Circulation

ORIGINAL RESEARCH ARTICLE

Idarucizumab for Dabigatran Reversal in the Management of Patients With Gastrointestinal Bleeding

Editorial, see p 757

Sake J. Van der Wall, MD
Renato D. Lopes, MD, PhD
James Aisenberg, MD
Paul Reilly, MD, PhD
Joanne van Ryn, PhD
Stephan Glund, PhD
Amelie Elsaesser, PhD
Frederikus A. Klok, MD, PhD
Charles V. Pollack Jr, MD, MA
Menno V. Huisman, MD, PhD

BACKGROUND: Although dabigatran has a favorable risk-benefit profile compared with vitamin K antagonist therapy for venous thromboembolism and nonvalvular atrial fibrillation, major bleeding events, including gastrointestinal (GI) bleeding, may occur. Therefore, our aim was to provide insights into the efficacy and safety of idarucizumab for urgent dabigatran reversal in patients with major GI bleeding.

METHODS: Patients with uncontrollable GI bleeding requiring reversal were enrolled from June 2014 through July 2016 in the RE-VERSE AD study (Reversal of Dabigatran Anticoagulant Effect With Idarucizumab), a prospective, multicenter, open-label study of idarucizumab, and were followed up for 90 days for primary and secondary outcomes. Patients were to receive a 5-g dose of intravenous idarucizumab, administered as 2 bolus infusions of 2.5 g no more than 15 minutes apart. The primary end point was the maximum reversal of dabigatran anticoagulation within 4 hours after administration of idarucizumab as measured by the dabigatran-specific assays diluted thrombin time and ecarin clotting time. Further end points included investigator-reported bleeding cessation within the first 24 hours and incidence of rebleeding, thromboembolic events, or mortality.

RESULTS: GI bleeding occurred in 137 patients enrolled in RE-VERSE AD, of which 84% was adjudicated as major or life-threatening, 48 (35.0%) was upper GI tract in origin, 43 (31.4%) was lower GI in origin, and 46 (33.6%) was either both or unknown. Complete reversal of dabigatran was observed in 118 of 121 patients (97.5%) with an elevated diluted thrombin time at presentation and 95 of 131 patients (72.5%) with an elevated ecarin clotting time and was similar for upper and lower GI bleeding. Bleeding cessation within 24 hours was reported in 92 of 134 evaluable patients (68.7%) after a median duration of 2.4 hours (interquartile range, 2.0–3.9 hours). During the 90-day follow-up, 6 patients (4.4%) had a postreversal thromboembolic event, and 20 patients (14.6%) died.

CONCLUSIONS: Idarucizumab showed a rapid and complete reversal of dabigatran activity in nearly all patients presenting with GI bleeding, facilitating emergency patient care without the additional presence of anticoagulation.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02104947.

Key Words: atrial fibrillation ■ dabigatran ■ gastrointestinal hemorrhage ■ idarucizumab

Sources of Funding, see page 755

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Idarucizumab showed a rapid and complete reversal of dabigatran activity in 98% of patients presenting with gastrointestinal bleeding who had an elevated diluted thrombin time, regardless of the gastrointestinal bleeding location, and can safely be administered in conjunction with hemostatic agents.

What Are the Clinical Implications?

- These data provide further insights to practicing physicians into the role of idarucizumab in the management of dabigatran-related major gastrointestinal bleeding.

Dabigatran etexilate (Pradaxa) is a direct thrombin inhibitor that has a favorable risk-benefit profile compared with vitamin K antagonists (VKAs) for the prevention of ischemic stroke in patients with nonvalvular atrial fibrillation and the treatment of patients with venous thromboembolism.[1,2] Even so, as with all anticoagulants, dabigatran still confers a risk of gastrointestinal (GI) bleeding that in rare cases can lead to hemodynamic instability and result in high risk for morbidity and mortality.[3] In patients with nonvalvular atrial fibrillation, the 150-mg twice-daily dose of dabigatran was associated with an increased risk of GI bleeding, and the 110-mg twice-daily dose was comparable to VKAs.[1] Thus, an agent that can rapidly counteract the anticoagulant effect of dabigatran in these patients would be a valuable tool in severe bleeding management.

Idarucizumab (Praxbind) is a humanized monoclonal antibody fragment that binds dabigatran with high affinity, neutralizing its ability to inhibit thrombin.[4,5] In the RE-VERSE AD study (Reversal of Dabigatran Anticoagulant Effect With Idarucizumab), idarucizumab provided rapid, effective, safe, and durable reversal of dabigatran activity in the presence of uncontrollable hemorrhage that warranted immediate reversal or the need for urgent surgery.[6] Before the availability of idarucizumab, treatment and prevention of severe bleeding in dabigatran-treated patients involved supportive care and nonspecific blood products.[1,7,8] Experience with the use of coagulation factors such as prothrombin complex concentrate (PCC) to antagonize dabigatran activity is limited, and its effectiveness has never been studied in clinical trials.[9]

In the large RE-VERSE AD study, GI bleeding accounted for 45.5% of all qualifying bleeding events, which was the most frequent organ system location.[6] The purpose of the present analysis is to provide insights from RE-VERSE AD into the extent of dabigatran reversal, the frequency of full bleeding cessation within the first 24 hours, and the occurrence of both thromboembolic events and mortality over a 90-day follow-up period in patients reversed for GI bleeding.

METHODS

Study Design and Population

The RE-VERSE AD study was a prospective, multicenter, open-label cohort evaluation of the efficacy and safety of idarucizumab in the reversal of dabigatran-related anticoagulation. The design and rationale for RE-VERSE AD and its main results have been published previously.[6,10] Briefly, 2 dabigatran-treated patient groups were evaluated: group A comprised patients who had uncontrollable bleeding that was judged by the clinician to warrant acute reversal, and group B consisted of patients who were about to undergo an intervention that could not be delayed for at least 8 hours. Every patient received intravenous idarucizumab, administered as two 50-mL bolus infusions, each containing 2.5 g idarucizumab, no more than 15 minutes apart. Patients were classified by the site investigator as having upper or lower GI tract bleeding, defined as bleeding that was presumed to originate from a source proximal or distal to the ligament of Treitz, respectively, as diagnosed clinically, by imaging, or by endoscopic examination as guided by clinical presentation.[11] All patients provided written informed consent. The study protocol was approved by all the relevant institutional review boards. The data, analytical methods, and study materials will be made available on request to other researchers for purposes of reproducing the results or replicating the procedure.

Study and Follow-Up Procedures

The primary end point of RE-VERSE AD was the maximum reversal of the anticoagulant activity of dabigatran as measured by the diluted thrombin time (dTT) or ecarin clotting time (ECT) within 4 hours after the end of the second infusion of idarucizumab. Complete reversal was achieved if assay results were at or below the upper limit of normal (ULN) for at least 1 of 5 time points during the first 4 hours after idarucizumab infusion. Both the dTT and ECT have previously been shown to correlate to actual dabigatran levels across a wide concentration range.[5] The activated partial thrombin time (aPTT; in both local and reference laboratories) was also evaluated as an end point in RE-VERSE AD. Because both ECT and aPTT are also subject to greater test variability, the main focus of the present study was the change in dTT. Reversal of ECT and aPTT values is reported in the online-only Data Supplement. The maximum reversal of dabigatran was calculated as follows: percentage reversal=[predose test result (in seconds)−minimum postdose test result (in seconds)]/[predose test result (in seconds)−ULN range (in seconds)]×100%. The ULN of the dTT in the reference laboratory was 36 seconds.[10] The minimum postdose test result is the lowest value from the 5 measurements within 4 hours. Patients without elevated dTT values were treated with idarucizumab on the basis of clinical necessity and were included in all safety analyses but were excluded from our primary analysis.

Further end points included (1) time to bleeding cessation, as assessed by the treating physician and defined by stabilization of pulse, blood pressure, or hemoglobin values or, if the site was endoscopically evaluable, visible determination; (2) postreversal rebleeding and thrombotic events occurring within 90 days of reversal; and (3) death. The extent of bleeding and hemodynamic stability was assessed by the site investigator between 10 and 30 minutes and at 1, 2, 4, 12, and 24 hours after idarucizumab administration or when considered clinically appropriate. All bleeding events were censored at a maximum duration of 24(+1) hours. Patients were enrolled on the basis of clinical presentation of uncontrolled bleeding that in the opinion of the treating clinician required immediate reversal of anticoagulation. The severity of bleeding was classified post hoc with the International Society on Thrombosis and Haemostasis criteria.[12] Patients were followed up from the time of idarucizumab infusion up to 90 days after the infusion. The occurrence of any suspected thrombotic events and deaths was recorded and adjudicated by an independent committee. Two patients died outside the protocol-specified 90-day follow-up and are not included in further analyses.

Statistics

Data were analyzed with descriptive statistics expressed as either the mean±SD or median (interquartile range [IQR]). For categorical variables, frequencies (number) and percentages (percent) were used. The primary end point of the maximum dabigatran reversal within 4 hours of idarucizumab administration was calculated only for patients in whom pretreatment values exceeded the ULN range in the central laboratory.[6] All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

The GI tract was the site of qualifying hemorrhage in 137 of 301 of bleeding patients (45.5%) enrolled in group A of the RE-VERSE AD cohort, representing the commonest organ source of hemorrhage.[6] Of the 137 patients, 43 (31.4%) presented with lower GI bleeding, 48 (35.0%) presented with upper GI bleeding, 4 patients (2.9%) had both upper and lower GI bleeding, and the bleeding site remained unidentified in 42 patients (30.7%). Patients' demographics did not differ by location of the GI bleeding. The mean age was 78 years (SD, 10 years), and 75 patients (54.7%) were male. Ninety-one patients (66.4%) were on the 110-mg twice-daily dose. Many patients had additional comorbidities, including 114 (83.2%) with hypertension, 68 (49.6%) with chronic heart failure, and 39 (28.5%) with prior stroke or transient ischemic attack (Table 1). Proton pump inhibitors were used at presentation in 38 patients (27.7%), and 20 patients (14.6%) were treated with antiplatelet therapy along with dabigatran. The median hemoglobin level at baseline was 8.1 g/dL (IQR, 6.7–10.1 g/dL). The patient-reported last dabigatran intake was at a median of 13 hours (IQR, 8–20 hours) before idarucizumab administration. A total of 121 patients (88.3%) had elevated dTT levels at enrollment with a median of 58 seconds (IQR, 44–86 seconds). International Society on Thrombosis and Haemostasis bleeding was classified as minor in 16% of patients with GI bleeds; however, dabigatran levels, time since the last dabigatran dose, and baseline dTT were similar regardless of whether the patients with minor bleeds were included in the cohort.

GI tract pathology was also recorded at the time of patient enrollment in the study, although this was not mandatory and may represent underreporting of actual pathology (Table I in the online-only Data Supplement). Gastric and duodenal ulcers were common in those with upper GI bleeding (25.0%), whereas polyps and diverticular disease were identified frequently in patients with lower GI bleeding (9.3% and 16.3%, respectively). Newly diagnosed luminal GI cancer was reported in at least 2 patients in source documentation, 1 patient with a GI stromal tumor, and 1 patient with pancreatic carcinoma involving the stomach. This information reporting was not mandatory and may represent underreporting; it was also not captured in the clinical database.

Dabigatran Reversal

The median time between the start of administering the first vial of idarucizumab to the end of the last vial was 19 minutes (IQR, 14–25 minutes) in patients with GI bleeding. Complete anticoagulation reversal was observed within 10 to 30 minutes in 118 of the 121 patients (97.5%) with elevated dTT values at baseline and was similar for all sites of GI bleeding (Figure). The 3 patients (2.5%) without complete initial reversal had 3- to 7-fold increased ULN dTT values but still had a reversal effect of at least 50%. This reversal persisted for at least 4 hours in 110 of 121 patients (90.9%) and up to 24 hours in 71 of 121 patients (58.7%). The extent of reversal with the ECT and (central laboratory) aPTT assays was comparable to reversal with dTT (Figures I and II in the online-only Data Supplement).

A re-elevation of dTT above the ULN occurred in 25 patients (20.7%) within 12 hours and in 50 patients (41.3%) within 24 hours. In 10 of these 50 patients (20.0%), rebleeding was reported within 48 hours after idarucizumab administration. These 10 patients with rebleeding had higher baseline dTT levels (median, 115.5 seconds [IQR, 79–134 seconds] versus 87 seconds [IQR, 65–101 seconds]), as well as higher dTT re-elevation levels at 24 hours (median, 66 seconds [IQR, 54–89 seconds] versus 41 seconds [IQR, 38–48 seconds]) compared with the 40 patients with re-elevation but no rebleeding. Three of these patients also received a second 5-g dose of idarucizumab after a rebleeding episode (Figure III in the online-only Data Supplement).

Table 1. Baseline Characteristics of 137 Patients Enrolled With GI Bleeding

Clinical Characteristic	Anatomic Location of Bleeding in GI Tract				
	Lower (n=43)	Upper (n=48)	Unknown (n=42)	Lower and Upper (n=4)	Total (n=137)
Age, mean±SD, y	80±7	77±13	79±9	78±7	78±10
Male sex, n (%)	22 (51.1)	28 (58.3)	24 (57.1)	1 (25.0)	75 (54.7)
BMI,* mean±SD, kg/m^2	27±4.9	27±6.7	29±11.6	27±4.3	28±7.9
Comorbidities, n (%)					
Hypertension	36 (83.7)	37 (77.1)	38 (90.5)	3 (75.0)	114 (83.2)
CHF	19 (44.2)	27 (56.3)	21 (50.0)	1 (25.0)	68 (49.6)
Diabetes mellitus	10 (23.3)	18 (37.5)	14 (33.3)	2 (50.0)	44 (32.1)
Prior ischemic stroke/TIA	14 (32.6)	11 (22.9)	13 (31.0)	1 (25.0)	39 (28.5)
Prior major bleeding	3 (7.0)	6 (12.5)	3 (7.1)	0	12 (8.8)
Active cancer	2 (4.7)	7 (14.6)	1 (2.4)	0	10 (7.3)
Creatinine clearance,† median (IQR), mL/min	49 (37–63)	49 (29–59)	39 (31–59)	37 (21–65)	46 (31–60)
Hemoglobin level,‡ median (IQR), g/dL	9.5 (7.7–10.4)	7.6 (6.0–10.1)	7.8 (6.7–9.2)	8.1 (4.7–10.5)	8.1 (6.7–10.1)
Bleeding severity (ISTH criteria), n (%)					
Minor	9 (20.9)	8 (16.7)	4 (9.5)	1 (25.0)	22 (16.1)
Major	28 (65.1)	27 (56.3)	26 (61.9)	1 (25.0)	82 (59.9)
Life-threatening	5 (11.6)	12 (25.0)	11 (26.2)	2 (50.0)	30 (21.9)
Not assessable	1 (2.3)	1 (2.1)	1 (2.4)	0	3 (2.2)
Dabigatran dose, n (%)					
150 mg twice daily	6 (14.0)	14 (29.2)	16 (38.1)	1 (25.0)	37 (27.0)
110 mg twice daily	35 (81.4)	30 (62.5)	23 (54.8)	3 (75.0)	91 (66.4)
75 mg twice daily	2 (4.7)	3 (6.3)	3 (7.1)	0	8 (5.8)
Missing	0	1 (2.1)	0	0	1 (0.7)
Time since last dabigatran dose,§ median (IQR), h	14 (9–24)	13 (8–17)	13 (7–30)	5 (4–10)	13 (8–20)
Elevated dTT at baseline,‖ n (%)	41 (95.3)	38 (79.2)	38 (90.5)	4 (100)	121 (88.3)
Baseline dTT,‖ median (IQR), s	56 (46–70)	55 (42–86)	65 (42–90)	72 (58–112)	58 (44–86)
Concomitant medication use, n (%)					
Antiplatelet	6 (14.0)	6 (12.5)	7 (16.7)	1 (25.0)	20 (14.6)
NSAID	0	0	1 (2.4)	0	1 (0.7)
Proton pump inhibitor	13 (30.2)	12 (25.0)	12 (28.6)	1 (25.0)	38 (27.7)

Data in patients with both upper and lower bleeding are presented as range instead of IQR because of small numbers. BMI indicates body mass index; CHF, congestive heart failure; dTT, diluted thrombin time; GI, gastrointestinal; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; NSAID, nonsteroidal anti-inflammatory drug; and TIA, transient ischemic attack.

*Seven patients with missing BMI.

†Three patients with missing creatinine clearance.

‡Two patients with missing hemoglobin level.

§One patient with missing time since last dabigatran dose.

‖Three patients with missing dTT at baseline.

These patients had a creatinine clearance at enrollment of 26, 43, and 29 mL/min and dTT at baseline of 133, 79, and 78 seconds. A second dose of idarucizumab was administered between 24 and 48 hours after the first dose. The dTT before the second dose was 74, 70, and 55 seconds. Cessation of bleeding occurred in all 3 patients within an hour, and reducing the dTT reversed to below the ULN. Of the 10 patients with rebleeding, 5 died, 1 of whom died because of the rebleeding.

Cessation of Bleeding

In patients with lower GI bleeding, 76.2% were assessable within 24(+1) hours, with a time of 2.1 hours (IQR, 1.3–7.9 hours) to bleeding cessation (Table 2). Bleeding cessation occurred in 9.5% of patients at time points >25 hours and could not be confirmed in 14.3% of patients. In the upper GI location, 82.6% were assessable within 24(+1) hours, with a median

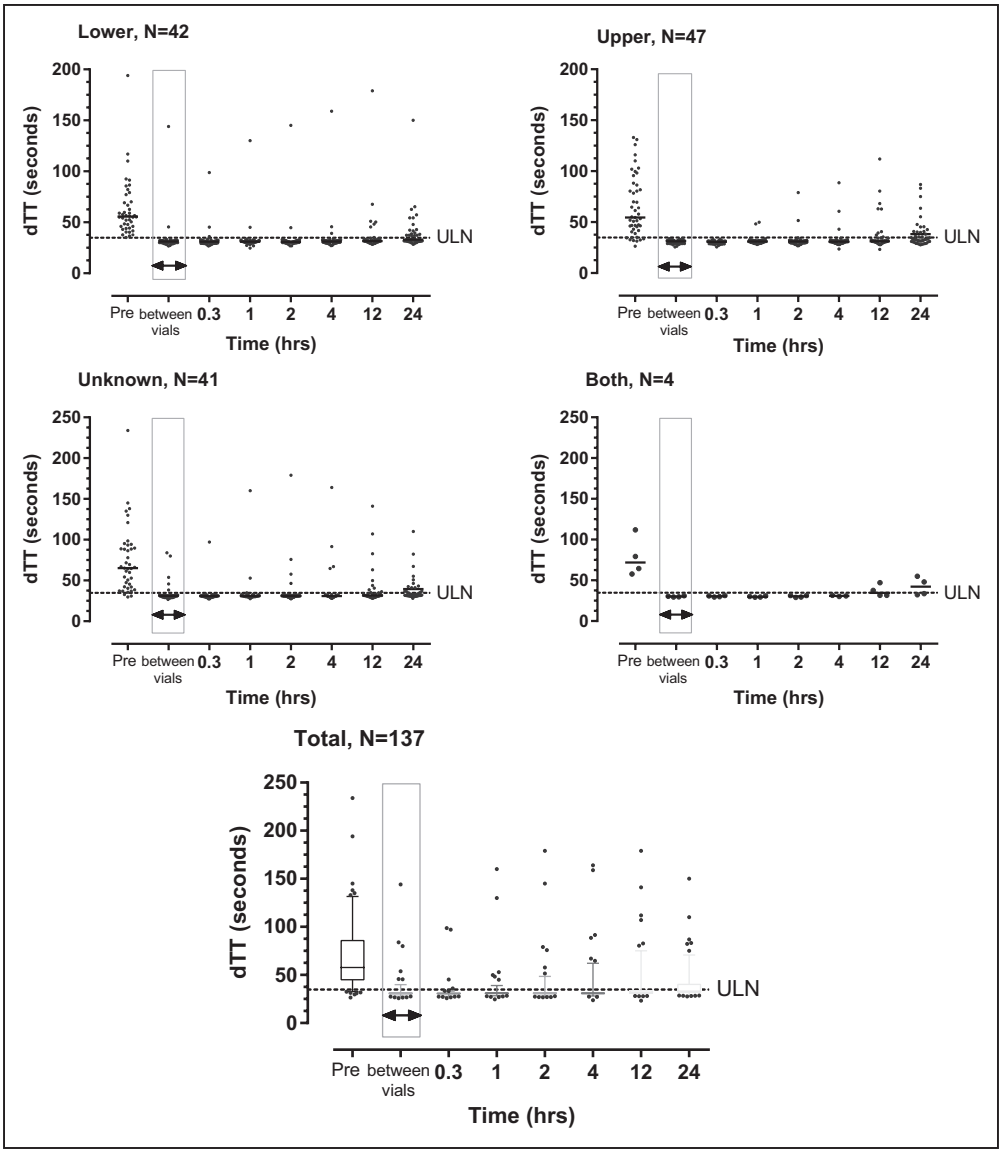

Figure. Reversal of diluted thrombin time (dTT) after administration of idarucizumab (rectangular box in each graph) in patients with lower or upper gastrointestinal bleeds, with unknown locations, or with both upper and lower bleeding.
Data points represent individual patients. The first time point after idarucizumab (0.3 hours) on the *x* axis represents a range between 10 and 30 minutes (0.16–0.5 hours). Upper limit of normal (ULN) for the dTT is identified as a dashed line. Pre indicates the blood sample taken prior to idarucizumab dosing.

time of 2.7 hours (IQR, 1.5–9.6 hours); 4.3% of patients stopped bleeding >25 hours; and 13.0% were not assessable. In patients with an unknown location of GI bleed, 52.4% were assessable within 24(+1) hours, with a median of 3.2 hours (IQR, 2.0–6.5 hours); 14.3% stopped bleeding at times >25 hours; and 33.3% were not confirmed. In patients with >1 location, bleeding cessation occurred within 24(+1) hours in 100% of patients after 6.4 hours (IQR, 0.8–16.0 hours).

Blood Product Management

A total of 117 patients (85.4%) in this cohort also received blood products: 113 (82.5%) received packed red blood cell transfusions; 6 (4.4%) received PCCs; 2 (1.5%) received activated PCCs; and 1 received recombinant activated factor VII (0.7%; Table 3). Administration of these procoagulant agents had no effect on dabigatran reversal by idarucizumab as demonstrated by dTT, ECT, and aPTT (data not shown).

Thromboembolic Events and Anticoagulation Resumption

A total of 6 patients (4.4%) experienced 7 thromboembolic events during the 90-day follow-up period, 4 of which occurred within 30 days (2.9%; Table 2). Five of these events in 4 patients occurred in the absence of anticoagulation: 1 myocardial infarction 1 day after the first idarucizumab dose, 2 deep vein thromboses (1 with concurrent pulmonary embolism) occurring at 2

Table 2. Time to Bleeding Cessation, Number of Thrombotic Events, and Mortality in 137 Patients With GI Bleeding After Receiving Idarucizumab

	Anatomic Location of Bleeding in GI Tract				
	Lower (n=42)	Upper (n=46)	Unknown (n=42)	Lower Plus Upper (n=4)	Total (n=134)
Cessation of bleeding					
Evaluated patients within 24(+1) h, n (%)	32 (76.2)	38 (82.6)	22 (52.4)	4 (100)	96 (71.6)
Time to cessation within 24(+1) h, median time (IQR), h	2.1 (1.3–7.9)	2.7 (1.5–9.6)	3.2 (2.0–6.5)	6.4 (0.8–16.0)	2.6 (1.5–9.5)
Cessation after 25 h, n (%)	4 (9.5)	2 (4.3)	6 (14.3)	0	12 (9.0)
Not assessable, n (%)	6 (14.3)	6 (13.0)	14 (33.3)	0	26 (19.4)
Patients with thrombotic events, n (%)					
0–5 d	0	2 (4.2)	1 (2.4)	0	3 (2.2)
0–30 d	0	2 (4.2)	2 (4.8)	0	4 (2.9)
0–90 d	0	3 (6.3)	3 (7.1)	0	6 (4.4)
Mortality, n (%)					
0–5 d	1 (2.3)	1 (2.1)	3 (7.1)	0	5 (3.6)
0–30 d	3 (7.0)	6 (12.5)	6 (14.3)	0	15 (10.9)
0–90 d	5 (11.6)	7 (14.6)	8 (19.0)	0	20 (14.6)

Patients could not be evaluated if bleeding stopped before idarucizumab (n=1) or no postbaseline bleeding assessment was performed (n=2). GI indicates gastrointestinal; and IQR, interquartile range.

days, and 1 ischemic stroke occurring at 35 days after idarucizumab. Two ischemic strokes occurred 19 and 74 days after idarucizumab while anticoagulant therapy was restarted (Table 4). Overall, 48 patients (35.0%) received parenteral anticoagulation during hospitalization, and 91 patients (66.4%) restarted some form of oral anticoagulant therapy after a median of 16 days (IQR, 7–34 days; Table II in the online-only Data Supplement). In 31 patients (22.6%), dabigatran was resumed after a median of 16 days (IQR, 6–38 days). Overall, patients were discharged from hospital after a median of 7 days (IQR, 4–12 days).

Table 3. Number of Patients Presenting With GI Bleeding Who Received Hemostatic Agents Both Before and After Idarucizumab Treatment

Patients Receiving Blood Products	Anatomic Location of Bleeding in GI Tract, n (%)				
	Lower (n=43)	Upper (n=48)	Unknown (n=42)	Lower Plus Upper (n=4)	Total (n=137)
Overall	36 (83.7)	41 (85.4)	37 (88.1)	3 (75.0)	117 (85.4)
Blood components					
Packed red blood cells	33 (76.7)	41 (85.4)	36 (85.7)	3 (75.0)	113 (82.5)
Fresh-frozen plasma	10 (23.3)	14 (29.2)	10 (23.8)	1 (25.0)	35 (25.5)
Platelets	1 (2.3)	2 (4.2)	5 (11.9)	0	8 (5.8)
Cryoprecipitate	1 (2.3)	1 (2.1)	1 (2.4)	0	3 (2.2)
Whole blood	1 (2.3)	0	1 (2.4)	0	2 (1.5)
Coagulation factor concentrates					
3- or 4-factor PCC	3 (7.0)	2 (4.2)	1 (2.4)	0	6 (4.4)
Recombinant activated factor VII	0	0	1 (2.4)	0	1 (0.7)
Activated PCC	1 (2.3)	0	1 (2.4)	0	2 (1.5)
Volume expanders, prohemostatic agents					
Volume expanders	12 (27.9)	10 (20.8)	1 (2.4)	0	23 (16.8)
Tranexamic acid	10 (23.3)	5 (10.4)	10 (23.8)	0	25 (18.2)
Other	0	0	1 (2.4)	0	1 (0.7)

GI indicates gastrointestinal; and PCC, prothrombin complex concentrate.

Table 4. Thrombotic Events Occurring in Patients After Receiving Idarucizumab for Management of GI Bleeding Associated With Dabigatran

Thrombotic Event	Anatomic Location of GI Bleed	Time of Adverse Event After Idarucizumab,* d	Time Until Restart of Anticoagulant Treatment,† d		Additional Blood Products Used to Manage Bleeding
			Parenteral	Dabigatran	
Myocardial infarction	Upper	1	…	6.4	Albumin
Deep venous thrombosis	Upper	2	…	13.7	PRBCs
Pulmonary embolism and deep venous thrombosis	Unknown	2	2	23.5	PRBCs, TxA, FFP
Fatal ischemic stroke	Unknown	19	5.3	…	PRBCs, FFP, Platelets
Ischemic stroke	Upper	35	35.2	…	PRBCs
Ischemic stroke	Unknown	74	48.9	55.0	Whole blood

FFP indicates fresh-frozen plasma; GI, gastrointestinal; PRBC, packed red blood cell; and TxA, tranexamic acid. The ellipsis indicate that the specified regimen was not restarted.

*Calculated as date of event minus date of start of idarucizumab treatment.

†Calculated as date and time of anticoagulant therapy start minus date and time of start of idarucizumab treatment.

Mortality

The 30-day and 90-day mortality was 10.9% (15 patients) and 14.6% (20 patients), respectively (Table 3). The median time of death was 18 days (IQR, 6–35 days) after idarucizumab. Causes of death included cardiac failure (4 patients), respiratory failure/infection (3 patients), myocardial infarction (3 patients), hemorrhage (2 patients), and kidney failure, sepsis, electrolyte imbalance, inanition, disseminated intravascular coagulation, ischemic stroke, Parkinson disease, and sudden death (1 patient each).

DISCUSSION

The main finding of this post hoc analysis of the RE-VERSE AD study is that idarucizumab showed a rapid and complete reversal of dabigatran activity in 97.5% of patients presenting with GI bleeding who had an elevated dTT regardless of the GI bleeding location.

This highly efficacious reversal is consistent with the published results of the entire RE-VERSE AD study, which included patients with bleeding into other organs and nonbleeding patients requiring urgent interventions while anticoagulated with dabigatran.[6] Overall, reversal was achieved rapidly and persisted up to 24 hours in the majority of patients after 1 dose of idarucizumab. The rapid and immediate decrease of dTT values demonstrates that reversal of dabigatran is directly related to the administration of idarucizumab and is consistent with its mechanism of action and previous results in healthy volunteers.[4,13] After 24 hours, 50 patients (41.3%) had a re-elevation of dTT values above the ULN. Re-elevation of dabigatran is possibly caused by the redistribution of unbound dabigatran from the peripheral tissues to the intravascular compartment over time, because idarucizumab is rapidly cleared (≈95% of the dose is cleared 4 hours after administration).[6] Re-elevation of the dTT was associated with rebleeding in 10 of 50 patients (20%). In general, patients with rebleeding had a high baseline dTT and higher re-elevated dTT levels at 24 hours. Measurement of anticoagulation in hospitalized patients after a GI bleed may be important for further clinical assessment. If rebleeding occurs and clotting assays are elevated, then a second dose of idarucizumab may be warranted.[14] However, if rebleeding occurs but clotting assays are not elevated, then rebleeding is likely anticoagulant-independent and should be addressed with bleeding management procedures. Clinical variables such as blood pressure, effect of the initial intervention, and thrombocyte count may also be important contributors to rebleeding.

A second dose of idarucizumab was administered to 3 patients with rebleeding, in whom the dTT reversed to below ULN and rebleeding stopped promptly within an hour. This illustrates that in rare cases, a second dose was indicated to stop the bleeding, which was well tolerated by patients.

The present study provides important information that dabigatran activity was completely reversed in patients presenting with predominantly uncontrollable GI bleeding. The frequency of GI bleeding from upper or lower GI tract locations in dabigatran-treated patients was comparable to and consistent with previous observations.[15,16] In addition, in accordance with earlier findings, upper GI bleeding was caused primarily by ulceration, whereas lower GI bleeding was frequently associated with diverticulosis and polyps.[17,18] The location of GI bleeding remained unidentified in 31% of the patients. This could be the result of a bleeding source within the small intestine at a site beyond the reach of traditional endoscopy or delayed or absent diagnostic evaluation.

Overall, 82.5% of the patients received red blood cell transfusions, which was higher than reported by other studies.[19,20] A study performed by Pannach et al[19] that included all major GI bleeding events documented in a prospective non-VKA oral anticoagulant registry found 44% red blood cell transfusions in 143 patients

using non-VKA oral anticoagulants. In addition, an observational study performed by Xu et al[20] found this rate to be 52% in 460 non-VKA oral anticoagulant–related bleeding events, which were located mostly in the GI tract. The majority of patients in this study (84%) presented with major or life-threatening bleeding and were deemed to warrant acute reversal; therefore, they had potentially more serious events than in other studies.[12] In the study by Xu et al,[20] PCC and recombinant factor VIIa were used more frequently than in our study, possibly because idarucizumab was not available in their study. In all cases of major GI bleeding, there is variation among clinicians in identifying and acting on thresholds for transfusion therapy.

Twenty of 137 patients with an index event of GI bleeding died during the 90-day follow-up. This underlines the poor prognosis of the critically ill patients in the present study, many of whom presented with hemodynamic instability and comorbidities despite normalization of coagulation. In addition, the long follow-up of the elderly patients in this study precludes direct comparisons with other studies, in which follow-up duration is often shorter. The in-hospital mortality in a study by Pannach et al[19] was 1.6% in non-VKA oral anticoagulant–treated patients and 5.6% in VKA-treated patients (mean hospital stay, 6.9 and 12.6 days, respectively). Although in-hospital mortality was not recorded in our study, the 5-day mortality was 3.6%, consistent with these results. Pannach et al also included patients with controllable GI bleeding, again reflecting the more severely ill patients enrolled in the present study and potentially explaining the higher mortality rate.

The incidence of thromboembolic events after 30 and 90 days was 2.9% and 4.4%, respectively, which is comparable to a pooled 2.3% (95% CI, 0.5–5.4) incidence reported in patients requiring urgent VKA reversal by PCCs in high-quality studies with varying follow-up durations.[21] Nearly all thromboembolic events occurred in patients in whom oral anticoagulation had not been restarted. One-third of the patients did not resume any form of anticoagulant therapy, consistent with findings of Pannach et al.[19] There is limited evidence to support the decision for and timing of resuming anticoagulation after GI bleeding. Current American College of Gastroenterology guidelines do not discuss the resumption of oral anticoagulation after GI bleeding, whereas current European Society of Cardiology guidelines suggest that an oral anticoagulant should be restarted as soon as the thrombotic risk outweighs the bleeding risk, mostly within 1 week.[22,23] Available scant evidence from VKA experience suggests that the optimal timing to restart oral anticoagulation after a GI bleeding is ≈7 to 15 days.[24] This is in line with our study in which oral anticoagulation was restarted after a median time of 16 days from the initial GI bleeding event.

Strengths and Limitations

This is the first analysis focusing on idarucizumab use in patients with GI bleeding. Because of the pragmatic design of this study, it reflects usual acute clinical care. These data may provide further insights to practicing physicians into the role of idarucizumab in the management of dabigatran-related major GI bleeding.

This study had several limitations. First, a control group is lacking because ethical aspects prohibited the inclusion of a placebo control group in very sick patients with no alternative targeted reversal treatment available.[6] Second, the study protocol did not require collection of specific details of diagnostic and interventional endoscopic procedures. Third, details of cessation of bleeding could not always be assessed accurately in nonvisible GI bleeding. Nonetheless, the clinical impact of bleeding events was always assessed by the attending physician.

CONCLUSIONS

Idarucizumab showed a rapid and complete reversal of dabigatran activity in nearly all patients presenting with GI bleeding, regardless of the localization, and can be safely administered in conjunction with hemostatic agents. Our findings provide relevant further insights to practicing physicians into the role of idarucizumab in the management of dabigatran-related major GI bleeding events.

ARTICLE INFORMATION

Received June 29, 2018; accepted October 2, 2018.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.118.036710.

Correspondence

Menno V. Huisman, MD, PhD, Department of Thrombosis and Hemostasis, Leiden University Medical Centre, Albinusdreef 2, 2300 RC Leiden, Netherlands. Email m.v.huisman@lumc.nl

Affiliations

Department of Thrombosis and Hemostasis, Leiden University Medical Center, the Netherlands (S.J.V.d.W., F.A.K., M.V.H.). Division Cardiology, Duke University Medical Center, Durham, NC (R.D.L.). Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY (J.A.). Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.R.). Boehringer Ingelheim International GmbH, Ingelheim and Biberach, Germany (J.v.R., S.G., A.E.). Emergency Medicine, Thomas Jefferson University and Sidney Kimmel Medical College, Philadelphia, PA (C.V.P.).

Acknowledgments

The authors acknowledge Corinna Miede and Karin Hoermann for providing statistical support for this analysis.

Sources of Funding

RE-VERSE AD was funded by Boehringer Ingelheim.

Disclosures

Dr Lopes reports research support from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, and Pfizer, as well as consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, and Portola. Drs van Ryn, Reilly, Elsaesser, and Glund are full-time employees of Boehringer Ingelheim. Dr Klok reports research grants from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, MSD, and Actelion. Dr Pollack reports grant support from Boehringer Ingelheim, Daiichi Sankyo, Portola, and CSL Behring; personal fees from Boehringer Ingelheim and BMS/Pfizer; and grant support and personal fees from Janssen Pharma and AstraZeneca. Dr Huisman has received research grants from ZonMW, Boehringer Ingelheim, Bayer Health Care, and Pfizer-Bristol-Myers Squibb and received consultancy and lecture fees from Pfizer-Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Health Care, and Aspen. Drs Van der Wall and Aisenberg report no conflicts.

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561
2. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–2352. doi: 10.1056/NEJMoa0906598
3. Cannon JW. Hemorrhagic shock. *N Engl J Med*. 2018;378:370–379. doi: 10.1056/NEJMra1705649
4. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, Nar H, Litzenburger T. A specific antidote for dabigatran: functional and structural characterization. *Blood*. 2013;121:3554–3562. doi: 10.1182/blood-2012-11-468207
5. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate: a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*. 2010;103:1116–1127. doi: 10.1160/TH09-11-0758
6. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI. Idarucizumab for dabigatran reversal: full cohort analysis. *N Engl J Med*. 2017;377:431–441. doi: 10.1056/NEJMoa1707278
7. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology*. 2013;145:105–112.e15.
8. Desai J, Granger CB, Weitz JI, Aisenberg J. Novel oral anticoagulants in gastroenterology practice. *Gastrointest Endosc*. 2013;78:227–239. doi: 10.1016/j.gie.2013.04.179
9. Weitz JI, Pollack CV Jr. Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. *Thromb Haemost*. 2015;114:1113–1126. doi: 10.1160/TH15-03-0222
10. Pollack CV Jr, Reilly PA, Bernstein R, Dubiel R, Eikelboom J, Glund S, Huisman MV, Hylek E, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Sellke F, Stangier J, Steiner T, Wang B, Weitz JI. 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. doi: 10.1160/TH15-03-0192
11. Davila RE, Rajan E, Adler DG, Egan J, Hirota WK, Leighton JA, Qureshi W, Zuckerman MJ, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO; Standards of Practice Committee. ASGE guideline: the role of endoscopy in the patient with lower-GI bleeding. *Gastrointest Endosc*. 2005;62:656–660. doi: 10.1016/j.gie.2005.07.032
12. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694. doi: 10.1111/j.1538-7836.2005.01204.x
13. Glund S, Stangier J, Schmohl M, Gansser D, Norris S, van Ryn J, Lang B, Ramael S, Moschetti V, Gruenenfelder F, Reilly P, Kreuzer J. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. *Lancet*. 2015;386:680–690. doi: 10.1016/S0140-6736(15)60732-2
14. Boehringer Ingelheim Pharmaceuticals Inc. PRAXBIND® (idarucizumab) injection, for intravenous use. 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf. Accessed January 21, 2019.
15. Kolb JM, Flack KF, Chatterjee-Murphy P, Desai J, Wallentin LC, Ezekowitz M, Connolly S, Reilly P, Brueckmann M, Ilgenfritz J, Aisenberg J. Locations and mucosal lesions responsible for major gastrointestinal bleeding in patients on warfarin or dabigatran. *Dig Dis Sci*. 2018;63:1878–1889. doi: 10.1007/s10620-018-5007-6
16. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial. *Circulation*. 2011;123:2363–2372. doi: 10.1161/CIRCULATIONAHA.110.004747
17. Strate LL. Lower GI bleeding: epidemiology and diagnosis. *Gastroenterol Clin North Am*. 2005;34:643–664. doi: 10.1016/j.gtc.2005.08.007
18. Lam SK. Differences in peptic ulcer between East and West. *Baillieres Best Pract Res Clin Gastroenterol*. 2000;14:41–52.
19. Pannach S, Goetze J, Marten S, Schreier T, Tittl L, Beyer-Westendorf J. Management and outcome of gastrointestinal bleeding in patients taking oral anticoagulants or antiplatelet drugs. *J Gastroenterol*. 2017;52:1211–1220. doi: 10.1007/s00535-017-1320-7
20. Xu Y, Schulman S, Dowlatshahi D, Holbrook AM, Simpson CS, Shepherd LE, Wells PS, Giulivi A, Gomes T, Mamdani M, Khuu W, Frymire E, Johnson AP; Bleeding Effected by Direct Oral Anticoagulants (BLED-AC) Study Group. Direct oral anticoagulant- or warfarin-related major bleeding: characteristics, reversal strategies, and outcomes from a multicenter observational study. *Chest*. 2017;152:81–91. doi: 10.1016/j.chest.2017.02.009
21. Dentali F, Marchesi C, Giorgi Pierfranceschi M, Crowther M, Garcia D, Hylek E, Witt DM, Clark NP, Squizzato A, Imberti D, Ageno W. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists: a meta-analysis. *Thromb Haemost*. 2011;106:429–438. doi: 10.1160/TH11-01-0052
22. Halvorsen S, Storey RF, Rocca B, Sibbing D, Ten Berg J, Grove EL, Weiss TW, Collet JP, Andreotti F, Gulba DC, Lip GYH, Husted S, Vilahur G, Morais J, Verheugt FWA, Lanas A, Al-Shahi Salman R, Steg PG, Huber K; ESC Working Group on Thrombosis. Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J*. 2017;38:1455–1462. doi: 10.1093/eurheartj/ehw454
23. Strate LL, Gralnek IM. ACG clinical guideline: management of patients with acute lower gastrointestinal bleeding. *Am J Gastroenterol*. 2016;111:755. doi: 10.1038/ajg.2016.155
24. Kido K, Scalese MJ. Management of oral anticoagulation therapy after gastrointestinal bleeding: whether to, when to, and how to restart an anticoagulation therapy. *Ann Pharmacother*. 2017;51:1000–1007. doi: 10.1177/1060028017717019