

# The newer direct oral anticoagulants: a practical guide

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## ABSTRACT

Anticoagulation therapy is one of the most important advances in modern medicine, saving thousands of lives from the complications of atrial fibrillation and mechanical heart valves and preventing recurrent venous thromboembolism. Warfarin and heparins have been the predominant anticoagulants used until the past decade. However, the arrival of newer target-specific anticoagulants has brought us easier and equally effective agents, although no specific antidotes are yet available. Being relatively newer drugs, physicians need to be familiar with the various practical issues that may be encountered with the prescription of these drugs, which are summarised in this review.

**KEYWORDS:** Anticoagulants, atrial fibrillation, bleeding, coagulation, thrombosis, warfarin

## Introduction

Warfarin and related coumarin derivatives have been the mainstay of the management of thromboembolic disease for more than five decades. Recently, several new drugs have been produced to overcome the well-known disadvantages of warfarin. Although these are usually described as novel oral anticoagulants (NOACs) in the medical literature, they will be described as direct oral anticoagulants (DOAs) in this article, as they are not entirely novel (trials published 4–5 years ago) and they work directly on specific sites in the coagulation pathway. The DOAs are mechanistically different from warfarin in that they act at the catalytic pocket of coagulation factors and inhibit their function. Warfarin produces an indirect anticoagulant effect by interfering with the metabolism of vitamin K, required for biological activity of coagulation factors.

## The three direct oral anticoagulants

Broadly, there are two classes of DOA. The anti-IIa drug dabigatran inhibits activated factor II (or IIa or thrombin). The anti-Xa drugs rivaroxaban and apixaban block activated factor X (or Xa); edoxaban is another anti-Xa agent but is not licensed for use in the UK. Table 1 summarises the pivotal

trials involving these agents and Table 2 summarises their key pharmacokinetic properties.

### Dabigatran

Dabigatran etexilate (Pradaxa®), a prodrug of dabigatran, is a small molecule that binds to the active site of thrombin and blocks free and clot-bound thrombin.<sup>14</sup> Dabigatran is predominantly excreted by the kidneys, so any reduction in renal function can affect plasma concentrations. Creatinine clearance (CrCl) should be checked in all patients before starting treatment with dabigatran; those with CrCl <30 ml/min should not receive this drug, while those with CrCl of 30–50 ml/min may be prescribed dabigatran but with close monitoring of renal function recommended. Dabigatran has low oral bioavailability, and tartaric acid is added to enhance absorption of the drug. Breaking the capsule formulation (or chewing) can result in a significant increase in bioavailability.<sup>14,15</sup> Until absorbed and metabolised to dabigatran, dabigatran etexilate remains a substrate for the P-glycoprotein efflux transporter and, as such, can interact with drugs that are known inducers of this efflux mechanism.<sup>15</sup> Dabigatran should be taken with food or water to minimise dyspepsia, although food does not affect its bioavailability. Blister packs should be used as dabigatran is hygroscopic, and the capsules should be discarded after 60 days of exposure (ie 60 days after bottle/container is opened).<sup>16</sup> Dabigatran can be continued without interruption in those undergoing cardioversion. If a dose is missed, the next dose should be taken within 6 hours, but the dose should be omitted if more than 6 hours have elapsed.

### Rivaroxaban

Rivaroxaban can inactivate free and clot-associated factor Xa.<sup>17</sup> It is dosed once daily, has a high bioavailability of 80% and is 90% bound to protein.<sup>18</sup> It is mainly eliminated through the liver. There is no accumulation of drug when CrCl is >15 ml/min, but a dose reduction to 15 mg once daily is recommended if CrCl is 15–30 ml/min.<sup>17,18</sup> The pharmacokinetics of rivaroxaban are affected by drugs that affect P-glycoprotein and cytochrome P450 3A4 (CYP3A4) but not CYP2C9 (like warfarin).<sup>18</sup> For this reason, drugs that act as inducers or inhibitors of these enzymes can significantly impact on plasma concentrations of rivaroxaban. It can be continued uninterrupted in patients undergoing cardioversion. Oral absorption of rivaroxaban is excellent for the 10 mg dose; however, higher doses of 15 mg and 20 mg should be taken with food to achieve high bioavailability. If a dose is missed, the next dose should be taken within 12 hours, but the dose should be omitted if more than 6 hours has elapsed.

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**Table 1. Studies with direct oral anticoagulants in patients with atrial fibrillation (AF), venous thromboembolism (VTE) and acute coronary syndrome (ACS)\* and for medical thromboprophylaxis.**

Setting	Drug	Study	Outcome†	Bleeding risk‡
AF	Dabigatran	RE-LY <sup>1</sup>	<ul style="list-style-type: none"> <li>&gt; 150 mg superior to warfarin for reduction of SSE (1.11 % vs 1.69 %)</li> <li>&gt; 110 mg non-inferior to warfarin (1.53 % vs 1.69 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Similar major bleeding rates with 150 mg and warfarin (3.11 % vs 3.36 %)</li> <li>&gt; Significantly lower bleeding rates with 110 mg than warfarin (2.71 % vs 3.36 %)</li> <li>&gt; More GI bleeding events with 150 mg than warfarin</li> <li>&gt; Significantly fewer ICH events with both doses than warfarin</li> </ul>
	Rivaroxaban	ROCKET-AF <sup>2</sup>	<ul style="list-style-type: none"> <li>&gt; Non-inferior to warfarin in relation to SSE (1.7 % vs 2.2 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Bleeding events similar for rivaroxaban and warfarin (14.9 % vs 14.5 %)</li> <li>&gt; Significantly fewer ICH events than warfarin (0.5 % vs 0.7 %)</li> </ul>
	Apixaban	ARISTOTLE <sup>3</sup>	<ul style="list-style-type: none"> <li>&gt; Superior to warfarin in preventing SSE (1.27 % vs 1.6 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Fewer bleeding events than warfarin (2.13 % vs 3.09 %)</li> <li>&gt; Compared with warfarin, significantly fewer: haemorrhagic strokes (0.24 % vs 0.47 %)</li> <li>&gt; ischaemic strokes (0.97 % vs 1.05 %)</li> </ul>
VTE	Dabigatran	RE-COVER <sup>4</sup>	<ul style="list-style-type: none"> <li>&gt; 150 mg non-inferior to warfarin in preventing VTE (2.4 % vs 2.1 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; No differences in major bleeds for dabigatran and warfarin</li> <li>&gt; Significant reduction in any bleeding (dabigatran &gt; warfarin)</li> </ul>
		RE-MEDY <sup>5</sup> RE-SONATE <sup>5</sup>	<ul style="list-style-type: none"> <li>&gt; Extended use: non-inferior to warfarin (1.8 % vs 1.3 %)</li> <li>&gt; better than placebo (0.4 % vs 5.6 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Fewer major bleeding events (0.9 % vs 1.8 %) (dabigatran &gt; warfarin)</li> <li>&gt; More bleeding events than placebo (0.3 % vs 0)</li> </ul>
	Rivaroxaban	EINSTEIN-DVT <sup>6</sup> EINSTEIN-PE <sup>7</sup>	<ul style="list-style-type: none"> <li>&gt; Non-inferior to warfarin for: DVT (2.1 % vs 3.0 %)</li> <li>&gt; PE (2.1 % vs 1.8 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Bleeding events: similar to warfarin for DVT</li> <li>&gt; lower than warfarin for PE</li> </ul>
		EINSTEIN extension <sup>6</sup>	<ul style="list-style-type: none"> <li>&gt; Superior to placebo (1.3 % vs 7.1 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; More bleeding events with rivaroxaban than placebo (6 % vs 1.2 %)</li> </ul>
	Apixaban	AMPLIFY <sup>8</sup>	<ul style="list-style-type: none"> <li>&gt; Non-inferior to placebo (2.3 % vs 2.7 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Significantly fewer bleeding events than placebo (4.3 % vs 9.7 %)</li> </ul>
		AMPLIFY-EXT <sup>9</sup>	<ul style="list-style-type: none"> <li>&gt; Superior to placebo (1.7 % vs 8.8 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Significantly less bleeding with apixaban than placebo</li> </ul>
ACS*	Rivaroxaban	ATLAS ACS 2 TIMI 51 <sup>10</sup>	<ul style="list-style-type: none"> <li>&gt; Reduced mortality from: cardiovascular causes (2.7 % vs 4.1 %)</li> <li>&gt; any cause (2.9 % vs 4.5 %)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; More major bleeding events (2.1 % vs 0.6 %)</li> <li>&gt; More ICH events (0.6 % vs 0.2 %)</li> </ul>
	Apixaban	APPRAISE-2 <sup>11</sup>	<ul style="list-style-type: none"> <li>&gt; No benefit in ischaemic events</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Early increase in major bleeding complications</li> </ul>
Medical thromboprophylaxis	Rivaroxaban	MAGELLAN <sup>12</sup>	<ul style="list-style-type: none"> <li>&gt; Non-inferior to enoxaparin</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Increased clinically relevant bleeding</li> </ul>
	Apixaban	ADOPT <sup>13</sup>	<ul style="list-style-type: none"> <li>&gt; Not superior to shorter course of enoxaparin</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Significantly more major bleeding events</li> </ul>

ACS = acute coronary syndrome; ADOPT = Apixaban Dosing to Optimize Protection from Thrombosis; AF = atrial fibrillation; AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; APPRAISE-2 = Apixaban for Prevention of Acute Ischemic Events – 2; ARISTOTLE = Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; ATLAS ACS 2 TIMI 51 = Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51; GI = gastrointestinal; ICH = intracranial haemorrhage; MAGELLAN = Multicenter, Randomized, Parallel-group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Medically Ill Patients Comparing Rivaroxaban With Enoxaparin; RE-LY = Randomized Evaluation of Long-term Anticoagulation Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SSE = stroke and systemic embolism; VTE = venous thromboembolism.

\*Already on antiplatelet therapy.

†Value for DOA always given first.

**Table 2. Pharmacokinetic properties of the newer direct oral anticoagulants.**

Property	Dabigatran	Rivaroxaban	Apixaban
Dosing frequency	Twice daily	Once daily	Twice daily
Dose (mg)	75*, 110 and 150	15 and 20	2.5 and 5
Food effect	Delays absorption	Delays absorption	None
Bioavailability (%)	6.5	80–100 at 10 mg 66 at 20 mg	50
Renal clearance (%)	85	33	27
Half life (hours)	11–17	5–9 (healthy) 9–13 (elderly)	8–15
Time to maximum effect (hours)	1–3 (6 in post-operative setting)	2–4	2–4
Protein binding (%)	35	90–95	87–93
Cytochrome metabolism (%)	No	30	15
Substrate for P-glycoprotein <sup>†</sup>	As a prodrug	Yes	Yes

\*Only in the US. <sup>†</sup>Major inhibitors of P-glycoprotein are amiodarone, clarithromycin, ciclosporin, diltiazem, erythromycin, indinavir, azoles, quinidine, ritonavir, sirolimus, tacrolimus and verapamil; inducers are rifampin and St John's wort.

### Apixaban

Apixaban is the other anti-Xa inhibitor currently approved in the UK for the management of patients with non-valvular atrial fibrillation (AF). It is an oral drug that is absorbed in the stomach and small intestine with bioavailability of about 50%.<sup>19</sup> Extreme body weights can cause fluctuations in the bioavailability of apixaban, which is metabolised predominantly through the liver and does not accumulate in patients with mild-to-moderate renal impairment. Apixaban is also metabolised through the CYP3A4 pathway and is a P-glycoprotein substrate, so adjustments are required for concomitant drugs metabolised by these enzymes.<sup>20</sup>

As noted in Table 1, the onset of action of all three agents is about 3 hours. In other words, all three act more or less immediately over the same time course as low molecular weight heparins (LMWHs), which is an important consideration, especially in patients receiving anticoagulants for thromboembolism.

### Bleeding in patients receiving direct oral anticoagulants

As the DOAs are drugs with anticoagulant function, they have similar risk factors for bleeding as warfarin. The main differences are in relation to increased bleeding from the gastrointestinal (GI) system and accumulation risk with renal impairment in the case of DOAs. However, DOAs have the benefit of lesser risks of intracranial haemorrhages. Since major morbidity and mortality in patients receiving anticoagulant drugs come from complications of intracranial bleeding, this is indeed a major advantage over warfarin. Probably the biggest disadvantage in this setting is the fact that the anticoagulant actions of DOAs are not easily reversible due to the lack of a specific antidote (although these are in preparation).

A meta-analysis to determine the efficacy and safety of DOAs in patients with AF identified a trend toward reduced major bleeding (relative risk [RR] 0.86), with a significant reduction of intracranial haemorrhage with DOAs compared with warfarin (RR 0.46).<sup>21</sup> In the same population, major GI bleeding was more

common with dabigatran and rivaroxaban than warfarin. In a meta-analysis of patients with venous thromboembolism (VTE) Fox *et al* concluded that rivaroxaban reduced the risk of major bleeding compared with warfarin while the other DOAs did not.<sup>22</sup>

In the case of dabigatran, post-hoc analysis of major bleeding events from the RE-LY trial showed that both doses of dabigatran have lower risks of intracranial and extracranial bleeding than warfarin in patients younger than 75 years.<sup>23</sup> However, in those older than 75 years, the risk of intracranial bleeding is lower but the risk of extracranial bleeding is similar or higher with both doses of dabigatran compared with warfarin. In addition, concomitant use of a single antiplatelet agent increases the risk of major bleeding (hazard ratio [HR] 1.60), with an even higher risk with dual antiplatelet therapy (HR 2.31); the absolute risk is lowest with 110 mg dabigatran.<sup>24</sup>

Although the real-world scenario is often described as different to the trial setting, post-marketing reports of patients taking dabigatran for AF reported similar bleeding rates as in the phase III trial.<sup>25,26</sup> An abstract published at the American Society of Hematology meeting in 2012 detailed a post-hoc analysis of major bleeding events from five phase III trials, with 30-day mortality for dabigatran lower than with warfarin.<sup>27</sup> Interestingly, and very much of practical benefit, most of the patients with major bleeding were treated only with general supportive measures, without the need for specific reversal agents or factor concentrates.

### Gastrointestinal bleeding

The unusual aspect of the site-specific bleeding is that, although DOAs are associated with a reduced risk of intracranial bleeding, at least rivaroxaban and dabigatran (150 mg twice daily) are associated with a 1.5-fold increased risk of GI bleeding compared with warfarin.<sup>23,28</sup> This difference may be due to the relative decreased absorption of DOAs compared with warfarin (95% absorbed) and the local effects on the gut mucosa, whereas GI bleeds with warfarin result only from a systemic anticoagulant effect.<sup>29</sup> In the case of dabigatran, bleeding in the RE-LY study also derived more from the lower GI tract than intracranial

bleeding (53% vs 47%), which contrasts with the bleeding pattern for warfarin and non-steroidal anti-inflammatory drugs (NSAIDs).<sup>30</sup> Although tartaric acid-induced caustic injury has been suggested as a mechanism, aspirin/extended-release dipyridamole (Aggrenox) – another drug with a similar formulation – does not cause any GI bleeds.<sup>29,30</sup> Apixaban is associated with reduced GI bleeding, possibly because more frequent dosing allows reduced anticoagulation peaks.<sup>29</sup> No data are available with regard to *Helicobacter pylori* status and the risk of DOA-related GI bleeding. Taking dabigatran sat upright and with food or water may help to decrease the risk of GI adverse events; whether combining with a proton pump inhibitor is beneficial in this scenario is not known, although antacid intake is not a contraindication for use of dabigatran.<sup>29</sup> The best way to minimise DOA-related GI bleeding probably is prevention:<sup>29,30</sup>

- Concurrent use of anti-platelet agents and NSAIDs increases the risk of major GI bleeding associated with DOA and is best avoided.
- Drug accumulation (in patients with moderate renal impairment) should be avoided.
- A thorough history – including previous GI symptoms, endoscopic evaluations, results of colonic screening, etc – should be taken before DOAs are prescribed.
- Patients should be given advice on lifestyle modification (eg reducing smoking and alcohol consumption), which may cause GI irritation.
- Patients should be informed of the early symptoms and signs of GI bleeding and advised to seek urgent help from healthcare professionals.

In a person who has developed a GI bleed related to a DOA, the drug should be discontinued and a search for the site of bleeding should be initiated (see ‘Management of bleeding’ below). If activated charcoal has been given, endoscopic visualisation may not be ideal and may need to be deferred. Timing of endoscopy in relation to DOA is before the next dose was due to minimise the risk of bleeding. Once the bleed has been dealt with, the dilemma is whether the DOA should be recommenced, with four possible options:<sup>30</sup>

- Recommence full-dose DOA if a GI lesion was identified and has been dealt with fully (eg a polyp).
- Recommence at a lower dose with a reduced risk of GI bleeding (eg 110 mg dabigatran).
- Switch to a DOA with a reduced risk of bleeding (eg apixaban).
- Switch to warfarin (which, at least currently, is easier to reverse than the DOAs).

### Risk of acute coronary events with direct oral anticoagulants

The original RE-LY trial suggested a small increase in the risk of myocardial infarction (MI) with dabigatran,<sup>1</sup> and a meta-analysis confirmed this increased risk (1.19% vs 0.79%),<sup>31</sup> which was also noted in the extended-use study for VTE, in which acute coronary syndromes occurred in 13 patients on dabigatran compared with three on warfarin.<sup>32</sup> This unusual difference has been suggested to be due to better risk reduction with warfarin rather than an increased risk due to dabigatran. When a patient taking dabigatran presents with an acute coronary syndrome, it may be necessary to switch to warfarin or a different DOA.<sup>32</sup> In this context, it may be noted that ‘real-world’ data from

post-marketing surveillance has not demonstrated excess MIs with dabigatran, which is an important finding but deserves explanation (eg whether this is due to selective prescribing).<sup>26</sup>

### Laboratory tests

Although it is widely publicised that these agents require no monitoring, monitoring may be relevant in certain clinical situations:<sup>33</sup>

- in bleeding patients to ensure there is no over-anticoagulation
- to determine the efficacy of reversal agents (antidotes are in the pipeline)
- in patients with thrombosis despite the drug (to identify under-anticoagulation or treatment failure, which may be difficult to ascertain due to the short half-life of the DOAs)
- before invasive procedures with a significant risk of bleeding to ensure the drug has been cleared
- in patients with overdose
- in patients with renal impairment, especially severe, which has developed while taking the drug
- in patients with extremes of body weight
- in children, if it may be used
- to assess compliance in some patient groups (eg patients with memory issues or psychiatric disorders)
- when coadministering drugs known to interact with the DOA in question
- in the future, when individualised tailoring of the treatment may be preferred.

As with warfarin, there is a correlation between the intensity of anticoagulation and bleeding, although significant differences in the amount of thrombin generated by patients can be seen with the same dose of DOA, which means that bleeding may be more likely in high responders and under-anticoagulation is possible in low responders.<sup>34</sup> Laboratory tests in patients taking DOAs require knowledge of the last dose, timing of the last dose, and the half-life and pharmacokinetics of the drug.

The popular clotting screen tests will be affected by ingestion of these drugs. Although the degree to which these tests will be affected by the DOAs depends on the blood concentrations of the drug, the relationship is not linear.<sup>35</sup>

- Among the commonly performed coagulation tests, thrombin time is most sensitive to dabigatran. Normal thrombin time may be used as an indicator to rule out the presence of any dabigatran in plasma. A diluted thrombin time test – Hemoclot Thrombin Inhibitors assay (Hyphen Biomed, France) – can be used to quantify concentrations of dabigatran in plasma.<sup>36</sup>
- In the case of rivaroxaban, prothrombin time (PT) is more sensitive. In most circumstances, a normal PT should exclude therapeutic intensity anticoagulation by rivaroxaban.<sup>37</sup> Although this has been questioned in some patients, a normal PT using Recombiplastin2G on IL-TOP analyser (Instrumentation Laboratory, USA) can exclude rivaroxaban in the plasma.<sup>38</sup> Quantification of rivaroxaban is possible with specific anti-Xa assays based on chromogenic substrates and calibrated with rivaroxaban calibrants.<sup>39</sup>
- Similar to rivaroxaban, PT would be expected to be sensitive to apixaban, although this may not be the case in all situations. Anti-Xa assay specific to apixaban with corresponding calibrators is in preparation but not yet commercially available.



Several laboratory issues need to be borne in mind when it comes to the use of assays in relation to DOAs:<sup>33</sup>

- Each laboratory should be familiar with the sensitivity of their assays and use the appropriate calibrated samples to avoid errors.
- Many routine tests, such as fibrinogen assays and D-dimer, may be affected by these drugs.
- Tests such as those in thrombophilia screening (lupus anticoagulant) can be affected.
- The international normalised ratio (INR) used for warfarin should not be used to monitor DOAs.
- Handheld devices (eg those used for finger-prick INR testing for warfarin) have not been validated for use with the DOAs.<sup>40</sup>

The subcommittee on control of anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis has recently published recommendations on measuring oral direct inhibitors of thrombin and factor Xa.<sup>41</sup>

### Older individuals and direct oral anticoagulants

In general, DOAs are useful drugs for older people at risk of arterial thromboembolism or VTE. At the same time, bleeding risks are also greater in older individuals due to various age-specific factors. First is the issue of polypharmacy. Although the DOAs are known to have fewer drug interactions than warfarin, some common drugs can interact with them and this needs to be borne in mind when prescribing and monitoring DOAs in this group. Although some inducers and inhibitors of P-glycoprotein and cytochrome P450 (CYP3A4) are already recognised to interact with the DOAs, some drugs may not yet have been examined in order to exclude interactions. As there are no easily available monitoring tests like INR, drug level monitoring may be relevant in these cases to ensure that levels of circulating drug are not in excess or inadequate.

The risk of bleeding may be greater with certain DOAs in patients older than 75 years. In a pooled analysis of studies with dabigatran, rates of major bleeding were increased in patients older than 75 years,<sup>23</sup> and in a recent case series of 44 patients with dabigatran-associated bleeding complications, two-thirds of patients were aged  $\geq 80$  years.<sup>42</sup> In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition – Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), older patients in both the rivaroxaban and warfarin groups also had higher rates of clinically relevant bleeding.<sup>2</sup> In both the Apixaban vs Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) and Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation (ARISTOTLE) trials, patients older than 75 years had higher rates of bleeding, although the differences were not significantly greater than with aspirin (2.6 % vs 2.2 %) or warfarin (3.3 vs 5.2%), respectively.<sup>3</sup> In summary, the increase in bleeding risk is similar for most DOAs and warfarin, except for dabigatran, with which the increased risk could be explained by the fact that the dose is not reduced in older populations and it has a higher likelihood of renal excretion. Because of the increased bleeding risk with dabigatran, the lower 110 mg twice-daily dose should be considered in patients older than 75–80 years of age (European licence).<sup>14</sup> The US Food and Drug Administration decided not to provide a licence

for the lower dose on the basis that any increase in bleeding has to outweigh the benefit from risk reduction from stroke and systemic embolism.

Despite the bleeding rates with DOAs, one of their attractive features is the reduced incidence compared with warfarin in all studies of the most feared intracranial bleed, which is probably due to the lack of inhibition of neuroprotective factor VII–tissue factor complexes that occurs with warfarin. Although the rates of GI bleeding are higher (and likely to be even higher in elderly patients due to likely underlying pathologies and increased gut transit time), this may be relatively easier to deal with than intracranial bleeds and so may favour DOAs over warfarin.

The most relevant concern in terms of prescribing DOAs in elderly patients probably relates to renal impairment. In the RE-LY trial, a twofold higher risk of bleeding was noted, even in patients with creatinine clearance (CrCl)  $< 50$  ml/min compared to those with CrCl  $> 80$  ml/min.<sup>1</sup> In the case of rivaroxaban, patients with CrCl 30–49 ml/min were older and had a higher bleeding rate, although the bleeding rate with apixaban was surprisingly less than with warfarin, even in patients with moderate renal impairment (3.2 vs 6.4 %), probably due to apixaban's reduced dependence on renal clearance.

### Renal impairment and direct oral anticoagulants

Patients with *severe* renal failure were excluded from all large clinical trials with DOAs. Elimination studies with dabigatran show an increase in clearance time of 15, 18 and 27 hours in patients with mild, moderate and severe renal impairment, respectively.<sup>43</sup> In relation to rivaroxaban, renal impairment increased plasma levels 1.44-, 1.52- and 1.64-fold in patients with mild, moderate and severe renal impairment, respectively.<sup>44</sup> The lower dose of 15 mg used in patients with creatinine clearance of 30–50 ml/min achieved similar levels as a 20 mg daily dose in patients with normal renal function.<sup>45</sup> Although estimated glomerular filtration rate (eGFR) is the standard method of determining renal function in the UK, the following suggestions for use of DOAs in patients with renal impairment are based on CrCl, as the trials with DOAs used this measure:<sup>46</sup>

- DOAs should not be used in patients with severe renal impairment (CrCl  $< 15$  ml/min) and those on dialysis.
- DOAs may be used in patients with mild to moderate renal impairment but with close monitoring of renal function, ideally every 6 months in patients with mild impairment and every 3 months in those with moderate impairment.
- Care should be taken when prescribing other drugs that may be nephrotoxic in such situations.
- Dabigatran, being predominantly renally cleared, may not be the drug of choice in patients with renal impairment, although the manufacturer has suggested 110 mg twice daily for patients with CrCl of 30–49 ml/min. The FDA suggested 75 mg dabigatran for patients with CrCl of 15–30 ml/min, but this dose is not used in the UK.
- In patients with CrCl of 15–49 ml/min, rivaroxaban should be given at a dose of 15 mg once daily for patients with non-valvular AF; in patients with VTE, the manufacturer recommends avoiding the drug if CrCl is  $< 30$  ml/min.
- In patients with CrCl of 15–29 ml/min, apixaban should be given at a dose of 2.5 mg twice daily.

## Peri-procedural management

Patients who receive one of the DOAs are likely to require a surgical procedure, endoscopic intervention or biopsy for various reasons. This may necessitate interruption of the DOA, a decision that is based mainly on the bleeding risk associated with the procedure and the thrombotic risk of the individual. In other words, if the patient were to require a procedure that is associated with a minor risk of bleeding, only a short period of discontinuation may be necessary and, in some cases, the DOA may be continued (similar to continuing warfarin with INR 2–3). However, if the procedure is associated with a major risk of bleeding, such as a neurosurgical intervention, the DOA has to be discontinued several days before and may even require bridging with an alternate anticoagulant, such as a LMWH. A similar management plan may be required for patients with a high risk of thrombosis, such as a patient who had a pulmonary embolism in the month before the procedure.

In all of these cases, it is important to bear in mind that moderate to severe renal impairment can lead to accumulation of drug in the plasma, which may necessitate measurement of drug levels, although this may be possible only in specialised laboratories. An analysis of the RE-LY trial is useful in this context, as it found no significant difference in the rates of peri-procedural major bleeding among the three treatment arms (3.8%, 5.1% and 4.6% with 110 mg and 150 mg dabigatran and warfarin, respectively) and no increased risk of thrombotic events, although only a few of the procedures were classified as urgent.<sup>47</sup> Fig 1 shows an algorithmic approach to peri-procedural management of patients on DOAs.

Restarting the DOA after the surgery or procedure depends on the risk of bleeding from the intervention and should be delayed until there are no signs of active bleeding and no bloody drainages. If the bleeding risk is minimal, the DOA may be recommenced about 6–8 hours after surgery. A lower dose may be considered if the bleeding risk is moderate (eg 10 mg rivaroxaban).<sup>48</sup> If the bleeding risk is high, the drug may be started 2–3 days after surgery. As these drugs are orally active, the fact that decreased gut transit time can impact on the bioavailability of the DOA needs to be borne in mind. The fast onset of action is a benefit in this context, as bridging with heparins is not necessary.

In the case of emergency surgery, the timing of the last dose of the DOA becomes even more relevant. An interval of two elimination half-lives is desirable but may not always be achievable.<sup>48</sup> A normal thrombin time usually excludes the presence of dabigatran and may be assumed to denote clearance of the drug. In the case of anti-Xa agents, only estimation of plasma levels can exclude clinical effects. Abnormal clotting

tests cannot be used as a guide for the risk of bleeding, as there is no correlation between these tests and clinical effects.

It needs to be stressed here that further prospective studies and observational data from ‘real-world’ clinical practice are necessary before a correct management strategy can be recommended in these scenarios.

## Reversal of direct oral anticoagulants

Currently, no clinically proven specific antidotes against the DOAs are available. If patients present with a bleed while receiving a DOA, several factors should be taken into consideration, including:

- > severity of bleeding
- > indication for anticoagulation
- > dosage and timing of the last dose
- > renal function
- > comorbidities
- > site of bleeding.

A haematologist should be involved in the management of these difficult cases, and, ideally, a hospital policy should be drafted depending on the availability of pro-haemostatic agents such as prothrombin complex concentrate (PCC), dialysis services, interventional radiologists, vascular surgeons, etc. Box 1 gives a suggested pathway depending on the severity of the bleeding.<sup>48</sup>

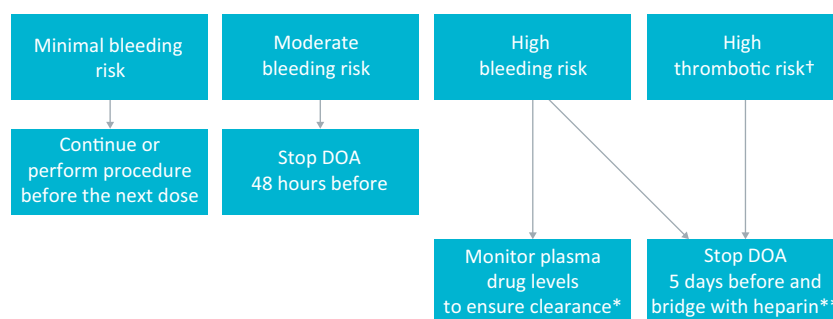
- > For minor bleeding that does not expose the patient to a vital risk, only discontinuation of the drug may be necessary.
- > With moderate to severe bleeding, activated charcoal may be helpful to remove drug that might remain in the gut, especially if it was ingested in the previous 2–3 hours. In the case of dabigatran, which is predominantly cleared renally, haemodialysis may be helpful, as reported in one study, in which 62% of a single dose of dabigatran was removed after 2 hours of dialysis and 68% after 4 hours<sup>49</sup> (see Box 1).

Different local measures can be adopted to stem the bleeding depending on the site. Antifibrinolytic agents such as tranexamic acid may be helpful, although their effectiveness has not been studied. Fresh frozen plasma is unlikely to be of benefit, as the DOAs enzymatically block the coagulation factors; however, red cell transfusions may help to keep the patient haemodynamically stable and maintain oxygenation.

Specific prohaemostatic drugs may be considered in patients who have serious bleeds while taking DOA, including PCC and activated PCC. Prothrombin complex concentrates contain inactive factors II, IX, X and VII, while activated PCC contains small amounts of these factors in active form. Most of the

**Fig 1. Bleeding risk is determined by the surgeon.**

Minimal bleeding risk does not put patient at risk of major morbidity. Moderate bleeding risk does put patient at risk of major morbidity. High bleeding risk does put patient at risk of mortality. Patients with a high thrombotic risk have had a thromboembolic episode in the previous month or have a high CHADS<sub>2</sub>-Vasc score. DOA = direct oral anticoagulant. \*Best strategy. \*\*If determination of plasma levels is not possible. †Some experts would recommend only discontinuation of DOA without bridging with heparin.



studies using these agents have been in animal models or healthy volunteers who have been given dabigatran or rivaroxaban, with the effects of the reversal agents determined using laboratory tests. In a randomised, double-blind, placebo-controlled study, Eerenberg *et al* demonstrated that PCC immediately and completely reverses the anticoagulant effect *in vitro* of rivaroxaban in healthy subjects (using thrombin generation tests) but has no influence on the anticoagulant action of dabigatran.<sup>50</sup> Although not evidence based, activated PCC or recombinant factor VIIa have been suggested to be useful. Recently, the British Committee for Standards in Haematology has published recommendations on the management of bleeding in patients on antithrombotic agents, including DOAs.<sup>51</sup>

### Which one should I prescribe – warfarin, dabigatran, rivaroxaban or apixaban?

DOAs may be preferred over warfarin in most cases (except valvular heart disease currently) once decision is made to commence an anticoagulant after taking into consideration the thrombotic and bleeding risks of individual patients. A systematic review of the six trials in patients with AF found lower risks of fatal bleeding and major bleeding with DOAs compared with warfarin (risk ratio (RR) 0.60 and 0.80, respectively) but higher risks of GI bleeding (RR 1.30) and discontinuation due to adverse events (RR 1.23).<sup>52</sup> In this context, it does need to be stressed that the higher discontinuation rates compared with warfarin were driven primarily by the studies relating to dabigatran and could be matched with patient intolerance from GI symptoms seen with this agent. A subgroup analysis of this study showed that fatal bleeding was significantly lower with anti-Xa drugs but not dabigatran. Another systematic review of the comparative effectiveness of DOAs and standard thromboprophylaxis with LMWHs showed that factor Xa inhibitors reduced the risk of symptomatic deep venous thrombosis (DVT) (four fewer episodes per 1,000 patients) but not the risks of mortality or non-fatal pulmonary embolism and that the risk of major bleeding increased (two more cases per 1,000 patients), while the outcomes with dabigatran were similar to those with LMWHs.<sup>53</sup> Indirect evaluation of these three agents by common comparison with LMWHs showed non-significantly reduced risks for VTE with rivaroxaban compared with dabigatran (RR 0.68) and apixaban (RR 0.59) but an increased risk of major bleeding.

Managing warfarin appropriately with good INR control is equally effective as the DOAs for patients with AF. The average individual time in therapeutic range (TTR) and the risks of stroke or major bleeding are inversely correlated – in other words, patients with high average individual TTR (>70%) will have a low risk of stroke and major bleeding.<sup>54</sup> There therefore may be more onus on anticoagulation clinics to achieve this high TTR for their patients. However, in patients who may not be able to achieve this high TTR, DOAs may be a better choice and have clearly been shown to be superior in the large trials. As yet, it is unclear whether the higher TTR translates to equally good outcomes only in patients who require anticoagulation for AF or also for those with VTE.

One of the often-quoted inconveniences of warfarin is the frequency of INR monitoring. However, Schulman *et al* have shown that INR monitoring every 4 weeks is as safe as every 12 weeks and that the percentage TTR does not differ much (74.1% with 4-weekly

### Box 1. Management of patients who present with severe or life-threatening bleeding on DOAs.

- > Ensure patient is haemodynamically stable
- > Transfuse red cells as necessary
- > Reduce drug exposure
  - Discontinue drug (delay next dose)
  - Stop any antiplatelet agents and other drugs that may cause bleeding (NSAIDs)
  - Activated charcoal orally if last dose of DOA less than 2–3 hours
  - Haemodialysis (only for dabigatran)
- > Local measures
  - Mechanical compression of the bleeding vessels
  - Injection of adrenalin, topical thrombin or fibrin glue
  - Endoscopy for gastrointestinal bleeding
  - Embolisation or coiling
  - Surgical intervention to stop bleeding
- > Antifibrinolytic agents
- > Prohaemostatic agents
  - PCC, activated PCC or recombinant factor VIIa

DOA = direct oral anticoagulant; NSAIDs = non-steroidal anti-inflammatory drugs; PCC = prothrombin complex concentrate.

monitoring vs 71.6 % for 12-weekly monitoring).<sup>55</sup> This suggests that patients with well-controlled INR do not require frequent monitoring, although compliance and various other factors that can affect INR should be taken into consideration in this regard.

When adjusted-dose warfarin is not suitable, one of the DOAs may be considered. Some situations when this may be relevant include:

- > patients with lifestyle issues for which INR monitoring may not be practical (work, distance, etc)
- > patients with side effects from warfarin (hair loss and skin rashes)
- > patients with wide fluctuations in INR (probably due to genetic polymorphisms well known to affect warfarin metabolism)
- > patients identified to have consistently poor TTR not due to compliance issues
- > patients taking other drugs that require frequent dose changes or that are used for short courses, such as antibiotics (eg patients with recurrent infections).

Any of the DOAs can be considered in these situations in patients with AF (only rivaroxaban is currently licensed in the UK for the treatment of VTE), except in the specific clinical scenarios detailed below:

- > A dose of 150 mg dabigatran twice daily may be considered, except in:<sup>56</sup>
  - elderly patients (older than 80 years)
  - patients receiving concomitant interacting drugs that may potentiate dabigatran's effects
  - patients with a high bleeding risk (HAS-BLED score >3)
  - patients in whom the bleeding risk is probably higher than the thrombotic risk
  - patients with moderate renal impairment (CrCl 30–49 ml/min), in whom 110 mg dabigatran daily may be prescribed.

- > A dose of 20 mg rivaroxaban daily should be considered unless a patient has a HAS-BLED score >3 or moderate renal impairment, when 15 mg once daily may be prescribed.<sup>56</sup>
- > The lower dose of 2.5 mg apixaban twice daily is given in patients with at least two of the following:
  - age ≥80 years
  - body weight ≤60 kg
  - serum creatinine ≥1.5 mg/dl.

Table 3 gives a snapshot guide to the choice of anticoagulant for different situations based on the above and results from trials.

The following plan may be followed when switching between anticoagulants:

- > To DOA from:
  - warfarin – when INR <2.0 or <3.0 for rivaroxaban
  - unfractionated heparin (UFH) – when it is discontinued, unless coexisting renal impairment (normal activated partial thromboplastin time (aPTT) may help the decision)
  - LMWH – just before the next dose is due
- > From DOA to:
  - warfarin – prescribe concomitantly until INR is in the appropriate range

**Table 3. Choosing between different direct oral anticoagulants and warfarin.**

Consideration	Recommendation	Comment/reason
Valvular heart disease	> Warfarin	<ul style="list-style-type: none"> <li>&gt; Dabigatran withdrawn following study in patients with mechanical heart valves</li> <li>&gt; No data on other DOAs</li> </ul>
Severe hepatic impairment with associated coagulopathy	> Warfarin or LMWH	> Close monitoring
Extremes of weight	> Warfarin or LMWH	> Close monitoring
Renal impairment		
CrCl >15 but <30 ml/min	> Rivaroxaban 15 mg or apixaban 2.5 mg	
CrCl <15 ml/min	> Warfarin	> All DOAs contraindicated
History of MI	> Apixaban, rivaroxaban or warfarin	> No increase in MI in trials with apixaban or rivaroxaban
Recent ischaemic stroke on warfarin	> Dabigatran 150 mg twice daily	> Dabigatran superior to other DOAs and warfarin but no specific studies conducted to address this endpoint
Medical thromboprophylaxis	> LMWH	> No benefits yet shown for DOA
Malignancy	> LMWH	<ul style="list-style-type: none"> <li>&gt; LMWH shown to be better than warfarin</li> <li>&gt; No studies yet with DOAs</li> </ul>
Antiphospholipid syndrome	> Warfarin or LMWH	<ul style="list-style-type: none"> <li>&gt; Likely that patients with antiphospholipid syndrome were included in DOA trials but clinico-laboratory lupus status was not documented</li> <li>&gt; Prospective studies underway</li> </ul>
Treatment of symptomatic DVT or PE	> Rivaroxaban*	
History of GI bleed	> Apixaban or warfarin	
Needs triple therapy (with concomitant antiplatelet agents)	> ? warfarin	
Poor compliance	> Warfarin or nothing	
Poor compliance with twice-daily dosing	> Rivaroxaban	
Patients stable on warfarin	> Continue warfarin or switch to DOA on patient preference	
Patients who require higher level of anticoagulation (eg INR 3.5)	> Warfarin	
Pregnancy	> No DOA is licensed in pregnancy	

CrCl = creatinine clearance; DOA = direct oral anticoagulant; DVT = deep vein thrombosis; GI = gastrointestinal; INR = international normalised ratio; LMWH = low molecular weight heparin; MI = myocardial infarction; PE = pulmonary embolism; VTE = venous thromboembolism.

\*Only DOA currently licensed in UK for treatment of VTE. Dabigatran, although effective, has the inconvenience of need for initial period of LMWH injections in patients who is treated for an acute venous thromboembolic episode. In the table, where warfarin or LMWH is indicated as preferred, it is, in most cases, because no clear data are yet available for the DOAs or studies have yet not been conducted in these settings to demonstrate benefits or lack of benefits.



- UFH or LMWH – just before the next dose is due
- another DOA – just before the next dose is due.

In all cases except warfarin, if the renal function is abnormal, special care needs to be taken, as heparins and DOAs can accumulate to varying degrees.

## Adherence

There is general argument that drug adherence is likely to be excellent in the setting of clinical trials because of surveillance, frequent follow up and the inclusion of motivated patients. When real-world adherence was examined in a recent study of patients taking dabigatran, 88% of patients were identified to have adequate adherence. Interestingly, although the prevalence of dyspepsia was high (33%), 91% of affected patients continued taking the medication.<sup>57</sup> However, 11 patients had <80% adherence and ≥30% acknowledged that they had sometimes missed taking the medication. This is worrying, as missing doses on a frequent basis can remove the anticoagulant effect from DOAs much more quickly than for warfarin. Whether this will translate to increased thrombotic events has not yet been studied.

Patient education about strict adherence is paramount. Leaflets and group education sessions may be useful, and digital long-distance monitoring tools may be developed. Family member awareness can also help with good compliance. In patients who prefer once-daily dosing, the DOA of choice is obviously rivaroxaban, but, at the same time, studies in patients taking other drugs in the long term have shown that patients missing doses in a twice-daily regimen is less harmful.<sup>58</sup>

## Who should start and monitor direct oral anticoagulants?

In recent years, there has been a tendency to shift the identification and management of patients with AF to primary care. Early attempts to allow GPs to diagnose VTE (at least DVT) and initiate treatment in straightforward cases have started in at least some parts of the UK. This would mean that primary care may lead the way in prescribing the DOAs much more than secondary care. This leads to the question of who should prescribe and continue to monitor the DOAs: primary care health care personnel, cardiologists, haematologists or anticoagulation clinics? Although no recommendations can be made, any prescriber who initiate DOAs (or any anticoagulant) should ideally:

- > obtain informed consent from patients who have been told about the benefits and risks of any anticoagulants (the National Patient Safety Alliance has provided booklets for use with warfarin, which may be adapted by each hospital for this purpose)
- > make special mention of the importance of compliance and current lack of antidote in the case of DOAs
- > give and advise patients to carry an alert card with details of the drug and contact details for themselves and other healthcare professionals who may need urgent advice in case of an emergency (the European Heart and Rhythm Association has suggested a very useful card, which can be downloaded in digital form from [www.NOACforAF.eu](http://www.NOACforAF.eu)).

Box 2 gives a checklist for before starting and when monitoring the DOAs.

## Box 2. Checklist before starting DOA.

- > Does the patient need an anticoagulant?
  - In patients with AF, use CHADS<sub>2</sub>/VASC score
  - In patients with VTE, discuss whether continuation of anticoagulation is necessary
- > Is the indication for anticoagulation valvular heart disease?
  - DOAs are not suitable
- > Is patient likely to comply and take medications in a timely manner?
  - if not, DOAs may be less preferable to warfarin
- > Assess renal function
  - In severe renal impairment, DOAs are unsuitable; special caution is recommended in patients with moderate renal impairment, which may worsen with dehydration or medical illnesses
- > Assess liver function
  - Severe hepatic impairment with associated coagulopathy was an exclusion criteria for using DOAs
- > Is the patient on drugs that may interact with DOAs?
  - Warn the patients that some drugs may interact with DOAs if they were to start them
- > If patients are on antiplatelet agents, do they need to continue them?
  - Increased risk of bleeding
- > Are they on or may they need NSAIDs or herbal medications?
  - Increased risk of bleeding
- > Do the patients have upper GI symptoms?
  - Dabigatran may be avoided in these cases
- > Do the patients have current or previous history of GI bleed?
  - Dabigatran and rivaroxaban may need to be avoided
- > Is the clotting screen completely normal?
  - Coagulopathy may be undiscovered
- > Has the HAS-BLED score been checked?

## Monitoring

After initiation, monitor at least once in 3 months and thereafter yearly, if none of the below is a problem:

- > Compliance
- > Has not started new drugs that may interact with DOAs
- > Renal function is normal and unlikely to deteriorate in the following months
- > Platelet count and liver function tests are normal
- > No new GI symptoms

AF = atrial fibrillation; DOA = direct oral anticoagulant; GI = gastrointestinal; NSAIDs = non-steroidal anti-inflammatory drugs; VTE = venous thromboembolism.

## Conclusion

In summary, a new era has begun in the field of anticoagulation. The arrival of the DOAs has brought us the convenience of dealing with many disadvantages associated with warfarin; however, they are not a panacea for all patients who require anticoagulation at the moment. Lessons need to be learnt from real-world cases, so it is important that any adverse event is reported to ensure that these drugs are given to the right patients. The DOAs should be the primary targets for grand rounds or similar educational events in various settings, as they may very often

be encountered by junior doctors and nursing staff who need to be as familiar with these agents as they are with warfarin. Most importantly, in addition to providing information to healthcare professionals, patient education is paramount. Hopefully, in the near future, the DOAs will help us manage anticoagulation with ease. ■

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