Drug therapy in anticoagulation: which drug for which patient?

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ABSTRACT

Four non-vitamin K oral anticoagulants (NOACs) are now licensed and available in the UK, offering unprecedented choices in anticoagulant therapy for clinicians and patients. NOACs have many clear benefits over warfarin, the most striking being the reduction in intracranial haemorrhage. However, a number of uncertainties remain: their efficacy in certain situations, utility of drug assays, significance of drug interactions and management of bleeding. In the absence of any direct comparative trials, it is not clear that any of the NOACs is significantly better than the others in any of the licensed indications. The differential activities, pharmacokinetics, metabolism, excretion and side effects of the agents should be considered when selecting the most appropriate anticoagulant. In this article, we discuss how, with careful selection for the relevant indication, NOACs can simplify therapy while improving outcomes. We aim to provide clinicians with the information needed to select the most suitable anticoagulant drug for an individual patient in a given situation.

KEYWORDS: Anticoagulant therapy, non-vitamin K oral anticoagulants, NOACs

Introduction

The non-vitamin K oral anticoagulants (NOACs)[1] are now established in UK practice and new members continue to arrive. Within their licensed indications they have clear benefits over warfarin, but a number of uncertainties remain: efficacy in some specific situations, the utility of drug assays, significance of drug interactions and the management of bleeding all suffer from a paucity of data.

This article provides an update on developments since the 2014 review in this journal.[2] Our aim is to provide the information needed to select the most suitable anticoagulant drug for an individual patient in a given situation.

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Properties of NOACs

Four NOACs are now licensed and available in the UK: the direct factor Xa (FXa) inhibitors apixaban, edoxaban and rivaroxaban, and the direct thrombin inhibitor dabigatran. The key to best choice of agent lies in their individual pharmacokinetic profiles, metabolism and routes of excretion. These properties, together with National Institute for Health and Care Excellence (NICE) approved indications, are summarised in Table 1.

Therapeutic indications for NOACs

Atrial fibrillation

Summary of phase III NOAC clinical trials in non-valvular atrial fibrillation

The phase III clinical trials comparing NOACs with warfarin for stroke prevention in non-valvular atrial fibrillation (AF) are summarised in Table 2.[3–6] All NOACs showed non-inferior or increased efficacy for the primary endpoint of stroke or systemic embolism (SSE) with similar or lower major bleeding risk when compared with warfarin. However, efficacy was driven primarily by a reduction in haemorrhagic stroke, while non-inferiority was reached for the reduction in ischaemic stroke. The exception was for the higher dose of dabigatran, which showed superior reduction in ischaemic stroke in all but the best controlled warfarin patients.[7] Although this was not associated with an increase in major or minor bleeding overall, along with rivaroxaban and high-dose edoxaban there was a significant increase in gastrointestinal bleeding.[3] The rate of ischaemic stroke did not differ significantly between high-dose edoxaban and warfarin, but was higher with low-dose edoxaban, which has consequently not been licensed.[6] Apixaban was the only NOAC to show a significant reduction in both SSE and major bleeding compared with warfarin.[5] These findings were shown to be independent of the quality of international normalised ratio (INR) control in patients receiving warfarin.[8]

Patients with valvular heart disease

Patients with AF and mechanical prosthetic heart valves or moderate to severe mitral stenosis were excluded from all of the AF trials (Table 2). However, they did include some patients with tissue valve replacements, previous valve repair or other valve disease. These constituted more than

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Table 1. Properties and licensed indications of NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	**Direct thrombin inhibitor**	**Factor Xa inhibitor**	**Factor Xa inhibitor**	**Factor Xa inhibitor**
T_{max}	2 hours	2–4 hours	1–4 hours	1–2 hours
Elimination half-life	12–17 hours	5–9 hours (young) 11–13 hours (elderly)	12 hours	10–14 hours
P-gp re-secretion	Yes	Yes	Yes	Yes
CYP3A4 metabolised	No	Yes	Yes	Minimal
Renal excretion	Up to 80%	66%	25%	35%
Plasma protein binding	35%	>90%	>90%	>90%
Intake with food required	No	Mandatory	No	No
Hepatic impairment	Not recommended in patients with elevated liver enzymes (>2×ULN)	Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients classified as Child-Pugh B and C.	Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk; not recommended severe hepatic impairment (Child-Pugh C); use with caution in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment or in patients with elevated liver enzymes (>2×ULN)	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk; not recommended In patients with severe hepatic impairment; use with caution in patients with mild to moderate hepatic impairment and patients with elevated liver enzymes (>2×ULN)
Antidote available	Yes	No	No	No
NICE approved indications and doses				
NVAF	150 mg bd, 110 mg bd[1]	20 mg od[2]	5 mg bd[3]	60 mg od[3]
VTE treatment and secondary prevention	150 mg bd (following ≥5d LMWH)	15 mg bd (initial 21 days), 20 mg od after 21 days	10 mg bd (initial 7 days), 5 mg bd (up to 6 months); 2.5 mg bd after 6 months)	60 mg od (following ≥5 days LMWH)
Prevention of VTE after elective hip or knee replacement	150 mg od	10 mg od	2.5 mg bd	Not licensed
ACS	Not licensed	2.5 mg od	Not licensed	Not licensed

[1]Dabigatran 110 mg bd dose in NVAF where ≥80 years; consider where CrCl 30–49 mL/min
[2]Dose reduction rivaroxaban in NVAF: 15 mg od where CrCl 30-49 mL/min
[3]Dose reduction apixaban in NVAF: 2.5 mg bd where CrCl 15–29 mL/min or where two of serum creatinine ≥1.5 mg/dL, age ≥80 years, body weight ≤60kg
[4]Dose reduction edoxaban in NVAF and VTE: 30 mg od where one of CrCl 15–49 mL/min, body weight ≤60kg, concomitant use of cyclosporin, dronedarone, erythromycin or ketoconazole
ACS = acute coronary syndrome; bd = twice per day; CrCl = creatinine clearance; LMWH = low molecular weight heparin; NICE = National Institute for Health and Care Excellence; NOAC = non-vitamin K oral anticoagulant; NVAF = non-valvular atrial fibrillation; od = once daily; P-gp = P glycoprotein; T_{max} = time to peak level post ingestion; ULN = upper limit of normal; VTE = venous thromboembolism

25% of the study population in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial; the efficacy and safety benefits of apixaban were preserved in these patients despite the greater risk of thromboembolic disease and bleeding associated with both apixaban and warfarin.[9]

Similar findings were obtained with dabigatran[10] and with rivaroxaban although bleeding was higher in the rivaroxaban arm.[11] In conclusion, NOACs are a reasonable choice of anticoagulant in patients with AF with some forms of valvular disease taking into account the individual drug properties. [12]

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Table 2. Non-valvular atrial fibrillation: comparison of NOAC phase III trials

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE-AF
Comparison	Dabigatran 150 mg bd, 110 mg bd vs warfarin	Rivaroxaban 20 mg od vs warfarin	Apixaban 5 mg bd vs warfarin	Edoxban 60 mg od, 30 mg od vs warfarin
Patients, n	18,113	14,264	18,201	21,105
Study design	Double blind, open-label with blinded endpoint evaluation	Double blind, double dummy	Double blind, double dummy	Double blind, double dummy
Reduced dose for selected patients	–	15 mg od: CrCl 30–49 mL/min	2.5 mg bd where two of: > serum creatinine ≥1.5 mg/dL > age ≥80 years > body weight ≤60 kg	Dose halved (30 mg, 15 mg) where one of: > CrCl 30–50 mL/min, > body weight ≤60 kg > concomitant verapamil, quinidine or dronedarone
Mean patient age, years	71	73	70 (median)	72
Mean $CHADS_2$ score	2.1	3.5	2.1	2.8
Mean time in therapeutic range, %	64.0	55.0	62.2	64.9
Valve exclusion	Severe valve disorder	Significant MS; any prosthesis	Moderate/Severe MS; mechanical	Moderate/Severe MS; mechanical
Paroxysmal AF, %	32	18	15	25
Primary endpoint SSE HR (95% CI)*	150 mg: 0.65 (0.52– 0.81)[S] 110 mg: 0.90 (0.74–1.10)	0.88 (0.75–1.03)	0.79 (0.66–0.95)[S]	60 mg: 0.79 (0.63–0.99) 30 mg: 1.07 (0.87–1.31)
Ischaemic stroke HR (95% CI)*	150 mg: 0.76 (0.60– 0.98)[S] 110 mg: 1.11 (0.89–1.40)	0.94 (0.75–1.17)	0.92 (0.74–1.13)	60 mg: 1.00 (0.83–1.19) 30 mg: 1.41 (1.19–1.67)
Major bleeding HR (95% CI)*	150 mg: 0.93 (0.81–1.07) 110 mg: 0.80 (0.70–0.93)[S]	1.04 (0.90–1.20)	0.69 (0.60–0.80)[S]	60 mg: 0.80 (0.71–0.91) 30 mg: 0.47 (0.41–0.55)
Major gastrointestinal bleeding HR (95% CI)*	150 mg: 1.48 (1.18–1.85) 110 mg: 1.08 (0.85-1.38)	1.61 (1.30–1.99)	0.89 (0.70–1.15)	60 mg: 1.23 (1.02–1.50) 30 mg: 0.67 (0.53–0.83)[S]
Intracranial bleeding HR (95% CI)*	150 mg: 0.40 (0.27–0.60)[S] 110 mg: 0.31 (0.20–0.47)[S]	0.67 (0.47–0.93)[S]	0.42 (0.30–0.58)[S]	60 mg: 0.47 (0.34–0.63)[S] 30 mg: 0.30 (0.21–0.43)[S]
Reduction in all-cause mortality	150 mg: 0.88 (0.77–1.00) 110 mg: 0.91 (0.80–1.03)	0.85 (0.70–1.02)	0.89 (0.80–0.99)	60 mg: No 30 mg: Yes

All comparisons versus warfarin and reached non-inferiority, unless otherwise stated.
*Data for dabigatran are presented as relative risk (95% CI)
[S]Superior
AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension history, age≥75 years, diabetes mellitus history, stroke or symptoms of transient ischaemic attack; CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; MS = mitral stenosis; NOAC = non-vitamin K oral anticoagulant; SSE = stroke or systemic embolism

In contrast, a trial comparing dabigatran to warfarin in patients following mechanical aortic or mitral valve replacement was terminated prematurely because of an excess risk of thromboembolic and bleeding complications in the dabigatran patients.[13] Warfarin remains the anticoagulant of choice in patients with mechanical heart valves.

Patients undergoing cardioversion

The use of NOAC or warfarin was not associated with any difference in ischaemic or bleeding events in the AF trial participants undergoing cardioversion.[14–16] This was reproduced in a prospective study of cardioversion comparing rivaroxaban with warfarin.[17] Trans-oesophageal echocardiography was performed according to standard protocols[18] and patients with left atrial thrombus were excluded.[17]

Criticisms of the AF trials

The manufacturers of dabigatran were criticised for withholding RE-LY (Randomized Evaluation of Long-term anticoagulant therapy) analyses that suggested that a major bleeding risk might be significantly reduced (with minimal effect on risk of ischaemic stroke) if dabigatran plasma levels were monitored and the dose adjusted accordingly.[19] The lower bioavailability of dabigatran and its administration as a pro-drug to facilitate absorption may account for the greater variability in plasma levels observed between patients taking dabigatran compared with the other NOACs.[20] Concerns regarding the validity of 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) data have recently been raised

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following recognition that the device used to monitor INR and administer warfarin dosage was faulty; in some cases it led to inflated doses of warfarin with consequent increased bleeding rates.[21,22] Subsequent investigations by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have determined the effects on stroke and bleeding risk to be minimal and insufficient to alter the trial findings.

Interpretation of trial findings

The AF studies differed somewhat in design, risk profile of participants and in outcome definitions, but results were broadly similar (Table 2). Nonetheless, in the absence of direct comparative head-to-head trials these differences may be significant. For example, both ARISTOTLE and RE-LY recruited fewer patients with heart failure or hypertension than ROCKET-AF and ENGAGE-AF (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48): consequently, in ROCKET-AF over 85% of patients had a $CHADS_2$ (congestive heart failure, hypertension history, age ≥75 years, diabetes mellitus history, stroke or symptoms of transient ischaemic attack) score ≥3 compared with 53% in ENGAGE-AF and 32% in RE-LY, while no ROCKET-AF patients had scores 0–1 compared with 32% in RE-LY.

Indirect comparative analyses have shown no significant difference in ischaemic stroke rates between NOACs, with the exception of the higher rate seen with edoxaban 30 mg.[23,24] Major bleeding was shown on indirect analyses to be significantly lower in apixaban when compared with dabigatran 150 mg (reduced by 26%), rivaroxaban (by 34%) and edoxaban 60 mg (by 21%).[23,24] Indirect comparison between apixaban and dabigatran 110 mg found no difference in major bleeding risk, while bleeding is higher in apixaban when compared with edoxaban 30 mg.[23,24]

While European guidance advocates a preference for NOACs over warfarin for stroke prevention in patients with non-valvular AF,[25] NICE guidance in the UK recommends that the decision between NOAC and warfarin be based on the patient's clinical features and preferences following discussion of the options.[26] This discussion will include how the individual characteristics of the patient match those of the individual anticoagulant.

Acute coronary syndrome

In patients with acute coronary syndrome (ACS), apixaban and dabigatran in addition to antiplatelet therapy resulted in unfavourable efficacy and safety profiles.[27,28] A lower dose of rivaroxaban (2.5 mg twice per day) in combination with dual antiplatelet therapy significantly improved ischaemic outcome in ACS, including rates of stent thrombosis,[29] albeit with an associated increase in bleeding;[30] this indication for rivaroxaban is licensed and approved in the UK.

Venous thromboembolism

Initial venous thromboembolism treatment

Phase III randomised controlled trials showed the non-inferiority of NOACs to low molecular weight heparin (LMWH) plus warfarin (or equivalent vitamin K antagonist) in preventing recurrent symptomatic venous thromboembolism (VTE) or death from VTE (Table 3).[31–35] As with the AF trials, there was an overall reduction in major, fatal and intracranial bleeding.[31–36] Unlike the AF trials, the risk of gastrointestinal bleeding did not appear to be increased when compared with warfarin, possibly reflecting less comorbidity in the younger population in these trials.

A key practical difference between NOACs is that dabigatran and edoxaban were both given after 5 days of conventional LMWH therapy, whereas apixaban and rivaroxaban were given as single agents throughout with higher doses given for the initial 7 and 21 days, respectively (Table 3).[31–35]

Again, there were differences in trial duration, outcome definition, blinding status and patient characteristics: for example the apixaban cohort in the AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) trial were older and included lower numbers of cancer patients (Table 3). Around 90% of patients in AMPLIFY had unprovoked VTE; this was lower for EINSTEIN and Hokusai-VTE, suggesting some variation in baseline VTE risk (Table 3). Nonetheless, all four NOACs are licensed and approved for the acute treatment of VTE (Table 3).

Prevention of recurrent VTE

The extension trials of apixaban, rivaroxaban and dabigatran for secondary prevention of VTE, following an initial anticoagulation period of 6 months after a first VTE episode, were all carried out against placebo in patients where the indication for long-term anticoagulation was uncertain (Table 4).[32,33,37,38] Dabigatran is the only agent to be also trialled against warfarin for patients definitely requiring anticoagulation (RE-MEDY, Table 4).[38]

Compared with placebo, all four significantly reduced VTE recurrence without excessive bleeding rates. In the AMPLIFY-EXT (Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment) study, the bleeding rate with 2.5 mg apixaban twice per day was not significantly different from placebo. It is likely that the low bleeding rates with these agents will reduce the threshold at which patients at risk of recurrent VTE will benefit from long-term anticoagulation.

In the RE-MEDY trial, dabigatran 150 mg twice per day was shown to be non-inferior to warfarin in preventing fatal or recurrent VTE in patients requiring long-term anticoagulation, with an associated reduction in significant bleeding.[38] There have been no studies of dabigatran 110 mg twice per day in the treatment or secondary prevention of VTE.

As yet, data are not available for patients with recurrent VTE, cerebral venous sinus thrombosis, portal vein thrombosis or other unusual sites and NOACs are not licensed for these indications. Moreover, there are no data to indicate whether NOAC dosing can be increased to match a target INR of >2.5.

Cancer

Cancer is associated with a high risk of VTE recurrence and recommended treatment is with LMWH, based largely on the results of the CLOT (Comparison of Low Molecular Weight Heparin Versus Oral Anticoagulant Therapy for

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Table 3. Venous thromboembolism initial treatment: comparison of NOAC phase III trials

	RE-COVER I RE-COVER II	EINSTEIN-DVT EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Comparison	Dabigatran 150 mg bd vs LMWH/ warfarin	Rivaroxaban 15 mg bd 21 days, then 20 mg od vs LMWH/warfarin or VKA	Apixaban 10 mg bd 7 days, then 5 mg bd vs LMWH/ warfarin	Edoxaban 60 mg od 30 mg od[1] vs LMWH/warfarin
Patients, n	RE-COVER I: 2,564 RE-COVER II: 2,568	EINSTEIN-DVT: 3,449 EINSTEIN-PE: 4,832	5,400	8,292
Study design	Double blind, double dummy	Open-label	Double blind,	Double blind, double dummy
Patient age, years	55.0 (median) 54.7	55.8 (mean) 57.9	57.2	55.8 (mean)
Unprovoked VTE, %	NS	60.9 64.7	89.8	65.9
Cancer, %	4.8	7.0	2.5	9.2
Heparin lead-in	At least 5 days	None	None	At least 5 days
Treatment duration	6 months	Pre-specified 3, 6, or 12 months	6 months	Flexible 3–12 months
Recurrent VTE or VTE-related death HR (95% CI)*	1.10 (0.65–1.84) 1.08 (0.64–1.80)	0.68 (0.44–1.04) 1.12 (0.75–1.68)	0.84 (0.60–1.18)	0.89 (0.70–1.13)
Major bleeding HR (95% CI)*	0.82 (0.45–1.48) 0.69 (0.36–1.32)	0.65 (0.33–1.30) 0.49 (0.31–0.79)	0.31 (0.17–0.55)	0.84 (0.59–1.21)
Major or clinically relevant non-major bleeding HR (95% CI)*	0.63 (0.51–0.77) 0.62 (0.45–0.84)	0.97 (0.76–1.22) 0.90 (0.76–1.07)	0.44 (0.36–0.55)	0.81 (0.71–0.94)
Intracranial bleeding, % (warfarin/VKA)	0.1 (0.2)	NS	0.1 (0.2)	0.1 (0.4)
Gastrointestinal bleeding, % (warfarin/VKA)	4.0 (2.8)	NS	0.3 (0.7)	NS

All comparisons versus LMWH/warfarin or vitamin K antagonist.
*Data for apixaban are presented as relative risk (95% CI)
[1]Dose of 30 mg od in patients with one of CrCl 15–50 mL/min, weight ≤60kg or concomitant treatment with potent P-glycoprotein inhibitors.
bd = twice per day; HR = hazard ratio; LMWH = low molecular weight heparin; NOAC = non-vitamin K oral anticoagulant; NS = not stated; od = once daily; VKA = vitamin K antagonist; VTE = venous thromboembolism

Table 4. Prevention of recurrent venous thromboembolism: comparison of NOAC phase III trials

	RE-SONATE	RE-MEDY	EINSTEIN-EXT	AMPLIFY-EXT
Comparison	Dabigatran 150 mg bd vs placebo	Dabigatran 150 mg bd vs warfarin	Rivaroxaban 20 mg od vs placebo	Apixaban 2.5 mg or 5mg bd vs placebo
Patients, n	1,343	2,856	1,196	2,482
Treatment duration before randomisation	6–18 months of VKA or dabigatran	3–12 months of VKA or dabigatran	6 or 12 months of VKA or rivaroxaban	6–12 months of standard therapy or apixaban
Treatment length, months	6	6–36	6 or 12	12
Recurrent VTE HR (95% CI)*	0.08 (0.02–0.25)[1]	1.44 (0.78–2.64)[2]	0.18 (0.09–0.39)	2.5 mg: 0.33(0.22–0.48)[3] 5 mg: 0.36 (0.25–0.53)[3]
Major bleeding HR (95% CI)*	NE	0.52 (0.27–1.02)	NE	2.5 mg: 0.49 (0.09–2.64) 5 mg: 0.25 (0.03–2.24)
Major or clinically relevant non-major bleeding HR (95% CI)*	2.92 (1.52–5.60)	0.54 (0.41–0.71)	5.19 (2.30–11.70)	2.5 mg: 1.20 (0.69–2.10) 5 mg: 1.62 (0.96–2.73)

Primary efficacy endpoint included [1]fatal VTE or unexplained death, [2]fatal VTE, [3]death from any cause
*Data for Apixaban is presented as Relative risk (95% C.I.)
bd = twice per day; CI = confidence interval; HR = hazard ratio; NE = not evaluable given zero major bleeds on placebo; od = once daily VKA = vitamin K antagonist; VTE = venous thromboembolism

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Long Term Anticoagulation in Cancer Patients With Venous Thromboembolism) trial.[39] A small number of patients with cancer were included in the VTE phase III trials (2–9%, Table 3), and pooled data suggest a significantly lower VTE recurrence in cancer patients receiving NOACs compared with warfarin.[36] However, this should not be extrapolated to all cancer patients because of inter-trial variation in cancer definition and exclusion of cancer patients deemed to require LMWH. Moreover, the potential for unreliable absorption and gastrointestinal toxicity of NOACs as well as drug interactions means that LMWH remains the treatment of choice in cancer-associated VTE.

Antiphospholipid syndrome

Around 10% of venous thromboembolic events occur in the context of the antiphospholipid syndrome (APS);[40] this patient subgroup was not specifically addressed in the VTE treatment trials and would not have entered the placebo controlled extension studies. A randomised clinical study comparing rivaroxaban and warfarin in over 100 APS patients with previous VTE showed the endogenous thrombin potential to be increased but the peak thrombin to be reduced in the rivaroxaban arm after 42 days of treatment.[41] The clinical significance of these results is not yet known. No data are available on NOACs in APS patients with arterial thrombosis; warfarin remains the anticoagulant of choice for both venous and arterial thrombosis in the APS setting.

NOACs and comorbidities

Age

Thrombotic and bleeding risks both increase significantly with age but there is a differential interaction with NOACs.[42,43] Investigations by the FDA and EMA have concluded that reported post-marketing increased bleeding rates in older patients taking dabigatran are consistent with the bleeding rates reported in RE-LY, in which the reduced risk of bleeding shown with dabigatran 110 mg was limited to patients <75 years of age, with bleeding risks similar to warfarin in patients ≥75 years.[3] However, the reduction in intracranial haemorrhage (ICH) with both dabigatran doses was shown to be independent of patient age. Dabigatran 110 mg is the recommended dose for AF patients ≥80 years of age, and should also be considered in patients ≥75 years (Table 5); this dose is not licensed for treatment of VTE.

Similar increases in bleeding with age have also been seen with edoxaban 60 mg[6] and rivaroxaban;[44] neither specifies dose adjustment. The lower risk of bleeding seen with apixaban compared with warfarin in ARISTOTLE prevailed in all age categories, including those aged ≥75 years;[5] apixaban dose reduction is recommended in patients ≥80 years of age in conjunction with an additional risk factor (Table 5).

Bleeding

All phase III studies in AF and VTE have shown there to be fewer bleeding complications with NOACs than warfarin

Table 5. Dosing in non-valvular atrial fibrillation: renal function, age and body weight

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg bd	20 mg bd	5 mg bd	60 mg od
Renal function				
CrCl 30–49 mL/min	Consider 110 mg bd	15 mg od	5 mg bd	30 mg od
CrCl 15–29 mL/min	Not recommended	Use with caution	2.5 mg bd	30 mg od
CrCl <15 mL/min	Not recommended	Not recommended	Not recommended	Not recommended
CrCl >95 mL/min	–	–	–	Not recommended
Age	≥80 years: 110 mg bd ≥75 years: consider 110 mg bd	–	2.5 mg bd where two of: > serum creatinine ≥1.5 mg/dL > age ≥80 years > weight ≤60 kg	–
Body weight	–	–	2.5 mg bd where two of: > serum creatinine ≥1.5 mg/dL > age ≥80 years > weight ≤60 kg	30 mg od: > weight ≤60 kg
Others	100 mg bd: > concomitant verapamil > consider where increased risk of bleeding			30 mg od: > concomitant use of cyclosporine, dronedarone, erythromycin or ketoconazole

bd = twice per day; CrCl = creatinine clearance; NVAF = non-valvular atrial fibrillation; od = once daily

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(reaching non-inferiority or superiority, Tables 2 and 3), with the outcome of bleeding appearing less serious in patients receiving NOACs.[45,46] Particularly striking is the reduction in ICH (around 50%) and other life-threatening bleeding.[47] The exception is gastrointestinal (GI) bleeding, which appears to vary considerably between NOACs with several studies showing higher GI bleeding risks than warfarin (Tables 2 and 3). The significantly higher incidence (approximately 1.5 fold) of GI bleeding with dabigatran 150 mg compared with warfarin found in RE-LY[3] has been reproduced in most post-marketing studies.[48,49] However, 12-month post-approval follow-up of a Danish registry cohort of over 14,000 anticoagulant naïve patients has shown both dabigatran doses to have comparable or lower GI bleeding rates than warfarin although these patients were younger and with lower $CHADS_2$ scores than the RE-LY patients.[50] A higher rate of GI bleeding symptoms was also shown in the rivaroxaban patients in ROCKET-AF[4] although rates of life-threatening and fatal GI bleeds were comparable to warfarin[44] and far fewer rivaroxaban-associated major GI bleeds met the criteria for life-threatening GI bleeding than for dabigatran 150 mg in the RE-LY trial (13% versus 50%). In contrast, a direct comparison between dabigatran 150 mg twice per day and rivaroxaban 20 mg once daily in over 100,000 'real world' patients with non-valvular AF has shown the risks of ICH and major extracranial bleeding, including major GI bleeding, to be significantly increased in patients treated with rivaroxaban.[51] The risk of GI bleeding in ENGAGE-AF was also shown to be significantly higher with edoxaban 60 mg compared with warfarin,[6] while no difference in GI bleeding was found between the apixaban and warfarin patients in ARISOTLE,[5] or dabigatran 110 mg and warfarin patients in RE-LY.[3]

As discussed above, the risk of major GI bleeding in the VTE studies was not increased compared with warfarin, possibly reflecting the younger population with fewer comorbidities in these trials. Overall, the risk of GI bleeding or underlying GI pathology is an important consideration when selecting a NOAC.

The different rates of GI bleeding between NOACs may reflect incomplete absorption of NOACs and persistence of active anticoagulant within the GI lumen following oral ingestion. Why the GI bleeding risks should differ between the direct FXa inhibitors is not clear; it is possible that this may in part reflect differences in P-glycoprotein (P-gp) transportation and peak anticoagulant concentration, which themselves are dependent on metabolism and dosing regimen.

Renal impairment

Patients with chronic kidney disease (CKD) are at an increased risk of both VTE and bleeding.[52] Moreover, it has been suggested that the relative benefit of NOACs may be greater in patients with mild and moderate CKD than those with normal renal function.[53] European licensing in AF requires dose adjustment of NOACs in patients with renal impairment with parallel consideration of patient age, weight and concomitant medications (Table 5). Renal function should be checked annually in uncomplicated patients, with more frequent testing advocated in patients with any impairment of renal function (eg creatinine clearance (CrCl) <60 mL/min) and older or frail patients.[12] Although there is a lack of comparative data showing differences in risks from CKD between NOACs, the suitability of agent may be guided by the clear differences in renal dependence (Table 1). Trial data may also help choice; for example, the lower rates of venous and bleeding complications with apixaban compared with warfarin have been shown to be independent of renal function.[54] Moreover, the relative reduction in bleeding with apixaban compared with warfarin has been shown to be greater in patients with impaired renal function as defined by CrCl<50 mL/min.[54] The lower bleeding rates observed with edoxaban compared with warfarin in patients with normal renal function are also seen in patients with renal impairment,[55] while this has not been shown to be the case for dabigatran 110 mg,[56] which has greater renal dependence. Poor renal function is a key predictor of bleeding in patients taking dabigatran.[57]

These findings suggest that selected NOAC use may be preferable to warfarin in some patients with CKD. NICE guidance suggests that use of apixaban should be considered in preference to warfarin in patients with mild/moderate CKD as defined by glomerular filtration rate of 30–50 mL/min.[58] There are currently insufficient data and experience to advocate the use of any of the NOACs in patients with CrCl<15 mL/min or in patients on haemodialysis. At the other end of the spectrum, the relative efficacy of edoxaban in stroke prevention has been shown to be reduced in patients with higher CrCl,[55] leading to summary of product characteristics (SmPC) advice to avoid edoxaban where CrCl>95 mL/min (Table 5).

Patients with hepatic impairment

All NOACs are contraindicated in patients with hepatic disease associated with coagulopathy and should be avoided in patients with severe hepatic impairment. Suitability in patients with mild and moderate hepatic impairment varies between NOACs (Table 1).

Drug-drug interactions

Despite being significantly fewer with NOACs than warfarin, there are a number of interactions that require appreciation when deciding upon NOAC suitability and dosage for an individual patient. The availability of pharmacokinetic data is continually expanding, but for many drugs currently remains insufficient to make specific recommendations. The role of drug assays in these circumstances is considered later in this article. Potential drug interactions should be considered in the context of other risk factors for bleeding that include age (≥75 years), body weight (<60 kg) and renal function (Table 5). Common to all NOACs is the potential for increased plasma levels when taken in combination with drugs that compete for the P-gp transporter, such as the frequently used antiarrhythmics verapamil, amiodarone and quinidine; dose reduction may be required, in particular with dabigatran or edoxaban.[12] Increased rivaroxaban levels may result from CYP3A4 inhibition,[59] whereas the CYP3A4 pathway makes minimal contribution towards edoxaban clearance and is not involved at all in the clearance of dabigatran. The diverse nature of non-renal clearance of apixaban reduces the impact of any CYP3A4 interactions,[60] such that use of apixaban should be avoided only when drugs that strongly inhibit both CYP3A4 and P-gp are used, such as the HIV protease inhibitors and

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azole antifungals. On the other hand, potent inducers of P-gp and CYP3A4, such as rifampicin and carbamazepine are likely to lower NOAC plasma levels to subtherapeutic levels. Proton pump inhibitors and antacids do not modify the clinical effects of NOACs.

Antiplatelet therapy

As with warfarin, the increased bleeding risk when NOACs are used together with antiplatelet agents is significant and an incremental increase in major bleeding risk results from the addition of a NOAC is added to single or dual antiplatelet agent, for example in the management of ACS.[27,28,30,61] There are presently insufficient available data to optimally guide clinical practice in such settings. All phase III AF trials allowed concomitant use of aspirin; however, only RE-LY included a substantial number of patients taking dual antiplatelet therapy (aspirin and clopidogrel) in addition to dabigatran.[61] Although antiplatelet use was associated with an increased risk of bleeding, the benefit of dabigatran over warfarin was not impacted significantly. There are currently no large-scale randomised studies evaluating the use of newer antiplatelet agents, such as prasugrel and ticagrelor, in combination with either NOAC or warfarin.

Ischaemic heart disease

Myocardial infarction (MI) risk appeared to be higher in the dabigatran than warfarin arm for both dabigatran doses in RE-LY although the difference was not shown to be statistically significant.[3] A subsequent meta-analysis of seven dabigatran trials across indications has similarly shown a higher MI event rate with dabigatran than warfarin with an absolute excess of around 3 per 1,000 patients; again this did not reach levels of statistical significance.[62] No difference in event rate was seen when RE-LY data were analysed using aggregated cardiac events (ACS, cardiac arrest or death) in addition to MI,[63] nor did the cardiac event rate associated with dabigatran appear to differ between patients with or without known ischaemic heart disease.[63] The Danish registry cohort, described earlier, reported lower MI rates in patients taking dabigatran than warfarin,[50] while switching from warfarin to dabigatran has been shown to increase the MI risk compared with continued warfarin usage.[64] A significant excess of MI has not been demonstrated for the FXa inhibitors.[4–6] This is despite the higher absolute numbers of MIs seen in the edoxaban and rivaroxaban arms in the ENGAGE-AF and ROCKET-AF trials, respectively.[4,6] No increased MI risk was shown with apixaban in the ARISTOTLE trial.[5]

INR control

Meta-analyses of the AF trials have shown NOACs to have a greater impact on reducing the risk of major bleeding when compared with patients taking warfarin in centres with poorer INR control as measured by time in therapeutic range (TTR) <66%.[65] As discussed earlier, the quality of INR control has been shown to impact on the relative benefit of dabigatran.[7] The beneficial effect of edoxaban also appears greater when compared to patients with poorer INR control, while similar effects are not seen with rivaroxaban or apixaban; apixaban offered a benefit on risk of stroke, bleeding or mortality irrespective of TTR in the comparator warfarin arm.[8] Studies have not identified a level of TTR with which warfarin is more effective than NOACs.

Practical applications

Measuring anticoagulant effect

A major advantage of the NOACs over warfarin is their fixed dosing without need for monitoring. However, there are times at which assessment of drug exposure and anticoagulant effect may be required, eg serious bleeding or urgent surgery, deterioration in renal function, consideration for thrombolysis, extremes of body weight or with certain concomitant medications. In general, the activated partial thromboplastin time (APTT) may provide a qualitative indication of the presence of direct thrombin inhibitors and the prothombin time (PT) the FXa inhibitors; however, there is considerable variability in the sensitivity of these assays between laboratories and the patient response. Importantly, normal PT and APTT times may be obtained in the presence of therapeutic amounts of NOACs. Although often not performed as part of the routine coagulation screen, a normal thrombin time can be interpreted as indicating minimal circulating concentration of dabigatran.

While quantitation of NOAC concentration is now available, using either anti-Xa assays (for FXa inhibitors) or a dilute thrombin time (for direct thrombin inhibitors), the utility of these assays is also limited by a lack of data correlating them with bleeding risk and the absence of defined therapeutic ranges. Moreover, significant inter-patient variability in NOAC levels has been reported,[20,66–68] and there is poor inter-laboratory agreement in quality assurance exercises. Access to these assays may not yet be routinely available, particularly out of hours, in which case clinical decision making should be based on the time of last dose, half-life and renal function (Table 1).

Specific guidance regarding laboratory measurement of NOACs is provided by the British Committee for Standards in Haematology.[69]

Management of bleeding complications

The approach to management of bleeding again require an appreciation of the pharmacokinetic properties of the NOACs, including their relatively short half-lives (Table 1). This is of particular importance where quantitative assays are not readily available. In normal subjects, haemostasis can be expected to be approaching normal at 24 hours following the last NOAC dose; however, consideration should be given to individual patient characteristics, such as renal impairment and concomitant medication.

The low protein binding of dabigatran facilitates its removal by dialysis although the effectiveness is not known and clinical evidence is limited.[70,71] Plasma levels of FXa inhibitors are not significantly reduced by dialysis. The only specific reversal agent currently available is idarucizumab, which should be used in patients who develop life-threatening bleeding while taking dabigatran. Life-threatening bleeding in patients receiving FXa inhibitors can be treated with prothrombin complex concentrates or the bypassing agents recombinant factor VIIa or factor eight inhibitor bypassing agent. Support for their use

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is limited, being largely derived from the effect on haemostatic parameters in NOAC-treated animal models. In one study, 50 u/kg of prothrombin complex concentrate was able to return bleeding after skin biopsy to normal in healthy volunteers receiving edoxaban.[72] There is less evidence for use of factor eight inhibitor bypassing agent or factor VIIa and a concern that such pre-activated agents may increase thrombotic events.

Antidotes

Idarucizumab, a humanised monoclonal antibody antigen-binding fragment that binds to dabigatran, is the first available NOAC antidote and should be used to restore haemostasis in patients presenting with serious bleeding or requiring urgent surgery.[73] Clinical trials showed near complete dabigatran reversal within minutes[74,75] and normal peak and trough plasma levels of dabigatran have been shown following recommencement of dabigatran 24 hours following idarucizumab administration.[76] Antidotes to the FXa inhibitors are in various stages of development; these include andexanet alfa, a recombinant human FXa analogue that binds to the FXa inhibitors but lacks procoagulant activity.[77] Studies in healthy volunteers taking standard doses of apixaban and rivaroxaban showed loss of anticoagulant activity within minutes of andexanet infusion.[78] However, both measures subsequently increased, necessitating infusion of andexant over a 2-hour period to sustain suppression.[78] Trials of andexanet in patients presenting with bleeding while receiving FXa inhibitors are currently underway with dose calculated according to the type of FXa inhibitor and, for rivaroxaban, the time from last dose, but this relies on obtainment of accurate clinical information.[79] While preliminary analysis has shown achievement of effective haemostasis in 79% of patients, thrombotic events occurred in 18%; notably, there was no comparator control arm.[79] A less specific reversal agent, ciraparantag – a small, synthetic molecule that binds to heparin through noncovalent interactions – also binds to the NOACs, and has thus far been shown to successfully reverse the anticoagulant effect of edoxaban.[80]

Perioperative management

It is generally recommended that NOACs be omitted for 24 hours prior to low-risk surgical procedures and 48 hours prior to high-risk procedures in patients with normal renal function.[81] For patients with impaired renal function, it is advised that this interval be prolonged by 24 hours (or longer for dabigatran).[81] Patients undergoing procedures that carry a high bleeding risk should not recommence full dose postoperative anticoagulation until 48–72 hours following the procedure. [81]

Thrombolysis in ischaemic stroke

Thrombolytic therapy with recombinant tissue plasminogen activator is not recommended in patients receiving warfarin with INR>1.7. The bleeding risks associated with thrombolysis in patients receiving NOACs are currently unknown. Patients taking dabigatran can be given idaracizumab. It is unlikely that plasma drug levels will be available within the approved time frame for thrombolysis so for FXa inhibitors, judgement relies on timing of most recent dose together with patient characteristics; in the absence of available evidence, it has been suggested that thrombolytic therapy not be given within 24–48 hours following last NOAC dose.[82]

Extremes of body weight

There are limited data on the efficacy and safety of fixed dose therapy at extremes of body weight. The apixaban and edoxaban SmPCs both recommend dose reduction at low body weight (Table 5). Reduced drug exposure, lower peak concentrations and shorter half-lives have been shown with increasing body weight[83] although their clinical relevance is unknown and there is high inter-patient variability as well as a lack of defined therapeutic ranges for NOAC drug levels. In the absence of randomised controlled trials, evidence is drawn from subgroup analyses of patients included in the large phase III clinical trials and the effect of body weight on pharmacokinetic parameters of NOACs. Guidance recommends that NOACs be avoided in patients with a body mass index greater than 40 kg/m^2 or those who weigh more than 120 kg.[83] Where NOACs are used in these patients, measurement of peak and trough drug levels is recommended and where the level is lower than expected, the patient should be switched to warfarin.[83]

Conclusion

The new direct acting oral anticoagulants offer significant advantages to both patients and doctors. Carefully chosen for the relevant indication, they can simplify therapy while improving outcomes. In the absence of any direct comparative trials, it is not clear whether any of the agents are significantly better than the others in any of the licensed indications. However, it is clear that they have differences in activity, pharmacokinetics, metabolism, excretion and side effects that can make appropriate patient selection critical. Careful screening of patients for bleeding diatheses (especially GI bleeding), concomitant medications, renal function and age are all important. The benefits and problems of once daily dosage regimens remain moot. Widespread acceptance has undoubtedly been limited by the lack of a reversal agent but this is now being addressed and post-marketing data show better outcomes from NOAC- than warfarin-associated bleeding even without this, confirming the overall benefit of the new agents. The most striking benefit, although unexplained, is the reduction in ICH compared with warfarin. We wait to discover how far the indications for NOACs will extend and whether they will be valuable for patients requiring more intensive anticoagulation than the standard INR of 2.5. ■

Conflicts of interest

CMM has received travel support from Boehringer Ingelheim, Leopharma, NovoNordisk, Pfizer and SOBI, speakers fees from Leopharma, LFB and Pfizer, and consultancy fees from Shire. MAL has received travel support from LFB and Bayer, speaker fees from Pfizer, Leopharma and Bayer and consultancy fees from SOBI.

Acknowledgements

CMM and MAL are supported by the NIHR Imperial College Biomedical Research Centre.

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