A pharmacist checklist for direct oral anticoagulant management: Raising the bar

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Background

Anticoagulation for atrial fibrillation (AF) is one of the most effective stroke prevention interventions available, with a relative risk reduction of more than 60% with warfarin versus placebo in patients with nonvalvular AF (NVAF).¹ Direct oral anticoagulant management (DOAC) therapy has been shown to be at least as good as or more effective than warfarin for stroke prevention in NVAF. The current Canadian Cardiovascular Society guidelines for the management of AF recommend DOACs over warfarin in the majority of NVAF patients.² In addition, with new evidence and recent changes to guidelines,³ the proportion of patients with venous thromboembolism (VTE) who are receiving indefinite DOAC anticoagulation is also increasing. Across Canada, prescriptions for any oral anticoagulant have increased from 4.8 million in 2008 to 7 million in 2013, with a continuous decline in warfarin prescriptions and a corresponding increase in DOAC prescriptions since 2011.⁴

In AF trials, major bleeding complications occurred in 2% to 4% of DOAC-treated patients annually—bleeding rates that were similar to, or lower than, the rates among warfarin-treated patients. All DOACs have been associated with a significantly lower incidence of intracranial hemorrhage (ICH) compared with warfarin. In practice, anticoagulation for AF is typically prescribed lifelong, often in older patients with multiple comorbidities who have greater bleeding risks and more complex medication regimens

than trial participants. While a number of guidelines are available to assist with patient selection and initial therapy, practice tools and recommendations specifically for follow-up and long-term monitoring of patients receiving DOACs are limited.

A critical issue with DOAC therapy is medication adherence because of their short elimination half-lives (7-17 hours on average) and absence of routine lab monitoring. The potential consequence of missed doses could be disabling or fatal strokes or VTE. In early postmarketing studies, up to one-quarter of dabigatran-treated AF patients had <80% adherence, and each 10% decrease in adherence was associated with a 13% greater risk of stroke or death.⁵ The lack of international normalized ratio (INR) monitoring is both a convenience of DOACs and a potential hazard because of elimination of adherence assessments and opportunities for support and reinforcement strategies. Thus, a key challenge for effective DOAC therapy is to help patients maintain persistent optimal adherence, including avoidance of missed doses and prolonged interruptions for procedures.

Pharmacists are the most accessible health care providers in the community and, as such, are in an excellent position to contribute to the long-term monitoring of DOAC-treated patients. Patients taking chronic therapies visit a pharmacy at least once every 3 months for medication refills and more often in many jurisdictions. Pharmacists have demonstrated

a significant impact on achieving improved medication adherence and outcomes in cardiovascular patients. In a recent study in which pharmacists assessed patient risk, recommended or prescribed lipid-lowering therapy and monitored and educated patients, more than 3 times as many patients reached their cholesterol targets.⁶ DOAC-specific programs delivered by pharmacists have demonstrated clinically significant improvements in appropriate dose selection at baseline as well as adherence.^{7,8} However, a Canadian survey of pharmacists found that only 20% of respondents felt very confident in managing DOAC therapy.⁹ Furthermore, access to patient-specific clinical information by community pharmacists can be challenging and is inconsistent across the country. Community pharmacists in Alberta and Saskatchewan, for example, have access to patients' creatinine values to calculate creatinine clearance, whereas in other provinces, community pharmacists do not have ready access to lab results and may need to rely on indirect information to assess a patient's renal function, such as patient self-report or presence of a nephrologist in their profile.

Given the increasing use of DOACs, the absence of routine laboratory coagulation monitoring and the potential for serious adverse events related to suboptimal adherence or bleeding, a systematic approach to DOAC monitoring, patient assessment and counselling appears warranted. With an interdisciplinary team, we developed a practice tool for DOAC patient monitoring that has been endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network and the Canadian Cardiovascular Society.¹⁰ We have adapted the original tool to facilitate cross-Canada use by community pharmacists with patients at the point of prescription refill. The pharmacist version of the tool was developed through a consensus process among the authors. The key principles and structure used to develop the original tool were maintained, and it was adapted to community pharmacist practice. Key edits were made to reflect the access of pharmacists to objective adherence data, to reflect limited access to clinical laboratory data in some regions of the country and to format the tool to be used to collect data and document drug therapy problems and the actions taken to prevent or resolve them. In addition, the tool underwent usability testing in both community practice and

long-term care, with the results informing the final design and content. To facilitate access, it is available on the Thrombosis Canada website.¹¹ The tool is organized into 5 domains (A to F) corresponding to key categories of DOAC refill assessments: Adherence, Bleeding risk, Creatinine clearance, Drug interactions, Examination of blood pressure and Final Assessment/Plan. It is accompanied by quick-reference tables summarizing dosing, interactions and periprocedural management (Appendix 1, available in the online version of the article).¹¹

A—Adherence Assessment and Counselling.

At each refill, ask patients about missed doses in a nonthreatening but direct way, acknowledging that taking chronic medications is challenging. Avoid asking leading questions such as, "You've been taking this medication twice a day, right?" Instead, try something like, "Some patients have challenges with taking this medication consistently. Do you have any questions about it? How many doses have you missed over the past week (or month)?" If no doses have been missed in an average week, provide positive reinforcement. If a patient is late in obtaining a refill, focus on potential reasons to facilitate a supportive interaction. When adherence is suboptimal, determine why and provide personalized counselling. Adherence is facilitated when patients understand their diagnosis, recognize the value of their therapy and trust their clinician.¹² Pharmacists should consider patient beliefs about health and medications as well as cost. Stressing the benefits and risks of the medication is key. For example, 1 in 5 AF-related strokes are fatal and 3 in 5 lead to permanent disability.¹³ While bleeding, including severe and life-threatening bleeding, is a risk with anticoagulant therapy, most anticoagulant-associated bleeds do not result in death or permanent disability.¹⁴ We prefer to use the term *anticoagulant* or *anticoagulating drug* rather than *blood thinner* since the latter is factually incorrect. To improve adherence, consider simplifying the medication regimen and providing adherence aids such as dosettes or blister packs.

Confirm that patients are following correct administration instructions (e.g., rivaroxaban should be taken with food for optimal absorption; dabigatran capsules should not be opened, crushed or chewed) and timing (the twice-daily

DOACs should be taken every 12 hours). Provide patients with a plan for missed doses. For patients on DOAC therapy for stroke prevention, a reasonable general approach to a missed dose is to take it as soon as they remember, but not if it is less than 6 hours before the next dose for twice-daily DOACs and not less than 12 hours before the next dose for once-daily DOACs. For patients on DOAC therapy for acute VTE, particularly in the early phase of therapy, ensure that patients complete the full course of therapy to prevent extension or embolization. Consult each DOAC product monograph for specific guidance on managing missed doses.

Support patients through periprocedural anticoagulant management to avoid lengthy interruptions that leave them unprotected. Ensure that patients have clear instructions and that their plan aligns with clinical guidelines on periprocedural DOAC management (such as Thrombosis Canada's clinical guides and online perioperative anticoagulant management algorithm accessible at www.thrombosiscanada.ca or the Canadian Cardiovascular Pharmacist Network SPAF app accessible at CCPN.ca).

B—Bleeding Risk Assessment. Use the checklist questions to screen for bleeding and bleeding risk factors, particularly those that are modifiable, such as excessive alcohol use, unnecessary antiplatelet or nonsteroidal anti-inflammatory drug (NSAID) use and uncontrolled hypertension (e.g., systolic blood pressure greater than 160 mmHg). Concomitant use of acetylsalicylic acid (ASA) increases the risk of bleeding in combination with DOACs by 30% to 60%.^{15,16} Therefore, the combined use of a DOAC and an antiplatelet agent should be employed only in select situations such as acute coronary syndrome (ACS), percutaneous coronary intervention (PCI or angioplasty) or specific high-risk patients, but not routinely for the majority of patients.

C—Creatinine Clearance (CrCL). As renal function influences the serum concentration of all of the DOACs, it should be assessed periodically during long-term therapy (annually at a minimum but more often in high-risk patients or if renal function is decreasing). Declining renal function may necessitate dose reduction or an alternate anticoagulant. Oral factor Xa inhibitors (~25%-50% renal elimination) may be a better choice than dabigatran (~80% renal elimination) when renal

function is moderately impaired (CrCL 30-50 mL/min) or unstable. In general, avoid DOACs in severe renal dysfunction (CrCL less than 30 mL/min, although specific DOACs may have lower CrCL cutoffs). Such patients should generally be followed by a medical specialist. Pharmacists with access to lab results (serum creatinine or estimated glomerular filtration rate [eGFR]) should check them at each follow-up. Pharmacists may identify those at greatest risk for renal function changes by being aware of concomitant illnesses such as hypertension, diabetes, and heart failure; identifying doses of other medications that are specific for renal dysfunction; and determining whether the patient has had a recent dehydrating illness and/or whether the patient has a nephrologist. Each DOAC has criteria for dose adjustments, generally based on renal function, age and weight. Patients who do not meet the specific criteria for adjusted dose of a DOAC should be taking the usual recommended dose to avoid complications related to underdosing. Remember that the priority is to prevent stroke (or treat an active VTE).

D—Drug Interaction Assessment and Education. Review the patient's medications for any that increase or decrease DOAC plasma concentrations and for ASA or NSAID use. In most anticoagulated AF patients, concomitant antiplatelet therapy is discouraged because it significantly increases bleeding risks with uncertain additional benefit. Exceptions include patients with recent ACS and/or coronary artery stents, high-risk mechanical heart valves and some other high-risk patients. Current guidelines recommend that patients with stable coronary artery disease in combination with AF should generally not receive ASA if they are receiving an anticoagulant for stroke prevention.² For DOAC-treated patients taking antiplatelet therapy, question the indication and assess whether the antiplatelet agent provides sufficient incremental benefit to warrant the definite increase in bleeding risk. Chronic NSAID use and excessive alcohol should be discouraged. Dabigatran and edoxaban serum levels are susceptible to change with coadministration of other drugs that either inhibit or induce P-glycoprotein (P-gp) activity. Rivaroxaban and apixaban are increased by strong inhibitors of both P-gp and cytochrome P450-3A4 and are decreased by strong inducers. As such, important classes of drugs that should prompt a

more detailed assessment are anticonvulsants, human immunodeficiency virus medications (particularly protease inhibitors), tuberculosis medications, azole antifungals, transplant immunosuppressants and macrolide antibiotics. However, as prescribing information regarding drug-drug interactions is continually updated, refer to the latest product monographs.

E—Examination. Measure blood pressure at each visit and encourage home monitoring for hypertensive patients. Hypertension is the leading risk factor for intracerebral hemorrhage and should be treated aggressively in anticoagulated patients. Conversely, in patients who have presyncope, check for orthostatic hypotension.

F—Final Assessment and Plan. Use the checklist to identify any “red flags” for real or potential drug therapy problems. The checklist data can help you decide whether the benefit-risk decision analysis favours continued DOAC therapy or if any specific intervention or physician review is warranted. We recommend assessing and documenting adherence using the checklist at each prescription refill.

In summary, anticoagulant management can be complex and the pharmacist can play a pivotal role in helping to maximize anticoagulant effectiveness and minimize adverse events. We encourage pharmacists to adopt this tool to achieve the goal of optimizing drug therapy outcomes. ■

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Acknowledgments: D. J. Gladstone gratefully acknowledges research support from the following sources: Mid-Career Award from the Heart & Stroke Foundation, Eaton Scholar Award from the University of Toronto Department of Medicine, Bastable-Potts Chair in Stroke, the Tory Family, and the Department of Medicine at Sunnybrook Health Sciences Centre, Toronto.

Author Contributions: Conception and design: K. Leblanc, D. J. Gladstone. Analysis and interpretation of the data: D. J. Gladstone, K. Leblanc, W. M. Semchuk, J. Papastergiou, B. Snow, V. Kapoor, L. Mandlsohn, L. M. Guirguis, W. H. Geerts, J. D. Douketis. Drafting of the article: K. Leblanc, D. J. Gladstone. Critical revision of the article for important intellectual content: D. J. Gladstone, K. Leblanc, W. M. Semchuk, J. Papastergiou, B. Snow, V. Kapoor, L. Mandlsohn, L. M. Guirguis, W. H. Geerts, J. D. Douketis. Final approval of the article: D. J. Gladstone, K. Leblanc, W. M. Semchuk, J. Papastergiou, B. Snow, V. Kapoor, L. Mandlsohn, L. M. Guirguis, W. H. Geerts, J. D. Douketis.

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Declaration of Conflicting Interests: K. Leblanc has received consulting fees and speaker honouraria from Boehringer Ingelheim, Bayer, Bristol Meyer Squibb/Pfizer Alliance and Servier. W. M. Semchuk, has received consulting fees and speaker honouraria from Boehringer Ingelheim, Bayer, Bristol Meyer Squibb/Pfizer Alliance, Servier and Sanofi. J. Papastergiou has received consulting and speaker honouraria from Bayer and Pfizer. B. Snow has received consulting and speaker honouraria from Bayer. V. Kapoor has received consulting fees from Boehringer Ingelheim and Bayer. L. Mandlsohn and L. M. Guirguis have no conflicts of interest to declare. J. D. Douketis has received consulting fees from Boehringer-Ingelheim, Bayer, Pfizer, Sanofi and Janssen Research and Development. He also receives royalties from The Merck Manual and Up-to-Date. W. H. Geerts has received consulting fees from Jansen Research and partial salary support from a hospital foundation account that has received donations from Sanofi. D. J. Gladstone has no disclosures from July 2016 onwards. Prior, he had received speaking and advisory honouraria from Boehringer Ingelheim, Bayer and Bristol Meyers Squibb/Pfizer Alliance.

Funding: The Pharmacist Checklist was supported by Thrombosis Canada through an unrestricted educational grant from Bayer Canada. The sponsors had no role in the content of the checklist or manuscript, which was conceived, written and edited by the authors as an academic project independent of industry. The checklist is available at <http://thrombosiscanada.ca/wp-content/uploads/2016/03/DOAC-Pharmacist-Checklist-27June2017.pdf>.

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