Anticoagulation

Introduction

Warfarin is used by around 1.5% of the population. Whilst anticoagulants are very important in reducing the risk of stroke and treating or preventing venous thromboembolism for many, they are also potentially dangerous drugs and need to be managed carefully to ensure maximum benefit whilst minimising side effects. Historically, patients on warfarin have been poorly managed. Between 1990 and 2002 around 600 incidents of harm, or near misses were reported to various authorities, and of these, 20% were fatal. The most common causes for these incidents in primary care were:

- Inadequate laboratory monitoring
- Drug interactions involving non-steroidal anti-inflammatory drugs (NSAIDs).

Anticoagulants are also frequently associated with adverse incidents in secondary care. Examples of serious errors at ULH recently include:

1. An elderly female patient was discharged with no anticoagulation plan, and GP not informed. She continued to take the initial (loading) dose of warfarin. The GP was called out when she collapsed due to an intracranial haemorrhage and was found to have an INR >8. She was admitted but died soon after.

2. A patient on warfarin for an aortic metallic valve was discharged to a nursing home following an admission not in the area of her usual GP. No discharge information was provided regarding warfarin management, and the home was unaware that she needed anticoagulants. She spent a month in the home with no anticoagulation. Fortunately she did not develop a valve thrombosis, but this was a near miss of another potentially fatal error.

Newer oral anticoagulants are now available for the prevention of stroke and treatment/prevention of venous thromboembolism (VTE) in selected patients. While these are potentially easier to use than warfarin since there is no need for monitoring, and the risk of bleeding may be lower, it is important that healthcare professionals are familiar with how to safely prescribe these newer drugs and review patients taking them long term

1. Types of anticoagulants
2. Indications for anticoagulants
3. How to anticoagulate
4. Maintaining anticoagulation on vitamin-k antagonists

1. TYPES OF ANTICOAGULANTS

Anticoagulant drugs are either oral or injectable.

Oral anticoagulants

Oral anticoagulants can be classified into:

- **Vitamin K antagonists**
  - Coumarins (eg warfarin and acenocoumarol)
  - Indanediones (egphenindione)
  -
- **NOACs** (oral direct inhibitors) – also known as DOACs (direct oral anticoagulants)
  - Direct thrombin inhibitors (dabigatran)
  - Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban).

Warfarin and the other vitamin K antagonists have been used for over 60 years. In contrast, the NOACs are newer anticoagulants that have been licensed only since 2010; however, NOACs have been thoroughly studied in large clinical trials whereas warfarin was introduced after minimal testing

Both groups of anticoagulants have their advantages and disadvantages and both are now recommended by NICE according to their licensed indications. In its patient decision aid for atrial fibrillation, NICE makes it clear that patients can choose between warfarin and the NOACs after an informed discussion.

Vitamin K antagonists

Vitamin K antagonists interfere with the cyclical conversion of vitamin K to reduce the biological activity of clotting factors II, VII, IX, and X and the anticoagulant proteins C and S. Because of their mechanism of action, the anticoagulant effects of this group of drugs can be overcome by small doses of vitamin K. However, vitamin K takes at least 6 hours for its action to begin.

Warfarin is the most commonly used oral anticoagulant in the UK. Since it acts by interfering with the activation of clotting factors, it takes on average five days before the clotting factors already present are degraded and the full effects of a dose are seen (table 1). This means that if an immediate effect is needed, low molecular weight heparin (LMWH) or more rarely unfractionated heparin (UFH) should be given concomitantly.

Table 1. Half lives of the vitamin K dependent clotting factors

Factor	Half life (hours)
II (prothrombin)	42 to 72
VII	4 to 6
IX	21 to 30
X	27 to 48
Protein C	8
Protein S	60

NOACs

Non-vitamin K oral anticoagulants (NOACs) have been licensed since 2010. They are easier to use than warfarin because they do not need regular monitoring. NICE now recommends that clinicians consider NOACs alongside warfarin for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation and for the treatment and prophylaxis of deep vein thrombosis and pulmonary embolism in adults. NOACs have much fewer food and drug interactions than vitamin K antagonists and they do not need therapeutic monitoring

The NOACs target individual clotting factors. The factor Xa inhibitors (Rivaroxaban, Apixaban and Edoxaban) inhibit activated factor X (factor Xa), thereby stopping the production of thrombin and the development of a thrombus. The direct thrombin inhibitor Dabigatran inhibits the action of thrombin, thereby preventing the conversion of fibrinogen to fibrin.

The NOACs are rapidly absorbed. Unlike the vitamin K antagonists, the onset of effect starts shortly after dosing with a maximum anticoagulant effect achieved within 0.5 to two hours. There is therefore no need to give low molecular weight heparin or unfractionated heparin on initiating anticoagulation with a NOAC,although for two of these agents, Dabigatran and Edoxaban, 5 days of LMWH is recommended when treating an acute venous thromboembolism (VTE).

The pharmacokinetics of both types of NOAC are predictable unlike warfarin, and can be taken orally without the need for regular monitoring. Remember that the INR was developed specifically to be sensitive to the action of warfarin and is not appropriate as a test to estimate the degree of anticoagulation for the NOACs. There is variable sensitivity to the basic clotting screen (APTT, PT) and this depends on individual reagents used by different hospitals as well as the different drugs , for example, rivaroxaban does have a measurable effect on the INR but this is not linear, and at its peak effect may vary from 1.3-1.7 in different hospitals. Apixaban, however, usually has no effect on any of the basic clotting screen tests. The APTT is sensitive to dabigatran but not to the anti-Xa agents. However, coagulation assays specific to these agents are available at bigger centres for use in emergency situations. (anti-Xa assays).

The NOACs are at least as effective as warfarin and safer with regard to major bleeds. One concern is the inability to reverse their action, although the drugs benefit from a shorter half-life than vitamin K antagonists so may not require an antidote. Also, in studies where life-threatening bleeding occurs, patients on NOACs have better outcomes than those on warfarin, with standard treatments of concentrated clotting agents (prothrombin concentrates, PCCs). In addition, Dabigatran now has a licenced reversal agent ,Idarucizumab (Praxbind), and agents are in development for the anti-Xa NOACs and likely to be available in late 2016. In the event of a major bleed, UK guidelines on managing bleeding recommend stopping the NOAC and taking general haemostatic measures:

- For minor bleeding this would be supportive measures, such as direct pressure, minor surgical intervention, and fluid replacement

- In life threatening bleeding pro-haemostatic agents such as prothrombin complex concentrate (PCC) or activated prothrombin complex concentrate (APCC) can be considered.

It is also important to note that the NOACs are partially cleared by the kidney (Dabigatran 80%, Edoxaban 50%, Rivaroxaban 33% and Apixaban 27%) It is vital that a patient's renal function is checked before starting on a NOAC, together with the baseline checks FBC, LFTs and basic clotting screen.Patients with significant renal impairment may need a dose reduction and careful monitoring of renal function. You should check the summary of product characteristics for specific details.

Table 2 - Summary information for the NOACs

	Apixaban[1,2]	Rivaroxaban[1,3]	Dabigatran[1,4]	Edoxaban[5]
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor
Oral bioavailability	~50%	80–100%	~6.5%	~62%
Pro-drug	No	No	Yes	No
Food effect	No	Yes (20 mg and 15 mg doses need to be taken with food)	No	No
Renal clearance	~27%	~33 %*	85%	50%
Mean half-life ($t_{1/2}$)	12 h	5–9 h (young) 11–13 h (elderly)	12–18 h (patients)†	10–14 h
T_{max}	3–4 h	2–4 h	0.5–2 h	1–2 h

*Direct renal excretion as unchanged active substance.
†Prolonged in patients with impaired renal function. The information in this table is based on the SmPC for apixaban, rivaroxaban, dabigatran and edoxaban. Please refer to the SmPC for further information.

Injectable anticoagulants

Injectable anticoagulants comprise:

- Heparins
  - Unfractionated heparin (UFH)
  - Low molecular weight heparin (LMWH)
- Heparinoids (egdanaparoid)
- Fondaparinux
- Hirudins.

Heparins

- These are the most commonly used injectable anticoagulants. **Unfractionated heparin** works by binding to antithrombin, which catalyses the inactivation of factors IIa, Xa, IXa, and XIIa. Thrombin and factor Xa are most sensitive to the effects of heparin. It initiates anticoagulation rapidly but has a short duration of action: at usual intravenous doses the half life of unfractionated heparin is 45 to 60 minutes. The bioavailability of subcutaneous unfractionated heparin is less than 50%. Unfractionated heparin may be used in patients with: Renal failure and occasionally in patients with massive deep vein thrombosis and pulmonary embolism

- The **low molecular weight heparins** (dalteparin, enoxaparin, and tinzaparin) work almost entirely through inhibiting factor Xa. They have a longer duration of action, with a half life of about four hours, and are 90 to 100% bioavailable after subcutaneous injection. Low molecular weight heparins come in pre-filled syringes that should be administered by subcutaneous injection. This should usually be given in the abdomen. It is not uncommon for patients to develop localised bruising at the injection site. No dose adjustments are necessary in elderly people unless they have renal impairment (CrCl< 30 ml/min). No dose adjustments are necessary for patients with obesity or low body weight. Treatment should be continued for at least five days and until the INR is greater than 2.0 for two successive days in patients who are being started on warfarin. There are minor differences between the different types of low molecular weight heparins. Low molecular weight heparins are used in patients (with normal renal function) with: 1)Venous thromboembolism 2)Acute coronary syndromes.

- **Heparinoids** such as danaparoid, have similar activity to that of low molecular weight heparins, but contain no heparin or heparin fragments. Danaparoid is indicated only for treating venous thromboembolism in patients with a history of heparin-induced thrombocytopenia.(HIT) – see below for details on diagnosis and treatment of HIT
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- **Fondaparinux** is a synthetic pentasaccharide that inhibits activated factor X. It is licensed for the prophylaxis of venous thromboembolism in medical patients and in patients undergoing major orthopaedic surgery of the legs. It is also licensed for treating deep vein thrombosis and for pulmonary embolism.
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- **Hirudins** are polypeptides that inhibit factor IIa and can therefore be classed as direct thrombin inhibitors. Bivalirudin is the only product available in the UK and is licensed for patients undergoing percutaneous coronary intervention

Monitoring heparin

Treatment with unfractionated heparin is monitored using the APTT. The target is a ratio of 1.5-2.5. Using protocols for dose adjustment according to APTT ratios helps you achieve therapeutic targets. However, the test should be calibrated locally to determine the recommended target APTT ratio.

There is generally no monitoring of low molecular weight heparins. The APTT is generally insensitive to low molecular weight heparins and cannot be used for monitoring. AntifactorXa monitoring is not routinely undertaken because it provides an incomplete picture of the anticoagulant effect and is poorly predictive of antithrombotic efficacy and risk of haemorrhage.

Because there is a risk of antibody mediated thrombocytopenia you should monitor platelet levels. Heparin induced thrombocytopenia, should it occur, usually appears between day five and 21 of treatment. You should monitor at baseline and regularly thereafter if unfractionated heparin or low molecular weight heparin is given for longer than four days. If heparin-induced thrombocytopenia is strongly suspected or confirmed, the heparin should be stopped and an alternative anticoagulant should be given.

Heparin can suppress adrenal secretions of aldosterone and lead to hyperkalaemia, particularly in patients with :

- Diabetes mellitus
- Chronic renal failure
- Pre-existing metabolic acidosis
- A raised plasma potassium.

The risk of hyperkalaemia appears to increase with the duration of therapy, but it is usually reversible. You should measure plasma potassium in at-risk patients before starting heparin therapy and you should monitor this regularly.

Heparin induced thrombocytopenia (HIT)

Recommendations from the British Society for Haematology with regards to monitoring for heparin induced thrombocytopenia include :

- Patients who are to receive any heparin should have a baseline platelet count

- Post-operative patients, including obstetric cases, receiving unfractionated heparin should have platelet count monitoring performed every two to three days from days four to 14 or until heparin is stopped

- Post-cardiopulmonary bypass patients receiving low molecular weight heparins should have platelet count monitoring performed every two to three days from days four to 14 or until heparin is stopped

- Post-operative patients (other than cardiopulmonary bypass patients) receiving low molecular weight heparins do not need routine platelet monitoring

- Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 days and are receiving any type of heparin should have a platelet count determined 24 hours after starting heparin

- Medical patients and obstetric patients receiving heparin do not need routine platelet monitoring

- If the platelet count falls by 30% or more and/or the patient develops new thrombosis or skin allergy or any of the other rarer manifestations of heparin induced thrombocytopenia between days four and 14 of heparin administration heparin induced thrombocytopenia should be considered and a clinical assessment made

- Heparin induced thrombocytopenia can be excluded by a low pre-test probability score without the need for laboratory investigation

- If the pre-test probability of heparin induced thrombocytopenia is not low, heparin should be stopped and an alternative anticoagulant started in full dosage whilst laboratory tests are performed.

2. INDICATIONS FOR ANTICOAGULANTS

The main indications for anticoagulation are as follows:

1.Following an episode of venous thromboembolism (VTE) – deep vein thrombosis (DVT) with or without pulmonary embolism (PE).Treatment for a minimum of three months is recommended for VTE, and if a reversible precipitating factor was present then this is probably sufficient treatment. For an unprovoked proximal deep vein thrombosis, long term anticoagulation should be considered, after taking into account the risk of bleeding versus risk of recurrence.. An assessment at 3 months is helpful to review the risk-benefit ratio and informed patient preference.

2.Long-term for stroke prevention in atrial fibrillation (non-valvular AF, NVAF), or because of mechanical prosthetic valves (which may cause valvular AF).

The clinical indications for the NOACs are similar to those for warfarin. NICE states that NOACs should be offered alongside warfarin as an option for treatment and prevention of VTE and for stroke prevention in AF.

In addition, Dabigatran, Rivaroxaban and Apixaban are recommended by NICE as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.

There is considerable variation in usage across the country. In ULH, NOACs are used as follows:

1. For thromboprophylaxis after hip or knee replacement apixaban 2.5mg bd – link

2. For treatment of provoked venous thromboembolism – deep vein thrombosis or pulmonary embolus – rivaroxaban 20mg od (15mg if reduced renal function) , and increasingly for unprovoked thrombotic events– link

3. for treatment of stroke prevention in atrial fibrillation – rivaroxaban, apixaban, dabigatran or warfarin–link

NB Definition of valvular atrial fibrillation is as follows: AF related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.

Table 3. Duration of anticoagulation for different clinical indications and target INR for patients on warfarin

Indication	Target INR	Duration of anticoagulation
Pulmonary embolus	2.5	At least three months
Proximal deep vein thrombosis	2.5	At least three months
Calf vein thrombus	2.5	Six weeks
Recurrence of venous thromboembolism when no longer on warfarin	2.5	Consider long term
Recurrence of venous thromboembolism while on warfarin	3.5	Consider long term
Antiphospholipid syndrome	2.5	Consider long term
Atrial fibrillation	2.5	Long term
Cardioversion†	2.5 or 3.0	Three weeks before and four weeks after procedure
Mural thrombus	2.5	Three months
Cardiomyopathy	2.5	Long term
Mechanical prosthetic heart valve	2.5 or 3.0	Long term

3. HOW TO ANTICOAGULATE

Starting anticoagulation

Introducing anticoagulation on warfarin safely is not a straightforward procedure, and although it is much easier with the NOACs (non-vitamin K anticoagulants) counselling is still important for these patients to understand the risks as well as the benefits of anticoagulation:

Warfarin (or other vitamin K antagonists)

Guidelines for anticoagulation have been produced by the British Committee for Standards in Haematology (BCSH) of the British Society for Haematology and by the American College of Chest Physicians.

Starting on warfarin: rapid induction

Rapid induction is the administration method of choice for:

1. treating venous thromboembolism
2. prophylaxis in patients with artificial heart valves.

The goal of rapid anticoagulation is to achieve the target INR as quickly as possible. It takes 5-10 days for the full effects of warfarin to be seen. In the early stages a relatively hypercoagulable state may be induced as a result of the rapid depletion of proteins C and S (natural anticoagulants) as they are also vitamin-K dependent factors. A quick acting anticoagulant, usually LMWH needs to be given at the same time a loading dose of warfarin. The parenteral anticoagulant should be continued for at least five days and until the INR is ≥ 2 for at least 24 hours, whichever is the longer.

Two warfarin dosing algorithms have been validated..These algorithms start from the basis that a healthy person would need 20 to 30 mg of warfarin over three days as a loading dose. This is often implemented as either 10 mg for two days and 5 mgs on the third day, or 9 mg for two days and 6 mg on the third day. Factors that increase sensitivity to the effects of warfarin, and therefore the ongoing dose are:

- Body weight less than 50 kg
- Low serum albumin
- Age older than 65
- Raised baseline INR
- Interacting drugs, especially drugs that inhibit the metabolism of warfarin (eg metronidazole and erythromycin)
- Liver disease
- Heart failure.

The elderly and those with comorbidities or liver disease should have a lower initiation doses or age adjusted doses.

NB High citrate concentrations will give spuriously high INRs so you must take care not to underfill the sample bottle or to pour two small samples into one bottle to make up the volume. This is the reason that the laboratory will reject these samples

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Starting warfarin – slow induction

The vast majority of patients with AF are suitable for anticoagulation. A **CHA_2DS_2-VASc** score should be calculated. The European Society of Haematology recommends the following algorithm:

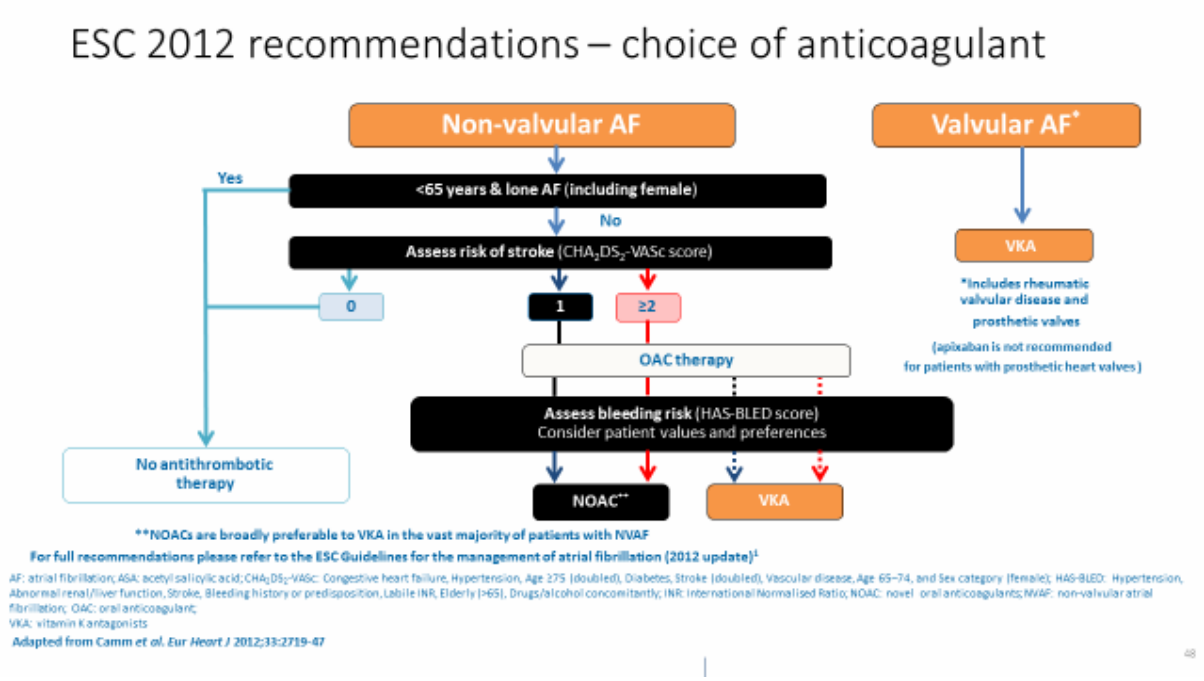
Assessing risk of stroke

NICE recommends that you assess the risk of stroke in people with any of the following

- Symptomatic or asymptomatic paroxysmal, persistent, or permanent atrial fibrillation
- Atrial flutter
- A continuing risk of the recurrence of arrhythmia after cardioversion back to sinus rhythm.

Until recently, the $CHADS_2$ score was generally advocated to assess risk of stroke in people with atrial fibrillation taking an anticoagulant. This tool allocates one point to each of **c**hronic heart failure, **h**ypertension, **a**ge over 75 years, and **d**iabetes mellitus, and two points for a history of **s**troke or transient ischemic attack. However, both NICE and the European Cardiology Society now recommend using the CHA_2DS_2-VASc tool. This modified version of the $CHADS_2$ tool includes additional risk factors (**v**ascular disease, **a**ge 65 to 74 years, and **s**ex **c**ategory), which helps to identify people at low risk of stroke who will not benefit from treatment with anticoagulants (table 7).

CHA_2DS_2-VASc	**Score**
Chronic heart failure or left ventricular ejection fraction ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Age 65 to 74 years	1
Diabetes	1
Stroke or transient ischaemic attack	2
Sex (female)	1
Vascular disease	1



After taking the risk of bleeding into account (see below), you should offer anticoagulation to:

- Anyone with a CHA_2DS_2-VASc score of 2 or more
- Men with a CHA_2DS_2-VASc score of 1.

Conversely, men with a CHA_2DS_2-VASc score of 0 and women with a score of ≤ 1 (ie people under the age of 65 with no risk factors other than their sex) should not be offered anticoagulation because their risk

In patients with atrial fibrillation who are starting on warfarin, the slow induction of anticoagulation is suitable. One advantage of this approach is that the potential hypercoagulability seen with rapid anticoagulation does not occur.

Several regimens have been shown to be safe and effective at producing stable INRs within two to four weeks with few episodes of over-anticoagulation. One way to start treatment is to give 1 or 2 mg of warfarin daily and then measure the INR after one week. You can then adjust the dose using either a recognised algorithm or computerised decision support system, or simply increase the daily dose by 1 mg per week and test after another week and so on until the therapeutic range is reached. After this you can increase the monitoring intervals. This is usually used when GPs are initiating the medication.

For patients with atrial fibrillation receiving a vitamin K antagonist for the prevention of stroke, it is recommended that the individual time in therapeutic range (TTR) is calculated at each visit. This can only practically be done using computerised decision support software. (Usually the DAWN system in secondary care, and INR star in primary care)

Starting anticoagulation on NOACs

This is much more straightforward than warfarin induction. For acute VTE patients, two of the NOACs, Rivaroxaban and Apixaban have an all-oral induction, with a higher dose for 3 weeks for Rivaroxaban and one week for Apixaban. Dabigatran and Edoxaban require a five day lead-in with LMWH.The introduction of a purely oral management strategy has led to the development of some care pathways for DVT where patients are managed completely in primary care, with secondary contact restricted to diagnostic imaging only. It is still very important that patients are counselled about the risks and potential side-effects on being on an anticoagulant.

NB:Women of childbearing age should be warned of the danger of teratogenicity with vitamin K antagonists because stopping these drugs before the sixth week of gestation may largely avoid the risk of foetal abnormality.Similarly, women should not conceive on a NOAC, as we do not know what potential harm to the fetus may result. These drugs are known to cross the placenta.

Adherence:NOACs may be considered more convenient for patients and clinicians because coagulation control does not need to be monitored. However, there is some concern that the lack of monitoring may result in poor adherence. This supports the need for effective counselling at the start of treatment to reduce the incidence of poor adherence.

Good adherence is even more important with the NOACs than with the vitamin K antagonists because NOACs have relatively short half-lives. The beneficial effects of warfarin will persist for 48 to 72 hours after missing a dose, whereas the anticoagulant effect of the NOACs fades after 12 to 24 hours.

Assessing the risk of a major bleed

NICE recommends using the HAS-BLED score to:

- Assess the risk of bleeding in people who are starting, or have started, anticoagulation and
- Highlight, correct, and monitor modifiable risk factors:
    - Uncontrolled hypertension
    - Poor renal function
    - Poor control of INR
    - Concurrent drugs, such as concomitant use of aspirin, a non-steroidal anti-inflammatory drug (NSAID), or a selective serotonin reuptake inhibitor (SSRI)
    - Harmful alcohol consumption.

Using the HAS-BLED tool, there is an increased one year bleed risk with a score of 3 or more on an anticoagulant (table 4)

Note that reducing the risk of bleeding in a patient by modifying the risk factors listed above means the HAS-BLED score reduces by one point (per risk factor modified). For example, controlling hypertension, improving renal function by altering the co-prescription, switching patients on warfarin with poor INR control to a NOAC, switching patients on medications that increase bleeding to alternative medications, and reducing harmful levels of alcohol consumption would each reduce the HAS-BLED score by 1 point.

Table 4 . HAS-BLED score for bleeding risk for patients with atrial fibrillation taking an anticoagulant

Feature	Score if present
Hypertension (systolic ≥ 160 mm Hg)	1
Abnormal renal function	1
Abnormal liver function	1
Stroke in past	1
Bleeding	1
Labile INRs	1
Elderly (age ≥ 65 years)	1
Drugs (eg aspirin/NSAIDs) Alcohol abuse	1

The HAS-BLED score should not be used to preclude people from receiving anticoagulant intervention but to assess how the bleeding risk can be minimised, and in combination with CHA_2DS_2-VASc as a way to balance the benefits and risks.

NICE states that:

- For most people with atrial fibrillation the benefit of anticoagulation outweighs the risks
- For people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important
- We should NOT withhold anticoagulation solely because the person is at risk of having a fall.

Once you have identified patients who will benefit from taking an anticoagulant, based on their risk of stroke and major bleeding, discuss drug options with the person (see later) and base your choice on their clinical features and preferences.

? aspirin for stroke prevention: NICE states that you should NOT offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation. Use of anticoagulants reduces the rate of stroke by around 50% in this population compared with aspirin. Aspirin is no longer considered a cost effective alternative to anticoagulation with warfarin or a NOAC, and continued use of aspirin is a barrier to appropriate stroke prevention with oral anticoagulants.

(See the full NICE guideline for recommendations of the role of left atrial appendage occlusion in people for whom anticoagulation is contraindicated or not tolerated.

Contraindications to anticoagulation

Anticoagulation is contraindicated in a number of situations where the risks of harm are likely to outweigh the benefits of treatment. However, there are many situations where contraindications are relative rather than absolute (tables 5 and 6).

Vena cava filters can be used to prevent pulmonary embolus in patients with venous thromboembolism who have a contraindication to anticoagulation. These filters are small cone shaped devices. The filters are inserted as a radiological procedure through a vein in the groin or neck and then guided to the vena cava. They should only be used when other measures are not possible, or fail, as they can be associated with complications. When inserted they should only be left in during the time of high risk.

Table 5: Absolute and relative contraindications to anticoagulation

Absolute contraindications to any anticoagulant	Relative contraindications to any anticoagulant
• Potential bleeding lesions • Active peptic ulcer, oesophageal varices, aneurysm, and proliferative retinopathy • Recent organ biopsy • Recent trauma or surgery to the head, orbit, or spine • Recent stroke • Confirmed intracranial or intraspinal bleed • Uncontrolled hypertension • Infective endocarditis	• History of gastrointestinal bleeding • Liver disease • Renal failure • Alcoholism • Mental impairment • Thrombocytopenia • Coagulation disorders • Interacting drugs, in particular NSAIDs • Poor concordance • Poor attendance for regular blood tests

Table 6: Absolute contraindications to specific anticoagulants

Heparin

- History of heparin induced thrombocytopenia or thrombosis

- **Fondaparinux**

- Homozygous protein C deficiency (risk of skin necrosis)
- History of warfarin related skin necrosis

- **Dabigatran**

- Severe renal impairment (creatinine clearance < 30 ml/min)
- Active clinically significant bleeding
- Organic lesions at risk of bleeding
- Impairment of haemostasis
- Hepatic impairment of liver disease expected to have an impact on survival
- Pregnancy
- Breast feeding

- **Rivaroxaban&Edoxaban**

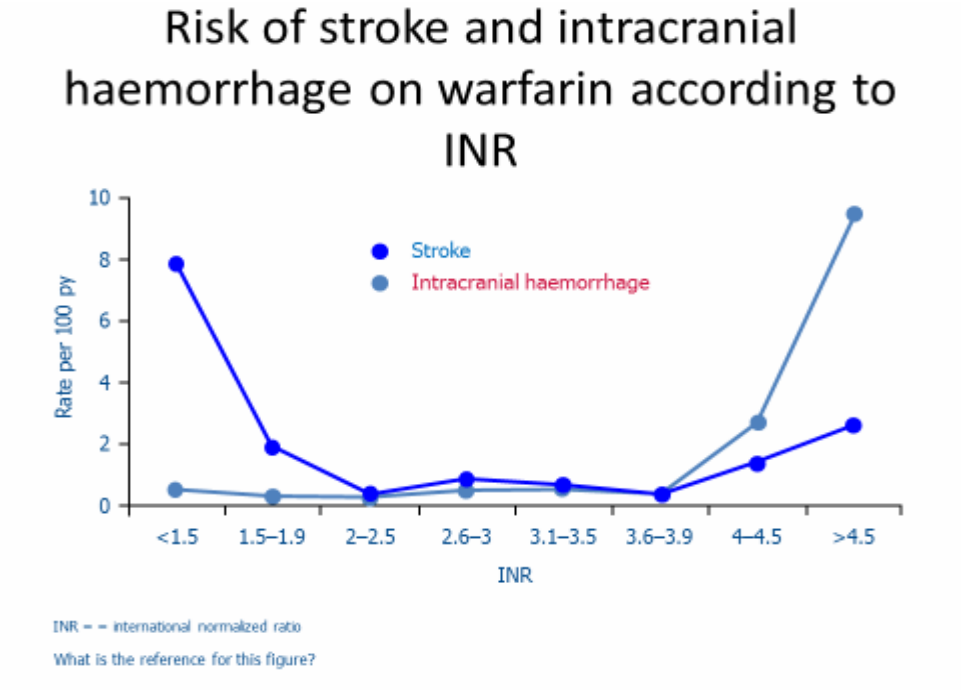
- Hypersensitivity to the active substance or to any of the excipients
- Active clinically significant bleeding
- Hepatic disease associated with coagulopathy
- Clinically relevant bleeding risk including patients with cirrhotic liver disease (Child-Pugh chronic liver disease score of B and C)
- Pregnancy
- Breast feeding

- **Apixaban**

- Hypersensitivity to the active substance or to any of the excipients
- Active clinically significant bleeding
- Hepatic disease associated with coagulopathy
- Clinically relevant bleeding risk
- Pregnancy
- Breast feeding

4. MAINTAINING ANTICOAGULATION ON VITAMIN-K ANTAGONISTS

Time in therapeutic range is very important – see figure 1 for an AF patient. Too little, and there is an increased risk of ischaemic stroke, too much and you risk intracranial haemorrhage.



Peri-operative anticoagulation with warfarin

Unless there is a very high risk of thromboembolism, anticoagulation should be temporarily stopped in preparation for surgery. British Committee for Standards in Haematology gives the following recommendations regarding peri-operative bridging (with low molecular weight heparin or unfractionated heparin):

- Pre-operative bridging carries a low risk of bleeding whereas post-operative bridging carries a high risk of bleeding and should not be started until at least 48 hours post surgery
- Consider bridging therapy in patients with:
  - Venous thromboembolism within the previous three months
  - Atrial fibrillation with previous stroke or transient ischaemic attack
  - Mitral mechanical heart valve
- Consider prophylactic dose low molecular weight heparin rather than bridging therapy in patients with:
  - Venous thromboembolism for more than three months
- Bridging therapy is not required in patients:
  - With low risk atrial fibrillation (no prior stroke or TIA)
  - With leaflet aortic mechanical heart valve.

Managing peri-operative anticoagulation on NOACs

This is much easier than with warfarin due to the shorter half-lives of these agents. Very few patients need ‘bridging’ with LMWHs. The local peri-operative guideline gives details.

Managing raised INR with and without bleeding

The main adverse effect of all oral anticoagulants is haemorrhage. The risk of major bleeding is greatest during the first three months of treatment with oral anticoagulants. It is essential to check the INR and omit doses when appropriate. If the anticoagulant is stopped but not reversed, the INR should be measured two or three days later to ensure that it is falling. The cause of an elevated INR should be investigated.

The anticoagulant effects of warfarin can be reversed by oral or intravenous vitamin K. Large doses of vitamin K (such as 10mg) can render a patient "warfarin resistant" for a week or more.

Table 5 summarises advice on high INRs or bleeding in patients on warfarin from the British National Formulary, which takes into account the recommendations of the British Society for Haematology.

Table 7. Recommended action following a high INR or bleeding in patients taking warfarin

INR/bleeding	Action
Major bleeding	• Stop warfarin • Admit to hospital • Give intravenous vitamin K 5 mg by slow intravenous injection plus dried prothrombin complex (factors II, VII, IX, and X) 25 to 50 units/kg; recombinant factor VIIa is not recommended for emergency anticoagulation reversal
INR > 8.0, minor bleeding	• Stop warfarin • Give intravenous vitamin K 1 to 3 mg by slow intravenous injection • Repeat dose if INR is still too high after 24 hours • Restart warfarin when INR is < 5.0
INR > 8.0, no bleeding	• Stop warfarin • Give oral vitamin K 1 to 5 mg by mouth using the intravenous preparation orally (unlicensed use) • Repeat dose of vitamin K if INR is still too high after 24 hours • Restart warfarin when INR is < 5.0
INR 5.0 to 8.0, minor bleeding	• Stop warfarin • Give vitamin K 1 to 3 mg by slow intravenous injection • Restart warfarin when INR is < 5.0
INR 5.0 to 8.0, no bleeding	• Withhold one or two doses of warfarin and reduce subsequent maintenance dose
Unexpected bleeding at therapeutic levels	• Always investigate the possibility of an underlying cause (eg unsuspected renal or gastrointestinal tract pathology)

NB Vitamin K takes at least 6 hours to start to work

Reversing the effects of heparin

The anticoagulant effects of unfractionated heparin can be fully reversed by intravenous injection of protamine. A dose of 1 mg of protamine neutralises 80 to 100 units of unfractionated heparin when given within 15 minutes of the heparin. Less protamine is needed if it is given after a longer period because of the short half life of intravenous heparin.

The anticoagulant effects of low molecular weight heparin are only partially reversible with protamine.There is anecdotal evidence of clinical benefits of using protamine in bleeding patients.1 mg protamine neutralises approximately 100 units of LMWH.

Warfarin tablet strengths

Warfarin is available as 1 mg tablets, 3 mg tablets, and 5 mg tablets. The tablets are different colours to help patients know which ones to take. In some centres newly anticoagulated patients are supplied with all three strengths so they can make up the dose required. Others use only 3 mg tablets and adjust the dose in increments of 1.5 mg. Patients whose vision is impaired should be prescribed or dispensed only 1 mg tablets to avoid the risk of mix ups.

A 0.5 mg warfarin tablet is also available. Some clinics are reluctant to use both 0.5 mg and 5 mg warfarin tablets in case there is confusion and accidental overdose. However, halving tablets leads to inaccurate doses. A small number of patients require large doses of warfarin and for these the 5 mg tablets may be most convenient.

NB ULH does not have an anticoagulation service, as this was devolved to primary care a number of years ago. However, it is extremely important to follow inpatient anticoagulant guidance and to have a clear plan at discharge for patients. An online discharge pack is available under VTE

Discharging a newly anticoagulated patient from hospital

Many patients with venous thromboembolism will have started treatment in hospital. Rapid induction of anticoagulation (for venous thromboembolism) involves giving a loading dose of warfarin (in addition to the parenteral anticoagulant the patient is already on) until INR is therapeutic to reach the desired degree of anticoagulation as quickly as possible.

Although patients who have started warfarin in hospital ideally are stabilised before discharge,they may be discharged before stabilisation as long as the discharge pack information is completed and the treatment will have been fully explained to them before they leave hospital. It is a secondary care responsibility to check on the patient's local anticoagulation service (usually their GP) and contacting this service directly. Points at which counselling should take place are advised in the National Patient Safety Alert Actions that can make anticoagulant therapy safer.

When anticoagulated patients are discharged, the hospital should send completeinformation about their anticoagulant treatment with warfarin to their long term healthcare provider so that it can be continued safely. Experience has shown that information provided to long term healthcare providers is often incomplete and this has led to dosing errors and adverse events.

Three important measures can help you avoid problems:

- if possible get the INR in range before the patient leaves hospital
- Ensure the patient understands the treatment and the system for monitoring
- Ensure a proper system of referral is established that keeps the GP fully informed.

When preparing for discharge you need to give patients information about:

- The purpose of anticoagulation for their situation and how long it will be needed
- What is expected of the patient
    - The dose of anticoagulant to take until the first monitoring visit – patients must be able to identify their tablets correctly and take the correct dose
- The arrangements for monitoring
- How to obtain further supplies of anticoagulant.

Ideally you should provide this information well in advance to ensure the patient has time to ask questions. Don't leave this until 30 minutes before discharge. Some hospitals have established procedures in which specialist nurses or pharmacists discuss the issues with the patient using a standard checklist.

The Department of Health yellow record book has an excellent education leaflet that covers this information. Take time to read through the booklet with the patient answering questions as you progress.

Discontinuing anticoagulant therapy

Provided there is no clinical reason to extend the period of anticoagulation, you can safely stop warfarin abruptly when the date for discontinuation is reached. There is no need to taper the dose.

Changing a patient's anticoagulant

Patients can be moved from warfarin to dabigatran or apixaban by stopping the warfarin and starting the NOAC once the INR is below 2.0. When converting patients from warfarin to rivaroxaban, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of this NOAC and therefore should not be used. Refer to the summary of product characteristics for more information.

When switching from a NOAC to warfarin it is recommended to wait for four half lives of the NOAC to pass before starting the warfarin, although in practice co-prescribing often occurs until the INR is above 2.0

Prescribing interacting medicines

Numerous drugs interact with the oral anticoagulants, although there are many more interactions with warfarin than with the NOACs.

Warfarin is metabolised by cytochrome p450 2C9 (CYP2C9). Patients with liver disease or those taking drugs that inhibit the activity of CYP2C9 (for example macrolide antibiotics or quinolones) will require less warfarin. Patients taking drugs that accelerate the metabolism of warfarin (for example rifampicin, barbiturates, and carbamazepine) will require more warfarin.

The NOACs do not interact with CYP2C9. However, their absorption can be altered by p-glycoprotein inhibitors or inducers. The British National Formulary contains a useful list of drug interactions for the oral anticoagulants.

A systematic review of warfarin and its drug and food interactions concluded: “While most reports are of poor quality and present potentially misleading conclusions, the consistency of reports of interactions with azole fungals, macrolides, quinolones, non-steroidal anti-inflammatory drugs, including selective cyclo-oxygenase-2 inhibitors, selective serotonin reuptake inhibitors, omeprazole, lipid-lowering agents, amiodarone, and fluorouracil, suggests that coadministration with warfarin should be avoided or closely monitored.”

The BCSH recommends that when prescribing warfarin :

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

As a general rule the most common medicines causing clinically significant drug interactions with warfarin include NSAIDs, antibiotics, and amiodarone

Prescribing for patients undergoing cardioversion, dental treatment, endoscopy, or surgery

You should follow the latest recommendations from the BCSH.

Cardioversion

A target INR of 2.5 is recommended for three weeks before and four weeks after cardioversion. To minimise cancellations due to low INRs on the day of the procedure, a higher target INR (for example 3.0) can be used before the procedure.

Dental treatment

The National Patient Safety Agency advises that if patients on warfarin who require dental surgery have an INR below 4.0, they can usually receive their dental treatment without needing to stop their warfarin or adjust their dose. The risk of thromboembolism after temporary withdrawal of warfarin therapy outweighs the risk of oral bleeding following dental surgery. Patients on warfarin may bleed more than normal, but bleeding is usually controlled with local measures.

Endoscopy without biopsy

Patients whose INR is in the therapeutic range (< 3.0) do not need to stop anticoagulation for endoscopy. See local guideline here:link

ANTICOAGULATION SERVICE MODELS

The provision of anticoagulant care within the UK has changed considerably over the last 20 years; previously hospital based outpatient clinics were standard practice in most parts of the UK. The introduction of point of care devices for INR testing and computerised decision support software for dosing decisions, plus the specialist nurse in secondary care clinics, have improved results in terms of INR control in both primary and secondary care.

Follow up **in Lincolnshire** is in primary care; at least annual reviews are necessary for all patients on ANY anticoagulant, in addition to regular INR monitoring for those on warfarin

Decision support systems are able to adjust doses more consistently than humans. In addition, they can:

- Track and recall patients
- Generate reminders about dates for stopping
- Enable audits.

The system generally used in primary care is INR star. We are also in the process of introducing this system to ULH, to improve communication between secondary and primary care, hence improving safety for the patients.

Annual review for anticoagulation

All people taking an anticoagulant long term should be reviewed at least annually. This should be more often if clinically relevant events that affect anticoagulation or bleeding risk occur. At this time the need for anticoagulation and the quality of anticoagulation should be considered, along with an assessment of the underlying condition requiring the anticoagulant. In its commissioning guide the NICE Topic Advisory Group recommended that the annual review should include:

- Reassessment of stroke or venous thromboembolism risk
- Reassessment of bleeding risk
- Assessment of renal function
- Incidence of adverse events relating to anticoagulation therapy since last review
- Assessment of compliance.

You should also assess cognitive function and lifestyle factors at each review. The European Heart Rhythm Association recommends the following for patients taking NOACs.

Check at each visit:

- Compliance (patient should bring remaining medication)
- Thromboembolic events
- Bleeding events
- Other side effects
- Concomitant medications and over the counter drugs.

Blood sampling:

- Monitoring of anticoagulation level is not required
- Yearly – haemoglobin, renal function, and liver function
- Renal function:

- Six monthly if creatinine clearance = 30-50 mL/min, > 75 years, or fragile
- Three monthly if creatinine clearance = 15-30 mL/min

Renal and liver function if a condition occurs that may have an impact.

Patient self management

The ready availability and reliability of near patient testing devices for INR measurement has made self management of oral anticoagulation with warfarin a feasible proposition for suitably motivated and counselled patients. A randomised controlled trial of 617 patients in the UK showed that self management of oral anticoagulation is as effective as routine care (in this case a mixture of hospital and primary care clinics).

Patients measured their INR values every two weeks (or every week if there were dose changes) and adjusted their doses. There were no significant differences in the time spent in the therapeutic range or the numbers of side effects. In addition, patients who had poor control of their INR values before the study improved in the intervention group. In another study (carried out in 2006), the cost of self management was £350 per year compared with about £100 for routine care.

In self management schemes patients are trained in the theoretical and practical aspects of anticoagulation and are provided with an approved near patient testing device and a personalised dose adjustment schedule. Patients remain in contact with a named doctor who takes clinical responsibility for their care. Patients must attend a clinic every three months. Recommendations for patients undertaking self management of oral anticoagulation with warfarin have been published.

In a Cochrane review, 18 randomised trials were found that compared self monitoring and self management with standard monitoring. The combined results of these trials showed that self monitoring or self management can improve the quality of treatment with a vitamin K antagonist such as warfarin, leading to fewer thromboembolic events and lower mortality, without a reduction in the number of major bleeds. Self monitoring and self management are not feasible for everyone, and you need to identify and educate suitable patients.

NICE supports the use of two point of care coagulometers - the Coaguchek XS system (Roche Diagnostics) and the InRatio2 PT/INR Monitor (Alere) - as options for self monitoring coagulation status in patients on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease if:

- The person prefers this form of testing
- The person or their carer is both physically and cognitively able to self-monitor effectively.

The weakness of self testing is that without the support of anticoagulant services these patients can be isolated when specialised care is needed during periods of high risk. It is essential that patients who self test have the support of a healthcare professional.

Recording INR results and communicating changes to the patient

Regardless of the source of the INR results, it is important that a continuous record of a patient's INR results is held both in their medical record and in the patient held anticoagulant record. The patient-held record is an important element of treatment. The yellow booklet can be used for this purpose; it contains information about anticoagulation and has a place to record doses and INR values. Some centres use a system in which patients keep a folder of computer printouts of doses and corresponding INR values. Regardless of the system used, the patient-held record is an important safeguard, provided that it is accurate and up to date. Results also need to be entered into the computer if you are using a computerised dosing support system.

When the dose needs to be changed the patient should be informed in the clinic or in writing. In the clinic you can also explore the reasons for an unusual result (such as temporary antibiotic treatment, binge drinking, or non-concordance) and to decide on an appropriate course of action.