An open learning programme for pharmacists and pharmacy technicians

Anticoagulation
Managing patients, prescribing and problems
Second edition 2008

Educational solutions for the NHS pharmacy workforce
Acknowledgements

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About CPPE

The Centre for Pharmacy Postgraduate Education (CPPE) is funded by the Department of Health to provide continuing education for practising pharmacists and pharmacy technicians providing NHS services in England. We are part of the Workforce Academy, within the School of Pharmacy and Pharmaceutical Sciences which is part of the Faculty for Medical and Human Sciences.

CPPE offers a wide range of learning opportunities for the pharmacy workforce. Our full learning portfolio is available on the internet at: http://www.cppe.ac.uk

Themes

We have allocated themes to all of our learning programmes. There are 28 themes in total and they allow you to navigate easily through our full learning portfolio. We have assigned a different colour to each of our themes, and this is used to identify the theme in the annual prospectus, in CPPE news&events, on our website, and on the covers of all the learning programmes.

This learning programme is part of the Cardiovascular disease theme. You will find additional learning programmes within this theme in our prospectus and on our website.

You can download this and other e-learning programmes in portable document format (PDF) from our website: http://www.cppe.ac.uk

CPPE 1 2 3

We recognise that people have different learning needs and not every CPPE learning programme is suitable for every pharmacist or pharmacy technician. Some of our programmes contain core learning, while others deliver more complex learning that is only required to support certain roles. So we have created three categories of learning – CPPE 1 2 3 – and allocated each programme to an appropriate category. The categories are:

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

This is a CPPE 2 learning programme.

Continuing professional development

You can use this learning programme to support your continuing professional development (CPD). Consider what your learning needs are in this area. You may find it useful to work with the information and activities here in a way that is compatible with the Royal Pharmaceutical Society of Great Britain’s approach to
continuing professional development ([http://www.rpsgb.org.uk/registrationand support/continuingprofessionaldevelopment](http://www.rpsgb.org.uk/registrationand support/continuingprofessionaldevelopment)) because you will be able to relate it to your personal circumstances more closely. Use your CPD record sheets or go to [http://www.uptodate.org.uk/home/welcome.shtml](http://www.uptodate.org.uk/home/welcome.shtml) to plan and record the actions you have taken.

**Activities**

**Exercises**

We have used exercises throughout this programme as a form of self-assessment. Use them to test your knowledge and understanding of key learning points.

Complete the exercises as fully as possible before looking at the suggested answers at the end of a section. Don’t be tempted to jump ahead until you have written your own answers.

**Practice points**

Practice points are an opportunity for you to consider your practical approach to the effective care of patients or the provision of a service. They are discrete activities designed to help you to identify good practice, to think through the steps required to implement new practice, and to consider the specific needs of your local population. Practice points are not essential learning; you must make your own decision about whether to do them, and how long to spend on them.

We have designed the practice points in this programme to help you and your team to make links between the learning and your daily practice and to co-ordinate with other healthcare professionals.

**Case studies**

We base case studies on actual or simulated events; they are a way of helping you to interpret protocols, deal with uncertainties and weigh up the balance of judgments needed to arrive at a conclusion. We design the case studies to prepare you for similar or related cases that you may face in your own practice.

**Reflective questions**

We have included questions in each section to give you an opportunity to reflect on what you have read so far, and to reinforce and extend your learning. Thinking about these questions will help you to meet the objectives of the programme.

**Assessment**

The assessment for this programme can only be accessed through our website at: [http://www.cppe.ac.uk](http://www.cppe.ac.uk). You can either use the e-assessment link on the tool bar or visit your CPD record on our website and access the assessment from there.
There are two anticoagulation e-assessments on our website.

- **Anticoagulants: supporting patients and ensuring safety**
  The successful completion of this assessment provides you with evidence that you have the core knowledge of anticoagulation. Successful completion of this assessment will show that you have an understanding of how to support patients and ensure safety with anticoagulants. This is a CPPE assessment.

- **Anticoagulation assessment**
  Successful completion will enable any pharmacist or pharmacy technician to demonstrate competence in managing patients and prescribing in the area of anticoagulation. This could be used as part of your portfolio of evidence for submission for local accreditation to provide anticoagulation services in primary or secondary care. This is a CPPE assessment.

Both of these are summative assessments of your learning. You will be informed whether your attempt has been successful or unsuccessful. If you are unsuccessful work through the suggested reading to help you broaden your knowledge before attempting the assessment again.

**Reference sources and further reading**

You can find reference sources for all the books, articles, reports and websites mentioned in the text, together with a list of further reading to support your learning, at the end of the programme. References are indicated in the text by a ‘superscript’ number (like this \(^3\)). For clarity, CPPE uses its own simplified format for references.

**Terminology used in this programme**

To aid your learning we have compiled a list of abbreviations used in the programme and a glossary of terms you may not be familiar with (it is assumed that you are familiar with terms routinely used within pharmacy). CPPE uses the nomenclature structure used in the *British national formulary*.

**Programme guardians**

CPPE has adopted a quality assurance process called ‘programme guardians’. A programme guardian is a recognised expert in an area relevant to the content of a learning programme who will review the programme every six months. Derek Meadows, a community pharmacist and an independent prescriber, is the programme guardian for this open learning programme. We will post any corrections, additions, deletions or further supporting materials that are needed as an update to the programme on the CPPE website.

We recommend that you refer to these updates if you are using this (or any other) learning programme significantly after its initial publication date. A full list of programme guardians is available on our website. You can email your comments about this programme to them at: info@cppe.ac.uk
Brand names and trademarks

CPPE acknowledges the following brand names and registered trademarks which are mentioned in this programme: Elantan LA®

External websites

CPPE is not responsible for the content of any non-CPPE websites mentioned in this programme or for the accuracy of any information to be found there. The fact that a website or organisation is mentioned in the programme does not mean that CPPE either approves of it or endorses it.

Disclaimer

CPPE recognises that local interpretation of national guidance may differ from the examples used in this learning programme and you are advised to check with your own relevant local guidelines. You are also advised to use this programme with other established reference sources. If you are reading this programme significantly after the date of initial publication you should refer to current published evidence. CPPE does not accept responsibility for any errors or omissions.

Feedback

We hope you find this learning programme useful for your practice. Please help us to assess its value and effectiveness by completing the feedback form (if enclosed) and returning it in the prepaid envelope. Otherwise, please email us at: feedback@cppe.ac.uk
This programme aims to improve your knowledge about anticoagulants, particularly warfarin and heparin, and their main indications. You will learn how to initiate warfarin therapy and how to monitor patients on long-term therapy. You will also gain an insight into how drugs and disease states interact with warfarin, and this will enable you to identify and solve common problems in patient care. Note, however, that the programme is designed to complement and not to replace any local arrangements or protocol training.

The programme does not cover the process of setting up anticoagulant clinics, blood sampling techniques, computer-aided decision-making, or the use of a coagulometer. However, it is a very useful starting point, both for pharmacists and for pharmacy technicians who wish to provide these services (for example, it will signpost you to appropriate websites for further information about setting up an anticoagulant clinic).

The programme is likely to take you about six hours to complete, depending on your learning style and pace (you should record the actual time in your CPD record).

**Target audience**

This programme is aimed at any pharmacist or technician working in the community, a primary care trust or a hospital who is interested in building up their knowledge and skills to achieve competency in this area of practice.

It has been designed as core learning to support the enhanced services template in the new pharmacy contractual framework or any other local arrangements or protocol training for the provision of an anticoagulant service.

**Learning style adopted in this programme**

This is a conventional open learning programme and is designed to be read from cover to cover with each section building on your knowledge and skills in this clinical area. There is extensive cross-referencing between the sections. It does not attempt to cover all the therapeutic issues associated with anticoagulation but focuses on the common medicines management issues that you will encounter in your everyday practice. We have included links to useful resources and references on the internet to further your learning.

**Learning objectives**

CPPE has linked all its learning programmes to the Royal Pharmaceutical Society of Great Britain’s competences for pharmacists and pharmacy technicians. This will make it easier for you to connect your professional practice to your learning needs and learning activities. We have selected only the competences for general pharmacists and pharmacy technicians, but we are aware that others exist.

We have also linked the learning to the dimensions of the NHS Knowledge and Skills Framework (KSF).
The competences and dimensions relevant to this programme are:

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<th>RPSGB competences</th>
<th>KSF dimensions</th>
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<td>Pharmacy technicians</td>
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<td>Recognise the main indications for anticoagulation (warfarin and heparin).</td>
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<td>TG7</td>
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<td>Evaluate the risks and benefits associated with anticoagulant prescribing.</td>
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<td>TG6, TG7</td>
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<td>Interpret laboratory data required to manage patients effectively.</td>
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<td>Understand how to manage elevated INRs.</td>
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<tr>
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<td>G1, G5, G7, G8</td>
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<tr>
<td>Learn how to manage patients on anticoagulants safely.</td>
<td>G1</td>
<td>TG9, TG14</td>
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<tr>
<td>Summarise the possible side-effects of anticoagulants and describe to patients the symptoms they may experience.</td>
<td>G1, G2, G8</td>
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<tr>
<td>Explain (teach) the key counselling points to a newly-anticoagulated patient.</td>
<td>G2</td>
<td>TG1</td>
</tr>
<tr>
<td>Propose a potential role for the pharmacist and pharmacy technician in a multiprofessional team supporting patients prescribed anticoagulants.</td>
<td>G1</td>
<td>TG1, TG13</td>
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</table>

The National Patient Safety Agency and Skills for Health* have developed six work competences for anticoagulant therapy:

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

Details are available at: http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant

* Skills for Health was set up in 2002 and is part of the NHS. It works with employers and other stakeholders to ensure that those working in the sector are equipped with the right skills to support the development and delivery of healthcare services.
Working through this programme

Take a few minutes to browse through the programme to get a feel for the contents. Although this is a traditional open learning programme you may wish to use it in different ways – to find out the answers to specific queries, for example, or as a training resource for your pharmacy staff.

There are 10 sections in this programme and some additional advice is given at the beginning of each section to guide your learning.

Online resources

Some of the references in this programme are to material which is only available online, and we assume that you have access to a computer connected to the internet. If you do not wish to retype all the web addresses into your browser you may find it helpful to download this programme from the CPPE website as a PDF document containing ‘live’ web links. Log on to: http://www.cppe.ac.uk

Where we think it will be helpful we have provided the URL to take you directly to an article or specific part of a website. However, we are also aware that web links can change (eg, the Department of Health links) so in some cases we have provided the URL for the organisation’s home page only. If you have difficulty accessing any web links, please go to the organisation’s home page and use appropriate key words to search for the relevant item.

Note on NICE guidance: To find any of the NICE guidelines or technology appraisals mentioned in this programme visit the NICE website at: http://www.nice.org.uk On their home page, under ‘Search NICE guidance’, enter the relevant topic and click ‘Search’.

Note on articles: If you have difficulty locating an article on the internet, search via: http://www.google.co.uk by typing in the title, author, date and name of the journal. It can also be helpful if you add in, at the end of the search criteria, the website where you think the information may be, eg, dh.gov.uk
Supporting you, your practice and the NHS

When devising this programme we paid special attention to how it would contribute both to your own professional development and to the overall improvement of NHS services. We have illustrated some of these benefits in the diagram below (you will find more detail as you progress through the programme).

**Supporting skill mix**

This programme will show you how you can involve your whole pharmacy team in managing patients taking anticoagulants.

**NHS Knowledge and Skills Framework**

Successful completion of the assessment may help you provide evidence that you are meeting the desired level of performance in relation to your current post.

**Evidence-base/guidelines**

This programme supports national guidelines provided by:
- British Committee for Standards in Haematology
- National Institute for Health and Clinical Excellence
- National Patient Safety Agency

**Commissioning**

You can provide an anticoagulant monitoring service which your PCT or PBC* group may wish to commission.

**Community pharmacy**

You will be able to embed clinical governance systems into your practice as part of the essential services tier in the pharmacy contract.

**Pharmacist prescribing**

Anticoagulant monitoring services could be expanded to meet increasing demand by the support of pharmacist prescribers.

**Policy drivers**

This learning supports numerous health initiatives such as; *Our health, our care, our say, Care closer to home* and the new GMS contract.

*Practice-based commissioning*
Activated partial thromboplastin time (aPTT)
Activated partial thromboplastin time is a performance indicator for measuring the clotting time in plasma, which focuses on a specific pathway in the blood clotting process. As well as detecting abnormalities in blood clotting, it is also used to monitor the treatment effects of heparin.

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 of less use in preventing thrombus formation in arteries because in faster flowing vessels thrombi are composed mainly of platelets.

Antiplatelet drugs
Antiplatelet drugs decrease platelet aggregation and may inhibit thrombus formation in the arterial circulation where anticoagulants have little effect.

Antithrombotic drugs
This term is used to cover both anticoagulant and antiplatelet drugs.

Atrial fibrillation
Atrial fibrillation is an abnormal heart rhythm (arrhythmia) which involves the two small, upper chambers of the heart. It is one of the most common arrhythmias seen in both general practice and in acute care.

Cardioversion
Cardioversion is the restoration of the normal heartbeat by electrical or pharmacological means.

Clinical knowledge summaries
Funded by the Department of Health, clinical knowledge summaries (CKS) are a central resource for the National Library for Health. They provide an up-to-date source of clinical knowledge for the NHS about the common conditions managed in primary and first contact care. CKS help healthcare professionals confidently make evidence-based decisions about the healthcare of their patients and provide the know-how to safely put these decisions into action.

Deep vein thrombosis (DVT)
Deep vein thrombosis is the formation of a blood clot or thrombus in a deep vein, commonly affecting leg veins such as the femoral or popliteal vein.

Distal DVT
These DVTs are found in the deep veins of the calf. They are the most common type of DVT.

Embryopathy
A developmental disorder in an embryo.

Euthyroid
This describes a situation where thyroid stimulating hormone test values are in the normal range. The thyroid is neither hyperthyroid nor hypothyroid and is considered ‘normal’.

Fennerty induction regimen
This is a method for the rapid initiation of warfarin therapy.
**Half-life**
This describes the time it takes for the concentration of a drug in the body to fall by half its initial value.

**International normalised ratio (INR)**
This is a system established by the World Health Organization and the International Committee on Thrombosis and Haemostasis for reporting the results of blood coagulation tests. In simple terms, it measures how long the blood takes to clot.

**‘Number needed to treat’ (NNT)**
The NNT is the number of people who need to be treated to produce one additional outcome. It is calculated as follows:

\[
NNT = \frac{100}{\%ARR \text{ (absolute risk reduction)}}
\]

where the \%ARR is calculated as: \%event rate (placebo) – \%event rate (drug).

**Organogenesis**
This describes the formation and development of organ systems during embryogenesis.

**Pharmacokinetics**
This is the process by which a drug is absorbed, metabolised, distributed and eliminated by the body – in other words, how the body handles drugs.

**Proximal DVT**
These DVTs are found in the popliteal, superficial femoral, common femoral or iliac veins.

**Sinoatrial node**
The sinoatrial node (also called the sinus node) is the impulse-generating (pacemaker) tissue located in the right atrium of the heart. It controls the rate of the heartbeat.

**Sinus rhythm**
This is a term used to describe the normal beating of the heart, as measured by an electrocardiogram.

**Thrombocytopenia**
A persistent decrease in the number of blood platelets that is usually associated with haemorrhagic conditions.

**Thrombophilia**
This term describes a group of conditions in which the blood clots easily or excessively due to an abnormality in the system of coagulation.

**Thromboembolic event**
The formation of a thrombus or blood clot.

**Valvular heart disease**
This describes any disease process affecting one or more valves of the heart.

**Venous thromboembolism**
DVT combined with pulmonary embolism or other thrombi.

**Ventricular arrhythmia**
This is a disorganised electrical activity in the atria leading to a rapid and irregular ventricular rate.
Section 1

Introduction

Objectives

On completion of this section you should be able to:

■ understand why the number of patients treated with warfarin is increasing

■ identify the main national policy drivers

■ start to consider how you and your staff can get involved in managing patients on warfarin.

This section looks at the increasing use of anticoagulants against a backdrop of the current policy drivers and the pressures on existing services. It finishes by briefly looking at the ways in which the pharmacy team can support patients who are taking anticoagulants.

1.1 Anticoagulant monitoring services

Anticoagulants are being used to treat an increasing number of long-term clinical conditions.

Warfarin is the most widely prescribed oral anticoagulant and its use has increased over the past decade. Due to its mechanism of action and narrow therapeutic index, patients who are prescribed warfarin need to have their blood clotting times checked on a regular basis using the international normalised ratio (INR).

Warfarin management includes:¹

- phlebotomy or finger-pricking
- accurate measurement of the INR by a coagulometer (with associated standards and quality control)
- interpretation of the result
- advice on the warfarin dose
- clinical management of the complications of treatment (predominantly overdose and drug interactions).

At present INR monitoring and dosage adjustments take place in a variety of settings, for example:

- outpatient clinics in hospital (however, many of these clinics are overstretched)
- ‘satellite’ clinics in the community run by hospital staff
- clinics run by GPs or nurses
- community pharmacy-led clinics
- the patient’s home (self-management).
1.2 Policy drivers

Because of 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. As a result, the service load for monitoring anticoagulation is predicted to increase by a factor of five over the next 10 years. There are also a number of policy initiatives driving this increase in the need for services to support patients taking warfarin. These include:

- a push by the government to treat patients with long-term conditions in the community, as reflected in the recent introduction of practice-based commissioning in GP practices. (Practice-based commissioning focuses on treating long-term conditions in the community and reducing the number of emergency admissions to hospital.)

- the inclusion of anticoagulant monitoring as one of the national enhanced services in the General Medical Service contract. (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.) In addition, the contract for 2006/2007 contains a quality standard in the quality and outcomes framework relating to the percentage of patients with atrial fibrillation who are currently treated with anticoagulants or antiplatelet drugs.

- the inclusion of anticoagulant monitoring as one of the template enhanced service specifications in the new pharmacy contract.

1.3 How the pharmacy team can support anticoagulated patients

This support may include:

- hospital pharmacists ensuring that adequate discharge counselling and written advice is given to patients who are newly-initiated on warfarin

- involving hospital pharmacists in pre-assessment clinics and stopping anticoagulation prior to elective surgery

- practice pharmacists targeting this group of patients in the GP practice to ensure they are managing their warfarin therapy appropriately

- community pharmacists using the new pharmacy contract to become more involved in the management of patients’ medication. For example:
  - by ensuring that suitable patients taking warfarin become part of the repeat dispensing service
  - by targeting this group of patients for a medicines use review to check that they understand their warfarin therapy and are complying with it
  - by being commissioned by the primary care trust to provide enhanced services in order to prescribe for this patient group, or to run anticoagulant monitoring clinics.
Practice point

Find out how patients taking anticoagulants are monitored and advised in your own local area. Do the current service providers feel overstretched, and what are their views on how pharmacy can get involved? Would patients prefer to use an easily-accessed service?

Summary

- The management of patients on warfarin is a complex process.
- The number of patients taking warfarin is on the increase.
- There is significant scope for pharmacy to become involved in supporting patients on anticoagulants.

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 current and future pressures on anticoagulant monitoring services and what your particular situation is locally.</td>
<td></td>
</tr>
<tr>
<td>Describe how pharmacy can become more involved in supporting patients who are taking anticoagulants.</td>
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</tbody>
</table>

Reflective questions

1. Are there any anticoagulant services run by pharmacy staff in your area?
2. What do you feel you can do now to improve the safe use of anticoagulants?
Section 2
Mode of action and pharmacokinetics of anticoagulants

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

- summarise the pharmacokinetics of warfarin and heparin, and the major contraindications, cautions and side-effects of treatment.

This section outlines some of the basic facts about the mode of action and the pharmacokinetics of anticoagulants to refresh your memory and support the learning in this programme. Further information is available on the websites mentioned in the text and in the reference section.

2.1 Warfarin

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 give protection against intravascular clotting without causing excessive suppression of these factors, which leads to haemorrhage.

The dose of warfarin should be titrated until the desired response for an individual is obtained (i.e., the ‘target INR’). This may take several days because warfarin does not have any effect on clotting factors already in the circulation. But it does have an effect on the rate of synthesis of the new factors by the liver.

A series of four articles in the *Pharmaceutical Journal* in 2004 reminded the pharmacy team about the basic principles of pharmacokinetics, pharmacodynamics and therapeutic drug monitoring. The articles available on the Pharmaceutical Journal website (http://www.pjonline.com) are entitled:


Warfarin is composed of a racemic mixture of two isomers, designated R and S. The S isomer is five times more potent than the R isomer, and both have different metabolic pathways. Warfarin is administered orally and with almost 100 percent absorption can be detected in plasma within one hour. It is extensively protein bound (99 percent), principally to albumin, and has a small volume of distribution.

The elimination of warfarin is almost entirely by metabolism in the liver to predominantly inactive metabolites. Therefore no dosage adjustment is required for
patients in renal failure, but hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.

The mean half-life of warfarin ranges from 25-60 hours, with a mean of about 40 hours. Thus the duration of action of warfarin is two to five days. When starting on warfarin therapy it normally takes five half-lives to accumulate the drug to steady state (i.e., when plasma concentration is constant). Therefore it would take 5 x 40 hours to reach steady state (which is about eight days). It is often desirable to initiate therapy with loading doses to bring the steady state forward (see Section 6 for further information).

The risk of bleeding is greater in patients recently initiated on warfarin and is related to the degree of anticoagulation. Bleeding while on oral anticoagulants increases significantly, with INR results greater than 5.0.

**Contraindications and cautions**

The contraindications and cautions for warfarin are described in the current edition of the *British national formulary*[^1] (http://www.bnf.org.uk). The relevant information can be downloaded from: http://www.cks.library.nhs.uk/deep_vein_thrombosis

The contraindications include:

- peptic ulcer (i.e., a potential bleeding lesion)
- severe hypertension (e.g., systolic greater than 200 mm/Hg or diastolic greater than 120 mm/Hg)[^4]
- bacterial endocarditis
- pregnancy (warfarin should be avoided if at all possible, especially in the first and third trimesters).

The cautions include:

- severe hepatic impairment
- severe renal impairment
- recent surgery
- not drinking cranberry juice – following advice from the Medicines and Healthcare Products Regulatory Agency (MRHA) in October 2004.[^5] This advice is available online from: http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomeopathicmedicines/Herbalmedicines/HerbalSafetyNews/Currentsafetyissues/CON1004343

Further discussions have taken place with the National Patient Safety Agency (NPSA) and the British Society for Haematology (BSH) about this topic and a decision reached that the wording in the booklet, *Oral anticoagulation therapy. Important information for patients*, states that drinking cranberry juice can affect an INR result and recommends avoidance of cranberry juice.

Other cautions to warfarin therapy can include:

- unco-operative/unreliable person – concordance and follow-up issues
- repeated falls or unstable gait – increased chance of injury and head trauma.

[^1]: The contraindications and cautions for warfarin are described in the current edition of the *British national formulary*[^1] (http://www.bnf.org.uk). The relevant information can be downloaded from: http://www.cks.library.nhs.uk/deep_vein_thrombosis

[^4]: The contraindications and cautions for warfarin are described in the current edition of the *British national formulary*[^1] (http://www.bnf.org.uk). The relevant information can be downloaded from: http://www.cks.library.nhs.uk/deep_vein_thrombosis

[^5]: The contraindications and cautions for warfarin are described in the current edition of the *British national formulary*[^1] (http://www.bnf.org.uk). The relevant information can be downloaded from: http://www.cks.library.nhs.uk/deep_vein_thrombosis
The concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided if at all possible due to the increased risk of gastrointestinal bleeding (see Section 5 for further information). If the benefits of an NSAID outweigh the risks, patients should be told to report signs and symptoms of bleeding and have their INR carefully monitored. Some centres advocate the use of a proton pump inhibitor with NSAIDs.

Exercise 1

NSAIDs taken with warfarin may result in an increased risk of bleeding. What is the mechanism of action of this interaction?

Side-effects
The side-effects of warfarin include:

- haemorrhage (see Section 8 for further information)
- hypersensitivity, rash, alopecia, diarrhoea, ‘purple toes’, skin necrosis, jaundice, hepatic dysfunction.

2.2 Heparin

Heparin is a parenterally administered anticoagulant that exerts its main action by binding to the body’s own anticoagulant, antithrombin III. Heparin potentiates the anticoagulant effect of antithrombin III and thereby prolongs the activated partial thromboplastin time (aPTT) when given in therapeutic doses.

Heparin initiates anticoagulation rapidly but has a short duration of action. It is referred to as standard or unfractionated heparin (UFH) to distinguish it from the low molecular weight heparins (LMWH) such as dalteparin, enoxaparin and tinzaparin, which have a longer duration of action. Therefore when rapid anticoagulation is required heparin and warfarin are usually administered at the same time, with heparin being withdrawn once a stable target INR is reached (see Section 6 for further information).

Adjusted dose subcutaneous heparin may be considered as an alternative therapy for patients in whom oral anticoagulants are either:

- contraindicated (eg, due to pregnancy)
- inconvenient (eg, because they live a distance from monitoring facilities)
- ineffective (eg, in some cancer patients).
Contraindications and cautions

The contraindications and cautions for heparin are described in the current edition of the British national formulary and the relevant summary of product characteristics maintained by the electronic Medicines Compendium (http://www.emc.medicines.org.uk).

The contraindications include:
- haemophilia and other haemorrhagic disorders
- thrombocytopenia (including history of heparin-induced thrombocytopenia)
- peptic ulcer
- recent cerebral haemorrhage
- severe hypertension
- severe liver disease.

The cautions include:
- old age
- hepatic impairment
- renal impairment
- heparin-induced thrombocytopenia – platelet counts are recommended for patients who receive heparin (including LMWH) for more than five days. Heparin should be stopped immediately and not repeated in patients who develop thrombocytopenia or who have a 50 percent reduction in platelet count.
- hyperkalaemia – the inhibition of aldosterone secretion by heparin (including LMWH) may result in hyperkalaemia. Patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium and those taking potassium-sparing drugs seem to be more susceptible. The risk appears to increase with the duration of therapy. The Committee on the Safety of Medicines has recommended that the plasma potassium of ‘at risk’ patients should be measured before starting heparin and monitored regularly thereafter, particularly if the heparin is to be continued for more than seven days.

Side-effects

The side-effects of heparins include:
- haemorrhage
- skin necrosis
- thrombocytopenia (see the list of cautions, above)
- hyperkalaemia (see the list of cautions, above)
- hypersensitivity reactions (including urticaria, angioedema and anaphylaxis)
- osteoporosis after prolonged use – heparin therapy for more than four months carries a high risk of osteoporosis and bone fractures. Guidelines published in 2006 by the British Committee for Standards in Haematology (BCSH) on the use and monitoring of heparin state that several lines of evidence now suggest that LMWHs are associated with a lower risk of osteoporosis than UFH. LMWH is preferred for long-term use and clinicians and patients should be aware of the risks of osteoporosis and consider this knowledge when determining the risk/benefit ratio of heparin therapy.
2.3 Other anticoagulants

Acenocoumarol (nicoumalone) and phenindione are rarely used but are options for people who are allergic to warfarin. See the current edition of the *British national formulary*³ for fuller prescribing details.

Two new classes of anticoagulants

Two new classes of anticoagulants are also being developed:

- dabigatran is a direct oral thrombin inhibitor. It has been approved by NICE for the prevention of venous thromboembolism, following elective total hip or knee replacement surgery, for up to 35 days after surgery. Its use is only initiated in secondary care.

- rivaroxaban is currently awaiting FDA approval. It is a direct Xa inhibitor indicated for the prevention of venous thromboembolism in adult patients undergoing an elective hip or knee replacement.

**Summary**

- Warfarin takes several days to have an observable effect because it does not act on the existing clotting factors that are present in the blood but on the rate of synthesis by the liver of new clotting factors.

- Loading doses of warfarin are sometimes used to bring the steady state forward and to achieve a target INR more quickly.

- The risk of bleeding is greater in patients recently initiated on warfarin and is related to the degree of anticoagulation.

- In 2004 the Committee on the Safety of Medicines issued advice stating that patients taking warfarin should not drink cranberry juice.

- Patients should be monitored for hyperkalaemia and thrombocytopenia if heparins are administered for more than seven days and five days, respectively.

- Osteoporosis can be a problem for patients taking heparin for more than four months.

**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 mode of action of warfarin and heparin.</td>
<td></td>
</tr>
<tr>
<td>Recognise the major contraindications, cautions and side-effects of treatment.</td>
<td></td>
</tr>
</tbody>
</table>
Reflective questions

1. What is the incidence of osteoporosis after prolonged use of heparin?
2. Which liver enzymes are predominantly involved in the metabolism of the S-isomer of warfarin?
3. Why is warfarin ineffective in some cancer patients?

Suggested answers

Exercise 1 (page 6)

The increased risk of bleeding is possibly due to the combination of gastric irritation, decreased platelet function, or the displacement of warfarin from plasma binding sites.
Section 3

Indications for anticoagulation, associated INR targets and duration of therapy

Objectives

On completion of this section you should be able to:

- outline the most common indications for anticoagulation
- describe the associated target INR and duration of therapy for each indication.

Venous thromboembolism, atrial fibrillation and the treatment of patients with mechanical heart valves are the main reasons that anticoagulants are prescribed. This section will help you to understand these conditions and the need for anticoagulant therapy.

3.1 Thromboembolism

The aim of anticoagulant therapy is to prevent the occurrence of a thromboembolic event (i.e., the formation of a thrombus or blood clot) in a patient who is at risk without overly increasing the incidence of haemorrhage.

The formation of a thrombus may result in, for example, a deep vein thrombosis, pulmonary embolism or a cerebrovascular accident/stroke.

Three primary factors influence the formation of thrombi. These are abnormalities of:

- blood flow (e.g., atrial fibrillation)
- surfaces in contact with blood (e.g., heart valve replacement)
- clotting components (e.g., Factor V Leiden and the less common protein S and protein C deficiencies). Thrombophilia is the term used to describe this group of conditions in which there is an increased tendency for excessive clotting. It usually presents in younger patients (less than 50 years of age) and is often recurrent. The most frequent causes of the syndrome are the factor V Leiden mutation and a prothrombin gene mutation, which together account for around 50 to 60 percent of cases.

Thromboembolism is a major cause of death and disability. Many people are hospitalised each year for stroke, which can be fatal or disabling, and 85 percent of strokes are due to thromboembolism. Similarly, each year thousands of people develop deep vein thrombosis of the lower limb or its sequel, pulmonary embolism.

Venous thromboembolism, atrial fibrillation and the treatment of patients with mechanical heart valves are the main reasons that anticoagulants are prescribed.
The following sections will help you to understand these conditions and the need for anticoagulant therapy.

3.2 Starting anticoagulation

The potential benefits of prevention from thromboembolic disease need to be balanced against the potential harm from induced haemorrhagic side-effects. Some questions to consider before starting a person on anticoagulation are described below.

**Considering anticoagulation**

- Is there a definite indication (e.g., atrial fibrillation)?
- Is there a high risk of bleeding or a strong contraindication against anticoagulation?
- Will concurrent medication or disease states increase the risk of bleeding or interfere with anticoagulation control?
- Is drug compliance and attendance at an anticoagulant clinic for monitoring likely to be a problem?
- Will there be a regular review of the patient, especially with regard to the risks and benefits of anticoagulation?


3.3 Routes of administration

Anticoagulants are given either by the parenteral route (e.g., heparin) or the oral route (e.g., warfarin).

**Parenteral anticoagulants**

Heparin initiates anticoagulation rapidly but has a short duration of action. It is referred to as standard or unfractionated heparin (UFH) to distinguish it from the low molecular weight heparins (LMWH) such as dalteparin, enoxaparin and tinzaparin, which have a longer duration of action.

Laboratory monitoring of UFH is essential, and preferably on a daily basis. Determination of the aPTT is the most widely used technique. aPTT ratios below 1.5 are associated with recurrent thromboembolism and ratios above 2.5 are associated with an increased risk of bleeding. Routine monitoring of the anticoagulant effects of LMWHs is not usually required.

When deciding on which heparin preparation and dose to use, clinicians must consider:

- the intrinsic risk to the patient of thrombosis and bleeding (patient risk)
- the risk of thrombosis and bleeding associated with the procedure or clinical condition of the patient (disorder risk)
- the relative efficacy of different heparin preparations and doses and the relative risk of bleeding associated with these (heparin risk).
For patients at high risk of bleeding, standard heparin is more suitable than low molecular weight heparin because its effect can be terminated rapidly by stopping the infusion.³

**Practice point**

*Read the latest edition of the British national formulary for product information and guidance on the licensed indications and dosing regimens for each heparin preparation in each clinical situation.*

**Oral anticoagulants**

The BCSH guidelines describe the indications for oral anticoagulation and suggest arrangements for the management of an anticoagulation service.⁹,¹⁰ Some of the indications described in these guidelines are listed in Table 1. (The guidelines themselves give a more detailed overview of all the indications, together with the evidence base and suggestions for the duration of therapy.)

Measuring prothrombin time is generally accepted as a means of controlling anticoagulant dosage. The international normalised ratio (INR) was developed to reduce variability in results and standardise the methods for comparison amongst different laboratories. One INR result can be compared to another INR result regardless of how or where the result was obtained.

The BCSH guidelines recommend ‘target INRs’. An INR within 0.5 INR units of the target is generally considered to be satisfactory. Therefore for a target INR of 2.5, a range of INR values between 2.0 and 3.0 would be acceptable.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid syndrome</td>
<td>2.5</td>
</tr>
<tr>
<td>Arterial grafts</td>
<td>2.5 if anticoagulated</td>
</tr>
<tr>
<td>Atrial fibrillation due to rheumatic heart disease, congenital heart disease and thyrotoxicosis</td>
<td>2.5</td>
</tr>
<tr>
<td>Bioprosthetic valve</td>
<td>2.5 if anticoagulated (see original 1998 guideline)</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>Coronary angioplasty and stents</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Coronary artery graft</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Coronary artery thrombosis</td>
<td>2.5 if anticoagulated</td>
</tr>
<tr>
<td>Ischaemic stroke without atrial fibrillation</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Mechanical prosthetic heart valve – aortic</td>
<td>3.0 or 2.5*</td>
</tr>
<tr>
<td>Mechanical prosthetic heart valve – mitral</td>
<td>3.5 or 3.0*</td>
</tr>
<tr>
<td>Mural thrombus</td>
<td>2.5</td>
</tr>
<tr>
<td>Non-rheumatic atrial fibrillation</td>
<td>2.5</td>
</tr>
<tr>
<td>Peripheral arterial thrombosis</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Proximal deep vein thrombosis</td>
<td>2.5</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>2.5</td>
</tr>
<tr>
<td>Recurrence of venous thromboembolism when no longer on warfarin therapy</td>
<td>2.5</td>
</tr>
<tr>
<td>Recurrence of venous thromboembolism while on warfarin therapy</td>
<td>3.5</td>
</tr>
<tr>
<td>Retinal vessel occlusion</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Symptomatic inherited thrombophilia</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Refer to the guidelines for recommendations for valve-location-specific target international INRs.

Source: Modified from Table 1 in the BCSH guidelines (1998)
3.4 Venous thromboembolism

Deep vein thrombosis of the lower limb and its acute complication, pulmonary embolism, are major causes of death and disability in this country.

Deep vein thrombosis is a serious condition where thrombi develop in the deep veins of the legs. It should be distinguished from blood clots in superficial varicose veins in the legs (called phlebitis), which is much less serious.

One in 100 people who develop deep vein thrombosis dies. The cause of death is usually a thrombus travelling from the legs to the lungs. This is called pulmonary embolism. Severe pulmonary embolism causes lung collapse and heart failure. Pulmonary embolism is an extremely common condition and a leading cause of death in all age groups, being the second most common cause of death after ischaemic heart disease.

Deep vein thrombosis combined with pulmonary embolism or other thrombi is often referred to as venous thromboembolism.

The prevention of venous thromboembolism

Recommendations of the expert working group on the prevention of venous thromboembolism (VTE) in hospitalised patient

An electronic copy of this report and separate annexes is available to view and download at: http://www.dh.gov.uk/

1. All medical patients should, as part of a mandatory risk assessment, be considered for thromboprophylaxis measures; in particular, patients likely to be in hospital for longer than four days and with reduced mobility, with either severe heart failure, respiratory failure (due either to exacerbation of chronic lung disease or pneumonia), acute infection, inflammatory illness or cancer (with additional risk factors for VTE) should be considered for the following regimen:
   - heparins (both unfractionated and low-molecular-weight forms) are effective preventive treatments. Low-molecular-weight heparins are the preferred prophylactic method.
   - aspirin is not recommended for thromboprophylaxis in medical patients
   - mechanical methods of prophylaxis have not to date been appropriately evaluated in acutely ill medical patients, and thus are not recommended at present.

2. All high risk surgical/orthopaedic patients should be managed according to the available evidence. The NICE clinical guideline CG46\(^\text{11}\) (see below) on the prevention of venous thromboembolism in patients undergoing orthopaedic surgery and other high risk procedures was published in April 2007.

3. Intermediate risk surgical patients or those with concomitant medical conditions should, as part of a mandatory risk assessment, be considered for the following thromboprophylaxis measures:
   - graduated compression stockings combined with heparins (both unfractionated or low-molecular-weight forms)
   - aspirin is not recommended for thromboprophylaxis in intermediate risk surgical patients.
4. Low risk surgical patients do not require specific prophylaxis other than early mobilisation because of the duration or nature of surgical procedure, unless other factors are present which increase overall risk and thus place them in intermediate or high risk categories.
   - Aspirin is not recommended for thromboprophylaxis in low risk surgical patients.

**National Institute for Health and Clinical Excellence (2007)**

*Venous thromboembolism: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery.*

Clinical guideline CG46 (London: NICE)\(^\text{11}\)

Available online at: [http://www.nice.org.uk/](http://www.nice.org.uk/)

The advice in this NICE guideline covers adults who are at risk of developing a blood clot because they are having an operation that requires an overnight stay in hospital.

These operations include:
- hip or knee surgery
- abdominal surgery
- gynaecological surgery (but not Caesarean section)
- surgery on the brain, spine, heart, lungs, kidneys or bladder
- surgery on the arteries or veins.

It does not specifically look at preventing blood clots in:
- children or young people under 18 years old
- adults who are at risk of developing blood clots for reasons other than having an operation.

**Key recommendations in the NICE guideline include:**

1. Patients should be assessed to identify their risk factors for developing venous thromboembolism.

2. Inpatients having surgery should be offered thigh-length graduated compression/ anti-embolism stockings from the time of admission to hospital unless contraindicated. If thigh-length stockings are inappropriate for a particular patient for reasons of compliance or fit, knee-length stockings may be used as a suitable alternative.

3. Intermittent pneumatic compression or foot impulse devices may be used as alternatives or in addition to graduated compression stockings while surgical patients are in hospital.

4. In addition to mechanical prophylaxis, patients at increased risk of venous thromboembolism because they have individual risk factors and patients having orthopaedic surgery should be offered low molecular weight heparin (LMWH). Fondaparinux, within its licensed indications, may be used as an alternative to LMWH.
5. LMWH or fondaparinux therapy should be continued for four weeks after hip fracture surgery.

6. Regional anaesthesia reduces the risk of venous thromboembolism compared with general anaesthesia. Its suitability for an individual patient and procedure should be considered, along with the patient’s preferences, in addition to any other planned method of thromboprophylaxis.

7. Healthcare professionals should encourage patients to mobilise as soon as possible after surgery.

**Practice point**

*Do you use LMWH in your hospital trust? Has it had any impact on the average length of stay for patients with deep vein thrombosis?*

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**The treatment of venous thromboembolism**

*Deep vein thrombosis*

Proximal DVTs occur in the popliteal, superficial femoral, common femoral or iliac veins. Distal DVTs occur in deep veins of the calf and are the most common type of deep vein thrombosis.12 *(See page 17 for further information.)*

**Who is at risk of deep vein thrombosis?**

Every year deep vein thrombosis occurs in about one to three in 1000 people in the general population. The risk of deep vein thrombosis and pulmonary embolism is greater in people who:

- are over 40 years of age
- have a history of thromboembolism
- have a family history of thromboembolism
- suffer from or have had treatment for cancer
- are being treated for heart failure and circulation problems
- have had surgery recently, especially on the hips or knees.

Deep vein thrombosis is also more common in women who:

- are pregnant
- have had a baby recently
- are taking the contraceptive pill or hormone replacement therapy.

These groups make up the majority of all those who get deep vein thrombosis and/or pulmonary embolism.
What are the signs of deep vein thrombosis?

The signs of deep vein thrombosis include swelling, pain, tenderness and redness, especially at the back of the leg below the knee (see picture). In some cases there may be no signs or symptoms at all in the legs and problems only become obvious when a pulmonary embolus develops from the thrombi in the legs.

Diagnosing deep vein thrombosis

People present with these symptoms in both primary care settings (eg, NHS walk-in centres) and at hospitals. Because several other conditions show similar symptoms to DVT, the condition may be difficult to diagnose without doing specific objective imaging studies.

The optimal diagnostic approach would include taking a detailed medical history, analysing the individual’s risk factors and undertaking a physical examination supplemented by selective imaging studies where appropriate.

In most patients with clinically suspected venous thrombosis, venous ultrasound is the diagnostic method of choice.

In addition, the D-dimer test is performed on blood obtained by finger-prick testing at the patient’s side. D-dimer assays are, in general, sensitive but non-specific markers of DVT. The D-dimer test is often false-positive after surgery or trauma, thereby limiting its value in these clinical situations. If applied properly, incorporation of D-dimer testing into a structured diagnostic approach simplifies the management of a patient presenting with suspected DVT. A low D-dimer level suggests a lower likelihood of DVT and should prompt other possible diagnoses (such as a ruptured Baker’s cyst, skin infections, phlebitis, etc).

Treatment of deep vein thrombosis

After a positive diagnosis of a deep vein thrombosis, patients are immediately treated with heparin (eg, LMWH). Warfarin is started simultaneously.

The first incidence of a proximal vein thrombosis in a patient requires six months of warfarin therapy with a target INR of 2.5. In calf vein thrombosis warfarin therapy is continued for three months in non-surgical patients who have no predisposing risk factors such as cancer or thrombophilia. Post-operative calf vein thrombosis in a patient with no persistent risk factors needs six weeks of warfarin therapy.

Patients may continue to experience swelling for some months after a deep vein thrombosis. If this is accompanied by pain and redness, the patient should be referred to an accident and emergency department.

Class 2 graduated elastic compression stockings should be worn on the affected leg following a proximal DVT. To reduce the incidence of further thrombotic events the evidence\(^4\) suggests that the stockings should be worn below the knee on the affected leg for at least two years.

The prescription for compression stockings should be renewed every three to six months if the stockings are used every day.
Pulmonary embolism

Pulmonary embolism is strongly associated with proximal DVT of the lower limb. Pulmonary embolism can cause breathlessness, chest and back pain and, in severe cases, collapse and death. Many patients are initially asymptomatic, and most of those who do have symptoms have an atypical presentation.

Diagnosing pulmonary embolism

Pulmonary angiography is considered the gold standard for pulmonary embolism diagnosis, but this invasive procedure is not without risk and may not be available at all hospitals. The ventilation/perfusion lung scan has been the preferred non-invasive test for pulmonary embolism but its diagnostic accuracy is limited. Several diagnostic tests have been recommended, including assays for circulating D-dimer, discussed previously under ‘Diagnosing deep vein thrombosis’.

After a positive diagnosis of a pulmonary embolism patients are immediately treated with LMWH and warfarin simultaneously. Warfarin therapy is continued for between three to six months, depending on the risk factors.

Recurrent deep vein thrombosis/pulmonary embolism while taking warfarin

After a patient has had a positive diagnosis of a recurrent deep vein thrombosis or pulmonary embolism while anticoagulated with warfarin, the target INR is increased to 3.5 (see Table 1 on page 13).

LMWH is given until the INR is within the new target range. Underlying reasons such as carcinoma or thrombophilia (eg, presence of factor V Leiden or antiphospholipid antibody syndrome) should be investigated. Recurrence of embolism while taking warfarin almost always means that long-term treatment with warfarin is needed.

Recurrent deep vein thrombosis/pulmonary embolism in patients who are not currently taking warfarin

After a positive diagnosis of a second deep vein thrombosis or pulmonary embolism patients are immediately treated with heparin and warfarin simultaneously, as before. A further episode of treatment is needed but the target INR remains the same as before.

Practice point

When a patient presents with a recurrence of a venous thromboembolism after stopping warfarin therapy the BCSH recommends a ‘further treatment episode’. Get a copy of your local protocol/guidance. How long is warfarin usually given in this clinical situation?
3.5 Prophylaxis of cardiac thromboembolism

Atrial fibrillation/paroxysmal atrial fibrillation

Warfarin should be considered first-line therapy to reduce the risk of stroke in moderate-to-high risk patients. Since the anticoagulant effect is not required immediately, warfarin therapy can be started without heparin unless the patient has presented with an embolic event.

Cardioversion

Cardioversion refers to the process of restoring the heart’s normal rhythm from an abnormal rhythm by electrical stimulation or by pharmacological means. For patients with atrial fibrillation it may prevent the need for long-term warfarin. However, there is an embolic risk associated with both the electrical and pharmacological termination of atrial fibrillation. Warfarin is therefore given for at least three weeks (within the target range, usually above 2.5) prior to cardioversion and for four weeks after it. There is a very good short-term success rate of restoring a sinus rhythm (about 75 percent), although after a year the number of patients remaining in sinus rhythm falls to only 10-30 percent. Cardioversion can be attempted a number of times on the same patient.

Valvular heart disease

Patients with valvular heart disease can be divided into those with a low, moderate or high risk of embolism.

Rheumatic mitral valve disease is associated with a high risk of stroke even in the absence of atrial fibrillation. The risk of embolism increases in the presence of atrial fibrillation or a previous history of embolism. Warfarin prophylaxis is indicated in patients with rheumatic mitral valve disease (especially mitral stenosis) who have a high risk of systemic embolisation.

Non-rheumatic heart valve disease with atrial fibrillation carries a moderate risk. Minor valve abnormalities in sinus rhythm are at low risk of systemic embolisation.

Mechanical prosthetic heart valves

There are many different types of mechanical prosthetic heart valves and the type and location determines the target INR. The position and age of the prosthesis are also factors that determine thrombotic risk.

The addition of aspirin or dipyridamole should be considered in patients with mechanical valves who suffer systemic embolism despite adequate intensity warfarin. The addition of aspirin increases the risk of bleeding.

Exercise 2

What duration of warfarin therapy is recommended for:

1. The secondary prevention of a venous thromboembolism?
2. A first episode of calf vein thrombosis?

3. Rheumatic mitral valve disease?

---

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

**Martin**

Martin is a 69-year-old male with permanent atrial fibrillation. His current drug therapy is:

- aspirin 75 mg once daily
- digoxin 125 micrograms daily
- ramipril 5 mg daily
- amiodarone 200 mg daily
- warfarin 1 mg tablets, taken as directed.

1. What is this patient’s target INR and duration of therapy?

2. Comment on his drug therapy and highlight any medicines management issues.

---

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

- Anticoagulant therapy is all about balancing the risks and benefits of therapy for each patient.
- Venous thromboembolism and atrial fibrillation are the main reasons that anticoagulants are prescribed.
- The attainment of target INRs for the relevant indications are recommended for oral anticoagulant therapy with an acceptable INR value within 0.5 INR units of the target.
- When rapid anticoagulation is needed heparin and warfarin are usually initiated at the same time. Heparin is taken for at least five days and is continued until the INR has been in the therapeutic range for two consecutive days.

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>Have a better understanding of venous thromboembolism and atrial fibrillation.</td>
<td></td>
</tr>
<tr>
<td>Understand the indications for anticoagulant therapy and the target INRs associated with oral therapy.</td>
<td></td>
</tr>
<tr>
<td>Appreciate that anticoagulant therapy is all about balancing the risks and benefits of therapy for each patient.</td>
<td></td>
</tr>
</tbody>
</table>

Reflective questions

1. What do you understand by the term ‘protein C deficiency’?
2. How are deep vein thrombosis and pulmonary embolism linked?
3. What is the main cause of atrial fibrillation?
4. Can you summarise the risks and benefits of anticoagulant therapy in the management of venous thromboembolism and atrial fibrillation?
5. What is the acceptable range of INR values for a target INR of 2.5?
Suggested answers

Exercise 2 (page 19)
1. Long-term.
2. At least six weeks.
3. Lifelong.

Case study 1: Martin (page 20)
1. What is this patient’s target INR and duration of therapy?
   Target INR is 2.5 (range 2.0-3.0) and warfarin therapy is indicated for life.

2. Comment on his drug therapy and highlight any medicines management issues.
   You may have noted the following:
   - confirm that the aspirin prescription is intended to continue when the warfarin is introduced. Aspirin and warfarin are frequently used in combination by cardiologists, but patients need extra education because the warfarin booklet says this combination should not be used together
   - aspirin makes the patient more likely to bleed without an elevated INR
   - altering the doses of amiodarone or digoxin will have an effect on the patient’s INR
   - be aware of the side-effects of amiodarone, particularly those that would alter the effects of warfarin (eg, thyroid disturbance and liver function)
   - recognise that ramipril may be prescribed for congestive cardiac failure and that INR control may fluctuate with changes in heart failure.
Section 4
Balancing the benefits and risks of anticoagulation in atrial fibrillation

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

- define the term atrial fibrillation
- evaluate the benefits and risks of anticoagulation in different patient groups with atrial fibrillation.

The risk of having a stroke varies and depends on the cause of atrial fibrillation, the patient’s age and other risk factors. This section highlights the various guidelines and risk management strategies to help you evaluate the benefits and risks of anticoagulation in different patient groups with atrial fibrillation.

4.1 Atrial fibrillation

Normally, the heart beats at a steady, regular rate (ie, at a ‘sinus rhythm’). This is controlled by electrical impulses which start from the sinoatrial node in the right atrium. In atrial fibrillation many random electrical impulses ‘fire off’ from the heart muscle in the atria. These cause the heartbeat to become much faster than normal; the normal regular sinus rhythm is lost, and the heartbeat becomes erratic (ie, there is ‘ventricular arrhythmia’). Atrial fibrillation is the most common cardiac arrhythmia seen in general practice.\textsuperscript{13, 14}

Hypertension is the most common cause of atrial fibrillation since it puts a strain on the cardiac muscle. Atrial fibrillation is also a common complication of various heart conditions (eg, ischaemic heart disease). Other causes include hyperthyroidism, over consumption of alcohol, pneumonia, and pulmonary embolism.

Possible symptoms include:
- palpitations
- dizziness
- angina
- breathlessness (often the first symptom that develops).

If left uncontrolled, atrial fibrillation can lead to complications such as heart failure from reduced cardiac output.

Compared to people in sinus rhythm, patients with atrial fibrillation are two to seven times more likely to have a stroke. Stasis of blood in the left atrium contributes to thrombus formation, increasing the risk.

The aims of treating atrial fibrillation are to:
- reduce palpitations
- reduce the symptoms of poor cardiac output
- reduce the risks of stroke and thromboembolism.
These are achieved by controlling the ventricular rate (eg, with digoxin) or by restoring the sinus rhythm using cardioversion, and by using aspirin and/or warfarin (drug choice should be based on a regular assessment of each patient’s risk of stroke and bleeding). Some cardiologists may use a combination of warfarin and aspirin or clopidogrel at the same time, but there is little evidence to support this practice.

Guidance from NICE on the management of atrial fibrillation was published in June 2006. This is available for download from: [http://www.nice.org.uk/](http://www.nice.org.uk/)

Atrial flutter

Atrial flutter occurs less frequently than atrial fibrillation but the two conditions often have similar underlying causes. The rapid atrial rate and the disturbance of conduction pathways in atrial flutter increase the risk of localised thrombus formation and secondary embolic events (ie, stroke) in patients with this condition.

**Exercise 3**

**How do you prevent thromboembolic complications in patients with atrial flutter?**

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

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

**4.2 Benefits of anticoagulation in atrial fibrillation**

The risk of stroke and the benefits of treatment for patients with atrial fibrillation are summarised in Table 2.
TABLE 2  Annual risk of stroke on no treatment, aspirin or warfarin in high, moderate and low-risk patients with non-valvular atrial fibrillation

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Untreated</th>
<th>Aspirin</th>
<th>Warfarin</th>
<th>NNT*</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 transient ischaemic attack</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>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age over 65, 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, other risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age under 65, no other risk factors</td>
<td>1·2%</td>
<td>1%</td>
<td>c. 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, 22-47 high-risk patients would need to be treated with warfarin instead of aspirin for one year in order to prevent one stroke.

Source: SIGN Publication 36. Antithrombotic therapy. A national clinical guideline

4.3 Risks of anticoagulation in atrial fibrillation

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 INR above 3.0, uncontrolled hypertension and, to some degree, increasing age.

4.4 Balancing the risks

The decision to use warfarin or aspirin should ultimately be based on the balance of an individual’s overall risk of stroke compared with the risk of adverse effects, and on their personal preference. There are many different guidelines available to aid clinicians and patients in the decision-making process (eg, the guidance on the management of atrial fibrillation published by NICE in June 2006 – see Figure 3).
Patients with paroxysmal, persistent, permanent AF

Determine stroke/thromboembolic risk

HIGH

MODERATE

LOW

High risk:
- previous ischaemic stroke/TIA or thromboembolic event
- age 75 or over with hypertension, diabetes or vascular disease*
- clinical evidence of valve disease or heart failure, or impaired left ventricular function on echocardiography.**

Moderate risk:
- age 65 or over with no high risk factors
- age under 75 with hypertension, diabetes or vascular disease.*

Low risk:
- age under 65 with no moderate or high risk factors.

Anticoagulation with warfarin

Consider anticoagulation or aspirin

Aspirin 75 to 300 mg/day if no contraindications

Reassess risk stratification whenever individual risk factors are reviewed

Contraindications to warfarin?

YES

NO

Warfarin, target INR 2.5 (range 2.0 to 3.0)

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 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 clinician must balance the risk 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.

* Coronary artery disease or peripheral artery disease

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

Source: Adapted from NICE Clinical guideline 36. Atrial fibrillation: the management of atrial fibrillation.
The clinical knowledge summaries (CKS) website contains the following guidance for antithrombotic prophylaxis in atrial fibrillation:

- **Warfarin is preferred in people at high risk of stroke** as the benefits usually outweigh the risks. This includes people with a previous ischaemic stroke or transient ischaemic attack, or people aged over 65 years with one other risk factor for stroke.

- **People at moderate risk of stroke** require antithrombotic therapy, but the decision to use warfarin or aspirin is less clear. Many would still choose warfarin in this situation. The decision to use warfarin or aspirin should ultimately be based on the balance of an individual’s overall risk of stroke compared with the risk of bleeding, and the individual’s personal preference.

- **People aged under 65 years with no other risk factors for stroke are at low risk** and should not be given antithrombotic prophylaxis unless aspirin is given for other indications.16

Clinical trials have shown that long-term anticoagulation reduces the risk of stroke associated with atrial fibrillation, but warfarin is taken by only 30-60 percent of appropriate patients. Because about 15 percent of all strokes are attributable to atrial fibrillation, the clinical and economic consequences of the underprescription of warfarin are profound.17

The overestimation of the risks of anticoagulation by doctors is the most consistently cited explanation for the observed patterns of warfarin use. Studies have also found that doctors are less likely to prescribe warfarin after one of their patients has had a major bleeding event associated with it.

**Practice point**

*Ask your local clinicians what their views are on the benefits and risks of warfarin treatment, how they decide which patients with atrial fibrillation should be treated with warfarin, and how they involve patients in this decision.*

**Summary**

- The evidence clearly shows that long-term anticoagulation reduces the risk of stroke associated with atrial fibrillation.

- The benefits of warfarin therapy in atrial fibrillation versus the increased risk of haemorrhage varies, depending on each patient’s characteristics.

- There are many different risk stratification schemes available to aid clinicians and patients in the decision-making process.

- The underprescribing of warfarin is a significant problem with only 30-60 percent of suitable patients taking the drug.
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 relative benefits and risks to patients with atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>compared with taking aspirin, or indeed taking nothing at all.</td>
<td></td>
</tr>
<tr>
<td>Appreciate that the under-use of warfarin in suitable patients is a significant</td>
<td></td>
</tr>
<tr>
<td>problem.</td>
<td></td>
</tr>
</tbody>
</table>

Reflective questions

1. What antithrombotic prophylaxis should be given to patients with atrial fibrillation aged under 65 years who have no other risk factors for stroke?
2. What factors may increase the risk of intracranial bleeds in patients taking warfarin?
3. How many patients at moderate risk of atrial fibrillation would need to be treated with warfarin instead of aspirin for one year in order to prevent one stroke?

Suggested answer

Exercise 3 (page 24)

Adequate anticoagulation has been shown to decrease thromboembolic complications in patients with persistent or paroxysmal atrial flutter. Patients with atrial flutter are anticoagulated in the same way as for atrial fibrillation.