Global Use of Idarucizumab in Clinical Practice: Outcomes of the RE-VECTO Surveillance Programme

Journal:	*Thrombosis and Haemostasis*
Manuscript ID	TH-19-03-0179.R1
Manuscript Type:	Original Article: Coagulation and Fibrinolysis
Category:	Clinical Studies
Date Submitted by the Author:	n/a
Complete List of Authors:	Fanikos, John; Brigham and Women's Hospital Murwin, Debra; Boehringer Ingelheim Pharmaceuticals Gruenenfelder, Fredrik; Boehringer Ingelheim International GmbH Tartakovsky, Igor; Boehringer Ingelheim International GmbH França, Lionel Riou; Boehringer Ingelheim International GmbH Reilly, Paul; Boehringer Ingelheim Pharmaceuticals Inc, Clinical Research Kermer, Pawel; Nordwest-Krankenhaus Sanderbusch and University Medicine Göttingen von Wowern, Frederik; University Hospitals of Skåne – Malmö Lane, Deirdre; Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital
Keywords:	anticoagulation, idarucizumab, dabigatran etexilate, real-world utilisation, reversal agent

SCHOLARONE™
Manuscripts

Fanikos_RE-VECTO ms_9July2019

Global Use of Idarucizumab in Clinical Practice: Outcomes of the RE-VECTO Surveillance

Programme

John Fanikos[1], Debra Murwin[2], Fredrik Gruenenfelder[3], Igor Tartakovsky[3], Lionel Riou

França[3], Paul A Reilly[2], Pawel Kermer[4], Frederik von Wowern[5], Deirdre A Lane[6], Ken Butcher[7]

[1]Brigham and Women's Hospital, Boston, Massachusetts, United States

[2]Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut, United States

[3]Boehringer Ingelheim International GmbH, Ingelheim, Germany

[4]Department of Neurology, Nordwest-Krankenhaus Sanderbusch and University Medicine

Göttingen, Göttingen, Germany

[5]University Hospitals of Skåne – Malmö, Skåne, Sweden

[6]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart &

Chest Hospital, Liverpool, United Kingdom

[7]Prince of Wales Clinical School, University of New South Wales, Sydney, Australia and

Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

Correspondence to: John Fanikos, RPh, MBA

Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA

Tel: +1 617 732-7165 (office); +1 617-605-3237 (mobile)

Email: jfanikos@bwh.harvard.edu; jfanikos@partners.org

Running head: The RE-VECTO surveillance programme

Target journal: *Thrombosis and Haemostasis*

Fanikos_RE-VECTO ms_9July2019

Word Count (max. 5000 excluding tables/figures/refs): 2984 (including headings and

subheadings)

References (max. 50): 22

Tables/Figures (no limit [online-only suppl. material is encouraged]): 4/2

Keywords (max. 5): anticoagulation, idarucizumab, dabigatran etexilate, real-world

utilisation, reversal agent

Summary table

What is known on this topic
- Limited data are available that describe idarucizumab utilisation in routine clinical practice.   - Post-marketing observational studies can provide insight into the use of medications in the real world where there is a broad patient population with various comorbidities and concomitant therapies.
What this paper adds
- It provides the first insight into how a NOAC reversal agent is used in the real-world setting, examining where idarucizumab is prescribed (across regions and within hospitals), the patients who receive idarucizumab, and why they received it.   - The RE-VECTO study confirmed that 5 g of idarucizumab was used appropriately in > 98% of dabigatran-treated patients with life-threatening bleeding or in need of emergency surgery.

Fanikos_RE-VECTO ms_9July2019

- Idarucizumab use was generally consistent with the data collected in the clinical trial

  setting with minimal off-label prescribing.

Fanikos_RE-VECTO ms_9July2019

Abstract

Idarucizumab was approved for the reversal of dabigatran in 2015. We investigated whether post-approval usage patterns of idarucizumab in a real-world setting reflect those observed in the pivotal trials. No safety or efficacy data were collected in this medical record-based observational study. RE-VECTO, a global post-approval, international, surveillance programme, involved hospital pharmacies in countries where idarucizumab was licensed and dispensed (August 2016 to June 2018). Characteristics of sites prescribing idarucizumab and of eligible patients (≥ 18 years old and receiving idarucizumab regardless of prior oral anticoagulant use), as well as idarucizumab utilisation data, were collected and analysed descriptively. Sixty-one sites enrolled 359 patients. Most pharmacies (85.2%) were centralised, and the median idarucizumab units stocked per hospital was 2.0 (interquartile range, 1.0 to 3.0). Almost three-quarters of patients were elderly (74.9% aged > 70 years), and only four (1.1%) had received idarucizumab before. Nearly all patients were treated with dabigatran (97.5%). There was low usage of unapproved dabigatran dosage regimens (3.3%). Life-threatening or uncontrolled bleeding was the most frequent indication for idarucizumab (57.7%), followed by emergency surgery/urgent procedure (35.9%). Of the life-threatening bleeding events, the most frequent were gastrointestinal tract (44.4%) and intracranial (38.6%). Most patients (95.0%) were given the full dose of two vials (2 × 2.5 g) of idarucizumab initially, and very few (1.7%) received a second dose. Of those patients requiring emergency or scheduled/planned surgery/procedures, 25.5% underwent gastrointestinal and/or abdominal surgery/procedures. Real-world usage patterns of idarucizumab provide valuable insights into emergency reversal strategies. Off-label use was minimal.

Fanikos_RE-VECTO ms_9July2019

Introduction

Anticoagulant reversal is central to the management of uncontrolled bleeding in

anticoagulated patients and, where possible, in those on anticoagulants who require

emergency surgery or other invasive procedures.[1] The strategy undertaken to attempt

reversal will vary according to the type of anticoagulant in use and availability of reversal

agents. Non-vitamin K antagonist oral anticoagulants (NOACs), including the direct thrombin

inhibitor dabigatran and the factor Xa antagonists (rivaroxaban, apixaban, edoxaban and

betrixaban), are now recommended in guideline statements as the preferred agents in most

clinical settings due to their similar efficacy and lower bleeding risk compared with vitamin K

antagonists (VKAs).[2-4] Reversal of NOACs was not possible until 2015, when idarucizumab

became commercially available in the United States of America (USA) and European Union

(EU) for the specific reversal of dabigatran.[5,6] Andexanet alfa was approved in 2018 in the

USA for the treatment of rivaroxaban- and apixaban-associated bleeding in patients, but is

not yet available elsewhere, nor is it approved for use in surgical patients.[7] Prior to this,

treatment was limited to non-specific empiric approaches (e.g. administration of blood or

blood derivatives, or waiting until anticoagulant activity had waned). Non-specific

approaches are still used in countries that have no approved specific reversal agents, and in

bleeding associated with oral anticoagulants (OACs) for which there are no specific reversal

agents available.

Idarucizumab is a humanised mouse monoclonal antibody fragment that binds directly

to dabigatran with high affinity, reversing its anticoagulant effects within minutes.[8,9] In the

phase III RE-VERSE AD (NCT02104947) trial, idarucizumab rapidly and completely reversed

dabigatran's anticoagulant effect in almost all patients with life-threatening or uncontrolled

Fanikos_RE-VECTO ms_9July2019

bleeding or those requiring emergency surgery or procedures. In addition, no safety

concerns, specifically anaphylaxis or pro-thrombotic effects, were reported.[10] Dabigatran is

indicated to reduce the risk of stroke and systemic embolism in non-valvular atrial

fibrillation, to treat deep venous thrombosis (DVT) and pulmonary embolism (PE), to

prevent recurrent DVT, and PE in adults (DVT/PE) and for primary prevention of VTE in

orthopaedic surgery.[11,12] Idarucizumab (5 g initially; two 50 mL vials each containing 2.5 g

idarucizumab constitute one complete 5 g dose [a second 5 g dose may be considered under

specific clinical circumstances]) is indicated in adult patients when rapid reversal of

dabigatran is required for life-threatening or uncontrolled bleeding or emergency

surgery/urgent procedures.[13,14]

In order to characterise the utilisation of idarucizumab and provide data on usage

patterns in a real-world setting, RE-VECTO, a global drug administration surveillance

programme, was initiated.

Methods and Analysis

Programme Design and Participants

RE-VECTO, an international, multicentre, cross-sectional surveillance programme, was a

post-approval study commitment for the European regulatory authorities. RE-VECTO

involved hospital pharmacies or departments in North America, the European Union, and

the Asia-Pacific region, where idarucizumab was dispensed between August 2016 and June

2018, depending on marketing authorisation, country regulations and requirements, and

availability of the protocol.

Fanikos_RE-VECTO ms_9July2019

In countries where idarucizumab was approved, potential sites where idarucizumab was dispensed were identified and invited to register; after which data were collected via a retrospective chart review. Initially, all centres who ordered idarucizumab were sent a welcome pack and invited to register on the website. The response rate was low and the process was redefined to include only those centres that ordered and then restocked idarucizumab. However, this was not necessarily indicative of use of idarucizumab as reorders could be for multiple reasons (i.e. supplying satellite locations within the hospital or towards the end of the trial- replacing expired product). In total, over 2000 invitations were sent, and other methods were used to narrow site selection to those with known patients receiving the product (i.e. claims data or medical science liaison conversations). All centres who registered, completed required training, and finalized the required trial documents were activated, regardless if they had an identified patient or not.

Idarucizumab was prescribed at the discretion of the treating physician and not influenced by participation in the programme. Prescription of idarucizumab other than indicated by the label was considered as off-label use, such as an unapproved indication (e.g. elective surgery), an unapproved dose (e.g. 2.5 g), or treatment of a patient who did not receive dabigatran. Patients aged ≥ 18 years receiving idarucizumab as part of their clinical care were eligible, regardless of prior OAC use. Any patients participating in a dabigatran or idarucizumab clinical trial were excluded.

Informed consent was not required because the programme was based on anonymised data. The protocol was approved by an independent ethics committee where necessary, based on country-specific regulations.

Data Collection

Fanikos_RE-VECTO ms_9July2019

In patients treated with idarucizumab, anonymised patient data were entered into an

electronic data capture system via an internet portal. A pre-specified data-management

plan and pre-specified rules generated auto-queries for missing fields, and data listing

reviews were conducted prior to database lock. Patient demographics such as age

categories and previous anticoagulant use (e.g., last intake of dabigatran etexilate or other

OACs), were collected. Previous antiplatelet treatment, safety and efficacy data were not

collected.

Idarucizumab utilisation, including the reason for idarucizumab use (life-threatening or

uncontrolled bleeding requiring medical intervention, or emergency surgery or other urgent

medical procedure necessitating rapid reversal of the anticoagulant effect of dabigatran),

was recorded. Information regarding the location of the bleeding event (gastrointestinal

tract, intracranial, post-procedural, skin, urogenital tract, undefined location, other defined

location) was also collected. In addition, the dosage and timing of idarucizumab

administration (total dose administered and the time interval between administration of the

first and second vials [the standard approved dosage is 2 × 2.5 g vials]), whether

idarucizumab administration was discontinued prematurely, and the care setting (for

example, emergency department, intensive care unit or operating Room) were recorded.

The characteristics of the hospital pharmacy were collected for each participating site

to evaluate the diversity of sites, including: country, whether the pharmacy was central or

decentralised, the number of pharmacy units within the hospital if there is no central

pharmacy (e.g. the emergency department, intensive care unit or operating room),

idarucizumab stocks, storage location, distribution channels within the hospital, type of

Fanikos_RE-VECTO ms_9July2019

practice (academic, non-academic, private or public) and availability of electronic

prescription records at the pharmacy.

Statistical Analysis

The programme sample size was driven by regulatory requirements, and idarucizumab

usage and provider participation. A minimum of 300 patients was requested by the

European Medicines Agency.

Data from all enrolled patients who received idarucizumab were analysed using

descriptive statistics (generated using SAS® version 9.2 or higher [SAS Institute, Cary, NC,

USA]). Categorical variables were summarised as numbers and proportions. Continuous

variables are reported as mean (standard deviation [SD]) or median (interquartile ranges

[IQR]). Subgroups analysed included; region, indication for use of idarucizumab, age, prior

administration of idarucizumab, department where idarucizumab was administered,

bleeding event location and type, and whether the bleeding was life-threatening. Missing

data were not imputed.

Results

Characteristics of Sites Prescribing Idarucizumab

Of the 132 registered hospitals, 61 sites enrolled 359 patients (eight sites in the Asia Pacific

region, 42 sites in the EU, and 29 sites in North America). Just over half (52.5%]) were non-

academic institutions, and the majority were public hospitals (67.2%]) (**Table 1**).

Most pharmacies (85.2%) were centralised. In sites with decentralised pharmacies, the

median number of pharmacy units per hospital was 8.0 (IQR 2.0–9.0) (**Table 1**). The majority

Fanikos_RE-VECTO ms_9July2019

of hospitals (78.7%) had electronic prescription and electronic medical records available,

and stored idarucizumab in the primary pharmacy (67.2%). Other storage locations including

satellite pharmacies, Emergency Department, Intensive Care Unit or Operating Room, and

other specialist departments (Cardiology and Neurology). The median total idarucizumab

units (one unit = 2 × 2.5 g vials) stocked per hospital pharmacy in all storage locations was

2.0 (IQR 1.0 to 3.0).

Characteristics of Patients Treated with Idarucizumab

Of the 359 enrolled patients, most were either in the EU (152/359 [42.3%]) or North

America (157/359 [43.7%], of whom 140 were enrolled in the USA) (**Table 2**). The majority

of patients were treated in hospitals that were academic (208/359 [57.9%]) and public

(238/359 [66.3%]).

Four (1.1%) patients had received idarucizumab previously, and this information was

missing for 50 (13.9%) patients. Most patients were aged > 70 years (74.9%) and 85.0% had

not received idarucizumab before (98.7% if excluding the 50 patients with unknown prior

use). The dose and last intake of previous anticoagulant medications (dabigatran and/or

other) is shown in **Table 3**. All patients had received an anticoagulant before recruitment.

Dabigatran was the last anticoagulant used by most patients (97.5%), and of these, only two

(0.6%) patients were taking dabigatran and another oral or parenteral anticoagulant (both

had life-threatening or uncontrolled bleeding). Of the nine patients without dabigatran

documented as their last anticoagulant medication, four had received rivaroxaban or an

unknown anticoagulant, and one had received apixaban. Dabigatran dosage regimens (eight

types were recorded) were known for 332 patients, with the most frequent being 150 mg

twice daily (bid; 52.4%) and 110 mg bid (35.8%). Of those patients receiving dabigatran 110

Fanikos_RE-VECTO ms_9July2019

mg bid or 150 mg bid, 89.9% and 60.3% were aged > 70 years. The dose of dabigatran was

not recorded for 18 (5.0%) patients.

Utilisation of Idarucizumab

Most patients (341/359 [95.0%]) received the full dose (2 × 2.5 g) of idarucizumab, with the

mean (SD) time between vials being 15.3 (8.6) minutes (**Table 4**); time between two vials

was missing for 123/341 (36.1%) patients. Of the 18 patients who were documented as not

receiving the full dose of idarucizumab initially, 12 received one vial (2.5 g) and the dose was

unknown for the other six. A second treatment with 5 g of idarucizumab, based on clinical

signs in combination with coagulation tests, was administered to six patients (1.7%), either

in the Emergency Department (*n* = 2) or Intensive Care Unit (*n* = 4). The mean (SD) time

between vials for the second treatment was 14.0 (7.1) minutes, with the time between two

vials missing in 2/6 (33.0%) patients. Of the six patients requiring a second full dose of

idarucizumab, five given idarucizumab for initial life-threatening or uncontrolled bleeding

required the second treatment for additional urgent intervention (*n* = 1) or for re-

bleeding/prolonged coagulation test (*n* = 4); one patient given idarucizumab initially for

emergency surgery/urgent medical procedures required the second treatment for

prolonged re-bleeding/prolonged coagulation test. No adverse events were reported in any

patient.

Idarucizumab was primarily administered in the Emergency Department (209/359

[58.2%]). Bleeding was the most frequent indication for the administration of idarucizumab

(207/359 [57.7%] patients), followed by emergency surgery/urgent procedure (129/359

[35.9%] patients). This pattern was consistent in most departments, except for the surgical

department.

Fanikos_RE-VECTO ms_9July2019

The most frequent bleeding events were gastrointestinal (GI) tract (92/207 [44.4%] of patients) and intracranial (80/207 [38.6%]) (**Fig. 1**). Most patients with GI bleeding (88/92 [95.7%]) received the full dose (2 × 2.5 g) of idarucizumab, with the mean (SD) time between vials being 15.2 (9.8) minutes. Similarly, the majority of patients with intracranial bleeding (76/80 [95.0%]) received the full dose of idarucizumab, with the mean (SD) time between vials being 16.3 (7.1) minutes. Of the 194/207 (93.7%) patients who received the full dose (2 × 2.5 g) of idarucizumab for a bleeding event, the time between two vials was not available for 68/194 (35.1%) patients. For those patients who received the full dose (2 × 2.5 g) of idarucizumab for GI or intracranial bleeding events, the time between two vials was not available for 28/88 (31.8%) and 25/76 (32.9%) patients, respectively. Four patients (1.1%) were reported to have prematurely discontinued idarucizumab, with none due to adverse events.

Of the 141 (39.3%) patients who were administered idarucizumab for emergency or for scheduled or planned surgery/procedure (**Fig. 2**), GI and/or abdominal surgery or procedures were most frequently performed (in 36 [25.5%] of patients), followed by orthopaedic procedures (in 31 [22.0%] patients), thoracic surgery including cardiac surgery (23 [16.3%] patients), and vascular operations (in 20 [14.2%] patients). Of the 23 patients who received idarucizumab for thoracic surgery including cardiac surgery, six patients underwent cardiac catheterization, three patients had a cardiac pacemaker insertion or removal, one patient had a central venous catheterization, and five patients had a pericardial excision and pericardial drainage. No intra-procedural bleeds were reported. The study also included patients who required rapid reversal of the anticoagulant effect of dabigatran prior to thrombolysis (*n* = 12) and thrombectomy (*n* = 2). On average, data were missing for 6.4% of patients with regard to the type of surgery/procedure; 8/129 (6.2%)

Fanikos_RE-VECTO ms_9July2019

patients who underwent emergency surgery or other urgent medical procedures, and 1/12

(8.3%) patients who underwent scheduled or planned surgery/procedures.

Discussion

The RE-VECTO post-approval surveillance study has shown that sites prescribing

idarucizumab were mainly non-academic institutions and public hospitals, with

approximately two doses of idarucizumab stored on-site. Most of the patients were

European or North American. More than half of the registered hospitals either registered

proactively prior to identification of a patient treated with idarucizumab or had historical

cases of patients treated with idarucizumab but did not enter patients into the registry. Of

those sites that entered patient data, as expected, dabigatran was the anticoagulant used

by most patients. Nearly all patients received the full dose (2 × 2.5 g) of idarucizumab, with

only one full dose required in almost all patients. There was minimal off-label dosing (e.g.,

use of 2.5 g in 12 patients), and administration of idarucizumab to seven patients using FXa

inhibitors (without dabigatran) was reported. . As expected, idarucizumab was most

frequently given in the Emergency Department, and bleeding (the most common locations

being GI tract and intracranial) was the most frequent reason for administering

idarucizumab.

The findings from RE-VECTO describing idarucizumab uptake, dabigatran prescribing

patterns and patient characteristics in the real-world setting add to the idarucizumab clinical

trial data and few case collections available to date.[10,15-22] While the patients in RE-VECTO

were less well characterized due to the limitations of data collection, outcomes were largely

consistent with those observed in the clinical trial setting with regard to indications, rates of

bleeding and emergent surgery events. In addition, RE-VECTO demonstrates that the real-

Fanikos_RE-VECTO ms_9July2019

world usage of idarucizumab was mostly as recommended in the label. Moreover, the

reversal of dabigatran in RE-VECTO rarely required a second round of idarucizumab dosing

(< 2% of patients), supporting the findings from the RE-VERSE-AD study in which a second

round of dosing was required in 1.6% patients.[10] In addition, the reversal of dabigatran in

the real-world setting involved a mainly elderly population treated with several different

dabigatran dosage regimens. In RE-VERSE-AD, the median age was 78 (range, 21–96) years,

and > 97% of patients received one of three approved dosage regimens of dabigatran

(150/110/75 mg bid).

Aside from idarucizumab, one other reversal agent, andexanet alfa, is available

commercially in the USA for the reversal of rivaroxaban- and apixaban-related bleeding only,

following positive results from clinical trials.[23,24] Another potential FXa inhibitor reversal

agent, ciraparantag, has yet to begin phase II or III evaluation in patient settings; phase II

data in healthy volunteers administered rivaroxaban (NCT03172910) or apixaban

(NCT03288454) are expected in 2019.

The RE-VECTO surveillance programme was designed to collect data on drug use in a

simple and effective way, although the voluntary registration design and/or resource

limitations may have reduced participation and resulted in some incomplete datasets. Some

recruited sites known to be prescribing idarucizumab did not enter patient data in the

registry during the specified time period for data collection, and were not actively surveyed.

Data listing reviews conducted prior to database lock did not involve an independent data

review committee, and on-site source data verification was not conducted. Administration

of idarucizumab is rare, and without patient data being entered into the registry, we are

unable to ascertain whether these sites were re-stocking idarucizumab, supplying satellite

Fanikos_RE-VECTO ms_9July2019

locations within the hospital, replacing expired idarucizumab, or administering idarucizumab

to patients. Nevertheless, drug surveillance programmes are one source of real-world

data,[25] that are particularly useful for identifying improper use. By identifying potential risks,

action can be taken to help minimise the risk of adverse drug reactions resulting from

medication errors. This study assessed idarucizumab utilization in a pre-defined sample of

prescriptions in the clinical practice setting, based on medical and pharmacy record review.

This approach was in line with post-marketing surveillance requested by the European

Medicines Agency.

Conclusion

Real-world information from the RE-VECTO surveillance programme adds to the data

obtained from idarucizumab clinical trials and provides valuable insights into the current

strategies employed to reverse the anticoagulation effects of dabigatran in emergency

situations. Usage patterns of idarucizumab were aligned with idarucizumab prescribing

information, with minimal off-label use.

Acknowledgements

Authors' contributions

All authors were involved with designing the surveillance programme, provided critical

review of the article and approved the final version for publication.

Funding

Fanikos_RE-VECTO ms_9July2019

Disclosure of interests

John Fanikos has consulted for Boehringer Ingelheim, Genentech, and Portola.

Debra Murwin, Fredrik Gruenenfelder, Paul A Reilly and Igor Tartakovsky are employees of

Boehringer Ingelheim.

L Riou França was an employee of Boehringer Ingelheim at the time of manuscript writing

and is now employed by Sanofi-Aventis.

Deirdre A Lane has received investigator-initiated educational grants from Bristol-Myers

Squibb and Boehringer Ingelheim; has been a speaker for Boehringer Ingelheim, Bayer, and

Bristol-Myers Squibb/Pfizer; and has consulted for Bristol-Myers Squibb, Bayer, Boehringer

Ingelheim, and Daiichi-Sankyo.

Pawel Kermer served as a speaker/has consulted for Boehringer Ingelheim, Bayer,

BMS/Pfizer and Portola.

Frederik Von Wowern served as a speaker/has consulted for Boehringer Ingelheim, Bayer,

BMS/Pfizer, Takeda and Leo Pharma.

Ken Butcher has served on advisory boards, received investigator-initiated research grants

and served as a speaker for Boehringer Ingelheim, Bayer and BMS/Pfizer.

Fanikos_RE-VECTO ms_9July2019

Fanikos_RE-VECTO ms_9July2019

References

1   Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. Thromb Haemost 2015;113:931-942

2   Das A, Liu D. Novel antidotes for target specific oral anticoagulants. Exp Hematol Oncol 2015;4:25

3   Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-2962

4   Macle L, Cairns J, Leblanc K, et al. 2016 Focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2016;32:1170-1185

5   European Medicines Agency. 2015. Idarucizumab summary of product characteristics. https://www.ema.europa.eu/documents/product-information/praxbind-epar-product-information_en.pdf. Accessed October 10, 2018.

6   US Food and Drug Administration. 2015. Idarucizumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf. Accessed October 10, 2018.

7   US Food and Drug Administration. 2018. Andexanet alfa prescribing information. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM606687.pdf. Accessed October 10, 2018.

8   Eikelboom JW, Quinlan DJ, van Ryn J, et al. Idarucizumab: the antidote for reversal of dabigatran. Circulation 2015;132:2412-2422

9   Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. Blood 2013;121:3554-3562

10   Pollack CV, Jr., Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med 2017;377:431-441

11   European Medicines Agency. Dabigatran etexilate. Summary of Product Chacrateristics. https://www.ema.europa.eu/documents/product-information/pradaxa-epar-product-information_en.pdf. Accessed October 10, 2018.

12   US Food and Drug Administration. Dabigatran etexilate prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022512s035lbl.pdf. Accessed October 10, 2018.

13   European Medicines Agency. Idarucizumab. Summary of Product Characteristics. https://www.ema.europa.eu/documents/product-information/praxbind-epar-product-information_en.pdf. Accessed October 10, 2018.

14   US Food and Drug Administration. Idarucizumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf. Accessed October 10, 2018.

15   Pollack CV, Jr., Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-520

16   Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet 2015;386:680-690
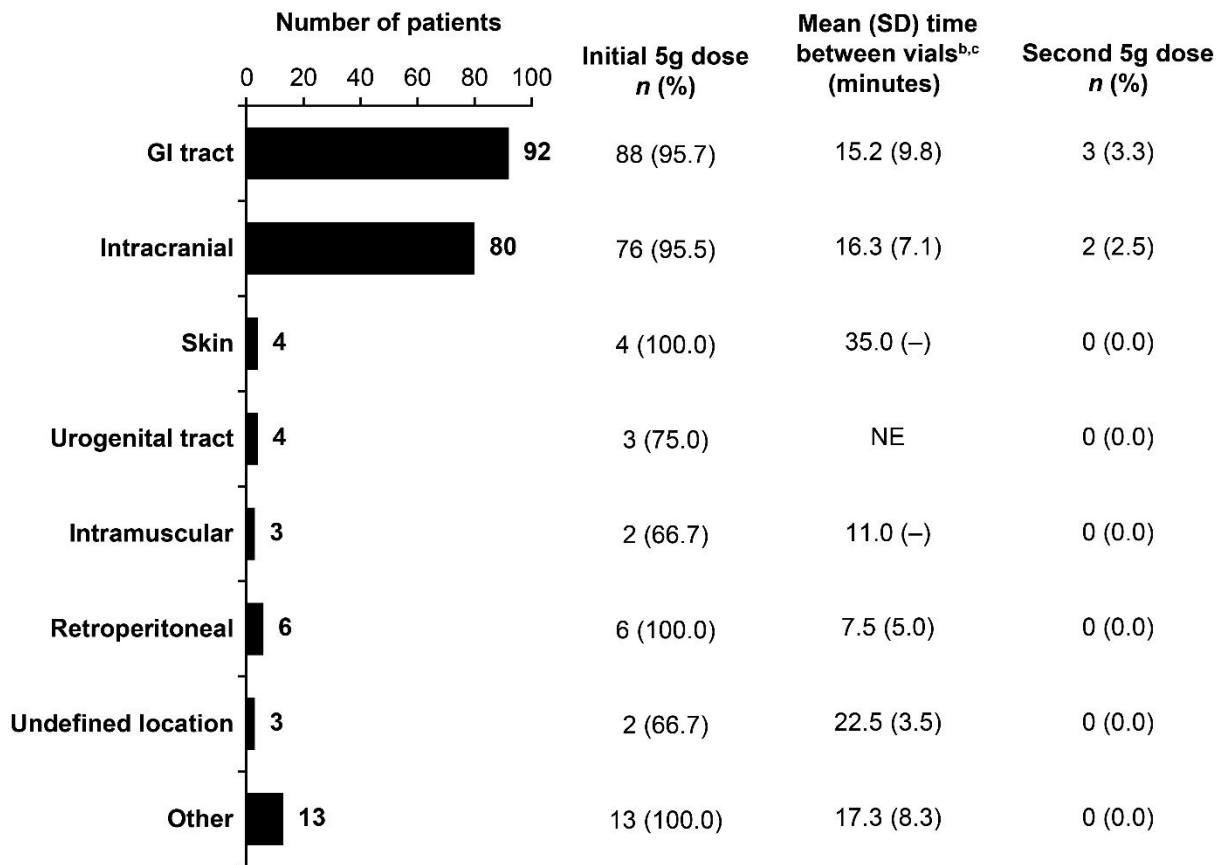
Fanikos_RE-VECTO ms_9July2019

17   van Ryn J, Yasaka M, Ikushima I, et al. Idarucizumab, a specific reversal agent for dabigatran: immediate, complete and sustained reversal of dabigatran-induced anticoagulation in Japanese healthy male volunteers. Blood 2016;128(suppl 22):2627

18   Glund S, Stangier J, van Ryn J, et al. Effect of age and renal function on idarucizumab pharmacokinetics and idarucizumab-mediated reversal of dabigatran anticoagulant activity in a randomized, double-blind, crossover phase Ib study. Clin Pharmacokinet 2017;56:41-54

19   Glund S, Stangier J, Schmohl M, et al. Idarucizumab, a specific antidote for dabigatran: immediate, complete and sustained reversal of dabigatran induced anticoagulation in elderly and renally impaired subjects. Blood 2014;124(suppl 21):344

20   Fang CW, Tsai YT, Chou PC, et al. Intravenous thrombolysis in acute ischemic stroke after idarucizumab reversal of dabigatran effect: Analysis of the cases from Taiwan. J Stroke Cerebrovasc Dis 2019;28:815-820

21   Kermer P, Eschenfelder CC, Diener HC, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany - A national case collection. Int J Stroke 2017;12:383-391

22   van der Wall SJ, van Rein N, van den Bemt B, et al. Performance of idarucizumab as antidote of dabigatran in daily clinical practice. Europace 2018

23   Connolly SJ, Milling TJ, Jr., Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;375:1131-1141

24   Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015;373:2413-2424

25   Martin K, Begaud B, Latry P, et al. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol 2004;57:86-92

Fanikos_RE-VECTO ms_9July2019

<FIGURE LEGENDS>

Fig. 1 Location of bleeding[a] events (*N* = 207) leading to idarucizumab use, and idarucizumab use by bleeding location.

Number of patients	Initial 5g dose n (%)	Mean (SD) time between vials[b,c] (minutes)	Second 5g dose n (%)
GI tract — 92	88 (95.7)	15.2 (9.8)	3 (3.3)
Intracranial — 80	76 (95.5)	16.3 (7.1)	2 (2.5)
Skin — 4	4 (100.0)	35.0 (–)	0 (0.0)
Urogenital tract — 4	3 (75.0)	NE	0 (0.0)
Intramuscular — 3	2 (66.7)	11.0 (–)	0 (0.0)
Retroperitoneal — 6	6 (100.0)	7.5 (5.0)	0 (0.0)
Undefined location — 3	2 (66.7)	22.5 (3.5)	0 (0.0)
Other — 13	13 (100.0)	17.3 (8.3)	0 (0.0)

[a]Life-threatening or uncontrolled bleeding requiring medical intervention.

[b] Calculated only for those patients administered total dose of 5 g (2 vials), and defined as the end time of second vial minus the start time of the first vial. If the start or end time of dosing was unknown, the estimated time of total infusion was used; if this estimate was not known, then time was set to missing.

[c] Missing data for 28 patients with gastrointestinal tract bleeding, 25 with intracranial bleeding, 3 with skin bleeding, 3 with urogenital tract bleeding, 1 with intramuscular bleeding, 2 with retroperitoneal bleeding, and 6 with other bleeding locations.
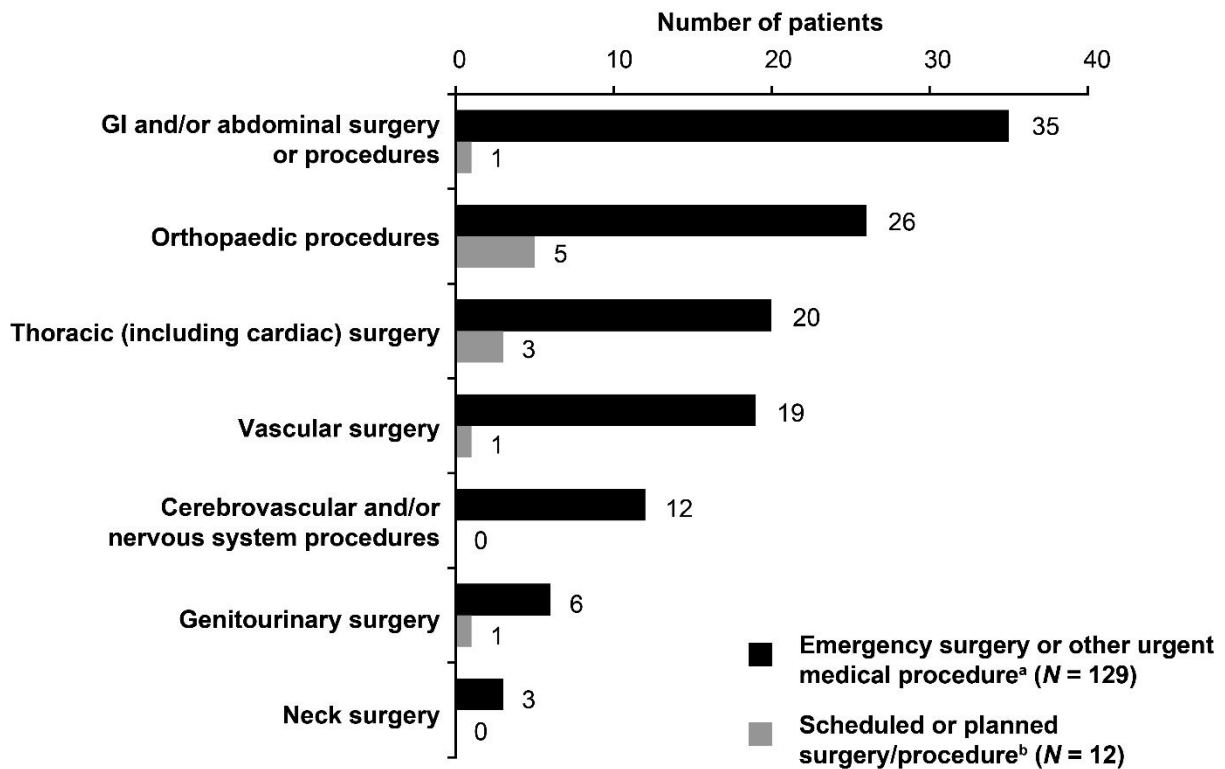
Fanikos_RE-VECTO ms_9July2019

Abbreviations: GI, gastrointestinal; NE, not evaluable; SD, standard deviation.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Fanikos_RE-VECTO ms_9July2019

Fig. 2 Type of surgery or procedure by indication for idarucizumab use.

Number of patients

Category	Value
GI and/or abdominal surgery or procedures	35 / 1
Orthopaedic procedures	26 / 5
Thoracic (including cardiac) surgery	20 / 3
Vascular surgery	19 / 1
Cerebrovascular and/or nervous system procedures	12 / 0
Genitourinary surgery	6 / 1
Neck surgery	3 / 0

Emergency surgery or other urgent medical procedure[a] (*N* = 129)

Scheduled or planned surgery/procedure[b] (*N* = 12)

[a] Missing data for 8 patients undergoing emergency surgery or other urgent medical procedures.

[b] Missing data for 1 patient undergoing scheduled or planned surgery/procedures.

Fanikos_RE-VECTO ms_9July2019

<TABLES>

Table 1 Hospitals treating patients with idarucizumab by region

Fanikos_RE-VECTO ms_9July2019

	Asia Pacific	Europe	North America	Total
	N = 8	*N* = 24	*N* = 29	*N* = 61
Hospital type 1[a], *n* (%)				
Academic	6 (75.0)	15 (62.5)	7 (24.1)	28 (45.9)
Non-academic	2 (25.0)	9 (37.5)	21 (72.4)	32 (52.5)
Other	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.6)
Hospital type 2[a], *n* (%)				
Private	0 (0.0)	1 (4.2)	18 (62.1)	19 (31.1)
Public	8 (100.0)	23 (95.8)	10 (34.5)	41 (67.2)
Other	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.6)
Type of pharmacy, *n* (%)				
Central pharmacy	7 (87.5)	23 (95.8)	22 (75.9)	52 (85.2)
Decentralised pharmacy	1 (12.5)	1 (4.2)	7 (24.1)	9 (14.8)

Fanikos_RE-VECTO ms_9July2019

Availability of electronic prescription records at the pharmacy, *n* (%)				
Yes	4 (50.0)	16 (66.7)	28 (96.6)	48 (78.7)
No	4 (50.0)	8 (33.3)	1 (3.4)	13 (21.3)
Availability of electronic medical records at the pharmacy, *n* (%)				
Yes	5 (62.5)	16 (66.7)	27 (93.1)	48 (78.7)
No	3 (37.5)	8 (33.3)	2 (6.9)	13 (21.3)
Number of pharmacy units per hospital[b], *n* (%)	1	1	7	9
Median (IQR)				
	9.0 (9.0, 9.0)	3.0 (3.0, 3.0)	8.0 (1.0, 10.0)	8.0 (2.0, 9.0)
Total number of idarucizumab units (2 × 2.5 g) stocked per hospital pharmacy in all storage locations[c], *n* (%)	8	24	28	60

Fanikos_RE-VECTO ms_9July2019

Median (IQR)	2.0 (1.0, 3.0)	2.0 (2.0, 3.5)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)
Storage location of idarucizumab stocks[c, d], n (%)				
Primary pharmacy	5 (62.5)	11 (45.8)	25 (86.2)	41 (67.2)
Satellite pharmacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Emergency room	2 (25.0)	9 (37.5)	7 (24.1)	18 (29.5)
Other	3 (37.5)	12 (50.0)	0 (0.0)	15 (24.6)

[a] Type 1: academic sector type; Type 2: practice hospital type.

[b] Only available when type of pharmacy is decentralised pharmacy.

[c] Data for 1 hospital pharmacy missing for North America.

[d] Multiple answers possible.

Abbreviations: IQR, interquartile range.

Fanikos_RE-VECTO ms_9July2019

Table 2 Characteristics of patients treated with idarucizumab by region

Fanikos_RE-VECTO ms_9July2019

	Asia Pacific	Europe	North America	Total
	N = 50	*N* = 152	*N* = 157	*N* = 359
Age group (years), *n* (%)				
18–50	2 (4.0)	4 (2.6)	5 (3.2)	11 (3.1)
51–70	11 (22.0)	28 (18.4)	40 (25.5)	79 (22.0)
> 70	37 (74.0)	120 (78.9)	112 (71.3)	269 (74.9)
Prior administration of idarucizumab, *n* (%)				
Yes	0 (0.0)	1 (0.7)	3 (1.9)	4 (1.1)
No	48 (96.0)	129 (84.9)	128 (81.5)	305 (85.0)
Unknown	2 (4.0)	22 (14.5)	26 (16.6)	50 (13.9)
Hospital Type 1[a], *n* (%)				
Academic	41 (82.0)	108 (71.1)	59 (37.6)	208 (57.9)
Non-Academic	9 (18.0)	44 (28.9)	93 (59.2)	146 (40.7)

Fanikos_RE-VECTO ms_9July2019

Other	0 (0.0)	0 (0.0)	5 (3.2)	5 (1.4)
Hospital Type 2[a], *n* (%)				
Private	0 (0.0)	10 (6.6)	87 (55.4)	97 (27.0)
Public	50 (100.0)	142 (93.4)	46 (29.3)	238 (66.3)
Other	0 (0.0)	0 (0.0)	24 (15.3)	24 (6.7)

[a] Type 1: academic sector type; Type 2: practice hospital type.

Fanikos_RE-VECTO ms_9July2019

Table 3 Last anticoagulant medication taken prior to recruitment, according to the reason for idarucizumab administration

Fanikos_RE-VECTO ms_9July2019

	Life-threatening or uncontrolled bleeding $N = 207$	Emergency surgery or other urgent medical procedure $N = 129$	Scheduled or planned surgery/ procedure $N = 12$	Other $N = 11$	Total $N = 359$

Fanikos_RE-VECTO ms_9July2019

Anticoagulant medication, *n* (%)

Dabigatran any dose[a]	203 (98.1)	124 (96.1)	12 (100.0)	11 (100.0)	350 (97.5)[a]
Rivaroxaban any dose	3 (1.4)	1 (0.8)	0 (0.0)	0 (0.0)	4 (1.1)
Apixaban any dose	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Edoxaban any dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vitamin K antagonist	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other anticoagulant	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Unknown	2 (1.0)	4 (3.1)	0 (0.0)	0 (0.0)	6 (1.7)[b]

[a] Includes two patients who received ≥ 1 dose dabigatran plus other anticoagulant.

[b] Includes two patients who were receiving another known anticoagulant medication.

Fanikos_RE-VECTO ms_9July2019

Table 4 Idarucizumab utilisation according to the reason for idarucizumab administration

Fanikos_RE-VECTO ms_9July2019

	Life-threatening or uncontrolled bleeding[a] N = 207	Emergency surgery or other urgent medical procedure[b] N = 129	Scheduled or planned surgery/ procedure N = 12	Other N = 11	Total N = 359
Idarucizumab total dose, *n* (%)					
2.5 g (1 vial)	7 (3.4)	5 (3.9)	0 (0.0)	0 (0.0)	12 (3.3)
5 g (2 vials)	195 (94.2)	123 (95.3)	12 (100.0)	11 (100.0)	341 (95.0)
Other	5 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)	6 (1.7)

Fanikos_RE-VECTO ms_9July2019

Time between 2 vials (minutes)[c, d]

N	127	83	7	1	218
Mean (SD)	15.80 (8.72)	14.20 (8.59)	16.14 (5.70)	25.00 (–)	15.25 (8.60)

Second round of idarucizumab 5 g, n (%)

No	198 (95.7)	125(96.9)	12 (100)	11 (100)	346 (96.4)
Yes	5 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)	6 (1.7)
Unknown	4 (1.9)	3 (2.3)	0 (0.0)	0 (0.0)	7 (1.9)

Reason for second round[e], n (%)

Additional urgent intervention	1 (20.0)	0 (0.0%)	0 (0.0)	0 (0.0)	1 (16.7)
Re-bleeding/coagulation test prolongation	4 (80.0)	1 (100.0)	0 (0.0)	0 (0.0)	5 (83.3)

Fanikos_RE-VECTO ms_9July2019

Time between 2 vials for second round (minutes)[c, e, f]					
N	4	0	0	0	4
Mean (SD)	14.00 (7.12)	–	–	–	14.00 (7.12)

[a] Life-threatening or uncontrolled bleeding requiring urgent medical intervention.

[b] Emergency surgery or other urgent medical procedure necessitating rapid reversal of dabigatran prior to surgery or procedure (emergency defined as within the next 8 hours).

[c] Calculated only for those patients administered total dose of 5 g (2 vials), and defined as the end time of second vial minus the start time of the first vial. If the start or end time of dosing was unknown, the estimated time of total infusion was used; if this estimate was not known, then time was set to missing.

[d] Missing data for 68 patients in the Emergency setting, 40 in the Operating setting, 5 in the intensive care setting, and 10 in the Other setting.

[e] Among patients who had second round of dosing with 5 g of idarucizumab.

[f] Missing data for 1 patient in the Emergency and ICU settings.

Abbreviations: SD, standard deviation.

Fanikos_RE-VECTO ms_9July2019

Global Use of Idarucizumab in Clinical Practice: Outcomes of the RE-VECTO Surveillance

Programme

John Fanikos[1], Debra Murwin[2], Fredrik Gruenenfelder[3], Igor Tartakovsky[3], Lionel Riou

França[3], Paul A Reilly[2], Pawel Kermer[4], Frederik von Wowern[5], Deirdre A Lane[6], Ken Butcher[7]

[1]Brigham and Women's Hospital, Boston, Massachusetts, United States

[2]Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut, United States

[3]Boehringer Ingelheim International GmbH, Ingelheim, Germany

[4]Department of Neurology, Nordwest-Krankenhaus Sanderbusch and University Medicine

Göttingen, Göttingen, Germany

[5]University Hospitals of Skåne – Malmö, Skåne, Sweden

[6]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart &

Chest Hospital, Liverpool, United Kingdom

[7]Prince of Wales Clinical School, University of New South Wales, Sydney, Australia and

Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

Correspondence to: John Fanikos, RPh, MBA

Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA

Tel: +1 617 732-7165 (office); +1 617-605-3237 (mobile)

Email: jfanikos@bwh.harvard.edu; jfanikos@partners.org

Running head: The RE-VECTO surveillance programme

Fanikos_RE-VECTO ms_9July2019

Word Count (max. 5000 excluding tables/figures/refs): 2984040 (including headings and

subheadings)

References (max. 50): 22

Tables/Figures (no limit [online-only suppl. material is encouraged]): 4/2

Keywords (max. 5): anticoagulation, idarucizumab, dabigatran etexilate, real-world

utilisation, reversal agent

Summary table

What is known on this topic   • Limited data are available that describe idarucizumab utilisation in routine clinical practice.   • Post-marketing observational studies can provide insight into the use of medications in the real world where there is a broad patient population with various comorbidities and concomitant therapies.
What this paper adds   • It provides the first insight into how a NOAC reversal agent is used in the real-world setting, examining where idarucizumab is prescribed (across regions and within hospitals), the patients who receive idarucizumab, and why they received it.   • The RE-VECTO study confirmed that 5 g of idarucizumab was used appropriately in > 98% of dabigatran-treated patients with life-threatening bleeding or in need of emergency surgery.

Fanikos_RE-VECTO ms_9July2019

- Idarucizumab use was <u>generally</u> consistent with the data collected in the clinical trial setting with minimal off-label prescribing.

Fanikos_RE-VECTO ms_9July2019

Abstract

Idarucizumab was approved for the reversal of dabigatran in 2015. We investigated whether post-approval usage patterns of idarucizumab in a real-world setting reflect those observed in the pivotal trials. No safety or efficacy data were collected in this medical record-based observational study. RE-VECTO, a global post-approval, international, surveillance programme, involved hospital pharmacies in countries where idarucizumab was licensed and dispensed (August 2016 to June 2018). Characteristics of sites prescribing idarucizumab and of eligible patients (≥ 18 years old and receiving idarucizumab regardless of prior oral anticoagulant use), as well as idarucizumab utilisation data, were collected and analysed descriptively. Sixty-one sites enrolled 359 patients. Most pharmacies (85.2%) were centralised, and the median idarucizumab units stocked per hospital was 2.0 (interquartile range, 1.0 to 3.0). Almost three-quarters of patients were elderly (74.9% aged > 70 years), and only four (1.1%) had received idarucizumab before. Nearly all patients were treated with dabigatran (97.5%). There was a low usagefrequency of unapproved dabigatran dosage regimens (3.3%). Life-threatening or uncontrolled bleeding was the most frequent indication for idarucizumab (57.7%), followed by emergency surgery/urgent procedure (35.9%). Of the life-threatening bleeding events, the most frequent were gastrointestinal tract (44.4%) and intracranial (38.6%). Most patients (95.0%) were given the full dose of two vials (2 × 2.5 g) of idarucizumab initially, and very few (1.7%) received a second dose. Of those patients requiring emergency or scheduled/planned surgery/procedures, 25.5% underwent gastrointestinal and/or abdominal surgery/procedures. Real-world usage patterns of idarucizumab provide valuable insights into emergency reversal strategies. Off-label use was minimal. provides valuable insights into the current strategies employed to

Fanikos_RE-VECTO ms_9July2019

reverse the anticoagulation effects of dabigatran in emergency situationsclosely matched

data from the clinical trial setting, with minimal off-label use.

Fanikos_RE-VECTO ms_9July2019

Introduction

Anticoagulant reversal is central to the management of uncontrolled bleeding in anticoagulated patients and, where possible, in those on anticoagulants who require emergency surgery or other invasive procedures.[1] The strategy undertaken to attempt reversal will vary according to the type of anticoagulant in use and availability of reversal agents. Non-vitamin K antagonist oral anticoagulants (NOACs), including the direct thrombin inhibitor dabigatran and the factor Xa antagonists (rivaroxaban, apixaban, edoxaban and betrixaban), are now recommended in guideline statements as the preferred agents in most clinical settings due to their similar efficacy and lower bleeding risk compared with vitamin K antagonists (VKAs).[2-4] Reversal of NOACs was not possible until 2015, when idarucizumab became commercially available in the United States of America (USA) and European Union (EU) for the specific reversal of dabigatran.[5,6] Andexanet alfa was approved in 2018 in the USA for the treatment of rivaroxaban- and apixaban-associated bleeding in patients, but is not yet available elsewhere, nor is it approved for use in surgical patients.[7] Prior to this, treatment was limited to non-specific empiric approaches (e.g. administration of blood or blood derivatives, or waiting until anticoagulant activity had waned). Non-specific approaches are still used in countries that have no approved specific reversal agents, and in bleeding associated with oral anticoagulants (OACs) for which there are no specific reversal agents available.

Idarucizumab is a humanised mouse monoclonal antibody fragment that binds directly to dabigatran with high affinity, reversing its anticoagulant effects within minutes.[8,9] In the phase III RE-VERSE AD (NCT02104947) trial, idarucizumab rapidly and completely reversed dabigatran's anticoagulant effect in almost all patients with life-threatening or uncontrolled

6

Fanikos_RE-VECTO ms_9July2019

bleeding or those requiring emergency surgery or procedures. In addition, no safety

concerns, specifically anaphylaxis or pro-thrombotic effects, were reported.[10] Dabigatran is

indicated to reduce the risk of stroke and systemic embolism in non-valvular atrial

fibrillation, to treat deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients

treated with a parenteral anticoagulant for 5–10 days, to prevent recurrent DVT, and PE in

adults (DVT/PE) and for primary prevention of VTE in orthopaedic surgery reduce the risk of

recurrence of DVT and PE in previously treated patients, and for the prophylaxis of DVT and

PE in patients who have undergone hip or knee replacement surgery.[11,12] Idarucizumab (5 g

initially; two 50 mL vials each containing 2.5 g idarucizumab constitute one complete 5 g

dose [a second 5 g dose may be considered under specific clinical circumstances]) is

indicated in adult patients when rapid reversal of dabigatran is required for life-threatening

or uncontrolled bleeding or emergency surgery/urgent procedures.[13,14]

In order to characterise the utilisation of idarucizumab and provide data on usage

patterns in a real-world setting, RE-VECTO, a global drug administration surveillance

programme, was initiated.

Methods and Analysis

Programme Design and Participants

RE-VECTO, an international, multicentre, cross-sectional surveillance programme, was a

post-approval study commitment for the European regulatory authorities. RE-VECTO

involved hospital pharmacies or departments in North America, the European Union, and

the Asia-Pacific region, where idarucizumab was dispensed between August 2016 and June

Fanikos_RE-VECTO ms_9July2019

2018, depending on marketing authorisation, country regulations and requirements, and availability of the protocol.

In countries where idarucizumab was approved, potential sites where idarucizumab was dispensed were identified and invited to register; after which data were collected via a retrospective chart review. Initially, all centres who ordered idarucizumab were sent a welcome packet and invited to register on the website. The rResponse rate was low and the process was redefined to include only those centres that ordered and then restocked idarucizumabproduct. However, this was not necessarily indicative of use of idarucizumab as reorders could be for multiple reasons (i.e. supplying satellite locations within the hospital or towards the end of the trial- replacing expired product). In total, over 2000 invitations were sent, and other methods were used to narrow site selection to those with known patients receiving the product (i.e. claims data or medical science liaisonMSL conversations). All centres who registered, completed required training, and finalized the required trial documents were activated, regardless if they had an identified patient or not.

Idarucizumab was prescribed at the discretion of the treating physician and not influenced by participation in the programme. Prescription of idarucizumab other than indicated by the label was considered as off-label use, such as an unapproved indication (e.g. elective surgery), an unapproved dose (e.g. 2.5 g), or treatment of a patient who did not receive dabigatran. Patients aged ≥ 18 years receiving idarucizumab as part of their clinical care were eligible, regardless of prior OAC use. Any patients participating in a dabigatran or idarucizumab clinical trial were excluded.

8

Fanikos_RE-VECTO ms_9July2019

Informed consent was not required because the programme was based on

anonymised data. The protocol was approved by an independent ethics committee where

necessary, based on country-specific regulations.

Data Collection

In patients treated with idarucizumab, anonymised patient data were entered into an

electronic data capture system via an internet portal. A pre-specified data-management

plan and pre-specified rules generated auto-queries for missing fields, and data listing

reviews were conducted prior to database lock. Patient demographics such as age

categories and previous anticoagulant use (e.g., last intake of dabigatran etexilate or other

OACs), were collected. Previous antiplatelet treatment, safety and efficacy data were not

collected.

Idarucizumab utilisation, including the reason for idarucizumab use (life-threatening or

uncontrolled bleeding requiring medical intervention, or emergency surgery or other urgent

medical procedure necessitating rapid reversal of the anticoagulant effect of dabigatran),

was recorded. Information regarding the location of the bleeding event (gastrointestinal

tract, intracranial, post-procedural, skin, urogenital tract, undefined location, other defined

location) was also collected. In addition, the dosage and timing of idarucizumab

administration (total dose administered and the time interval between administration of the

first and second vials [the standard approved dosage is 2 x 2.5 g vials]), whether

idarucizumab administration was discontinued prematurely, and the care setting (for

example, emergency department, intensive care unit or operating Room) were recorded.

The characteristics of the hospital pharmacy were collected for each participating site

to evaluate the diversity of sites, including: country, whether the pharmacy was central or

Fanikos_RE-VECTO ms_9July2019

decentralised, the number of pharmacy units within the hospital if there is no central

pharmacy (e.g. the emergency department, intensive care unit or operating room),

idarucizumab stocks, storage location, distribution channels within the hospital, type of

practice (academic, non-academic, private or public) and availability of electronic

prescription records at the pharmacy.

Statistical Analysis

The programme sample size was driven by regulatory requirements, and idarucizumab

usage and provider participation. A minimum of 300 patients was requested by the

European Medicines Agency.

Data from all enrolled patients who received idarucizumab were analysed using

descriptive statistics (generated using SAS® version 9.2 or higher [SAS Institute, Cary, NC,

USA]). Categorical variables were summarised as numbers and proportions. Continuous

variables are reported as mean (standard deviation [SD]) or median (interquartile ranges

[IQR]). Subgroups analysed included; region, indication for use of idarucizumab, age, prior

administration of idarucizumab, department where idarucizumab was administered,

bleeding event location and type, and whether the bleeding was life-threatening. Missing

data were not imputed.

Results

Characteristics of Sites Prescribing Idarucizumab

Fanikos_RE-VECTO ms_9July2019

Of the 132 registered hospitals, 61 sites enrolled 359 patients (eight sites in the Asia Pacific

region, 42 sites in the EU, and 29 sites in North America). Just over half (52.5%]) were non-

academic institutions, and the majority were public hospitals (67.2%]) (**Table 1**).

Most pharmacies (85.2%) were centralised. In sites with decentralised pharmacies, the

median number of pharmacy units per hospital was 8.0 (IQR 2.0— to 9.0) (**Table 1**). The

majority of hospitals (78.7%) had electronic prescription and electronic medical records

available, and stored idarucizumab in the primary pharmacy (67.2%). Other storage

locations including satellite pharmacies, Emergency Department, Intensive Care Unit or

Operating Room, and other specialist departments (Cardiology and Neurology). The median

total idarucizumab units (one unit = 2 xx 2.5 g vials) stocked per hospital pharmacy in all

storage locations was 2.0 (IQR 1.0 to 3.0).

Characteristics of Patients Treated with Idarucizumab

Of the 359 enrolled patients, most were either in the EU (152/359 [42.3%]) or North

America (157/359 [43.7%], of whom 140 were enrolled in the USA) (**Table 2**). The majority

of patients were treated in hospitals that were academic (208/359 [57.9%]) and public

(238/359 [66.3%]).

Four (1.1%) patients had received idarucizumab previously, and this information was

missing for 50 (13.9%) patients. Most patients were aged > 70 years (74.9%) and 85.0% had

not received idarucizumab before (98.7% if excluding the 50 patients with unknown prior

use). Four (1.1%) patients had received idarucizumab previously, and this information was

missing for 50 (13.9%) patients. The dose and last intake of previous anticoagulant

medications (dabigatran and/or other) is shown in **Table 3**. All patients had received an

anticoagulant before recruitment. Dabigatran was the last anticoagulant used by most

Fanikos_RE-VECTO ms_9July2019

patients (97.5%), and of these, only two (0.6%) patients were taking dabigatran and another

oral or parenteral anticoagulant (both had life-threatening or uncontrolled bleeding). Of the

nine patients without dabigatran documented as their last anticoagulant medication, four

had received rivaroxaban or an unknown anticoagulant, and one had received apixaban.

Dabigatran dosage regimens (eight types were recorded) were known for 332 patients, with

the most frequent being 150 mg twice daily (bid; 52.4%) and 110 mg bid (35.8%). Of those

patients receiving dabigatran 110 mg bid or 150 mg bid, 89.9% and 60.3% were aged >

70 years. The dose of dabigatran was not recorded for 18 (5.0%) patients.

Utilisation of Idarucizumab

Most patients (341/359 [95.0%]) received the full dose (2 × 2.5 g) of idarucizumab, with the

mean (SD) time between vials being 15.3 (8.6) minutes (**Table 4**); time between two vials

was missing for 123/341 (36.1%) patients. Of the 18 patients who were documented as not

receiving the full dose of idarucizumab initially, 12 received one vial (2.5 g) and the dose was

unknown for the other six. A second treatment with 5 g of idarucizumab, based on clinical

signs in combination with coagulation tests, was administered to six patients (1.7%), either

in the Emergency Department (*n* = 2) or Intensive Care Unit (*n* = 4). The mean (SD) time

between vials for the second treatment was 14.0 (7.1) minutes, with the time between two

vials missing in 2/6 (33.0%) patients. Of these six patients requiring a second full dose of

idarucizumab, five given idarucizumab for initial life-threatening or uncontrolled bleeding

required the second treatment for additional urgent intervention (*n* = 1) or for re-

bleeding/prolonged coagulation test (*n* = 4); one patient given idarucizumab initially for

emergency surgery/urgent medical procedures required the second treatment for

Fanikos_RE-VECTO ms_9July2019

prolonged re-bleeding/prolonged coagulation test. No adverse events were reported in any

patient.

Idarucizumab was primarily administered in the Emergency Department (209/359

[58.2%]). Bleeding was the most frequent indication for the administration of idarucizumab

(207/359 [57.7%] patients), followed by emergency surgery/urgent procedure (129/359

[35.9%] patients). This pattern was consistent in most departments, except for the surgical

department.

The most frequent bleeding events were gastrointestinal (GI) tract (92/207 [44.4%] of

patients) and intracranial (80/207 [38.6%]) (**Fig. 1**). Most patients with GI bleeding (88/92

[95.7%]) received the full dose (2 × 2.5 g) of idarucizumab, with the mean (SD) time between

vials being 15.2 (9.8) minutes. Similarly, the majority of patients with intracranial bleeding

(76/80 [95.0%]) received the full dose of idarucizumab, with the mean (SD) time between

vials being 16.3 (7.1) minutes. Of the 194/207 (93.7%) patients who received the full dose (2

× 2.5 g) of idarucizumab for a bleeding event, the time between two vials was not available

for 68/194 (35.1%) patients. For those patients who received the full dose (2 × 2.5 g) of

idarucizumab for GI or intracranial bleeding events, the time between two vials was not

available for 28/88 (31.8%) and 25/76 (32.9%) patients, respectively. Four patients (1.1%)

were reported to have prematurely discontinued idarucizumab, with none due to adverse

events.

Of the 141 (39.3%) patients who were administered idarucizumab for emergency or

for scheduled or planned surgery/procedure (**Fig. 2**), GI and/or abdominal surgery or

procedures were most frequently performed (in 36 [25.5%] of patients), followed by

orthopaedic procedures (in 31 [22.0%] patients), thoracic surgery including cardiac surgery

Fanikos_RE-VECTO ms_9July2019

(23 [16.3%] patients), and vascular operations (in 20 [14.2%] patients). Of the 23 patients who received ~~idaricizumab~~idarucizumab for thoracic surgery including cardiac surgery, six patients underwent cardiac catheterization, three patients had a cardiac pacemaker insertion or removal, one patient had a central venous catheterization, and five patients had a pericardial excision and pericardial drainage. No intra-procedural bleeds were reported. The study also included patients who required rapid reversal of the anticoagulant effect of dabigatran prior to thrombolysis (n = 12) and thromb~~o~~ectomy (n = 2). On average, data were missing for 6.4% of patients ~~were missing data~~ with regard to~~ing~~ the type of surgery/procedure; 8/129 (6.2%) patients who underwent emergency surgery or other urgent medical procedures, and 1/12 (8.3%) patients who underwent scheduled or planned surgery/procedures.

Discussion

The RE-VECTO post-approval surveillance study has shown that sites prescribing idarucizumab were mainly non-academic institutions and public hospitals, with approximately two doses of idarucizumab stored on-site. Most of the patients were European or North American. More than half of the registered hospitals either registered proactively prior to identification of a patient treated with idarucizumab or ~~who~~ had historical cases of patients treated with idarucizumab ~~and actively prescribing idarucizumab~~ but did not enter patients into the registry. ~~, perhaps due to organisational reasons. A~~Of those sites that entered patient data, a~~s~~ expected, dabigatran was the anticoagulant used by most patients. Nearly all patients received the full dose (2 ~~xx~~ 2.5 g) of idarucizumab, ~~O~~with only one full dose ~~was~~ required in almost all patients. ~~with~~ There was minimal off-label ~~use~~ dosing (e.g., use of 2.5 g in 12 patients), and administration of idarucizumab to

14

Fanikos_RE-VECTO ms_9July2019

seven patients usinge of anti FXa inhibitors (without dabigatran) was reported. for seven

patients. Only one full dose was required in almost all patients. As expected, idarucizumab

was most frequently given in the Emergency Department, and bleeding (the most common

locations being GI tract and intracranial) was the most frequent reason for administering

idarucizumab.

The findings from RE-VECTO describing idarucizumab uptake, dabigatran prescribing

patterns and patient characteristics in the real-world setting add to the idarucizumab clinical

trial data and few case collections available to date.[10,15-22] While the patients in RE-VECTO

were less well characterized due to the limitations of data collection, outcomes were largely

consistent with those observed in the clinical trial setting with regard to indications, rates of

bleeding and emergent surgery events. In addition, RE-VECTO indicatesdemonstrates that

the real-world usage of idarucizumab was mostly as recommended in the label. Moreover,

the reversal of dabigatran in RE-VECTO rarely required a second round of idarucizumab

dosing (< 2% of patients), supporting the findings from the RE-VERSE-AD study in which a

second round of dosing was required in 1.6% patients.[10] In addition, the reversal of

dabigatran in the real-world setting involved a mainly elderly population treated with

several different dabigatran dosage regimens. In RE-VERSE-AD, the median age was 78

(range, 21–96) years, and > 97% of patients received one of three approved dosage

regimens of dabigatran (150/110/75 mg bid).

Aside from idarucizumab, one other reversal agent, andexanet alfa, is available

commercially in the USA for the reversal of rivaroxaban- and apixaban-related bleeding only,

following positive results from clinical trials.[23,24] Another potential FXa inhibitor reversal

agent, ciraparantag, has yet to begin phase II or III evaluation in patient settings; phase II

15

Fanikos_RE-VECTO ms_9July2019

data in healthy volunteers administered rivaroxaban (NCT03172910) or apixaban

(NCT03288454) are expected in 2019.

The RE-VECTO surveillance programme was designed to collect data on drug use in a

simple and effective way, although the voluntary registration design and/or resource

limitations may have reduced participation and resulted in some approximately 10% of

patients having incomplete datasets., and Some recruited sites known to be prescribing

idarucizumab that did not enter patient data in the registry during the specified time period

of time of for data collection, and were not actively surveyed. Data listing reviews

conducted prior to database lock did not involve an independent data review committee,

and on-site source data verification was not conducted. Administration of idarucizumab is

rare, and without patient data being entered into the registry, we are unable to ascertain

whether these sites wereare re-stocking idarucizumab, supplying satellite locations within

the hospital, replacing expired idarucizumab, or administering idarucizumab to patients. In

addition, this surveillance programme had no pre-specified data management plan or

independent review as part of the protocol, and some patient information was missing.

Nevertheless, dDrug surveillance programmes are one source of real-world data,[25] that are

particularly useful for identifying improper use. By identifying potential risks, action can be

taken to help minimise the risk of adverse drug reactions resulting from medication errors.

This study assessed idarucizumab utilization in a pre-defined sample of prescriptions in the

clinical practice setting, based on medical and pharmacy record review. This approach was

in line with post-marketing surveillance requested by the European Medicines Agency.

Conclusion

Fanikos_RE-VECTO ms_9July2019

Real-world information from the RE-VECTO surveillance programme adds to the data obtained from idarucizumab clinical trials and provides valuable insights into the current strategies employed to reverse the anticoagulation effects of dabigatran in emergency situations. Usage patterns of idarucizumab were ~~closely~~ aligned with ~~data from the clinical trial setting~~idarucizumab prescribing information, with minimal off-label use.

Acknowledgements

Authors' contributions

All authors were involved with designing the surveillance programme, provided critical review of the article and approved the final version for publication.

Funding

Disclosure of interests

John Fanikos has consulted for Boehringer Ingelheim, Genentech, and Portola.

Debra Murwin, Fredrik Gruenenfelder~~, L Riou França~~, Paul A Reilly and Igor Tartakovsky are employees of Boehringer Ingelheim.

L Riou França was an employee of Boehringer Ingelheim at the time of manuscript writing and is now employed by Sanofi-Aventis.

Fanikos_RE-VECTO ms_9July2019

Fanikos_RE-VECTO ms_9July2019

References

1   Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. Thromb Haemost 2015;113:931-942

2   Das A, Liu D. Novel antidotes for target specific oral anticoagulants. Exp Hematol Oncol 2015;4:25

3   Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-2962

4   Macle L, Cairns J, Leblanc K, et al. 2016 Focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2016;32:1170-1185

5   European Medicines Agency. 2015. Idarucizumab summary of product characteristics. https://www.ema.europa.eu/documents/product-information/praxbind-epar-product-information_en.pdf. Accessed October 10, 2018.

6   US Food and Drug Administration. 2015. Idarucizumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf. Accessed October 10, 2018.

7   US Food and Drug Administration. 2018. Andexanet alfa prescribing information. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM606687.pdf. Accessed October 10, 2018.

8   Eikelboom JW, Quinlan DJ, van Ryn J, et al. Idarucizumab: the antidote for reversal of dabigatran. Circulation 2015;132:2412-2422

9   Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. Blood 2013;121:3554-3562

10   Pollack CV, Jr., Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med 2017;377:431-441

11   European Medicines Agency. Dabigatran etexilate. Summary of Product Chacrateristics. https://www.ema.europa.eu/documents/product-information/pradaxa-epar-product-information_en.pdf. Accessed October 10, 2018.

12   US Food and Drug Administration. Dabigatran etexilate prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022512s035lbl.pdf. Accessed October 10, 2018.

13   European Medicines Agency. Idarucizumab. Summary of Product Characteristics. https://www.ema.europa.eu/documents/product-information/praxbind-epar-product-information_en.pdf. Accessed October 10, 2018.

14   US Food and Drug Administration. Idarucizumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf. Accessed October 10, 2018.

15   Pollack CV, Jr., Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-520

16   Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet 2015;386:680-690
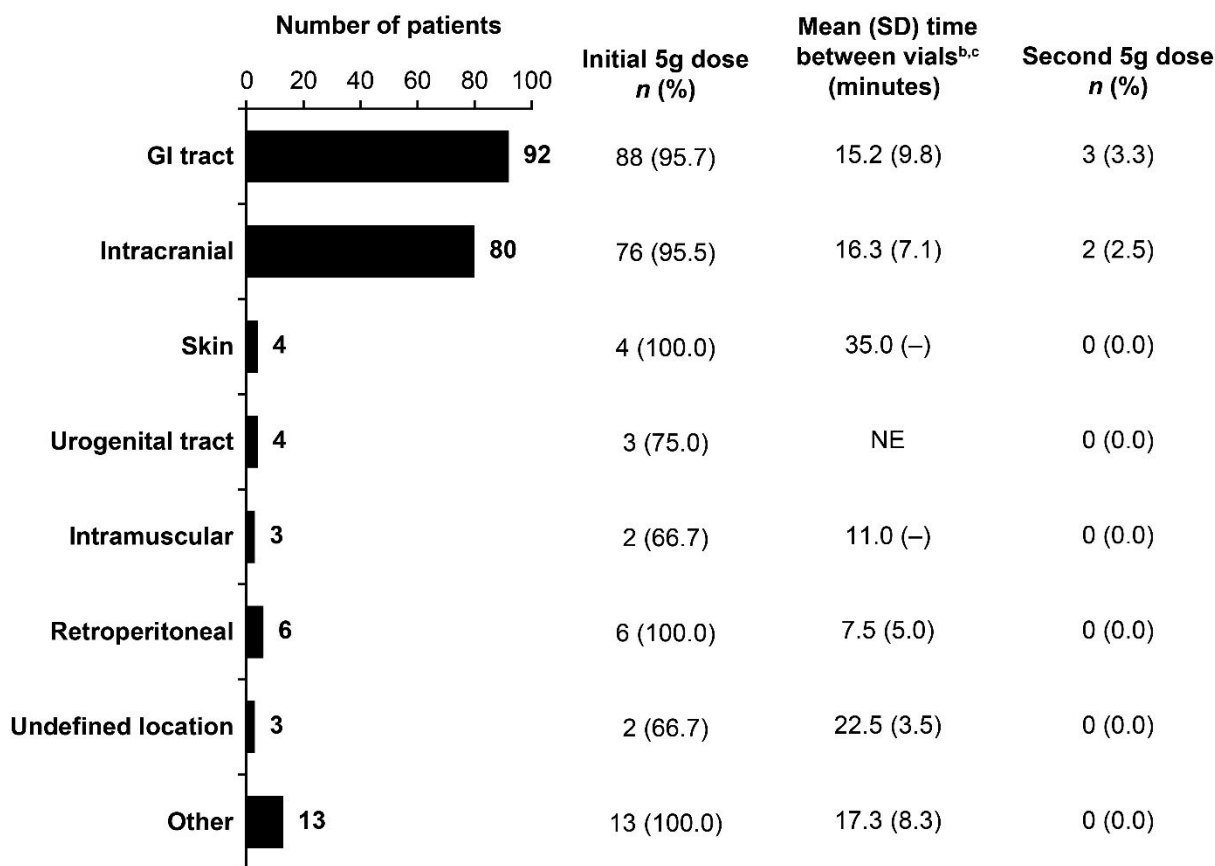
Fanikos_RE-VECTO ms_9July2019

17   van Ryn J, Yasaka M, Ikushima I, et al. Idarucizumab, a specific reversal agent for dabigatran: immediate, complete and sustained reversal of dabigatran-induced anticoagulation in Japanese healthy male volunteers. Blood 2016;128(suppl 22):2627

18   Glund S, Stangier J, van Ryn J, et al. Effect of age and renal function on idarucizumab pharmacokinetics and idarucizumab-mediated reversal of dabigatran anticoagulant activity in a randomized, double-blind, crossover phase Ib study. Clin Pharmacokinet 2017;56:41-54

19   Glund S, Stangier J, Schmohl M, et al. Idarucizumab, a specific antidote for dabigatran: immediate, complete and sustained reversal of dabigatran induced anticoagulation in elderly and renally impaired subjects. Blood 2014;124(suppl 21):344

20   Fang CW, Tsai YT, Chou PC, et al. Intravenous thrombolysis in acute ischemic stroke after idarucizumab reversal of dabigatran effect: Analysis of the cases from Taiwan. J Stroke Cerebrovasc Dis 2019;28:815-820

21   Kermer P, Eschenfelder CC, Diener HC, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany - A national case collection. Int J Stroke 2017;12:383-391

22   van der Wall SJ, van Rein N, van den Bemt B, et al. Performance of idarucizumab as antidote of dabigatran in daily clinical practice. Europace 2018

23   Connolly SJ, Milling TJ, Jr., Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;375:1131-1141

24   Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015;373:2413-2424

25   Martin K, Begaud B, Latry P, et al. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol 2004;57:86-92

Fanikos_RE-VECTO ms_9July2019

<FIGURE LEGENDS>

Fig. 1 Location of bleeding[a] events (*N* = 207) leading to idarucizumab use, and idarucizumab use by bleeding location.

Number of patients	Initial 5g dose *n* (%)	Mean (SD) time between vials[b,c] (minutes)	Second 5g dose *n* (%)
GI tract — 92	88 (95.7)	15.2 (9.8)	3 (3.3)
Intracranial — 80	76 (95.5)	16.3 (7.1)	2 (2.5)
Skin — 4	4 (100.0)	35.0 (–)	0 (0.0)
Urogenital tract — 4	3 (75.0)	NE	0 (0.0)
Intramuscular — 3	2 (66.7)	11.0 (–)	0 (0.0)
Retroperitoneal — 6	6 (100.0)	7.5 (5.0)	0 (0.0)
Undefined location — 3	2 (66.7)	22.5 (3.5)	0 (0.0)
Other — 13	13 (100.0)	17.3 (8.3)	0 (0.0)

[a]Life-threatening or uncontrolled bleeding requiring medical intervention.

[b] Calculated only for those patients administered total dose of 5 g (2 vials), and defined as the end time of second vial minus the start time of the first vial. If the start or end time of dosing was unknown, the estimated time of total infusion was used; if this estimate was not known, then time was set to missing.

[c] Missing data for 28 patients with gastrointestinal tract bleeding, 25 with intracranial bleeding, 3 with skin bleeding, 3 with urogenital tract bleeding, 1 with intramuscular bleeding, 2 with retroperitoneal bleeding, and 6 with other bleeding locations.

Fanikos_RE-VECTO ms_9July2019

Abbreviations: GI, gastrointestinal; NE, not evaluable; SD, standard deviation.

Fanikos_RE-VECTO ms_9July2019

Fig. 2 Type of surgery or procedure by indication for idarucizumab use.

^a Missing data for 8 patients undergoing emergency surgery or other urgent medical

procedures.

^b Missing data for 1 patient undergoing scheduled or planned surgery/procedures.

Fanikos_RE-VECTO ms_9July2019

<TABLES>

Table 1 Hospitals treating patients with idarucizumab by region~~Participating hospitals by region~~

24

Fanikos_RE-VECTO ms_9July2019

	Asia Pacific	Europe	North America	Total
	N = 8	*N* = 24	*N* = 29	*N* = 61
Hospital type 1[a], *n* (%)				
Academic	6 (75.0)	15 (62.5)	7 (24.1)	28 (45.9)
Non-academic	2 (25.0)	9 (37.5)	21 (72.4)	32 (52.5)
Other	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.6)
Hospital type 2[a], *n* (%)				
Private	0 (0.0)	1 (4.2)	18 (62.1)	19 (31.1)
Public	8 (100.0)	23 (95.8)	10 (34.5)	41 (67.2)
Other	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.6)
Type of pharmacy, *n* (%)				
Central pharmacy	7 (87.5)	23 (95.8)	22 (75.9)	52 (85.2)
Decentralised pharmacy	1 (12.5)	1 (4.2)	7 (24.1)	9 (14.8)

Fanikos_RE-VECTO ms_9July2019

Availability of electronic prescription records at the pharmacy, n (%)				
Yes	4 (50.0)	16 (66.7)	28 (96.6)	48 (78.7)
No	4 (50.0)	8 (33.3)	1 (3.4)	13 (21.3)
Availability of electronic medical records at the pharmacy, n (%)				
Yes	5 (62.5)	16 (66.7)	27 (93.1)	48 (78.7)
No	3 (37.5)	8 (33.3)	2 (6.9)	13 (21.3)
Number of pharmacy units per hospital[b], n (%)	1	1	7	9
Median (IQR)				
	9.0 (9.0, 9.0)	3.0 (3.0, 3.0)	8.0 (1.0, 10.0)	8.0 (2.0, 9.0)
Total number of idarucizumab units (2 × 2.5 g) stocked per hospital pharmacy in all storage locations[c], n (%)	8	24	28	60

Fanikos_RE-VECTO ms_9July2019

Median (IQR)	2.0 (1.0, 3.0)	2.0 (2.0, 3.5)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)
Storage location of idarucizumab stocks[c, d], n (%)				
Primary pharmacy	5 (62.5)	11 (45.8)	25 (86.2)	41 (67.2)
Satellite pharmacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Emergency room	2 (25.0)	9 (37.5)	7 (24.1)	18 (29.5)
Other	3 (37.5)	12 (50.0)	0 (0.0)	15 (24.6)

[a] Type 1: academic sector type; Type 2: practice hospital type.

[b] Only available when type of pharmacy is decentralised pharmacy.

[c] Data for 1 hospital pharmacy missing for North America.

[d] Multiple answers possible.

Abbreviations: IQR, interquartile range.

Fanikos_RE-VECTO ms_9July2019

Table 2 Characteristics of patients treated with idarucizumab by region

For Peer Review

28

Fanikos_RE-VECTO ms_9July2019

	Asia Pacific	Europe	North America	Total
	N = 50	*N* = 152	*N* = 157	*N* = 359
Age group (years), *n* (%)				
18–50	2 (4.0)	4 (2.6)	5 (3.2)	11 (3.1)
51–70	11 (22.0)	28 (18.4)	40 (25.5)	79 (22.0)
> 70	37 (74.0)	120 (78.9)	112 (71.3)	269 (74.9)
Prior administration of idarucizumab, *n* (%)				
Yes	0 (0.0)	1 (0.7)	3 (1.9)	4 (1.1)
No	48 (96.0)	129 (84.9)	128 (81.5)	305 (85.0)
Unknown	2 (4.0)	22 (14.5)	26 (16.6)	50 (13.9)
Hospital Type 1[a], *n* (%)				
Academic	41 (82.0)	108 (71.1)	59 (37.6)	208 (57.9)
Non-Academic	9 (18.0)	44 (28.9)	93 (59.2)	146 (40.7)

Fanikos_RE-VECTO ms_9July2019

Other	0 (0.0)	0 (0.0)	5 (3.2)	5 (1.4)
Hospital Type 2[a], *n* (%)				
Private	0 (0.0)	10 (6.6)	87 (55.4)	97 (27.0)
Public	50 (100.0)	142 (93.4)	46 (29.3)	238 (66.3)
Other	0 (0.0)	0 (0.0)	24 (15.3)	24 (6.7)

[a] Type 1: academic sector type; Type 2: practice hospital type.

Fanikos_RE-VECTO ms_9July2019

Table 3 Last anticoagulant medication taken prior to recruitment, according to the reason for idarucizumab administration

Fanikos_RE-VECTO ms_9July2019

	Life-threatening or uncontrolled bleeding *N* = 207	Emergency surgery or other urgent medical procedure *N* = 129	Scheduled or planned surgery/ procedure *N* = 12	Other *N* = 11	Total *N* = 359

32

Fanikos_RE-VECTO ms_9July2019

Anticoagulant medication, *n* (%)

Dabigatran any dose[a]	203 (98.1)	124 (96.1)	12 (100.0)	11 (100.0)	350 (97.5)[a]
Rivaroxaban any dose	3 (1.4)	1 (0.8)	0 (0.0)	0 (0.0)	4 (1.1)
Apixaban any dose	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Edoxaban any dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vitamin K antagonist	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other anticoagulant	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Unknown	2 (1.0)	4 (3.1)	0 (0.0)	0 (0.0)	6 (1.7)[b]

[a] Includes two patients who received ≥ 1 dose dabigatran plus other anticoagulant.

[b] Includes two patients who were receiving another known anticoagulant medication.

33

Fanikos_RE-VECTO ms_9July2019

Table 4 Idarucizumab utilisation according to the reason for idarucizumab administration

34

Fanikos_RE-VECTO ms_9July2019

	Life-threatening or uncontrolled bleeding[a] $N = 207$	Emergency surgery or other urgent medical procedure[b] $N = 129$	Scheduled or planned surgery/ procedure $N = 12$	Other $N = 11$	Total $N = 359$
Idarucizumab total dose, *n* (%)					
2.5 g (1 vial)	7 (3.4)	5 (3.9)	0 (0.0)	0 (0.0)	12 (3.3)
5 g (2 vials)	195 (94.2)	123 (95.3)	12 (100.0)	11 (100.0)	341 (95.0)
Other	5 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)	6 (1.7)

Fanikos_RE-VECTO ms_9July2019

Time between 2 vials (minutes)[c, d]					
N	127	83	7	1	218
Mean (SD)	15.80 (8.72)	14.20 (8.59)	16.14 (5.70)	25.00 (–)	15.25 (8.60)
Second round of idarucizumab 5 g, *n* (%)					
No	198 (95.7)	125(96.9)	12 (100)	11 (100)	346 (96.4)
Yes	5 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)	6 (1.7)
Unknown	4 (1.9)	3 (2.3)	0 (0.0)	0 (0.0)	7 (1.9)
Reason for second round[e], *n* (%)					
Additional urgent intervention	1 (20.0)	0 (0.0%)	0 (0.0)	0 (0.0)	1 (16.7)
Re-bleeding/coagulation test prolongation	4 (80.0)	1 (100.0)	0 (0.0)	0 (0.0)	5 (83.3)

Fanikos_RE-VECTO ms_9July2019

Time between 2 vials for second round (minutes)[c, e, f]					
N	4	0	0	0	4
Mean (SD)	14.00 (7.12)	–	–	–	14.00 (7.12)

[a] Life-threatening or uncontrolled bleeding requiring urgent medical intervention.

[b] Emergency surgery or other urgent medical procedure necessitating rapid reversal of dabigatran prior to surgery or procedure (emergency defined as within the next 8 hours).

[c] Calculated only for those patients administered total dose of 5 g (2 vials), and defined as the end time of second vial minus the start time of the first vial. If the start or end time of dosing was unknown, the estimated time of total infusion was used; if this estimate was not known, then time was set to missing.

[d] Missing data for 68 patients in the Emergency setting, 40 in the Operating setting, 5 in the intensive care setting, and 10 in the Other setting.

[e] Among patients who had second round of dosing with 5 g of idarucizumab.

[f] Missing data for 1 patient in the Emergency and ICU settings.

Abbreviations: SD, standard deviation.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

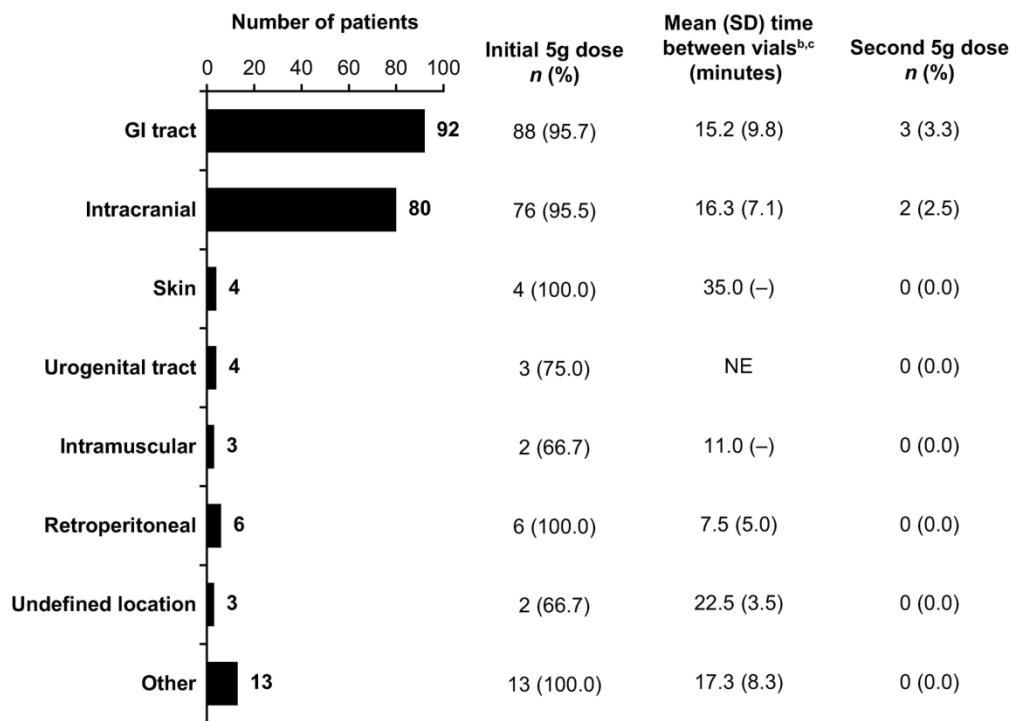| Number of patients	Initial 5g dose n (%)	Mean (SD) time between vials[b,c] (minutes)	Second 5g dose n (%)
GI tract — 92	88 (95.7)	15.2 (9.8)	3 (3.3)
Intracranial — 80	76 (95.5)	16.3 (7.1)	2 (2.5)
Skin — 4	4 (100.0)	35.0 (–)	0 (0.0)
Urogenital tract — 4	3 (75.0)	NE	0 (0.0)
Intramuscular — 3	2 (66.7)	11.0 (–)	0 (0.0)
Retroperitoneal — 6	6 (100.0)	7.5 (5.0)	0 (0.0)
Undefined location — 3	2 (66.7)	22.5 (3.5)	0 (0.0)
Other — 13	13 (100.0)	17.3 (8.3)	0 (0.0)

Fig. 1 Location of bleeding[a] events (N = 207) leading to idarucizumab use, and idarucizumab use by bleeding location.

aLife-threatening or uncontrolled bleeding requiring medical intervention.
b Calculated only for those patients administered total dose of 5 g (2 vials), and defined as the end time of second vial minus the start time of the first vial. If the start or end time of dosing was unknown, the estimated time of total infusion was used; if this estimate was not known, then time was set to missing.
c Missing data for 28 patients with gastrointestinal tract bleeding, 25 with intracranial bleeding, 3 with skin bleeding, 3 with urogenital tract bleeding, 1 with intramuscular bleeding, 2 with retroperitoneal bleeding, and 6 with other bleeding locations.
Abbreviations: GI, gastrointestinal; NE, not evaluable; SD, standard deviation.

170x121mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
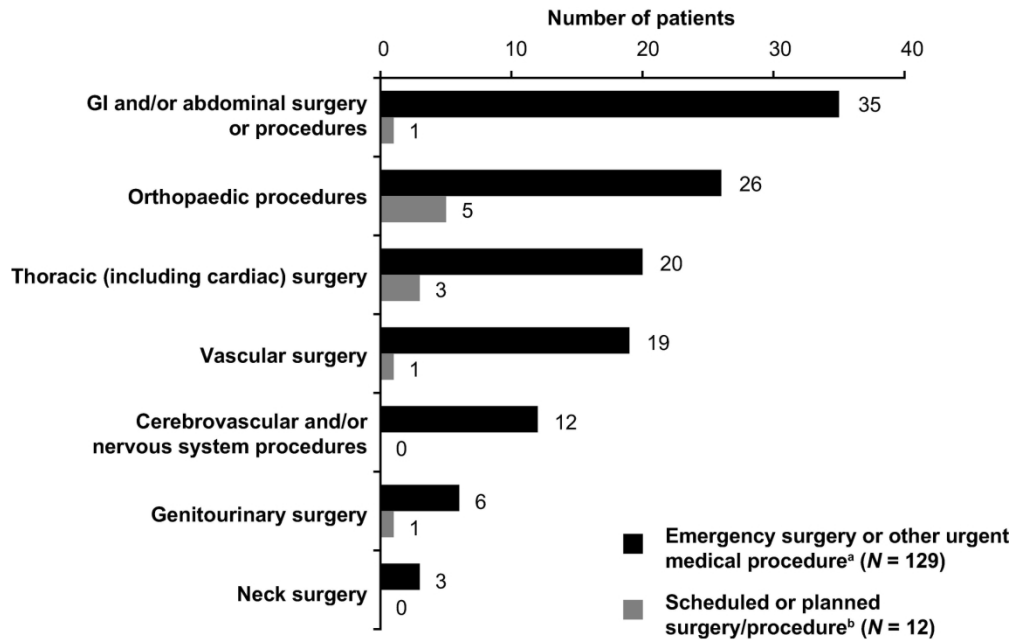51
52
53
54
55
56
57
58
59
60

Fig. 2 Type of surgery or procedure by indication for idarucizumab use.

a Missing data for 8 patients undergoing emergency surgery or other urgent medical procedures.
b Missing data for 1 patient undergoing scheduled or planned surgery/procedures.

170x107mm (300 x 300 DPI)