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Stroke Prevention in Atrial Fibrillation

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Abstract Vitamin K antagonists (VKA) have been the primary anticoagulant for the past few decades, and to a lesser degree aspirin, in preventing thrombotic events from atrial fibrillation. In spite of our experience with warfarin over the years, its use has been limited by multiple challenges: its need for frequent international normalized ratio (INR) monitoring, its narrow therapeutic range, variation with metabolism, diet, and other medications, and the need for frequent dosage adjustment. With the advent of newer/novel oral anticoagulants such as oral direct thrombin inhibitors (dabigatran) and oral factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), we are at the dawn of a new era in anticoagulation. Compared with VKAs, they do not need INR monitoring, have a rapid onset of action, are a fixed-dose therapy, and for unclear reasons, have been shown to cause significantly less intracranial hemorrhage than VKAs.

Keywords Atrial fibrillation · Stroke · Anticoagulation · Thromboembolism · Vitamin K antagonist · Direct thrombin inhibitors · Factor Xa inhibitors

Introduction

Atrial fibrillation (AF) increases the risk of embolic stroke, and is the commonest clinically relevant heart rhythm abnormality [1]. The prevalence is 4 % for patients under 60 years of age and 9 % for those over 80 years of age. It is estimated this burden will increase by a factor of 2.5 over the next four decades [2]. Patients with AF are at up to fivefold increased risk of developing a stroke. This puts an enormous burden on patients with poor functional outcome, morbidity, mortality, and subsequent financial impact resulting from stroke-related complications. Although there are multiple strategies to mitigate this risk, quite often the strategy is limited to administration of antithrombotic medications. Vitamin K antagonists (VKAs) were the only antithrombotic agents available until early in the twenty-first century, when the oral direct thrombin inhibitor ximeligatran was introduced. However, because of its potential hepatotoxicity, it was subsequently withdrawn from clinical use. This formed a proof of concept and subsequently dabigatran, with a better safety profile from the same class, entered the market. Oral factor Xa inhibitors (rivaroxaban, apixiban, edoxaban), as the name implies, inhibit factor Xa and appear to have better safety profiles. After a phase III clinical trial (ROCKET AF), the Food and Drug Administration (FDA) approved rivaroxaban for treatment of nonvalvular AF. Apixaban has similarly completed phase III clinical trials (ARISTOTLE and AVERROES) and has recently been granted approval both in Europe and in the USA for use in patients with nonvalvular AF for prevention of stroke. The results of the phase III clinical trial for edoxaban (ENGAGE AF-TIMI 48) are expected in 2013.

Thromboembolism in AF

Owing to uncoordinated or lack of contraction of the atria in AF, the primary site of clot formation is in the left atrium and especially the left atrial appendage. Patients with AF have reduced flow in both the left atrium and the left atrial

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appendage [3]. This effect is amplified in patients with systolic heart failure and rheumatic mitral stenosis [4]. It is thought that because of the above-mentioned factors and also Virchow's triad of stasis, hypercoagulable state and endothelial dysfunction play a role in thrombus formation, albeit to a lesser role for the third component. Irrespective of the type of heart failure, multiple trials have shown that the higher the New York Heart Association (NYHA) heart failure class the patients have, the higher is the risk of stroke [4, 5].

There are several ways to minimize the risk of thromboembolism in patients with AF. They can be divided into rhythm control, where the primary strategy is to convert the patient to normal sinus rhythm with direct current cardioversion or medications, surgical procedures (maze, left atrial appendage exclusion, watchman devices, etc.), or the use of antithrombotic medications. Several novel mechanical approaches to prevent cardioembolic stroke have been evaluated, including various models of percutaneous left atrial appendage occluding devices, minimally invasive surgical isolation of the left atrial appendage, and implantation of carotid devices which divert large emboli so they do not reach the intracranial circulation [6].

Thromboembolic Risk Stratification

Estimating the risk of stroke for patients with AF is a crucial step in providing appropriate anticoagulant therapy. There are different clinical and echocardiographic models for predicting thromboembolism. In patients at risk of stroke, reduced left ventricular function on transthoracic echocardiography and the presence of spontaneous echo contrast, thrombus, reduced flow in the left atrial appendage, and the presence of complex atheroma in the thoracic aorta on transesophageal echocardiography have been associated with increased risk of thromboembolism [5]. Of the clinical risk predication models, the two major risk schema which are being used currently are $CHADS_2$ and CHA_2DS_2-VASc (see Table 1). Both models have been validated in subsequent prospective studies: $CHADS_2$ has been adopted in the American College of Cardiology guidelines and CHA_2DS_2-VASc has been adopted in the European Society of Cardiology guidelines [7]. One of the caveats with both models is poor stroke rate prediction in secondary prevention. For someone with a score of 2, either from previous stroke or from other risk factors, the stroke rate is approximately 4 % (see Table 2). For patients with prior stroke (score of 2), their risk of another stroke is 14 % [8]. The advantage of CHA_2DS_2-VASc is its ability to predict "low-risk" patients, where the stroke rates are low.

Antithrombotic Medications

At least 15 % of ischemic strokes have been attributed to AF. Over the course of the past few decades, VKAs have been established as the anticoagulant of choice owing to their superiority over antiplatelets or placebo, but patients at low risk of stroke/thromboembolism will not require VKAs [5].

Aspirin reduces the risk of stroke in AF by a factor of only 19 % [95 % confidence interval (CI), −1 to 35 %] compared with placebo, whereas warfarin reduces the risk of stroke by 64 % (95 % CI, 49–74 %) [9, 42]. Its efficacy is further limited in secondary prevention of strokes. In a meta-analysis which included five randomized trials, aspirin reduced stroke in secondary prevention trials by a factor of only 11 % (stroke rate of 14 % for participants receiving placebo), whereas in primary prevention studies the stroke rate was reduced by 33 % (stroke rate of 5 % for participants receiving placebo) [8]. The efficacy of aspirin in preventing strokes in the setting of AF is weaker and its role is primarily in patients who are at low risk of thromboembolism with a $CHADS_2$ score of either 0 or 1, although the American College of Cardiology Foundation/American Heart Association recommendation is to preferably use a VKA for the second category [5]. Aspirin is also suitable for patients who refuse anticoagulant medications.

The utility of combination antiplatelets in stroke prevention was studied in the following trials. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A), in patients who were deemed "unsuitable" for a VKA in prevention of stroke from AF, combining clopidogrel and aspirin was found to be superior to aspirin alone in reducing ischemic strokes (1.9 vs 2.8 %/year, $p < 0.001$), but at the expense of increased but nonfatal bleeding, negating the net benefit gained [10]. Conversely in VKA-eligible patients in the ACTIVE W trial, warfarin was found to be superior to aspirin plus clopidogrel, and the trial was terminated early because of the clear evidence of superiority with the warfarin arm [11].

VKAs have been the standard oral anticoagulant medication until recently. VKAs have been demonstrated to be superior to both placebo and antiplatelet agents in reducing the incidence of stroke and also mortality [9, 11, 12]. In a meta-analysis by Hart et al. [9], treatment with adjusted-dose warfarin was associated with 64 % (95 % CI, 49–74 %) reduction in all strokes and 67 % (95 % CI, 54–77 %) reduction in ischemic strokes when compared with placebo. This roughly translated to treating 37 patients and preventing one stroke (absolute risk reduction of 2.7 %) for primary prevention and treating 12 patients and preventing one stroke for secondary prevention (absolute risk reduction of 8.4 %).

Table 1 Risk stratification models

$CHADS_2$ schema		CHA_2DS_2-VASc schema	
Risk factor	Score	Risk factor	Score
Congestive heart failure	1	Congestive heart failure/LV dysfunction	1
Hypertension	1	Hypertension	1
Age ≥75 years	1	Age ≥75 years	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke or TIA	2		
		Stroke or TIA or TE	2
		Vascular disease[a]	1
		Age 65–74 years	1
		Sex category (if female gender)	1

TIA transient ischemic attack, *LV* left ventricle, *TE* thromboembolism

[a] Prior myocardial infarction, peripheral arterial disease, or aortic plaque

Use of adjusted-dose warfarin showed a nearly two thirds reduction in both disabling and nondisabling stroke. Despite its superiority and benefit in preventing ischemic stroke and thromboembolism, there are multiple challenges associated with administration of warfarin. Variations in metabolism and interactions with food and other medications while patients were taking warfarin negatively influence the time in the therapeutic range (TTR). In spite of careful monitoring, 1–3 % of patients have adverse bleeding outcomes. Although VKAs have demonstrated superiority in preventing stroke, only 50–60 % of patients are prescribed warfarin and only 60–70 % of these patients have adequate TTR [13]. TTR has a direct correlation to the incidence of ischemic and total strokes. For example, in the SPAF III trial, only 61 % of patient's INR were in therapeutic range, with an annual ischemic stroke event rate of 1.9 % (2.4 % total stroke), whereas in the SPORTIF V trial 68 % of patient's INR were in therapeutic range, with a lower annual ischemic stroke event rate of 1.1 % (1.2 % total stroke) [13]. TTR of less than 58 % is less effective than combination antiplatelet therapy [11]. Hylek et al. [14] assessed the intensity of anticoagulation to severity of stroke in nonvalvular AF and mortality. In this study, only 38 % of patients had an international normalized ratio (INR) of 2.0 or greater (mean INR 1.7). Fifteen percent of patients with INR < 2.0 either died before discharge or had a severe stroke as opposed to 5 % of patients with INR ≥ 2.0. One third of patients with severe stroke died within 30 days.

Despite their limitations, VKAs are still considered the drug of choice for patients with valvular AF, AF patients with end-stage renal disease, and patients with mechanical prosthetic heart valves.

Table 2 TE rate based on the risk categories/cumulative risk

$CHADS_2$ schema		CHA_2DS_2-VASc schema	
Score	Adjusted stroke rate[a] (%)	Score	TE rate[b] (%)
0	1.9	0	0
1	2.8	1	0.7
2	4.0	2	1.9
3	5.9	3	4.7
4	8.5	4	2.3
5	12.5	5	3.9
6	18.2	6	4.5
		7	10.1
		8	14.2
		9	100

TE thromboembolism

[a] Rate adjusted for no aspirin usage [5]

[b] Adjusted for no therapy. For patients on aspirin, rates adjusted assuming aspirin confers a 22 % risk reduction from TE [41]

Newer Oral Anticoagulants

Although effective, VKA use has been limited by the slow onset of action requiring overlap with another anticoagulant, interaction with other cardiac medications (e.g., amiodarone), food interaction based on vitamin K intake necessitating frequent dosage adjustment, and also frequent drug monitoring. With the advent of newer, novel oral anticoagulants, both oral direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixiban, edoxaban) provide several advantages over VKAs.

Oral Direct Thrombin Inhibitors

Ximeligatran, an oral direct thrombin inhibitor, was the first newer, novel oral anticoagulant approved, albeit briefly for use in nonvalvular AF. Pooled analysis from two studies showed ximelagatran to be noninferior to adjusted-dose warfarin (TTR of 67 %) in both primary and secondary prevention of strokes [15, 16]. Patients receiving ximelagatran developed significantly abnormal liver enzyme levels compared with those receiving warfarin (6.1 vs 0.8 %). Because of its potential hepatotoxicity, ximelagatran was withdrawn from the market [15, 17]. This served as a proof of concept and facilitated further development of newer oral anticoagulants.

Dabigatran

Dabigatran is a potent competitive direct thrombin (factor IIa) inhibitor. Dabigatran etexilate is a prodrug, which after

intestinal absorption is hydrolyzed by the plasma esterase to its active metabolite dabigatran [18]. The oral bioavailability is 7 %, peak drug level is reached at 2 h, it has a plasma half-life or 12–17 h, and 85 % of the drug is renally excreted [19]. It has drug–drug interaction with P-glycoprotein inhibitors, and its concentration can be increased by inhibitors such as dronedarone, amiodarone, verapamil, and ketoconazole and can be decreased by rifampin [20].

Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a randomized trial which compared two fixed, blinded doses of dabigatran (110 or 150 mg twice daily) with open-label warfarin in patients with nonvalvular AF with at least one risk factor (prior stroke or transient ischemic attack, left ventricular ejection fraction less than 40 %, New York Heart Association heart failure class II or higher, age 75 years or older or 65–74 years plus diabetes mellitus, hypertension or coronary artery disease), and the primary outcome was stroke or systemic embolism [21]. Patients with a severe stroke within 6 months or stroke within 14 days, creatinine clearance of less than 30 mL/min, increased bleeding risk, and active liver disease were excluded from the trial. A total of 18,113 patients with a mean age of 71 years (63.6 % males) and a mean $CHADS_2$ score of 2.1 were enrolled.

Dabigatran, 110 mg, was found to be noninferior [1.53 %/year, relative risk (RR), 0.91; 95 % CI, 0.74–1.11, $p \leq 0.001$ for noninferiority] to adjusted-dose warfarin for primary outcome. The rate of major bleeding was lower at this dose (2.71 %/year, RR, 0.80; 95 % CI, 0.69–0.93; $p = 0.003$). Dabigatran, 150 mg, was found to be superior to warfarin (1.11 %/year; RR, 0.66; 95 % CI, 0.53–82; $p \leq 0.001$) in relation to primary outcome of stroke and systemic embolism, and the rate of major bleeding (3.11 %/year, RR, 0.93; 95 % CI, 0.81–1.07; $p = 0.31$) was similar to that for warfarin (3.36 %/year) [21]. The rate of intracranial hemorrhage was significantly lower for patients assigned to both 110 mg dabigatran (0.23 %/year, RR, 0.3; 95 % CI, 0.19–0.45) and 150 mg dabigatran (0.31 %/year, RR, 0.4; 95 % CI, 0.27–0.59) when compared with warfarin (0.76 %/year).

Although in the RE-LY trial there was increased rate of myocardial infarction with both doses of dabigatran [21], in a subsequent detailed analysis the annual rates of a composite of myocardial infarction, unstable angina, cardiac arrest, and cardiac death were found to be 3.16 %/year with 110 mg dabigatran, 3.33 %/year with 150 mg dabigatran, and 3.41 %/year with warfarin [hazard ratio (HR), 0.93, 95 % CI, 0.80–1.06, $p = 0.28$ for 110 mg dabigatran; HR, 0.98, 95 % CI, 0.85–1.12, $p = 0.77$ for 150 mg dabigatran] [22].

The commonest adverse event was dyspepsia, which is likely related to the tartaric acid core in the dabigatran pellets (to create an acidic environment and help absorption) [19], and there was no significant elevation of liver enzyme levels compared with use of warfarin. Unfortunately, there is no antidote for dabigatran, but it can be removed by hemodialysis. Although the data are limited, either recombinant activated factor VII or prothrombin complex concentrates can be used in cases of life-threatening bleeding [23]. Dabigatran has been approved by the FDA at a dosage of 150 mg twice daily for patients with a creatinine clearance of more than 30 mL/min and 75 mg twice daily for patients with a creatinine clearance of 15–30 mL/min.

Oral Factor Xa Inhibitors

Factor X is positioned at a unique spot in the coagulation cascade (see Fig. 1), at the convergence of both the extrinsic and the intrinsic pathway. Therefore, factor Xa has emerged as an attractive target for anticoagulation. Antistasin and tick anticoagulant peptide were the first direct factor Xa inhibitors, and were isolated from Mexican leech and soft tick, respectively [24]. Preclinical studies with these agents were promising, and subsequently fondaparinux, a parenteral, antithrombin-dependent factor Xa inhibitor, underwent successful phase III clinical trials for treatment of venous thromboembolism [25, 26] and acute coronary syndrome [27, 28]. Following the success with fondaparinux, the race was on to develop oral factor Xa inhibitors.

Rivaroxaban

Rivaroxaban, an oral factor Xa inhibitor, was found to be superior to enoxaparin in preventing venous thromboembolism following orthopedic surgery [29] and noninferior to the standard treatment of enoxaparin followed by adjusted-dose warfarin for the treatment of deep venous thrombosis [26] and also pulmonary embolism [30]. Rivaroxaban Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) [31] was a double blind, randomized controlled trial, where patients with nonvalvular AF were randomized to a fixed dose of 20 mg rivaroxaban daily (15 mg daily for patients with a creatinine clearance of 30–49 mL/min) or adjusted-dose warfarin with a primary end point of all strokes and systemic embolism. Patients with no prior transient ischemic attack or stroke or systemic embolism and who had no more than two risk factors constituted only 10 % of the patients, and the remainder had either prior thromboembolic events or three or more risk factors. A total of 14,264 patients with a mean age of 73 years (61.3 % males) and a mean $CHADS_2$ score of 3.5 (as opposed to 2.1 for RE-LY and ARISTOTLE) were enrolled. The median follow-up

was 1.9 years. Average TTR was low (55 %) in the warfarin group compared with the other trials.

Rivaroxaban was found to be noninferior to warfarin, with a stroke rate of 1.7 and 2.2 %/year, respectively (HR in the rivaroxaban group, 0.79; 95 % CI, 0.66–0.96; $p \leq 0.001$ for noninferiority). There was no difference in the rates of major bleeding between the two groups (3.6 and 3.4 %, respectively, $p = 0.58$). Patients receiving rivaroxaban when compared with patients receiving warfarin had a significantly lower rate of fatal hemorrhage (0.2 and 0.5 %, respectively, $p = 0.003$) and hemorrhagic stroke and intracranial bleeding (0.5 and 0.7 %, respectively, $p = 0.02$). Major gastrointestinal bleeding was higher in the rivaroxaban group (3.2 %) than in the warfarin group (2.2 %, $p \leq 0.001$) [31]. A greater proportion of patients receiving rivaroxaban discontinued use of the drug prematurely (23.9 %) than did patients receiving warfarin (22.4 %) [7]. Rivaroxaban has been approved by the FDA for prevention of thromboembolism in patients with nonvalvular AF. There is currently no antidote available for rivaroxaban.

Apixaban

Apixaban, another novel oral factor Xa inhibitor, is rapidly absorbed with a peak effect within 2 h, has a bioavailability of approximately 50 %, has a short half-life of 12 h, and has a renal excretion rate of 25 % [32]. In the initial trials of thromboprophylaxis in orthopedic surgical procedures, 2.5 mg apixaban twice daily was found to be superior to 40 mg enoxaparin daily, but had similar efficacy when used with enoxaparin at a twice daily dosing of 30 mg [33–35].

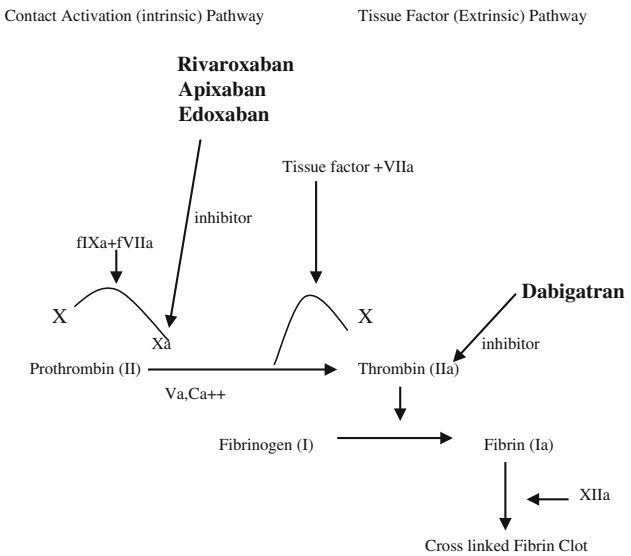

Fig. 1 Coagulation cascade and sites of action of different anticoagulants

Apixaban has been evaluated in two trials for stroke prevention in patients with nonvalvular AF. In the first trial (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes, AVERROES) [36], 5,599 patients with AF and with at least one stroke risk factor, who were either "unsuitable" for or unwilling to receive VKA treatment, were randomly assigned in a double blind, double dummy fashion to treatment with either apixaban (5 mg twice daily or 2.5 mg twice daily for patients aged 80 years or older, with a weight of 60 kg or less, or with a serum creatinine level of 1.5 mg/dL or greater) or aspirin (81–324 mg/day, with 91 % taking 162 mg or less per day). The primary end point was either stroke or thromboembolism. The trial was stopped early after apixaban was found to be superior to aspirin in regard to primary outcome (1.6 and 3.7 %/year, respectively; $p \leq 0.001$). Major bleeding rates were similar in both groups (1.4 and 1.2 %, respectively; $p = 0.57$). Medication discontinuation was less with apixaban than with aspirin (17.9 and 20.9 %/year, respectively; $p = 0.03$).

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [37], 18,201 patients with nonvalvular AF, with a median age of 70 years (64.7 % male) and a mean $CHADS_2$ score of 2.1 were randomly assigned to either fixed-dose apixaban, 5 mg twice daily (2.5 mg twice daily if patients had two of the following: age 80 years or older, weight 60 kg or less, or a serum creatinine level of 1.5 mg/dL or greater), or to adjusted-dose warfarin. Patients in the warfarin arm had a mean TTR of 62.2 %. Apixaban was found to be superior to warfarin for primary outcome, with an annual rate of 1.27 versus 1.60 %, respectively (HR, 0.69; 95 % CI, 0.66–0.95; $p \leq 0.001$ for noninferiority and $p = 0.01$ for superiority). The major bleeding rate was significantly less in the apixaban group (2.13 %/year, HR, 0.69; 95 % CI, 0.60–0.80; $p \leq 0.001$) than in the warfarin group (3.09 %/year) and the intracranial bleeding rate was significantly lower than in the warfarin group (0.33 and 0.80 %, respectively; $p \leq 0.001$). Although there was a trend of improved mortality in the previous trials with other newer anticoagulants, apixaban was the first drug to show a statistically significant reduction in death from all-cause mortality (HR, 0.89; 95 % CI, 0.80–0.99; $p = 0.047$).

Gastrointestinal bleeding rates were similar in both groups (0.76 vs 0.86 %). Apixaban was better tolerated than warfarin, with slightly fewer early discontinuations (25.3 vs 27.5 %). On the basis of the above results, apixaban was recently approved for clinical use in both the USA and Europe.

Edoxaban

Edoxaban, the third novel factor Xa inhibitor to enter the market, has pharmacokinetic and pharmacodynamic

Table 3 Pharmacological properties of warfarin and newer, novel oral anticoagulants

Characteristics	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	VKORC1	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Bioavailability (%)	100	~6.5	~80	~50	~50
Time to peak	4–5 days	0.5–2 h	2–3 h	1–2	1–2 h
Half-life (h)	40	12–14	7–11	12 h	5–11
Renal elimination	No	85 %	33 %	25 %	35 %
Antidote	Vitamin K	No	No	No	No
Monitoring	INR	No	No	No	No
Dosing	Variable/once daily	Twice daily	Twice daily	Twice daily	Once daily

Modified from [18, 24]

VKORC1 C1 subunit of vitamin K epoxide reductase enzyme, *INR* international normalized ratio

properties similar to those of apixaban (see Table 3). A phase III clinical trial is under way for evaluation of edoxaban in AF—Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48) [38]. The results of this trial are expected in 2013.

Betrixaban

Betrixaban, another factor Xa inhibitor, has undergone phase II studies, and so far seems to be safe in one venous thromboembolism prevention study [39]. A significant advantage with this drug is its potential use in patients with renal failure as less than 5 % of the drug is renally cleared and the rest is excreted in bile [40].

Conclusions

Although VKAs have been the primary anticoagulant for decades, we are entering an era when there are different therapeutic options. With therapy targeted at different levels of the coagulation cascade (see Fig. 1), the two new classes of novel oral anticoagulants have provided promising results and have opened the door for newer drugs. Dabigatran and apixaban at the approved doses have been shown to be superior to warfarin and rivaroxaban has been shown to be noninferior to warfarin in prevention of stroke and thromboembolism in nonvalvular AF. Although there was a trend toward improved all-cause mortality with dabigatran and rivaroxaban, apixaban showed a statistically significant reduction in all-cause mortality. All the novel oral anticoagulants have shown a significant reduction in the rate of intracranial bleeding compared with warfarin. With predictable pharmacodynamics and pharmacokinetics, all the drugs can be administered in fixed doses and routine coagulation monitoring is not needed.

There are no specific antidotes for the novel oral anticoagulants. With relatively short half-lives, in cases of a nonsignificant bleeding, withholding the medication is all that is needed. In cases of significant or life-threatening bleeding, dabigatran can be dialyzed and although they have not been very well studied, either activated factor VII or procoagulant prothrombin complex can be administered.

Finally, although the newer, novel anticoagulants appear to have a favorable safety profile, we need to await data from postmarketing surveillance to assess their role in antithrombotic treatment regimens.

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