

BRIEF REPORT

Safety of idarucizumab in the reversal of dabigatran at six tertiary care Ontario hospitals

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Abstract

Background: Idarucizumab, a monoclonal antibody fragment that reverses the anticoagulant effect of dabigatran, was approved for use in Canada in 2016.

Objective: Our objective was to assess the safety of idarucizumab among patients who received the drug within the first 3 years of its use in Canada.

Patients/Methods: We performed a retrospective health records review of all idarucizumab use, excluding use in those <18 years of age, between May 16, 2016, and August 1, 2019, at six Ontario tertiary care hospitals. The primary outcome was mortality. The secondary outcomes were in-hospital arterial thrombotic event (ATE), in-hospital venous thromboembolism (VTE), length of hospital stay, and length of critical care stay.

Results: A total of 85 patients received idarucizumab during the study period for the following indications: 37 (43.5%) for spontaneous bleeding, 28 (32.9%) for traumatic bleeding, 11 (12.9%) for emergency surgeries/procedures, 5 (5.9%) for elective surgeries/procedures, and 4 (4.7%) for other indications. Nineteen patients (22.4%; 95% confidence interval [CI], 14.8%-32.3%) did not survive their hospitalization. During hospitalization, two patients (2.4%; 95% CI, 0.7%-8.2%) had ATE, and three patients (3.5%; 95% CI, 1.2%-9.9%) had VTE. The median length of stay was 8 (interquartile range [IQR], 2.5-13) days in hospital and 3 (IQR, 2-5) days in critical care.

Conclusions: Compared with clinical trial data, we found a numerically higher rate of mortality and similar rate of ATE and VTE among patients treated with idarucizumab in the real world.

KEYWORDS

anticoagulant, antidote, bleeding, dabigatran, idarucizumab

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Essentials

- Real-world analysis of idarucizumab use outside of clinical trials is needed.
- We retrospectively reviewed outcomes of all idarucizumab use at six tertiary care hospitals.
- Almost a quarter of patients died, but the rate of venous and arterial thrombosis was low.
- Mortality in patients with bleeding was almost double that of the RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) study.

1 | INTRODUCTION

The direct oral anticoagulants (DOACs) have demonstrated efficacy as anticoagulation in atrial fibrillation and venous thromboembolism (VTE).¹⁻³ They have several advantages over traditional vitamin K antagonists (VKAs) including fixed dosing without the need for routine monitoring and are increasingly replacing VKAs as the oral anticoagulant of choice.⁴ Despite their advantages, outcomes are poor in DOAC-associated bleeding with supportive care alone, with a case fatality rate of 10% after a major bleed and 40% after an intracranial bleed.^{5,6}

Idarucizumab is a humanized monoclonal antibody fragment that reverses the anticoagulant effect of dabigatran, an oral direct thrombin inhibitor.⁷ The RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) study demonstrated that idarucizumab can rapidly reverse dabigatran's anticoagulant effect in patients with life-threatening bleeding or requiring urgent surgeries; however, within 30 days of receiving the drug, 13.3% had died, 3.0% had arterial thrombotic events (ATEs), and 2.0% had VTE.⁸

While large trials are crucial in establishing the efficacy and safety of new drugs, real-world practice can differ from what is seen within the realm of clinical studies, including different patient demographics, clinical circumstances, and practice patterns.^{9,10} To assess real-world use of idarucizumab, we analyzed its use at six tertiary care centers.

Our objective was to assess the safety of idarucizumab in the reversal of dabigatran among patients for all indications since its approval for use in Canada.

2 | METHODS

This was a retrospective chart review performed at six Ontario tertiary care hospitals and was approved by the appropriate research ethics boards.

No calculations were performed to calculate a sample size. All patients who received idarucizumab between May 16, 2016, and August 1, 2019, for any indication and in any setting within the participating hospitals were included. We excluded patients under the age of 18 years. An initial list of patients who were prescribed idarucizumab was identified through hospital pharmacy records, and drug administration was then confirmed by electronic medical record review.

Data were collected from the electronic medical records by three authors (JA, SZ, and CE). Data collection followed a detailed data dictionary and involved a systematic review of pharmacy records, physician progress notes, laboratory results, blood bank records, and diagnostic imaging reports. Ambiguous data were resolved through discussion with the site principal investigator.

Clinical data included the indications for idarucizumab (spontaneous bleeding, traumatic bleeding, emergency surgeries/procedures, elective surgeries/procedures, other); classification of spontaneous and traumatic bleeding events as major, as defined by the ISTH; appropriateness of use of idarucizumab based on Health Canada approved indications; time to idarucizumab administration; and adjunctive therapies including tranexamic acid, blood components, and blood products.^{11,12} Time to idarucizumab administration was calculated for the spontaneous bleeding, traumatic bleeding, and emergency surgeries/procedures groups, and was defined as the time from emergency triage (or if indication occurred while inpatient, from confirmation of bleeding or requirement for urgent surgery/procedure as adjudicated by site investigator) to drug administration as per nursing records.

The primary outcome was all-cause in-hospital mortality. The secondary outcomes were in-hospital ATE, in-hospital VTE, length of hospital stay, and length of critical care stay. ATE was defined as ischemic stroke, transient ischemic attack, myocardial infarction, or peripheral arterial embolism. VTE was defined as pulmonary embolism, deep vein thrombosis, or unusual site venous thrombosis. Mortality, ATE, and VTE outcomes were adjudicated by the site investigators based on clinical reports and diagnostic imaging. The site investigators were not involved in the treatment of the patients.

All data were deidentified and entered into a spreadsheet for analysis. No statistical methods were performed to account for missing data. Descriptive statistics were used to summarize the patient demographics and study outcomes. We reported the 95% confidence intervals (CIs) (using the Wilson score calculation without continuity correction) for mortality, and ATE and VTE outcomes. We reported the median number of days in hospital and in critical care with interquartile range (IQR).

3 | RESULTS AND DISCUSSION

A total of 85 patients received idarucizumab at the participating centers (Table 1). The indications for idarucizumab are described in Table 2. Idarucizumab use adhered to Health Canada recommendations in 74 (87%) cases.

TABLE 1 Baseline characteristics

Characteristic	Total (n=85)
Female, n (%)	37 (43.5)
Age, y, mean (SD)	78.8 (9.7)
Dabigatran indication, n (%)	
Atrial fibrillation	82 (96.5)
Venous thromboembolism	2 (2.4)
Other	1 (1.2)
Dabigatran dose, n (%)	
110 mg twice daily	54 (63.5)
150 mg twice daily	23 (27.1)
Unknown	8 (9.4)
Aspirin or antiplatelet use, n (%)	11 (12.9)
NSAID use, n (%)	3 (3.5)
Hemoglobin, g/L, mean (SD)	111.0 (29.7)
Platelets, $\times 10^9$ /L, mean (SD)	217.0 (87.5)
Creatinine, n (%)	
<50 $\mu\text{mol/L}$	1 (1.2)
50–<100 $\mu\text{mol/L}$	45 (52.9)
100–<150 $\mu\text{mol/L}$	29 (34.1)
≥ 150 $\mu\text{mol/L}$	10 (11.8)
Creatinine clearance, ^a n (%)	
<30 mL/min	4 (4.7)
30–<50 mL/min	20 (23.5)
50–<80 mL/min	32 (37.6)
≥ 80 mL/min	8 (9.4)
Insufficient information to calculate	21 (24.7)
Coagulation tests conducted at baseline, n (%)	
Dilute thrombin time/dabigatran level	12 (14.1)
Thrombin time	17 (20)
INR	75 (88.2)
APTT	82 (96.5)
Coagulation tests prolonged among those tested (%)	
Dilute thrombin time/dabigatran level ^b	11/12 (91.7)
Thrombin time	14/17 (82.4)
INR	59/75 (78.7)
APTT	57/82 (69.5)

Abbreviations: APTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

^aAs per Cockcroft-Gault formula.

^bElevated defined as >30 ng/mL.

The median times to administration of idarucizumab were 288 (IQR, 124–676) minutes for spontaneous bleeding, 260 (IQR, 129–406) minutes for traumatic bleeding, and 789 (IQR, 281–913) minutes for emergency surgeries/procedures.

Almost all patients received the standard 5-g dose of idarucizumab divided into two doses of 2.5 g ($n = 80$, 94.1%). Overall, 22 (26%) of patients were coadministered tranexamic acid with

TABLE 2 Indications for idarucizumab

Indication	Total (n=85)
Spontaneous bleeding, n(%)	37 (43.5)
Major spontaneous bleeding, n (%)	26 (70.3)
Spontaneous bleeding location, n (%) ^a	
Gastrointestinal	24 (64.9)
Intracranial	9 (24.3)
Genitourinary	3 (8.1)
Retroperitoneal	1 (2.7)
Musculoskeletal	1 (2.7)
Traumatic bleeding, n (%)	28 (32.9)
Major traumatic bleeding, n (%)	25 (89.3)
Traumatic bleeding location, n (%) ^a	
Intracranial	17 (60.7)
Musculoskeletal	3 (10.7)
Intraperitoneal	3 (10.7)
Gastrointestinal	2 (7.1)
Retroperitoneal	2 (7.1)
Genitourinary	1 (3.6)
Other	6 (21.4)
Emergency surgery/procedures, n (%)	11 (12.9)
Type of surgery/procedure, n (%)	
General	4 (13.3)
Cardiac	2 (6.7)
Orthopedic	2 (6.7)
Systemic thrombolysis for stroke	2 (6.7)
Elective surgery, n (%)	5 (5.9)
Type of surgery/procedure, n (%)	
Cardiac	2 (40.0)
Vascular	2 (40.0)
Other	1 (20.0)
Other ^b	4 (4.7)

^aSome patients had multiple bleeding locations.

^bTwo patients had acute kidney injury, and the third had cardiogenic shock but none had bleeding or urgent requirement for surgery/procedure. The fourth received idarucizumab during cardiac surgery in the setting of an aortic injury, although dabigatran had been held appropriately preoperatively.

idarucizumab (10 [27%] with spontaneous bleeding, 11 [39%] with traumatic bleeding, and 1 [9%] with emergency surgeries/procedures). The use of blood components and products are summarized in Figure 1.

During hospitalization, 19 of 85 patients who received idarucizumab died (22.4%; 95% CI, 14.8%–32.3%), with idarucizumab indications as follows: seven for spontaneous bleeding (five of which were major spontaneous bleeding), seven for traumatic bleeding (seven of which were major traumatic bleeding), two for elective surgeries/procedures, one for an emergency surgery/procedure, and two for other indications. Most deaths occurred early, with a median of 2

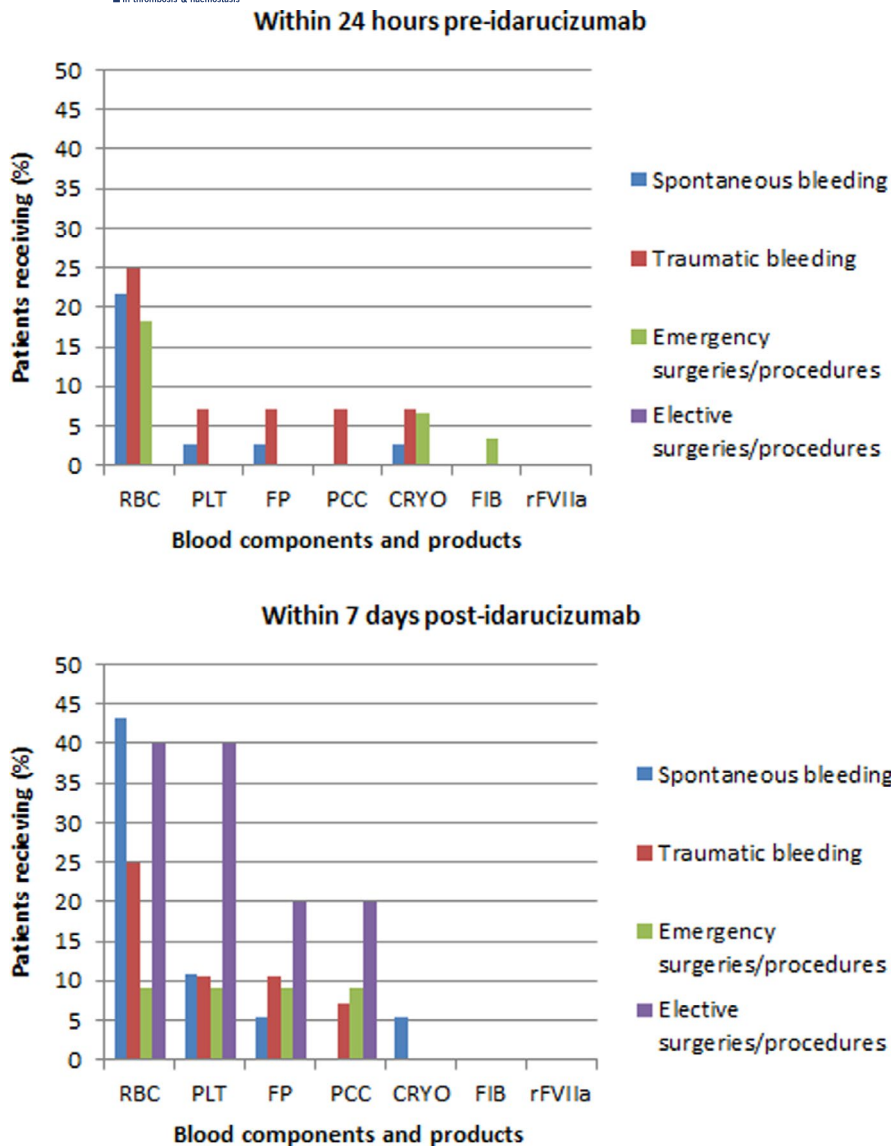


FIGURE 1 Coadministration of blood components and blood products by indication for idarucizumab. CRYO, cryoprecipitate; FIB, fibrinogen; FP, frozen plasma; PCC, prothrombin complex concentrate; PLT, platelets; RBC, red blood cells; rFVIIa, recombinant factor VIIa

(IQR, 1–6) days. Nine deaths were attributed to hemorrhage, two to ischemic strokes, and eight to nonhemorrhagic and nonthrombotic causes. Of the nine deaths attributed to hemorrhage, the initial indications for idarucizumab were spontaneous bleeding in four patients and traumatic bleeding in five patients.

Two patients were diagnosed with ischemic strokes, for an in-hospital incidence of ATE of 2.4% (95% CI, 0.7%–8.2%) (Table 3). Three patients (3.5%; 95% CI, 1.2%–9.9%) had VTE during their hospitalization.

The median length of stay in hospital was 8 (IQR, 2.5–13) days. Forty-six (54%) patients required admission to critical care. The median length of stay in critical care was 3 (IQR, 2–5) days.

We analyzed real-world data to provide an alternate lens to view the safety of idarucizumab outside of protocolized clinical trials. This real-world analysis, including 85 patients who received idarucizumab for any indication, demonstrated an all-cause mortality of 22.4% (95% CI, 14.8%–32.3%), and rates of ATE and VTE at 2.4% (95% CI, 0.7%–8.2%) and 3.5% (95% CI, 1.2%–9.9%), respectively. Hospital stay varied greatly among

patients, but had a median of 8 days, with a median of 3 days in critical care.

All centers had protocols in place to guide appropriate idarucizumab use, whether by clinical parameters, laboratory parameters, or approval by either the hematology, transfusion medicine, or thrombosis service. Despite this, in our cohort, 11 (13%) of the patients who received idarucizumab did not meet Health Canada specified indications for rapid reversal of dabigatran in the setting of emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding.¹³ This was primarily due to two main reasons: (i) early approval and use of idarucizumab for suspected major bleeding in patients on dabigatran, in whom subsequent investigations failed to identify the presence of major bleeding; and (ii) patients presenting for major elective surgery who had failed to discontinue dabigatran, and in whom it was felt that surgery could not be delayed for clinical or logistical reasons.

Almost one in four patients who received idarucizumab did not survive. It is unclear if idarucizumab itself played a role in mortality, as this analysis did not include a comparator group. In

TABLE 3 Thrombotic outcomes

Thrombotic Event	Idarucizumab indication	Received tranexamic acid at presentation	Blood products transfused within 24 hours before idarucizumab	Post-idarucizumab day thrombotic event occurred	Anticoagulation at time of thrombosis (day started following idarucizumab)	Survived hospitalization
Ischemic stroke	Traumatic bleed	No	Yes	2	None	No
Ischemic stroke	Spontaneous bleed	Yes	No	5	Therapeutic dabigatran (1)	No
Pulmonary embolus	Traumatic bleed	Yes	No	8	Prophylactic LMWH (2)	Yes
Pulmonary embolus	Emergency surgery/procedure	No	No	9	None	No
Pulmonary embolus	Traumatic bleed	No	No	24	Therapeutic dabigatran (18)	Yes

Abbreviation: LMWH, low-molecular-weight heparin.

prior studies involving idarucizumab administration to healthy volunteers, no serious adverse events were observed.^{14,15} The high mortality may have been a reflection of our elderly cohort with a mean age of 78.8 and their presentation with life-threatening bleeding or other serious clinical events requiring urgent use of a reversal agent.

In our analysis, the proportions of patients who experienced ATE or VTE were low. Again, it is difficult to determine if idarucizumab itself is prothrombotic without a control group, but data from prior studies suggests it is not.^{7,14,15} Idarucizumab did not demonstrate platelet aggregation activity or prothrombotic abnormalities on coagulation tests, and no ATEs or VTE were observed in healthy volunteers receiving idarucizumab.^{7,14,15} The thrombotic events observed in our analysis may have been a result of anticoagulation withdrawal and exposure to thrombotic risk factors including surgeries, immobilization, and admissions to critical care.

The findings of in our cohort can be compared to the RE-VERSE AD cohort (n = 503), as well as real-world cohorts from the Netherlands (n = 88) and Denmark (n = 46).^{8,16,17} The idarucizumab indications varied by cohort, with bleeding being the indication in 76.5% in our cohort, 59.8% in the RE-VERSE AD cohort, 60.2% in the Netherlands cohort, and 43% in the Denmark cohort.^{8,16,17} Across the cohorts, the most common bleeding site was gastrointestinal, followed by intracranial, except for the Denmark cohort, in which half was intracranial.^{8,16,17} Abdominal/gastrointestinal, orthopedic, and cardiovascular surgeries were the most common types of surgeries requiring anticoagulant reversal.^{8,16,17} Mortality in the urgent surgery/procedure groups were similar in the RE-VERSE AD cohort with 12.6% at 30 days, the Netherlands cohort with 14.3% at 90 days, and our cohort with 9.1% (95% CI, 0.5%-42.9%) during hospitalization, but much lower in the Denmark cohort with 4.5% at 30 days; however, almost a quarter of surgeries/procedures in this cohort were invasive imaging procedures.^{8,16,17} Mortality in the bleeding groups was approximately double in the real-world cohorts, with 22.6% at 90 days in the Netherlands cohort, 25% at

30 days in the Denmark cohort, and 21.5% (95% CI, 12.7%-33.8%) during hospitalization in our cohort compared to 13.5% at 30 days in the RE-VERSE AD cohort.^{8,16,17} It is unclear why mortality in the bleeding groups was higher in the real-world studies. All the cohorts were similar in terms of age and indication for dabigatran, but the Denmark cohort had a greater male prevalence.^{8,16,17} While the Netherlands cohort and ours did not assess comorbidities, the Denmark cohort seemed healthier than that of RE-VERSE AD, with much lower rates of heart failure, hypertension, ischemic heart disease, and renal clearance <30 mL/min.^{8,16,17} It is possible that time to drug could account for the mortality difference; however, as the RE-VERSE AD study does not comment on time to drug in the bleeding group, we can only speculate if the protocolized nature of the trial optimized time to drug delivery.⁸ Conversely, in the real world, especially given the lack of familiarity with idarucizumab as a recently approved drug, delays are expected. In our cohort, the median time to idarucizumab from presentation was 288 (IQR, 124-676) minutes for spontaneous bleeding, and 260 (IQR, 129-406) minutes for traumatic bleeding. The time to idarucizumab in the bleeding groups was not reported in the Netherlands or Denmark cohorts.^{16,17}

Thrombotic outcomes were similar across the cohorts.^{8,16,17} ATE and VTE, respectively, occurred in 3.0% and 2.0% at 30 days in RE-VERSE AD, 2.3% and 1.1% at 30 days in the Netherlands cohort, 0% and 0% in the Denmark cohort, and 2.4% (95% CI, 0.7%-8.2%) and 3.5% (95% CI, 1.2%-9.9%) during hospitalization in our cohort.^{8,16,17} The similarity in the risk of thrombotic outcomes may be due to similarities in patient demographics and idarucizumab indications.^{8,16} Comparatively, the thrombotic risk after reversal of warfarin using prothrombin complex concentrate or frozen plasma is 4.2% and 4.8%, respectively.¹⁸ Of note, resuming anticoagulation did not eliminate the risk of thrombosis, with 33%, 50%, and 60% of thrombotic events occurring despite anticoagulation in RE-VERSE AD, the Netherlands cohort, and our cohort, respectively.^{8,16}

To the best of our knowledge, this is one of the largest cohorts of idarucizumab use in the clinical setting.^{16,17,19-22} Although the study analyzed idarucizumab use exclusively at Canadian centers, the data presented from this study may be generalizable to other developed countries. This was also the only study to capture time from presentation to idarucizumab administration in the bleeding group.

The limitations of this study must be kept in mind when interpreting the results. First, the data are derived from a retrospective review of patient records. Therefore, their completeness is limited by the information available in the medical records. Second, our study did not assess hemostatic effect as an outcome as was done in the other cohorts; therefore, we could not completely report on idarucizumab effectiveness.^{8,16,17} However, even in prospective studies with prespecified outcomes and independent adjudication, it is difficult to accurately assess hemostatic efficacy, as most types of bleeding are challenging to measure.²³ Third, as with the other large idarucizumab cohorts, this study did not include a control group, historical or otherwise.^{8,16,17,22} Without a control group, we could not determine if the adverse effects were secondary to idarucizumab use or a complication of other treatments or comorbidities.

In summary, this study provides further data regarding the safety of idarucizumab use in a real-world setting. Compared with clinical trial data, we found a higher rate of mortality in patients receiving idarucizumab for bleeding but a similar overall rate of ATE and VTE. Further studies assessing comparator groups, time to idarucizumab, and time to resumption of anticoagulation are necessary to fully understand the safety of idarucizumab.

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AUTHOR CONTRIBUTIONS

JA, SZ, KdW, and RS conceptualized and designed research. JA, SZ, and CE analyzed data. JA, KdW, and RS wrote the manuscript, and all authors critically edited the manuscript.

RELATIONSHIP DISCLOSURE

YL has received research grants from Novartis and consulting fees from Pfizer. KdW has received a research grant from Bayer. JA, SZ, CE, MS, and RS declare no conflicts of interest.

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