

New oral anticoagulants: how safe are they?

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Introduction of the new oral anticoagulants (NoACs) to prevent and treat thromboembolic phenomena is one of the most significant innovations in clinical practice in the past 50 years. It has been about 6 years since the first new oral anticoagulant gained approval for stroke prevention in atrial fibrillation (AF) in the United States. The new anti-coagulants (Factor Xa inhibitors and factor IIa inhibitors) have major pharmacologic advantages over vitamin K antagonists (inhibiting clotting factors II, VII, IX, and X) and a very few disadvantages. Warfarin is still the drug of choice for patients with mechanical heart valves. If the patients' compliance is debatable NoACs will not be the drugs of choice as the off-set toxicity is high to create new clots. Cost of the NoACs is higher than warfarin but somewhat similar to low molecular weight heparin (which is administered subcutaneously). With increasing familiarity among the practitioners NoACs will establish a bigger market, and long term effects of using these drugs will be known.

In this article we have compared warfarin with the commonly used new oral anticoagulants to determine whether their use is safe in Sri Lanka.

Keywords: Stroke; bleeding; atrial fibrillation; pulmonary embolism; prevention

Introduction

AF is the most common sustained cardiac arrhythmia and is associated with an increased risk of stroke and other thromboembolic events.¹

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are serious but preventable conditions. Prophylactic treatment is cheaper than treating them.

There are new drugs that have been introduced to the market in the recent past that have made a difference to the patient's life styles when compared with the existing treatment regimes.

The high risk patients who are on these drugs can present for surgical interventions which pose a challenge for the clinicians to time the procedures and offer them an uneventful outcome.

Warfarin Sodium

The most widely prescribed oral anti-coagulant is warfarin sodium.² It is a synthetic vitamin K antagonist. It was discovered accidentally by

observing the cows dying of haemorrhagic shock after ingestion of straw spoiled by sweet clover^{3,5} when they underwent minor surgical procedures. In 1948 the research carried out at the University of Wisconsin discovered warfarin and hence it gained the name WARF (Wisconsin Alumni Research Foundation) and "arin" because it is derived from coumarin (natural substance found in many plants).^{4,5}

Mechanism of action

Warfarin acts by inhibiting the synthesis of vitamin K dependent clotting factors II, VII, IX and X and the anticoagulant proteins C and S.⁴

It is best known to anticoagulate in stagnant blood flow. Stagnant blood flow would occur in patients with DVT, patients with replaced heart valves with blood pooling behind the valves and those having dysfunctional cardiac atria giving



rise to thrombo-embolic events. Warfarin is also used in anti-phospholipid syndrome.⁵

Warfarin is not effective after myocardial infarction. Anti-platelet drugs are more effective in preventing new thrombus formation in coronary arteries.⁴

Dosing of warfarin

Warfarin therapy has many limitations. Dosing of the drug is difficult due to most of the commonly used medications (macrolide and many other broad spectrum antibiotics, anti fungals and corticosteroids) and food items (beef liver, leafy green vegetables, cabbage, ginger, starflower oil, fish oil, cranberries and soya beans) interacting with warfarin and as a result the anticoagulant effect can be varied^{5,6}. Therefore close monitoring of the international normalised ratio (INR) is required until a stable targeted INR (usually 2-3 and in patients with mechanical heart valves a higher value of 3-4) is achieved.⁷ The patients should be educated well about the drug and food interactions. And if any unknown food items or drugs were ingested INR monitoring should be carried out.

During the first 3 days of warfarinization the levels of anticoagulation factors (protein C and protein S) drop faster than procoagulation proteins - factors II, VII, IX and X. There is a temporary hypercoagulable state in this initial period which needs bridging with another anticoagulant (usually heparin).^{7,8}

Contraindications

Warfarin is contra indicated in pregnancy. When administered in the first trimester at 6-9 weeks of gestation foetus acquires skeletal abnormalities (nasal hypoplasia, narrowed nasal bridge, scoliosis, calcifications in the vertebral column, femur or heel bone and brachydactyly). In the third trimester if administered the foetus can get central nervous system disorders (spasticity, seizures) and eye defects.⁵ Any patient with malignant hypertension or has suffered sequel due to hypertension like

haemorrhagic stroke should not receive warfarin at any cost.⁶

Adverse Effects

Commonest side effect is bleeding. Risk of severe bleeding is not high unless the INR is above 4-5.^{7,9} When patients are on anti-platelet or anti-inflammatory drugs or have a high alcohol consumption the risk of bleeding is high. Bleeding can occur anywhere and most catastrophic is into the brain and spinal cord.⁹

Rare but a serious complication associated with warfarin therapy is necrosis. This is seen in patients with protein C (innate anticoagulant) deficiency. Skin necrosis and gangrene of limbs are being reported. Heparin is added when starting warfarin therapy to combat this⁵

In the recent past there have been various new oral anticoagulants introduced to the market. They have become popular due to the rapid onset and off set of action, few drug interactions, predictable pharmacokinetics and eliminating the requirement for regular coagulation monitoring.¹⁰

The most commonly used drugs are Rivaroxaban, Dabigatran and Apixaban.

Rivaroxaban

This was the first available oral factor Xa inhibitor that came to the market. It is well absorbed by the gut and the maximum effect is seen in 4 hours after administration and the effect lasts for 8-12 hours. Since the factor Xa activity doesn't return to normal by 24 hours once daily dosing is adequate.¹¹

Rivaroxaban is licensed for use to prevent deep vein thrombosis in patients undergoing elective hip and knee surgery in the post-operative period and in the prevention of embolic events in patients with non-valvular atrial fibrillation (AF) with one or more risk factors such as congestive cardiac failure, age (more than 75 years), diabetes mellitus and transient ischaemic events.¹²



Rivaroxaban is an oxizolidinone derivative that is highly selective in inhibiting the action of Factor Xa. It has a high bioavailability and has a rapid onset of action with no effects on the platelets or on factor II (thrombin).¹¹

Being a potent anticoagulant rivaroxaban is associated with bleeding. A possible antidote is still under research (and exanat alpha- antidote for factor Xa inhibitors) in phase 3 trials and is yet to be approved by US Food and Drug administration¹². Major or life threatening bleeding will require antidote therapy.

Patients with reduced kidney function should be given lower doses. If the Creatinine clearance (CrCl) is less than 30 ml/min rivaroxaban shouldn't be prescribed.

Dosing of Rivaroxaban

Any dose above 10mg is given with food.

DVT prophylaxis in orthopaedic surgery.¹³

Initial dose 6 hours after surgery after haemostasis is established. After knee replacement 10mg a day should be given for 12 days. After hip replacement - 10mg a day for 35 days.

Prophylactic therapy for non valvular AF- 20 mg

Treatment of DVT and Pulmonary embolism (PE)

15mg a day for 21 days, then 20mg a day for 6 months.

Dose modifications¹²

If the CrCl is 15-50ml/min in Non valvular AF- 15mg a day

If Crcl< 15ml/min avoid rivaroxaban

For post-operative thrombo prophylaxis

If CrCl is 30-50 ml/min no dose adjustments but use with caution. If Crcl<30ml/min avoid rivaroxaban for post-operative thrombo prophylaxis.

Any liver failure or coagulopathy should be contraindications for rivaroxaban therapy and it should be avoided in pregnancy and lactation.

Dabigatran

This is a direct thrombin inhibitor that is used to reduce the risk for stroke and systemic embolism in patients with non valvular AF and to prevent and treat venous thromboembolism.¹⁴

A laboratory test to assess anti coagulation is not available for dabigatran.

Most commonly reported side effect of dabigatran is gastro intestinal symptoms. When compared to warfarin patients treated with dabigatran has fewer life threatening bleeds or other major bleeds but gastro intestinal bleeding tends to be higher than with warfarin.¹⁴

Dabigatran produces an optimal effect within 2-3 hours of ingestion and has a half-life of 12-14 hours. Fatty foods can delay the absorption but bioavailability is unaffected. If combined with a proton pump inhibitor the absorption is moderately decreased and therefore is not recommended. Dabigatran capsule has tartaric acid which lowers the pH of the stomach and is required for absorption, but can give rise to effects like dyspepsia.

Renal impairment requires dose adjustments with dabigatran.¹⁴

Dosing of dabigatran

Creatinine clearance of over 50mls/min – 150 mg twice daily can be given.

If creatinine clearance is 30-50mls/min – 75mg twice daily

If the clearance is less than 15mls/min – should be avoided.

Dabigatran is the only novel anti-coagulant that has a Food and Drug Administration (USA) approved reversal agent. Idarucizumab can be used when reversal of the anticoagulant effects are needed for emergency surgery or urgent procedures, or in the event of life-threatening or uncontrolled bleeding.¹⁵



Apixaban

Apixaban is a highly selective, orally bioavailable, and reversible direct inhibitor of free and clot-bound factor Xa. Factor Xa catalyzes the conversion of prothrombin to thrombin, the final enzyme in the coagulation cascade that is responsible for fibrin clot formation. Apixaban has no effect on platelet aggregation.

Apixaban and other novel oral anticoagulants appear equally effective in prevention of non-haemorrhagic stroke in people with AF and have a lower risk of intra cranial bleeding.¹⁶

Apixaban is also effective in prevention of DVT in post hip and knee surgery, treatment of DVT and PE and reducing the risk of recurring DVT and PE after initial therapy.¹⁶

When different products were available in the market there is a choice for the clinicians. There were 3 major randomised trials carried out, ROCKET-AF (rivaroxaban versus warfarin), RE-LY (dabigatran versus warfarin) and ARISTOTLE (apixaban versus warfarin).¹⁷

The trials helped to compare the risks, benefits, long term effects and the cost to evaluate the long term effectiveness of these drugs compared to warfarin on patients with non valvular AF.

Dabigatran showed a significant reduction in thrombotic stroke. Apixaban showed a reduction in major bleeding and mortality. Also gastro intestinal bleeding was much less compared to other drugs. They also showed that Factor X inhibitors are less dependent on renal elimination and have fewer gastro intestinal effects. There was more compliance with rivaroxaban as it is given once daily. New oral anticoagulants dosing have to be adjusted in renal insufficiency but warfarin can be given in renal impairment. All the oral anti-coagulants are not safe in pregnancy.

Premature discontinuation of the new oral anticoagulants increases the risk of thrombosis for reasons other than pathological bleeding or completion of therapy course. It is not due to any rebound effect from discontinuation, but due to having no protection against the causative factor for embolic process. To reduce this risk, administering another anticoagulant is advised.

Comparison of the new oral anticoagulants with warfarin¹⁸

	Rivaroxaban	Apixaban	Dabigatran
Non valvular atrial fibrillation	Non inferior to warfarin	20% reduction ARISOTLE	34% reduction RE-LY
Heart valve replacement	No studies	No studies	No studies
Rheumatic valvular disease	No studies	No studies	No studies
Gastro intestinal bleeding	Can be increased	Minor	Can be increased
Intra cranial haemorrhage	40% reduced than warfarin	50% reduced than warfarin	74% reduced than warfarin
Major Bleeding	similar	30% reduction	similar
Drug Dose	Once daily	Twice daily	Twice daily
Renal Excretion	Less dependent. Dose modifications required	Less dependent. Dose modifications required	Mainly renal elimination. Reduce dose according to Cr clearance
Risk of embolism	High with missing a dose	High with missing a dose	High with missing a dose
Drug and food interactions	Minimal	Minimal	Minimal

New oral anticoagulants and neuraxial blocks

There are no contra indications for neuraxial blocks for patients on aspirin or non-steroidal anti-inflammatory drugs without other risk factors like hepatic insufficiency or excess alcohol consumption.

When spinal/epidural anaesthesia or puncture is utilized, patients who are being treated with anti-thrombotic agents for the prevention of thromboembolic complications are at risk for developing a haematoma, which can cause long-term or permanent paralysis. The risk of this may be increased by using epidural or



intrathecal catheters after a surgical operation or from the concurrent use of medicinal agents that affect haemostasis.

Timing of the drug administration, special investigations and monitoring of the bleeding risk will enable us to find a safe time to initiate the regional technique.

We have summarised the data in the table below^{19,20}

Drug	Pre-neuraxial blockage test	Timing of procedure	Bridging Therapy	After catheter removal when to restart	Monitoring
Low Molecular Weight Heparin (LMWH)	Most specific is Factor X, but not routinely performed	12 hours after prophylactic (0.5mg/kg) 24hrs after therapeutic(1mg/kg) dose	Not required	4 hours	No additional monitoring
Warfarin	INR	5 days or INR < 1.5 before procedure.	Yes with LMWH for about 2 days till INR> 1.5	When INR <1.4	Daily INR until dose stable
Rivaroxaban	No-test	24 hour(2x half-life) for regional blocks	Not required	after 6 hours (24hrs if traumatic inj)	None available
Apixaban	No-test	Ideally 48 hours, but 24hrs in emergency	Not required	after 6 hours (24hrs if traumatic inj)	None available
Dabigatran	No test	1-2 days (CrCl>50ml/min) 4-5 days (CrCl<30ml/min) before regional blocks and surgical procedures	Not required	Restart after 6 hours (24hrs if traumatic inj)	None available
Clopidogrel	No test	7 days following cessation	Not required	2 hours	P2Y12 assay not routinely done
Unfractionated iv Heparin	APTT	Administration of Heparin should be 1 hour after the block	Not required	1 hour before subsequent dose or 2-4 hours after last dose of Heparin	APTT
Subcutaneous heparin	APTT	Performed before subcut Heparin is administered(5000u/12hrly)	Not required	Follow same as for iv heparin	APTT

No anticoagulation should be carried out while an epidural catheter is in place other than sc heparin<5000 units.¹⁹

New oral anticoagulants have proved to be superior in treating non valvular AF compared to warfarin in many aspects. But the cost of the drugs is the only limiting factor compared to warfarin. Regular point of care testing requires the patients to attend outpatient clinics in developing countries. Educating the patients about the numerous food and drug interactions with warfarin also can be challenging which imposes close monitoring of INR. If the cost can balance the ease of use with the new oral anticoagulants they will have a role in thromboprophylaxis for non valvular AF, following hip and knee replacement and treating and preventing DVT and PE.

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