CLINICAL REVIEW

Novel Anticoagulants in Atrial Fibrillation: A Primer for the Primary Physician

Martina Mookadam, MD, Fadi E. Shamoun, MD, and Farouk Mookadam, MD, MSc (HRM), FRCPC

Atrial fibrillation is a common arrhythmia encountered in clinical practice. The prevalence increases with age. A devastating complication of atrial fibrillation is cardioembolic stroke with central nervous system sequelae. Based on stroke risk scores (CHADS and CHA_2DS_2VASc) and bleeding risk (HAS-BLED), the optimal use of anticoagulation in atrial fibrillation is feasible. Warfarin is a proven medication for this specific indication but requires frequent monitoring and dose adjustments, and it has multiple food, drug, and disease-state interactions. In addition, management of anticoagulation during the perioperative period may be challenging. In this regard, novel oral anticoagulants (NOACs) have shown promise in the shift toward the "ideal" anticoagulant therapy, in that fixed dosing is the norm, drug interactions are few, food interactions are absent, onset is fairly immediate and offset predictable, and, in the majority of patients, therapeutic monitoring is not required. This article provides a review of recent published trials of the use of NOACs in atrial fibrillation. Practical points on indications, contraindications, mechanism of action, interactions, and perioperative management tips are discussed with a view toward the safe and effective use of these new medications. When patients are transitioned between different anticoagulant medications, the risks of thrombosis and bleeding need to be considered. When switching from warfarin to a NOAC, the NOAC can be started once the international normalized ratio is ≤2.0.(J Am Board Fam Med 2015;28:510–522.)

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Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice, affecting in excess of 2.3 million people in the United States[1] and over 6 million patients in Europe.[2] AF occurs in 0.4% to 2% of the general population, with higher prevalence rates as the population ages.[1,2] Ischemic stroke is one of the major complications of AF because of the propensity for cerebral thromboembolism. AF increases the risk of stroke 5-fold, and 15% to 20% of patients with stroke have AF.[1,2] Hence, patients with AF should be aggressively stratified for stroke risk and, where indicated, maintained on long-term therapeutic anticoagulation for stroke prevention.[3]

Warfarin, a vitamin K antagonist, was until recently the only commercially available oral anticoagulant (OAC) for stroke prevention in atrial fibrillation. Warfarin is still the preferred method of anticoagulant in patients with mechanical heart valves; however, it is far from being the "ideal" anticoagulant. As a result, patients with AF who meet criteria for chronic anticoagulation may lead providers to choose alternatives to warfarin.[4] In the past few years novel OACs (NOACs) that offer an alternative for chronic anticoagulation have been developed, overcoming many of the drawbacks of warfarin while maintaining efficacy. The US Food and Drug Administration (FDA) has approved a few NOACs for use in AF, whereas others are in various phases of investigation.

As the population continues to age, a 6-fold increase in the prevalence of AF, from 2.3 million

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From the Department of Family Medicine (MM) and the Division of Cardiovascular Diseases (FES, FM), Mayo Clinic, Scottsdale, AZ.
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Corresponding author: Martina Mookadam, MD, Department of Family Medicine, Mayo Clinic, 13400 East Shea Blvd, Scottsdale, AZ 85259 (E-mail: mookadam.martina@mayo.edu).

Table 1. Comparison of the $CHADS_2$ and CHA_2DS_2-VASc* Risk Stratification Scores for Subjects With Nonvalvular Atrial Fibrillation[5]

Definition	Possible Score	Stroke Risk Stratification: $CHADS_2$ and CHA_2DS_2-VASc Scores	Stroke Risk Stratification: Adjusted Stroke Rate (% per year)
$CHADS_2$ acronym		$CHADS_2$ acronym†	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 years	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2
CHA_2DS_2-VASc acronym		CHA_2DS_2-VASc acronym‡	
Congestive HF	1	0	0
Hypertension	1	1	1.3
Age ≥75 years	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65 to 74 years	1	6	9.8
Sex category (eg, female sex)	1	7	9.6
Maximum score	9	8	6.7
		9	15.20

†These adjusted stroke rates are based on data for hospitalized patients and atrial fibrillation and were published in 2001.[8] Because stroke rates are decreasing, actual stroke rates in contemporary nonhospitalized cohorts might vary from these estimates.
‡Adjusted stroke rate scores are based on data from Lip and colleagues.[9] Actual rates of stroke in contemporary cohorts might vary from these estimates.
AF = atrial fibrillation
*$CHADS_2$ = congestive heart failure; hypertension; age ≥75 years; diabetes mellitus, prior stroke or transient ischemic attack (TIA), or thromboembolism (doubled). CHA_2DS_2-VASc = congestive heart failure; hypertension; age ≥75 years (doubled); diabetes mellitus; prior stroke or TIA or thromboembolism (doubled); vascular disease; age 65 to 74 years; sex category.
HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolic.[9,10]

to 15.9 million, by the year 2050 is projected.[4,5] Hence, the imperative to reduce the burden of stroke in nonvalvular atrial fibrillation with NOACs is now at hand. In this review we highlight the NOAC drugs that are currently available or may be in the process of approval for thromboembolism prophylaxis in patients with nonvalvular AF. Patients with AF have an increased propensity to form a thrombus in the left atrial appendage that may result in cerebral ischemia. Several other putative etiologies, including relative vascular stasis caused by "fibrillating," uncoordinated and ineffective atrial contraction, endothelial dysfunction, and atrial endocardial inflammation may all increase the risk of a left atrial appendage thrombus in AF. These clots can propagate through the arterial circulation and cause distant thromboembolism, the most important being ischemic stroke.[6,7]

The 2 major categories of drugs that have been studied for the long-term prevention of thromboembolic events in patients with AF are antiplatelet agents (aspirin, clopidogrel) and a vitamin K antagonist (warfarin). Different dosages of aspirin as well as different intensities of warfarin treatment have been studied in prospective, randomized clinical trials over the past 20 years; warfarin showed superior efficacy in all clinical trials.[8]

Risk Stratification for Anticoagulation in AF

Several factors contribute to the added risk of thromboembolism in patients with AF. The most widely used risk stratification strategies include $CHADS_2$ and CHA_2DS_2VASc (class 1B recommendation). Table 1 was proposed in the 2011 European Society of Cardiology recommendations[2] that especially recog-

Table 2. Assessment of Bleeding Risk (HAS-BLED) in Patients With Atrial Fibrillation

Letter	Risk	Points	HAS-BLED Score	Bleeds per 100 Patient-Years
H	Hypertension (uncontrolled, systolic blood pressure >160 mmHg)	1	0	1.13
A	Abnormal ± renal function* Abnormal liver function†	1 or 2	1	1.02
S	Stroke history	1	2	1.88
B	Bleeding (major bleed: anemia or predisposition to bleed)	1	3	3.74
L	Labile INRs (time in therapeutic range <60%)	1	4	8.7
E	Elderly (age >65 years)	1	5–9	Insufficient data‡
D	Drugs or alcohol (antiplatelets or NSAIDs, or excess alcohol§)	1 or 2	—	—

*Abnormal renal function is classified as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 μmol/L (2.26 mg/dL).
†Abnormal liver function is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin 2 to 3 times the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase raise/alkaline phosphatase 3 times the upper limit of normal).
‡Insufficient events at HAS-BLED scores of >5 in initial validation cohort.
§Excess alcohol is defined as the consumption of ≥8 alcoholic units/wk.
Reproduced with permission from Lip.[11]
INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory agent.

nize patients with AF who seemingly have low to moderate risk for thromboembolism ($CHADS_2$ score 0 to 1; Table 1).

In addition to the variables used in the $CHADS_2$ scheme, this scoring system includes a few other risk factors, such as the presence of vascular disease and female sex. Greater emphasis is placed on age of the patient. Patients who are >75 years of age are assigned 2 points, whereas those who are 65 to 74 years old are given 1 point. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society atrial fibrillation guidelines for risk stratification recommend using the more sensitive CHA_2DS_2VASc score. Based on the aggregate CHA_2DS_2VASc score, no antithrombotic therapy is recommended for patients with a score of 0, an OAC or aspirin 75 to 325 mg daily (with a preference for OACs) for those with a score of 1, and either warfarin or one of the NOACs is advised for those with a CHA_2DS_2VASc score of ≥2.[8]

The European Society of Cardiology guidelines also include a scoring system to assess patients who are at high risk for major bleeding (Table 2). The HAS-BLED bleeding risk score[12] includes (class 1C recommendation): hypertension (1 point); abnormal renal or liver function (1 point each); stroke (1 point); bleeding (1 point); labile international normalized ratio (INR) (1 point); elderly (>65 years old, 1 point); concomitant drugs, that is, antiplatelet drugs, nonsteroidal anti-inflammatory drugs, or alcohol (1 point each) (Table 2). A cumulative score ≥3 suggests a higher risk of bleeding; hence, caution in prescribing OACs should be exercised, and more frequent follow-up for these patients is necessary. These scoring systems can help clinicians make a judicious decision for chronic anticoagulation in patients with AF after weighing the risks and the benefits.[9] When both bleeding and stroke risk are high, NOACs seem to have a net clinical benefit over warfarin.[13]

Warfarin

Warfarin acts by inhibiting vitamin K epoxide reductase, thereby suppressing the effective synthesis of biologically active forms of vitamin K–dependent clotting factors (II, VII, IX, and X), as well as the regulatory factors protein C and protein S. Although one can see the change in INR within the first 1 to 2 days after the initial administration of warfarin, it can take up to 5 days for a clinically relevant antithrombotic effect to occur because the circulating coagulation factors are not affected by the drug. Warfarin[14] has a long half-life; however, its anticoagulation can be quickly reversed using parenteral vitamin K, fresh frozen plasma, or concentrated factor VII. The efficacy of warfarin treatment is monitored by testing the INR of the prothrombin time; the recommended range of INR for thromboembolic prophylaxis in patients with AF is

2.0 to 3.0.[10] Warfarin follows nonlinear pharmacokinetics and has significant food, drug, and disease-state interactions that affect INR. Consuming a stable vitamin K diet without much fluctuation in the consumption of vitamin K–dense foods is recommended for patients. A thorough review is recommended when a patient on warfarin is introduced to new medication. The narrow therapeutic range of warfarin and its multiple food, drug, and disease-state interactions require patients to undergo at least monthly testing of INR when dosing has stabilized. Self-monitoring and management of INR through a third-party, home-based kit is an alternative for patients who are willing and able to do the necessary training and who have a history of stable INRs.[15,16] In patients with a stable INR, extended follow-up intervals of 60 to 90 days may be adequate. Major bleeding is the most common serious side effect of chronic warfarin anticoagulation. Intracranial bleeding increases when the INR exceeds 4.0, but there is no increase in bleeding risk with INR values between 2.0 and 3.0 compared with lower INRs.[2]

The complexities of warfarin may discourage its use even in high-risk patients with AF.[17] A retrospective cohort study of inpatients performed at 21 teaching hospitals, 13 community hospitals, and 4 Veterans Administration hospitals in the United States reported that among the 945 patients with AF, 86% had factors that stratified them as at high risk of stroke, and only 55% of those received warfarin.[18] Similar data come from the registry of the Canadian Stroke Network that studied use of warfarin and admission INR in high-risk patients with AF who were admitted to the hospital with stroke and had no contraindications to anticoagulation. Warfarin usage before admission was only 40%, of which three-fourths had a subtherapeutic INR (<2.0) at the time of admission for stroke. In a subset of patients with a history of previous transient ischemic attack or stroke, only 18% were taking warfarin and had a therapeutic INR.[4,19] Both patient and physician factors contribute to the underuse of warfarin.[20] Patients may find using warfarin inconvenient because of its food, drug, and disease-state interactions, risk of bleeding, and the regular need for laboratory visits. Physicians may tend to overestimate the bleeding risks caused by warfarin or may not prescribe it to patients who are perceived to be noncompliant with INR testing.[20]

In patients with atrial fibrillation for whom vitamin K antagonist therapy was deemed unsuitable, a combination of aspirin and clopidogrel was studied in the ACTIVE (effect of clopidogrel added to aspirin in patients with atrial fibrillation) trial.[21] This placebo-controlled trial enrolled 7554 patients who were followed for a median of 3.6 years. The addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, but increased the risk of major hemorrhage. The ACTIVE W[22] trial, which compared clopidogrel plus aspirin versus warfarin in patients with AF, was stopped early because of clear evidence of the superiority of warfarin therapy both in stroke prevention and in lower risk of major bleeding.

NOAC Class

NOACs have been available for a few years and are increasingly being used for thromboembolic risk reduction in patients with AF. NOACs have different pharmacologic actions, and to optimally use these medications, a better understanding of their characteristics is important to allow for their safe and effective use when indicated (Table 3). An ideal anticoagulant should be available in an oral, fixed-dose formulation; have a rapid onset of action; have predictable pharmacokinetics and pharmacodynamics; and offer a wide therapeutic window without a need for regular monitoring of drug concentrations. It should have a safe antidote, be easily reversible, and be available at a low cost to consumers. A schematic of the coagulation cascade pathway and the areas of action of the newer anticoagulants are shown in Figure 1. Dabigatran, rivaroxaban, and apixaban have already received FDA and European Union approval for use in patients with nonvalvular AF to prevent thromboembolic events.

Direct Thrombin Inhibitors

Thrombin (factor II) converts fibrinogen to fibrin and amplifies the process of coagulation by direct activation of platelets and other clotting factors in the coagulation cascade. direct thrombin inhibitors (DTIs) inactivate clot-bound as well as soluble thrombin. The first DTI that was extensively studied in clinical trials for thromboembolic prophylaxis was ximelagtran (class 3B recommendation). The potential of ximelagtran (Exanta; AstraZeneca, London, UK) for stroke prevention in patients with

Table 3. Review of Novel Oral Anticoagulant Pharmacokinetics[23]

Characteristics	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Synthesis of II, VII, IX, X	IIa (thrombin)	Xa	Xa	Xa
Dose (mg)	Variable	150 110* 75†	20 (15)	5 (2.5)	30 60
Frequency	Once a day	Twice a day	Once a day	Twice a day	Once a day
Hour to C_{max}	72–96	22–4.5	1–3	1–2	—
Half-life (hours)	40	12–14 >24 if creatinine <30	5–9 9–13 (Elderly)	8–15	10–14
Interactions	CYP2C9/3A4/1A2	P-gP	CYP3A4/2J2 P-gP	CYP3A4 P-gP	P-gP
Renal elimination (%)	<1	80	33	25	35

*The 110-mg dose not available in the United States.
†Use 75-mg dose in patients with creatinine clearance 15–30 mL/min.
P-gP, P-glycoprotein; CYP, cytochrome P; IIa, factor IIa (thrombin); Xa, factor Xa.

AF was demonstrated in 2 phase III clinical trials[24,25]; because of concerns of hepatotoxicity, however, further development of this drug was terminated and it was withdrawn from all markets in 2006.[26]

Dabigatran (Pradaxa; Boehringer Ingelheim Pharmaceuticals, Inc., Richfield, CT).

Dabigatran etexilate is a DTI that is converted to the active form dabigatran by esterase-catalyzed hydrolysis in plasma and within the liver independent of cytochrome P-450. Hence, dabigatran is less affected by food and drug interactions, a contradistinction to warfarin, and does not require monitoring in patients with normal renal function. It is administered orally in a fixed dose twice a day, and it has a low bioavailability, a rapid onset of action (1 to 2 hours), and a half-life of 12 to 14 hours. In healthy older volunteers the elimination half-life was 13 hours. It is renally cleared, and a lower dose is recommended in patients with renal insufficiency.[27]

The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial was a landmark trial that compared different dosages of dabigatran with warfarin in patients with nonvalvular AF[28]; 18,113 patients with AF were enrolled to receive fixed doses of dabigatran (110 or 150 mg twice daily) or adjusted-dose warfarin (Table 4). After a 2-year follow-up, the primary outcome of stroke or systemic embolism was similar in the group that received a lower dose of dabigatran (110 mg) compared with warfarin's relative risk with dabigatran; however, those receiving 150 mg of dabigatran had significantly fewer primary outcome events compared with those receiving warfarin. The risk of major bleeding was lower in the low-dose dabigatran group and similar in the higher-dose dabigatran group when compared with those taking warfarin (class 1B recommendation). A subanalysis of the RE-LY trial based on age concluded that both doses of dabigatran have lower risks of bleeding compared with warfarin in patients aged <75 years. In those aged >75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar with the 110 mg dabigatran dose and higher with the 150 mg dabigatran dose compared with warfarin.[35] The RE-LY trial also specifically looked at renal function in patients with an estimated glomerular filtration rate >80, 50 to 80, and <50 mL/min. Risk of stroke, systemic embolism, major bleeding, and all-cause mortality increased as renal function decreased. Rate of stroke or systemic embolism was lower with dabigatran 150 mg bid and similar with 110 mg bid compared with warfarin, regardless of renal function.[36] In 2010 the FDA approved 2 dosages of dabigatran for reduction of systemic stroke and systemic embolism in patients with nonvalvular AF (class 1B recommendation): 150 mg twice a day for patients with normal renal function and 75 mg twice daily for those with impaired renal function; however, this is not a studied dose but rather a dose based on pharmacokinetic modeling.[37]

Although dabigatran has been welcomed with great enthusiasm by many clinicians, there are some areas of concern. The twice-a-day dosing

Table 4. Review of the Landmark Trials in Atrial Fibrillation and the Use of Novel Anticoagulants[28–34]

Drug	Trial	Design	Treatment	Duration	TTR (%)	Patients	Mean $CHAD_2$ Score	Efficacy/Outcome	Safety/Outcome
Dabigatran	RE-LY	Blinded	VKA/dabigatran (150 mg bid)	24 months	64	18,113 patients with nonvalvular Afib	2.1	Stroke or systemic emboli, 1.11% Dabigatran 1.69% VKA group	Major bleeding in 2.71% Dabigatran in 3.36% of VKA group
Rivaroxaban	Rocket AF	DB	VKA/rivaroxaban (20 mg daily)	30 months	55	14,264 patients with nonvalvular Afib	3.5	Stroke or systemic emboli 1.7% rivaroxaban 2.2% VKA group	Major bleeding: 3.6% in rivaroxaban group, 3.4% in VKA group
	X-Vert	DB	VKA/rivaroxaban (20 mg daily)	Months	55	1504 patients needed cardioversion for Afib	3.2	Stroke or systemic emboli: 0.5% in rivaroxaban group and 1.02 in the VKA group	Major bleeding: 0.61% in rivaroxaban group vs 0.8% in VKA group
Apixaban	AVVEROUS	DB	ASA/apixaban 5 mg bid or 2.5 mg bid	13 months	62	5,599 patients with nonvalvular Afib could not take warfarin	2.1	Stroke or systemic emboli: 1.6% in apixaban group vs 3.7% in the ASA group	Major bleeding: 1.4% in apixaban group vs 1.2% in ASA group
	ARISTOTLE	DB	VKA/apixaban 5 mg bid or 2.5 mg bid	22 months	62	18,201 patients with nonvalvular Afib	2.1	Stroke or systemic emboli 1.27% apixaban 1.6% VKA group	Major bleeding 2.1 apixaban 3.09% VKA group
Edoxaban	ENGAGE-TIMI 48	DB	VKA/edoxaban 60 mg daily and 30 mg daily	34 months	64	21,105 patients with nonvalvular Afib	2.8	Stroke or systemic emboli: 1.18% in edoxaban group vs 1.5% in VKA group	Major bleeding: 2.75% in edoxaban group vs 3.43% in VKA group

Afib, atrial fibrillation; ASA, aspirin; DB, double blind; TTR, time in therapeutic range; VKA, Vitamin K antagonist.

Table 5. Common Drug–Drug Interactions With Novel Oral Anticoagulants

	Novel Oral Anticoagulants			
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Ketoconazoles	Avoid	Avoid	Avoid	Avoid
Clarithromycin	No adjustment	Precaution*	Avoid	Avoid
Erythromycin	Precaution*	Precaution*	*Precaution*	Avoid
Fluconazole	Avoid	Precaution*	Avoid	Avoid
Rifampin	Avoid	Avoid	Avoid	Safe
NSAIDs/ASA	Caution	Caution	Caution	Caution
Clopidogrel/antiplatelet agents	Caution	Caution	Caution	Caution
Diltiazem	NK	Caution	Caution	NK
Verapamil	Avoid†	Caution	Caution	Avoid
Heparin/anticoagulants/ticagrelor	Avoid	Avoid	Avoid	Avoid

*Especially in renal impairment.
†Administer novel oral anticoagulant 2 hours before if choosing to use both agents; caution implies increased bleeding risk
ASA, aspirin; NK, not known; NSAID, nonsteroidal anti-inflammatory drug.

may not be convenient for some patients. Drug storage may not be convenient and may be prohibitive for patients who use medication reminder boxes to assist with adherence. Dosing in patients with severe renal dysfunction (estimated glomerular filtration rate <30 mL/min) has not been adequately evaluated in trials, and many patients in this cohort have chronic kidney disease. Dabigatran etexilate is a substrate for the efflux pump P-glycoprotein. Hence, caution should be used while taking inhibitors (ketoconazole, amiodarone, and verapamil) or inducers (rifampin) of P-glycoprotein. In general, dabigatran is contraindicated in patients taking ketoconazole and rifampin[38–41] (Table 5). Although no dose adjustment is recommended in patients taking verapamil or amiodarone, dabigatran should be given at least 2 hours prior to taking either of these medications to minimize potential interactions.[38] Unlike warfarin, there is no antidote available for this drug. Other concerns include significant dyspepsia, and a small but insignificant increase in the rate of myocardial infarct was associated with dabigatran in the RE-LY trial.[42] The RE-LY-ABLE (Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients with Atrial Fibrillation) study is currently underway to establish the long-term safety of dabigatran in patients who completed the RE-LY trial.[43] In addition, the FDA is currently conducting an independent medical product assessment of dabigatran as part of its Mini-Sentinel Program.[44]

While the RE-LY study outlines the bleeding risk of warfarin compared with dabigatran within the close follow-up of a clinical trial, a recent article looking at bleeding risk between these drugs with "real life" use should be highlighted.[17,45] In essence this is a retrospective look at a random sampling of medicare beneficiaries over a 1-year period with atrial fibrillation who were prescribed either of these medications. Among dabigatran users (n = 1302) and warfarin users (n = 8102), risk of both major and minor bleeding was higher for dabigatran. Dabigatran users had fewer intracranial bleeds than warfarin, with hazard ratios of 1.30 (95% confidence interval [CI], 1.20–1.41) for any bleeding, 1.58 (95% CI, 1.36–1.83) for major bleeding, and 1.85 (95% CI, 1.64–2.07) for gastrointestinal bleeding. The risk of intracranial hemorrhage was higher among warfarin users, with a hazard ratio of 0.32 (95% CI, 0.20–0.50) for dabigatran compared with warfarin. Dabigatran was consistently associated with an increased risk of major bleeding and gastrointestinal hemorrhage. Thus, this after-market assessment of the risk of bleeding while taking dabigatran relative to warfarin must be taken into account, especially among older patients (>75 years of age), African Americans, and those with renal impairment.[45]

The following are practical points about dabigatran that physicians should consider:

- Renal function should be assessed in all patients before initiating dabigatran therapy.
- Dabigatran is contraindicated in patients with severe renal impairment.

- Avoid dabigatran in patients with elevated risk for gastrointestinal bleeding.[33]
- In elderly patients (>75 years old) or in patients with renal impairment, an adjusted dose of 75 mg bid is preferred.
- Activated partial thromboplastin time (aPTT) and ecarin time correlate with dabigatran blood concentrations.[28]
- Dabigatran should be stopped 2 to 5 days before elective surgical intervention (Table 6).
- Fresh frozen plasma during hemoperfusion should be considered in cases of life-threatening bleeding.
- Dabigatran should not be used in patients with mechanical heart valves.[28]
- Dabigatran must be stored in the tightly closed original bottle or a blister pack to avoid moisture. Patient cannot use pill organizers.

Factor Xa Inhibitors

Factor Xa plays an important role in the coagulation cascade because it lies at the convergence of the intrinsic and the extrinsic pathways. Factor Xa catalyzes the conversion of prothrombin to thrombin, which in turn plays a critical role in clotting, as discussed above. The 2 factor Xa inhibitors that have been studied in phase III trials are rivaroxaban (Xarelto; Janssen Pharmaceuticals, Titusville, NJ) and apixaban (Eliquis; Pfizer and Bristol Myers Squibb, New York City, NY).

Rivaroxaban (Xarelto)

Rivaroxaban is a direct factor Xa inhibitor that selectively and reversibly inhibits both free and clot-bound factor Xa. It is administered orally in a fixed, once-daily dose, with food to ensure adequate absorption. Rivaroxaban has a relative bioavailability of 80%, achieves peak plasma concentrations within 2 hours, and has a half-life ranging from 5 to 9 hours in healthy volunteers (9 to 13 hours in the elderly). It is excreted via both the renal and hepatic routes. Rivaroxaban is metabolized through CYP3A4/3A5 and to a lesser extent through CYP2J2; hence, caution should be used when concomitantly using rivaroxaban with other CYP3A4 or P-glycoprotein substrates. Routine monitoring of anticoagulation is not required (Table 3).

The Rivaroxaban—Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism in

Table 6. Suggestions for Novel Oral Anticoagulation Discontinuation Prior to Planned Surgical Intervention[46,47]*

	Dabigatran		Rivaroxaban		Apixaban	
Creatinine Clearance (mL/min)	Low Risk	High Risk	Low Risk	High Risk	Low Risk	High Risk
>50	≥2 Days	≥3 Days	≥2 Days	≥3 Days	≥2 Days	≥3 Days
30–50	≥3 Days	≥4 to 5 Days	≥2 Days	≥3 Days	≥3 Days	≥4–5 Days
15–30	Not indicated	Not indicated	≥3 Days	≥4 Days	Not indicated	Not indicated
<15			No official indication for use			

*No important bleeding risk and/or adequate local hemostasis possible. Perform at trough level (ie, ≥12 hours or 24 hours after last intake).

Atrial Fibrillation (ROCKET-AF) trial was a large, randomized, double-blind, phase III, non-inferiority trial that enrolled 14,264 patients with nonvalvular AF to receive rivaroxaban (20 mg/day) or dose-adjusted warfarin (Table 4). The primary end of stroke or systemic embolism occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 patients in the warfarin group (2.2% per year) ($P < .001$ for noninferiority). There was no significance in the risk of major bleeding between the 2 groups ($P = .44$), although intracranial and fatal bleeding occurred less often in the rivaroxaban group. The trial concluded that rivaroxaban was not inferior to warfarin for the prevention of stroke or systemic embolism in patients with AF.[31] Based on the results of this trial, rivaroxaban was approved in 2011by the FDA for use in AF for stroke prevention (class 1B recommendation).

The following are practical points about rivaroxaban that physicians should consider:

- Administer with food.
- Monitor renal function.
- Adjust dose based on renal function: creatinine clearance (Cr Cl) ≥50 mL/min, 20 mg daily; Cr Cl 15 mL/min to 50, 15 mg daily; Cr Cl ≤15 mL/min, avoid.[39]
- Rivoraxaban use increases risk of gastrointestinal bleeding compared with warfarin.[31]
- Rivoraxaban should not be used in patients with mechanical heart valves or valvular AF (it is not approved for this use).
- Rivoraxaban should be stopped 1 to 2 days before elective surgery (Table 6).
- Possible reversal agents being developed, including 4-factor prothrombin complex concentrate (4F-PCC).[48,49]
- Avoid combined use with ketoconazole and rifampin (Table 5).

Apixaban (Eliquis)

Apixaban is a direct factor Xa inhibitor that is administered orally in a fixed, twice-a-day dose, with an onset of effect of 3 hours, bioavailability of 49%, and a half-life of 8 to 15 hours (Table 6). Clearance is predominantly nonrenal; hence, the drug can be used in patients with moderate renal dysfunction. It is metabolized mainly through the CYP3A4/3A5 pathway, so caution should be used when apixaban is administered concomitantly with other CYP3A4 inducers or inhibitors. Routine monitoring of anticoagulation is not required.

The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVVEROUS) (class 1B recommendation) was a double-blind study that compared apixaban with aspirin in patients with AF for whom vitamin K antagonist therapy was unsuitable because of a difficult-to-control INR, patient refusal, or increased bleeding risk (Table 4). Over 5500 patients randomly assigned in a double-blind study were subject to apixaban 5 mg twice a day or aspirin 81 to 324 mg/d to determine whether apixaban was superior. Mean $CHADS_2$ score was 2.05. The study was stopped prematurely because of the clear advantage of apixaban over aspirin in reducing the risk of stroke or systemic events by >50%. There was no increased risk of major bleeding with apixaban over aspirin.[33] The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study compared apixaban with warfarin in >18,000 patients with AF. This trial was conducted for 1.8 years in over 1000 centers in 39 countries. The rate of the primary outcome (stroke/systemic embolism) was 1.27% per year in the apixaban group compared with 1.60% per year in the warfarin group ($P < .001$ for noninferiority; $P = .01$ for superiority). The rate of major bleeding was significantly less in the apixaban group ($P < .001$), and the rate of death from any cause was less as well ($P = .047$).[30] Apixaban proved itself as the first OAC to reduce the risk of death from any cause. In 2012 the FDA approved apixaban for use in patients with nonvalvular AF (class 1B recommendation)

The following are practical points about apixaban that physicians should consider:

- The recommended dose is 2.5 mg twice daily for any 2 of the following: age >80 years; body weight <60 kg; or serum creatinine >1.5 mg/dL.[30]
- The recommended dose for patients with end-stage renal disease maintained on hemodialysis is 5 mg twice daily.[30]
- Similar to rivaroxaban, a normal prothrombin time would indicate the absence of the drug from the body. Chromogenic Xa can be used to monitor the drug concentration; however, the values are not well understood.

- Avoid use in combination with ketoconazole, clarithromycin, clopidogrel, or rifampin (Table 5).
- Apixaban should be held 2 days before elective surgical intervention (Table 6).
- 4F-PCC can be considered in cases of live threatening bleeding because there is no antidote or true reversal agent.

Other Oral Factor Xa Inhibitors

Edoxaban (Lixana; Daiichi Sankyo Tokyo, Japan) is an oral, direct factor Xa inhibitor that is currently undergoing a phase III clinical trial. It has a short onset of action (1 to 1.5 hours), a half-life of 10 to 14 hours[50] (Table 3), and 35% renal excretion. Routine anticoagulation monitoring is not needed. Caution should be used when administered concomitantly with other CYP3A4 inducers or inhibitors. In a phase II trial of 1146 patients with AF, the safety of 4 fixed-dose regimens of edoxaban was compared with warfarin for 12 weeks.[34] The results suggested that the safety profiles of edoxaban once-daily dosing in patients with AF were similar to those of warfarin. By contrast, the edoxaban bid regimens were associated with more bleeding than warfarin. Hence, a phase III trial (ENGAGE AF-TIMI 48 [Edoxoban versus Warfarin in Patients with Atrial Fibrillation]) was designed to compare stroke and systemic embolism outcomes between edoxaban (30 or 60 mg daily) and warfarin in patients with AF.[29] About 20,500 subjects will be enrolled and followed up for 24 months. Both daily doses of edoxaban were not inferior to warfarin and were associated with significantly less major bleeding. Edoxaban 60 mg was associated with more gastrointestinal bleeding when compared with warfarin (no recommendation; not approved in the United States).

The following are practical points about edoxaban that physicians should consider:

- Edoxaban is approved for nonvalvular AF only in Japan.
- Caution should be used when administering concomitantly with other CYP3A4 inducers or inhibitors (Table 5).

Betrixaban

Betrixaban (PRT-054021) is another oral direct factor Xa inhibitor; it has a bioavailability of 47% and a half-life of 19 hours, and it is excreted almost unchanged in bile, making it particularly suitable for use in patients with renal failure. Betrixaban was shown to be safe, with a dose-dependent risk of bleeding comparable to that of warfarin, in the phase II trial EXPLORE Xa (Bertrixaban Compared With Warfarin in Patients with Atrial Fibrillation), where a once-daily dose of betrixaban 40 mg demonstrated significantly less bleeding than warfarin ($P = .035$) in patients with AF. The risk of bleeding for the 60- and 80-mg doses of betrixaban was similar to that of warfarin.[32] No information is available regarding phase III trials of this drug in AF (no recommendation).

Reversibility of NOACs

There is no specific antidote for dabigatran. Because of its short half-life (12 to 14 hours after multiple doses), cessation of dabigatran therapy for 2 to 4 days is sufficient to reverse its action in nonurgent cases.[51] Suggested treatments in the case of major bleeding include administration of 4F-PCC, recombinant-activated factor VII, or hemodialysis in patients with kidney failure. Administration of activated charcoal is recommended if the last dose was within 2 hours. A potential dabigatran antidote (proposed international nonproprietary name "idarucizumab") is also undergoing clinical studies.[52] For rivaroxiban, although monitoring of medication concentrations is not required, measurement of antifactor Xa, prothrombin time, and INR is useful in certain circumstances. Possible reversal agents are 4F-PCC and activated prothrombin complex concentrate (PCC). Apixaban can be monitored by testing prothrombin time, aPTT, INR, and antifactor Xa. Similar to other NOACs, there is no specific antidote for apixaban, and cessation of therapy for 3 days is usually all that is required to reverse its action. In cases of severe bleeding, the use of 4F-PCC or activated PCC is recommended. Andexanet α (PRT4445) is a recombinant factor Xa protein that may be able to partially reverse the action of factor Xa inhibitors.[49] Phase II clinical trials to evaluate this new medication as an antidote for rivaroxaban and apixaban are ongoing.[48] For edoxaban, monitoring the plasma concentration could be achieved by testing INR, prothrombin time, and antifactor Xa activity. Reversal with recombinant human factor VIIa, anti-inhibitor coagulant complex, and 4F-PCC is possible in preclinical studies.[53]

Treatment Interruption for Surgical Procedures

It is estimated that 20% of patients >70 years old will require some sort of anticoagulation interruption for minor or major surgical interventions annually. Open heart surgery, abdominal vascular surgery, neurosurgery, major cancer surgery, and urologic procedures are considered high risk for bleeding (class 1C recommendation), keeping in mind that many procedures with low bleeding risk use neuroaxial anesthesia. Recommendations for discontinuing NOACs based on pharmacokinetics, renal function, and the risk of the surgery are shown in Table 4. For spinal, epidural, or major surgery where complete hemostasis is needed, >48 hours of NOAC discontinuation is warranted in patients with normal renal function, and in those with renal impairment an even longer discontinuation time before elective surgery is needed. In the case of dabigatran, aPTT and, in the case of rivaroxaban and apixaban, prothrombin time may be helpful if the blood concentrations before surgery are close to normal, suggesting a very low serum concentrations.[46,47]

Transitioning Between Warfarin and NOACs

When transitioning from a NOAC to warfarin, concomitant therapy is generally recommended until the INR reaches the desired level. This can be done by overlapping the NOAC and warfarin or by bridging with low-molecular-weight heparin during warfarin initiation.[42] So far, because of the lack of direct comparison trials, there are no clinical practice guidelines on how to transition between NOACs. A reasonable approach is to make a direct switch when changing from a drug dosed bid, such as dabigatran, to one such as apixaban. If switching from once-a-day rivoraxaban, the patient can be advised to wait 24 hours before starting their new NOAC. Future guidelines will need to address safe transitioning between oral anticoagulants.

Conclusion

NOACs have been long anticipated as an alternative to warfarin and are now here in full force. Several studies show equal or slightly better efficacy compared with warfarin, with fewer bleeding side effects, especially intracranial bleeds.

NOACs are generally not indicated in patients with mechanical valves, valvular atrial fibrillation, or when INR is well controlled and stable (within the therapeutic range). On occasion, patient preference to be on a NOAC in place of warfarin may be considered, with a detailed discussion of benefit risk and cost in particular that may be traded for convenience. Dabigatran is contraindicated in advanced renal failure compared with other NOACs. Dabigatran, rivaroxaban, and epixaban are contraindicated in patients taking ketoconazole and rifampin.

The NOACs fulfill many but not all the criteria of an ideal anticoagulant. They are oral, fixed-dose medications; do not require regular monitoring of drug concentrations; have rapid onset of action, with predictable pharmacodynamics and pharmacokinetics; and offer a wide therapeutic window. Important remaining challenges include the need for dose adjustment in both renal and hepatic impairment. Contraindication in end-stage renal disease (with or without renal replacement), medication cost, and the lack of a specific antidote remain as limitations. Nevertheless, it is anticipated that over the next few years, assays that measure serum NOAC concentrations and specific reversal agents will become available for general use. Based on phase III trials, the FDA has approved dabigatran, rivaroxaban, and apixaban for use in patients with nonvalvular AF. In the next few years, as clinicians gain familiarity with NOACs, the long-term safety, adverse reactions, as well as the cost benefit advantages will become apparent. The quest for the ideal anticoagulant should continue. In the meantime, these new anticoagulants do go a long way to provide essential anticoagulation with greater convenience and less monitoring in patients with AF with appropriate indications.

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