REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will weigh the pros and cons of the new oral anticoagulants compared with vitamin K antagonists

**BERNARDINO ROCA, MD, PhD**
Hospital General, University Jaume I, Castellon, Spain

**MANUEL ROCA, MD**
Hospital Provincial, University Jaume I, Castellon, Spain

# The new oral anticoagulants: Reasonable alternatives to warfarin

## ABSTRACT

Dabigatran (a direct thrombin inhibitor) and rivaroxaban, apixaban, and edoxaban (direct activated factor X inhibitors) are increasingly being used in clinical practice. Compared with vitamin K antagonists, they are more convenient, do not require laboratory monitoring, have limited drug and food interactions, and have fixed dosages suitable for most patients. But the shortcomings of these agents can jeopardize their efficacy and increase the risk of bleeding. Their future role in preventing and treating thromboembolic disease will depend on building clinical experience, but current evidence indicates that they are reasonable alternatives to vitamin K antagonists.

## KEY POINTS

The new oral anticoagulants have favorable pharmacologic properties and similar efficacy and safety as vitamin K antagonists.

The new agents are indicated for preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation and preventing and treating deep vein thrombosis and pulmonary embolism (the indications regarding venous thromboembolism differ somewhat among agents).

Except for dabigatran, lack of an antidote in case of bleeding or emergency surgery is a major drawback.

Be cautious when using these drugs in patients with renal or liver disease and in those taking an inhibitor or inducer of the P-glycoprotein transporter or the cytochrome P450 enzymes.

doi:10.3949/ccjm.82a.14052

For decades, vitamin K antagonists such as warfarin, acenocoumarol, phenindione, and phenprocoumon have been the only available oral anticoagulants. These drugs have similar pharmacologic profiles and share significant drawbacks in clinical use: a narrow therapeutic window, food and drug interactions, and the need for repeated blood testing to ensure the desired international normalized ratio.

Such problems have fostered research in the field of coagulation, and new oral agents that selectively target coagulation factors have become available. At least three such products are already available in most countries: dabigatran (a thrombin or factor IIa inhibitor) and rivaroxaban and apixaban (factor Xa inhibitors).[1,2] Other factor Xa inhibitors, including edoxaban[3] (available in the United States and Japan) and betrixaban,[4] may also soon become available worldwide.

The new oral anticoagulants are more effective than vitamin K antagonists in preventing several thromboembolic conditions, have fewer drug interactions, and likely have fewer side effects.[5] Indications for these new agents are expected to expand as new clinical trial results become available.[6,7]

This review summarizes the clinically relevant characteristics of the new oral anticoagulants (**Table 1**) and provides guidance on their usage (**Table 2**).

## THROMBIN (FACTOR IIa) INHIBITORS

### Dabigatran

Dabigatran etexilate is a prodrug that is rapidly and completely converted by esterases in the plasma and liver into its active metabolite, dabigatran. It competitively and reversibly binds to freely circulating and clot-bound

TABLE 1

**Characteristics of thrombin inhibitors and factor Xa inhibitors**

| Characteristic | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| **Target** | Factor IIa | Factor Xa | Factor Xa | Factor Xa |
| **Prodrug** | Dabigatran etexilate | No | No | No |
| **Approximate bioavailability** | 5% | 90% | 50% | 45% |
| **Metabolism** | Hepatic | Hepatic | Hepatic | Hepatic |
| **Approximate plasma protein binding** | 35% | 95% | 85% | 50% |
| **Approximate plasma half-life** | 15 hours | 10 hours | 12 hours | 10 hours |
| **Renal excretion** | 80% | 33% | 27% | 35% |
| **Dose monitoring** | Not needed | Not needed | Not needed | Not needed |
| **Approximate time to peak effect** | 2 hours | 3 hours | 3 hours | 1–2 hours |
| **Use of P-glycoprotein transporter** | Yes | Yes | Yes | Yes |
| **Metabolism through cytochrome P450** | No | 30% | 15% | 3% |
| **Antidote** | Idarucizumab | None | None | None |
| **Time to hemostasis after stopping the drug** | 12 hours | 5–9 hours | 8–15 hours | 4–10 hours |
| **Reversal of action by hemodialysis** | Yes | No | No | No |

**Indications for the new agents are likely to expand**

thrombin, thereby blocking thrombin's procoagulant properties (**Figure 1**).

Clinical trials have shown dabigatran to be similar to warfarin and enoxaparin in efficacy and safety in preventing and treating thromboembolic disease.[8–10]

**Indications.** Dabigatran is approved by the US Food and Drug Administration (FDA) for:

- Preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Treating deep vein thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5 to 10 days
- Preventing recurrence of deep vein thrombosis and pulmonary embolism in patients who have previously been treated with other medications.

**Precautions.** Dabigatran should not be used, or should be used only in a reduced dosage, in patients with renal failure. It can be used in patients with moderate liver impairment but should be avoided in patients with advanced liver disease (cirrhosis), especially if they have coagulopathy. Its use in pregnant and nursing women is not recommended.

**Adverse effects.** Bleeding, including gastrointestinal and intracranial hemorrhage, is the most important adverse effect,[11] but the incidence is similar to that with vitamin K antagonists and low-molecular-weight heparins.[1,12] Dyspepsia is common and may be severe enough to require stopping treatment.[13] Other possible

TABLE 2

**Approved indications for and doses of the new oral anticoagulants**

| Indication | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| **Atrial fibrillation** | 150 mg twice a day if creatinine clearance is > 30 mL/min, 75 mg twice a day if creatinine clearance is 15–30 mL/min | 20 mg daily if creatinine clearance is > 50 mL/min, 15 mg daily if creatinine clearance is 15–50 mL/min | 5 mg twice a day [a] | 60 mg daily if creatinine clearance is 50–95 mL/min, 30 mg daily if creatinine clearance is 15–50 mL/min, avoid if creatinine clearance is > 95 mL/min |
| **Prevention of venous thromboembolism** | Not indicated | 10 mg daily | 2.5 mg twice a day | Not indicated |
| **Treatment of venous thromboembolism** | 150 mg twice a day after parenteral treatment if creatinine clearance is > 30 mL/min | 15 mg twice a day for 21 days, then 20 mg daily | 10 mg twice a day for 7 days, then 5 mg twice a day | 60 mg daily after parenteral treatment, 30 mg daily if creatinine clearance is 15–50 mL/min |
| **Preventing recurrence of venous thromboembolism** | 150 mg twice a day if creatinine clearance is > 30 mL/min | 20 mg daily | 2.5 mg twice a day | Not indicated |

[a] 5 mg daily if the patient has end-stage renal disease maintained on hemodialysis, and 2.5 mg twice a day if any two of the following three circumstances are present: age 80 or older, body weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dL

effects are pain or burning in the throat, skin rash, and syncope. The risk of acute coronary syndrome is slightly increased but is outweighed by the benefit of ischemic stroke prevention.[14,15]

**Drug interactions.** Normally, permeability (P)-glycoprotein intestinal transporter extrudes substrate drugs back into the gut lumen after initial absorption, thereby interfering with drug bioavailability. Strong P-glycoprotein inhibitors (eg, ketoconazole, cyclosporine, tacrolimus, dronedarone, amiodarone, verapamil, clarithromycin) increase the plasma concentration of dabigatran. Despite that, giving these drugs with dabigatran is generally safe except in patients with renal failure (and especially with ketoconazole and dronedarone). To reduce interaction with verapamil, dabigatran should be taken at least 2 hours before this drug.

Potent P-glycoprotein transporter inducers such as rifampicin, carbamazepine, and phenytoin reduce the plasma concentration of dabigatran, and concomitant use of dabigatran with these drugs should be avoided.[1]

### Another selective thrombin inhibitor

Ximelagatran was extensively investigated and approved in several countries in 2006. However, it was withdrawn after reports of severe hepatotoxicity.[16] No other selective thrombin inhibitors are currently in an advanced stage of development.

## FACTOR Xa INHIBITORS

Factor Xa is an ideal target for anticoagulants because of its important role in thrombin formation (**Figure 1**). Selective or direct factor Xa inhibitors significantly reduce the number of strokes and systemic embolic events compared with warfarin in patients with atrial fibrillation. They also may cause fewer major bleeding events than warfarin, although evidence supporting this is less robust.[17] These agents have shown an advantage over enoxaparin for thromboprophylaxis after elective hip or knee replacement surgery and after hip fracture surgery without increasing the rate of bleeding events.[18]

## Selected steps in the blood coagulation pathway

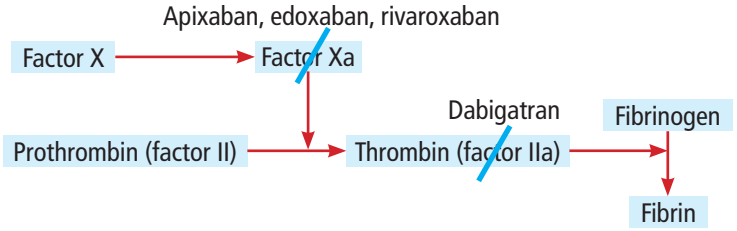


**FIGURE 1.** Selected steps in the blood coagulation pathway. Sites of action of thrombin inhibitors and factor Xa inhibitors are denoted by blue slashes.

### Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor. It reversibly binds to factor Xa with high specificity and inhibits free and clot-bound factor Xa as well as factor Xa in the prothrombinase complex (which catalyzes the conversion of prothrombin to thrombin).[19]

**Indications.** Clinical trials have shown rivaroxaban to have suitable efficacy and safety in several clinical situations.[20–23] It is FDA-approved for:

- Reducing the risk of stroke and systemic embolism in nonvalvular atrial fibrillation
- Preventing deep vein thrombosis after hip or knee replacement surgery
- Treating deep vein thrombosis and pulmonary embolism
- Reducing the risk of recurrence of deep vein thrombosis and pulmonary embolism.

In addition, the European Medicines Agency has approved the use of rivaroxaban together with antiplatelet medications to prevent atherothrombotic events after an acute coronary syndrome with elevated cardiac biomarkers.

**Avoid dabigatran—or use a lower dosage—in patients with renal failure**

**Precautions.** Rivaroxaban should be taken with food to maximize its absorption. Like dabigatran, it should be avoided or used cautiously in patients with renal failure and liver disease, and it is not recommended for pregnant and nursing women.

**Adverse effects.** The most common adverse event is bleeding, although the incidence of major hemorrhage is similar to that with vitamin K antagonists and low-molecular-weight heparins.[1] Other effects include osteoarticular pain, weakness, wound secretion, skin rash, pruritus, abdominal pain, and syncope.

**Drug interactions.** Inhibitors of the P-glycoprotein transporter or the cytochrome P450 enzymes can alter the metabolism of rivaroxaban, making its levels too high. Rivaroxaban is not recommended for patients receiving systemic treatment with azole-antimycotics (eg, ketoconazole) or protease inhibitors to treat human immunodeficiency virus (HIV) infection (eg, ritonavir), as these drugs are strong inhibitors of both systems and may considerably increase plasma rivaroxaban concentrations.[24] Interactions of rivaroxaban with most other inhibitors of the P-glycoprotein transporter or the cytochrome P450 enzymes are considered clinically inconsequential, but caution is still recommended, especially in patients already at risk of bleeding (eg, those taking antiplatelet agents).[25]

Strong inducers of the P-glycoprotein transporter and the cytochrome P450 enzymes (eg, rifampicin, phenytoin) can reduce plasma rivaroxaban concentrations and thus decrease its efficacy. Caution is needed if rivaroxaban is taken with these drugs.

### Apixaban

Apixaban also selectively and reversibly inhibits free and clot-bound factor Xa, as well as factor Xa in the prothrombinase complex.

**Indications.** Apixaban has a suitable efficacy and safety profile, and in clinical trials fewer patients died while taking it than those taking warfarin.[26–28] It is FDA-approved for:

- Reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Prophylaxis of deep vein thrombosis and pulmonary embolism in patients who have undergone hip or knee replacement
- Treating deep vein thrombosis and pulmonary embolism
- Reducing the risk of recurrent deep vein thrombosis and pulmonary embolism after initial therapy.

**Precautions.** Apixaban can be used in most patients with renal failure, but at a lower dosage in some circumstances (**Table 2**). It can be used without dosage adjustment for patients with mild hepatic impairment but should be avoided in those with moderate or advanced liver failure. It is contraindicated in pregnant and nursing women.

**Adverse effects.** As with other anticoagulants, the most common adverse effect is

bleeding, but the incidence is similar to that with vitamin K antagonists and low-molecular-weight heparins.[1,26–28] Other adverse reactions, such as nausea, skin rash, and liver enzyme elevation, are uncommon.

**Drug interactions** are similar to those of rivaroxaban but are generally less intense. Concomitant use with strong dual inhibitors of the P-glycoprotein transporter or the cytochrome P450 enzymes, especially azole-antimycotics and HIV protease inhibitors, should be avoided, but if used, the apixaban dosage may be halved. Caution is also recommended if using apixaban with dual inducers of the P-glycoprotein transporter and the cytochrome P450 enzymes.[29]

### Edoxaban

Edoxaban, another direct factor Xa inhibitor, has a rapid onset of action. It is taken orally once daily and has antithrombotic efficacy similar to other agents in this group.[1,30]

**Indications.** Edoxaban has been approved by the Japanese Pharmaceuticals and Medical Devices Agency and the FDA for:

- Reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Treating deep vein thrombosis and pulmonary embolism after 10 days of initial therapy with a parenteral anticoagulant.

**Precautions**. Edoxaban should not be used in patients with creatinine clearance above 95 mL/min because patients with this excellent level of renal function may clear the drug too well and therefore have a higher risk of ischemic stroke than those receiving warfarin.[31]

**Adverse effects and drug interactions** are similar to those of other factor Xa inhibitors.

### Other factor Xa inhibitors

**Betrixaban** is similar to other factor Xa inhibitors but has some unique pharmacokinetic characteristics, including minimal metabolism through the cytochrome P450 system, limited renal excretion, and a long half-life. This profile may have the advantages of fewer drug interactions and greater flexibility for use in patients with poor renal function, as well as the convenience of once-daily dosing.[4,32] The drug has not yet been approved for clinical use by the FDA or the European Medicines Agency.

Additional oral factor Xa inhibitors, including letaxaban, darexaban, and eribaxaban, are being developed with the aim of overcoming the limitations of available drugs in the group.[33]

## COAGULATION MONITORING

Given their rapid onset of action, stable pharmacokinetic properties, and few significant drug interactions, the new oral anticoagulants do not generally require coagulation monitoring. However, these drugs may produce alterations in coagulation tests: thrombin inhibitors tend to prolong the activated partial thromboplastin time, and factor Xa inhibitors tend to prolong the prothrombin time. These alterations vary from laboratory to laboratory, depending on the reagents used.[34,35]

The new agents have also been reported to cause false-positive results on lupus anticoagulant assays and falsely elevated activated protein C ratio assays, misclassifying patients with the factor V Leiden mutation as normal.[36,37]

Anticoagulation from dabigatran therapy can be monitored with the ecarin clotting time test, which yields a dose-dependent prolongation of clotting time.[38] Rivaroxaban, apixaban, and edoxaban can be monitored using modified chromogenic anti-Xa assays.[25] These tests may help manage overdoses, bleeding events, and emergency perioperative situations, but their usefulness in clinical practice is limited at this time because they are not widely available and they are not validated for this use.

**Anticoagulation with the new oral agents can be monitored, but the clinical usefulness of the monitoring tests is limited**

## SWITCHING FROM VITAMIN K ANTAGONISTS TO THE NEW AGENTS

Important issues to consider when switching anticoagulant agents are the delayed onset of action after initiating treatment and the persistent anticoagulant effect after stopping it. In both cases, the international normalized ratio can be used to monitor the anticoagulant effect of the drugs. Renal failure should also be considered, as it can prolong the plasma half-life of the agents.[1,39]

## MANAGING BLEEDING

Dabigatran is the only new anticoagulant with an antidote commercially available: idarucizumab can completely reverse the anticoagulant effect of dabigatran within minutes.

The other new oral anticoagulants lack antidotes, which can present a major problem if a patient has a major bleed or needs emergency surgery. Giving vitamin K is probably useless in this situation. In general, patients taking one of the new oral anticoagulants who present with bleeding should be treated with traditional measures—eg, oral activated charcoal to retard absorption of recently ingested drugs and cauterization and packing of localized bleeding sites. Dialysis may be useful for patients taking dabigatran[40] but probably not the other drugs, because they are more highly protein-bound.

Other measures to consider include giving:

- Fresh frozen plasma, which may have some potential for reversing the action of thrombin inhibitors and factor Xa inhibitors but lacks data in humans[41]
- Activated prothrombin complex concentrate for reversing thrombin inhibitors
- Nonactivated prothrombin complex concentrates and factor Xa analogues for reversing anti-factor Xa agents[42–44]
- Recombinant factor VIIa, but serious adverse effects—disseminated intravascular coagulation and systemic thrombosis—limit its usefulness.[45]

More research is needed to assess the efficacy and safety of these measures.[46,47]

**Except for dabigatran, the new oral anticoagulants lack antidotes**

## STOPPING THERAPY BEFORE SURGERY

How long to withhold a new oral anticoagulant before patients undergo surgery depends on the type and urgency of the procedure, the indication for anticoagulation, the patient's renal function, and the drug used.

For procedures with a low risk of bleeding (eg, laparoscopy, colonoscopy), dabigatran should be stopped at least 48 hours before the procedure, and factor Xa inhibitors at least 24 hours before. More time should be allowed for patients with renal failure to clear the drug, according to creatinine clearance.

For procedures entailing a high bleeding risk (eg, major surgery, insertion of pacemaker or defibrillator, neurosurgery, spinal puncture), any new oral anticoagulant should be stopped at least 48 hours before the procedure, with a longer time needed for patients with renal failure.

If urgent surgery is needed and performed within a few hours after the last dose of a drug, bleeding complications should be anticipated.

Resuming anticoagulation therapy after surgery should also be individualized depending on the procedure, the indication for anticoagulation, and renal function. In most patients, if good hemostasis is achieved, the drug may be resumed 4 to 6 hours after surgery. Generally, the first dose should be reduced by 50%, after which the usual maintenance dose can be resumed.[39]

## OTHER POSSIBLE USES

**Cardioversion.** Anticoagulation with dabigatran before and after cardioversion in patients with atrial fibrillation[48] appears as effective and safe as anticoagulation with warfarin.[49] There are insufficient data for the other new oral anticoagulants.

**Heparin-induced thrombocytopenia.** The new oral anticoagulants do not affect the interaction of platelets with platelet factor 4 or antibodies to the platelet factor 4-heparin complex, indicating that they may be an appropriate option for anticoagulation in patients with heparin-induced thrombocytopenia.[50–53]

**Other conditions.** The new oral anticoagulants have demonstrated efficacy in preventing or treating thromboembolic disease in patients with cancer[54] and critical illnesses,[55] and in treating acute coronary syndrome[56–58] and other conditions.[59] However, their role in these settings is not well established.[60,61]

## SITUATIONS TO AVOID

**Valvular heart disease.** The new oral anticoagulants should not be prescribed for patients with a prosthetic heart valve or other significant valvular heart disease because of an increased risk of thrombotic complications with dabigatran and the lack of evidence of efficacy and safety of factor Xa inhibitors.[62–64]

**Concurrent thrombolytic therapy** along with any of the new oral anticoagulants poses a very high risk of bleeding. Some cases in which dabigatran was used successfully in this situation have been reported, but definitive recommendations are lacking.[65]

**Elderly patients.** The safety of the new oral anticoagulants in the elderly is of concern

because of the high prevalence of renal failure and other comorbidities and the underrepresentation of this population in many clinical trials assessing these drugs. Data on interactions with foods or other drugs in this population are also scant.[66]

## CHOOSING AN ORAL ANTICOAGULANT

New oral anticoagulants are now a viable alternative to vitamin K antagonists for preventing and treating thromboembolic disease.[67,68]

When oral anticoagulation is indicated, the choice of drug should be individualized. Cost is an important consideration: direct costs of the new drugs are substantially higher than those of vitamin K antagonists and heparin, but their cost-effectiveness may be comparable or superior to that of warfarin or enoxaparin when clinical efficacy and savings in avoiding coagulation tests are considered.[18]

Many experts estimate that the new oral anticoagulants are not remarkably superior to vitamin K antagonists, and thus patients whose coagulation is well controlled and stable on a traditional drug would probably not benefit much from changing.[1,18]

There is currently no conclusive evidence to determine which new oral anticoagulant drug is more effective and safe for long-term treatment, as head-to-head studies of the different medications have not yet been performed.[17,69,70] However, there are factors to consider when choosing a drug:

- Rivaroxaban and edoxaban can be taken once daily and so may be better choices for patients who may have difficulties with compliance.
- Dabigatran should be avoided in patients with dyspepsia because of gastrointestinal adverse effects.[13]
- Dabigatran should be avoided in patients at risk of myocardial infarction because of a possible additional increase in risk.[1,71]

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***ADDRESS**: Bernardino Roca, MD, PhD, Hospital General, University Jaume I, Catalunya, 33-4, 12004 Castellon, Spain; e-mail: broca@uji.es*