8-3-2017

Idarucizumab for Dabigatran Reversal - Full Cohort Analysis.

Charles V. Pollack
Thomas Jefferson University

Paul A. Reilly
Boehringer Ingelheim

Joanne van Ryn
Boehringer Ingelheim

John W. Eikelboom
Boehringer Ingelheim

Stephan Glund
Boehringer Ingelheim

See next page for additional authors

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D., John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Chak-Wah Kam, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Gordon Royle, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., Peter Verhamme, M.D., Bushi Wang, Ph.D., Laura Young, M.D., and Jeffrey I. Weitz, M.D.

ABSTRACT

BACKGROUND

Idarucizumab, a monoclonal antibody fragment, was developed to reverse the anticoagulant effect of dabigatran.

METHODS

We performed a multicenter, prospective, open-label study to determine whether 5 g of intravenous idarucizumab would be able to reverse the anticoagulant effect of dabigatran in patients who had uncontrolled bleeding (group A) or were about to undergo an urgent procedure (group B). The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, on the basis of the diluted thrombin time or ecarin clotting time. Secondary end points included the restoration of hemostasis and safety measures.

RESULTS

A total of 503 patients were enrolled: 301 in group A, and 202 in group B. The median maximum percentage reversal of dabigatran was 100% (95% confidence interval, 100 to 100), on the basis of either the diluted thrombin time or the ecarin clotting time. In group A, 137 patients (45.5%) presented with gastrointestinal bleeding and 98 (32.6%) presented with intracranial hemorrhage; among the patients who could be assessed, the median time to the cessation of bleeding was 2.5 hours. In group B, the median time to the initiation of the intended procedure was 1.6 hours; periprocedural hemostasis was assessed as normal in 93.4% of the patients, mildly abnormal in 5.1%, and moderately abnormal in 1.5%. At 90 days, thrombotic events had occurred in 6.3% of the patients in group A and in 7.4% in group B, and the mortality rate was 18.8% and 18.9%, respectively. There were no serious adverse safety signals.

CONCLUSIONS

In emergency situations, idarucizumab rapidly, durably, and safely reversed the anticoagulant effect of dabigatran. (Funded by Boehringer Ingelheim; RE-VERSE AD ClinicalTrials.gov number, NCT02104947.)

From Thomas Jefferson University, Philadelphia (C.V.P.); Boehringer Ingelheim, Ridgefield, CT (P.A.R., R.D., B.W.); Boehringer Ingelheim, Biberach (J.R., S.G., J.S.), Boehringer Ingelheim, Ingelheim am Rhein (J.K.), Klinikum Frankfurt Höchst, Frankfurt (T.S.), and Heidelberg University Hospital, Heidelberg (T.S.) — all in Germany; McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada (J.W.E., J.I.W.); Feinberg School of Medicine, Northwestern University, Chicago (R.A.B.); Leiden University Medical Center, Leiden (M.V.H.), and Tergooi Hospital, Hilversum (P.W.K.) — both in the Netherlands; Boston University School of Medicine, Boston (E.M.H.); Tuen Mun Hospital, Hong Kong (C.-W.K.); Duke University School of Medicine, Durham, NC (J.H.L.); Middlemore Hospital (G.R.) and the University of Auckland (L.Y.) — both in Auckland, New Zealand; Warren Alpert Medical School of Brown University and Rhode Island Hospital, Providence (F.W.S.); and KU Leuven, Center for Molecular and Vascular Biology, Leuven, Belgium (P.V.). Address reprint requests to Dr. Pollack at Thomas Jefferson University, 1020 Walnut St., 6th Fl., Philadelphia, PA 19107, or at charles.pollack@jefferson.edu.

This article was published on July 11, 2017, at NEJM.org.

N Engl J Med 2017;377:431-41.
DOI: 10.1056/NEJMoa1707278

Patients who are receiving oral anticoagulant therapy for the prevention or treatment of thrombosis may benefit from anticoagulant reversal if they present with life-threatening bleeding or if they will be undergoing urgent surgery or intervention. Therefore, the availability of specific reversal agents has the potential to improve the benefit–risk profile of long-term anticoagulant therapy and to increase patient and physician acceptance of such treatment. Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with high affinity and specificity and rapidly reverses its anticoagulant activity.[1] Idarucizumab has been licensed in many countries, in part on the basis of the results of an interim analysis of data on the first 90 patients enrolled in the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study.[2] This report provides data on the entire cohort of 503 patients included in that study and validates the results of the interim analysis.

Methods

Study Design and Oversight

We conducted a multicenter, prospective, single-cohort study.[3] The rationale for not including a control group has been described previously.[2,3] A steering committee composed of representatives from academia and the sponsor (Boehringer Ingelheim) assumes final responsibility for the design and conduct of the study. The study protocol, which is available with the full text of this article at NEJM.org, was approved by all the relevant institutional review boards. All the authors contributed to the drafting of the manuscript, made the decision to submit the manuscript for publication, and vouch for the completeness and accuracy of the data, the accuracy of the analyses, and the fidelity of the study to the protocol. No one who is not an author contributed to the writing of the manuscript.

Patients

The study included two groups of adults, 18 years of age or older, who were receiving dabigatran. The patients in group A were those with uncontrollable or life-threatening bleeding that was judged by the treating clinician to require rapid anticoagulant reversal. The patients in group B were those who were about to undergo surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal hemostasis was required. All the patients or their authorized representative provided written informed consent.

Study Treatment

All patients were to receive 5 g of intravenous idarucizumab, which was administered as two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 minutes apart. The 5-g dose was calculated to reverse the total body load of dabigatran that was associated with the 99th percentile of the dabigatran levels measured in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.[4]

Assessments and Study End Points

The primary efficacy end point was the maximum percentage reversal of the anticoagulant effect of dabigatran, determined at any point from the end of the first idarucizumab infusion until 4 hours after the end of the second infusion, with the percentage reversal assessed on the basis of the diluted thrombin time or the ecarin clotting time. These measurements were chosen because they correlate linearly with dabigatran concentrations measured with the use of mass spectroscopy.[5,6] Blood samples for pharmacokinetic and pharmacodynamic assessments were obtained at baseline, after the first infusion of idarucizumab, and between 10 and 30 minutes and at 1, 2, 4, 12, and 24 hours after the second infusion. Diluted thrombin time, ecarin clotting time, activated partial-thromboplastin time, and concentrations of unbound dabigatran were measured at a central laboratory, as described previously.[3] Reasons that an assessment could not be performed at any given time point included death, a missing sample, a small-volume sample, and technical difficulties. Treating clinicians were unaware of the results at the central laboratory. In parallel, the activated partial-thromboplastin time was assessed locally at baseline, after the first infusion of idarucizumab, and between 10 and 30 minutes and at 12 hours after the second infusion of idarucizumab. Complete reversal was defined as a decrease in the diluted thrombin time or ecarin clotting time to a normal level. A second 5-g dose of idarucizumab was permitted if there was recurrent or continued bleeding and objective evidence of a residual anticoagulant effect of dabi-

gatran or if a second surgical procedure was necessary and residual anticoagulant activity was suspected or confirmed.

Clinical outcomes, as assessed by the treating clinician, were secondary end points. In group A, the extent of bleeding and hemodynamic stability were assessed between 10 and 30 minutes and at 1, 2, 4, 12, and 24 hours after the second idarucizumab infusion or when deemed clinically appropriate. The severity of bleeding was classified with the use of the International Society on Thrombosis and Haemostasis criteria (for more details, see the Supplementary Appendix, available at NEJM.org).[7] In group B, periprocedural hemostasis was classified by the clinician as normal or as mildly, moderately, or severely abnormal. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 18.0.[8] Adverse events occurring within 5 days after the administration of idarucizumab were considered to have occurred during treatment. The severity of bleeding at presentation (in group A) and any suspected thrombotic events or deaths occurring from the time of idarucizumab infusion to 90 days after the infusion were to be adjudicated by an independent committee. Deaths were classified as vascular (including bleeding) or nonvascular in origin.

STATISTICAL ANALYSIS

The primary efficacy end point of maximum percentage reversal of dabigatran was calculated for patients in whom pretreatment diluted thrombin times or ecarin clotting times were above the upper limit of the normal range as assessed at a central laboratory; descriptive statistics with confidence intervals or percentiles were used as appropriate. Clotting-time measurements that exceeded the maximum measurable range were imputed with the use of the maximum measurable clotting time of 500 seconds only if the imputation was consistent with the concomitant results of other coagulation tests and unbound-dabigatran concentrations.[3]

The sample size was based on regulatory feedback and practical considerations, including recruitment rates and the frequency of serious bleeding complications and emergency surgery among patients receiving dabigatran. On the basis of data from the RE-LY trial, the annual rates of life-threatening bleeding among patients receiving dabigatran at a dose of 150 mg and 110 mg are 1.5% and 1.25%, respectively, and the annual rate of emergency surgery among patients receiving dabigatran is 1.5%.[9]

RESULTS

CHARACTERISTICS OF THE PATIENTS

From June 2014 through July 2016, a total of 503 patients (301 in group A and 202 in group B) were enrolled at 173 sites (of 369 initiated sites) in 39 countries. More than 95% of the patients were receiving dabigatran for stroke prevention in the context of atrial fibrillation, and the median age was 78 years. The median patient-reported time from the last dose of dabigatran to the first infusion of idarucizumab was 14.6 hours in group A and 18.0 hours in group B. Of the enrolled patients, 43.3% had a creatinine clearance, calculated with the use of the Cockcroft–Gault equation, that was less than 50 ml per minute. Many patients had coexisting conditions at the time of enrollment (Table 1).

Of the 301 patients in group A, 137 (45.5%) had gastrointestinal bleeding, 98 (32.6%) had intracranial hemorrhage, and 78 (25.9%) had trauma as the cause of bleeding (Table 2). Bleeding was adjudicated as major or life-threatening in 265 patients (88.0%) and resulted in surgical intervention in 61 (20.3%); 114 patients (37.9%) had hemodynamic instability at presentation.

Of the 202 patients in group B, 197 (97.5%) underwent the intended surgery or intervention. The median time from the first infusion of idarucizumab to the initiation of the procedure was 1.6 hours. The indications for urgent surgery or intervention are listed in Table 2.

REVERSAL OF ANTICOAGULATION

At study entry, 461 of the 503 patients (91.7%; 276 in group A and 185 in group B) had a prolonged diluted thrombin time or ecarin clotting time and were included in the primary efficacy analysis (Table 1). The median maximum percentage reversal within 4 hours after the administration of idarucizumab was 100% (95% confidence interval [CI], 100 to 100), as assessed on the basis of either the diluted thrombin time (Fig. 1A and 1B) or the ecarin clotting time (Fig. S1 in the Supplementary Appendix). Reversal was rapid and occurred independently of age, sex, renal function, and dabigatran concentration at baseline. Reversal based on the activated partial-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Group A (N=301)	Group B (N=202)	Total (N=503)
Age — yr			
Median	79	77	78
Range	24–96	21–96	21–96
Male sex — no. (%)	172 (57.1)	102 (50.5)	274 (54.5)
Weight — kg			
Median	74	77	75
Range	35–231	39–169	35–231
Race or ethnic group — no. (%)†			
White	239 (79.4)	175 (86.6)	414 (82.3)
Asian	29 (9.6)	8 (4.0)	37 (7.4)
Hawaiian or Pacific Islander	16 (5.3)	14 (6.9)	30 (6.0)
Other	17 (5.6)	5 (2.5)	22 (4.4)
Coexisting condition — no. (%)			
Hypertension	237 (78.7)	157 (77.7)	394 (78.3)
Congestive heart failure	117 (38.9)	65 (32.2)	182 (36.2)
Diabetes	95 (31.6)	57 (28.2)	152 (30.2)
Coronary artery disease	110 (36.5)	68 (33.7)	178 (35.4)
Previous stroke	73 (24.3)	36 (17.8)	109 (21.7)
Previous transient ischemic attack	27 (9.0)	20 (9.9)	47 (9.3)
Previous systemic embolism	20 (6.6)	16 (7.9)	36 (7.2)
Previous major bleeding	27 (9.0)	10 (5.0)	37 (7.4)
Current cancer	23 (7.6)	20 (9.9)	43 (8.5)
Creatinine clearance			
Value — ml/min			
Median	50.8	56.0	52.6
Range	6.1–216.9	7.9–198.7	6.1–216.9
Distribution — no. (%)			
≥80 ml/min	58 (19.3)	50 (24.8)	108 (21.5)
50 to <80 ml/min	95 (31.6)	68 (33.7)	163 (32.4)
30 to <50 ml/min	86 (28.6)	41 (20.3)	127 (25.2)
<30 ml/min	53 (17.6)	38 (18.8)	91 (18.1)
Missing data	9 (3.0)	5 (2.5)	14 (2.8)
Dose of dabigatran — no. (%)			
150 mg twice daily	94 (31.2)	57 (28.2)	151 (30.0)
110 mg twice daily	185 (61.5)	126 (62.4)	311 (61.8)
75 mg twice daily	16 (5.3)	8 (4.0)	24 (4.8)
Other	3 (1.0)	11 (5.4)	14 (2.8)
Indication for dabigatran — no. (%)			
Atrial fibrillation	288 (95.7)	190 (94.1)	478 (95.0)
Orthopedic surgery	0	3 (1.5)	3 (0.6)
Venous thromboembolism	5 (1.7)	4 (2.0)	9 (1.8)
Other	8 (2.7)	5 (2.5)	13 (2.6)

Table 1. (Continued.)

Characteristic	Group A (N=301)	Group B (N=202)	Total (N=503)
Time since last intake of dabigatran — hr‡			
Median	14.6	18.0	15.6
Range	1.5–90.4	2.6–105.8	1.5–105.8
Elevated ecarin clotting time at baseline — no. (%)	276 (91.7)	185 (91.6)	461 (91.7)
Elevated diluted thrombin time at baseline — no. (%)	244 (81.1)	152 (75.2)	396 (78.7)
Elevated ecarin clotting time or diluted thrombin time at baseline — no. (%)	276 (91.7)	185 (91.6)	461 (91.7)

* Group A included patients who had uncontrolled bleeding, and group B included patients who required urgent surgery or intervention.
† Race or ethnic group was reported by the patient.
‡ Data were available for 501 patients (299 in group A, and 202 in group B).

thromboplastin time (Fig. 1D) and reversal based on the thrombin time (Fig. S2 in the Supplementary Appendix), as measured at the central laboratory, were similar to that based on the diluted thrombin time; the activated partial-thromboplastin time was prolonged at baseline in 373 of the 503 patients (232 in group A and 141 in group B).

DABIGATRAN AND IDARUCIZUMAB CONCENTRATIONS

Only one patient, who was subsequently found to be receiving apixaban, had no measurable plasma concentration of dabigatran at study entry. Unbound-dabigatran concentrations for all other patients correlated with the results of the clotting assays. The median baseline concentration of unbound dabigatran was 110 ng per milliliter in group A and 73.6 ng per milliliter in group B; after the administration of idarucizumab, the concentration was 20 ng per milliliter or less in all but three patients who could be assessed (Fig. 1C). With these low concentrations of unbound dabigatran, impairment of hemostasis is unlikely, because corresponding clotting times are at or below the upper limit of the normal range.

Unbound-dabigatran concentrations remained below 20 ng per milliliter for 24 hours in the majority of patients; however, reappearance of levels above 20 ng per milliliter was observed in 114 of 497 patients (23.0%), mainly after 12 hours, with 67 patients having elevated levels only at the 24-hour measurement. These recurrent elevations were associated with recurrent or continued bleeding in 10 patients in group A and in no patients in group B; of the 10 patients, 3 received an additional dose of idarucizumab. At 24 hours, the median idarucizumab concentration had decreased to less than 1% of the peak median, a finding consistent with the short half-life of idarucizumab (Fig. S3 in the Supplementary Appendix).[10]

Only 9 of the 503 patients (1.8%) received more than 5 g of idarucizumab, including the 3 in group A who had recurrent bleeding; 7 received a second dose of idarucizumab and 1 received two additional doses because they had recurrent bleeding or were undergoing a second urgent surgical procedure (Table 3). One patient received a second dose in error.

CLINICAL OUTCOMES

The time to the cessation of bleeding could not be assessed in the 98 patients with intracranial bleeding, because there is dissociation between the clinical course and the extent of bleeding. Although hematoma expansion on early follow-up imaging studies of the head can be used as a surrogate for the determination of the time to bleeding cessation, such imaging studies were not mandated. Of the remaining 203 patients in group A, 134 (67.7%) had confirmed bleeding cessation within 24 hours; among those 134 patients, the median time to hemostasis after the administration of idarucizumab was 2.5 hours (95% CI, 2.2 to 3.9). In the remaining 69 patients, bleeding stopped before treatment in 2 patients and could not be determined in 67 patients. Because bleeding could not be visualized (either directly or with imaging), it was not possible to

Table 2. Indications for Dabigatran Reversal.

Indication	Group A (N=301)*
	no. of patients (%)
Bleeding	
Intracranial	98 (32.6)
Subdural	39 (13.0)
Subarachnoid	26 (8.6)
Intracerebral	53 (17.6)
Gastrointestinal	137 (45.5)
Lower	47 (15.6)
Upper	52 (17.3)
Unknown	42 (14.0)
Intramuscular	9 (3.0)
Retroperitoneal	10 (3.3)
Intrapericardial	7 (2.3)
Intraarticular	5 (1.7)
Intraocular	1 (0.3)
Other	52 (17.3)
Not identified	4 (1.3)
Trauma-related	78 (25.9)
	Group B (N=202)†
Reason for procedure‡	
Abdominal condition or infection: hernia, peritoneal infection	49 (24.3)
Fracture or septic arthritis: involvement of the hip or femur	41 (20.3)
Cardiovascular condition: pacemaker implantation, aneurysm repair	37 (18.3)
Central nervous system condition: craniotomy	17 (8.4)
Pancreatic or hepatobiliary disease: cholecystitis, cholangitis	14 (6.9)
Respiratory condition: chest trauma	14 (6.9)
Kidney and urinary tract condition: acute renal failure	11 (5.4)
Septicemia or sepsis	8 (4.0)
Skin condition: abscess, hematoma	6 (3.0)
Postoperative complications	3 (1.5)
Uterine condition	1 (0.5)
Poisoning: deliberate overdose	1 (0.5)

* Patients may have had more than one type of bleeding.
† Procedure was canceled for five patients.
‡ For some categories, frequent events are listed as examples.

know at a given time point whether bleeding had stopped or was still ongoing.

Among the 197 patients in group B who underwent surgery or an intervention, periprocedural hemostasis was assessed as normal in 184 patients (93.4%), mildly abnormal in 10 (5.1%), and moderately abnormal in 3 (1.5%); no patients had severely abnormal hemostasis. Many patients received transfusions and other blood products. The use of blood products and volume expanders is described in Table S2 in the Supplementary Appendix.

The 30-day mortality rate was 13.5% in group A and 12.6% in group B, and the corresponding 90-day mortality rate, as estimated by the Kaplan–Meier method, was 18.8% and 18.9%, respectively. The number of deaths that occurred within 5 days after treatment was 19 (6.3%) in group A and 16 (7.9%) in group B (Table S2 in the Supplementary Appendix). The 30-day mortality rate was 16.4% among patients with intracranial hemorrhage, 11.1% among patients with gastrointestinal bleeding, and 12.7% among patients with bleeding at other sites.

THROMBOTIC EVENTS

Thrombotic events occurred in 24 of the 503 patients (4.8%; 14 in group A and 10 in group B) within 30 days after treatment and in 34 patients (6.8%; 19 in group A and 15 in group B) within 90 days. Details of the 30-day events are provided in Figure 2. During the 90-day follow-up, antithrombotic therapy (including treatment with prophylactic or therapeutic doses of an anticoagulant or with an antiplatelet drug) was restarted in 72.8% of the patients in group A and in 90.1% in group B, at a mean of 13.2 days and 3.5 days, respectively, after the administration of idarucizumab. By 72 hours after the administration of idarucizumab, antithrombotic therapy was restarted in 69 of the 301 patients in group A (22.9%), with 10.1% of those patients receiving dabigatran, and in 135 of the 202 patients in group B (66.8%), with 25.9% receiving dabigatran.

IMMUNOGENICITY AND HYPERSENSITIVITY

Anti-idarucizumab antibodies were detected in 28 of the 501 patients who could be assessed (5.6%). Of those 28 patients, 19 tested positive for preexisting antibodies that were cross-reactive with idarucizumab before its administration, and 9 had antibodies that developed during treatment. The antibody titers were generally low (median, 4; interquartile range, 2 to 8), and the preexisting antibodies had no detectable effect on idarucizumab activity.

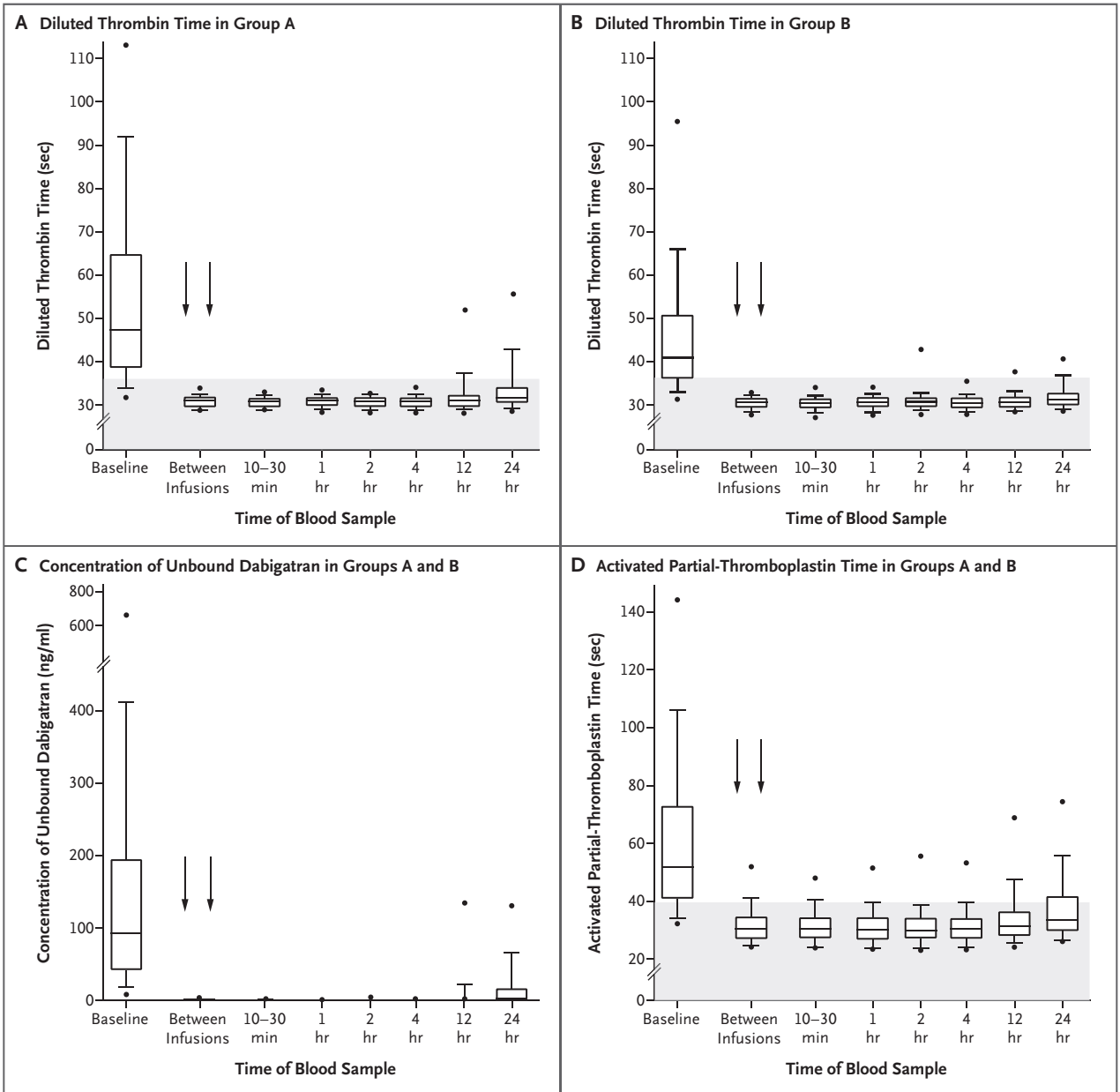

Figure 1. Key Measurements before and after the Administration of Idarucizumab.

The diluted thrombin time in 293 patients who had uncontrolled bleeding and in 195 patients who were about to undergo urgent surgery or intervention are shown in Panels A and B, respectively. Panel C shows the plasma concentration of unbound dabigatran in the 485 patients in groups A and B who could be assessed. Panel D shows the activated partial-thromboplastin time in the 486 patients in groups A and B who could be assessed. The arrows show the timing of the two infusions of idarucizumab. Blood samples were obtained at baseline, after the first infusion, and between 10 and 30 minutes and at 1, 2, 4, 12, and 24 hours after the second infusion. Data are presented as box-and-whisker plots, in which the top and bottom of the rectangles indicate the 75th and 25th percentiles, respectively; the horizontal lines within the rectangles indicate the 50th percentile; the lines above and below the rectangles indicate the 90th and 10th percentiles, respectively; and the dots above and below the lines indicate the 95th and 5th percentiles, respectively. The shaded areas show the normal ranges for each of the measures, which are based on data from 208 volunteers. The upper limits of the normal range for diluted thrombin time and activated partial-thromboplastin time are 35.5 seconds and 39.8 seconds, respectively.

Table 3. Patients Who Received More Than One Dose of Idarucizumab.*

Patient No.	Age	Sex	Previous Dose of Dabigatran	Index Event	Baseline Level of Unbound Dabigatran	Creatinine Clearance	Approximate Time to Additional Dose	Reason for Additional Dose
	yr		*mg twice daily*		*ng/ml*	*ml/min*		
Group A								
1	60	Male	110	Gastrointestinal bleeding	955	25.7	48 hr	Recurrent bleeding
2	79	Male	110	Gastrointestinal bleeding	325	43.4	36 hr	Recurrent bleeding
3	76	Male	110	Hematuria	1360	15.2	24 hr	Recurrent bleeding
4	73	Male	110	Gastrointestinal bleeding	329	29.0	24 hr	Recurrent bleeding
Group B								
5	85	Female	75	Intestinal occlusion	51	31.2	5 days	New procedure
6	73	Female	150	Ischemic large bowel	1630	34.0	12 hr	Postoperative bleeding
7	82	Female	110	Catheter placement for dialysis	271	8.0	6 days	Postoperative bleeding
8	70	Male	110	Catheter placement for dialysis	240	18.6	3 days (dose 2); 8 days (dose 3)	Postoperative bleeding and new procedure

* One patient who received two doses in error is not included in the table.

Three potential hypersensitivity events, each of which occurred within 5 days after the administration of idarucizumab, were reported by the investigator as being drug-related. These included a rash that lasted 1 day in a patient in whom therapy with ondansetron and tramadol had been initiated 2 days previously, vomiting and loss of consciousness in a patient who had a large intracranial hemorrhage at study entry, and hypotension during the infusion of idarucizumab that was reported as an anaphylactic reaction. An additional case of anaphylaxis, which was characterized by rash, vomiting, respiratory distress, and loss of consciousness, was reported in a patient who was receiving amoxicillin.

OTHER SAFETY OUTCOMES

Serious adverse events that occurred within 5 days after the administration of idarucizumab were reported in 117 patients (23.3%): 66 in group A (21.9%) and 51 in group B (25.2%). Events that occurred at a frequency of at least 1% in either group are listed in Table S3 in the Supplementary Appendix. Most of the events appeared to be a worsening of the index event or a coexisting condition. No other consistent pattern emerged. In group A, the most frequent event was delirium (which occurred in 2.3% of the patients); in group B, the most frequent events were cardiac arrest and septic shock (which occurred in 3.5% and 3.0% of the patients, respectively).

DISCUSSION

The results of the RE-VERSE AD study show that, among 503 patients who were receiving dabigatran, had uncontrolled bleeding or were about to undergo an urgent procedure, and had a prolonged diluted thrombin time at baseline, idarucizumab reversed anticoagulation rapidly and completely (to a median maximum percentage of 100%) in more than 98% of the patients. A single 5-g dose of idarucizumab was sufficient in 98% of the patients, and reversal was maintained for 24 hours in most patients. The robust, rapid, and durable reversal observed in this study is consistent with the results of an interim analysis in this study and with the results of studies of the use of idarucizumab in healthy volunteers.[2,10,11]

The study protocol, which was designed to mimic routine emergency care and to avoid delay in treatment, did not mandate that the results of

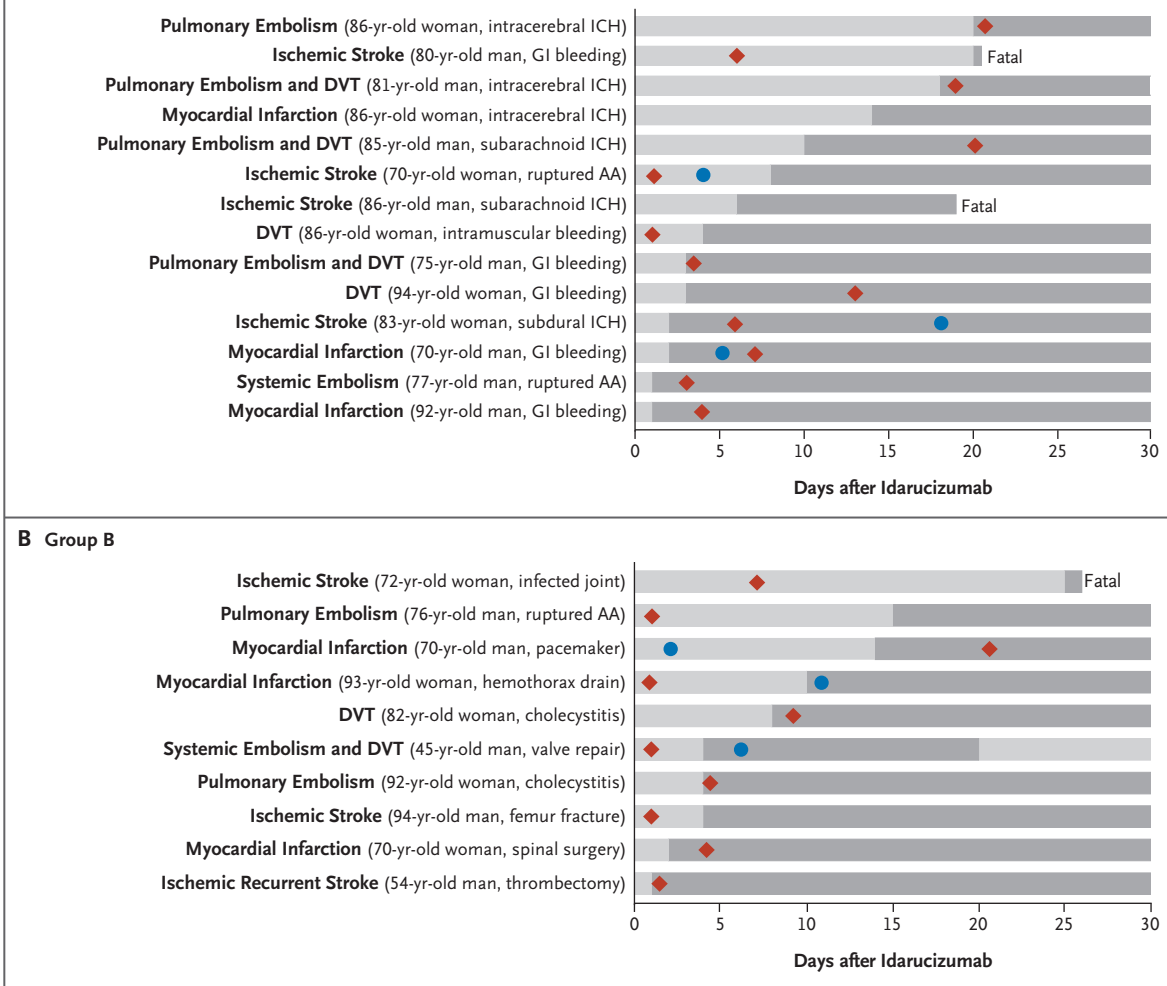

Figure 2. Adjudicated Thrombotic Events within 30 Days after the Administration of Idarucizumab.

Panels A and B list the thrombotic events that occurred among patients in group A and group B, respectively. Patient age, sex, and type of index event are listed in parentheses after the type of thrombotic event. The light gray portion of the bar indicates the time before the event, and the dark gray portion the time after the event. Red diamonds indicate the initiation of parenteral or oral anticoagulant therapy, and blue circles the initiation of antiplatelet therapy. AA denotes aortic aneurysm, DVT deep-vein thrombosis, GI gastrointestinal, and ICH intracranial hemorrhage.

baseline coagulation tests had to be available before idarucizumab was administered. Therefore, some patients had normal clotting times at entry. The safety of idarucizumab observed in this study supports its urgent use even if patients later prove to have had little or no circulating dabigatran.

Among patients with overt bleeding who could be evaluated in the first 24 hours, the median time to the cessation of bleeding was 2.5 hours. The administration of idarucizumab enabled surgery or an intervention in 197 of the 202 patients in group B; the median time to the initiation of the procedure was 1.6 hours, and 95% had normal or mildly abnormal hemostasis during the procedure. Therefore, the use of idarucizumab permitted rapid and safe intervention in the majority of patients.

The most likely explanation for a recurrent elevation in clotting time, which was seen mainly between 12 and 24 hours after treatment in 114 patients, is redistribution of unbound dabigatran from the extravascular to the intravascular compartment. However, recurrent elevation was as-

sociated with bleeding in only 10 patients. Therefore, among patients with a recurrent elevation in clotting time, only those with new-onset or recurrent bleeding should be considered for a second dose of idarucizumab.

The 30-day mortality rate was similar in group A and group B (13.5% and 12.6%, respectively), as was the 90-day mortality rate (18.8% and 18.9%, respectively). Patients enrolled in this study were elderly, had numerous coexisting conditions, and presented with serious index events, such as intracranial hemorrhage, multiple trauma, sepsis, acute abdomen, or open fracture. Most of the deaths that occurred within 5 days after enrollment appeared to be related to the severity of the index event or to coexisting conditions (e.g., respiratory failure or multiple organ failure), whereas deaths that occurred after 30 days were more likely to be independent events or related to coexisting conditions. The 30-day mortality rate observed in this study is lower than the 30-day mortality rate of 50% observed among patients who were receiving warfarin and presented with intracranial hemorrhage and than the 30-day mortality rate of 30% observed among patients who were receiving warfarin and were about to undergo emergency intervention.[12-17] However, it is similar to the 30-day mortality rate of 15% observed among the first 67 patients enrolled in a study of andexanet for the reversal of factor Xa inhibitors in patients with serious bleeding.[18]

The rate of thrombotic events was 4.8% at 30 days and 6.8% at 90 days, and the 30-day rate was similar in group A and group B (5.0% and 4.6%, respectively). These rates are consistent with those reported after major surgical procedures or hospitalization for uncontrolled bleeding.[16,17] The low rate of reinitiation of anticoagulation, particularly in group A, may have contributed to the thrombotic events. Idarucizumab has a half-life of approximately 45 minutes,[10] and all the thrombotic events that occurred within 72 hours after its administration occurred in patients in whom anticoagulation had not been restarted. Subsequent thrombotic events are more likely to reflect the underlying prothrombotic state than to be a direct effect of reversal, because idarucizumab had no procoagulant activity when it was given to animals and healthy human volunteers.[10,11]

Rates of thrombosis after the administration of idarucizumab are lower than those reported in studies evaluating prothrombin complex concentrate for the reversal of vitamin K antagonists.[12,16,17] For example, in one such study, the 30-day rate of thrombotic events was 7.8%.[17] The 30-day rate of thrombotic events in this study was lower than the rates of 18% and 12% that were observed among the first 67 and 102 patients, respectively, who received andexanet in the ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors) study.[18,19]

The strengths of this study include the broad inclusion criteria and the pragmatic study design, which reflects usual clinical practice. With this pragmatic design, patients with uncontrolled bleeding due to trauma could be enrolled in group A or group B at the discretion of the treating physician, depending on the urgency of any planned surgery. The major limitation of this study is the lack of a control group. Although guidelines recommend prothrombin complex concentrate for dabigatran reversal if idarucizumab is unavailable,[20] high-quality evidence of its effectiveness is limited.

In summary, idarucizumab is effective for dabigatran reversal among patients who have uncontrolled bleeding or will be undergoing urgent surgery. Although case reports suggest that thrombolysis and thrombectomy can be performed safely after dabigatran reversal with idarucizumab,[21] postmarketing surveillance would be helpful to monitor the effectiveness of idarucizumab for this and other indications and to further assess its safety.

Supported by Boehringer Ingelheim.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Campbell Joyner, M.D. (Sunnybrook Health Sciences Center, Toronto), and Renato Lopes, M.D. (Duke University, Durham, NC), for their service on the RE-VERSE AD Clinical Events Adjudication Committee.

REFERENCES

1. Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. Blood 2013;121:3554-62.
2. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-20.
3. Pollack CV Jr, Reilly PA, Bernstein R, et al. Design and rationale for RE-VERSE AD: a phase 3 study of idarucizumab, a specific reversal agent for dabigatran. Thromb Haemost 2015;114:198-205.
4. Reilly PA, Lehr T, Haertter S, et al. 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 2014;63:321-8.
5. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet 2008;47:285-95.
6. Stangier J, Feuring M. Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran. Blood Coagul Fibrinolysis 2012;23:138-43.
7. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8:202-4.
8. MedDRA. Introductory guide: MedDRA version 18.0. March 2015 (https://www.meddra.org/sites/default/files/guidance/file/intguide_18_0_english.pdf).
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
10. Glund S, Stangier J, van Ryn J, et al. Effect of age and renal function on idarucizumab pharmacokinetics and idarucizumab-mediated reversal of dabigatran anticoagulant activity in a randomized, double-blind, crossover phase Ib study. Clin Pharmacokinet 2017;56:41-54.
11. Glund S, Moschetti V, Norris S, et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. Thromb Haemost 2015;113:943-51.
12. Steiner T, Poli S, Griebe M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurol 2016;15:566-73.
13. Lopes RD, Guimarães PO, Kolls BJ, et al. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. Blood 2017;129:2980-7.
14. Mehta KD, Patel S, Patel K, Wang H, Parikh RA, Smith RE. Trends of inpatient venous thromboembolism in United States before and after Surgeon General's call to action. Blood 2016;128:1177. abstract.
15. Heit JA, Crusan DJ, Ashrani AA, Petterson TM, Bailey KR. Effect of near-universal hospitalization-based prophylaxis on annual number of venous thromboembolism events in the US. Blood 2017 May 8 (Epub ahead of print).
16. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-43.
17. Goldstein JN, Refaai MA, Milling TJ Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet 2015; 385:2077-87.
18. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;375:1131-41.
19. Connolly SJ, Gibson CM, Crowther M. Andexanet alfa for factor Xa inhibitor reversal. N Engl J Med 2016;375:2499-500.
20. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;17:1467-507.
21. Vosko MR, Bocksrucker C, Drwiła R, et al. Real-life experience with the specific reversal agent idarucizumab for the management of emergency situations in dabigatran-treated patients: a series of 11 cases. J Thromb Thrombolysis 2017;43: 306-17.