

Minimizing bleeding risk in patients receiving direct oral anticoagulants for stroke prevention

Jeffrey Steven Habert

Department of Family and Community
Medicine, University of Toronto,
Toronto, ON, Canada

Abstract: Many primary care physicians are wary about using direct oral anticoagulants (DOACs) in patients with nonvalvular atrial fibrillation (AF). Factors such as comorbidities, concomitant medications, and alcohol misuse increase concerns over bleeding risk, especially in elderly and frail patients with AF. This article discusses strategies to minimize the risk of major bleeding events in patients with AF who may benefit from oral anticoagulant therapy for stroke prevention. The potential benefits of the DOACs compared with vitamin K antagonists, in terms of a lower risk of intracranial hemorrhage, are discussed, together with the identification of reversible risk factors for bleeding and correct dose selection of the DOACs based on a patient's characteristics and concomitant medications. Current bleeding management strategies, including the new reversal agents for the DOACs and the prevention of bleeding during preoperative anticoagulation treatment, in addition to health care resource use associated with anticoagulation treatment and bleeding, are also discussed. Implementing a structured approach at an individual patient level will minimize the overall risk of bleeding and should increase physician confidence in using the DOACs for stroke prevention in their patients with nonvalvular AF.

Keywords: anticoagulants, atrial fibrillation, bleeding, primary care

Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with a fivefold increase in the risk of stroke.^{1,2} At least one in five strokes occurs in patients with AF, and these strokes are twice as likely to have fatal or disabling consequences (30%–50% 1-year mortality rates).^{1,3–6} The risk of stroke in patients with nonvalvular AF can be reduced effectively with anticoagulants, such as vitamin K antagonists (VKAs; eg, warfarin) or direct oral anticoagulants (DOACs; eg, apixaban, dabigatran, edoxaban, and rivaroxaban),^{7,8} although the benefits of therapy should always be balanced against the increased risk of bleeding associated with all anticoagulants.⁹ Nevertheless, physicians should remember that the principal goal of anticoagulation in patients with AF is the prevention of stroke, and they should be mindful of the patient's perspective on stroke and bleeding events; many patients view their reduced quality of life after major stroke as tantamount to or worse than death,¹⁰ and available data indicate that patients with AF place more value on the avoidance of stroke than the avoidance of bleeding, compared with physicians who treat patients with AF.¹¹ The phrase “we can replace blood, but we cannot replace brain” serves as a useful reminder for physicians that an increase in the risk of bleeding may be an acceptable side effect of achieving this goal, and that most bleeding events can be managed easily using standard methods.¹²

Correspondence: Jeffrey Steven Habert
Department of Family and Community
Medicine, University of Toronto, 206-
2900 Steeles Avenue East, Thornhill, ON,
L3T4X1, Canada
Mob +1 905 881 6667
Email jhabert@rogers.com

The risks of serious bleeding (ie, intracranial hemorrhage [ICH] or other critical site bleeding) that are associated with all anticoagulants are of concern to physicians.^{13,14} This review aims to address these concerns through discussion of the potential benefits offered by the DOACs in terms of improved safety profiles compared with VKAs. The use of bleeding risk scores to identify and manage a patient's reversible risk factors for bleeding (separate from the general risk common to all anticoagulants) is explored and consideration is given to correct DOAC dose selection, which – together with correction of reversible risk factors for bleeding – can reduce the risk of DOAC-associated bleeding. Finally, the different approaches and agents used in the prevention and management of bleeding, including the recently developed DOAC reversal agents, are discussed. Using this personalized approach to minimize a patient's overall risk of bleeding should help to instill confidence among physicians in the use of the DOACs for stroke prevention in patients with nonvalvular AF.

Safety of the DOACs for the prevention of stroke in patients with nonvalvular AF

The safety and efficacy of the DOACs (rivaroxaban, dabigatran, apixaban, and edoxaban) are well established from large Phase III studies in patients with nonvalvular AF.^{15–18} The DOACs were superior to or as effective as warfarin for the prevention of stroke and systemic embolism, and rates of major bleeding were similar or lower in DOAC-treated patients compared with those in warfarin-treated patients.

Importantly, all four DOACs were associated with significantly lower incidences of ICH and numerically lower or significantly lower rates of fatal bleeding (Table 1).^{15–21} However, rivaroxaban and the higher tested doses of dabigatran (150 mg twice daily [bid]) and edoxaban (60 mg once daily [od]) were all associated with significantly higher rates of major gastrointestinal (GI) bleeding.^{17,19,22}

Meta-analysis, pooling data from the four trials, reinforces the favorable benefit–risk profile of the DOACs compared with warfarin; importantly, the DOACs were associated with a 50% reduction in the risk of ICH, the most feared type of bleeding event.²³ Although the overall rates of major bleeding in DOAC-treated patients were similar to those seen in warfarin-treated patients, the DOACs were associated with an increased risk of GI bleeding in this meta-analysis.²³ Efficacy and safety outcomes for the DOACs were found to be consistent across a wide range of patients, including the elderly (aged ≥ 75 years), those with mild or moderate renal impairment, and those at a high risk of stroke.²³

Physicians are often concerned that patients enrolled in Phase III clinical trials are not representative of those they see daily in clinical practice. Encouragingly, accumulating real-world data on the use of the DOACs (predominantly available for rivaroxaban and dabigatran) for stroke prevention in patients with AF suggest that their safety profiles in unselected patients seen in routine care are consistent with those observed in the Phase III studies. For example, the recently published results from XANTUS (N=6,784), the first completed prospective, multinational (excluding

Table 1 Key safety outcomes in the Phase III clinical trials comparing the use of DOACs with warfarin for stroke prevention in patients with nonvalvular atrial fibrillation

| Parameter | Dabigatran (RE-LY) ^{16,19–21} | | Rivaroxaban (ROCKET AF) ^{15,22,70} | Apixaban (ARISTOTLE) ¹⁸ | Edoxaban (ENGAGE AF-TIMI) ¹⁷ | |
|---|---|-----------------------|---|------------------------------------|--|-----------------------|
| Patients randomized | 18,113 | | 14,264 | 18,201 | 21,105 | |
| Comparator | Dose-adjusted warfarin (target INR 2.0–3.0) | | | | | |
| Doses tested | 110 mg bid | 150 mg bid | 20 mg od ^a | 5 mg bid ^b | 30 mg od ^c | 60 mg od ^c |
| Patients eligible for reduced dose | NA | NA | 2,950 (20.7%) | 831 (4.6%) | 5,330 (25.3%) at randomization; 7.1% after randomization | |
| Major bleeding outcomes (DOAC vs warfarin; % per year) | | | | | | |
| Major bleeding | 2.92 vs 3.61; P=0.003 | 3.40 vs 3.61; P=0.41 | 3.6 vs 3.4; P=0.58 | 2.13 vs 3.09; P<0.001 | 1.61 vs 3.43; P<0.001 | 2.75 vs 3.43; P<0.001 |
| Fatal bleeding | 0.19 vs 0.33; P=0.039 | 0.23 vs 0.33; P=0.15 | 0.2 vs 0.5; P=0.003 | NR (34 vs 55 patients) | 0.13 vs 0.38; P<0.001 | 0.21 vs 0.38; P=0.006 |
| ICH | 0.23 vs 0.76; P<0.001 | 0.32 vs 0.76; P<0.001 | 0.5 vs 0.7; P=0.02 | 0.33 vs 0.80; P<0.001 | 0.26 vs 0.85; P<0.001 | 0.39 vs 0.85; P<0.001 |
| Major GI bleeding | 1.15 vs 1.07; P=0.52 | 1.56 vs 1.07; P=0.001 | 2.00 vs 1.24; P<0.0001 | 0.76 vs 0.86; P=0.37 | 0.82 vs 1.23; P<0.001 | 1.51 vs 1.23; P=0.03 |

Notes: ^a15 mg od for patients with CrCl 30–49 mL/min at randomization; ^b2.5 mg bid for patients with ≥ 2 of: weight ≤ 60 kg, age ≥ 80 years, or serum creatinine ≥ 1.5 mg/dL at randomization; and ^cdose was halved if any of the following characteristics were present at randomization or during study: CrCl 30–50 mL/min, weight ≤ 60 kg, or concomitant use of potent P-glycoprotein inhibitors (verapamil, quinidine, or dronedarone).

Abbreviations: bid, twice daily; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; GI, gastrointestinal; ICH, intracranial hemorrhage; INR, international normalized ratio; NA, not applicable; NR, not reported; od, once daily.

the United States), noninterventional study of a DOAC in patients with nonvalvular AF, show that rivaroxaban is associated with low rates of major bleeding (2.1%/year), including ICH (0.4%/year) and major GI bleeding (0.9%/year), as well as a low risk of stroke (0.7%/year).²⁴ These findings are supported by data from a United States postmarketing surveillance study (N=27,467); retrospective analysis of electronic medical records, using an algorithm that allows identification of major bleeding events resulting in hospitalization, showed that the rate of major bleeding in rivaroxaban-treated patients was 2.9% per year.²⁵ In the case of dabigatran, several large, retrospective, propensity-matched, or adjusted analyses suggest that the relative safety of dabigatran versus VKAs is similar to that observed in the Phase III RE-LY trial, including superior or noninferior protection from stroke and systemic embolism, significantly reduced rates of ICH, and similar or higher rates of GI bleeding.^{26–30} Because of the increased risk of GI bleeding identified in DOAC-treated patients in the Phase III ROCKET AF and RE-LY studies, two recently published retrospective studies have focused specifically on this outcome; reassuringly, GI bleeding rates between warfarin- and both rivaroxaban- and dabigatran-treated patients were similar in both studies, although elderly (≥ 75 years old) DOAC-treated patients were shown to be at higher risk.^{31,32}

Using risk scores to identify patients at increased risk of bleeding

Bleeding at critical sites is a major concern, but such concerns should never preclude the use of an oral anticoagulant; instead, physicians should focus on modifying/minimizing

existing risk factors for bleeding. Several validated scoring systems are available that can be used to assess risk of bleeding in patients with AF, including the HAS-BLED score, the ATRIA score, and the recently described ORBIT bleeding score, all of which include advanced age, impaired renal function, bleeding history, and anemia as risk factors for bleeding (Table 2).^{33–35} Owing to its simplicity and its inclusion of modifiable risk factors (eg, uncontrolled hypertension, concurrent antiplatelet agents or nonsteroidal anti-inflammatory drugs, harmful alcohol consumption, and labile international normalized ratios for patients on VKAs), European and UK guidelines recommend the use of the HAS-BLED score to assess the risk of bleeding in patients with AF.^{36,37} However, data from real-world practice indicate that approximately half of physicians estimate or guess bleeding risk in their patients with AF without using any risk scores; furthermore, in one-third of cases physician-estimated bleeding risk did not align with HAS-BLED-estimated bleeding risk, with one-quarter of physicians overestimating the risk of bleeding.³⁸ Patients with a high risk of bleeding can be identified by a HAS-BLED score of ≥ 3 ; however, a patient's bleeding risk score should not be used to preclude the use of anticoagulants. Instead, in most cases, an anticoagulant should be used with appropriate caution – regular follow-up appointments should be scheduled and actions taken to resolve any modifiable risk factors contributing to the patient's elevated risk, as discussed further in the following section.³⁶ Very rarely will an individual's risk of bleeding greatly outweigh their risk of stroke, in which case the benefit–risk ratio may favor no thromboprophylaxis.³⁹

Table 2 Bleeding risk scores validated for use in patients with nonvalvular atrial fibrillation

| HAS-BLED ³³ | | ATRIA ³⁴ | | ORBIT ³⁵ | |
|---|--------|--|----|---|---|
| Hypertension – uncontrolled (>160 mmHg systolic) | 1 | Anemia ^a | 3 | Older age (≥ 75 years old) | 1 |
| Abnormal renal function (SCr ≥ 200 μ mol/L or dialysis or transplantation) or abnormal hepatic function ^b | 1 or 2 | Severe renal disease (eGFR <30 mL/min or dialysis) | 3 | Reduced hemoglobin ^a , reduced hematocrit ^c , or anemia | 2 |
| Stroke history | 1 | ≥ 75 years old | 2 | Bleeding history | 2 |
| Bleeding history or predisposition to bleeding (eg, anemia and bleeding diathesis) | 1 | Any prior hemorrhage | 1 | Insufficient kidney function (eGFR <60 mL/min/1.73 m ²) | 1 |
| Labile INRs | 1 | Diagnosed hypertension | 1 | Treatment with antiplatelets | 1 |
| Elderly (>65 years old) | 1 | – | – | – | – |
| Drugs or alcohol (antiplatelet agents or NSAIDs; alcohol ≥ 8 units per week) | 1 or 2 | – | – | – | – |
| Maximum score | 9 | Maximum score | 10 | Maximum score | 7 |

Notes: Potentially modifiable bleeding risk factors are shown with green shading; criteria that may mandate the use of a reduced-dose DOAC to reduce bleeding risk are shown with orange shading; in the case of older patients, dose reductions may only be mandated in patients ≥ 80 years old on certain DOACs. ^aHemoglobin <13 g/dL in men and <12 g/dL in women; ^bchronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin $>2\times$ upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase $>3\times$ upper limit normal); and ^c $<40\%$ for men and $<36\%$ for women.

Abbreviations: DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; SCr, serum creatinine.

Minimizing existing risk factors for bleeding in patients receiving DOACs for stroke prevention

Reversible risk factors for bleeding, including concomitant medications, comorbidities (eg, hypertension), and alcohol misuse, can be corrected.⁴⁰ Most patients diagnosed with nonvalvular AF are elderly with multiple comorbidities; the increased risk of bleeding associated with comorbidities (such as hypertension and diabetes), polypharmacy, and falls can complicate the care of these patients and make bleeding management difficult. However, many strategies for the management of reversible bleeding risk factors are available within primary care to help lower the overall risk. If physicians refocus on managing modifiable risk factors for bleeding, outside of the general risk associated with anticoagulant use, the risks of bleeding can be minimized. Actions to correct bleeding risk factors in patients receiving the DOACs may include controlling blood pressure, reducing alcohol intake, and minimizing concomitant use of drugs affecting hemostasis or increasing the risk of

bleeding (eg, antiplatelet agents, including acetylsalicylic acid and nonsteroidal anti-inflammatory drugs) and drugs inhibiting the P-glycoprotein and cytochrome P450 3A4 pathways that may lead to increased DOAC plasma concentrations (Table 3).³⁶

Although not identified as a bleeding risk factor per se, many physicians may be reluctant to prescribe an anticoagulant in frail, elderly patients perceived as being at risk of falling. However, it has been estimated that an elderly patient with a 6% annual risk of stroke (ie, a CHA₂DS₂-VASc score of between 4 and 5) would have to fall 295 times a year for the risks of warfarin therapy to outweigh the potential benefits.⁴¹ These data are supported by real-world evidence showing that, although patients at risk of falls have a higher incidence of ICH, the benefits of warfarin significantly outweigh the risks in patients with a CHADS₂ score of ≥ 2 .⁴² Therefore, a potential danger of subdural hematoma as a consequence of a fall should not preclude the use of an oral anticoagulant;³⁷ instead, steps should be taken to minimize the risk of falls, such as correction of visual impairment and use of mobility aids (Table 3).

Table 3 Reversible risk factors and management strategies for bleeding in patients with AF receiving DOACs

| Reversible risk factors for bleeding in patients with AF | Management |
|--|--|
| Hypertension | |
| A systolic blood pressure of ≥ 140 mmHg is associated with an increase in the risk of both hemorrhagic and ischemic stroke among patients with AF ⁴⁰ | <ul style="list-style-type: none"> Regular monitoring for patients with a history of hypertension Adequate control of blood pressure to the recommended level |
| Diabetes | |
| Diabetes is associated with an increased risk of bleeding in patients with AF receiving anticoagulation therapy ⁷¹ | <ul style="list-style-type: none"> Review medication and dosing regularly to ensure good glycemic control |
| Gastrointestinal bleeding | |
| Risk of gastrointestinal bleeding is increased: <ul style="list-style-type: none"> In patients with <i>Helicobacter pylori</i> infection and/or existing/previous stomach/peptic ulcers and/or dyspepsia By ASA and NSAID use and alcohol consumption⁷² | <ul style="list-style-type: none"> Prescribe proton pump inhibitors Treat for <i>H. pylori</i> Manage diet and alcohol intake Avoid concomitant use of NSAIDs and ASA unless indicated⁷² |
| Polypharmacy | |
| Concomitant use of P-gp and/or CYP3A4 inhibitors may lead to increased DOAC plasma concentrations Drug–drug interactions may increase the risk of falls ^{40,73} | <ul style="list-style-type: none"> Regular medicines management reviews should be performed to ensure no contraindications or unnecessary medicine usage and that the appropriate doses are being administered |
| Lifestyle | |
| Poor adherence to anticoagulant therapy may increase the risk of bleeding (ie, if the patient overdoses) Drug and alcohol misuse may increase the risk of falls/trauma ⁴⁰ | <ul style="list-style-type: none"> Patient communication and education may improve treatment adherence Reduce the risk of substance misuse; refer patient for alcohol/drug dependency counseling |
| Risk of falls | |
| Postural hypotension, visual impairment, reduced mobility/frailty, and psychotropic medications (such as benzodiazepines, antidepressants, and antipsychotics) and drug–drug interactions may be associated with an increased risk of falls ^{73,74} | <ul style="list-style-type: none"> Check for low blood pressure to prevent dizziness and fainting Correct visual impairment Provide mobility aids such as walking sticks or handrails Reconsider need for any psychotropic medications Review medicine use regularly to optimize combinations |

Abbreviations: AF, atrial fibrillation; ASA, acetylsalicylic acid; CYP3A4, cytochrome P450 3A4; DOAC, direct oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein.

Dosing considerations to minimize bleeding risk in patients treated with DOACs for stroke prevention

Patient characteristics associated with increased bleeding risk can influence not only their suitability for a DOAC but also the prescribed dosing regimen. Characteristics increasing the risk of bleeding and influencing DOAC suitability include hepatic and renal impairment and certain concomitant medications; physicians need to be aware that the different

DOACs are contraindicated, not recommended or should be used with caution at differing degrees of hepatic and renal impairment, and with different concomitant medications (Table 4).^{43–46} Similarly, dependent on the DOAC, certain patient characteristics and certain concomitant medications can mandate the use of a reduced DOAC dose.^{43–46} For rivaroxaban, the reduced dose (15 mg od) is only approved for use in patients with moderate or severe renal impairment, and all other patients, provided they have a creatinine clearance

Table 4 Recommendations for use and dosing regimens of the DOACs for stroke prevention in patients with nonvalvular atrial fibrillation according to patient characteristics and concomitant medications that may be associated with an increased risk of bleeding

| Recommended use | Dabigatran ⁴⁵ | Rivaroxaban ⁴³ | Apixaban ⁴⁴ | Edoxaban ⁴⁶ |
|---|--|--|--|---|
| Standard dose | 150 mg bid | 20 mg od to be taken with food | 5 mg bid | 60 mg od |
| Patients with active bleeding | | | | |
| Contraindications | Active clinically significant bleeding or a lesion or condition considered to be a high risk for major bleeding (including current or recent GI ulceration, presence of malignant neoplasms at high risk of bleeding, recent CNS injury or surgery, recent ICH, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms, or major intracerebral or intraspinal abnormalities) | | | |
| Patients with hepatic impairment | | | | |
| Contraindications | Hepatic impairment or liver disease expected to have an impact on survival | Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with moderate-to-severe hepatic impairment (Child–Pugh B and C) | Hepatic disease associated with coagulopathy and clinically relevant bleeding risk | Hepatic disease associated with coagulopathy and clinically relevant bleeding risk |
| Not recommended | Elevated liver enzymes (>2× ULN) | NA | Severe hepatic impairment | Severe hepatic impairment |
| Use with caution | NA | NA | Mild or moderate hepatic impairment (Child–Pugh A or B) Elevated liver enzymes ALT/AST >2× ULN or total bilirubin ≥1.5× ULN | Mild-to-moderate hepatic impairment Elevated liver enzymes ALT/AST >2× ULN or total bilirubin ≥1.5× ULN |
| Patients with renal impairment | | | | |
| Dose adjustments | A dose reduction to 110 mg bid should be considered in patients with CrCl 30–49 mL/min and a high risk of bleeding | 15 mg od in patients with CrCl 15–49 mL/min | 2.5 mg bid in patients with ≥2 of the following criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL (133 μmol/L) 2.5 mg bid in patients with CrCl 15–29 mL/min | 30 mg od in patients with CrCl 15–50 mL/min |
| Contraindications | CrCl <30 mL/min | NA | NA | NA |
| Not recommended | NA | Patients with CrCl <15 mL/min | Patients with CrCl <15 mL/min | Patients with CrCl <15 mL/min |
| Use with caution | NA | Patients with CrCl 15–29 mL/min | NA | NA |
| Elderly patients | | | | |
| Dose adjustments | Age ≥80 years: 110 mg bid In patients aged 75–80 years a dose reduction to 110 mg bid may be considered when thromboembolic risk is low and bleeding risk is high | No dose adjustment based on age alone | 2.5 mg bid in patients with ≥2 of the following criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL (133 μmol/L) | No dose adjustment based on age alone |

(Continued)

Table 4 (Continued)

| | Dabigatran ⁴⁵ | Rivaroxaban ⁴³ | Apixaban ⁴⁴ | Edoxaban ⁴⁶ |
|--|--|---|--|---|
| Patients receiving concomitant P-gp or CYP3A4 inhibitors that increase DOAC plasma concentrations | | | | |
| Dose adjustments | 110 mg bid in patients receiving concomitant verapamil | No dose adjustment based on use of concomitant P-gp or CYP3A4 inhibitors alone | No dose adjustment based on use of concomitant P-gp or CYP3A4 inhibitors alone | 30 mg od in patients receiving concomitant cyclosporine, dronedarone, erythromycin, or ketoconazole |
| Contraindications | Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, and dronedarone | NA | NA | NA |
| Not recommended | Concomitant treatment with tacrolimus | Concomitant systemic treatment with azole antimycotics (eg, ketoconazole, itraconazole, voriconazole, and posaconazole) or HIV protease inhibitors (eg, ritonavir) Coadministration with dronedarone should be avoided | Concomitant systemic treatment with azole-antimycotics (eg, ketoconazole, itraconazole, voriconazole, and posaconazole) or HIV protease inhibitors (eg, ritonavir) | NA |
| Use with caution | Caution advised with concomitant treatment with amiodarone, quinidine, posaconazole, verapamil, clarithromycin, or ticagrelor, especially in patients with mild-to-moderate renal impairment | Caution advised in patients with renal impairment concomitantly receiving clarithromycin, erythromycin, or fluconazole | NA | NA |
| Patients receiving concomitant treatment with drugs affecting hemostasis | | | | |
| Dose reductions | Consider dose reduction to 110 mg bid in patients receiving concomitant treatment with clopidogrel, ASA, or NSAIDs, especially if patient is ≥ 75 years old | No dose adjustment based on use of drugs affecting hemostasis | No dose adjustment based on use of drugs affecting hemostasis | No dose adjustment based on use of drugs affecting hemostasis |
| Not recommended | NA | NA | Concomitant use of thienopyridines (eg, clopidogrel) or dipyridamole | Concomitant chronic use of high-dose ASA (325 mg/d) or NSAIDs |
| Use with caution | Concomitant administration with drugs affecting hemostasis by inhibition of platelet aggregation | Concomitant treatment with NSAIDs, ASA, or platelet aggregation inhibitors | Concomitant administration of NSAIDs or ASA | Concomitant administration of ASA in elderly patients |
| Other patients at increased risk of bleeding or elevated DOAC concentrations | | | | |
| Dose adjustments | Consider dose reduction to 110 mg bid in patients with gastritis, esophagitis, or gastroesophageal reflux and in other patients at increased risk of bleeding (eg, patients receiving concomitant treatment with SSRIs or SNRIs) | No dose adjustments based on bleeding risk alone | No dose adjustments based on bleeding risk alone | 30 mg od in patients with low body weight (≤ 60 kg) |

Abbreviations: ALT, alanine aminotransferase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; bid, twice daily; CNS, central nervous system; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; DOAC, direct oral anticoagulant; GI, gastrointestinal; HIV, human immunodeficiency virus; ICH, intracranial hemorrhage; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; od, once daily; P-gp, P-glycoprotein; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; ULN, upper limit of normal.

>50 mL/min, are recommended to receive 20 mg od.⁴³ For the other DOACs (apixaban, edoxaban, and dabigatran), a patient's renal function, age, body weight, and concomitant medications may need to be considered to ensure selection of the correct dosing regimen to best balance ischemic and bleeding risks (Table 4).^{44–46}

When considering use of a DOAC in a patient with a high HAS-BLED score, many physicians may wonder whether it is appropriate to prescribe a reduced-dose DOAC. In the case of the Factor Xa inhibitors apixaban and rivaroxaban, the lower doses are only approved in patients fulfilling certain criteria as tested in their respective Phase III clinical trials – and these did not include an elevated bleeding risk in the absence of factors specifically mandating a dose reduction (Tables 1 and 4).^{15,18,43,44} Consequently, there is no evidence to support the efficacy of apixaban 2.5 mg bid or rivaroxaban 15 mg od in patients not meeting the criteria for a dose reduction; therefore, a patient with a high bleeding risk (but no other factors mandating use of a reduced dose) should receive the higher approved dose of apixaban (5 mg bid) or rivaroxaban (20 mg od).^{43,44} In the RE-LY trial, patients treated with dabigatran were randomized to one of two dabigatran doses (110 mg bid or 150 mg bid) and the results showed dabigatran 150 mg bid to be superior to warfarin for the prevention of stroke or systemic embolism with a similar rate of major bleeding, whereas dabigatran 110 mg bid was noninferior to warfarin for prevention of stroke or systemic embolism but associated with significant reductions in major bleeding.^{16,20} Based on these data, the European label suggests that, in patients with an increased bleeding risk (including those aged 75–80 years or with gastritis, esophagitis, or gastroesophageal reflux), a daily dose of 150 mg bid or 110 mg bid should be selected based on an individual assessment of a patient's thromboembolic and bleeding risks.⁴⁵ In Canada, the product monograph for dabigatran recommends the use of the 110 mg bid dabigatran dose in patients aged 75 years or older with one or more risk factor for bleeding.⁴⁷ In ENGAGE-AF-TIMI 48, patients treated with edoxaban were randomized to either edoxaban 60 mg od or edoxaban 30 mg od, and, in either arm, the dose was halved if patients met the criteria for dose reduction (Table 1).¹⁷ Although the lower dose of edoxaban was shown to be noninferior to warfarin for the prevention of stroke or systemic embolism,¹⁷ data in the European Medicines Agency public assessment report indicate that edoxaban 30 mg od was inferior to warfarin for the prevention of ischemic stroke or systemic embolism (1.89%/year vs 1.36%/year; $P < 0.0001$), was associated with a higher number of disabling strokes (82 vs 57 patients), and a greater number

of patients experienced ≥ 2 primary efficacy events (21 vs eight patients); moreover, analysis by HAS-BLED score did not identify a group of patients who would benefit from edoxaban 30 mg od.⁴⁸ Therefore, the available data do not support the use of a reduced dose of edoxaban (30 mg od) in patients at high risk of bleeding but not fulfilling criteria for dose reduction, owing to the increased risk of thromboembolic events, and edoxaban 60 mg od should be prescribed.^{46,48}

Bleeding management strategies and health care resource use

There are a range of bleeding management strategies available for both VKA and DOACs (it should also be noted that the fatal bleeding rate was lower for DOACs vs warfarin in three pivotal trials).^{15–17} These vary in terms of suitability for different patient groups and treatment situations, and their costs also differ, impacting on treatment availability and choices.

Management of bleeding with anticoagulants can be achieved in a variety of ways, with some overlap between the approaches for VKAs and DOACs. These include treatment cessation, as well as more infrequently used measures such as reversal agents or administration of coagulation factors.⁴⁹ Restoration of coagulation function after cessation of warfarin takes several days, and therefore, it is not suitable for rapid reversal. Coagulation factors are a third option; these can be administered in the form of prothrombinase complex concentrate (PCC), which is derived from plasma and contains clotting factors II, VII, IX, and X, and results in immediate warfarin reversal. However, as the effect wears off after 6–12 hours, guidelines advise a combination of vitamin K and PCC.⁵⁰ Activated PCC (Factor VIII inhibitor bypassing activity) is derived from Factor VIII and has a similar profile to the one described earlier for PCC; both PCC and activated PCC carry a thrombotic risk. Fresh–frozen plasma can also be considered, but is not advised unless PCC is unavailable; recombinant Factor VIIa can be used with agents such as heparin and fondaparinux in instances of critical bleeding.⁴⁹

For the DOACs, as described earlier, some patient groups may benefit from dose reductions to balance bleeding risk and treatment efficacy, although this is not appropriate for all patients or with all DOACs. Specific reversal agents are also a potential option: idarucizumab, a Fab fragment targeted specifically against dabigatran,⁵¹ has recently been approved for use in emergency surgery/urgent procedures and for life-threatening or uncontrolled bleeding; the RE-VERSE AD trial showed complete reversal of dabigatran plasma levels within minutes.⁵¹ Andexanet alfa, a Factor Xa decoy targeted against Factor Xa inhibitors,⁵² and ciraparantag (PER977),

which antagonize multiple anticoagulants (unfractionated and low molecular weight heparins, and all four DOACs), are currently in clinical development.⁵³ PCC may be used, although it is unclear whether its reversal of DOAC action corresponds to improved clinical outcomes as much of the relevant data are from healthy volunteers, *in vitro* studies, and animal models.^{54,55} Activated Factor VIIa or Factor VIII inhibitor bypassing activity may also be considered;⁵⁵ oral activated charcoal can be used to prevent further absorption if the dose has been administered within the previous 2 hours.^{49,56}

Dose cessations or reductions are limited in terms of sensitivity, not appropriate for all patients, and may not offer the best cost–benefit balance owing to impacts on treatment effectiveness. Estimates from studies on warfarin reversal in hip replacement surgery have shown dose cessation to be the most expensive approach when direct costs arising during hospitalization are accounted for;⁵⁷ low-dose PCC has also been shown to be cost effective for management of VKA-induced bleeding versus a variable high-dose strategy.⁵⁸ However, a recent study suggests that management of dabigatran-associated major bleeding with dose cessation is as effective as or superior to drug withdrawal plus administration of red cell concentrates, plasma, or coagulation factor concentrates.⁵⁹ Cessation alone is not sufficient when rapid reversal of anticoagulant action is needed. PCC is expensive in terms of unit costs and is associated with a risk of thrombogenicity and concerns around transmission of prions or pathogens originating from pooled plasma; however, cost–benefit modeling has shown it to be more cost effective than fresh–frozen plasma for warfarin reversal.^{60,61} Vitamin K is inexpensive, but has no clinical usefulness in situations requiring rapid warfarin reversal.⁶²

The reversal agents for the DOACs are effective and have a rapid onset of action, but are associated with higher costs (cost of idarucizumab is ~\$3,500 per dose).⁶³ The costs have not yet been determined for andexanet alfa or ciraparantag, but they are likely to be similarly priced once approved. The high costs of these agents may therefore restrict their use in some hospitals or regions, and cost–benefit analyses will also need to be conducted versus other approaches such as the nonspecific reversal agent PCC.

Preprocedural maintenance of anticoagulation and management of bleeding

Another key consideration for physicians is anticoagulation use prior to surgical/invasive procedures: treatment interruption transiently exposes patients to an increased risk of thromboembolism, whereas continuing treatment increases the risk

of surgical bleeding.⁶⁴ Additionally, different anticoagulants require different approaches. VKAs take several days for their anticoagulant effects to diminish,⁶³ whereas the DOACs have shorter half-lives, meaning that their anticoagulant effects abate more rapidly following treatment cessation (although this is impacted by factors such as renal impairment).^{56,65} Specific reversal agents are not yet approved for the Factor Xa inhibitors, creating difficulties for patients requiring urgent procedures. For urgent surgeries associated with a high risk of bleeding, nonspecific reversal agents, such as PCC, may be considered.

Thrombosis and bleeding risks must be assessed prior to surgery; higher thrombosis risk reduces the duration that anticoagulation can safely be stopped for, whereas a higher bleeding risk requires a longer period of treatment cessation. For those with transiently increased high risk of thrombosis, delaying elective surgery can allow continuation of anticoagulation treatment and the risk to return to baseline.⁶⁶ Patients at low risk of bleeding may be suitable to continue anticoagulation treatment prior to surgery, depending on the nature of the procedure.⁶⁶ For the reasons discussed earlier, timing of treatment interruption must also be considered depending on which therapy the patient is receiving. Algorithms are available to help address this often complex issue of perioperative anticoagulation.^{67,68} Bridging therapy with a fast-acting parenteral agent (eg, low molecular weight heparin) can be considered for patients at a very high risk of thromboembolism and receiving VKA, but is not necessary for most patients owing to the increased risk of bleeding and lack of impact on thromboembolic risk that has been reported in some studies.⁶⁹

Conclusion

Bleeding risk is often a concern for physicians when considering the use of the DOACs in high-risk patients with nonvalvular AF. This concern may be heightened if the patient is elderly, has comorbidities, is prescribed many medications, or is perceived to be at high risk of falling. Proper assessment of bleeding risk and taking steps to minimize any modifiable risk factors, together with selection of the correct dose of DOAC for stroke prevention based on a patient's characteristics and concomitant medications, should reduce the risk of DOAC-associated bleeding. These simple recommendations should give physicians greater confidence in the use of the DOACs, to optimize adequate protection against stroke.

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