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Published in:
Europace

DOI:
10.1093/europace/euy220

Publication date:
2019

ESC European Society of Cardiology

Europace (2019) **21**, 414–420
doi:10.1093/europace/euy220

CLINICAL RESEARCH
Atrial fibrillation

Performance of idarucizumab as antidote of dabigatran in daily clinical practice

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Received 12 July 2018; editorial decision 30 August 2018; accepted 12 September 2018; online publish-ahead-of-print 17 October 2018

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

Methods and results 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 International Society on Thrombosis and Haemostasis (ISTH) recommendations. Patients were followed for 90 days for occurrence of thromboembolism, (re-)bleeding and death. 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 haemostasis 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 haemostasis (five intracranial) died, compared with two of 32 patients with effective haemostasis (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 5 days.

Conclusion In this practice-based cohort, idarucizumab use was considered inappropriate in 28% of patients. Effective haemostasis 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.

Keywords Idarucizumab • Dabigatran • Bleeding • Reversal

Introduction

Because of its favourable benefit-risk profile compared with vitamin K antagonists (VKA), dabigatran etexilate (Pradaxa®) is widely used for the prevention of ischaemic stroke in patients with non-valvular atrial fibrillation (AF) 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

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What's new?

- This largest practice-based cohort of consecutive patients treated with idarucizumab revealed inappropriate use in 28% of patients.
- Effective haemostasis 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.

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 insights 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 ischaemic 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 haemostatic 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, haemostatic 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 DOACs.[11] These guidance indications include life-threatening/uncontrollable bleeding, bleeding into a critical organ or closed space, prolonged bleeding despite local haemostatic 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 haemoglobin (Hb) of at least 5 g/dL, transfusion of at least four 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 h. 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 (i) to assess haemostatic efficacy after administration for urgent reversal in bleeding events and (ii) to evaluate the incidence of 90-day clinical outcomes, comprising thromboembolism, (re-)bleeding and death. Haemostatic 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 ischaemic 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.

Statistical analysis

Means [standard deviation (SD)] and medians [interquartile range (IQR)] were used to present continuous variables and analysed 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 (CIs). Data were analysed 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 2 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 AF as primary indication for dabigatran use. The last self-reported dabigatran intake was > 24 h 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, most had

Table 1 Proposed criteria for proper idarucizumab usage

Reason for idarucizumab usage	Adjudication category	
	Appropriate usage	Inappropriate usage
Intervention	(1) Proper indication ISTH guidance • Need for urgent intervention that cannot be delayed for drug clearance (within 8 h) • Emergency intervention in patients at high risk for procedural bleeding (2) Indicators for presence of circulating dabigatran • Dabigatran intake <72 h • Prolonged aPTT, ECT, or dTT[a]	(1) Improper indication ISTH guidance • Intervention that can be delayed to permit dabigatran clearance • Elective surgery (2) Absence of indicators for circulation dabigatran
Bleeding	(1) Proper indication ISTH guidance • Uncontrollable haemorrhagehage • Closed space or critical organ (intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, and intramuscular with compartment syndrome) • Persistent major bleeding or risk of recurrent bleeding because of delayed dabigatran clearance (2) Indicators for presence of circulation dabigatran • Dabigatran intake <72 h • Prolonged aPTT, ECT, or dTT[a]	(1) Improper indication ISTH guidance • Major (GI) bleeds that respond to supportive measures • Absence of indicators for circulating dabigatran

aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; GI, gastrointestinal; ISTH, International Society on Thrombosis and Haemostasis.
[a]If test result is available prior to administration.

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 g).

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 (see Supplementary material online, *Table S1*). All 14 interventions could have been delayed for at least 8 h 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 h 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%).

Haemostatic 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 haemostasis died compared with two of 31 patients (6.5%) with effective haemostasis (RR 7.0, 95% CI 1.6–30). Effective haemostasis of appropriate idarucizumab usage was comparable to all administrations, achieved in 28 of 38 patients (74%).

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 ischaemic 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 man who developed ischaemic stroke at the first day after idarucizumab administration also developed a major pericardial re-bleeding after 6 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.

Deaths

During the 90-day follow-up, 17 patients died (19%); 10 (11%) within 5 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 5 days were: sepsis (three patients), post-operative shock (three patients; one possibly related to bleeding), intracranial bleeding (two patients), pericardial bleeding (one patient), and lung

Table 2 Baseline characteristics of 88 patients who received idarucizumab

Characteristics	Intervention (*n* = 35)	Bleeding (*n* = 53)	Total (*n* = 88)
Age (years), mean ± SD	74 ± 9	78 ± 9	76 ± 9
Male, *n* (%)	19 (54)	32 (60)	51 (58)
eGFR (mL/ms), *n* (%)			
>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, *n* (%)			
150 mg	18 (52)	18 (34)	36 (41)
110 mg	16 (46)	34 (64)	50 (57)
Other	1 (2.9)[a]	1 (1.9)[b]	2 (2.3)
Dabigatran indication, *n* (%)			
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), *n* (%)			
<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)			
n (%)	8 (22)	30 (57)	38 (43)
Above normal range, *n* (%)	8 (100)	24 (80)	32 (84)
Dabigatran (ECT/dTT) (s)			
n (%)	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)

AF, atrial fibrillation; aPTT, activated partial thromboplastin time; bid, twice a day; dTT, diluted thrombin time; ECT, ecarin clotting time; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drugs; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; TT, thrombin time; VTE, venous thromboembolism.
[a]Patient used 75 mg dabigatran bid.
[b]Patient used rivaroxaban.

bleeding (one patient). Other causes of death after 5 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.

Table 3 Bleeding events and interventions of 88 patients who received idarucizumab

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)

All data is presented as *n* (%).

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 haemostasis 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, 40% of interventions could have been delayed for at least 8 h 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 dTT and the 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

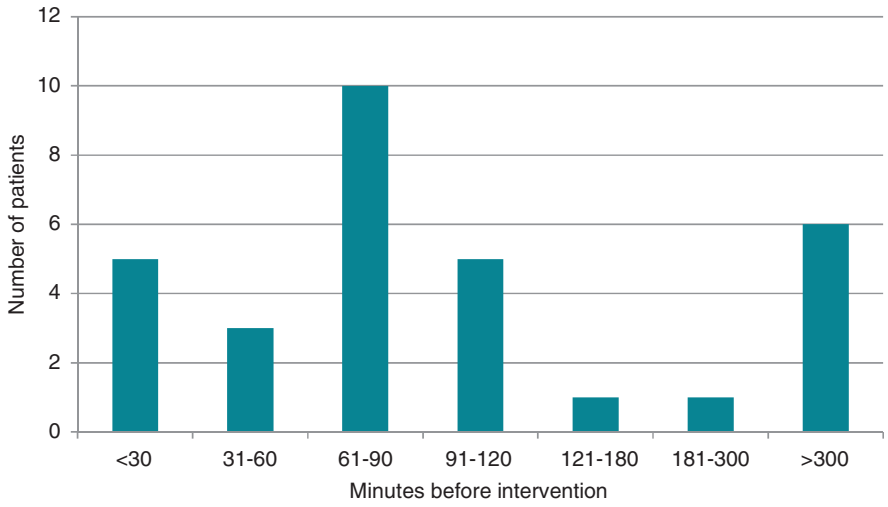

Figure 1 Time between first idarucizumab infusion and initiation of procedure in 31 patients in whom this duration could be determined.

Table 4 Effectiveness of haemostasis in 53 patients with bleeding events

	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[a]	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)

GI, gastrointestinal; ICH, intracranial haemorrhage; IQR, interquartile range.
[a]Other bleedings were: lung, retroperitoneal, and skin or fractures.

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 haemostasis 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.*[15,16] evaluating the use of prothrombin complex concentrates (PCC) in VKA. This similar effectiveness indicates that these reversal agents are all effective or, alternatively, have minimal or no effect. In this study, bleeding localization was not related to effectiveness. However, as may be expected, failure to achieve effective haemostasis 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 REVERSE 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 analyse 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 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 whom 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 European Society of Cardiology (ESC) consensus recommends resumption after major bleeding as soon as the

Table 5 Characteristics of patients with 90-day adverse outcome

Event	Time from idarucizumab (days)	Time until restart of anticoagulation (days)		Age (years)	Dabigatran dose bid (mg)	Type of index bleeding
		Parenteral[a]	Dabigatran			
Thromboembolism						
Ischaemic stroke	1	2	Unknown	65	150	Pericardial
Fatal pulmonary embolism	5	–	–	92	110	ICH
Ischaemic 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

bid, bid, twice a day; GI, gastrointestinal; ICH, intracranial haemorrhage.
[a]Therapeutic dosage.

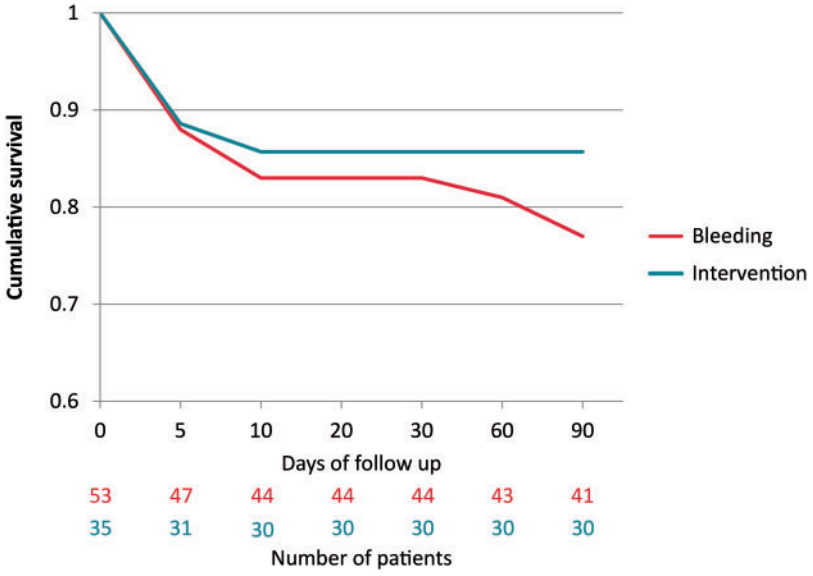

Figure 2 The Kaplan–Meier 90-day survival curve of 88 patients after idarucizumab administration, stratified by reason for usage.

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.

Limitations

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 haemostatic 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.

Conclusion

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 haemostasis, which was associated with a lower mortality risk compared with patients with ineffective haemostasis. Clinical outcome of patients treated with idarucizumab was similar to those observed in the REVERSE AD trial,[6] comprising (fatal) re-bleeds and thromboembolism, and a high-mortality rate.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

We would like to acknowledge the help received from Dr Paula Ypma (Department of Hematology, Haga Medical Center, The Netherlands), Dr Cilia Henkens (Department of Hematology, Rivierenland Hospital, The Netherlands), Dr Peter Westerweel (Department of Hematology, Albert Schweitzer Hospital, The Netherlands), and Dr Evert-Jan de Kruijf (Department of Hematology, Hospital Gelderse Vallei, The Netherlands) who contributed to data retrieval for the present analysis.

Conflict of interest: none declared.

References

1. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta- analysis. *J Thromb Haemost* 2014;**12**:320–8.
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**:1139–51.
3. Boehringer Ingelheim Inc. *Praxbind (idarucizumab) prescribing information: Food and Drug Administration (FDA)*. 2015. http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf (16 July 2015, date last accessed).
4. van Ryn J, Stangier J, Haertter S, Liesenfeld K-H, Wienen W, Feuring M *et al.* Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010;**103**:1116–27.
5. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J *et al.* A specific antidote for dabigatran: functional and structural characterization. *Blood* 2013; **121**:3554–62.
6. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA *et al.* Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med* 2017; **377**:431–41.
7. Vornicu O, Larock AS, Dincq AS, Douxfils J, Dogne JM, Mullier F *et al.* Idarucizumab for the treatment of hemorrhage and dabigatran reversal in patients requiring urgent surgery or procedures. *Expert Opin Biol Ther* 2017;**17**: 1275–96.
8. Kermer P, Eschenfelder CC, Diener HC, Grond M, Abdalla Y, Althaus K *et al.* Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany—a national case collection. *Int J Stroke* 2017;**12**: 383–91.
9. Raval AN, Cigarroa JE, Chung MK, Diaz-Sandoval LJ, Diercks D, Piccini JP *et al.* Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: a scientific statement from the American Heart Association. *Circulation* 2017;**135**:e604–33.
10. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
11. Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JI. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost* 2016;**14**:623–7.
12. Khorsand N, Majeed A, Sarode R, Beyer-Westendorf J, Schulman S, Meijer K. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. *J Thromb Haemost* 2016;**14**:211–4.
13. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–4.
14. Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. *Thromb Haemost* 2015;**113**:931–42.
15. Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL *et al.* Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013;**128**:1234–43.
16. Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A *et al.* Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med* 2016;**375**:1131–41.
17. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M *et al.* Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015;**46**:2032–60.
18. Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L *et al.* Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost* 2018;**118**:842–51.
19. Majeed A, Agren A, Holmstrom M, Bruzelius M, Chaireti R, Odeberg J *et al.* Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood* 2017;**130**:1706–12.
20. Halvorsen S, Storey RF, Rocca B, Sibbing D, Ten Berg J, Grove EL *et al.* Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J* 2017;**38**: 1455–62.