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

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Millions of US patients are prescribed oral anticoagulants. Traditionally, oral anticoagulation was achieved with vitamin K antagonists (VKAs). In recent years, non–VKA oral anticoagulants (NOACs) have emerged that provide an effective and convenient alternative to VKAs. These agents possess very different pharmacologic properties from what the medical community has grown accustom to with the VKAs. Thus, a new knowledge base is required for NOACs. One particular challenge with the NOACs is the lack of specific reversal agent, resulting in difficulties correcting the coagulopathy induced by these drugs when needed. A review of the current literature is presented to assist clinicians in gaining knowledge of the NOACs to care for patients.

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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.[1] 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.[2] No specific agent is available to reverse its effects.

Rivaroxaban's pharmacokinetic (PK) and pharmacodynamic (PD) properties are predictable, permitting fixed dosing. Thus, this agent does not require routine coagulation monitoring.[3] It has a rapid onset of 2 to 4 hours and a half-life ranging from 7 to 11 hours, and up to 13 hours in elderly patients. It is eliminated by means of renal (66%) and hepatic (33%) pathways (*Table 1*). Rivaroxaban should be avoided in patients with a creatinine clearance (CrCl) rate less than 15 mL/min or moderate to severe (Child-Pugh class B or C) hepatic impairment or associated coagulopathy (*Table 2*).[4]

Rivaroxaban is a substrate (neither an inducer nor inhibitor) of CYP3A4 and drug transporter P-glycoprotein (P-gp). Because of interactions with these systems, agents to be avoided include azole antimycotics and protease inhibitors for human immunodeficiency virus. Less potent interacting drugs (eg, rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort [*Hypericum perforatum*], macrolide antibiotics) should be used with caution.[1,5]

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.[5,12,13] 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 inbitors.[12] Factor Xa chromogenic assay, performed with appropriate calibration and plasma control samples, can be used to measure the effect of rivaroxaban (*Table 1*),[3] and rotational thrombelastometry may help determine its associated coagulopathic deficiencies.[14]

Apixaban

Apixaban (Eliquis; Bristol-Myers Squibb) is another oral direct factor Xa inhibitor.[15] In the United States, 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.[2] It has the same predictable PD and PK effects as other NOACs, so no routine coagulation monitoring is required.[15] Again, no specific reversal agent is available.[6]

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 2 of the following criteria: aged 80 years or older, bodyweight 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.[6] Mild hepatic impairment requires no dose adjustment, but apixaban should be avoided in patients with moderate to severe hepatic impairment (*Table 2*).[15]

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) decrease the efficacy of the apixaban, and their use should be avoided.[6,15]

Apixaban causes dose-dependent prolongation of PT with varying sensitivity, though to a lesser extent than rivaroxaban.[5] Unlike warfarin, INR does not correlate with apixaban's activity. Its effect on aPTT is concentration dependent, small, and less sensitive than that on PT. The results of these tests vary based on the reagent used, and ECT and TT are insensitive markers for apixaban effects. Chromogenic anti–factor Xa assays are sensitive tests of apixaban activity, but no specific calibration is currently available for apixaban (*Table 1*).[7] Rotational thrombelastometry may help identify coagulopathy caused by apixaban.[14]

Table 1.
Properties of Non–Vitamin K Oral Anticoagulants[1-11]

Property	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Mechanism of Action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
T_{max}	0.5-2	1-3	2-4	1-2
Half-life, h	12-17	8-15	7-13	10-14
Clearance Time, h	Renal 80%, bile 20%	Hepatic 66%, renal 33%	Hepatic 75%, renal 25%	Hepatic 50%, renal 50%
Usefulness of Laboratory Assay				
PT	Not useful	Useful	Possibly useful	Useful
aPTT	Useful	Not useful	Not useful	Possibly useful
ACT	Useful	Not useful	Not useful	NA
ECT	Useful	NA	NA	NA
TT	Most useful	NA	NA	NA
Chromographic anti-Xa	NA	Most useful	Most useful	Most useful

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; NA, not available; PT, prothrombin time; T_{max}, 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.[8] 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.[16] 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.[8]

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.[7] As with other agents, no specific reversal agent is available for edoxaban.[17]

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.[18] It is approved in the United States for

Table 2.
Recommended Dosages for Non–Vitamin K Oral Anticoagulants by Indication[4,6,8,9]

Property	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
NVAF	150 mg twice daily for CrCl >30 mL/min; 75 mg twice daily for CrCl 15-30 mL/min	20 mg/d for CrCl ≥50 mL/min; 15 mg/d for CrCl ≥15-50 mL/min	5 mg twice daily; 2.5 mg twice daily for ≥ risk factors[a]	60 mg/d for CrCl 50-95 mL/min; 30 mg/d for CrCl 15-50 mL/min
VTE treatment	150 mg twice daily for CrCl >30 mL/min (after >5-d parenteral treatment)	15 mg twice daily for 21 d, then 20 mg/d[b]	10 mg twice daily for 7 d, then 5 mg/d[b]	60 mg/d; 30 mg/d for CrCl 15-50 mL/min or weight <60 kg (after >5-d parenteral treatment)
VTE prophylaxis after hip or knee arthroplasty	NA	10 mg/d (12 d for knee and 35 d for hip arthroplasty)	2.5 mg/d (12 d for knee and 35 d for hip arthroplasty)	NA
Reducing risk of recurrent VTE	150 mg twice daily for CrCl >30 mL/min	20 mg/d	2.5 mg twice daily	NA
Conditions with which to avoid use	NVAF: CrCl <15 mL/min; VTE: CrCl <30 mL/min	Child-Pugh class B or C; NVAF: CrCl <15 mL/min; VTE: CrCl <30 mL/min	Severe hepatic impairment	NVAF: CrCl >95 mL/min

[a] 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.

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 CYP3A[4] 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]

Dabigatran can prolong aPTT/activated clotting time, PT, ECT, and TT; results vary based on the reagent 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.[7,11] 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]

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, hysterectomy, 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.[23] The NOAC treatment should be resumed 24 hours after these low-bleeding-risk procedures.[24] In patients with impaired elimination pathways, clinicians should hold the NOAC for more than 24 hours, especially dabigatran in patients with renal impairment.[23]

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).[25-28] 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.[25] 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.[23]

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.[24,25] 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.[25]

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.[23-25] Postoperative bridging should be considered in patients with postoperative ileus or other reasons for prolonged limitation of enteral medications.[23] The NOAC can be restarted 12 hours after the last dose of LMWH.[24] 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.[29-31] The

Figure provides a management algorithm that may assist in the care of bleeding complications associated with these medications.

The approach to acute hemorrhage in a patient taking NOACs begins with basic assessment, including hemodynamic status; location of bleeding; concurrent medications, particularly those affecting hemostasis; medical history, including renal function; and timing of the last NOAC dose. Laboratory tests are essential, including hemoglobin level, platelet count, aPTT, PT/INR, electrolyte panel, and renal function tests.[30,31] In general, normal aPTT and PT values preclude a substantial clinical effect by the NOACs.[32] Where thrombelastometry is readily available, its findings can shed light on the coagulation cascade. More specialized testing as listed previously may not be readily available in emergency situations.

One advantage of NOACs is their short half-lives compared with VKAs. Discontinuing the NOAC might be sufficient in patients with minor and non–life-threatening hemorrhage.[33] Such cessation must be balanced against the risk of thrombotic complications. Intravenous fluid resuscitation and red blood cell transfusion, when applicable, are used to maintain circulating volume. Maintaining an appropriate body temperature avoids exacerbation of coagulopathy. Hemodynamic support with vasopressors may be needed.[29,30] If the NOAC was ingested several hours before the bleeding event, gastric lavage and administration of activated charcoal may be helpful.[33]

Local hemostatic pressure and agents can also be used. Diagnostic studies and therapeutic procedures can help identify and possibly manage the source of bleeding. Endoscopic interventions may be used to locate and treat areas of gastrointestinal bleeding.[37] Interventional radiographic procedures have the potential to stop bleeding through embolization techniques, but they require vascular access, which carries a bleeding risk.[31]

Dabigatran is primarily excreted by the kidneys. Diuresis may speed elimination,[19] as may HD.[30] Unfortunately, HD requires dialysis access, risking additional hemorrhage. It also may not be feasible given the time needed to prepare and perform the treatment.

No specific agent is currently available to attenuate the anticoagulant effect of NOACs, but empiric reversal strategies have been used. All of the proposed agents have varying effects on the coagulation cascade, and they are all procoagulants that may result in unintended thrombotic events.

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.[7,29] Fresh frozen plasma contains factor II. Direct thrombin inhibitors prevent conversion of factor II to IIa; thus, they will prevent activation of the administered factor II.[38] Cryoprecipitate contains fibrinogen, factors VIII and XIII, and von Willebrand factor. Although helpful in patients with factor deficiencies, it theoretically has no role in the correction of NOAC-associated coagulopathy.[12]

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.[29]

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.[26,30] Unfortunately, little data support their standard use.

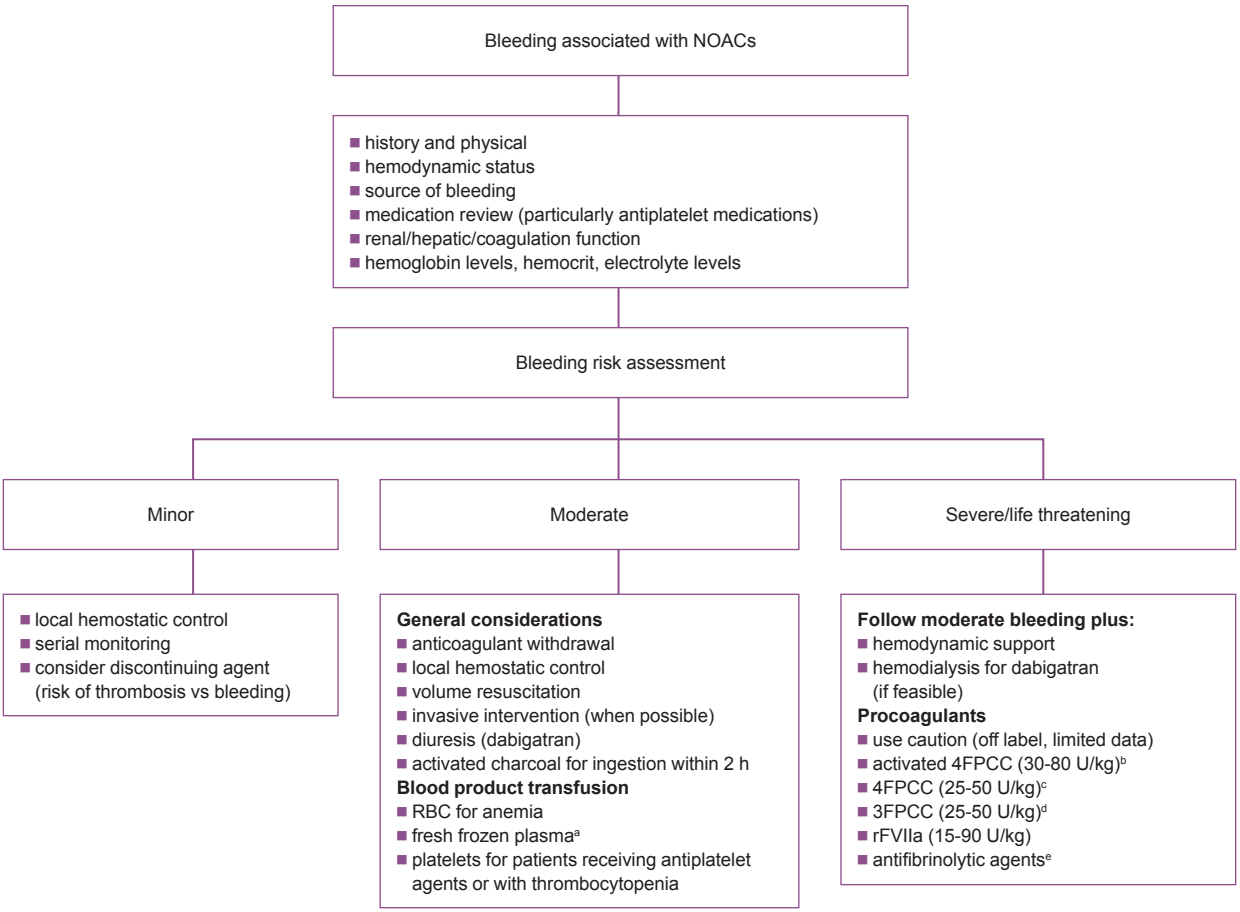

Figure.
Bleeding management strategy for non–vitamin K antagonist oral anticoagulants (NOACs).[29,31-36]
[a]For associated coagulopathy (eg, disseminated intravascular coagulation, dilutional coagulopathy).
[b]Activated 4-factor prothrombin complex concentrate (FPCC) (FEIBA, Baxter); possibly superior in dabigatran.
[c]4FPCC (Kcentra, CSL Behring); possibly superior in Xa inhibitors. [d]3FPCC (Profilnine, Grifols Therapeutics & Bebulin, Baxter). [e]Tranexamic and aminocaproic acid. *Abbreviations*: RBC, red blood cell; rfVIIa, recombinant factor VIIa. Adapted with permission.[36]

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.[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.[12] In the United States, these agents are approved only for treating or preventing bleeding in patients with hemo-

philia A or B.[29] Nonactivated 4FPCC (Kcentra; CSL Behring) is approved for the treatment of VKA-induced major bleeding.[39] In theory, however, the agents may reduce NOAC-induced bleeding by providing large amounts of factors II and X.[35]

Limited data exist on the efficacy of PCCs in reversing the effects of NOACs in humans. In a small randomized trial, 12 healthy volunteers were given rivaroxaban (20 mg twice per day) or dabigatran (150 mg twice per day) for 2.5 days and were then treated with 50 IU/kg of 4FPCC or saline solution. Patients given rivaroxaban and then treated with the PCC had reversal of their elevated PTT. Those given dabigatran and then PCC continued to have elevated PTT, ECT, and TT values.[40] Another study showed that the administration of activated 4FPCC (FEIBA; Baxter) corrected aPTT and PT values in healthy volunteers given the same 2 NOACs.[41] Among available nonspecific reversal agents, limited data suggest that 4FPCC can improve coagulation profiles in patients given NOACs, particularly activated 4FPCC in patients receiving dabigatran.[38,42,43]

Recombinant factor VIIa is currently approved in the United States to manage and prevent procedure-related bleeding in congenital factor VII deficiencies, hemophilia A or B with inhibitors, and acquired hemophilia. It has a black box warning against use outside those approved situations.[30,34] Data supporting its use in patients taking NOACs are limited; therefore its use is not clearly indicated. Some advocate it as salvage therapy in life-threatening situations.[26,35] However, a review of 35 randomized controlled trials of its off-label use identified a statistically significant increase in the risk of arterial thrombotic events, particularly in elderly patients.[44]

Specific Antidotes

Currently under investigation but not approved by the US Food and Drug Administration are specific antidotes to the NOACs. Idarucizumab, a humanized antibody fragment, is currently in late-phase trials evaluating its use in reversing the effects of dabigatran.[45] 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.[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.[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.[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.[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.

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