New oral anticoagulants: an alternative to warfarin

New agents have been introduced for the prevention of inappropriate thrombosis in the vascular tree and the heart. This article reviews, compares and contrasts the newer agents which inhibit activated factor X (Xa) or activated factor II (thrombin).

The need to reduce thrombotic risk has increased because of the ageing population with an attendant rise in the prevalence of atrial fibrillation, the commonest reason for anticoagulation. Other clinical indications for antithrombotic therapy include the treatment and prevention of deep venous thrombosis, pulmonary emboli and patients with prosthetic heart valves.

Whereas vitamin K antagonists such as warfarin have been used to provide anticoagulation for many decades newer agents have been developed which do not need blood monitoring and have no important interactions with other medication, making them more acceptable to patients and potentially improving compliance and safety.

This article focuses on the use of the new agents in treating atrial fibrillation and acute coronary syndromes.

Atrial fibrillation and thromboembolic risk

Atrial fibrillation can be associated with a five-fold increased risk of stroke and this risk is substantially reduced with appropriate treatment. This has historically been provided with warfarin, with recent reviews suggesting that low risk patients do not need any therapy and that aspirin may be of little or no value in these patients. Clinicians have used the CHADS2 score for some years to guide them as to which patients have a high enough thromboembolic risk to warrant warfarin but recently the CHA2DS2-VASc score has been introduced. The latter gives a higher score in most patients because a figure of 1 is allocated to an age over 65 years and 2 if the patient is over 75 years of age, leading to yet more patients being given anticoagulation to reduce the risk (Lip and Halperin, 2010).

Andersson et al (2012) have shown an overall atrial fibrillation prevalence of 2.5% in a stable population of 65 532 people living in northern Sweden, rising from 6.3% in those over 55 years to 13.8% over 80 years. The indication to provide antithrombotic therapy rose from 56.3% using CHADS2 to 85.1% with CHA2DS2-VASc.

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The other main use of anticoagulation has been in the perioperative period to prevent venous thromboembolism which has traditionally been provided with low molecular weight heparin.

Warfarin

The effect of anticoagulation was discovered by serendipity (Lin, 2005). Cattle in the United States were found to be suffering from excessive haemorrhage and this proved to be caused by fermented silage from sweet clover. Coumarin dicoumarol was found to be the active ingredient and warfarin (Wisconsin Alumni Research Foundation) was synthesized, turning out to be the most popular anticoagulant.

However, warfarin has several drawbacks. The first of these is that many patients are aware that it is used as a rat poison and find this an unattractive thought. Second the dose has to be monitored by measuring the INR (international normalized ratio) on a regular basis which patients find irksome, and last there are numerous interactions with other medicines (including non-prescription medication), alcohol and some dietary ingredients which can cause problems with poor control and on occasions dangerous bleeding.

It is therefore no surprise that considerable efforts have been made to find more suitable compounds to take the place of formal anticoagulation.

Antithrombin agents and factor Xa inhibitors

The advantages of these drugs are that they have a fixed dose, do not need blood to be taken for monitoring and have no interactions with food or most drugs. It is recommended that the P-glycoprotein inducers such as rifampin should be used with caution with them. The main disadvantage is that there is no antidote. The drugs most advanced in clinical testing are dabigatran, which directly inhibits thrombin, and rivaroxaban and apixaban which interfere with factor Xa. The end result of both approaches is to inhibit thrombin generation and fibrin formation (Eikelboom and Weitz, 2007).

Ximelagatran was the first to be formally tested in a clinical setting but concerns were raised about changes in liver function and the drug was withdrawn.

Dabigatran

Dabigatran (Baetz and Spinler, 2008) is rapidly effective within 0.5–2 hours with 80% of the dose excreted by the kidneys; its serum half-life is 12–17 hours. It was initially approved in the UK for venous thrombosis prevention after hip and knee replacement and more recently for thromboembolic prevention in atrial fibrillation.

The initial trials focussed on postoperative venous thrombosis prevention (Eriksson et al, 2007). The RE-NOVATE study randomized 3494 patients undergoing total hip replacement to either dabigatran (220 mg or 150 mg once daily) or enoxaparin (40 mg subcutaneous once daily) given for 1 month. The assessment was either with venography or objectively confirmed symptomatic thromboembolism and 24% of patients could not be assessed mainly because of the need to perform a venogram. The study found that both dabigatran doses were non-inferior to enoxaparin for the primary efficacy outcome – a composite of total venous thromboembolic events, defined as deep vein thrombosis – venographic or symptomatic – and/or symptomatic pulmonary embolism, and all-cause mortality during treatment.

Further trials including postoperative knee replacements followed (RE-MOBILIZE; Ginsberg et al, 2009) and a National Institute for Health and Clinical Excellence (2008) assessment concluded that dabigatran was likely to be clinically and economically equivalent to low molecular weight heparin or fondaparinux.

More recently data have been published comparing dabigatran with warfarin in preventing thromboembolism in atrial fibrillation, a clinical situation requiring long-term treatment rather than a short postoperative course.

The RE-LY study (Connolly et al, 2009) randomized 18 113 patients with atrial fibrillation who had a higher than average risk of thromboembolism (similar to CHADS2 score of 2 or more) to either blinded dabigatran 110 mg twice daily or 150 mg twice daily or unblinded warfarin. The primary outcome was stroke or systemic embolism and the primary safety outcome was major haemorrhage. Whereas both doses of the study drug were non-inferior to warfarin, the 150 mg twice daily dose was actually superior in terms of the primary outcome. Major bleeding occurred in 3.36% on warfarin, 2.71% on dabigatran 110 mg twice daily and 3.11% on 150 mg twice daily leading to a significant reduction comparing the lower dose of dabigatran with warfarin.

As compared with warfarin, the 110 mg dose of dabigatran was therefore associated with similar rates of stroke and systemic embolism and lower rates of major haemorrhage; the 150 mg dose was associated with lower rates of stroke and systemic embolism but with a similar rate of major haemorrhage. The authors suggested that this would allow clinicians to choose the most appropriate dose for individual patients according to their perceived risk of bleeding or thromboembolism.

Of importance was that the rate of intracranial haemorrhage, a particularly dangerous event, taking either dose of dabigatran was one third that of warfarin. Dyspepsia proved to be significantly more common on dabigatran (11.3 and 11.8%) compared with warfarin (5.8%), possibly because of the acidic core of the pellets.

An editorial comment (Gage, 2009) suggested that because of the need to take the drug twice a day and the increased symptoms of dyspepsia patients who were well controlled on warfarin would have little to gain by switching to dabigatran. However, that leaves a number of patients in whom control has been challenging who would benefit.

National Institute for Health and Clinical Excellence (2011) recommended that dabigatran can be used in patients with non-valvular atrial fibrillation as long as they have one or more of the following risk factors:

- Previous stroke, transient ischaemic attack or systemic embolism
- Left ventricular ejection fraction below 40%
- Symptomatic heart failure of New York Heart Association (NYHA) class II or above
- Age 75 years or older
- Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

In its final guidance published in March 2012 National Institute for Health and Clinical Excellence confirmed that dabigatran is an option for the prevention of stroke and systemic embolism in people with atrial fibrillation. The guidance also recommends that the decision about whether to start treatment with dabigatran should be made after an informed discussion about the risks and benefits of dabigatran compared with warfarin, and in light of a person's current level of INR control if he/she is already taking warfarin.

Rivaroxaban

This drug, a factor Xa inhibitor, has followed closely behind dabigatran in clinical trials. The EINSTEIN trial (EINSTEIN Investigators, 2010) showed it to be as effective for the treatment of deep venous thrombosis as warfarin.

The Rivaroxaban ROCKET AF study (Patel et al, 2011) had similar entry criteria to RE-LY and randomized 14 264 patients who had atrial fibrillation and a CHADS2 score of 2 or above. In this study the patients were randomly assigned to receive fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with reduced renal function) or blinded adjusted-dose warfarin (INR 2–3). Analysis showed that rivaroxaban was non-inferior to warfarin in the primary end points and there was no difference in the bleeding rates, although fatal and intracranial bleeding was less in patients taking the study drug.

One reason for giving a fixed dose drug is that there is significant variation of the time within therapeutic

range of the INR when taking warfarin. In a Veterans study in the United States (Rose et al, 2011) the mean time that patients on warfarin were within the therapeutic range was only 58% compared with 55% as found by Patel et al (2011). However, it is feasible to maintain patients in the therapeutic INR range of 2–3 for up to 76% of the time and if this is the case the benefits of these new agents could be less than claimed (Weiloch et al, 2011).

The associated leading article (del Zoppo and Eliasziw, 2011) points out that this class of drugs has no antidote unlike warfarin and if patients have haemorrhagic problems this could cause problems in their management.

Whereas rivaroxaban has been licensed for use in the UK in atrial fibrillation, National Institute for Health and Clinical Excellence has requested further information about the drug before producing its final recommendations. The problems stem from the fact, as noted above, that the time within therapeutic range for INR was deemed poor in relationship to UK practice and that the population studied was not representative of the type of patient who might be offered therapy in the UK.

Attention is now turning to the use of rivaroxaban, dabigatran and apixaban in acute coronary syndromes. In ATLAS ACS–TIMI 46 (Mega et al, 2012) 15 526 patients who had a non-ST elevation myocardial infarction, an ST myocardial infarction or unstable angina were randomized to either 2.5 mg twice daily or 5 mg twice daily of rivaroxaban or placebo on top of standard therapy which included low dose aspirin plus either clopidogrel or ticlopidine. Those patients who were under 55 years of age either had diabetes or a previous myocardial infarction on top of the study criteria. Enrollment started within 7 days of the event with revascularization complete and the patient stable.

Rivaroxaban, at both doses, reduced the primary end point which was a composite of death from cardiovascular causes, myocardial infarction or stroke. The 2.5 mg twice daily dose reduced the rates of death from cardiovascular causes (2.7% *vs* 4.1%, P=0.002) and from any cause (2.9% *vs* 4.5%, P=0.002) whereas this was not seen with the 5 mg twice daily dose. As expected increased rates of both major bleeding (2.1% *vs* 0.6%, P<0.001 – a factor of four times) and intracranial haemorrhage (0.6% *vs* 0.2%, P=0.009 – a factor of three times) were seen, but not fatal bleeding (0.3% *vs* 0.2%, P=0.66).

Evidence has just been published about the use of rivaroxaban in the treatment of pulmonary embolism (EINSTEIN-PE Investigators, 2012). The EINSTEIN-PE study randomized 4832 patients who had acute symptomatic pulmonary embolism to rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily or a vitamin K antagonist and found non-inferiority between the treatments. Rivaroxaban was given without pre-treatment with heparin unlike the vitamin K antagonist group.

Apixaban

Apixaban is the latest in the current crop of this class to report results. The ARISTOTLE trial (Granger et al, 2011) reported 18 201 patients with atrial fibrillation and at least one additional risk factor for stroke who were randomized to either apixaban 5 mg twice daily or warfarin. The primary outcome was systemic embolism or ischaemic or haemorrhagic stroke. Although the trial was designed to assess non-inferiority it revealed that apixaban compared with warfarin significantly reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31% and death by 11%.

Apixaban has also been compared with aspirin, which is regarded as producing a relatively weak effect, in patients with a higher than average risk thromboembolic risk in atrial fibrillation who are either reluctant to take vitamin K antagonists or were deemed unsuitable (Connolly et al, 2011). The AVERROES study enrolled 5599 patients in a double dummy design with patients either randomized to apixaban 5 mg twice daily or aspirin 81–324 mg daily. The study was stopped prematurely as the primary end point of stroke or systemic embolism was noted in 1.6% of patients on apixaban compared with 3.7% on aspirin (P<0.0001). However, the rates of major and intracranial bleeding were similar (P=0.57).

Apixaban, like rivaroxaban, has also been tested in acute coronary syndromes (Alexander et al, 2011). In the APPRAISE-2 study, which was terminated prematurely, there was no significant difference in the primary end point of cardiovascular death, myocardial infarction or ischaemic stroke by adding apixaban to standard antiplatelet therapy, although there was an increased major bleeding rate of 1.3% on the active drug compared with 0.5% on placebo (P=0.001).

Conclusions

The need for antithrombotic treatment for atrial fibrillation has increased and this has been the main driver for new agents to replace warfarin.

The new drugs, dabigatran, rivaroxaban and apixaban, have significant advantages to the patient with a fixed dose and no interaction with other therapies. However, they naturally cost more and if patients are well controlled on vitamin K antagonists there is no significant benefit. A potential problem is that they have no antidote unlike the vitamin K antagonists but they do have a relatively short half-life. Doctors are used to dealing with patients who are on drugs with no antidote such as aspirin, clopidogrel and low molecular weight heparin. The short half-life means that compliance must be good to maintain therapeutic levels and unlike using INR with vitamin K antagonists there is no test to confirm that the patient is taking the drug regularly.

The main evidence base at present is in the prevention and treatment of peripheral venous thrombosis and thromboembolism in atrial fibrillation where

dabigatran and rivaroxaban have been licensed in the UK. Further studies should tell us if this class is suitable for use in patients with acute coronary syndromes, pulmonary emboli and in those who are undergoing cardioversion for atrial fibrillation where the uncertainty of warfarin control may delay the correction of the arrhythmia. **BJHM**

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KEY POINTS

- The need for drugs to reduce thromboembolic risk is increasing.
- Vitamin K antagonists have significant drawbacks because of the need to have regular blood tests and the risk of poor control.
- The newer agents are easier to take with no need for blood tests and have at least equivalent if not improved efficacy in atrial fibrillation.
- They have proved effective in postoperative prevention of deep venous thrombosis.
- The newer agents have no antidote and are considerably more expensive than vitamin K antagonists.
- It is likely that other indications will be sought such as their use in the treatment of pulmonary embolus and before cardioversion.

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