Day 3</td>
</tr>
<tr>
<td>Wednesday Day 4</td>
</tr>
<tr>
<td>Friday Day 6</td>
</tr>
</tbody>
</table>

Mr SL continued taking 5 mg of warfarin a day until his next appointment three days later (day 9). Because his INR measured 2.3 (within target range) his maintenance dose was continued at 5 mg a day. His next appointment was scheduled for a week later (week 3). As his subsequent INR measurements remained within the target range, Mr SL’s INR monitoring continued every eight weeks.
6.2 Maintaining treatment

The effectiveness and safety of warfarin therapy is critically dependent upon maintaining the INR within the target range. Sensitivity to warfarin varies widely between individuals (and within the same person) due to variables such as age, diet, disease state and drugs. As previously described, a well-stabilised patient may need an INR check only every eight to 12 weeks; however, any change in their clinical state or medication can prompt the need for more frequent checks.

Before adjusting the dose of warfarin you should review:

- the previous doses of warfarin
- earlier INR results
- any changes in the patient’s clinical condition
- any changes in medication
- any changes in lifestyle
- alcohol consumption.

Changes to the maintenance dose should generally be made in small increments. Dose adjustments should be increased or decreased by looking at the weekly dose, not the daily dose. Adjusting the total weekly dose by five to 20 percent should cause a measurable change in the INR. Adjusting the total weekly dose by five to twenty percent should cause a measurable change in the INR. For example, a patient stabilised on 3.5 mg daily and who requires a dose increase would go up to 4 mg daily. Alternate daily dosing should be avoided.

A booster dose is occasionally used when a more rapid increase in INR is needed. For example, if a patient with a second-generation mechanical heart valve whose target INR is 3.0 (associated range 2.5-3.5) had an unexpectedly low INR (eg, 1.6) then a boost dose of 25-50 percent of the maintenance dose would be advised for one night only.

Care should be taken not to overreact to an INR that is just within or only slightly out of the target range. (Remember to consider the many factors that may affect the INR value before changing the dose of warfarin.) Since it takes at least three days for the effect of a change in dosage to be reflected in the INR the minimum time to re-check the INR is approximately three days after therapy has been adjusted. The maximum should be no longer than two weeks.

The effectiveness and safety of warfarin therapy is critically dependent on maintaining the INR within the therapeutic range. Two approaches have been developed in an attempt to improve anticoagulant control. The first is to use specialist anticoagulant clinics; the second is to use computerised dosage support systems to aid dosage adjustment.
6.3 INRs above and below the normal target range

The possibility of an INR value not being within the target range is increased if (for example):

- the patient’s characteristics are not adequately taken into consideration (e.g., poor concordance with other drug therapy, health beliefs, medical history, etc)
- there is poor communication between the anticoagulant clinic practitioner, the patient, and the other clinicians involved in his or her care.

The tinted panel below describes how patients outside their target INR ranges are typically managed.

Managing INRs outside the target range

If the INR is low:

- the patient should be asked if they have missed any doses
- depending on the level, the warfarin dose may need to be (temporarily) increased and sometimes a booster dose may be needed. The INR should be measured two or three days later to ensure that it is increasing.

If the INR is high:

- the patient should be asked if they have any signs of bleeding
- depending on the level, the warfarin dose may need to be (temporarily) reduced and/or one or two doses may need to be omitted. The INR should be measured two or three days later to ensure that it is falling.

Source: Clinical knowledge summary. Deep vein thrombosis*

Practice point

Compare this advice with what happens in your own local clinics. Find out how soon patients are brought back to the clinic when they present with a high or low INR.

6.4 Stopping treatment

Warfarin can be stopped abruptly when the duration of treatment is completed. There is no evidence to suggest that the abrupt discontinuation of warfarin leads to any increased risk or harm.*
**William**

**Patient**
70-year-old male

**Indication**
Atrial fibrillation (recently diagnosed)

**Target INR**
2.5 (Range 2.0 - 3.0)

**Duration**
Lifelong

**History**
William was admitted to hospital with shortness of breath on 22 August. It was discovered that he had paroxysmal atrial fibrillation. A computerised tomography brain scan showed two small infarcts and excluded haemorrhagic stroke. He was started on a loading regimen of amiodarone on 27 August while in hospital. Thyroid function tests showed him to be euthyroid. His biochemistry results were all normal and his liver function tests were also normal.

**Patient medication record**
- Aspirin 75 mg daily
- Furosemide 40 mg daily
- Warfarin variable doses
- Ramipril 2.5 mg daily

An excerpt from his ‘yellow booklet’:

<table>
<thead>
<tr>
<th>Date</th>
<th>INR</th>
<th>Recommended dose</th>
<th>Next appointment</th>
<th>Clinic record</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 September</td>
<td>1.0</td>
<td>2 mg</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>25 September</td>
<td>2.5</td>
<td>2 mg</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>1 October</td>
<td>6.1</td>
<td>Miss 2 days</td>
<td>2 day</td>
<td>No bleeding or bruising</td>
</tr>
<tr>
<td>3 October</td>
<td>6.2</td>
<td>Miss 1 day</td>
<td>1 day</td>
<td></td>
</tr>
<tr>
<td>4 October</td>
<td>5.6</td>
<td>Miss 1 day</td>
<td>1 day</td>
<td></td>
</tr>
<tr>
<td>5 October</td>
<td>5.4</td>
<td>Miss 3 day</td>
<td>3 days</td>
<td></td>
</tr>
<tr>
<td>8 October</td>
<td>5.7</td>
<td>Miss 1 day</td>
<td>1 day</td>
<td>Vitamin K 1 mg orally</td>
</tr>
<tr>
<td>9 October</td>
<td>3.0</td>
<td>0.5 mg</td>
<td>1 day</td>
<td></td>
</tr>
<tr>
<td>10 October</td>
<td>2.5</td>
<td>STOP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Liver function test normal. Urea and electrolytes normal. Going on holiday for one week. Restart after return from holiday.
1. According to his ‘yellow booklet’, what regimen was used to start William on warfarin? What are the advantages/disadvantages of this regimen?

2. Why was warfarin not started while he was in hospital in August?

3. What information should have been obtained when he attended the clinic on 1 October when his INR had unexpectedly increased to 6.1?
4. What information should have been obtained from him on 8 October?

(For more information on the use of vitamin K in cases of excessive bleeding see Section 8.)

Turn to the end of the section for suggested answers.

Summary

- Warfarin takes several days to have a therapeutic effect. Therefore, depending on the urgency of the need for anticoagulation, it is usually initiated with loading doses to achieve a stable target INR more quickly, with the possible addition of heparin on a short-term basis from day 1.

- The Fennerty induction regimen is a rapid induction regimen that starts with repeated loading doses of 10 mg a day of warfarin. However, recent guidelines advise that for certain patient groups requiring this type of rapid regimen (eg, people over 60 years of age, those with liver disease or cardiac failure and those at high risk of bleeding) it may be preferable to start with 5 mg doses or a single 10 mg dose followed by 5 mg doses.

- As patients are stabilised on warfarin the frequency of INR measurements may decrease from once a day to once a week, and then to a maximum recall frequency of 12 weeks. Therefore all anticoagulant clinics must be able to operate in a way that can accommodate these variable recall frequencies.

- Sensitivity to warfarin varies widely between individuals (and within the same person) due to variables such as age, diet, disease state and drugs. A well-stabilised patient may need an INR check only every eight to 12 weeks; however, any change in their clinical state or medication can prompt the need for more frequent checks.
Intended outcomes

By the end of this section you should be able to:

<table>
<thead>
<tr>
<th>Learning objective</th>
<th>Well can you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand why it may be necessary to give a loading dose of warfarin (with the potential addition of heparin) when anticoagulant therapy is initiated.</td>
<td></td>
</tr>
<tr>
<td>Describe some of the different types of induction regimen.</td>
<td></td>
</tr>
<tr>
<td>Understand why anticoagulant services may need to accommodate the frequent INR monitoring of newly-initiated patients.</td>
<td></td>
</tr>
<tr>
<td>Describe how patients with INR values outside their target range are managed.</td>
<td></td>
</tr>
</tbody>
</table>

Reflective questions

1. How is heparin therapy incorporated into a warfarin induction regimen?
2. How often do INR measurements need to be taken when patients are initiated on the Fennerty induction regimen?
3. What is the recommended maximum recall frequency for patients on warfarin to have their INR values checked?
Suggested answers

Case study 5: William (page 47)

1. According to his ‘yellow booklet’, what regimen was used to start William on warfarin? What are the advantages/disadvantages of this regimen?

Warfarin was started on 17 September using a low slow-start regimen. William took 2 mg of warfarin a day for two weeks and had his INR checked weekly. (If INR is greater than 5.0 after week 1 then the dose would be adjusted for week 2.) Thereafter his INR values would determine the frequency of testing.

This regimen is ideal for elderly patients who have not actually had an embolic event (e.g., atrial fibrillation) since there is no need to get their INR into the therapeutic range immediately. The advantage for patients with mobility problems is that they only need to attend the clinic once a week during the induction period compared with the Fennerty regimen, which requires clinic attendance four or five times in the first week. This regimen is not considered suitable for younger patients or for patients with atrial fibrillation who are candidates for cardioversion. Although William has had an embolic event he is already on amiodarone so a low slow start was considered suitable.

2. Why was warfarin not started while he was in hospital in August?

After an acute cerebral ischaemic event, warfarin therapy should be delayed until most of the deficit has resolved. In the case of more severe strokes, more than two weeks should elapse so that the risk of intracranial bleeding is reduced.

3. What information should have been obtained when he attended the clinic on 1 October when his INR had unexpectedly increased to 6.1?

The clinic practitioner would have tried to identify a reason for the large increase in INR by asking specific questions such as:

- How many and what colour tablets are you taking?
- Have there been any changes to your current medicines? Have you bought any over-the-counter products or herbal medicines?
- Have you drunk any alcohol within the previous few days?
- Has there been any change in your diet?
- How have you been keeping in general – any recent problems?
- Have you changed your smoking habits?
- Have you been experiencing any bleeding or bruising?

The answers to all of the above questions could not identify a definite cause for the increased INR. Over the next seven days the patient’s INR remained above 5.0.

4. What information should have been obtained from him on 8 October?

The clinic practitioner should have repeated all the questions listed in question 3 in case anything had changed. Liver function tests should also have been repeated to ensure there were definitely no liver function abnormalities. It was presumed that
this patient showed extreme sensitivity to warfarin. Since he was due to go on holiday for a week the decision was taken to stop warfarin and administer vitamin K (1 mg orally) on 8 October in order to ensure his INR would drop to an acceptable level prior to his leaving. He was restarted on 22 October and is presently prescribed 0.5 mg a day, which maintains his INR within the therapeutic range of 2.0–3.0.

To sum up. Perhaps the practitioner should have realised in week 1 that the patient’s INR was higher than expected, since it takes about two weeks to reach steady state. The point of doing a week 1 level is to gauge whether the patient is likely to need less than 2 mg. Although his week 2 level was higher than most of us would expect there were warning signs in week 1.
Section 7
Patient education and other management strategies

Objectives

On completion of this section you should be able to:

- summarise the vast amount of information that patients newly-initiated on warfarin need to deal with
- appreciate the important role of the pharmacy team in informing and educating patients about warfarin therapy
- understand and use the key patient counselling points
- advise and educate patients taking warfarin on the implications of travel, surgery and visiting the dentist.

This section focuses on patient education – one of the key factors in minimising adverse outcomes and keeping patients on warfarin well. There is a key role for pharmacy staff to improve concordance as well as ensuring the safety and efficacy of warfarin therapy.

7.1 The ‘yellow booklet’

Patients, relatives and carers should be educated on the advice in the ‘yellow booklet’ (Oral anticoagulant therapy. Important information for patients) issued by the British Society for Haematology and the NPSA.21

Although we refer to the ‘yellow booklet’ throughout this programme, the information is now presented in an A5 yellow folder with four sections:

- the anticoagulant alert card. This credit card-size alert is designed to be carried by the patient at all times to inform health professionals that the patient is taking oral anticoagulants. It also provides an emergency telephone number (which is inserted locally).
Oral anticoagulant therapy: Important information for patients

This A5 size yellow booklet provides general information about the safe use of oral anticoagulants. It is intended to be kept at home by the patient as a reference source when needed. It provides concise information about the practical issues of taking anticoagulants and reinforces the key advice that should be given to the patient by the prescriber and other healthcare professionals:

- before the first dose of anticoagulant is given (it is important that the healthcare practitioner who first provides this information makes a note in the patient’s healthcare record)
- upon discharge from hospital
- at the first anticoagulant clinic appointment
- whenever necessary throughout the course of treatment.

Oral anticoagulant therapy: record book

This small yellow booklet provides a record of anticoagulant treatment and should pass between the patient and the anticoagulant healthcare provider.

- blood test results and dosage information. The final section provides space for a written record of the patient’s latest INR test results, dosage information and next clinic appointment by use of loose anticoagulation record sheets. These may be handwritten records made by a healthcare professional or the patient, or a computer-generated record sent to the patient by the anticoagulant clinic. *It is essential that a written record is always made following an INR blood test or dose adjustment.* To enable continuity of care it is best practice for these patient-held records to be maintained even when the patient is admitted to hospital as an inpatient.

The new folders also have space to include information about the local anticoagulant service and clinic contact details. The NPSA also intends to make available electronic versions of the ‘yellow booklet’. For more information about foreign language editions go to: [http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant/](http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant/)

This website address links to all the important documents and references relating to Patient Safety Alert 18: *Actions that can make anticoagulant use safer.* This includes links to relevant standards and guidelines, e-learning modules, information for patients and carers and risk assessment reports.
Practice point

Using the ‘yellow booklet’ as a guide, prepare a checklist of the key points you should tell a patient who is taking warfarin. Keep a copy with your standard operating procedures. How does your checklist compare with the advice from the clinical knowledge summary reproduced in Section 7.2 overleaf?

7.2 Advice that should be given to patients while they are taking warfarin

There is an important role for pharmacy staff in reinforcing key patient education points when repeat dispensing patients collect their batch issues, or during a medicines use review (MUR), or when patients are discharged from hospital care.

Pharmacists and pharmacy technicians must ensure that it is safe to dispense repeat prescriptions for anticoagulants. There may be a delay between the prescription being issued and the drugs being dispensed. It cannot be assumed that the prescriber has undertaken the safety checks in all cases. Reviewing the patient-held record (which contains details of the date of their last clinic appointment, their latest INR test result and current dose) and confirming this information with the patient is recommended as safe practice.

In addition, pharmacists and pharmacy technicians need to ensure that patients understand the differences in colour and strength of warfarin tablets. Supplying warfarin tablets in more than one strength may increase the risk of accidental overdose especially in older people who may be confused. And while patients generally know the colour of the warfarin tablets they take, less than half know the strength of their tablets, the reason for taking them, or the effect on their body.17 (The ‘yellow booklet’ describes the strengths and colours of warfarin tablets.)

To avoid confusion, doses should always be expressed as the total number of mg and not as the number of tablets (see Figure 4 below).

FIGURE 4 Warfarin tablets: colours and doses

In the UK, the colours of warfarin tablets are:

- 0.5 mg (500 micrograms) – white
- 1 mg – brown
- 3 mg – blue
- 5 mg – pink

Different brands of warfarin tablets may have different markings to those shown above. Other anticoagulants may come in different strengths and colours.

You may need a mixture of different coloured tablets make up your dose. Your healthcare professional will explain this to you.

Do not confuse the dose in mg with the number of tablets that you take.

Source: BSH and NPSA (2007)17
Key patient counselling points

Advise people while they are on warfarin that:

- it is very important to have their blood tested regularly (preferably in a warfarin clinic)
- they should always carry their yellow anticoagulant treatment booklet or anticoagulant alert card with them
- they should take warfarin at the same time each day
- if a dose is accidentally missed they should continue with the regimen as prescribed, and NEVER take a double dose (unless specifically advised)
- they must inform anticoagulant healthcare staff if they think they have taken too much warfarin or have missed any doses
- women of childbearing age should tell a healthcare professional if they are pregnant or planning a pregnancy – they will need to stop taking warfarin (as it is dangerous to fetuses and pregnant women) and to start low molecular weight heparin
- they must inform the relevant healthcare professionals if they start, stop or change the dose of other medicines, or if their diet changes substantially (eg, intake of broccoli, lettuce or spinach). ‘Other medicines’ include not only prescribed drugs but also products that may be bought without prescription, such as aspirin and medicines containing aspirin, vitamins, food supplements and herbal or homoeopathic remedies
- if they require surgery, dental work, or any other invasive procedure they may need to stop taking warfarin temporarily. Patients should discuss their warfarin management with a healthcare professional prior to the procedure.

If the effect of warfarin is enhanced, the individual may notice the following signs:

- bruising
- bleeding gums
- nosebleeds
- prolonged bleeding from cuts
- blood in the urine and stools.

Advise the person to get medical advice as soon as possible if spontaneous bleeding occurs, and the bleeding does not stop or recurs.

Lifestyle advice

- People on vitamin K-rich diets should not change their eating habits without at the same time reducing the warfarin dosage, because excessive anticoagulation and bleeding may occur (first seek medical advice).
- People should limit the amount of alcohol to a maximum of one or two drinks a day and never binge drink.
- People should avoid activities which could cause abrasion, bruising or cuts (eg, contact sports, gardening, sewing), or at least use protection.
- People should take extra care when brushing teeth or shaving and should consider using a soft toothbrush and an electric razor.
- If people do injure or cut themselves, especially the lower leg, and the wound continues to bleed or ooze, they must seek help from their GP, practice nurse or accident and emergency department immediately. In the interim they should keep the affected part raised above the level of the heart.
- People should avoid insect bites, especially on their legs, and should use a repellent when exposed to insects.

Source: Clinical knowledge summary. Deep vein thrombosis

**Note.** Patients with deep vein thrombosis should be given the following additional lifestyle advice:
- regular walking exercise helps to reduce the risk of further deep vein thrombosis and improves circulation in the affected limb
- the affected leg should be elevated when sitting.

---

**Exercise 4**

One of your patients who is taking warfarin has been told to restrict her dietary intake of vitamin K. She is concerned that she will not be able to continue with her vegetarian diet. How can you help her to take a sensible approach to dietary considerations during her warfarin therapy?

---

**Before you read on, please compare your answer with the suggested answer provided at the end of this section.**

**7.3 International travel**

Warfarin should be taken at the same time each day. While travelling it is extremely important to continue to take warfarin at 24-hour periods. One way of dealing with crossing international time zones is to take an extra wristwatch and keep it set to Greenwich Mean Time.
Patients who are travelling for any length of time will need to move their dosing time gradually – say by an hour a day – to a time that is convenient to the new time zone. They may also need to have an INR check while they are away.

**Advice on travel-related deep vein thrombosis**

A possible link between deep vein thrombosis (DVT) and long-haul air travel was first suggested by reports in medical journals in the 1950s. These early reports generally pointed to immobility as the common underlying risk factor. DVT may be associated with any form of long distance travel, whether by air, car, coach or train, and new research, largely funded by the Departments of Transport and Health, has confirmed that all forms of transport involving a journey of four hours or more led to an increase in the risk of blood clots forming in the veins of the legs.

**The risk of DVT from air travel**

There is evidence that long-haul flights, especially when passengers have little or no exercise, may increase the risk of developing DVT. Information on the proportion of people who develop DVT related to air travel has been limited until recently; new research carried out by a consortium of medical research scientists under the auspices of the World Health Organization has found one case of DVT for every 6000 journeys that lasted four hours or more. Nevertheless, it is difficult to decide whether the flight itself caused the deep vein thrombosis/pulmonary embolism or whether these people were at risk for other reasons. This is because:

- deep vein thrombosis and pulmonary embolism are relatively common conditions anyway, and
- more people than ever now travel by air every year.

While it is difficult to be certain what the exact causes of travel-related DVT are, experts agree that lack of exercise or immobility are major underlying risks. They have also identified that people at increased risk of deep vein thrombosis/pulmonary embolism, in general, are those more likely to develop travel-related DVT/pulmonary embolism.

*Source: Advice on travel-related DVT*

**Practice point**


**7.4 General surgery**

When patients who are receiving long-term warfarin therapy require surgery, a variety of approaches may be considered. If the risk of subsequent thromboembolism is low it may be acceptable to discontinue the warfarin in advance of the
procedure. For patients with a greater risk, the dose may be lowered and the operation performed when the INR is at an acceptable level (ie, below 2.5). A third alternative is to reduce the anticoagulant effect with vitamin K just prior to surgery and operate under prophylactic cover of heparin, with the aim of reintroducing warfarin in the immediate post-operative period.

Patients should always seek advice about their warfarin therapy from whoever is carrying out the surgical procedure.

**Practice point**

*Find out your trust’s policy or visit the surgical directorate or surgical wards and find out what happens to patients on long-term warfarin who need to undergo surgery.*

**7.5 Dental advice**

Many dentists appear to be unaware of the specific needs of patients who are receiving anticoagulants and perform procedures from dental hygiene to multiple extractions without managing the treatment or referring to others.¹⁸,²²

Minor dental surgical procedures can be carried out safely as long as the patient’s INR is below 4.0. Examples of the procedures likely to be carried out in primary care would be the simple extraction of up to three teeth, crown work, and cosmetic dentistry. An INR measurement should be taken within 72 hours of the procedure. Figure 5 *(overleaf)* shows how patients on warfarin who are undergoing dental treatment should be managed.
FIGURE 5 Managing patients who are taking warfarin and undergoing minor oral surgery or dental extractions

Is the patient known to have liver impairment/high alcohol intake, renal failure, thrombocytopenia, haemophilia or other haemostasis disorders, or are they receiving chemotherapy or taking more than one antiplatelet drug?

YES

Refer to specialist services.

NO

Obtain an INR measured no more than 72 hours before the dental procedure.

Does the patient have an INR of 4.0 or below?

YES

Follow local antibiotic policy or current guidelines in BNF, taking account of any potential drug interaction

NO

Refer to anticoagulation service. Reschedule the procedure when INR is less than 4.0. Refer to specialist services for dental treatment if INR remains above 4.0 or control is erratic.

Does the patient need prophylactic antibiotics, for example for endocarditis?

YES

Drug therapy: if the patient requires analgesia, use paracetamol. Avoid non-steroidal anti-inflammatories, for example, ibuprofen, aspirin and diclofenac. The use of dihydrocodeine should only be considered for second line pain relief when other drugs are unsuitable. Codeine has no role in dental analgesia. There is no indication for routine prescribing of antibiotics for dental procedures in this group of patients.

NO

Consider the timing of the dental procedure. It is recommended treatment takes place in the morning at the beginning of the week when re-bleeding problems can be managed during the working day and working week.

Use a local anaesthetic containing a vasoconstrictor. Where possible use an infiltration, intraligamentary or mental nerve injection. If there is no alternative and an inferior alveolar nerve block is used, the injection should be administered slowly using an aspirating technique.

For extractions, gently pack the socket with an absorbable haemostatic dressing. Carefully suture the socket.

Practice point

Speak to a local dentist or visit your local hospital’s dental department to find out what specific advice they give to warfarin patients following dental treatment.

Source: Adapted by courtesy of the NPSA and the British Dental Association

NB This information was correct at the time of going to press, but may have since been revised. Please check the NPSA website at: http://www.npsa.nhs.uk for the latest guidance.
Pharmaceutical advice for patients on the management of clots in the post-operative dental period

You should advise the patient to:

- rest while the local anaesthetic wears off and the clot fully forms (this usually takes two to three hours)
- take paracetamol if pain control is needed (NSAIDs and aspirin or products containing these medicines should be avoided)
- avoid rinsing the mouth for 24 hours unless specifically advised to do so by a healthcare professional
- avoid sucking hard or disturbing the clot with the tongue or anything else
- avoid hot liquids and hard foods for the rest of the day
- avoid chewing on the affected side until they are sure that a stable clot has formed
- rinse the mouth with warm salty water three or four times the day after treatment.

If the bleeding continues or restarts you should advise the patient to apply pressure over the bleeding area using a clean, damp folded handkerchief or gauze pad. The pad should be placed over the site of the bleeding and the patient should bite down firmly for 20 minutes while sitting quietly in a chair.

The use of tranexamic mouthwash (which acts as a local antifibrinolytic) has been investigated. It should not be used routinely in primary dental care; it is expensive, difficult to obtain and of no more benefit than other local haemostatic measures.

Source: Oral anticoagulant therapy. Important information for dental patients

Drug interactions of particular relevance to this patient group

- **Amoxicillin.** Patients requiring a course of amoxicillin should be advised to be vigilant for signs of increased bleeding and may require closer monitoring. However, a single 3 g dose for prophylaxis should not produce a clinically significant interaction.

- **Clindamycin.** Clindamycin does not interact with warfarin when given as a single dose for endocarditis prophylaxis. Clindamycin is restricted to specialist use and should not be used routinely for dental infections.

- **Metronidazole.** Caution is needed as metronidazole interacts with warfarin and should be avoided wherever possible. If it cannot be avoided, the patient’s GP or anticoagulant clinic should be consulted to arrange additional INR testing and dose review. The warfarin dose may need to be reduced by a third to a half and the dose readjusted when the antibiotic is discontinued.

- **Erythromycin.** Erythromycin and other macrolides (eg azithromycin) interact with warfarin unpredictably and only affect certain individuals. Patients should be advised to be vigilant for any signs of increased bleeding. If increased bleeding
occurs then patients should be advised to contact their GP or anticoagulant clinic to arrange additional INR testing and dose review.

- **Fluconazole.** A significant interaction occurs with warfarin and fluconazole (capsules and oral gel). The patient’s INR should be checked no longer than three days after starting a course.

- **Non-steroidal anti-inflammatory drugs.** NSAIDs such as aspirin, ibuprofen and diclofenac should be avoided. Care should be taken due to the increased risk of bleeding from the gastrointestinal tract.

### Case studies

#### James

**Patient** 58-year-old male  
**Indication** Atrial fibrillation and left ventricular systolic dysfunction  
**Target INR** 2.5 (range 2.0-3.0)  
**Duration** Lifelong  
**History** James has been on warfarin for the last eight months and his INR has remained reasonably stable between 2.0-3.0 on a maintenance dose of 8 mg daily. He returned to the anticoagulant clinic on 16 January after a 10-week interval.

**Patient medication record**  
Warfarin

An excerpt from his ‘yellow booklet’:

<table>
<thead>
<tr>
<th>Date</th>
<th>INR</th>
<th>Recommended dose</th>
<th>Next appointment</th>
<th>Clinic record</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 November</td>
<td>2.2</td>
<td>8 mg</td>
<td>10 weeks</td>
<td></td>
</tr>
<tr>
<td>16 January</td>
<td>1.2</td>
<td>Boost 10 mg for two days then 8 mg</td>
<td>5 days</td>
<td>May have taken at different times. Just returned from holiday in Australia</td>
</tr>
<tr>
<td>21 January</td>
<td>1.4</td>
<td>Boost 12 mg for two days then 8.5 mg daily</td>
<td>2 days</td>
<td>White warfarin tablets (0.5 mg) were mixed with blue tablets (3 mg). He had taken 3 mg dose for a few days instead of 8 mg</td>
</tr>
<tr>
<td>23 January</td>
<td>1.5</td>
<td>9 mg</td>
<td>2 days</td>
<td></td>
</tr>
<tr>
<td>25 January</td>
<td>1.8</td>
<td>9 mg daily</td>
<td>4 days</td>
<td></td>
</tr>
<tr>
<td>29 January</td>
<td>2.4</td>
<td>9 mg daily</td>
<td>2 weeks</td>
<td></td>
</tr>
<tr>
<td>13 February</td>
<td>2.7</td>
<td>9 mg daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. According to the recent NICE guidelines on atrial fibrillation, what is James’s risk category for a stroke?

2. What advice would you have given this patient about travelling abroad and getting his INR checked?

3. What specific questions should have been asked at the clinic on 16 January when his INR was so low?

A Turn to the end of the section for suggested answers.
**Frank**

Patient 70-year-old male

Indication Atrial fibrillation

Target INR 2.5 (range 2.0-3.0)

Duration Lifelong

History Frank is known to be a ‘binge’ drinker. If he cannot control his excessive drinking and his anticoagulation control remains poor, his cardiologist may recommend that his warfarin therapy is discontinued. He has had previous gastrointestinal bleeds so aspirin is not considered to be an option for this patient.

Patient medication record

Digoxin 250 micrograms daily

Warfarin 1 mg

An excerpt from his ‘yellow booklet’:

<table>
<thead>
<tr>
<th>Date</th>
<th>INR</th>
<th>Recommended dose</th>
<th>Next appointment</th>
<th>Clinic record</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 September</td>
<td>1.8</td>
<td>3 mg</td>
<td>2 weeks</td>
<td></td>
</tr>
<tr>
<td>26 September</td>
<td>DNA</td>
<td></td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>3 October</td>
<td>2.7</td>
<td>3 mg</td>
<td>3 weeks</td>
<td></td>
</tr>
<tr>
<td>24 October</td>
<td>2.4</td>
<td>3 mg</td>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>21 November</td>
<td>11.7</td>
<td></td>
<td></td>
<td>Admitted to hospital for vitamin K$_1$ intravenously. No bleeding or bruising. Discharged from hospital on 22 November</td>
</tr>
<tr>
<td>26 November</td>
<td>2.7</td>
<td>2 mg</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>3 December</td>
<td>4.4</td>
<td>Miss one day then 2 mg</td>
<td>3 days</td>
<td></td>
</tr>
<tr>
<td>6 December</td>
<td>3.1</td>
<td>2 mg</td>
<td>4 days</td>
<td></td>
</tr>
<tr>
<td>10 December</td>
<td>1.8</td>
<td>3 mg</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>17 December</td>
<td>2.0</td>
<td>3 mg</td>
<td>1 week</td>
<td></td>
</tr>
</tbody>
</table>

(DNA = Did not attend)

1. Explain what could have caused the increase in Frank’s INR (do not just consider his alcohol intake).
2. What action should have been taken on 21 November when his INR was 11.7?

3. What education point would you consider to be essential for this patient?

4. What questions would you have asked Frank when he was seen on 3 December?

(For more information on the use of vitamin K₁ in cases of excessive bleeding see Section 8.)

Turn to the end of the section for suggested answers.
Barrie

Barrie is a 64-year-old man with a history of bladder problems. He is seen by the pharmacist at a pre-assessment clinic prior to his admission for a transurethral resection of a tumour of the prostate.

Drug history:
- Warfarin to be taken as directed (usual dose is 5.5 mg daily)
- Atorvastatin 10 mg at night
- No known drug allergies
- Barrie takes anticoagulant therapy for a mechanical heart valve

Target INR: 3.0-4.0
Duration: Long-term

1. What action should the pharmacist take? What should Barrie’s target INR be before surgery? When should his warfarin be stopped? Does Barrie need prophylactic cover with heparin?

2. When should Barrie restart his warfarin therapy and what induction regimen should he follow?

3. Barrie develops a temperature and a urinary tract infection is suspected. *Pseudomonas* infection is identified which is sensitive to gentamicin, ciprofloxacin and ceftazidime. The doctor asks your advice about the choice of antibiotic for this patient. What would you advise?
Summary

- Education is one of the key factors in minimising adverse outcomes and keeping patients on warfarin well.
- Each patient on warfarin should possess a copy of the ‘yellow booklet’ (*Oral anticoagulant therapy. Important information for patients*). It should be readily available for reference.
- Patients taking warfarin should appreciate the added complications when flying or undergoing surgery or dental treatment.
- Patients requiring dental surgical procedures in primary care and who have an INR below 4.0 should continue warfarin therapy without dose adjustment.

Intended outcomes

By the end of this section you should be able to:

<table>
<thead>
<tr>
<th>Learning objective</th>
<th>Well can you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand the key role that pharmacy staff have to play in helping patients understand all the information they will need to manage their warfarin safely and effectively.</td>
<td></td>
</tr>
<tr>
<td>Be more confident when counselling patients about their warfarin therapy.</td>
<td></td>
</tr>
<tr>
<td>Appreciate the implications of air travel, surgery and visiting the dentist for patients taking warfarin, and know how to counsel them appropriately.</td>
<td></td>
</tr>
</tbody>
</table>
Reflective questions

1. How would you counsel a patient on:
   - what to do when a dose of warfarin is missed?
   - alcohol consumption?
   - considering overseas travel for three months?
   - the signs they may notice if the effect of warfarin has been enhanced?

2. Is it safe for patients to continue taking warfarin during minor dental procedures?

Suggested answers

Exercise 4 (page 57)

Pharmacists and technicians must be aware of the dietary factors which may affect the action of warfarin and the resultant INR. Some foods contain large amounts of vitamin K (listed in the ‘yellow booklet’) which can affect the way warfarin works. The more vitamin K there is in the diet, the less effective warfarin becomes.

Therefore the most important advice you should give this patient is to maintain a regular, healthy diet. She should avoid binge eating and crash dieting and report any significant dietary changes to her healthcare practitioner.

Case study 6: James (page 62)

1. According to the recent NICE guidelines on atrial fibrillation, what is James’s risk category for a stroke?

   He is at moderate risk of having a stroke as he is under 65 years old, but he has the following risk factors: atrial fibrillation and left ventricular systolic dysfunction. Untreated, his annual risk is three to five percent. Treatment with warfarin reduces this risk to one to two percent.

2. What advice would you have given this patient about travelling abroad and getting his INR checked?

   All patients should be reminded to carry their anticoagulant alert card at all times. They should also be encouraged to take their ‘yellow booklet’ when visiting any healthcare professional so that they have an accurate record of recent INRs and warfarin doses with them. The use of INR means that patients who travel can obtain accurate comparisons from different laboratories.

   While travelling it is extremely important to continue to take warfarin at 24-hour intervals. One way of dealing with crossing international time zones is to take an extra wristwatch and keep it set to Greenwich Mean Time.
If James was travelling abroad for any length of time the dosing time for warfarin would need to be moved to a convenient time of day within the new time zone. It may also be necessary for him to have an INR check while abroad.

3. What specific questions should have been asked at the clinic on 16 January when his INR was so low?

He should have been asked about missed doses and/or late doses. Changes in medication and the colour of the tablets he has been taking (ie, the dose) should have been confirmed. This case illustrates why it is important for patients to pay attention to the different colours of the tablets they are taking.

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**Case study 7: Frank (page 64)**

1. Explain what could have caused the increase in Frank’s INR (do not just consider his alcohol intake).

Excessive alcohol intake was thought to be the reason for the increase in Frank’s INR. However, upon questioning him it became apparent that he was taking the wrong dose of warfarin. He had visited his GP practice for a flu vaccination and at the same time had requested a new supply of warfarin. When the practice nurse saw that he was taking 3 mg a day she thought it would be helpful to supply 3 mg tablets. Previously Frank had only ever been prescribed 1 mg (brown) tablets, and this was the first time he had been given 3 mg strength (blue) tablets. He thought both kinds of tablets were the same strength (ie, 1 mg) but just a different colour, so for one week he took three times his normal dose (ie, 9 mg instead of 3 mg).

2. What action should have been taken on 21 November when his INR was 11.7?

Any patient with an INR greater than 5.0 has an increased risk of bleeding. According to the local hospital’s protocol (based on the British Committee for Standards in Haematology’s guidelines). Frank should have been admitted to hospital to be given vitamin K₁, as his INR was greater than 8.0.

The effect of vitamin K₁ (orally or by intravenous route) is rapid and will return prothrombin time to normal (and reduce INR) within four to 24 hours. Caution has to be taken when administering vitamin K₁ as warfarin therapy may be rendered ineffective for seven to 14 days subsequently.

3. What education point would you consider to be essential for this patient?

Frank needs to be re-educated about the colour of his tablets. Even though a patient may have been taking warfarin for a number of years they can still make mistakes. You could also inform his GP of what happened and ask him to only prescribe 1 mg tablets.
4. What questions would you have asked Frank when he was seen on 3 December?

He should have been asked about his alcohol intake, any changes in his medicines and to confirm the colour of the tablets he has been taking. In this particular case the same issue that had caused Frank’s admission to hospital in November had arisen again. He was not given any 1 mg tablets on his discharge from hospital because he had stated that he had warfarin tablets at home. He had still not requested a new supply of 1 mg tablets from his GP practice. He was advised to contact his GP urgently to obtain a supply of 1 mg tablets and to return the 3 mg tablets to his community pharmacist.

Case study 8: Barrie (page 66)

1. What action should the pharmacist take? What should Barrie’s target INR be before surgery? When should his warfarin be stopped? Does Barrie need prophylactic cover with heparin?

Prior to surgery the patient’s INR should be less than 2.0. Because Barrie has a mechanical heart valve it is essential that he receives alternative prophylaxis. The pharmacist needs to follow the hospital’s procedure for the perioperative management of patients on warfarin. In this case the following procedure was followed:

*Patients with mechanical prosthetic heart valves.* Admit two days prior to surgery. Stop warfarin three days prior to surgery. Start intravenous heparin and aim to keep the aPTT ratio at 1.5-2.0 (refer to heparin infusion guidelines for detailed dose adjustment). Heparin to be stopped at least six hours prior to surgery and then re-started as soon as the risk of post-operative haemorrhage has passed. This decision will be made by a senior member of the team.

2. When should Barrie restart his warfarin therapy and what induction regimen should he follow?

Warfarin may be introduced once oral intake has started. Reloading this patient with a more aggressive schedule like the Fennerty regimen will achieve a therapeutic INR much more quickly and it may be possible to discharge Barrie from the hospital earlier.

3. Barrie develops a temperature and a urinary tract infection is suspected. *Pseudomonas infection is identified which is sensitive to gentamicin, ciprofloxacin and ceftazidime.* The doctor asks your advice about the choice of antibiotic for this patient. What would you advise?

In routine practice, any antibiotic can interfere with INR control. However, ciprofloxacin may cause an unpredictable increase in INR and is best avoided. Barrie was started on gentamicin and ceftazidime intravenously and the urinary tract infection resolved quickly, allowing him to be discharged.
Dealing with emergencies

Objectives

On completion of this section you should be able to:

- identify the signs of excessive anticoagulation in patients
- counsel patients appropriately about the risks of bleeding when taking warfarin.

Bleeding is the most serious and common complication of warfarin treatment. This section considers how excessive bleeding is dealt with and looks at the role of the pharmacy team in this area.

8.1 The action patients need to take if they bleed

Bleeding complications that occur in patients receiving oral anticoagulants increase substantially when INR levels exceed 5.0. The most serious major bleed is an intracranial haemorrhage.

Clinically speaking, most problems with bleeding are minor, though patients are unlikely to view them in these terms. The problems include nose bleeds, bruising and excessive bleeding from minor injuries such as shaving. Patients should be made aware of these common problems by the anticoagulant clinic or their GP and reassured that they are to be expected in patients receiving warfarin treatment.

Advice in the ‘yellow booklet’ (see Section 7 for further information) states: 21

If you experience any of the following, seek medical attention and have an urgent INR test:

- prolonged nosebleeds (more than 10 minutes)
- blood in vomit
- blood in sputum
- passing blood in your urine or faeces
- passing black faeces
- severe or spontaneous bruising
- for women, heavy or increased bleeding during your period or any other vaginal bleeding.

If you cut yourself apply firm pressure to the site for at least five minutes using a clean and dry dressing. Seek medical advice immediately if you suffer a major injury or are unable to stop the bleeding.

The tinted panel overleaf describes the factors that predispose patients to a high risk of bleeding. The most important variables determining a patient’s risk of major life-threatening bleeding complications while they are receiving anticoagulation treatment are probably: advanced age (over 75 years), the intensity of the anticoagulation (especially if the INR exceeds 5.0), a history of cerebral vascular disease, and the simultaneous use of drugs that interfere with haemostasis (particularly aspirin and NSAIDs).
Factors which predispose patients to a high risk of bleeding with warfarin

- Age over 75 years
- A history of uncontrolled hypertension (defined as systolic blood pressure greater than 180 mm/Hg or diastolic blood pressure greater than 100 mm/Hg)
- Alcohol excess (acute or chronic), liver disease
- Poor drug compliance or clinic attendance
- Bleeding lesions, especially gastrointestinal blood loss (eg, peptic ulcer disease or recent cerebral haemorrhage)
- A tendency to bleed (including coagulation defects, thrombocytopenia), or concomitant use of NSAIDs
- Instability of INR control and INR greater than 3.0

8.2 Dealing with excessive bleeding

Proposals for the management of bleeding and excessive anticoagulation that take into account the recommendations of the British Society for Haematology can be found in the current edition of the British national formulary. They are based on the result of the INR and whether there is major or minor bleeding. The action taken may vary from the omission of doses to the administration of vitamin K₁, for example:

- Major bleeding – stop warfarin; give phytonadione (vitamin K₁) 5-10 mg by slow intravenous injection; give prothrombin complex concentrate (factors II, VII, IX and X) 30-50 units/kg or (if no concentrate is available) fresh frozen plasma 15 mL/kg.
- INR > 8.0, no bleeding or minor bleeding – stop warfarin, restart when INR < 5.0; if there are other risk factors for bleeding give phytonadione (vitamin K₁) 500 micrograms by slow intravenous injection or 5 mg by mouth (for partial reversal of anticoagulation give smaller oral doses of phytonadione e.g. 0.5-2.5 mg using the intravenous preparation orally); repeat dose of phytonadione if INR still too high after 24 hours.
- INR 6.0-8.0, no bleeding or minor bleeding – stop warfarin, restart when INR < 5.0.
- INR < 6.0 but more than 0.5 units above target value – reduce dose or stop warfarin, restart when INR < 5.0.

If there is unexpected bleeding at therapeutic levels you should always investigate the possibility of an underlying cause (eg, unsuspected renal or gastrointestinal tract pathology).

Practice point

There are several guidelines available on ways to manage excessive bleeding. Do you have a clinic protocol? How does it compare to the guidance in the British national formulary?
The role of pharmacy

Pharmacists should follow the advice in the ‘yellow booklet’, paying particular attention to spontaneous bruising, any bleeding that is difficult to arrest, and any evidence of gastrointestinal bleeding.

Pharmacists and technicians who are not involved in INR monitoring clinics should in the first instance gather the facts about the event. In all cases an INR may help to better inform the situation.

The prime action should be to arrest the bleeding; treat occasional bleeding from cuts and minor nose bleeds with first aid methods and if they cannot be resolved refer to the GP or the nearest accident and emergency department.

For minor bleeds (eg, occasional nose bleeds, slight bruising, bloodshot eye) patients should be advised to contact their anticoagulant clinic for monitoring and advice.

In the event of large unexpected bruising, obvious bleeding, abdominal pain or loss of consciousness, refer the patient urgently to their GP or to an accident and emergency department.

Your local trust may operate a patient group direction for the administration of oral vitamin K₁ (usually 1 mg).

Wilma

Wilma is a 76-year-old woman with atrial fibrillation. She presents at your pharmacy and shows you a large haematoma on her side which is weeping slightly. Her INR was within the target range the last time she attended the anticoagulant clinic, which was two weeks ago.

Patient medication record

- Captopril 25 mg three times a day
- Clopidogrel 75 mg daily
- Elantan LA 50 mg in the morning
- Furosemide 40 mg in the morning
- Metoprolol 50 mg three times a day
- Simvastatin 20 mg at night
- Warfarin 1 mg and 3 mg

1. What is Wilma’s INR target range and duration of therapy?

2. What questions would you ask her?
3. What is your advice to Wilma? Could any of her medication have contributed to this bleeding episode?

---

**Summary**

- Bleeding is the most serious and most common complication of warfarin treatment. The most serious major bleed is an intracranial haemorrhage.
- It is essential that patients are clear about what action to take if they bleed, and understand the relative seriousness of bleeds.
- The patient-held *Oral anticoagulant therapy. Important information for patients* booklet provides clear advice to patients on what signs to be alert for. Pharmacists should make themselves aware of this guidance.
- Signs that need urgent assessment include spontaneous bruising, any bleeding that is difficult to arrest, and any evidence of gastrointestinal bleeding.
- The most important variables determining a patient’s risk of major life-threatening bleeding complications while they are receiving anticoagulation treatment are probably: advanced age (over 75 years), the intensity of the anticoagulation (especially if the INR exceeds 5.0), a history of cerebral vascular disease, and the simultaneous use of drugs that interfere with haemostasis (particularly aspirin and NSAIDs).
Intended outcomes

By the end of this section you should be able to:

<table>
<thead>
<tr>
<th>Learning objective</th>
<th>Well can you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe the relevant advice in the patient-held Oral anticoagulant therapy. Important information for patients booklet.</td>
<td></td>
</tr>
<tr>
<td>Educate patients on the relative risks of different types of bleeding events.</td>
<td></td>
</tr>
</tbody>
</table>

Reflective questions

1. What advice would you give a patient who had cut himself shaving and who was concerned that the bleeding did not stop for a few minutes?
2. What guidance would you give a patient who had a nosebleed for 30 minutes?
Case study 9: Wilma (page 73)

1. What is Wilma’s INR target range and duration of therapy?
   Target range 2.5 (2.0-3.0) with lifelong duration.

2. What questions would you ask her?
   Questions should include:
   - Have there been any recent changes in her medication (eg, a course of antibiotics)? Has she purchased any new medications or remedies recently?
   - Is she taking the correct dose and the correct number and colours of tablets?
   - How much alcohol has she drunk recently? Has there been any alteration in her smoking habits?

3. What is your advice to Wilma? Could any of her medication have contributed to this bleeding episode?
   Send her to the accident and emergency department or the local anticoagulant clinic to have her INR checked and the bleeding treated.

   She attended the nearest accident and emergency department where her INR was checked and found to be within her normal therapeutic range (2.0-3.0). Clopidogrel is an antiplatelet drug that can increase the likelihood of bleeding in patients on warfarin without having an effect on their INR measurement. The haematoma was dressed and she was instructed to stop taking clopidogrel. She was seen at the anticoagulant clinic three days later.
Section 9
Clinical governance issues

Objectives
On completion of this section you should be able to:

- plan a clinical governance framework in your workplace to help overcome some of the problems associated with the management of anticoagulants
- name the relevant work competences needed to support anticoagulation therapy
- be aware of the use of safety indicators in auditing anticoagulant services
- appreciate the needs of patients and carers with respect to the use of warfarin
- understand the procedures that must take place when co-prescribing interacting drugs with warfarin.

Clinical governance is a fundamental part of every service in the NHS. This section looks at the main risks associated with the use of anticoagulants and introduces the concept of safety indicators to audit anticoagulant services.

9.1 Definitions of clinical governance

The Department of Health defines clinical governance as ‘a framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care can flourish’.23

Clinical governance is an essential element of any service in the NHS. It is important to be able to demonstrate the quality of a service, to manage the risks within a service, and to continually monitor a service to ensure that standards are maintained or improved when failures or lapses are identified.

Clinical governance is now a core part of the new pharmacy contract, which is built around the seven key components of clinical governance in the NHS. For more information go to either http://www.dh.gov.uk or http://www.psnc.org

9.2 Specific clinical governance issues with anticoagulants

Anticoagulation is associated with a significant morbidity and mortality, and anticoagulants are one of the classes of medicines that are most commonly associated with fatal medication errors. In order to manage and minimise these risks it is essential to define standards of care and to regularly audit the care of patients on anticoagulants.

In January 2006 the NPSA published its Risk assessment of anticoagulant therapy in order to identify the risks associated with the use of anticoagulant medicines.18 The full report is available online at: http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant
In a recent (2007) patient safety alert the NPSA has identified areas to reduce the risk of harm to patients (http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant). Some of the key areas for action are listed below.

**Training and work competences**

Healthcare staff who prescribe, adjust the dosage, dispense, prepare, administer, monitor and discharge patients on anticoagulant therapy must receive adequate training and have the necessary work competences to undertake their duties safely.

The NPSA, using a Skills for Health Framework, has developed six work competences for anticoagulant therapy:

- initiating anticoagulant therapy
- maintaining oral anticoagulant therapy
- managing anticoagulants in patients requiring dental surgery
- dispensing oral anticoagulants
- preparing and administering heparin therapy
- reviewing the safety and effectiveness of an anticoagulant service.

Full details of these work competences are available at: http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant/

There are additional competences required when using anticoagulants in children, such as dose calculation and use of liquid formulations.

All of these work competences can be adapted and developed for local use.

The NPSA has commissioned two e-learning modules on initiating and maintaining anticoagulant therapy.

- *Starting patients on anticoagulants: how to do it*
- *Maintaining patients on anticoagulants: how to do it*

These are available from BMJ Learning at http://www.bmjlearning.com/ Registration is required but it is free.

**Procedures and clinical protocols**

Your local healthcare trusts should have written procedures and clinical protocols for the safe use of both oral and injectable anticoagulant therapies. These documents should be based on the guidelines for anticoagulant therapy that have been published by the British Society of Haematology Standards Taskforce. These procedures and protocols should include the following:

- a risk assessment of the benefits and the risks of anticoagulant therapy for individual patients
- providing information for the patient before anticoagulant therapy begins, prior to hospital discharge, and at their first visit to the anticoagulant clinic
- how to safely initiate anticoagulant loading doses, including the use of low-dose loading for patients with atrial fibrillation
Clinical Governance Issues

- how to monitor anticoagulation and adjust dosage to achieve the patient’s target INR range
- safe systems for documenting results and treatment
- systems to ensure that there is effective communication when clinical responsibility for anticoagulant therapy is being transferred (e.g., upon discharge from hospital)
- annual clinical review of patients on oral anticoagulants
- how to discontinue anticoagulant therapy.

Use of safety indicators to audit anticoagulant services

The British Society of Haematology Standards Taskforce in collaboration with the NPSA has developed safety indicators for the use of oral anticoagulants for inpatients and outpatients that include laboratory, documentation and clinical indicators (see the tinted panel below). Monitoring these indicators will help to identify risks and promote appropriate action to reduce risks. Full details can be found at: [http://www.bcsghguidelines.com/pdf/Anticoagulant_310806.pdf](http://www.bcsghguidelines.com/pdf/Anticoagulant_310806.pdf)

A template service audit form for auditing these safety standards can be downloaded as a Microsoft Word document from the BCSH website and modified for local use. Go to: [http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant/](http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant/)

**Practice point**

*The routine audit of clinical management should be an integral part of your anticoagulation service. Using your incident reporting system, analyse the percentage of errors with warfarin and identify any common causes. Introduce corrective changes in practice to reduce risk.*

A clinical audit in one hospital trust found that intravenous drug users on oral anticoagulant therapy were poorly managed due to issues of non-compliance and ongoing injection of drugs. The trust drafted a paper to support the use of low molecular weight heparins (LMWH) in this patient group for the duration of their treatment.

**Safety indicators for patients starting oral anticoagulant treatment**

1. Percentage of patients following a loading protocol appropriate to indication for anticoagulation.
2. Percentage of patients developing INR > 5.0 within first 2 months of therapy.
3. Percentage of patients in therapeutic range at discharge (for inpatients being transferred to outpatient care).
4. Percentage (incidence) of patients suffering a major bleed in first month of therapy and percentage suffering major bleed with INR above therapeutic range.

5. Percentage of new referrals to anticoagulant service (hospital or community based) with incomplete information, eg diagnosis, target INR, stop date for anticoagulant therapy, dose of warfarin on discharge, list of other drugs on discharge.

6. Percentage of patients that were not issued with patient held information and written dose instructions at start of therapy.

7. Percentage of patients that were discharged from hospital without an appointment for next INR measurement or for consultation with appropriate health care professional to review and discuss treatment plan, benefits, risks and patient education.

8. Percentage of patients with subtherapeutic INR when heparin stopped (fast loading patients only, eg treatment of acute venous thromboembolism).

**Safety indicators for patients established on oral anticoagulant treatment**

1. Proportion of patient-time in range (if this is not measurable because of inadequate decision/support software then secondary measure of percentage of INRs in range should be used).

2. Percentage of INRs>5.0.

3. Percentage of INRs>8.0.

4. Percentage of INRs>1.0 INR unit below target (e.g. percentage of INRs<1.5 for patients with target INR of 2.5).

5. Percentage of patients suffering adverse outcomes, categorised by type, e.g. major bleed.

6. Percentage of patients lost to follow up (and risk assessment of process for identifying patients lost to follow up).

7. Percentage of patients with unknown diagnosis, target INR or stop date.

8. Percentage of patients with inappropriate target INR for diagnosis, high and low.

9. Percentage of patients without written patient educational information.

10. Percentage of patients without appropriate written clinical information, eg, diagnosis, target INR, last dosing record.

*Source: Safety indicators for inpatient and outpatient oral anticoagulant care*
Procedures for co-prescribing and dispensing interacting medicines

Many medicines interact with oral anticoagulant therapy. In many cases the practitioner who prescribes other medicines for a patient on anticoagulants (e.g., a GP) is not the same practitioner who monitors and adjusts the dosage of the therapy (an anticoagulant clinic practitioner).

If possible, medicines should be selected that do not produce clinically significant interactions. If this is not possible, the prescriber, who initiates or discontinues a prescription for an interacting medicine, is responsible for ensuring that the patient is informed that an interacting medicine has been commenced or discontinued. They should also tell the patient to arrange an INR test within four to seven days of the start of the interacting medicine. The patient should be instructed to provide details of the change in therapy when the blood sample is taken. This information can then be recorded on the test request form to inform the anticoagulant clinic. Once notified in this way, the anticoagulant clinic may require additional INR tests and may need to adjust the dose of the oral anticoagulant accordingly.

In the same way, pharmacists or technicians who dispense other medicines for patients who are being maintained on anticoagulants must not assume that additional INR tests have been arranged or that the anticoagulant clinic has been informed. When dispensing a new medicine or noting the discontinuation of an interacting medicine you must check that the additional safety precautions have been taken. Where this has not happened you must inform the patient—and, where necessary, the prescriber—that an additional INR test is required. The anticoagulant clinic also needs to be informed of the change.

Standardised methods of medicine product supply and dosage adjustment

The wide variations in the methods of supply and dosing for warfarin tablets leads to complexity and confusion for patients, carers and healthcare professionals alike.

Patient and carer groups have reported that they would prefer warfarin regimens to have the following characteristics:

- to use the least number of tablets each day
- to use constant daily dosing and not alternate day dosing
- not to require the use of half tablets. (Patients find it difficult to break tablets in half and, when necessary, would rather use 0.5 mg tablets instead.)

*To avoid confusion, doses should always be expressed as the total number of mg and not as the number of tablets.*

Safe practice procedures for anticoagulants in care homes

The safe use of oral anticoagulants in social care settings requires particular mention. This includes care homes and when homecare workers support patients in their own homes.

National minimum standards for care homes and domiciliary care agencies require providers to have written policies and procedures for medicines. The NPSA recommends that local policies should incorporate a specific section on oral anticoagulants.
The dose of oral anticoagulants is likely to change from time to time and it is safe practice that anticoagulant clinics provide clear written dosing instructions for care workers. It is safe practice to attach the written confirmation of the oral anticoagulant dosage, supplied by the anticoagulant clinic, to the medicine administration record (MAR) used by the care provider. Verbal dose changes should only be used in emergencies, and always confirmed in writing as soon as possible.

There is widespread use of monitored dosage systems in care homes and in the community at large. Although the use of these systems may be beneficial for other types of medicines, where dose changes are infrequent, the use of anticoagulants in these dosage systems is not recommended. These systems are usually not flexible enough to facilitate frequent dose changes. It is recommended that oral anticoagulants are administered from the original packs dispensed for individual patients.

There may be some patients in the community, outside of care home settings, that use compliance aids to help them manage their medicines. Oral anticoagulants may still be used in these compliance aids provided that whoever fills these aids ensures that the tablets in the compliance aid matches the latest prescribed dose.

**Summary**

- Clinical governance is an essential element of any service in the NHS. It is important to be able to demonstrate the quality of a service, to manage the risks within a service, and to continually monitor a service to ensure that standards are maintained or improved when failures or lapses are identified.

- Clinical governance is now a core part of the new pharmacy contract, which is built around the seven key components of clinical governance in the NHS.

- Anticoagulants are one of the classes of medicines that are most commonly associated with fatal medication errors.

- The NPSA has identified the main risks associated with the use of anticoagulant medicines and has set out action points to deal with these in a recent (2007) patient safety alert.
Intended outcomes

By the end of this section you should be able to:

<table>
<thead>
<tr>
<th>Learning objective</th>
<th>Well can you?</th>
</tr>
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<tbody>
<tr>
<td>Identify how clinical governance in your workplace will help you to overcome some of the problems associated with the management of anticoagulants.</td>
<td></td>
</tr>
<tr>
<td>Name the relevant work competences needed to support anticoagulation therapy.</td>
<td></td>
</tr>
<tr>
<td>Understand the use of safety indicators in auditing anticoagulant services.</td>
<td></td>
</tr>
<tr>
<td>Appreciate the needs of patients and carers with respect to the use of warfarin.</td>
<td></td>
</tr>
<tr>
<td>Understand the procedures that must take place when co-prescribing interacting drugs with warfarin.</td>
<td></td>
</tr>
</tbody>
</table>

Reflective questions

1. *Do you have the necessary work competences to provide an anticoagulant service?*
2. *What safety indicators are audited in your practice?*
3. *What additional precautions must be taken when an interacting drug is prescribed with warfarin?*
Section 10
Overview of service models

Objectives
On completion of this section you should be able to:

- better understand how anticoagulant services can be offered to patients
- describe how pharmacy can become more closely involved in improving anticoagulant control.

This section completes the learning programme by taking a brief look at the various service models for providing anticoagulant services and the role of pharmacists and technicians in improving anticoagulant control. The concept of ‘near patient’ testing is also mentioned.

10.1 Anticoagulant clinics

Around 950,000 people in the UK are taking warfarin and the service load for monitoring anticoagulation is predicted to increase by a factor of five over the next 10 years. Outpatient anticoagulant clinics based in hospitals are well established, but attending them is an inconvenient and time-consuming process for many patients; in addition, hospital-based services are struggling to cope with an increasing workload.

Alternative service models are required. A survey of anticoagulation clinics in the UK in 2005 revealed that the service was at ‘breaking point’ because of increased patient demand. Furthermore, the need to bring patients to the hospital is no longer necessary as a result of the development of ‘near patient’ testing devices (see below).

There are several options for developing services in primary care. These include:

- ‘satellite’ clinics run by hospital staff
- clinics at a GP surgery delivered by a GP, nurse or practice pharmacist
- community pharmacy-led clinics.

10.2 How pharmacy can get involved

Pharmacists and technicians can play an important role in improving anticoagulant control both in hospital and in primary care by, for example:

- taking drug histories
- dosage titration according to INR
- advising on return dates for monitoring
- patient education and the safe dispensing of continuing supplies.

Hospital pharmacists have increasingly become involved in the provision of anticoagulant services over a number of years. Indeed, the NPSA, in its report Risk assessment of anticoagulant therapy, advocated the use of pharmacists and nurses to provide anticoagulant services to hospital inpatients as one way of overcoming the
poor documentation and quality of treatment plans at the commencement of anticoagulant therapy. However, with the increasing use of anticoagulant therapy and the improvements in patient convenience and choice in the NHS, alternative service models are being sought by primary care trusts.

To improve ease of access to this service some pharmacists are already involved in monitoring warfarin in a variety of primary care settings. In addition to enhancing their knowledge about warfarin and gaining experience in warfarin dosing, some have achieved competency in the use of ‘near patient’ testing technology. This has given them the flexibility to run warfarin clinics both in community pharmacies and in GP practices. It has also enabled them to make domiciliary visits to housebound patients in order to measure their INR and to advise them on their warfarin dosage requirements.

There are many advantages to pharmacist-led anticoagulant clinics in primary care (see page 90 for the relevant resources). These include:

- patient convenience
- continuity of care
- maintenance of accurate patient records
- identification of drug interactions
- identification and minimisation of adverse effects.

And, of course, the introduction of supplementary and independent prescribing means that pharmacy will have an even bigger role to play in the future.

**Practice point**

Are any pharmacists in your area involved in providing anticoagulation services? Set some time aside to talk to them and find out what they do. (It may also be useful to ‘shadow’ them to get some first-hand experience of dealing with this type of service.)

### 10.3 ‘Near patient’ testing

Anticoagulant clinics in primary care are being run with the use of ‘near patient’ testing equipment such as the CoaguChek and Protime. However, the availability of these self-testing kits enables patients to monitor and adjust their own treatment. In guidelines published in 2005 (An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation) the BCSH stated that ‘available data suggest that patient self testing and management of oral anticoagulation is an option for a significant minority of patients if underpinned by structured training and follow-up’. In addition, the guidelines highlight a number of gaps that currently prevent a safe and effective roll-out of such technology to patients. These include issues around the lack of standardised formal training programmes for patients in the UK, and a lack of internal and external quality control for patients measuring their own INR.
Summary

- Hospital-based services are struggling to cope with the increasing workload and alternative service models are required.
- To improve access to anticoagulant services some pharmacists are already involved in monitoring warfarin in a variety of primary care settings.
- There are many advantages to having pharmacist-led anticoagulant clinics in primary care.
- Anticoagulant clinics in primary care are being run with the use of ‘near patient’ testing equipment such as the CoaguChek and Protim. It is also possible for patients themselves to use these kits. However, the evidence suggests that patient self-testing and the self-management of oral anticoagulation is an option for a minority of patients only.

Intended outcomes
By the end of this section you should be able to:

<table>
<thead>
<tr>
<th>Learning objective</th>
<th>Well can you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciate why alternative service models for anticoagulant clinics are urgently needed.</td>
<td></td>
</tr>
<tr>
<td>Outline how pharmacy can support patients taking anticoagulants and the advantages of pharmacy-led anticoagulation clinics in primary care.</td>
<td></td>
</tr>
</tbody>
</table>

Reflective questions

1. Which elements of an anticoagulation service are you able to offer immediately?
2. How would you like to extend the service and what are the associated training requirements?
3. Who would you initially involve from both primary and secondary care when setting up a pharmacist-led anticoagulant clinic in your locality?
i. Reference sources


**ii. Further reading**

**Clinical guidelines/evidence-based reviews**

- Clinical knowledge summary on the management of atrial fibrillation and deep vein thrombosis. Available at: [http://cks.library.nhs.uk/](http://cks.library.nhs.uk/)
- Reviews of the latest clinical evidence in the management of atrial fibrillation and thromboembolism. Available at: [http://www.clinicalevidence.org](http://www.clinicalevidence.org)

**Guidelines from the British Committee for Standards in Haematology** – all available at: [http://www.bcsghguidelines.com](http://www.bcsghguidelines.com)


**Relevant MeReC Bulletin resources** – all available at: [http://www.npc.co.uk](http://www.npc.co.uk)

- National Prescribing Centre (2002). Anticoagulation monitoring strips. *MeReC Extra 5*
Relevant articles from the British Medical Journal – all available at: http://www.bmj.com


Relevant articles from Hospital Pharmacist – all available at: http://www.pjonline.com


For advice on setting up an anticoagulant clinic

- The enhanced service specification under the new pharmacy contract on anticoagulation monitoring is available at: http://www.psnco.org.uk
- The relevant details about the anticoagulant monitoring service, as part of the national enhanced service of the GMS contract can be downloaded from the British Medical Association website: http://www.bma.org.uk
• National Institute for Health and Clinical Excellence (NICE) commissioning
guides – supporting service re-design: Anticoagulant therapy service.
Available at: http://www.nice.org.uk/

• National Pharmacy Association (1999). Providing anticoagulant monitoring
services in community pharmacy: A resource pack for LPCs and community
pharmacists. Available on request by emailing the NHS Service Development
Department at: nhs.dev@npa.co.uk

Primary Care Pharmacy 1 (3): 70-72

Background articles from the Pharmaceutical Journal (referred to in Section 2.1) –
all available at: http://www.pjonline.com/

(272) 7304: 769-771

• Thomson A (2004b). Variability in drug dosage requirements. Pharmaceutical
Journal (272) 7305: 806-808

Journal (273) 7310: 153-155

• Thomson A (2004d). Examples of dosage regimen design. Pharmaceutical
Journal (273) 7311: 188-190
Appendix 1

Checklist to assess if you are ready to deliver an NHS funded anticoagulant monitoring service

Answer the following reflective questions to assess your knowledge and readiness to implement and operate an anticoagulant monitoring service and identify any learning needs. This may provide evidence to your primary care trust or commissioning body about your ability to deliver an anticoagulant monitoring service.

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Yes/No</th>
<th>Learning need</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>I understand why an anticoagulant monitoring service is needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>I can describe how an anticoagulant monitoring service fits into government health policies and pharmacy modernisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>I have successfully completed an accredited training course – please specify</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>I can summarise the main contraindications, cautions and side-effects of warfarin therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>I am aware of the common indications for anticoagulation, associated INR targets and duration of therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>I can evaluate the benefits and risks of anticoagulation in different patient groups.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>I can describe how warfarin therapy is initiated and illustrate the different types of induction regimen.</td>
<td></td>
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<tr>
<td>8.</td>
<td>I can demonstrate an understanding of the main factors affecting warfarin therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>I can manage patients whose INR values are outside their target range.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/No</td>
<td>Learning need</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>10. I understand the important role of the pharmacy team in informing and educating patients about warfarin therapy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. I know and can use the key patient counselling points.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I can advise and educate patients taking warfarin on the implications of travel, surgery and visiting the dentist.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I am able to identify the signs of excessive anticoagulation in patients taking warfarin.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. I can list five clinical governance measures that relate specifically to an anticoagulant monitoring service.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>15. I can describe and provide evidence of clinical governance processes to support a quality anticoagulant monitoring service and help overcome some of the problems associated with the management of anticoagulants.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. I have put processes in place to train my pharmacy team with regard to certain aspects of managing patients taking anticoagulants to enable them to actively participate in the implementation/delivery of this service.</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Points 17-23 are not covered in the CPPE anticoagulant learning programme, but would be useful to consider.

<table>
<thead>
<tr>
<th></th>
<th>Yes/No</th>
<th>Learning need</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.</td>
<td>I am able to operate an appropriate INR analyser – please specify which type, e.g. CoaguChek and Protame.</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>I am able to operate the software and interpret the results from the computerised clinical decision support system.</td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>I can take adequate blood samples (phlebotomy) to determine INR values.</td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>I know how to deal with the disposal of clinical waste.</td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>I have worked under the direct supervision of a trained practitioner.</td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>I am aware of local procedures, documentation and training policies.</td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>My professional indemnity insurer will cover me for provision of this service.</td>
<td></td>
</tr>
</tbody>
</table>

You may wish to add some of your own additional points

Signed

Dated
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