

New oral anticoagulants for Atrial Fibrillation

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Review Article

ABSTRACT

ARTICLE INFO

Keywords:

Atrial fibrillation
anticoagulants

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DOI : 10.20885/JKKI.Vol8.Iss2.art5

History:

Received: April 15, 2017

Accepted: May 22, 2017

Online: June 15, 2017

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the world. Four new oral anticoagulants have become available as alternatives for warfarin in patients with AF. Although the newer aspects have higher acquisition cost, the benefits of cost savings may be derived from potential for decreasing the bleeding incidence and reducing the need for anticoagulation monitoring.

Fibrilasi atrial (AF) adalah aritmia jantung yang paling umum didunia. Terdapat empat antikoagulan oral baru tersedia sebagai alternatif warfarin pada pasien dengan AF. Meskipun harga obat baru tersebut lebih mahal, namun terdapat manfaat penghematan biaya yang disebabkan penurunan kejadian pendarahan dan penurunan kebutuhan untuk monitoring penggunaan antikoagulan.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, currently affecting in 1 – 2% of the general population.¹ The lifetime risk of AF in patients 40 years of age and older is estimated at 25%.^{2,3} Stroke is a major complication associated with AF, which contributes to the morbidity and mortality associated with the disease. Patients with AF have a five-fold increased risk of stroke. In consequence, the risk of death from AF-related stroke is doubled and the cost of care is increased 1.5 fold. This risk varies among patient populations, according to age, sex, and the presence of comorbid disease states (e.g., diabetes, hypertension, congestive heart failure, and vascular disease).^{2,4,5}

Anticoagulation is recommended for stroke prevention for intermediate risk and high risk patients (CHADS2 score \geq 1, see Table 1).^{4,6-10} Previously, warfarin was the only option for oral

anticoagulation in these patients. An assessment of bleeding risk should be part of the patient assessment before starting anticoagulation. Despite anticoagulation of more elderly patients with AF, rates of intracerebral haemorrhage are considerably lower than in the past, typically between 0.1 and 0.6% in contemporary reports. This may reflect lower anticoagulation intensity, more careful dose regulation, or better control of hypertension. Using a 'real-world' cohort of 3978 European subjects with AF from the EuroHeart Survey, a new simple bleeding risk score, HAS-BLED (see Table 2), has been derived. It would seem reasonable to use the HAS-BLED score to assess bleeding risk in AF patients, whereby a score of \geq 3 indicates 'high risk', and some caution and regular review of the patient is needed following the initiation of anticoagulation therapy.¹

Currently, four oral anticoagulants are

available on the market as alternatives to warfarin in patients with AF. Dabigatran was the first new oral anticoagulant approved for stroke prevention in AF, followed by the oral anti-factor Xa inhibitors rivaroxaban, apixaban and edoxaban. Rivaroxaban is also approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), along with prevention of DVT/PE in patients undergoing knee or hip replacement surgeries.¹¹ Apixaban was approved for stroke prevention in December 2012.¹² Edoxaban was approved for the prevention of stroke and for the treatment of symptomatic venous thromboembolism in 2013.^{38,39} None of the new agents are approved for use in patients with AF secondary to valvular heart disease or mechanical heart valves. A summary of indications and doses of these oral agents is provided in Table 3.^{10-12,38,39}

Table 1. CHADS2 Score

| | |
|-----------------------------|----|
| Congestive Heart Failure | +1 |
| Hypertension | +1 |
| Age ≥ 75 years | +1 |
| Diabetes Mellitus | +1 |
| Stroke/TIA/Thrombo-embolism | +2 |

Table 2. HAS-BLED Score

| | |
|-------------------------|----|
| Hypertension | +1 |
| Abnormal liver function | +1 |
| Abnormal renal function | +1 |
| Stroke | +1 |
| Bleeding | +1 |
| Labile INRs | +1 |
| Elderly (Age >65) | +1 |
| Drugs | +1 |
| Alcohol | +1 |

Table 3. Indications and doses for the new oral anticoagulant

| | Atrial fibrillation | VTE prevention | VTE treatment |
|--------------------|--|----------------------------|---|
| Dabigatran | 150 mg b.i.d., 75 mg b.i.d. ^a | - | - |
| Rivaroxaban | 20 mg daily; 15 mg daily ^b | 10 mg daily ^{d,e} | 15 mg b.i.d. x 21 days, then 20 mg daily ^e |
| Apixaban | 5 mg daily; 2.5 mg daily ^c | - | - |
| Edoxaban | 60 mg daily; 30 mg daily ^f | - | 60 mg daily; 30 mg daily ^f |

^aFor patients with a CrCl of 15 to 30 mL/minute or a CrCl of 30 to 50 mL/minute and concomitantly receiving a strong P-glycoprotein inhibitor.

^bFor patients with a CrCl of 15 to 50 mL/minute.

^cIf the patient is taking a strong dual inhibitor of CYP3A4 and a permeability glycoprotein (P-gp) inhibitor, or has two or more of these characteristics: 80 years of age or older, body weight ≤ 60kg, or serum creatinine 1.5 mg/dL or greater.

^dPost-operative thromboprophylaxis following hip or knee replacement surgery.

^eAvoid use in patients with a CrCl of 30 mL/minute or lower.

b.i.d. = twice daily; CrCl = creatinine clearance; CYP = cytochrome P450; VTE = venous thromboembolism.

^fFor patients with a CrCl of 30 to 50 mL/minute, bodyweight ≤ 60kg or concomitantly receiving a strong P-glycoprotein inhibitor.

Comparison of warfarin and the new oral anticoagulant

An ideal oral anticoagulant has a rapid onset and predictable pharmacokinetics with easily quantifiable and reversible therapeutic effects. Above all, the medication should be efficacious.

When compared with warfarin, the new oral anticoagulants have a faster onset and predictable pharmacokinetics.¹¹⁻¹³ In addition, a routine anticoagulation monitoring is not required, and these agents are at least as efficacious as warfarin.

Warfarin exerts its anticoagulation effect by inhibiting the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X. The primary pharmacological effect of warfarin results from the inhibition of factor II or thrombin.¹⁴ More frequent monitoring of the International Normalized Ratio (INR) may be required at the initiation of therapy in order to determine the patient's individual steady-state dose.

Inhibition of multiple vitamin K-dependent coagulation factors and genetic variations of the VKORC1 and cytochrome P450 (CYP) 2C9 enzymes contribute to the variation in dosing required for therapeutic anticoagulation.¹⁵⁻¹⁸ The amount of dietary vitamin K consumed can also affect the dosing requirements of warfarin; therefore, dietary intake should remain consistent. Sub-therapeutic anticoagulation therapy may result in thrombosis, yet over-anticoagulation can lead to bleeding complications.

Warfarin also inhibits natural anticoagulant proteins C and S, resulting in an increased risk of thrombosis at the initiation of therapy.^{19,20} Patients at a high risk of thrombosis (who have

a high risk for AF and acute thrombosis or who have a mechanical heart valve) may need bridge therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) until a steady-state concentration is achieved.

A slow onset of action, a narrow therapeutic index, numerous drug and food interactions, variable pharmacokinetics, and the need for monitoring INR are major limitations of the warfarin use in patients with AF. The newer anticoagulants exert their therapeutic effects by directly inhibiting a single factor in the coagulation cascade; dabigatran targets factor IIa, and rivaroxaban, apixaban and edoxaban bind to factor Xa. These new agents also have a more reliable pharmacodynamic profile and provide a less complicated dosing regimen (see Table 4).¹¹⁻¹³ However, limitations to their use include a higher acquisition cost, its contraindication for patients with severe renal impairment, a lack of an antidote for reversal, and an inability to quantify their effects in routine coagulation testing and limited experience with drug-drug and drug-disease interactions.

Table 4. Pharmacokinetic properties of new oral anticoagulants

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|------------------------|---------------------------|----------------------------|----------------------------|----------------------------|
| Mechanism of action | Direct thrombin inhibitor | Direct factor Xa inhibitor | Direct factor Xa inhibitor | Direct factor Xa inhibitor |
| Oral bioavailability | 6% | 60%–80% | 50% | 62% |
| Volume of distribution | 50–70 L | 50 L | 21 L | 107 L |
| Half-life | 12–17 hours | 5–13 hours | 9–14 hours | 10–14 hours |
| Metabolism/elimination | 80% renal | 33% renal; 66% hepatic | 25% renal; 75% fecal | 50% renal; 50% hepatic |
| Protein binding | 35% | > 90% | 87% | 55% |
| Approval year by FDA | Oct 2010 | Nov 2011 | DeC 2012 | Jan 2015 |

Direct thrombin inhibitors

Dabigatran

Dabigatran, a competitive and reversible inhibitor of free and clot-bound thrombin, prevents soluble fibrinogen from converting to fibrin.^{13,21} It is a prodrug that is converted to its active form through esterase catalyzed hydrolysis.^{13,22} Dabigatran is formulated as

encapsulated pellets with a tartaric acid core to enhance its oral absorption and to ensure consistent and pharmacologically desirable concentrations.²³ Crushing or breaking the capsules and administration via a nasogastric (NG) tube should be avoided, because pellet administration outside of the capsule can increase bioavailability by up to 75%.^{13,23}

In patients with AF, dabigatran 150 mg is taken twice daily with or without food. A reduced dose of 75 mg is recommended if the patient's creatinine clearance (CrCl) is 15 to 30 mL/minute. Clearance is primarily renal, and the drug is a substrate of permeability glycoprotein (P-gp). The use of dabigatran with P-gp inducers (such as rifampin) should be avoided. The combination of renal impairment and P-gp inhibition has a greater tendency to achieve undesirable concentrations when compared with each factor separately.^{11-13,24}

For patients with moderate renal impairment (a CrCl of 30–50 mL/minute) who are concomitantly taking P-gp inhibitors such as dronedarone or systemic ketoconazole, a reduced dose of 75 mg is recommended. Approval of the 75-mg dose was based on pharmacokinetic modeling data.^{13,24} The clinical efficacy of the reduced dose regimen has not been studied.^{6,9-13} Significant adverse effects occurring with dabigatran at a rate exceeding 15% include dyspepsia and gastritis-like symptoms.¹³

Routine monitoring of anticoagulation activity is not necessary if dabigatran is administered according to the manufacturer's recommendations. Dabigatran prolongs thrombin clotting time (TCT), prothrombin time (PT), activated partial thromboplastin time (aPTT), and ecarin clotting time (ECT). TCT, aPTT, and ECT can be used to estimate the drug's serum concentration. However, the degree of aPTT elevation is not linearly correlated with the dabigatran concentration, and it is particularly inaccurate at higher concentrations of the drug.^{13,15}

A boxed warning cautions against interruptions in dabigatran therapy to avoid an increased risk of stroke resulting from the drug's short half-life. Therefore, with holding dabigatran for bleeding or invasive surgery should be minimized when possible.¹³ Dabigatran should be withheld for 1 to 2 days before an invasive procedure in patients with normal renal function and for 3 to 5 days if the CrCl is 50 mL/minute or below.¹³ TCT and aPTT can be used to determine the residual anticoagulation activity

of dabigatran before the procedure.^{15,25}

There is no known reversal agent for dabigatran. Symptomatic management is the primary approach for bleeding because of dabigatran's relatively short half-life. Recombinant factor VIIa (rFVIIa), prothrombin complex concentrates (PCCs), or hemodialysis can be considered for reversing life-threatening bleeding.²⁵⁻²⁸

Factor Xa Inhibitors

Rivaroxaban

Rivaroxaban (Xarelto) was the first oral reversible factor Xa inhibitor for stroke prevention in nonvalvular AF. It is also approved for treatment of VTE, PE and VTE prophylaxis in patients undergoing knee or hip replacement.⁹ For patients with AF, rivaroxaban 20 mg once daily should be taken with food. Because of the drug's partial renal elimination, the dose should be reduced to 15 mg once daily in patients with a CrCl of 15 to 50 mL/minute.¹¹⁻¹³

Rivaroxaban, also a P-gp substrate, is metabolized by CYP3A4 pathways. The concomitant use with a P-gp and a strong CYP3A4 inhibitor (e.g., a protease inhibitor, ketoconazole, or itraconazole) can lead to increased rivaroxaban exposure by 30% to 160%, resulting in increased bleeding risk and, therefore, should be avoided. Clinicians should weigh the risks and benefits in patients with renal impairment who are receiving concomitant P-gp and weak-to-moderate CYP3A4 inhibitors such as amiodarone, diltiazem, verapamil, quinidine, erythromycin, and azithromycin. Conversely, rivaroxaban concentrations can be reduced by 50% with dual P-gp and strong CYP3A4 inducers such as rifampin, phenytoin, carbamazepine; concomitant administration should be avoided.¹¹

The use of rivaroxaban in patients with hepatic impairment (a Child–Pugh class of B or C) is not recommended. Additional warnings include an increased risk of thrombotic events with the cessation of rivaroxaban therapy. The drug's half-life is 5 to 9 hours in young, healthy patients (20–45 years of age); its half-life is 11 to 13 hours in elderly people. The peak effect occurs

2 to 4 hours after administration. Rivaroxaban can also be given by nasogastric tube or a gastric feeding tube.¹¹

The most common adverse events with rivaroxaban were related to bleeding and occurred at rates similar to those of warfarin in clinical trials. Non-hemorrhagic adverse drug events reported at a rate of 5% or more included peripheral edema, dizziness, nasopharyngitis, cardiac failure, bronchitis, dyspnea, and diarrhea, which occurred at rates similar to those receiving warfarin.¹¹

Rivaroxaban causes concentration-dependent prolongation of PT and aPTT. Neither the manufacturer nor any organization recommends routine anticoagulation monitoring during rivaroxaban therapy. Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) have a more pronounced effect on PT than on aPTT. Abnormalities in coagulation tests can be observed with therapeutic doses.³¹ Interruption of therapy should be minimized to reduce the risk of thrombosis. Anticoagulation activity may be prolonged in patients with renal dysfunction because of partial renal clearance.¹¹⁻¹³ Rivaroxaban should be withheld for at least 1 day before an invasive procedure for patients with normal renal function and longer for patients with renal dysfunction (2 days if the CrCl is 60–90 mL/minute, 3 days if the CrCl is 30 to 59 mL/minute, and 4 days if the CrCl is 15 to 29 mL/minute).^{25,32}

There is no specific antidote for rivaroxaban. It is not dialyzable, because its protein binding is nearly 95%. Limited data suggest that four-factor prothrombin complex concentrates (PCCs) and recombinant factor VIIa can be used in cases of life-threatening bleeding.^{28,33,34}

Apixaban

Apixaban is the second oral selective inhibitor of free and clot-bound factor Xa. In patients with AF, apixaban 5 mg twice daily is recommended. A reduced dose of 2.5 mg twice daily is recommended in patients with two or more of the following: age 80 years or older, body weight 60 kg or less, and a serum Cr level

of 1.5 mg/dL or higher.

Apixaban is metabolized primarily by the liver CYP enzyme 3A4 and is a substrate of P-gp. A reduced dose of 2.5 mg twice daily is also recommended when apixaban is used concomitantly with a strong dual inhibitor of CYP3A4 and P-gp (i.e., ketoconazole, itraconazole, ritonavir, or clarithromycin). Manufacturers also advise against the concomitant use of apixaban with strong inducers of P-gp and CYP3A4 if the recommended dose for the patient is 2.5 mg (based upon age, body weight, and renal function). Apixaban is not recommended for patients with severe hepatic impairment.

The drug's biological half-life is 12 hours in vivo.¹² Adverse events with its use were related primarily to bleeding.^{12,29,30}

Apixaban produces dose-dependent elevations in aPTT, PT and chromogenic anti-factor Xa assay. Abnormalities in coagulation tests (PT and aPTT) can be observed with therapeutic doses. Anticoagulation monitoring with routine tests is not recommended because of the high degree of variation; however, drug-specific chromogenic anti-factor Xa assay can be used to estimate the extent of anticoagulation.³⁵ Renal and hepatic impairment may result in an extended biological half-life.

Apixaban should be withheld 1 to 2 days before an invasive procedure in patients with normal renal function and longer for patients with renal impairment (3 days if the CrCl is 50 to 59 mL/minute and for 4 to 5 days if the CrCl ranges from 30 to 49 mL/minute).²⁵

No antidote is currently available for apixaban; however, PCCs (prothrombin complex concentrates) can be considered for reversal of a life-threatening bleeding episode. In vitro data supporting its use are lacking.^{25,28,36}

Edoxaban

Edoxaban, a once daily non-vitamin K antagonist oral anticoagulant, is a direct, selective, reversible

inhibitor of factor Xa (FXa).³⁸⁻⁴⁰ In healthy subjects, single oral doses of edoxaban result in peak plasma concentrations within 1.0–2.0 hour

of administration, followed by a biphasic decline. Exposure is approximately dose proportional for once daily doses of 15–150 mg.

Edoxaban is predominantly absorbed from the upper gastrointestinal tract, and oral bioavailability is approximately 62 %.^{64,66} Food does not affect total exposure to edoxaban. The terminal elimination half-life in healthy subjects ranges from 10 to 14 h, with minimal accumulation upon repeat once daily dosing up to doses of 120 mg. Its clearance mechanisms involve both renal and non-renal pathways to almost equal extents. Intrinsic factors, such as age, sex and race, do not affect edoxaban pharmacokinetics after renal function is taken into account.

Pharmacokinetic modeling and simulation showed that patients with low body weight, moderate-to-severe renal dysfunction, or concomitant use of a potent P-glycoprotein inhibitor should have the edoxaban dose reduced by 50%.³⁸ Oral administration of edoxaban results in rapid changes in anticoagulatory biomarkers, with peak effects on anticoagulation markers (such as anti-FXa), PT and aPTT occurring within 1–2 h of dosing.⁴⁰ Although no specific antidote for edoxaban is currently available, hemostatic agents reverse its anticoagulant effect.³⁸

CONCLUSION

Four new oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) provide several advantages over warfarin, including their predictable pharmacokinetic profile, the fact that no routine monitoring is needed, and the incidence of fewer drug–food interactions. Although renal function, bleeding, and compliance may still need to be monitored in patients, the comfort of use may improve persistence with their anticoagulant regimen.³⁷

Some limitations to the use of these newer anticoagulants include the lack of a reversal agent, an inability to use them in specific patient populations (such as those with severe renal impairment), a lack of coagulation tests to quantify their effect, and little experience with drug–drug and drug–disease interactions.

Information about the impact of noncompliance, especially given the short half-lives of these agents, is also lacking.

Taking their limitations into consideration, the new agents still offer several advantages when used appropriately in selected patients. Their role is likely to grow as more data become available regarding their long-term use, drug–drug interactions and use in specific patient populations.

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