·Drug and Clinical Medicine·

New anticoagulants in the treatment of stroke: future promise

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Keywords

Atrial fibrillation; Anticoagulants; Stroke.

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Received: 21 February, 2013.

DOI:10.3969/j.issn.1672-6731.2013.04.004

Abstract

Recent evidence is leading to the replacement of vitamin K antagonists, the efficacy of which in preventing stroke in patients with atrial fibrillation (AF) is well established, with better tolerated and more manageable new anticoagulant drugs, with a lower risk of intracranial bleeding, no clear interactions with food, fewer interactions with medications, and no need for frequent laboratory monitoring and dose adjustments. Among new anticoagulants, dabigatran etexilate is a direct, competitive inhibitor of thrombin. It was evaluated for patients with AF in the RE-LY trial, showing lower rates of stroke and systemic embolism at a dose of 150 mg twice daily with similar rates of major hemorrhage compared with warfarin; and non-inferiority compared with warfarin for the prevention of stroke and systemic embolism at a dose of 110 mg twice daily, with lower rates of major bleeding. Beside dabigatran, oral factor X a inhibitors are also emerging for the prevention of thromboembolic events in AF. Despite the obvious advantages of these new oral anticoagulants over vitamin K antagonists, further information is still needed on how to prioritize the patients deriving the greatest benefit from these novel agents on the basis of patient characteristics or drug pharmacokinetics. There is also a need for assessing their long-term efficacy and safety over decades in the real-world setting.

Atrial fibrillation (AF) is the most common arrhythmia with a 25% lifetime risk in adults. AF increases stroke risk by 5-fold and accounts for 15% of stroke, rising with age [1]. Twenty-first century will be remembered as a significant milestone in the treatment and prevention of thromboembolic diseases. Until recently, vitamin K antagonists (eg. warfarin) were the only oral anticoagulants available, but using warfarin in elderly patients could be challenging. For more than 60 years, vitamin K antagonists were the only available oral anticoagulation (OAC). Recommendations for OAC in AF [2] are based on unequivocal evidence for benefit of warfarin versus both placebo and antiplatelet therapy in stroke prevention. However, the limitations of warfarin [3] result in poor adherence. It has two major limitations: a narrow therapeutic window of adequate anticoagulation without bleeding, and a highly variable dose-response relation among individuals that requires monitoring by laboratory testing.

The approval of target-specific oral anticoagulants means that patients with AF have multiple treatment options for the prevention of embolic stroke. Recent evidence is leading to the replacement of vitamin K antagonists, the efficacy of which in preventing stroke in AF is well established, with better tolerated and more manageable new anticoagulant drugs, with a lower risk of intracranial bleeding, no clear interactions with food, fewer interactions with medications, and no need for frequent laboratory monitoring and dose adjustments, they offer both convenience and, possibly, a public health benefit if they are used by patients who otherwise would have declined to take warfarin. However, patients on a highly stable, therapeutic dose of warfarin should not expect better health outcomes if switching to a new OAC.

This article reviews recent advances in stroke prevention in patients with AF brought about by novel antithrombotic agents. Despite the obvious advantages of these new oral anticoagulants over vitamin K antagonists, further information is still needed on how to prioritize the patients deriving the greatest benefit from these novel agents on the basis of patient

characteristics or drug pharmacokinetics. There is also a need for assessing their long-term efficacy and safety over decades in the real-world setting. The growing burden of AF and stroke, and new hypotheses regarding the development and progression of AF will continue to make stroke prevention in patients with AF fertile ground for new research.

Antithrombotic therapy and stroke risk assessment

Compared with placebo, OAC (essentially, the vitamin K antagonists, eg. warfarin) results in a significant reduction in stroke by 64% however, antiplatelet therapy results in a reduction of 22% . Compared with antiplatelet therapy, OAC reduces stroke by 37% [4]. Thus, the most effective therapy for stroke prevention in AF is OAC. As age increases, stroke risk rises, and absolute benefit of OAC increases [5]. Major bleeding risk increases with age, but to a lesser extent than absolute benefit of OAC on stroke [5].

The increased stroke risk with AF is heterogeneous and dependent on cumulative risk of various risk factors. In patients with AF, several scoring systems, such as the $CHADS_2$ and CHA_2DS_2-VASc scores, are currently used to evaluate thromboembolic risk. The CHA_2DS_2-VASc score stratifies patients at intermediate-low thromboembolic risk more accurately than the $CHADS_2$ score [6-7]. The most recent European and US guidelines on AF have extended the indications for OAC, which is recommended not only for patients at high risk, but also for those at intermediate risk, with $CHADS_2$ score $\geqslant 1$ [8].

Current guidelines recommend an optimal international normalized ratio (INR) range of 2.0 to 3.0 for stroke prevention in AF, balancing thrombotic risk with low INR and hemorrhagic risk with high INR. Compared with standard INR monitored by health professionals, self-monitoring or self-management can improve quality of OAC and reduce thromboembolic events [9], but are only recommended where appropriate training and support are available [8-9].

Risk factors for bleeding should be assessed before initiation of OAC. The simple HAS-BLED score reliably incorporates risk factors for real-world patient populations, performing better than existing scores and improving predictive value among warfarin-naive patients [10]. One recent analysis examining the risk of ischemic stroke versus intracranial hemorrhage found a neutral/positive clinical benefit with OAC in patients with a $CHADS_2$ score of $\geqslant 0$ and CHA_2DS_2-VASc score of $\geqslant 1$ and a negative clinical benefit only with a CHA_2DS_2-VASc score = 0 (given the "truly low risk" for these patients) [11] (Table 1). Interestingly, the clinical benefit was even greater at HAS-BLED scores of $\geqslant 3$, given that higher risk individuals would have a much greater absolute reduction in stroke risk with warfarin, which would outweigh the small absolute increase in major bleeding events. OAC is still recommended if there is risk of stroke and thromboembolism regardless of other rate and rhythm control medication for AF and regardless of a rate or rhythm control strategy such as catheter ablation [8].

Table 1. The $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED Scores

Scoring system	Score
$CHADS_2$	
Congestive cardiac failure*	1
Hypertension (blood pressure consistently > 140/90 mm Hg or treated hypertension on medication)	1
Age $\geqslant$ 75 years	1
Diabetes mellitus	1
Stroke/transient ischemic attack/thromboembolism	2
Maximum score	6
CHA_2DS_2-VASc	
Congestive cardiac failure*	1
Hypertension (blood pressure consistently >140/90 mm Hg or treated hypertension on medication)	1
Age $\geqslant$ 75 years	1
Diabetes mellitus	1
Stroke/transient ischemic attack/thromboembolism	2
Vascular disease (previous myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Age 65–74 years	1
Sex category (ie, female)	1
Maximum score	9
HAS-BLED	
Hypertension (systolic >160 mm Hg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile international normalized ratio (if on warfarin)	1
Elderly (age > 65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

*Congestive cardiac failure is moderate to severe systolic left ventricular dysfunction (left ventricular ejection fraction $\leqslant$ 40%). $CHADS_2$ score and risk of stroke and thromboembolism: 0, low risk; 1, moderate risk; $\geqslant$ 2, high risk. $CHA2DS_2$-VASc score and risk of stroke and thromboembolism: 0, low risk; 1, moderate risk; $\geqslant$ 2, high risk. HAS-BLED score and risk of major bleeding: 0–2, low risk; $\geqslant$ 3, high risk.

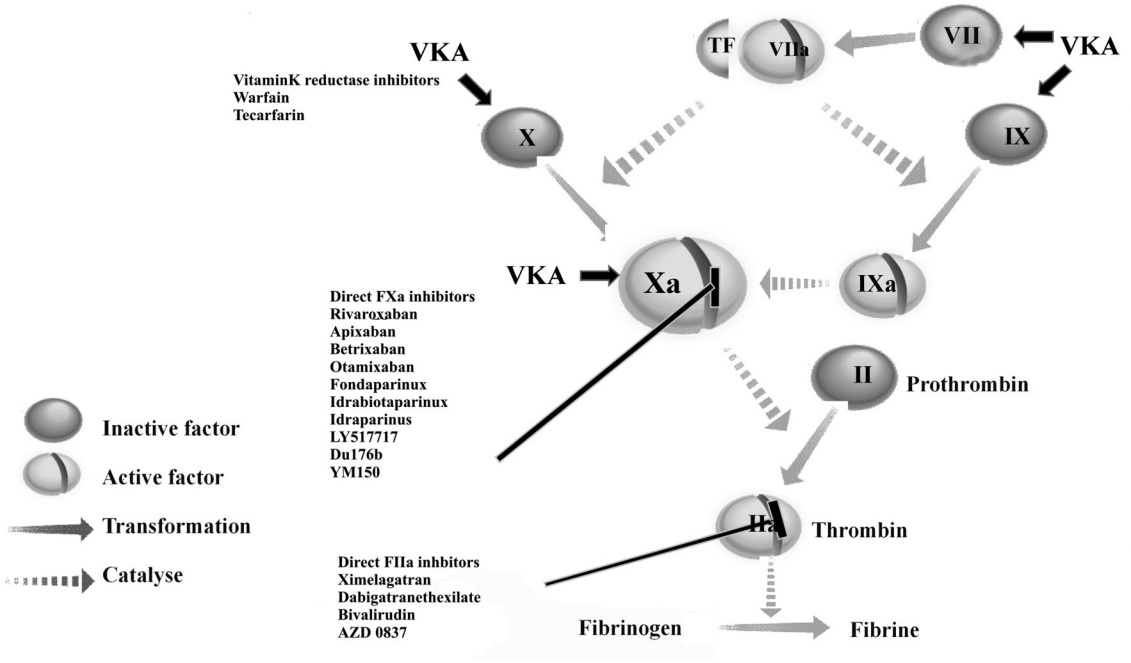

Figure 1 Coagulation cascade and sites of action for vitamin K antagonists (VKAs), direct factor Xa and factor Ⅱa inhibitors. Factor Xa has a critical role in the generation of thrombin and some direct factor Xa inhibitors block this pathway. Direct thrombin inhibitors block transformation of fibrinogene to fibrine by inhibition of thrombin. Tecarfarin is a new VKA. Dabigatran is an oral thrombin inhibitör, and rivaroxaban, apixaban and others are oral inhibitors. Dabigatran is a substrate of the P-glycoprotein (Pgp) efflux transporter.

Novel oral anticoagulants

Due to the various well known limitations of the vitamin K antagonists, attention has been directed toward new oral anticoagulants. Thrombin is the final enzyme of the clotting cascade. The structure of thrombin has been defined by X-ray crystallography. There is a deep groove on one side of the molecule, and the active site of the enzyme is buried deep within this groove. Access to the active site is protected by the surrounding amino acids, some of which protrude into the opening and shield the active site. Restricted access gives rise to some of the specificity of the enzyme [12]. Residues important in thrombin-activatable fibrinolysis inhibitor (TAFI) activation are located above the active site cleft, whereas residues involved in protein C activation are located below the active site cleft [13].

The two major classes of novel oral agents are direct thrombin inhibitors (eg. dabigatran) and factor Xa inhibitors (eg. apixaban or rivaroxaban) with more predictable pharmacodynamics than vitamin K antagonists [14]. The direct thrombin inhibitors, directly interacts with and inhibits the active site of thrombin and exosite Ⅰ [15]. And indirect thrombin inhibitors: heparin interacts with exosite Ⅱ and antithrombin (AT) to inhibit thrombin; low molecular weight heparin and fondaparinux interact with AT to inhibit factor Xa; and the heparinoid danaparoid has an anticoagulant effect that is partially mediated by inhibition of thrombin via a combination of AT (heparin cofactor Ⅰ) and heparin cofactor Ⅱ. Direct factor Xa inhibition may cause more coagulation-specific effects, whereas direct thrombin inhibition may have beneficial effects outside the coagulation cascade [16] (Fig. 1).

Direct thrombin inhibitors

There are a number of small molecule direct thrombin inhibitors orally active. Dabigatran etexilate is an orally active direct thrombin inhibitor that has been employed for prevention and treatment of venous and arterial thromboembolic disorders in (eg. prevention of venous thromboembolism [VTE] after total knee or total hip arthroplasty, treatment of acute VTE, prevention of stroke in AF) [17-19]. It was concluded that a fixed dose of dabigatran was as effective as warfarin for the treatment of acute VTE, with a safety profile similar to that of warfarin, without requiring laboratory monitoring. Dabigatran has not yet been approved by the United States FDA for this indication, although it has been approved for use in patients with nonvalvular AF.

Dabigatran does not interact with the cytochrome P450 system. However, its use in those taking certain P-glycoprotein inducers or inhibitors and those agents that alter dabigatran bioavailability (eg. rifampin, quinidine, ketoconazole, verapamil, amiodarone,

clarithromycin), has been considered contraindicated in some labeling (eg. quinidine in the European Medicines Agency labeling).

In the RE-LY (Randomized Evaluation of Long-term anticoagulant therapY) trial, patients with AF were randomized to take low-dose (110 mg) or high-dose (150 mg) dabigatran versus warfarin [14, 20]. As a result, low-dose dabigatran was not inferior to warfarin for stroke, and high-dose dabigatran was actually superior to warfarin [20]. Major bleeding was similar with high-dose dabigatran versus warfarin and less with low-dose dabigatran. Dabigatran was superior to warfarin for hemorrhagic stroke and intracranial hemorrhage at both dosages [20].

A network Meta-analysis showed effectiveness of dabigatran versus antiplatelet therapy for stroke prevention without significant bleeding risk [21]. Compared with placebo, the numbers-needed-to-treat were 16 and 18 for any stroke and 28 and 29 for all-cause mortality at 150 mg and 110 mg of dabigatran, respectively. Compared with no treatment, 1 additional extracranial hemorrhage occurred for every 71 (150 mg dose) or 97 (110 mg dose) patients on dabigatran [21]. High-dose dabigatran was estimated to reduce stroke risk compared with aspirin monotherapy by 63% and compared with aspirin plus clopidogrel by 61%.

In patients with previous stroke/transient ischemic attack, there was a trend toward reduced risk of stroke or systemic embolism with dabigatran at 110 mg and 150 mg compared with warfarin [22], and 110 mg dabigatran showed reduction in vascular death. Compared with warfarin, major hemorrhage was less at 110 mg dabigatran and similar at 150 mg, highlighting potential roles for dabigatran in secondary prevention.

In the RE-LY trial, there were numerically more myocardial infarction events in the dabigatran-treated patients compared to warfarin [20]. A Meta-analysis of contemporary trials of warfarin versus other OAC or OAC-equivalent regimes showed that warfarin was associated with significant reduction in myocardial infarction (relative risk, 0.77; 95% confidence interval [CI], 0.63-0.95; P = 0.01) [23], suggesting a possible protective effect of warfarin for myocardial infarction.

Dabigatran has a half-life of approximately 12 to 14 h in adult volunteers with normal renal function, which requires twice daily dosing. Dabigatran at 150 mg twice a day (with 75 mg twice a day for patients with creatinine clearance 15-30 ml/min) is recommended in current US guidelines as an alternative to warfarin [24], but the dose regime with 110 mg twice a day is not approved by the Food and Drug Administration [25]. In the Canadian, UK and European Medicines Agency labeling, dabigatran is contraindicated for use in patients with a creatinine clearance < 30 ml/min. In recent European guidelines, 150 mg dabigatran twice a day is recommended for patients at low bleeding risk (HAS-BLED score 0-2), whereas 110 mg twice a day is recommended for those at elevated bleeding risk (HAS-BLED score ≥ 3) [8].

There is no antidote for dabigatran. Drug discontinuation is usually sufficient to control bleeding in most clinical settings, since its half-life is relatively short (12 to 14 h) in subjects with normal renal function.

Another direct thrombin inhibitor, AZD0837, has completed Phase Ⅱ trials [26] with good safety, low incidence of bleeding, and effective anticoagulation.

Factor Ⅹa inhibitors

Factor Ⅹa can be inhibited indirectly through antithrombin or by direct inactivation per se, blocking conversion of prothrombin to thrombin. Similar to the direct thrombin inhibitors, they all have rapid onset of action, with peak anticoagulant effect achieved within 2 to 4 h, thus potentially obviating the need for a parenteral anticoagulant (eg. heparin or low molecular weight heparin) in the initial treatment of VTE. These agents are also designed to have relatively stable pharmacodynamic profiles so that routine monitoring is not required, making them theoretically superior to warfarin for long-term use. However, the cost of these new factor Ⅹa inhibitors will likely be substantially higher than that of warfarin.

Rivaroxaban is an orally available direct factor Ⅹa inhibitor with a peak plasma concentrations occurring 2.5 to 4 h after oral administration. Dose-finding studies in patients undergoing orthopedic procedures suggested that an oral dose of 10 mg/d was suitable for investigation in phase III trials for the prevention of VTE [27] and a dose of 20 to 40 mg/d was for the treatment of VTE [8]. In the ROCKET-AF trial (Rivaroxaban Once daily oral direct factor Ⅹa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), rivaroxaban was not inferior to warfarin and achieved superiority in the on-treatment analysis but not in the more conventional intention-to-treat analysis [28]. Intracranial hemorrhage occurred less with rivaroxaban compared with warfarin (0.49% versus 0.74%).

Rivaroxaban has been approved in the United States, European Union (EU), and Canada for the prevention of venous thromboembolism in adults undergoing elective hip or knee replacement surgery, at a fixed oral dose of 10 mg/d beginning after hemostasis has been established. This dose does not require laboratory monitoring or adjustment [29]. The study protocol of the ROCKET-AF trial suggested discontinuation of the drug approximately two days before elective surgery without bridging anticoagulation [30].

The use of rivaroxaban is not recommended for those with a creatinine clearance < 30 ml/min, and is

Table 2. Comparison of risk of stroke and bleeding between novel anticoagulants and warfarin in different trials N(%)

Complication	RE-LY Trial*			ROCKET-AF Trial#		ARISTOTLE Trial▲	
	Dabigatran 110 mg (N = 6015)	Dabigatran 150 mg (N = 6076)	Warfarin (N = 6022)	Rivaroxaban (N = 7081)	Warfarin (N = 7090)	Apixaban (N = 9120)	Warfarin (N = 9081)
Stroke	183 (1.5)	134 (1.1)	202 (1.7)	269 (1.7)	306 (2.2)	212 (1.2)	265 (1.6)
Major hemorrhage	342 (2.8)	399 (3.3)	421 (3.5)	395 (3.6)	386 (3.4)	327 (2.1)	462 (3.0)

*Study criteria: AF, $CHADS_2 \geqslant 1$ (mean score: 2.1). #Study criteria: AF, $CHADS_2 \geqslant 1$ (mean score: 3.5). ▲Study criteria: AF, $CHADS_2 \geqslant 1$ (mean score: 2.1)

considered contraindicated in those with a creatinine clearance < 15 ml/min, as well as in those with significant hepatic impairment[31].

Apixaban, an oral Factor Xa inhibitor, was compared to warfarin in the ARISTOTLE trial[32] which showed superiority for apixaban over warfarin in reducing stroke and systemic thromboembolism (by 21%) which was driven by a 50% reduction in hemorrhagic stroke but no significant difference in ischemic stroke. Major bleeding rates were significantly lower with apixaban (by 31%). All-cause mortality was also significantly lower (by 11%). The AVERROES (Apixaban versus aspirin to reduce the risk of stroke) trial comparing apixaban with aspirin in patients with AF unsuitable for warfarin was terminated early after a 55% reduction in stroke or systemic embolism with apixaban with no difference in major bleeding and poorer tolerability of aspirin[33]. In addition, ARISTOTLE is the first study to show a significant reduction in the rate of all-cause death compared to warfarin (3.5 versus 3.9 percent per year) (Table 2). Based on the trial outcomes, dabigatran, rivaroxaban and apixaban were not inferior to warfarin. Dabigatran 150 mg and apixaban and on-treatment rivaroxaban were superior to warfarin. They were both safer than warfarin. Apixaban caused less bleeding, and resulted in lower mortality.

Edoxaban is an orally active factor Xa inhibitor approved in Japan for the prevention of VTE after major orthopedic surgery, at a dose of 30 mg daily[34]. The half life of edoxaban is in the range of the other factor Xa inhibitors (ie. 6 to 10 h), but unlike apixaban and the direct thrombin inhibitor dabigatran, edoxaban is administered once daily. Edoxaban is renally excreted and is a substrate for P-glycoprotein. Edoxaban also appears to have similar efficacy in reducing cardiovascular risk, and a safety profile similar to the other direct factor Xa inhibitors. A Phase Ⅲ trial (Effective aNticoaGulation with factor XA next GEneration in Atrial Fibrillation [ENGAGE-AF TIMI 48]) of edoxaban against warfarin is underway[35].

Both betrixaban is a factor Xa inhibitor at early stages of development[11, 36-37]. A Phase Ⅱ trial (EXPLORE-Xa [A phase 2, randomized, parallel group, dose finding, multicenter, multinational study of the safety, tolerability and pilot Efficacy of three blinded doses of the oral factor Xa inhibitor betrixaban comPared with open Label dOse-adjusted waRfarin in patiEnts with non-valvular atrial fibrillation]) comparing betrixaban with warfarin for stroke prevention in patients with AF has been presented[35]. Results showed that a once-daily dose of oral betrixaban, given to patients with nonvalvular AF, reduced the incidence of major and clinically relevant non-major bleeds compared to dose-adjusted warfarin. Another oral Factor Xa inhibitor, YM150, is being investigated against warfarin in patients with AF in Phase Ⅱ trials[38].

Rate and rhythm control are other considerations in the management of patients with AF. OAC is still recommended if there is risk of stroke and thromboembolism regardless of other concurrent therapy for AF and regardless of a rate or rhythm control strategy[8].

Conclusions

Unlike warfarin, novel oral anticoagulants such as dabigatran and rivaroxaban have predictable and consistent anticoagulant effects with a rapid onset of action, short half-life, and consequently no need for routine laboratory testing. The pharmacologic profiles of these drugs represent an advantage for patients on chronic oral anticoagulant treatment who are undergoing invasive procedures. These drugs may minimize patient time without the antithrombotic effects of oral anticoagulants spent during the perioperative period, potentially eliminating the need for bypass therapy althogether.

Novel agents are changing treatment guidelines and choices available to both patients and clinicians, but bringing new considerations, for example, concerns regarding monitoring and how to treat bleeding with new anticoagulants that do not have an antidote. Dabigatran etexilate, rivaroxaban and apixaban affect major laboratory tests for clotting. However, at present we do not know whether and how this information may be clinically useful. Although current trials show favorable safety profiles for newer agents, long-term data are required, because most patients with AF require lifelong OAC. The use of novel antiarrhythmic treatments will similarly be determined by longer-term

data. Their high cost is another major issue, and newer pharmacoeconomic studies are needed to evaluate their cost-effectiveness ratio versus warfarin.

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