A FOCAL POINT LEARNING PROGRAMME

ANTICOAGULATION
SECOND EDITION

BOOK 1
March 2013
FP119/1
Content contributor
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We thank Eve Knight at AntiCoagulation Europe for her help finding an expert patient to support this programme.

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Learning with CPPE

The Centre for Pharmacy Postgraduate Education (CPPE) offers a wide range of learning opportunities for the pharmacy workforce. We are based in the University of Manchester’s School of Pharmacy and Pharmaceutical Sciences and are funded by the Department of Health to provide continuing education for practising pharmacists and pharmacy technicians providing NHS services in England. For further information about our learning portfolio, visit http://www.cppe.ac.uk.

We recognise that people have different levels of knowledge and not every CPPE programme is suitable for every healthcare professional. We have created three categories of learning to cater for these differing needs:

- **CPPE 1** Core learning (limited expectation of prior knowledge)
- **CPPE 2** Application of knowledge (assumes prior learning)
- **CPPE 3** Supporting specialties (CPPE may not be the provider and will direct you to other appropriate learning providers).

This is a **CPPE 2** learning programme and assumes that you already have some knowledge of the topic area.

**Continuing professional development (CPD)** – You can use this focal point unit to support your CPD. Consider what your learning needs are in this area. Use your CPD record sheets to plan and record your learning.

**Programme guardians** – A programme guardian is a recognised expert in an area relevant to the content of a learning programme. They will review the programme every six months to ensure quality is maintained. We will post any alterations or further supporting materials that are needed as an update on our website. We recommend that you check for these updates if you are using a programme more than six months after its initial publication date.

**Feedback** – We hope you find this learning programme useful for your practice. Please help us to assess its value and effectiveness by visiting the *my CPPE record* page on our website. Alternatively, please email us at feedback@cppe.ac.uk.
About CPPE focal point programmes

We have developed focal point to give you short, clinically focused learning sessions. It will help you learn with your colleagues and improve the services you offer your patients. Each unit presents information and activities that are relevant for healthcare professionals working in primary care and in the community. There are two types of learning event for you to choose between when using focal point units – you can either attend a CPPE tutor-led event or can learn as part of a CPPE ‘learning community’. Have a look at the CPPE website: http://www.cppe.ac.uk/ for more information about how to set up a learning community.

Reference sources for all the books, articles, reports and websites mentioned in the text can be found at the end of the programme. References are indicated in the text by a superscript number (like this 3).

This book gets you started. It provides key information to help you meet the learning objectives presented overleaf, but it also encourages you to identify your own learning needs. It then challenges you to relate what you have learnt to your own area of practice and professional development. We have included practice points and talking points to stimulate your thinking and we will refer to these again at the focal point event. Make sure you have studied these activities before your event.

You will receive Book 2 when you attend the focal point event. It uses a case study and ‘clinical vignettes’ to help you apply what you have learnt and encourages you to make changes to improve your practice. We also include some suggested answers to the learning activities.

About this focal point unit on anticoagulation

In this unit we consider:

- the indications for anticoagulation treatment and principles of monitoring warfarin therapy
- National Patient Safety Agency guidance on anticoagulants, patient concordance and communication
- the identification and management of key issues related to anticoagulant treatment.
Learning objectives

You can meet the learning objectives that we identify here by reading the information that we provide and refer you to, undertaking the various activities that we suggest and putting what you have learnt into practice. We have split our learning objectives into appropriate sections. This should help you determine how to meet them. We have also linked the learning objectives in this programme to the General Level Framework (GLF) and the NHS Knowledge and Skills Framework (KSF) dimensions. We have suggested some competences, but you may be able to apply your learning to other aspects of these frameworks.

Moving into focus and Reading

<table>
<thead>
<tr>
<th>Objective</th>
<th>KSF</th>
<th>GLF</th>
</tr>
</thead>
</table>
| Demonstrate an understanding of the National Patient Safety Agency guidance for anticoagulation medication and how it relates to your workplace and practice | Communication Level 3    | Cluster: Delivery of patient care
|                                                                           |                          | Competency: Medicines information and patient education |
| Explain the recall period for patients receiving warfarin based on their international normalised ratio (INR) result | HWB 7 Level 4            | Cluster: problem solving
|                                                                           |                          | Competency: Gathering information              |
| Demonstrate a knowledge of the latest oral anticoagulants treatments and their role in therapy | HWB 7 Level 2            | Cluster: Delivery of patient care
|                                                                           |                          | Competency: Drug specific issues               |
| State the main indications for warfarin and target INR values             | HWB 7 Level 4            | Cluster: Delivery of patient care
|                                                                           |                          | Competency: Monitoring drug therapy            |
Practice points, talking points, case study and clinical vignettes

You’ll find these in this book and Book 2, and will work on them during the event.

<table>
<thead>
<tr>
<th>Objective</th>
<th>KSF</th>
<th>GLF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify and consider resolutions to common medicines issues in the anticoagulated patient</td>
<td>HWB 7 Level 2</td>
<td>Cluster: Problem solving Competency: Gathering information</td>
</tr>
<tr>
<td>Describe how you can improve safety for the anticoagulated patient by following best practice and principles of medicines optimisation</td>
<td>Service improvement Level 3</td>
<td>Cluster: Management and organisation Competency: Service provision</td>
</tr>
</tbody>
</table>

Directing change scenarios and follow-up activities

You will achieve practical outcomes after completing this unit, when you apply what you have learnt to your everyday practice. You will find advice in Book 2.

<table>
<thead>
<tr>
<th>Objective</th>
<th>KSF</th>
<th>GLF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement improvements in the care provided to patients prescribed anticoagulation in your area of practice</td>
<td>Service improvement Level 3</td>
<td>Cluster: Management and organisation Competency: Service development</td>
</tr>
</tbody>
</table>
Useful resources

We have selected some resources that you can use when developing improved services in your area for people taking an anticoagulant.

Patient support

Patient UK – http://www.patient.co.uk/

This website is designed to provide health information for patients, their carers and health professionals. It makes available details on different anticoagulant medicines and patient information leaflets on clinical conditions – for example, atrial fibrillation (AF). It provides materials of a complexity suitable for both the public and professionals. The website also lists links to further information and support.

AntiCoagulation Europe – http://anticoagulationeurope.org

This patient support organisation provides information for patients, their carers and health professionals. It actively promotes the use of self-testing and self-management of anticoagulant therapy in patients where appropriate to do so. It produces a wide range of patient information leaflets, available to download from the website, on clinical conditions and offering practical advice, such as how to get an INR test abroad. The website hosts patient experience videos and area contacts for patients taking anticoagulation.

Services support


The National Patient Safety Agency (NPSA) alert on anticoagulation (2007) is an essential resource for this learning programme. There are a number of documents included with the alert. You may wish to focus on the documents that are most relevant to your area of practice: Anticoagulant therapy: information for community pharmacists; Anticoagulant therapy: information for GPs; Managing patients who are taking warfarin and undergoing dental treatment and Anticoagulant template service audit form. Some of the documents are presented in a poster format, which you can print and display in your consultation room.


The British Committee for Standards in Haematology (BCSH) provides information on the management of oral anticoagulation, safety indicators for oral anticoagulant care and advice about INR self-testing in the management of patients taking warfarin. The website links closely to articles published in the British Journal of Haematology.
Checklist for planning

To meet the learning objectives you will need to carry out the activities listed in the table below. We’ve given you this list now so that you can start to plan your learning. Although it will only take you about two hours to work through Book 1, feedback from other users suggests that it is useful to plan your activities over a timescale that suits you – perhaps over several days. Try to set yourself a realistic deadline for each task.

<table>
<thead>
<tr>
<th>You will need to:</th>
<th>This will take about</th>
<th>I will do this by (Insert date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Answer the Moving into focus questions</td>
<td>5 minutes</td>
<td></td>
</tr>
<tr>
<td>List three learning needs</td>
<td>5 minutes</td>
<td></td>
</tr>
<tr>
<td>Read the whole booklet</td>
<td>60 minutes</td>
<td></td>
</tr>
<tr>
<td>Undertake the practice points</td>
<td>20 minutes</td>
<td></td>
</tr>
<tr>
<td>Make notes for the talking points</td>
<td>10 minutes</td>
<td></td>
</tr>
<tr>
<td>Work through your own</td>
<td>20 minutes</td>
<td></td>
</tr>
<tr>
<td>Directing change scenario</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Moving into focus

Consider the following questions. Use them to focus your thoughts and stimulate your learning. Are you confident you know the answers?

1. “Renee is prescribed a 3.5 mg dose of warfarin each day, therefore she should take one blue tablet on one day, then one blue and one brown tablet the next day.” Do you agree with this statement? Why (or why not)?

2. If a patient being treated with warfarin is having a crown replaced at a local dentist, what checks should be carried out prior to the procedure and why?

3. Anja takes warfarin for a pulmonary embolism she had four weeks ago. Her current INR reading is 1.8. Anja is normally stable in range on 3 mg of warfarin each day. What adjustments would you make and why?

4. A patient with a prosthetic heart valve is being treated with warfarin. What is the maximum length of time allowed between INR checks?

5. Jayesh is a 76-year-old who has been newly diagnosed as having AF. He has read about a new treatment called Pradaxa for stroke prevention in AF. According to the National Institute for Health and Clinical Excellence (NICE), is Jayesh eligible to receive this medication?
What do you want to learn?

Write down three things that you would like to gain from this focal point learning unit. These will help you plan your own CPD entry. You will need to tell others about them at the focal point event.

1.

2.

3.

Now you have completed your reflection and planning for this focal point unit, it's time to undertake the background reading.
Reading

1. Introduction

Anticoagulants are being used to treat an increasing number of long-term clinical conditions. It is estimated that 1.25 million patients in the UK, many of them elderly, are currently prescribed oral anticoagulant medication.\(^1\) Due to an increasingly elderly population, better detection of disease and robust evidence of the effectiveness of anticoagulant therapy for a number of indications, a growing number of patients are taking warfarin. However, anticoagulation therapy is associated with risks, with an estimated ten percent of medication incidents causing severe harm or death being attributable to anticoagulants.\(^2\) In primary care, deaths associated with warfarin use have been linked to inadequate laboratory results and drug interactions typically involving non-steroidal anti-inflammatory drugs or antibiotics.\(^3\)

In 2004, the Department of Health identified oral anticoagulation therapy as a high risk requiring additional safety management.\(^4\) This resulted in the NPSA risk assessment, alert document and support material detailing ‘actions that can make anticoagulant therapy safer’ to manage the risks associated with anticoagulant use and to reduce patient harm.\(^3\) You can find information about the alert and documents online at [http://www.npsa.nhs.uk](http://www.npsa.nhs.uk).

There are a number of policy initiatives driving the need for services to support patients taking oral anticoagulants. These include the:

- inclusion of anticoagulation monitoring as one of the national enhanced services in the General Medical Service contract
- inclusion of anticoagulants in the list of high-risk medicines highlighted as a national target group for medicines use reviews – an advanced service in the community pharmacy contract
- inclusion of anticoagulants as a therapy area for the new medicine service – an advanced service in the community pharmacy contract
- development by the Department of Health of a cross-government long-term conditions strategy to support people living with long-term conditions, with a goal for them to remain as independent as possible: [http://longtermconditions.dh.gov.uk](http://longtermconditions.dh.gov.uk)
1.1 Definitions
Below we have provided a list of commonly used terms that we will refer to throughout this unit.

**Anticoagulant drugs**
Anticoagulant drugs prevent thrombus formation or the extension of an existing thrombus in the slower moving venous side of the circulation. They are less effective in preventing thrombus formation in arteries because, in faster flowing vessels, thrombi are composed mainly of platelets.

**Antiplatelets**
Antiplatelet drugs are agents that reduce platelet aggregation and inhibit thrombus formation. Examples include aspirin, clopidogrel and a combination of aspirin with sustained-release dipyridamole.

**INR**
The INR is a system established by the World Health Organization and the International Committee on Thrombosis and Haemostasis to report the results of blood coagulation tests. It measures how long a patient’s blood takes to clot compared with a theoretical standard patient not on an anticoagulant. This is then corrected for an international sensitivity index to ensure that INR values tested in different laboratories are comparable. A patient not on an anticoagulant will have an INR value of one. A patient on an anticoagulant will have an INR value greater than one.

**Recall period**
The time between each appointment to measure a patient’s INR.
2. Anticoagulant properties

Warfarin is the most widely prescribed oral anticoagulant and its use has increased over the past decade. In this section we will look closely at anticoagulation with warfarin but will also consider other anticoagulants that you may come across in practice – in particular, the newly emerging oral anticoagulant treatments.

2.1 Warfarin

Pharmacokinetics

Warfarin exerts its anticoagulant effect by interfering with the hepatic synthesis of vitamin K-dependent clotting factors. It reduces the concentration of clotting factors II (prothrombin), VII, IX and X to levels that are believed to protect people against intravascular clotting, without causing excessive suppression of these factors, which leads to haemorrhage. Figure 1 below indicates the stages of the clotting cascade that warfarin disrupts.

**Figure 1:** The clotting cascade with action sites of different anticoagulants
Warfarin also inhibits protein C and protein S formation. These factors have short half-lives and are natural anticoagulants. Therefore, in the very early phases of warfarin initiation, warfarin may act as a procoagulant, rather than an anticoagulant. To counteract this, patients may be started on a low molecular weight heparin (LMWH – see Section 2.2) for rapid anticoagulation at the same time as warfarin is initiated.

Warfarin is taken orally and is almost 100 percent absorbed. It can be detected in plasma within one hour of administration. It is 99 percent protein-bound, principally to albumin, and has a small volume of distribution. The body eliminates warfarin almost entirely by metabolism in the liver, predominantly producing inactive metabolites. Hepatic dysfunction can increase the response to warfarin, because the synthesis of clotting factors is impaired and because the metabolism of the anticoagulant is decreased.

The half-life of warfarin ranges from 25 to 60 hours, with a mean of about 40 hours. As a result, it normally takes between two and five days for the action of warfarin to become therapeutic. When starting a patient on warfarin therapy it normally takes five half-lives to accumulate the drug to steady state (ie, when a constant plasma concentration is achieved).
Therefore it would take $5 \times 40$ hours to reach steady state (which is about eight
days). Loading doses of 10 mg were historically used to achieve steady state more
rapidly; however, the BCSH no longer recommends this approach to initiation,
recommending instead a lower dose of 5 mg for initiation.$^5$ In the elderly, a slow
loading protocol is often preferred as this is shown to be less likely to result in
potentially dangerous over-anticoagulation.

Warfarin does not affect activated clotting factors already in circulation, meaning
that there is a delay in the rise of the INR when therapy is initiated. This delay is an
important consideration when altering warfarin doses during therapy and you should
titrate the dose until the desired response in the patient is obtained (i.e., their target
INR is achieved).

Anticoagulation therapy is intended to reduce the risk and effects of a thromboembolic
event in at-risk patients, but these benefits must be balanced against the risk of a
serious bleed. When reviewing a patient, the contraindications and cautions for
anticoagulation use must be considered. Contraindications and cautions for warfarin
are described in the British National Formulary (BNF) – the most up-to-date BNF
information can be found online at http://bnf.org/ and

Patient UK also produces patient information leaflets on anticoagulation therapy,
available at: http://www.patient.co.uk/showdoc/30002751/.

**Practice point 1**

List four cautions and four contraindications to anticoagulant therapy with
warfarin.
Adverse-effects

The most common side-effects related to warfarin treatment include:

- alopecia
- diarrhoea
- nausea and vomiting
- rash
- minor bleeding or bruising.

The most serious adverse effect related to warfarin treatment is the risk of major bleeding. A meta-analysis of warfarin studies in AF found the incidence of major bleeding varied from 1.4 to 3.4 percent per year. The risk of bleeding is greater in patients recently initiated on warfarin and is related to the degree of anticoagulation, meaning that bleeding risk increases significantly with INR results greater than 5.0. The BNF and BCSH guidelines recommend vitamin K to reverse anticoagulation in patients whose INR is excessive. Further information on the management of over-anticoagulation can be found in the BNF.
2.2 Heparin

Pharmacokinetics

Heparin is a parenterally administered anticoagulant that exerts its main action by binding to the body's own anticoagulant, antithrombin III. Heparin initiates anticoagulation rapidly but acts for only a short time. It is referred to as standard or unfractionated heparin to distinguish it from the LMWHs such as dalteparin (Fragmin), enoxaparin (Clexane) and tinzaparin (Innohep), which have a longer duration of action. When a patient requires rapid anticoagulation, heparin and warfarin are usually administered at the same time, with heparin being withdrawn once a stable target INR is reached. Patients being treated for a venous thromboembolism (VTE) should continue with both warfarin and heparin for at least five days or until the INR is in range for at least 24 hours, whichever is longer.

Longer-term subcutaneous LMWH may be considered as an alternative therapy for patients in whom oral anticoagulants are either:

- contraindicated (eg, due to pregnancy)
- inconvenient (eg, because the patient lives too far from monitoring facilities)
- less effective (eg, in some cancer patients).

Contraindications and cautions

Heparin has similar contraindications to warfarin. An additional concern with heparin and LMWH is the potential for heparin-induced thrombocytopenia (HIT) and hyperkalaemia. HIT occurs typically five to ten days after beginning heparin treatment and requires medical intervention. Therefore patients should have a platelet count check before starting heparin, and twice weekly after day 5 of treatment. The highest risk of HIT is in the first three weeks of treatment. If the platelet count is found to be reduced, treatment should be stopped and the diagnosis confirmed by an HIT assay. If HIT is confirmed, heparin must not be used for anticoagulation in these patients. Hyperkalaemia can occur because heparin inhibits aldosterone secretion.
2.3 Dabigatran, rivaroxaban and apixaban

Dabigatran, rivaroxaban and apixaban are new oral anticoagulant treatments that have emerged in recent years. Unlike warfarin, they do not require frequent monitoring for INR, have no dietary restrictions and have fewer significant drug interactions than warfarin. These proposed benefits over warfarin potentially make these medicines the future of oral anticoagulation. However, unlike with warfarin, there is no specific reversal agent for these treatments, which makes the management of a potential major bleed less clear.8

Dabigatran

Dabigatran (Pradaxa) is a direct oral thrombin inhibitor (see Figure 1). It has a half-life of 12 to 14 hours and exerts its maximum effect within two hours of administration. It is important to discuss with patients that dabigatran capsules should not be opened as this potentially increases absorption.

Dabigatran is currently approved by NICE for the prevention of VTE following elective total hip or knee replacement surgery9 and as an option for the prevention of stroke and systemic embolism in people with non-valvular AF.10

To qualify for AF treatment with dabigatran, patients must have one or more of the following risk factors:

- previous stroke, transient ischaemic attack (TIA) or systemic embolism
- left-ventricular ejection fraction below 40 percent
- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- age 75 or older
- age 65 or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.10
Rivaroxaban

Rivaroxaban (Xarelto) is an orally active direct factor Xa inhibitor, which inhibits thrombin formation and development of thrombi (see Figure 1). Maximum inhibition of factor Xa occurs four hours post dose, with effects lasting 8 to 12 hours. However, factor Xa activity does not return to normal within 24 hours, which makes once-daily dosing possible.

Like dabigatran, rivaroxaban is currently approved by NICE for the prevention of venous thromboembolism following elective total hip or knee replacement surgery and as an option for the prevention of stroke and systemic embolism in people with non-valvular AF.

To qualify for AF treatment with rivaroxaban, patients must have one or more of the following risk factors:

- 75 years or over
- diabetes mellitus
- congestive heart failure
- hypertension
- history of previous stroke or TIA.11

In addition, rivaroxaban is recommended by NICE as an option for treating deep vein thrombosis (DVT) and preventing recurrent DVT and pulmonary embolism after an acute diagnosis of DVT.12

Apixaban

Apixaban (Eliquis), like rivaroxaban, is an oral, highly selective active-site inhibitor of factor Xa, which inhibits thrombin formation and development of thrombi. Apixaban is rapidly absorbed with peak concentrations appearing three to four hours after oral intake and has a half-life of approximately 12 hours. Currently apixaban has only been reviewed by NICE for the prevention of VTE after total hip or knee replacement in adults.

Cautions and contraindications of dabigatran, rivaroxaban and apixaban

As with other anticoagulants, dabigatran, rivaroxaban and apixaban should be used with caution in conditions with increased risk of haemorrhage and patients should be monitored for signs of bleeding. The BNF has details of cautions, contraindications and side-effects. However, it is worth bearing in mind that these are relatively new medicines and side-effects which have not yet been identified may become apparent through use in practice.
Practice point 2

Consider the possible advantages and disadvantages of the new oral anticoagulant treatments when compared to warfarin. Make a list of these below.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.4 Other anticoagulants

Acenocoumarol and phenindione are rarely used but are options for people who are allergic to warfarin. See the *BNF* for fuller prescribing details.
3. Indications for therapy

In this section we will look at the indications for anticoagulant use, specific INR targets and durations of therapy.

Table 1: Some common indications for oral anticoagulant therapy and target INRs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>2.5</td>
</tr>
<tr>
<td>Calf vein thrombus</td>
<td>2.5</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>2.5</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>2.5 or 3.0</td>
</tr>
<tr>
<td>Mechanical heart valve – no patient risk factors</td>
<td>2.5, 3.0 or 3.5*</td>
</tr>
<tr>
<td>Mechanical heart valve – patient-related risk factors</td>
<td>3.0 or 3.5*</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>2.5</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>2.5</td>
</tr>
<tr>
<td>Recurrence of VTE when no longer on warfarin therapy</td>
<td>2.5</td>
</tr>
<tr>
<td>Recurrence of VTE while on warfarin therapy</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Depending on the type of valve employed.

You will find a comprehensive review of the clinical indications for oral anticoagulants in the BCSH guidelines, available online at http://www.bcsghguidelines.com. A full list of target INRs is also available in the BNF.

3.1 Atrial fibrillation

Warfarin is widely used in patients with AF to reduce the risk of a stroke. In this section we will consider the role of anticoagulation in patients with AF.

The decision to start patients on an anticoagulant for prevention of stroke in AF is not always a clear-cut one and should always be made in conjunction with the patient. Possible options for stroke prevention are long-term aspirin or anticoagulation (most commonly with warfarin, but dabigatran and rivaroxiban may also be treatment options). Table 2 highlights the annual stroke risk for patients with AF with no treatment or on aspirin or warfarin.
Table 2: Annual risk of stroke with no treatment, aspirin or warfarin in high, moderate and low-risk patients with non-valvular atrial fibrillation\textsuperscript{13}

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Untreated</th>
<th>Aspirin</th>
<th>Warfarin</th>
<th>NNT warfarin vs. aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very high</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous ischaemic stroke or TIA</td>
<td>12%</td>
<td>10%</td>
<td>5%</td>
<td>13</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age over 65 and one other risk factor:</td>
<td>5-8%</td>
<td>4-6%</td>
<td>2-3%</td>
<td>22-47</td>
</tr>
<tr>
<td>▪ Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Left-ventricular dysfunction</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age over 65 years with no other risk factors</td>
<td>3-5%</td>
<td>2-4%</td>
<td>1-2%</td>
<td>47-83</td>
</tr>
<tr>
<td>Age under 65 years with other risk factors</td>
<td></td>
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</tr>
<tr>
<td><strong>Low</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age under 65 years with no other risk factors</td>
<td>1.2%</td>
<td>1%</td>
<td>0.5%</td>
<td>200</td>
</tr>
</tbody>
</table>

NNT = number needed to treat with warfarin instead of aspirin for one year to prevent one stroke. Therefore, for example, 22 to 47 high-risk patients would need to be treated with warfarin instead of aspirin for one year to prevent one stroke.
The decision to use warfarin or aspirin to treat patients with AF should ultimately be based on the balance of an individual’s overall risk of stroke compared with adverse events, and on their personal preference. There are several resources available to aid clinicians and patients in the decision making process. The flowchart published by NICE on the management of AF (Figure 2) is designed to inform healthcare decisions made when commencing anticoagulation therapy for those at risk of stroke.

1 Note that risk factors are not mutually exclusive, and are additive to each other in producing a composite risk. Since the incidence of stroke and thromboembolic events in patients with thyrotoxicosis appears similar to that in patients with other aetiologies of AF, antithrombotic treatments should be chosen based on the presence of validated stroke risk factors.

2 Owing to lack of sufficient clear-cut evidence, treatment may be decided on an individual basis, and the physician must balance the risks and benefits of warfarin versus aspirin. As stroke risk factors are cumulative, warfarin may, for example, be used in the presence of two or more moderate stroke risk factors. Referral and echocardiography may help in cases of uncertainty.

3 Coronary artery disease or peripheral artery disease.

4 An echocardiogram is not needed for routine assessment, but refines clinical risk stratification in the case of moderate or severe LV dysfunction and valve disease.

Figure 2: NICE guidance for assessing the risk of stroke and thromboprophylaxis

Reproduced with the permission of NICE.
In its guidelines on the management of AF, the European Society of Cardiology has adopted the CHA2DS2-VASc risk algorithm as a means of stratifying a patient’s risk of stroke.\textsuperscript{15}

\textbf{Table 3: CHA2DS2-VASc score for stroke risk in AF}

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age over 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Age between 65 and 74 years</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
</tbody>
</table>

- **Score of 2 or more:** \textbf{high risk of stroke}. Anticoagulation with warfarin is preferred as the benefits usually outweigh the risks.

- **Score of 1:** \textbf{intermediate risk of stroke}. Antithrombotic therapy is required, but the decision to use warfarin or aspirin is less clear. The decision should be based on risk versus benefit and patient preference.

- **Score of 0:** \textbf{low risk}. Offer aspirin as antithrombotic of choice.

Bleeding is the most serious and most common complication of warfarin treatment. The most serious major bleed is an intracranial haemorrhage. In primary prevention trials comparing warfarin to placebo, the annual risk of intracranial haemorrhage increased from 0.1 percent in controls to 0.3 percent in patients taking warfarin. This increased risk was particularly associated with an INR reading above 3.0, uncontrolled hypertension (and a non-significant association with increasing age).\textsuperscript{16, 17} However, as the data in Table 2 shows, AF patients prescribed warfarin have a lower risk of stroke than those prescribed aspirin.\textsuperscript{13}
Talking point A

Involving patients in the decision to start treatment with warfarin is an important aspect of patient-centred care. How could you explain the risks and benefits of starting treatment with warfarin for a patient who is at an intermediate risk of having a stroke?

Clinical trials have shown that long-term anticoagulation reduced the risk of stroke associated with anticoagulation but warfarin is only taken by 30 to 60 percent of appropriate patients. Because about 15 percent of all strokes are attributable to AF, the clinical and economic consequences of the underprescription of warfarin are profound.

Dabigatran, rivaroxaban and apixaban in stroke

The long-term use of the new oral anticoagulants for the prevention of stroke has been evaluated in three large randomised controlled trials: ARISTOTLE (apixaban), RE-LY (dabigatran) and ROCKET AF (rivaroxaban). These trials considered the efficacy and safety of each new oral anticoagulant when compared to warfarin in patients with moderate to high risk of stroke. A meta-analysis of these trials looking at the efficacy and safety of the new oral anticoagulant versus warfarin found that the new oral anticoagulants are at least non-inferior to warfarin in preventing stroke and systemic embolism. All three medicines were associated with a significantly decreased risk of haemorrhagic stroke when compared to warfarin, but a higher risk of gastrointestinal bleeding.
4. Monitoring and maintaining therapy

In this section we will focus on treatment with warfarin and will look at recall periods for INR testing and factors that affect anticoagulant therapy.

The effectiveness and safety of warfarin is critically dependent upon maintaining the INR within the target range, typically 0.5 either side of the target INR value. The dose of warfarin to achieve a target INR will vary from patient to patient.

4.1 Maintenance and recall of patients

As a healthcare professional monitoring a patient’s anticoagulant therapy, you should take into account the trend of their previous INR results and the reason that they are taking warfarin when considering their next dose and the length of time between assessments.

During induction and initial stabilisation of patients on warfarin, daily INR measurements are often necessary, particularly with more aggressive induction regimes. The time between recalls increases as the patient remains stable and decreases if the patient becomes less stable.

Once a patient is within the therapeutic range the frequency of the INR measurements may decrease. The maximum recall period for patients is typically 12 weeks, though patients with a prosthetic heart valve have a shorter maximum recall period of six weeks.
Refer to local protocols or guidelines provided in your area on frequency of monitoring for further information. Local resources should also provide information for managing over and under-anticoagulated patients.

**Practice point 3**

Self-monitoring of INR and self-management of warfarin dosing may be a possibility for suitable patients.

Scan the QR code to watch the following video, in which Peter talks about his experience of self-monitoring his INR (or visit [http://www.cppe.ac.uk/anticoagulation](http://www.cppe.ac.uk/anticoagulation)). Has watching this video changed your perception of self-monitoring? What would you want to consider if a patient wishes to self-monitor?

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4.2 **Factors affecting warfarin therapy**

Several factors can affect an individual's response to warfarin. These include drug interaction, herbal/alternative remedies, physical or lifestyle changes and disease states.

**Drug interactions**

It is very difficult to avoid medication that interacts with warfarin in patients with multiple disease states and in patients receiving several medicines. The INR of a patient prescribed warfarin must be closely monitored when any interacting medicine (e.g., amiodarone or metronidazole) is introduced, discontinued or has its dosage adjusted. Up-to-date information on drug interactions can be found in the *BNF*.
The BCSH guidelines on oral anticoagulants state that:\textsuperscript{5}

- when prescribing, a non-interacting drug should be chosen where possible
- for short courses of a new drug, warfarin dose adjustment is not essential
- for a drug change lasting more than seven days, an INR test should be performed three to seven days after starting the new medication so that the warfarin dose may be adjusted on the basis of INR result.

It is important to understand the mechanism of any drug interaction with warfarin and to know what advice to give to patients about their warfarin when other medication is altered in any way. Warfarin is metabolised by several P450 isoenzymes 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.

**Practice point 4**

Selected examples of drugs which may interact with warfarin are listed in Table 4 overleaf.

Indicate whether the warfarin dose is likely to increase, decrease or stay the same and state what action you would take if a patient who takes warfarin presents with a prescription for this drug for the first time.
Table 4: Selected drugs and their effect on warfarin doses required

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on warfarin dose required</th>
<th>Action you would take (if any)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Allopurinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin (14-day course)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole (14-day course)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
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<td></td>
</tr>
</tbody>
</table>

Herbal/alternative remedies

Some alternative medicines, including food supplements, may interact with warfarin. The strength and quantities of active ingredients are not regulated for most alternative health products, so monitoring the effects of added alternative remedies in a patient stabilised on warfarin can be difficult. Some widely used alternative medicines that can affect INR include:

- chondroitin
- ginger
- garlic
- ginseng
- ginkgo biloba
- glucosamine (you should advise patients to avoid this completely)
- St John’s wort (you should advise patients to avoid this completely).
Talking point B
What resources are available for you to use when patients ask you for advice on taking herbal and alternative remedy products while on warfarin?

Physical/lifestyle changes and disease states

Many conditions can alter the effects of warfarin, including:

*Pregnancy*
Oral anticoagulants should be avoided in pregnancy. Patients who become pregnant while taking warfarin must seek immediate medical advice. These patients should be managed with LMWH as it does not cross the placenta. It is stopped prior to delivery.

*Breastfeeding*
Women may breastfeed their babies while they are taking warfarin.

*Age*
Generally, elderly people have an increased sensitivity to warfarin and require a lower mean daily dose to achieve a given anticoagulant effect. Since many older patients are prescribed multiple medicines, the chance of drug interactions increases. The decline in cognitive function in some elderly patients makes this a particularly challenging patient group for whom to manage anticoagulant therapy safely and effectively.
Hypothyroidism
This medical condition results in a reduced metabolic rate, which means clotting factors that are dependent on vitamin K remain in the circulation longer. A patient with an underactive thyroid will require a higher dose of warfarin as a result. 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 marked increase in metabolic activity, which may accelerate the clearance of clotting factors that are dependent on vitamin K. Consequently, the amount of warfarin required to produce an anticoagulant effect decreases. When a patient starts to take carbimazole or propylthiouracil to correct their thyroid function, their warfarin requirement will increase as their thyroid function normalises.

Heart failure
Heart failure can cause congestion of blood flow around the liver 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.

Antiphospholipid syndrome (also known as Hughes syndrome).
This disorder of the clotting cascade results in excessive clotting in both the arteries and veins. The condition is often associated with other autoimmune disorders, as well as pregnancy-related complications, such as miscarriage and severe pre-eclampsia due to small clots forming in the placenta.

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

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

Alcohol
Alcohol can act both as an enzyme inhibitor and an enzyme inducer. Binge drinking results in hepatic dysfunction and can increase the effects of warfarin through impaired synthesis of coagulation factors, producing an increase in INR. A chronic alcoholic (heavy abuser) may show a diminished effect from warfarin and, in such cases, INR decreases.
Diet
Patients who are taking warfarin should be encouraged to eat a sensible, well-balanced diet and not to go on crash diets or start binge eating. 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, as well as in those on weight-reduction diets that are rich in green vegetables and vitamin K. If patients need to lose weight, encourage them to contact their doctor or practice nurse for advice.

Concordance
Poor concordance may be a reason for unexpected and marked variations in anticoagulant control. The best way to avoid complications with oral therapy is to be certain that the patient clearly understands the risks of too much or too little anticoagulation. You should 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.
4.3 Managing anticoagulants in patients requiring dental surgery

The NPSA is particularly concerned about managing patients who are taking warfarin and undergoing dental treatment. It has produced a flow diagram for dentists, which details how to manage dental patients taking anticoagulants. This includes information on drug interactions with some of the medicines commonly used in dentistry. Patient information leaflets are also available for dental patients taking anticoagulants. As a rule of thumb, if the INR is 4.0 or less then dental treatment can usually be carried out in the community without altering or stopping the patient’s dose of warfarin.

**Figure 3: Flow diagram provided by the NPSA for display and use in dental clinics**
5. Supporting patients to manage their treatment

Patient education is one of the key factors in minimising adverse outcomes and keeping patients on warfarin well. A key role for healthcare professionals is to provide education and support patients with a view to improving adherence as well as ensuring the safety and efficacy of warfarin therapy. With oral anticoagulants finding use in an increasing number of conditions and a drive within the NHS towards shared decision-making, patients are becoming more medically aware and involved in their condition and its management.

Providing patients with appropriate education about their medication and condition empowers them to make appropriate decisions and choices regarding their care. For example, healthcare professionals can provide advice to patients on interactions with medicines they are aware the patient is taking, but will not be aware of medicines bought from a supermarket or herbal remedies. Real dialogue with patients is needed to engage them in understanding and managing their anticoagulation in an informed way. There are many available resources to support you in doing this effectively, including the ‘Yellow Book’ which contains a range of information for patients. Patient information leaflets are also available to download from Patient.co.uk and AntiCoagulation Europe.
Practice point 5

When counselling patient on warfarin you may find it useful to have a checklist of key points to cover. If you do not already have one of these in your practice, construct one now using resources such as the Yellow Book to help you.

Summary

In this book we have reviewed the key points relating to the main anticoagulants used in the UK, including the indications for treatment, evidence to support their use, principles of monitoring warfarin therapy and factors that may affect therapy management. We have looked closely at the example of AF, a common indication for anticoagulant treatment, to discuss treatment selection choice and risk evaluation. We have also considered the importance of patient involvement in the safe and effective management of anticoagulant treatment.
Directing change

Here we give you the opportunity to reflect and consider how you could improve your practice in this area.

At the focal point event we would like you to share with your colleagues an experience that you have had regarding the management of anticoagulated patients. Take some time to make some notes to support you on the evening.

You should include the following information:

- the type of anticoagulation the patient was taking
- the condition being treated and any co-existing medical conditions
- issues that you encountered and how you resolved them
- how you involved the patient in any action you took.
# Checklist for action

At this point in the learning programme you will have carried out the following.

<table>
<thead>
<tr>
<th>Activity</th>
<th>I completed this on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have answered the Moving into focus questions</td>
<td></td>
</tr>
<tr>
<td>I have listed three learning needs</td>
<td></td>
</tr>
<tr>
<td>I have read the whole booklet</td>
<td></td>
</tr>
<tr>
<td>I have undertaken the practice points</td>
<td></td>
</tr>
<tr>
<td>I have made notes for the talking points ready to share at the event</td>
<td></td>
</tr>
<tr>
<td>I have worked through the Directing change exercise</td>
<td></td>
</tr>
</tbody>
</table>

Signed:  

Date:  

Take this booklet with you to your *focal point* event. Make sure that you know when and where it is and what time it starts. Enjoy your learning.
References


Notes
For information on your orders or bookings, or any general enquiries, please contact us by email, telephone, fax or post. A member of our customer services team will be happy to help you with your enquiry.

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Fax: 0161 778 4030

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The University of Manchester
Oxford Road
Manchester M13 9PT

Do you have any comments on your focal point learning experience? email: feedback@cppe.ac.uk

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