ORIGINAL ARTICLE

# Idarucizumab for Dabigatran Reversal

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## ABSTRACT

### BACKGROUND

Specific reversal agents for non–vitamin K antagonist oral anticoagulants are lacking. Idarucizumab, an antibody fragment, was developed to reverse the anticoagulant effects of dabigatran.

### METHODS

We undertook this prospective cohort study to determine the safety of 5 g of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required 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 determination at a central laboratory of the dilute thrombin time or ecarin clotting time. A key secondary end point was the restoration of hemostasis.

### RESULTS

This interim analysis included 90 patients who received idarucizumab (51 patients in group A and 39 in group B). Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100% (95% confidence interval, 100 to 100). Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients in group A who could be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.

### CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes. (Funded by Boehringer Ingelheim; RE-VERSE AD ClinicalTrials.gov number, NCT02104947.)

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A non–vitamin K antagonist oral anticoagulant, dabigatran etexilate (dabigatran) is an oral thrombin inhibitor that is licensed for the prevention of stroke in patients with nonvalvular atrial fibrillation and for the prevention and treatment of venous thromboembolism. Although dabigatran is associated with less serious bleeding than warfarin,[1-3] life-threatening bleeding can occur; in addition, dabigatran-treated patients may require urgent surgery or intervention, and dabigatran can increase the risk of perioperative bleeding. To improve the treatment of such patients, a specific dabigatran-reversal agent would be beneficial.

Idarucizumab, a monoclonal antibody fragment, binds dabigatran with an affinity that is 350 times as high as that observed with thrombin.[4,5] Consequently, idarucizumab binds free and thrombin-bound dabigatran and neutralizes its activity.[4,5] In healthy young volunteers with normal renal function, in volunteers who were 65 to 80 years of age, and in volunteers who were 45 to 80 years of age with mild or moderate renal impairment, the administration of idarucizumab produced immediate and complete reversal of the anticoagulant effects of dabigatran without procoagulant effects.[6-8]

Given these findings, a prospective cohort study was undertaken to examine the efficacy and safety of idarucizumab for the reversal of the anticoagulant effects of dabigatran in patients who presented with serious bleeding or who required urgent surgery or intervention. We present the results from the first 90 patients enrolled in the study of the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD).

## METHODS

### STUDY DESIGN AND OVERSIGHT

In this ongoing, multicenter, prospective cohort study, we plan to recruit up to 300 patients at more than 400 centers in 38 countries. A steering committee composed of members from academia and the sponsor (Boehringer Ingelheim) assumes final responsibility for the design and conduct of the trial. 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 wrote all the drafts of the manuscript, made the decision to submit the manuscript for publication, and vouch for the completeness of the data, the accuracy of the analyses, and the fidelity of this report to the study protocol.

### PATIENTS

The study included two groups of adults, 18 years of age or older, who were taking dabigatran. The patients in group A were those with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent. The patients in group B were those who required surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal hemostasis was required. These inclusion criteria were chosen to mirror the real-world population in which the reversal agent would be used. All the patients or their authorized representative provided written informed consent.

### STUDY TREATMENT

Patients received 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.[1,9]

### STUDY END POINTS

Blood samples for pharmacokinetic and pharmacodynamic assessments were obtained at baseline, after the first infusion of idarucizumab, and then between 10 and 30 minutes and at 1, 2, 4, 12, and 24 hours after the second infusion. The results of the clotting tests from the central laboratory were not available to clinicians when they made the decision to administer idarucizumab. The activated partial-thromboplastin time was assessed locally in parallel except at 1, 2, 4, and 24 hours. The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran, as determined at any point from the end of the first idarucizumab infusion to 4 hours after the second infusion, with the percentage reversal assessed on the basis of the measurement of the dilute thrombin time or ecarin clotting time at a central laboratory. The

maximum percentage reversal of the anticoagulant effect was calculated with the use of the following equation:

$$\text{percentage reversal} = (\text{predose test result [in seconds]} - \text{minimum postdose test result [in seconds]}) / (\text{predose test result [in seconds]} - \text{upper limit of the normal range [in seconds]}) \times 100.$$

Calculated values of 100% or higher were interpreted as complete reversal. For all patients with complete reversal, the value 100% was used in further calculations.

The upper limit of the normal range was calculated at the central laboratory as the mean +2 SD of all the baseline values measured in healthy volunteers.[6-8] The dilute thrombin time and ecarin clotting time were chosen because they are highly correlated with the concentrations of unbound dabigatran (i.e., dabigatran and its conjugates that did not bind to plasma proteins or idarucizumab).[8] A description of these assays is provided in the Supplementary Appendix (available at NEJM.org). The thrombin time, activated partial-thromboplastin time, and plasma concentrations of total and unbound dabigatran and idarucizumab were measured at central laboratories. The plasma concentrations of dabigatran were determined by means of high-performance liquid chromatography–tandem mass spectrometry,[8] and the plasma concentrations of idarucizumab by means of enzyme immunoassay.[6] Secondary end points included the proportion of patients who had complete normalization of the dilute thrombin time or ecarin clotting time in the first 4 hours and the reduction in the concentration of unbound dabigatran.

Clinical outcomes, as assessed by the treating clinicians, were secondary end points. In the patients in group A, the extent of bleeding and hemodynamic stability was assessed at 10 and 30 minutes and at 1, 2, 4, 12, and 24 hours after the second infusion or when deemed appropriate. The severity of bleeding was classified with the use of the International Society on Thrombosis and Haemostasis[10] and the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) scales[11] (Tables S1 and S2 in the Supplementary Appendix). The outcome of patients with intracranial hemorrhage was assessed by a comparison of the baseline score on the modified Rankin scale[12,13] (Table S3 in the Supplementary Appendix) with the score at 90 days. In the patients in group B, hemostasis during the intervention was classified by the physician as normal or as mildly, moderately, or severely abnormal. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 17.1. 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 maximum percentage reversal was calculated for patients with pretreatment dilute thrombin times or ecarin clotting times above the upper limit of the normal range, with the use of descriptive statistics with confidence intervals or percentiles 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.

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

From June 2014 through February 2015, a total of 90 patients (51 patients in group A and 39 in group B) were enrolled at 184 sites in 35 countries. More than 90% of the patients were receiving dabigatran for stroke prevention in the context of atrial fibrillation. The median age of the patients was 76.5 years, and the median creatinine clearance was 58 ml per minute (Table 1). The condition of 16 of the patients in group A was hemodynamically unstable, and these patients had ongoing blood loss at study entry. A total of 18 patients in group A had intracranial hemorrhage, 20 had gastrointestinal bleeding, 9 had bleeding from trauma, and 11 had other causes of bleeding. The indications for emergency surgery in the patients in group B are listed in Table S4 in the Supplementary Appendix. The median time since the last dose of dabigatran, as reported by the patients, was 15.4 hours.

**Table 1. Clinical Characteristics of the Patients.***

| Characteristic | Group A (N=51) | Group B (N=39) | Total (N=90) |
|---|---|---|---|
| Age — yr | | | |
| Median | 77.0 | 76.0 | 76.5 |
| Range | 48–93 | 56–93 | 48–93 |
| Male sex — no. (%) | 32 (63) | 18 (46) | 50 (56) |
| Race or ethnic group — no. (%)† | | | |
| Asian | 5 (10) | 1 (3) | 6 (7) |
| Hawaiian or Pacific Islander | 3 (6) | 3 (8) | 6 (7) |
| White | 43 (84) | 35 (90) | 78 (87) |
| Weight — kg | | | |
| Median | 70.5 | 73.0 | 71.9 |
| Range | 42.4–127.5 | 49.5–116.0 | 42.4–127.5 |
| Creatinine clearance‡ | | | |
| Value — ml/min | | | |
| Mean | 59±33 | 65±36 | 62±35 |
| Median | 54 | 60 | 58 |
| Range | 16–187 | 11–171 | 11–187 |
| Distribution — no. (%) | | | |
| <30 ml/min | 5 (10) | 7 (18) | 12 (13) |
| 30 to <50 ml/min | 14 (27) | 6 (15) | 20 (22) |
| 50 to <80 ml/min | 16 (31) | 11 (28) | 27 (30) |
| ≥80 ml/min | 6 (12) | 9 (23) | 15 (17) |
| Missing data | 10 (20) | 6 (15) | 16 (18) |
| Dose of dabigatran — no. (%) | | | |
| 150 mg twice daily | 14 (27) | 15 (38) | 29 (32) |
| 110 mg twice daily | 34 (67) | 24 (62) | 58 (64) |
| 75 mg twice daily | 1 (2) | 0 | 1 (1) |
| Other | 2 (4) | 0 | 2 (2) |
| Indication for dabigatran — no. (%) | | | |
| Atrial fibrillation | 47 (92) | 39 (100) | 86 (96) |
| Venous thromboembolism | 1 (2) | 0 | 1 (1) |
| Other | 3 (6) | 0 | 3 (3) |
| Time since last intake of dabigatran | | | |
| Median — hr | 15.2 | 16.6 | 15.4 |
| Distribution — no. (%) | | | |
| <12 hr | 17 (33) | 15 (38) | 32 (36) |
| 12 to <24 hr | 21 (41) | 10 (26) | 31 (34) |
| 24 to <48 hr | 12 (24) | 10 (26) | 22 (24) |
| ≥48 hr | 1 (2) | 4 (10) | 5 (6) |
| Elevated dilute thrombin time at baseline — no. (%) | 40 (78) | 28 (72) | 68 (76) |
| Elevated ecarin clotting time at baseline — no. (%) | 47 (92) | 34 (87) | 81 (90) |
| Type of bleeding — no. (%)§ | | | |
| Intracranial | 18 (35) | — | 18 (20) |
| Trauma-related | 9 (18) | — | 9 (10) |
| Gastrointestinal | 20 (39) | — | 20 (22) |
| Other | 11 (22) | — | 11 (12) |

* Plus–minus values are means ±SD. Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.
† Race or ethnic group was self-reported.
‡ Creatinine clearance was estimated by the Cockroft–Gault equation.
§ Patients may have had more than one type of bleeding.

### FOLLOW-UP

All the patients received 5 g of idarucizumab and were followed until death or for at least 1 month, except for 1 patient who withdrew informed consent and 1 who declined further follow-up and received palliative care. Among 90 treated patients, excluding 3 with missing information, the median duration of hospitalization (based only on dates, not times) was 8 calendar days (range, 2 to 93).

### REVERSAL OF ANTICOAGULATION

At study entry, 22 patients had dilute thrombin times that were subsequently determined by central laboratory analysis to be within normal limits; likewise 9 patients (all of whom had normal dilute thrombin times) were found to have normal ecarin clotting times. These patients were enrolled and given idarucizumab on the basis of the inclusion criteria for the study but were excluded from the efficacy analysis because their baseline clotting tests were within the normal range. Therefore, the percentage reversal with idarucizumab as assessed by means of the dilute-thrombin-time test could be determined in 68 of the 90 patients (40 patients in group A and 28 in group B), and the percentage reversal as assessed by means of the ecarin-clotting-time test could be determined in 81 of 90 (47 in group A and 34 in group B).

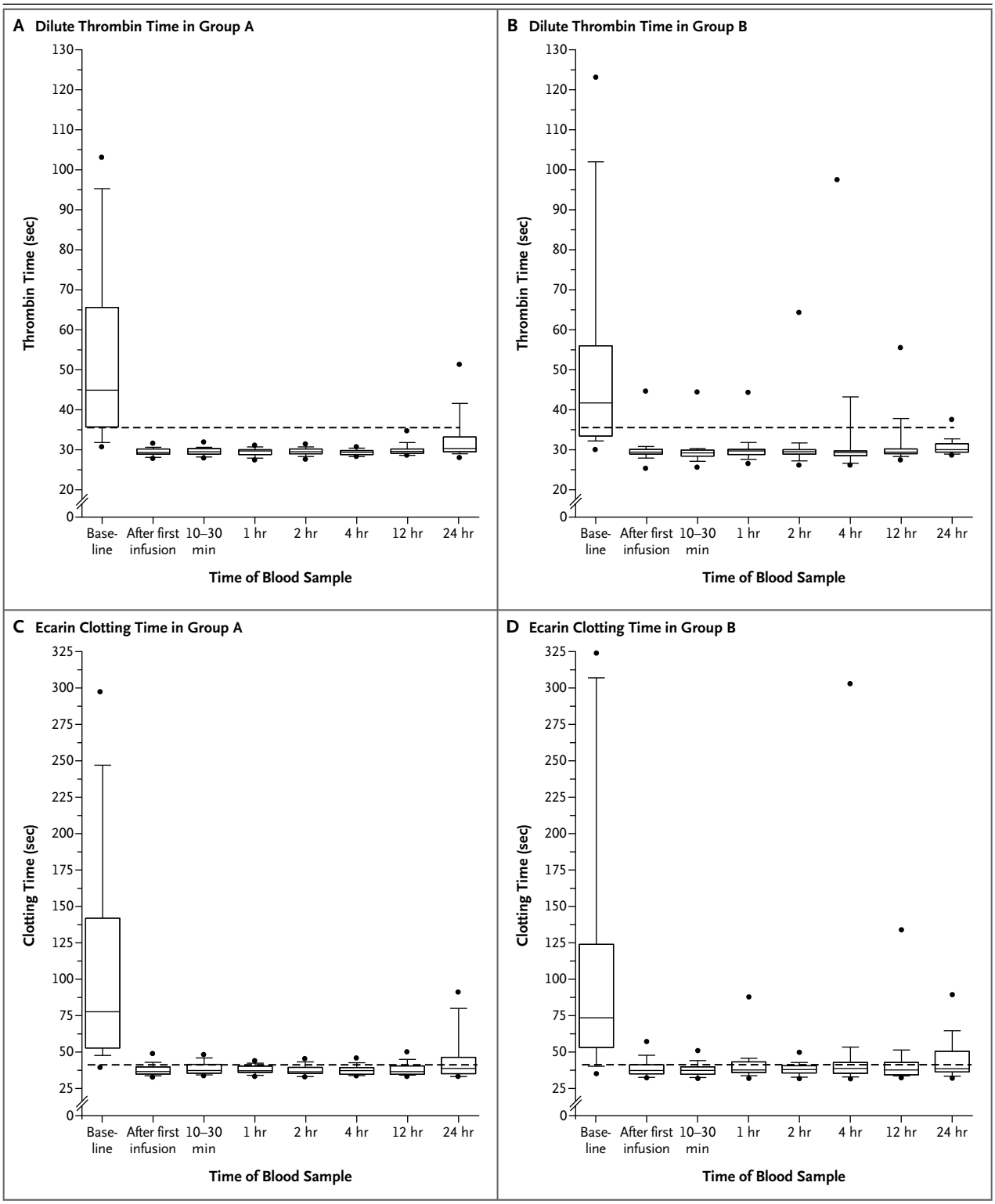
The median maximum percentage reversal in the patients in group A and in those in group B was 100% (95% confidence interval, 100 to 100), as assessed by both the dilute thrombin time and ecarin clotting time, and reversal was evident on the sample taken after the first infusion (Fig. 1). The dilute thrombin time was normalized in 98% of the patients in group A who could be evaluated and in 93% of those in group B who could be evaluated, and the ecarin clotting time was normalized in 89% and 88% of the patients who could be evaluated, respectively (Fig. 1, and Tables S5 and S6 in the Supplementary Appendix). At 12 hours and 24 hours, the dilute thrombin time was below the upper limit of the normal range in 90% of the patients in group A who could be evaluated and in 81% of those in group B, and the ecarin clotting time was below the upper limit of the normal range in 72% and 54% of the patients who could be evaluated, respectively. Similar results were observed with respect to the activated partial-thromboplastin time and the thrombin time as measured at the central laboratory (Fig. S1 in the Supplementary Appendix) or at the local hospitals (data not shown).

Clearance of dabigatran is influenced by renal function. As compared with the 68 patients with elevated results on the clotting tests at baseline, the 22 patients with normal results had better renal function (median creatinine clearance, 48 ml per minute in patients with elevated results vs. 67 ml per minute in those with normal results) and a longer time since the last dose of dabigatran (median, 12.8 hours vs. 30.3 hours). In group A, the proportion of patients with intracranial bleeding was higher among the 11 patients who had normal results on the clotting tests at baseline than among the 40 who had elevated results at baseline (64% vs. 28%). One death and 2 thrombotic events occurred among the 22 patients with normal results on either of the clotting tests at baseline, and 17 deaths and 3 thrombotic events occurred among the 68 patients with elevated results.

### DABIGATRAN AND IDARUCIZUMAB CONCENTRATIONS

At baseline, the median plasma concentration of total dabigatran was 132 ng per milliliter (range, 5 to 886) in group A and 114 ng per milliliter (range, 7 to 3600) in group B. Except for the plasma concentrations of total dabigatran of more than 1000 ng per milliliter in two patients in group B, the dabigatran concentrations were similar to those measured in the RE-LY trial.[9] The median plasma concentration of unbound dabigatran at baseline was 84 ng per milliliter (range, 3 to 641) in group A and 76 ng per milliliter (range, 4 to 2880) in group B (Fig. 2A and 2B, and Fig. S2 in the Supplementary Appendix). In samples obtained after the first vial of idarucizumab was administered, the concentration of unbound dabigatran was less than 20 ng per milliliter — a level that produces little or no anticoagulant effect — in all but one patient.

Blood samples were available from 86 patients at 4 hours, 83 patients at 12 hours, and 78 patients at 24 hours; the reasons for missing samples included death or technical difficulties (Table S7 in the Supplementary Appendix). At 4 hours after treatment, 83 of the 86 patients had a concentration of unbound dabigatran near the lower limit of quantification, 1 had a concentration of 31 ng per milliliter, and 2 had high concentrations of 848 ng per milliliter and 1510 ng per milliliter (Fig. 2A and 2B, and Table S8 in the




Supplementary Appendix). The concentration of unbound dabigatran was less than 20 ng per milliliter in 77 of the 83 patients (93%) at 12 hours and in 62 of the 78 (79%) at 24 hours. By 4 hours after administration, the geometric mean plasma concentration of idarucizumab had decreased by 80% from the peak level (Fig. 2C and 2D, and Table S9 in the Supplementary Appendix).

**Figure 1 (facing page). Time Course of the Dilute Thrombin Time and Ecarin Clotting Time before and after the Administration of Idarucizumab.**

The analyses included 51 patients who had serious bleeding (group A; Panels A and C) and 39 who required urgent surgery or intervention (group B; Panels B and D). Idarucizumab was administered in two 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. 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 dashed lines indicate the upper limit of the normal range for the tests.

### CLINICAL OUTCOMES

Among the 51 patients in group A, 3 had no bleeding assessment at baseline. The time to the cessation of bleeding could not be ascertained in 13 patients, of whom 5 had intracranial hemorrhage, 4 had gastrointestinal bleeding, 2 had intramuscular bleeding, 1 had pericardial bleeding, and 1 had retroperitoneal bleeding. In the remaining patients, the median investigator-reported time to the cessation of bleeding was 11.4 hours.

Idarucizumab obviated the need for emergency dialysis in 1 patient in group B who had ingested a massive overdose of dabigatran; the condition of 2 other patients in group B remained too unstable for surgery despite the reversal of anticoagulation. The remaining 36 patients in group B underwent urgent procedures, and normal intraoperative hemostasis was reported in 33 (92%). Mildly or moderately abnormal hemostasis during the procedure was reported in 2 patients and 1 patient, respectively.

There were 18 deaths overall, with 9 in each study group (Table 2); 10 deaths were due to vascular causes, including 5 fatal bleeding events. Death within 96 hours after treatment appeared to be related to the index event (2 patients had septic shock, 3 had intracranial hemorrhage, and 1 each had multiorgan failure, hemodynamic collapse, respiratory failure, and cardiac arrest), whereas all the later deaths appeared to be associated with coexisting conditions. Data regarding blood-product use and the reinitiation of antithrombotic therapy are provided in Tables S10 and S11, respectively, in the Supplementary Appendix.

### THROMBOTIC EVENTS AND SERIOUS ADVERSE EVENTS

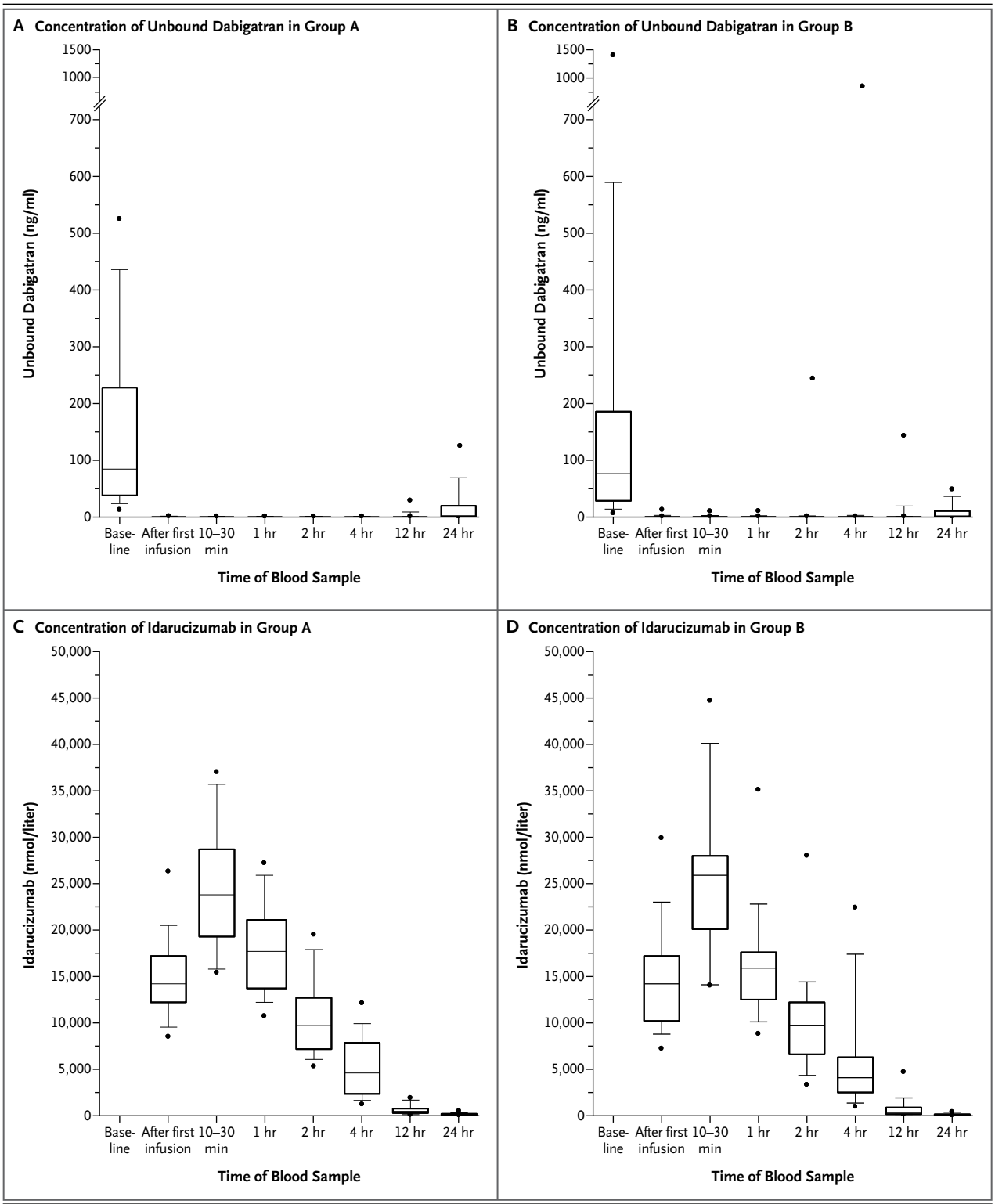
Thrombotic events, classified as early (≤72 hours after idarucizumab administration) or late (>72 hours after administration), occurred in five patients: deep-vein thrombosis and pulmonary embolism occurred in one patient 2 days after treatment; deep-vein thrombosis, pulmonary embolism, and left atrial thrombus occurred in one patient 9 days after treatment; deep-vein thrombosis alone occurred in one patient 7 days after treatment; non–ST-segment elevation myocardial infarction occurred in one patient 13 days after treatment; and ischemic stroke occurred in one patient 26 days after treatment. None of these patients were receiving antithrombotic therapy when the events occurred.

A total of 21 patients (13 patients in group A and 8 in group B) had serious adverse events during study participation. In addition to the 18 deaths and the thrombotic events that occurred in 5 patients, these events included gastrointestinal hemorrhage (in 2 patients) and postoperative wound infection, delirium, right ventricular failure, and pulmonary edema (in 1 patient each). Some patients had more than one event.

## DISCUSSION

The RE-VERSE AD study was undertaken to examine the efficacy and safety of idarucizumab in dabigatran-treated patients who had serious bleeding or required urgent procedures. Most hospitals lack tests for the rapid assessment of dabigatran levels apart from the activated partial-thromboplastin time. Consequently, patients were enrolled on the basis of their history of dabigatran intake and the assumption that the drug may have been contributing to bleeding or could increase the risk of surgery — scenarios that are likely to mirror clinical practice.

Idarucizumab rapidly and completely reversed the anticoagulant effect of dabigatran in 88 to 98% of the patients who had had elevated clotting times at baseline. Idarucizumab obviated the need for intervention in 1 of the 3 patients in group B who did not undergo a procedure. Among the 36 patients who underwent a procedure, normal hemostasis was reported in 92% and mild-to-moderate impairment in the remaining 8%. Although the median time to the cessation of bleeding in group A was 11.4 hours, this variable was difficult to assess in many patients, such as




those with intracranial or retroperitoneal bleeding. Only 1 of the 90 patients (1%) had a thrombotic event within 72 hours after idarucizumab administration, and antithrombotic therapy had not been reinitiated in that patient.

Few trials of anticoagulation-reversal agents

**Figure 2 (facing page). Time Courses of Plasma Concentrations of Unbound Dabigatran and Idarucizumab before and after the Administration of Idarucizumab.**

The analyses included 51 patients who had serious bleeding (group A; Panels A and C) and 39 who required urgent surgery or intervention (group B; Panels B and D). 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.

have been conducted. In a previous randomized trial in which four-factor prothrombin complex concentrate was compared with fresh-frozen plasma for warfarin reversal in patients who had bleeding or required urgent procedures,[14] patients with acute trauma, as well as those who were expected to die within 3 days or to require surgery within 24 hours were excluded; in contrast, we included such patients in our study. Furthermore, patients enrolled in our study were older than those in the previous randomized study (mean age, 76.7 years vs. 69.8 years), and a higher proportion had intracranial bleeding (35% vs. 12%).[14] In the previous trial, among warfarin-treated patients who had serious bleeding, prothrombin complex concentrate normalized the international normalized ratio within 30 minutes in 62% of patients, and hemostasis was restored in 72% within 24 hours. Among patients undergoing procedures, prothrombin complex concentrate normalized the international normalized ratio within 30 minutes in 55%, and 90% had effective hemostasis during the procedure.[14]

The 5-g dose of idarucizumab that was used in this study to reverse the effects of dabigatran was chosen on the basis of the highest range of

**Table 2. Serious Adverse Events Leading to Death.**

| Event | Characteristics of the Patients | | Study Group* | Time from Treatment to Death |
|---|---|---|---|---|
| | Age | Sex | | |
| | *yr* | | | *days* |
| Cardiac arrest | 82 | Female | B | <1 |
| Circulatory collapse | 93 | Male | B | <1 |
| Hemodynamic collapse | 88 | Female | B | <1 |
| Septic shock | 87 | Female | B | 1 |
| Sepsis, shock, and gastrointestinal bleeding | 60 | Male | B | 1 |
| Progression of respiratory failure | 60 | Male | A | 1 |
| New intracranial hemorrhage | 77 | Male | A | 1 |
| Progression of intracranial hemorrhage | 69 | Male | A | 2 |
| Multiorgan failure | 87 | Male | B | 2 |
| Progression of intracranial hemorrhage | 69 | Male | A | 4 |
| Pulmonary edema | 83 | Female | A | 11 |
| Cardiac arrest | 78 | Female | B | 21 |
| Ischemic stroke | 72 | Female | B | 26 |
| Congestive heart failure | 73 | Male | A | 30 |
| Parkinson's disease | 80 | Male | A | 43 |
| General health deterioration | 83 | Male | A | 42 |
| Pneumonia | 86 | Female | A | 94 |
| Progression of cancer | 80 | Male | B | 101 |

* Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.

plasma concentrations measured in the RE-LY trial.[1,9] Immediately after the administration of idarucizumab, the concentration of unbound dabigatran was reduced to a level at or near the lower limit of quantification in all but 1 patient, resulting in normalization of the dilute thrombin time and the ecarin clotting time. The subsequent increases in dabigatran concentrations that occurred 12 hours after the administration of idarucizumab in 6 patients and 24 hours after the administration of idarucizumab in 16 patients were also evident by increases in the clotting times (Fig. 1) and may reflect the redistribution of extravascular dabigatran into the intravascular compartment. It is uncertain whether patients with such a response would benefit from additional idarucizumab.

The strengths of our study include the broad inclusion criteria, simple study design, and confirmation that normalization of the results of the coagulation tests reflected dabigatran reversal by determination of the concentrations of unbound drug. The major limitation is the lack of a control group. Although some guidelines recommend prothrombin complex concentrate for the management of serious bleeding in dabigatran-treated patients, high-quality evidence for its efficacy is lacking. In the absence of a proven alternative to idarucizumab, a cohort design was selected because it was deemed unethical to randomly assign patients to receive placebo or no active treatment.

In conclusion, idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 88 to 98% of patients. There were no safety concerns among the 90 patients involved in this study — including patients who were given idarucizumab on clinical grounds but were later found to have had normal results on clotting tests at baseline — or among the more than 200 volunteers who were administered idarucizumab in previous studies.[6-8]

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

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