

# New oral anticoagulants: their role and future

Susie Shapiro and Mike Laffan

**ABSTRACT** – After 60 years in which warfarin has been the only practical oral anticoagulant, a number of new oral anticoagulants are entering practice. These drugs differ in a several important respects from warfarin; most notably they have a reliable dose-response effect which means they can be given without the need for monitoring. Their simpler metabolism and mode of action also results in fewer interactions with other drugs and with diet. However, some of their other properties such as renal clearance (to varying degrees), short half-life and lack of an available antidote may slow their rate of introduction. Large trials have established their non-inferiority to warfarin in a number of indications and in some cases their superiority. To date they have been licensed for prophylaxis following high risk orthopaedic procedures, non-valvular atrial fibrillation and treatment of venous thromboembolism, but is not clear that they will supplant warfarin in all areas.

**KEY WORDS:** Anticoagulation, warfarin, rivaroxaban, dabigatran, apixaban

## Introduction

The new oral anticoagulants (NOAC) offer significant advantages when compared to previously available agents, but their introduction will also be accompanied by a new set of problems and limitations. The NOAC are referred to as ‘new’ primarily in reference to warfarin, which has been the only practical agent for long-term anticoagulation for more than 50 years. They will be judged therefore by comparison with warfarin and will have to compete with warfarin for their place in therapy. It is essential to understand the properties of the drugs in order to make the best choice for individual patients.

## The comparator: warfarin

Warfarin acts as an anticoagulant because it is similar in structure to vitamin K, which is required for the post-translational modification of several coagulation proteases, specifically factors II, VII, IX and X. Vitamin K is also required for manufacture of the anticoagulants protein C and protein S. Warfarin blocks the recycling of vitamin K and the resulting deficiency reduces the liver’s capacity to perform the essential gamma-carboxylation of

these proteins, which are therefore reduced in quantity and activity. Warfarin is thus an indirect anticoagulant that has no anticoagulant effect of its own.<sup>1</sup>

After warfarin administration, the onset of the anticoagulant effect is determined by the half-lives of the coagulation factors, some of which are 2–3 days. As a result, the onset of warfarin anticoagulation is always gradual, even if large doses are given. These factors make warfarin unsuitable for situations in which rapid anticoagulation is required, but they do add stability to its anticoagulation effect and tend to minimise the effect of delayed or missed doses. Nevertheless, this complicated mechanism of action and warfarin’s own metabolism result in a very narrow therapeutic index and, as is well known, the dose required for an appropriate level of anticoagulation varies greatly between individuals and from time to time in any individual patient. This necessitates monitoring using the International Normalised Ratio (INR) system. Success in maintaining the optimum level of anticoagulation is judged by the INR’s time in therapeutic range (TTR), and clearly this must be taken into account when comparing warfarin with other anticoagulants.

Another very important result of warfarin’s mode of action is that it provides convenient and effective methods for its reversal. Specifically, administration of intravenous vitamin K will largely reverse the effect within 12–24 hours; in an emergency, intravenous administration of the missing factors using prothrombin complex concentrate can completely and safely reverse the effect in a matter of minutes.<sup>2</sup> After 60 years of experience, we know a great deal about how to manage warfarin anticoagulation.

## The new oral anticoagulants

At present, there are three alternative oral anticoagulants licensed in the UK. These are rivaroxaban and apixaban, which are direct inhibitors of activated factor X (Xa), and dabigatran, which is a direct inhibitor of thrombin (IIa). Thrombin and FXa are both important enzymes in the coagulation cascade. FXa is responsible for the conversion of prothrombin into thrombin which then cleaves fibrinogen to create the fibrin clot. Although the introduction of these drugs was preceded by much discussion as to whether thrombin FXa was the preferable target, both have proved effective. The properties of the three drugs are summarised in Table 1.<sup>3</sup> They are all direct and immediate-acting anticoagulants that achieve maximum concentrations in the blood only 2–4 hours after ingestion. In this respect, they achieve an anticoagulant effect as quickly as a subcutaneous injection of low molecular weight heparin (LMWH). They also all have plasma half-lives of less than 24 hours; the shortest being that of

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**Table 1. Properties of the new oral anticoagulants.**

	<b>Dabigatran</b>	<b>Rivaroxaban</b>	<b>Apixaban</b>
Mode of action	Factor IIa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Time to peak	2 hours	2–4 hours	1–3 hours
Half-life	12–14 hours	7–11 hours	12 hours
Dosing for atrial fibrillation	Twice daily	Once daily	Twice daily
Metabolism	Prodrug, requires acid for absorption esterase catalysed hydrolysis	CYP P450 dependent and independent mechanisms	CYP P450 dependent
Excretion	85% renal	33% renal	25% renal
Dose	150 mg 110 mg if >80 years old, with verapamil or at increased bleed risk	20 mg 15 mg if CrCl 30–49 ml/min	5 mg 2.5 mg with two or more of: >80 years old, weight <60 kg, Cr >133 µm/l or CrCl 15–39 ml/min)
Protein bound	35%	90%	87%

Cr = creatinine; CrCl = creatinine clearance.

rivaroxaban at approximately 10 hours. This may be of benefit in some circumstances (eg where there is bleeding) and problematic in others (eg if a dose is missed). As with LMWH, relatively little anticoagulant effect remains after 24 hours. An important way in which these NOAC differ from warfarin is that they are all, to some extent, dependent on renal excretion (most markedly, dabigatran, 85% of which is excreted by this route).

The most attractive property of the NOAC is that their simpler mode of action and metabolism results in a more reliable dose response, dispensing with the need for monitoring, largely removing the interactions with lifestyle and diet and limiting drug interactions to a few specific drugs (Table 1).<sup>4</sup> Moreover, they are taken orally and have an immediate onset of action, so that in acute situations, it is possible to dispense with an initial period of heparin anticoagulation followed by a difficult transition to warfarin. Some physicians, however, will be uneasy about the lack of monitoring and the consequent loss of a check on compliance and anticoagulation effect. The lack of monitoring also means that we currently have no ready way of increasing the anticoagulant effect for difficult patients with higher thrombotic risks, whereas with warfarin we have considerable experience of increasing the target INR. Further trials will be required for these patients. The direct mode of action has the above advantages, but it also means that we have no ready means of removing or reversing the effect of these drugs. This problem is currently unsolved although it is worth noting that the half-lives are relatively short<sup>5</sup> and that novel reversal agents are under development.<sup>6</sup> Renal dependence will add another area of concern and caution. Finally, and not to be easily dismissed, the new agents will be more expensive than warfarin, notwithstanding the reduction in costs of monitoring, and this aspect has been thoroughly investigated by NICE.<sup>7</sup>

## New oral anticoagulants in practice

### *Thromboprophylaxis in orthopaedic surgery*

All three drugs have successfully completed trials and have been licensed for use in knee and hip replacement surgery. Comparisons

were complicated by changes in practice and differences in LMWH regimens on either side of the Atlantic, but it appears clear that the overall efficacy of NOAC is at least as good as that of existing LMWH regimens. They are more convenient for post-discharge completion of the 14- and 35-day regimens currently recommended.<sup>8</sup>

### *Atrial fibrillation*

All three drugs have completed successful trials and NICE evaluations for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF).<sup>9–11</sup> A comparison of the trials is summarised in Table 2.<sup>12</sup> Although the entry criteria for these trials differed somewhat, with rivaroxaban tackling a higher risk group (CHADS2 score 3.5 vs 2.1 in the other two trials), the licensed indication in each case is for non-valvular AF plus one or more additional risk factors. Dabigatran was given in two different regimens, 110 mg and 150 mg, and the higher dose achieved superiority over warfarin in terms of efficacy and non-inferiority in terms of safety. The only drug to achieve superiority for both efficacy and safety was apixaban, which also resulted in a significant reduction in all-cause death.<sup>9</sup> As noted above, the TTR in the comparative warfarin arm is important to take into account: this was 62% and 64%, respectively, in the apixaban and dabigatran trials, levels that are comparable to those currently achieved in UK practice. The TTR for the warfarin arm was lower in the rivaroxaban trial at 55%. This may have made it easier for rivaroxaban to achieve non-inferiority with warfarin but this trial constituted a higher risk group with more comorbidity. Subgroup analysis from the REL-Y trial showed overall benefit for dabigatran when the TTR was <57% and equivalence when better TTR was achieved. There was no level of warfarin control identified for which warfarin was superior.<sup>13</sup>

The AF trials also provided interesting data that will be useful in introducing the new drugs. For example, it is notable that the benefit of the NOAC accrues almost entirely from a reduction in haemorrhagic stroke, with the frequency of ischaemic stroke

**Table 2. Summary of NOAC trials for atrial fibrillation.**

	Dabigatran		Rivaroxaban	Apixaban
	110 mg	150 mg		
Design	Open label		Double blind	Double blind
Patient inclusion criteria	Non-valvular AF + 1 risk factor		Non-valvular AF + 2 risk factors	Non-valvular AF + 1 risk factor
Inclusion (mean CHADS2 score)	2.1		3.5	2.1
Warfarin control (mean TTR)	64%		55%	62%
Primary endpoint HR (95% CI)	0.91 (0.74–1.1) p<0.001 (NI)	0.66 (0.53–0.82) p<0.001 (S)	0.79 (0.66–0.96) p<0.001 (NI)	0.79 (0.66–0.95) p=0.01 (S)
Safety endpoint HR (95% CI) (major or cnm bleeding)	0.80 (0.69–0.93) p=0.003	0.93 (0.81–1.07) p=0.31	1.03 (0.96–1.11) p=0.44 (NI)	0.68 (0.61–0.75) p<0.001
Composite endpoint	0.92 (0.84–1.02) p=0.1	0.91 (0.82–1.00) p=0.04	–	0.85 (0.82–0.92) p<0.001
Concomitant aspirin use	40%		36%	31%

95% CI = 95% confidence interval; AF = atrial fibrillation; cnm = critical non-major; HR = hazard ratio; NI = non inferior; S = superior; TTR = time in therapeutic range. Primary endpoint was stroke and systemic embolism.

largely unchanged. Both dabigatran and rivaroxaban, but curiously not apixaban, resulted in an increase in gastrointestinal (GI) bleeding. The only hint of a class effect is the slightly increased incidence of myocardial infarction seen with dabigatran. This was an unspecified endpoint in the original trial but appears to be confirmed in a subsequent meta-analysis, although it is not sufficient to reduce the overall benefit.<sup>14</sup>

### Venous thrombosis

All three agents have been trialled for the treatment of venous thromboembolism but are currently at different stages of development and licensure. At the time of writing, only rivaroxaban has a UK license for this indication. In the EINSTEIN-DVT trial, rivaroxaban was used as the sole agent for treatment of deep vein thrombosis (DVT), starting at a dose of 15 mg twice daily for 3 weeks before reducing to 20 mg once daily for longer-term prevention.<sup>15</sup> The success of this trial, which demonstrated non inferiority for both efficacy and safety compared to the standard LMWH- vitamin K antagonist (VKA) treatment, offers the opportunity to simplify DVT management greatly because it omits the need for injections and therefore avoids the difficult transition from heparin to warfarin. Thus, patients are freed from repeated return visits to hospital for LMWH injections and blood tests for INR monitoring. Similarly, patients who are admitted will not have their discharge delayed while waiting for warfarin stabilisation (a fact that also applies to patients with AF and patients who have had their anticoagulation stopped for surgery). The rivaroxaban trial for pulmonary embolism (PE) was similarly successful<sup>16</sup> and it is now licensed for both indications, although the introduction of use for outpatient management of PE will be more circumspect. Apixaban has been trialled for acute treatment of thromboembolism using a similar regimen (results awaited) whereas the dabigatran trial for thromboembolism used LMWH as a conventional initial agent.<sup>17</sup>

All three drugs have been successfully tested for long-term secondary prevention; dabigatran against warfarin and the other agents against placebo.<sup>16,18,19</sup> Although not yet licensed, a low dose of apixaban (2.5 mg twice daily) appeared to reduce the risk of recurrent thrombotic events significantly, while producing no significant increase in bleeding. This example suggests that the balance of risk and benefit for long-term secondary prevention may need revision and a far larger number of patients may benefit from long-term treatment.

### Other indications

There are a number of other areas in which new anticoagulants may be deployed, but as yet there is little evidence to support their wider use. It cannot be expected that data from one area can be easily extrapolated into another. In particular, trials of these three agents in thromboprophylaxis for medical inpatients,<sup>20,21</sup> patients with cardiac valves and patients with acute coronary syndromes<sup>22,23</sup> have been unsuccessful or of limited benefit. It is also worth noting that, as mentioned above, we have no NOAC regimens for patients requiring higher levels of anticoagulation.

### How should the new anticoagulants be introduced and chosen for individual patients?

The relatively high cost of the new anticoagulants means that it will be impossible to support a major change in practice in the short term. Moreover, it is clear from sub-group analyses of the trials that patients with good INR control, as judged by a TTR of >60%, have little to gain from switching to the new drugs other than the convenience of being freed from monitoring. For some patients whose control is poor, efforts should be made to improve this by education and possibly by adopting self-testing and self-dosing.<sup>24</sup> On the other hand, for patients who have genuine difficulty in maintaining an INR in the therapeutic

range despite reasonable efforts, or whose control is confounded by irregular diet or frequent changes in medication, there is the potential to improve anticoagulation by switching to a NOAC. Clearly, switching is unlikely, in itself, to improve adherence and physicians are likely to be anxious about losing the ability to check the degree of anticoagulation easily in patients who are irregular in this respect.

When switching is contemplated, there are several points from the trials that should be taken into consideration. For example, these drugs are not suitable for patients with severe renal impairment (clearance <15 ml/min) and are potentially problematic with milder renal impairment. All patients should have their renal function checked at initiation and if this is likely to be unstable, these agents should be avoided. If there is a history of gastrointestinal bleeding, then rivaroxaban and dabigatran should definitely be avoided. Single daily dosing of rivaroxaban may be of benefit to some patients but the relatively short half-life of this drug makes it particularly important that doses are taken on time. The transition between warfarin and NOAC requires careful attention because it is important to maintain effective anticoagulation throughout, and the NOAC may affect the INR.<sup>25</sup>

## Coagulation tests and the NOAC

One of the principal attractions of the NOAC is that they do not need monitoring, but it is likely that there will be a number of situations in which it will be necessary or desirable to assess the amount of drug present: prior to emergency surgery, after trauma or spontaneous bleeding and in the event of deteriorating renal function. Preliminary results suggest that if the activated partial thromboplastin time (APTT) is normal, then the amount of anticoagulant present is likely to be no more than a prophylactic level, although reagents may differ significantly in sensitivity.<sup>26</sup> Rivaroxaban and apixaban can be measured using a standard anti-Xa assay as is used for heparin, provided calibrants are obtained from the manufacturer, and dabigatran can be measured using a dilute thrombin time (Haemoclot). These tests should be available in all hospital laboratories and physicians should liaise closely with haematologists.

## Emergency correction of coagulation

In contrast to warfarin, the NOAC have a direct anticoagulant action and thus there is no simple way of reversing their effect. The relatively short half-life of these drugs is of some benefit in this respect, but in situations such as intracranial bleeding, additional measures will be required. The best strategies at present utilise prothrombin complex concentrates or activated prothrombin complex concentrates to achieve high levels of X/Xa and II/IIa to overcome the inhibitory effect of the drugs.<sup>5</sup> There are some *in vitro* and animal data suggesting that recombinant VIIa may also force enough coagulation factor activation to achieve an effect.<sup>27</sup> Because only 25% of dabigatran is protein-bound, it is possible to remove approximately 50% with a 4-hour dialysis session.<sup>28</sup> More specific inhibitors or antibodies for reversal are in development.<sup>6</sup>

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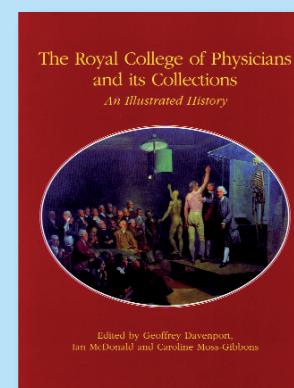
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