Cardiol Ther (2013) 2:111–124
DOI 10.1007/s40119-013-0016-1

CASE REPORT

Dabigatran Excess: Case Report and Review of the Literature

Amy Sarma · Jeffrey E. Rossi · Jean M. Connors · Robert P. Giugliano

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Received: April 3, 2013 / Published online: June 1, 2013

ABSTRACT

Introduction: Novel oral anticoagulants are increasingly used for stroke prophylaxis in patients with non-valvular atrial fibrillation. While these agents offer a more predictable pharmacokinetic profile, the lack of readily available laboratory tests to monitor the level of anticoagulation and absence of an antidote or established therapies to reverse the anticoagulant effect make management of cases of over-anticoagulation challenging.

Case Report: In this case report an 87-year-old man with a history of atrial fibrillation presented with dabigatran excess in the setting of life-threatening, acute renal and hepatic failure. The authors review the use of dabigatran in elderly patients, the available data on management of patients with excess anticoagulation, and the potential options for reversal of the anticoagulation effect.

Conclusion: Further investigation into reliable means of monitoring and reversing the anticoagulant effect of dabigatran is crucial to the management of such patients.

Keywords: Anticoagulants; Anticoagulation; Atrial fibrillation; Dabigatran; Elderly; Renal failure; Stroke

A. Sarma and J. E. Rossi contributed equally to the writing of this paper.

A. Sarma · J. E. Rossi · J. M. Connors · R. P. Giugliano (✉)
Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
e-mail: rgiugliano@partners.org

J. M. Connors
Hematology Division, Brigham and Women's Hospital, Boston, MA, USA

R. P. Giugliano
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

R. P. Giugliano
TIMI Study Office, 350 Longwood Avenue, 1st Floor Offices, Boston, MA 02115, USA

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INTRODUCTION

Dabigatran etexilate is an oral direct thrombin inhibitor approved for use as an alternative to the vitamin K antagonist, warfarin, for stroke

prophylaxis in patients with non-valvular atrial fibrillation. Its predictable pharmacokinetic profile provides significant user appeal since routine monitoring of its anticoagulant effect and dose titration are not required. Furthermore, when compared with warfarin in the Randomized Evaluation of the Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran was superior to warfarin in preventing stroke and systemic embolization at 150 mg twice-daily (1.11% versus 1.69% per year, relative risk (RR) 0.66, 95% CI 0.53–0.82, $P < 0.001$ for superiority) and non-inferior to warfarin at 110 mg twice-daily (1.53% versus 1.69% per year, RR 0.91, 95% CI 0.74–1.11, $P < 0.001$ for noninferiority) [1]. With respect to bleeding, patients randomized to 110 mg twice-daily experienced a lower rate of major bleeding as compared to warfarin (2.71% versus 3.36% per year, $P = 0.003$), while those randomized to 150 mg twice-daily had a similar rate of major bleeding (3.11% versus 3.36%, $P = 0.31$). In a recent Mini-Sentinel analysis of adverse post-marketing events, dabigatran was not associated with a higher risk of bleeding as compared to warfarin in clinical use [2]. Despite a similar or superior safety profile, two major disadvantages of dabigatran include the lack of a reversal agent and no validated, clinically available measure to monitor anticoagulant activity, both of which are critical to the care of patients presenting with active bleeding. Here, the authors report a case of an 87-year-old man on dabigatran who presented with a coagulopathy in the setting of acute renal and hepatic failure. Given that 80% of dabigatran is renally cleared, the authors caution clinicians to carefully monitor renal function and adjust dosing accordingly, especially in elderly patients who are particularly susceptible to asymptomatic changes in renal function.

CASE REPORT

An 87-year-old man with a history of atrial fibrillation with CHA_2DS_2-VASc score of 5, heart failure with preserved ejection fraction, and hypertension presented to the emergency room with weakness, decreased oral intake, and mild cough. Consent for publication of this case report was obtained from the patient's wife. Five months earlier, the patient started dabigatran etexilate 150 mg orally twice-daily for thromboembolic prophylaxis of atrial fibrillation [which is the dose approved by the US Food and Drug Administration (FDA) for patients with normal or mildly impaired renal function—the 110 mg dose is not available in the US]. One week prior, the patient was seen by his primary care physician for increased lower extremity edema and found to have atrial fibrillation with a rapid ventricular response averaging 120 beats per minute. The serum creatinine (Cr) at the time was measured at 1.20 mg/dL [estimated glomerular filtration (eGFR) = 57 mL/min/1.73 m^2 as reported by the hospital laboratory based on the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease [MDRD] study equation]. The daily doses of verapamil, metoprolol, and furosemide were increased from 120 to 240, 25 to 100, and 40 to 60 mg, respectively. Two days prior to presentation, the patient fell while getting out of bed, but did not seek medical attention. On the day of admission, the patient was too weak to stand and vomited three times, prompting his family to seek emergency medical care. The last dose of dabigatran was reportedly taken 2 days prior to admission.

On initial evaluation, the axillary temperature was 95.7 °F, blood pressure 102/48 mmHg, ventricular rate 36 beats/min with atrial fibrillation (Fig. 1), and oxygen

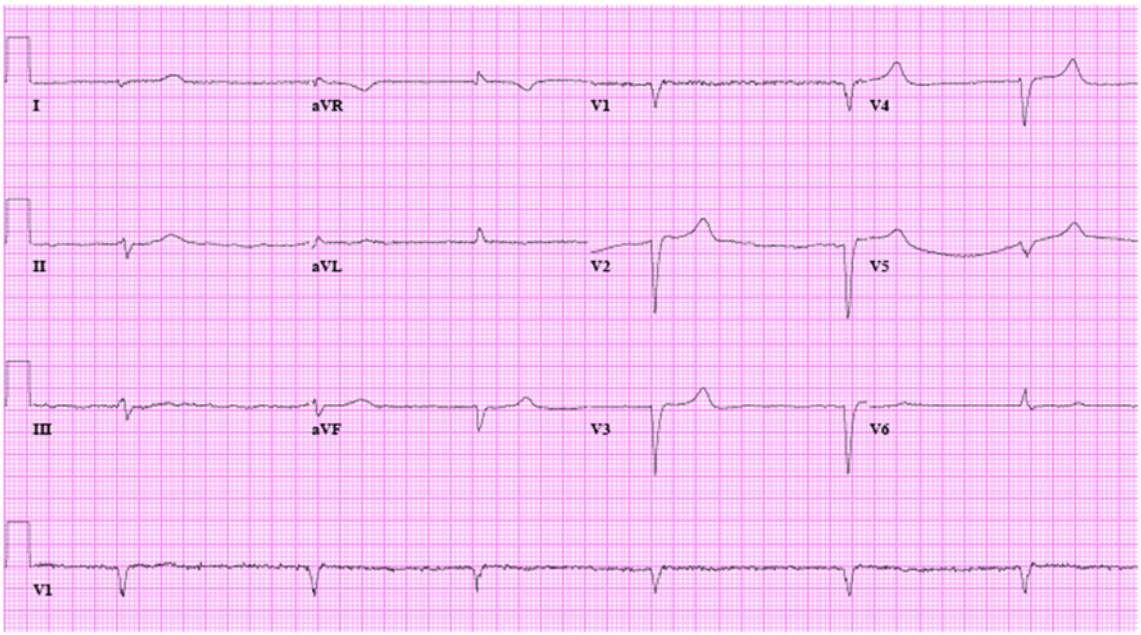

Fig. 1 Admission electrocardiogram revealed atrial fibrillation with a ventricular response rate of ~36 beats/min. The QRS morphology, duration, axis, voltage, and R wave progression across the precordium are consistent with nonspecific interventricular conduction delay and right axis deviation

saturation 96% on 2 L/min of supplemental oxygen. On examination, the patient was ill appearing but in no acute distress. The patient had 10 cm of jugular venous distension with monophasic waves and hepatojugular reflux. There were bibasilar crackles present on lung examination. Cardiac auscultation revealed a bradycardic, irregular rhythm, normal first heart sound with a physiologically split second heart sound, and a III/VI systolic murmur loudest at the upper sternal border. The abdomen was benign without organomegaly. There was 3+ pitting edema of the extremities with normal pulses bilaterally.

Upon arrival to the emergency department 2 L of intravenous (IV) normal saline and 1 mg of IV glucagon were administered. A chest X-ray revealed a right lower lobe infiltrate (Fig. 2), cultures were obtained, and treatment was initiated with ceftriaxone and levofloxacin. Laboratory studies were notable for acute renal failure and hepatic dysfunction, which likely developed in the setting of septic shock from pneumonia, potentially compounded by recently increased diuretic therapy and bradycardia in the setting of uptitration of nodal blockade (Table 1; Fig. 3). In conjunction, laboratory studies revealed electrolyte disturbances, elevated serum lactate, and profound coagulopathy (Table 1; Fig. 3). The patient received 10 units of IV insulin, 50 g of IV dextrose, 2 g of IV calcium gluconate, and 50 mEq of IV sodium bicarbonate to manage hyperkalemia. Computed tomography of the head, neck, and cervical spine did not show evidence of acute hemorrhage or fracture.

On admission to the cardiac intensive care unit, the heart rate was irregular at 48 beats/min and the blood pressure was 90/50 mmHg. The patient rapidly developed worsening hypoxia and was placed on 70% oxygen at 35 L/min delivered by high flow nasal cannula. During a phlebotomy, the patient became acutely unresponsive with a loss of palpable pulses.

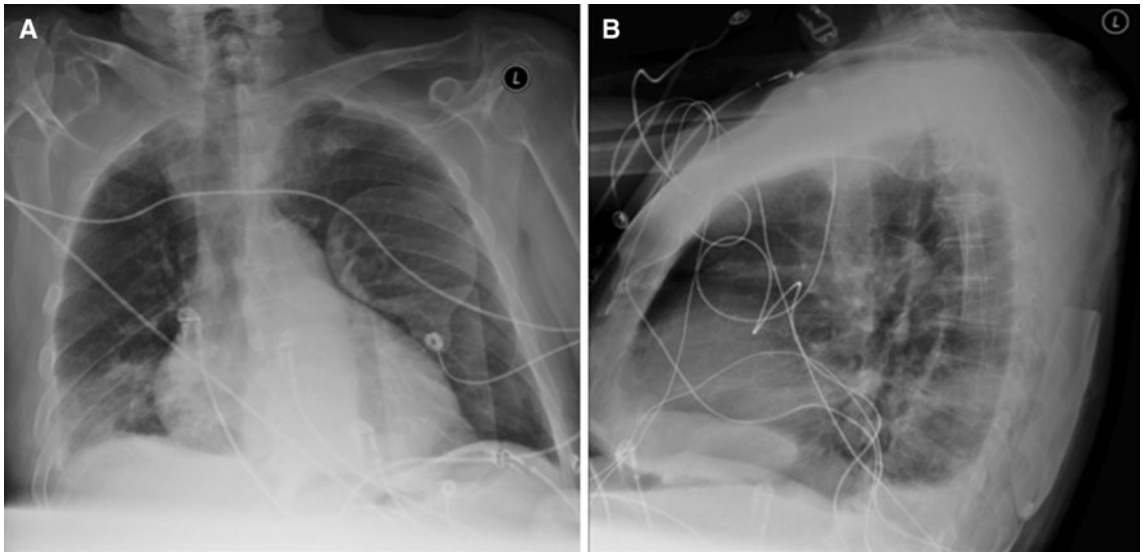

Fig. 2 Posteroanterior (**a**) and lateral (**b**) admission chest radiograph. Admission chest radiograph revealed a small right pleural effusion with right basilar opacity consistent with pneumonia

The cardiac monitor revealed progressive bradycardia to less than 30 beats/min. The patient received approximately 2.5 min of chest compressions with return of spontaneous circulation, was intubated, and placed on mechanical ventilation.

The patient did not demonstrate any overt signs of active bleeding at any point during the hospitalization. On admission, the hematocrit was 43.5%, consistent with the patient's baseline value. In the setting of receiving a total of 4.5 L of IV normal saline during the first day of hospitalization, the hematocrit dropped to a nadir of 33.9%, but gradually improved without infusion of red blood cells to 38.3% on day of discharge. However, taking into account the history of a recent fall, need for central venous access, and presence of multi-organ failure in the elderly gentleman with possible need for dialysis, the decision was made to reverse the coagulopathy. A reversal strategy was pursued that attempted to counteract both dabigatran toxicity and the potential for decreased hepatic synthesis of clotting factors given concern for hepatic injury in the setting of an acute transaminitis. The patient's history of heart failure and acute renal failure limited the amount of high volume blood products that could be administered and more concentrated forms of coagulation factor replacement were considered. A total of 4 units of fresh frozen plasma (FFP), 15 mg of vitamin K (initially 5 mg orally, then 10 mg IV), and 5,020 international units (IU) of IV inactivated prothrombin complex concentrates (PCC; Profilnine®, Grifols Biologicals, Inc, Los Angeles, CA, USA) were administered on the first day of hospitalization (Fig. 3). The prothrombin time (PT) and partial thromboplastin time (PTT) peaked in the first 24 h and then gradually returned to normal (Fig. 3). Coagulopathy was further measured using the thrombin time at 7, 24, and 26 h after admission and was >150 s (normal range 15–30) at all three measurements. A diluted thrombin time (one part patient plasma to three parts normal plasma) was measured at 24 and 26 h and was 125.0 and 113.1 s, respectively (Table 1).

Table 1 Selected initial laboratory results

Test	Result	Reference range
Sodium (mmol/L)	137	135–145
Potassium (mmol/L)	6.6	3.4–5.0
Chloride (mmol/L)	100	98–107
Total CO_2 (mmol/L)	10	22–31
Blood urea nitrogen (mg/dL)	45	6–23
Creatinine (mg/dL)	3.05	0.50–1.20
Glucose (mg/dL)	102	70–100
Magnesium (mg/dL)	2.6	1.7–2.6
ALT (U/L)	546	10–50
AST (U/L)	422	10–50
Alkaline phosphatase (U/L)	111	35–130
Total bilirubin (mg/dL)	1.4	0.0–1.0
Direct bilirubin (mg/dL)	0.5	0.0–0.3
CK (U/L)	170	39–308
CKMB (ng/mL)	5.9	0.0–6.6
Troponin T (ng/mL)	0.08	0.00–0.00
NT-proBNP (pg/mL)	3,695	0–1,799
White blood cell count (K/μL)	18.52	4–10
Hemoglobin (g/dL)	14.0	13.5–18.0
Hematocrit (%)	43.5	40–54
Platelet count (K/μL)	214	150–450
PT (s)	**54.4**	**12.2–14.6**
PTT (s)	**100.6**	**23.8–36.6**
INR	**6.0**	**0.9–1.1**
Fibrinogen (mg/dL)	279	200–450
Diluted TT (s)	**125.0 (at 24 h) 113.1 (at 26 h)**	**15–30**

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CK* creatine kinase, *CKMB* creatine kinase myocardial band, *INR* international normalized ratio, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *PT* prothrombin time, *PTT* partial thromboplastin time, *TT* thrombin time

The hepatic transaminases and renal function also peaked on the first day with an alanine aminotransferase (ALT) of 4,590 U/L, aspartate aminotransferase (AST) of 4,965 U/L, and Cr of 3.07 mg/dL (eGFR $\leq$20 mL/min/1.73 m^2). Thereafter, the patient's Cr, transaminases, and coagulation parameters trended downward over the course of 10 days (Fig. 3).

The patient was stabilized and treated for pneumonia in the intensive care unit for 7 days. The patient was extubated on day 5, had no signs of bleeding, and was discharged home on hospital day 19. On hospital day 5, the patient's international normalized ratio (INR) was 1.8 (see Fig. 3 for trend) with a PTT of 46.9 s, at which time an unfractionated heparin infusion was started for stroke prevention secondary to atrial fibrillation given a CHA_2DS_2-VASc score of 5 (indicating a high yearly risk of stroke), and concern that the patient was unable to reliably take oral medications in the setting of acute illness and deconditioning. However, the patient regained ability to take oral medications more quickly than anticipated and was, therefore, started on warfarin on hospital day 7. On the day of discharge, the Cr was 0.70 mg/dL (eGFR $\geq$60 mL/min/1.73 m^2) with a PTT of 41.3 s and INR of 1.8 on warfarin. The ALT and AST were last measured on hospital day 10 at 271 and 32 U/L, respectively.

DISCUSSION

Monitoring of Anticoagulant Assays

There is no established laboratory method for monitoring dabigatran's activity. While its short half-life and reliable pharmacokinetics render this unnecessary for routine clinical use, it may be advantageous in the setting of a potential overdose or clinically significant bleeding. PT/INR, activated partial thromboplastin time (aPTT), thrombin clotting time (TT), ecarin clotting time (ECT), activated clotting time (ACT), and fibrinogen tests have all been evaluated as potential measures of the anticoagulant effect of dabigatran.

While monitoring of the PT/INR is standard for warfarin therapy, it is relatively insensitive

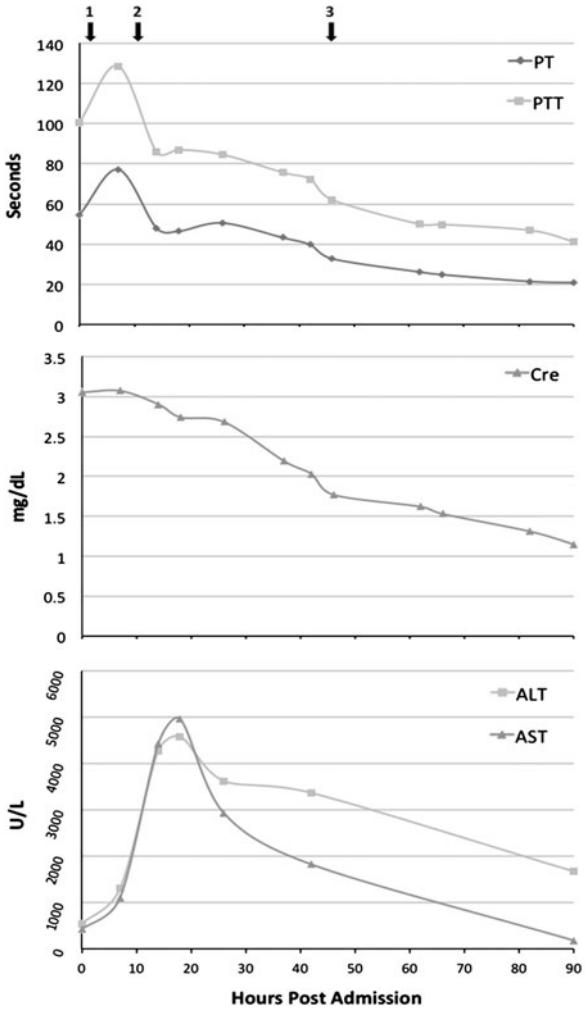

Fig. 3 Coagulation parameters, creatinine and liver enzymes over time. 2 units (total 400 cc) of FFP and 5 mg of oral vitamin K were administered at *arrow 1*; 5,020 international units of Profilnine®, 2 units of FFP and 10 mg of intravenous vitamin K were administered at *arrow 2*; 2 units of FFP were administered at *arrow 3* (prior to central venous catheter placement). Thrombin time was measured (not shown) at hours 7, 24, and 26 and remained >150 s and the diluted TT was 125.0 and 113.1 s at 24 and 26 h, respectively. Of note, 8 months prior to admission the PT and international normalized ratio were 25.2 and 1.1, respectively. *PTT* partial thromboplastin time, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Cre* creatinine, *FFP* fresh frozen plasma, *PT* prothrombin time, *TT* thrombin clotting time

to dabigatran's effect at therapeutic levels [3–5]. In contrast, the aPTT increases in a curvilinear fashion with increasing dabigatran concentration, but the concentration-response curve plateaus at dabigatran concentrations above 200 ng/mL [3–7], which is close to the peak therapeutic level achieved by most patients [8]. Thus, the aPTT is a sensitive test for detecting dabigatran activity, but its value may not accurately reflect dabigatran concentrations above therapeutic levels. Similarly, in vitro studies show a linear relationship between the ACT and dabigatran concentrations up to 250 ng/mL, with a flattening of the concentration-response curve above 500 ng/mL [3]. However, the ACT has not been systematically tested in patients and, therefore, its clinical utility remains uncertain.

The TT directly assesses thrombin activity and exhibits a linear relationship with increasing dabigatran concentration up to 600 ng/mL, at which point the value generally exceeds the maximum measurement time of most coagulometers [3, 6]. Thus, the standard TT may be most useful in determining the presence or absence of circulating dabigatran, but may be too sensitive for overdose evaluations [3–5, 7, 9]. The HemoClot® thrombin inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France) is not yet commercially available in the US, but holds promise as a useful assay for determining drug concentration [3, 4, 7, 9]. The diluted TT assay exhibits a linear relationship with dabigatran concentrations, even at high levels. Thus, dabigatran standards can be supplied to run a calibration curve and thereby determine plasma dabigatran concentration. The ECT is another promising assay of thrombin generation that exhibits a linear relationship with plasma concentrations of dabigatran [3, 5]. However, ECT is currently only available in the research setting [9] and was not available at the authors' institution.

Dabigatran was developed with the expectation that routine laboratory monitoring of its anticoagulant effect would not be needed. However, the present patient's case demonstrates the utility of adopting standardized testing to determine plasma dabigatran concentration. Although initial fibrinogen concentration was in the normal range at 279 mg/dL, the presence of hepatic failure in the present patient made it difficult to determine the degree of coagulopathy attributable to dabigatran versus the contribution from impaired hepatic synthetic function.

Use of Dabigatran in Elderly Patients

Numerous case reports of serious bleeding on dabigatran have been reported in the elderly [7, 10–16]. As in the present patient, these events are frequently precipitated by development of acute renal failure. In patients with normal renal function, dabigatran's half-life is 12–17 h [12]. In patients with a creatinine clearance (CrCl) between 30–50 mL/min, the half-life increases to 13–23 h [12]. As the CrCl falls below 30 mL/min, dabigatran's half-life increases to 22–35 h [12]. For patients with a baseline CrCl of 15–30 mL/min or CrCl of 30–50 mL/min receiving concomitant treatment with strong inhibitors of P-glycoprotein (P-gp), the FDA has approved a dabigatran dose of 75 mg twice-daily [17]. Of note, the RE-LY trial excluded patients with a CrCl less than 30 mL/min and, thus, both the efficacy and relative bleeding risk as compared with warfarin have not been established in this population [1].

Although several case reports implicate development of acute renal failure as the cause for excessive anticoagulation with dabigatran use in the elderly, there are no established guidelines for monitoring renal function while on dabigatran [10–12]. The Italian Federation of Thrombosis Centers recommends annual assessment of renal function in patients with mild renal failure and bi-annual assessments in patients with moderate renal failure [18]. In November of 2011, the prescribing information for dabigatran was revised to recommend calculation of CrCl prior to drug initiation, in any clinical situation potentially associated with a decline in renal function, and annual monitoring in patients greater than 75 years of age or with a CrCl less than 50 mL/min [12, 19]. Close monitoring of CrCl may enable detection of asymptomatic changes in renal function that warrant dose adjustments or cessation of the drug.

In an analysis from the RE-LY trial, patients aged less than 75 years experienced less bleeding with both dabigatran 110 and 150 mg as compared to warfarin (1.89% versus 3.04%, $P < 0.001$ for 110 mg; 2.12% versus 3.04%, $P < 0.001$ for 150 mg) [20]. Among patients aged 75 years and older, however, the risk of bleeding with dabigatran 110 mg was similar to that of warfarin (4.43% versus 4.37%, $P = 0.89$), but a trend toward increased risk of bleeding with age emerged with dabigatran 150 mg as compared with warfarin (5.10% versus 4.37%, $P = 0.07$; P for interaction <0.001) [20]. When the type of bleeding was further analyzed, an increased risk of extracranial bleeding with age emerged, but the risk of intracranial bleeding remained lower for dabigatran as compared with warfarin regardless of age [20]. Interestingly, patients with CrCl <50 mL/min experienced a more than twofold increased risk of major bleeding with both dabigatran and warfarin as compared to patients with CrCl ≥80 mL/min even though warfarin, unlike dabigatran, is not renally excreted [20]. Given a lack of association between treatment and CrCl with major bleeding, factors other than a

tendency toward impaired renal function may contribute to the increased risk of extracranial bleeding that elderly patients experience with dabigatran therapy [20].

Because dabigatran is not metabolized by the cytochrome (CYP) P450 system, drugs affecting CYP enzymes should not affect dabigatran [5, 21]. Dabigatran is, however, a substrate of the efflux transporter P-gp [17]. Inducers of P-gp (e.g., rifampin) decrease peak dabigatran concentrations, while P-gp inhibitors (e.g., ketoconazole and dronedarone) increase peak concentrations. This latter interaction is of particular importance in patients with renal impairment in whom dose adjustments of dabigatran or avoidance of the P-gp inhibitor should be considered depending on the specific co-administered drug and degree of renal impairment [5, 17, 21]. Of note, no dose adjustment of dabigatran is recommended in combination with moderate P-gp inhibitors (e.g., verapamil, amiodarone, quinidine, and clarithromycin) [17].

Methods for Reversal of Dabigatran's Anticoagulant Effect

Reports of major bleeding in patients receiving dabigatran have garnered attention in large part due to the fact that, unlike warfarin, there is currently no antidote for its anticoagulant effect. Given its relatively short half-life (12–17 h) compared to vitamin K antagonists, drug cessation and supportive care is often sufficient in patients with normal renal function who will excrete the drug within hours [3, 10, 12, 14, 22]. By 12 h, dabigatran plasma concentrations fall below 100 ng/mL and aPTT falls to 1.5 times baseline values in patients with normal renal function taking 150 mg of dabigatran twice-daily [3]. Even with impaired CrCl, promoting diuresis when possible is encouraged as a means of eliminating the drug [7]. As shown in Fig. 3, the present patient's coagulation parameters improved in conjunction with improving renal function. When overdose is suspected, dabigatran can be absorbed by activated charcoal given within 1–2 h of ingestion, although this has only been tested in vitro [3, 6, 23]. However, case reports of dabigatran overdose cite new renal failure rather than either intentional or accidental ingestion as the usual culprit, limiting the utility of this potential method [12, 13, 15, 16].

Many therapies used to reverse other anticoagulants are ineffective with dabigatran. Vitamin K and protamine sulfate, well-known antidotes of warfarin and heparin, respectively, are not beneficial for over-anticoagulation with dabigatran [3, 22]. Use of cryoprecipitate has been cited in two case reports without clinical benefit [16, 24]. While the 2011 focused update on the management of patients with atrial fibrillation (update on dabigatran) from the American College of Cardiology, American Heart Association, and Heart Rhythm Society suggest the use of FFP, many cases report utilization of FFP without a significant change in the aPTT or INR [3, 6, 22, 23, 25].

Recombinant activated factor VII (rFVIIa) was developed for treatment of bleeding in hemophiliac patients with inhibitors to factors VIII and IX. Exogenous factor VIIa can directly activate thrombin on the surface of platelets in the absence of tissue factor and has, therefore, gained interest as a potential means of reversing dabigatran's effect [3, 6, 23]. However, rFVIIa did not reverse the antithrombotic effects of melagatran (the active form of the oral direct thrombin inhibitor, ximelagatran, which is not available for clinical use) in a single-blind, randomized study of 47 healthy male volunteers [26].

In an ex vivo study of eight patients with atrial fibrillation taking dabigatran 150 mg twice-daily, Davis et al. [27] investigated the Rapid Thromboelastographic-derived activated clotting time (RapidTEG-ACT) as a method of measuring both the anticoagulant activity of dabigatran and the potential for reversibility with human inactivated thrombin (HTI), rFVIIa, and a four-factor PCC. In concert with aPTT, PT, TT, and ACT, measurement of reaction time from test initiation to initial fibrin formation using thromboelastography (called the TEG *R*-value) is a potentially useful laboratory value for assessing dabigatran's anticoagulant activity. The addition of HTI (currently only available topically and, therefore, unsuited for in vivo testing for this indication) and rFVIIa to patients' peripheral blood significantly reduced the TEG *R*-value while the PCC analog did not. This study suggests a potential utility for rFVIIa that requires further investigation in vivo and clinically.

In a case report of a 79-year-old participant in the RE-LY trial who unintentionally underwent cardiac surgery with therapeutic levels of circulating dabigatran, the authors reported initially trying three doses of 2.4 mg/dose of rFVIIa without success in controlling the patient's post-operative bleeding [24]. The authors subsequently administered two doses of 7.2 mg/dose and, although they did not report coagulation parameters, they cited a reduction in the patient's bleeding as a favorable sign that high-dose rFVIIa may reduce dabigatran-associated bleeding. However, the patient also underwent hemodialysis (HD), which may have contributed to the reduction in bleeding. Furthermore, given the potential of rFVIIa to precipitate myocardial infarction and stroke, care should be taken in using rFVIIa for bleeding events in non-hemophiliacs. The FDA has issued a black box warning due to an increased potential for thrombotic events when rVIIa is used outside of the product's approved indications [28].

Several cases reports, including the present, have commented on the utilization of PCC, of which there are two types available [12, 23]. In the US, only three-factor concentrates are available. They contain II, IX, and X but very low levels of VII. Profilnine is a three-factor PCC used in the authors' institution. Cofact® (Sanquin, Amsterdam, The Netherlands) is a four-factor PCC that contains higher levels of factor VII and is available in Canada and several European countries. In a randomized, double-blind trial of 12 healthy male volunteers, 50 IU/kg of Cofact did not reverse the anticoagulant effects of dabigatran as measured using aPTT, ECT, or TT [29]. In the present case, the patient's coagulopathy did rapidly correct, but the independent contribution of Profilnine could not be determined as it was administered concomitantly with vitamin K and FFP (Fig. 3).

An activated PCC (aPCC) available in the US is Factor Eight Inhibitory Bypassing Activity (FEIBA®; FEIBA NF®, Baxter, West Lake Village, CA, USA). This product is an aPCC concentrate containing factors II, activated VII, IX, and X that was developed for hemophiliac patients with inhibitors to factors VIII or IX. FEIBA has the theoretical benefit of combining the effects of rFVIIa and PCC [23, 30]. In vitro, FEIBA decreased the aPTT of plasma containing factor VIII inhibitor [30]. Marlu et al. [31] assessed whether PCC, rFVIIa, or FEIBA could reverse the anticoagulant effect of dabigatran 150 mg in vitro using venous blood from ten, healthy, white male patients. Four-factor PCC and FEIBA increased the endogenous thrombin potential of dabigatran-anticoagulated plasma, with low

doses successfully reducing levels back to baseline and regular or half doses actually increasing thrombin generation. The highest dose of rFVIIa (3 U/mL) and the three highest doses of FEIBA (0.5–2 U/mL) corrected lag time in thrombin generation nearly to baseline. This study suggests that these products remain promising with respect to reversal of dabigatran-induced thrombin inhibition.

Finally, a number of novel reversal agents are currently in various stages of development. Van Ryn et al. [32] reported that a humanized monoclonal antibody fragment (Fab) against dabigatran can completely inhibit the anticoagulant activity of the drug in both human plasma and whole blood. A synthetic small molecule, PER977, is being developed as a potential antidote to all novel oral anticoagulant drugs, with activity against factor Xa and IIa inhibitors [33]. In addition, a truncated, inactive form of factor Xa known as PRT064445 is currently being tested in phase 2 clinical trials. Early in vitro and in vivo studies have shown this compound to be an effective reversal agent for both the newer direct factor Xa inhibitors and indirect factor Xa inhibitors, such as low molecular weight heparin and fondaparinux [33–36].

Table 2 Summary of case reports of dabigatran over-anticoagulation treated with HD

Authors	Patient	Treatment
Wychowski et al. [12]	66-year-old woman (CrCl ~15 mL/min) with upper GI bleeding	Four sessions of HD over 5 days resulted in resolution of bleeding, decrease in INR from 2.2 to 1.3, decrease in aPTT from 74.7 to 34.8, no change in corrected TT from >60 s
Maddry et al. [13]	74-year-old man (Cr 3.1 mg/dL) with hematemesis	After 4 h of HD, the dabigatran level decreased from 370 to 130 ng/mL
Louet et al. [15]	86-year-old man (CrCl 13.8 mL/min) with GI bleeding	6 h of HD resulted in 60% drug removal
Warkentin et al. [24]	79-year-old man (CrCl 36 mL/min) underwent cardiac surgery with therapeutic dabigatran levels and suffered severe post-op bleeding	After 6 h of high-flux dialysis, the dabigatran level decreased from 76 to 27 ng/mL
Harinstein et al. [16]	84-year-old man (CrCl 25 mL/min) with GI and surgical site bleeding	After 51 h of continuous renal replacement therapy (HD could not be performed due to hemodynamic instability) TT dropped from >120 to 109.7 s
Wanek et al. [37]	59-year-old woman (CrCl 40 mL/min) presented for cardiac transplant 36 h after last dabigatran dose	After 1 h of HD, TT decreased from 90.6 to 65.6 s; after 2.5 h, TT decreased to 60.2 s
Chang et al. [38]	94-year-old man with normal renal function presented with a subdural hematoma	After 1 h of HD, the dabigatran level was 49 ng/mL; after 2 h, the dabigatran level was 20 ng/mL. Dabigatran levels rebounded after dialysis cessation, causing the authors to suggest a longer duration of therapy for future cases

aPTT activated partial thromboplastin time, *ARF* acute renal failure, *CrCl* creatinine clearance, *GI* gastrointestinal, *HD* hemodialysis, *INR* international normalized ratio, *TT* thrombin clotting time

Use of HD in the Management of Severe Bleeding with Dabigatran

Given its lipophilic structure and the fact that a large fraction is not protein bound, up to 62% of plasma dabigatran levels can be removed over 2 h of HD [13, 22, 30]. Several case reports have explored this modality and consistently reported reductions in dabigatran levels with HD (Table 2) [12, 15, 16, 21, 23, 24, 37, 38]. While evidence in support of HD is limited to case reports, the consistently cited benefit of this modality makes it a promising treatment option in cases of dabigatran-associated bleeding. Given the bleeding risk associated with placing a dialysis catheter in a patient with severe coagulopathy, other methods to reverse the anticoagulant effect of dabigatran will be necessary complements to a treatment strategy incorporating HD. In addition, although typically utilized for patients experiencing bleeding in the setting of acute renal failure, it is possible that HD confers a benefit over supportive therapy and promotion of diuresis in patients presenting with bleeding in the context of normal renal function.

Elevations in Liver Enzymes with Oral Direct Thrombin Inhibitors

The first developed oral direct thrombin inhibitor, ximelagatran, was associated with ALT elevations in 6.4% of patients (as compared to 1.2% taking placebo) [39]. Some patients developed clear evidence of drug-induced liver injury (occasionally fatal), resulting in removal of the drug from the European market [39–41] (ximelagatran was never approved for use in the US). However, dabigatran has not been associated with an increased rate of liver function abnormalities in the RE-LY trial or in other studies of venous thromboembolism prevention and treatment [1, 42]. The present patient presented with elevations of both ALT and AST in a clinical context, most suggestive of hepatic hypoperfusion. However, the authors cannot exclude a direct toxic effect of dabigatran.

CONCLUSION

The authors present a case of an elderly gentleman on dabigatran 150 mg twice-daily who developed a significant coagulopathy in the setting of acute renal and hepatic failure. Given that numerous case reports involving elderly patients implicate fluctuations in renal function as a precursor to adverse bleeding events, it is important for clinicians to carefully follow renal function in older patients on dabigatran. Although routine monitoring of dabigatran's anticoagulant effect is not required, a better understanding and availability of laboratory tests specific for dabigatran activity would prove beneficial in managing adverse bleeding events. Finally, a means of reliably and safely reversing the anticoagulant effects of dabigatran will be crucial in effectively managing bleeding in patients taking this medication. While dabigatran carries an equal or lower rate of bleeding compared to warfarin, bleeding events on dabigatran will continue to pose a clinical challenge until optimal monitoring tests and reversal strategies are better defined.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or publication of this article. The authors would like to thank Dr. Stuart Mushlin for his comments and suggestions during the preparation of this manuscript. Dr. Giugliano

is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of interest. Dr. Giugliano is a member of the TIMI Study Group and Principal Investigator of the ENGAGE AF-TIMI 48 Trial, which is supported by a research grant from Daiichi-Sankyo to the TIMI Study Group. Dr. Giugliano has received honoraria for CME lectures and/or consulting from Daiichi-Sankyo and Janssen Pharmaceuticals. Dr. Amy Sarma declares no conflict of interests. Dr. Jeffrey E. Rossi declares no conflict of interests. Dr. Jean M. Connors declares no conflict of interests.

Compliance with ethics guidelines. Consent for publication of this case report was obtained from the patient's wife.

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