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ORIGINAL RESEARCH

Idarucizumab for Emergency Reversal of the Anticoagulant Effects of Dabigatran: Final Results of a Japanese Postmarketing Surveillance Study

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ABSTRACT

Introduction: Idarucizumab, a monoclonal antibody fragment that rapidly reverses the anticoagulant effects of dabigatran, was approved in Japan in September 2016, at which time an all-case, postmarketing surveillance (PMS) study was initiated to collect data on idarucizumab in Japanese patients. Interim results were published previously, and the final results are reported herein.

Methods: This multicenter, open-label, uncontrolled, non-interventional PMS study was conducted in Japanese patients who received idarucizumab at the approved dose (2 × 2.5 g/50 ml) and had uncontrolled bleeding (group A) or required an emergency procedure (group B). The primary endpoint was the frequency of adverse drug reactions (ADRs). The secondary endpoint was the maximum extent of reversal of the anticoagulant effects of dabigatran, within 4 h of idarucizumab administration, based on activated partial thromboplastin time (aPTT).

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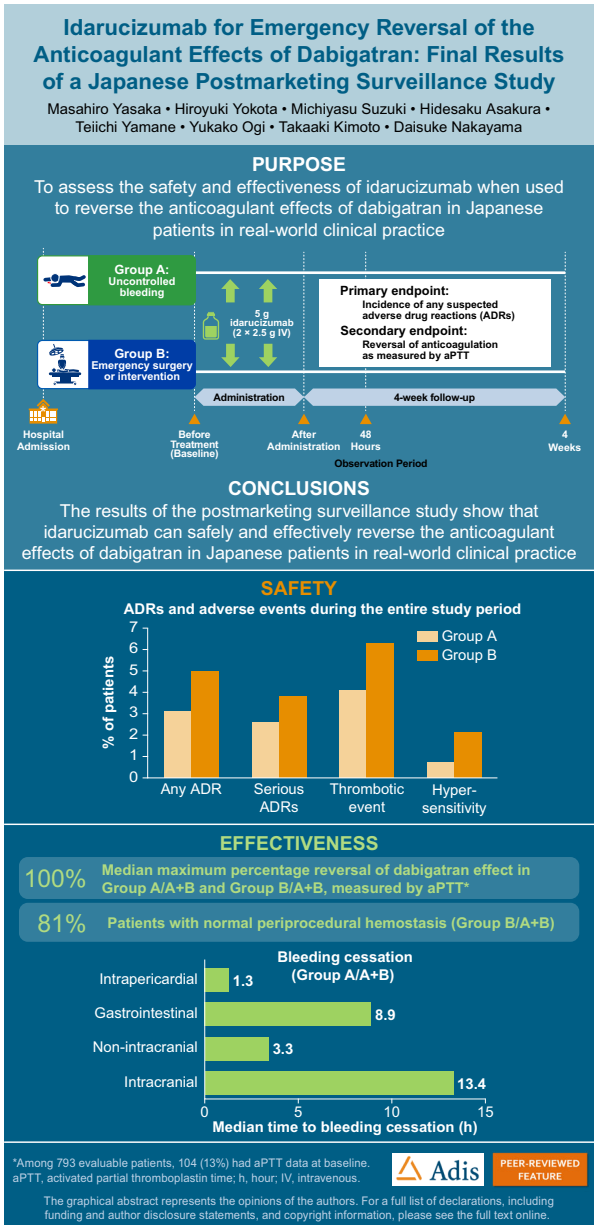
Results: The final analysis included 804 patients. ADRs during the idarucizumab treatment and post-treatment periods were reported in 17 of 542 patients (3.1%) in group A and 12 of 240 patients (5.0%) in group B. Thrombotic events were reported in 22 patients (4.1%) in group A and 15 patients (6.3%) in group B, and hypersensitivity occurred in four (0.7%) and five patients (2.1%), respectively. Among 793 patients evaluated for effectiveness, 78 in group A and 26 in group B had aPTT data at baseline (immediately before idarucizumab administration) and within 4 h of idarucizumab administration; in these patients, median maximum percentage reversal within 4 h of idarucizumab administration was 100%.

Conclusions: The final analysis from the PMS study confirms previous findings suggesting that idarucizumab can safely and effectively reverse the anticoagulant effects of dabigatran in Japanese patients in clinical practice. The results support the continued use of idarucizumab in Japan.

Trial Registration: This study is registered with ClinicalTrials.gov (NCT02946931).

Graphical Abstract:



PLAIN LANGUAGE SUMMARY

Atrial fibrillation is an irregular heart rhythm (arrhythmia), and the type of atrial fibrillation not caused by a heart valve problem is known as "non-valvular atrial fibrillation" or NVAF. People with NVAF have an increased risk of ischemic stroke, in which a blood clot (thrombus) blocks an artery in the brain. Drugs that inhibit blood clots, known as anticoagulants,

are prescribed to people with NVAF to prevent ischemic stroke. Historically, warfarin has been one of the most prescribed anticoagulant drugs. However, a novel anticoagulant drug, known as dabigatran, has clinical advantages over warfarin and is approved in many countries for people with NVAF. People who take anticoagulants may experience life-threatening bleeding or need urgent surgery, and thus rapid and effective reversal of the anticoagulant effects is critical. The drug idarucizumab specifically binds to dabigatran to reverse its anticoagulant effects in people with uncontrolled bleeding or who require an urgent procedure. Idarucizumab was approved for use in Japan in September 2016. In Japan, drug companies are obligated to collect data after a new drug is launched as an approval condition, which is done through a postmarketing surveillance study. Here, we report the final results of a postmarketing surveillance study conducted between September 2016 and November 2020 to evaluate the safety and effectiveness of idarucizumab in Japanese patients receiving dabigatran. The results of our study show that idarucizumab can safely and effectively reverse the anticoagulant effects of dabigatran in Japanese patients, and support the continued use of idarucizumab in Japan in clinical practice.

Keywords: Anticoagulation; Dabigatran; Emergency reversal; Idarucizumab; Japanese postmarketing surveillance

Key Summary Points

Why carry out this study?

Dabigatran is a direct thrombin inhibitor used to prevent ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Idarucizumab rapidly reverses the anticoagulant effects of dabigatran in patients with uncontrolled bleeding or who require an urgent procedure.

A postmarketing surveillance study was conducted to evaluate idarucizumab in Japanese patients.

What was learned from the study?

Idarucizumab safely and effectively reversed the anticoagulant effects of dabigatran in Japanese patients.

The results of this study support the continued use of idarucizumab to reverse the anticoagulant effects of dabigatran in Japanese patients in real-world clinical practice.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24065562.

INTRODUCTION

Dabigatran etexilate is a direct oral anticoagulant that acts as a potent, competitive, and reversible thrombin inhibitor to prevent thrombus development [1]. The drug is approved worldwide for the prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) [2]. The long-term effectiveness and safety of dabigatran in Japanese patients with NVAF has been shown in postmarketing surveillance (PMS) studies [3, 4].

Idarucizumab is a humanized, monoclonal antibody fragment with specificity for dabigatran and its metabolites, rapidly reversing the anticoagulant effects of dabigatran [5]. As idarucizumab is specific to dabigatran, it does not promote or inhibit thrombosis. The global, open-label, phase III study RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) was the first trial to prospectively evaluate

the ability of idarucizumab to reverse the anticoagulant effects of dabigatran in patients with uncontrolled bleeding or who required urgent surgery or a procedure [6, 7]. Among 503 patients, the median maximum percentage reversal of the anticoagulant effect of dabigatran was 100% based on diluted thrombin time (dTT) or ecarin clotting time (ECT) [7]. This study showed that idarucizumab can rapidly and durably reverse the anticoagulant effects of dabigatran, with no safety concerns.

Idarucizumab was approved in Japan in September 2016 [8]. Because a limited number of Japanese patients were treated with idarucizumab in clinical trials, an all-case PMS study was required by the Japanese regulatory authority to collect data on these patients in a clinical setting in order to assess the safety and effectiveness of idarucizumab when used according to the Japanese label. Interim results of the study in 262 patients were published previously [9], and the final results in the full cohort of patients are reported herein.

METHODS

Study Design and Patient Population

We conducted a multicenter, open-label, uncontrolled, all-case, non-interventional surveillance study within the conditions of the approved marketing authorization in Japan (Supplemental Fig. S1). Enrolled patients were classified as either those who presented with life-threatening or uncontrolled bleeding (group A) or those who were to undergo emergency surgery or an invasive procedure where significant bleeding was anticipated (group B). Idarucizumab was given intravenously in two consecutive infusions (2×2.5 g/50 ml) over 5–10 min each, or as a bolus injection (total dose of 5 g), according to the Japanese label [10].

This study was conducted according to the Declaration of Helsinki (1964 and its later amendments). The study also complied with Japanese Good Post-marketing Study Practice regulations, and the protocol was approved by the Japanese Ministry of Health, Labour and Welfare. Anonymous data were collected from clinical settings, and thus it was not necessary to obtain informed consent from the patients. The medical institutions that agreed to provide anonymized data signed a contract with the sponsor (Nippon Boehringer Ingelheim Co., Ltd.). This study is registered with ClinicalTrials.gov (NCT02946931).

Information was collected via case report forms (CRFs) for patients who had been administered idarucizumab through April 2019. For patients administered idarucizumab after April 2019, no prespecified information was collected via CRFs. While the original target number of patients was 300, enrollment continued until the conditions of the regulatory approval were satisfied according to the Japanese authority. The study period was from September 2016 to April 2022, but the registration period continued until November 2020, when the conditions of the approval were removed. All sites that administered idarucizumab to patients after the drug was approved in Japan participated in the study; if a study site had already administered idarucizumab at the time of contracting with the sponsor, data were collected retrospectively. There were no exclusion criteria.

Study Endpoints

The primary endpoint of the study was the incidence of adverse drug reactions (ADRs). The secondary endpoint was the maximum extent of reversal of the anticoagulant effect of dabigatran, based on activated partial thromboplastin time (aPTT), within 4 h of idarucizumab administration. The maximum reversal effect was calculated as follows:

$$\text{Maximum reversal effect} = \frac{(\text{predose aPTT}) - (\text{minimum postdose aPTT})}{(\text{predose aPTT}) - (\text{ULN})} \times 100\%$$

(ULN, upper limit of normal in each site.)

Other endpoints were the time to recorded cessation of bleeding in group A, periprocedural hemostasis in group B, the percentage of patients who restarted anticoagulant therapy, time to restart of anticoagulant therapy, and

re-exposure to idarucizumab after resumption of dabigatran.

Data Collection, Management, and Analysis

Physicians used paper CRFs to collect patient data. Observations were made at prespecified time points: at baseline (prior to first idarucizumab administration), during idarucizumab administration, and 4 weeks after administration or discontinuation of the drug. Data included patient demographics, bleeding assessment, surgery or intervention, idarucizumab administration, baseline coagulation tests, relevant medical history/concomitant disease, concomitant medications/therapy, blood pressure and pulse rate, laboratory tests, adverse events (AEs), and restart of anticoagulant therapy.

All AEs were recorded throughout the observation period and coded using Version 24.1 of the Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term. ADRs were defined as AEs that the investigator or sponsor assessed as related to idarucizumab, in which there was at least a reasonable probability of a causal relationship between idarucizumab and an AE. The assessment of a reasonable causal relationship was based on whether (1) the event was consistent with the known pharmacology of the drug, (2) the event was known to be caused by or attributed to the drug class, (3) there was a plausible time to onset of the event relative to the time of drug exposure, (4) there was evidence that the event was reproducible when the drug was re-introduced, (5) there was no medically sound alternative etiology that could explain the event, (6) the event was typically drug-related and infrequent in the general population not exposed to drugs, and (7) there was an indication of a dose response.

AEs reported up to 5 days after the last treatment were considered as on-treatment AEs. A serious AE was defined as any AE that (1) resulted in death, (2) was life-threatening, (3) resulted in patient hospitalization or prolongation of existing hospitalization, (4) resulted in persistent or significant disability or incapacity, or (5) was a congenital anomaly/birth defect. The safety dataset was the basis of all demographic, baseline, and safety analyses, which included all patients who were registered, received at least one dose of idarucizumab, and had available CRFs.

The effectiveness dataset included all patients in the safety analysis who had at least one of the following effectiveness data items available: extent of anticoagulation reversal effect assessed by aPTT, time to recorded bleeding cessation since first infusion (group A), periprocedural hemostasis (group B), frequency of restarting anticoagulant therapy, or time to when anticoagulant therapy was restarted.

Statistical Analyses

A sample size of 300 patients was planned considering the postmarketing occurrence rate of hemorrhagic AEs observed with dabigatran and on the basis of feasibility [3]. Important potential risks (thrombosis [2.8–9.0%] and hypersensitivity [8.4–17.1%]) were considered as the key survey items as described in the Report on the Deliberation Results from the Japanese Ministry of Health, Labour & Welfare [8]. A sample size of 300 patients was required to ensure the same accuracy in this study as these estimations. All data are reported using descriptive statistics.

RESULTS

Between September 2016 and November 2020, a total of 1393 patients were enrolled across 697 medical institutions (Fig. 1). CRFs were collected for 805 patients across 494 medical institutions by April 2019, of which 804 forms were validated. The safety analysis set included 804 patients: 542 in group A and 240 in group B; 16 patients were included in both group A and group B (shown as group A + B), and six patients were classified as "Other" as determined by the investigators. The effectiveness set included 793 patients: 541 in group A, 236 in group B, and 16 in both group A and group B; 11 patients were excluded from the effectiveness

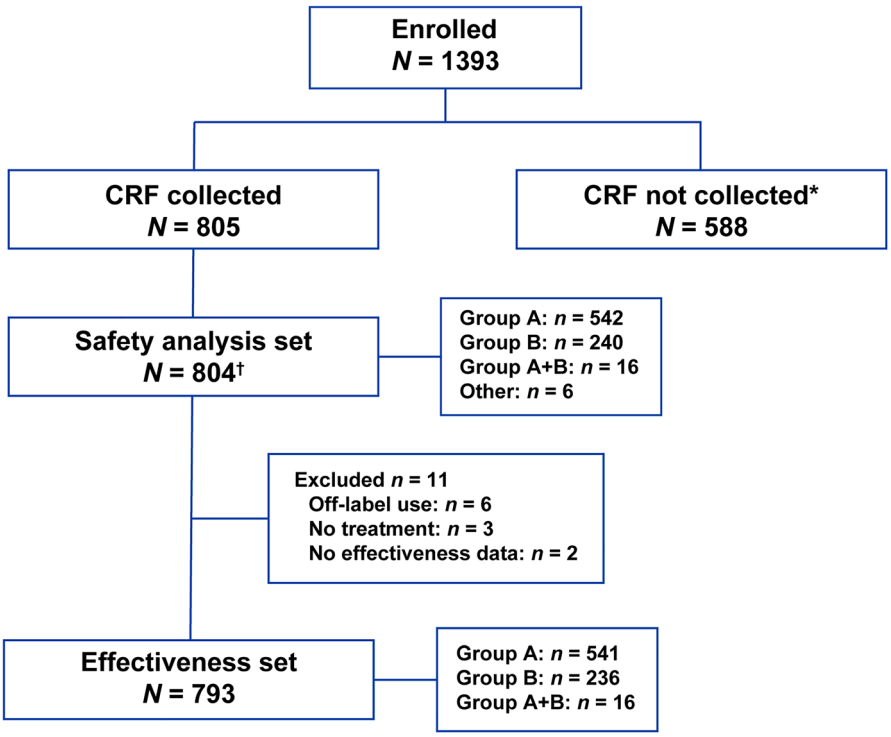


Fig. 1 Patient disposition. *CRF* case report form, *PMDA* Pharmaceuticals and Medical Devices Agency. *CRF required for cases in which idarucizumab was used from the time of approval of idarucizumab (September 2016) through April 14, 2019. After consultation with the PMDA, a CRF was no longer required after April 15, 2019. †One CRF could not be validated

set due to off-label use, no treatment with dabigatran, or no all-effectiveness data (Fig. 1).

Baseline characteristics of the patients are shown in Table 1. The median age of the patients was 78 years and 67% were male. Most patients had reduced renal function (among evaluable patients, 62% had a creatinine clearance of < 80 ml/min, with 12% having a creatinine clearance of < 30 ml/min). Median time from last dose of dabigatran to the first infusion of idarucizumab was 9.2 h in group A and 9.7 h in group B. A baseline coagulation test was performed in 78% of patients.

Idarucizumab Indications

Among the 558 patients in group A and group A + B (group A/A + B), idarucizumab was indicated for the reversal of dabigatran due to intracranial hemorrhage in 208 patients (37.3%), gastrointestinal (GI) bleeding in 133 patients (23.8%), and intrapericardial bleeding in 106 patients (19.0%) (Fig. 2). Other bleeding sites were mainly in the chest, such as pulmonary hemorrhage in 21 patients (3.8%), and intrathoracic bleeding in ten patients (1.8%). In group A/A + B, 134 patients (24.0%) had trauma-related bleeding, including 86 of 208 patients (41.3%) with intracranial hemorrhage. In an assessment of bleeding severity, 108 patients (19.4%) in group A/A + B had ongoing blood loss and were hemodynamically stable, whereas 171 patients (30.6%) had ongoing blood loss and were hemodynamically unstable. Changes in the reasons for using idarucizumab on or before April 15, 2017, through April 15, 2019, are shown in Supplementary Table S1.

In group B/A + B, the most frequent emergency surgery/intervention required by the patients was neurological (53.1%), followed by vascular (19.0%), abdominal (18.0%), orthopedic (3.8%), respiratory (3.3%), and gynecological-urological (2.8%) (Fig. 2). Among the 16

Table 1 Patient characteristics at baseline

	Group A (*N* = 542)	**Group B (*N* = 240)**	**Group A + B (*N* = 16)**	**Total[a] (*N* = 804)**
Age, years–median (range)	78 (37–101)	78 (44–94)	75 (59–90)	78 (24–101)
Age ≥ 70	430 (79.3)	198 (82.5)	11 (68.8)	644 (80.1)
Age class				
< 65	52 (9.6)	20 (8.3)	1 (6.3)	74 (9.2)
65 to < 75	137 (25.3)	59 (24.6)	6 (37.5)	206 (25.6)
75 to < 85	253 (46.7)	115 (47.9)	6 (37.5)	375 (46.6)
≥ 85	100 (18.5)	46 (19.2)	3 (18.8)	149 (18.5)
Sex, male	359 (66.2)	169 (70.4)	10 (62.5)	540 (67.2)
BMI[b], kg/m^2–mean ± SD	22.7 ± 3.7	22.9 ± 4.1	21.2 ± 3.3	22.7 ± 3.8
Creatinine clearance[c], ml/min–median (range)	53.4 (2.8–166.7)	57.6 (2.4–149.2)	55.0 (26.3–80.4)	54.9 (2.4–166.7)
Distribution				
≥ 80	73 (13.5)	32 (13.3)	1 (6.3)	108 (13.4)
50 to < 80	167 (30.8)	69 (28.8)	7 (43.8)	244 (30.3)
30 to < 50	114 (21.0)	43 (17.9)	4 (25.0)	161 (20.0)
< 30	74 (13.7)	17 (7.1)	2 (12.5)	94 (11.7)
Unknown	114 (21.0)	79 (32.9)	2 (12.5)	197 (24.5)
Daily dose of dabigatran				
220 mg	369 (68.1)	158 (65.8)	10 (62.5)	541 (67.3)
300 mg	115 (21.2)	48 (20.0)	4 (25.0)	169 (21.0)
Other	46 (8.5)	28 (11.7)	1 (6.3)	75 (9.3)
Unknown/missing	12 (2.2)	6 (2.5)	1 (6.3)	19 (2.4)
Duration of dabigatran use, days				
< 14	118 (21.8)	29 (12.1)	4 (25.0)	154 (19.2)
14 to < 30	21 (3.9)	5 (2.1)	0	26 (3.2)
30 to < 91	36 (6.6)	9 (3.8)	0	45 (5.6)
91 to < 182	18 (3.3)	4 (1.7)	0	22 (2.7)
182 to < 365	18 (3.3)	4 (1.7)	0	24 (3.0)
365 to < 730	10 (1.8)	4 (1.7)	0	14 (1.7)
730 to < 1095	11 (2.0)	10 (4.2)	1 (6.3)	22 (2.7)
≥ 1095	68 (12.6)	23 (9.6)	2 (12.5)	93 (11.6)
Unknown/missing	242 (44.6)	152 (63.3)	9 (56.3)	404 (50.2)

Table 1 continued

	Group A (*N* = 542)	**Group B (*N* = 240)**	**Group A + B (*N* = 16)**	**Total[a] (*N* = 804)**
Time from last dabigatran dose to first administration of idarucizumab[d], hours – median (range)	9.2 (0.0–435.0)	9.7 (0.2–98.8)	9.1 (4.5–16.0)	9.3 (0.0–435.0)
Distribution				
< 12	206 (38.0)	79 (32.9)	5 (31.3)	293 (36.4)
12 to < 24	81 (14.9)	32 (13.3)	1 (6.3)	114 (14.2)
24 to < 48	26 (4.8)	15 (6.3)	0	41 (5.1)
≥ 48	6 (1.1)	2 (0.8)	0	8 (1.0)
Exact timing unknown	220 (40.6)	107 (44.6)	10 (62.5)	339 (42.2)
Day of administration of idarucizumab	101 (45.9)	59 (55.1)	5 (50.0)	166 (49.0)
Day before administration of idarucizumab	73 (33.2)	30 (28.0)	2 (20.0)	105 (31.0)
≥ 2 days before administration of idarucizumab	8 (3.6)	3 (2.8)	0	11 (3.2)
Unknown	38 (17.3)	15 (14.0)	3 (30.0)	57 (16.8)
Missing	3 (0.6)	5 (2.1)	0	9 (1.1)
Department[c]				
Cardiovascular	184 (33.9)	34 (14.2)	1 (6.3)	223 (27.7)
Neurosurgery	156 (28.8)	97 (40.4)	10 (62.5)	263 (32.7)
Emergency	76 (14.0)	14 (5.8)	2 (12.5)	93 (11.6)
Neurology	20 (3.7)	15 (6.3)	1 (6.3)	36 (4.5)
Gastroenterology	35 (6.5)	8 (3.3)	1 (6.3)	44 (5.5)
Other	75 (13.8)	75 (31.3)	1 (6.3)	152 (18.9)
Performed coagulation test	441 (81.4)	167 (69.6)	13 (81.3)	626 (77.9)
Elevated aPTT at baseline				
> ULN in each site	259 (47.8)	97 (40.4)	6 (37.5)	364 (45.3)
≤ ULN in each site	154 (28.4)	63 (26.3)	6 (37.5)	226 (28.1)
Unknown	129 (23.8)	80 (33.3)	4 (25.0)	214 (26.6)
PT-INR[f], median (range)	1.30 (0.89–27.69)	1.22 (0.96–7.40)	1.19 (0.97–1.77)	1.27 (0.89–27.69)
Fibrinogen[g], mg/dl–median (range)	288 (72–936)	339 (129–1018)	266 (127–328)	298 (72–1018)

Table 1 continued

	Group A (*N* = 542)	Group B (*N* = 240)	Group A + B (*N* = 16)	Total[a] (*N* = 804)
Fibrin degradation products[h], μg/ml–median (range)	5.8 (0.3–251.8)	6.6 (0.4–222.0)	6.7 (3.5–15.4)	6.3 (0.3–251.8)
D-dimer[i], ng/dl–median (range)	1.40 (0.00–89.81)[j]	1.44 (0.00–50.40)[j]	2.70 (0.72–24.55)	1.42 (0.00–89.81)[j]
$CHADS_2$–mean (SD)	1.9 (1.3)	2.2 (1.3)	2.9 (1.7)	2.0 (1.3)
$CHADS_2$ score class				
0	65 (12.0)	16 (6.7)	1 (6.3)	83 (10.3)
1	163 (30.1)	61 (25.4)	3 (18.8)	230 (28.6)
2	149 (27.5)	76 (31.7)	2 (12.5)	227 (28.2)
3	95 (17.5)	48 (20.0)	4 (25.0)	149 (18.5)
4–6	70 (12.9)	39 (16.3)	6 (37.5)	115 (14.3)
Coexisting condition				
Hypertension	287 (53.0)	129 (53.8)	13 (81.3)	432 (53.7)
Stroke	110 (20.3)	76 (31.7)	9 (56.3)	196 (24.4)
Diabetes	98 (18.1)	46 (19.2)	5 (31.3)	150 (18.7)
Congestive heart failure	84 (15.5)	37 (15.4)	2 (12.5)	125 (15.6)
Coronary artery disease	67 (12.4)	23 (9.6)	1 (6.3)	91 (11.3)
Active cancer	47 (8.7)	18 (7.5)	1 (6.3)	66 (8.2)
Systemic embolism	3 (0.6)	1 (0.4)	0	4 (0.5)
Previous TIA	1 (0.2)	0 (0.0)	1 (6.3)	2 (0.2)
Concomitant treatment with antiplatelet drug	70 (12.9)	28 (11.7)	2 (12.5)	100 (12.4)

Data are presented as *n* (%) unless otherwise specified. Group A: Patients with life-threatening or uncontrolled bleeding. Group B: Patients requiring emergency surgery or intervention. Sixteen patients were included in both group A and group B (shown as group A + B)

aPTT activated partial thromboplastin time, *BMI* body mass index, *$CHADS_2$* Congestive heart failure, Hypertension, Age (> 65 = 1 point, > 75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points), *PT-INR* prothrombin time international normalized ratio, *SD* standard deviation, *TIA* transient ischemic attack, *ULN* upper limit of normal

[a]Six patients were classified as "Other" (neither group A nor group B). Enrollment in the "Other" group versus group A or group B was determined by the investigators. The reasons for patients being classified as "Other" were "untreated with dabigatran", "international normalized ratio level increased to > 9.90", "blood pressure decreased", "overdose of dabigatran", "abnormal coagulation accompanied by severe multiorgan disorder", and "shock during intervention"

[b–d]Data were available for 717 patients (477 in group A, 220 in group B, and 15 in group A + B)[b], 607 patients (428 in group A, 161 in group B, and 14 in group A + B)[c], and 456 patients (319 in group A, 128 in group B, and 6 in group A + B)[d], respectively

[e]Patients may have been treated in more than one department

[f–i] Data were available for 600 patients (422 in group A, 162 in group B, and 11 in group A + B)[f], 267 patients (187 in group A, 72 in group B, and 7 in group A + B)[g], 128 patients (91 in group A, 33 in group B, and 3 in group A + B)[h], and 340 patients (229 in group A, 101 in group B, and 9 patients in group A + B)[i], respectively

[j]Seven cases with D-dimer values > 50 ng/dl were reported, of which six were trauma cases (head injury in five cases and femur fracture in one case). The remaining case was one of intra-abdominal bleeding due to rupture of hepatocellular carcinoma

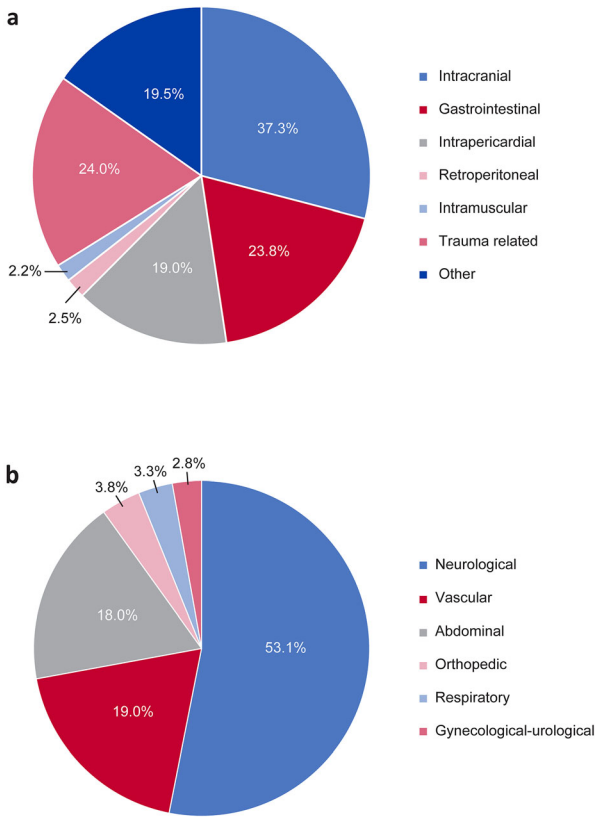


Fig. 2 Idarucizumab indication for reversal effect of dabigatran. **a** Location of bleeding events in group A/A + B (N = 558) and **b** types of surgery/procedures in group B/A + B (N = 211). Patients may have experienced more than one type of bleeding and thus the percentages in **a** exceed 100%. Among 208 patients (37.3%) with intracranial bleeding, the locations of intracranial bleeding (N, %) were intracerebral (139, 24.9%), subdural (78, 14.0%), and subarachnoid (55, 9.9%). Among 133 patients (23.8%) with gastrointestinal (GI) bleeding, 61 (10.9%) had lower GI bleeding only, 53 (9.5%) had upper GI bleeding only, 5 (0.9%) had both lower and upper GI bleeding, and 14 (2.5%) had an unknown GI bleeding location. In **b**, the types of surgery or procedures and number of patients for each were: Neurological—intracranial hemorrhage (78), cerebral infarct (23), hydrocephalus (3), abscess (2), for diagnosis (2), other (4); Vascular—aortic dissection/ruptured aortic aneurysm (24), cardiac tamponade/pericardial effusion (4), intracardiac thrombus (3), coronary artery disease (2), valvular disease (2), other (5); Abdominal–cholecystitis/cholangitis (12), gastrointestinal perforation (9), bowel obstruction (8), incarcerated hernia (4), other (5); Orthopedic—fracture (5), other (3); Respiratory—pneumothorax (2), other (5); Gynecological-urological—dialysis (2), other (4)

patients in group A + B, 11 had intracranial hemorrhage and required surgical intervention.

Safety

Adverse Drug Reactions

ADRs during the entire study period were reported in 17 patients (3.1%) in group A and 12 patients (5.0%) in group B, of which 14 (2.6%) and nine (3.8%) were considered serious (Table 2). ADRs during the idarucizumab treatment period (i.e., within 5 days of idarucizumab treatment) were reported in 13 patients (2.4%) in group A and ten patients (4.2%) in group B, which were serious in 11 (2.0%) and eight (3.3%) patients, respectively (Table 2). No ADRs were reported for patients included in group A + B.

The ADRs reported in group A and group B are listed in Supplementary Table S2. The most commonly reported ADRs were in the system organ class of nervous system disorders – six patients (1.1%) in group A and five patients (2.1%) in group B. Four of the five patients in group B experienced a cerebral infarction, compared with one patient in group A. The second most commonly reported ADRs by system organ class were vascular disorders—four (0.7%) in group A and one (0.4%) in group B. GI disorders occurred in two patients in each group. All of the ADRs reported as nervous system disorders (11) or as vascular disorders (five) were considered serious. Two patients in group B experienced a subdural hematoma. All other serious ADRs occurred in one patient in each group, including a patient in group A who experienced a serious GI disorder—rectal ulcer hemorrhage. ADRs by bleeding location and type of surgery/procedure are listed in Supplementary Tables S3 and S4, respectively.

AEs led to death in 73 patients (13.5%) in group A and 24 patients (10.0%) in group B, of which 58 (10.7%) and 16 (6.7%) occurred within 5 days of idarucizumab treatment (Table 2). A list of the AEs that led to death within 5 days of idarucizumab treatment for each patient is provided in Supplementary Table S5. The most common AEs that led to death were subdural hematoma (ten patients in

Table 2 Summary of safety outcomes

	Group A (*N* = 542)	Group B (*N* = 240)	Group A + B (*N* = 16)	Total (*N* = 804)
Patients with ADRs				
Within 5 days	13 (2.4)	10 (4.2)	0	23 (2.9)
Entire study period	17 (3.1)	12 (5.0)	0	29 (3.6)
Patients with serious ADRs				
Within 5 days	11 (2.0)	8 (3.3)	0	19 (2.4)
Entire study period	14 (2.6)	9 (3.8)	0	23 (2.9)
Patients with AEs leading to death				
Within 5 days	58 (10.7)	16 (6.7)	3 (18.8)	78 (9.7)
Entire study period	73 (13.5)	24 (10.0)	4 (25.0)	102 (12.7)
Patients with a thrombotic event				
Within 5 days	9 (1.7)	11 (4.6)	0	20 (2.5)
Entire study period	22 (4.1)	15 (6.3)	0	37 (4.6)
Patients with hypersensitivity				
Within 5 days	3 (0.6)	4 (1.7)	0	7 (0.9)
Entire study period	4 (0.7)	5 (2.1)	0	9 (1.1)

Data are presented as *n* (%). ADRs and AEs were coded using Version 24.1 of the Medical Dictionary for Regulatory Activities

ADR adverse drug reaction, *AE* adverse event

group A and zero patients in group B), pneumonia aspiration (six patients and two patients), cerebral hemorrhage (six patients and one patient), hemorrhagic shock (five patients and zero patients), multiorgan dysfunction syndrome (three patients and one patient), brain herniation (one patient and three patients), pulmonary alveolar hemorrhage (three patients and zero patients), brain edema (two patients and one patient), cerebral infarction (two patients and one patient), cardiac failure (two patients and one patient), hemorrhage (one patient and two patients), peritonitis (one patient and two patients), pneumonia (one patient and two patients), and malignant neoplasm progression (one patient and two patients).

Thrombotic Events and Hypersensitivity

Thrombotic events (ischemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, systemic embolism) were reported in 22 patients (4.1%) in group A and 15 patients (6.3%) in group B, of which nine (1.7%) and 11 (4.6%) patients, respectively, experienced thrombotic events within 5 days of idarucizumab treatment (Table 2). Of these thrombotic events, five (0.9%) in group A and five (2.1%) in group B were reported as ADRs. The details of thrombotic events are provided in Supplementary Table S6. Hypersensitivity (including shock and anaphylaxis) occurred in four patients (0.7%) in group A and five patients (2.1%) in group B—circulatory collapse (one and two patients, respectively), rash (two patients in group B), shock (two patients in group A), urticaria (one patient in each group), and drug eruption (one patient in group B). One

Table 3 Reversal of anticoagulation as measured by aPTT[a]

	Group A/A + B (*N* = 557)	Group B/A + B (*N* = 252)	Total (*N* = 793)
Elevated aPTT at baseline			
> ULN in each site	264 (47.4)	103 (40.9)	361 (45.5)
≤ ULN in each site	160 (28.7)	69 (27.4)	223 (28.1)
Unknown	133 (23.9)	80 (31.8)	209 (26.4)
Maximum effect on the anticoagulant activity < 4 h after idarucizumab administration[a]			
No. of patients	78	26	102
Median (interquartile range)	100.0 (80.1–100.0)	100.0 (100.0–100.0)	100.0 (82.5–100.0)
No. of cases at 100%	46 (59.0)	20 (76.9)	64 (62.8)
No. of cases between 80% and < 100%	13 (16.7)	3 (11.5)	16 (15.7)
No. of cases between 50% and < 80%	7 (9.0)	2 (7.7)	9 (8.8)
No. of cases < 50%	12 (15.4)	1 (3.9)	13 (12.8)

Data are presented as *n* (%) unless otherwise specified
aPTT activated partial thromboplastin time, *h* hour, *ULN* upper limit of normal
[a]If calculated reversal was > 100, it was set to 100

additional patient experienced a hypersensitivity-related AE after receiving idarucizumab again following restart of dabigatran. Thrombotic events and hypersensitivity by bleeding location and type of surgery/procedure are listed in Supplementary Tables S7 and S8, respectively.

Effectiveness

In the effectiveness dataset (*N* = 793), 78 patients in group A and 26 patients in group B had both aPTT data at baseline and within 4 h of idarucizumab administration; in these patients, the median maximum percentage reversal within 4 h of idarucizumab administration was 100% (Table 3). Cessation of bleeding was confirmed in 146 of 208 patients (70%) who had intracranial hemorrhage, 271 of 349 patients (78%) who had non-intracranial hemorrhage, 104 of 132 patients (79%) who had any GI bleed, and 86 of 106 patients (81%) who had intrapericardial bleed (Table 4). Median time to recorded cessation of bleeding was 13.4, 3.3, 8.9, and 1.3 h in patients with intracranial hemorrhage, non-intracranial hemorrhage, any GI bleed, and intrapericardial bleeds, respectively (Table 4).

Among 252 patients in group B/A + B, 211 (84%) underwent surgery or had a procedure; 205 of the 211 patients who underwent surgery or required a procedure had at least one hemostasis assessment. Periprocedural hemostasis was normal in 166 of 205 patients (81%). The median time from administration of the first vial of idarucizumab to surgery or a procedure was 1.24 h (interquartile range, 0.50–2.50). For patients who required neurological surgery/procedure, vascular surgery/procedure, or abdominal surgery/procedure, the median times were 1.05, 1.40, and 1.43 h, respectively (Table 5). Many patients received transfusions and other blood products (48% in group A and 34% in group B), including packed red blood cells (37% in group A and 25% in

Table 4 Time to cessation of all bleeding – group A/A + B

	ICH (*N* = 208)	Non-ICH (*N* = 349)	GI bleeds (*N* = 132)	Intrapericardial (*N* = 106)	Total (*N* = 557)
Bleeding stopped					
Yes	146 (70.2)	271 (77.7)	104 (78.8)	86 (81.1)	417 (74.9)
No	43 (20.7)	57 (16.3)	19 (14.4)	16 (15.1)	100 (18.0)
Unknown	19 (9.1)	21 (6.0)	9 (6.8)	4 (3.8)	40 (7.2)
Time to cessation of bleeding since first infusion					
< 1 h	7 (4.8)	73 (26.9)	18 (17.3)	37 (43.0)	80 (19.2)
< 2 h	16 (11.0)	104 (38.4)	28 (26.9)	49 (57.0)	120 (28.8)
< 3 h	26 (17.8)	121 (44.7)	32 (30.8)	57 (66.3)	147 (35.3)
< 4 h	38 (26.0)	131 (48.3)	34 (32.7)	60 (69.8)	169 (40.5)
< 12 h	67 (45.9)	169 (62.4)	48 (46.2)	67 (77.9)	236 (56.6)
< 24 h	101 (69.2)	213 (78.6)	70 (67.3)	79 (91.9)	314 (75.3)
≥ 24 h	141 (96.6)	250 (92.3)	93 (89.4)	83 (96.5)	391 (93.8)
Time to stop bleeding, hours					
No. of patients	141	250	93	83	391
Median (95% CI)	13.4 (8.1–16.6)	3.3 (2.4–5.0)	8.9 (5.0–16.9)	1.3 (0.8–2.8)	5.8 (4.4–7.3)

Data are presented as *n* (%) unless otherwise specified
CI confidence interval, *GI* gastrointestinal, *h* hour, *ICH* intracranial hemorrhage

group B), fresh frozen plasma (21% in each group), and platelets (7% in group A and 14% in group B). The use of blood products and volume expanders is described in Supplementary Table S9.

The 30-day mortality rate, estimated by the Kaplan–Meier method, was 12.0% in all patients included in the safety dataset. In group A/A + B, the mortality rate was 13.1% at day 30. At day 30, the mortality rate was 14.1% for patients who had intracranial hemorrhage, 16.7% for patients who had GI bleeding, and 4.8% for patients who had intrapericardial bleeding. In group B/A + B, the estimated mortality rate at day 30 was 10.4%. Patients who underwent neurological, vascular, or abdominal surgery/procedures had mortality rates of 8.4, 15.3, and 5.3% at day 30, respectively.

During the 4-week follow-up period after idarucizumab treatment, anticoagulation therapy was restarted in 329 patients (59%) in group A/A + B and 173 patients (69%) in group B/A + B, of which > 50% received dabigatran in each group (Table 6). After idarucizumab administration, median time to the restart of any anticoagulation therapy was 3.6 days in group A/A + B and 2.5 days in group B/A + B (Table 6). Restart of anticoagulation therapy and median time to restart of any anticoagulation therapy by bleeding location and type of surgery/procedure are provided in Supplementary Tables S10 and S11, respectively. Seven patients received idarucizumab again after dabigatran was restarted (Supplementary Table S12). One patient received an additional 5 g of idarucizumab before dabigatran was restarted, for a total of 10 g.

Table 5 Median time to surgery or invasive procedure after idarucizumab – group B/A + B

	Time to surgery after idarucizumab (h)[a] Median (range)	Hemostasis during surgery/procedure, *n* (%)			
		Normal	Mildly abnormal	Moderately abnormal	Severely abnormal
Total (*n* = 252)	1.24 (– 0.2 to 92.3)	166 (81.0)	15 (7.3)	16 (7.8)	8 (3.9)
Neurological (*n* = 112)	1.05 (– 0.1 to 24.7)	92 (86.0)	8 (7.5)	5 (4.7)	2 (1.9)
Vascular (*n* = 40)	1.40 (– 0.2 to 92.3)	25 (62.5)	2 (5.0)	8 (20.0)	5 (12.5)
Abdominal (*n* = 38)	1.43 (0.0–23.3)	31 (81.6)	5 (13.2)	1 (2.6)	1 (2.6)
Other (*n* = 21)	1.32 (– 0.1 to 44.7)	18 (90.0)	0	2 (10.0)	0

h hour

[a]Time after administration of the first vial of idarucizumab

DISCUSSION

The data from this full analysis of the Japanese PMS study in 804 patients confirms the results previously reported from an interim analysis in 262 patients [9]. Among the 804 patients, 30% required urgent surgery or an invasive procedure, of which more than half required neurological surgery or a procedure (primarily for intracranial hemorrhage). Compared with the results of the interim analysis [9], a lower percentage of patients experienced thrombotic events in the full cohort (4.6 vs. 6.1%) and a higher percentage of patients were able to restart anticoagulant therapy in both groups.

The regulatory approval of idarucizumab in Japan in 2016 was based on an interim analysis of data from the RE-VERSE AD trial (unpublished data). Within the limitations of comparing our real-world, observational study with clinical trials, the data on patient characteristics, safety, and effectiveness were consistent with those of the RE-VERSE AD trial [6, 7]. The patient populations were generally similar between studies: median age of the patients was 78 years in both studies and the majority had impaired renal function. Notably, creatinine clearance was < 30 ml/min in 12% of patients in our study and in 18% of patients in RE-VERSE AD [7]. The majority of dabigatran (80%) is eliminated unchanged by renal excretion [11]. Low or deteriorating renal function, which can occur during anticoagulation treatment with dabigatran [12], may increase the risk of bleeding complications due to reduced renal excretion of dabigatran. Thus, close laboratory monitoring of creatine clearance is needed.

In RE-VECTO, a global, postmarketing registry conducted after the approval of idarucizumab [13], the reasons for the use of idarucizumab were consistent with the results of the RE-VERSE AD study: GI bleeding was most common in the bleeding group, followed by intracranial hemorrhage. In the emergency surgery group, abdominal surgery was the most common reason for using idarucizumab, followed by orthopedic surgery. Compared with the RE-VERSE AD study and the RE-VECTO registry, the reasons for using idarucizumab in our study were relatively higher rates of intracranial and intrapericardial bleeding and lower rates of GI bleeding. Patients requiring emergency surgery had relatively higher rates of neurosurgical procedures and lower rates of orthopedic procedures. This difference in usage trends may reflect regional differences or differences in the timing of the survey. With regard to intracranial hemorrhage, a higher frequency has been reported in Asians compared with non-Asians [14]. The relatively higher rates of intracranial hemorrhage and neurosurgical procedures in our study are consistent with a shorter median time from the last dose of dabigatran to the first infusion of idarucizumab than in the RE-VERSE AD study (9.3 vs. 15.6 h, respectively) [7].

Table 6 Restart of anticoagulation therapy

	Group A/A + B (*N* = 557)	Group B/A + B (*N* = 252)	Total (*N* = 793)
Restarted anticoagulant therapy, *n* (%)			
Any anticoagulant therapy	329 (59.1)	173 (68.7)	494 (62.3)
Dabigatran	181 (55.0)	103 (59.5)	280 (56.7)
Apixaban	56 (17.0)	10 (5.8)	64 (13.0)
Edoxaban	41 (12.5)	9 (5.2)	49 (9.9)
Heparin	31 (9.4)	34 (19.7)	65 (13.2)
Warfarin	11 (3.3)	8 (4.6)	18 (3.6)
Rivaroxaban	10 (3.0)	7 (4.1)	17 (3.4)
Other	0 (0.0)	2 (1.2)	2 (0.4)
Time to restart any anticoagulant therapy, days			
No. of patients	216	105	318
Median (interquartile range)	3.6 (1.7–8.0)	2.5 (1.4–7.6)	3.4 (1.6–7.6)

For GI bleeding, it is relatively easy to identify the source of bleeding by endoscopy, which is used in most hospitals in Japan, and thus bleeding is typically stopped by clipping rather than using idarucizumab. Intrapericardial bleeding may have been caused by catheter ablation for NVAF. Due to the results of the RE-CIRCUIT trial and the presence of a reversal agent, dabigatran may be widely chosen in the peri-ablation period of catheter ablation in patients with NVAF, as Japanese guidelines recommend continued anticoagulation with dabigatran (the only direct oral anticoagulant with a class 1A recommendation) in the peri-ablation period. In fact, the proportion of patients using idarucizumab for intrapericardial bleeding has increased since early 2017, when the RE-CIRCUIT trial results were published [15].

In group B, surgical procedures for intracranial hemorrhage were the most common in our study, and about 40% of these patients were trauma cases. The prognosis for head trauma patients on anticoagulation is poor, and reversal of anticoagulation may be important. In our study, 23 patients were treated with idarucizumab before treatment of ischemic stroke (thrombolysis, thrombectomy, or bypass for ischemic stroke). Recommendations have been published regarding acute reperfusion therapy with idarucizumab for patients with ischemic stroke receiving dabigatran [16].

The incidence of ADRs, serious ADRs, and AEs leading to death were similar between RE-VERSE AD [7] and our study. The majority of events appeared to be a worsening of the index event or were associated with coexisting conditions, similar to what was reported in the RE-VERSE AD study [7]. Additionally, the rates of thrombotic events were similar between studies: 4.6% for all patients in our study and 4.8% in RE-VERSE AD within 4 weeks or 30 days of idarucizumab treatment. Seventeen patients (46%) who presented with thrombotic events had not reinitiated anticoagulation therapy. The rates of restarting anticoagulant therapy were lower in our study at 59% in group A and 69% in group B, compared with 73% and 90% in RE-VERSE AD, respectively. A recent meta-analysis of reversal agents against anticoagulants reported that the risk of thrombotic events was 4.3, 3.8, and 10.7% for four-factor prothrombin complex concentrates, idarucizumab, and andexanet alfa, respectively [17]. The frequency of thrombotic events in our study was consistent with the results of this meta-analysis.

In RE-VERSE AD, the effectiveness of idarucizumab in reversing the anticoagulant effects of dabigatran was assessed based on dTT or ECT, neither of which are available in clinical practice in Japan. Therefore, we used aPTT to assess the effectiveness of idarucizumab. However, reversal of anticoagulation based on aPTT was shown to be similar to that based on dTT in RE-VERSE AD [7]. In both our study and RE-VERSE AD, the median maximum percentage reversal within 4 h of idarucizumab administration was 100%.

The median time to cessation of bleeding in our study was similar to that reported in RE-VERSE AD. Among patients with non-

intracranial hemorrhage in group A, median time to bleeding cessation was 3.3 h in our study and was 2.5 h in RE-VERSE AD. We further reported a median time to cessation of bleeding of 13.4 h for patients with intracranial hemorrhage, but this was not assessed in RE-VERSE AD. In both studies, early follow-up imaging was not mandated, and thus the recorded time to cessation of intracranial hemorrhage may have been prolonged.

In our study, the median time to surgery after idarucizumab administration was 1.24 h in group B/A + B, generally consistent with the results of RE-VERSE AD. Periprocedural hemostasis in group B/A + B was assessed as normal in 81% of patients in our study and in 93% of patients in RE-VERSE AD [7]. Hemostasis was manageable in patients at high risk for bleeding. Idarucizumab facilitates management of patients requiring urgent procedures by providing rapid dabigatran reversal, and is the only agent of its class studied in surgical patients.

The 30-day mortality rate was similar between our study and RE-VERSE AD (in group A, 13.1 and 13.5%, respectively, and in group B, 10.4 and 12.6%, respectively). The mortality rates for patients with intracranial hemorrhage in our study and RE-VERSE AD were 14.1 and 16.4%, respectively. These mortality rates are not high compared with the results of the aforementioned meta-analysis [15], in which the mortality rate was 17.7% for overall bleeding patients and 20.2% for patients with intracranial hemorrhage [17].

The Japanese risk-management plan for idarucizumab lists idarucizumab re-exposure as "missing information" in clinical trials. Based on seven cases in our study where idarucizumab was readministered after dabigatran was restarted, the risk of readministering idarucizumab was suggested to be low.

LIMITATIONS

Our PMS study has limitations inherent to real-world, observational studies, particularly the extent of missing data compared with clinical studies. The exact timing from the last dose of dabigatran to the first administration of idarucizumab was unknown in 42% of patients. For the effectiveness dataset, aPTT could only be measured in 13% of patients. Moreover, our evaluation of the effectiveness of idarucizumab was not based on dTT or ECT, nor did we measure the concentration of unbound dabigatran. Finally, some patients were discharged or transferred from the hospital before the 4-week observation period could be completed.

CONCLUSIONS

Despite the limitations of our study, the effectiveness and safety data of idarucizumab were similar to that of clinical trials. The results of the full analysis of the Japanese PMS study confirm previous findings that suggest idarucizumab can safely and effectively reverse the anticoagulant effects of dabigatran in Japanese patients in real-world clinical practice. The data support the continued use of idarucizumab in Japan, with no new safety concerns having been identified.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Masahiro Yasaka has received lecture, advisory, and travel fees from Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Bayer, Daiichi Sankyo, and CSL Behring, as well as scholarship funds or non-restricted grants from Nippon Boehringer Ingelheim. Hiroyuki Yokota has received lecture fees, consulting fees, and grants from Herusu-Shuppan, MEDIC MEDIA, MEDICAL VIEW, Stryker Japan, and UCB Japan. Michiyasu Suzuki has received lecture fees from Nippon Boehringer Ingelheim and CSL Behring. Hidesaku Asakura has received lecture fees from Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Bayer, Nippon Boehringer Ingelheim; scholarships from Pfizer, Daiichi Sankyo, Nippon Boehringer Ingelheim, CSL Behring; and grants from Bristol-Myers Squibb. Teiichi Yamane has received lecture and consulting fees from Daiichi Sankyo, Nippon Boehringer Ingelheim, Abbott Japan, Bristol-Myers Squibb, Bayer Pharmaceutical Company, and Medtronic Japan. Yukako Ogi and Daisuke Nakayama are employees of Nippon Boehringer Ingelheim. Takaaki Kimoto is an employee of the EPS Corporation. Current affiliation for Masahiro Yasaka: Department of Cerebrovascular Medicine, Fukuoka Neurosurgical Hospital, 5-3-15 Osa, Minami-ku, Fukuoka 811–1313, Japan.

Ethical Approval. This study was conducted according to the Declaration of Helsinki (1964 and its later amendments). The study also complied with Japanese Good Post-marketing Study Practice regulations, and the protocol was approved by the Japanese Ministry of Health, Labour and Welfare. Anonymous data were collected from clinical settings, and thus it was not necessary to obtain informed consent from the patients. The medical institutions that agreed to provide anonymized data signed a contract with the sponsor (Nippon Boehringer Ingelheim Co., Ltd.). This study is registered with ClinicalTrials.gov (NCT02946931).

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