Dabigatran-Associated Intracranial Hemorrhage: Literature Review and Institutional Experience

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Abstract

Dabigatran etexilate is an oral direct thrombin inhibitor approved for prevention of stroke and systemic embolization in patients with nonvalvular atrial fibrillation and for the treatment of venous thromboembolism. Although dabigatran has a favorable safety profile, predictable pharmacokinetics, fewer drug interactions than warfarin, and does not require monitoring, clinical data regarding dabigatran reversal are limited. In addition, currently available laboratory assays allow measurement of the presence, but not extent, of dabigatran-associated anticoagulation. Patient age, renal function, weight, concurrent drug therapy, adherence, and concomitant disease states can affect dabigatran's efficacy and safety. Management of dabigatran-related intracranial hemorrhage must be approached on a case-by-case basis and include assessment of degree of anticoagulation, severity of hemorrhage, renal function, timing of last dabigatran dose, and risk of thromboembolic events. Initial management includes dabigatran discontinuation and general supportive measures. Oral activated charcoal should be administered in those who ingested dabigatran within 2 hours. Four-factor prothrombin complex concentrates (4PCCs), activated PCC, or recombinant activated factor VII use may be reasonable but is not evidence based. Reserve fresh frozen plasma for patients with dilutional coagulopathy. If readily available, hemodialysis should be considered, particularly in patients with advanced kidney injury or excessive risk of thromboembolic events. More clinical studies are needed to determine a standardized approach to treating dabigatran-associated intracranial hemorrhage. Institutional protocol development will facilitate safe, efficacious, and timely use of the limited management options.

Keywords

dabigatran, thrombin inhibitors, subarachnoid hemorrhage, intracerebral hemorrhage, intracranial hemorrhage

Introduction

Until recently, warfarin, an oral vitamin K antagonist, was the mainstay of stroke prevention in high- and moderate-risk patients with nonvalvular atrial fibrillation (NVAf). It is also commonly used to prevent and treat venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). However, warfarin is associated with multiple food and drug interactions, inter- and inpatient dosing variability, and the need for frequent monitoring.¹ These limitations led to the development of novel oral anticoagulants (NOACs) with specific activity on a single clotting factor and more reliable safety profiles. Dabigatran etexilate is an oral prodrug that is rapidly hydrolyzed to dabigatran, which directly inhibits thrombin. It was the first NOAC approved by the US Food and Drug Administration (FDA) for prevention of ischemic stroke and systemic embolism in patients

with NVAf. It is also approved for treatment of DVT and PE. Although dabigatran has a favorable safety profile, predictable pharmacokinetics, fewer drug interactions than

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warfarin, and no monitoring requirements, it has no antidote and clinical data regarding its reversal are limited.² We present 4 cases of dabigatran-associated intracranial hemorrhage managed at our institution and review the literature regarding management of this patient population. Waiver of informed consent was granted by the institutional review board. Baseline characteristics and pertinent admission data are described in Tables 1 and 2, respectively.

Cases

Case 1

A 79-year-old man with chronic kidney disease (CKD) who received dabigatran 75 mg orally twice daily for new-onset atrial fibrillation (AF) following coronary artery bypass grafting (CABG) and aortic valve replacement (AVR) 3 weeks before admission presented with left-sided basal ganglia intracerebral hemorrhage (ICH) measuring $3 \times 2.1 \text{ cm}^2$ with no midline shift. Dabigatran was discontinued and a 3-hour hemodialysis (HD) session was initiated 18 hours after admission and 30 hours after dabigatran ingestion. A second HD session was completed 24 hours later secondary to persistently elevated thrombin time (TT). Neither activated partial thromboplastin time (aPTT) nor TT decreased after the second HD session. The patient was discharged to a rehabilitation facility.

Case 2

An 80-year-old woman who received dabigatran 150 mg twice daily for NVAF, aspirin for coronary artery disease (CAD), and celecoxib for arthritis presented with traumatic subarachnoid hemorrhage (SAH). Dabigatran, aspirin, and celecoxib were discontinued. The patient received 4 units of fresh frozen plasma (FFP), 10 units of platelets, and phytonadione 5 mg orally once daily for 7 days. Eight hours after admission, the patient reported worsening headache; repeat noncontrast head CT showed progression of SAH. Hemodialysis was initiated 18 hours after admission and 29 hours after dabigatran ingestion, resulting in normalization of aPTT and international normalized ratio (INR) with persistent elevation in TT. A second HD session was completed 24 hours later with aPTT and INR remaining normal; TT was not remeasured. The patient was discharged to a rehabilitation facility.

Case 3

An 84-year-old woman who received dabigatran 150 mg orally twice daily for NVAF presented with acute left thalamic hemorrhage measuring $1.7 \times 2.4 \text{ cm}^2$ with ventricular extension and no midline shift. Dabigatran was discontinued. The patient received no HD, blood products, or coagulation factor products. Activated partial thromboplastin time remained elevated for 37 hours. The patient was discharged to a rehabilitation facility.

Case 4

A 90-year-old woman who received dabigatran 150 mg orally twice daily and dronedarone for NVAF presented with acute left temporoparietal subdural hematoma (SDH) measuring 7 mm in thickness, with SAH and trace intraventricular hemorrhage (IVH). Dabigatran and dronedarone were discontinued. Hemodialysis was initiated 3.75 hours after presentation. Time of last dabigatran dose is unknown. Postdialysis, the patient received 4 units of FFP. No additional blood products or coagulation factor products were administered. The aPTT did not significantly decrease after HD and remained elevated for the next 21 hours. The patient was discharged to a rehabilitation facility.

Discussion

The most recent guidelines for the management of AF recommend dabigatran as a first-line option for primary stroke prevention in patients with a CHA₂DS₂-VASc score 2 or higher or recurrent stroke in patients with NVAF.³ In addition, dabigatran is recommended for VTE treatment in certain situations.⁴ Dabigatran's FDA approval was based on results of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, which concluded that dabigatran 150 mg twice daily was superior to warfarin (dose adjusted for INR 2-3) for prevention of stroke or systemic embolization in patients with NVAF. In addition, there was no significant difference in major bleeding between groups and greater than 50% lower incidence of hemorrhagic stroke with dabigatran. The RE-LY trial also evaluated dabigatran 110 mg twice daily. At this dose, which was not FDA approved, dabigatran was noninferior to warfarin with respect to prevention of stroke and systemic embolization and had significantly lower rates of major bleeding and hemorrhagic stroke.⁵ Dabigatran was associated with increased rates of myocardial infarction (MI) in the RE-LY trial, but this was not statistically significant in a post hoc analysis.^{5,6} In the Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism (RE-COVER) trial, dabigatran 150 mg was noninferior to dose-adjusted warfarin for the treatment of acute VTE and was associated with lower bleeding rates. In addition, there were low overall rates of intracranial hemorrhage and a trend toward increased rates of gastrointestinal hemorrhage associated with dabigatran.⁷ A meta-analysis of direct thrombin inhibitors found that increased risk of MI appears to be a drug class effect.⁸ Approximately 20% of patients enrolled in the RE-LY trial had a prior stroke or transient ischemic attack (TIA).⁵ A subgroup analysis of this population found that dabigatran 150 mg was superior to warfarin for the prevention of subsequent stroke or thromboembolism, while dabigatran 110 mg was noninferior. In addition, when compared to warfarin, dabigatran 150 mg had similar rates of major bleeding while dabigatran 110 mg had lower rates.⁹ These findings are consistent with the overall findings of the RE-LY trial. A retrospective analysis examining in-hospital mortality among

Table 1. Baseline Characteristics of Patients Presenting With Dabigatran-Associated Intracranial Hemorrhage.

Patient	Age, Gender (M/F)	Type of Hemorrhage	Weight, kg	Outpatient Dabigatran Dose/Timing of Last Dose	Admission Creatinine, mg/dL/Creatinine Clearance, mL/min	Admission PT, Seconds/INR	Admission aPTT, Seconds	Additional Baseline Coagulation Parameters	Outpatient Medications (Medications With Pharmacokinetic or Pharmacodynamic Interactions With Dabigatran Are Italicized)	Past Medical/Surgical History (Dabigatran Indication Italicized)
1	79, M	ICH	70	75 mg twice daily/30 hours prior to HD	3.4/19	17.5/1.48	54	None measured	Metoprolol, albuterol, ipratropium, pravastatin, lisinopril	NVAF s/p CABG and AVR, CAD, CKD, COPD, HTN
2	80, F	Aneurysmal SAH	95	150 mg twice daily/29 hours prior to HD	0.9/43	16.8/1.4	60	None measured	Aspirin, celecoxib, diltiazem, lisinopril, hydrochlorothiazide, simvastatin, ezetimibe, metaxolone	NVAF, HTN, B/L CEA, dyslipidemia, arthritis, breast cancer (in remission)
3	84, F	ICH, IVH	74	150 mg twice daily/timing of last dose not known	0.7/47	17.9/1.5	57	TT = 225.4 seconds, dTT 35.1 seconds, ECT 22 seconds	Cyclosporine, levothyroxine, nadolol, duloxetine	NVAF, cutaneous vasculitis, hypothyroidism, HTN, depression
4	90, F	Traumatic SAH, SDH, IVH	59	150 mg twice daily/timing of last dose not known	0.8/33	22.3/2.1	65.2	None measured	Simvastatin, dronedarone, escitalopram, metoprolol, mirtazapine, digoxin	NVAF, CKD, depression, dyslipidemia, HTN

Abbreviations: aPTT, activated partial thromboplastin time; AVR, aortic valve replacement; CABG, coronary artery bypass graft; CAD, coronary artery disease; CEA, carotid endarterectomy; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; dTT, dilute thrombin time; ECT, ecarin clotting time; F, female; HD, hemodialysis; HTN, hypertension; ICH, intracerebral hemorrhage; INR, international normalized ratio; IVH, intraventricular hemorrhage; M, male; NVAF, nonvalvular atrial fibrillation; PT, prothrombin time; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; TT, thrombin time.

Table 2. Inpatient Laboratories, Treatments and Outcomes in Patients Presenting with Dabigatran-Associated Intracranial Hemorrhage.

Patient	Duration of Elevated aPTT, hours	Additional Coagulation Parameters Measured	HD During Admission (Yes/No)	HD Characteristics	Additional Interventions (eg Blood Products, Coagulation Factor Products, and Vitamin K)	Outcomes
1	37	TT = 99.3 sec after first HD session; TT = 89.1 sec after second HD session	Y	First session started 18 hours after admission. Second session 42 hours after admission. Each session was 3 hours long on high-flux dialyzer with no fluid removal.	None	Hematoma expanded between outside facility and our facility. No hematoma expansion after HD. Discharged to rehabilitation facility.
2	28	TT = 58.4 sec after first HD session	Y	First session started 18 hours after admission. Second session 42 hours after admission. Each session was 3 hours long on high-flux dialyzer with no fluid removal.	4 units FFP and 10 units platelets given prior to hemodialysis Vitamin K 5 mg orally × 7 days starting on day of admission	Hematoma expansion after blood product administration. No further expansion after HD. Discharged to rehabilitation facility.
3	37	None measured	N	NA	None	No hematoma expansion. Discharged to rehabilitation facility.
4	21	None measured	Y	Single dialysis session started 3 hours and 45 minutes after admission. Session was 3 hours long on high- flux dialyzer with no fluid removal.	4 units FFP administered after HD due to persistent elevation in aPTT	No hematoma expansion after HD. Discharged to rehabilitation facility.

Abbreviations: aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; HD, hemodialysis; NA, not applicable; TT, thrombin time.

patients with AF and intracranial hemorrhage associated with dabigatran or warfarin found that mortality was similar between the groups, even when stratified based on the type of hemorrhage.¹⁰

Since its approval, numerous reports of dabigatran-associated hemorrhagic stroke have been published and reported via FDA's Adverse Event Reporting System.¹¹⁻¹⁷ Consequently, FDA investigated actual rates of hemorrhage in new dabigatran users versus new warfarin users using insurance claims and administrative data. The investigation found similar rates of gastrointestinal and intracranial hemorrhage between the groups.^{18,19} These findings were confirmed by a retrospective cohort study comparing treatment naive patients who received dabigatran (110 or 150 mg) and a propensity-matched group of patients treated with warfarin. Comparing warfarin with each dose of dabigatran, the study found similar rates of stroke and systemic embolization, similar rates of major bleeding, and lower rates of intracranial bleeding with both dabigatran doses.²⁰ In contrast, the Institute for Safe Medication Practices reports that adverse events associated with dabigatran were significantly more likely to result in death when compared to warfarin, even when adjusted for age and gender.²¹

In December 2012, a randomized clinical trial in which patients with bi-leaflet mechanical prosthetic heart valves received either dose-adjusted warfarin or dabigatran was terminated early due to higher rates of VTE and major bleeding in dabigatran-treated patients.²²⁻²⁴

Considerations for Use

Renal function. Approximately 80% of dabigatran is excreted unchanged in the urine. As renal function declines with age or renal disease, dabigatran exposure increases, necessitating decreased dosages (Table 3).^{2,25} Notably, patients with creatinine clearance (CrCl) less than 30 mL/min were excluded from phase III studies of dabigatran.²⁶⁻²⁹ Dosing recommendations for this patient population are based on a pharmacokinetics study conducted in patients who received a single dabigatran dose. Area under the plasma concentration-time curve, C_{max}, and half-life increased as renal function decreased.³⁰ Although the half-life of dabigatran is 12 to 17 hours in healthy patients, it can be prolonged to over 24 hours in patients with severe renal dysfunction and over 34 hours in patients with end-stage renal disease requiring HD, as seen in Table 4.^{2,25,30} Increased dabigatran exposure due to impaired

Table 3. Dosing Considerations for Dabigatran Etxilate for Nonvalvular Atrial Fibrillation.^{2,a,b}

Condition	Recommended Dose
CrCl > 30 mL/min	150 mg by mouth twice daily
CrCl 15 to 30 mL/min	75 mg by mouth twice daily
CrCl < 15 mL/min	Dosing recommendations not provided by manufacturer
Renal replacement therapy	Dosing recommendations not provided by manufacturer
CrCl 30 to 50 mL/min with concurrent use of P-gp inhibitors dronedarone or systemic ketoconazole	Consider administering 75 mg by mouth twice daily
CrCl 30 to 50 mL/min with concurrent use of P-gp inhibitors other than dronedarone or systemic ketoconazole	150 mg by mouth twice daily
CrCl < 30 with concurrent use of P-gp inhibitors	Avoid concurrent use
P-gp inducers	Avoid concurrent use

Abbreviations: CrCl, creatinine clearance; P-gp, permeability glycoprotein.

^aP-gp inducers include: carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir.

^bP-gp inhibitors include: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ritonavir, quinidine, ranolazine, and verapamil.

Table 4. Influence of Renal Impairment on Dabigatran's Half-Life.³⁰

Creatinine clearance, mL/min	>80	>50-≤80	>30-≤50	≤30	ESRD
T½, hours	13.8	16.6	18.7	27.5	34.1

Abbreviations: ESRD, end-stage renal disease; T½, half-life.

renal function is directly linked to its safety. Worsening renal function is a risk factor for major bleeding and a contributor to increased trough dabigatran concentrations, which is itself a risk factor for major bleeding.³¹⁻³³ In a prespecified analysis of the RE-LY trial, worsening renal function was associated with increased risk of hemorrhage in patients in all treatment arms. Despite this, efficacy results for dabigatran were consistent with the results of the overall trial and neither dose of dabigatran was associated with an increased risk of hemorrhage when compared to warfarin.³⁴

Age. The mean age of patients enrolled in the RE-LY trial was 71.4 years, with 40% of patients aged 75 years or older.^{2,5} Among these older patients, the risk of intracranial bleeding was lower with dabigatran when compared to warfarin. However, increasing age was associated with increased risk of hemorrhage across all patients enrolled in the trial, regardless of the drug therapy that they received.³⁵ A meta-analysis examining the efficacy and safety of dabigatran in patients aged 75 and older found that dabigatran was more effective

than conventional anticoagulants and had similar rates of major or clinically significant bleeding.³⁶ The manufacturer does not recommend adjusting dabigatran dosages based on age.² However, the risk-benefit profile must be considered for each patient, particularly those in the extremes of age. Age and renal function are intricately related as renal function declines with age.

Weight. The mean weight of RE-LY trial participants, dabigatran-treated patients, was approximately 82 kg.⁵ Compared to patients weighing 50 to 100 kg, those weighing less than 50 kg had higher dabigatran trough concentrations, while those weighing over 100 kg had lower dabigatran trough concentrations. Higher dabigatran trough concentrations were associated with increased major bleeding risk, while the risk of stroke or systemic embolism increased with lower dabigatran trough concentrations.³³ While the manufacturer does not recommend dosage adjustments for patients with extremely low or high weight, it is important to note that elderly patients with low body weight and impaired renal function may be at particular risk of dabigatran-associated hemorrhage due to increased trough concentrations.

Drug-drug interactions. Although dabigatran has fewer drug interactions than warfarin, it is subject to pharmacokinetic and pharmacodynamic drug interactions (Table 3). Dabigatran is a substrate of the permeability glycoprotein (P-gp) efflux transporter. Permeability glycoprotein inducers, such as rifampin, decrease dabigatran concentrations and should be avoided due to increased risk of VTE. Permeability glycoprotein inhibitors increase dabigatran concentrations, potentially leading to increased bleeding complications. Studies have implicated P-gp inhibitor use as a risk factor for bleeding in patients taking dabigatran.^{31,32,37} Dabigatran also has pharmacodynamic drug interactions when concurrently administered with other anticoagulants, antiplatelets, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, or systemic corticosteroids.^{31,32,37} Selective serotonin reuptake inhibitors (SSRIs) theoretically could interact pharmacodynamically with dabigatran. Among patients enrolled in the RE-LY trial, 38.4% received concomitant aspirin or clopidogrel. In terms of efficacy, dabigatran 110 mg remained noninferior to warfarin regardless of receipt of concomitant antiplatelet therapy. Among patients who received dabigatran 150 mg plus concomitant aspirin or clopidogrel, there was a trend toward a reduced benefit. Patients who received dabigatran with or without antiplatelets experienced fewer major bleeds than warfarin-treated patients. However, all patients treated with antiplatelets had higher rates bleeding when compared to patients who did not receive antiplatelets.³⁸ The decision to use dabigatran in combination with an agent that may increase bleeding risk must be based on a patient-specific risk-benefit analysis. Whenever possible, the concurrent therapy should be administered for the shortest appropriate duration.³⁹

Adherence. Because of dabigatran's short half-life, missed doses could decrease efficacy, leading to the drug's black box warning for increased risk of thromboembolic events associated with premature drug discontinuation.² However, a study of adherence rates to dabigatran using pharmacy- and patient-reported information found that 11% of patients missed at least 20% of dabigatran doses over the course of 3 months to 6 years; none of these patients experienced VTE or stroke during the study period.⁴⁰

Among the patients treated at our institution, dabigatran was prescribed for NVAf in 3 patients and off-label use in 1 patient. Patients ranged in age from 79 to 90 years, older than the mean age of patients enrolled in the RE-LY trial. Our patients weighed 59 to 90 kg and had impaired renal function with CrCl ranging from 19 to 47 mL/min. Increasing age, worsening renal function, and low body weight are associated with increased risk of hemorrhage, and their effects may be additive, such that an elderly patient with low body weight and decreased renal function may be at a higher risk of hemorrhage due to multiple risk factors. In 3 of our patients, dabigatran was dosed correctly, including patient 1 who received a reduced dose secondary to CKD. Patient 4 received concomitant dronedarone and dabigatran 150 mg twice daily. Because her CrCl was 33 mL/min, the patient should have received dabigatran 75 mg twice daily. This dosing error may have caused increased plasma dabigatran levels and contributed to the SDH. Patient 4 had additional risk factors for dabigatran-associated hemorrhage, including advanced age (90 years), low body weight (59 kg), and concomitant use of escitalopram, an SSRI. Two additional patients treated at our institution had drug interactions with dabigatran that could have contributed to their hemorrhages. Patient 2 received concomitant aspirin and celecoxib that likely caused platelet dysfunction and contributed to her SAH. Patient 3 received concomitant duloxetine, a serotonin-norepinephrine reuptake inhibitor that could have contributed to increased risk of hemorrhage through similar mechanisms as SSRIs. These cases highlight the importance of considering patient-specific risk factors when prescribing dabigatran, along with the potential that risk factors may have an additive effect.

Monitoring Considerations

One widely touted benefit of dabigatran is that it does not require routine monitoring of drug concentration or measures of coagulation. However, safety and efficacy are related to trough concentrations, suggesting that patient outcomes could be improved by establishing a therapeutic range and measuring dabigatran trough concentrations or by adjusting dosages based on patient factors.³³ Two studies have reported therapeutic ranges observed in patients taking dabigatran 150 mg orally twice daily, although these ranges have not been correlated with efficacy or toxicity, and monitoring of dabigatran concentrations is not readily available.^{41,42}

Dabigatran prolongs aPTT, prothrombin time (PT), TT, dilute thrombin time (dTT), ecarin clotting time (ECT), and activated clotting time (ACT). Prothrombin time and TT do not accurately quantify dabigatran-associated anticoagulation and should be avoided.⁴¹ Several investigations demonstrate that while aPTT becomes less sensitive at supratherapeutic dabigatran concentrations, it provides a qualitative assessment of dabigatran concentrations.^{41,43-45} Conversely, a recent study found that, depending on the reagent used, up to 35% of patients with normal aPTT have therapeutic dabigatran concentrations.^{41,42} Ecarin clotting time and dTT are sensitive at higher concentrations but they are not validated, widely available, or FDA approved for use with dabigatran.⁴¹ Dilute thrombin time is the most sensitive test to evaluate the degree of dabigatran-associated anticoagulation and could be used to distinguish between nonadherence and treatment failure in patients with stroke or systemic embolism, measure the degree of anticoagulation in patients with intracranial hemorrhage, and evaluate the effectiveness of reversal strategies in a patient with intracranial hemorrhage. Elevated TT or aPTT indicate the presence of dabigatran in the plasma but cannot provide quantitative information regarding the extent of anticoagulation. Normal aPTT levels cannot be used to rule out the presence of dabigatran.

Management of Dabigatran-Associated Intracranial Hemorrhage

Dilute thrombin time should be measured in patients with suspected dabigatran-associated intracranial hemorrhage. If dTT is not available, aPTT and TT should be measured, with elevated levels indicating the presence of therapeutic dabigatran concentrations and normal levels not ruling out therapeutic levels of anticoagulation. Particularly in the setting of normal aPTT or TT, the neurointensivist must determine the timing of the last dabigatran dose, since patients are fully anticoagulated within 1 to 3 hours of ingesting dabigatran. In patients with normal renal function, the clinical effects of dabigatran dissipate within 24 to 48 hours of the last dose, and reversal may not be required or indicating depending on the timing of the last dose.² Conversely, patients with impaired renal function could remain anticoagulated for 3 to 5 days.² This is in contrast to warfarin, which is associated with therapeutic INR and clinical efficacy even in the setting of 1 or more missed doses, regardless of renal function, and reversal is indicated in the majority of patients with intracranial hemorrhage.

Dabigatran antidotes are under development. A humanized monoclonal antibody fragment (anti-Dabi-Fab) inhibited anticoagulant activity of dabigatran in vitro and in rhesus monkeys and reduced blood loss in animal studies. This agent does not have procoagulant properties.^{41,46} Another investigative molecule, PER977, reverses multiple anticoagulants, including dabigatran.⁴⁷ No clear guidance for acute dabigatran reversal is provided by the manufacturer.² Recognizing this, our institution developed a protocol for the management of

dabigatran-associated hemorrhage (Appendix A). The protocol states that dabigatran should be immediately discontinued and supportive care administered, including volume or RBC replacement, and local methods to stop bleeding.^{3,43} Activated charcoal prevents drug absorption, *in vitro*, and should be considered if dabigatran ingestion occurred within 2 hours.^{41,48} Our protocol recommends HD next, if possible, to accelerate dabigatran's plasma clearance. This is based on studies indicating that HD removed 48% to 68% of dabigatran.^{30,49} Case reports and series describe HD use for dabigatran removal in patients with hemorrhagic stroke.^{13,15,16,50} Because of the risk of early hematoma expansion in intraparenchymal hemorrhage, the viability of HD may be limited by the risk of obtaining vascular access in an anticoagulated patient, delayed availability of HD, and duration of HD. Despite these limitations, our institutional guidelines recommend HD before the use of factor products and FFP due to the lack of proven efficacy and safety concerns associated with these agents.

Three- and four-factor prothrombin complex concentrates (3PCC, 4PCC), activated PCC (aPCC, FEIBA), and recombinant activated factor VII (rFVIIa) are options to reverse the anticoagulant effects of dabigatran in intracranial hemorrhage. These agents have an immediate onset of action and small infusion volumes. However, arterial and venous thromboembolic events are associated with rFVIIa, 4PCC, and aPCC, and the products available in the United States have associated black box warnings for their approved indications.⁵¹⁻⁵³ Evidence to support the use of coagulation factors is limited and inconsistent. In animals, 4PCC improved blood loss and time to hemostasis, prevented ICH expansion, and decreased 24-hour mortality.^{54,55} However, in human studies, 4PCC failed to correct aPTT, ECT, or dabigatran-induced lag time of thrombin generation, although the clinical significance of this is unknown.^{56,57} A case report describes the successful reversal of dabigatran-associated hemorrhage with aPCC during cardiac ablation.⁵⁸ In human blood samples, aPCC corrected dabigatran-induced lag time of thrombin generation; however, the clinical significance of this is unknown.⁵⁷ In addition, aPCC reversed prolonged bleeding time in dabigatran-anticoagulated rats.⁵⁹ In 1 animal study, rFVIIa reversed prolonged bleeding time and aPTT.⁵⁹ Additionally, rFVIIa corrected dabigatran-induced lag time of thrombin generation in human blood samples.⁵⁷ However, in other animal studies, rFVIIa did not reduce blood loss, prevent ICH expansion in dabigatran-associated hemorrhage, or normalize aPTT, TT, or ECT.^{55,56,60} In an animal model of intracerebral bleeding, FFP reduced the volume of dabigatran-associated ICH with no effect on mortality.⁵⁵ However, FFP plus rFVIIa did not restore hemostasis in a patient with dabigatran-related epidural hematoma and spinal cord compression after traumatic injury.⁶¹ Drawbacks of FFP administration include need for thawing and cross-matching, prolonged infusion time, risk of transfusion-related acute lung injury and allergic reaction, and large volume load.^{62,63} Guidelines recommend FFP administration only in patients with dilutional coagulopathy.⁴³

Based on this limited data, it seems reasonable to administer 4PCC, aPCC, or rFVIIa to treat intracranial hemorrhage; however, the lack of human efficacy data and risk of thromboembolism must be considered.

Dabigatran was immediately discontinued in all of our patients. In 2 of the 3 patients who received FFP, lack of efficacy was demonstrated. In patient 2, hematoma expansion occurred after FFP administration. In patient 4, aPTT remained elevated after FFP administration. No patients received activated charcoal, recombinant factor VIIa, or PCCs. Patient 2 received vitamin K and platelets, despite lack of data to support these interventions. Patients 1, 2, and 4 received HD. Based on their impaired renal function, these patients had estimated dabigatran half-lives of 18.7 to 34 hours. In patients 1 and 2, HD was initiated 29 to 30 hours after dabigatran ingestion. However, these patients had elevated aPTT at the time of HD, and aPTT was effectively decreased by HD. In patient 4, HD was administered within 4 hours of emergency department presentation. The aPTT increased after HD, indicating dabigatran redistribution after HD.

Management of Acute Ischemic Stroke in Patients Taking Dabigatran

Three cases of thrombolysis with recombinant tissue-type plasminogen activator (rtPA) for acute ischemic stroke (AIS) in patients taking dabigatran have been reported. All patients received rtPA without symptomatic hemorrhagic transformation.^{64,65} Due to increased risk of hemorrhage, guidelines for early management of AIS recommend against use of rtPA in anticoagulated patients.⁶⁶ Guidelines state that careful history, including time of last ingested dabigatran dose, history of renal dysfunction, and assessment of coagulation parameters is essential. Normal aPTT cannot rule out therapeutic dabigatran concentrations and dTT may not be readily available. Therefore, if a patient's history, coagulation parameters, or renal function indicate that therapeutic dabigatran concentrations may be present, then risk of hemorrhage likely outweighs benefits of thrombolysis.⁶⁶ Based on dabigatran's half-life, it is unlikely that a patient would be a candidate for intravenous rtPA unless they missed at least 2 dabigatran doses. Uncertainties remain, including the safety of dabigatran reversal prior to rtPA administration and of endovascular therapy.

Restarting Dabigatran After AIS

The optimal timing of restarting anticoagulation after AIS is unknown. Clinical factors including stroke size, risk factors for recurrent thrombosis (eg, presence of mechanical valves), and blood pressure control must be considered when deciding when to restart anticoagulation.^{67,68} Patients were excluded from the RE-LY trial if they had AIS within 6 months of enrollment.⁵ Based on the lack of safety data in this time

period, it is reasonable to avoid dabigatran use within 6 months of AIS.

Restarting Anticoagulation After Intracranial Hemorrhage

It is not known whether or when anticoagulation can be safely restarted after intracranial hemorrhage. Oral anticoagulation is a risk factor for recurrent ICH.⁶⁹ Additional factors for recurrent ICH include advancing age, uncontrolled hypertension (HTN), spontaneous hemorrhage, lobar hemorrhage, cerebral amyloid angiopathy, microhemorrhages, malignancy, severe leukoaraiosis, and need for concurrent antiplatelet therapy.⁷⁰ When deciding whether or when to restart anticoagulation, the neurohospitalist must balance the risk of recurrent ICH against the risk of thromboembolism. Factors that may increase the risk of thromboembolism include vascular risk factors, advanced age, mechanical heart valve, left ventricular assist device, intracardiac thrombus, NVAf with very high CHADS2 score, prior AIS, hypercoagulable disorder, and malignancy.⁷⁰ Notably, uncontrolled HTN, advanced age, and malignancy increase risk of both recurrent ICH and thromboembolism. In addition, although dabigatran was associated with lower rates of intracranial hemorrhage than warfarin in the RE-LY trial, it is not known if this remains true for recurrent intracranial hemorrhage.^{5,70} These factors must be assessed for each patient in whom anticoagulation may be restarted after hemorrhagic stroke.

Management of Anticoagulation for Surgical Procedures

Dabigatran should be discontinued 24 to 48 hours or 3 to 5 days prior to nonurgent procedures for patients with CrCl greater than or less than 50 mL/min, respectively. Longer delays are necessary for patients undergoing major surgery, spinal puncture, or insertion of spinal or epidural ports or catheters. However, these patients may require coverage with another anticoagulant such as intravenous heparin. For more urgent procedures, anticoagulation must be reversed as described previously.² When restarting dabigatran after surgical procedures, timing should take into account the rapid onset of anticoagulation within 1 to 3 hours of dabigatran ingestion.

Conclusions

Management of dabigatran-related intracranial hemorrhage must be approached on a case-by-case basis and include assessment of degree of anticoagulation, severity of hemorrhage, renal function, timing of last dabigatran dose, and risk of thromboembolic events. Initial management includes dabigatran discontinuation and general supportive measures. Oral activated charcoal should be administered in those who ingested dabigatran within 2 hours. Administration of four-factor prothrombin complex concentrates, aPCC, or rFVIIa may be reasonable but is not evidence based. Reserve FFP for

patients with dilutional coagulopathy. If readily available, HD should be considered, particularly in patients with advanced kidney injury or excessive risk of thromboembolic events. More clinical studies are needed to determine a standardized approach to treat dabigatran-associated intracranial hemorrhage. Institutional protocol development will facilitate safe, efficacious, and timely use of the limited management options.

Appendix A

Protocol for the Use of Dabigatran for Nonvalvular Atrial Fibrillation, Section on Management of Major or Life-Threatening Hemorrhagic Events

Minor bleed	Hold or discontinue treatment with dabigatran, if clinically appropriate. Order PTT to determine degree of elevation.
Moderate to severe bleed	Symptomatic management mainly consists of supportive care by attempting to control the source of bleeding and provide hemodynamic support. Administration of PRBCs as needed for significant blood loss is appropriate. Administer activated charcoal if administration of dabigatran was within 2 hours. Hemodialysis should be considered in all major dabigatran-associated hemorrhages. Order a stat consult from nephrology. Consult hematology or vascular medicine for further management options, especially in patients with thrombocytopenia or on concomitant antiplatelet therapy.
Life-threatening bleed	In addition to steps listed previously under moderate to severe bleed category, consult hematology, or vascular medicine for further recommendations. FFP, recombinant factor VIIa, or prothrombin complex concentrates may be considered, but are likely not effective in reversing the anticoagulant effect of dabigatran and should only be considered as a last resort when all other measures as listed previously have been ineffective.

Authors' Note

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