PERSPECTIVE

Practical issues with using novel oral anticoagulants

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Appropriate patient selection is key to accessing the benefits of the novel oral anticoagulants without increasing the risks. Understanding how managing patients who are taking these novel anticoagulants differs from managing those taking warfarin is crucial to achieving optimal anticoagulation.

Key points

- **The pharmacokinetic characteristics of the novel oral anticoagulants (NOACs) and warfarin differ significantly and this has important implications for patient management.**
- **Current indications for NOACs in Australia are limited to patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke and primary prophylaxis of venous thromboembolism following elective hip or knee replacement surgery. Rivaroxaban is the only NOAC currently approved for the treatment and secondary prevention of venous thromboembolism.**
- **Patient selection should take into account renal and liver function, the few known drug interactions and the clinical characteristics of patients who were excluded from clinical trials.**
- **Routine laboratory monitoring in patients taking NOACs is not required.**
- **NOACs have a more rapid onset and offset of action than warfarin, which means perioperative management is simplified, eliminating the need for bridging anticoagulation.**
- **Antidotes to NOACs are in development but are not currently available for clinical use.**

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For more than 50 years, warfarin has been the principal oral anticoagulant and is used for a range of indications, despite its limitations of a narrow therapeutic index, delayed onset and offset of action, numerous food and drug interactions and wide interindividual variation in dosing. Novel oral anticoagulant (NOAC) agents have been developed to address these issues but they have different modes of action, pharmacokinetic profiles and limited clinical experience to date. This has implications for patient management because the protocols for laboratory monitoring, reversal of anticoagulant effect and periprocedural management of warfarin are not directly applicable to these new agents. If patients are to benefit from the convenience and efficacy of NOACs without increased risks, clinicians must learn new methods for anticoagulant management, as well as selection of the appropriate patients.

What are NOACs?

NOACs are agents that directly inhibit a single specific target in the coagulation pathway, either thrombin (dabigatran) or factor Xa (rivaroxaban and apixaban). This is in contrast to warfarin, which antagonises vitamin K, impairing hepatic production of coagulation factors II, VII, IX and X (Figure). The pharmacokinetic characteristics of NOACs differ significantly from warfarin and this has important implications for patient management (Table 1).

Indications for NOACs

Outcomes from large multicentre trials evaluating NOACs compared with standard therapy for each of the indications described below are summarised in the appendix in the online version of this article.[1-20] Direct comparisons of results from NOAC trials are not possible because of differences in trial design, patient populations, definitions of endpoints and availability of published data for some endpoints.

Nonvalvular atrial fibrillation

Dabigatran, rivaroxaban and apixaban are all approved for use in patients with nonvalvular atrial fibrillation and at least one additional

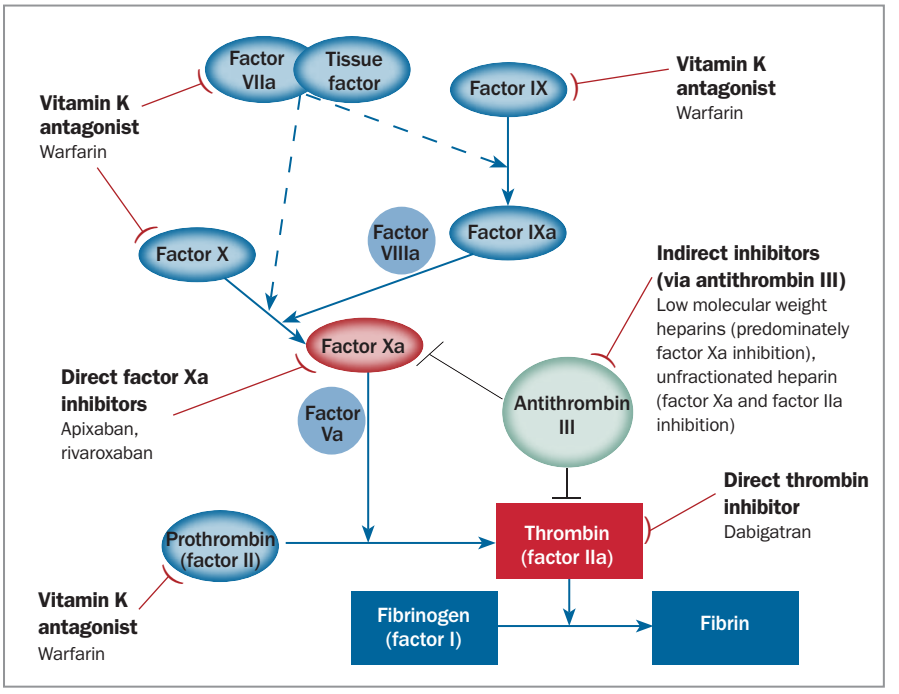

Figure. Targets for oral anticoagulants in the coagulation pathway.

Table 1. Comparative pharmacokinetic characteristics for warfarin and NOACs

Pharmacokinetic characteristics	Anticoagulants			
	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	Vitamin K epoxide reductase	Thrombin	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No
Bioavailability	>95%	6.5%	80%	About 66%
Time to C_{max}	72 to 96 hours	1 to 2 hours	2.5 to 4 hours	3 hours
Half-life	40 hours	9 to 13 hours	7 to 11 hours	8 to 15 hours
Monitoring	Routine	No	No	No
Dosing	Once daily, INR adjusted	Fixed, once or twice daily	Fixed, once daily*	Fixed, twice daily
Elimination	None	80% renal	67% renal, 33% faecal	25% renal, 75% faecal
Potential drug interactions	Extensive drug interactions: CYP 2C9, 3A4, 1A2	Potent P-gp inhibitors: amiodarone, verapamil, quinidine	Potent CYP 3A4 and P-gp inhibitors	Potent CYP 3A4 inhibitors

* Initial treatment dose for venous thromboembolism is twice daily for three weeks.
Abbreviations: INR = International normalised ratio; NOAC = novel oral anticoagulant.

risk factor for stroke. All NOACs reduce intracranial haemorrhage rates compared with warfarin, although large numbers of patients need to be treated to achieve this population benefit.[1-3] For patients with prosthetic valves, warfarin remains the anticoagulant of choice. In this high-risk population, dabigatran was associated with increased thromboembolism and bleeding rates compared with warfarin; however, other NOACs have not been studied in this patient population.[21]

Venous thromboembolism

Dabigatran, rivaroxaban and apixaban are all approved for prophylaxis of primary venous thromboembolism (VTE) in the context of elective hip and knee replacement surgery. NOACs are not approved in other surgical VTE prophylaxis settings as no major studies in this area have been carried out. NOACs are also not approved for primary VTE prophylaxis in medical ward inpatients because bleeding rates were increased with extended prophylaxis using rivaroxaban and apixaban.[11,12] Dabigatran has not been studied in these patients.

Rivaroxaban is the only NOAC currently approved for the treatment and secondary prevention of VTE; however, dabigatran and apixaban have been studied and may subsequently become approved for this indication in Australia.[13,14,16-18,20,21] The single-drug approach to VTE treatment with oral direct Xa inhibitors shows efficacy comparable with warfarin and similar or reduced risk of bleeding (see appendix). Patients at high thrombotic risk, such as those with antiphospholipid syndrome and recurrent thrombotic events, were excluded from clinical trials. Warfarin should remain the standard of care for these patients until NOACs are evaluated in this patient population. In patients with cancer-associated VTE, low molecular weight heparins are the treatment of choice and have not yet been compared with NOACs.[23] Rivaroxaban has not been compared with warfarin for long-term prevention of recurrent VTE in high-risk patients. Patient follow up should include regular reassessment of the risk–benefit ratio of continued anticoagulation.

Table 2. Laboratory assessment of the anticoagulant effect of NOACs

	Dabigatran	Rivaroxaban	Apixaban
Significant anticoagulant effect unlikely	APTT and TT normal	PT normal	Normal PT does not exclude presence of therapeutic apixaban
Anticoagulant effect present	TT prolonged APTT prolonged	PT prolonged	PT prolonged or normal
Specific assays to quantify drug presence and intensity	Dilute thrombin clotting time (Hemoclot assay)	Modified antifactor Xa assay specific for rivaroxaban	Modified antifactor Xa assay specific for apixaban

Abbreviations: APTT = activated partial thromboplastin time; NOAC = novel oral anticoagulant; PT = prothrombin time; TT = thrombin time.

Acute coronary syndromes

NOACs are not currently approved for the treatment of acute coronary syndromes in Australia. Studies have shown increased bleeding risk in patients in whom concomitant single or dual antiplatelet agents are used.[19,23,24] Some patients receiving dual antiplatelet therapy after coronary stenting will develop indications for anticoagulation, such as atrial fibrillation or acute VTE. These circumstances should be discussed with the patient's cardiologist and consideration given to cessation of one antiplatelet agent.

Patient selection

Patients taking long-term warfarin may benefit from changing to a NOAC if control of the international normalised ratio (INR) has been difficult, despite good compliance. These patients will require education about use of the novel agent. Patient preference will be a strong driver for use of a NOAC; however, appropriate patient selection should take into account drug pharmacokinetics and characteristics of patients who were excluded from clinical trials due to concerns about safety or anticoagulant efficacy, as discussed below.

In some cases, patient compliance may contribute to poor INR control. As warfarin has a much longer half-life than the NOACs, a single missed dose of warfarin will have less impact than missed doses of NOACs. When choosing between NOACs, once-daily treatment (rivaroxaban) may be more appealing to patients than a twice-daily regimen (dabigatran and apixaban). However, pharmacokinetic modelling suggests that missing one dose of a once-daily medication is equivalent to missing two or three consecutive doses of a twice-daily medication with a similar half-life.[25]

Taking warfarin may be difficult for some patients due to interactions with food or concomitant medications. There are no significant food interactions with NOACs, although rivaroxaban should be taken with food. Only a few NOAC drug interactions are significant. Rivaroxaban and apixaban should be avoided in patients taking azole antifungals, HIV protease inhibitors and rifampicin. Combination of dabigatran with azole antifungals or rifampicin should also be avoided. Verapamil, amiodarone and quinidine may all increase concentrations of dabigatran; however, the effect is lessened by administering dabigatran at least two hours before these drugs are taken.[26] Dabigatran should not be exposed to air before administration and therefore is not suitable for use in dosette boxes.

Use of all NOACs is contraindicated during pregnancy and while breastfeeding. NOACs are small molecules that cross the placenta and whether they are excreted in breast milk remains unknown.

Warfarin remains the anticoagulant of choice for patients with severe renal impairment or chronically declining renal function because all NOACs are renally excreted. Dose adjustments were made in the NOAC trials for patients with moderate stable chronic kidney disease. Patients with hepatic impairment or alanine transaminase levels more than twice the upper limit of normal were excluded from the NOAC trials.

Patients with significant anaemia, thrombocytopenia, recent surgery or gastrointestinal bleeding were also excluded from major treatment studies because of increased risk of bleeding. The risk–benefit ratio of using any anticoagulant in such patients should be evaluated on an individual basis. In addition, both dabigatran and rivaroxaban were associated with an increase in gastrointestinal bleeding compared with warfarin in the atrial fibrillation trials. If patients require anticoagulation but have a history predisposing them to gastrointestinal bleeding, warfarin or apixaban may be preferable.

Laboratory testing

Although people taking NOACs do not require routine monitoring, laboratory testing is informative in the context of bleeding, urgent surgery or recurrent thromboembolism. Standard coagulation assays are variably affected by NOACs but the results are not equivalent to INR testing for warfarin and do not indicate anticoagulant intensity.[27-29] At present, assays for drug quantitation are performed in specialised coagulation laboratories (Table 2). When planning the transition between NOACs and warfarin, effects of NOACs on prothrombin time and INR should be taken into consideration.

Transitioning between anticoagulants

If low molecular weight heparins have been used while awaiting a confirmatory test for VTE, rivaroxaban may be commenced when

Table 3. Preoperative interruption of novel anticoagulants use[31]

Novel anticoagulants and doses	Surgery	Renal function (creatinine clearance, mL/min)	Half-life of novel anticoagulant*	Timing of dose before surgery
Dabigatran 150 mg twice daily	Major†	>50	12 to 17 hours	72 hours
		30 to 50	13 to 23 hours	96 to 120 hours
	Minor†	>50	12 to 17 hours	48 hours
		30 to 50	13 to 23 hours	72 hours
Rivaroxaban 20 mg daily	Major†	>50	5 to 9 hours	48 to 72 hours
		30 to 50	9 to 13 hours	72 hours
	Minor†	>50	5 to 9 hours	24 to 48 hours
		30 to 50	9 to 13 hours	48 hours
Apixaban 5 mg twice daily	Major†	>50	7 to 8 hours	48 to 72 hours
		30 to 50	17 to 18 hours	72 to 96 hours
	Minor†	>50	7 to 8 hours	24 to 48 hours
		30 to 50	17 to 18 hours	48 to 72 hours

*Estimated half-life based on calculated renal clearance using the Cockcroft–Gault equation.
†Minor surgery: aiming for mild to moderate residual anticoagulant effect (<12 to 25%) at surgery.
†Major surgery: aiming for no or minimal residual anticoagulant effect (<3 to 6%) at surgery.

the next dose of low molecular weight heparin is due. When converting from warfarin to a NOAC, a current INR should be available. When the INR is between 2.0 and 2.5, warfarin can be ceased and the NOAC commenced the next day. If the INR is subtherapeutic (less than 2.0), the NOAC should be commenced the same day. Conversion from a NOAC to warfarin is more complicated because of the delayed onset of action of warfarin and the fact that both drugs may affect the INR. Haematology advice should also be sought.

Management of bleeding

Evaluation of the cause of bleeding and assessment for residual or excessive anticoagulant effect should be undertaken. Minor bleeding may be managed with local measures and temporary drug cessation. Patients with clinically significant bleeding may be managed with administration of activated charcoal, standard resuscitation measures, and surgical, radiological or endoscopic intervention. Prohaemostatic agents may be used but have no proven efficacy. Approximately 60% of active dabigatran may be removed from the plasma with dialysis but factor Xa inhibitors are too highly protein bound.[30] Vitamin K has no effect on NOACs. Reversal agents have now been developed for NOACs but they are just entering clinical trial evaluation.

Perioperative management

In contrast to warfarin, NOACs have a rapid onset of action, achieving full anticoagulant effect within hours of dosing. Residual drug effect after cessation is regarded as minimal after four to five half-lives have elapsed and thus the offset of the NOAC effect is also much more rapid. Consequently, bridging anticoagulation is unnecessary in most patients taking NOACs. The timing of preoperative drug interruption depends on the individual patient's thrombotic risk, bleeding risk associated with the intended surgery, degree of renal impairment and specific drug half-life (Table 3).[31] NOACs may be resumed 24 hours after minor procedures and surgery and at least 48 to 72 hours after major surgery.[32-34]

Conclusion

NOACs are a convenient alternative to warfarin for many patients but they are not suitable for all indications for anticoagulation. Appropriate patient selection is key to accessing NOAC benefits without increasing risks.[35] Understanding how managing patients who are taking NOACs differs from managing those taking warfarin is crucial to achieving optimal anticoagulation. **CT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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APPENDIX

Appendix. Outcomes of major NOAC studies according to indication for anticoagulation

Indication	Study name	Drug	Dose	Comparateur	Efficacy outcome	Safety outcome
Nonvalvular AF with at least one additional stroke risk factor	RE-LY[1]	Dabigatran Dabigatran	150 mg bd 110 mg bd	Warfarin Warfarin	Superior (150 mg bd) Noninferior (110 mg bd)	Noninferior (150 mg bd) Superior (110 mg bd)
Nonvalvular AF	ROCKET[2]	Rivaroxaban	20 mg daily (15 mg*)	Warfarin	Noninferior	Noninferior
Nonvalvular AF	ARISTOTLE[3]	Apixaban	5 mg bd (2.5 mg bd†)	Warfarin	Superior	Superior
Primary prophylaxis VTE post knee arthroplasty	RE-MODEL[4]	Dabigatran	220 mg daily (150 mg daily*)	Enoxaparin 40 mg daily	Noninferior	Noninferior
Primary prophylaxis VTE post hip arthroplasty	RE-NOVATE[5]	Dabigatran	220 mg daily (150 mg daily*)	Enoxaparin 40 mg daily	Noninferior	Noninferior
Primary prophylaxis VTE post hip arthroplasty	RECORD 1[6]	Rivaroxaban	10 mg daily	Enoxaparin 40 mg daily	Superior	Noninferior
Primary prophylaxis VTE post hip arthroplasty	RECORD 2[7]	Rivaroxaban	10 mg daily	Enoxaparin 40mg daily	Superior	Noninferior
Primary prophylaxis VTE post knee arthroplasty	RECORD 3[8]	Rivaroxaban	10 mg daily	Enoxaparin 40 mg daily	Superior	Noninferior
Primary prophylaxis VTE post knee arthroplasty	ADVANCE 2[9]	Apixaban	2.5 mg bd	Enoxaparin 40 mg daily	Superior	Noninferior
Primary prophylaxis VTE post hip arthroplasty	ADVANCE 3[10]	Apixaban	2.5 mg bd	Enoxaparin 40 mg daily	Superior	Noninferior
Primary prophylaxis VTE in acutely ill medical patients	MAGELLAN[11]	Rivaroxaban	10 mg daily (days 1 to 35)	Enoxaparin 40 mg daily (for 6 to 14 days)	Superior	Inferior
Primary prophylaxis VTE in acutely ill medical patients	ADOPT[12]	Apixaban	2.5 mg bd (days 1 to 30)	Enoxaparin 40 mg daily (for 6 to 14 days)	Noninferior	Inferior
Treatment of acute VTE	RECOVER I[13] RECOVER II[14]	Dabigatran	150 mg bd (initial heparin given)	Warfarin	Noninferior	Noninferior
Treatment of acute VTE	EINSTEIN DVT[15] EINSTEIN PE[16]	Rivaroxaban	15 mg bd for 21 days then 20 mg daily	Warfarin	Noninferior	Superior
Treatment of acute VTE	AMPLIFY[17]	Apixaban		Warfarin	Noninferior	Superior
Secondary prevention of VTE	RE-MEDY[18]	Dabigatran	150 mg bd	Warfarin	Noninferior	Noninferior
Secondary prevention of VTE	RE-SONATE[19]	Dabigatran	150 mg bd	Placebo	Superior	Inferior
Secondary prevention of VTE	EINSTEIN extension[15]	Rivaroxaban	20 mg daily	Placebo	Superior	Inferior
Secondary prevention of VTE	AMPLIFY-EXT[20]	Apixaban	2.5 mg bd, 5 mg bd	Placebo	Superior	Inferior

* Dose adjusted in patients with creatinine clearance 30 to 50 mL/min.

† Dose adjusted in patients with two of the following: reduced creatinine clearance, low body weight, advanced age.

Abbreviations: AF = atrial fibrillation; bd = twice daily; VTE = venous thromboembolism.

AF studies: efficacy outcome: recurrent stroke or systemic embolism; safety outcome: major bleeding.
VTE primary prophylaxis studies: efficacy outcome: symptomatic or asymptomatic VTE or death related to VTE; safety outcome: major bleeding.
VTE treatment studies: efficacy outcome: recurrent symptomatic VTE or death; safety outcome: major bleeding.