Management of Bleeding Associated with Dabigatran and Rivaroxaban: A Survey of Current Practices

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Dedication

This thesis is dedicated to my husband and sons for their unending support and my patients for whom my research is intended to benefit.

Abstract

Dabigatran and rivaroxaban are two new oral anticoagulants that have been recently approved as alternatives to warfarin. Clinical trials have shown non-inferiority of the new oral anticoagulants to warfarin for anti-thrombotic effects with equal to decreased bleeding risk. Unfortunately no standard method to assess the level of anticoagulation or reverse the effects of dabigatran or rivaroxaban is available. Current recommended management of bleeding patients taking dabigatran or rivaroxaban is based on expert opinion. To gain information from experience of physicians who have managed hemorrhaging patients, U.S. non-malignant hematologists were surveyed with a 31% response rate. In total, 43 cases of dabigatran associated hemorrhage and 5 cases of rivaroxaban associated bleeding were reported. Factor concentrates were used in 9 cases of dabigatran hemorrhage with perceived effectiveness ranging from 50-80%. A national registry is needed to track management of hemorrhages until antidotes become available.

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Thesis Introduction

The management and prevention of thrombosis has dramatically changed over the last two years with the approval of the new oral anticoagulants, dabigatran and rivaroxaban, as alternatives to warfarin. Advantages of the new oral anticoagulants include uniform dosing, lack of need for monitoring, and limited medication interactions. However in patients who bleed while taking dabigatran or rivaroxaban, no approved laboratory assay can determine the level of anticoagulation and an antidote does not exist. The manuscript below titled, "New Anticoagulants: A Concise Review" was published in the Journal of Trauma and Acute Care Surgery in October 2012 and is reproduced with permission from Lippincott Williams & Wilkins. This review provides a summary of the phase II and III clinical trials testing the new oral anticoagulants, review of laboratory testing, and proposes a bleeding management algorithm. As information regarding the use of factor concentrates available in the United States to treat bleeding in patients is limited to case reports and series, my thesis research project involved a survey to non-malignant hematologists about their experience with assessment and management of bleeding. The associated thesis manuscript titled, "Management of Bleeding Associated with Dabigatran and Rivaroxaban: A Survey of Current Practices" has been submitted but is not yet accepted for publication. While drug antidotes and clinical trials on reversal strategies are being developed, disseminating the combined experience of hematologists is crucial to inform current management strategies.

New Anticoagulants: A Concise Review

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Introduction

Fifty-seven years since warfarin was approved by the FDA, two new oral anticoagulants have entered the U.S. market. These drugs have given patients and providers alternatives to heparin and warfarin for prophylaxis against stroke in patients with atrial fibrillation and venous thromboembolism (VTE) after orthopedic procedures. As more patients have switched to these anticoagulants, issues have arisen such as management of bleeding and perioperative management. This review will focus on dabigatran and rivaroxaban as they are approved for clinical use and apixaban as it has completed phase III studies. The pharmacokinetic data for these agents is summarized in Table 1. A review of the coagulation cascade and the sites of action of these agents are seen in Figure 1. The new oral drugs are very effective anticoagulants because they inhibit proteins at the end of the coagulation cascade. Reversal of the anticoagulant effect is challenging because antidotes for these anticoagulants do not exist. This review will summarize available clinical trial evidence as well as a proposed approach to management of bleeding and the perioperative setting.

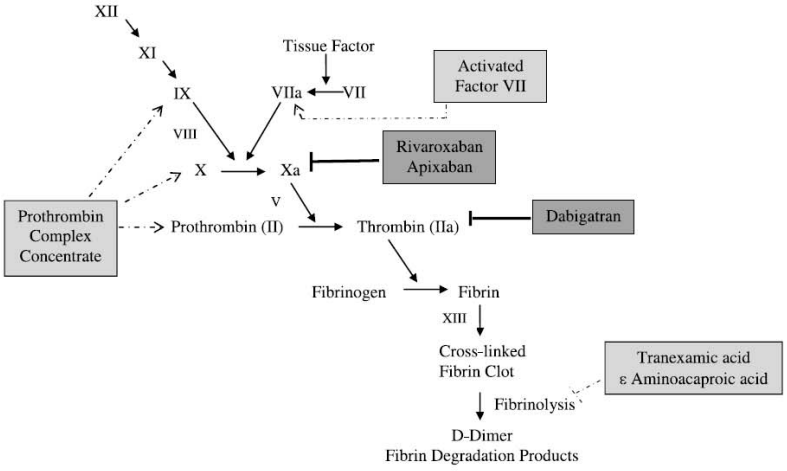

Figure 1. Clotting cascade and location of activity of new oral anticoagulants and hemostatic agents. Proteins are depicted by their zymogen symbols. The new oral anticoagulants are depicted in dark gray boxes with bold inhibition lines. Hemostatic agents are in light gray boxes with dashed lines in the area of activity. The PCC is depicted as containing nonactivated proteins for simplicity but can contain activated proteins and factor VII also depending on the product.

Dabigatran

Clinical Trials

Dabigatran is an oral direct thrombin inhibitor that is FDA approved for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation. The RE-LY trail randomized over 18,000 patients with non-valvular atrial fibrillation to blinded treatment with dabigatran 150 mg or 110 mg orally twice daily or open label warfarin (Table 2). Dabigatran 150 mg was superior to warfarin in prevention of stroke or systemic embolism with the primary end-point occurring in 1.11%/year of patients managed with dabigatran compared to 1.69%/year in patients treated with warfarin ($p<0.001$ superiority). The 110 mg dose was non-inferior to warfarin. The rate of ischemic stroke was significantly less only in patients treated with 150 mg of dabigatran. Life threatening hemorrhage occurred less often with either dose of dabigatran. Intracranial hemorrhage occurred significantly less in the dabigatran 110 mg and 150 mg groups compared to warfarin with a rate of 0.23%/year, 0.3%/year, and 0.74 %/year, respectively.[1] The FDA approved dabigatran (Pradaxa®; Boehringer Ingelheim, Ingelheim, Germany) 150 mg orally twice daily in October 2010 for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The 110 mg dose was not approved as subset analyses did not find a group in which the risk-benefit profile was superior to the 150 mg dose.[2] Based on pharmacokinetic data, 75 mg orally twice daily was approved for patients with creatinine clearance between 15-30 ml/min, but other authors suggest caution with use in this group.[3] Subsequent analysis has shown that poorly controlled patients on warfarin with INR measurements in therapeutic range <65% of the time benefited the most and may be the best candidates for dabigatran therapy.[4]

A phase II placebo-controlled dose escalation study (50 to 150 mg twice daily) of dabigatran in patients after myocardial infarction showed equal rates of cardiovascular death, myocardial infarction and stroke, but a dose dependent increase in bleeding rates.[5]

Additional studies of dabigatran for secondary prevention after acute coronary syndromes are not currently available.

Dabigatran has also been studied in prophylaxis of VTE after knee and hip replacement. The RE-MODEL and RE-MOBILIZE trials compared 150mg and 220 mg of dabigatran to enoxaparin 40 mg subcutaneously daily or 30 mg subcutaneously twice daily, respectively. Both dabigatran doses were found have equal bleeding rates in comparison to enoxaparin. However, enoxaparin 30 mg twice daily was superior to dabigatran whereas dabigatran was non-inferior to enoxaparin 40 mg daily (Table 2).[6] In a study of 2000 patients treated after total hip replacement VTE or death occurred in 2.2% of patients treated with dabigatran 220 mg compared to 4.2% of patients treated with enoxaparin 40 mg daily (risk difference -1.9%, p=0.03 superiority). Major bleeding was similar between the groups (1.4% dabigatran, 0.9% enoxaparin, p=0.4).[7] Overall this data suggests similar efficacy to enoxaparin 40 mg daily in VTE prophylaxis after orthopedic surgery with similar bleeding risk. Dabigatran has been approved in Europe and Canada for prevention of VTE after orthopedic surgery based on this data.

The RE-COVER trial examined the use of dabigatran to treat VTE in 2500 patients with proximal DVT or pulmonary embolism. All patients were treated with low-molecular weight heparin and then randomized to dabigatran 150 mg twice daily or warfarin for 6 months in a double-blind, double-dummy design. Recurrent VTE occurred in 2.4 % in the dabigatran arm and 2.1% in the warfarin group ($p<0.001$, non-inferiority). Major bleeding was equal but the location of bleeding was more often in a critical organ (9 intracranial hemorrhages with warfarin versus 1 intracranial hemorrhage with dabigatran). The incidence of any bleeding was also higher in the warfarin group (21.9% versus 16.1%, Hazard Ratio (HR) 0.71).[8] The RE-MEDY trial is an extension of the RE-COVER trial examining the use of dabigatran for secondary prevention of VTE. The study completed in October 2010 and we anticipate results in the next year.

Laboratory Testing

One of the major benefits of dabigatran over warfarin is that laboratory monitoring is not required during therapy. However, there are many instances in which knowing the degree of anticoagulation is paramount. For patients on dabigatran, the activated partial thromboplastin time (aPTT) increases with larger doses; however, the dose response is not linear and plateaus at higher concentrations of dabigatran.[3,9] The prothrombin time (PT/INR) is variably affected but has been shown to rise with therapeutic doses.[9] The INR is an insensitive measure of dabigatran activity and should not be used to monitor patients. Elevations in activated clotting time measured by thromboelastography (TEG) have been reported[10] but animal studies showed similar TEG profiles in pigs on dabigatran and without anticoagulation.[11] The thrombin time (TT) measures the direct activity of thrombin and is the most sensitive to the effects of dabigatran. If the TT is normal there is no dabigatran in the sample. At high concentrations of dabigatran, however, the thrombin time may be above a measurable level. The ecarin clotting time (ECT) also directly measures the anticoagulant effect of direct thrombin inhibitors but is less sensitive than the TT, thus, a more accurate measure of the concentration of dabigatran. The ECT is not widely available, thus, most hospitals may be limited to aPTT and TT to interpret the extent of anticoagulation in patients on dabigatran.[3]

Rivaroxaban

Clinical Trials

Rivaroxaban is an oral direct inhibitor of activated Factor X (Xa), that is FDA approved for stroke and systemic embolization prevention in non-valvular atrial fibrillation and VTE prevention after knee and hip replacement. The ROCKET-AF trial randomized over 14,000 patients with atrial fibrillation and two stroke risk factors to rivaroxaban 20 mg daily or warfarin (Table 3). Rivaroxaban was non-inferior to warfarin in prevention of stroke and systemic embolism (2.1%/year rivaroxaban versus 2.4%/year warfarin, $p<0.001$ non-inferiority). Major bleeding was equal between the rivaroxaban and warfarin groups at 5.6% and 5.4%, respectively. Fatal bleeding was 50% lower in the

rivaroxaban group (0.4% versus 0.8%, p=0.003). Intracranial hemorrhage rates were also decreased with rivaroxaban (0.8% versus 1.2%, p=0.02).[12] Rivaroxaban was approved for prevention of stroke in patients with non-valvular atrial fibrillation in November 2011 (20 mg orally daily or 15 mg daily if creatinine clearance 15-50 ml/min).[13] After discontinuation of rivaroxaban in the ROCKET-AF trial, an increased risk of stroke was found, leading to a black box warning.[13] In order to maintain blinding in the trial at its completion, patients were not bridged when switching from rivaroxaban to warfarin. Inadequate anticoagulation in high risk patients likely led to increased stroke risk.

The ATLAS-TIMI 46 and 51 studies used rivaroxaban in patients after acute coronary syndromes to reduce cardiovascular endpoints.[14,15] Compared to placebo, rivaroxaban decreased the composite endpoint of cardiovascular death, myocardial infarction and stroke, but caused significantly higher major bleeding. The use of rivaroxaban after acute coronary syndromes currently is not standard of care.

In the RECORD trials, rivaroxaban was compared to enoxaparin for VTE prophylaxis after total knee and hip replacement.[16-19] Rivaroxaban 10 mg orally daily was found to be superior to enoxaparin 40 mg daily and 30 mg twice daily. In a systematic review of these studies, the relative risk of VTE was 0.38 compared to enoxaparin 40 mg daily ($p<0.0001$) and 0.77 in comparison to enoxaparin 30 mg twice daily ($p=0.05$). No significant difference in post-operative bleeding was noted. In all of these studies, rivaroxaban was started within 6-8 hours of surgery and continued for an average of 12 days after knee replacement and 35 days after hip replacement.[20] In July 2011, the FDA approved rivaroxaban (Xarelto®; Janssen Pharmaceuticals, Titusville, NJ) for VTE prophylaxis after orthopedic surgery.

Rivaroxaban has also been tested against warfarin in the treatment of VTE. The EINSTEIN trial was an open label randomized non-inferiority study of rivaroxaban 15 mg twice daily for 3 weeks then 20 mg daily, compared to enoxaparin bridged to

warfarin. Recurrent VTE occurred in 3% of patients treated with enoxaparin/warfarin and 2.1% patients treated with rivaroxaban ($p<0.001$ non-inferiority). Major and clinically relevant bleeding was similar between the groups (major bleed 0.8% rivaroxaban versus 1.2% enoxaparin/warfarin, $p=0.21$). The EINSTEIN extension study showed that rivaroxaban was effective for secondary VTE prophylaxis, with recurrent VTE in 7.1% of the placebo group versus 1.3% on rivaroxaban ($p<0.001$). Major bleeding occurred in 0.7% of patients on rivaroxaban and zero patients on placebo ($p=0.11$).[21] This suggests that bleeding risk is low with rivaroxaban, but comparison to bleeding rates for long term anticoagulation on warfarin would require extrapolation from other studies.

Laboratory Testing

Routine laboratory monitoring of rivaroxaban is not required. As Factor X is a part of the common coagulation pathway, inhibitors of Factor Xa should prolong the PT and aPTT. The degree of prolongation is dependent on the reagent used. No effect was seen on the TT or fibrinogen activity assays.[22] Dose-dependent prolongation of TEG parameters (R and K times) has been reported. [23] Chromogenic anti-Xa assays can be standardized to measure rivaroxaban, but this test may not be routinely available.[24]

Apixaban

Clinical Trials

Apixaban is an oral direct Factor Xa inhibitor that has completed several phase III trials but has not yet been approved by the FDA (Table 4). Apixaban has been studied in two large trials in patients with atrial fibrillation. The AVERROES trial randomized 5600 patients unsuitable for warfarin therapy to apixaban 5 mg twice daily versus aspirin. With a mean follow-up of 1.1 years, the trial was stopped early for benefit as the rate of stroke or systemic embolism was 3.7%/year in the aspirin group versus 1.6%/year with apixaban. Similar rates of bleeding were seen in both treatment groups including rates of intracranial hemorrhage (0.4%/year in both groups).[25] This trial has been criticized because of the lack of standardization of the aspirin dose and the use of enteric-coated

aspirin. The ARISTOTLE trial compared apixaban 5 mg twice daily to warfarin in over 18,000 patients with atrial fibrillation and one stroke risk factor. Apixaban was superior to warfarin in prevention of stroke or systemic embolization. The rate of hemorrhagic stroke was reduced by half with apixaban (0.24%/year apixaban versus 0.47%/year warfarin; $p<0.001$). The rate of death from any cause was also lower in the apixaban group (HR 0.89, $p=0.047$). Intracranial hemorrhage was reduced from 0.8%/year with warfarin to 0.33%/year with apixaban ($p<0.001$). Major bleeding occurred significantly less often with apixaban compared to warfarin and a 7.7% absolute risk reduction for all bleeding was noted with apixaban ($p<0.001$).[26] Overall, apixaban appears to be an effective alternative to warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation.

A phase II and III study tested the use of apixaban with antiplatelet therapy after acute coronary syndromes.[27,28] The APPRAISE-2 study was discontinued early due to increased major bleeding without a decrease in the composite primary endpoint of cardiovascular death, recurrent myocardial infarction and stroke.

Apixaban has been evaluated in prevention but not treatment of VTE. The ADVANCE trials have examined the use of apixaban 2.5 mg twice daily versus enoxaparin in prophylaxis of VTE after orthopedic surgery. When compared to enoxaparin 30 mg twice daily, apixaban failed non-inferiority to enoxaparin with rates of VTE and all-cause mortality in 9% of the apixaban and 8.9% of the enoxaparin groups[29]. However, when compared to the European regimen of enoxaparin 40 mg daily, apixaban was found to be superior with equal bleeding rates after total knee and hip replacement.[30,31]

Laboratory Testing

Apixaban has a mechanism of action similar to rivaroxaban with direct inhibition of Factor Xa. Apixaban also prolongs the aPTT and PT levels with variability in the PT depending on the reagents used in testing. The linear correlation of the plasma

concentration of apixaban and anti-Xa levels standardized to apixaban or to low molecular weight heparin are equally strong (r=0.967). Therefore, recalibration of anti-Xa testing may not be necessary to determine the degree of anticoagulation with apixaban.[32]

Management of Bleeding With New Oral Anticoagulants

The bleeding rates with the new oral anticoagulants are generally equal to or less than bleeding rates with warfarin, but antidotes are not available. Figure 1 shows the sites of action of the new oral anticoagulants and hemostatic agents that could be utilized. Algorithms for managing hemorrhage in patients on dabigatran have been developed.[33] A proposed management guideline is presented in Figure 2.

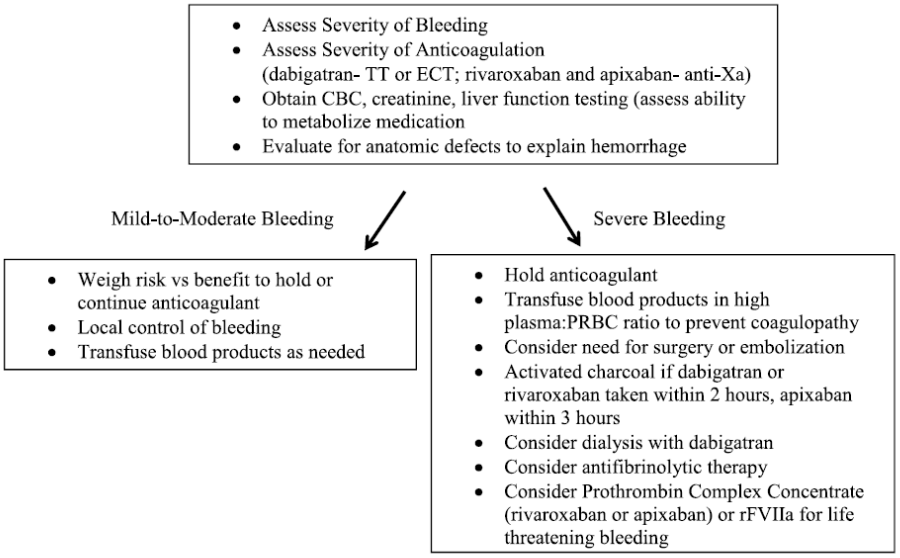

Figure 2. Management guideline for bleeding while taking dabigatran, rivaroxaban, or apixaban.

Initial evaluation for bleeding patients on the new oral anticoagulants includes an assessment of hemodynamic stability, severity of bleeding, and level of anticoagulation. Life threatening bleeding (i.e. intracranial hemorrhage) requires the most aggressive response. Baseline clotting times, fibrinogen activity, complete blood count, creatinine, and liver function tests should be obtained. Alteration in renal function will affect the metabolism of dabigatran the most and apixaban the least. Apixaban and rivaroxaban

metabolism is altered by changes in liver function. Assessment for anatomic etiology of the hemorrhage should be sought with use of local control measures if possible. Activated charcoal will decrease absorption of the anticoagulants if administered within 2-3 hours of ingestion of the anticoagulant. Dialysis will remove dabigatran due to its low plasma protein binding whereas rivaroxaban and apixaban are likely not dialyzable.[3,34] The volume of distribution of dabigatran is large (60-70L)[3]; therefore, multiple sessions of dialysis may be required. Extrapolating from the trauma literature, if massive transfusion is required, we recommend transfusion in 1:1 plasma:PRBC ratio to prevent dilutional and consumptive coagulopathy.[35]

In cases of significant bleeding, additional hemostatic agents should be considered (Table 5). Antifibrinolytic medication provides clot stabilization if fibrin is able to form. In a large randomized trial of injured patients not taking the new oral anticoagulants, tranexamic acid was shown to decrease the risk of death due to hemorrhage when given within the first 3 hours of injury.[36] Antifibrinolytic agents have been ineffective in reducing bleeding times with direct thrombin inhibitors and may not be useful for patients taking dabigatran.[3] A recent prospective case series suggests decreased post-operative blood loss in patients treated with both rivaroxaban prophylaxis and tranexamic acid.[37] Reversal agents for the new oral anticoagulants including an inactivated Xa product are in development, but are not currently available.[38] In healthy subjects, the anticoagulant effect of rivaroxaban can be reversed with administration of 50 units/kg of Cofact® (Sanquin, Amsterdam, Netherlands), a non-activated 4-factor prothrombin complex concentrate (PCC) (Table 5). In patients on dabigatran, clotting times remained prolonged after PCC infusion showing inadequate reversal of anticoagulation effect.[39] In a rat tail model of bleeding, recombinant activated Factor VII, non-activated 4-factor PCC and activated PCC were shown to significantly reduce bleeding times in dabigatran treated animals.[3,40] Laboratory coagulation tests did not predict the reversal of bleeding in the mice, however.[40] In a mouse model of intracranial hemorrhage with dabigatran use, a non-activated 4-factor PCC prevented hematoma expansion but activated Factor VII did

not have an effect.[41] Clinical data on dabigatran and rivaroxaban reversal using PCCs and activated Factor VII in humans is not available. Additionally, 4-factor PCCs are not available in the US (Table 5). Thrombosis and disseminated intravascular coagulation have occurred with administration of activated Factor VII and activated and non-activated PCCs. Therefore, the risk of hemorrhage needs to be weighed against the risk of using any of these procoagulant agents and patients must be monitored closely.

Perioperative Management

Timing of anticoagulant discontinuation prior to surgery depends on the half-life of the anticoagulant, the patient's renal function, and the surgical risk of bleeding. Creatinine clearance plays the largest role in perioperative management of dabigatran. Table 6 summarizes recommendations regarding timing of discontinuation in standard risk procedures. High risk procedures including cardiac surgery, neurosurgery, abdominal surgery or procedures requiring spinal anesthesia may require 2-4 days off dabigatran in patients with normal renal function and 4 days off therapy with creatinine clearance 30-50 ml/min.[3] Checking an ECT or TT in patients with renal impairment on dabigatran is an option to ensure that minimal anticoagulant effect remains prior to the procedure. Rivaroxaban has a significantly shorter half-life than dabigatran and thus could be discontinued 24 hours prior to surgery.[13] The half-life of rivaroxaban in elderly patients increases, so 48 hours may be necessary to allow for proper elimination. An increased risk of stroke has been reported after discontinuation of rivaroxaban, thus, minimizing the duration without anticoagulation in high risk patients is recommended.[13] In elderly patients, higher levels of apixaban have been reported. Providers should consider discontinuing apixaban for 48 hours or checking an anti-Xa level prior to surgery.[42]

Timing of resumption of the new anticoagulants after surgery is dependent on bleeding risks and the dose used. It is important to remember that these drugs fully anticoagulate the patient in 2 – 4 hours. In clinical trials for VTE prophylaxis after orthopedic surgery dabigatran was initiated at a half dose 1-4 hours after surgery and full dose 12 hours

later.[6] Rivaroxaban was initiated 6-8 hours after wound closure and apixaban was started 12-24 hours postoperatively.[20,43] For procedures with low bleeding risk, full anticoagulation with apixaban could be restarted after 24 hours; whereas resumption of anticoagulation after major surgery could be considered 48 hours post-operatively.[43] Additional clinical data and experience with the new anticoagulants will influence perioperative and postoperative management in the future.

Conclusion

Two new oral anticoagulants are available in the U.S. with additional agents likely to be approved in the near future. Each of these agents has the benefit of oral administration and uniform dosing. A majority of the clinical benefit is likely secondary to consistent anticoagulant effect. Monitoring of anticoagulant activity is not required but may be necessary in specific instances such as bleeding. Determining the anticoagulant effect of dabigatran requires special coagulation testing using the thrombin or ecarin clotting times. Rivaroxaban and apixaban can be monitored through standardized anti-Xa assays. Perioperative and post-operative management of anticoagulation should be determined by the surgical risk of bleeding and renal function of the patient which may be affected by age. In the bleeding patient, reversal of anticoagulant effect depends on the severity of hemorrhage, hepatic and renal function which will determine metabolism of the drugs. In healthy volunteers, PCC can reverse the effects of rivaroxaban but it is unknown if this can be extrapolated to bleeding individuals on any Xa inhibitor if severe hemorrhage occurred. Reversal of dabigatran with activated PCC and Factor VII has only been shown in animals. Until additional clinical data becomes available, physicians will need to rely on a hemorrhage management algorithm and clinical judgment.

Author Contributions

Lisa Baumann Kreuziger completed a literature search, primary manuscript writing, and revisions. Colleen Morton assisted with literature search and content review and revisions. David Dries initiated the project and completed content review and revisions.

Table 1: Pharmacokinetic properties of new oral anticoagulants.

	Dabigatran	**Rivaroxaban**	**Apixaban**
FDA approved indications	Prevention of stroke and systemic embolism in nonvalvular atrial fibrillation	Venous thromboembolism prophylaxis after hip and knee replacement, Stroke and systemic embolism prophylaxis in nonvalvular atrial fibrillation	Pending
Activity	Inhibits free and clot bound thrombin (Factor IIa)	Inhibits Factor Xa	Inhibits Factor Xa
Dosing for atrial fibrillation	150 mg twice daily, 75 mg twice daily if CrCl 15-30 ml/min	20 mg daily, 15 mg daily if CrCl 15-50 ml/min	5 mg twice daily^
Dosing for VTE prophylaxis		10 mg daily	2.5 mg twice daily^
Onset of Action	1.5-3 hours	2-4 hours	3 hours
Half life	14-17 hours	5-9 hours, 11-13 hours elderly#	8-15 hours
Metabolism and excretion	80% renal 20% fecal	66% renal 33% fecal	25% renal 75% biliary, fecal
Drug Interactions	P-glycoprotein inhibitors*	Potent CYP3A4 inhibitors+, P-glycoprotein inhibitors*	Potent CYP3A4 inhibitors+, P-glycoprotein inhibitors*
Detection of anticoagulant effect	ECT if available, TT most sensitive	Anti-Xa assay	Anti-Xa assay
Unique issues	Must be stored in original bottle	Highly protein bound and not dialyzable, take with evening meal	Highly protein bound and not dialyzable

CrCl= creatinine clearance ECT- ecarin clotting time, TT- thrombin time ^ Dosing not approved by FDA # Despite half life, daily dosing due to persistance of anti-Xa activity

*rifampin, amiodarone + ketoconazole, itraconazole, voriconazole, ritonavir

Table 2: Phase II and III clinical trials using dabigatran

Trial Name	Indication	Dabigatran Dose	Comparator	Treatment duration	Thrombotic outcome	Major Bleeding
PETRO[44] Phase II	Non-valvular atrial fibrillation	50 mg, 150 mg or 300 mg BID	Warfarin (INR 2-3)	12 weeks	Stroke and systemic embolism 50 mg: 1.7% 150 mg: 0% 300 mg: 0% Warfarin: 0 %	50 mg: 0% 150 mg: 0% 300 mg: 0% Warfarin: 0 %
RE-LY[1] Phase III	Non-valvular atrial fibrillation	110 mg or 150 mg BID	Warfarin (INR 2-3)	Median follow-up 2 years	Stroke and systemic embolism 110 mg: 1.53%/year^ 150 mg: 1.11%/year* Warfarin: 1.69%/year	110 mg: 2.71%/year* 150 mg: 3.11%/year Warfarin: 3.36%/year
RE-DEEM[5] Phase II	Secondary prevention after ACS	50 mg, 75 mg, 110 mg, 150 mg BID	Placebo	6 months	CV Death, MI or Stroke 50 mg BID: 4.6% 75 mg BID: 4.9% 110 mg BID: 3.0% 150 mg BID: 3.5% Placebo: 3.8%	50 mg BID: 0.8% 75 mg BID: 0.3% 110 mg BID: 2.0%+ 150 mg BID: 1.2%+ Placebo: 0.5%
BISTRO I[45] Phase II	VTE prevention after THR	Dose escalation 12.5-300 mg twice daily, 150 mg or 300 mg daily	N/A	6-10 days	All VTE 12.5 mg BID: 20.8% 25 mg BID: 9.5% 50 mg BID: 14.8% 100 mg BID: 19.4% 150 mg Daily: 9.1% 150 mg BID: 9.5% 200 mg BID: 19.0% 300 mg Daily: 0%	0% in all groups

BISTRO II[46] Phase II	VTE prevention after THR or TKR	50 mg, 150 mg, or 225 mg twice daily, 300 mg daily	Enoxaparin 40 mg daily	6-10 days	All VTE 50 mg BID: 28.5% 150 mg BID: 17.4%* 300 mg daily: 16.6%* 225 mg BID: 13.1%* Enoxaparin: 24%	50 mg BID: 0.3%* 150 mg BID: 4.1% 300 mg daily: 4.7% 225 mg BID: 3.8% Enoxaparin: 2%
RE-MODEL[47] Phase III	VTE prevention after TKR	150 mg or 220 mg daily	Enoxaparin 40 mg daily	6-10 days	VTE and all-cause mortality 150 mg: 40.5%^ 220 mg: 36.4%^ Enoxaparin: 37.7%	150 mg: 1.3% 220 mg: 1.5% Enoxaparin: 1.3%
RE-NOVATE[48] Phase III	VTE prevention after THR	150 mg or 220 mg daily	Enoxaparin 40 mg daily	28-35 days	VTE and all-cause mortality 150 mg: 8.6%^ 220 mg: 6%^ Enoxaparin: 6.7%	150 mg: 1.3% 220 mg: 2% Enoxaparin: 1.6%
RE-MOBILIZE[49] Phase III	VTE prevention after TKR	150 mg or 220 mg daily	Enoxaparin 30 mg BID	12-15 days	VTE and all-cause mortality 150 mg: 34%$^{+}$ 220 mg: 31%$^{+}$ Enoxaparin: 25%	150 mg: 0.6% 220 mg: 0.6% Enoxaparin: 1.4%
RE-NOVATE II[50] Phase III	VTE prevention after THR	220 mg daily	Enoxaparin 40 mg daily	28-35 days	VTE and all-cause mortality 220 mg: 7.7%^ Enoxaparin: 8.8%	220 mg: 1.4% Enoxaparin: 0.9%
RE-COVER[8] Phase III	Acute VTE treatment	150 mg BID	Warfarin (INR 2-3)	6 months	Recurrent VTE Dabigatran: 2.4%^ Warfarin: 2.1%	Dabigatran: 1.6% Warfarin: 1.9%
RE-MEDY Phase III	Secondary VTE prophylaxis	150 mg BID	Warfarin (INR 2-3)	18 months	Not Reported	Not Reported

VTE= venous thromboembolism, ACS=acute coronary syndrome, TKR=total knee replacement, THR=total hip replacement, BID=twice daily, +statistically significant inferiority demonstrated over comparator ^statistically significant noninferiority demonstrated to comparator *statistically significant superiority demonstrated over comparator

Table 3: Phase II and III clinical trials using rivaroxaban

Trial Name	Indication	Rivaroxaban Dose	Comparator	Treatment Duration	Thrombotic outcome	Major Bleeding
ROCKET-AF[12] Phase III	Non-valvular atrial fibrillation	20 mg daily	Warfarin (INR 2-3)	Median treatment 19.7 months	Stroke and Systemic embolism Rivaroxaban: 2.12%/year^ Warfarin: 2.42%/year	Rivaroxaban: 3.6%/year Warfarin: 3.4%/year
ATLAS ACS–TIMI 46[14] Phase II	Secondary prevention after ACS	5-20 mg total daily dose	Placebo	6 months	CV Death, MI, Stroke, Revascularization 5 mg: 5.8% 10 mg: 3.8% 15 mg: 6.2% 20 mg: 5.5% Placebo: 5.1%	5 mg: 0.7%+ 10 mg: 1.5%+ 15 mg: 1.8%+ 20 mg: 1.8%+ Placebo: 0.1%
ATLAS ACS–TIMI 51[15] Phase III	Secondary prevention after ACS	2.5 mg and 5 mg BID	Placebo	31 months	CV Death, MI, Stroke 2.5 mg BID: 9.1%* 5 mg BID: 8.8%* Placebo: 10.7%	2.5 mg BID: 1.8%+ 5 mg BID: 2.4%+ Placebo: 0.6%
RECORD1[16] Phase III	VTE prevention after THR	10 mg daily	Enoxaparin 40 mg daily	31-39 days	VTE and all-cause mortality Rivaroxaban: 1.1%* Enoxaparin: 3.7%	Rivaroxaban: 0.3% Enoxaparin: 0.1%
RECORD2[17] Phase III	VTE prevention after THR	10 mg daily	Enoxaparin 40 mg daily	31-39 days, enoxaparin 10-14 days	VTE and all-cause mortality Rivaroxaban: 2%* Enoxaparin: 9.3%	Rivaroxaban: <0.1% Enoxaparin: <0.1%
RECORD3[18] Phase III	VTE prevention after TKR	10 mg daily	Enoxaparin 40 mg daily	10-14 days	VTE and all-cause mortality Rivaroxaban: 9.6%* Enoxaparin: 18.9%	Rivaroxaban: 0.6% Enoxaparin: 0.5%
RECORD4[19] Phase III	VTE prevention after TKR	10 mg daily	Enoxaparin 30 mg BID	10-14 days	VTE and all-cause mortality Rivaroxaban: 6.9%* Enoxaparin: 10.1%	Rivaroxaban: 0.7% Enoxaparin: 0.3%

MAGELLAN[51] Phase III	VTE medical patients	10 mg daily	Enoxaparin 40 mg daily	35-39 days, enoxaparin 10-14 days	VTE death and all VTE Rivaroxaban: 4.4%* Enoxaparin: 5.7%	Rivaroxaban: 1.1%+ Enoxaparin: 0.4%
ODIXa-DVT [52] Phase II	Acute VTE treatment	10 mg, 20 mg, 30 mg BID or 40 mg daily	Enoxaparin/Warfarin (INR 2-3)	12 months	Thrombotic burden and VTE death 10 mg BID: 53% 20 mg BID: 59.2% 30 mg BID: 56.9% 40 mg: 43.8% Warfarin: 45.9%	10 mg BID: 1.7% 20 mg BID: 1.7% 30 mg BID: 3.3% 40 mg: 1.7% Warfarin: 0%
EINSTEIN[21] Phase III	Acute VTE treatment	15 mg BID for 3 weeks, 20 mg daily	Enoxaparin/Warfarin (INR 2-3)	3-12 months	Recurrent VTE Rivaroxaban: 2.1%^ Warfarin: 3.0%	Rivaroxaban: 0.8% Warfarin: 1.2%

VTE= venous thromboembolism, ACS=acute coronary syndrome, TKR=total knee replacement, THR=total hip replacement, BID=twice daily, +statistically significant inferiority demonstrated over comparator ^statistically significant noninferiority demonstrated to comparator *statistically significant superiority demonstrated over comparator

Table 4: Phase II and III clinical trials of apixaban

Trial Name	Indication	Dose	Comparator	Treatment duration	Thrombotic outcome	Major Bleeding
AVERROES[25] Phase III	Non-valvular atrial fibrillation	5 mg BID	Aspirin 81-324 mg	Median follow-up 1.1 years	Stroke or systemic embolism Apixaban: 1.6%/year* Aspirin: 3.7%/year	Apixaban: 1.4%/year Aspirin: 1.2%/year
ARISTOTLE[26] Phase III	Non-valvular atrial fibrillation	5 mg BID	Warfarin (INR 2-3)	Median follow-up 1.8 years	Stroke or systemic embolism Apixaban: 1.3%/year* Warfarin: 1.6%/year	Apixaban: 2.1%/year* Warfarin: 3.1%/year
APPRAISE[27] Phase II	Secondary prevention after ACS	5-20 mg daily	Placebo	26 weeks	CV Death, MI, revascularization and Stroke 2.5 mg BID: 7.6% 10 mg Daily: 6.0% Placebo: 8.7%	2.5 mg BID: 0.8% 10 mg Daily: 0% 10 mg BID: 2.9%+ 20 mg Daily: 4.1%+ Placebo: 0%
APPRAISE-2[28] Phase III	Secondary prevention after ACS	5 mg BID	Placebo	Median follow-up 241 days	CV Death, MI and Stroke Apixaban: 7.5% Placebo: 7.9%	Major Bleeding Apixaban: 1.3%+ Placebo: 0.5%
ADVANCE1[29] Phase III	VTE prevention after TKR	2.5 mg BID	Enoxaparin 30 mg BID	12 days	VTE and all-cause mortality Apixaban: 9% Enoxaparin: 8.8%	Apixaban: 0.7%* Enoxaparin: 1.4%
ADVANCE-2[30] Phase III	VTE prevention after TKR	2.5 mg BID	Enoxaparin 40 mg daily	12 days	VTE and all-cause mortality Apixaban: 15%* Enoxaparin: 24%	Apixaban: 0.6% Enoxaparin: 0.9%
ADVANCE-3[53] Phase III	VTE prevention after THR	2.5 mg BID	Enoxaparin 40 mg daily	35 days	VTE and all-cause mortality Apixaban: 1.4%* Enoxaparin: 3.9%	Apixaban: 0.8% Enoxaparin: 0.7%
Botticelli DVT[54] Phase II	Acute VTE treatment	5 mg or 10 mg BID, 20 mg daily	Enoxaparin/warfarin	84-91 days	VTE and increased thrombotic burden: 5 mg BID: 6% 10 mg BID: 5.6% 20 mg Daily: 2.6% Warfarin: 4.2%	5 mg BID: 0.7% 10 mg BID: 0% 20 mg Daily: 1.6% Warfarin: 0%

Metastatic cancer[55] Phase II	VTE prevention metastatic cancer	5-20 mg	Placebo	12 weeks	Symptomatic VTE Apixaban: 0% Placebo: 10%	5 mg: 0% 10 mg: 0% 20 mg: 6% Placebo: 3%

VTE= venous thromboembolism, ACS=acute coronary syndrome, TKR=total knee replacement, THR=total hip replacement, BID=twice daily, +statistically significant inferiority demonstrated over comparator ^statistically significant noninferiority demonstrated to comparator *statistically significant superiority demonstrated over comparator

Table 5: Potential useful medications for bleeding while on new anticoagulants

Name	**Agent Category**	**Clotting Factors in Product**	**Available in US?**
Tranexamic acid	Anti-fibrinolytic	None	Yes
ε Aminoacaproic acid	Anti-fibrinolytic	None	Yes
NovoSeven	Activated Factor VII	Activated VII	Yes
Cofact®	4-Factor PCC	Non-activated II, VII, IX, X	No
Beriplex®, Octaplex®	4-Factor PCC	Non-activated II, VII, IX, X, Protein C and S	No
Profilnine®, Bebulin®	3-Factor PCC	Non-activated II, IX, X, small amounts VII	Yes
Feiba®	Activated PCC	Activated VII, non-activated II, IX, X	Yes

PCC- Prothrombin complex concentrate

Table 6: Timing of discontinuation of new oral anticoagulants prior to standard risk procedures. Additional duration of discontinuation may be needed for high risk procedures.[3,13,42]

Creatinine Clearance	**Dabigatran**	**Rivaroxaban**	**Apixaban**
>50 ml/min	24 hours	24 hours	24-36 hours
30-50 ml/min	48 hours	48 hours	48 hours
<30 ml/min	5 days		

Case Reports of Factor Concentrate Use in Bleeding Patients

Since publication of my manuscript, "New Anticoagulants: A Concise Review," several case reports of management of bleeding patients taking dabigatran have been reported. The reported effectiveness of recombinant activated factor VIIa (rfVIIa) has varied depending on the clinical situation. In a patient with atrial fibrillation on dabigatran and excessive bleeding post-operatively, 5 doses of recombinant activated factor VIIa (rfVIIa) decreased bleeding sufficiently to allow transfer from the operating room; however, hemodialysis lead to the most significant decrease in dabigatran concentration and bleeding.[56] Two case reports from the neurosurgical literature showed persistent hemorrhage after rfVIIa in elderly patients on dabigatran.[57,58] Only three case reports of use of other factor concentrates in dabigatran associated hemorrhage have been published. In a patient with cardiac perforation during an atrial fibrillation ablation, administration of aPCC lead to hemostasis within minutes of administration.[59] Use of a 3-factor PCC in a patient with an upper gastrointestinal hemorrhage lead to improvement in the INR and aPTT and no further bleeding occurred.[60] In a similar clinical situation, administration of 3-factor PCC lead to hemoglobin stabilization after an upper gastrointestinal hemorrhage, but the patient died of multiorgan failure.[61] No case reports of management of rivaroxaban associated hemorrhage have been published. Overall, human data on the most effective management strategies for bleeding in patients taking the new oral anticoagulants is limited and conflicting.

Thesis Research Project

Post-marketing surveillance has reported major bleeding events in patients taking dabigatran.[62] Anecdotally, physicians have also cared for patients hemorrhaging after taking rivaroxaban. Because the bleeding events are rare, one physician is unlikely to gather experience sufficient to base recommendations. Even if primary care physicians or cardiologists currently prescribe a majority of the new oral anticoagulants for patients with atrial fibrillation, hematologists are likely to be consulted if bleeding occurs. Therefore, I surveyed adult non-malignant hematologists across the United States to combine their experiences of the assessment and management of bleeding patients taking

the new oral anticoagulants. The Hemostasis and Thrombosis Research Society (HTRS) is the US professional organization for physicians interested in coagulation. Additionally, directors of Hemophilia Treatment Centers (HTC) specialize in management of bleeding and have significant experience with use of factor concentrates. Thus, HTRS members and HTC directors were the target population for my survey. With approval of the HTRS leadership and the University of Minnesota Institutional Review Board, I contacted physicians via Survey Monkey. HTC directors are listed on the CDC website and emails were located via the internet. Physicians were excluded from the recipient list if they only practiced at a children's hospital or were personally known to not treat adult hematology patients. As many institutions do not have a significant number of coagulation experts available, many pediatric non-malignant hematologists also see adult patients. Therefore, physicians were not excluded based on pediatric training alone. Figure 3 shows the breakdown of the contacted physicians and the response to the survey. The manuscript below titled "Management of Bleeding on the New Oral Anticoagulants: A Survey of Current Practices" has been submitted to Blood as a Brief Report and summarizes the survey results and implications of the findings.

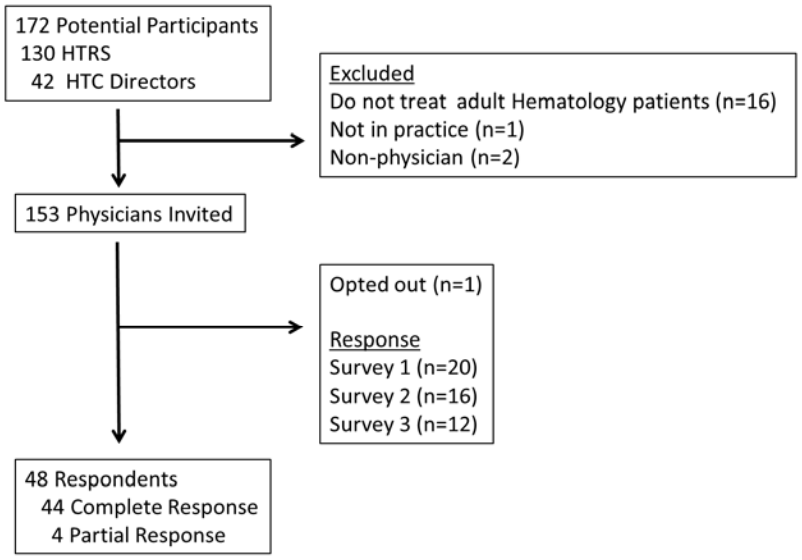

Figure 3: Survey Flow Diagram
HTRS= Hemostasis and Thrombosis Research Society
HTC= Hemophilia Treatment Center Director

Management of Bleeding Associated with Dabigatran and Rivaroxaban: A Survey of Current Practices

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Abstract

Expert opinion underlies current recommended management of bleeding patients taking dabigatran or rivaroxaban. We surveyed US non-malignant hematologists regarding their experience treating hemorrhages associated with the new anticoagulants. In total, 43 cases of dabigatran-associated hemorrhage and 5 cases of rivaroxaban-associated bleeding were reported. Respondents used thrombin time and aPTT most frequently to assess the level of dabigatran anticoagulation as ecarin clotting time and dilute thrombin assays were not widely available. Rivaroxaban was evaluated using aPTT and anti-Xa levels in all reported patients. Factor concentrates were used in 9 cases of dabigatran hemorrhage with perceived effectiveness ranging from 50-80%. Over half of survey respondents had moderately high to high levels of concern regarding their ability to manage bleeding associated with dabigatran and rivaroxaban, highlighting the need for a national registry to track management of hemorrhages until antidotes are available.

Introduction

Dabigatran and rivaroxaban are anticoagulant alternatives to warfarin with advantages including uniform dosing and lack of required monitoring.[3,63] Assessment and management of dabigatran and rivaroxaban-associated bleeding is challenging because standard coagulation studies do not accurately reflect the level of anticoagulation and reversal agents are not available.[64] Established methods to manage dabigatran and

rivaroxaban-associated bleeding do not exist due to lack of human studies. Therefore, we surveyed hematologists across the US to gauge how bleeding patients have been evaluated and managed.

Methods

Physician members of the Hemostasis and Thrombosis Research Society (HTRS) and hemophilia center directors were queried electronically regarding the number of patients treated for dabigatran or rivaroxaban-associated bleeding, bleeding management and perceived effectiveness of management, and institutional treatment algorithms. Cases were identified as those experiencing major bleeding[65] or renal failure (creatinine clearance <30 ml/min). Availability and use of laboratory testing to measure the level of anticoagulation were assessed. Lastly, we evaluated physicians' level of concern regarding their ability to manage bleeding patients (scale 1-5). The survey was pre-announced and sent electronically three times. Participants were considered responders if one question was answered. The University of Minnesota Institutional Review Board approved the study.

Results and Discussion

Overall response rate was 31.5% (48/152 surveyed) and 92% of respondents completed the survey. Our response rate was within previously published ranges of physicians' response to electronic surveys without incentives.[66,67] No significant differences in demographic or practice characteristics were found between survey respondents and non-respondents (Table 7). The lack of difference in baseline characteristics between respondents and non-respondents decreases but does not eliminate the possibility of non-response bias in our survey results.

Detailed management information was provided in 22 of 43 reported cases of dabigatran-associated bleeding (Table 8). Years in practice or participation in clinical trials was not associated with number of cases managed. No fatal bleeds were reported, and all patients

stopped bleeding. Because dabigatran undergoes 80% renal excretion but is only 35% protein bound, dialysis can remove dabigatran.[3] All of the patients with renal failure had dialysis and required a median of 4-5 sessions (range 1 to >7) to remove dabigatran's effect. Dialysis was reported as the most effective management strategy in 4/5 of dabigatran-associated bleeding episodes managed with dialysis (Table 2). Dabigatran was withheld in all reported cases of dabigatran bleeding and was considered the most effective strategy in 82% of patients. Factor concentrates were used in 9 patients experiencing major bleeding on dabigatran. Reported doses were lower than recommended to treat hemophilia,[68-70] and multiple doses of activated prothrombin complex concentrates (aPCC) and recombinant activated factor VII (rfVIIa) were used. Factor concentrates were perceived as effective in 50-80% of the patients bleeding with dabigatran. In the 2 cases where both prothrombin complex concentrates (PCC) and rfVIIa were given, both were considered effective by the treating physician. Unfortunately, the limited number of bleeding patients managed with factor concentrates does not allow for recommendations of one concentrate over another.

Fewer cases of rivaroxaban-associated bleeding were reported (Table 8). Similar to dabigatran, management of bleeding involved withholding the drug and local measures. aPCC was administered in 1 case. All interventions used to treat rivaroxaban-associated bleeding were perceived as effective. These patients are the first reported cases of managing rivaroxaban-associated bleeding in the literature.

Algorithms to manage bleeding patients have been proposed by several authors based on animal data and expert opinion.[64,63] Management algorithms were available at 12 (25%) of the respondents' institutions. Only 25% of the algorithms recommended antifibrinolytic medication, whereas all but one algorithm contained the use of factor concentrate (50% aPCC, 66% PCC, and 83% rfVIIa). Nine of the 12 institutional algorithms contained more than one factor concentrate. Factor concentrates were widely available; 62% of institutions had PCC, 87% had aPCC, and 98% had rfVIIa on-site.

Only three bleeding patients were managed at hospitals with treatment algorithms; thus, inferences as to the influence of the treatment algorithm on the management strategy cannot be made.

Due to predictable pharmacokinetics, dabigatran and rivaroxaban do not require monitoring during treatment but understanding the degree of anticoagulation is essential in a bleeding patient.[71] Dabigatran increases the prothrombin time (PT/INR) variably and the activated partial thromboplastin time (aPTT) in a non-linear fashion.[3] In the reported dabigatran bleeding cases, the PT/INR and aPTT were used to assess level of anticoagulation in 59% and 100% of cases, respectively. The thrombin time (TT) is the most sensitive assay to measure dabigatran's effects[3] and was used in 91% of dabigatran bleeding cases. At high dabigatran concentrations, the TT may be unmeasureable. A diluted TT can be used reliably to measure dabigatran even at high concentrations;[72] however, this assay was only available in 4 institutions and was not used in any of the bleeding cases. The ecarin clotting time (ECT) may more effectively assess dabigatran concentrations in overdose settings because of decreased sensitivity compared to the TT.[3] ECT was used in only 23% of dabigatran bleeding episodes, and these cases were managed in 2 of the 10 hospitals that had ECT available on-site. Laboratory assessment of bleeding patients on dabigatran is challenging because the assays most efficacious in overdose settings, ECT and diluted TT, are not widely available even at academic centers.

Similar to the dabigatran bleeding cases, 60% of the rivaroxaban bleeding patients were evaluated with PT/INR and 100% with aPTT. Chromogenic anti-Xa assays can be standardized to measure rivaroxaban[24] and rivaroxaban anticoagulation was assessed using an anti-Xa assay in all reported bleeding cases. Anti-Xa assays were available on-site in 91% of the respondents' hospitals including academic, academic affiliated and community practices. Therefore, the ability to measure rivaroxaban anticoagulation via anti-Xa is more accessible than assays for dabigatran.

A majority of physicians remain concerned about their ability to manage bleeding patients on the new oral anticoagulants; 27% of physicians reported moderate concern, 30% noted moderately high and 25% reported high concern. Only 9% of physicians reported mild and no concern. Physicians with moderate to high levels of concern attributed their apprehension to lack of established effective management, antidote, or experience with managing bleeding patients. Whereas physicians with only mild concern referenced infrequent major bleeding rates as the reason for their minimal concern. Average level of concern was lower in physicians who participated in clinical trials than in physicians who had not participated in trials, but this was not statistically significant (Mean 2.6 vs 3.6, p=0.07). Level of concern was not associated with years in practice, number of cases managed, or availability of treatment algorithm. Respondents' high level of concern regarding their ability to manage hemorrhage illustrates the unease associated with widespread use of the new anticoagulants.

Our survey results show management of dabigatran and rivaroxaban-associated bleeding varies. Effective management included withholding the drug or local measures in most cases. Factor concentrates were prescribed in 41% of dabigatran-associated bleeding, but a specific product cannot be recommended because of similar frequency of concentrate use and perceived effectiveness. Surprisingly, most academic institutions do not have diluted TT or ECT to measure elevated concentrations of dabigatran; whereas anti-Xa assays are widely available. Non-malignant hematologists remain concerned about their ability to manage patients, which reiterates the need for national registries or multicenter trials to determine the best management strategy for dabigatran and rivaroxaban-associated bleeding.

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Authorship Contributions

LBK completed the survey, analysis, manuscript writing and revisions. MTR completed survey and manuscript review and revisions.

Disclosure of Conflicts of Interest

A NIH T32 training grant supported LBK's fellowship. MTR served as consultant, speaker, advisory board member, and has received research funding from Novo Nordisk, Baxter, Bayer, Biogen Idec, Octapharma, and Pfizer.

Tables

Table 7: Baseline characteristics of survey respondents and non-respondents. Chi-square testing compared respondents to non-respondents.

	Respondent (n=48)	**Non-Respondent (n=104)**	**p-value**
Male n (%)	24 (50%)	56 (54%)	0.66
Academic Practice n (%)	37 (77%)	88 (85%)	0.26
Hemophilia Treatment Center n (%)	42 (88%)	88 (85%)	0.64
Level 1 Trauma Center n (%)	30 (63%)	71 (69%)	0.43
Duration in Practice median (range) years	15.5 (1-40)		
Clinical Trial Participants n (%)	6 (13%)		

Table 8: Reported dabigatran and rivaroxaban-associated bleeding episodes and perceived effectiveness of management strategies used in bleeding.

	Dabigatran	**Rivaroxaban**
Reported Cases n	43	5
Available Management Information n	22	5
Bleeding stopped n (%)	22 (100%)	5 (100%)
Major Bleeding[4] n (%)	11/21 (52%)	3/5 (60%)
Renal failure n (%)	5/21 (24%)	2/5 (40%)
Effectiveness of Management Strategies		
Withholding Medication	18/22 (82%)	4/4 (100%)
Local Measures	7/10 (70%)	2/2 (100%)
Invasive Procedure	0/1 (0%)	
Dialysis	4/5 (80%)	
Antifibrinolytic	1/2 (50%)	
PCC	3/4 (75%)	
Reported Dose	20-50 Units/kg	
Mean Number of Doses	1	
aPCC	1/2 (50%)	1/1(100%)
Mean Number of Doses	2	
rfVIIa	4/5 (80%)	
Reported Dose	10-40 mcg/kg	
Mean Number of Doses	2 (range 1-3)	

Fractions represent cases perceived effective/cases when intervention used.

PCC=prothrombin complex concentrate, aPCC= activated prothrombin complex concentrate, rfVIIa=recombinant activated Factor VII.

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