J R Coll Physicians Edinb 2016; 46: 113–8
http://dx.doi.org/10.4997/JRCPE.2016.211

A practical approach to the new oral anticoagulants used for stroke prevention in patients with atrial fibrillation

[1]S Bashir, [2]A Al-Mohammad, [3]S Gupta
[1]Cardiology Registrar, Castle Hill Hospital, Cottingham, UK; [2]Consultant Cardiologist and Honorary Senior Clinical Lecturer, Sheffield Teaching Hospitals NHS Foundation Trust, UK; [3]Consultant Cardiologist, York General Hospital, York, UK

ABSTRACT This review evaluates the research undertaken in the last six years on the use of new oral anticoagulants for stroke prevention in atrial fibrillation and provides evidence-based answers to common clinical questions. Two types of new oral anticoagulants – direct thrombin (IIa) inhibitors, and Xa inhibitors – are currently available. These drugs have similar pharmacokinetics and pharmacodynamics. They are more predictable than, though in many respects comparable to, warfarin. They do not require frequent laboratory tests, nor do they have a narrow therapeutic window. When a patient requires surgery, new oral anticoagulants are easier to manage than warfarin due to their short half-lives. Short half-lives reduce the length of bleeding events. Information obtained from risk calculators such as CHA_2DS_2-VASc and HAS-BLED should be considered before prescribing. New oral anticoagulants are useful in every day clinical practice, but there are complex factors that should be considered in each patient before prescribing to implement the best practice and achieve the best results.

KEYWORDS atrial fibrillation, clinical practice, NOACs, stroke prevention

DECLARATION OF INTERESTS SB reports non-financial support from Servier, outside the submitted work. AA has accepted hospitality from Servier to attend the Euro Hf meetings in Athens (2014) and in Seville (2015). SG has received speaker fees and given educational lectures on behalf of four pharmaceutical companies which produce the NOACS; Boehringer Ingleheim, Daichii Sankyo, Bayer and Pfizer/Bristol Myers Squibb. SG has accepted hospitality from all of the above mentioned companies to attend educational masterclasses and conferences.

***Correspondence to** S Bashir*
Department of Cardiology
Castle Hill Hospital
Castle Rd
Cottingham
Yorkshire HU16 5JQ
UK

e-mail ***shaza.khider@gmail.com***

INTRODUCTION

For 50 years, the main oral anticoagulant used to prevent stroke and systemic embolism in patients with atrial fibrillation was warfarin, a vitamin K antagonist. In the coagulation cascade, there are two different primary pathways that lead to the formation of fibrin. These are the extrinsic, tissue factor pathway, and the intrinsic, contact activation pathway. The former is the primary target. The extrinsic pathway works to create a thrombin burst, rapidly releasing thrombin for the purposes of clotting. New oral anticoagulants (NOACs) work to inhibit such clotting, reducing the likelihood of stroke due to the presence of a clot or systemic embolism. Warfarin is effective at preventing thrombosis, but is inconvenient to manage because of its unpredictability.[1]

Three NOACs, dabigatran, rivaroxaban and apixaban, have been in use since their approval by the National Institute for Health and Care Excellence (NICE) for prevention of embolism in persons with non-valvular atrial fibrillation. The pharmacokinetics and oral bioavailability of NOACs are more predictable than warfarin[2] and they have fewer interactions with food and other drugs which can increase or decrease their bioavailability. For example, if a patient steadily consumes the same amount of leafy greens weekly, the effects on warfarin's bioavailability and its effectiveness will remain stable. If there is dietary fluctuation, this can decrease the bioavailability of the drug and potentially cause additional risks for the patient. Similarly, NOACs can have shifting effects as a result of absorption rates based on differences in diet of the individual, creating potential concerns about their effects.[2–4]

Although the NOACs have been thoroughly examined in randomised clinical trials,[3–5] less attention has been given to methods to facilitate their use in everyday clinical practice. We searched the PubMed database for clinical studies relating to use of NOACs for stroke prevention in atrial fibrillation, published in the last six years.

DRUG INFORMATION

Dabigatran (as etexilate) is a direct thrombin (factor IIa) inhibitor; rivaroxaban and apixaban are Xa inhibitors.[3–5] Dabigatran has low bioavailability (3–7%) unless it is

taken without the surrounding capsule.[6] The bioavailability of the Xa inhibitors is 60–80%.[6,7] The half-life of NOACs (11–14 hrs) is considerably shorter than the half-life of warfarin (20–60 hrs). The time required to reach peak concentration is similar in both NOACs and warfarin (0.5–4 hrs).[1–5] NOACs are metabolised by permeability glycoproteins and CYP3A4, while warfarin has multiple metabolic pathways.[3,4,5,8] There are two different licensed dosages for dabigatran, 150 mg and 75 mg, both taken by mouth twice daily. The two doses have slightly dissimilar side effects and bleeding risks, based on the dosage being taken by the patient, though it is important to note that the 75 mg dose is not currently licensed for use in the UK.[3–5]

Compared to warfarin, dabigatran has an increased incidence of dyspepsia. Apixaban and rivaroxaban have side effect profiles similar to the side effects of warfarin. Overall, the NOACs have a comparative risk of major bleeding.[2–4] Dabigatran and rivaroxaban have increased risk of gastrointestinal bleeding and decreased risk of intracranial bleeding compared to warfarin. Apixaban has a lower risk of intracranial bleeding but no difference in gastrointestinal bleeding.[3,4,6,7]

INDICATIONS/CONTRAINDICATIONS

How should risks be identified?

Since the choice of anticoagulant depends on balancing the risk factors for stroke/thromboembolism and the risk factors for bleeding, a risk-benefit analysis should be conducted for each patient.[7,9] Risk calculators for both thromboembolic stroke and bleeding have been developed and tested through prospective studies. NICE recommends the use of the CHA_2DS_2-VASc score to estimate stroke risk and the HAS-BLED score to estimate bleeding risk.[10–12] A higher CHA_2DS_2-VASc score raises the likelihood of embolism, a lower HAS-BLED score indicates the chance of bleeding is lower. NOACs, like warfarin, reduce the likelihood of thromboembolism and increase the chance of bleeding.[10,13,14] The HAS-BLED score should not serve as the sole barrier to the use of anticoagulants but should be taken into consideration in conjunction with the patient's lifestyle and diet in order to determine the best way to reduce the risks identified by the CHA_2DS_2-VASc risk score.

When can NOACs be prescribed?

NOACs are licensed by NICE for patients with non-valvular atrial fibrillation when other risk factors, such as prior stroke or transient ischaemic attack, age ≥ 75 years, heart failure (NYHA Class ≥ II), diabetes mellitus, or hypertension, are present.[9,10]

When should NOACs not be prescribed?

NOACS should not be used in patients with a history of poor medication compliance (unless poor compliance relates to difficulty managing flexible warfarin dosage).[9–11] NOACs should not be substituted for warfarin if the patient has had a bleeding event related to warfarin treatment or cannot take warfarin due to a high bleeding risk, alcohol or drug abuse.[11] NOACs should not be used in pregnancy.[9,10]

What factors influence the choice of NOACs versus warfarin?

The presence of advanced renal disease, a history of gastrointestinal bleeding, the need for drugs that interact with NOACs, and extremes of body mass index are negative factors for use of NOACs as their dosage is not easily adjusted and effects cannot be monitored. Warfarin may be preferred in these instances. The options for anticoagulation and the appropriate pros and cons should be outlined for the patient. Whenever possible, patient preference should be a primary factor in the choice of anticoagulant.[9,11,12] It is important to note, however, that the decision to use a NOAC over warfarin or vice versa is not as simple as it may seem. The physician should discuss with the patient the most appropriate medication and treatment plan for that patient.

INITIATING NOAC THERAPY

What patient education is required?

Once the NOAC has been chosen, patients must be educated about possible side effects, missed dose procedures and symptoms of covert bleeding.[9,15] Patients should be told when to seek healthcare input and when to go to the emergency department. In addition, patients should be encouraged to wear a medical alert notice around their neck or wrist indicating that they are taking anticoagulants.[15,16]

What laboratory tests are suggested prior to prescribing NOACs and during NOAC therapy?

The international normalised ratio (INR) should not be used in patients taking NOACs.[17] The following tests and parameters should be checked before initiating NOACs and at annual follow-up intervals: clotting screen, blood counts, urea and electrolytes, liver function, kidney function (CrCl, creatinine clearance, or eGFR, estimated glomerular filtration rate), blood pressure and body weight.[15,17]

J R Coll Physicians Edinb 2016; 46: 113–8

TABLE 1 Dosage considerations

	Warfarin[3,4,6]	Dabigatran[2,8]	Rivaroxaban[5,7]	Apixaban[4]
Dose and frequency	Variable dose, dependent on INR once daily	Patients < 80 years: 150 mg twice daily Patients > 80 years: 75–110 mg twice daily *note: the 75 mg dosage is not currently licensed in the UK	20 mg once daily	5 mg twice daily
Indications for dose reduction[3–7]	INR over 3.0 or target	If CrCl 30–50 mL/min or body weight < 50kg: lower dose to 110 mg twice daily	If CrCl 30–49 mL/min: lower dose to 15 mg once daily	If 2 or more of: *age ≥ 80 years, *body weight ≤ 60 kg, or *serum Cr of ≥ 133 µmol/L, lower dose to 2.5 mg twice daily or less
Renal function caution or contraindication[6,7]	Use with caution	Contraindicated if CrCl is < 30 mL/min	Contraindicated if CrCl is < 15 mL/min	Contraindicated if CrCl is < 15 mL/min
Food and drug restrictions[7,12,13]	Caution should be taken with CYPP450 cytochromes inhibitors and inducers; avoid high vitamin K foods	No dietary restriction apart from moderating alcohol intake; drugs that compete for permeability glycoprotein and/or inhibit CYP3A4 may require dosage adjustment		

TABLE 2 Serious drug interactions with NOACs

Type of interaction	Dabigatran[2,3]	Rivaroxaban[5,7]	Apixaban[4]
Increased risk of bleeding	Verapamil, ticagrelor, quinidine, ketoconazole, dronedarone, amiodarone	Voriconazole,clarithromycin, itraconazole, ketoconazole, ritonavir, posaconazole	Posaconazole, ketoconazole, voriconazole, itraconazole, ritonavir
Increased risk of stroke and systemic embolism	Carbamazepine, St John's wort, rifampicin	Carbamazepine, St John's wort, rifampicin, phenytoin, phenobarbital	Carbamazepine, St John's wort, rifampicin, phenytoin, phenobarbital

How often should follow-up visits be scheduled?

For the first year, patients should return every three months for visual bleeding checks and faecal occult blood tests. Laboratory tests do not need to be done at every visit unless the patient's renal status warrants.[7,9,11] Patients with mild to moderate chronic kidney disease should be tested every 3–6 months.[15,16]

What factors affect dosage of NOACs?

Table 1 indicates the suggested dose and frequency of each drug, when the dosage should be adjusted, renal contraindications and required food or drug restrictions.

What drugs are known to interact with NOACs?

NOACs including dabigatran, rivaroxaban and apixaban are less prone to drug interactions compared with warfarin.

Pharmacodynamic interactions The concomitant use of NOACs with other anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory agents is expected to increase the risk of bleeding, potentially as much as 60%. Thus, their concurrent use with NOACs should be avoided.[18–20]

Pharmacokinetic interactions The main pharmacokinetic drug interactions are focused on drugs affecting the permeability glycoprotein efflux transporter protein and/or cytochrome P-450 enzymes. Table 2 highlights clinically significant drug interactions that justify avoiding concomitant therapy.[7,9,12,13] For the less serious drug interaction, the decision should be based on the indication and the patient's bleeding risk.

How should the transition from a vitamin K antagonist to a NOAC and from a NOAC to a vitamin K antagonist be handled?

Warfarin has a long half-life, so administration of the NOAC must be delayed until the INR has fallen below the therapeutic range.[20,21] When switching from a NOAC back to a vitamin K antagonist, it is crucial to maintain adequate anticoagulation by giving warfarin and a NOAC simultaneously until the INR, taken just before the next NOAC dose, reaches the appropriate range.[21,22]

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TABLE 3 Pre-operative management of NOACs – when to stop

	Kidney function	Dabigatran[29–32]	Rivaroxaban[29–32]	Apixaban[29–32]
Minor surgery/ procedure (low-moderate bleeding risk)	Normal/Stage 1 (CrCl >80)	24 hrs	24–48 hrs	24–48 hrs
	Stage 2/3A (CrCl 50–80 mL/min)	36 hrs	24–48 hrs	24–48 hrs
	Stage 3B (CrCl 30–50 mL/min)	48 hrs	36–72 hrs	24–48 hrs
	Stage 4 (CrCl 15–30 mL/min)	72 hrs	48–72 hrs	36–48 hrs
Major surgery or spinal anaesthetics (high bleeding risk)	Normal/Stage 1 (CrCl > 80 mL/min)	48 hrs	48–72 hrs	48–72 hrs
	Stage 2/3A (CrCl 50–80 mL/min)	72 hrs	48–72 hrs	48–72 hrs
	Stage 3B (CrCl 30–50 mL/min)	96 hrs	48–72 hrs	48–72 hrs
	Stage 4 (CrCl 15–30 mL/min)	96 hrs	At least 96 hrs	At least 96 hrs

MANAGEMENT OF ADVERSE EVENTS:

What measures should be taken for minor bleeding?

If a patient taking a NOAC develops minor bleeding, such as a sub-conjunctival, gingival, nasal, or haemorrhoidal bleed, there is usually no action required, since minor haemorrhages usually stop by themselves.[23–25] It is also important to note that the short half-life of NOACs means that many of these bleeding concerns, either major or minor, fail to materialise. However, the physician must still be aware of these risks for the patient and how to effectively address those risks.[21,22,26,27]

What if a patient develops major bleeding?

If a patient develops major bleeding, such as intracranial bleeding or severe gastrointestinal bleeding, the response should focus on local haemostatic measures, fluid replacement, platelets substitution and packed red cells. Tranexamic acid and fresh frozen plasma may be used as adjuncts.[21–23]

Research suggests that prothrombin complex concentrates containing coagulation factors II, VII, IX, and X may overwhelm the inhibitory effects of the NOACs, although their value in prevention of morbidity and mortality is unproven.[29]

If the bleeding is caused by dabigatran, then there seems to be an 89% chance of stopping it within 4 hours through the use of the specific antidote idarucizumab, approved by the US Food and Drug Administration in October 2015.[28] In many patients, NOAC-related anticoagulant effects will rapidly dissipate because of the drugs' short half-lives. Nevertheless, major bleeding should be treated immediately.[21,22,26,27]

NOACS AND SURGERY

How should NOACs be managed before major or minor surgery?

Management should be individualised depending on the NOAC used, the patient's renal function, the type of surgery (higher or lower bleeding risk) and the type of anaesthetic administered (general, spinal, or regional).[29–32] For dental procedures, tranexamic acid 5% mouth wash may be prescribed. The patient should use 10 ml four times a day for 5 days.[29] Table 3 gives specific pre-operative cut-off times for stopping the agents according to type of surgery/anaesthesia, kidney function and NOAC.

Should coagulation testing be done before surgery?

Pre-operative coagulation testing is unnecessary in patients taking NOACs because they have short half-lives, so there should be little residual anticoagulant effect at the time of surgery. Also, standard coagulation tests may not reflect the true risk of bleeding.[7,24,25]

Is a bridging protocol necessary?

Because NOACs have swift offset and onset of effect, patients undergoing surgery and who require temporary interruption of a NOAC do not usually need bridging anticoagulation. However, if the surgical procedure requires substantial immobilisation, an intermediate dose of low molecular weight heparin may begin 6–8 hours after surgery, once haemostasis is reached.[29,32]

POSTOPERATIVE MANAGEMENT OF NOACS

The rapid action of NOACs (1–3 hours after intake) can increase the risk of bleeding if treatment is resumed too soon after surgery. For this reason, care must be taken in the postoperative period that haemostasis had been reached prior to restarting the NOAC, and the potential risks of bleeding need to be weighed against the risk of thromboembolism in those patients left without anticoagulation. Generally, treatment with a NOAC should be delayed for at least 48 hours after a low risk surgery or procedure and for 72 hours after a high risk surgery or procedure.[29–32]

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GAPS IN RESEARCH

There remain gaps in the research in several areas. For example, the use of NOACs in specific ethnic populations has not been examined, with the exception of one study that addressed the likelihood of negative outcomes in Asians vs non-Asians.[33] There is also an absence of evidence comparing the three major NOACs, which are available in the UK, in a single randomised, double-blind controlled study.

Most of the recent studies summarised above examined the effects of dabigatran, the direct thrombin (IIa) inhibitor but additional research is needed on the cardiovascular safety of the Xa inhibitors and further work is required to identify antidotes to Xa inhibitors. We still lack knowledge with regards to the long-term effects of NOACs after > 10 years.

CONCLUSION

The NOACs are superior to warfarin in that their usage does not require frequent blood tests or significant dietary restrictions, and their short half-lives make them easier to manage in the context of surgery. However, with the exception of dabigatran there is no antidote for the NOACs if a major bleed occurs. A thorough risk-benefit analysis should be conducted, using risk calculators, before prescribing these drugs.

EDUCATION

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