Approach to the new oral anticoagulants in family practice

Part 2: addressing frequently asked questions

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Abstract

Objective To address common "what if" questions that arise relating to the long-term clinical follow-up and management of patients receiving the new oral anticoagulants (NOACs).

Sources of information For this narrative review, we searched the PubMed database for recent (January 2008 to week 32 of 2013) clinical studies relating to NOAC use for stroke prevention in atrial fibrillation and for the treatment of acute venous thromboembolism. We used this evidence base to address prespecified questions relating to NOAC use in primary care settings.

Main message Dabigatran and rivaroxaban should be taken with meals to decrease dyspepsia and increase absorption, respectively. There are no dietary restrictions with any of the NOACs, beyond moderating alcohol intake, and rivaroxaban and apixaban can be crushed if required. The use of acid suppressive therapies does not appear to affect the efficacy of the NOACs. As with warfarin, patients taking NOACs should avoid long-term use of nonsteroidal anti-inflammatory and antiplatelet drugs. For patients requiring surgery, generally NOACs should be stopped 2 to 5 days before the procedure, depending on bleeding risk, and the NOAC should usually be resumed at least 24 hours after surgery. Preoperative coagulation testing is generally unnecessary. In patients who develop bleeding, minor bleeding typically does not require laboratory testing or discontinuation of NOACs; with major bleeding, the focus should be on local measures to control the bleeding and supportive care, and coagulation testing should be performed. There are currently no antidotes to reverse NOACs. The NOACs should not be used in patients with valvular heart disease, prosthetic heart valves, cancer-associated deep vein thrombosis, or superficial thrombophlebitis.

Conclusion Management of "what if" scenarios for patients taking NOACs have been proposed, but additional study is needed to address these issues, especially periprocedural management and bleeding.

EDITOR'S KEY POINTS

- As the new oral anticoagulants (NOACs) are being increasingly encountered in primary care, many questions are arising about how patients receiving NOACs should be managed in everyday practice. This review addresses many such questions, providing concise, evidence-based replies.
- Concomitant food and drug issues, management of patients requiring surgery or other invasive procedures, management of patients who develop bleeding or thrombosis, and possible additional clinical uses of NOACs are reviewed.

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Case description

A 73-year-old obese man with chronic atrial fibrillation (AF), type 2 diabetes, and hypertension requires a colonoscopy for removal of multiple polyps. His medications include 10 mg of ramipril once daily, 1000 mg of metformin 3 times daily, and 150 mg of the new oral anticoagulant (NOAC) dabigatran twice daily. You are asked to manage his anticoagulation around the time of his procedure.

Since 2010, 3 NOACs—dabigatran,[1] rivaroxaban,[2] and apixaban[3]—have become available for clinical use in Canada for stroke prevention in AF and for the prevention and treatment of venous thromboembolism (VTE). Despite comprehensive evaluation of the NOACs in well designed randomized trials, relatively little attention has been given to the use of NOACs in everyday practice and, in particular, to how to address common questions that arise in primary care settings. Addressing such questions is important because of the increasing uptake of the NOACs in Canadian clinical practice.[4] In part 1 of this 2-part review (**page 989**),

the NOACs were compared in terms of key pharmacologic properties and their use according to clinical indication and individual patient characteristics.[5] The objective of this article is to pose common questions that arise relating to NOAC use in primary care settings and to provide concise, evidence-based replies.

Sources of information

For this narrative review, we searched the PubMed database for the past 5 years (January 2008 to week 32 of 2013) for clinical studies relating to NOAC use for stroke prevention in AF and for the treatment of acute VTE. We used this evidence base to address our prespecified questions relating to NOAC use in primary care settings.

Main message

Administration of NOACs and concomitant food and drug issues

Does it matter if NOACs are taken with meals? Dabigatran capsules should be taken with meals to reduce the risk of dyspepsia.[6] Rivaroxaban should be taken with a meal to enhance absorption.[7] Rivaroxaban pills also can be crushed and taken with soft food such as applesauce. Apixaban can be taken with or without meals, and the pills can be crushed if required.[8] Dyspepsia can occur in approximately 10% of patients who receive dabigatran but it is often self-limited.[1] Dyspepsia is less common with rivaroxaban or apixaban.[9-11] The use of acid suppressive therapies such as ranitidine or proton pump inhibitors might alleviate gastrointestinal symptoms and is not known to affect NOAC efficacy.[12-14]

Are there any foods or beverages that should be avoided by NOAC users? There are no known restrictions for foods or beverages (eg, green vegetables and grapefruit juice, as with warfarin) in patients taking NOACs.[15] Alcohol use should be moderated, as for warfarin users, because of the increased risk of bleeding and trauma with excessive alcohol consumption.

Can NOAC users take nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen? Long-term use of NSAIDs should be avoided in patients treated with NOACs because the combination increases the risk of bleeding. However, it is probably safe to combine an NOAC with an NSAID for several days (eg, to treat acute joint pain).[16] Acetaminophen is preferred over an NSAID for joint pain, headache, and flulike symptoms because it does not have antiplatelet effects and does not cause peptic ulcer disease.[17]

Can NOAC users take acetylsalicylic acid or other antiplatelet drugs? As for warfarin users, concomitant long-term use of an NOAC with acetylsalicylic acid or other antiplatelet drugs (clopidogrel, ticagrelor, prasugrel) should be avoided in patients with AF because combination therapy increases the risk of bleeding and does not improve efficacy for stroke or thromboembolism prevention.[17,18] The combination might be justified in selected patient groups, including those with recent acute coronary syndrome, coronary stenting, or coronary artery bypass surgery.[19-21]

Managing patients taking NOACs who need surgery or other invasive procedures

What if a patient who is taking an NOAC needs dental work? For patients who need teeth cleaning, tooth extraction, or root canal procedures, NOACs can be continued around the time of the procedure as long as patients receive oral prohemostatic mouthwash (eg, tranexamic acid) before and after the procedure.[22,23] This is similar to the approach used in warfarin-treated patients who require minor dental procedures.[22] If substantial bleeding is expected, the patient should skip 1 to 2 days of the NOAC before the procedure and resume the NOAC on the evening after the procedure.[22] Periprocedural continuation of NOACs (as with warfarin) is usually safe for patients who require other minor procedures such as skin cancer removal, joint injection, or cataract removal.[22]

What if a patient who is taking an NOAC needs surgery? For such patients, management should be individualized depending on the NOAC used, the type of surgery (higher or lower bleeding risk), and the type of anesthetic administered (general, spinal, or regional).[22] Suggested perioperative management of NOAC-treated patients who require surgery is shown in **Tables 1** and **2**.[22,24] Before surgery, the timing of NOAC interruption depends on the degree of bleeding risk and patients' estimated glomerular filtration rate.[25] Caution should be used when resuming an NOAC after surgery because the rapid onset of action of these drugs (1 to 3 hours after intake) can increase the risk of bleeding if treatment is resumed too soon after surgery, especially after major surgeries (eg, hip or knee replacement). In general, resumption of an NOAC should be delayed for at least 24 hours after a surgery or procedure.[22]

The suggested management protocol for dabigatran-treated patients is based on a study of patients in the RELY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial who required interruption of anticoagulation for surgery or procedures. Perioperative outcomes in dabigatran- and warfarin-treated patients were similar when the management plan shown in **Tables 1** and **2**[22,24] was followed.[26]

Does a patient taking an NOAC need routine coagulation blood testing before surgery? Preoperative coagulation testing is unnecessary in patients taking NOACs who are undergoing elective surgery, as long as the suggested preoperative interruption schedule is followed. With this approach there should be minimal residual anticoagulant effect at the time of surgery.[22]

If additional reassurance is required that there is no clinically important residual anticoagulant effect (eg, if the

Table 1. Suggested preoperative management of patients taking NOACs

DRUG (DOSE REGIMEN)	RENAL FUNCTION	MINOR SURGERY OR PROCEDURE (LOW BLEEDING RISK)	MAJOR SURGERY OR PROCEDURE OR SPINAL ANESTHESIA (HIGH BLEEDING RISK)
Dabigatran (twice daily)			
• Half-life = 14 h	Normal renal function or mild impairment (eGFR > 50 mL/min)	Last dose: 2 d before surgery (skip 2 doses)	Last dose: 3 d before surgery (skip 4 doses)
• Half-life = 15-18 h	Moderate renal impairment (eGFR 30-50 mL/min)	Last dose: 3 d before surgery (skip 4 doses)	Last dose: 4-5 d before surgery (skip 6-8 doses)
Rivaroxaban (once daily)			
• Half-life = 9 h	Normal renal function or mild to moderate impairment (eGFR > 30 mL/min)	Last dose: 2 d before surgery (skip 1 dose)	Last dose: 3 d before surgery (skip 2 doses)
Apixaban (twice daily)			
• Half-life = 9 h	Normal renal function or mild to moderate impairment (eGFR > 30 mL/min)	Last dose: 2 d before surgery (skip 1 dose)	Last dose: 3 d before surgery (skip 4 doses)

eGFR—estimated glomerular filtration rate, NOAC—new oral anticoagulant.
Data from Douketis[22] and Thrombosis Canada.[24]

Table 2. Suggested postoperative management of patients receiving NOACs

NOAC	MINOR SURGERY OR PROCEDURE (LOW BLEEDING RISK)	MAJOR SURGERY OR PROCEDURE OR SPINAL ANESTHESIA (HIGH BLEEDING RISK)*
Dabigatran	Resume 1 d after surgery (24 h postoperative), 150 (or 110) mg twice daily	Resume 2 d after surgery (48 h postoperative), 150 (or 110) mg twice daily
Rivaroxaban	Resume 1 d after surgery (24 h postoperative), 20 mg once daily	Resume 2 d after surgery (48 h postoperative), 20 mg once daily
Apixaban	Resume 1 d after surgery (24 h postoperative), 5 mg twice daily	Resume 2 days after surgery (48 h postoperative), 5 mg twice daily

NOAC—new oral anticoagulant.
*An alternative approach would be to give a reduced dose of an NOAC for the initial 1-3 d. For example, dabigatran, 75 mg twice daily; rivaroxaban, 10 mg daily; or apixaban, 2.5 mg twice daily.
Data from Douketis[22] and Thrombosis Canada.[24]

timing of the last NOAC dose is uncertain), coagulation tests can be done. Patients taking dabigatran can have partial thromboplastin time measured, and if results are normal or near normal this suggests no important residual anticoagulant effect.[27] Patients taking rivaroxaban should have prothrombin time measured, and if it is not prolonged this probably indicates no residual anticoagulant effect, but the validity of this measurement is reagent specific.[28,29] For patients taking apixaban, routinely available coagulation tests do not provide a reliable measure of the anticoagulant effect.[30] A more specific measure of the anticoagulant effect of dabigatran is a direct thrombin inhibitor assay (a dilute thrombin time assay),[31] and for rivaroxaban and apixaban anti–factor Xa level can be measured using specific rivaroxaban or apixaban calibrators.[30,32,33]

Does a patient who needs NOAC interruption for surgery require heparin bridging? Patients who require temporary interruption of an NOAC for surgery do not require bridging anticoagulation because the NOACs have a rapid offset and onset of effect.[22]

Managing patients taking NOACs who develop bleeding or thrombosis

What if a patient develops minor bleeding? If patients who are receiving an NOAC develop minor bleeding, such as a subconjunctival, gingival, nasal, or hemorrhoidal bleed, the NOAC can usually be continued, as these are typically self-limiting.[22,23] This management mirrors that of warfarin-treated patients. There is usually no need to perform laboratory tests, as these will not affect management.

What if a patient develops major bleeding? In patients who develop major (or life-threatening) bleeding, the focus should be on local measures to control bleeding and supportive care with fluids and packed red cells.[23,34] Patients should have coagulation testing (prothrombin time, activated partial thromboplastin time, thrombin time) to assess if there is an excessive anticoagulant effect from the NOAC or other causes of acquired coagulopathy, and a complete blood count to assess hemoglobin and platelet count.[23,34] Specific tests to measure

NOAC blood levels (direct thrombin inhibitor assay for dabigatran, anti–factor Xa levels for rivaroxaban and apixaban) could also be considered if these tests are available. Serum creatinine measurement is useful to help estimate the half-life of the NOAC.

Vitamin K does not reverse the anticoagulant effect of NOACs,[1-3] and fresh frozen plasma is of unproven benefit.[15] Prothrombin complex concentrates that contain coagulation factors II, VII, IX, and X might overwhelm the inhibitory effects of the NOACs and should be considered for patients with intracranial or other serious bleeding, although their efficacy for prevention of morbidity and mortality is unproven.[35-37] In most patients NOAC-related anticoagulant effects will rapidly dissipate because of the drugs' short half-lives; patients with severe renal insufficiency are the exception, but NOACs are contraindicated in such patients.[23,34]

What if a patient develops a stroke or an acute coronary syndrome? For patients who are receiving an NOAC and who have a suspected stroke or an acute coronary syndrome, management should be the same as for other patients with these conditions. Patients should be assessed promptly in an urgent care facility because NOAC use might not preclude thrombolysis for acute ischemic stroke[38-41] or either thrombolysis or percutaneous coronary intervention for an acute coronary syndrome.[18] The issue of thrombolysis should be considered in the context of when the patient last received a dose of the NOAC and the expected or measured residual anticoagulant effect.[42]

Possible additional clinical uses for NOACs

Can NOACs be used in patients with AF and valvular heart disease? In general, only patients with AF and moderate-to-severe mitral stenosis are considered to have *valvular AF*. Warfarin is recommended in patients with valvular AF because NOACs have not been assessed for this indication.[43] Most patients with mitral insufficiency or aortic stenosis are considered to have nonvalvular AF and are eligible to receive NOACs.

Can NOACs be used in patients with mechanical prosthetic heart valves? The NOACs are contraindicated in patients with mechanical prosthetic heart valves.[44] A study that compared dabigatran (150, 220, or 300 mg twice daily) with warfarin in patients with mechanical heart valves was prematurely terminated because of an increase in the risk of thromboembolism and bleeding in dabigatran-treated patients.[45] No clinical studies assessing rivaroxaban or apixaban in patients with mechanical heart valves have been done.

Can NOACs be used in patients with bioprosthetic heart valves? In patients with previous (not recently implanted) bioprosthetic heart valves who have AF, NOACs can be used because the clinical indication for anticoagulation is the AF, not the bioprosthetic valve.

Can NOACs be used in patients with cancer-associated deep vein thrombosis (DVT)? First-line treatment of cancer-associated DVT is 3 to 6 months of low-molecular-weight heparin (longer in patients with ongoing disease), which can be problematic because of the inconvenience of daily injections.[46] Although NOACs provide an appealing alternative to low-molecular-weight heparins for cancer-associated DVT, NOACs should not be routinely used for such patients because their efficacy is unproven.

Can NOACs be used for patients with superficial thrombophlebitis? The NOACs should not be used for patients with superficial thrombophlebitis. Although it is likely that NOACs will be efficacious and safe for this indication, there are no completed studies in such patients and the appropriate dose regimens and treatment duration are not known.

Case resolution

Returning to our patient, it is clear that interruption of NOAC therapy is required because of the potential for considerable bleeding with multiple polypectomies if anticoagulation is continued. Based on the suggested periprocedural management protocol for dabigatran-treated patients, which is anchored on the type of procedure (high or low bleeding risk) and the patient's renal function, you ask the patient to stop dabigatran 4 days before the colonoscopy. The endoscopist removes 3 polyps and applies endoscopic clips to the remaining polyp stalks to prevent bleeding. Dabigatran is resumed 48 hours after the colonoscopy when there is no clinically overt bleeding.

Conclusion

For more information about using NOACs and other antithrombotic drugs in a primary care setting, visit the Thrombosis Canada website (**www.thrombosiscanada.ca**) to view the clinical guides,[24] which are designed to provide concise and easy-to-implement advice for use at the point of care when managing such patients taking NOACs or with thrombosis. You can also download a free smartphone clinical guides application.

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Contributors

All authors contributed to the literature review, analysis, and interpretation, and to preparing the manuscript for submission.

Competing interests

Dr Douketis has been a consultant or has attended advisory meetings (in the past 10 years) for Bayer, Boehringer Ingelheim, Biotie, AstraZeneca, Pfizer, Medicines Co, Bristol-Myers Squibb, and Sanofi-Aventis. **Dr Bell** has received research funding and consulting fees from the Canadian Cardiovascular Society, Thrombosis Canada, Boehringer Ingelheim, Bayer, Pfizer, and Bristol-Myers Squibb. **Dr Eikelboom** has received honoraria or consulting fees from

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