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# Novel Oral Anticoagulants for Stroke Prophylaxis and Venous Thromboembolism Prevention and Treatment

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**Abstract** Novel oral anticoagulants (NOACs) are becoming popular management options for stroke prophylaxis in nonvalvular atrial fibrillation as well as deep vein thrombosis and pulmonary embolism treatment and prophylaxis. NOACs have similar efficacy to warfarin along with noninferior safety profiles. Patient comorbidities, size, renal and hepatic function, and concomitant drug regimen play a role in which NOAC a physician may choose.

**Keywords** novel oral anticoagulants, atrial fibrillation, deep vein thrombosis, pulmonary embolism, dabigatran, Pradaxa, rivaroxaban, Xarelto, apixaban, Eliquis, edoxaban, Savaysa, Lixiana

For decades, vitamin K antagonists, namely warfarin, had been the only oral anticoagulants available for stroke prevention in the setting of atrial fibrillation, deep vein thrombosis (DVT) and pulmonary embolism (PE) prophylaxis after orthopedic procedures, as well as for the treatment of DVT and PE. Although warfarin offers anticoagulation benefits and fairly predictable reversibility in cases of bleeding, its drawbacks include multiple drug-drug interactions, food interactions, poorly predictable therapeutic response and the need for constant international normalized ratio (INR) monitoring given a fairly narrow therapeutic window.

In the 1990s and early 2000s, subcutaneously injectable anticoagulants, e.g. enoxaparin, dalteparin and fondaparinux, offered more predictable anticoagulant effects than warfarin without the need for monitoring. However, these medications were less readily reversible, were costlier, were not as easily transported and had to be injected at least once daily, which made them suboptimal for many patients. Still, the subcutaneously injectable anticoagulants continue to be excellent choices for patients bridging to or from warfarin or as monotherapy for anticoagulation in the settings of warfarin failure, cancer, and short- or long-term venous thromboembolism (VTE) prophylaxis.

Over the past few years, however, the U.S. Food and Drug Administration (FDA) has approved the use of four novel oral anticoagulants (NOACs) that appear to offer new hope for patients needing anticoagulant therapy. These new medications offer the benefit of predictable oral anticoagulation with less drug-drug and food interactions and essentially no monitoring.

The four FDA-approved NOACs include one direct thrombin inhibitor — dabigatran (Pradaxa) — and three selective factor Xa inhibitors — rivaroxaban (Xarelto), apixaban (Eliquis) and edoxaban (Savaysa/Lixiana). This review of the current knowledge on these four anticoagulants will discuss their characteristics (Table 1), including mechanisms of action (Figure 1), indications, contraindications, dosing recommendations and surgical precautions, as well as the trials that led to their FDA approval. It also will briefly touch on andexanet alfa (Annexa), an antidote to the anticoagulant effects of factor Xa inhibitors.

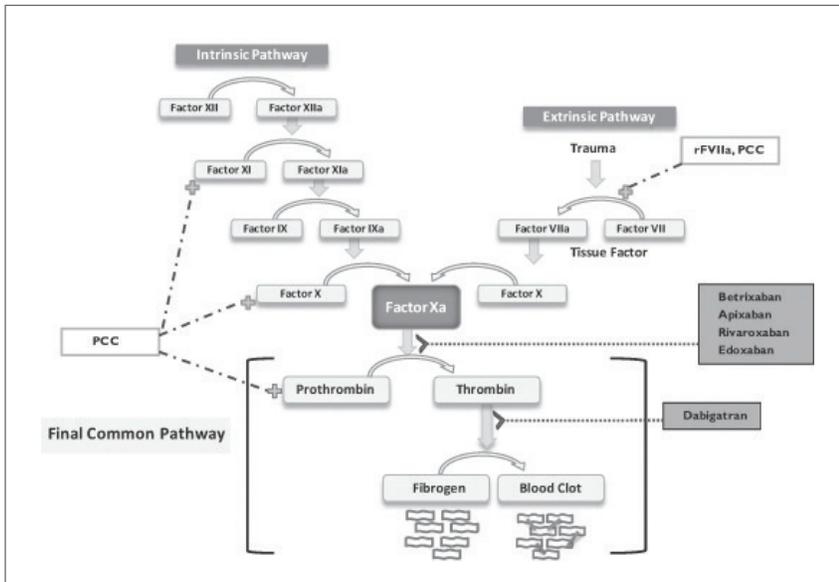
## DABIGATRAN ETEXILATE

### Pharmacodynamics/Mechanism of Action

Dabigatran is a competitive direct thrombin inhibitor. It inhibits free and clot-bound thrombin as well as thrombin-induced platelet aggregation, thereby preventing thrombus formation.

Dabigatran prolongs the coagulation markers activated partial thromboplastin time (aPTT) and thrombin time. aPTT provides an approximate anticoagulant effect,

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**Figure 1.** Diagram depicting where existing reversal agents and novel oral anticoagulants interact with the coagulation cascade. Betrixaban is a once daily oral factor Xa inhibitor being studied in phase 3 trials; the drug is not FDA approved. (Reprinted from U.S. Securities and Exchange Commission filing by Portola Pharmaceuticals Inc. [Oct. 7, 2013], available at <http://www.sec.gov/Archives/edgar/ata/1269021/000119312513393061/d601496ds1.htm>.)

## Box 1. Dabigatran

### Indications<sup>1</sup>

1. Reduction in risk of stroke and systemic embolism in NVAf.
2. Treatment of DVT and PE following 5–10 days of parenteral anticoagulation.
3. Reduction in risk of recurrence of DVT and PE in previously treated patients.

### Contraindications<sup>3</sup>

1. Active pathological bleeding (i.e. clinically significant bleeding secondary to a disease process or injury).
2. Known serious hypersensitivity reaction to dabigatran (e.g. anaphylaxis).
3. Mechanical prosthetic heart valve.

DVT, deep vein thrombosis; NVAf, nonvalvular atrial fibrillation; PE, pulmonary embolism.

with a median of 52 seconds (range: 40–76 seconds) in patients receiving the 150-mg dose.<sup>1</sup> Although routine monitoring is not required, an aPTT  $\geq 2.5$  times that of control may suggest supra-therapeutic anticoagulation. INR is typically insensitive to dabigatran exposure. The drug is metabolized in the liver, where the prodrug is converted to dabigatran. It is excreted mostly renally and has a half-life of 12–17 hours.<sup>2</sup>

## Indications/Contraindications

Indications and contraindications for dabigatran are listed in Box 1.<sup>1,3</sup>

## Dosing

Dabigatran's 110-mg dose is not available in the United States. The FDA approved the 150-mg dose but not the 110-mg dose due to its "inability to identify any subgroup in which the use of the lower dose would not represent a substantial disadvantage."<sup>4</sup>

Dosing guidelines<sup>1</sup> are as follows:

- For stroke and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation (NVAf): 150 mg orally twice a day. For renal dosing in those with creatinine clearance (CrCl) of 15–30: 75 mg orally twice a day (dosing is based on pharmacokinetic rather than clinical trial data). For those with CrCl < 15 or in hemodialysis, dosing is not defined.
- For recurrent DVT/PE prophylaxis: 150 mg orally twice a day. For those with CrCl < 30 or in hemodialysis, dosing is not defined.
- For DVT/PE treatment: 150 mg orally twice a day. For those with CrCl < 30 or in hemodialysis, dosing is not defined.
- Dosing for hepatic impairment is not defined.

## Discontinuation for Surgery, Procedures

Dabigatran should be discontinued 1 to 2 days (if CrCl

≥ 50 mL/min) or 3 to 5 days (if CrCl < 50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consideration should be given for longer times of anticoagulant cessation for those undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, as complete hemostasis may be required in these patients.<sup>1</sup>

### Clinical Trials

Dabigatran has been studied in multiple clinical trials and compared to warfarin in most of them. In the RE-LY trial, dabigatran was noninferior to warfarin in stroke and systemic embolism prophylaxis in NVAF patients at a dose of 110 mg and was superior to warfarin in stroke and systemic embolism prophylaxis in NVAF patients at a dose of 150 mg.<sup>5</sup> In the RE-COVER and RE-COVER II trials, dabigatran was shown to have similar efficacy to warfarin in the treatment of VTE.<sup>6,7</sup> In the REMEDY (vs. warfarin) and RESONATE (vs. placebo) trials, dabigatran was found to be effective in the extended treatment of VTE.<sup>8</sup>

The risk of major bleeding was similar with dabigatran 150 mg and warfarin except for patients 75 years or older, in whom there was a trend toward higher incidence of major bleeding on dabigatran (hazard ratio [HR]: 1.2, 95% confidence interval [CI]: 1.0–1.4). There also was a higher rate of major gastrointestinal bleeding in patients taking dabigatran 150 mg than in patients taking warfarin (1.6% vs. 1.1%, respectively) and a higher rate of any gastrointestinal bleeding (5.7% vs. 3.9%, respectively).<sup>1</sup>

## RIVAROXABAN

### Pharmacodynamics/Mechanism of Action

Rivaroxaban is a selective factor Xa inhibitor. It does not require antithrombin for activity, but it inhibits both free and clot-bound factor Xa and prothrombinase activity. It has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, rivaroxaban decreases thrombin generation.<sup>9</sup>

Rivaroxaban reaches maximum plasma concentrations and inhibits factor Xa activity at 2–4 hours.<sup>9</sup> The half-life of rivaroxaban is 5–9 hours in healthy subjects 20–45 years of age and 11–13 hours in the elderly. Coagulation markers, including aPTT, thrombin

time and INR, are typically not used to monitor its anticoagulant effects.<sup>9</sup> The drug is metabolized in the liver by the cytochrome P450 enzyme's 2J2, 3A4/5 substrate. Excretion is 66% renal and 28% fecal.<sup>2</sup>

### Indications/Contraindications

Indications and contraindications for rivaroxaban are listed in Box 2.<sup>9</sup>

### Dosing

Dosing guidelines<sup>9</sup> for rivaroxaban are as follows:

- For stroke reduction in NVAF: 20 mg once daily with dinner. For renal dosing in those with CrCl 15–50: 15 mg once daily. Avoid use in patients with CrCl < 15 ml/min.
- For DVT and PE treatment: 15 mg twice daily with food for the first 21 days; on day 22, transition to 20 mg once daily with food at the same time each day. Avoid use in patients with CrCl < 30 ml/min.
- For reduction in the risk of recurrence of DVT and PE: 20 mg once daily with food at the same time each day. Avoid use in patients with CrCl < 30 ml/min.
- For DVT prophylaxis after knee or hip replacement surgery: 10 mg once daily. Avoid use in patients with CrCl < 30 ml/min.
- Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

#### Box 2. Rivaroxaban

##### Indications<sup>9</sup>

1. Stroke risk reduction in NVAF.
2. DVT and PE treatment.
3. Reduction in risk of DVT and PE recurrence.
4. DVT prophylaxis after knee and hip replacement surgery.

##### Contraindications<sup>9</sup>

1. Active pathological bleeding.
2. Severe hypersensitivity reaction to rivaroxaban (e.g. anaphylactic reactions).
3. Mechanical heart valves.

DVT, deep vein thrombosis; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism.

## Discontinuation for Surgery, Procedures

Rivaroxaban should be stopped at least 24 hours before procedures. Consider stopping the drug 48 hours before a procedure in patients with renal dysfunction. The drug should be restarted as soon as adequate postoperative hemostasis has been established. Consideration should be given to a parenteral anticoagulant if oral medications cannot be taken immediately after the procedure.<sup>9</sup>

## Clinical Trials

Rivaroxaban was compared to warfarin in the ROCKET AF trial, where it showed efficacy in the reduction of stroke and non-central nervous system embolism in patients with NVAF at moderate or high risk for stroke. Major bleeding rates were comparable to warfarin.<sup>10</sup>

In a pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies, the single-drug approach with rivaroxaban resulted in similar efficacy to standard therapy (enoxaparin 1 mg/kg twice daily and warfarin) and was associated with a lower rate of major bleeding (46% relative risk reduction, 0.7% absolute risk reduction).<sup>11-13</sup> In EINSTEIN-EXT, patients on placebo had a significantly greater rate of recurrent VTE than patients on rivaroxaban (42 events vs. 8 events, HR [95% CI]: 0.18 [0.09–0.39],  $P < 0.0001$ ).<sup>11</sup>

In the RECORD trials, patients taking rivaroxaban 10 mg daily had significantly lower rates of postoperative VTE than patients taking enoxaparin 40 mg daily, with comparable bleeding events.<sup>14-16</sup>

## APIXABAN

### Pharmacodynamics/Mechanism of Action

Apixaban is a selective factor Xa inhibitor. It does not require antithrombin to exert its antithrombotic activity. The drug inhibits free and clot-bound factor Xa as well as prothrombinase activity. It has no direct effect on platelet aggregation but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban decreases thrombin generation and thrombus development.<sup>17</sup>

As a result of factor Xa inhibition, apixaban prolongs clotting tests such as prothrombin time, INR and aPTT. However, changes observed in these clotting tests at the expected therapeutic dose are small, subject to a

high degree of variability and not useful in monitoring the anticoagulation effect of apixaban.<sup>17</sup> The drug is metabolized in the liver by the cytochrome P450 enzyme's 1A2, 2C8, 2C9, 2C19, 2J2 and 3A4 (primary) substrates. Excretion is 27% renal and the rest fecal. The half-life of apixaban is 12 hours.<sup>2</sup>

## Indications/Contraindications

Indications and contraindications for apixaban are listed in Box 3.<sup>18</sup>

## Dosing

Dosing guidelines<sup>19</sup> for apixaban are as follows:

- For stroke reduction in NVAF: 5 mg twice daily in most patients; 2.5 mg twice daily in patients with at least two of the following — age  $\geq 80$  years, body weight  $\leq 60$  kg, serum creatinine  $\geq 1.5$  mg/dL — or in patients taking drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (e.g. ketoconazole, itraconazole, ritonavir and clarithromycin). No dose adjustment is required for patients with mild, moderate or severe renal impairment alone. There is also no dose adjustment in NVAF patients with end-stage renal disease maintained on hemodialysis, unless they satisfy two of the aforementioned dose-reduction criteria.
- For DVT/PE treatment and reduction in risk of recurrence: 10 mg twice daily for 7 days, followed by 5 mg twice daily. Following 6 months of treatment, a dose of 2.5 mg twice daily is recommended to reduce the risk of recurrent DVT/PE. No dose adjustment is needed in patients with renal impairment.
- For prophylaxis of DVT after hip or knee replacement surgery: 2.5 mg twice daily, 12 to 24 hours after surgery, for 35 days after hip replacement or for 12 days after knee replacement surgery. No dose adjustment is needed in patients with renal impairment.
- No dose adjustment is required in mild hepatic impairment (Child-Pugh A). Dosing recommendations cannot be provided in patients with moderate hepatic impairment (Child-Pugh B). Apixaban is not recommended in patients with severe hepatic impairment (Child-Pugh C).

## Discontinuation for Surgery, Procedures

Apixaban should be discontinued at least 48 hours prior

### Box 3. Apixaban

#### Indications<sup>18</sup>

1. Stroke risk reduction in NVAF.
2. DVT/PE treatment and reduction in risk of recurrence.
3. Prophylaxis of DVT after hip or knee replacement surgery.

#### Contraindications<sup>18</sup>

1. Active pathological bleeding.
2. Severe hypersensitivity reaction to apixaban (e.g. anaphylactic reactions).
3. Mechanical heart valves.

DVT, deep vein thrombosis; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism.

to surgery and interventions with moderate or high risk of unacceptable or clinically significant bleeding. The drug can be discontinued at least 24 hours prior to surgery and interventions with low risk of bleeding or where bleeding would not be in a critical site and could be easily controlled. Bridging therapy is not needed. Apixaban should be restarted postoperatively as soon as adequate hemostasis has been established.<sup>19</sup>

#### Clinical Trials

In the ARISTOTLE study, apixaban was found to be superior to warfarin (21%/year relative risk reduction, 0.33%/year absolute risk reduction) in reducing the risk of stroke and systemic embolism in the setting of NVAF. Purely ischemic strokes occurred with similar rates on both drugs. Major bleeding rates were less with apixaban than with warfarin (31%/year relative risk reduction, 0.96%/year absolute risk reduction).<sup>20</sup>

In the AVERROES study, apixaban was superior to aspirin (81–324 mg daily) in reducing the risk of stroke and systemic embolism (55%/year relative risk reduction, 2.01%/year absolute risk reduction). The study was stopped early given the significant outcome discrepancy.<sup>21</sup>

In the AMPLIFY study, fixed-dose apixaban was noninferior to conventional therapy (subcutaneous enoxaparin followed by warfarin) for the treatment

of acute VTE and was associated with less major or clinically relevant nonmajor bleeding (5.4% absolute risk reduction).<sup>22</sup> The AMPLIFY-EXT study (apixaban at 5 mg or 2.5 mg vs. placebo) showed that extended anticoagulation with apixaban at either the treatment dose or the prophylactic dose reduced the risk of recurrent VTE without increasing the rate of major bleeding.<sup>23</sup>

In the ADVANCE-2 (post-knee replacement surgery) and ADVANCE-3 (post-hip replacement surgery) studies, fixed-dose apixaban at 2.5 mg twice daily was associated with lower rates of postoperative VTE and comparable bleeding rates to enoxaparin 40-mg subcutaneous injections daily.<sup>24,25</sup>

## EDOXABAN

### Pharmacodynamics/Mechanism of Action

Edoxaban is an oral anticoagulant that reversibly and directly inhibits factor Xa.<sup>26</sup> By inhibiting factor Xa, edoxaban decreases thrombin generation and thrombus development. The drug also indirectly inhibits platelet aggregation. Edoxaban is minimally metabolized in the liver by the cytochrome P450 enzyme's 3A4 substrate. Its half-life is 10–14 hours, with 50% of the drug being renally excreted.<sup>2</sup>

### Indications/Contraindications

Indications and contraindications for edoxaban are listed in Box 4.<sup>27</sup>

### Box 4. Edoxaban

#### Indications<sup>27</sup>

1. Reduction in risk of stroke and systemic embolism in patients with NVAF.
2. Treatment of DVT and PE following 5–10 days of initial therapy with a parenteral anticoagulant.

#### Contraindications<sup>27</sup>

1. Patients with active pathological bleeding.
2. Mechanical heart valves.
3. Moderate to severe mitral stenosis.

DVT, deep vein thrombosis; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism.

## Dosing

Dosing guidelines<sup>27</sup> for edoxaban are as follows:

- For stroke prophylaxis in NVAF: 60 mg once daily in patients with CrCl > 50 to ≤ 95 ml/min. Edoxaban should not be used in patients with a CrCl > 95 ml/min, as the higher rate of drug metabolism in such patients was associated with an increased rate of ischemic stroke compared to patients treated with warfarin. Reduce the dose to 30 mg once daily in patients with CrCl of 15–50 ml/min. Avoid use in patients with a CrCl < 15 ml/min. There is no data regarding the use of edoxaban in hemodialysis patients.
- For treatment of DVT and PE: 60 mg once daily. The dose is reduced to 30 mg once daily in patients with CrCl of 15–50 ml/min or body weight ≤ 60 kg or who use certain P-glycoprotein inhibitors.
- Edoxaban should not be used in patients with moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C).

## Discontinuation for Surgery, Procedures

Edoxaban should be discontinued at least 24 hours before invasive or surgical procedures because of the risk of bleeding. It should be restarted afterward as soon as adequate hemostasis has been established.<sup>28</sup>

## Clinical Trials

In the ENGAGE AF-TIMI 48 study, edoxaban was noninferior to warfarin for the primary efficacy endpoint of stroke or systemic embolization in the setting of NVAF (HR: 0.68, 95% CI: 0.55–0.84), and the rates of cardiovascular death with edoxaban and warfarin were 2.95% per year versus 3.59% per year, respectively. Edoxaban also was associated with less major bleeding in NVAF patients compared to warfarin (HR: 0.80, 95% CI: 0.70–0.91, P<0.001). In the same study population, edoxaban was associated with lower rates of intracranial hemorrhage (0.5% vs. 1% per year) but with a higher rate of gastrointestinal bleeding events (1.8% vs. 1.3% per year) compared to warfarin, respectively. In patients with CrCl > 95 ml/min, the use of edoxaban was associated with an increased risk of ischemic stroke compared to warfarin.<sup>26</sup>

In the overall Hokusai-VTE study population, edoxaban 60 mg daily was noninferior to warfarin for the primary efficacy endpoint of recurrence of symptomatic VTE (3.2% vs. 3.5%, respectively), with a 19% relative risk reduction (1.8% absolute risk reduction) of clinically relevant bleeding events in patients with VTE.<sup>26</sup>

**Table 1.** Properties of four FDA-approved novel anticoagulants

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
FDA approval	Stroke prophylaxis in NVAF; DVT/PE treatment and prophylaxis	Stroke prophylaxis in NVAF; DVT/PE treatment and prophylaxis	Stroke prophylaxis in NVAF; DVT/PE treatment and prophylaxis	Stroke prophylaxis in NVAF; DVT/PE treatment only
Half-life	12–17 hours	5–13 hours	12 hours	10–14 hours
Dosage forms	75 mg, 150 mg	10 mg, 15 mg, 20 mg	2.5 mg, 5 mg	15 mg, 30 mg, 60 mg
Dosing frequency	Twice a day	Twice a day for 3 weeks (loading dose in DVT/PE treatment); otherwise daily	Twice a day	Daily
Pregnancy class <sup>2</sup>	C	C	B	C

DVT, deep vein thrombosis; FDA, U.S. Food and Drug Administration; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism.

## ANDEXANET ALFA

Andexanet alfa is a recombinant engineered version of human factor Xa that acts as a factor Xa decoy and retains high affinity for all factor Xa inhibitors.<sup>29</sup> Therefore, the drug acts as a novel antidote to the anticoagulant effects of factor Xa inhibitors.<sup>29</sup>

The results of the phase 3 ANNEXA-R study demonstrated that andexanet alfa met the primary endpoint with high statistical significance. An intravenous bolus of andexanet alfa was associated with significant and immediate reversal of the anticoagulant activity of rivaroxaban.<sup>30</sup> Andexanet alfa also is being studied in the (phase 3) ANNEXA-A study for the reversal of the anticoagulant effects of apixaban. The drug is not yet approved by the FDA.

## CONCLUSIONS

Novel oral anticoagulants appear to offer physicians and patients multiple new options for anticoagulation in the setting of nonvalvular atrial fibrillation, deep vein thrombosis and pulmonary embolism treatment as well as venous thromboembolism prophylaxis post-hip/knee replacement surgery. In general, the new agents offer similar clinical outcomes to warfarin or enoxaparin with comparable bleeding profiles. The decision on what agent to use depends on indication, comorbid conditions, availability and physician experience. The cost of the NOACs is similar across the board, approximately \$300/month. Warfarin is ultimately less costly to use chronically, but has its drawbacks as previously noted.

The current lack of approved, standardized “NOAC level” tests makes use in some populations, such as the morbidly obese or the extremely underweight, quite challenging. In addition, the lack of such testing does not allow for objective stroke or venous thromboembolism risk assessment in the setting of missed doses or bleeding risk assessment in the setting of overdosage. Although there are no strong data to suggest NOAC dose adjustments or recommendations against NOAC use in morbidly obese patients, the use of warfarin in this population is likely safer and more predictable. The ability to readily check INR in patients on warfarin anticoagulation provides valuable information about the patient’s status and, thus, risk of thrombosis versus bleeding.

The advent of reliable reversal agents and potential “NOAC level” laboratory tests would certainly make their use more attractive in the future.

### Patient-Friendly Recap

- Patients with atrial fibrillation require anticoagulant medication to prevent stroke and other complications from blood clots.
- Warfarin is the drug traditionally prescribed to these patients despite having certain drawbacks, such as interactions with other medications and the need for constant monitoring.
- The authors reviewed the literature on a series of novel oral anticoagulants, new drugs developed for these conditions.
- Overall, clinical outcomes are similar among the novel and traditional anticoagulants. Choosing the best drug depends on individual patient factors.

### Conflicts of Interest

None.

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