Thromboembolic events reported in association with idarucizumab and andexanet alfa: disproportionality analysis of the Food and Drugs Administration Adverse Event Reporting System (FAERS) database

Protocol version 1.1

Title	Thromboembolic events reported in association with idarucizumab and andexanet alfa: disproportionality analysis of the Food and Drugs Administration Adverse Eventr Resporting System (FAERS) database
Medicinal product(s) / Device(s)	idarucizumab and andexanet alfa
Event(s) of interest	Any thromboembolic event
Research question and objectives	To describe the pattern of use of incretin-based drugs in large sample of the Italian general population.
Country(ies) of study	Italy
Protocol author(s)	Giuseppe Roberto, Alessandra Flaccavento, Marco Tuccori, Rosa Gini, Gianni Virgili

List of abbreviations:

MedDRA	Medical Dictionary for Regulatory Activities
RxNorm	medical prescription normalized Medical prescription
FDA	Food and Drugs Administration
FAERS	FDA Adverse Event Resporting System
SMQ	strandrdized MedDRA queries
DOAC	direct oral anticoagulant
PCC	prothrombin complex concentrate
3PCC	3 factors- prothrombin complex concentrate
4PCC	4 factors- prothrombin complex concentrate
aPCC	activated prothrombin complex concentrate

Responsible parties

Name	Institution	Activity
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Amendments and updates

Version	Description of changes	Study protocol section	Date of effectiveness
1.1	Added sections “Assessment of disproportionate signals” and “Case-by-case analyses”	Method section	4 January 2024

Background

Idarucizumab and andexanet alfa are drugs for the emergency reversal of pharmacological effect of direct oral anticoagulant (DOAC) drugs (1,2). In particular, idarucizumab is a humanized monoclonal antibody with very high affinity for dabigatran, an DOAC that acts as a direct inhibitor of thrombin (coagulation factor IIa). Idarucizumab is approved for the treatment of adult patients treated with dabigatran who require rapid inactivation of the anticoagulant effect due to emergency surgery/urgent procedures or in cases of potentially fatal or uncontrolled bleeding (2). Andexanet alfa, on the other hand, is a recombinant form of human factor Xa, which is devoid of enzymatic activity. It is indicated in adult patients treated with a direct factor Xa inhibitor, i.e., the DOACs apixaban or rivaroxaban, when reversal of anticoagulant therapy is required due to potentially fatal or uncontrollable bleeding (2).

Patients treated with DOACs who receive idarucizumab or andexanet alfa may subsequently experience thromboembolic events due to both activation of bleeding coagulation, pre-existing prothrombotic conditions, and/or a possible 'rebound' effect due to the administration of the anticoagulant therapy antidote (3). However, given the recent commercialization of these two antidotes (2015 for idarucizumab (2), 2018 for andexanet(4)) and their rare use in clinical practice, as they are restricted to emergency situations, evidence on the safety of idarucizumab regarding thromboembolic risk is still limited (3,5,6).

In this context, spontaneous reporting analysis can provide new hypotheses regarding the possible association between the use of idarucizumab and specific thromboembolic events, which can be subsequently verified through ad hoc observational studies.

Materials and Methods

Data source

The Food and Drug Administration Adverse Event Reporting System (FAERS) spontaneous reporting database will be used. The row data from FAERS database are publicly available(7) and contains reports of adverse events, therapeutic error reports, and reports on the quality of medicinal products that can be submitted by healthcare providers (such as physicians, pharmacists, nurses, and others), consumers (such as patients, family members, lawyers, and others), and pharmaceutical

companies. The database is widely used by the FDA to support post-marketing safety surveillance of drugs and biological products(8).

Study design

A case/non-case analysis will be conducted to identify specific thromboembolic events reported disproportionately in the reports of patients treated with the drug(s) of interest compared to reports of patients treated with drugs other than the drug(s) of interest (9,10).
For the purpose of this study reports from 2014 through to the end of 2022 will be conssidered.

Exposure

Reports in which idarucizumab or andexanet alfa, respectively, are reported as suspected, concomitant, or interacting drugs will be considered (see Table 1 in the appendix for the RxNorm(11) codes of the drugs of interest).

Events of interest

A list of thromboembolic events coded according to MedDRA terminology (version 26.1) and identified through the use of Standardized MedDRA Queries (SMQs) will be considered(12). In particular, in addition to the 3 SMQs 'Embolic and thrombotic events, arterial', 'Embolic and thrombotic events, venous', and 'Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous', all preferred terms (PTs) contained in each of the three SMQs will also be considered.

Statistical Analysis

Using all reports of suspected adverse drug reactions in the database, the Reporting Odds Ratios (RORs) will be calculated, with 95% confidence intervals (9,10), for idarucizumab and andexanet alfa, respectively, in association with the three relevant SMQs and subsequently in association with each of the PTs contained within each of the three SMQ. Drug-event pairs with ROR>1 and at least 3 reports will be considered as signals of disproportionate reporting.

ROR=

$$\left(\frac{\text{n. reports with drug of interest + event of interest}}{\text{n. reports with drug of interest + any other event}} \right)$$

$$\left(\frac{\text{n. reports with drugs other than drug of interest + event of interest}}{\text{n. reports with drugs other than drug of interest + any other event)}} \right)$$

$$\text{n. reports with drug of interest + event of interest}$$

Sensitivity Analysis

First, the analyses will be restricted to the set of reports concerning any DOAC (i.e. dabigatran, rivaroxaban, apixaban, edoxaban) as reported among suspected, interacting or concomitant drugs.

Second, the analyses will be further restricted to the set of reports concerning any DOAC and at least one among idarucizumab, andexanet alfa or a prothrombin complex concentrate, i.e. the therapeutic alternative to idarucizumab, andexanet alfa, listed as suspected or interacting drug (see Table 2 in the appendix)

The above reported sensitivity analyses has the objective of addressing the bias of indication for which thromboemboembolic events may be more frequently observed following idarucizumab or andexanet alfa administration than expected from the backgroung frequency in the FAERS database. The rationale for the sensitivity analyses lies in the hypothesized pathophysiological mechanism of thromboembolic events that can be potentially observed after the use of idarucizumab and andexanet alfa (3), namely:
-Baseline thromboembolic risk of patients (addressed with the first sensitivity analysis),
-Activation of the coagulation process due to ongoing bleeding and/or discontinuation of the NOAC (addressed with the second sensitivity analysis),
-Rebound effect due to the administration of the anticoagulant therapy antidote (addressed with the second sensitivity analysis).

Assessment of disproportionate signals

Signals of disproportionate reporting will be assessed with respect to information already available in the published literature and in the relevant SmPC. Signals of disproportionate reporting corresponding to dug-event pairs with no or scarce information available in the published literature

for which a possible biological plausibility cannot be excluded will be selected. The corresponding reports will be retrieved further assessed through a case-by-case analysis.

Case by case analysis

The original reports corresponding to the selected drug-event pairs will be retrieved through a FOIA request using the available on-line form on the FDA website (https://www.fda.gov/regulatory-information/freedom-information/how-make-foia-request).
Information from each original case safety report will be extracted and reported in a tabular format (e.g. concomitant drugs, comorbidities, time-to-onset of the suspected adverse drug reaction). The Naranjo scale for causality assessment will be also applied(13).

Data management and processing

Data will be managed using Google Bigquery and analyzed using Microsoft Excel sheet.

Limitations of study methods

The data used for this study can only be intended for hypothesis-generating purposes. Therefore, no inference can be made on any association that will be highlighted in the results of this work. Rather, evidence from this study should be intended as the basis for future research on specific drug-event pair.

Ethical considerations

Since the FAERS database is accessible to the public and patient records are anonymized and de-identified, ethical clearance and informed consent are not required for this study.

Disseminations and communication strategy

Results generated through this research will be shared among all study participants before December 2023. A study report summarizing all main results will be drafted by February 2023. Findings from this study will be submitted to a peer-review international journal before June 2023.

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Appendix

Table 1. Drugs of interest and corresponding RxNorm codes

Active substance	rxcui	description
Dabigatran	1037046	Pradaxa
	1037042	dabigatran etexilate
	1037041	dabigatran etexilate mesylate
	1037049	Pradaxa 150 MG Oral Capsule
	1037181	Pradaxa 75 MG Oral Capsule
	1723478	Pradaxa 110 MG Oral Capsule
	2590619	Pradaxa 110 MG Oral Pellet
	2590621	Pradaxa 150 MG Oral Pellet
	2590625	Pradaxa 20 MG Oral Pellet
	2590629	Pradaxa 30 MG Oral Pellet
	2590633	Pradaxa 40 MG Oral Pellet
	2590637	Pradaxa 50 MG Oral Pellet
	1037047	dabigatran etexilate 150 MG [Pradaxa]
	1037180	dabigatran etexilate 75 MG [Pradaxa]
	1723477	dabigatran etexilate 110 MG [Pradaxa]
	2590624	dabigatran etexilate 20 MG [Pradaxa]
	2590628	dabigatran etexilate 30 MG [Pradaxa]
	2590632	dabigatran etexilate 40 MG [Pradaxa]
	2590636	dabigatran etexilate 50 MG [Pradaxa]
	1037048	dabigatran etexilate Oral Capsule [Pradaxa]
	2590618	dabigatran etexilate Oral Pellet [Pradaxa]
	1184616	Pradaxa Oral Product
	1184617	Pradaxa Pill
	2590617	Pradaxa Pellet Product
	1037045	dabigatran etexilate 150 MG Oral Capsule
	1037179	dabigatran etexilate 75 MG Oral Capsule
	1723476	dabigatran etexilate 110 MG Oral Capsule
	2590616	dabigatran etexilate 110 MG Oral Pellet
	2590620	dabigatran etexilate 150 MG Oral Pellet
	2590623	dabigatran etexilate 20 MG Oral Pellet
	2590627	dabigatran etexilate 30 MG Oral Pellet
	2590631	dabigatran etexilate 40 MG Oral Pellet
	2590635	dabigatran etexilate 50 MG Oral Pellet
	1037043	dabigatran etexilate 150 MG
	1037178	dabigatran etexilate 75 MG
	1723475	dabigatran etexilate 110 MG
	2590622	dabigatran etexilate 20 MG
	2590626	dabigatran etexilate 30 MG

	2590630	dabigatran etexilate 40 MG
	2590634	dabigatran etexilate 50 MG
	1037044	dabigatran etexilate Oral Capsule
	2590615	dabigatran etexilate Oral Pellet
	1156646	dabigatran etexilate Oral Product
	1156647	dabigatran etexilate Pill
	2590614	dabigatran etexilate Pellet Product
Rivaroxaban	1114199	Xarelto
	1549683	Xarelto 30-Day Starter Pack Kit
	1549682	{42 (rivaroxaban 15 MG Oral Tablet) / 9 (rivaroxaban 20 MG Oral Tablet) } Pack
	1114195	rivaroxaban
	1114202	Xarelto 10 MG Oral Tablet
	1232084	Xarelto 15 MG Oral Tablet
	1232088	Xarelto 20 MG Oral Tablet
	2059017	Xarelto 2.5 MG Oral Tablet
	2588066	Xarelto 1 MG/ML Oral Suspension
	1114200	rivaroxaban 10 MG [Xarelto]
	1232083	rivaroxaban 15 MG [Xarelto]
	1232087	rivaroxaban 20 MG [Xarelto]
	2059016	rivaroxaban 2.5 MG [Xarelto]
	2589628	rivaroxaban 1 MG/ML [Xarelto]
	1114201	rivaroxaban Oral Tablet [Xarelto]
	2589630	rivaroxaban Oral Suspension [Xarelto]
	1186304	Xarelto Oral Product
	1186305	Xarelto Pill
	2589629	Xarelto Oral Liquid Product
	1114198	rivaroxaban 10 MG Oral Tablet
	1232082	rivaroxaban 15 MG Oral Tablet
	1232086	rivaroxaban 20 MG Oral Tablet
	2059015	rivaroxaban 2.5 MG Oral Tablet
	2588062	rivaroxaban 1 MG/ML Oral Suspension
	1114196	rivaroxaban 10 MG
	1232081	rivaroxaban 15 MG
	1232085	rivaroxaban 20 MG
	2059014	rivaroxaban 2.5 MG
	2589624	rivaroxaban 1 MG/ML
	1114197	rivaroxaban Oral Tablet
	2589626	rivaroxaban Oral Suspension
	1157968	rivaroxaban Oral Product
	1157969	rivaroxaban Pill
	2589625	rivaroxaban Oral Liquid Product

Apixaban	1364436	Eliquis
	1992428	Eliquis 30-Day Starter Pack
	1992427	{74 (apixaban 5 MG Oral Tablet) } Pack
	1364430	apixaban
	1364441	Eliquis 2.5 MG Oral Tablet
	1364447	Eliquis 5 MG Oral Tablet
	1364437	apixaban 2.5 MG [Eliquis]
	1364446	apixaban 5 MG [Eliquis]
	1364438	apixaban Oral Tablet [Eliquis]
	1364439	Eliquis Oral Product
	1364440	Eliquis Pill
	1364435	apixaban 2.5 MG Oral Tablet
	1364445	apixaban 5 MG Oral Tablet
	1364431	apixaban 2.5 MG
	1364444	apixaban 5 MG
	1364434	apixaban Oral Tablet
	1364432	apixaban Oral Product
	1364433	apixaban Pill
Edoxaban	1599538	edoxaban
	1599564	edoxaban tosylate
	1599549	Savaysa 15 MG Oral Tablet
	1599553	Savaysa 30 MG Oral Tablet
	1599557	Savaysa 60 MG Oral Tablet
	1599545	edoxaban 15 MG [Savaysa]
	1599552	edoxaban 30 MG [Savaysa]
	1599556	edoxaban 60 MG [Savaysa]
	1599546	edoxaban Oral Tablet [Savaysa]
	1599547	Savaysa Oral Product
	1599548	Savaysa Pill
	1599543	edoxaban 15 MG Oral Tablet
	1599551	edoxaban 30 MG Oral Tablet
	1599555	edoxaban 60 MG Oral Tablet
	1599539	edoxaban 15 MG
	1599550	edoxaban 30 MG
	1599554	edoxaban 60 MG
	1599542	edoxaban Oral Tablet
	1599540	edoxaban Oral Product
	1599541	edoxaban Pill
	1599564	edoxaban tosylate
Idarucizumab	1716196	Praxbind
	1716191	idaruCIZUmab

	1716200	50 ML Praxbind 50 MG/ML Injection
	1716197	idaruCIZUmab 50 MG/ML [Praxbind]
	1716198	idaruCIZUmab Injection [Praxbind]
	1716199	Praxbind Injectable Product
	1716195	50 ML idaruCIZUmab 50 MG/ML Injection
	1716192	idaruCIZUmab 50 MG/ML
	1716194	idaruCIZUmab Injection
	1716193	idaruCIZUmab Injectable Product
Andexanet alfa	2045130	Andexxa
	2045114	andexanet alfa
	2045125	coagulation factor Xa (recombinant), inactivated-zhzo
	2108130	Andexxa 200 MG Injection
	2108129	coagulation factor Xa (recombinant), inactivated-zhzo 200 MG [Andexxa]
	2045132	andexanet alfa Injection [Andexxa]
	2656279	coagulation factor Xa (recombinant), inactivated-zhzo Injection [Andexxa]
	2656279	coagulation factor Xa (recombinant), inactivated-zhzo Injection [Andexxa]
	2045133	Andexxa Injectable Product
	2108128	coagulation factor Xa (recombinant), inactivated-zhzo 200 MG Injection
	2108127	coagulation factor Xa (recombinant), inactivated-zhzo 200 MG
	2045128	andexanet alfa Injection
	2045127	andexanet alfa Injectable Product
aPCC	968897	Feiba
	314504	anti-inhibitor coagulant complex
	1660001	Feiba 1 UNT Injection
	1659999	anti-inhibitor coagulant complex 1 UNT [Feiba]
	1660000	anti-inhibitor coagulant complex Injection [Feiba]
	1176000	Feiba Injectable Product
	1659998	anti-inhibitor coagulant complex 1 UNT Injection
	1659996	anti-inhibitor coagulant complex 1 UNT
	1659997	anti-inhibitor coagulant complex Injection
	1153633	anti-inhibitor coagulant complex Injectable Product
4PCC	1484959	Kcentra
	1484957	factor IX / factor VII / factor X / protein C / protein S / prothrombin
	1484963	Kcentra 1 UNT Injection
	1673581	coagulation factor IX, human 1 UNT / coagulation factor X, human 1 UNT / factor VII, human 1 UNT / protein C, human 1 UNT / protein S, human 1 UNT / prothrombin, human 1 UNT [Kcentra]
	1670055	factor IX / factor VII / factor X / protein C / protein S / prothrombin Injection [Kcentra]
	2657599	coagulation factor IX, human / coagulation factor X, human / factor VII, human / protein C, human / protein S, human / prothrombin, human

		Injection [Kcentra]
	2657599	coagulation factor IX, human / coagulation factor X, human / factor VII, human / protein C, human / protein S, human / prothrombin, human Injection [Kcentra]
	1484962	Kcentra Injectable Product
	1484958	coagulation factor IX, human 1 UNT / coagulation factor X, human 1 UNT / factor VII, human 1 UNT / protein C, human 1 UNT / protein S, human 1 UNT / prothrombin, human 1 UNT Injection
	1670052	factor IX / factor VII / factor X / protein C / protein S / prothrombin Injection
	2647373	coagulation factor IX, human-lans / coagulation factor X, human-lans / factor VII, human-lans / protein C, human-lans / protein S, human-lans / prothrombin, human-lans Injection
	2648925	coagulation factor IX, human / coagulation factor X, human / factor VII, human / protein C, human / protein S, human / prothrombin, human Injection
	2647373	coagulation factor IX, human-lans / coagulation factor X, human-lans / factor VII, human-lans / protein C, human-lans / protein S, human-lans / prothrombin, human-lans Injection
	2648925	coagulation factor IX, human / coagulation factor X, human / factor VII, human / protein C, human / protein S, human / prothrombin, human Injection
	1484955	factor IX / factor VII / factor X / protein C / protein S / prothrombin Injectable Product
	2663113	coagulation factor IX, human / coagulation factor X, human / factor VII, human / protein C, human / protein S, human / prothrombin, human Injectable Product
	2663686	coagulation factor IX, human-lans / coagulation factor X, human-lans / factor VII, human-lans / protein C, human-lans / protein S, human-lans / prothrombin, human-lans Injectable Product
	2663113	coagulation factor IX, human / coagulation factor X, human / factor VII, human / protein C, human / protein S, human / prothrombin, human Injectable Product
	2663686	coagulation factor IX, human-lans / coagulation factor X, human-lans / factor VII, human-lans / protein C, human-lans / protein S, human-lans / prothrombin, human-lans Injectable Product
	2643205	Balfaxar
	2643209	Balfaxar 1 UNT Injection
	2643207	Balfaxar Injectable Product
PCC	1670388	Profilnine
	1670383	factor IX complex
	1670392	Profilnine 1 UNT Injection
	1670389	factor IX complex 1 UNT [Profilnine]
	1670390	factor IX complex Injection [Profilnine]
	1670391	Profilnine Injectable Product

	1670387	factor IX complex 1 UNT Injection
	1670384	factor IX complex 1 UNT
	1670386	factor IX complex Injection
	1670385	factor IX complex Injectable Product

4F-PCC=four-factor prothrombin complex concentrate; 3F-PCC=three-factor prothrombin complex concentrate; PCC= prothrombin complex concentrate; aPCC=activated prothrombin complex concentrate.