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The incidence of thrombotic events with idarucizumab and andexanet alfa: A systematic review and meta-analysis

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ABSTRACT

Introduction: Direct thrombin inhibitor, dabigatran and factor Xa inhibitors, apixaban, edoxaban, and rivaroxaban (DOACs/NOACs), are currently the first-choice drugs in some indications. Life-threatening bleeding occurring during DOACs treatment may benefit from the use of reversal agents, however there are some concerns regarding potential rebound thrombotic events. In this systematic review we aimed to estimate the incidence of thrombotic events in patients treated with idarucizumab or andexanet alfa.

Methods: This systematic review included all prospective and retrospective studies, enrolling patients that received specific antidotes (idarucizumab, andexanet alfa and cirapantag) for anticoagulation reversal, published until October 2019 in CENTRAL, MEDLINE and PsycINFO. Studies in healthy individuals and those with less than 10 patients were excluded. The primary outcome was the incidence of thrombotic events and the secondary outcome was all-cause mortality. Studies screening and data extraction was performed in duplicate by reviewers. A random-effects meta-analysis was performed using the Freeman-Tukey transformation of the data. The results are expressed in percentages, with 95%-confidence intervals (CI), limited between 0 and 100% due to the data transformation.

Results: Overall 16 studies with 1774 patients were included (13 studies enrolling 1384 patients that received idarucizumab; 3 studies enrolling 390 patients that received andexanet alfa; cirapantag studies were not found). The pooled incidence rate of thrombotic events in the patients treated with specific antidote was 5.5% (95% CI 2.0–10.1%) until 30–90 days. The incidence of all-cause mortality was 13.3% (95% CI 9.6–17.5%).

Conclusions: In patients requiring idarucizumab or andexanet alfa to reach haemostasis, our data shows that there were 5.5% thrombotic events. The causality of harm associated to antidotes remains to be established due to the design of studies without a control group.

1. Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs/DOACs), including direct thrombin inhibitor dabigatran and factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, are already the first-choice drugs in the prevention of stroke in patients with non-valvular atrial fibrillation and are frequently used in the treatment of venous thromboembolism (VTE: deep venous thrombosis and/or pulmonary embolism) and in the prevention of postoperative VTE, particularly after orthopaedic surgery [1,2].

All DOACs have a predictable effect (onset and offset) without need for regular anticoagulation monitoring [1], and they seem to be safer than vitamin K antagonists (VKA) with significant lower risk of major bleeding, namely intracranial haemorrhage [3,4].

Nevertheless, patients treated with DOACs can have severe bleeding events, which are among the most common reason for withholding or discontinuing oral anticoagulants, and it is known that anticoagulation-related bleeding is associated with an increased risk of death [2].

Patients with life-threatening bleeding while treated with anticoagulants may require its reversal (with specific or non-specific agents),

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in addition to the standard measures. However, such circumstances, thrombotic events may occur either due to the activation of the coagulation of bleeding, prothrombotic baseline conditions and/or the rebound effect of the reversal agent (specific or non-specific). Prothrombin complex concentrates (PCCs) are non-specific reversal agents that have been used in clinical practice for indications beyond VKAs reversal, including for DOACs associated major bleeds [5]. Some studies evaluating PCC have shown thrombotic events ranging from 4 to 8%, although these studies only included patients with bleeding [6–8].

Regarding specific reversal agents the incidence of thrombotic events is not well established. Therefore, we aimed to systematically evaluate the incidence of thrombotic events in patients requiring idarucizumab, andexanet alfa or ciraparantag, in the clinical practice.

2. Methods

This systematic review has been developed based on the applicable aspects of Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines and Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) Checklist [9,10].

2.1. Types of studies included

This systematic review is based on all interventional or observational studies, including randomized controlled trials, controlled clinical trials, cohort/nested case-control studies, case-control studies, and case series, either prospective or retrospective. Studies had to include patients treated with anticoagulants (dabigatran, apixaban, edoxaban, rivaroxaban or low-molecular-weight-heparin) experiencing active haemorrhagic events, undergoing surgery/invasive procedures or other causes for anticoagulation reversal, deemed by the investigators to be eligible for reversal with specific antidotes (idarucizumab, andexanet alfa and ciraparantag). In contrast, studies with healthy individuals, studies with less than 10 patients, and case reports were excluded.

2.2. Types of outcome measures

The primary outcome was the incidence of thrombotic events occurring until discharge or within 30 days after the administration of the antidote. The secondary outcomes were the type of individual thrombotic event (pulmonary embolism, deep vein thrombosis, systemic embolism, ischemic stroke, transient ischemic attack and myocardial infarction) and all-cause mortality during the same timeframe. Whenever data for this time stratum was not available, we chose the closest follow-up to retrieve information.

2.3. Search methods for identification of studies

We searched for studies in the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (R), PsycINFO; from inception until October 2019. The full search strategy is presented in Table 1 of the Supplementary data appendix.

2.4. Data extraction and risk of bias evaluation

Two reviewers (AOR and DC) screened the titles and abstracts yielded by the searches against the inclusion criteria. In a second phase, the full text reports were assessed by independently by the reviewers to determine whether these met the inclusion criteria. The reasons for exclusion at this stage were recorded and are detailed in Table 2 of the Supplementary data appendix.

The data from the individual studies identified for inclusion was introduced into a pre-piloted form. This information included: study design; year of publication; length of follow-up; sample size; participants' characteristics; anticoagulant used; reason for the need of antidote; type of antidote; outcomes of interest.

The risk of bias was performed for the primary outcome and assessed independently by the reviewers using an adapted Critical Appraisal Skills Programme (CASP) Checklist [11] (Table 3 of the Supplementary data appendix).

In all these stages disagreements were solved by consensus or through a third party (CD).

2.5. Meta-analysis

The OpenMeta-analyst software was used to synthesize the results and to determine the pooled estimated incidence of thrombotic events and mortality [12].

The results of the incidence of the individual and pooled studies were expressed in percentages with 95% confidence intervals (CI). Freeman-Turkey transformation (double arcsine transformation) was used to adjust the dataset and estimate the frequency of the events, limiting the CI among 0–100% [13].

The DerSimonian and Laird model was used by default, as this approach is the simplest and most commonly used method for fitting the random effects model [14]. If studies reported to have zero events, we applied a correction factor of 0.5 to allow for the inclusion of those studies in the analysis [15]. Statistical heterogeneity was assessed using I^2 (based on chi-squared statistic and its degrees of freedom), which describes the percentage of the variability, and in effect estimates, heterogeneity rather than chance.

3. Results

Electronic database search yielded a total of 605 published references. After removal of duplicates, screening of title and abstract, and evaluation for full-text eligibility, we included 16 studies for qualitative analysis. Fig. 1 shows the detailed results of the search strategy.

3.1. Characteristics of included studies

After the screening and full-text assessment stages, 16 cohort studies (2 prospective and 14 retrospective) fulfilled the inclusion criteria. Thirteen studies included 1384 treated with idarucizumab, and 390 patients from 3 studies received andexanet alfa. None of the included studies reported the use of ciraparantag.

Overall these 1774 patients were previously treated with anticoagulants: 1754 of them were treated with DOACs (78.0% dabigatran; 12.6% apixaban; 7.7% rivaroxaban; 0.6% edoxaban) and the remaining 20 patients were treated with a low-molecular weight heparin (LMWH). The mean age of the patients enrolled in the studies ranged between 69 years and 81 years (4 studies did not report age data). The follow-up lasted until discharge in 5 studies, until 30 days in 7 studies and 90 days in 4 studies.

The characteristics of the studies and patient population are presented in Tables 1 and 2.

Regarding the reasons for the use of specific antidotes, among the included studies 1327 patients had active bleeding, 399 patients requiring anticoagulation reversal for urgent surgery and 48 patients with other causes for anticoagulation reversal or without the reason reported.

In 10 of the 16 studies, information on resumption of oral anticoagulation was provided. The time for this resumption was heterogeneous and it was related with the occurrence of events in larger studies [16,17].

The most important risk of bias features of the included studies rely on the absence of a control group, imprecision due to the small sample size of some studies and the absence of clear data in some studies where outcomes were not reported (reporting bias) (Supplementary Table 3 for other features).

Table 1
Main characteristics of included studies.

Reference	Year	Type of study	Total patients (males)	Mean age (range)	DOAC	Cause for antidote		
						Bleeding	Undergoing surgery	Other causes
Brennan [18]	2018	Retrospective cohort	23 (13)	77 (50–91)	Dabigatran	17	6	0
Fanikos [19]	2019	Retrospective cohort	359 (ND)	ND	Dabigatran	207	129	23
Oberladstatter [20]	2019	Retrospective cohort	15 (9)	81 (SD ± 10)	Dabigatran	7	8	0
Okishige [21]	2019	Retrospective cohort	21 (6)	73 (51–88)	Dabigatran	21	0	0
Kermer [22]	2017	Retrospective cohort	31 (14)	75 (40–94)	Dabigatran	12	0	19
Kupper [23]	2019	Retrospective cohort	32 (22)	78 (SD ± 9)	Dabigatran	23	0	9
Pollack [16]	2017	Prospective cohort	503 (274)	78 (21–96)	Dabigatran	301	202	0
Raco [24]	2018	Retrospective cohort	11 (8)	81 (71–85)	Dabigatran	5	6	0
Sheikh-taha [25]	2018	Retrospective cohort	13 (12)	77 (SD ± 7)	Dabigatran	11	2	0
Singh [26]	2019	Retrospective cohort	265 (ND)	ND	Dabigatran	265	0	0
Sowerby [27]	2019	Retrospective cohort	12 (4)	73 (56–83)	Dabigatran	6	5	1
van der Wall [28]	2018	Retrospective cohort	88 (51)	76 (SD ± 9)	Dabigatran	53	35	0
Wheeler [29]	2019	Retrospective cohort	14 (ND)	ND	Dabigatran	11	3	0
Brown [30]	2020	Retrospective cohort	25 (10)	75 (71–83)	Apixaban	17	3	0
					Rivaroxaban	5	0	0
Connolly [17]	2019	Prospective cohort	352 (187)	77 (SD ± 10)	Apixaban	194	0	0
					Rivaroxaban	128	0	0
					Edoxaban	10	0	0
					Enoxaparin	20	0	0
Stevens [31]	2019	Retrospective cohort	13 (7)	69 (59–79)	Apixaban	9	0	0
					Rivaroxaban	4	0	0

ND: not described; SD: standard deviation.

3.2. Incidence of thrombotic events

The pooled analysis included 11 studies and the incidence rate of thrombotic events in the patients treated with specific antidote was 5.5% (95% CI 2.0–10.1%) (Fig. 2).

We performed an exploratory analysis considering that studies not reporting events had zero events. The incidence of thrombotic events using this assumption was 3.7% (95% CI 1.1–7.4%) (Supplementary Fig. 1). Including only studies with outcomes at discharge or 30 days (i.e. excluding thrombotic events at 90 days) the incidence of thrombotic events was 4.4% (95% CI 1.2–9.0%).

The incidence of thrombotic events according to the use of each specific antidote was 3.3% (95% CI 0.7–7.2%) for idarucizumab, and 10.6% (95% CI 1.9–23.7%) for andexanet alfa (Supplementary Table 4).

Regarding the incidence of thrombotic events according to the cause for which an antidote was needed, we reached the following results: 0.7% (95% CI 0–3.3%) (Supplementary Fig. 2) for patients undergoing surgery and 5.9% (95% CI 1.8–11.6%) (Supplementary Fig. 3) for bleeding patients.

3.3. Incidence of all-cause mortality

The pooled analysis of all-cause mortality included 14 studies and the mortality incidence in this circumstance was 13.3% (95% CI 9.6–17.5%) (Fig. 3), with a moderate to high statistical heterogeneity (I^2 = 58.99%).

4. Discussion

In this systematic review of observational studies enrolling patients that required the treatment with Idarucizumab or Andexanet alpha we found that the incidence of thrombotic events was 5.5% and overall mortality rate was 13.3%. This means that the thrombotic events occur at a non-negligible frequency among a population with a substantial short-term mortality risk, highlighting that risk minimization strategies

Table 2
Antidote used, follow-up and outcomes.

Reference	Total patients	Antidote used	Follow-up time after infusion	ATE	PE	DVT	SE	IS	MI	TIA	Non-specific VTE	All-cause mortality
Brennan [18]	23	Idarucizumab	Until discharge	0	–	–	–	–	–	–	–	6
Kermer [22]	31	Idarucizumab	Until discharge	NR	NR	NR	NR	NR	NR	NR	NR	2
Kupper [23]	32	Idarucizumab	90 days	NR	NR	NR	NR	NR	NR	NR	NR	10
Pollack [16]	503	Idarucizumab	30 days	28	6	7	2	7	6	–	–	66
Raco [24]	11	Idarucizumab	90 days	4	–	2	–	2	–	–	–	4
Singh [26]	265	Idarucizumab	Until discharge	NR	NR	NR	NR	NR	NR	NR	NR	22
			30 days	3	–	–	–	–	–	–	3	NR
van der Wall [28]	88	Idarucizumab	90 days	4	2	–	–	2	–	–	–	17
Wheeler [29]	14	Idarucizumab	30 days	NR	NR	NR	NR	NR	NR	NR	NR	3
Oberladstatter [20]	15	Idarucizumab	Until discharge	0	–	–	–	–	–	–	–	0
Okishige [21]	21	Idarucizumab	30 days	0	–	–	–	–	–	–	–	0
Sheikh-taha [25]	13	Idarucizumab	Until discharge	0	–	–	–	–	–	–	–	0
Sowerby [27]	12	Idarucizumab	90 days	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fanikos [19]	359	Idarucizumab	Until discharge	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brown [30]	25	Andexanet alfa	30 days	0	–	–	–	–	–	–	–	6
Connolly [17]	352	Andexanet alfa	30 days	40	5	13	–	14	7	1	–	49
Stevens [31]	13	Andexanet alfa	30 days	5	1	1	–	1	1	–	1	2

NR: not reported; ATE: all thrombotic events; PE: pulmonary embolism; DVT: deep venous thrombosis; SE: systemic embolism; IS: ischemic stroke; MI: myocardial infarction; TIA: transient ischemic attack; VTE: venous thromboembolism.

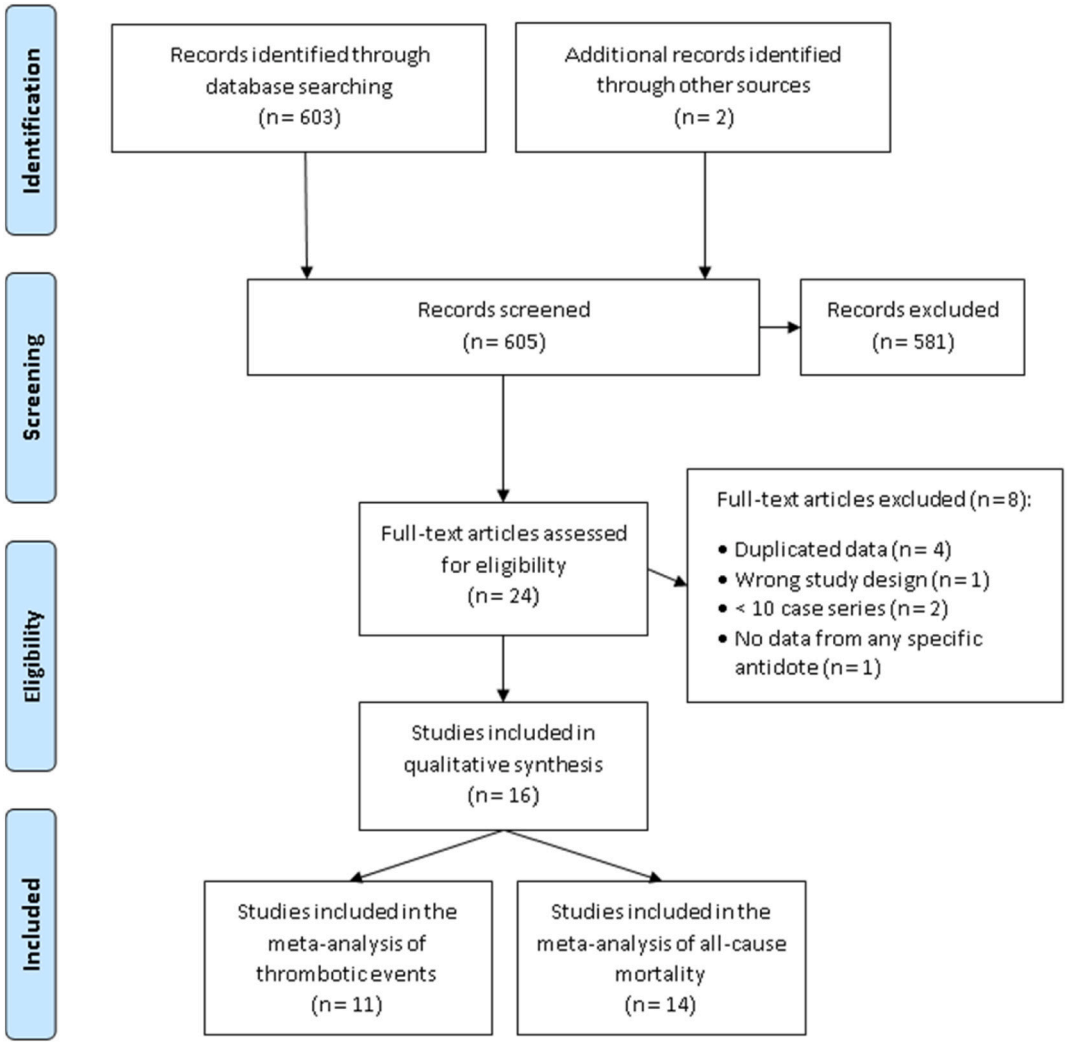

Fig. 1. Flowchart of study selection.

are a clear priority in this setting and that robust evidence should be pursued.

Most of the data were derived from studies and patients with major bleeding events which are medical emergencies that may have a poor prognosis, with limited treatment options for such patients [17]. Strategies to manage bleeding complications in patients treated with DOACs require the adequate assessment of patients characteristics including the bleeding location and severity, the time of the last DOAC intake, the prescribed dosage regimen, renal function and other factors influencing haemostasis, such as concomitant use of antiplatelet drugs [1]. This clinical assessment is essential to prevent inappropriate/unnecessary antidote usage and to better select the treatments proposed for these patients and prevent possible side/thrombotic rebound effects.

It is important to stress that the body of evidence is larger for

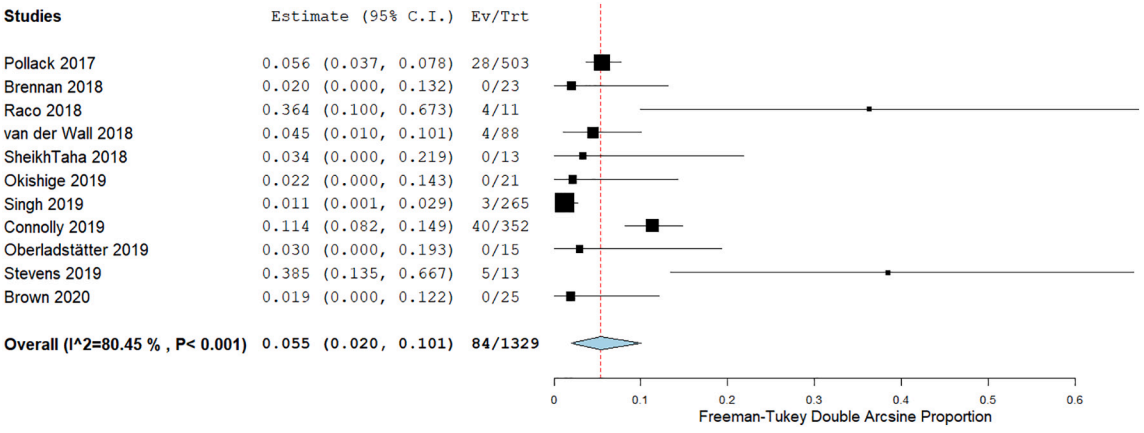

Fig. 2. Incidence of thrombotic events with DOAC antidotes.

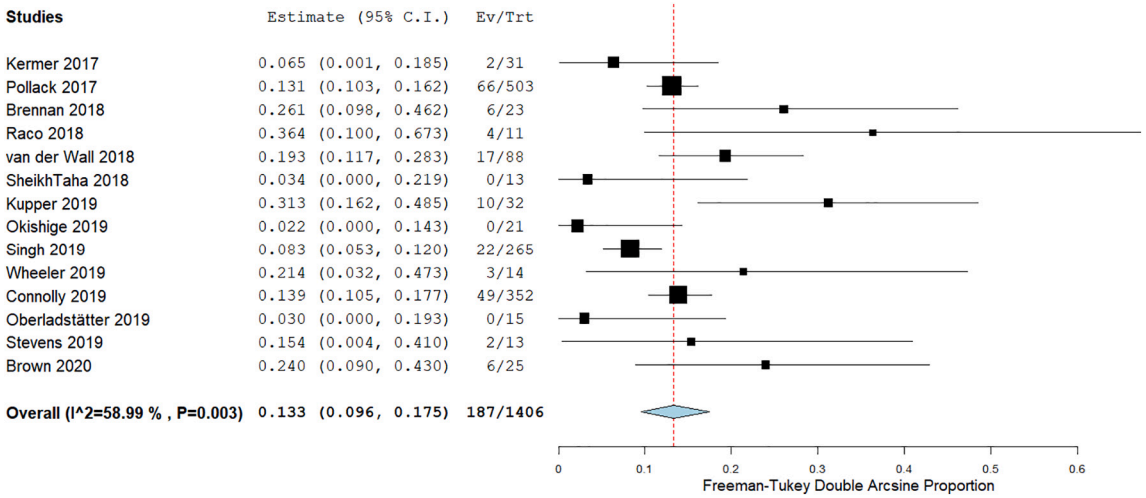

Fig. 3. Incidence of all-cause mortality with DOAC antidotes.

idarucizumab than andexanet alfa, and that no ciraparantag studies fulfilled the inclusion criteria. Within the three studies with andexanet alfa, the incidence of thrombotic events was as high as 10.6%. In the ANNEXA-4 study, most events occurred in patients when resumption of oral anticoagulation was delayed or in patients who did not restart anticoagulation, suggesting that thrombotic events may not be directly related to the usage of antidotes. After restarting oral anticoagulation, no patient had a thrombotic event during the 30-day follow-up [17]. Therefore, the resumption of oral anticoagulation after major bleeding should be pursued as soon as clinically appropriate [31]. The data from ANNEXA-4 study [17] led to andexanet alfa approval in the United States but a black-box warning was added for putative thromboembolic risks [32].

It is relevant to inform that the population studied had a short-term high mortality rate of 13.3%. It is difficult for infer whether the deaths were due to the bleeding events, thrombotic events or other causes and most studies did not report the cause of death. Nevertheless, it seems relevant to state that in the studies RE-VERSE AD and van der Wall et al. [16,28], there were no deaths related to thrombotic events in the first 5 days after enrolment and within this timeframe, many deaths were related to the severity of bleeding.

Regarding patients requiring specific antidotes due to the need to urgent/emergent surgery, the majority data were derived from the RE-VERSE AD [16], which together with the remaining surgical patients in the other studies, showed a incidence of thrombotic events of 0.7% in this context, lower than the incidence of 5.9% of thrombotic events in bleeding patients that received idarucizumab or andexanet alfa. Once again, the resumption at earlier stages might explain, at least partially these results. In RE-VERSE AD the antithrombotic therapy was restarted in 90.1% of the surgical patients at an average of 3.5 days, while in bleeding patients the antithrombotic treatment resumption occurred in 72.8% of the patients at an average of 13.2 days [16]. In the other hand, the precision of the data for thrombosis in the surgical setting is low which may lead spurious comparisons with the bleeding stratum which has more data.

We did not perform analyses according to each type of thrombotic events due to the data scarcity when assessing each one individually. Nevertheless, the pattern of thrombotic events ascertained from the largest studies (RE-VERSE AD [16] and ANNEXA-4 [17]) showed that stroke and venous thromboembolism were the most frequent thrombotic events. Stroke can be explained by the indication for oral anticoagulation which was atrial fibrillation in most of these patients (95% in RE-VERSE AD; 80% in ANNEXA-4), while VTE may be related to the immobility of the hospitalization/critically illness, in both circumstances activation of coagulation due bleeding may have a role, while the share attributable to the rebound effects of specific antidotes is unknown.

Our findings are important because they inform all stakeholders about the incidence of thrombotic events based on the best available evidence which is currently based on non-controlled studies. While it is advantageous to use randomized controlled trials to study the relative efficacy and safety of the specific antidotes, there are many challenges in the application of this study design to a highly vulnerable population mainly because of logistic and ethical issues, given the perceived risks of placebo assignment. Nonetheless, we recommend that a possible comparison with the standard therapy (also with inherent challenges) should not be excluded. In fact there is an ongoing open-label randomized controlled trial (ANNEXA-I; NCT03661528) comparing andexanet to usual care for patients with intracranial haemorrhage previously treated with Xa inhibitors, which will push the standards of trials in this setting for a higher stratum in terms of establishing benefits and harms. Our data also contains insights related to clinical practice, namely, the importance of re-initiating oral anticoagulation as early as possible, and whenever possible, to prevent earlier thrombotic events.

The limitations of this systematic review are inherent to the included studies, such as, the absence of a control group and the small sample size of some studies. Other constraints are related to the nature and aims of the studies that were not designed to detect adverse events of the specific antidotes, specifically, thrombotic events, this includes some studies where outcomes were not reported (reporting bias). Also, most of the included studies did not report clear data about the type of bleeding or the coexisting conditions (reporting bias). These issues will be overcome, at least partially, with the randomized controlled trials. Nevertheless we believe that the data that we provided through the meta-analyses is relevant and intends to quantify and inform the potential risks associated to this specific circumstance, despite the differences in the setting (active bleeding, urgent/emergent surgery), baseline oral anticoagulants, specific antidotes, study designs, and duration of follow-up which may explain the statistical heterogeneity found. Finally, none of studies and nor the pooled incidence accounted for the competing risk of death when analysing thrombotic events.

5. Conclusions

In patients requiring Idarucizumab and Andexanet alfa, our data shows that the incidence of thrombotic events in this context was 5.5% and the incidence of death was 13.3%. Therefore, clinicians should remain vigilant, as well as consider close monitoring and follow-up of these patients not only for haemorrhagic events but also for thrombotic events. Nevertheless, it is relevant to stress that the causality of harm

associated to specific antidotes in this context remains to be established due to the fragility of studies design without a control group.

Declaration of competing interest

JJF had speaker and consultant fees with Grunenthal, Fundação MSD (Portugal), TEVA, MSD, Allergan, Medtronic, GlaxoSmithKline, Novartis, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie, Sunovion-Pharmaceuticals. FJP had consultant and speaker fees with Astra Zeneca, Bayer, BMS, Boehringer Ingelheim and Daiichi Sankyo. DC has participated in educational meetings and/or attended a conferences or symposia (including travel, accommodation) with Daiichi Sankyo, Menarini, Merck Serono and Roche, in the last 3 years. The remaining authors have nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.09.003.

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