Checklists for the use of novel oral anticoagulants by the front-line clinician

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Background

After approval of warfarin in 1954, vitamin K antagonists (VKAs) remained the only oral anticoagulant option for over half a century, despite challenges to safely and effectively manage them in daily practice.^{1,2} In the past decade, 3 novel oral anticoagulants (NOACs)—apixaban, dabigatran and rivaroxaban—have been studied in large-scale clinical trials against standard therapy and have received Health Canada approval for the following indications: elective orthopedic (hip and knee arthroplasty) venous thromboembolism (VTE) prophylaxis, stroke prevention for nonvalvular atrial fibrillation (AF) and acute treatment and prevention of recurrent VTE.³⁻⁵ While all 3 of these agents pose many advantages relative to the VKAs, they must be applied to the right patient populations, with the right dosing and appropriate follow-up, to facilitate efficacy and safety in clinical practice.

Given the vast amount of information about NOACs in recent years (including clinical trials, meta-analyses, systematic reviews and alterations/updates in product monographs), it is paramount that the generalist front-line clinician have ready access to a succinct overview that compiles important prescribing information. While detailed reviews of NOACs have previously been published,⁶⁻⁸ our purpose is to highlight a tool we created to be used as checklists for apixaban, dabigatran and rivaroxaban. The intent of these checklists is to guide the generalist clinician in determining the appropriateness of therapy, making dose recommendations and managing commonly encountered scenarios.

Checklist development, scope and access

These checklists were developed by a group of 10 pharmacists who comprise the Collaborative Learning On Thrombosis (CLOT) group. The CLOT group was established in 2003 and consists of pharmacists who have a clinical practice/focus in thrombosis. Membership identified a need for a succinct, user-friendly resource to guide the appropriate use of the NOACs for front-line clinicians. The CLOT group used primary literature, Canadian product monographs and Canadian clinical practice guidelines as resources to create the checklists. The content was based on consensus of key elements necessary to make informed decisions in commonly encountered clinical situations. The following sections are consistent across the 3 checklists: indications, requirements, contraindications, potential limitations, potential advantages over warfarin, dosing recommendations, pertinent patient information, monitoring parameters, switching between anticoagulant agents (to and from warfarin plus to and from a parenteral anticoagulant), management of bleeding and periprocedural management. Importantly, these tools were not designed to direct the clinician to select one NOAC over another but rather to outline clinical considerations for each agent. The checklists are reviewed and revised every 6 months and more frequently, if warranted, based on new and evolving literature.

Initial distribution of the checklists was informal and was done by the CLOT members. Beginning in 2012, CLOT collaborated with RxFiles to reach

a broader audience and enable ready access to a current downloadable portable document format (PDF) (Figure 1). Downloadable checklists can be found as Appendices 1 to 3 of this article (available online at cph.sagepub.com/supplemental) and on the RxFiles website:

- www.rxfiles.ca/rxfiles/uploads/documents/CLOT-Apixiban-Checklist-Final-CPP.pdf
- www.rxfiles.ca/rxfiles/uploads/documents/CLOT-Dabigatran-Checklist-Final-CPP.pdf
- www.rxfiles.ca/rxfiles/uploads/documents/CLOT-Rivaroxaban-Checklist-Final-CPP.pdf

As of the fall of 2014, each checklist had been downloaded from the RxFiles website an average of 201 times per month (range, 139-255).

Application of the tool/checklist

These checklists may be used in a variety of practice settings (community pharmacies, primary health care teams) to aid in the initial prescribing and dispensing of a NOAC, to monitor patients, to provide patient information and to manage clinical situations (e.g., switching between agents, periprocedural management).

Scenario: Mrs. Smith has come to your pharmacy today with a prescription for [NOAC name] to be taken [dose and timing of administration]. Your technician has taken the prescription, filled it and placed it in the queue for you, and you see 4 prescriptions ready to go after Mrs. Smith's. As you just finish counselling another patient, you are directed to deal with a phone call on hold. You then turn to retrieve Mrs. Smith's prescription from the queue, walk into the counselling room with her and begin by . . .

Initial assessment of NOAC therapy

Ensuring appropriate selection of both the agent and dose requires the pharmacist to discern the indication for therapy, the patient's renal function (and degree of stability of renal function), and concomitant medications.

- Indication and dose³⁻⁵: Mrs. Smith's indication can be determined by asking her a few questions. If she's recently had elective

orthopedic (hip or knee) surgery, the NOAC dose to prevent VTE following elective orthopedic (hip and knee) arthroplasty is lower and a shorter duration of time is indicated. In contrast, if she's had an acute clot (e.g., deep vein thrombosis [DVT] or pulmonary embolus [PE]), full treatment NOAC doses should be used. Importantly, for those treated for acute VTE, varying therapy regimens are needed specific to each NOAC during the initial treatment phase (within 1-3 weeks, dependent on the agent), followed by dosing specific to the long-term phase of VTE treatment (out to 3-6 months), then the extended phase (long-term prevention of recurrent VTE), if applicable. Should Mrs. Smith have AF, and the pharmacist is uncertain of the diagnosis, several inquiries could be made. After the indications related to VTE treatment/prophylaxis are ruled out, asking Mrs. Smith whether she has an arrhythmia or "irregular heartbeat" alongside common risk factors for stroke (hypertension, heart failure, knowledge of advanced age, etc.) may support the indication of AF. If she has permanent AF, the pharmacist may assess Mrs. Smith's pulse for irregularity to support the diagnosis.⁹ To ensure appropriate dosing of a NOAC for AF, the pharmacist requires more information, most notably renal function.

- Renal function³⁻⁵: All of the NOACs have a component of renal elimination (27% for apixaban, 33% for [active] rivaroxaban, 80% for dabigatran). Neither dabigatran nor rivaroxaban is approved for use in Canada if creatinine clearance (CrCl) is below 30 mL/min, and for those having CrCl of 30-50 mL/min, dosage adjustments are indicated for the AF indication. For apixaban, once the CrCl is between 15 and 25 mL/min, limited clinical data are available to guide dosing. Importantly, if Mrs. Smith's CrCl is below 50 mL/min, the pharmacist should gauge the stability of renal function and use this as a marker to determine the appropriateness of NOAC therapy and dosing as well as the frequency of future CrCl assessments.
- Concomitant medications^{3-5,10}: While the NOACs have very few drug-drug interactions compared with warfarin, important interactions exist that contraindicate concomitant administration with a NOAC.

FIGURE 1 CLOT checklists

CLOT

Is Apixaban (Eliquis®) an Option for Your Patient?
Prior to prescribing, please review the following information

Indications¹

- ☐ Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism
- ☐ Prevention of
- ☐ Acute VTE treat

*CCS definition: A fib

Requirements¹ - NC

- ☐ Stable creati
- ☐ Stable liver fi

Contraindications¹

- ☐ Prosthetic he
- ☐ Apixaban, lik
- ☐ Pregnant/Bre
- ☐ Moderate to with severe l
- ☐ Drug Interacti

CLOT

Is Dabigatran (Pradaxa®) an Option for Your Patient?
Prior to prescribing, please review the following information

Indications¹

- ☐ Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism
- ☐ Prevention of
- ☐ Acute VTE treat

*CCS definition: A Fib

Requirements¹ - NO

- ☐ Stable creatini

Contraindications¹

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- ☐ Dabigatran, lik
- ☐ Pregnant/Bre
- ☐ Drug Interacti

CLOT

Is Rivaroxaban (Xarelto®) an Option for Your Patient?
Prior to prescribing, please review the following information

Indications¹

- ☐ Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism
- ☐ Prevention of venous thromboembolic events (VTE) in elective total hip or knee replacement surgery (THR, TKR)
- ☐ Acute VTE treatment & prevention of recurrent VTE [for deep vein thrombosis (DVT) and pulmonary embolism (PE)]

*CCS definition: Afib without rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, or mitral valve repair²

Requirements¹ - NOTE: Rivaroxaban accumulates in hepatic and/or renal dysfunction

- ☐ Stable creatinine clearance (CrCl) 30 mL/min or more
- ☐ Stable liver function or Child-Pugh A (i.e. score less than 7) [refer to Contraindications section below]

Contraindications¹

- ☐ Prosthetic heart valves, with/without atrial fibrillation: No data that rivaroxaban provides adequate anticoagulation
- ☐ Rivaroxaban, like other anticoagulants, is contraindicated in patients at high risk for bleeding
- ☐ Pregnant/Breastfeeding: Safety & dosing has not been studied. Use is NOT recommended
- ☐ Moderate to severe hepatic impairment (including Child-Pugh Class B and C: Score 7 or greater) associated with coagulopathy and clinically relevant bleeding risk. Patients with severe hepatic impairment have not been studied.
- ☐ Drug Interactions: Concomitant use of strong inducers or inhibitors of both CYP 3A4 and P-glycoprotein - See below

CLOT

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- ☐ Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism
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For dabigatran, drugs that are either strong inhibitors or inducers of P-glycoprotein should not be coadministered, as increased or reduced dabigatran levels, respectively, will result. For both rivaroxaban and apixaban, agents that are strong inhibitors (or inducers) of both P-glycoprotein and cytochrome P450 3A4 should be avoided.

As with any drug, the pharmacist should be aware of contraindications for appropriate use.³⁻⁵ To complete the initial assessment of the NOAC, the pharmacist should be aware of potential advantages over warfarin (if applicable) and potential limitations to the NOAC.

Inform your patient

Mrs. Smith should be well informed of the benefits of her NOAC, with clear explanation of the signs and symptoms of thrombosis that would be indicative of treatment failure and are dependent upon the

indication (e.g., stroke for AF; DVT or PE for VTE) and the need to seek medical attention. Counselling Mrs. Smith to ensure a general awareness of side effects, with bleeding most common to OAC therapy, is important so she knows what to look for and how to react based on her signs and symptoms. Drug-specific information should be covered. Should Mrs. Smith be prescribed rivaroxaban at either 15 mg or 20 mg dosing, she needs to take it with food to ensure adequate absorption.⁵ If dabigatran is prescribed, Mrs. Smith should be instructed to administer the capsule whole right after taking it out of the manufacturer's original packaging and should be informed not to open or crush the capsule.⁴ The pharmacist should be prepared to address dyspeptic symptoms such as heartburn or abdominal pain. Strategies such as administration with food or the use of an acid-suppressing agent (e.g., proton pump inhibitor) may be helpful to mitigate this side effect.¹¹ Above all, regardless of the NOAC prescribed, Mrs. Smith must be convinced of the importance of adherence,

given the short half-life of these agents and the risk of subtherapeutic anticoagulation in the event of missed doses.

While warfarin therapy requires ongoing assessment of the level of coagulation (and hence constant patient reinforcement), long-term therapy with a NOAC may impart a more cavalier attitude toward anticoagulant therapy, given the lack of ongoing reinforcement. As the duration of NOAC therapy continues, it is important that Mrs. Smith have ongoing reinforcement that she is taking an anticoagulant and that she should 1) notify all of her health care providers and 2) carry a wallet card or wear some sort of medical alert jewelry.

Ongoing monitoring of NOAC therapy

While routine coagulation testing is unnecessary for patients prescribed NOACs (note: if you deem coagulation testing necessary, the patient should likely not be prescribed a NOAC), clinicians should monitor renal function and hemoglobin at least annually, and more frequently if results are not within normal ranges or if patients suffer from diseases or conditions known to affect these parameters. Doses of NOACs may vary with indication and timing of treatment, mandating that the pharmacist ensure the appropriate dose is prescribed. The pharmacist should continue to reinforce to Mrs. Smith factors specific to her NOAC therapy, such as taking rivaroxaban with food or ensuring that dabigatran remains in the foil packaging until administration. Recent data indicate that dabigatran appears to be stable outside of the manufacturer's blister packs; however, the clinical implications of this storage are not yet known.¹² Assessment of adherence should be ongoing, with strategies implemented to optimize drug administration where appropriate.

Clinical scenarios of switching anticoagulants and periprocedural management

Special clinical situations occur among patients who are anticoagulated that require individualized management. When patients are switching between NOACs, the general goal is to ensure appropriate anticoagulant effect with one of the agents yet minimize the risk of bleeding. Subsequently, the new agent would be initiated at the point of near or actual subtherapeutic

anticoagulant coverage with the old agent. Depending on the individual patient's risk of thrombosis and bleeding, the clinician may elect to err on the side of having some anticoagulant activity with the old anticoagulant when starting the new (if high clot risk) or ensure adequate washout of the old agent prior to initiation of the new (if high bleed risk). Generally, for transitions between NOACs, the new agent is taken when the next dose of the old agent would have been scheduled. Transitioning from warfarin to a NOAC should be done based on the international normalized ratio (INR). Dabigatran and apixaban should be started once the INR drops below 2.0,^{3,4} while it is suggested that rivaroxaban be started once the INR falls below 2.5, owing to the higher risk population studied in the AF trial, where investigators reported strokes with suboptimal anticoagulant coverage during the transition from rivaroxaban to warfarin at the end of the study.⁵

Should Mrs. Smith require management of her NOAC around an invasive procedure, she may need to temporarily stop taking it. Assuming the NOAC must be stopped in advance, the pharmacist must determine the risk of bleeding for the procedure and, in turn, based on Mrs. Smith's ability to clear the drug (based on her renal function), the pharmacist must determine how long she must withhold her NOAC in advance of the procedure to minimize the risk of bleeding during the procedure. Afterward, the NOAC should be restarted once hemostasis is intact, with knowledge of the risk of bleeding from the procedure (e.g., for high bleed risk procedures, waiting 2-3 days to restart is common). Notably, once therapy is restarted with a NOAC, therapeutic anticoagulation will occur within hours, contrary to warfarin, where several days are required.

Summary

Anticoagulation drugs are lifesaving when used appropriately. However, misadventure with oral anticoagulants will result in devastating consequences to our patients. With the vast amount of information for NOACs released in the recent past, it is our hope that these practice tools will serve as a user-friendly resource for the front-line pharmacist to optimize patient outcomes in a variety of practice settings. ■

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