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Managing New Oral Anticoagulants in the Perioperative and Intensive Care Unit Setting

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ABSTRACT

Managing patients in the perioperative setting receiving novel oral anticoagulation agents for thromboprophylaxis or stroke prevention with atrial fibrillation is an important consideration for clinicians. The novel oral anticoagulation agents include direct Factor Xa inhibitors rivaroxaban and apixaban, and the direct thrombin inhibitor dabigatran. In elective surgery, discontinuing their use is important, but renal function must also be considered because elimination is highly dependent on renal elimination. If bleeding occurs in patients who have received these agents, common principles of bleeding management as with any anticoagulant (including the known principles for warfarin) should be considered. This review summarizes the available data regarding the management of bleeding with novel oral anticoagulation agents. Hemodialysis is a therapeutic option for dabigatran-related bleeding, while *in vitro* studies showed that prothrombin complex concentrates are reported to be useful for rivaroxaban-related bleeding. Additional clinical studies are needed to determine the best method for reversal of the novel oral anticoagulation agents when bleeding occurs.

ANTICOAGULATION is routinely used in diverse clinical settings, including perioperative venous thromboembolism (VTE) prophylaxis and stroke prevention in patients with atrial fibrillation (AF). Unfractionated heparin, low-molecular-weight heparin, and vitamin K antagonists such as warfarin are widely used but have disadvantages. Although there is no "ideal" anticoagulant, an optimal profile includes, in addition to established efficacy and safety, oral administration, no routine monitoring requirement, a predictable anticoagulant effect, a rapid onset and offset of action, and reversibility.[1] Only a few anticoagulants are acutely reversible, including unfractionated heparin with protamine and vitamin K antagonists with four-component prothrombin complex concentrates. The newer oral anticoagulants (NOACs) include the direct thrombin inhibitor dabigatran etexilate (Pradaxa®, Boehringer-Ingelheim Pharma GmbH, Ingelheim am Rhein, Germany) and the direct factor Xa inhibitors rivaroxaban (Xarelto, Johnson and Johnson/Bayer HealthCare AG, Leverkusen, Germany) and apixaban (Eliquis, Bristol Myers Squibb/Pfizer, Bristol-Myers Squibb House, Uxbridge, United Kingdom).[2] Advantages of these new agents include their relatively rapid onset and offset of action and predictable anticoagulant effect so that routine coagulation monitoring is not required. However, laboratory monitoring may be relevant in certain clinical situations, where an assessment of the anticoagulation status is needed. As the NOACs are

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increasingly replacing older parenteral agents and vitamin K antagonists in clinical practice, it is important to consider that patients treated with these agents will be exposed to different clinical situations (spontaneous or postoperative bleeding, overdose, trauma, and elective or emergent surgical procedures) that require an intervention. There are also increasing concerns about managing patients on these therapeutic agents following trauma or in a perioperative setting. The purpose of this review is (1) to examine the NOACs, focusing on key pharmacologic properties, and (2) to provide management approaches for users of NOACs in the perioperative and critical care settings based on the available literature.

Oral Direct Thrombin Inhibitors

Thrombin has a pivotal role in hemostasis, making it an appealing target for anticoagulant drugs. When thrombin is activated from prothrombin, it converts soluble fibrinogen to insoluble fibrin; activates coagulation factors V, VIII, and XI (which generate more thrombin); and activates platelets (fig. 1).[3] Dabigatran is a reversible direct thrombin inhibitor that directly inhibits free and fibrin-bound thrombin without the need for antithrombin. Dabigatran etexilate is a prodrug that has a rapid onset of action, no reported food interactions, few drug interaction, and does not require routine coagulation monitoring. The peak plasma concentration is reached 1.25–3 h after administration, and it has a half-life of 12–14 h in healthy volunteers.[4] Dabigatran is 35% bound to plasma proteins and undergoes renal excretion, with 80% of the drug entering the urine unchanged. The anticoagulant effect of dabigatran accumulates in the setting of renal insufficiency, and such bioaccumulation correlates well with the degree of renal dysfunction.[5] In contrast to other NOACs that are highly protein bound, the relatively low protein binding of dabigatran allows it to be eliminated to a large extent by hemodialysis.[6] In cases of moderate hepatic impairment, dabigatran can be administered safely and no dose adjustment is necessary.[7]

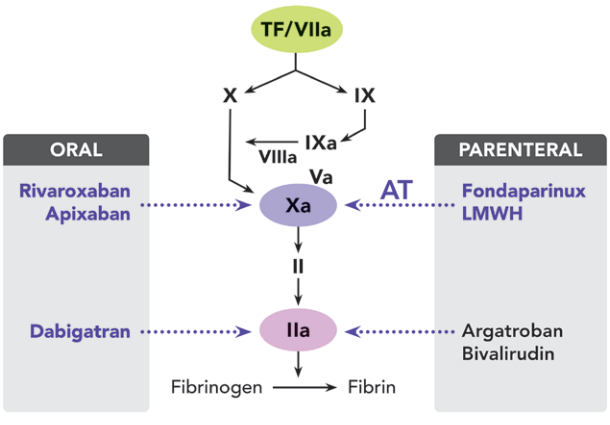

Fig. 1. Effect sites of anticoagulation agents. The new oral anticoagulation agents directly inhibit one of two major targets in the coagulation cascade. Rivaroxaban and apixaban directly inhibit factor Xa, and dabigatran directly inhibits thrombin. The parenteral anticoagulants that inhibit factor Xa include low-molecular-weight heparin (LMWH) and fondaparinux by antithrombin (AT)-dependent binding. Parenteral direct thrombin inhibitors include argatroban, bivalirudin, and desirudin that also directly inhibit thrombin independent of AT.

Dabigatran is approved in the United States, Canada, Europe, and Japan for stroke prevention in patients with non-valvular AF based on the results of the Randomized Evaluation of Long-term anticoagulant therapY (RE-LY) trial in which 150 mg of dabigatran twice-daily was superior to dose-adjusted warfarin with a similar rate of major bleeding.[8] Dabigatran, 75 mg twice-daily, is approved for use in the United States for patients with severe renal insufficiency (CrCl 15–30 ml/min), based on indirect pharmacokinetic modeling and the assumed anticoagulant effect with this level of renal dysfunction. In Europe and Canada, the 75-mg dose is not approved for clinical use and dabigatran is contraindicated in patients with a CrCl < 30 ml/min. Dabigatran is also is approved for VTE prophylaxis following total hip or knee replacement surgery in Europe and Canada, but not the United States. A recent indirect network meta-analysis suggests that treatment with dabigatran offers benefit for the prevention of stroke, systemic embolism, and mortality over antiplatelets and placebo without increased intracranial or extracranial hemorrhage compared to antiplatelet agents.[9] Further investigations are needed to confirm these results.

Oral Direct Factor Xa Inhibitors

Factor Xa is another important target for anticoagulant drugs due to its role as the rate-limiting factor in thrombin generation and amplification, generating the Xa complex that converts prothrombin to thrombin (fig. 1).[2] The direct factor Xa inhibitors inhibit free Factor Xa, Factor Xa in the prothrombinase complex, and Factor Xa found in clots, independent of an antithrombin cofactor.[2,10] This is in contrast to low-molecular-weight heparin, unfractionated heparin, and fondaparinux, which all are dependent on antithrombin to inhibit Factor Xa.

Rivaroxaban

Rivaroxaban is an oral, direct Factor Xa inhibitor that has good bioavailability (80%), is highly protein-bound, and has few drug interactions. Peak plasma concentrations occur within 2–4 h of administration, and rivaroxaban has a half-life of 5–9 h in healthy subjects and 11–13 h in the elderly.[10] It is selective for Factor Xa in relation to other serine proteases.[2] Clearance of rivaroxaban may be decreased to some extent in patients with renal impairment,[11] but its primary mode of clearance is by non-renal mechanisms. It should be noted that although some reports may indicate that approximately 67% of rivaroxaban is eliminated by the kidney, such total renal clearance reflects 33% clearance of active drug and 33% clearance of inactive rivaroxaban, which is not clinically important. Thus, two-thirds of the active rivaroxaban

are cleared by nonrenal mechanisms. Based on pharmacokinetic study, 10-mg rivaroxaban administered once daily offers the best efficacy profile while avoiding excessive bleeding complications.[12] In patients with AF, the recommended rivaroxaban dose is 20 mg daily, although a reduced dose (15 mg daily) is recommended in patients with a CrCl 15–30 ml/min.[13] Due to high plasma protein binding (>90%), rivaroxaban cannot be eliminated during hemodialysis.

Rivaroxaban is approved in the United States, Canada, and Europe for VTE prophylaxis after hip or knee replacement surgery and for stroke prevention in patients with non-valvular AF. Rivaroxaban was recently approved for treatment of deep vein thrombosis, pulmonary embolism, and reduction in the risk of recurrence. In the Regulation of Coagulation in Orthopedic surgery to pRevent Deep venous thrombosis and pulmonary embolism (RECORD) trials, rivaroxaban, 10 mg daily, was superior to enoxaparin 30 mg twice-daily, and 40 mg once-daily for the prevention of VTE after knee and hip replacement, respectively, without a significant increase in the rate of major bleeding.[14–17] In terms of stroke prevention, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial randomly allocated (in a double-blind manner) 14,264 patients with AF to rivaroxaban 20 mg daily (15 mg daily if CrCl 15–50 ml/min) compared to dose-adjusted warfarin and found that rivaroxaban was not inferior to warfarin in efficacy, with no significant difference in major bleeding events.[18] In patients with an acute coronary syndrome, the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS2–TIMI 51) compared rivaroxaban, 2.5 mg or 5 mg daily, to placebo in patients who were receiving aspirin and a thienopyridine (usually clopidogrel). Although the 2.5-mg dose regimen conferred a significant reduction in cardiovascular and all-cause mortality (and also led to more bleeding), the Food and Drug Administration issued a "complete response letter" and requested additional data.[19]

Apixaban

Apixaban is another oral, direct Factor Xa inhibitor with good oral bioavailability (80%), is highly protein bound, reaches peak plasma concentration within 2–3 h after intake, and has limited potential for drug interactions.[10] Apixaban 2.5 mg twice-daily is the recommended dose for VTE prophylaxis based on pharmacokinetic study.[20] In patients who received apixaban 2.5 mg twice-daily for VTE prophylaxis, the risk of major bleeding was not influenced by renal function.[21] Moreover, in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, assessing apixaban 5 mg twice-daily for stroke prevention, patients were excluded only if they had a CrCl < 25 ml/min. For these reasons, no dose adjustment is recommended in patients with mild (CrCl, 50–80 ml/min) or moderate (CrCl, 30–50 ml/min) renal impairment. The half-life in healthy subjects is 8–15 h.[10] Apixaban has been approved in Canada and Europe for VTE prophylaxis after total hip and knee replacement surgery based on the results of the ADVANCE trials.[22,23] Apixaban is currently under Food and Drug Administration review in the United States for this indication. In the ARISTOLE trial, apixaban was superior to dose-adjusted warfarin in preventing stroke and systemic embolism, with a decrease in bleeding complications, and a lower mortality.[24] The Apixaban *Versus* Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) study is noteworthy as it is the only trial comparing treatment with a NOAC, in this case apixaban 5 mg twice-daily, against aspirin (81–325 mg) for stroke prevention in AF.[25] Although it would be expected that apixaban conferred a lower risk for stroke, what is surprising, perhaps, is that this treatment was not associated with more bleeding compared with aspirin.[25]

Monitoring Anticoagulation with the NOACs

Although routine laboratory testing is not required in NOAC-treated patients, except for periodic monitoring of renal function (especially in patients with preexisting renal impairment), coagulation function tests should be ordered for any anticoagulated patient presenting with an acute bleed, suspected overdose, or requiring emergency surgery.[26] Due to the effect of dabigatran on thrombin-mediated conversion of fibrinogen to fibrin, most of the routine coagulation assays will be prolonged except the prothrombin time.[27] The maximum effect of dabigatran on coagulation parameters occurs at the same time as peak plasma concentration. For this reason, the delay between the last dabigatran dose and the time of blood sampling is needed to interpret the tests. The effects of dabigatran can be best measured using the thrombin time or a dilute thrombin time, available as the Hemoclot assay.[28] Other assays that have been studied include the ecarin clotting time, although this test is not widely available.[2,29] The thrombin time provides a direct assessment of thrombin activity and increases linearly with increasing dabigatran concentration; however, experience with this assay indicates that it is overly sensitive to dabigatran levels and, consequently, the thrombin time may be prolonged in the setting of a clinically insignificant dabigatran effect.[28] The Hemoclot assay has better linear correlation to plasma levels of dabigatran and is probably the most reliable method to measure the anticoagulant effect of dabigatran.[28] In the ecarin clotting time assay, prothrombin is converted to meizothrombin, a prothrombin–thrombin intermediate, by the snake venom ecarin, and dabigatran directly inhibits this meizothrombin intermediate in a dose-dependent fashion but this assay is not frequently used.[30] A more universally available test, the activated partial thromboplastin time, can also be used; however, the relationship between dabigatran

Table 1. Preoperative Discontinuation of Dabigatran Based on Renal Function

Renal Function (CrCl, ml/min)	Half-life, h	Timing of Last Dose before Surgery: Normal Bleeding Risk	Timing of Last Dose before Surgery: High Bleeding Risk
>80	13 (11–12)	1 d	2–4 d
50–80	15 (12–34)	1 d	2–4 d
30–50	18 (13–23)	>2 d	>4 d
<30	27 (22–35)	2–5 d	>5 d

CrCl = creatinine clearance (ml/min); d = days.

concentration and partial thromboplastin time is curvilinear, resulting in decreased precision of the assay as plasma dabigatran concentrations increase,[29] and there may be interassay variability in measurements. Nonetheless, the partial thromboplastin time provides a reasonable alternative if other tests are not available and a normal partial thromboplastin time will likely indicate the absence of a clinically important anticoagulant effect. Additional laboratory studies are urgently needed to correlate coagulation assay results with varying plasma levels of dabigatran.

Rivaroxaban and apixaban inhibit factor Xa directly, which is in complex with FVa and independ of antithrombin.[2] Rivaroxaban causes a prolongation of the prothrombin time, although there may be considerable inter-assay variability in such measurements, and has less of an effect on the partial thromboplastin time. However, these tests are not useful for measuring the pharmacodynamic effects of oral factors Xa inhibitors.[31] More recently, a specific assay has been developed for the direct Xa inhibitors that is different from an antiXa assay used to monitor low-molecular-weight heparin, and may provide the optimal method for determining the effect of rivaroxaban, although further studies are needed.[2,32,33] Rivaroxaban produces a concentration-dependent prolongation of clotting parameters on thromboelastometry, including R and K time without significant modification of maximal amplitude, making this assay not useful for routine monitoring.[31] Until now, the lack of readily available means for assessing the degree of anticoagulation remains a notable concern, especially in a life-threatening bleed where point-of-care monitoring or rapid laboratory assays might be required.

Temporary Discontinuation before Surgery and Neuraxial Anesthesia

Before discontinuing any anticoagulant medication, the risk of bleeding must be carefully weighed against the risk of thrombosis. For dabigatran, which is eliminated primarily by renal mechanisms, the timing of discontinuation should be based on patients' CrCl and the bleeding risk associated with the procedure (table 1).[34,35] Renal impairment may be less important in patients taking rivaroxaban, in which a decreased creatinine clearance appears to have a limited effect on the half-life of the drug. In a study of patients with renal impairment who are receiving a single 10-mg dose of rivaroxaban, the mean half-life only increased very slightly from 8.3 h in healthy controls to 9.5 h in patients with severe renal impairment (CrCl < 30 ml/min).[11]

The Working Group on perioperative hemostasis and the French Study Group on thrombosis and hemostasis published recommendations about the perioperative management of NOACs.[36,37] For scheduled surgery or invasive procedures with low risk of bleeding, they recommend interruption 24 h (≈2 half-lives) before the procedure and to restart 24 h after. In case of scheduled surgery or invasive procedures at moderate or high risk of bleeding, a 5 days interruption before surgery is recommended, while treatment should be restarted according to the bleeding risk. For patients at higher thrombosis risk, unfractionated heparin or low-molecular-weight heparin at curative dose should be initiated 12 h after the last dose of oral anticoagulants. Although these recommendations are easy to use and appear sensible, there is a need for prospective studies assessing the efficacy and safety of these (and other) perioperative management protocols for NOAC-treated patients who require an elective surgery/procedure.

The safety of neuraxial anesthesia for patients treated with NOACs will be based on the pharmacokinetic properties of the anticoagulant (table 2).[36] Catheter placement and, to a lesser extent, removal should be considered when anticoagulant concentrations are at their lowest, and patients should be monitored closely for signs of hematoma in the initial days after catheter removal. Specific recommendations for

Table 2. Pharmacokinetics of the New Oral Anticoagulation Agents

	Dabigatran	Rivaroxaban	Apixaban
Route of administration	Oral twice daily	Oral once daily	Oral twice daily
Bioavailability	6.5%	80%	66%
Time to maximal concentration (Tmax)	1.25–3 h	2–4 h	1–3 h
Half-life	12–14 h	5–13 h	8–15 h
Renal excretion	80%	66%	25%
Plasma protein binding	35%	>90%	87%

Table 3. Recommendations for Novel Anticoagulants for Venous Thromboembolic Prophylaxis in the Setting of Peridural/Regional Anesthesia[36]

	Dabigatran	Rivaroxaban	Apixaban
Time between epidural anesthetic technique and next anticoagulant dose	2–4 h	4–6 h	6 h
Time before last anticoagulant dose and epidural catheter removal	NR*	22–26 h	26–30 h
Time between removal of epidural catheter and next anticoagulant dose	6 h	4–6 h	4–6 h

* Dabigatran in not recommended in patients undergoing anesthesia with postoperative indwelling catheters.
NR = not recommended.

managing these agents for venous thromboembolic prophylaxis in the setting of peridural/regional anesthesia are listed in table 3. Rosencher[38] suggests allowing at least two half-lives to pass before catheter removal, at which point only 25% of the drug remains active. Allowing a longer interval would only slightly reduce the drug concentration, because elimination slows after this point.[38] The risk of the residual anticoagulant activity and neuraxial hematoma needs to be weighed against the risk of VTE. However, the authors suggest that anticoagulation should be restarted after 8 h minus the time to reach maximum activity (Tmax), based on the their suggestion that it takes 8 h to establish a stable clot, and allowing time for the peak of anticoagulation to be reached.[38] However, there may be considerable variability in the time needed to attain a dry vascular bed, especially after major orthopedic or oncologic surgery, and longer times may be needed because of the risk of bleeding compared to the risk of VTE.[38] Recommendations for the use of the new anticoagulants in the setting of neuraxial anesthesia have been proposed by Llau *et al.*[39] based on existing guidelines and the pharmacokinetics of each drug (table 3).

A recent report evaluated bleeding rates from 7 days prior until 30 days following invasive procedures for patients receiving dabigatran.[40] Based on 4,591 patients who had a first treatment interruption for an elective surgery or invasive procedure, 24.7% of patients were receiving dabigatran—110 mg, 25.4% were on dabigatran—150 mg, and 25.9% were on warfarin. The procedures included the following: pacemaker/defibrillator insertion (10.3%), dental procedures (10.0%), diagnostic procedures (10.0%), cataract removal (9.3%), colonoscopy (8.6%), and joint replacement (6.2%). The last dose of dabigatran was given a mean of 49 (range: 35–85) h before the procedure, compared to a mean of 114 (range: 87–144) h for the last preprocedure dose of warfarin ($P < 0.001$). There was no significant difference in the rates of periprocedural major bleeding between patients receiving dabigatran, 110 mg (3.8%), or dabigatran, 150 mg (5.1%), or warfarin (4.6%). The relative risk for major bleeding with dabigatran-110 mg *versus* warfarin was 0.83 (95% CI, 0.59–1.17; $P = 0.28$), and with dabigatran-150 mg *versus* warfarin, it was 1.09 (95% CI, 0.80–1.49; $P = 0.58$). Among patients having urgent surgery, major bleeding occurred in 17.8% with dabigatran-110, 17.7% with dabigatran-150, and 21.6% with warfarin: dabigatran-110. There are no published data on perioperative outcomes in patients receiving rivaroxaban or apixaban who require elective or urgent surgery/procedures, although the same management principles should apply that incorporate procedure bleeding risk and drug elimination as with dabigatran-treated patients.

Reversal of the Novel Anticoagulants and Management of Acute Bleeding

Immediate reversal of anticoagulation is often needed in the bleeding patient or patient requiring emergency surgery. Current dosing and indications for these agents are listed in

Table 4. Current Dosing Guidelines for New Oral Anticoagulation Agents

	Dabigatran	Rivaroxaban	Apixiban*
Dosing for atrial fibrillation: normal renal function	150 mg BID	20 mg QD	5 mg BID
Dosing for atrial fibrillation: renal dysfunction	110 mg BID United States: 75 mg BID with CrCl 15–30 ml/min	15 mg QD with CrCl 15–50 ml/min	2.5 mg BID
DVT prophylaxis	220 mg QD	10 mg QD†	2.5 mg BID
Renal dysfunction	150 mg QD Not approved in the United States for this indication	Avoid with CrCl < 30 ml/min	

* For apixaban, no data available for use with CrCl < 15 ml/min or on dialysis. † For hip and knee surgery.
BID = twice a day; CrCl = creatinine clearance; QD = daily.

table 4. Although managing any anticoagulation agent in a bleeding patient is a challenge, it is important to note that warfarin and other vitamin K antagonist agents are not easily reversible with therapies available in the United States, such as vitamin K and/or fresh frozen plasma. Four-component prothrombin complex concentrates (PCCs) are currently preferred in Canada and most European countries and recommended in recent guidelines.[37,41,42] Stopping a NOAC and providing supportive care are the most important consideration and are often sufficient if the bleeding is not severe or if surgery can be delayed. However, when patients present with a major bleeding episode related to these agents and/or require emergency surgery, other measures must be taken.

For any significant bleeding event, initial measures should include volume resuscitation with fluids and/or packed red blood cells, identification of the bleeding source, and attempts at local hemostatic control. If an anticoagulant overdose is the suspected cause, activated charcoal may be effective in preventing additional drug absorption when administered within 1–2 h of ingestion. Activated charcoal has not been used in the clinical setting and is limited by its narrow window of use and inability to use in a perioperative setting.

Hemodialysis or hemoperfusion is another potential option for the emergent removal of anticoagulants. Rivaroxaban and apixaban are too highly protein bound to be effectively removed by these methods, but dabigatran is an appropriate candidate for these therapies.[10] In a study of six volunteers with end-stage renal disease who were given a 50-mg dose of dabigatran before routine hemodialysis, an average of 62% of the active dabigatran was removed after 2 h and 68% after 4 h.[5] Unfortunately, attempting to perform either of these procedures in a bleeding patient in shock may not be possible.[29] Therefore, the use of procoagulant agents should be considered for a life-threatening bleed. However, unlike when fresh frozen plasma or PCCs are used to replace depleted factors II, VII, IX, and X in warfarin-treated patients, the effectiveness of such clotting factor replacement therapies may be limited in NOAC-treated patients who do not harbor deficiencies of clotting factors but in whom there is an ongoing clotting factor inhibitory effect. It may be argued, therefore, that providing supraphysiologic levels of clotting factors may be ineffective in the setting of an ongoing NOAC-related inhibitory effect. On the contrary, such clotting factors may overwhelm such an ongoing inhibitory effect and, in cases of severe bleeding, may replace clotting factors that are depleted due to consumption.

Although fresh frozen plasma is commonly administered for initial control of bleeding in anticoagulated patients, its use as a reversal agent for the NOACs has not been studied in humans.[43] In a study of mice pretreated with dabigatran (4.5 mg/kg or 9.0 mg/kg) before induction of intracranial hemorrhage, fresh frozen plasma administration successfully limited hematoma expansion in the low-dose group but had no effect in the high-dose group and did not significantly decrease mortality. There is insufficient evidence to recommend its use.[43,44]

Recombinant factor VIIa (rFVIIa) is increasingly used in an "off-label" manner as a universal hemostatic and reversal agent. However, it has not been studied in humans for reversal of NOACs, and the results of studies in animal models are inconclusive. The benefit-to-risk balance for rFVIIa must be carefully weighed, as rFVIIa has been associated with an increased risk of arterial thrombosis among elderly patients.[45,46] In several animal models, rFVIIa reversed bleeding time prolongation associated with dabigatran and rivaroxaban, but it did not correct the underlying coagulopathy as suggested by other laboratory markers.[44] In one study, rats received high-dose dabigatran before a standard tail incision, prolonging the bleeding time from 125 s in controls to 1455 s. A 0.5 mg/kg dose of rFVIIa decreased this bleeding time to 135 s. The partial thromboplastin time was 58 s after dabigatran exposure, *versus* 7 s in controls, and administration of rFVIIa reduced this to 27 s. In a similar study that exposed rats to supratherapeutic dabigatran levels, administration of rFVIIa rapidly corrected the bleeding time and preserved this effect for the entire 2-h study period.[47] However, of the coagulation markers examined, only the prothrombin time was completely corrected. The partial thromboplastin time, the ecarin clotting time, and the thrombin time all failed to normalize.[47]

PCCs are available as three-factor (II, IX, X) and four-factor (II, VII, IX, X) varieties that are procoagulant and enhance thrombin generation.[42] The four-factor PCCs have activated and nonactivated forms, and only three-factor PCCs are available in the United States.[44] Small quantities of heparin, antithrombin, protein C, and protein S are added to the concentrates to reduce coagulation activation through endogenous pathways,[48] but caution is required for off-label use as thrombotic events in 1–3% of treated patients have been reported with both formulations.[49,50]

Unlike the other procoagulant agents, four-factor PCCs have been studied as potential reversal agents in humans. In a small, randomized, double-blinded, placebo-controlled trial, 12 healthy men were given dabigatran 150 mg twice-daily or (supratherapeutic) rivaroxaban 20 mg twice-daily for 2.5 days, and subsequently received either a 50 IU/kg bolus of a four-factor PCC or saline.[51] They were switched to the other anticoagulant following a wash-out period and the procedure was repeated. The addition of the PCC completely reversed both the prothrombin time prolongation and inhibition of endogenous thrombin potential associated with rivaroxaban, but only laboratory parameters were evaluated in this study, and no bleeding outcomes were measured in the volunteers. However, dabigatran-associated prolongations in the clotting assays and endogenous thrombin potential lag time were not corrected by the administration of the PCC. Recently, in an animal model, although both rFVIIa and PCC partially corrected laboratory assays (thromboelastography and thrombin generation assay), none of them reduced bleeding induced by rivaroxaban.[52]

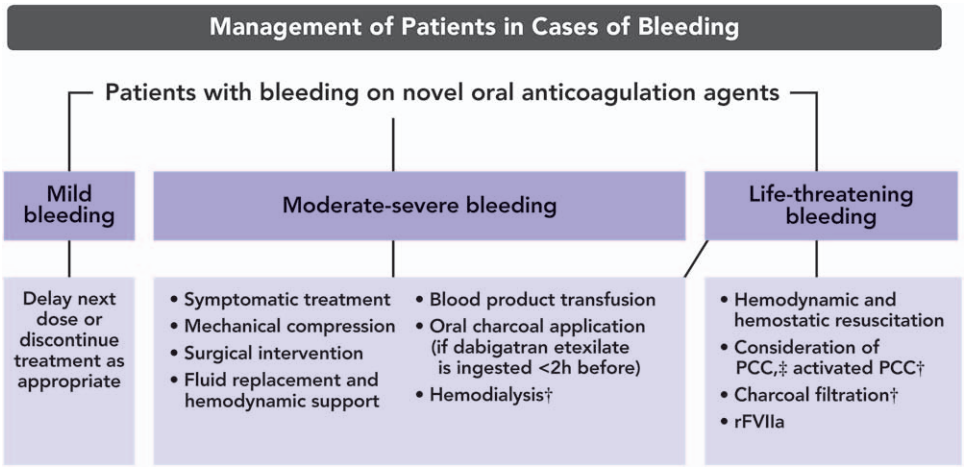

Fig. 2. Management strategies for patients bleeding who have received the novel oral anticoagulation agents. In cases of mild bleeding, stopping or delaying the next dose should be considered. The new agents including dabigatran, rivaroxaban, and recently approved apixiban have relatively short half-lives, so stopping the drug in patients with normal renal function, the anticoagulant effect rapidly decreases compared to warfarin. In patients with moderate to severe bleeding, standard therapeutic approaches should be considered, including supportive care that includes volume resuscitation, hemodynamic support with vasoactive therapy, blood product transfusions as determined by testing, and identification of bleeding source that may require surgical or another intervention. If the agents were taken within ≈2 h of admission, administration of oral activated charcoal should be considered. For dabigatran,† hemodialysis can remove ≈60% of the drug after several hours of dialysis and should be considered in patients with impaired renal function who are bleeding and will have altered clearance. Apixaban and rivaroxaban are highly protein bound and will not be cleared by hemodialysis. However, emergency access for hemodialysis requires vascular access with large bore catheters that may pose additional risk in the anticoagulated patient. For patients with life-threatening bleeding, hemodynamic and hemostatic resuscitation should be considered, with therapy similar to that for a trauma patient including the use of a massive transfusion protocol. Based on current data as discussed in the manuscript, the use of either three-factor or four-factor prothrombin complex concentrates (PCCs) depending on their availability should be considered as they have been shown to reverse or partially reverse the anticoagulation effect of the newer agents. ‡ In patients receiving dabigatran, the use of an activated PCC may be more effective. † However, there are no studies reporting the use of PCCs on actual bleeding in patients, and further studies including the development of specific reversal agents are underway currently. In hypotensive patients, hemodialysis is unlikely to be tolerated, and alternate methods for hemofiltration should be considered if needed. † The use of recombinant activated factor VIIa (rVIIa) decreases bleeding times in animal models, but there are no human studies to determine if this is effective. † = for dabigatran. ‡ = for rivaroxaban and apixiban.

Marlu *et al.*[53] evaluated dabigatran and rivaroxaban reversal using thrombin generation tests evaluating 10 healthy volunteers randomized to receive rivaroxaban (20 mg) or dabigatran (150 mg) orally in a cross-over study, and blood was collected 2 h post-ingestion. Anticoagulation reversal was tested *in vitro* using PCC, rFVIIa, or factor eight inhibitory bypass activity at different concentrations.[53] In rivaroxaban-treated patients, PCC and factor eight inhibitory bypass activity corrected thrombin generation, but rFVIIa only modified the kinetic parameters. In dabigatran-treated patients, PCC increased thrombin generation as determined by area under the curve, but only rFVIIa and factor eight inhibitory bypass activity corrected the altered lag time.[53]

Summary

Common principles of bleeding management as with any anticoagulant (including the known principles for warfarin) should be followed in patients receiving dabigatran. Hemodialysis is an additional, unique therapeutic option for urgently reducing exposure to dabigatran that has not been shown to be useful for other new oral anticoagulants. Ongoing clinical studies are needed to determine the best method for reversal of the NOACs when bleeding occurs. Based on the available evidence, supportive care and interventions as discussed including dialysis for dabigatran should be considered in a bleeding patient and potential therapeutic approaches as listed in figure 2. For rivaroxaban-treated patients, studies in volunteers suggest the PCCs may be effective, but additional studies are needed. When possible, these drugs should be stopped preoperatively at times based on renal function and procedure.[54] Additional drug-specific antidotes are also under investigation.

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