

Idarucizumab The Antidote for Reversal of Dabigatran

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Four non-vitamin K antagonist oral anticoagulants (NOACs), including the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, are currently licensed as alternatives to heparins and vitamin K antagonists for the prevention and treatment of venous thromboembolism and for the prevention of stroke in patients with nonvalvular atrial fibrillation. Dabigatran is the only NOAC that inhibits thrombin; the others inhibit factor Xa. All of the NOACs are at least as effective as vitamin K antagonists for the prevention of stroke in patients with atrial fibrillation and for the treatment of venous thromboembolism, and they are associated with less life-threatening bleeding, in particular less intracranial hemorrhage.^{1,2} Nonetheless, serious bleeding can occur with NOACs. In addition, patients taking NOACs may sustain trauma and may require urgent surgery or interventions. Consequently, the availability of specific reversal agents for NOACs could improve patient management during these emergency situations.

Idarucizumab is a humanized monoclonal antibody fragment that has been developed as a specific reversal agent for dabigatran. In vitro and ex vivo studies have demonstrated that idarucizumab promptly restores dabigatran-prolonged coagulation parameters to baseline values,³⁻⁵ and studies in healthy volunteers and patients with life-threatening bleeding or requiring emergency surgery or invasive procedures show that it completely reverses the anticoagulant effects of dabigatran within minutes in the majority of patients. Idarucizumab was recently licensed in the United States and Europe. This article summarizes the pharmacology and clinical data on the use of idarucizumab to reverse dabigatran.

Development of Idarucizumab

The first step in the development of idarucizumab was to immunize mice with dabigatran-derived haptens coupled to carrier proteins to produce antibodies against dabigatran.³ Monoclonal antibodies exhibiting the highest affinity for dabigatran were selected, and the antigen-binding fragment (Fab) was isolated (Figure 1). Murine protein sequences were replaced with human sequences, first in the constant region resulting in a chimeric Fab and then in the variable region where the amino acids were humanized through a design and screening process. The dabigatran-binding humanized Fab

was then expressed in a mammalian cell line with the use of recombinant DNA technology. The use of a humanized Fab instead of an intact antibody results in a shorter half-life and a reduced potential for immunologic reactions.

Pharmacology of Idarucizumab

The mechanism of action and pharmacological properties of idarucizumab are summarized in Table 1.

Mechanism of Action

Idarucizumab binds dabigatran with an affinity \approx 350-fold higher than the affinity of dabigatran for thrombin (binding affinity [K_D] values of 2 pmol/L and 0.7 nmol/L, respectively). Idarucizumab binds unbound and thrombin-bound dabigatran and the active glucuronide metabolites of dabigatran to form 1:1 stoichiometric complexes (Figure 2).³ Once dabigatran is complexed to idarucizumab, the anticoagulant effects of unbound and protein-bound dabigatran and its active metabolites are neutralized.

Idarucizumab is specific for dabigatran and does not bind thrombin or its substrates, nor does it activate platelets or convert fibrinogen to fibrin, making off-target side effects unlikely.^{3,5} In animals and human volunteers, idarucizumab did not promote or attenuate thrombin generation, suggesting that it has no intrinsic anticoagulant or procoagulant effects.

Formulation

Idarucizumab is available as a ready-to-use solution in a package containing two 50-mL glass vials each with 2.5 g idarucizumab at a concentration of 50 mg/mL. No reconstitution is required, which enables rapid delivery. Vials must be refrigerated (2°C–8°C [36°F–46°F]) and have a shelf life of 24 months.⁶ Before use, the unopened vials may be maintained at room temperature for up to 48 hours if they are stored in the original package to protect them from light or for up to 6 hours if exposed to light. In the phase 3 clinical study, a total dose of 5 g was administered intravenously as 2 consecutive 2.5-g infusions no more than 15 minutes apart.⁷ The infusion of each vial, via a syringe, infusion pump, or other appropriate equipment, should take no longer than 5 to 10 minutes. The 5-g total dose of idarucizumab is expected to reverse all of the available dabigatran (ie, all unbound and

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protein-bound dabigatran and its active metabolites) up to the 99th percentile of dabigatran plasma concentrations measured in patients enrolled in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.⁸ The large dose of idarucizumab reflects the ≈ 100 -fold higher molecular weight of idarucizumab relative to dabigatran (47 800 and 472 Da, respectively), the large extravascular pool of dabigatran, and the 1:1 binding (Figure 2).⁹ The use of a fixed-dose regimen simplifies idarucizumab administration.

Pharmacokinetics

The interaction of idarucizumab with dabigatran is characterized by a rapid on-rate (milliseconds) and a very slow off-rate, consistent with the high-affinity binding. With the slow off-rate, binding is effectively irreversible. Therefore, the idarucizumab-dabigatran complex is stable, and there is minimal dissociation of dabigatran from the complex.

In healthy volunteers, peak plasma concentrations of idarucizumab are achieved at the end of a 5-minute infusion, which ensures immediate availability in plasma for binding to dabigatran.¹⁰ Idarucizumab reverses dabigatran in a dose-dependent manner; a 2-g dose is equimolar to the mean peak steady-state concentrations of dabigatran (≈ 155 ng/mL) in healthy volunteers given dabigatran at a dose of 220 mg twice daily.⁹

Idarucizumab has a volume of distribution of ≈ 0.06 L/kg, which approximates the blood volume, and is found primarily in plasma.¹⁰ In contrast, dabigatran is a small hydrophilic molecule with a volume of distribution of ≈ 1 L/kg, and it moves freely between the blood and extravascular compartments.^{11,12} The concentration of unbound dabigatran decreases when idarucizumab binds dabigatran in plasma (Figure 3). Any residual unbound dabigatran re-establishes equilibrium by moving from the extravascular compartment into the plasma where it is bound by idarucizumab, provided that idarucizumab

is administered in excess.⁹ This process continues until all of the dabigatran is bound and its anticoagulant activity is neutralized.

In volunteers with normal renal function, idarucizumab plasma concentrations decline in a biphasic manner with a rapid, initial half-life of ≈ 45 minutes and only 4% of the peak concentration remaining in plasma after 4 hours.¹⁰ Despite its relatively short half-life, idarucizumab binds all of the dabigatran in plasma and that drawn from the extravascular compartment within minutes, as evidenced by the rapid reduction in unbound dabigatran plasma concentrations (ie, dabigatran and its conjugates that are not bound to plasma proteins or to idarucizumab) and the parallel reduction in the anticoagulant effects of dabigatran. Unbound dabigatran concentrations remain low because the idarucizumab binds dabigatran so tightly that the complex is essentially irreversible. This rapid movement of dabigatran from the extravascular compartment into the plasma results in a paradoxical increase in plasma concentrations of total dabigatran, which includes inactive plasma protein-bound dabigatran (and metabolites), idarucizumab-bound dabigatran, and residual active dabigatran. However, the residual concentration of active dabigatran after idarucizumab administration is low, as evidenced by the prompt decline in the plasma concentration of unbound active dabigatran and by the parallel rapid normalization of clotting tests such as the diluted thrombin time (dTT), ecarin clotting time (ECT), and activated partial thromboplastin time (aPTT). The last point is most relevant to clinicians because few will have access to mass spectrometry assays for unbound active dabigatran levels but all will be able to monitor the aPTT before and after idarucizumab administration and some may have access to the dTT or ECT.

Like most proteins $< 50\,000$ Da in molecular weight, idarucizumab is eliminated mainly renally.^{10,13} Idarucizumab is either reabsorbed and degraded in the proximal renal

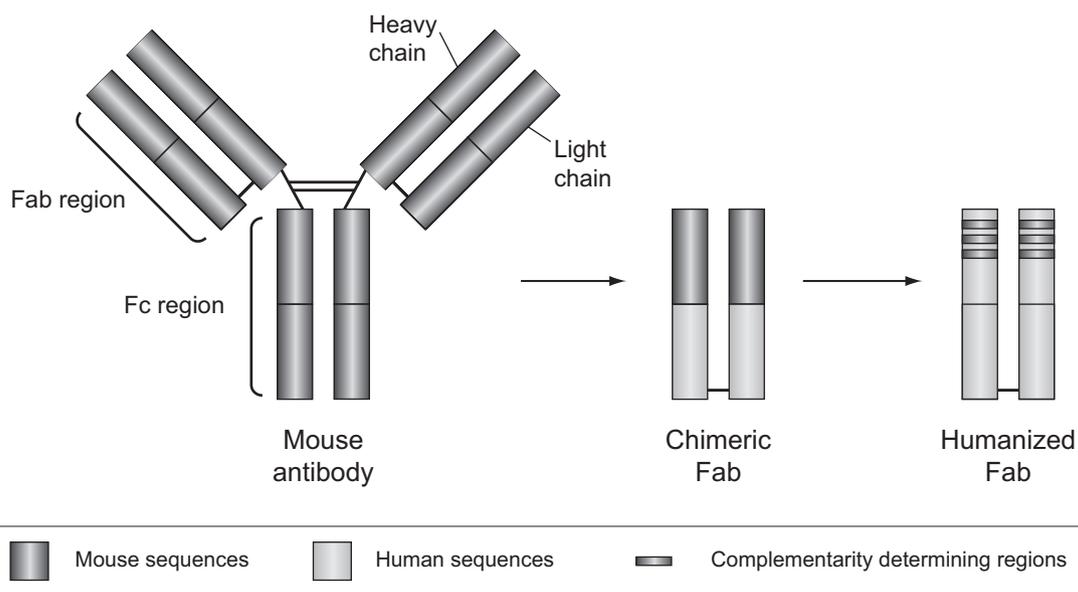


Figure 1. Development of idarucizumab. The fragment antigen-binding (Fab) region is composed of a light and heavy chain and contains the part of the antibody that binds to dabigatran. It also contains a constant region, which, when murine sequences are replaced with human ones, is called a chimeric Fab. The fragment constant (Fc) region interacts directly with the immune system; however, such non-specific binding is avoided by removal of the Fc region.

Table 1. Pharmacological and Pharmacokinetic Properties of Idarucizumab

Properties	
Target	Dabigatran
Structure	Humanized Fab fragment
Mechanism of action	Noncompetitive inhibitor
MW, Da	47 800
K_D , pmol/L	2.1
k_{on}	1.5×10^6 /ms
k_{off} (calculated)	3×10^{-6} /s
Administration	Intravenous (bolus or rapid infusion)
Dosing	Fixed dose, 5 g, administered as two 2.5-g vials no more than 15 min apart
Onset of action	Within minutes
Pharmacokinetics	Stable, predictable*
Reversal of anticoagulant effect	Reduces dTT, ECT, aPTT, and TT within minutes
Elimination half-life	Biphasic; initial, ≈ 45 min \dagger , terminal, ≈ 4.4 – 8.1 h \ddagger
Interaction with other drugs	None reported
Monitoring	No routine monitoring required
Storage	Requires refrigeration (2°C–8°C [36°F–46°F])
Stability	Stable for 2 y
Cost	US wholesale acquisition cost, \$3500
Clinical status	Approved in United States and Europe; undergoing regulatory review in a 10 further countries§

aPTT indicates activated partial thromboplastin time; dTT, dilute thrombin time; ECT, ecarin clotting time; Fab, fragment antigen-binding; K_D , binding affinity; k_{off} , dissociation constant; k_{on} , association constant; MW, molecular weight; and TT, thrombin time.

*Exposure (area under the idarucizumab plasma concentration curve) is increased in patients with renal impairment.

\dagger Accounts for $\approx 90\%$ of the drug.

\ddagger Based on healthy volunteers receiving a dose of 1 to 4 g as a 5-minute infusion. Likely to be increased slightly in patients with renal impairment.

§As of November 2015.

tubules or excreted unchanged in the urine. With a 1-g dose, $\approx 10\%$ unchanged idarucizumab was recovered in the urine, whereas after a 2- or 4-g dose, $\approx 20\%$ and 40% , respectively, was excreted unchanged into the urine. This dose-proportional increase in the percentage of unchanged idarucizumab excreted in the urine reflects saturation of the proximal renal tubule receptors responsible for reuptake of protein fragments. Once these receptors are saturated, excess idarucizumab is eliminated unchanged in the urine.^{10,14}

The majority of idarucizumab recovered in the urine is found within 4 hours of administration. As a result of its predominantly renal excretion, idarucizumab clearance is attenuated in patients with renal impairment, resulting in increased plasma concentrations of idarucizumab. Compared with healthy subjects, idarucizumab exposure, defined as the area under the curve, is increased by 43.5% and 83.5% in subjects with mild or moderate renal impairment, respectively.⁶ However, because patients with renal impairment often have elevated dabigatran plasma concentrations, the higher idarucizumab exposure may be advantageous.

Because idarucizumab envelops the much smaller dabigatran molecule on formation of the 1:1 idarucizumab-dabigatran complex, the complex is cleared in a manner analogous to that of free idarucizumab.^{15,16} After degradation of the complexes in the renal tubules, dabigatran is released into the collecting system and recovered in the urine.¹⁵ The complexes are cleared more slowly in patients with renal impairment. Patient age, body weight, sex, and race (white versus Asian) do not have a clinically relevant

impact on systemic idarucizumab exposure on the basis of population pharmacokinetic analyses in healthy volunteers.⁶

Pharmacodynamic Effect

The reversal of dabigatran can be assessed by monitoring the anticoagulant effects of dabigatran or by measuring dabigatran plasma concentrations before and after idarucizumab administration. Global coagulation tests that measure the anticoagulant effects of dabigatran include the aPTT, thrombin time (TT), and activated clotting time. Of these, the aPTT and TT are readily available with rapid turnaround in most hospitals. Plasma dabigatran concentrations can be quantified with the Hemoclot dTT and ecarin assays. The dTT can accurately quantify dabigatran over a broad range of concentrations, but its sensitivity is reduced with plasma dabigatran concentrations <50 ng/mL.¹⁷ The Hemoclot assay is commercially available in many countries, including Canada and Europe, but it is not approved for patient use in the United States. The ECT and ecarin chromogenic assay determine the capacity of dabigatran to inhibit meizothrombin-induced conversion of fibrinogen to fibrin and chromogenic substrate hydrolysis, respectively, and are accurate over a broad range of dabigatran concentrations.¹⁸

Idarucizumab, given as either a bolus or a 5-minute infusion, normalizes dabigatran-induced prolongation of the dTT, ECT, aPTT, TT, and activated clotting time within minutes in a dose-dependent fashion.^{9,10,19} If the dTT or ecarin-based assays are unavailable, the aPTT or TT can be used to monitor dabigatran reversal with idarucizumab.

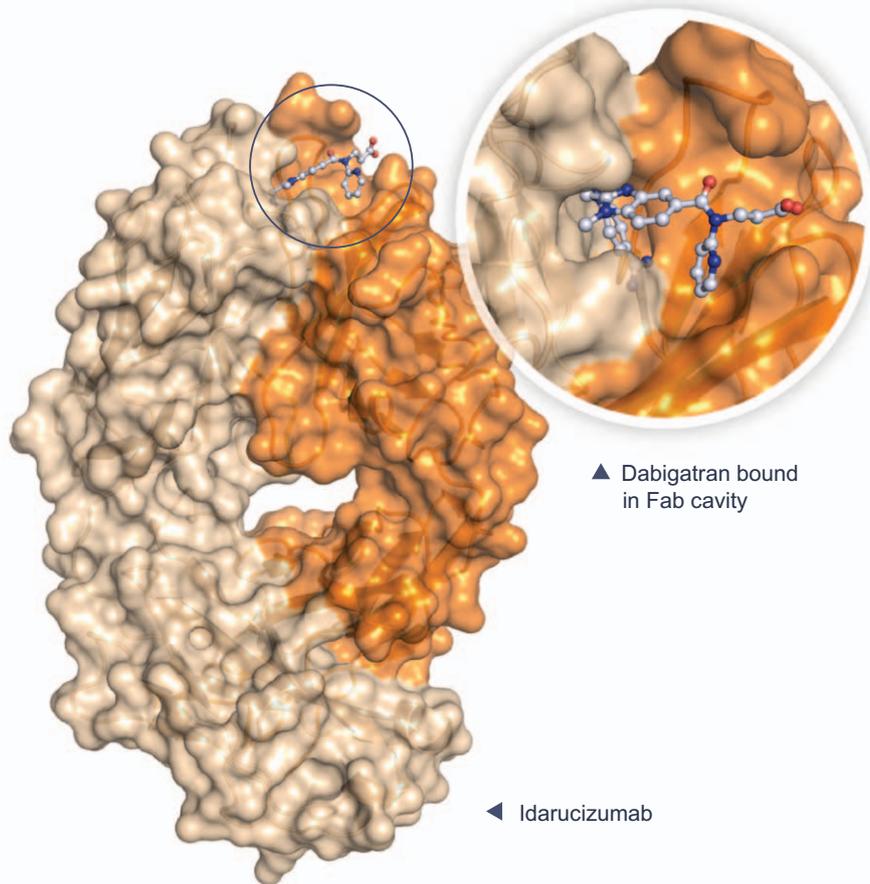


Figure 2. X-ray crystallography surface representations of dabigatran (stick representation) bound to idarucizumab. Inset, A zoom into the cavity formed by the interface of the light (orange) and heavy chains of the fragment antigen-binding into which the benzamidine moiety of dabigatran fits. When dabigatran is bound in this cavity, only $\approx 20\%$ of the molecule is exposed, and it does not protrude from the binding site. Fab indicates fragment antigen-binding.

Animal Studies

Initial studies in rats demonstrated that a single intravenous bolus of idarucizumab completely reversed the anticoagulant activity of 200 ng/mL dabigatran within 1 minute, as measured by TT and aPTT.³ Subsequent studies in a trauma model in pigs that involved crush injury to the liver confirmed the potential of idarucizumab to rapidly reverse the hemorrhagic effects of dabigatran. In pigs given high doses of dabigatran, standardized liver injury resulted in death caused by hemorrhagic shock. Administration of a single intravenous bolus of idarucizumab (30, 60, or 120 mg/kg) reduced blood loss in a dose-dependent manner and improved survival up to 100% compared with untreated controls ($P < 0.0001$ for all groups).²⁰ With administration of idarucizumab 30, 60, or 120 mg/kg, plasma concentrations of unbound active dabigatran decreased by 75%, 80%, and 93%, respectively, compared with the pretreatment levels. Dabigatran-induced prolongation of coagulation tests such as the aPTT and dTT was rapidly reversed by idarucizumab in a dose-dependent fashion. Similar results were obtained with idarucizumab in a double liver injury model of hemorrhagic shock in pigs,²¹ and idarucizumab reduced hemorrhage more rapidly than 4-factor prothrombin complex concentrate in a polytrauma model in which pigs were subjected to both liver injury and femoral fracture.²² Replacing 50% of the blood

volume with crystalloid, colloids, or retransfused washed red blood cells in such models did not interfere with the binding of idarucizumab to dabigatran.²³ Finally, compared with saline, idarucizumab significantly attenuated intracerebral hematoma expansion in dabigatran-treated mice.²⁴ Therefore, the preclinical studies support the potential of idarucizumab to attenuate dabigatran-induced bleeding.

Volunteer Studies

The results of phase 1 studies with idarucizumab are summarized in Table 2. The first was a 2-part placebo-controlled study performed in 110 healthy male volunteers (18–45 years of age); 83 received an intravenous infusion of idarucizumab (20 mg–8 g over 1 hour or 1–4 g over 5 minutes), and 27 were given placebo.¹⁰ Thereafter, 47 volunteers were given 220 mg dabigatran twice daily for 3 days. This dose was chosen because it resulted in peak plasma dabigatran concentrations of ≈ 160 ng/mL in these young healthy volunteers,¹⁰ levels similar to those obtained in older individuals in the RE-LY trial taking the drug at a dose of 150 mg twice daily.⁸ On the fourth day, 2 hours after the morning dose of dabigatran, volunteers were given an intravenous infusion of placebo or idarucizumab (at doses of 1, 2, or 4 g over 5 minutes or 5 g plus 2.5 g each given over 5-minutes, 1 hour apart).⁹ Idarucizumab

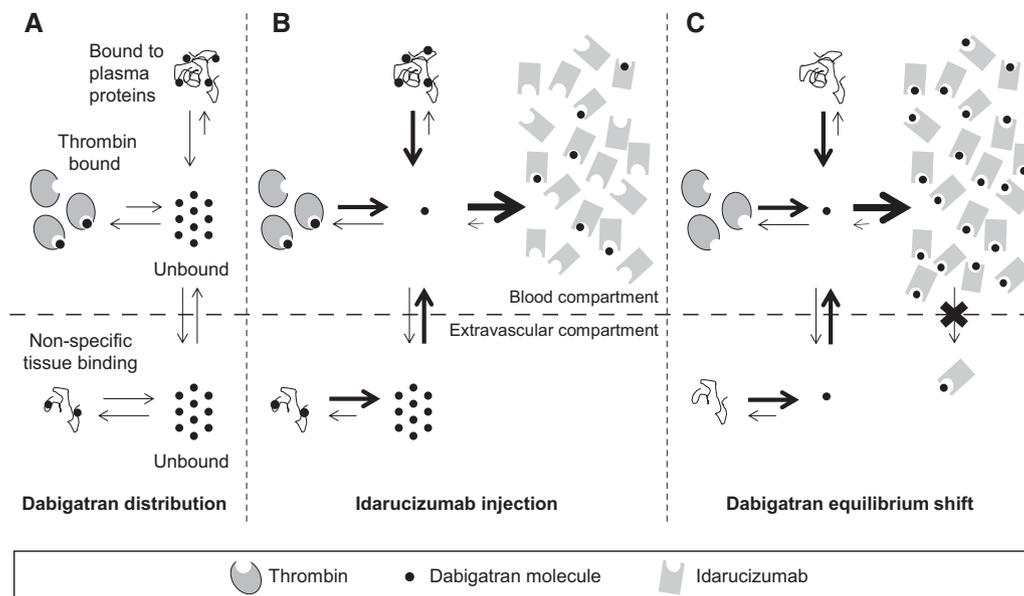


Figure 3. Changes in the distribution of dabigatran after idarucizumab administration. **A**, Circulating dabigatran exists in a state of equilibrium between the plasma and the extravascular compartments. Only unbound dabigatran in the plasma is able to bind thrombin and to inhibit coagulation. **B**, Idarucizumab rapidly binds dabigatran in the plasma. This alters the equilibrium, causing dabigatran in the extravascular compartment to move into the plasma and to potentially dissociate from thrombin (larger arrows). **C**, Because of the high affinity of idarucizumab for dabigatran, thrombin is no longer inhibited, and it regains its capacity to trigger clotting.

reversed the anticoagulant effect of dabigatran, as measured by dTT, aPTT, ECT, TT, and activated clotting time, within 5 minutes in a dose-dependent manner. With doses of ≥ 2 g, reversal of anticoagulant activity, defined as a mean clotting time below the upper limit of normal, was sustained for >72 hours. Plasma concentrations of idarucizumab were reduced to <5% of peak within 4 hours of administration. The treatment was well tolerated, and there was no change in endogenous thrombin potential measured 15 minutes after idarucizumab administration, consistent with its lack of procoagulant or anticoagulant activity. In an *ex vivo* substudy, idarucizumab was shown to restore wound-site fibrin formation, as measured by fibrinopeptide A generation in the shed blood, in dabigatran-treated volunteers.

As with all proteins, idarucizumab may be immunogenic. Natural antibodies with Fab cross-reactivity, including idarucizumab, were detected in 13 of 110 subjects (12%) before the administration of idarucizumab or placebo in part 1¹⁰ and 6 of 47 in part 2 (13%).⁹ These antibodies are directed against the C-terminus of the Fab and do not affect the interaction of idarucizumab with dabigatran because the reversal effect of idarucizumab was maintained in such patients. The majority of these pre-existing antibodies were of low titer, and there were no hypersensitivity reactions. In 3 of 35 subjects receiving idarucizumab in part 2, anti-idarucizumab antibodies were first detected after the infusion and were no longer present at 30 and 90 days. In 1 of the 35 subjects, anti-idarucizumab antibodies were first detected after 30 days and were still present at the 90-day follow-up. The clinical significance of this finding is unclear, and evaluations are ongoing.

The second study investigated the effect of idarucizumab in 46 older volunteers (45–80 years of age), some of whom also had renal dysfunction.¹⁹ Volunteers with normal renal function were given dabigatran 220 mg twice daily for 3

days, and those with mild to moderate renal impairment were given 150 mg twice daily for 3 days. On day 4, 2 hours after the morning dabigatran dose, volunteers received a 5-minute intravenous infusion of placebo or idarucizumab, given as single 1-, 2.5-, or 5-g doses or two 2.5-g doses 1 hour apart in those with moderate renal impairment. Idarucizumab reversed the anticoagulant effect of dabigatran within minutes, and the effect was sustained with doses of ≥ 2.5 g. When dabigatran was again given 24 hours after the 2.5- or 5-g doses of idarucizumab, therapeutic anticoagulation was re-established. Rechallenge of 6 dabigatran-treated volunteers 2 months later with the same dose of idarucizumab again resulted in a similar degree of dabigatran reversal. All doses of idarucizumab were well tolerated, with no events indicative of immunogenicity or prothrombotic effects.

A further study in 80 healthy Japanese subjects investigated the effect of single doses of idarucizumab, administered both alone and after dabigatran.²⁵ The dosing regimens were similar to those used in the first study, but the findings have not yet been reported.

In summary, idarucizumab was tested in >200 volunteers and was well tolerated in doses up to 8 g. No hypersensitivity reactions or severe antidrug antibody reactions have been reported.

Phase 3 Study

The Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study is an ongoing phase 3, global, prospective, cohort study (<http://www.clinicaltrials.gov>; NCT02104947) investigating idarucizumab in 2 groups of dabigatran-treated patients (Figure 4): those who present with uncontrolled or life-threatening bleeding (group A) and those who are not bleeding but require emergency surgery or other invasive procedures that cannot be delayed for at least 8 hours and for which normal hemostasis is desirable (group B).¹⁶ A cohort design was chosen

Table 2. Key Clinical Findings With Idarucizumab in Healthy Volunteers*

Study	Design	Population	Subjects, n	Idarucizumab Dose	Results			
					PK	PD	Safety	Other
1 ¹⁰	R, DB, PC	Healthy male subjects, 18–45 y of age	110	Part 1: Single doses, 20 mg–8 g over 1 h or 1–4 g over 5 min	Dose-proportional increase in C_{max} , AUC, initial $t_{1/2}$ 45 min†	No effect on coagulation parameters	Idarucizumab AE similar to placebo	
1 ⁹			47	Part 2: 1-, 2-, or 4-g 5-min infusion, or 5 g plus 2.5 g in two 5-min infusions given 1 h apart, ≈2 h after final dabigatran dose‡	Dabigatran concentration parallel PD results†	Dose-dependent decrease in ECT, dTT, aPTT, and TT§	Idarucizumab was well tolerated; no unexpected or clinically relevant safety concerns	No increase in thrombin generation vs placebo
2 ¹⁹	R, DB, PC, 2-way CO	Healthy, 45–65 y of age Healthy elderly, 65–80 y of age Mild renal impairment, 45–80 y of age Moderate renal impairment, 45–80 y of age	46	Single 1-, 2.5-, or 5-g doses or two 2.5 g doses 1 h apart as 5-min infusions 2 h after final dabigatran dose¶	Dabigatran concentrations reduced immediately after end of infusion, parallel PD results†	Dose-dependent decrease in ECT, dTT, aPTT, and TT.§ Sustained reversal over 72 h for doses >2 g. Partial reversal for 2–4 h with 1-g dose Complete reversal after idarucizumab re-exposure 2 mo after initial administration	All doses of idarucizumab were safe and well tolerated No hypersensitivity after idarucizumab re-exposure 2 mo after initial administration	Readministration of dabigatran 24 h after idarucizumab 2.5 and 5 g restored dabigatran-related anticoagulation

AE indicates adverse effects; aPTT, activated partial thromboplastin time; AUC, area under the concentration-time curve in plasma; C_{max} , maximum measured concentration in plasma; CO, crossover; DB, double-blind; dTT, dilute thrombin time; ECT, ecarin clotting time; PC, placebo controlled; PD, pharmacodynamic; PK, pharmacokinetic; R, Randomized; TT, thrombin time; and $t_{1/2}$, half-life.

*A further study was performed in 80 healthy Japanese men (20–45 years of age).²⁵ The study had a similar design to the study 1 design (part 1: single doses, 20 mg to 8 g over 1 hour or from 1 to 4 g over 5 minutes [n=36]; part 2: 1-, 2-, or 4-g 5-minute infusion, or 5 g plus 2.5 g in two 5-minute infusions given 1 hour apart, ≈2 h after final dabigatran dose [n=44]), but the study results have not been reported.

†Measured as concentrations of unbound dabigatran as a measure of pharmacologically active dabigatran.

‡All participants received oral dabigatran etexilate 220 mg twice daily for 3 days and a final dose on day 4.

§Assessed by measuring the area under the effect curve from 2 to 12 hours after dabigatran etexilate ingestion on days 3 and 4.

¶Dabigatran etexilate 220 mg twice daily in healthy and elderly subjects and 150 mg twice daily in subjects with mild renal impairment (creatinine clearance, 60–90 mL/min) or moderate renal impairment (creatinine clearance, 30–60 mL/min) was given over 4 days.

because it was considered unethical to include a control group who received placebo or no active treatment in the absence of a known alternative to idarucizumab. It is expected that ≈500 patients from 400 centers will be entered in this trial, which will complete enrollment in 2016. All patients receive 5 g idarucizumab administered as 2 intravenous boluses of 2.5 g, each given as a rapid infusion, no more than 15 minutes apart. The primary end point is maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours of completion of the idarucizumab infusions on the basis of central laboratory measurement of the dTT or ECT, tests chosen because they showed excellent correlation with dabigatran concentrations measured by mass spectrometry. Time to cessation of bleeding and assessment of hemostasis during interventions are key secondary end points in groups A and B, respectively.

Data for the first 90 patients receiving idarucizumab in the phase 3 trial were reported.⁷ More than 90% of patients had a diagnosis of atrial fibrillation and were receiving dabigatran for stroke prevention. Group A included 51 patients, of whom 16 were hemodynamically unstable. Enrolled in this group were 18 patients with intracranial hemorrhage, 20 with gastrointestinal bleeding, and 9 with trauma. Group B included 39 patients who required urgent procedures (including 8 with bone fractures and 5 with acute cholecystitis) but were not bleeding at presentation. The mean age was 77 years in group A and 76

years in group B. The median patient-reported time since the last dose of dabigatran was 15.2 and 16.6 hours in groups A and B, respectively. Median plasma concentrations of dabigatran were 132 and 114 ng/mL in groups A and B, respectively.

Overall, 68 (76%) and 81 (90%) of the 90 patients had an elevated dTT or ECT at study entry. In the group A bleeding patients, 11 had normal coagulation tests, and in group B non-bleeding patients, 11 presented with normal tests. However, patient enrollment was based only on clinical presentation, and these assays were performed centrally at a later time point and were not used to guide therapy. After administration of idarucizumab, the median maximum reduction in these assays within 4 hours was 100% (95% confidence interval, 100–100; Figure 5). Reversal was evident immediately after the first vial of idarucizumab was given, and 100% reversal was achieved in all but 1 patient. Idarucizumab normalized these assays in 88% (ECT) to 98% (dTT) of patients who had elevated levels at baseline. At 4 hours after treatment, 83 of the 86 patients with elevated dabigatran levels at baseline had a concentration of unbound dabigatran that was ≈1 ng/mL, the lower limit of quantification (Figure 6). By 24 hours, 79% of patients had plasma concentrations of active dabigatran that were <20 ng/mL, a level that produces little or no anticoagulant activity.

In the group A patients, bleeding cessation could be determined in 38 patients (13 patients had bleeding at sites not

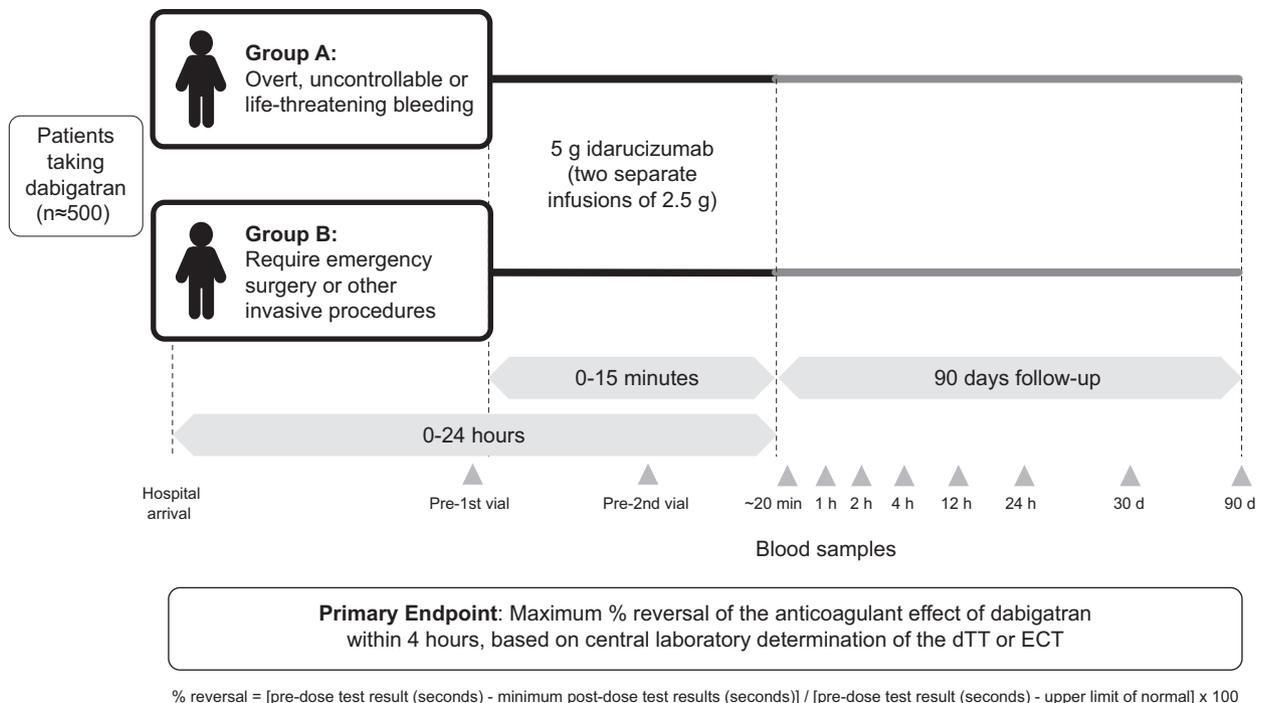


Figure 4. Design of the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study.¹⁶ dTT indicates diluted thrombin time; and ECT, ecarin clotting time.

readily accessible). The investigator-reported median time to cessation of bleeding was 11.4 hours. In group B, normal intraoperative hemostasis was reported in 92% of the 36 patients who underwent procedures after the administration of idarucizumab. The median time between administration of idarucizumab and the start of the procedure was 1.7 hours, and no postsurgical bleeding complications were reported in the 24 hours after surgery.

Thrombotic events (including deep vein thrombosis, pulmonary embolism, myocardial infarction, or ischemic stroke) occurred in 5 patients: 1 after 48 hours of idarucizumab administration and the rest >72 hours after dosing. None of the 5 patients had restarted anticoagulant therapy at the time of the thromboembolic event, and in each of these cases, the thrombotic event could be attributed to the underlying medical condition. Of the 90 patients, 18 died (9 in each group). Therefore, the mortality rate was 20%, with about half of the deaths caused by vascular events. Half of the deaths occurred >96 hours after the administration of idarucizumab, and all of the deaths appeared to be associated with pre-existing medical conditions.

Implications for Practice

On October 16, 2015, the US Food and Drug Administration granted accelerated approval to idarucizumab (Praxbind) for use in patients who are taking dabigatran during emergency situations when there is a need to reverse the anticoagulant effects of dabigatran.⁶ This approval was based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers. On November 20, 2015, the European Medicines Agency approved idarucizumab after accelerated assessment.²⁶ Regulatory submissions have also been made in a 10 further countries. Idarucizumab is currently

available for clinical use in the United States and some European countries and will become more widely available in Europe and the rest of the world in 2016.

As always, the management of bleeding complications in patients receiving dabigatran should be individualized on the basis of the location and severity of the hemorrhage.²⁷ It is important to point out that coexisting medical conditions may have a greater effect on prognosis than the ability to rapidly neutralize the anticoagulant effect of dabigatran.²⁸ This concept is underscored by the high mortality rate observed in the first 90 patients enrolled in the RE-VERSE AD study.

Current protocols for the management of bleeding and of patients who require urgent surgery will need to be updated to provide guidance on the use of idarucizumab when it becomes available. Figure 7 shows a proposed algorithm for inclusion of idarucizumab in current bleeding management protocols in patients treated with dabigatran. When available, idarucizumab will be the treatment of choice for dabigatran reversal.

In rare cases in which idarucizumab administration fails to completely reverse the anticoagulant effects of dabigatran or if there is a rebound increase in the tests of coagulation and reappearance of clinically relevant bleeding or the need for a second urgent procedure, an additional 5-g dose of idarucizumab may be considered.⁶

In the first 90 patients receiving idarucizumab in RE-VERSE AD, the results of coagulation tests were normal in about one quarter of patients considered eligible for idarucizumab. Such patients have little or no circulating dabigatran and are unlikely to benefit from idarucizumab administration.²⁸ Nonetheless, once licensed, it is likely that idarucizumab will be given before the results of coagulation tests are known in patients who present with life-threatening

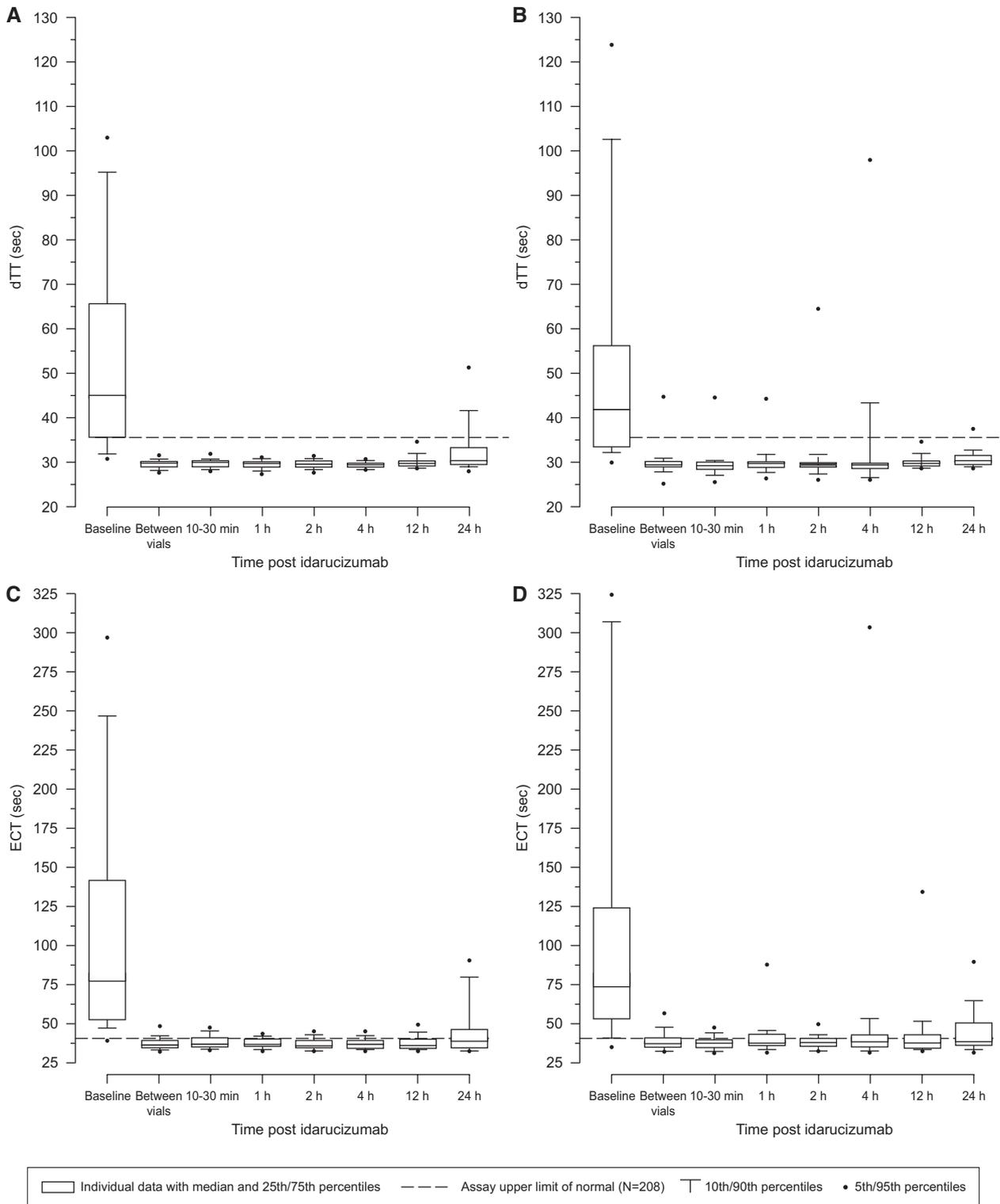


Figure 5. Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) primary end-point results. Time course of the ecarin clotting time and diluted thrombin time before and after idarucizumab administration. The analyses included 51 patients in group A with serious bleeding (**A** and **C**) and 39 in group B who required urgent surgery or intervention (**B** and **D**). Idarucizumab was administered as 2 intravenous bolus infusions. Blood samples were obtained at baseline; after the first infusion; at 10 to 30 minutes after the administration of the second infusion; and at 1, 2, 4, 12, and 24 hours thereafter. Data are presented as box-and-whisker plots in which the tops and bottoms of the rectangles indicate the 75th and 25th percentiles, respectively; the horizontal lines within the rectangles, the 50th percentile; the lines above and below the rectangles, the 90th and 10th percentiles, respectively; and the dots above and below the lines, the 95th and 5th percentiles, respectively. The dashed lines indicate the upper limit of the normal range for the tests. dTT indicates diluted thrombin time; and ECT, ecarin clotting time. Reprinted with permission from Pollack et al.⁷ Copyright © 2015, Massachusetts Medical Society.

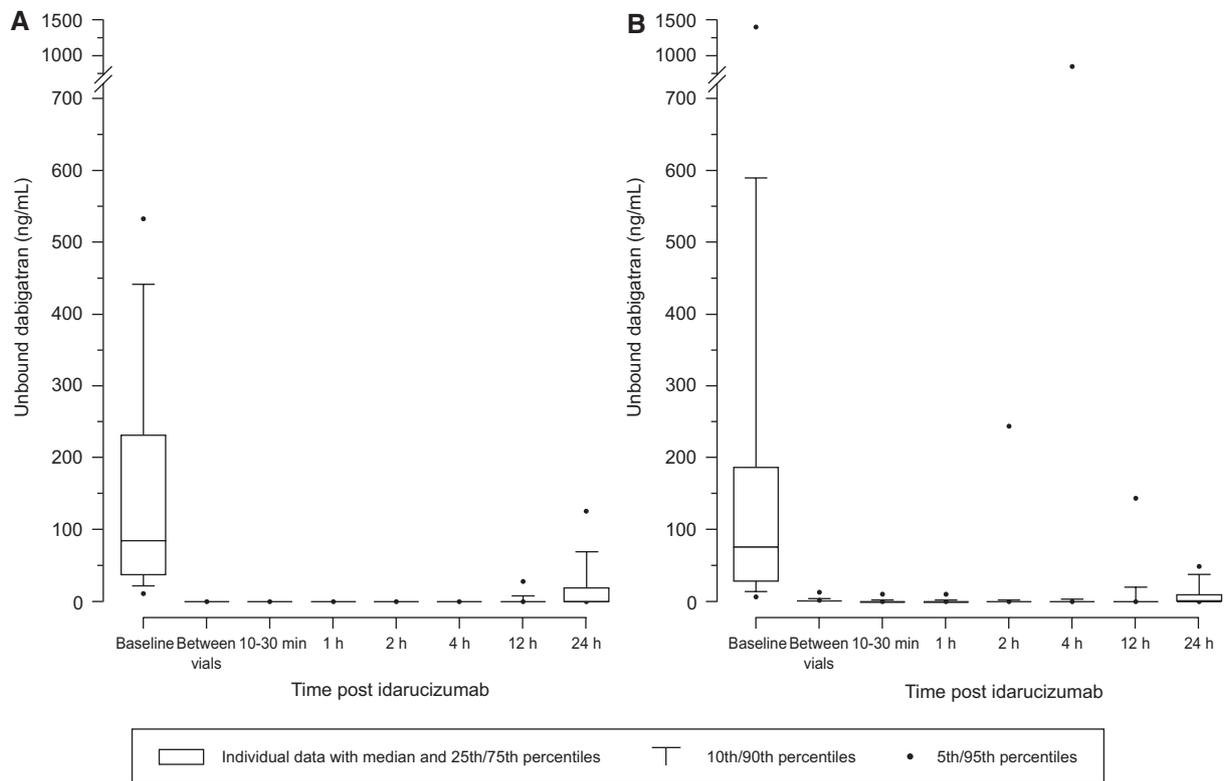


Figure 6. Plasma concentrations of unbound dabigatran before and after idarucizumab administration. The analyses include 51 patients in group A with serious bleeding (**A**) and 39 patients in group B who required urgent surgery or intervention (**B**). Data are presented as box-and-whisker plots in which the tops and bottoms of the rectangles indicate the 75th and 25th percentiles, respectively; the horizontal lines within the rectangles, the 50th percentile; the lines above and below the rectangles, the 90th and 10th percentiles, respectively; and the dots above and below the lines, the 95th and 5th percentiles, respectively. Reprinted with permission from Pollack et al.⁷ Copyright © 2015, Massachusetts Medical Society.

bleeding such as those with intracranial hemorrhage or with multiple trauma.

Depending on the clinical condition of the patient with a life-threatening bleed, coagulation testing can be of value to determine the presence or absence of circulating dabigatran and to help evaluate its potential contribution to the bleeding. The aPTT approximates dabigatran levels and is a useful tool to quickly obtain an anticoagulant status. The TT can determine the presence or absence of dabigatran in the circulation and, together with an aPTT, may also be useful.²⁹ A normal TT essentially eliminates a contribution of dabigatran to the bleeding.³⁰ The results of abnormal coagulation tests need to be cautiously interpreted in patients with liver disease or severe blood loss because coagulopathies can occur even in nonanticoagulated patients. More specific tests such as the ECT or dTT are useful but rarely are available 24 hours a day.

A key consideration when faced with patients who are bleeding is the timing of the last dose of dabigatran. If >48 hours have elapsed in patients with normal renal function or >72 hours in those with impaired renal function, dabigatran is unlikely to be a major contributor to the bleeding.

The short half-life of idarucizumab in patients with normal renal function allows the resumption of dabigatran treatment within 24 hours of its administration. This is important to avoid the potential risk of thrombosis inherent in reversing anticoagulation in a patient with an underlying predisposition

to thrombosis.³¹ In the RE-VERSE AD study, 5 of the 17 patients who did not restart anticoagulation 2 to 26 days after treatment subsequently developed a thrombotic event.⁷

A similar strategy exists for the management of patients taking dabigatran who require emergency surgery or an invasive procedure (Figure 7). The effect of idarucizumab is extremely rapid and sustained for 12 hours, meaning that surgical procedures can be started shortly after administration. Evidence of a normal aPTT and TT before surgery can help to confirm reversal.

Provided that the risk of thrombosis outweighs the risk of bleeding, anticoagulant treatment should resume after surgery or invasive procedures once adequate hemostasis is restored. In patients at high risk for bleeding after surgery, treatment can start with a low dose of an anticoagulant for thromboprophylaxis, and the dose can then be increased to a therapeutic level once the bleeding risk subsides. Because idarucizumab is specific for dabigatran, the anticoagulant activity of other anticoagulants will not be affected.

In patients with renal impairment, the idarucizumab half-life is prolonged, meaning that reinitiation of dabigatran may need to be delayed or an alternative anticoagulation may need to be considered.

Implications for Future Research

The potential exists for use of idarucizumab in patients with moderate bleeding that fails to stop with general measures.¹⁵

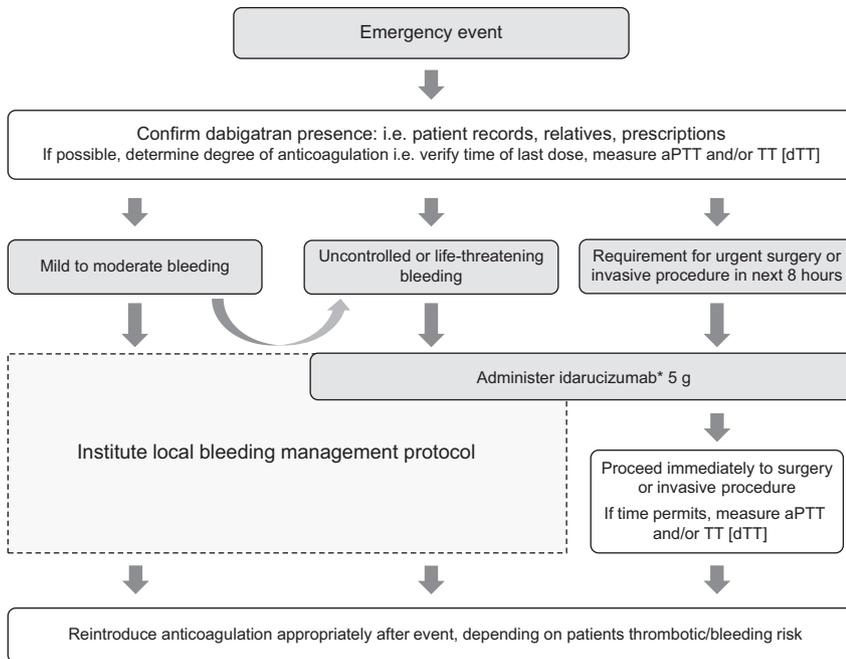


Figure 7. Proposed algorithm for management of patients treated with dabigatran who present with bleeding episodes or require urgent surgery/invasive procedures. *Administer two 50-mL vials of idarucizumab (each containing 2.5 g) intravenously. In rare cases when dabigatran anticoagulation remains present after idarucizumab and bleeding continues in the patient, a second 5-g dose of idarucizumab may be considered. aPTT indicates activated partial thromboplastin time; dTT, diluted thrombin time; and TT, thrombin time.

Idarucizumab has not been tested in this setting, and further study is required. It is uncertain whether an idarucizumab dose of 2.5 g is sufficient for reversal in some patients, and it is unknown whether idarucizumab can be safely used to reverse dabigatran before thrombolytic therapy is given to patients with acute ischemic stroke.

After approval, additional real-world data will help to increase our understanding of the role of idarucizumab in situations and patient groups in which it can improve clinical outcomes.

Conclusions

The development of idarucizumab to rapidly and completely reverse the anticoagulant activity of dabigatran is an important clinical advance. When available, idarucizumab is likely to be the treatment of choice for patients who present with dabigatran-induced uncontrolled or life-threatening bleeding or for those who require urgent surgery or invasive procedures.

Besides idarucizumab, other reversal agents are in development to reverse both dabigatran and the other NOACs.¹⁵ These include andexanet alfa, a recombinant truncated form of enzymatically inactive factor Xa, which binds and reverses the anticoagulant action of the factor Xa inhibitors,³² and PER977 (ciraparantag), a synthetic small molecule that is reported to bind to all of the NOACs and has been shown to reduce the whole-blood clotting time to background levels in volunteers given edoxaban.³³

Although there is less serious bleeding with the NOACs than with vitamin K antagonists, the lack of specific reversal agents has raised concerns about the inability to promptly reverse their anticoagulant effect in patients with life-threatening bleeding and in those requiring emergency surgery.³⁴ The impending availability of specific reversal agents for the NOACs should allay these concerns and enhance their uptake, particularly in patients with nonvalvular atrial fibrillation.³⁵

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