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Choosing Non–Vitamin K Antagonist Oral Anticoagulants: Practical Considerations We Need to Know

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Background: Warfarin is a well-established agent for use in the prevention of stroke or systemic embolic event (SEE) in patients with nonvalvular atrial fibrillation (NVAF) and for the treatment of venous thromboembolism (VTE). However, management of patients requiring oral anticoagulation with warfarin can be complicated by the need for frequent monitoring, drug-drug and drug-food interactions, and a variable response based on genetic polymorphisms. The non–vitamin K antagonist oral anticoagulants (NOACs) were developed as alternatives to warfarin; they do not require routine monitoring and have predictable pharmacokinetics, fewer drug-drug interactions, and limited drug-food interactions. Four NOACs—dabigatran, rivaroxaban, apixaban, and edoxaban—have received approval from the US Food and Drug Administration for the prevention of stroke or SEE in NVAF and for the treatment of VTE. Selecting the most appropriate agent for each patient should be done in consideration of patient preferences and characteristics, including renal function, bleeding risk, and the need for other medications.

Methods: A search was performed on the terms atrial fibrillation and venous thromboembolism with individual terms dabigatran, apixaban, edoxaban, or rivaroxaban to identify relevant manuscripts; large randomized clinical trials, metaanalyses, and treatment guideline recommendations were given preference. Searches to identify registries, treatment guidelines, and metaanalyses relevant to specific subgroups were also used.

Results: NOACs are effective in reducing the risk of stroke or SEE in patients with NVAF and are associated with fewer incidents of intracranial bleeding vs warfarin.

Conclusion: NOACs provide a convenient and safe alternative to warfarin and may result in improved therapeutic outcomes for patients with NVAF or VTE. The use of NOACs in other indications and patient populations is under investigation, and clinical trials investigating their use in acute coronary syndrome, medically ill patients, percutaneous coronary intervention, cardioversion, catheter ablation, coronary arterial disease, and heart failure have been announced.

Keywords: *Anticoagulants, apixaban, atrial fibrillation, dabigatran, drug interactions, edoxaban, food-drug interactions, rivaroxaban, venous thromboembolism, warfarin*

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INTRODUCTION

Between 2010 and 2015, the non–vitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban were approved in the United States for reduction of the risk of stroke and systemic embolic event (SEE) in patients with nonvalvular atrial fibrillation (NVAF) and for the treatment of acute venous thromboembolism (VTE). In phase 3 clinical trials, dabigatran, rivaroxaban, apixaban, and edoxaban were at least as effective as warfarin in reducing the risk of stroke or SEE in patients with NVAF.[1-4] Additionally, the NOACs were associated with similar or lower rates of major or clinically relevant nonmajor bleeding and significantly decreased rates of intracranial bleeding compared with warfarin.[1-4] The NOACs were also noninferior to warfarin for the treatment of acute symptomatic VTE and significantly decreased bleeding risk relative to warfarin.[5-8]

This review focuses on the practical considerations for NOAC use, including dosing guidelines, transitions of care, and management of bleeding.

METHODS

PubMed searches were conducted with the terms atrial fibrillation and venous thromboembolism with individual terms for the NOACs dabigatran, apixaban, edoxaban, or rivaroxaban. Separate searches identified registries, treatment guidelines, and metaanalyses relevant to specific subgroups. Large randomized clinical trials, metaanalyses,

and treatment guideline recommendations were given preference in data selection. Data included in this review were chosen to provide guidance on practical considerations for selecting the most appropriate agent for each patient.

ANTICOAGULANTS AND THE COAGULATION CASCADE

The antithrombotic and anticoagulant effects of warfarin are mediated by the reduction of prothrombin, factor X, factor VII, and factor IX (Figure 1).[9] A heparin lead-in is recommended for the initiation of warfarin for the treatment of VTE, as the antithrombotic effect of warfarin is driven primarily by reducing prothrombin, which has a half-life of approximately 60-72 hours.[9] Warfarin has a half-life of 36-42 hours.[9] In contrast, the NOACs act downstream of warfarin in the coagulation cascade on factor X and factor IIa (Figure 1) and have a faster onset of action and half-lives ranging from 5-17 hours.[10-13] Warfarin interferes with the conversion of vitamin K and its 2,3-epoxide; thus, variations in dietary vitamin K intake can affect anticoagulation levels in patients receiving warfarin.[9,14] Further, although warfarin is a long-established and effective treatment for the management of NVAF and VTE, it has a number of drug-drug interactions, and its exposure is affected by several genetic polymorphisms in enzymes responsible for its metabolism that can lead to excessive bleeding or decreased efficacy.[14] As a result, patients receiving warfarin require frequent monitoring of anticoagulation levels and dose adjustments to maintain optimal anticoagulation. The NOACs provide alternatives to treatment with warfarin that do not require routine monitoring and have predictable pharmacokinetics, fewer drug-drug interactions, and limited food-drug interactions.[13,15]

DOSING CONSIDERATIONS AND RISK FACTORS FOR BLEEDING

Patient dosing considerations for the NOACs are shown in Table 1. For the treatment of VTE, a period of parenteral anticoagulation is required prior to the initiation of administration of dabigatran or edoxaban.[10,13] Neither rivaroxaban nor apixaban requires this period of parenteral anticoagulation; however, both require a transition from a higher starting dose to a lower dose following an initial treatment period (Table 1).[11,12] These differences in treatment initiation are based on the study designs from the phase 3

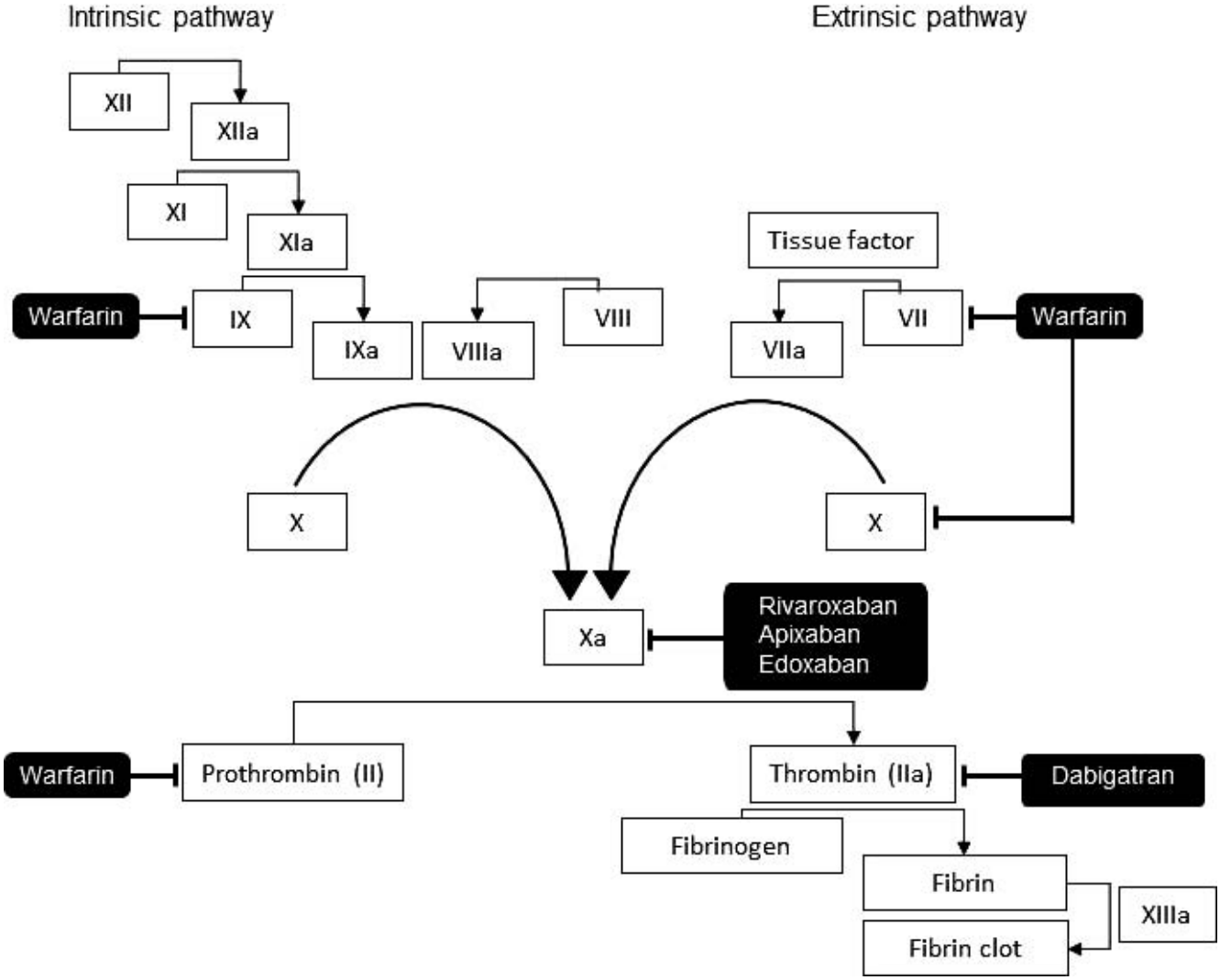

Figure 1. Coagulation cascade.

Table 1. Patient Dosing Considerations[10-13]

	Elderly	Hepatic Function	Low Body Weight	Renal Function
Nonvalvular Atrial Fibrillation				
Dabigatran, 150 mg, twice daily	No dose adjustment: bleeding risk increases with age	No dose adjustment: moderate hepatic impairment (Child-Pugh B)	No dose adjustment	150 mg twice daily: CrCl >30 mL/min Reduce dose to 75 mg twice daily: CrCl 15-30 mL/min No dose recommendation provided: CrCl <15 mL/min or on dialysis
Rivaroxaban, 20 mg, once daily with the evening meal	No dose adjustment: bleeding risk increases with age	Avoid use: moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or any hepatic disease associated with coagulopathy	No dose adjustment	20 mg once daily with the evening meal: CrCl >50 mL/min Reduce dose to 15 mg once daily with the evening meal: CrCl 15-50 mL/min Avoid use: CrCl <15 mL/min
Apixaban, 5 mg, twice daily	Reduce dose to 2.5 mg/dL twice daily when at least 2 of the following: age ≥80 years and either body weight ≤60 kg or serum creatinine ≥1.5 mg/dL	No dose adjustment: mild (Child-Pugh A) hepatic impairment No dose recommendation provided: moderate (Child-Pugh B) hepatic impairment	Reduce dose to 2.5 mg twice daily when at least 2 of the following: body weight ≤60 kg and either age ≥80 years or serum creatinine ≥1.5 mg/dL	Reduce dose to 2.5 mg twice daily when at least 2 of the following: serum creatinine ≥1.5 mg/dL and either age ≥80 years or body weight ≤60 kg 5 mg twice daily: end-stage renal disease maintained on hemodialysis
Edoxaban, 60 mg, once daily for CrCl >50 to ≤95 mL/min	No dose adjustment	No dose adjustment: mild (Child-Pugh A) hepatic impairment Not recommended: moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment	No dose adjustment	Reduce dose to 30 mg once daily: CrCl 15-50 mL/min Not recommended: CrCl <15 mL/min Avoid use: CrCl >95 mL/min
Venous Thromboembolism				
Dabigatran, 150 mg, twice daily[a]	No dose adjustment: bleeding risk increases with age	No dose adjustment: moderate hepatic impairment (Child-Pugh B)	No dose adjustment	150 mg twice daily: CrCl >30 mL/min No dose recommendation provided: CrCl ≤30 mL/min or on dialysis
Rivaroxaban, 15 mg, twice daily with food for 21 days; 20 mg, once daily with food	No dose adjustment: more bleeding events in the elderly	Avoid use: moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or any hepatic disease associated with coagulopathy	No dose adjustment	Avoid use: CrCl <30 mL/min

Table 1. Continued

	Elderly	Hepatic Function	Low Body Weight	Renal Function
Apixaban, 10 mg, twice daily for 7 days; 5 mg, twice daily	No dose adjustment	No dose adjustment: mild (Child-Pugh A) hepatic impairment No dose recommendation provided: moderate (Child-Pugh B) hepatic impairment	No dose adjustment	No dose adjustment
Edoxaban, 60 mg, once daily[a]	No dose adjustment	No dose adjustment: mild (Child-Pugh A) hepatic impairment Not recommended: moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment	Reduce dose to 30 mg once daily: patients ≤60 kg	Reduce dose to 30 mg once daily for patients with 1 or more of the following: CrCl 15-50 mL/min, body weight ≤60 kg, or use of certain P-glycoprotein inhibitors

[a]Five to 10 days parenteral anticoagulation prior to treatment initiation.
CrCl, creatinine clearance.

VTE trials[5-7,16,17] rather than on the pharmacology of these anticoagulants. The bioavailability of rivaroxaban is increased with food; thus, patients with NVAF are recommended to take doses with the evening meal.[11]

The NOACs are generally associated with fewer bleeding events compared with warfarin. Overdose of NOACs and the concomitant administration of other anticoagulants, antiplatelets, and thrombolytics increase the risk of bleeding.[10-13] An analysis of case reports suggests that the majority of hemorrhagic complications during administration of dabigatran or rivaroxaban were either precipitated by prescriber error related to comedication or dose or occurred in patients with impaired renal function, advanced age, or low body weight.[18] Thus, education of both the patient and caregiver is important for decreasing risks.

Dabigatran and apixaban are administered twice daily; edoxaban and rivaroxaban are administered once daily, although dosing at initiation of treatment may vary.[10-13] One study supports a twice-daily dosing regimen for a better risk-benefit profile for stroke prevention and intracranial hemorrhage rather than once-daily dosing[19]; in general, data are limited. Overall, the introduction of dabigatran, rivaroxaban, and apixaban into clinical practice increased the use of oral anticoagulation for patients with NVAF at a high risk of stroke, although rates of undertreatment remain high.[20] Using sample patient profiles, we provide guidance for selecting the best NOAC for each patient in the sections that follow.

RENAL IMPAIRMENT: PATIENT EXAMPLE 1

An 85-year-old woman with a body weight of 59 kg and moderate renal impairment (creatinine clearance [CrCl] of 49 mL/min) presents to the hospital with NVAF. Optimal anticoagulant choice in this case is affected by several factors, including level of renal function, body weight, and need for concomitant medication. Many patients who require anticoagulation are older (≥80 years of age)[15] and may have age-related reductions in renal function.[21] Current American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines recommend checking renal function prior to administration of an NOAC and periodically thereafter.[15] In a study of patients treated with dabigatran, rivaroxaban, or apixaban, the frequency of major and nonmajor bleeding events was increased in patients who experienced a decline in renal function to <50 mL/min during treatment (21%) relative to those whose renal function remained ≥50 mL/min (8%) during a 2-year period.[22] All 4 NOACs are dependent on renal function for clearance, albeit to varying degrees. Apixaban has the least renal dependence, with 27% renal excretion; however, patients with renal impairment and low body weight (≤60 kg) or patients of advanced age (≥80 years)—such as the example patient—may still require a dose adjustment of apixaban for treating NVAF.[12] Apixaban is also the only NOAC that can be administered to a patient undergoing dialysis, based on pharmacokinetic and pharmacodynamic data in subjects with end-stage renal disease maintained on dialysis, although this dosing guidance is not based on clinical efficacy or safety data.[12] In general, use of this information has not been applied to everyday practice given the lack of clinical data in the real-world setting. In one indirect comparison analysis, apixaban or edoxaban 30 mg had the most favorable safety profiles in patients with moderate (CrCl=25-49 mL/min) or mild (CrCl=50-79 mL/min) renal impairment.[23]

Dabigatran has the greatest renal dependence relative to the other NOACs, with 80% of an absorbed dose of dabigatran eliminated by the kidneys.[11] A reduced dose of dabigatran is available for patients with reduced renal function (CrCl=15-30 mL/min) and NVAF (Table 1).[11] Dabigatran can be removed by dialysis; thus, dosing recommendations cannot be given for patients receiving dialysis.[11]

Rivaroxaban, edoxaban, or apixaban may be better choices than dabigatran for a patient with renal dysfunction, as these NOACs are less dependent on the kidneys for

clearance. Absorbed doses of rivaroxaban and edoxaban are cleared 66% and 50%, respectively, by the kidneys.[11,13] Patients with NVAF and a CrCl=15-50 mL/min should receive a dose reduction of rivaroxaban or edoxaban, and an edoxaban 30-mg dose is also available for patients with VTE and reduced renal function (Table 1). In the United States, edoxaban is not recommended for patients with NVAF and a CrCl >95 mL/min; in the edoxaban NVAF stroke prevention phase 3 study, patients with CrCl >95 mL/min receiving edoxaban 60 mg once daily had an increased ischemic stroke hazard ratio (HR) of 2.16 (95% confidence interval [CI] 1.17-3.97) relative to warfarin, compared with patients with CrCl >50 to ≤80 mL/min (HR=0.63, 95% CI 0.44-0.89).[13] Within the approved population, edoxaban is noninferior to warfarin (HR=0.94, 95% CI 0.76-1.16, *P*=0.54).[24]

DRUG-DRUG INTERACTIONS: PATIENT EXAMPLE 2

A 64-year-old patient receiving medication for high cholesterol was diagnosed with silent NVAF while hospitalized for bacterial pneumonia. When choosing an NOAC for this patient, the potential for drug-drug interactions may be an important factor for consideration. Polypharmacy is not uncommon, particularly among elderly patients, increasing the risk of drug-drug interactions. All 4 NOACs interact with the P-glycoprotein (P-gp) transporter and, to varying degrees, with cytochrome P450 isoenzyme 3A4 (CYP3A4). Apixaban has the greatest interaction with CYP3A4, followed by rivaroxaban and edoxaban; dabigatran is not a CYP3A4 substrate (Table 2).[10-13] As a result, NOACs should be administered with caution in patients taking drugs that interact with P-gp, such as certain beta-adrenergic blockers, statins, antibiotics, calcium channel blockers, and antiarrhythmic agents.[10-13] Use of strong dual P-gp and CYP3A4 inhibitors and inducers may also require dose adjustments. Edoxaban does not require dose reductions in patients with NVAF using P-gp inhibitors, while for patients with VTE using specific P-gp inhibitors, the once-daily dose of edoxaban should be reduced from 60 mg to 30 mg; for either indication, as with the other NOACs, edoxaban should not be used concomitantly with the P-gp inducer rifampin (Table 2).[13]

Patients taking apixaban and 6-8 or ≥9 concomitant medications have higher rates of stroke or SEE (1.48/100 patient years, HR=1.270, 95% CI 1.022-1.577 and 1.57/100 patient years, HR=1.539, 95% CI 1.190-1.991 for 6-8 medications and ≥9 medications, respectively) and hemorrhagic complications (21.40/100 patient years, HR=1.167, 95% CI 1.092-1.247 and 29.63/100 patient years, HR=1.452, 95% CI 1.348-1.565 for 6-8 medications and ≥9 medications, respectively) relative to patients taking 0-5 medications (1.29/100 patient years and 17.41/100 patient years for ischemic stroke and any bleeding, respectively), with the magnitude of benefit decreasing progressively as the number of drugs taken increases (interaction *P*=0.02).[25] In a subgroup analysis of the phase 3 dabigatran VTE clinical trial, increased numbers of concomitant medications correlated with increased bleeding risk and a slightly increased risk of VTE-related death for all patients; dabigatran exhibited better safety and equivalent efficacy relative to warfarin.[26] Subgroup analyses for edoxaban and rivaroxaban have not yet been presented.

HIGH RISK FOR BLEEDING: PATIENT EXAMPLE 3

A patient with NVAF, a history of falling, and a high risk of major bleeding score (≥3) requires a careful balance of bleeding and stroke risks. Assessment of bleeding risk by HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], drugs/alcohol concomitantly) is recommended by European Heart Rhythm Association and European Society of Cardiology guidelines; however, it is not recommended by the US-based AHA/ACC/HRS NVAF guidelines.[15,27-29] Patients with NVAF and increased risk of stroke tend to have increased risk for bleeding, as many of the respective risk factors overlap.[30] Further, anticoagulant treatment increases bleeding risk relative to no anticoagulant treatment. Elderly and fragile patients are particularly vulnerable to bleeding complications related to the use of warfarin and are at a high risk of bleeding in the first 3 months of treatment.[31]

Guidelines recommend stroke risk stratification based on the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, prior stroke or transient ischemic attack [TIA] or thromboembolism [doubled], vascular disease, age 65-74 years, sex category) scoring system.[15,32] In the phase 3 NVAF trials, patient inclusion was based on $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism) scores rather than CHA_2DS_2-VASc scores, with a minimum required $CHADS_2$ score ≥1 for dabigatran and apixaban and ≥2 for rivaroxaban and edoxaban.[1-4] Thus, mean $CHADS_2$ scores for patients enrolled in the rivaroxaban and edoxaban trials were higher relative to those in the dabigatran and apixaban trials. Increased risks for stroke and SEE, major and intracranial bleeding, and death were associated with higher $CHADS_2$ scores.[33]

As a group, the NOACs reduce intracranial bleeding (relative risk [RR]=0.48, 95% CI 0.39-0.59, *P*<0.0001) and all-cause mortality (RR=0.90, 95% CI 0.85-0.95, *P*=0.0003) relative to warfarin.[34] The summary odds ratio (OR) for a fatality following a major bleeding event was 0.65 (95% CI 0.52-0.81), favoring the NOACs (*P*=0.0001).[35] In a meta-analysis, the RR for a gastrointestinal (GI) bleed from an NOAC vs warfarin was 1.25 (95% CI 1.01-1.55, *P*=0.04).[34] In phase 3 NVAF studies, approved US doses of dabigatran, rivaroxaban, and edoxaban 60 mg were associated with higher rates of GI bleeding relative to warfarin, while there was no difference in the rate of major GI bleeding between apixaban, edoxaban 30 mg, and warfarin.[1-4] In elderly patients with NVAF or VTE, dabigatran has been associated with a higher risk of GI bleeding compared with warfarin.[36] For patients receiving dabigatran for NVAF, an increased risk of GI bleeding was highly associated with increased age, renal impairment, heart failure, alcohol abuse, *Helicobacter pylori* infection, antiplatelet therapy, and digoxin use.[37] Dabigatran is also associated with instances of dyspepsia, suggesting that this drug may be less suitable than other NOACs for patients with GI disorders.[10]

Table 2. Drug-Drug Interactions[a10-13]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
P-gp substrate	Yes	Yes	Yes	Yes
CYP3A4 metabolism	None	Yes	Yes	Minimal
P-gp inhibitors	Avoid use: patients taking P-gp inhibitors and CrCl <50 mL/min (VTE only) Avoid use: patients with CrCl <30 mL/min No dose adjustment: patients taking ticagrelor	No dose adjustment	No dose adjustment	No dose adjustment
Dual P-gp/CYP3A4 inhibitors	Consider reduced dose of 75 mg twice daily: patients with moderate renal impairment (CrCl 30-50 mL/min) and concomitant ketoconazole or dronedarone (AF only) No dose adjustment required for clarithromycin, amiodarone, quinidine, verapamil	Avoid use: P-gp and strong CYP3A4 inhibitors ketoconazole, itraconazole, lopinavir/ritonavir, indinavir, conivaptan	Recommended 50% dose reduction for patients receiving >2.5 mg twice daily: when coadministered with strong dual inhibitors of CYP3A4 and P-gp (ketoconazole, itraconazole, ritonavir, or clarithromycin); avoid use of these drugs when dosage is 2.5 mg twice daily	Reduce dose to 30 mg once daily: patients taking P-gp inhibitors verapamil and quinidine or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole[b]
Dual P-gp/CYP3A4 inducers	Avoid coadministration with rifampin	Avoid strong dual inducers of P-gp and CYP3A4 carbamazepine, phenytoin, rifampin, St. John's wort	Avoid strong dual inducers of P-gp and CYP3A4 carbamazepine, phenytoin, rifampin, St. John's wort	Avoid concomitant use of rifampin

[a]The concomitant use of non–vitamin K antagonist oral anticoagulants and all other anticoagulants, platelet inhibitors, and nonsteroidal antiinflammatory drugs increases the risk of bleeding. Patients receiving these medications should be carefully monitored.
[b]For patients with VTE only.
AF, atrial fibrillation; CrCl, creatinine clearance; CYP3A4, cytochrome C P450 isoenzyme 3A4; P-gp, P-glycoprotein; VTE, venous thromboembolism.

PRIOR HISTORY OF MYOCARDIAL INFARCTION OR ACUTE CORONARY SYNDROME: PATIENT EXAMPLE 4

A patient with atrial fibrillation and a history of myocardial infarction (MI) is at an increased risk of stroke. All 4 phase 3 NVAF clinical trials included patients with prior MI.[1-4] In prespecified subanalyses of patients with or without a prior history of MI, no differences in efficacy or safety between edoxaban or warfarin were seen.[4] Likewise, no significant differences in efficacy or safety were found between rivaroxaban and warfarin.[3] No subgroup analysis of prior MI was performed for dabigatran or apixaban.[1,2]

In the dabigatran NVAF stroke prevention phase 3 study, rates of MI occurring during the study were increased for dabigatran 150 mg (0.74% per year, RR 1.38, 95% CI 1.00-1.91, P=0.05) relative to warfarin (0.53% per year).[1] In 2010, following reevaluation of the database for possible under-reporting of events, the RR of MI was revised to a lower value of 1.27 (95% CI 0.94-1.71, P=0.12).[38] Relative to the rest of the study population, patients who had at least 1 MI were older and had more coronary risk factors, including more prior MIs and use of antiplatelet medications, beta blockers, and statins.[39] In a metaanalysis including 14 randomized controlled trials of dabigatran, dabigatran 150 mg was associated with a 1.43 OR for MI (95% CI 1.08-1.89, P=0.01) relative to warfarin in a fixed-effect model.[40] However, in a large-scale cohort study in Europe, patients previously treated with warfarin who switched to dabigatran 150 mg exhibited higher rates of MI (HR 1.30, 95% CI 0.84-2.01) relative to warfarin.[41] Within the first 60 days of initiating dabigatran use, patients switching to dabigatran 150 mg had a higher rate of MI relative to warfarin (HR 2.97, 95% CI 1.31-6.73).[41] The rates of MI with warfarin (1.63%) were similar to those with a pooled analysis of apixaban, rivaroxaban, or edoxaban (1.69%).[42]

The use of NOACs for patients with acute coronary syndrome (ACS) who require triple therapy is not currently supported. The APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) placebo-controlled apixaban trial in patients with ACS treated with aspirin and clopidogrel

was terminated early because of higher bleeding rates with apixaban relative to placebo.[43] Although results from the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51) trial demonstrated a reduction in the composite of cardiovascular death, MI, and stroke in patients treated with rivaroxaban,[44] a high rate of missing data was observed, raising concerns among US Food and Drug Administration (FDA) clinical and statistical reviewers.[45] Bleeding increased in a dose-dependent manner in the phase 2 RE-DEEM (Randomized Dabigatran Etexilate Dose-Finding Study in Patients With Acute Coronary Syndromes) trial, in which patients with ACS received dabigatran in conjunction with clopidogrel and aspirin.[46] Participants are being recruited for a clinical trial to assess the safety of rivaroxaban vs aspirin in combination with clopidogrel or ticagrelor in patients with ACS (ClinicalTrials.gov NCT02293395).

PATIENTS WHO ARE BLEEDING: PATIENT EXAMPLE 5

Patients on anticoagulants with emergent bleeds are of particular concern. Routinely available laboratory tests may not adequately assess the anticoagulant effect of NOACs, which is a potential drawback to managing bleeding events.[47] A flowchart for the treatment of bleeding for patients receiving NOACs is provided in Figure 2.[10-13,27,47-49] A summary of reversal strategies for each NOAC is provided in Table 3.[10-13,15,47,48] Only dabigatran has an approved reversal agent, the dabigatran-specific antibody fragment idarucizumab.[50] In an interim analysis of a prospective cohort trial, reversal of dabigatran anticoagulation occurred within minutes of a 5-g idarucizumab infusion in 88%-98% of patients who had overt, uncontrolled bleeding or who required surgery, with restoration of hemostasis at a median of 11.4 hours in patients with overt, uncontrolled bleeding.[51]

A catalytically inactive version of human recombinant FXa (andexanet alfa, Portola Pharmaceuticals) and a synthetic small molecule (ciraparantag [PER977], Perosphere Inc.) are also under investigation.[52-57] Andexanet alfa was submitted to the FDA for approval in February 2016.[58] In phase 3 trials in healthy older volunteers anticoagulated with apixaban or rivaroxaban, andexanet alfa reduced anti–factor Xa activity more effectively than placebo within 2-5 minutes.[57] A follow-up clinical trial in patients with factor Xa inhibitor-induced acute major bleeding is ongoing.[57] Ciraparantag reverses the anticoagulant effects of edoxaban based on whole blood clotting time and restores hemostasis in healthy subjects.[54] Although not developed as reversal agents for direct FXa inhibitors, hemostatic agents such as factor VIII inhibitor bypassing activity, prothrombin complex concentrates, and an active recombinant form of factor VII have also been evaluated for reversal of NOACs.[13,15,59,60]

ECONOMIC CONSIDERATIONS

Among adults aged 65 years of age or older, warfarin is implicated in roughly one-third of emergency hospitalizations for adverse events,[61] suggesting that NOACs may provide a significant benefit in this population. Economic data are limited, but analyses of clinical trial data suggest that NOAC use can decrease total yearly medical expenditures relative to standard therapies for VTE, with the greatest reductions generally deriving from costs associated with major bleeding.[62] Based on an analysis matching clinical trial data to outcomes, annual total medical cost reductions of $146, $344, $482, and $918 for dabigatran, edoxaban, rivaroxaban, and apixaban, respectively, would result from

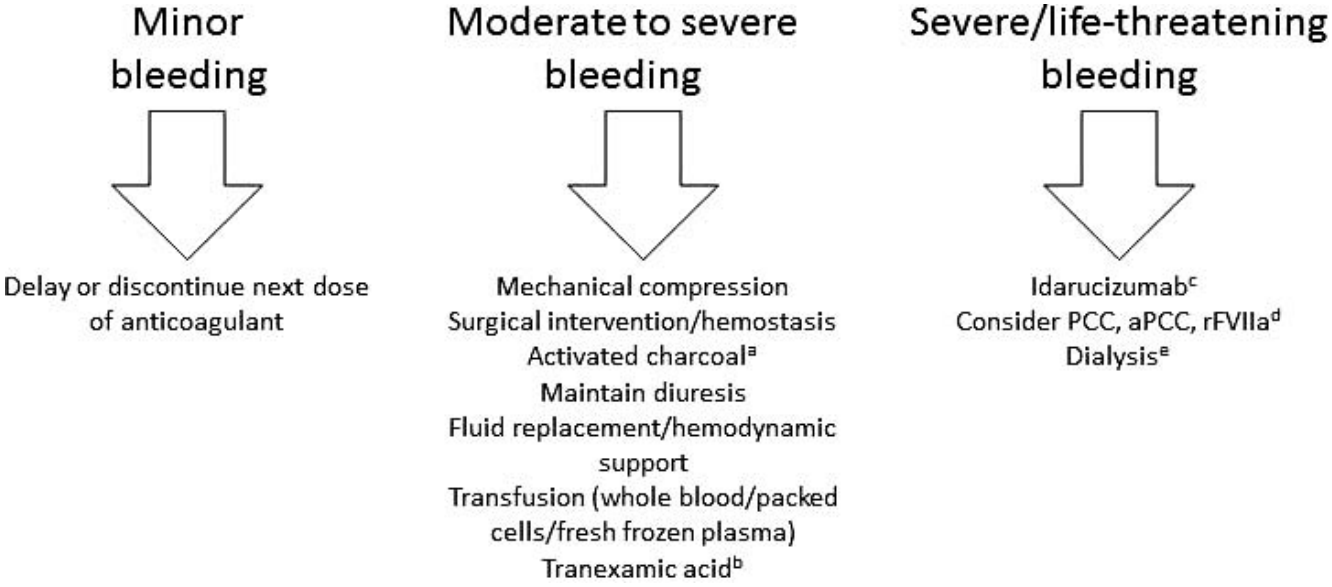

Figure 2. Flowchart for treatment of bleeding for patients taking non–vitamin K oral anticoagulants.[10-13,27,47-49] [a]May be considered in case of rivaroxaban or apixaban overdose. [b]For dabigatran only, 1 g intravenously in case of significant bleeding; not expected to reverse edoxaban. [c]For dabigatran only. [d]Based on limited preclinical studies and clinical studies in healthy volunteers. [e]For dabigatran only; clinical evidence is limited. aPCC, activated PCC; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

Table 3. Reversal and Non–Vitamin K Antagonist Oral Anticoagulants[10-13,15,47,48]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Reversal agent	Idarucizumab	None available	None available	None available
Antifibrinolytic agents	No guidance provided	No guidance provided	No experience	Not expected to affect reversal
Protamine sulfate/vitamin K	No	No	No	Not expected to affect reversal
Systemic hemostatics	No guidance provided	No guidance provided	No experience with desmopressin or aprotinin	No guidance provided
Platelet concentrates	Consider if thrombocytopenia is present or long-acting antiplatelets are used	No guidance provided	No guidance provided	No guidance provided
Prothrombin complex concentrates	aPCC, factor VIII inhibitor bypass activity, rFVIIa may be considered; not evaluated in clinical trials	Clinical trials in healthy subjects; aPCC, rFVIIa not evaluated	May be considered; not evaluated in clinical trials	Clinical trials in healthy subjects
Activated charcoal	Yes	Yes	Yes	No guidance provided
Hemodialysis	Yes; limited support	No	No	No

aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

decreased outlays driven by a reduction in overall clinical events.[62] Medical costs associated with NOAC use compared with warfarin for NVAF—based on reductions in annual total medical costs associated with reduced hemorrhagic stroke and major bleeding—are estimated at $140, $204, $340, and $495 less per patient for rivaroxaban, dabigatran, edoxaban, and apixaban, respectively.[63] These data suggest that apixaban may provide the greatest decrease in costs for patients with NVAF or VTE; rivaroxaban and edoxaban have similar cost effectiveness for NVAF and VTE.

The underuse of warfarin and nonadherence to therapy among patients with NVAF are known to be prevalent and costly, resulting in a significant economic burden.[64] Patients may be more likely to comply with a once-daily dosing regimen, such as for rivaroxaban (taken with the evening meal) and edoxaban, than a twice-daily regimen such as for dabigatran or apixaban (Table 1).[10-13] Studies of relative compliance between once-daily and twice-daily dosing show a 39%-61% higher likelihood of patient compliance with once-daily dosing in patients with VTE and a 22% greater likelihood of adherence for patients with NVAF compared with twice-daily dosing.[65,66] A fixed effects metaanalysis, however, showed that patients with NVAF had a greater preference for once-daily intake, no bridging, and no interactions with food.[67] Limited data on NOAC persistence are available; however, NOACs have significantly higher persistence than warfarin (83.0% vs 65.3%, $P<0.0001$) at 1 year; in this study, persistence with rivaroxaban was 83.7%, persistence with dabigatran was 73.1%, and persistence with apixaban could not be determined based on the short period of follow-up during the study period.[68] In a phase 3 clinical trial subanalysis, patients reported greater satisfaction with oral rivaroxaban therapy compared with conventional therapy for the treatment of pulmonary embolism; however, similar data on patient satisfaction with the other NOACs are not yet available.[69]

CONCLUSION

The NOACs were effective in clinical trials in reducing the risk of stroke or SEE in patients with NVAF and were associated with fewer incidents of intracranial bleeding relative to warfarin. These agents were also as effective as warfarin in treating VTE and were associated with fewer bleeding events. NOACs provide a convenient and safe alternative to warfarin and may result in improved therapeutic outcomes for patients with NVAF or VTE. The use of NOACs in further indications and patient populations is under investigation, and clinical trials investigating their use in ACS, medically ill patients, percutaneous coronary intervention, cardioversion, catheter ablation, coronary artery disease, and heart failure have been announced.

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