module 243

Welcome to the two hundred and forty third module in the Pharmacy Magazine Continuing Professional Development Programme, which looks at medicines optimisation in anticoagulation.

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The commonest uses of oral anticoagulants are for the treatment of deep vein thrombosis or pulmonary embolism, collectively known as venous thromboembolism (VTE), and the secondary treatment of stroke in non-valvular atrial fibrillation.

Vitamin K antagonists
Warfarin is the only licensed vitamin K antagonist (acenocoumarol and phenindione are other members of the group). Warfarin has a half-life of 40 hours, an onset of action of two to five days and a mode of action that reduces the availability of vitamin K, thereby reducing the production of active clotting factors II, VII, IX and X. Warfarin is metabolised in the liver by cytochrome P450 and metabolites are excreted in the...
Table 2 summarises key features of the DOACs.

**Direct oral anticoagulants**
Direct oral anticoagulants (DOACs) have a direct action on factors in the clotting cascade: Apixaban, edoxaban and rivaroxaban are direct inhibitors of Factor Xa, preventing thrombin production and thrombus formation. Dabigatran is a direct thrombin inhibitor.

The half-life of this drug group ranges from seven to 14 hours, with the onset of action between one and four hours. DOACs are metabolised in the liver to form active metabolites, which are excreted by the kidneys.

**Indications for use of anticoagulants**

**Aetiology of thrombosis**
A thrombus is formed when soluble fibrinogen is converted to insoluble fibrin by thrombin factor IIa, the end point of the clotting cascade. A clot is formed when insoluble fibrin is converted to fibrin by thrombin. A thrombus is formed when soluble fibrin is converted to fibrin by thrombin. A thrombus is formed when soluble fibrin is converted to fibrin by thrombin.

**Venous thromboembolic events**
Deep vein thrombosis (DVT) is the term used to describe the formation of a thrombus in a deep vein. DVT occurs in approximately one in 1,000 people and is a major cause of morbidity and mortality. Venous thromboembolism can be described as provoked or unprovoked. Provoking factors include significant immobilisation, surgery, trauma, pregnancy or puerperium, the combined contraceptive pill and hormone replacement therapy. These risk factors can be modified, reducing the risk of recurrence, in which case anticoagulation would normally be limited to three months (pharmacists should check their local anticoagulation guidelines).

If the event was deemed to be unprovoked in the absence of any transient risk factors, then long-term anticoagulation may need to be considered if the cause is not easily correctable or unknown.

**Secondary prevention of stroke in non-valvular atrial fibrillation**
Non-valvular atrial fibrillation (AF) is the commonest clinically significant cardiac arrhythmia, with an estimated lifetime risk of 22-26 per cent conferring a five-fold risk of stroke. The estimated prevalence for the population of England is 1.6 per cent. Through its effects on rate and rhythm, atrial fibrillation itself is associated with a five-fold increase in the risk of stroke. Atrial fibrillation is a major cause of stroke, and atrial fibrillation itself is a major cause of stroke.

**Indication**

**Target INR**

**Duration**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>2.5</td>
<td>Long-term</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>2.5</td>
<td>Pending cardioversion (check if local guidelines suggest an increase to avoid cancellations due to low INR)</td>
</tr>
<tr>
<td>First distal DVT</td>
<td>2.5</td>
<td>3 months (check local guidance as some may indicate 6 weeks)</td>
</tr>
<tr>
<td>First provoked proximal DVT/PE</td>
<td>2.5</td>
<td>3 months</td>
</tr>
<tr>
<td>First unprovoked DVT/PE</td>
<td>2.5</td>
<td>6 months and review</td>
</tr>
<tr>
<td>Recurrent VTE (when not anticoagulated)</td>
<td>2.5</td>
<td>Consider indefinite – seek haematology advice</td>
</tr>
<tr>
<td>Recurrent VTE (when fully anticoagulated and anticoagulant control is within target)</td>
<td>3.5</td>
<td>Seek clarification. In some localities this may require haematologist review</td>
</tr>
</tbody>
</table>

**Confusing terminology**
When they first became available, the non-vitamin K antagonists were referred to as novel or new oral anticoagulants (NOACs). Now that these medicines have been in use for several years, the term NOAC is considered to mean ‘non-vitamin K oral anticoagulants’. It has been recognised that the abbreviation NOAC has the potential to be misinterpreted as NO-anticoagulation, and some people argue that DOAC (direct anticoagulants) may be a safer abbreviation for this drug group.
Until DOACs became available, all patients referred back to their haematologist. The move away from routine monitoring of anticoagulant activity presents a paradigm shift. The HAS-BLED assessment tool is used to guide a decision where the risk of bleeding outweighs the benefit of anticoagulation.

| Table 2: Summary of the direct oral anticoagulants (DOACs) |
|-----------------|-----------------|-----------------|-----------------|
| Rivaroxaban     | Edoxaban        | Thrombacin      | Apixaban        |
| Target          | Factor Xa       | Factor Xa       | Factor Xa       |
| Bioavailability | 80-100%         | 55%             | 3-7%            |
| Renal clearance | 36%             | 50%             | 80%             |
| Hepatic clearance | • Review SPC, avoid concomitant treatment with strong inhibitors of both CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors) • Caution with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John’s wort) as they may lead to reduced rivaroxaban concentrations • Caution with dronedarone | • Review SPC, dose reduction is required with concomitant treatment with strong inhibitors of both CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors) • Caution with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John’s wort) as they may lead to reduced edoxaban concentrations | • Review SPC, potential for P-gp interactions (e.g. amiodarone, verapamil, quinidine, ketoconazole, clarithromycin, rifampicin, phenytoin and carbamazepine) • Concomitant treatment with systemic ketoconazole, ciclosporin, itraconazole, tacrolimus and dronedarone is contraindicated | • Review SPC, avoid concomitant use with strong inhibitors of both CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors) • Caution with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John’s wort) as they may lead to reduced apixaban concentrations |
| Compliance aid compatibility | Yes – shelf-life of 3 years and no special storage requirements | Yes – shelf-life of 3 years and no special storage requirements | No | Yes – shelf-life of 3 years and no special storage requirements |
| Compliance | Once daily – except during 21-day course of 15mg twice daily, needed for acute VTE | Once daily | Twice daily dosing | Twice daily dosing |
| Missed dose | Missed dose should be taken immediately and then continued on the following day with once a day dosing | Missed dose should be taken immediately and then continued on the following day with once a day dosing | Missed dose may still be taken up to 6 hours prior to next scheduled dose | Missed dose should be taken immediately and then continued twice a day as before |
|               | Do not double dose within the same day to make up for missed dose | Do not double dose within the same day to make up for missed dose | If within 6 hours of next dose, the missed dose should be omitted | Do not double dose within the same day to make up for missed dose |

American Society of Cardiology (acc.org/tools-and-practice-support/clinical-toolkits/atrial-fibrillation-afib)

The NICE guidelines recommend that anticoagulation should be considered for men who have a CHA2DS2-VASc score of 1 and be offered to male and female patients who have a CHA2DS2-VASc of 2. It is anticipated that the number of patients prescribed anticoagulants is set to increase, particularly with an ageing population.

The HAS-BLED assessment tool is used to guide a decision where the risk of bleeding outweighs the benefit of anticoagulation. If the HAS-BLED score is above 3, the risk may outweigh the benefit. In such cases patients should be informed of the risk factors and referred back to their haematologist.

**Medicines optimisation**

Medicines optimisation is a person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines. The success of oral anticoagulant treatment can be determined by the prevention of stroke or transient ischaemic attack and the amount of time the patient spends safely anticoagulated.

You can complete this module online at pharmacymagazine.co.uk and record your learning outcomes and the impact on your practice in your personal learning log.
Reinforcing safety messages in a range of settings, including community pharmacies, may make oral anticoagulants safer.

Without the security associated with regular INR testing, there is no system in place to identify patients who are not taking their anticoagulants. Patients who are prescribed DOACs need support and access to information to develop sustained, informed adherence.

Patients may have their DOAC treatment initiated by specialist anticoagulant services but, following the initiation phase, the drug may then be prescribed by the patient’s GP. A community pharmacist could be the only healthcare professional to have regular contact with the patient, so it is important not to assume that the hospital pharmacist or another member of the hospital team has been able to have a full discussion with the patient about his/her medicine.

Patients who are prescribed DOACs should be identified as soon as possible and offered support via the NMS or given a MUR. Where possible, the NMS and MURs should be built into integrated care pathways.

**Evidence-based treatment**

In recent NICE clinical guidance (2014), oral anticoagulants (warfarin or DOACs) were recommended as first-line treatment for patients with AF and at an increased risk of stroke. Evidence now indicates that patients with AF should not be offered aspirin as a monotherapy for stroke prevention as it is a barrier to appropriate stroke prevention with oral anticoagulation.

Audit data collected in 2013 found that only 36 per cent of patients with AF admitted to hospital with stroke were prescribed an oral anticoagulant.

Patients with AF should also not be prescribed antiplatelet drugs because this drug group is considered ineffective in stroke reduction. It is essential therefore that community pharmacy teams identify patients with AF, especially those who buy low-dose aspirin OTC, and ensure that they have their treatment reviewed.

There are also instances when patients should have their anticoagulation therapy reassessed. NICE recommends a review of warfarin anticoagulation in the following circumstances:

- A time-in-therapeutic-range (TTR) of less than 65 per cent
- Two INRs less than 1.5
- Two INRs greater than 3
- One INR reading greater than 8 in the past six months.

Patients should be considered for a DOAC if appropriate but have their anticoagulation therapy reassessed if they are non-adherent.

In July 2015 NICE published quality standard 93: ‘Atrial fibrillation: treatment and management’. Community pharmacists can support local anticoagulation services by ensuring:

- Adults with non-valvular atrial fibrillation and a CHA2D2-VASc stroke risk score of 2 or above are offered anticoagulation
- Adults with atrial fibrillation are not prescribed aspirin as monotherapy for stroke prevention
- Adults with atrial fibrillation who are prescribed anticoagulant discuss the options with their healthcare professional at least once a year
- Adults with atrial fibrillation taking a vitamin K antagonist who have poor anticoagulation control have their anticoagulation reassessed
- Adults with atrial fibrillation whose treatment fails to control their symptoms are referred for specialised management within four weeks
- Adults with atrial fibrillation on long-term vitamin K antagonist therapy are supported to self-manage with a coagulometer.

**Ensuring safe anticoagulant use**

The International Normalized Ratio (INR) can be used to advise what dose of warfarin is required. Current practice recommends that prescribers and pharmacists should check patients’ INR values at the point of prescribing and dispensing warfarin. Some community pharmacy-based services include point-of-care INR monitoring using a coagulometer.

Vitamin K antagonists have a narrow therapeutic range so need close monitoring to
ensure that a patient is not under- or over-anticoagulated. Moreover, patients who are initiated on DOACs or are being switched from warfarin to a DOAC may be concerned about achieving the right level of anticoagulation. Such patients need to be reassured that, due to the pharmacokinetics of DOACs, their coagulation does not need to be monitored – but they will need to have their renal and liver function monitored annually. Liver and kidney function tests may be needed more frequently with older people.

Patients may also be concerned that there are no reversing agents for DOACs. Community pharmacists are well placed to discuss these issues during a NMS consultation or MUR. The safety profile of DOACs relies on patients understanding the differences between warfarin and DOACs and the importance of adhering to their treatment to reduce the frequency of missed and skipped doses.

Community pharmacists have a role to play in ensuring patients have their liver and renal function monitored. They are also well placed to help patients understand that DOACs are metabolised by the liver into an active metabolite, and if their renal function deteriorates this will lead to an accumulation of active drug and an increased risk of haemorrhage. This may help patients to understand the importance of recognising indications of over-anticoagulation and that dose adjustment may be necessary in cases of renal or hepatic impairment.

Table 3 summarises adverse event and side-effect management.

### Understanding the patient experience

Only 16 per cent of patients are fully adherent after starting a new medicine, even when they have all of the information that they need. One-third are non-compliant 10 days after starting a new medication. Of these, 55 per cent are unaware that they are even taking their medication incorrectly and 45 per cent are intentionally non-adherent.

A typical model for patients prescribed warfarin who do not attend for INR tests would be to offer them three further chances to attend their appointment. If at that point they have still
not been tested, the GP should be notified that the patient has stopped attending and therefore they would not be able to prescribe warfarin safely for this patient.

While available data suggests that DOACs are as effective as warfarin, the lack of INR monitoring may mean patients’ medicines-taking behaviour is different. The short half-life of DOACs means patients who omit doses intentionally or unintentionally are at risk of thrombosis through inadequate anticoagulation.

Given that the anticoagulant effects of DOACs fade rapidly on cessation, it is imperative that poor adherence is identified at any patient contact opportunities. Pharmacists should be familiar with missed dose guidance.

Evidence suggests that patients initiated on dabigatran are more likely to persist with oral anticoagulation in comparison to those initiated on warfarin. However, studies documenting ‘real world’ experience suggest that adherence to DOACs is similar to that for other chronic conditions that require long-term medication management.

One study found that 28 per cent of patients with non-valvular atrial fibrillation were non-adherent within one month following initiation of dabigatran. (Non-adherence was defined as having a proportion of days covered by medication as less than 80 per cent.) Throughout a median follow-up period of eight months, approximately two in 10 patients had a gap longer than 30 days without medication.

Another study established that 30 per cent of patients prescribed dabigatran discontinued treatment in consultation with their doctor at some time between three and 12 months of initiation. When interviewed, patients gave the following reasons for discontinuation, in descending order:
- GI symptoms (which led to discontinuation within days of the first dose)
- Concerns that there was no antidote available
- Worsening renal function
- Myocardial infarction
- Itching
- Major haemorrhage.

Not all patients who experienced GI symptoms discontinued treatment. Some patients were initiated on a proton pump inhibitor and the alleviation of GI symptoms allowed them to persist with dabigatran. These issues could be discussed with patients during NMS and MUR consultations.

When discussing oral anticoagulant treatment options with patients, the following issues should also be considered:
- Burden of INR monitoring
- Ability to develop sustained, persistent adherence
- Use of compliance devices
- Polypharmacy medicines burden:
  - Daily vs twice daily dosing
  - Beliefs about stroke prevention:
    - Accept that those with a low CHA2DS2-VASc score may be less willing to consider treatment
    - HAS-BLED risk
- Patients who have taken aspirin for years may be unwilling to switch to an oral anticoagulant.

Drug interactions

A broad range of medicines interact with warfarin. Patients prescribed warfarin should have their INR re-checked three to five days after starting any new medication and be encouraged to notify their anticoagulation clinic to review the date of their next INR test.

As each DOAC has a slightly different profile, community pharmacists should review the SPC for the DOAC required for specific guidance regarding drug interactions.

Local anticoagulation services

Although practice varies, patients prescribed DOACs are monitored routinely by specialist anticoagulation services for the first two to three months of therapy, after which they may be transferred to primary care where they will not be monitored routinely. Some providers do not provide specialist monitoring in the initial phase, and in some localities GPs may also prescribe from initiation on the basis that they feel competent to do so.

Patients managed by specialist anticoagulation services may have their DOACs dispensed on-site, but delays in appointment systems may result in patients running out of medication before their next appointment. Patient safety can also be compromised if documentation of an anticoagulant switch from warfarin to a DOAC is not received by GPs.
before they prescribe a repeat supply of warfarin, resulting in duplicated anticoagulation.

Ideally, patients who are started on a DOAC in secondary care should be referred to their local community pharmacy for the NMS in accordance with the service specification but, in reality, this is not common practice.

To improve patient safety, there is a need for community pharmacy teams to adopt a proactive approach to case-finding patients who have been instigated on a DOAC. When dispensing regular repeat medicines, pharmacy teams should consider how they can capture and record all prescribed medicines, including DOACs, irrespective of where they are dispensed.

Members of the pharmacy team could consider asking patients questions, such as:
• Have you been seen by any members of the anticoagulation team?
• Have you changed your blood thinning medicines?
• Do you take any medicines that are dispensed in other places, including hospital services?
• Do you take any medicines that are delivered to you at home?
• Do you take any medicines other than the ones that are dispensed by this pharmacy?

The NMS is a valuable tool to determine if therapy is particularly important with DOACs, years after being initiated on oral anticoagulant therapy. There is a need to embed the NMS and MUR services into care pathways that enable community pharmacists to identify patients who require anticoagulant dose titration. Recent guidance highlighted safety concerns associated with PGDs for drugs that required regular monitoring and dose adjustment. The guidance suggests that developing non-medical independent prescribing services for high-risk groups could be safer. This may provide community pharmacists with an opportunity to develop a non-medical prescribing anticoagulation service linked with other service providers (see panel below).

New medicine service

The NMS is a valuable tool to determine if a patient is tolerating an anticoagulant and to reinforce understanding with regards to the indication, duration and what to do in the event of a minor or major bleed (see Figure 1).

If, during a NMS consultation, it transpires that the patient is suffering intolerable side-effects, he/she can be referred back to the GP in accordance with the service specification. The NMS provides an opportunity to ensure that patients are aware that they must carry with them at all times an anticoagulation alert card and tell other healthcare professionals that they are on an anticoagulant, particularly where they may be having an invasive procedure. A discussion around compliance and how a patient plans to fit the medicines into his/her daily routine is also beneficial.

Conclusion

There is a need to embed the NMS and MUR services into care pathways that enable community pharmacists to support anticoagulated patients. The importance of maintaining persistent adherence months and years after being initiated on oral anticoagulant therapy is particularly important with DOACs, and community pharmacists have an important role in supporting this patient group. Where problems arise with side-effects, bleeding or a patient’s own beliefs regarding their medication, community pharmacists can signpost appropriately.

**Reflection exercise 4**

How many of your patients prescribed DOACs have had a NMS? Discuss with the local anticoagulant lead pharmacist how you can develop or improve the referral pathway should any problems occur.
MEDICINES OPTIMISATION IN ANTICOAGULATION

**assessment questions**

1. Which of the following is not a DOAC?
   a. Apixaban
   b. Acenocoumarol
   c. Edoxaban
   d. Rivaroxaban

2. Find the TRUE statement regarding DOACs:
   a. They have a direct action on the clotting cascade
   b. If one causes a specific side-effect, so will all of the others
   c. If a patient has renal impairment, one DOAC may be safer than another
   d. DOACs are licensed to treat secondary stroke prevention in all types of atrial fibrillation

3. Patients prescribed warfarin should have their treatment reviewed if in the past six months:
   a. Three INR values have been higher than 5
   b. Two INR values have been higher than 8
   c. INR values have been less than 1.5
   d. Time-in-therapeutic-range is less than 65 per cent

4. Which is NOT a licensed use of dabigatran?
   a. Primary prevention of a venous thromboembolic event in adults who have undergone elective knee replacement surgery
   b. Prevention of stroke and systemic embolism in adults with atrial fibrillation
   c. Treatment of deep vein thrombosis and pulmonary embolism in adults
   d. Prevention of recurrent DVT and pulmonary embolism in adults

5. The acidic coating of which anticoagulant can cause intolerable GI discomfort?
   a. Rivaroxaban
   b. Dabigatran
   c. Apixaban
   d. Edoxaban

6. Which statement is FALSE?
   a. Anticoagulation should be considered for men who have a CHA2DS2-VASc score of 1
   b. Edoxaban inhibits Factor Xa
   c. Apixaban has once daily dosing
   d. Warfarin has a half-life of 40 hours

7. Which of the following issues does NOT have to be considered when discussing DOAC treatment options with patients?
   a. GI symptoms
   b. Concerns that there is no antidote available
   c. Monitoring renal function
   d. Ability to cope with a three-time-a-day dosing regimen

8. Which of the following does not require urgent medical attention in patients on anticoagulants?
   a. Nosebleeds lasting less than five minutes
   b. Blood in vomit
   c. Passing blood in the urine or faeces
   d. Unusual headaches

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