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Newer oral anticoagulants

This bulletin principally discusses the use of the three newer oral anticoagulants licensed for use in the UK – dabigatran etexilate, apixaban▼, and rivaroxaban▼ – for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). It also contains information likely to be of use when managing patients prescribed these medicines for other licensed indications.

The newer oral anticoagulants have been developed in an attempt to address some of the perceived limitations of anticoagulation with vitamin K antagonists, specifically warfarin, including:

- a longer onset and offset of action, necessitating bridging therapy with parenteral agents for some indications,
- variability in dosing requirements and a narrow therapeutic window, requiring routine anticoagulant monitoring,
- food-drug and drug-drug interactions, requiring dietary precautions, restrictions on use with certain other medicines, and/or the requirement for additional monitoring.[1]

In Wales, over 890 000 prescriptions for oral anticoagulants were dispensed in primary care in the year to August 2013; newer agents accounted for less than 1% of the total, but this is increasing.[2]

Licensed indications

Dabigatran etexilate, apixaban, and rivaroxaban have been accepted by the National Institute for Health and Care Excellence (NICE) as an option for use within the NHS for the following licensed indications.[3-9] All are licensed for the prevention of stroke and systemic embolism in patients with non-valvular AF with one or more cardiovascular risk factor/s (which vary very slightly between agents) and the prophylaxis of venous thromboembolism following knee or hip surgery. Rivaroxaban is additionally licensed for the treatment – and prevention of recurrent – deep vein thrombosis and pulmonary embolism.

Summary

- The benefits and risks of anticoagulation should be carefully assessed using validated tools.
- An informed discussion, of risks and benefits relative to warfarin, should take place with the patient if a newer anticoagulant is to be used.
- Patients who are already well controlled on warfarin should not have their therapy changed.
- Renal function should be measured prior to initiation of the newer anticoagulants and periodically thereafter; where required, the dose should be adjusted as recommended.
- It should be noted that significant drug-drug interactions may occur with the newer agents.
- Switching from warfarin to a newer agent and vice versa should be done with care and monitoring of renal function and international normalised ratio (INR) where appropriate.

Some useful pharmacology

Dabigatran etexilate is an inactive pro-drug, which is converted *in vivo* into the direct thrombin inhibitor dabigatran; **apixaban** and **rivaroxaban** are both direct inhibitors of factor Xa.

Approximately 80% of active dabigatran, 25% of the apixaban dose, and one-third of the rivaroxaban dose are excreted unchanged in the urine. It is essential to assess kidney function using creatinine clearance (CrCl) prior to initiation; serum creatinine should be measured and the Cockcroft-Gault formula used. The dose should then be adjusted as recommended.[1,10-13] Renal function should be monitored periodically thereafter – the product literature for dabigatran etexilate suggests at least annually in most patients, but more frequent monitoring is recommended in certain situations where renal function may decline or deteriorate (e.g. dehydration, hypovolaemia, co-administration of medicines affecting the kidney, etc.).[11,14]

Dabigatran does not undergo substantial metabolism via the hepatic pathway, but both apixaban and rivaroxaban are metabolised in the liver.[1,15] Liver function tests are required before initiating apixaban.[12] Changes to dose and/or contraindications and cautions in hepatic impairment vary between agents.[11-13]

The newer agents are not without associated **drug-drug interactions** and, as they enter more routine practice, it is likely that others will be identified. Table 1 illustrates some of the medicines which may interact.

As apixaban and rivaroxaban undergo hepatic metabolism, predominantly via the CYP3A4/3A5 pathway; inhibitors and inducers of this system may respectively increase or decrease plasma levels. Dabigatran has a low potential for interactions through the hepatic pathway but is likely to be affected to a greater extent than apixaban and rivaroxaban by combinations of medicines affecting the kidney. All three agents are substrates of P-glycoprotein and co-administration with medicines that inhibit or induce this pathway can respectively increase or decrease plasma concentration.[1,15]

Table 1. Examples of possible drug-drug interactions with the newer anticoagulants[10-13]

Drugs directly affecting bleeding risk	Drugs affecting the kidney	Inducers of hepatic metabolism	Inhibitors of hepatic metabolism	Inducers of P-glycoprotein	Inhibitors of P-glycoprotein
other anticoagulants[A] NSAIDs antiplatelets thrombolytic agents selective serotonin re-uptake inhibitors serotonin-noradrenaline re-uptake inhibitors	diuretics NSAIDs ACE inhibitors angiotensin-II-receptor antagonists	rifampicin St John's Wort carbamazepine phenytoin phenobarbital	azole antifungals[B,E,F] verapamil[C] amiodarone[D] ciclosporin[B] tacrolimus[B] HIV protease inhibitors[E,F]	rifampicin, St John's Wort, carbamazepine, phenytoin, phenobarbital	dronedarone[B,F] quinidine[D] azole antifungals[B,E,F] amiodarone[D] diltiazem verapamil[C] clarithromycin ticagrelor HIV protease inhibitors[E,F]

A. Contraindicated except when switching between agents.
B. Contraindicated with dabigatran etexilate.
C. Dose adjustment of dabigatran etexilate required.
D. Dose adjustment of dabigatran etexilate required in orthopaedic use.
E. Not recommended with apixaban.
F. Not recommended with rivaroxaban.

Prophylaxis in atrial fibrillation

Antithrombotic therapy should be considered for the prophylaxis of embolism in all patients with AF.[16] The choice of treatment depends on individual risk assessment for both stroke and bleeding, together with an informed discussion with the patient.

Patients at the highest risk of stroke are likely to derive most benefit from anticoagulation. NICE recommends that antiplatelet therapy may be considered for low risk patients. However, the European Society of Cardiology (ESC) 2012 guideline recommends that an anticoagulant is considered for all patients other than those at 'truly low risk', i.e. aged under 65 years with lone AF, who should receive no antithrombotic.[17]

The Quality and Outcomes Framework (QOF) for Wales (2013-14) recommends the use of the $CHADS_2$ tool (see Box 1) to assess stroke risk in patients with AF.[18] Anticoagulation should be considered in patients with a score of ≥ 2.[19] The CHA_2DS_2-VASc tool (see Box 2) includes more risk factors for stroke and may be used for patients with a $CHADS_2$ score of 0 or 1 to identify those at truly low risk; it is at least as good as $CHADS_2$ at identifying patients who develop stroke and thromboembolism.[17]

Box 1. $CHADS_2$ scoring system

	Risk factor	Score
C	Congestive HF	1
H	Hypertension	1
A	Age ≥ 75	1
D	Diabetes mellitus	1
S_2	Stroke/TIA/thromboembolism	2

Box 2. CHA_2DS_2-VASc scoring system

	Risk factor	Score
C	Congestive HF/left-ventricular dysfunction	1
H	Hypertension	1
A_2	Age ≥ 75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thromboembolism	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	Age 65 - 74	1
Sc	Sex category, i.e. female gender	1

An assessment of bleeding risk using a tool such as HAS-BLED (see Box 3) should be undertaken before anticoagulation. In general, if the HAS-BLED score ≥ 3, caution and regular review is advised.[17,20] Modifiable risk factors should be addressed.

Box 3. HAS-BLED bleeding risk score

	Risk factor	Score
H	Hypertension (systolic > 160 mmHg)	1
A	Abnormal renal/hepatic function* (1 each)	1 or 2
S	Stroke	1
B	Previous or predisposition to bleeding	1
L	Labile INR (unstable/high/poor TTR)	1
E	Elderly (age > 65 years)	1
D	Drugs or alcohol (1 each) (e.g. antiplatelets, NSAIDs, or alcohol ≥ 8 units/week)	1 or 2

* Abnormal renal function: chronic dialysis, transplantation, or serum creatinine ≥ 200 µmol/l. Abnormal hepatic function: chronic disease (e.g. cirrhosis) or significant biochemical derangement (e.g. bilirubin > 2x upper limit of normal, in association with aminotransferase/alanine aminotransferase/alkaline phosphatase > 3x upper limit of normal, etc.).

Social and clinical risk factors should also be assessed.[19] It is useful to ask questions such as:

- Is the patient registered with a GP?
- Any investigations for cancer?
- Is the patient taking over-the-counter medicines?
- Any evidence of trips and falls?
- Any sensory, visual, or literacy deficits?
- Alzheimer's or problems with mental capacity?
- Is the patient of child-bearing age?[21]

Benefits and risks of newer agents in AF

The three key clinical trials comparing the newer agents with warfarin in patients with AF were based on a non-inferiority design, i.e. they were designed to show equivalence within specified limits for the primary endpoint of stroke and systemic embolism.

Non-inferiority versus warfarin was demonstrated for all three of the newer agents.[22-24] Dabigatran etexilate 110 mg twice daily was associated with a slightly lower risk of major bleeding, and at 150 mg twice daily there was a decrease in the risk of stroke and systemic embolism with no difference in the rate of major bleeding compared with warfarin.[22] The apixaban trial also reported a decrease in the risk of stroke and systemic embolism but with a lower rate of major bleeding compared with warfarin.[23] The rivaroxaban trial reported similar rates of stroke and systemic embolism and major bleeding to warfarin.[24]

A systematic review and meta-analysis of efficacy and safety data from 12 phase II and III trials of four newer anticoagulants (one not licensed in the UK) suggested a small advantage over warfarin in terms of stroke and systemic embolism and all-cause mortality.[25] Intracranial bleeding rates were lower than seen with warfarin but the risk of major bleeding was similar. These results provide a limited estimate of clinical efficacy.[26]

Choosing an anticoagulant in AF

The All Wales Medicines Strategy Group (AWMSG) currently advises warfarin as first-line therapy for the majority of patients where the decision has been made to start an anticoagulant in AF (see guidance at www.awmsg.org).[19] Patients who are already well controlled on warfarin should not have their therapy changed.[19] However, in certain carefully selected patients, e.g. those taking warfarin but unable to maintain an INR within the target therapeutic range despite good adherence, the newer agents may be considered. In such cases an informed discussion should take place between the patient and clinician regarding the risks and benefits of the newer agent relative to warfarin.[4,6,8,19] When monitoring warfarin therapy it is important to use a computer dosing system that is capable of measuring time in therapeutic range (TTR). The TTR should not be assessed within the first one to three months post-initiation; an assessment period of six months following this initiation phase is a better indication of ability to maintain target INR.[19]

Poor adherence to any anticoagulant is likely to be associated with an increased risk of thrombosis or bleeding.[19]

Evidence suggests that warfarin is not an effective intervention when TTR < 58%.[19] If there are extreme spikes in INR and/or TTR is below this threshold, the issue of adherence should be explored. Poor adherence alone is not an indication that one of the newer agents will be suitable; indeed, the newer agents have comparatively short half-lives and it has been suggested that missed doses could lead to a greater risk of thrombosis compared with missed doses of warfarin.[1] Prescribers should make efforts to understand and address reasons for warfarin non-adherence before considering a switch.[19]

Prescribing responsibility

The decision to initiate one of the newer agents should be on the advice of a secondary care specialist but this should not preclude primary care prescribing where appropriate; a first prescription may be issued in primary care on the advice of a specialist.[19] For people with existing AF in whom the decision is made to switch from current therapy to dabigatran etexilate, apixaban, or rivaroxaban it may be appropriate for practices providing level 3 and 4 anticoagulation services to make the switch if the clinician is familiar with the use of these agents.[19]

In the year to July 2013, the MHRA received 33 **Yellow Cards** regarding the newer anticoagulants from within Wales.[27] To report suspected adverse effects, go to www.yellowcardwales.org.

Table 2. Initiation of newer anticoagulants and switching from and to warfarin in AF[10-13]

	Initiation doses **in AF**	Switching **from** warfarin **in AF**	Switching **to** warfarin **in AF**
Dabigatran etexilate	**150 mg twice daily**, or **110 mg twice daily** if: patient > 80 years, at higher risk of bleeding, or receiving verapamil **Contraindicated** if: CrCl < 30 ml/min	Stop warfarin and start dabigatran etexilate when INR < 2.0.	If CrCl ≥ 50ml/min, start warfarin 3 days prior to dabigatran withdrawal. If CrCl ≥ 30 to < 50ml/min, start warfarin 2 days prior to dabigatran withdrawal. Dabigatran etexilate can affect INR; do not measure until 48h after withdrawal.
Apixaban▼	**5 mg twice daily**, or **2.5 mg twice daily** if: CrCl 15-29 ml/min, or at least two of: age ≥ 80 years, weight ≤ 60kg or, serum creatinine ≥ 1.5mg/dL. **Not recommended** if: CrCl < 15ml/min	Stop warfarin and start apixaban when INR < 2.0.	Co-administer apixaban and warfarin for two days, then measure INR. Warfarin can be continued as monotherapy when INR ≥ 2.0. Apixaban can affect the INR; measure at least 24h after the previous dose but prior to the next dose.
Rivaroxaban▼	**20 mg daily**, or **15 mg daily** if: CrCl 30-49 ml/min CrCl 15-29 ml/min (use with caution) **Not recommended** if: CrCl < 15ml/min	Stop warfarin and start rivaroxaban when INR ≤ 3.0.	Co-administer rivaroxaban and warfarin until INR ≥ 2.0. Rivaroxaban can affect the INR; measure at least 24h after the previous dose but prior to the next dose.

Monitoring activity

One of the postulated advantages of the newer agents is that there is no need for routine coagulation monitoring and this may be of benefit to many. However, the lack of the ability to monitor these agents using routine tests may be of concern to some.

All three of the newer agents prolong the activated partial thromboplastin time (aPTT) and the INR to some extent; thrombin time is increased by dabigatran and prothrombin time by the factor Xa inhibitors. With an appropriate reagent, the aPTT may be used to indicate whether anticoagulation is supratherapeutic, therapeutic, or subtherapeutic, but cannot determine plasma concentration.[14,15,28] Such urgent qualitative assessment may be useful:

- before surgery or invasive procedures
- when a patient is bleeding
- if a patient has overdosed
- if a patient has developed renal failure
- when a patient has a thrombosis on treatment.[14]

The ecarin clotting time and diluted thrombin time can be used to measure the effect of dabigatran, and specifically calibrated anti-factor Xa assays may be used with rivaroxaban and apixaban.[14,28] However, the relationship of these tests with the thrombotic event risk and bleeding risk remains to be established[29] and availability is variable. These less urgent quantitative tests may be useful:

- for patients with deteriorating renal function
- where interacting medicines are to be given
- for patients at extremes of body weight.[14]

Managing bleeding

Experience with the newer agents is still limited and managing bleeding should concentrate on prevention, i.e. prescribing the correct dose to a suitable patient. Special care should be taken when prescribing the newer agents to patients with co-morbidities, undergoing procedures, or with other medicines, which may increase the risk of bleeding.[30] Careful attention should also be paid to renal function and to the contraindications, posology, and warnings for use specific to each agent, together with the individual's risk factors for bleeding.[30]

There is no specific antidote for any of the newer agents – product information should be consulted for advice on treatment in the event of a bleed.[30] Local guidelines may also exist and all prescribers should be familiar with these. Bleeding patients should be rapidly assessed for haemodynamic stability, source of bleeding, time elapsed since last dose, and renal function. All three agents have comparatively short half-lives and **minor bleeding** such as epistaxis, ecchymosis, and menorrhagia may be controlled with local haemostatic measures, possibly combined with a short cessation of therapy with due regard given to thrombotic risk. Patients with **moderate** and **severe/life-threatening** bleeding should be urgently referred to secondary care.[31]

Again, local guidelines may exist regarding the **peri-operative** management of anticoagulation with the newer agents. The risk of bleeding from the procedure, together with renal function, should be taken into account – as should the risk of thrombosis if anticoagulation is to be temporarily withdrawn.[29,32]

Consult Summaries of Product Characteristics for full prescribing information.

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