Enhanced Elimination of Dabigatran Through Extracorporeal Methods

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Abstract Several pharmacokinetic studies have suggested that dabigatran possesses a number of ideal properties for expedited removal via extracorporeal methods. However, this practice has not been prospectively evaluated in patients with life-threatening bleeding or requiring emergency surgery secondary to dabigatran-associated coagulopathy. The purpose of this literature review is to evaluate the published evidence surrounding extracorporeal removal of dabigatran in the setting of emergency surgery or life-threatening bleeding. A query of MEDLINE, Web of Science, International Pharmaceutical Abstracts, and Google Scholar using the terms dabigatran, dabigatran etexilate, hemodialysis, renal replacement therapy, hemorrhage, and atrial fibrillation was used to retrieve relevant literature. Furthermore, a manual search of

the references of the identified literature was performed to capture additional data. Current evidence suggests that extracorporeal removal of dabigatran may play a role in the setting of life-threatening bleeding and emergent surgery. Conflicting evidence exists with regard to the potential for redistribution based on serum dabigatran concentrations. In addition, a number of practicalities must be considered before incorporating this technique in the clinical setting. Extracorporeal removal of dabigatran may be a treatment modality in selected patients who require emergency reversal.

Keywords Dabigatran · Hemodialysis · Hemofiltration · Toxicity · Renal replacement therapy

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Introduction

Dabigatran is an orally administered direct thrombin inhibitor approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF), and for treatment and secondary prevention of venous thromboembolism [1]. Dabigatran's pharmacologic profile is summarized in Table 1 [1–4]. Although target-specific oral anticoagulants represent an important advance over vitamin K antagonists [5], they carry limitations that may place patients at risk for hemorrhage or treatment failure. These include limited outcome data in special populations, no readily available measure of the adequacy of anticoagulation, and lack of a specific reversal agent [6].

Since dabigatran's approval for clinical use by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), numerous reports have appeared of bleeding complications [7–17]. In the Randomized Evaluation of Long-term anticoagulation therapy (RE-LY) study, the rate of overall major bleeding was similar between dabigatran and warfarin. Further, while intracranial bleeding was reduced (0.3

Table 1 Pharmacologic properties of dabigatran [1–4]

Oral bioavailability	3–7 %
$T_{\max}$	1–3 h
Protein binding	35 %
Volume of distribution	0.7–1.0 L/kg (based on a 70-kg patient)
Onset of effect	0.5–2 h
Time to steady state	Approximately 3 days
Metabolism	Carboxylesterase 1 converts dabigatran etexilate to dabigatran (active)
Renal elimination	80 %
Dialyzability	62 % (at 2 h) and 68 % (at 4 h)
Drug interactions	P-glycoprotein inhibitors and inducers, and antiplatelets
Dosing	CrCl >30 mL/min; 150 mg twice daily CrCl ≤30 mL/min; 75 mg twice daily ^a CrCl <15 mL/min; contraindicated

^a Patients with CrCl <30 mL/min were excluded from the RE-LY study. The use of dabigatran in patients with a CrCl <30 mL/min is considered contraindicated in the European and Canadian product labeling. The US dose adjustment (75 mg twice daily) for patients with a CrCl 15 to 30 mL/min is based on a pharmacokinetic model. The predicted peak and trough dabigatran concentrations with this dosage are similar to those obtained in patients with moderate renal impairment receiving 150 mg twice daily. The safety and efficacy of the dosage reduction have not been formally evaluated

versus 0.8 %), gastrointestinal bleeding was greater (1.6 versus 1.1 %) in dabigatran-treated patients [18]. The majority of data suggest that the risk of major hemorrhage with dabigatran is at least similar to warfarin [7, 10, 19–21]. Although voluntary reporting of dabigatran-related adverse events is almost certainly prone to bias, these cases provide clinicians with valuable information [10, 21, 22]. Most reports suggest that patients often had multiple risk factors for hemorrhage. The most commonly reported risk factor was renal impairment, which leads to significant dabigatran accumulation [23].

One of the challenges with dabigatran is the lack of data on the optimal management of dabigatran-related hemorrhage. Although several authors have suggested prothrombin

complex concentrates (PCC), factor eight inhibitor bypassing activity (FEIBA), and other hemostatic agents, evidence supporting these options is limited [24–27]. Nonetheless, hemostatic agents may be considered in the setting of life-threatening bleeding and is discussed elsewhere [25–27]. Dabigatran is extensively absorbed by activated charcoal in vitro; however, dabigatran's rapid absorption (time to peak plasma level, 1 h) limits the use of this modality to patients presenting with dabigatran overdose [2]. Extracorporeal removal is a potential consideration for treatment in the setting of dabigatran toxicity. An evaluation of dabigatran's pharmacological profile suggests that extracorporeal removal can expedite its clearance from plasma (Table 2) [1, 2, 28–32]. Several authors have provided evidence to support extracorporeal removal as a strategy to manage dabigatran-related hemorrhage [32–34]. We offer a narrative review of the published literature evaluating extracorporeal removal as a therapeutic modality in the management of dabigatran-related hemorrhage.

Data Extraction

We performed a comprehensive search strategy to identify any pertinent literature discussing the management of dabigatran-related bleeding using renal replacement therapy. Relevant literature was identified with MEDLINE (1950–July 2014), Web of Science (1900–July 2014), International Pharmaceutical Abstracts (1970–July 2014), and Google Scholar using combinations of the key words dabigatran, dabigatran etexilate, hemodialysis, renal replacement therapy, hemorrhage, and atrial fibrillation. In addition, annual meeting abstracts (1990–July 2014) presented at the American Society of Hematology, International Society of Thrombosis and Hemostasis, American College of Cardiology, and American Heart Association were searched using the same key words. References of identified citations were manually searched to identify any other relevant publications. Preference was

Table 2 Comparison of dabigatran with ideal characteristics for hemodialysis [1, 2, 28–32]

	Ideal characteristics	Dabigatran	Dialyzability?
Molecular weight (daltons)	<500	471.5	Yes
Protein binding	<80 %	35 %	Yes
Volume of distribution (V_d)	<1.0 L/kg	0.7–1.0 L/kg ^a	Questionable ^b
Water solubility	Yes	Slightly soluble ^c	Questionable
Net increase in plasma clearance by hemodialysis	≥30 %	62–67 %	Yes

^a Based on a 70-kg patient and V_d reported in product labeling of 50–70 L

^b Apparent volume of distribution during the terminal phase has been reported as 2.4–26.6 L/kg (based on a 70-kg patient) depending on the population studied [32]

^c The water solubility for dabigatran etexilate (prodrug) is 1.8 mg/mL. There is no value reported in the literature for dabigatran (active moiety)

placed on the inclusion of data obtained from controlled clinical studies and humans.

Pharmacologic Basis for Extracorporeal Removal

Dabigatran etexilate is a prodrug rapidly converted to the active moiety (dabigatran) via esterase-catalyzed hydrolysis in the intestine. Dabigatran is a potent competitive thrombin inhibitor [2], inhibiting both fibrin-bound and unbound thrombin. Dabigatran has a low oral bioavailability, ranging from 3 to 7 % and is predominantly cleared (80 %) by the kidneys [1, 2, 29, 35]. The recommended dosage for prevention of stroke in patients with nonvalvular AF and for treatment and secondary prevention of venous thromboembolism is 150 mg twice daily [1].

A therapeutic range for dabigatran has not been established, but current evidence suggests a correlation between plasma concentrations and the incidence of both thrombosis and hemorrhage [36]. Dabigatran is not significantly protein bound, has a low-to-moderate steady state volume of distribution ($V_d=0.7\text{--}1.0$ L/kg; based on a 70-kg patient), and has a low molecular weight (Table 1). All of these attributes make dabigatran a candidate for extracorporeal removal, although the low protein binding and variable moderate-to-high V_d during the terminal phase (2.4–26.6 L/kg; based on a 70-kg patient) suggest redistribution of dabigatran into the plasma post extracorporeal removal may occur [32]. Redistribution is typically seen in medications with large V_d (>1 L/kg) [37].

Dabigatran is a highly polar compound that does not undergo oxidative metabolism and is primarily excreted unchanged in the urine [29, 31]. The predominant route of dabigatran metabolism is conjugation to glucuronic acid [29], with *UGT2B15* serving as the major enzyme for metabolism and *UGT1A9* and *UGT2B7* serving as minor contributors to this process [38]. In fact, acyl glucuronides have been shown to prolong activated partial thromboplastin time to a similar extent as dabigatran, and as such may contribute to the drug's effect [29]. Dabigatran's elimination half-life ranges from 12 to 28 h, depending on renal function [1, 39].

Dabigatran etexilate (but not dabigatran itself) is a substrate for the multidrug efflux transporter P-glycoprotein, which is extensively distributed in the intestinal epithelium [1, 40]. As a result of this active process, administration of the drug with potent inhibitors or inducers of P-glycoprotein may result in increased or decreased plasma concentrations, respectively [41]. Specifically, administration of dabigatran etexilate with potent P-glycoprotein inducers (i.e., rifampin) should be avoided [1]. Administration of dabigatran with potent P-glycoprotein inhibitors (i.e., ketoconazole, verapamil, amiodarone, quinidine) may significantly increase dabigatran exposure and subsequent risk of toxicity [41]. Cases of dabigatran toxicity have been reported in patients taking

concomitant P-glycoprotein inhibitors [42, 43]. Additive effects are expected if dabigatran etexilate is administered with other drugs known to inhibit coagulation, such as antiplatelet agents [1, 41]. Dabigatran requires an acidic environment for optimal absorption; therefore, administration with acid suppression therapies (i.e., proton pump inhibitors and histamine receptor antagonists) may decrease absorption (up to 35 %).

Genetic polymorphisms have been shown to impact the bioavailability and effects of dabigatran within the systemic circulation. For example, a recent analysis demonstrated that the single-nucleotide polymorphism of carboxylesterase-1, rs2244613, was present in 32.8 % of subjects enrolled in the RE-LY trial, which was found to be protective as lower trough concentrations of dabigatran and correlate with a lower risk of bleeding [35]. In addition, polymorphisms in *ABCB1*, the gene that encodes P-glycoprotein, can influence the bioavailability of dabigatran [23, 44]. Collectively, although dabigatran possesses some of the attributes of an ideal anticoagulant, genetic polymorphisms and drug-drug interactions may place patients at an increased risk for iatrogenic events. The clinical application of genetic polymorphisms has not been elucidated.

Laboratory Assessment to Determine Presence of Dabigatran

Coagulation assays are available to measure the impact of dabigatran on hemostasis. The utility of coagulation assays for assessing the effects of dabigatran has been discussed in detail previously [25, 45, 46]. The activated partial thromboplastin time (aPTT) and thrombin time (TT) assays are useful for qualitative effect of dabigatran. Unlike partial thromboplastin time, the aPTT assay uses an activator to speed up the clotting time resulting in a more sensitive test with a narrower therapeutic range [47]. The relation between aPTT and dabigatran concentration is curvilinear, with a flattening of the curve above dabigatran concentrations of 200 ng/mL [2]. The aPTT is useful for identifying the presence of dabigatran, but not the degree of anticoagulation. TT reflects the conversion of fibrinogen to fibrin. Because dabigatran catalyzes the conversion of fibrinogen to fibrin, the TT is too sensitive for dabigatran concentrations above 25 ng/mL and is most useful when the result is within the normal reference interval, which argues against the presence of dabigatran [48].

Ecarin clotting time (ECT) and dilute thrombin time (dTT) are useful for quantitative assessment of the response to dabigatran [45]. ECT and dTT have strong linear correlations with dabigatran plasma concentrations ($r^2=0.92$ and 0.99 , respectively) [2, 44]. Both of these assays can be useful determining excess anticoagulant activity in life-threatening bleeding or for emergency surgical procedures. The major limitation of these assays is their availability to clinicians,

standardization with dabigatran, FDA and EMEA approval status, and lack of clearly defined therapeutic ranges for dabigatran [2, 45].

Although definitive therapeutic ranges have not been validated with dabigatran, both ischemic and bleeding outcomes were highly correlated with dabigatran plasma concentrations in the RE-LY study [36, 49]. Mean dabigatran trough levels achieved in patients with any and major bleeding were 111 and 141 ng/mL in the RE-LY trial, respectively [50]. Expected peak and trough concentrations in patients receiving dabigatran 150 mg twice daily are approximately 180 and 90 ng/mL; respectively [51]. The mean dabigatran trough concentration in the RE-LY study was 91 ng/mL (28.2–155 ng/mL, 10th and 90th percentile) [36]. However, a therapeutic range of 30 to 130 ng/mL at trough has been suggested [46]. Levels above 200 ng/mL at trough are associated with an increase in bleeding [52]. The values can be used to interpret the dabigatran plasma concentration to coagulation assay curve.

In general, the monitoring of dabigatran with coagulation assays is not necessary, but may be useful in special circumstances [45, 53]. For example, a normal aPTT and TT is suggestive of no meaningful dabigatran effect, negating the utility of extracorporeal removal in a bleeding patient. The international normalized ratio (INR) is not useful in the monitoring of dabigatran because INR values do not correlate with dabigatran activity [2, 44, 54]. Some have suggested the use of coagulation assays (aPTT and TT) to determine safety of surgical intervention [55]. The authors suggest that if both aPTT and TT are normal, no dabigatran effect is present and surgery can be performed without concerns of dabigatran-related hemorrhage. This strategy has not been validated; however, it is reasonable based on our understanding of the coagulation assays and their relationship to dabigatran concentrations. In general, the discontinuation of dabigatran prior to surgery ranges from 24 to 96 h depending on the patient's renal function and surgical bleeding risk. A more detailed discussion of perioperative management in the setting of dabigatran therapy may be found elsewhere [25]. Table 3 provides the reader with a summary and interpretation of laboratory parameters in the setting of dabigatran toxicity [2, 25, 45, 56].

Pharmacokinetics of Dabigatran in Kidney Disease and Hemodialysis

The pharmacokinetics of dabigatran have been evaluated in several studies [23, 30, 39, 57–63]. In an open-label, parallel group study [39], subjects given one dose of dabigatran (150 mg) were stratified by severity of renal impairment (mild, creatinine clearance (CrCl) >50 to ≤80 mL/min; moderate, CrCl >30 to ≤50 mL/min; severe, CrCl ≤30 mL/min). Patients

Table 3 Interpretation of coagulation assays in the setting of dabigatran toxicity [2, 25, 45, 56]

	Qualitative effect			Quantitative effect		
	PT/INR	aPTT	TT	Dilute TT	ECT	
Typical reference ranges	9.5–13.8 s/0.8–1.2	28–38 s	15–23 s	NA ^a	NA ^a	
Relation to dabigatran plasma concentration	Linear	Curvilinear	Linear	Linear ($r^2 > 0.90$)	Linear ($r^2 > 0.90$)	
Utility in the setting of toxicity	Not useful and should not be used. PT/INR does not correlate with dabigatran activity	Higher risk of bleeding with aPTT levels at troughs greater than two- to three-fold greater than baseline	At dabigatran concentrations >600 ng/mL, the maximum measurement of the TT is exceeded. TT is too sensitive for dabigatran concentrations >20 ng/mL	Values >65 s are associated with an excess risk of bleeding. Hemoclot® DTT assays are not approved for clinical use in the USA	Higher risk of bleeding with levels >3 times the upper limit of reference	
Interpretation	Not relevant	If both tests are within reference ranges, this suggests no significant dabigatran effect is present. If results are elevated, then the degree of dabigatran's effects is unclear		If either test result is within the reference range, then it suggests no significant effect from dabigatran is present		

aPTT activated partial thromboplastin time, ECT ecarin clotting time, INR international normalized ratio, PT prothrombin time, TT thrombin time

^aNo reference values can be provided due to significant inter-laboratory variability. Reference ranges are determined from a calibration curve

with end-stage renal disease were given 50 mg of dabigatran just prior to commencement of hemodialysis. Compared with healthy subjects, patients with mild, moderate, or severe renal impairment had 1.5-, 3.2-, and 6.3-fold higher area under the curve (AUC) values, respectively. Although there was no change in $T_{\max}$ or $C_{\max}$, the elimination half-life was twofold higher in patients with $\text{CrCl} \leq 30$ mL/min compared to healthy subjects (mean of 28 versus 14 h, respectively). In patients with end-stage renal disease, the mean fraction of dabigatran removed by hemodialysis was 62 % at 2 h and 68 % of the total initial amount at 4 h.

Wilson and colleagues further characterized the effects of hemodialysis on dabigatran pharmacokinetics and pharmacodynamics in 10 adult patients with end-stage renal disease after administration of a single dose of dabigatran etexilate 110 mg [64]. Unlike the study completed by Stangier and colleagues [39], no heparin was used in the dialysis circuit enabling the correlation of TT ratio with dabigatran. The mean half-life of dabigatran was substantially reduced with hemodialysis from 30.2 ± 7.8 to 2.6 ± 1.3 h. The hemodialysis extraction ratio was calculated as 0.63 ± 0.07 and the TT ratio was found to have strong linear relationship ($r^2 = 0.741$) with dabigatran concentration. The TT ratio was similar to baseline at the end of hemodialysis, but was significantly higher at 8 h post dialysis indicating a redistribution effect might exist. The study was not designed to formally evaluate redistribution; therefore, no information on the magnitude and duration of this effect was provided. These data support hemodialysis as an effective means to accelerate dabigatran elimination.

An open-label, single-center, multiple dose study designed to mimic concentrations achieved in subjects with atrial fibrillation receiving 150 mg twice daily provided additional data on the influence of hemodialysis on dabigatran elimination [57]. Four hours of hemodialysis removed 48.8 and 59.3 % of dabigatran, depending on targeted blood flow (200 and 400 mL/min, respectively). Redistribution of dabigatran was insignificant (<16 %) after the end of the hemodialysis session. A pharmacometric approach was applied to evaluate the influence of various blood flow rates on the pharmacokinetics of dabigatran [58]. The study concluded that altering filter properties or flow rates had only a minor impact on the amount of dabigatran removed; the most important variable associated with dabigatran removal was the duration of hemodialysis.

Anecdotal Experience with Extracorporeal Removal of Dabigatran

Extracorporeal removal of dabigatran has been used in emergent situations, as described in case reports involving emergency surgery (Table 4) and life-threatening hemorrhage (Table 5). In three cases in which dabigatran removal was

Table 4 Reported cases in the literature of extracorporeal removal of dabigatran for emergency surgery

Reference	Case	Type of surgery	Serum creatinine at presentation	Baseline coagulation parameters ^a	Method and duration of extracorporeal removal	Laboratory parameters after extracorporeal removal	Outcome
Carrizo et al. [67]	85-year-old male	Emergency surgery for perforated diverticulitis	1.19 mg/dL	aPTT=70 s TT >120 s	Hemodialysis, 3 h	aPTT=48 s TT=60 s	No bleeding complications. Patient discharged after 5 days of hospitalization
Esnault et al. [66]	62-year-old female	Urgent surgery for hematoma removal	NR ^b	Plasma dabigatran concentration=123 ng/mL aPTT=63 s TT=90.6 s	Hemodialysis, 2 h	Plasma dabigatran concentration=11 ng/mL aPTT=41 s TT=60.2 s	Patient discharged after 10 days of hospitalization
Wanek et al. [34]	59-year-old female	Cardiac transplantation	NR ^c		Hemodialysis, 2.5 h		TT remained prolonged and sustained for nearly 24 h after surgery. No bleeding complications

aPTT activated partial thromboplastin time, TT thrombin time

^a Reference ranges: aPTT=23–38 s; PT=9.5–13.8 s; TT=1.5–2.3 s. A plasma dabigatran concentration greater than 200 ng/mL increases a patient's risk for bleeding. ECT reference range determined from a calibration curve and is laboratory-specific. Please note that these values are generally institution-specific and can vary [56]

^b Serum creatinine was not reported; however, the authors reported a creatinine clearance of 39 mL/min

^c Serum creatinine was not reported; however, the authors reported a creatinine clearance of 40 mL/min

Table 5 Reported cases in the literature of extracorporeal removal of dabigatran for life-threatening bleeding

Reference	Case	Type of bleed	Serum creatinine at presentation	Baseline coagulation parameters ^a	Method and duration of extracorporeal removal	Laboratory parameters after extracorporeal removal	Outcome
Bachelierie et al. [65]	80-year-old male	Gross hematuria with obstructive acute kidney injury and a preexisting bladder tumor	12.8 mg/dL	Plasma dabigatran concentration = 429.31 ng/mL TT >60 s	Hemodialysis ^c	Plasma dabigatran concentration = 174.35 ng/mL	Redistribution in plasma dabigatran concentrations occurred, prompting four sessions of intermittent hemodialysis over a 72-h period
Chang et al. [32]	94-year-old male	ICH (traumatic)	0.74 mg/dL	TT >300 s aPTT = 39.8 s Plasma dabigatran concentration = 312 ng/mL	Hemodialysis, 3 h	Plasma dabigatran concentration = 43 ng/mL	Redistribution occurred within 2 h after completion of hemodialysis with an increase in the plasma dabigatran concentration. However, this resolved at 8 and 12 h. Patient remained stable and discharged after 10 days of hospitalization
Chen et al. [9]	80-year-old male, unintentional acute overdose	Hemoptysis, pulmonary hemorrhage	1.28 mg/dL	TT >20 s aPTT = 132.9 s Plasma dabigatran concentration = 1100 ng/mL	Hemodialysis, 4 h	aPTT = 75.2 s Plasma dabigatran concentration = 18 ng/mL	Redistribution in plasma dabigatran concentration to 100 ng/mL at approximately 20 min after cessation of hemodialysis. Patient discharged one month later
Chiew et al. [72]	66-year-old male	Altered mental status with coagulopathy from an intentional polysubstance overdose	1.78 mg/dL	aPTT = 115.4 s TT >240 s	Continuous venovenous hemodiafiltration, 32 h	aPTT = 73 s	An increase in plasma dabigatran concentrations was initially observed during extracorporeal removal, but it consistently decreased throughout the remaining duration of therapy. Patient discharged 5 days later
Kumar et al. [71]	Case series	ICH (4 patients) GI (1 patient) Perforated colon (1 patient) Foot ulcer (1 patient)	0.9 to 2.2 mg/dL	Plasma dabigatran concentrations = 41 to 1200 ng/mL TT >150 s aPTT = 36.5 to 82.5 s	Hemodialysis, 2 to 4 h	Plasma dabigatran concentrations decreased by up to 77 %, reaching undetectable levels in 2 cases	Two patients required continuous venovenous hemodialysis. Redistribution observed in four patients, with levels increasing by up to 87 %. Two patients died, and the remaining five were discharged
Lal et al. [73]	Case series ^b	ICH (1 patient)	3.4 mg/dL	PT = 25.1 s aPTT = 92 s	Hemodialysis ^c	aPTT = 40 s PT = 17.3 s	Complicated hospital course leading to comfort care only and death within 1 week of presentation
		ICH, intraglottal hemorrhage (1 patient)	10.5 mg/dL	PT = 117 s aPTT = 100.2 s	Hemodialysis ^c	PT = 22 s aPTT = 60 s	Despite two weeks of aggressive care, patient died 4 weeks later
Lillo Le-Louet et al. [16]	86-year-old male	GI	NR ^d	Plasma dabigatran concentration = 2350 ng/mL	Continuous venovenous hemodiafiltration, 6 h	Plasma dabigatran concentration = 960 ng/mL	Bleeding resolved 10 h post-initiation of renal replacement therapy. Plasma dabigatran concentrations continued to decrease over the course of 3 days post cessation of renal replacement therapy. After a complicated hospitalization, patient deceased after 18 days

Table 5 (continued)

Reference	Case	Type of bleed	Serum creatinine at presentation	Baseline coagulation parameters ^a	Method and duration of extracorporeal removal	Laboratory parameters after extracorporeal removal	Outcome
Ross et al. [70]	Case series ^e	ICH (1 patient)	NR	ECT=125.5 s	Hemodialysis	ECT=83.1 s	Patient received recombinant factor VIIa and underwent surgery in efforts to reverse the bleed, but expired after 48 h
		ICH (1 patient)	NR	ECT=84.1 s Plasma dabigatran concentration=60 ng/mL	Hemodialysis, 5 h; continuous renal replacement therapy, 26 h	6 h post extracorporeal removal: ECT=55.2 s Plasma dabigatran concentration=60 ng/mL TT=81.2 s	TT and plasma dabigatran concentrations increased after 11 and 12 h, respectively. Coagulation parameters continued to decline, but the patient did not survive to hospital discharge
Singh et al. [33]	Case series	ICH (2 patients) GI (2 patients) Perforated colon (1 patient)	1.4 to 3.1 mg/dL	Plasma dabigatran concentrations=149 to 1200 ng/mL TT >150 s	Hemodialysis, 2 to 5 h	Plasma dabigatran concentrations decreased by up to 77 %	Redistribution occurred within 2 h after completion of hemodialysis, with concentrations increasing by up to 87 % from baseline. In two cases, a second session of intermittent hemodialysis was necessary due to substantial redistribution effect and incomplete resolution of hemorrhage. One case required continuous venovenous hemodiafiltration for 30 h. Two patients died, and the remaining three patients were discharged
Verma et al. [68]	64-year-old male	ICH (traumatic)	NR	aPTT=44.3 s PT=14.9 s ECT=125.5 s	Hemodialysis, 3 h	aPTT=49.3 s PT=15.7 s ECT=83.1 s	Intubation during hemodialysis because of worsening neurological status. Comfort care measures initiated followed by patient death
Warkentin et al. [69]	79-year-old male	Coronary artery bypass graft surgery	NR ^f	TT=129 s aPTT=52 s Plasma dabigatran concentration=95 ng/mL	Hemodialysis, 6 h	Plasma dabigatran concentration=27 ng/mL	Bleeding continued to recede during hemodialysis. Because of complications, the patient was discharged nearly two months following the surgery

aPTT activated partial thromboplastin time, ECR extracorporeal removal, ECT ecarin clotting time, GI gastrointestinal, ICH intracranial hemorrhage, NR not reported, PT prothrombin time, TT thrombin time

^a Reference ranges: aPTT=23–38 s; PT=9.5–13.8 s; TT=15–23 s. A plasma dabigatran concentration greater than 200 ng/mL increases a patient's risk for bleeding. ECT reference range determined from a calibration curve and is laboratory-specific. Please note that these values are generally institution-specific and may vary [56]

^b Among the four patients included in this case series of life-threatening bleeding from dabigatran toxicity, two patients received renal replacement therapy, and their outcomes were included in the table

^c Duration of extracorporeal removal not provided

^d Serum creatinine was not reported; however, the authors reported a creatinine clearance of 13.8 mL/min

^e Among the 11 patients included in this case series of life-threatening bleeding from dabigatran toxicity, two patients received renal replacement therapy, and their outcomes were included in the table

^f Serum creatinine was not reported; however, the authors reported a creatinine clearance of 36 mL/min

expedited with extracorporeal removal prior to emergency surgery, hemodialysis was used for 2 to 3 h. These patients experienced no bleeding complications following the surgery. In the setting of life-threatening bleeding secondary to dabigatran (Table 4), 23 cases were reviewed, and hemodialysis was the primary mode of removal in most reported cases. In the majority of cases, reduction in plasma dabigatran concentrations and correction of coagulation parameters that included aPTT, PTT, TT, and ECT (where available) were used as surrogate markers to determine the effectiveness and need for continuation of extracorporeal removal. A correction in coagulation parameters was observed in most cases. When available, plasma dabigatran concentrations dramatically decreased following initiation of extracorporeal removal. However, a redistribution effect in plasma dabigatran concentrations was observed in several cases, with an observed increase of 50 to over 500 % occurring within 20 min to 12 h post cessation of renal replacement therapy. This observed phenomenon is a finding inconsistent with the pharmacokinetic studies that led to the approval of dabigatran by the FDA and EMEA. Continuous renal replacement therapy was utilized in six cases, and there is limited reported data related to coagulation parameters and pharmacokinetics of dabigatran following this chosen mode of extracorporeal removal. Of the 23 cases reviewed, 10 patients did not survive to hospital discharge.

Practical Considerations Limiting Utility of Extracorporeal Removal of Dabigatran

Although extracorporeal removal may be an effective means of removing dabigatran, practical considerations should be taken into account. The amount of time needed to prepare the patient to receive extracorporeal therapy to expedite the eliminations of dabigatran presents itself as a challenge. Patients with life-threatening hemorrhage may present with hemodynamic instability such as hypotension that would make initiation of extracorporeal removal difficult. Another challenge includes placement of the catheter for the chosen mode of extracorporeal removal, which could be associated with life-threatening hemorrhage in the setting of coagulopathy. In one case, a hemostatic agent (8 units/kg FEIBA) [32] was administered to decrease the risk of bleeding associated with this process. Micropuncture technique and/or ultrasound-guided approaches may reduce the risk of bleeding associated with insertion of the catheter.

With the published case reports, the duration of extracorporeal removal in patients requiring emergency surgery and those who present with life-threatening bleeding has not been consistent. Patient-specific factors such as the timing of the last dose of dabigatran, coagulation parameters, bleeding severity, and hemodynamic status should be taken into account

in determining the initial duration of extracorporeal removal via renal replacement therapy.

It is important to note that coagulation parameters may not necessarily correlate with the clinical outcomes of attenuation of bleeding and mortality, as reflected in the cases described in Tables 4 and 5.

Furthermore, although the redistribution of dabigatran has been described in several reports following extracorporeal removal, there is no clear characterization of patients who may develop this effect. Although redistribution did occur in two reported cases of acute ingestion of dabigatran [9, 72], this observation is unlikely secondary to continued absorption through the gastrointestinal tract because this effect was observed in several cases of toxicity that were not due to overdose. Although this redistribution effect was observed with an increase in plasma concentrations of dabigatran, this was not demonstrated to correlate with reported coagulation parameters in the cases described. Regardless of what treatment strategy is utilized to reverse coagulopathy associated with dabigatran toxicity, this observed phenomenon will continue to be a challenge because coagulation parameters are imperfect in displaying the effect of redistribution. In addition, institutions may not have the capability of measuring plasma dabigatran concentrations in a timely fashion relative to the urgency necessary for reversal. Furthermore, the clinical significance of this observation as well as its relation to the necessary length of renal replacement therapy is still not clearly understood.

In addition, should institutions consider extracorporeal removal as an option for expedited removal of dabigatran, an institutional plan will be needed with consensus from clinicians within the specialties of emergency medicine, hematology, and nephrology. Should such an institution have the capability of testing for the presence of dabigatran via any or all of the laboratory parameters described above, a mechanism will be needed to ensure that these parameters are measured at the initiation and conclusion of the chosen mode of extracorporeal removal. Laboratory personnel should be prepared to report the results of these coagulation parameters to clinicians in a timely fashion during the duration of the treatment strategy utilized. In addition, medical toxicologists should be consulted to provide guidance on the interpretation of available assays in the presence of dabigatran toxicity, especially if continuous renal replacement therapy is warranted in the setting of incomplete resolution of coagulopathy following a period of intermittent hemodialysis.

Summary

The utility of extracorporeal removal as a mechanism for expedited elimination of dabigatran may be an option for patients undergoing emergency surgery or in the setting of

life-threatening bleeding. Dabigatran displays many properties of a dialyzable substance, and several case reports describe its removal in emergent settings.

There are several limitations with the practical application and with regard to the availability of indicators demonstrating the effectiveness of extracorporeal removal for managing dabigatran-related bleeding. Most importantly, the use of extracorporeal removal as a treatment modality has not been prospectively evaluated in this clinical setting. The consideration to utilize extracorporeal removal should not preclude or delay the use of other supplemental hemostatic therapies in these patients when indicated. In addition, the modality of extracorporeal therapy should be individualized and based on patient presentation and clinical parameters such as the nature of the exposure, the level of renal dysfunction, and the severity of the coagulopathy.

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References

- Pradaxa® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2011 March. In.
- van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A (2010) Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 103(6):1116–1127
- Pradax® Canadian prescribing information [http://www.boehringer-ingelheim.ca/en/Home/Human_Health/Our_Products/Product_Monographs/Pradax-pm.pdf]
- Hankey GJ, Eikelboom JW (2011) Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation* 123(13):1436–1450
- Granger CB, Armaganjian LV (2012) Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke or thromboembolism. *Circulation* 125(1):159–164
- Schulman S, Majeed A (2012) The oral thrombin inhibitor dabigatran: strengths and weaknesses. *Semin Thromb Hemost* 38(1):7–15
- Southworth MR, Reichman ME, Unger EF (2013) Dabigatran and postmarketing reports of bleeding. *N Engl J Med* 368(14):1272–1274
- Van Heukelom J, Lal Y (2013) Dabigatran and bleeding: still an emergent situation? *Am J Med Sci* 346(3):259
- Chen BC, Sheth NR, Dadzie KA, Smith SW, Nelson LS, Hoffman RS, Winchester JF (2013) Hemodialysis for the treatment of pulmonary hemorrhage from dabigatran overdose. *Am J Kidney Dis* 62(3):591–594
- Larsen TB, Rasmussen LH, Skjoth F, Due KM, Callreus T, Rosenzweig M, Lip GY (2013) Efficacy and safety of dabigatran etexilate and warfarin in “real-world” patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol* 61(22):2264–2273
- Fellows SE, Rosini JM, Curtis JA, Volz EG (2013) Hemorrhagic gastritis with dabigatran in a patient with renal insufficiency. *J Emerg Med* 44(2):e221–225
- Wychowski MK, Kouides PA (2012) Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. *Ann Pharmacother* 46(4):e10
- Barton CA, McMillian WD, Sadi Raza S, Keller RE (2012) Hemopericardium in a patient treated with dabigatran etexilate. *Pharmacotherapy* 32(5):e103–107
- Harper P, Young L, Merriman E (2012) Bleeding risk with dabigatran in the frail elderly. *N Engl J Med* 366(9):864–866
- Bene J, Said W, Rannou M, Deheul S, Coupe P, Gautier S (2012) Rectal bleeding and hemostatic disorders induced by dabigatran etexilate in 2 elderly patients. *Ann Pharmacother* 46(6):e14
- Lillo-Le Louet A, Wolf M, Soufir L, Galbois A, Dumenil AS, Offenstadt G, Samama MM (2012) Life-threatening bleeding in four patients with an unusual excessive response to dabigatran: implications for emergency surgery and resuscitation. *Thromb Haemost* 108(3):583–585
- Legrand M, Mateo J, Aribaud A, Ginisty S, Eftekhari P, Huy PT, Drouet L, Payen D (2011) The use of dabigatran in elderly patients. *Arch Intern Med* 171(14):1285–1286
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361(12):1139–1151
- (2012) QuarterWatch™ (First Quarter 2011) Signals for dabigatran and metoclopramide. ISMP Medication Safety Alert! 17(1).
- Sipahi I, Celik S, Tozun N (2014) A comparison of results of the US food and drug administration’s mini-sentinel program with randomized clinical trials: the case of gastrointestinal tract bleeding with dabigatran. *JAMA Internal Med* 174(1):150–151
- Sorensen R, Gislason G, Torp-Pedersen C, Olesen JB, Fosbol EL, Hvidtfeldt MW, Karasoy D, Lamberts M, Charlott M, Kober L et al. (2013) Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. *BMJ Open* 3(5)
- Berger R, Salhanick SD, Chase M, Ganetsky M (2013) Hemorrhagic complications in emergency department patients who are receiving dabigatran compared with warfarin. *Ann Emerg Med* 61(4):475–479
- Stangier J, Clemens A (2009) Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost* 15(Suppl 1):9S–16S
- Siegal DM, Crowther MA (2013) Acute management of bleeding in patients on novel oral anticoagulants. *Eur Heart J* 34(7):489–498b
- Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P (2013) European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 15(5):625–651
- Weitz JJ, Quinlan DJ, Eikelboom JW (2012) Periprocedural management and approach to bleeding in patients taking dabigatran. *Circulation* 126(20):2428–2432
- Siegal DM, Garcia DA, Crowther MA (2014) How I treat target-specific oral anticoagulant-associated bleeding. *Blood* 123(8):1152–1158
- van Ryn J, Goss A, Huel N, Wienen W, Pripke H, Nar H, Clemens A (2013) The discovery of dabigatran etexilate. *Front Pharmacol* 4:12
- Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W (2008) The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 36(2):386–399
- Stangier J (2008) Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* 47(5):285–295

31. Remko M, Broer R, Remkova A (2014) A comparative study of the molecular structure, lipophilicity, solubility, acidity, absorption and polar surface area of coumarinic anticoagulants and direct thrombin inhibitors. *RSC Adv* 4(16):8072–8084
32. Chang DN, Dager WE, Chin AI (2013) Removal of dabigatran by hemodialysis. *Am J Kidney Dis* 61(3):487–489
33. Singh T, Maw TT, Henry BL, Pastor-Soler NM, Unruh ML, Hallows KR, Nolin TD (2013) Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: a single center experience. *Clin J Am Soc Nephrol* 8(9):1533–1539
34. Wanek MR, Horn ET, Elapavaluru S, Baroody SC, Sokos G (2012) Safe use of hemodialysis for dabigatran removal before cardiac surgery. *Ann Pharmacother* 46(9):e21
35. Pare G, Eriksson N, Lehr T, Connolly S, Eikelboom J, Ezekowitz MD, Axelsson T, Haertter S, Oldgren J, Reilly P et al (2013) Genetic determinants of dabigatran plasma levels and their relation to bleeding. *Circulation* 127(13):1404–1412
36. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L (2014) The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol* 63(4):321–328
37. Brenner BM, Rector FC (2008) Brenner & Rector's The Kidney, 8th edn. Saunders Elsevier, Philadelphia
38. Ebner T, Wagner K, Wienen W (2010) Dabigatran acylglucuronide, the major human metabolite of dabigatran: in vitro formation, stability, and pharmacological activity. *Drug Metab Dispos* 38(9):1567–1575
39. Stangier J, Rathgen K, Stahle H, Mazur D (2010) Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 49(4):259–268
40. Zhou SF (2008) Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. *Xenobiotica* 38(7–8): 802–832
41. Nutescu E, Chuatrisorn I, Hellenbart E (2011) Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. *J Thromb Thrombolysis* 31(3):326–343
42. Fountzilas C, George J, Levine R (2013) Dabigatran overdose secondary to acute kidney injury and amiodarone use. *N Z Med J* 126(1370):110–112
43. (2013) Dabigatran: life-threatening bleeding. *Prescrire Int* 22(135): 41–43.
44. Huisman MV, Lip GY, Diener HC, Brueckmann M, van Ryn J, Clemens A (2012) Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. *Thromb Haemost* 107(5):838–847
45. Brunetti L, Bandali F (2013) Dabigatran: is there a role for coagulation assays in guiding therapy? *Ann Pharmacother* 47(6):828–840
46. Chin PK, Wright DF, Patterson DM, Doogue MP, Begg EJ (2014) A proposal for dose-adjustment of dabigatran etexilate in atrial fibrillation guided by thrombin time. *Br J Clin Pharmacol* 78(3):599–609
47. Kamal AH, Tefferi A, Pruthi RK (2007) How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. *Mayo Clin Proc* 82(7):864–873
48. Hapgood G, Butler J, Malan E, Chunilal S, Tran H (2013) The effect of dabigatran on the activated partial thromboplastin time and thrombin time as determined by the Hemoclot thrombin inhibitor assay in patient plasma samples. *Thromb Haemost* 110(2):308–315
49. Eikelboom JW, Connolly SJ, Hart RG, Wallentin L, Reilly P, Oldgren J, Yang S, Yusuf S (2013) Balancing the benefits and risks of 2 doses of dabigatran compared with warfarin in atrial fibrillation. *J Am Coll Cardiol* 62(10):900–908
50. US Food and Drug Administration, Center for Drug Evaluation and Research. Dabigatran etexilate. Advisory committee briefing document, August 27, 2010. <http://www.Fda.Gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm226009.pdf>. Accessed Oct 30, 2013
51. Eisert WG, Haul N, Stangier J, Wienen W, Clemens A, van Ryn J (2010) Dabigatran: an oral novel potent reversible nonpeptide inhibitor of thrombin. *Arterioscler Thromb Vasc Biol* 30(10):1885–1889
52. Cohen D (2014) Dabigatran: how the drug company withheld important analyses. *BMJ* 349:g4670. doi: [org/10.1136/bmj.g4670](https://doi.org/10.1136/bmj.g4670)
53. Pengo V, Crippa L, Falanga A, Finazzi G, Marongiu F, Palareti G, Poli D, Testa S, Tiraferri E, Tosetto A et al (2011) Questions and answers on the use of dabigatran and perspectives on the use of other new oral anticoagulants in patients with atrial fibrillation. A consensus document of the Italian Federation of Thrombosis Centers (FCSA). *Thromb Haemost* 106(5):868–876
54. van Ryn J, Baruch L, Clemens A (2012) Interpretation of point-of-care INR results in patients treated with dabigatran. *Am J Med* 125(4):417–420
55. New Zealand Pharmaceutical Management Agency. Guidelines for testing and perioperative management of dabigatran. <http://www.pharmac.govt.nz/2011/06/13/Dabigatran%20testing%20and%20perioperative%20management.pdf>. Accessed Feb 22, 2014.
56. Fischbach FT, Dunning MB (2014) A manual of laboratory and diagnostic tests. 9th edn. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia
57. Khadzhynov D, Wagner F, Formella S, Wiegert E, Moschetti V, Slowinski T, Neumayer HH, Liesenfeld KH, Lehr T, Hartter S et al (2013) Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. *Thromb Haemost* 109(4):596–605
58. Liesenfeld KH, Staab A, Hartter S, Formella S, Clemens A, Lehr T (2013) Pharmacometric characterization of dabigatran hemodialysis. *Clin Pharmacokinet* 52(6):453–462
59. Dansirikul C, Lehr T, Liesenfeld KH, Haertter S, Staab A (2012) A combined pharmacometric analysis of dabigatran etexilate in healthy volunteers and patients with atrial fibrillation or undergoing orthopaedic surgery. *Thromb Haemost* 107(4):775–785
60. Liesenfeld KH, Lehr T, Dansirikul C, Reilly PA, Connolly SJ, Ezekowitz MD, Yusuf S, Wallentin L, Haertter S, Staab A (2011) Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. *J Thromb Haemost* 9(11):2168–2175
61. Troconiz IF, Tillmann C, Liesenfeld KH, Schafer HG, Stangier J (2007) Population pharmacokinetic analysis of the new oral thrombin inhibitor dabigatran etexilate (BIBR 1048) in patients undergoing primary elective total hip replacement surgery. *J Clin Pharmacol* 47(3):371–382
62. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W (2007) The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 64(3):292–303
63. Stangier J, Stahle H, Rathgen K, Fuhr R (2008) Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet* 47(1): 47–59
64. Wilson JA, Goralski KB, Soroka SD, Morrison M, Mossop P, Sleno L, Wang Y, Anderson DR (2014) An evaluation of oral dabigatran etexilate pharmacokinetics and pharmacodynamics in hemodialysis. *J Clin Pharmacol* 54(8):901–909
65. Bachellerie B, Ruiz S, Conil JM, Crognier L, Seguin T, Georges B, Fourcade O (2014) Patient with acute renal injury presenting dabigatran overdose: hemodialysis for surgery. *Ann Fr Anesth Reanim* 33(1):44–46
66. Esnault P, Gaillard PE, Cotte J, Cungi PJ, Beaume J, Prunet B (2013) Haemodialysis before emergency surgery in a patient treated with dabigatran. *Br J Anaesth* 111(5):776–777

67. Carrizo A, Campbell S (2014) Hemodialysis to remove anti-coagulant dabigatran during emergencies. *Medicina (B Aires)* 74(2):121–123
68. Verma A, Chhibber V, Emhoff T, Klinger D (2012) Promise and challenges of anticoagulation with dabigatran. *Clin Kidney J* 5:336–338
69. Warkentin TE, Margetts P, Connolly SJ, Lamy A, Ricci C, Eikelboom JW (2012) Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood* 119(9):2172–2174
70. Ross B, Miller MA, Ditch K, Tran M (2014) Clinical experience of life-threatening dabigatran-related bleeding at a large, tertiary care, academic medical center: a case series. *J Med Toxicol* 10(2):223–228
71. Kumar R, Smith RE, Henry BL (2014) A review of and recommendations for the management of patients with life-threatening dabigatran-associated hemorrhage: a single-center university hospital experience. *J Intensive Care Med*. <http://www.ncbi.nlm.nih.gov/pubmed/24668159>
72. Chiew AL, Khamoude D, Chan BS (2014) Use of continuous venovenous haemodiafiltration therapy in dabigatran overdose. *Clin Toxicol (Phila)* 52(4):283–287
73. Lal Y, Van Heukelom J (2013) Dabigatran: a cause of hematologic emergency. *Am J Med Sci* 346(3):190–193