Reviews

Oral Anticoagulants to Reduce the Risk of Stroke in Atrial Fibrillation: How Should a Clinician Choose?

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ABSTRACT

Atrial fibrillation (AF), a common arrhythmia that occurs with increasing frequency in the aging population, is associated with increased mortality and morbidity. To ensure that patients receive adequate anticoagulant prophylaxis, clinical guidelines for anticoagulation advocate use of validated scoring systems to stratify patients by cardiovascular risk and predict the individual patient's risk of adverse effects of therapy. Recently approved oral anticoagulants — a direct thrombin inhibitor and the factor Xa inhibitors — may offer advantages over the 50-year standard, warfarin, for efficacy, safety, and ease of administration. Clinical trial experience with the newly approved agents and others, yet to be approved, will define their relative value in reducing the risk of thromboembolism associated with AF. This article discusses issues that may help clinicians choose among these newer agents and individualize treatment appropriately.

Clinical Vignette

A 52-year-old woman with a history of hypertension, diabetes mellitus, advanced emphysema, on long-term oxygen therapy with normal renal and left ventricular function, and diagnosed with atrial fibrillation of more than 2 days duration has decided to pursue a rate control strategy after discussions with her physician. She is reluctant to use warfarin because of the need for frequent monitoring, and is keen to know about the newer oral anticoagulants for atrial fibrillation. Which anticoagulant would be ideal for this patient?

Introduction

Atrial fibrillation (AF) is a common arrhythmia, with an estimated US prevalence of 3 million, which is expected to rise to 7 million by 2050.[1] AF is associated with increased mortality and morbidity due to complications in the form of hemodynamic changes, ventricular dysfunction, and thromboembolic events.[2] Thromboembolic stroke is the most serious and debilitating complication, the risk of which is increased 3 to 5 times in patients with AF.[3] During the last 2 to 3 decades, there has been considerable interest in preventive strategies to reduce the risk of stroke in patients with AF.[4,5]

Recent years have seen new risk prediction models for bleeding and stroke prevention, as well as the approval of new oral anticoagulants (OACs) to reduce the risk of stroke in patients with AF in addition to nonpharmacologic therapies that are under investigation. The challenge for physicians is to choose the appropriate OAC agent for individual patients. Attempts have been made to do indirect comparisons of these agents from the available data of individual trials. However, this kind of comparison has its own limitations because cross-trial comparisons could be inaccurate due to confounding.[6]

This article briefly reviews the newer, validated models for predicting risk of bleeding as well as stroke, in addition to clinical trial data on the efficacy and safety of the new OACs, to provide clinicians with a means of choosing an OAC to ensure optimal therapy for every patient with AF.

Stroke Risk Assessment

Stroke risk associated with AF varies among the AF population and depends on several factors.[7] Traditional stroke risk scores stratify patients into low-, moderate-, and high-risk groups, although the risk of stroke is a continuum and such an artificial categorization has only

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Received: April 16, 2013
Accepted with revision: June 20, 2013

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22173

Table 1. Comparison of Risk Scores Between $CHADS_2$ and CHA_2DS_2-Vasc Models[10]

$CHADS_2$ Risk	Score	CHA_2DS_2-Vasc Risk	Score
Congestive heart failure	1	Congestive heart failure or left ventricular ejection fraction <40%	1
Hypertension	1	Hypertension	1
Age ≥75 years	1	Age ≥75 years	2
Diabetes	1	Diabetes	1
Stroke/TIA	2	Stroke/TIA/thromboembolism	2
		Vascular disease	1
		Age 65–74 years	1
		Female sex	1

Abbreviations: TIA, transient ischemic attack.

modest predictive value for thromboembolism. In older guidelines, OAC therapy is recommended for high-risk patients, whereas OAC or acetylsalicylic acid (ASA) is recommended for moderate-risk patients and ASA alone for low-risk patients.[8]

The most commonly used score in United States, $CHADS_2$ (Tables 1 and 2), excludes several common stroke risk factors and has only modest predictive value for stroke.[9] The expanded CHA_2DS_2-Vasc score is consistently better at identifying truly low-risk subjects and performs at least as well as $CHADS_2$ for prediction in high-risk patients, and is included in current European guidelines.[10,11]

Bleeding Risk Score Assessment

To better identify patients in whom the benefits of anticoagulation may be outweighed by a high risk for bleeding, clinicians need risk models that can be applied conveniently and meaningfully in practice. Risk models for estimating bleeding risk have not achieved wide acceptance.[12] Several authors proposed bleeding risk assessment models that appeared too complex or lacked validation in AF patients. Recent efforts have resulted in simpler and more robust models, as discussed below.

HAS-BLED Bleeding Risk Model: Four independent risk factors for major bleeding were identified in a cohort of 3978 patients with AF from the Euro Heart Survey. On the basis of these risk factors, in addition to other established risk factors from systematic reviews and multivariate analyses, a bleeding risk score, termed HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history/predisposition, labile international normalized ratio [INR], elderly [>65 years old], use of drugs/alcohol), was proposed as an easy-to-use clinical tool for the assessment of bleeding risk in patients with AF who are under consideration for anticoagulant therapy. Table 3 lists the clinical characteristics used in developing HAS-BLED.[13]

ATRIA Bleeding Risk Model: The ATRIA risk score model outperformed earlier validated scores in predicting the risk of warfarin-associated hemorrhages in a cohort of 9186 patients with AF. On the basis of earlier validated risk stratification models, 5 specific risk factors were identified for warfarin-associated bleeding in patients with AF. Each of these variables was assigned points as follows: anemia (3), renal disease with estimated glomerular filtration rate <30 mL/min or on dialysis (3), age >75 years (2), history of bleeding (1), and hypertension (1). In both the derivation and validation groups, events per 100 patient-years ranged from 0.4 for patients with a score of 0, through 2.6 for a score of 4, and up to 12.4 and 17.25 for risk scores of 9 and 10, respectively. On the basis of these event rates, patients were considered to be at low risk for bleeding with scores of 0 to 3, and at high risk with scores from 5 to 10.[14]

Table 2. Comparison of Stroke Rates per Year Between $CHADS_2$ and CHA_2DS_2-Vasc Models[10]

CHA_2DS_2-Vasc Score	Patients, N = 7329	Adjusted Stroke Rate, %/Year	$CHADS_2$ Score	Patients, N = 1733	Adjusted Stroke Rate, %/Year
0	1	0	0	120	1.9
1	422	1.3	1	463	2.8
2	1230	2.2	2	532	4.0
3	1730	3.2	3	337	5.9
4	1718	4.0	4	220	8.5
5	1159	6.7	5	65	12
6	679	9.8	6	5	18.2
7	294	9.6			
8	82	6.7			
9	14	15.2			

Oral Anticoagulants

Warfarin, a vitamin K epoxide reductase inhibitor (termed a vitamin K antagonist [VKA]), was the only oral anticoagulant available for half a century. Despite benefits seen with warfarin in multiple trials, problems encountered in its use included the need for anticoagulation monitoring, interactions with foods and medications, and genetic polymorphism, all of which may interfere with medication adherence and limit the use of warfarin in clinical practice.[15] In a community database study of more than 3600 patients with AF or atrial flutter, antithrombotic treatment was given in accordance with guideline recommendations to only 53% of patients, a large proportion of whom were undertreated.[16] Newer anticoagulants have been developed to overcome warfarin's limitations.

The 2 main classes of novel oral anticoagulants are direct thrombin inhibitors (DTIs) and factor Xa (FXa) inhibitors. Agents in both classes have shown more predictable pharmacodynamics than VKA. Direct FXa inhibition has coagulation-specific effects, whereas direct thrombin inhibition may have beneficial effects outside the coagulation cascade.[17] These features do not necessarily translate into better safety or efficacy as will be discussed

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DOI:10.1002/clc.22173

Table 3. Clinical Characteristics Used in the HAS-BLED Bleeding Risk Score*

HAS-BLED Risk Score			Estimated Bleeding Risk	
Acronym	Characteristic	Points	HAS-BLED Score (Total Points)	Bleeds/100 Point-Years[a]
H	Hypertension	1	0	1.13
A	Abnormal renal or liver function (1 point each)	1 or 2	1	1.02
S	Stroke	1	2	1.88
B	Bleeding	1	3	3.74
L	Labile INR	1	4	8.70
E	Elderly	1	5 to 9	Insufficient data[b]
D	Drugs or alcohol use (1 point each)	1 or 2		
		Maximum 9		

Abbreviations: INR, international normalized ratio.
[a]Reproduced with permission from Lip GY.[13] [b]Based on initial validation cohort (reported in Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score [HAS-BLED] to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100) with insufficient events at HAS-BLED scores ≥5 to give the rates.

below. The pharmacokinetics and target sites of oral anticoagulants are shown in Table 4 and the Figure 1.

Direct Thrombin Inhibitors

Ximelagatran was the first DTI that had shown efficacy in decreasing thromboembolic events in AF.[18] However, it was noted to be associated with significant elevations in liver transaminases and was subsequently not approved for clinical use. Dabigatran etexilate is the sole example in this class that is approved for clinical use currently.

Dabigatran

Dabigatran is an orally available, small-molecule DTI, which has a high affinity for thrombin with reversible binding. Dabigatran etexilate, a prodrug, is converted into the active metabolite, dabigatran, which displays low bioavailability (6%). This accounts for the high doses needed to maintain therapeutic plasma concentrations. The intestinal absorption of dabigatran is pH sensitive. Tartaric acid included in the preparation may account for the dyspepsia frequently reported by patients. Peak plasma concentrations are reached within 2 to 3 hours after oral administration, with a half-life of 12 to17 hours. The active metabolite is predominantly (80%) excreted renally, which is an important consideration when patients have impaired renal function.[19]

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) was a noninferiority study that compared 2 doses of dabigatran etexilate (110 mg and 150 mg) to adjusted-dose warfarin for prevention of stroke and systemic embolism (SSE) in nonvalvular AF (ie, AF in the absence of rheumatic mitral valve disease, prosthetic heart valve, or mitral valve repair). The dabigatran 110 mg dose was associated with rates of SSE similar to those with warfarin, but lower rates of major hemorrhage. The dabigatran 150 mg dose, compared with warfarin, was associated with lower rates of SSE and similar rates of major hemorrhage.[20]

Dabigatran was approved by the US Food and Drug Administration (FDA) in 2010 as an alternative to warfarin to reduce the risk of stroke in patients with AF. Doses for clinical use in the United States are 150 mg and 75 mg twice daily; the latter dose is indicated for patients with decreased renal function (creatinine clearance [CrCl] 15 to 30 mL/min). Dabigatran is contraindicated in patients with severe renal impairment (CrCl <15 mL/min).

FXa Inhibitors

Rivoraxaban

This agent is an oral anticoagulant with competitive and reversible binding to FXa. Rivaroxaban has bioavailability of 60% to 80% and reaches peak plasma concentrations after approximately 3 hours. A higher, but delayed, maximum plasma concentration of rivaroxaban was observed in fed patients compared to fasting patients, which translates to slightly lower anti-Xa activity in fasting patients. In clinical trials, therefore, rivaroxaban was administered within 2 hours of food intake. The half-life of rivaroxaban is between 5 and 9 hours in patients with normal renal and hepatic function. Thus, higher plasma levels of rivaroxaban may be expected in patients with impaired renal function—which, to a certain extent, naturally occurs in elderly patients—or impaired hepatic function, as one-third of the drug is excreted unchanged renally, and about two-thirds is metabolized in the liver primarily via cytochrome P450.[21]

The Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) trial was a randomized, double-blind, double-dummy, event-driven, noninferiority comparison of rivaroxaban (20 mg/day, 15 mg/day if CrCl 30–49 mL/min) with warfarin for stroke prevention in AF. Rivaroxaban was found to be noninferior to warfarin for the prevention of stroke or systemic embolism with no significant differences in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.[22]

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DOI:10.1002/clc.22173

Table 4. Comparison of Pharmacokinetics of Oral Anticoagulants

Agent	Target	Prodrug	Dosing	Oral Bioavailability, %	Monitoring	Half-life, h	Metabolism/Elimination	Time to Peak Plasma, h	Drug-Drug Interactions
Warfarin	Vitamin K epoxide reductase	No	Once/day	>95.0	INR-adjusted	40	CYP 2C9, 3A4, 1A2	72–96	CYP2C9, 1A2, 3A4
Dabigatran etexilate	Thrombin	Yes	Fixed, once or twice/day	6.5	None	14–17	80% renal/20% fecal	2	Potent P-glycoprotein inhibitor, rifampicin, quinidine, amiodarone, dronedarone, ketoconazole, verapamil
Rivaroxaban	Factor Xa	No	Fixed, once or twice/day	80.0	None	5–9 in younger pts; 9–13 in older adults	CYP3A4; 66% renal/33% fecal	2.5–4.0	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors
Apixaban	Factor Xa	No	Fixed, twice/day	~66.0	None	8–15	CYP3A4; 75% fecal/25% renal	3	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors
Edoxaban	Factor Xa	No	Fixed, twice/day	50.0	None	9–11	CYP3A4; 65% fecal/35% renal	1–2	

Abbreviations: INR, international normalized ratio.
Reproduced with permission from Weitz JI, Eikelboom JW, Samama MM. New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e120S–e151S.

Figure 1. Pharmacokinetics and target sites of oral anticoagulants. Abbreviations: LMWH, low molecular weight heparin.

Rivaroxaban was approved by the FDA in 2011 for use in patients with AF. The recommended doses are 20 mg/d in patients with CrCl >50 mL/min, and 15 mg/d in patients with CrCl between 15 and 50 mL/min. Rivaroxaban should be avoided in patients with CrCl <15 mL/min.

Apixaban

Apixaban is an oral direct FXa inhibitor with reversible binding and oral bioavailability of approximately 50%. Apixaban achieves its peak plasma level at around 3 hours after oral administration and has a half-life of 9 to 14 hours. Similar to rivaroxaban, the drug is metabolized in the liver via a cytochrome P450-dependent pathway. Approximately 25% of the drug is eliminated via the kidneys and the remainder by intestinal excretion.[23]

The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial assessed the efficacy and safety of apixaban in 5599 patients with AF who were at an increased risk of stroke, and for whom VKA therapy was unsuitable. Apixaban was found to reduce the risk of stroke or systemic embolism without a significantly higher risk of major bleeding or intracranial hemorrhage compared with aspirin.[24]

Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) was a randomized, double-blind trial that compared apixaban 5 mg twice daily with warfarin in patients with nonvalvular AF. The trial was designed to test for noninferiority for primary outcomes specified as ischemic/hemorrhagic stroke or systemic embolism, with key secondary objectives of testing for superiority with respect to the primary outcome and the rates of major bleeding and death from any cause. Apixaban was not only found to be superior to warfarin in preventing stroke or systemic embolism, but also caused less bleeding and resulted in lower mortality.[25]

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DOI:10.1002/clc.22173

Table 5. Comparison of Factors Favoring Use of Available Oral Anticoagulants in Atrial Fibrillation

Characteristics	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Cost	+	−	−	−
Once-daily use	+	−	+	+
No need for monitoring	−	+	+	+
Drug interaction/enzyme substrates				
CYP 2C9, 1A2	+	−	−	−
CYP 3A4	+	−	+	+
P-glycoprotein	−	+	+	+
Measure of anticoagulation	+	−	−	−
Reversibility	+	−	−	−
Precardioversion	+	+	−	−
Compared to warfarin:				
Superior ischemic stroke prevention		+	−	−
Less intracranial bleeds		+	+	+
Less GI bleeds		−	−	+
Drug tolerance	+	−	+	+
Other indications				
VTE/PE treatment	+	−	+	−
Medically ill patient VTE prophylaxis	−	−	+	−
Acute coronary syndrome	−	−	+	−
Use in end-stage renal disease (CrCl <15)	+	−	−	−

Abbreviations: +, advantage; −, disadvantage; CrCl, creatinine clearance; GI, gastrointestinal; PE, pulmonary embolism; VTE, venous thromboembolism.

Edoxaban

Edoxaban, not yet approved in the United States, is a reversible direct inhibitor of FXa; it is rapidly absorbed with good bioavailability, has a half-life of 8 to 10 hours, and is eliminated largely via the kidneys. The Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE-AF TIMI 48) is a phase 3, randomized, double-blind, double-dummy trial comparing edoxaban (30 mg or 60 mg once daily adjusted for drug clearance) versus warfarin (adjusted to INR 2.0–3.0) in approximately 20 500 patients with nonvalvular AF. Results for this study should be available within the next 2 years.[26]

Factors in the Choice of Novel Oral Anticoagulants

Table 5 summarizes factors favoring 1 available OAC agent over the other.

Convenience

Dabigatran, rivaroxaban, and apixaban all have more predictable and reliable anticoagulant properties compared to warfarin, with much shorter half-lives. The convenience of quicker initiation and cessation of anticoagulant effect obviates the need to monitor the level of blood thinning, which can be very appealing to patients and care providers.

Ease of Use

Rivaroxaban is taken once daily, whereas dabigatran and apixaban are taken twice daily. Clinicians hypothesize that it may be more favorable for certain patients to use a once-daily rather than a twice-daily medication, irrespective of any marginal benefits.

Cost

Acquisition costs of novel agents will be higher than for warfarin; thus, many patients who lack drug coverage will probably remain on warfarin, despite evidence that from a broader perspective, the novel agents are cost-neutral or cost-effective in many settings. However, the upfront costs of individual drugs, prescription plans, and copays may be deciding factors for many patients.

Drug Interactions

Although the level of interactions with food substances and drugs is much less compared to warfarin, the risk of drug interactions is still present and must be considered in the

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DOI:10.1002/clc.22173

selection of therapy for individual patients. Dabigatran is known to interact with inhibitors or inducers of the transporter P-glycoprotein (P-gp) alone, whereas rivaroxaban and apixaban are subject to interactions via P-gp as well as to inducers and inhibitors of the microsomal enzyme CYP3A4.

Renal Insufficiency

Dabigatran is mainly excreted renally (75%–80%); therefore, patients with higher degrees of renal impairment may be better served by rivaroxaban or apixaban. In patients with CrCl <15 mL/min, all the new OACs are contraindicated, and warfarin remains the only choice.

Patient Adherence to Medication

Although routinely available coagulation tests can predict complete lack of medication effect as in the case of total noncompliance for the available new OACs, questions remain whether this can be used for assessing patient compliance. However, factors such as convenience and ease of use may translate into better compliance for a large proportion of patients.

Monitoring of Anticoagulation in Special Situations

In situations such as trauma, active bleeding, or emergent surgeries, no blood tests routinely available in hospitals or clinical practice provide a consistent and reliable quantitative assay of anticoagulation correlating with serum levels of the new oral anticoagulants. Warfarin, in contrast, can be followed with a quantitative test in the form of prothrombin time (PT) or INR. For dabigatran, thrombin clotting time (TCT) has been suggested for qualitative assay, as a normal TCT essentially rules out significant anticoagulation with dabigatran. There is no equivalent, widely available test for checking the effect of rivaroxaban, as PT and anti-FXa assays have limitations that make them unreliable for this purpose.[27]

Lack of Reversal Agents

Although warfarin does not have a true antidote, its effects can be reversed with administration of vitamin K, over more than 24 hours, or in urgent situations, with administration of blood products such as fresh frozen plasma. None of the new OACs have a proven antidote or can the anticoagulant effects be reversed with blood products. In case of emergency or dabigatran overdose, dialysis can be attempted to reduce the serum drug levels and anticoagulation to an extent, because 35% of the drug is protein bound and cannot be removed. Neither rivaroxaban nor apixaban can be dialyzed, as a major proportion of these drugs is bound to plasma proteins. Recent data in healthy volunteers have shown that prothrombin concentrate can reverse the effects of rivaroxaban; however, definitive data from patients with AF are lacking.[28,29] On the other hand, these drugs have a much shorter half-life and will be eliminated faster than warfarin, and despite the lack of an antidote, the rates of bleeding deaths in the trials were not increased when compared with warfarin.

Bridging

Increased incidence of stroke was clearly noted on discontinuation of rivoraxaban as well as apixaban in the clinical trials, and therefore both carry a black-box warning about the higher incidence of strokes on discontinuation of the drug and urge consideration of bridging with an alternative anticoagulant. Even though dabigatran does not have a similar warning, one needs to understand that discontinuation of any oral anticoagulant can be hazardous, and patients at higher risk of thromboembolism must be handled very carefully in such conditions regardless of which oral anticoagulant is chosen.

All 3 agents—dabigatran, rivoraxaban, and apixaban—have short as well as equally comparable half-lives and time to peak drug effects, making them equally comparable with regard to avoiding the need for bridging with unfractionated heparin or low molecular weight heparin for loading, as well as in situations requiring brief interruption of oral anticoagulants.

Cardioversion

There are no data from any prospective randomized control studies on the safety and efficacy of the new oral anticoagulants compared to warfarin in cardioversion patients. However, a post hoc analysis from RE-LY suggests that the 30-day outcomes for stroke and major bleeding were similar in patients taking dabigatran compared to warfarin. Although not FDA approved for this indication, dabigatran can be considered as a reasonable alternative for this indication.[30] On the other hand, there is very limited information regarding rivaroxaban's or apixaban's use in cardioversion, although they would be expected to be safe in this situation given their equally comparable pharmacodynamics.

Efficacy and Safety in Patient Subgroups

No significant interaction was noted on the efficacy of dabigatran, rivaroxaban, or apixaban with regard to patient age, sex, weight or body mass index, renal impairment, or type of AF. However, 1 or the other anticoagulant may be preferred in certain of the following specific situations.

Higher $CHADS_2$ Scores/History of Stroke: Patients in ROCKET-AF had higher $CHADS_2$ scores (average 3.5, with greater history of strokes) compared with patients in RE-LY (average 2.1); therefore, more information is available about the efficacy of rivaroxaban in patients with high $CHADS_2$ scores than for dabigatran or apixaban.

Efficacy in Preventing Ischemic Strokes: Dabigatran at the 150-mg dose was found to be superior to warfarin in the RE-LY trial. Dabigatran at the 110-mg dose and rivaroxaban (ROCKET-AF) were found to be noninferior in the prevention of ischemic and overall strokes. Apixaban was also found to be superior to warfarin for overall strokes, the benefit being derived mainly from hemorrhagic strokes.

Use in Patients With Coronary Artery Disease: Rivaroxaban was noted to decrease risk of cardiovascular events, stroke, and death in acute coronary syndrome (ACS).[31] However, there was an increased incidence of major bleeding with apixaban with no significant reduction in ischemic events in patients with ACS.[32] On the other hand, an unfavorable trend

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DOI:10.1002/clc.22173

was noted with dabigatran, with a slightly higher incidence of myocardial infarction (MI) compared to warfarin in the RE-LY patient subsets.[33]

Mortality: Death from any cause was lower with both dabigatran and rivaroxaban compared to warfarin, although values did not reach statistical significance. Apixaban reached nominal significance with regard to reduction in all-cause mortality.

Long-Term Safety: The safety and efficacy data on rivaroxaban and apixaban are available from a follow-up period of approximately 2 years from the clinical trials, whereas the RE-LY extension study confirmed similar safety and efficacy of dabigatran as compared to its pilot study, up to a duration of 4.3 years, as noted in the Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial (RE-LY ABLE) study.[34]

Bleeding Risk

Intracranial Bleeding: Risk of intracranial bleeding was lower with dabigatran, rivaroxaban, and apixaban compared to warfarin.

Gastrointestinal Bleeding: Risk of gastrointestinal (GI) bleeding was slightly higher with both dabigatran and rivaroxaban compared to warfarin, which makes use of these agents less favorable in patients prone to GI bleeding. However, the risk was lower with apixaban, which could potentially favor the choice of apixaban for patients at higher risk of GI or extracranial bleeding.[35]

Drug Tolerability

A substantial proportion (10%–20%) of patients who take dabigatran experience nausea, reflux, bloating, and abdominal pain. To clinicians and AF patients, these effects can be real barriers. Neither rivaroxaban nor apixaban have significant GI adverse effects.

Use in Other Indications

The benefits of the new oral anticoagulants have been acknowledged in clinical situations other than atrial fibrillation as discussed below. Formularies and healthcare providers may prefer a single agent that can be used for different clinical situations.

Venous Thromboembolism: Both dabigatran and rivaroxaban have been shown to be noninferior to warfarin for venous thromboembolism (VTE) treatment, whereas rivaroxaban was also shown to be noninferior to warfarin in the treatment of acute pulmonary embolism.[36,37] However, rivaroxaban is the only new OAC currently approved for treatment of deep vein thrombosis (DVT)/pulmonary embolism (PE) in addition to DVT prophylaxis in patients undergoing knee or hip replacement surgeries.

ACS: In the future, rivaroxaban may also be considered in patients with ACS, given the favorable outcomes observed in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction (ATLAS ACS 2-TIMI 51) trial.[38] This agent may be more appealing in patients with a higher risk of coronary artery disease or after ACS.

The Medically Ill: Rivaroxaban has been studied in medically ill patients and found to be superior to enoxaparin therapy for VTE prophylaxis. However, this benefit was overshadowed by an increased risk of bleeding in this study. In the future, this feature may gain popularity as patients may be more selectively identified without a higher risk of bleeding, providing an oral alternative to medically ill patients for VTE prophylaxis.[39]

Currently, in the United States dabigatran, rivaroxaban, and apixaban are all approved for stroke prevention in nonvalvular AF. In addition, rivaroxaban is approved for treatment and prevention of VTE, PE, and DVT prophylaxis in patients undergoing hip and knee replacement surgeries.

Referring back to the clinical vignette presented above, in this particular patient, dabigatran at 150 mg twice daily may be preferred because of its superior benefit in ischemic stroke compared to warfarin at its 150-mg dose. However, either rivaroxaban or apixaban could also be used with anticipated efficacy and safety.

Summary

Results from large-scale trials comparing the novel oral anticoagulants have demonstrated efficacy and overall safety in comparison to warfarin for reducing the risk of stroke in patients with AF. However, concerns still exist regarding both the lack of a readily available antidote when patients experience bleeding in emergent situations as well as long-term safety, as these agents are often proposed for lifelong use by patients with AF. In the absence of direct comparison studies of these new oral anticoagulants, patient characteristics, such as risk of GI bleeding, frequency of drug administration, and risk of MI, as discussed, may have a bearing on the selection of an anticoagulant in clinical practice. We hope this review will help clinicians choose the most appropriate oral agents, individualizing therapy while maintaining awareness of their potential disadvantages.

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DOI:10.1002/clc.22173 © 2013 Wiley Periodicals, Inc.

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DOI:10.1002/clc.22173