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Mini-Review

Management of Bleeding Complications in Patients on New Oral Anticoagulants

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Abstract

Until recently, the Vitamin K antagonist (VKA) warfarin was the only oral anticoagulant available for clinical use. However, with the US FDA approval of new oral anticoagulants (NOAs) such as dabigatran, rivaroxaban and apixaban, there currently exist several choices. With any anticoagulant, bleeding complications are anticipated and require well defined management guidelines. Unlike warfarin, the NOAs present a clinical challenge in the management of bleeding issues due to their lack of specific antidotes/reversal agents. Given the increasing use of NOAs and anticipated challenges associated with bleeding complications, we provide a management overview for physicians based on current evidence based practices.

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INTRODUCTION

The vitamin K antagonist, warfarin, remains the gold standard for oral anticoagulation for more than half a century. However its narrow therapeutic index, multiple food and drug interactions and need for frequent coagulation monitoring negatively impacts its efficacy, safety and compliance [1]. These limitations prompted the development of new oral anticoagulants (NOAs) with improved efficacy and safety profiles that do not require coagulation monitoring. The NOAs currently approved in the US include dabigatran (Pradaxa®, Boehringer Ingelheim), rivaroxaban (Xarelto®, Bayer, J&J) and apixaban (Eliquis®, Pfizer and Bristol-Myers Squibb) [2]. These agents have been approved for short-term thromboprophylaxis after hip and knee arthroplasty [3-10], treatment of venous thromboembolism (VTE) [11,12] and prevention of VTE in atrial fibrillation (AF) [13-15]. Edoxaban (Lixiana®, Daiichi Sankyo) is another NOA approved for clinical use only in Japan for the prevention of VTE after major orthopedic surgery. The characteristics of these NOAs are summarized in Table 1.

Apart from the aforementioned indications, several clinical studies are being conducted to extend the approved indications for these NOAs, thus a wider use is expected in the future [16-18]. Bleeding complications secondary to anticoagulant use is common and is associated with significant morbidity and mortality [19]. Physicians have become familiar with the management of such issues in patients on conventional anticoagulants such as warfarin, heparin or low molecular weight heparin (LMWH). However, there remains a lack of experience in managing patients treated with NOAs. A recent study indicated that majority (>90%) of non-malignant hematology physician members of the Hemostasis and Thrombosis Research Society (HTRS) and US hemophilia center directors remain concerned about their ability to manage bleeding complications secondary to NOAs due to the lack of established management protocols and experience [20]. Thus, this review provides an evidence based overview to clinicians to help them deal with this pressing issue.

Challenges in managing bleeding complications due to NOAs

Unlike warfarin, managing bleeding complications in patients on NOAs poses several different challenges. First, there are no specific antidotes for reversing the anticoagulant effects of NOAs [21]. Second, conventional coagulation monitoring assays such as the activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin time (TT) are unable to accurately measure the degree of anticoagulation, making it difficult to gauge the severity [22]. Finally, there is increasing use of NOAs for patients with AF and those requiring VTE prophylaxis after knee and hip arthroplasty. This patient group tends to be elderly with multiple comorbidities sometimes requiring concurrent antiplatelet therapies, further complicating bleeding issues [23,24].

Measuring the anticoagulation effect of NOAs during bleeding complications

Though traditional coagulation assays are incapable of accurately measuring the anticoagulant effect of NOAs, rapid assessment of the degree of anticoagulation is still required when assessing bleeding complications. The prothrombin time (PT) is relatively insensitive at therapeutic levels of dabigatran compared to rivaroxaban and apixaban; whereas the

Table 1: Comparative properties of the NOAs dabigatran, rivaroxaban, apixaban and edoxaban.

Characteristic	*Dabigatran*	*Rivaroxaban*	*Apixaban*	*Edoxaban**
Target	Factor IIa (Free and clot -bound thrombin)	Factor Xa	Factor Xa	Factor Xa
Half-life (t ½)	14 –17 hours	5 –9 hours 9-13 hours (elderly)	10 – 14 hours	9 – 11 hours
Elimination	80% renal 20% fecal	66% renal 33% fecal	27% renal 63% fecal	33% renal 66% fecal
Monitoring	Not needed	Not needed	Not needed	Not needed
Peak effect	2 hours	2 - 4 hours	3 – 4 hours	1 – 2 hours
Antidote	None	None	None	None

* Approved only in Japan

activated partial thromboplastin time (aPTT) is more sensitive to dabigatran[25,26]. Unfortunately, different aPTT and PT reagents used amongst different laboratories have different responsiveness to these NOAs making it difficult to standardize results [22].

Given these limitations, modified or novel assays have been developed to help accurately measure the degree of anticoagulation in patients on NOAs though none are standardized or routinely available [27]. The ecarin clotting time (ECT) is a TT-like assay that uses a metalloprotease derived from the venom of the *Echis carinatus* snake that generates meizothrombin from prothrombin, which then converts fibrinogen to fibrin, leading to clot formation[28]. Direct thrombin inhibitors like dabigatran can inactivate meizothrombin prolonging the clotting time, thus making it useful as a monitoring assay [28]. Newer chromogenic based ECT assays prevent influence of results by the levels of fibrinogen and prothrombin [29].

The HEMOCLOT direct thrombin inhibitor assay (HYPHEN BioMed, Neuville Sur Oise, France) is a dilute thrombin time assay that provides accurate, reproducible measures of dabigatran anticoagulant activity and plasma concentrations. It shows linear effects with dabigatran plasma concentrations but no activity to rivaroxaban or apixaban [30]. It is licensed for commercial use in Europe and Canada but not the US. For factor Xa inhibitors such as rivaroxaban and apixaban, commercially available chromogenic anti-factor Xa assays can be used to measure their serum levels based on their respective calibration curves, thus making them sensitive and specific [31-33].

Management of bleeding complications or overdoses in patients on NOAs

Patients bleeding due to NOA use need to undergo rapid clinical assessment in order to confirm hemodynamic stability, identify the bleeding source and evaluate the severity of blood loss (Figure 1) [34]. If hemodynamically unstable, patients should receive life supporting therapies in an intensive care setting such as volume replacement, vasopressors or mechanical ventilation [35]. Packed red blood cells (PRBCs) and platelets can be transfused in response to severe anemia and impaired platelet function secondary to anti-platelet therapies respectively. Hemostasis of the bleeding source for minor bleeding e.g. epistaxis, can be obtained by addressing the potential anatomical defects e.g. cauterization or nasal packing [36]. However, more severe bleeding may necessitate referrals for procedural and surgical hemostasis [36]. Finally, further NOA exposure must be held based on the co-morbidities and assessment of risks of drug discontinuation. For moderate to severe bleeding, given the relatively short half-lives of the NOAs, most of the anticoagulant effect should dissipate within 48 hours [37]. Adjunctive medications such as antiplatelet drugs that may exacerbate the bleeding events should also be held.

Other supportive measures that can be employed to manage bleeding complications are described in **Table 2** and include the following:

Activated charcoal: Though this method has not been evaluated prospectively in clinical trials, *in vitro* experiments have shown that activated charcoal can absorb 99.9% of dabigatran suspended in acidic water [38]. Thus, it can be used to decrease the absorption of recently ingested dabigatran within a couple hours of presentation [39] and may be especially useful in cases of intoxication. Though there is no data regarding the use of activated charcoal to reverse the anticoagulant effect of rivaroxaban, there is preliminary data with apixaban. A study evaluated 18 healthy subjects in a randomized, crossover study of single-dose apixaban (20 mg) administered alone and with activated charcoal given at 2 or 6 hours post-dose to healthy subjects [40]. The area under the concentration-time curve for apixaban without activated charcoal decreased by 50% and 28 %, respectively, when charcoal was administered at 2 and 6 hours post-dose. Furthermore, the mean half-life for apixaban alone which is about 10 to 14 hours decreased to around 5 hours when activated charcoal was administered at 2 or 6 hours post-dose [40]. Thus, activated charcoal may be useful in cases of intoxication with apixaban and potentially with rivaroxaban.

Hemodialysis: Given that only 35% of dabigatran is bound to plasma proteins, hemodialysis should be considered, especially in patients with impaired renal function [41,42]. In an open-label, single-center phase I study, four hour hemodialysis sessions rapidly eliminated a substantial amount of dabigatran with a concomitant marked reduction in its anticoagulant activity [43]. These results suggest that hemodialysis is a suitable approach to eliminate dabigatran in emergency situations. However, this method is limited by the need for placing a central dialysis catheter in a patient who is fully or excessively anticoagulated placing the patient at risk for further bleeding. Although there are no data, dialysis is unlikely to be effective for rivaroxaban and apixaban as they are over 85-90% protein-bound.

Pro-haemostatic agents: Recombinant activated factor VIIa (rFVIIa) activates Factor X leading to thrombin generation

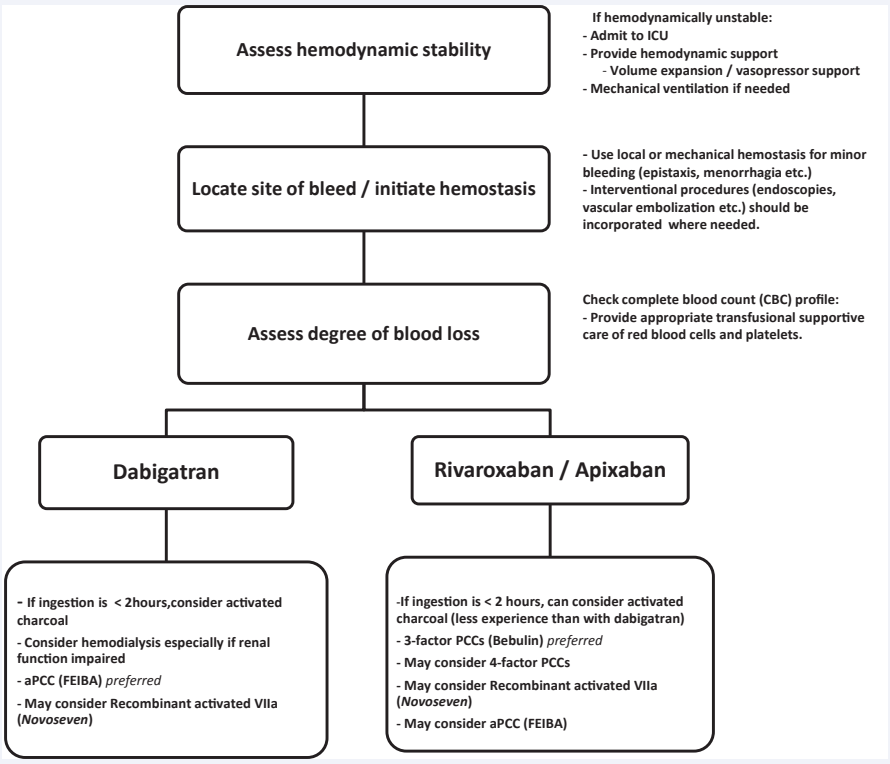

Figure 1 Flow Diagram of New Oral Anticoagulants.

Table 2: Choice of interventions available for the reversal of anticoagulation based on the type of NOA causing the clinical bleeding.

Intervention used	Type of New Oral Anticoagulant (NOA)		
	Dabigatran	**Rivaroxaban**	**Apixaban**
Activated Charcoal	If < 2 hours since last dose ingested	If < 2 hours since last dose ingested	If < 2 hours since last dose ingested
Desmopressin	No clinical evidence	No clinical evidence	No clinical evidence
Hemodialysis	Yes, is dialyzable	Not dialyzable	Not dialyzable
FFP	If DIC or dilutional coagulopathy seen	If DIC or dilutional coagulopathy seen	If DIC or dilutional coagulopathy seen
PRBCs	If symptomatic anemia or Hemoglobin < 8 g/dL	If symptomatic anemia or Hemoglobin < 8 g/dL	If symptomatic anemia or Hemoglobin < 8 g/dL
Platelets	If on anti-platelet therapy or if platelet count < 20,000	If on anti-platelet therapy or if platelet count < 20,000	If on anti-platelet therapy or if platelet count < 20,000
Activated Factor VII (*Novo Seven*)	Anecdotal cases; Not preferred	Anecdotal cases; Not preferred	Anecdotal cases; Not preferred
Non-activated PCCs *(3 or 4 factor PCCs)*	Not preferred	3-factor PCCs (*Bebulin*) preferred	3-factor PCCs (*Bebulin*) preferred
Activated PCCs	Yes; FEIBA preferred	Not preferred	Not preferred
Potential agents available in future	• aDabi-Fab • PER977	• PRT4445 • PER977	• PRT4445 • PER977

and was developed for the treatment of bleeding episodes in hemophiliac patients with Factor VIII and IX inhibitors. It has been used off-label in clinical practice to help reverse life-threatening bleeds caused by NOAs. It decreases the bleeding time in animal models but does not reverse the anticoagulation effect on most other laboratory coagulation tests [44,45]. Other than anecdotal case reports [46,47], there are no randomized controlled studies confirming its benefit in these situations. Furthermore, one must keep in mind, potential serious side effects of rVIIa, including disseminated intravascular coagulation and systemic thrombosis.

Activated 4-factor prothrombin complex concentrate (aPCC) (Factor eight inhibitor bypass activity, FEIBA NF) is a coagulation concentrate that contains activated factor VII and inactive factors II, IX and X. It corrects the anticoagulant effect in animal models[48] as well as plasma from healthy volunteers treated with NOAs [47,49]. Our recommendations for reversing the anticoagulant effects of dabigatran or other Factor Xa inhibitors with aPCC are, an initial dose of 50 units/kg of actual body weight with an additional 50 units/kg being administered every 6-12 hours (up to 200 units/kg/day) until the bleeding ceases. Patients should

be monitored closely for disseminated intravascular coagulation

Coagulation factor replacements: There are no studies evaluating the use of fresh frozen plasma (FFP) in patients with bleeding complications secondary to NOAs. Given that FFP carries risks of volume overload, infusion reactions (including TRALI) and infections, its use is generally not recommended. On the other hand, prothrombin complex concentrates (PCC) seem to be attractive option. The 3-factor PCCs (Bebulin, Baxter and Profilnine SD, Grifols) have relatively similar concentrations of non-activated factors II, IX, and X, with low concentrations of non-activated factor VII. Similarly, 4-factor PCCs (Beriplex) contains large amounts of four non-active vitamin K dependent procoagulant factors (factors II, VII, IX and X) that stimulate thrombin formation.

In a randomized, double-blind, placebo-controlled study, 6 healthy volunteers received rivaroxaban 20 mg twice daily and another 6 volunteers received dabigatran 150 mg twice daily for two and a half days followed by either a single bolus of 50 IU/kg 4-factor PCC or a similar volume of saline [50]. After a washout period, this procedure was repeated with the other anticoagulant treatment. The thrombin formation and prothrombin time was inhibited by rivaroxaban but normalized with the administration of PCC whereas saline infusions had no effect [50]. On the contrary, even though dabigatran increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time, the administration of PCC did not restore these coagulation tests to their normal values [50].

The use of either 3 or 4 factor PCC may increase the risk of thrombosis, with the 3-factor PCC being less likely to do so [51]. In spite of the pre-clinical and human volunteer data on the ability of PCCs to reverse the effects of Factor Xa inhibitors, there are no randomized controlled trials evaluating the various PCCs in human patients with clinically relevant bleeding. Furthermore, there are variations in the amount of factors II, VII, IX and X, and antithrombotic proteins (proteins C and S) contained in the different PCCs making it likely that the different PCCs are not all equivalent in their reversal effects. Nevertheless, it is reasonable to use either 3-factor or 4-factor PCCs in the setting of serious bleeding related to Factor Xa inhibitors. We recommend based on our practice that in order to reverse the anticoagulant effects of rivaroxaban or apixaban, 3-factor PCCs such as Bebulin can be used with an initial dose of 25 units/kg of actual body weight for moderate bleeding not requiring massive transfusion or 50 units/kg if the bleeding is severe enough requiring massive transfusion. This concentrate can be re-dosed every 12 hours for ongoing hemorrhage but patients should be monitored closely for disseminated intravascular coagulation and thrombosis.

EXPERIMENTAL AGENTS IN THE FUTURE

Several novel antidotes to reverse NOAs are in development and early clinical trials. PRT4445 (Portola Pharmaceuticals) or "Andexanet alfa", a novel recombinant protein, binds to Factor Xa inhibitors preventing them from inhibiting the activity of the native Factor Xa, but has no *in vivo* effects on coagulation parameters due to its unique structure [52]. This drug is currently in phase II evaluation as an antidote for the anticoagulant effect of factor Xa inhibitors. Preliminary data released by the company on their phase 2 studies including more than 80 volunteers using andexanet alfa with apixaban or rivaroxaban suggest a dose-dependent and well-tolerated short-term or sustained reversal of their anticoagulation activity [53]. A thrombin double mutant, W215A/E217A, is being developed which shortens thrombin inhibitor-associated aPTT prolongation by thrombin generation in vitro [54]. Recently, a dabigatran-specific antidote known as "aDabi-Fab" has been created to mimic the thrombin structure but not function *in vitro* and binds with a greater affinity for dabigatran than for thrombin [55]. In a rat model, continuous dabigatran infusion prolonged the TT and aPTT over controls. However, the addition of a single bolus injection of "aDabi-Fab" completely reversed the prolonged anticoagulant activity within one minute [55]. Finally, PER977 is a small molecule that is able to bind to various NOAs and reduces clinical bleeding in a rat tail injury model [56]. Development of such antidotes, if shown to be safe and effective in early phase studies, will be evaluated in later-phase clinical trials thus providing additional options for emergency reversal of NOAs.

CONCLUSION

The new oral direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors, rivaroxaban and apixaban have shown favorable safety and efficacy profiles compared to warfarin for the prevention and treatment of VTE. However, like all anticoagulants, there remains an increased risk of bleeding complications. Instilling routine practices to decrease the chance of bleeding complications remains the most effective way of curbing this issue. Some such measures include prescribing the NOAs at their recommended dosages while limiting the duration of treatment to the shortest time for which anticoagulation is needed. Also, frequent monitoring of the renal function and various drug interactions in patients while on NOAs could help determine the need for dose adjustments thus limiting the risk of over anticoagulation. In the future, the emergence of newer laboratory assays as well as the development of specific reversal agents will play a major role in improving our clinical ability to manage bleeding complications due to NOAs.

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