# Practical Recommendations on Incorporating New Oral Anticoagulants Into Routine Practice

Jaskirat Randhawa, MD, Nirosshan Thiruchelvam, MD, Michael Ghobrial, MD, Timothy Spiro, MD, Bernadette Clark, PharmD, Abdo Haddad, MD, and Hamed Daw, MD

Dr Randhawa is a fellow in hematology oncology at the University of Cincinnati in Cincinnati, Ohio. Drs Thiruchelvam and Ghobrial are senior residents in internal medicine at the Fairview/Cleveland Clinic Hospital in Cleveland, Ohio. Dr Spiro is a medical hematologist oncologist, Dr Clark is a pharmacist, Dr Haddad is a medical hematologist oncologist, and Dr Daw is a medical hematologist oncologist at the Moll Cancer Center at the Cleveland Clinic in Cleveland, Ohio.

Address correspondence to:
Jaskirat Randhawa, MD
Department of Hematology/Oncology
University of Cincinnati
Cincinnati, OH 45220
Tel: 216-501-0886
E-mail: randhajs@ucmail.uc.edu

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**Abstract**: The use of new oral anticoagulants (NOACs) is expected to rise significantly in upcoming years. Therefore, it is important to understand the potential uses, side effects, and management of these agents in routine practice. NOACs have major pharmacologic advantages over warfarin, including a rapid onset and offset of action, fewer drug interactions, and predictable pharmacokinetics. These agents are gaining popularity among both physicians and patients because of their ease of administration and the advantage of eliminating the requirement for regular coagulation monitoring. NOACs work to prevent and treat thrombosis by targeting either thrombin (as with dabigatran) or factor Xa (as with rivaroxaban and apixaban). In this review, we discuss practical recommendations for the use of NOACs and the risks and benefits of incorporating them into routine practice.

## Introduction

Venous thromboembolism (VTE) is the third most common cardiovascular disease after myocardial infarction and stroke, affecting at least 700,000 people annually in North America.[1] The annual incidence of VTE is approximately 0.1%, a rate that increases to 1% among patients who are at least 60 years old.[2] Anticoagulation is also widely used in patients with atrial fibrillation (AF). The estimated number of individuals with AF globally in 2010 was 33.5 million. Evidence exists of an increase in overall disease burden, incidence, and prevalence of AF, as well as in AF-associated mortality. Between 1990 and 2010, the mortality associated with AF increased by 2-fold in women and 1.9-fold in men.[3]

The oral vitamin K antagonist (VKA) warfarin is still in use despite its many limitations. The 2 major limitations are a narrow therapeutic window of adequate anticoagulation without increasing the risk of bleeding and a highly variable dose-response relationship that requires frequent monitoring. Other common problems reported with warfarin use are drug-food interactions, the need for frequent monitoring of international normalized ratio (INR) by either laboratory testing or self-testing, a slow onset of action, and prolonged bridging or transition to a therapeutic level.

The available new oral anticoagulants (NOACs) are dabigatran (Pradaxa, Boehringer Ingelheim), rivaroxaban (Xarelto, Janssen), and apixaban (Eliquis, Bristol-Myers Squibb). Dabigatran is a direct inhibitor of thrombin in the coagulation cascade, whereas rivaroxaban and apixaban are factor Xa inhibitors. The effective management of these newer drugs requires an understanding of their mechanism of action, pharmacokinetics, and pharmacodynamics.[4] The advantages of NOACs are their convenience, lower number of drug interactions, rapid onset of action, fixed dosages, and lack of food restrictions. The rapid onset of anticoagulation and the short half-life also make initiation and interruption of anticoagulation considerably easier than with VKAs.[5]

Below is an overview of the indications, contraindications, precautions, and drug interactions for dabigatran, rivaroxaban, and apixaban.

## Dabigatran

The direct thrombin inhibitor dabigatran has been studied in a number of different clinical settings, including treatment and prophylaxis of deep vein thrombosis (DVT), prevention of embolic stroke in patients with AF, and acute management of patients with unstable angina or myocardial infarction.[6] In a trial comparing 2 doses of dabigatran with warfarin in 18,113 patients with AF who were at risk for stroke, dabigatran was found to be equivalent or superior to warfarin as a function of dose. Patients who took dabigatran 110 mg twice daily had a rate of stroke or systemic embolism that was similar to that with warfarin, along with a lower rate of major hemorrhages. Patients who took dabigatran 150 mg twice daily had a rate of stroke or systemic embolism that was lower than that with warfarin, along with a similar rate of major bleeding.[7]

### *Indications*

Dabigatran has several indications that have been approved by the US Food and Drug Administration (FDA).

First, it has been approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF. The approved dose is 150 mg twice daily, except for elderly patients and/or those with underlying renal impairment.[8]

Second, it has been approved for use in VTE prophylaxis and treatment. Two doses of dabigatran—150 mg and 220 mg once daily—were studied in the RE-MODEL and RE-NOVATE trials. The trials found that both doses were as effective as enoxaparin 40 mg once daily in reducing the risk of total VTE and all-cause mortality after hip[9] or knee arthroplasty,[10] with a similar safety profile. However, in the RE-MOBILIZE trial, dabigatran was found inferior to enoxaparin 30 mg twice daily with respect to VTE prophylaxis after unilateral knee arthroplasty.[11]

Dabigatran is approved in the European Union and Canada for VTE prevention (220 mg once daily, with half the dose on the day of surgery) in patients who have undergone hip or knee arthroplasty.[12]

Since April 2014, dabigatran has been FDA-approved for the treatment of DVT and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5 to 10 days, and to reduce the risk of recurrent DVT and PE in patients who have been previously treated.[13]

### *Contraindications and Precautions*

Dabigatran is contraindicated in patients with mechanical prosthetic valves and in patients with severe renal impairment (creatinine clearance [CrCl] <15 mL/min).[8]

Because the majority of the drug is excreted renally (80%), a reduced dose (75 mg twice daily) should be considered in patients with moderate renal impairment (CrCl, 15-30 mL/min).[8]

The use of dabigatran for VTE prophylaxis in patients with AF in the setting of other forms of valvular heart diseases, including bioprosthetic heart valves, has not been studied and therefore is not recommended.[8]

If a dose is missed, the next dose of dabigatran should be taken as soon as possible on the same day. However, the missed dose should be skipped if the next scheduled dose is due in less than 6 hours. The dose of dabigatran should not be doubled to make up for a missed dose.[8]

### *Drug Interactions*

The concomitant use of dabigatran and permeability glycoprotein (P-gp) inducers (Table 1) falls into drug interaction category *X* and generally should be avoided because P-gp inducers decrease the effectiveness of dabigatran.[8] The combination of dabigatran and P-gp inhibitors falls into category *D* because P-gp inhibitors may increase serum concentrations of active metabolite(s) of dabigatran. As a result, an alternative therapy should be considered.[8] Additionally, P-gp inhibitors and impaired renal function (CrCl, 30-50 mL/min) are independent factors that can increase the exposure to dabigatran, causing toxicity. The concomitant use of dabigatran and P-gp inhibitors in patients with severe renal impairment (CrCl <30 mL/min) should be avoided.[8]

## Rivaroxaban

In a double-blind trial of 14,264 patients with nonvalvular AF, the factor Xa inhibitor rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was a nonsignificant difference in major and non-major bleeding events between the groups (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; *P*=.44), although patients in the rivaroxaban group had significantly lower rates of intracranial hemorrhage (0.5% vs 0.7%, *P*=.02)

**Table 1.** P-Glycoprotein and CYP3A4 Inducers and Inhibitors

| Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|
| **P-gp inducers** | **CYP3A4 strong inducers** | **CYP3A4 strong inducers** |
| carbamazepine, dexamethasone (systemic), doxorubicin, fosphenytoin, nefazodone, phenobarbital, phenytoin, prazosin, primidone, rifampin, St John's wort, tenofovir, tipranavir, and vinblastine | carbamazepine, dexamethasone (systemic), enzalutamide, fosphenytoin, mitotane, nafcillin, nevirapine, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, primidone, rifabutin, rifampin, and rifapentine | carbamazepine, dexamethasone (systemic), enzalutamide, fosphenytoin, mitotane, nafcillin, nevirapine, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, primidone, rifabutin, rifampin, and rifapentine |
| **P-gp inhibitors** | **CYP3A4 strong inhibitors** | **CYP3A4 strong inhibitors** |
| abiraterone acetate, amiodarone, atorvastatin, carvedilol, clarithromycin, cobicistat, crizotinib, cyclosporine (systemic), darunavir, dipyridamole, dronedarone, erythromycin (systemic), grapefruit juice, itraconazole, ivacaftor, ketoconazole (systemic), lapatinib, lomitapide, lopinavir, mefloquine, nelfinavir, nicardipine, nilotinib, progesterone, propranolol, quinidine, quinine, ranolazine, reserpine, ritonavir, saquinavir, simeprevir, sunitinib, tacrolimus (systemic), tamoxifen, telaprevir, ulipristal, vandetanib, vemurafenib, and verapamil | atazanavir, boceprevir, chloramphenicol, cobicistat, conivaptan, darunavir, delavirdine, fosamprenavir, indinavir, itraconazole, ketoconazole (systemic), lopinavir, nefazodone, nelfinavir, nicardipine, posaconazole, ritonavir, saquinavir, stiripentol, telaprevir, telithromycin, and voriconazole (exception: clarithromycin) | atazanavir, boceprevir, chloramphenicol, clarithromycin, cobicistat, conivaptan, darunavir, delavirdine, fosamprenavir, indinavir, itraconazole, ketoconazole (systemic), lopinavir, nefazodone, nelfinavir, nicardipine, posaconazole, ritonavir, saquinavir, stiripentol, telaprevir, telithromycin, and voriconazole |

P-gp, p-glycoprotein.

Based on the package inserts for Pradaxa,[8] Xarelto,[16,18] and Eliquis.[22]

**Table 2.** NOAC Dose-Adjustment Recommendations in Renal Impairment and AF

| Degree of impairment | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| **Mild** (CrCl, 60-89 mL/min) | No adjustment required | No adjustment required | No adjustment required[a] |
| **Moderate** (CrCl, 30-59 mL/min) | Dose reduction recommended 75 mg twice daily (AF), 150 mg daily (VTE prophylaxis) | No adjustment required, except 15 mg/day for AF | No adjustment required[a] |
| **Severe** (CrCl, 15-29 mL/min) | Contraindicated | Contraindicated (some studies have used 15 mg/day for AF with high precautions) | No adjustment required[a] (use with caution) |
| (CrCl <15 mL/min or dialysis patients) | Contraindicated | Contraindicated | No data available |

AF, atrial fibrillation; CrCl, creatinine clearance; NOAC, new oral anticoagulant drug.

[a] The recommended dose is 2.5 mg twice daily for patients with 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dL.

Based on data from Poulsen BK et al. *Drugs*. 2012;72(13):1739-1753[28] and the package inserts for Pradaxa,[8] Xarelto,[16] and Eliquis.[22]

and fatal bleeding events (0.2% vs 0.5%, *P*=.003) than those in the warfarin group.[14] Rivaroxaban is excreted predominantly by the kidneys (70%), with a small component excreted by the liver (30%).[15]

### *Indications*

Rivaroxaban has several FDA-approved indications.

First, it has been approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF. The dose for this indication is 20 mg once daily, except in elderly patients and in those with renal impairment, who need a reduced dose (Table 2).[16]

Second, it has been approved for the treatment and reduction in recurrence risk of DVT and PE (see Table 3 for drug doses).[16]

Third, it has been approved for VTE prophylaxis. The approved dose of rivaroxaban for this use is 10 mg daily, beginning 6 to 10 hours after surgery and continuing for 5 weeks after total hip arthroplasty and 2 weeks after total knee arthroplasty).[15]

### *Contraindications and Precautions*

Rivaroxaban should not be used in patients with a CrCl below 30 mL/min, who were not included in studies of this agent.

**Table 3.** Application of NOACs in VTE Prophylaxis and Treatment and PE Management

| NOAC Agent | Drug Dose | Clinical Application |
|---|---|---|
| **Dabigatran**[46-48] (dose reduction is advised in patients with renal insufficiency) | 1. 150 mg daily[a]<br>2. 150 mg twice daily | 1. VTE prophylaxis (FDA approved)<br>2. Symptomatic VTE treatment (FDA approved) |
| **Rivaroxaban**[46,49-51] | 1. 10 mg once daily<br>2. 15 mg twice daily for 3 weeks, followed by 20 mg once daily | 1. VTE prophylaxis[b] (FDA approved)<br>2. Symptomatic VTE and PE treatment (FDA approved) |
| **Apixaban**[20,46,52] | 1. 2.5 mg per day<br>2. 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months | 1. VTE prophylaxis (FDA approved)<br>2. Symptomatic VTE treatment (FDA approved) |
| **Edoxaban**[53,54] | 1. 15 mg once daily<br>2. 60 mg once daily, or 30 mg once daily (in patients with creatinine clearance of 30 to 50 mL per minute or a body weight below 60 kg) | 1. VTE prophylaxis (not FDA approved)<br>2. Symptomatic VTE and PE treatment (not FDA approved) |

FDA, US Food and Drug Administration; NOAC, new oral anticoagulant; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Dabigatran is approved in Europe for VTE prophylaxis at an oral dose of 220 mg once daily. For patients older than 75 years and with creatinine clearance of 30-50 mL/min, the total daily dose is reduced to 150 mg once daily.

[b] Extended-duration rivaroxaban showed reduced risk of VTE, but was associated with an increased risk of bleeding.

Elderly patients may be at increased risk for bleeding. People aged 75 years and older may exhibit elevated plasma concentrations of rivaroxaban, with the mean area under the curve (AUC) being approximately 50% higher than in younger patients.[16,17] In the ROCKET AF (Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study, the concomitant use of aspirin and rivaroxaban was identified as an independent risk factor for major bleeding.[14,16]

### *Drug Interactions*

The combination of rivaroxaban and strong inducers of CYP3A4 (Table 1) falls into drug interaction category *X*. Strong inducers of CYP3A4 decrease the serum concentration of rivaroxaban, so concurrent use of rivaroxaban with these drugs should be avoided when possible.[16,18] US prescribing information recommends avoiding concurrent use of rivaroxaban and any drugs that are strong inducers of both CYP3A4 and P-gp.[18]

The combination of rivaroxaban and moderate inhibitors of CYP3A4 also falls into drug interaction category *X*, and concurrent use should be avoided when possible.[18] Moderate inhibitors of CYP3A4 include abiraterone acetate (Zytiga, Janssen Biotech), aprepitant, bicalutamide, cimetidine, clotrimazole (oral), crizotinib (Xalkori, Pfizer), cyclosporine (systemic), desipramine, diltiazem, dronedarone, efavirenz, fluconazole, fosaprepitant, grapefruit juice, haloperidol, iloperidone, imatinib (Gleevec, Novartis), lomitapide, norfloxacin, sitaxsentan, tetracycline, and verapamil, as well as systemic erythromycin, which can be used in combination with rivaroxaban. Patients with impaired renal function (CrCl, 15-80 mL/min) should not use moderate inhibitors of P-gp and CYP3A4 unless the potential benefits outweigh the potential risks.[18]

Strong inhibitors of CYP3A4 (Table 1) should be avoided, as many such agents are inhibitors of P-gp as well.[18]

## Apixaban

In a randomized, double-blind trial of 18,201 patients with AF called ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation), the factor Xa inhibitor apixaban was found to be superior to warfarin at preventing stroke or systemic embolism, decreasing bleeding, and decreasing mortality.[19] A fixed-dose regimen of apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) has been shown to be noninferior to conventional therapy (subcutaneous enoxaparin, followed by warfarin) in the treatment of acute VTE, and was associated with significantly less bleeding.[20] When prescribed twice daily, apixaban can be the drug of preference in renal impairment because only approximately 30% of the drug is excreted through the kidneys.[15] Apixaban can reach maximal plasma concentration in 2 to 4 hours after administration, and has a bioavailability ranging from 80% to 100%.[21]

### *Indications*

Apixaban has the following FDA-approved indications. First, it is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF. The suggested dose for this indication is 5 mg twice daily, except for elderly patients with renal impairment, for whom a reduced dosage of 2.5 mg twice daily is suggested (Table 2).[22] Second, it is approved for the treatment of VTE, to reduce the risk

**Table 4.** Transition From or to NOACs

| | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| **From warfarin to NOACs** | Discontinue warfarin and start dabigatran when INR is below 2.0 | Discontinue warfarin and start rivaroxaban when INR is below 3.0 | Discontinue warfarin and start apixaban when INR is below 2.0 |
| **From NOACs to warfarin** | The warfarin start time should be adjusted based on CrCl. Dabigatran affects INR, so INR measurement may not be appropriate. | No clinical trial data available to guide switching at this time. Rivaroxaban affects INR, so INR measurement may not be appropriate. Possible approach is to discontinue rivaroxaban, and start both parenteral anticoagulant and warfarin at the time of next dose of rivaroxaban. | Discontinue apixaban, and start both parenteral anticoagulant and warfarin at time of next dose of apixaban. Discontinue parenteral anticoagulant when INR reaches an acceptable range. |

Creatinine clearance, CrCl; INR, international normalized ratio; NOAC, new oral anticoagulant.

Based on data from the package inserts for Pradaxa,[8] Xarelto,[16] and Eliquis.[22]

of recurrent VTE following initial therapy, and for VTE prophylaxis in patients who have undergone hip or knee arthroplasty (see drug doses in Table 3).[22]

### *Contraindications and Precautions*

The contraindications to apixaban are active bleeding and severe hypersensitivity reaction to the drug. Because there are few data on the use of apixaban in patients on dialysis or in those with CrCl of less than 15 mL/min, caution is advised in these patients.

### *Drug Interactions*

The concurrent use of apixaban with any strong inducers of CYP3A4 (Table 1) should be avoided wherever possible.[22] The concurrent use of apixaban with strong dual inducers of CYP3A4 and P-gp (eg, rifampin, carbamazepine, phenytoin, and St John's wort) should be avoided in all circumstances. The product labeling in both the United States and Canada advises against such usage.[22]

The use of apixaban with drugs that are strong dual inhibitors of CYP3A4 and P-gp may increase the risk of bleeding. Per apixaban US prescribing information, the dose of apixaban should be decreased to 2.5 mg twice daily in patients receiving strong dual inhibitors of CYP3A4 and P-gp who would otherwise receive 5 mg twice daily.[22] Common strong inhibitors of CYP3A4 are listed in Table 1.

## Discussion

NOACs are gaining popularity because of their advantages over the VKA warfarin. In this section, we will discuss how to switch between NOACs and warfarin when necessary; the salient features one should keep in mind while prescribing NOACs in patients with hepatic impairment, renal impairment, or heart failure; perioperative management of patients taking NOACs; the role of NOACs in bridging to warfarin; the need for blood coagulation assays; and toxicity and reversal.

### *Switching Patients Between a NOAC and Warfarin*

To switch patients from a NOAC to warfarin, the agents can be administered concomitantly until the INR is therapeutic. NOACs may have an additional affect on the INR (especially if they are factor Xa inhibitors); therefore they can influence the measurement while on combined treatment during the overlap phase. The INR measurement should be just before the next intake of the NOAC during concomitant administration, and should be retested 24 hours after the last dose of the NOAC (ie, therapy with warfarin alone) to assure adequate anticoagulation (Table 4).[23]

To switch patients from warfarin to a NOAC, warfarin should be discontinued. Dabigatran or apixaban should be started when the INR is below 2.0, and rivaroxaban should be started when the INR is below 3.0 (Table 4).[8,22]

### *Patients With Liver Impairment*

Moderate hepatic impairment (Child-Pugh class B) does not affect the safety profile of dabigatran, and the drug can be prescribed without the need for dose adjustment in these patients.[24] Because dabigatran is not metabolized by cytochrome P450 isoenzymes, the small differences in pharmacokinetics seen with this drug are associated with age-related variations in renal function.[25] Dabigatran is not recommended for use in patients with abnormal liver enzymes (ie, patients with >2 times the upper limit of normal [ULN]), and is contraindicated in patients with hepatic impairment or liver disease, which can impact patient survival.[26]

In moderate liver impairment, the AUC for plasma concentration time is increased by 2.27-fold for rivaroxaban (10-mg single dose) and by 1.09-fold for apixaban (5-mg single dose). Therefore, rivaroxaban is contraindicated in patients with hepatic disease associated with clinically relevant bleeding risk, including the cirrhotic patients classified as Child-Pugh class B and C.[26]

Apixaban should be used with caution in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment or in patients with transaminase

**Table 5.** Dose Adjustment Recommendations in Hepatic Impairment

| Degree of Impairment | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| **Mild** (Child-Pugh A) | No dose adjustment required | Caution advised | No dose adjustment required[a] |
| **Moderate** (Child-Pugh B) | No dose adjustment required, but caution is advised | Avoid or discontinue the drug | Limited data with apixaban (caution is advised) |
| **Severe** (Child-Pugh C) | Avoid or discontinue the drug | Avoid or discontinue the drug | Avoid or discontinue the drug |

CrCl, creatinine clearance.

[a] The recommended dose is 2.5 mg twice daily for patients with 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dL.

Based on data from Stangier J et al. *J Clin Pharmacol*. 2008;48(12):1411-1419,[24] Graff et al. *Clin Pharmacokinet*. 2013;52(4):243-254,[26] and the package inserts for Pradaxa,[8] Xarelto,[16] and Eliquis.[22]

levels more than 2 times the ULN. It should be avoided in patients with severe hepatic impairment, and is contraindicated in those with hepatic disease associated with coagulopathy with clinically relevant bleeding risk.[26] Caution should be taken while treating patients who are at risk owing to moderate hepatic impairment because of diminished synthesis of coagulation factors in the liver (Table 5).

### *Patients With Renal Impairment*

In most of the clinical trials of dabigatran and rivaroxaban for stroke prevention in AF, the drug eligibility and dosing were determined using the Cockcroft-Gault formula to estimate CrCl as a measure of renal function. However, determining these based on estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula alters the dosing of the renally excreted NOACs, potentially imposing serious side effects in elderly patients. The uses of MDRD-derived eGFR instead of the Cockcroft-Gault formula in prescribing these new agents would cause many elderly patients with AF either to incorrectly become eligible for them or to receive too high a dose.

Patients with severe renal impairment have an AUC for dabigatran that is 6.3 times that of the normal baseline. Furthermore, the half-life of dabigatran increases from 13 hours with normal renal function to 27 hours with severe renal impairment.[8] Therefore, prescribers in the primary care setting need to be educated on the use of the Cockcroft-Gault formula to calculate eligibility and dosing of NOACs in the elderly population.[27] In patients who are younger than 80 years and have a Cockcroft-Gault estimated CrCl of 30 to 50 mL/min, the dabigatran dose should be reduced on an individual basis, particularly if there is an additional bleeding risk. In patients aged 80 years and older with AF, the dabigatran dosage should be reduced from 150 mg to 110 mg twice daily (estimated CrCl >30 mL/min); the agent is contraindicated if the estimated CrCl is less than 30 mL/min.[27] The rivaroxaban dose in AF patients should be reduced to 15 mg daily (from 20 mg daily) if the Cockcroft-Gault estimated CrCl is 15 to 49 mL/min; the agent is contraindicated if the estimated CrCl is less than 15 mL/min. Another factor to consider is that rivaroxaban, unlike dabigatran, has high plasma protein binding and is not expected to be dialyzable.[16] No dose adjustment is recommended for apixaban in AF patients except those with 2 of the following characteristics: age 80 years or older, serum creatinine 1.5 mg/dL or greater, and body weight 60 kg or lower (Table 2).[28]

**Table 6.** Characteristics of NOACs

| Feature | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| Mechanism of inhibition | Direct IIa | Direct Xa | Direct Xa |
| Prodrug? | Yes | No | No |
| Frequency | Twice daily | Once daily | Twice daily |
| Available doses for AF, mg | 150, 110, 75 | 20, 15 | 5, 2.5 |
| Bioavailability, % | 6.5 | 80-100 | 50 |
| t(max), h | 0.5-2 | 2-4 | 3-4 |
| t(1/2), h | 11-17 | 5-13 | 5-13 |
| Renal excretion, % | 80 | 33 | 27 |
| Protein binding, % | 35 | 90-95 | 87-93 |

AF, atrial fibrillation; h, hours; NOAC, new oral anticoagulant; t(1/2), half-life; t(max), time to maximum plasma concentration.

This table is adapted with permission from Cairns JA. *Can J Cardiol*. 2013;29(10):1165-1172,[45] and contains data from the package inserts for Pradaxa,[8] Xarelto,[16] and Eliquis.[22]

### *Patients With Heart Failure*

Although routine monitoring is not necessary with NOACs, plasma levels of these agents may fluctuate in patients with heart failure.[29] Because these patients are at constant risk for renal impairment due to inadequate cardiac output, physicians must carefully monitor renal function when prescribing a NOAC.[30] Patients with heart failure and mechanical heart valves should be continued on

**Table 7.** Discontinuation of NOACs for Surgery or Other Invasive Interventions

| Bleeding risk (with normal renal and hepatic function) | Dabigatran | Rivaroxaban[a] | Apixaban[a] |
|---|---|---|---|
| **Low risk** | Discontinue 24 h prior | Discontinue 24 h prior | Discontinue 24 h prior |
| **Moderate to high risk** | Discontinue at least 48 h prior | Discontinue 48 h prior | Discontinue at least 48 h prior |

h, hours; NOAC, new oral anticoagulant.

[a] Warning: An increased rate of stroke was observed following discontinuation of rivaroxaban/apixaban in clinical trials in patients with atrial fibrillation. If rivaroxaban/apixaban is discontinued for a reason other than pathological bleeding, consider administering another anticoagulant agent.[16,22]

Based on data from the package inserts for Pradaxa,[8] Xarelto,[16] and Eliquis.[22]

warfarin. The use of dabigatran in patients with mechanical heart valves has been associated with increased rates of thromboembolic and bleeding complications when compared with warfarin.[31] Of the above 3 NOACs, apixaban may be most suitable for stroke prevention in patients with heart failure, AF, and associated renal dysfunction because only 27% of the drug is renally excreted (Table 6).

### *Perioperative Management of Patients*

Dabigatran should be stopped for at least 24 hours prior to an invasive procedure with a low risk of bleeding, and at least 48 hours prior to a procedure that carries a high risk of bleeding (Table 7).[8] The duration of discontinuation is dependent on the renal function, and CrCl levels should be monitored for 5 days after surgery. Although rivaroxaban has a shorter half-life than dabigatran, it can be discontinued using the same schedule as for dabigatran.

For procedures in which immediate and complete hemostasis has been achieved, NOACs can be resumed after 6 to 8 hours.[23] For invasive procedures with a high risk of bleeding, NOACs are usually deferred for 48 to 72 hours and should be resumed only after validation of complete hemostasis. There are no data on the safety and efficacy of the postoperative use of reduced-dose NOACs (such as used for the prevention of VTE after hip or knee arthroplasty) in patients with AF undergoing surgery.[23]

### *The Role of NOACs in Bridging to Warfarin*

Controlled studies are not available on bridging to warfarin using NOACs, so this advice is based on expert opinion only.

If a patient prefers to stay on warfarin, the physician should respect this decision. Patients who are hospitalized for other medical conditions often are found to have a subtherapeutic INR on warfarin. These patients frequently require intravenous heparin or subcutaneous low-molecular-weight heparin for their transition to a therapeutic INR. Theoretically, NOACs may help to allow for a rapid transition to therapeutic levels. However, the use of a NOAC as a replacement for heparin or low-molecular-weight heparin in bridging therapy has not been studied. This is merely a hypothetical proposal, and studies are required to investigate the bleeding risk and safety of combining NOACs with warfarin.

### *Blood Coagulation Assays*

There is no need for blood coagulation assays in routine clinical practice, but they may be useful in cases of emergency or drug overdose. One study found a linear relationship between activated prothrombin time and the square root of dabigatran plasma concentration.[32]

### *Toxicity and Reversal*

The overall incidence of NOAC-related intracranial hemorrhage (ICH) is between 2 to 9 per 100,000 population per year, and is expected to increase as the number of patients treated with NOACs increases.[33] Some of the common risk factors for ICH are age, hypertension, intensity of anticoagulation, remote ischemic stroke, and other cerebral vasculopathies (eg, amyloid angiopathy and subcortical hypertensive arteriopathy). The Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) bleeding risk assessment score is a practical tool to evaluate the individual bleeding risk of patients with AF.[34,35] There is no specific antidote or reversal agent available in the market. The current emergency treatment in NOAC-related bleeding is rapid discontinuation of the offending drug and rapid implementation of some of the measures discussed below.

Controlled data in humans are not available. Hemodialysis can be used to remove dabigatran from the circulation, but clinical experience for this approach is limited.[8] Activated prothrombin complex concentrates (PCCs), recombinant factor VIIa, or factor II, IX, or X concentrates may be considered for use in life-threatening bleeds, although they have not been evaluated in this situation.[8,23] Table 8 describes measures to control bleeding secondary to NOACs. Platelet concentrates can be considered when thrombocytopenia is present, or if long-acting antiplatelet drugs were on board.[8] The use of fresh frozen plasma for the management of bleeding resulting from NOACs is not recommended. However, there are reports suggesting the efficacy of fresh frozen plasma in combination with PCCs.[36] In one study, the use of an activated PCC was found promising for the reversal

**Table 8.** Measures to Control Bleeding Secondary to NOACs

| General Measures |
|---|
| Assess vital signs and resuscitate as appropriate |
| Discontinue the offending anticoagulant |
| Measure baseline kidney function and hepatic function |
| Periodically assess blood counts and coagulation cascade |
| Gastric lavage and activated charcoal can be considered within 4 hours of ingestion |
| **Measures for severe or life-threatening bleeding** |
| Consider a multidisciplinary team approach in an intensive care unit setting |
| Mechanical compression of accessible sites |
| Surgical interventions as appropriate |
| Consider hemodialysis in case of dabigatran. Rivaroxaban, being >90% protein bound, cannot be dialyzed. |
| Frequent monitoring of vitals and replacement of blood products as needed. This can help to borrow time until the drug is naturally eliminated by the body. |
| In case of dabigatran, measure aPTT and thrombin time (consider dabigatran assay if available); consider activated charcoal, with sorbitol, if within 4 hours of dabigatran ingestion; maintain renal perfusion and urine output to facilitate dabigatran excretion |
| **Nonspecific prohemostatic agents: (data limited to healthy human volunteers, animal models, and in vitro studies)[4,57,58]** |
| Activated PCC 50-100 U/kg IV (preferred) |
| PCC 50 U/kg (reversed dabigatran in animal model) |
| Recombinant factor VIIa 120 U/kg |
| **Specific antidotes in pipeline[59,60]** |
| aDabi-Fab (antidote for dabigatran) successful reversal in animal model only |
| r-Antidote (PRT064445)for apixaban and rivaroxaban |
| Following use of prohemostatic/specific antidotes, patients may be monitored for possible risk of thromboembolic complications |

aPTT, activated prothrombin time; IV, intravenously; PCC, prothrombin complex concentrate; NOAC, new oral anticoagulant.

Based on data from Fawole A et al. *Cleve Clin J Med.* 2013;80(7):443-451,[4] Kaatz S et al. *Am J Hematol.* 2012;87(S1)(suppl 1):S141-S145,[55] and Alikhan R et al. *Emerg Med J.* 2014;31(2):163-168.[56]

of dabigatran, and the nonactivated PCC appeared to help reverse anti–factor Xa.[37]

## Investigational NOACs

The investigational oral factor Xa inhibitor edoxaban was recently studied in a randomized, double-blind trial. The drug was administered once daily after initial treatment with heparin, and was found to be noninferior to high-quality standard therapy. It caused significantly less bleeding than warfarin in patients with VTE and severe PE.[38] The once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism, and were associated with significantly lower rates of bleeding and death from cardiovascular causes.[39]

Ximelagatran, which was the first member of the direct thrombin inhibitor drug class, was initially approved in several countries. This drug was withdrawn after reports of hepatotoxicity, however.[40, 41]

Razaxaban, a selective, oral inhibitor of coagulation factor Xa, has been shown in animal models to be effective in combination with aspirin and/or clopidogrel for prevention of occlusive arterial thrombosis.[42]

Betrixaban is an oral, specific, and direct inhibitor of Xa, with an oral bioavailability of 47%. This agent, which is near totally eliminated through the hepatobiliary route, could be another potential drug for patients with renal failure.[28]

## Conclusion

The NOACs are novel agents that are easy to administer, have significantly fewer food and drug interactions than warfarin, and are likely to have a better side effect profile. As the population ages, the need increases for an agent that can strike a balance between anticoagulation and the risk of bleeding. NOACs have emerged as popular agents that produce a greater quality-adjusted life expectancy than warfarin, although their cost and the lack of a specific antidote have been concerning to some physicians.[43,44] The availability of multiple medications, with different pharmacodynamics and pharmacokinetics profiles, will allow these agents to be individualized based on patients' comorbidities.

### *Disclosures*

*The authors have declared no conflicts of interest.*

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