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CME ARTICLE

Novel oral anticoagulants for atrial fibrillation

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Mr Yang, an elderly man, visited your clinic to follow up on his chronic condition, accompanied by his daughter, who seemed unusually angry. After reading some materials on the Internet, Ms Yang was upset that her father had been taking 'rat poison' for his irregular heartbeat for the past eight years when better blood thinners were available. She wanted to know your opinion on this.

HOW COMMON IS THIS IN MY PRACTICE?

What are oral anticoagulants?

Anticoagulation therapy is effective in preventing primary and secondary thromboembolic events from atrial fibrillation. In 1954, warfarin was approved by the United States Food and Drug Administration (FDA);[1] it remained the only option for long-term oral anticoagulation therapy until the approval of dabigatran, a direct thrombin inhibitor, in 2010 and direct factor Xa inhibitors such as rivaroxaban from 2011 onwards. This newer class of drugs is referred to as non-vitamin K antagonist oral anticoagulants or novel oral anticoagulants (NOAC).

Warfarin is an effective anticoagulant with a narrow therapeutic index that may cause serious bleeding complications. It was first introduced in 1848 as a rodenticide and thought to be too potent for use as medication for humans.[1] Warfarin has many known interactions with food and drugs, including both western and herbal preparations. Vitamin K is administered to treat warfarin toxicity. The international normalised ratio (INR) is used to measure the therapeutic effectiveness of warfarin and its bleeding risk. The target range for most clinical indications is between 2.0 and 3.0;[1] however, this range should be individualised according to the patient's bleeding and thrombotic risks.

NOAC are new alternatives to the use of warfarin in patients with nonvalvular atrial fibrillation (AF). They have been shown to be superior to warfarin in the prevention of systemic embolism resulting in strokes, but no statistical differences have been found in the rate of prevention of ischaemic strokes and myocardial infarction.[2] Patients on NOAC had fewer haemorrhagic strokes and intracranial haemorrhage, and a slightly lower all-cause mortality, but a higher risk of gastrointestinal bleeding.[2] Other clinical indications for NOAC include venous thromboembolic events after surgery, deep vein thrombosis and pulmonary embolism, which will not be covered in this article.

WHAT CAN I DO IN MY PRACTICE?

Patient selection

The following four groups of patients could be considered for NOAC or referred to a cardiologist for advice on their suitability for NOAC: patients who (a) have poor venous access; (b) have difficulty receiving regular INR monitoring; (c) are on drug treatments that interact with warfarin, e.g. antiepileptics, thyroxine and recurrent antibiotics; and (d) cannot be stably anticoagulated on warfarin (within therapeutic range > 65% over three months) due to drugs or dietary interactions.

NOAC are contraindicated in patients with mechanical prosthetic valves and those with moderate-to-severe mitral stenosis. No antidote was available for NOAC until 16 October 2015, when the FDA gave accelerated approval for the use of idarucizumab (Praxbind®) for emergency reversal of the anticoagulation effects of dabigatran in life-threatening or uncontrolled-bleeding situations in the US.[3] In Singapore, haemodialysis may be used in cases of overcoagulation for patients on dabigatran,[4] but is not used to treat bleeding related to direct factor Xa inhibitor NOAC such as rivaroxaban and apixaban.

Before starting patients on NOAC, baseline renal and liver function levels should be obtained in order to correct the dosing regimen. Baseline haemoglobin levels are also useful for evaluating episodes of bleeding complications. NOAC should not be used in the presence of severe renal impairment (glomerular filtration rate < 30 mL/min),[4,5] as even patients who are initially stable on NOAC have a higher risk of bleeding complications when their renal function worsens. Rivaroxaban is metabolised by the liver and not suitable for patients with moderate-to-severe liver impairment. Prothrombin time (PT) and activated partial thromboplastin time (APTT) are tested to diagnose bleeding complications due to NOAC. An APTT that is more prolonged than PT is suggestive of dabigatran effect, in the absence of the use of heparin and low-molecular-weight fibrinogen, while a PT that is more prolonged than APTT is suggestive of a direct factor Xa inhibitor effect, in the absence of warfarin use or acute liver diseases.[6]

NOAC have fewer drug-drug interactions than warfarin, but are still affected by P-glycoprotein and CYP3A4 interactions. The concurrent use of ketoconazole is contraindicated with dabigatran (due to P-glycoprotein inhibition), and with

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rivaroxaban (due to P-glycoprotein inhibition and CYP3A4 inhibition), as drug levels may increase by more than 150%.[7] Other drugs that may increase drug levels when used concurrently are verapamil, amiodarone and quinidine with dabigatran and human immunodeficiency virus protease inhibitors, and clarithromycin with rivaroxaban. Rifampicin, which is commonly used in protracted tuberculosis treatment, may reduce drug levels by 50% for all NOAC.[7]

Discussions with patients and family members

Any discussion with patients and their family members about switching to NOAC should include an explanation on their clinical performance as compared to warfarin. As NOAC are significantly more expensive than long-term warfarin, the long-term financial burden of the switch must be taken into account. Providing a monthly or yearly estimated cost may be helpful for the patient or family in evaluating affordability. Another possible consideration is that local retail pharmacies may require time to bring in NOAC, as they usually do not have available stock. In addition, NOAC generally have a short half-life; hence, noncompliance to the twice-a-day regime and skipping medication may quickly result in a prothrombotic state.

An obvious advantage of switching to NOAC is the reduction in the number of clinic visits for regular blood investigations, which are required for the safe administration of warfarin within its narrow therapeutic range. This may translate to considerable monetary and time savings for patients who need additional help (e.g. wheelchair-bound or bedridden individuals) and their families, or those who spend considerable effort arranging for family members to accompany a patient to clinic consultations. In such cases, the option must be discussed with the patient and the accompanying next-of-kin.

Making the switch

For the clinical indication of nonvalvular atrial fibrillation, the switch from warfarin to NOAC generally involves stopping warfarin until the patient's INR drops below 2.0, at which time the patient is started on NOAC. There are recommendations that advocate starting rivaroxaban once the patient's INR is less than 3.0.[7]

Ms Yang was impressed with your explanation and information about oral anticoagulants. Mr Yang politely chided his daughter for being rude and decided that he will continue with warfarin therapy for his irregular heartbeat.

TAKE HOME MESSAGES

1. NOAC are new clinical alternatives to warfarin for nonvalvular atrial fibrillation.
2. NOAC do not require the frequent investigations and titrations of warfarin regimens.
3. NOAC have a twice-a-day fixed dosing and there is higher risk of a prothrombotic state when the dose is missed, due to their short half-life.
4. NOAC cost more than warfarin, but this has to be weighed against the cost of the regular clinic visits and investigations that are necessary for a safe warfarin regime.
5. NOAC have fewer food and drug interactions as compared to warfarin.
6. There is no locally available antidote for NOAC, although one has recently been approved for use in the US.

ABSTRACT Anticoagulation therapy is effective in preventing primary and secondary thromboembolic events due to atrial fibrillation. Warfarin, which was approved by the United States in 1954, was the only long-term oral anticoagulation therapy till the approval of dabigatran in 2010, and of rivaroxaban and other direct factor Xa inhibitors from 2011, forming a group known as novel oral anticoagulants (NOAC). NOAC have fewer food and drug interactions compared to warfarin; hence, the patient will require fewer clinic visits. However, the short half-life of NOAC means that twice-a-day dosing is needed and there is higher risk of a prothrombotic state when doses are missed. Other disadvantages are the lack of long-term data on NOAC, their high cost and the current lack of locally available antidotes.

Keywords: anticoagulation, atrial fibrillation, NOAC, non-VKA oral anticoagulants

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201512A)

	True	False
1. Common anticoagulation therapies, including warfarin, aspirin, ticlopidine and clopidogrel, are used in the prevention of stroke.	☐	☐
2. Warfarin is not effective in preventing primary and secondary thromboembolic events from atrial fibrillation.	☐	☐
3. Novel oral anticoagulants (NOAC) is a broad class of drugs that works either as a direct thrombin inhibitor or direct factor Xa inhibitor.	☐	☐
4. Non-vitamin K antagonist oral anticoagulants are older generation NOAC.	☐	☐
5. Warfarin was first introduced in 1848 as a rodenticide and thought to be too potent for use as medication for humans.	☐	☐
6. The antidote for anticoagulation from the use of warfarin and NOAC is administration of vitamin K.	☐	☐
7. The international normalised ratio (INR) measures the therapeutic effectiveness of NOAC.	☐	☐
8. Different clinical indications for NOAC regimens should have different individualised targets of INR according to bleeding and thrombotic risks.	☐	☐
9. NOAC have been shown to be superior to warfarin in the prevention of systemic embolism resulting in strokes.	☐	☐
10. Patients on NOAC had fewer haemorrhagic strokes and intracranial haemorrhage, a slightly lower all-cause mortality, but a higher risk of gastrointestinal bleeding.	☐	☐
11. Other clinical indications for NOAC include venous thromboembolic events after surgery, deep vein thrombosis and pulmonary embolism.	☐	☐
12. Switching from warfarin to NOAC regimens should be considered for patients with poor venous access or who have difficulty receiving regular INR monitoring.	☐	☐
13. Patients on treatment with drugs that interact with NOAC, e.g. antiepileptics, thyroxine and recurrent antibiotics, should be kept on warfarin regimes.	☐	☐
14. NOAC are safer than warfarin in patients with mechanical prosthetic valves.	☐	☐
15. The United States Food and Drug Administration gave accelerated approval for the use of idarucizumab (Praxbind) on 16 October 2015 for emergency reversal of the anticoagulation effects of dabigatran in life-threatening or uncontrolled-bleeding situations in the US.	☐	☐
16. Haemodialysis may be used in cases of overcoagulation for patients on dabigatran in Singapore, but it is not used to treat bleeding related to rivaroxaban and apixaban.	☐	☐
17. NOAC should not be used in the presence of severe renal impairment (glomerular filtration rate < 30 mL/min).	☐	☐
18. Prothrombin time (PT) and activated partial thromboplastin time (APTT) are more useful than INR to differentiate bleeding complications due to NOAC.	☐	☐
19. An APTT that is more prolonged than PT is suggestive of a direct factor Xa inhibitor effect, in the absence of warfarin use or acute liver diseases.	☐	☐
20. The concurrent use of ketoconazole is contraindicated with dabigatran (from P-glycoprotein inhibition) and with rivaroxaban (P-glycoprotein inhibition and CYP3A4 inhibition), as drug levels may increase by more than 150%.	☐	☐

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