Venous and arterial thrombotic complications. Solutions in clinical practice

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Chapter 7

Performance of idarucizumab as antidote of dabigatran in daily clinical practice

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ABSTRACT

Aims

Because practice-based data on the usage of idarucizumab for urgent dabigatran reversal are unavailable we evaluated the appropriateness of idarucizumab usage, its hemostatic effectiveness and clinical outcomes.

Methods

An observational cohort study was performed including consecutive patients who were treated with idarucizumab between 2016 and 2018. Appropriate usage was assessed with predefined criteria. Post-reversal effectiveness was evaluated according to ISTH recommendations. Patients were followed for 90 days for occurrence of thromboembolism, (re-)bleeding and death.

Results

Idarucizumab was used in 88 patients, of whom 53 (60%) presented with severe bleeding (20 gastrointestinal and 18 intracranial) and 35 (40%) requiring urgent surgical intervention. Use of idarucizumab was judged inappropriate in 25 patients (28%). Effective hemostasis was achieved in 32 of 48 (67%) bleeding patients in whom assessment was possible. Seven of 16 patients with major bleeding who did not achieve effective hemostasis (five intracranial) died, compared to two of 32 patients with effective hemostasis (relative risk: 7.0, 95% confidence interval 1.6-30). Four patients (4.2%) developed thromboembolism (2 (2.1%) within 30 days) and four patients (4.2%) re-bleeding, all within 10 days. Seventeen patients (19%) died; 10 (11%) within five days.

Conclusion

In this practice-based cohort, idarucizumab use was considered inappropriate in 28% of patients. Effective hemostasis was achieved in two third of bleeding patients and was associated with lower mortality risk. Clinical outcomes were similar to those observed in the RE-VERSE AD trial, comprising re-bleeds and thromboembolism, and a high mortality rate.

INTRODUCTION

Because of its favourable benefit-risk profile compared to vitamin K antagonists (VKA), dabigatran etexilate (Pradaxa®) is widely used for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation and for the prevention and treatment of venous thromboembolism (1, 2). However, as for all anticoagulants, bleeding, including life-threatening or fatal bleeding, remains a relevant side effect. The lack of a reversal agent has been perceived as a concern to both patients and clinicians which until recently has been an obstacle for direct oral anticoagulant (DOAC) use in many patients.

The specific reversal agent Idarucizumab (Praxbind®), a monoclonal antibody fragment that binds dabigatran with high affinity, has been approved by the U.S. Food and Drug Administration and the European Medicines Agency for urgent dabigatran reversal (3-5). This approval was based on the results of the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial which showed rapid and complete reversal of dabigatran activity in patients with uncontrolled or life-threatening bleeding or undergoing an emergency procedure (6). Further insight on the clinical use of idarucizumab is only available from case reports and one small retrospective study demonstrating safe and effective idarucizumab administration in 31 patients with intracranial bleeding or ischemic stroke prior to thrombolysis (7, 8). Even so, current international guidelines recommend idarucizumab usage for urgent dabigatran reversal in the presence of life-threatening bleeding or urgent surgery associated with high risk of bleeding (9, 10). It remains nonetheless to the clinician's discretion to decide in which clinical setting usage of idarucizumab is appropriate.

Since data on idarucizumab in daily practice are scarce, we set out to perform an observational study aiming to determine the appropriateness of idarucizumab usage as well as the hemostatic effectiveness and clinical outcomes in daily practice.

METHODS

Study design and population

This was an observational, multicentre cohort study including consecutive patients who were treated with idarucizumab between 2016 and 2018, with the aim of evaluating appropriate usage, hemostatic effectiveness and 90-day clinical outcomes. A representative from manufacturer Boehringer Ingelheim provided a list of 20 major idarucizumab distributing Dutch hospital pharmacies which were all approached for participation. Five of them replied not to have dispensed idarucizumab, three did not comply with the request and 12 provided all available information. Subsequently, data were collected by scrutinizing medical records, including medical notes, laboratory results, radiology

reports and other relevant details. No exclusion criteria were applied. The institutional review board of the LUMC centrally approved the study and waived the need for informed consent because of its observational non-interventional design.

Study outcomes

The primary objective was to assess the appropriateness of idarucizumab usage. Each individual administration was adjudicated independently by two expert physicians (F.K. and M.V.) using criteria listed in **Table 1.** These criteria were predefined and based on an expert consensus of the International Society on Thrombosis and Haemostasis (ISTH) for reversal of direct oral anticoagulants (DOACs) (11). These guidance indications include life-threatening/uncontrollable bleeding, bleeding into a critical organ or closed space, prolonged bleeding despite local hemostatic measures, high risk of recurrent bleeding because of overdose or delayed clearance of dabigatran, and need for an urgent intervention associated with a high risk of bleeding.

In line with the RE-VERSE AD trial (6), bleeding was considered uncontrollable if one or more of the following criteria were met: symptomatic intracranial bleeding, a reduction in hemoglobin (Hb) of at least 5 g/dL, transfusion of at least 4 units of blood or packed cells, bleeding requiring use of intravenous inotropic agents or necessitating surgical intervention. An urgent intervention was defined as one that could not be delayed for at least 8 hours. We added indicators for the presence of dabigatran plasma levels as a criterion for appropriateness. These indicators comprised a sensitive activated Partial Thromboplastin Time (aPTT), diluted Thrombin Time (dTT) or ecarin clotting time (ECT) laboratory test result above the upper limit of normal (according to fixed cut-off points of individual hospitals) and/or a self-reported time of last dabigatran intake. Discrepancies were resolved independently by a third party, consisting of a relevant specialized expert physician who was selected ad hoc.

Secondary objectives were 1) to assess hemostatic efficacy after administration for urgent reversal in bleeding events, and 2) to evaluate the incidence of 90-day clinical outcomes, comprising thromboembolism, (re-)bleeding and death. Hemostatic efficacy was assessed in accordance with standardized definitions published by the ISTH (12). Additional chart data were collected for bleeding course, need for blood products, additional procedures, and , for intracranial bleeding solely, results from repeat computed tomography scans and change in neurological status. Thromboembolic events comprised objectively verified arterial (i.e. stroke, transient ischemic attack, myocardial infarction or arterial thromboembolism) or venous thromboembolisms (i.e. deep vein thrombosis and pulmonary embolism). Bleeding complications were classified using the ISTH criteria for major bleeding (13). The cause of death was verified by reviewing the pathology report. In case autopsy had not been performed, the likely cause of death was verified with the treating physician.

Table 1. Proposed criteria for proper idarucizumab usage. *If test result is available prior to administration

Reason for idarucizumab usage	Adjudication category	
	Appropriate usage	**Inappropriate usage**
Intervention	Proper indication ISTH guidance Need for urgent intervention that cannot be delayed for drug clearance (within eight hours) Emergency intervention in patients at high risk for procedural bleeding Indicators for presence of circulating dabigatran Dabigatran intake <72h Prolonged aPTT, ECT or dTT*	Improper indication ISTH guidance Intervention that can be delayed to permit dabigatran clearance Elective surgery Absence of indicators for circulation dabigatran
Bleeding	Proper Indication ISTH guidance Uncontrollable hemorrhage Closed space or critical organ (intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, intramuscular with compartment syndrome Persistent major bleeding or risk of recurrent bleeding because of delayed dabigatran clearance Indicators for presence of circulation dabigatran Dabigatran intake <72h Prolonged aPTT, ECT or dTT*	Improper indication ISTH guidance Major (GI) bleeds that respond to supportive measures Absence of indicators for circulating dabigatran

Note: ISTH=International Society on Thrombosis and Haemostasis, aPTT=activated Partial Thromboplastin Time, dTT=diluted Thrombin Time, ECT=ecarin clotting time, GI=Gastrointestinal.

Statistical analysis

Means (standard deviation (SD)) and medians (interquartile range (IQR)) were used to present continuous variables and analyzed with t-test for normal and the Mann-Whitney test for skewed distributions. The categorical variables were described by proportions (n) and percentages (%), and compared using relative risks (RRs) with associated 95% confidence intervals (CI). Data were analyzed using SPSS version 23 (SPSS, Chicago, IL, USA). A *P*-value below 0.05 was considered to be significant.

RESULTS

Study population

Demographic and clinical characteristics of all consecutive 88 patients who were treated with idarucizumab for urgent dabigatran reversal are listed in **Table 2**. Among the 12 hospitals, the number of administrations varied from one to 14 during the two year

study period. Fifty-three (60%) patients presented with bleeding and 35 (40%) patients required urgent intervention. The mean age was 76 (SD ± 9) years and 51 patients (58%) were males. Nearly all patients (96%) had atrial fibrillation (AF) as primary indication for dabigatran use. The last self-reported dabigatran intake was > 24 hours in 11 patients (13%). Administration of idarucizumab occurred at the hospital ward (49%), the emergency room (34%), operating theatre (9.1%) or intensive care unit (6.8%). The aPTT was measured in 38 patients (43%) and was prolonged in 32/38 patients (84%). Specific dabigatran tests (ECT or dTT) were available in 10 of 12 included hospitals (83%) but were used in only 16 patients (18%). Of the 53 patients who presented with bleeding,

Table 2. Baseline characteristics of 88 patients who received idarucizumab. Patient used *75mg dabigatran BID and †rivaroxaban.

Characteristic		**Intervention (n=35)**	**Bleeding (n=53)**	**Total (n=88)**
Age, mean ± SD		74 ± 9	78 ± 9	76 ± 9
Male, no. (%)		19 (54)	32 (60)	51 (58)
eGFR (ml/ms), no. (%)	>90	5 (14)	5 (9.4)	10 (11)
	61-90	16 (46)	23 (43)	39 (44)
	30-60	7 (20)	20 (38)	27 (31)
	<30	5 (14)	3 (5.7)	8 (9.1)
	Missing	2 (5.7)	2 (3.8)	4 (4.5)
Dabigatran dosage BID, no. (%)	150mg	18 (52)	18 (34)	36 (41)
	110mg	16 (46)	34 (64)	50 (57)
	Other	1 (2.9)*	1 (1.9) †	2 (2.3)
Dabigatran indication, no. (%)	AF	32 (91)	52 (98)	84 (96)
	VTE	2 (5.7)	1 (1.9)	3 (3.4)
	Unknown	1 (2.9)	0	1 (1.1)
Last intake of dabigatran until administration (h), no. (%)	<24	32 (91)	44 (83)	76 (86)
	24-47	3 (8.6)	4 (7.5)	7 (8.0)
	48-71	0	2 (3.8)	2 (2.3)
	>72	0	2 (3.8)	2 (2.3)
	Missing	0	1 (1.9)	1 (1.1)
Laboratory tests prior to idarucizumab administration				
aPTT (s)	No (%)	8 (22)	30 (57)	38 (43)
	Above normal range, no (%)	8 (100)	24 (80)	32 (84)
Dabigatran (ECT/ dTT) (s)	No (%)	8 (23)	8 (15)	16 (18)
	> 30 ng ml^{-1}	7 (88)	8 (100)	15 (94)
	> 50 ng ml^{-1}	5 (63)	7 (88)	12 (75)

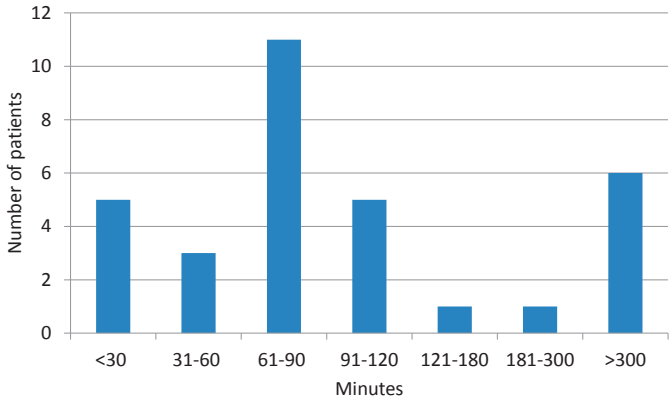
Note: eGFR=estimated Glomerular Filtration Rate, BID=Twice a day, AF=Atrial Fibrillation, VTE=Venous Thromboembolism, aPTT=activated Partial Thromboplastin Time, TT= Thrombin Time, dTT=diluted Thrombin Time, ECT=ecarin clotting time, NSAID=Non-Steroidal Anti-inflammatory Drugs, SSRI=Selective Serotonin Reuptake Inhibitors

most had gastrointestinal (38%) or intracranial bleeding (34%; **Table 3**). Of the 35 urgent interventions, most were performed in the abdominal region (39%). The time between administration of idarucizumab and initiation of intervention varied greatly (**Figure 1**). Each patient received the recommended dosage of idarucizumab (single administration of two times 2.5 grams).

Table 3. Bleeding events and interventions of 88 patients who received idarucizumab. All data is presented as n (%).

Intervention (n=35)		**Bleeding (n=53)**	
Abdominal	14 (40)	Gastrointestinal	20 (38)
Cardiovascular	8 (23)	Intracranial	18 (34)
Fractures	5 (14)	Pericardial	7 (13)
Nervous system	3 (8.6)	Lung	2 (3.8)
Skin	2 (5.7)	Other	6 (11)
Lung	1 (2.9)		
Eye	1 (2.9)		
Pancreatic/hepatobiliary	1 (2.9)	Traumatic	9 (17)

Figure 1. Time between first idarucizumab infusion and initiation of procedure in 31 patients in whom this duration could be determined.



Appropriateness of idarucizumab usage

Inappropriate usage of idarucizumab occurred in 25 patients (28%): 14 of 35 patients (40%) requiring intervention and 11 of 53 patients (21%) presenting with bleeding (**Supplemental table S1**). All 14 interventions could have been delayed for at least eight hours and eight of these 11 (72%) bleeding complications were not considered uncontrollable. Three bleeding patients (5.7%) had no dabigatran plasma levels; two had a last intake >72 hours as well as normalized aPTT levels, and one patient used

rivaroxaban instead of dabigatran. Nearly all bleeding events in which the administration was considered inappropriate were located in the gastrointestinal tract (73%).

Hemostatic effectiveness

Treatment with idarucizumab was considered effective in 32 of 48 (67%) bleeding patients in whom assessment was possible (**Table 4**). No significant difference was observed between the effectiveness of intracranial and extracranial bleeding (RR: 1.2, 95%CI 0.53-2.7) as well as traumatic and non-traumatic bleeding (RR: 1.5, 95%CI 0.40-6.1). Seven of 16 patients (44%) with bleeding (five intracranial) who did not achieve effective hemostasis died compared to two of 31 patients (6.5%) with effective hemostasis (RR: 7.0, 95%CI 1.6-30). Effective hemostasis of appropriate idarucizumab usage was comparable to all administrations, achieved in 28 of 38 patients (74%).

Table 4. Effectiveness of hemostasis in 53 patients with bleeding events. *Other bleedings were: lung, retroperitoneal, skin or fractures.

		Effective	Ineffective	Unclear
Bleeding type, n (%)	GI bleeding	15 (75)	5 (25)	0
	ICH	10 (56)	6 (33)	2 (11)
	Pericardial	4 (57)	1 (14)	2 (29)
	Other*	3 (38)	4 (50)	1 (13)
	Traumatic	3 (33)	4 (44)	2 (22)
	Non-traumatic	12 (29)	27 (64)	3 (7.1)
Mortality, n (%)		2 (6.3)	7 (44)	3 (60)
Additional procedures, n (%)		9 (75)	2 (17)	1 (8.3)
Days of hospital stay, mean (IQR)		9 (4-13)	10 (3-11)	6 (3-11)
Total, n (%)		32 (60)	16 (30)	5 (9.4)

Note: GI=Gastrointestinal, ICH=Intracranial Hemorrhage, IQR=Inter-Quartile Range

CLINICAL OUTCOMES

Thromboembolic and bleeding complications

Four thrombotic and four (re-)bleeding complications occurred during the 90-day follow up, all in patients who initially had presented with bleeding (**Table 5**). Thrombotic events comprised two ischemic strokes, occurring on day one (before anticoagulation resumption) and 41 (after anticoagulation resumption), and two pulmonary embolisms (one fatal), occurring on day five (before anticoagulation resumption) and 21 (after dabigatran resumption). A 65-year old male who developed ischemic stroke at the first day after idarucizumab administration also developed a major pericardial re-bleeding after six days after restart of anticoagulation therapy. Other re-bleeding events comprised

of a fatal pericardial (after dabigatran resumption) and two minor bleedings (before anticoagulation resumption), all occurring within 10 days and at the same anatomical location of the index presentation.

Table 5. Characteristics of patients with 90-day adverse outcome. *Therapeutic dosage.

Event	Time from idarucizumab (days)	Time until restart of anticoagulation (days)		Age (y)	Dabigatran dose BID (mg)	Type of index bleeding
		Parenteral*	Dabigatran			
Thromboembolism						
Ischemic stroke	1	2	Unknown	65	150	Pericardial
Fatal pulmonary embolism	5	-	-	92	110	ICH
Ischemic stroke	21	-	4	73	150	ICH
Pulmonary embolism	41	-	1	79	110	GI
Re-bleeding						
GI (minor)	3	-	-	73	150	GI
Lung (minor)	6	-	6	85	110	Lung
Pericardial (major)	6	2	-	65	150	Pericardial
Fatal pericardial (major)	9	-	-	82	110	Pericardial

Note: ICH=Intracranial Hemorrhage, GI=Gastrointestinal

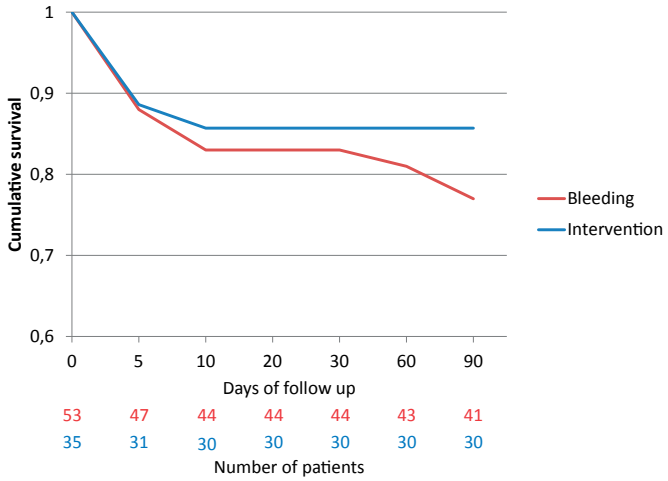
Deaths

During the 90-day follow up, 17 patients died (19%); 10 (11%) within five days. Of these 17 patients, 12 had presented with bleeding (six intracranial) and five underwent urgent intervention. The Kaplan-Meier curve of cumulative survival is shown in **Figure 2**. Causes of death within five days were: sepsis (three patients), postoperative shock (three patients; one possibly related to bleeding), intracranial bleeding (two patients), pericardial bleeding (one patient) and lung bleeding (one patient). Other causes of death after five days were sepsis (three patients), unknown (two patients), intracranial bleeding (one patient), pericardial bleeding (one patient) and pulmonary embolism (one patient).

Antithrombotic therapy resumption

Overall, antithrombotic therapy was restarted in 60 of 88 patients (68%); in 31 of 35 patients (89%) requiring intervention after a median of 3 days (IQR 1-5) and in 30 of 53 patients (57%) presenting with bleeding after a median of 6 days (IQR 3-11). A total of 51 patients (58%) restarted dabigatran and nine patients were switched to other antithrombotic regimens; five to VKA, three to LMWH (one prophylactic and two therapeutic) and one to apixaban.

Figure 2. Kaplan Meier 90-day survival curve of 88 patients after idarucizumab administration, stratified by reason for usage.



DISCUSSION

The main findings of this practice based cohort study were that idarucizumab usage was considered inappropriate in 28% of patients, mostly due to interventions that could have been delayed and gastrointestinal bleeding complications that might also have responded to supportive measures alone. For patients presenting with bleeding, two third achieved effective hemostasis after idarucizumab administration, which was associated with lower mortality risk. In line with the REVERSE-AD study, we observed a 4.2% rate of thromboembolic and bleeding events, and a mortality rate of 19% within 90 days (6).

The predefined criteria for appropriateness were based on the recent ISTH guidance for DOAC reversal which is in line with international guideline recommendations of the European Society of Cardiology (2016) and the American Heart Association (2017) (9-11). After adjudication, forty percent of interventions could have been delayed for at least eight hours and 15% of bleedings were located in the gastrointestinal tract that might also have responded to supportive measures alone. Inappropriate usage is likely the result of the acute critical care setting in which a prompt decision is required, as is illustrated by one patient who incorrectly received idarucizumab while using rivaroxaban. In addition, hospital logistics might also have played an important role in the decision not to delay interventions, as operating room schedules may not always allow awaiting full dabigatran clearance. Moreover, it might have been difficult to foresee the time needed to await dabigatran clearance in patients with moderate to severe renal impairment. In order to prevent inappropriate idarucizumab usage, clinicians should attentively manage dabigatran intake and assess the urgency of the intervention as well

as the bleeding severity when deciding upon administration. Ideally, the decision to administer idarucizumab should be made by a multidisciplinary team.

Results of laboratory test may guide the decision whether or not to administer idarucizumab, except for patients with life-threatening conditions in whom a rapid decision is required. Specific dabigatran tests for accurate estimation of dabigatran plasma concentrations, i.e. the diluted thrombin time (dTT) and the ecarin clotting time (ECT), were infrequently used in our study, although these tests were available in 10 of 12 included hospitals. Applying these tests however requires careful preparation of the specific reagents and materials as well as the presence of an experienced laboratory worker to perform the procedure and analyses. This probably resulted in the low rate of use in the acute setting. The fact that the aPTT test was frequently used to estimate dabigatran plasma levels supports this conclusion.

Inappropriate usage has some important drawbacks. Despite an observed non-procoagulant activity of idarucizumab (5), the attributable thrombotic risk has not yet accurately been determined. Inappropriate usage also significantly increases health care costs as the average wholesale price package of two idarucizumab 2.5 g/50 mL vials is approximately €2600. In addition, there is still insufficient knowledge about the risk of hypersensitivity and significant drug interactions associated with idarucizumab (14). Hereditary fructose intolerance could, for instance, induce a serious adverse reaction due to sorbitol excipients that are processed in the idarucizumab compound (3). Thus, inappropriate usage has impact on both patients' safety as well as healthcare cost.

Our observation of effective hemostasis is similar to those reported in the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors (ANNEXA-4) study and to Sarode *et al.* (2013) evaluating the use of prothrombin complex concentrates (PCC) in VKA (15, 16). This similar effectiveness indicates that these reversal agents are all effective or, alternatively, have minimal or no effect. In the present study, bleeding localization was not related to effectiveness. However, as may be expected, failure to achieve effective hemostasis was associated with higher mortality risk. These comprised mostly patients with intracranial bleeding who are generally at high risk of poor outcomes (17).

The 90-day thromboembolic (4.2%), bleeding (4.2%) and mortality (19%) rates were consistent with those reported by the large RE-VERSE AD trial (6). This clearly reflects the similarities between study populations, involving comparable baseline characteristics and a similar distribution of bleedings and interventions. The observed 5-day mortality rate of 11% underlines the poor prognosis of the patients enrolled with uncontrollable bleeding or requiring emergency interventions. Moreover, the most frequent cause of death does not seem related to bleeding or thromboembolism, but may be driven by the underlying disease. Importantly, it is difficult to analyze the real impact of idarucizumab on patient outcome as there can be no control group for ethical reasons. The 2.1% 30-day thromboembolic rate in our study was lower than those reported in previous

studies evaluating prothrombin complex concentrate (PCC) for the reversal of VKA or Xa-inhibitors, in which thrombotic rates between 4% and 8% were demonstrated (15, 18, 19). Although an indirect comparison, this difference might be explained by the fact that we observed a large part of patients requiring interventions, in which anticoagulation therapy was more rapidly and frequently resumed, whereas these studies only included patients with bleeding (15, 18, 19). The timing of resumption after a bleeding episode is clearly more difficult. A recent ESC consensus recommends resumption after major bleeding as soon as the thrombotic risks outweigh the re-bleeding risks, in most cases within one week (20). Although this was consistent with an observed median duration of six days in our study, all thrombotic and (re-) bleeding events occurred in patients presenting with bleeding. Results of randomized trials evaluating optimal anticoagulation resumption after severe bleeding are eagerly awaited.

To our knowledge, this is the largest practice-based cohort of consecutive patients treated with idarucizumab. No exclusion criteria were applied, which makes the study generalizable to the population treated with idarucizumab. Also, standardized ISTH criteria were used for the evaluation of appropriate usage (11). Each case was independently adjudicated. Our data provide further insight into clinical practice in different situations in which idarucizumab currently is used and its role for the management of urgent dabigatran reversal.

The most important limitation of our study was the retrospective design. Inherently, we might not have accurately reconstructed the line of clinical reasoning in the acute setting. To deal with this issue, medical reports were meticulously scrutinized before the independent adjudication process occurred. In addition, the hemostatic effectiveness could not be determined in 10% of patients because required ISTH criteria for this assessment could not completely be retrieved from the medical reports.

In conclusion, idarucizumab usage was considered inappropriate in 28% of patients, mostly due to interventions that could have been delayed and gastrointestinal bleeding complications that might have responded to supportive measures alone. Of note, the criteria applied to judge appropriateness have not been tested in clinical trials and may not fully reflect daily clinical care on crowded emergency rooms. Two third of bleeding patients achieved effective hemostasis which was associated with a lower mortality risk compared to patients with ineffective hemostasis. Clinical outcome of patients treated with idarucizumab was similar to those observed in the RE-VERSE AD trial(6), comprising (fatal) re-bleeds and thromboembolism, and a high mortality rate.

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