Non–Vitamin K Antagonist Oral Anticoagulants: The Clinician’s New Challenge

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Oral anticoagulation medications are commonly prescribed to patients for a variety of conditions. The mainstay of such therapy has been vitamin K antagonists (VKAs), primarily warfarin. The emergence of non-VKA oral anticoagulants, also referred to as novel oral anticoagulants (NOACs) has changed many patients’ therapeutic options for anticoagulation. These drugs have proven efficacy in the prevention and management of thrombus, with similar risks of bleeding.

Patients taking these medications present a unique challenge for clinicians, especially in the performance of invasive procedures and during acute hemorrhage. Moreover, standard coagulation studies provide an unclear picture of the NOACs’ effects. For clinicians, it is important to understand the pharmacologic properties of these agents and their effects on common coagulation tests. In the present review, we cover NOACs’ approved use in the United States, pharmacologic properties, and contraindications, along with periprocedural management and treatment strategies for patients with bleeding complications.

Factor Xa Inhibitors

**Rivaroxaban**

Rivaroxaban (Xarelto; Janssen Pharmaceuticals) is an oral direct factor Xa inhibitor. It is approved in the United States for anticoagulation for thrombus prevention in nonvalvular atrial fibrillation (NVAF) and prevention of venous thromboembolism (VTE) in patients undergoing elective total hip or knee arthroplasty. It is also approved for the treatment and reduction of recurrent of deep vein thrombosis and pulmonary embolism. No specific agent is available to reverse its effects.
Apixaban

Apixaban (Eliquis; Bristol-Myers Squibb) is another oral direct factor Xa inhibitor. It is approved for reduction of embolic complications caused by NVAF and for the management and prevention of VTE, including recurrent VTE and VTE after total hip or and total knee arthroplasty. It has the same predictable PD and PK effects as other NOACs, so no routine coagulation monitoring is required. Again, no specific reversal agent is available.

Apixaban has a peak plasma concentration at 1 to 3 hours, and its half-life is approximately 12 hours, up to 15 hours in elderly patients. It is metabolized mainly by the liver and excreted in urine and feces. Dose reductions are indicated for patients with NVAF and any of the following criteria: aged 80 years or older, body weight less than 60 kg, serum creatinine level more than 1.5 mg/dL, and end-stage renal disease managed with hemodialysis (HD); no dose reduction is required in patients receiving HD who meet none of the other criteria. Mild hepatic impairment requires no dose adjustment, but apixaban should be avoided in patients with moderate to severe hepatic impairment (Table 2).

When apixaban is administered with a strong dual inhibitor of CYP3A4 and P-gp (ketoconazole, itraconazole, or clarithromycin), a reduced dose of 2.5 mg twice per day is recommended, and patients already receiving a reduced apixaban dose should avoid concomitant use with these agents. Strong dual inducers of CYP3A4 and P-gp (rifampin, carbamazepine, phenytoin, and St John’s Wort [Hypericum perforatum], macrolide antibiotics) should be used with caution.

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Rivaroxaban prolongs prothrombin time (PT), with a greater sensitivity than activated partial thromboplastin time (aPTT). Its effects on these clotting assays are strongly influenced by the reagents used, making quantitative assessment unreliable. The international normalized ratio (INR) should not be applied to NOACs, because it is validated only for VKAs. Thrombin time (TT) and ecarin clotting time (ECT) are not affected by Xa inhibitors. Factor Xa chromogenic assay, performed with appropriate calibration and plasma control samples, can be used to measure the effect of rivaroxaban (Table 1), and rotational thrombelastometry may help determine its associated coagulopathic deficiencies.
ment. It has been shown to be less effective in patients with NV AF and a CrCl rate above 95 mL/min, whose kidney function should be assessed before treatment is started.

Changes in PT, aPTT, and anti–factor Xa activity have been reported to be correlated closely with plasma edoxaban concentrations, with anti–factor Xa activity the most sensitive indicator, followed by PT. As with other agents, no specific reversal agent is available for edoxaban.

### Table 1.
**Properties of Non–Vitamin K Oral Anticoagulants**

<table>
<thead>
<tr>
<th>Property</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.5-2</td>
<td>1-3</td>
<td>2-4</td>
<td>1-2</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>12-17</td>
<td>8-15</td>
<td>7-13</td>
<td>10-14</td>
</tr>
<tr>
<td>Clearance Time, h</td>
<td>Renal 80%, bile 20%</td>
<td>Hepatic 66%, renal 33%</td>
<td>Hepatic 75%, renal 25%</td>
<td>Hepatic 50%, renal 50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usefulness of Laboratory Assay</th>
<th>PT</th>
<th>aPTT</th>
<th>ACT</th>
<th>ECT</th>
<th>TT</th>
<th>Chromographic anti-Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>Not useful</td>
<td>Useful</td>
<td>Possibly useful</td>
<td>Useful</td>
<td>NA</td>
<td>Most useful</td>
</tr>
<tr>
<td>aPTT</td>
<td>Useful</td>
<td>Not useful</td>
<td>Not useful</td>
<td>NA</td>
<td>NA</td>
<td>Most useful</td>
</tr>
<tr>
<td>ACT</td>
<td>Useful</td>
<td>Not useful</td>
<td>Not useful</td>
<td>NA</td>
<td>NA</td>
<td>Most useful</td>
</tr>
<tr>
<td>ECT</td>
<td>Useful</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Most useful</td>
</tr>
<tr>
<td>TT</td>
<td>Most useful</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Most useful</td>
</tr>
<tr>
<td>Chromographic anti-Xa</td>
<td>NA</td>
<td>Most useful</td>
<td>Most useful</td>
<td>Most useful</td>
<td>Most useful</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACT, activated clotting time; aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; NA, not available; PT, prothrombin time; T<sub>max</sub>, time to maximum concentration; TT, thrombin time.

### Edoxaban
In the United States, Edoxaban (Savaysa; Daiichi Sankyo) is approved for the prevention of NVAF embolic complications and VTE management after initial management with parenteral anticoagulation for 5 to 10 days. A direct factor Xa inhibitor, its peak plasma concentration is achieved after approximately 1 to 2 hours, and its half-life is 10 to 14 hours. Edoxaban has lower protein binding than the other drugs in the class, which is important for patients undergoing HD. Its excretion is approximately 50% renal and 50% hepatic. Possible interaction with P-gp inhibitors (eg, quinidine, verapamil, amiodarone), may cause an increase in edoxaban exposure. Dose reduction is recommended in patients with concomitant use of these inhibitors, moderate renal impairment, or bodyweight less than 60 kg. Edoxaban is not recommended in Child-Pugh class B or C hepatic impairment. It has been shown to be less effective in patients with NVAF and a CrCl rate above 95 mL/min, whose kidney function should be assessed before treatment is started.

Changes in PT, aPTT, and anti–factor Xa activity have been reported to be correlated closely with plasma edoxaban concentrations, with anti–factor Xa activity the most sensitive indicator, followed by PT. As with other agents, no specific reversal agent is available for edoxaban.

### Direct Thrombin Inhibitors
#### Dabigatran
An oral, competitive, and reversible direct thrombin inhibitor, dabigatran (Pradaxa; Boehringer Ingelheim) is a prodrug, converted to the active form after oral administration. It is approved in the United States for
Table 2. Recommended Dosages for Non–Vitamin K Oral Anticoagulants by Indication*4,8,9

<table>
<thead>
<tr>
<th>Property</th>
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<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVAF</td>
<td>150 mg twice daily for CrCl &gt;30 mL/min; 75 mg twice daily for CrCl 15-30 mL/min</td>
<td>20 mg/d for CrCl ≥50 mL/min; 15 mg/d for CrCl ≥15-50 mL/min</td>
<td>5 mg twice daily; 2.5 mg twice daily for ≥ risk factors*</td>
<td>60 mg/d for CrCl 50-95 mL/min; 30 mg/d for CrCl 15-50 mL/min</td>
</tr>
<tr>
<td>VTE treatment</td>
<td>150 mg twice daily for CrCl &gt;30 mL/min (after &gt;5-d parenteral treatment)</td>
<td>15 mg twice daily for 21 d, then 20 mg/db</td>
<td>10 mg twice daily for 7 d, then 5 mg/dc</td>
<td>60 mg/d; 30 mg/d for CrCl 15-50 mL/min or weight &lt;60 kg (after &gt;5-d parenteral treatment)</td>
</tr>
<tr>
<td>VTE prophylaxis after hip or knee arthroplasty</td>
<td>NA</td>
<td>10 mg/d (12 d for knee and 35 d for hip arthroplasty)</td>
<td>2.5 mg/d (12 d for knee and 35 d for hip arthroplasty)</td>
<td>NA</td>
</tr>
<tr>
<td>Reducing risk of recurrent VTE</td>
<td>150 mg twice daily for CrCl &gt;30 mL/min</td>
<td>20 mg/d</td>
<td>2.5 mg twice daily</td>
<td>NA</td>
</tr>
<tr>
<td>Conditions with which to avoid use</td>
<td>NVAF: CrCl &lt;15 mL/min; VTE: CrCl &lt;30 mL/min</td>
<td>Child-Pugh class B or C; NVAF: CrCl &lt;15 mL/min; VTE: CrCl &lt;30 mL/min</td>
<td>Severe hepatic impairment</td>
<td>NVAF: CrCl &gt;95 mL/min</td>
</tr>
</tbody>
</table>

* Risk factors include age older than 80 years, weight less than 60 kg, serum creatinine level above 1.5 mg/dL, and end-stage renal disease with hemodialysis.

b For the remainder of treatment

Abbreviations: CrCl, creatinine clearance; NA, not applicable; NVAF, nonvalvular atrial fibrillation; VTE, venous thromboembolism.

Dabigatran can prolong aPTT/activated clotting time, PT, ECT, and TT; results vary based on the agent used.10,11,18 The TT assay is most sensitive, given that it directly assesses the activity of thrombin.19 If TT and ECT values are normal, dabigatran does not have an anticoagulant effect.11 After TT, the order of sensitivity is ECT, aPTT, and PT.11,19 The HEMOCLOT (HYPHEN BioMed) thrombin inhibitor assay is the preferred assay for monitoring when it is calibrated with dabigatran,9,20 but it is currently unavailable for patient care in the United States.21 Dabigatran affects thromboelastography, yielding a hypocoagulable picture on the graph.22

preventing embolic complications associated with NVAF, managing VTE in patients treated with parenteral anticoagulation for 5 to 10 days, and reducing the risk of recurrent VTE. Like the other agents, it has predictable PD and PK effects, so no routine coagulation monitoring is necessary.9

Dabigatran has its peak effect within 0.5 to 2 hours. In healthy volunteers, a steady state is achieved after administration for approximately 3 days.18 Its half-life is approximately 8 hours (ranging from 12 to 14 hours after multiple doses) and can increase to approximately 13 hours in older adults. It is excreted primarily through the renal route (Table 1). In patients with renal impairment (CrCl, <30 mL/min), its half-life is extended to more than 24 hours. Thus, dosing for this agent is based on the CrCl rate (Table 2).9,18 Coadministration of potent P-gp or CYP3A4 inhibitors (eg, quinidine, ketoconazole, amiodarone, verapamil) increases dabigatran’s plasma concentration, and caution should be exercised in this situation, particularly in patients with renal impairment.18 Its use should be avoided with rifampin.9

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Perioperative Management

The literature lacks evidence-based recommendations for periprocedural management in patients receiving NOACs. The suggested guidelines are largely based on expert opinion and case reports. The basic underlying principles driving these guidelines include assessing the risk of bleeding associated with a procedure and understanding the PK effects of these agents (Table 1).

For minor procedures not associated with a clinically important bleeding risk, recommendations include discontinuing NOACs 18 to 24 hours before the procedure and restarting them 6 hours later. For elective procedures with minor bleeding risk (eg, hernia repairs, hysterec- tomy, endoscopy with biopsy, bladder or prostate biopsy), the NOAC should be discontinued at least 24 hours beforehand, allowing 2 elimination half-lives to pass before the procedure in patients with normal elimination. The NOAC treatment should be resumed 24 hours after these low-bleeding-risk procedures. In patients with impaired elimination pathways, clinicians should hold the NOAC for more than 24 hours, especially dabigatran in patients with renal impairment.

For procedures associated with a moderate or high risk of bleeding, recommendations include discontinuing NOACs at least 48 hours before the scheduled surgical procedure (approximately ≥3 elimination half-lives). At this point, plasma levels should decrease to less than 15% of initial levels; any longer cessation is unlikely to provide additional hemostatic benefit. Conservative recommendations extend the discontinuation period for 5 days before the procedure, particularly in higher-risk populations (eg, patients with CrCl <50 mL/min or aged >75 years), in which elimination of NOACs can be less predictable and more prolonged. Procedures that involve a high risk of bleeding in critical areas (eg, eye, neurologic procedures) may warrant a 5-day discontinuation. Dabigatran should be discontinued at least 72 hours beforehand in patients with a CrCl rate of 50 to 79 mL/min, and at least 96 hours beforehand in those with a CrCl rate of 30 to 49 mL/min.

With a longer disruption of anticoagulation in moderate- to high-risk procedures, the risk of thrombosis must be assessed, and an alternative anticoagulant must be considered. Discontinuing these agents in patients with a moderate risk of thrombosis is based on individual risk. For high-risk patients, including those with proximal deep vein thrombosis (with or without pulmonary embolism in the previous 3 months), recurrent idiopathic VTE, or atrial fibrillation with a history of cardioembolic disease, bridging with another anticoagulant is strongly recommended.

For low–molecular-weight heparin (LMWH), the first dose should be administered 12 hours after the last NOAC dose if LMWH is given twice daily and 24 hours after the last NOAC dose if it is given once daily. In patients with a high risk of bleeding, some recommend starting LMWH 24 hours after the last NOAC dose, regardless of the dosing schedule.

Recommendations for when to restart NOACs after procedures with a moderate to high bleeding risk range from 24 to 72 hours after the procedure. The key to restarting NOACs is the certainty that the bleeding risk is controlled. Postoperative bridging should be considered in patients with postoperative ileus or other reasons for prolonged limitation of enteral medications. The NOAC can be restarted 12 hours after the last dose of LMWH. There should be no overlap in the administration of bridging heparin agents and NOACs, given the rapid onset of action for NOACs.

Management of Acute Hemorrhage

General Considerations

Hemorrhage is a difficult complication in patients receiving anticoagulation treatment, and it can be life threatening. The NOACs lack specific reversal agents. Most current recommendations for managing bleeding complications associated with NOACs stem from small trials involving healthy participants, limited retrospective case series, or expert opinion.
Blood Product Transfusion
Platelet transfusion should be considered for patients with thrombocytopenia or concomitant antiplatelet agents. Administration of fresh frozen plasma containing factors II, VII, IX, and X does not specifically reverse the effect of NOACs, but fresh frozen plasma may be needed if coagulation factors are depleted. No findings in humans support the effectiveness of fresh frozen plasma in reversing the effects of NOACs.

Procoagulant Agents
Vitamin K treatment is effective only with agents or disease that impair vitamin K–dependent coagulation factors (factors II, VII, IX, and X, and proteins C and S); it does not seem to have any effect in reversing the action of NOACs. Antifibrinolytic drugs, such as aminocaproic acid and tranexemic acid, act by inhibiting plasminogen-binding sites, decreasing plasmin formation and fibrinolysis. Some advocate their use in life-threatening hemorrhage with NOACs. Unfortunately, little data support their standard use.
Desmopressin, or DDAVP, acts by enhancing levels of von Willebrand factor and factor VIII. It can be an adjunct, particularly in patients with uremia. Again, a paucity of data supports its use in NOAC-associated bleeding, but its use should be considered in severe bleeding.\textsuperscript{26,31,34}

Prothrombin complex concentrates (PCCs) are pooled plasma products containing various coagulation factors that have been examined as possible reversal agents. Several preparations of PCCs exist, containing various amounts of clotting factors, in both active and nonactive forms; PCCs may also contain varying amounts of low-dose heparin, antithrombin, and proteins C and S. Three-factor PCC contains mainly factors II, IX, and X; 4-factor PCC (4FPCC) adds factor VII.\textsuperscript{12} In the United States, these agents are approved only for treating or preventing bleeding in patients with hemo-

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Figure.
Bleeding management strategy for non–vitamin K antagonist oral anticoagulants (NOACs).\textsuperscript{29,31-36}
\textsuperscript{a}For associated coagulopathy (eg, disseminated intravascular coagulation, dilutional coagulopathy).
\textsuperscript{b}Activated 4-factor prothrombin complex concentrate (FPCC) (FEIBA, Baxter); possibly superior in dabigatran.
\textsuperscript{c}4FPCC (Kcentra, CSL Behring); possibly superior in Xa inhibitors. \textsuperscript{d}3FPCC (Proflnine, Grifols Therapeutics & Bebulin, Baxter). \textsuperscript{e}Tranexamic and aminocaproic acid. Abbreviations: RBC, red blood cell; rFVIIa, recombinant factor VIIa. Adapted with permission.\textsuperscript{36}
use in reversing the effects of dabigatran.\textsuperscript{43} Andexanet alfa is a recombinant, modified factor Xa molecule. It acts as an Xa decoy that targets and sequesters both direct and indirect factor Xa inhibitors with high specificity. When bound to this agent, the inhibitors cannot bind to or inhibit the patient’s factor Xa, thus allowing normal hemostatic processes to be restored.\textsuperscript{46,47}

**Management of Bleeding**

**Minor or Moderate Bleeding**

Largely symptom based, the management of minor bleeding can be achieved in most cases with local hemostatic measures along with discontinuation of the NOAC.\textsuperscript{34} Moderate bleeding may present the most challenging management algorithm. If a patient is not experiencing life-threatening bleeding, the risk of thrombosis may be too high to justify the off-label use of procoagulant agents. As with minor bleeding, local control of hemorrhage and supportive care, including transfusion when needed, may provide enough time for the effect of the NOAC to abate.\textsuperscript{34,38}

**Life-Threatening Bleeding**

Aggressive therapeutic intervention is required for severe, life-threatening hemorrhage, including intensive care monitoring, transfusion of blood products, and the off-label use of nonspecific procoagulants. A risk-benefit analysis must be performed in each case to determine whether the use of procoagulants is warranted.\textsuperscript{30,31}

**Conclusion**

With the increasing use of NOACs as a therapeutic option for anticoagulation, it is important to understand their properties and current approved uses in the United States. Although these agents are easy to administer and require no regular monitoring, they present difficulties for clinicians when patients taking them experience acute hemorrhage or need emergency or urgent interven-
tions. Until specific reversal agents become available, management of hemorrhagic complications in these patients will remain nonselective and empiric, requiring a multidisciplinary approach to minimize both bleeding and thrombotic complications.

References


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