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Introduction to New Oral Anticoagulants (NOAC's)

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Abstract: To produce a high quality article for physicians that reviews the current literature pertaining to NOAC's, in particular, their use in clinical practice, known drug interactions and side effect profile. Medline, Cochrane and PubMed databases were searched for the most recent and clinically sound articles pertaining apixaban, rivaroxaban and dabigatran. Researchers found the trials for each of these NOAC's to be sound and have results that can be translated into clinical practice.

Key words: PubMed databases, rivaroxaban, NOAC's, physicians, potential

INTRODUCTION

Patients with atrial fibrillation are at an increased risk of stroke (Wolf *et al*., 1991). Warfarin reduces the risk of stroke and death but increases the risk of haemorrhage (Hart *et al*., 2007). Due to multiple food and drug interactions and need for patient monitoring, warfarin is often difficult to use for patients and general practitioners in clinical practice (Piccini *et al*., 2009).

Case: Mrs Smith is an 81 years old woman with atrial fibrillation and hypertension. She has been on warfarin for several years with some difficulty in maintaining the INR levels within the therapeutic range. Upon hearing about the Novel Oral Anticoagulants (NOAC), she comes to you requesting to be switched from warfarin to a new agent. Is it practical for this 81 years old woman to be prescribed a NOAC instead of warfarin?

PATHOPHYSIOLOGY AND EPIDEMIOLOGY

Atrial Fibrillation (AF) is a supraventricular tachyarrythmia characterised by uncoordinated atrial activation with consequent deterioration of mechanical function. It is often associated with structural heart disease and can lead to hemodynamic instability and thromboembolic events resulting in significant morbidity and mortality (Fuster *et al*., 2001). AF can be classified as a first-episode or recurrent (≥2 episodes) and further sub-classified as paroxysmal, persistent or permanent depending on time until reversion to sinus rhythm.

AF is the most common arrhythmia in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbances. The incidence and prevalence of AF has been steadily increasing over the past several decades (Medi *et al*., 2011).

Oral anticoagulation is required for stroke prevention in those at risk due to AF. Anticoagulation should be considered in those with no active bleeding or significant risk of bleeding.

PHARMACOKINETICS

Dabigatranetexilate is an oral pro-drug that is rapidly converted by a serum esterase to dabigatran. It is a potent reversible direct thrombin inhibitor that inhibits free and fibrin-bound thrombin without need for antithrombin. The peak plasma concentration is reached 1.25-3 h after administration and it has a half-life of 12-14 h (Levy *et al*., 2013). Dabigatran has a bioavailability of 6.5% with 80% of the given dose being renally excreted (Connolly *et al*., 2009).

Rivaraoxaban is an oral, direct factor Xa inhibitor that has good bioavailability (80%) is highly protein bound and has few drug interactions. It has a half-life of 5-9 h and peak plasma concentrations occur within 2-4 h of administration. Its primary mode of clearance is by non-renal mechanisms (Levy *et al*., 2013).

Apixaban is an oral, direct factor Xa inhibitor with good oral bioavailability (80%). It is highly protein bound, has a half-life of 8-15 h and reaches peak plasma concentration within 2-3 h after intake. It is primarily metabolised by the liver (Levy *et al*., 2013).

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CLINICAL TRIALS

The Randomised Evaluation of Long-Term Anticoagulation therapy (RE-LY) (Connolly *et al*., 2009) was a non-inferiority randomised trial comparing two fixed doses of dabigatran (110 and 150 mg twice daily) with adjusted dose warfarin in patients who had atrial fibrillation and were at increased risk of stroke or systemic embolism. Dabigatran given at a dose of 110 mg was associated with similar rates of stroke and systemic embolism as warfarin (1.53 vs. 1.69% per year, $p<0.001$ for non inferiority) but with lower rates of major haemorrhage. Dabigatran administered at a dose of 150 mg as compared with warfarin was associated with lower rates of stroke and systemic embolism (1.11 vs. 1.69% per year, $p<0.001$ for superiority) but with similar rates of major haemorrhage. The study concluded that dabigatran was non-inferior to warfarin in the prevention of stroke and systemic embolism with lower or similar rates of major haemorrhage.

The rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) (Patel *et al*., 2011) was a randomised control trial that compared rivaroxaban to warfarin in patients with non-valvular AF. Rivaroxaban at a daily dose of 20 mg was demonstrated to be non-inferior to dose adjusted warfarin for the prevention of stroke and systemic embolism (1.7 vs. 2.2% per year, $p<0.001$). The rivaroxaban group as compared to warfarin, had lower rates of intracranial haemorrhage and fatal bleeding. The study concluded rivaroxaban to be non-inferior to warfarin for the prevention of stroke or systemic embolism with no significant between group difference in the risk of major bleeding.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) (Granger *et al*., 2011) trial was a non-inferiority trial that compared apixaban with warfarin for the prevention of stroke and systemic embolism in patients at increased risk. Apixaban was demonstrated to be superior to warfarin in preventing stroke or systemic embolism (1.27 vs. 1.60% per year, $p<0.001$), caused less major bleeding (2.13 vs. 3.09% per year, $p<0.001$) and resulted in lower mortality rates (3.52 vs. 3.94%, $p = 0.047$).

PEAK BODY GUIDELINES

Practice guidelines published by the American College of Cardiology Foundation and American Heart Association suggest dabigatran as a useful alternative to warfarin in patients with atrial fibrillation who do not have a prosthetic heart valve, hemodynamically significant valvular disease, severe renal disease or advanced liver disease. They have not made any recommendations pertaining to other NOAC's (Anderson *et al*., 2013). Guidelines by the American College of Chest Physicians recommend dabigatran 150 mg twice a day rather than vitamin K antagonist therapy. They have not made recommendations pertaining to other NOAC's (You *et al*., 2012).

The Australian Pharmaceutical Benefits Scheme has published a document which reviews NOAC's safety, efficacy and pharmacology but do not make any recommendations regarding their use (Heidbuchel *et al*., 2013). The Australian National Prescribing Service have published a document outlining the initiation and monitoring of NOAC's and state that the place in therapy of the newer oral anitcoagulants is currently uncertain. Therapeutic Guidelines recommend dabigatran and rivaroxaban as second line agents in anticoagulation in non-valvular AF in patients at moderate to high risk of stroke.

The European Society of Cardiology has recommended NOAC's as preferable to warfarin in the vast majority of patients with non-valvular AF given their non inferiority and safety profile (Camm *et al*., 2012).

INITIATION AND MONITORING

Once decided that anticoagulation is appropriate each of the NOAC's can be initiated ensuring all contraindications have been excluded. Baseline renal and liver function tests should be performed to tailor dose adjustment and exclude coagulopathy. Given their short half life patients should be educated on compliance. Recommended doses have been outlined in Table 1.

NOAC's do not require routine monitoring of coagulation. However, in emergency situations such as serious bleeding or thrombotic events, coagulation studies should be performed and interpreted accordingly. In this process it is paramount to know the exact time of administration relative to the time of blood sampling. The maximal effect of the NOAC will occur at its maximal plasma concentration which is ~3 h after the intake of each of these drugs while trough levels occur 12-24 h after intake. Interpretation of coagulation tests for different NOACs can be found in Table 2 (Heidbuchel *et al*., 2013). When switching from warfarin, a NOAC can be started immediately once the INR is <2.0. If the INR is 2.0-2.5 a NOAC can be started immediately or the next day. If the INR is >2.5 a NOAC should not be initiated. For patients on intravenous unfractionated heparin a NOAC can be started once the

Table 1: Recommended dosages for NOACs

Dose		
Dabigatran	Apixaban	Rivaroxaban
150 mg orally twice daily or 110 mg orally twice daily in patients: age >75 renal function 30-50 mL min^{-1} pts with higher risk of bleeding -	5 mg orally twice a day or 2.5 mg orally twice daily in patients with two or more of the following risk factors: reduced renal function age >80 years weight<60 kg	20 mg orally once a day or 15 mg orally once daily in patients with renal fuction 30-49 mL min^{-1}

Table 2 : Coagulation test interpretation (Heidbuchel *et al*., 2013)

Levels	Dabigatran	Apixaban	Rivaroxaban
Plasma peak level	2 h after ingestion	1-4 h after ingestion	2-4 h after ingestion
Plasma trough level	12-24 h after ingestion	12-24 h after ingestion	12-24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged: may indicate bleeding INR risk but local calibration required
INR	Cannot be used	Cannot be used	Cannot be used
aPTT -	At trough 2xULN suggests excessive bleeding risk	Cannot be used	Cannot be used
Anti-FXa	Not applicable	No data yet	Quantitative: no data on threshold values for bleeding or thrombosis

Table 3: Clearance in renal dysfunction

	New Oral Anticoagulants (NOACs)		
Creatinine clearance	Dabigatran	Rivaroxaban	Apixaban
CrCl ≥80 mL min^{-1}	≥24 h (L), ≥48 h (H)	≥24 h (L), ≥48 h (H)	≥24 h (L), ≥48 h (H)
CrCl 50-80 mL min^{-1}	≥36 h (L), ≥ 72 h (H)	≥24 h (L), ≥48 h (H)	≥24 h (L), ≥48 h (H)
CrCl 30-50 mL min^{-1}	≥48 h (L), ≥96 (H)	≥24 h (L), ≥48 h (H)	≥24 h (L), ≥48 h (H)
CrCl 15-30 mL min^{-1}	Not indicated	≥36 h (L), ≥ 48 h (H)	≥36 h (L), ≥48 h (H)
CrCl<15 mL min^{-1}	Not indicated	-	-

L = Low bleeding risk surgery: endoscopy, radiofrequency ablation, angiography, pacemaker and ICD insertion; H = High bleeding risk surgery: complex left sided ablation, spinal/epidural anaesthesia, thoracic/abdominal/orthopaedic, TURP: liver/kidney biopsy

Table 4: Common drug interactions of NOACs (Heidbuchel *et al.*, 2013)

Drugs	Consider dose reduction if more than one interaction	Dose reduction recommended	Contraindicated/ not recommended
Dabigatran	Quinidine, amiodorone, clarithromycin and erythromycin	Verapamil	Dronedarone, ketoconazole, itraconazole, voriconazole, posaconazole, rifampicin, St. John; sWort, carbamazipine, phenytoin and phenobarbital
Rivaroxaban	Quinidine, fluconazole, cyclosporine, tacrolimus, clarithromycin, erythromycin, rifampicin, St. John; sWort, carbamazipine, phenytoin and phenobarbital		Ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors (e.g., ritonavir)
Apixaban	Diltiazem		Ketoconazole, itraconazole, voriconazole, posaconazole, rifampicin, St. John; sWort, carbamazipine, phenytoin, phenobarbital

heparin has been discontinued and for those on low molecular weight heparin a NOAC can be initiated when the next dose is due to be given.

When switching from a NOAC to warfarin, both should be given until the INR is above 2.0 then the NOAC is ceased. Parenteral anticoagulation can be given when the next dose of NOAC was due. As for switching between NOACs, the new agent can be given when the next dose of the old agent is due.

PERI OPERATIVE MANAGEMENT

For procedures with a minor bleeding risk it is recommended to discontinue NOACs 24 h before the elective procedure in patients with normal kidney function. In procedures that carry a high bleeding risk it is recommended to take the last NOAC 48 h prior. Patients on rivaroxaban and apixaban with a creatinine clearance of 15-30 mL min^{-1} are advised to cease the medication earlier for interventions with low or high risk of bleeding (>36 and >48 h, respectively). For dabigatran, timing of cessation is titrated against kidney function as outlined in Table 3. Anticoagulation can be recommenced once hemostasis is achieved and postoperative bleeding risk reduced (Heidbuchel *et al*., 2013).

DRUG INTERACTIONS

An important interaction mechanism for all NOAC's except rivaroxaban consists of significant resecretion over a P-glycoprotein (P-gp) transporter after absorption in the gut. Many drugs used in AF are P-gp substrates and so competitively inhibit this pathway and result in increased plasma levels. Notable examples include amiodarone, verapamil and quinidine.

CYP3A4 type cytochrome P450 dependent elimination in involved in rivaroxaban and apixaban hepatic clearance. Hence, any drugs which induce or inhibit this enzyme can significantly affect the plasma levels of these agents and should be used with caution in these patients. Table 4 outlines some common drug interactions of NOAC's.

Case study (answer): Yes it is useful and safe for this elderly lady to be treated with a NOAC upon ceasing her warfarin. It is important to check her renal function to ensure that she is not in severe renal impairment. A thorough physical examination is required to ensure that she has no severe valve disease and if required an echocardiogram may be helpful if there is an audible murmur. Since, the three agents have not been compared head-to-head with each other for superiority it is reasonable to consider any one agent provided that there are no contra-indications and concerns of drug-drug interactions.

CONCLUSION

NOAC's can be used in clinical practice. However, physicians should be aware of their potential side effects and toxicity.

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