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Review Article

Idarucizumab for dabigatran reversal: A systematic review and meta-analysis of indications and outcomes

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ABSTRACT

Background: Idarucizumab has been approved to reverse the anticoagulant effect of dabigatran. However, there is little knowledge of the effectiveness and safety of idarucizumab in daily practice.
Aims: This systematic review and meta-analysis aims to evaluate the use, effectiveness and outcomes of idarucizumab.
Methods: A systematic literature search was performed up to September 8th 2022. Original studies including patients prescribed idarucizumab, evaluating prescription indications, prescription appropriateness, haemostatic efficacy and/or the occurrence of adverse events were eligible. Case-reports and studies performed in patients ≤18 years or in healthy volunteers were excluded. Study selection and data extraction were performed by two independent reviewers. Pooled estimates were calculated using the random-effects model, after Freeman-Tukey double-arcsine transformation.
Results: Thirty studies comprising 3602 patients were included. Idarucizumab was prescribed for bleeding (63.1 %, 95%CI 57.0 %–69.0 %), invasive procedures (30.5 %, 95%CI: 24.1 %–37.2 %), to enable thrombolysis (range: 2.0 %–27.3 %), dabigatran intoxication without bleeding (range: 3.6 %–7.0 %) or unspecified reasons (range: 0.4 %–18.8 %). Overall, 2.8 % (95%CI 0.5 %–6.2 %) of prescription indications were reported to be inappropriate upon post-hoc evaluation. Hemostatic effectiveness was achieved in 77.7 % (95%CI 66.7 %–87.2 %) and peri-procedural haemostasis was normal in 98.5 % (95%CI 86.6 %–100 %) of patients. The pooled incidences of all-cause mortality and thromboembolic events at any follow-up duration were 13.6 % (95%CI 9.6 %–17.9 %) and 2.0 % (95%CI 0.8 %–3.4 %), respectively.
Conclusion: Idarucizumab was mainly prescribed in the setting of bleeding. The reported hemostatic effectiveness was good, especially perioperatively, and the incidence of thromboembolic events was low. Patients with dabigatran-associated bleeding or requiring an urgent procedure nonetheless face a high mortality risk.

1. Introduction

Idarucizumab has been approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) to rapidly reverse the anticoagulant effect of dabigatran [1,2]. The results of the RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) trial, a phase III observational study in patients with uncontrollable bleeding or who required an urgent procedure with high bleeding risk, were decisive for this approval. In this study, idarucizumab was found to be effective and safe for the reversal of dabigatran [3]. Randomized controlled trials to accurately evaluate the efficacy and outcomes of idarucizumab are, however, unavailable. Even so, since the approval in 2015 and in the absence of alternative strategies to reverse the effect of dabigatran, idarucizumab has been widely introduced in clinical practice and several observational studies have reported on the indications and outcomes of idarucizumab administration.

With this present systematic review and meta-analysis we aimed to evaluate the literature on the use and outcomes of idarucizumab. We provide insight into prescription indications, appropriateness of prescriptions, hemostatic efficacy, the need for repeated administration, the occurrence of adverse events associated with idarucizumab administration, and the re-initiation of anticoagulant therapy.

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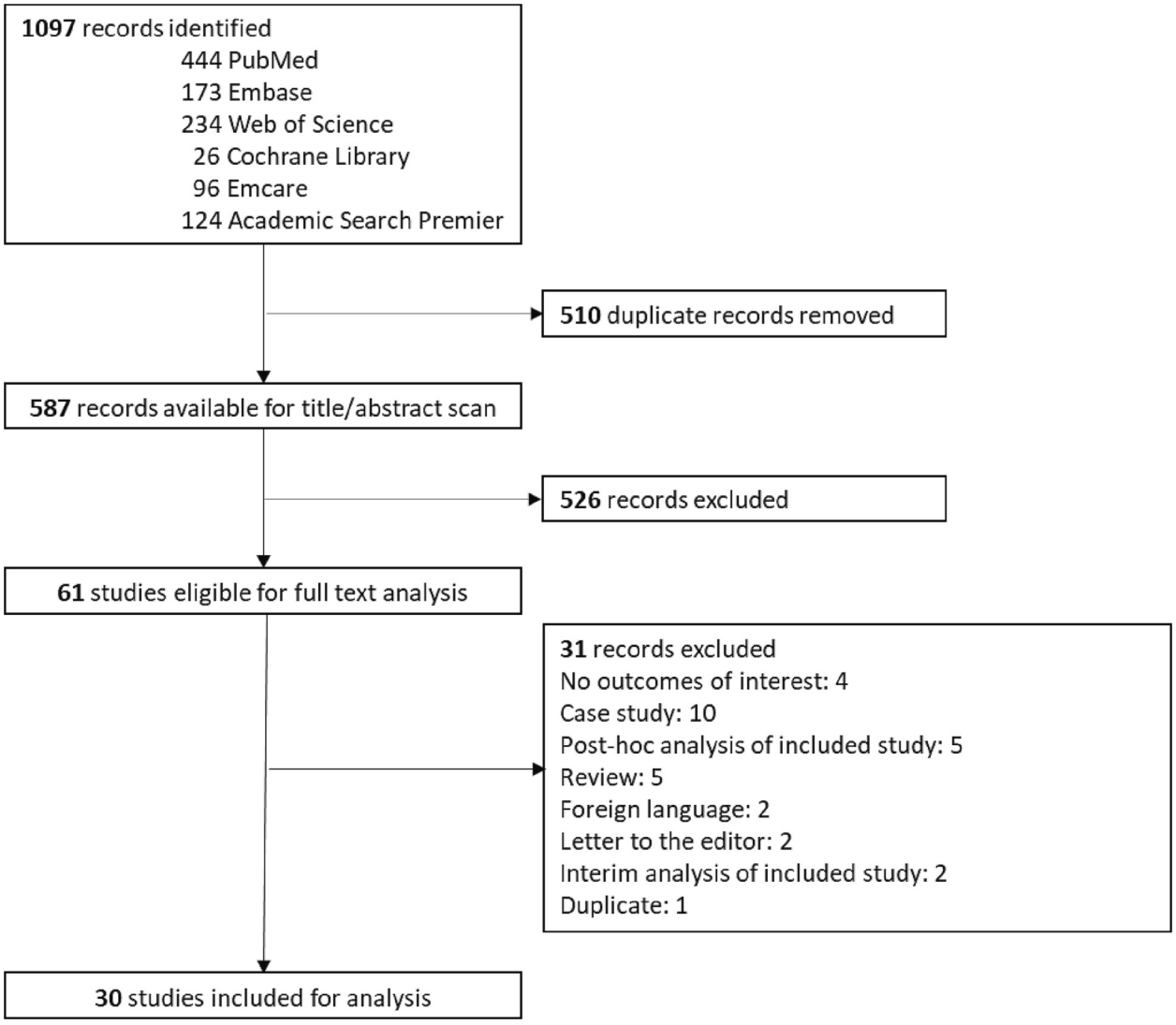

Fig. 1. Flowchart of literature search and study selection.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [4]. The review protocol was registered a priori in the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42022359668).

2.1. Data sources and search strategy

A systematic literature search in the MEDLINE (PubMed), Embase, Web of Science, Cochrane Library, Emcare and Academic Search Premier databases was performed from inception to September 8th 2022 with the help of a research librarian. Search terms consisted of "idarucizumab", "Praxbind", "BI 655075" and "ADABI-FAB". The search was limited to original articles, with the exception of case-reports. The full search terms are available in the Supplementary Materials. All identified records were exported to a bibliographic EndNote database, and duplicates were removed.

2.2. Selection criteria

Included studies were required to meet specific criteria. The study population were patients who were prescribed idarucizumab. One of the following outcomes had to be measured and reported: a) prescription indication; b) efficacy of idarucizumab; c) need for a second administration of idarucizumab; d) retrospective appropriateness of prescribing idarucizumab; or e) adverse events after administration of idarucizumab. Clinical trials, cohort studies, case-control studies, cross-sectional studies and case series published in English or Dutch language were eligible for inclusion. Case-reports and studies performed in patients under 18 years or in healthy volunteers were excluded.

Furthermore, studies that exclusively enrolled patients with ischaemic stroke who were prescribed idarucizumab to allow for thrombolysis were excluded, as this is a highly specific population with outcomes that may not be generalizable to the broader population prescribed idarucizumab for bleeding management or prevention.

2.3. Study selection

The study selection was performed by two independent and blinded reviewers (S.H., E.M.), using the Rayyan application. Titles and abstract of the identified records were screened for eligibility. The remaining articles were then analyzed by full text, applying the predefined inclusion criteria, to select articles for inclusion. Any disagreement was handled by discussion or involvement of a third reviewer (F.K.) until

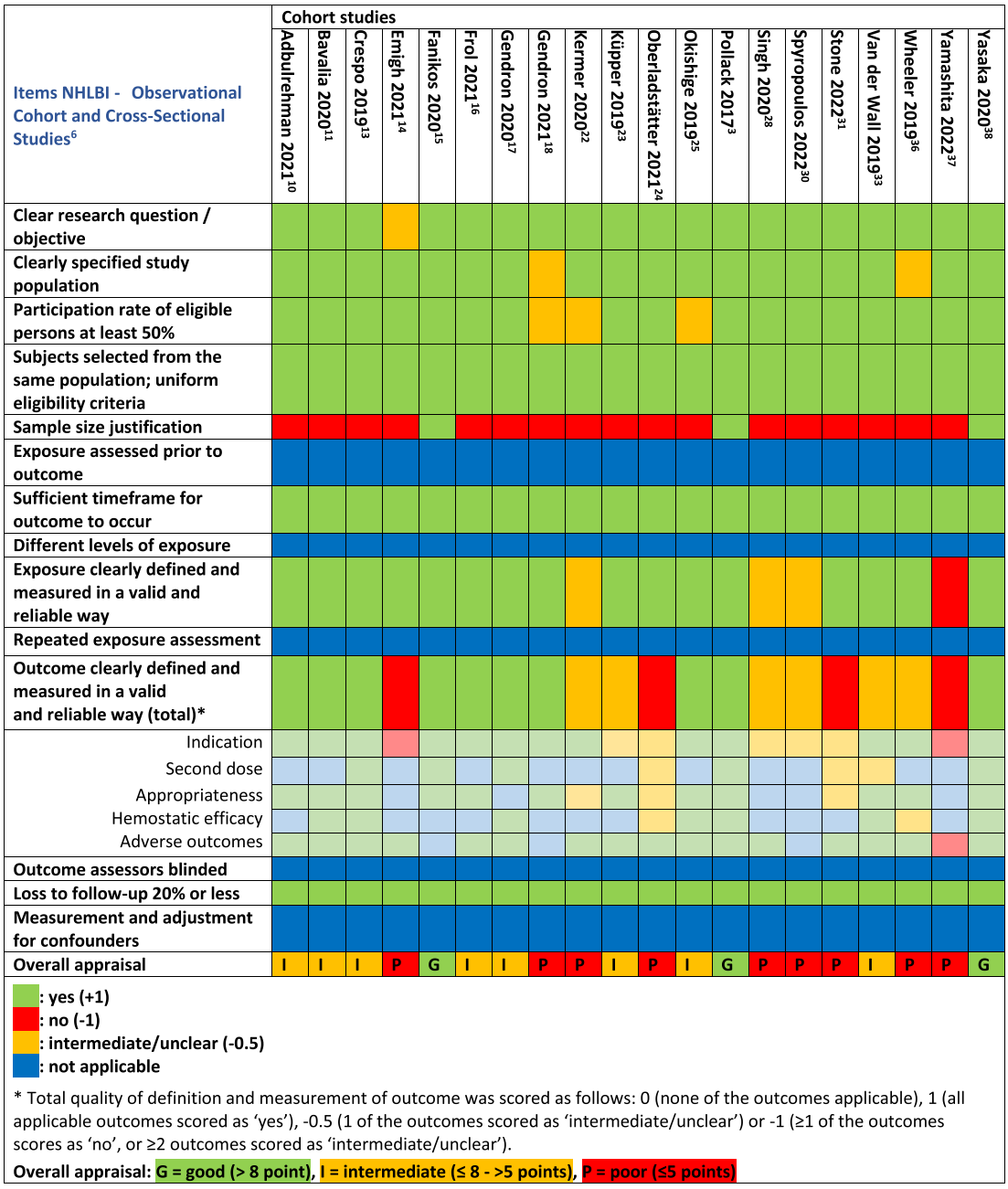

Fig. 2. Quality assessment cohort studies, using the NIH Quality Assessment Tool.

consensus was reached.

2.4. Data extraction

Two reviewers independently extracted data from each included study (S.H., E.M.). A predesigned extraction table was used to this end to collect the following data: first author; publication year; study design; sample size of patients prescribed idarucizumab; prescription indications; need for repeated idarucizumab administration; inappropriate idarucizumab prescriptions (i.e., guideline/protocol non-adherence, inappropriate indication, prescription in patients not using dabigatran, inappropriate dosage, laboratory testing prior to idarucizumab administration indicating no or irrelevant dabigatran activity); percentage in which treatment with idarucizumab was reported to be effective (i.e. hemostatic efficacy, peri-procedural efficacy as defined in the included studies); incidence and types of adverse events (e.g. thromboembolic events, mortality). Conflicting opinions were resolved by discussion or involvement of a third reviewer (F.K.).

2.5. Study quality

Included studies were subjected to methodological quality assessment by two independent reviewers (S.H., E.M.), using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case series, and the NIH Quality Assessment Tool developed by the National Heart, Lung and Blood Institute for observational cohort or cross-sectional studies [5,6]. Each item was rated as yes, no, moderate/unclear or not applicable. The overall quality appraisal was allocated as follows: good quality (>8 point), intermediate quality (≤ 8 to >5 points), or poor quality (≤5 points).

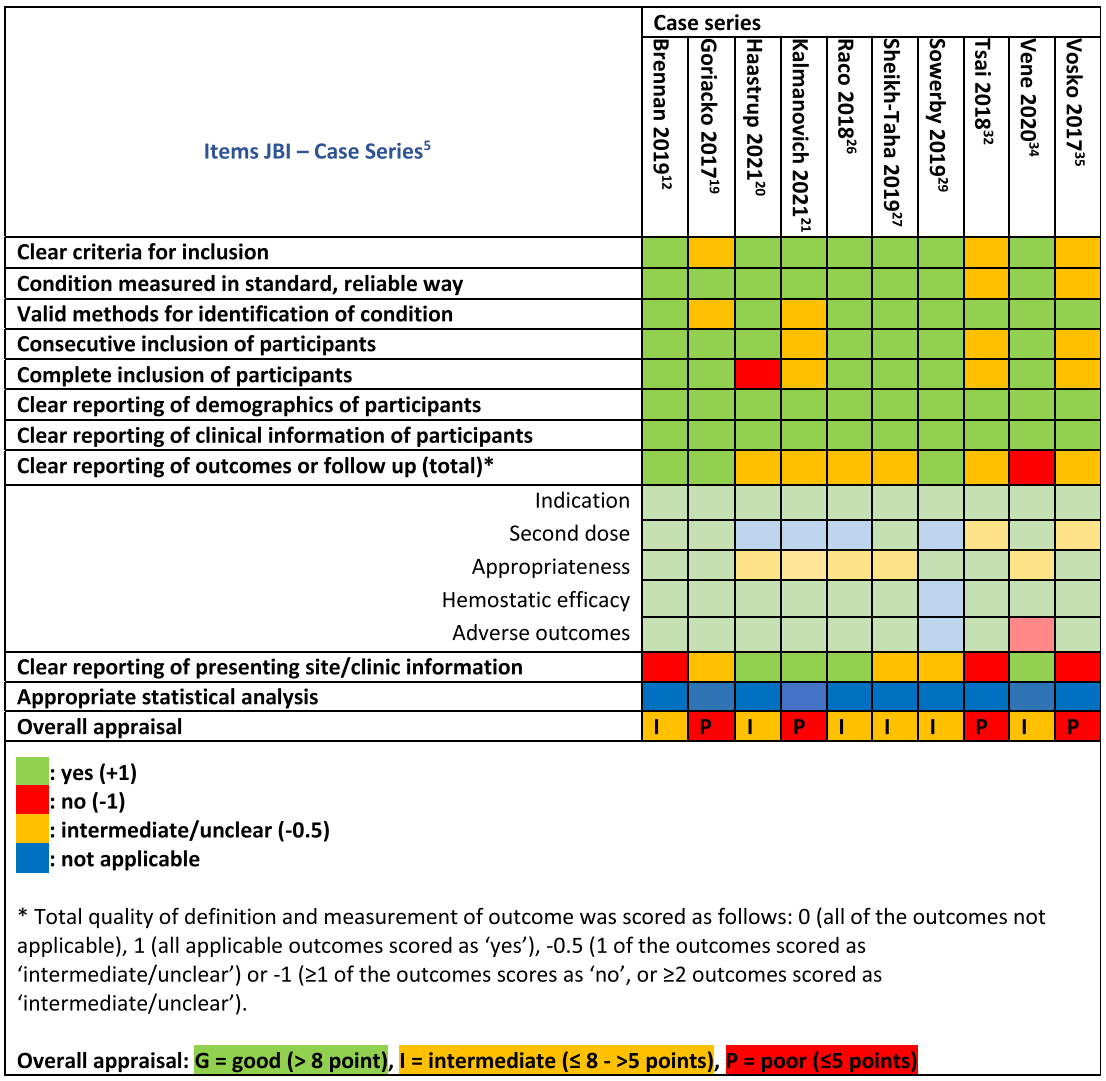

Fig. 3. Quality assessment case series, using JBI Critical Appraisal Checklist.

2.6. Statistical methods

The Freeman-Tukey double arcsine transformation was applied to the proportional data obtained from each study to stabilize variances [7,8]. To calculate the pooled estimates and corresponding 95 % confidence intervals (CIs), the random effects model with restricted maximum likelihood (REML) was utilized [9]. Between-study heterogeneity was assessed with the I^2 statistic and *Q*-test. All statistical analyses were performed using the Metafor package in R, version 4.2.2.

3. Results

3.1. Study selection and characteristics

The initial literature search resulted in 587 records after removing duplicates. After screening titles and abstracts of the remaining records, the full texts of 61 articles were assessed for eligibility. Finally, 30 studies were included in this systematic review (Fig. 1) [3,10–38]. All selected studies, comprising a total of 3602 patients receiving idarucizumab, were published between 2017 and 2022. Of the 30 included studies, 18 were cohort studies, 10 were case series, 1 was a cross-sectional study and 1 was a registry study. The sample size of the included studies ranged from 7 to 1232 patients receiving idarucizumab.

3.2. Quality assessment

The results of the quality assessment are shown in Figs. 2 and 3. Three of the cohort studies were appraised as of good quality, eight of intermediate quality and nine of poor quality. Of the case series six and four studies were considered as of good and intermediate respectively, while none of the case series met the requirements for a good quality appraisal.

3.3. Prescription indications and inappropriateness of prescriptions

The indications for idarucizumab prescription, as reported by the included studies, are summarised in Table 1 [3,10–12,15,17,19,20,23,24,26–38]. Bleeding was the most common reason to prescribe idarucizumab, with a pooled proportion of 63.1 % (95 % CI 57.0 % – 69.0 %, I^2: 82 %; 22 studies, n = 3190, Fig. 4) [3,10–12,15,17,19,20,23,24,26,27,29–38]. Idarucizumab was prescribed prior to invasive procedures in 30.5 % of cases (95%CI: 24.1 % – 37.2 %, I^2: 91 %; 22 studies, n = 3190, Fig. 5) [3,10–12,15,17,19,20,23,24,26,27,29–38]. Even though the majority of procedures were classified as urgent, idarucizumab was prescribed in the context of elective procedures as well (3.3 % – 5.9 %) [10,15]. Other indications for idarucizumab administration were acute ischaemic stroke in order to allow for intravenous thrombolysis or thrombectomy

Table 1
Included studies and prescription indications.

Study	Study design	Sample size idarucizumab	Prescription indication (n, %)
Abdulrehman et al., 2021 [10]	Retrospective cohort	85	Bleeding: 65 (76.5 %) Procedure: 16 (18.8 %) – Urgent procedure: 11 (12.9 %) – Elective procedure: 5 (5.9 %) Other indication (unspecified): 4 (4.7 %)
Bavalia et al., 2020 [11]	Prospective cohort	21	Bleeding: 16 (76.2 %) Procedure: 5 (23.8 %)
Brennan et al., 2019 [12]	Case series	23	Bleeding: 17 (74.0 %) Procedure: 6 (26.0 %)
Crespo et al., 2019 [13]	Retrospective cohort	53	Procedure: 53 (100 %), all cardiac transplant surgery
Emigh et al., 2021 [14]	Prospective cohort	9	N.A.
Fanikos et al., 2020 [15]	Cross-sectional	359	Bleeding: 207 (57.7 %) Procedure: 117 (35.3 %) – Urgent procedure: 115 (32.0 %) – Elective procedure: 12 (3.3 %) Thrombolysis/ thrombectomy: 14 (3.9 %) Other indication (unspecified): 11 (3.1 %)
Frol et al., 2021 [16]	Prospective cohort	13	Bleeding: 13 (100 %), all intracranial hemorrhage
Gendron et al., 2020 [17]	Retrospective cohort	87	Bleeding: 61 (70.1 %) Procedure: 24 (27.6 %) Dabigatran intoxication without bleeding: 2 (2.3 %)
Gendron et al., 2021 [18]	Retrospective cohort	87	N.A.
Goriacko et al., 2017 [19]	Case series	7	Bleeding: 6 (85.7 %) Procedure: 1 (14.3 %)
Haastrup et al., 2021 [20]	Case series	46	Bleeding: 20 (43.0 %) Procedure: 22 (48.0 %) Dabigatran intoxication without bleeding: 3 (7.0 %) Thrombolysis/ thrombectomy: 1 (2.0 %)
Kalmanovich et al., 2021 [21]	Case series	10	Procedure: 10 (100 %), all cardiac transplant surgery
Kermer et al., 2020 [22]	Retrospective cohort	40	Bleeding: 40 (100 %), all intracranial hemorrhage
Küpper et al., 2019 [23]	Cohort (registry)	32	Bleeding: 20 (62.5 %) Procedure: 4 (12.5 %) Thrombolysis/ thrombectomy: 8 (25.0 %)
Oberladstätter et al., 2021 [24]	Retrospective cohort	15	Bleeding: 7 (46.7 %) Procedure: 8 (53.3 %)
Okishige et al., 2019 [25]	Retrospective cohort	21	Bleeding: 21 (100 %), all periprocedural cardiac tamponade
Pollack et al., 2017 [3]	Prospective cohort, observational, open-label, phase 3	503	Bleeding: 301 (59.8 %) Procedure: 202 (40.2 %)
Raco et al., 2018 [26]	Case series	11	Bleeding: 6 (54.5 %) Procedure: 5 (45.5 %)
Sheikh-Taha et al., 2019 [27]	Case series	13	Bleeding: 11 (84.6 %) Procedure: 2 (15.4 %)
Singh et al., 2020 [28]	Retrospective cohort	266	Bleeding: 266 (100 %)
Sowerby et al., 2019 [29]	Case series	12	Bleeding: 6 (50.0 %) Procedure: 5 (41.7 %) Other indication (unspecified): 1 (8.3 %)
Spyropoulos et al., 2022 [30]	Retrospective cohort	1232	Bleeding: 626 (50.8 %) Procedure: 270 (21.9 %) Both bleeding and procedure: 105 (8.5 %) Other indication (unspecified): 231 (18.8 %)
Stone et al., 2022 [31]	Retrospective cohort	329	Bleeding: 123 (37.4 %) Procedure: 206 (62.6 %)
Tsai et al., 2018 [32]	Case series	11	Bleeding: 5 (45.5 %) Procedure: 1 (9.1 %) Both bleeding and procedure: 3 (27.3 %) Thrombolysis/ thrombectomy: 2 (18.2 %)
van der Wall et al., 2019 [33]	Retrospective cohort	88	Bleeding: 53 (60.2 %) Procedure: 35 (39.8 %)
Vene et al., 2020 [34]	Case series	17	Bleeding: 11 (64.7 %) Procedure: 4 (23.5 %) Thrombolysis/ thrombectomy: 2 (11.8 %)
Vosko et al., 2017 [35]	Case series	11	Bleeding: 4 (36.4 %) Procedure: 4 (36.4 %) Thrombolysis/ thrombectomy: 3 (27.3 %)

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Table 1 (*continued*)

Study	Study design	Sample size idarucizumab	Prescription indication (n, %)
Wheeler et al., 2019 [36]	Retrospective cohort (audit review)	14	Bleeding: 11 (78.6 %) Procedure: 3 (21.4 %)
Yamashita et al., 2022 [37]	Prospective cohort	12	Bleeding: 11 (91.7 %) Procedure: 1 (8.3 %)
Yasaka et al., 2020 [38]	Prospective cohort (post-marketing surveillance study; interim analysis)	262	Bleeding: 173 (66.0 %) Procedure: 83 (81.7 %) Both bleeding and procedure: 5 (1.9 %) Other indication (unspecified): 1 (0.4 %)

Abbreviations: N.A.: not applicable.

(2.0 % – 27.3 %) and dabigatran intoxication in the absence of bleeding (2.3 % - 7.0 %) [15,17,20,23,32,34,35]. Idarucizumab was prescribed for unspecified reasons in 0.4 % to 18.8 % of cases [10,15,29,30,38].

According to product labels, idarucizumab is indicated for reversal in dabigatran-treated patients with a life-threatening or uncontrollable bleeding, or requirement for an emergency invasive procedure [1,2]. Overall, 2.8 % (95%CI 0.5 % – 6.2 %, I^2: 86 %; 22 studies, $n = 1707$, Fig. 6) of idarucizumab prescription indications deviated from the product label and were deemed inappropriate [3,10–13,15,16,18–22,25–27,29,32–36,38–44]. The following inappropriate indications were reported: bleeding was not major nor uncontrollable, the invasive procedure could have been delayed, dabigatran intoxication in the absence of bleeding, an unspecified indication for prescribing idarucizumab, or, in retrospect, the patient was using another DOAC or other type of anticoagulant instead of dabigatran (Supplementary Table 1). Idarucizumab was rarely prescribed to patients not using dabigatran (incidence range: 0–4.8 %, assessed in 28 studies) [3,10–16,18–29,31–38]. Four studies included coagulation tests as indicators for circulating dabigatran presence in the assessment of appropriateness Overall, idarucizumab was prescribed despite laboratory findings indicative of insignificant or no dabigatran activity in 3.2 % of patients (95%CI 0.8 % – 6.6 %, I^2: 9 %; 4 studies, $n = 201$, Supplementary Fig. 1) [18,29,33,36]. In the prospective RE-VERSE AD study, quantifications of circulating dabigatran was routinely performed, yet treating clinicians were unaware of the results. Retrospectively, idarucizumab was prescribed in the absence of indicators for circulating dabigatran in 1 patient (0.2 %), and this patient used apixaban instead of dabigatran [3]. In daily clinical practice, non-specific coagulation tests (activated partial thromboplastin time (aPTT), International Normalized Ratio (INR) or thrombin time (TT)) were measured in the majority of patients prior to idarucizumab administration (43.2 % – 100 %), while dabigatran-specific tests (ecarin clotting time (ECR), diluted thrombin time (dTT) or dabigatran plasma levels) were less commonly obtained (14.1 % - 86.7 %) (Supplementary Table 1) [10–13,16,18–20,22–29,31–36,38]. As prompt decisions are commonly required in this setting, it is reasonable to think that idarucizumab was already administered before laboratory test results had become available in the majority of patients.

Twenty studies provided data regarding idarucizumab dosing. According to product labels, the recommended dose of idarucizumab is 5 g, administered intravenously as two consecutive vials each containing 2.5 g and infused over 5–10 min, or as a bolus injection [1,2]. Overall, the pooled proportion of patients who received an initial dosage other than 5 g was 2.3 % (95%CI 0.0 % – 8.2 %, I^2 97%; 20 studies, $n = 1959$, Supplementary Fig. 2) [3,10–13,15,16,18,19,21,23–25,29,31–35,38]. The majority of these patients received a halved dosage of 2.5 g, while initial dosages of 7.5 g and 10 g were reported as well [12,15,24,31]. Time interval between infusions, evaluated in 5 studies, was appropriate in 83.3 % to 100 % of administrations (Supplementary Table 1)

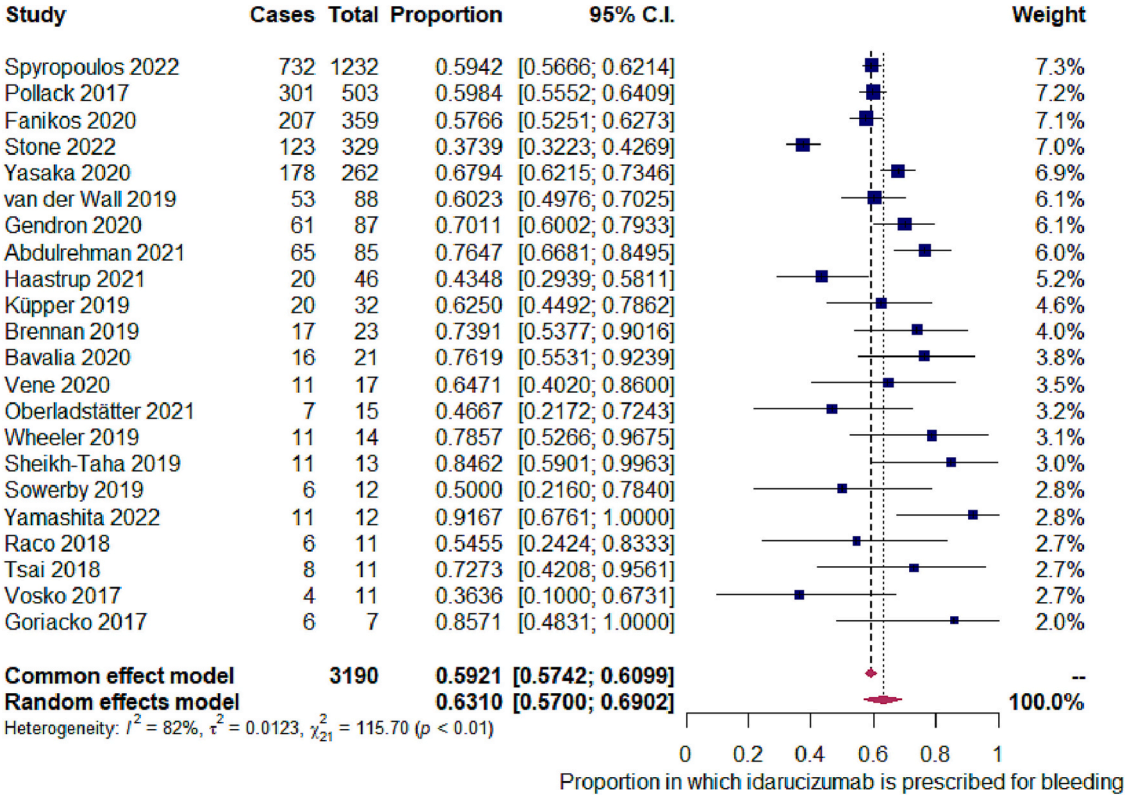

Fig. 4. Forest plot with pooled proportion of bleeding as prescription indication for idarucizumab.

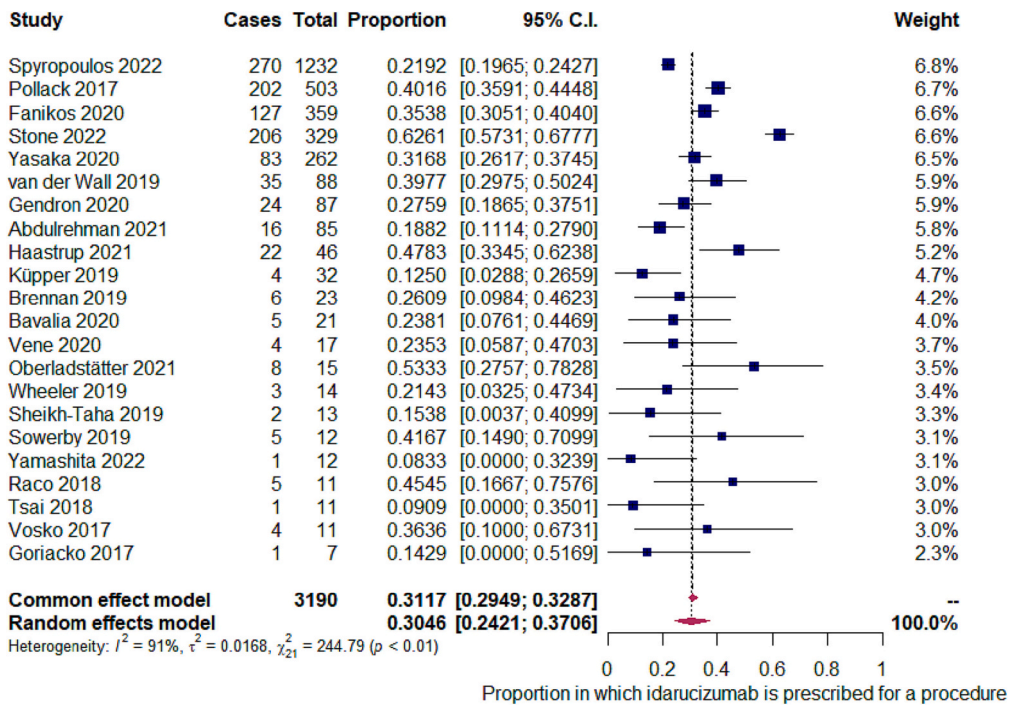

Fig. 5. Forest plot with pooled proportion of invasive procedure as prescription indication for idarucizumab.

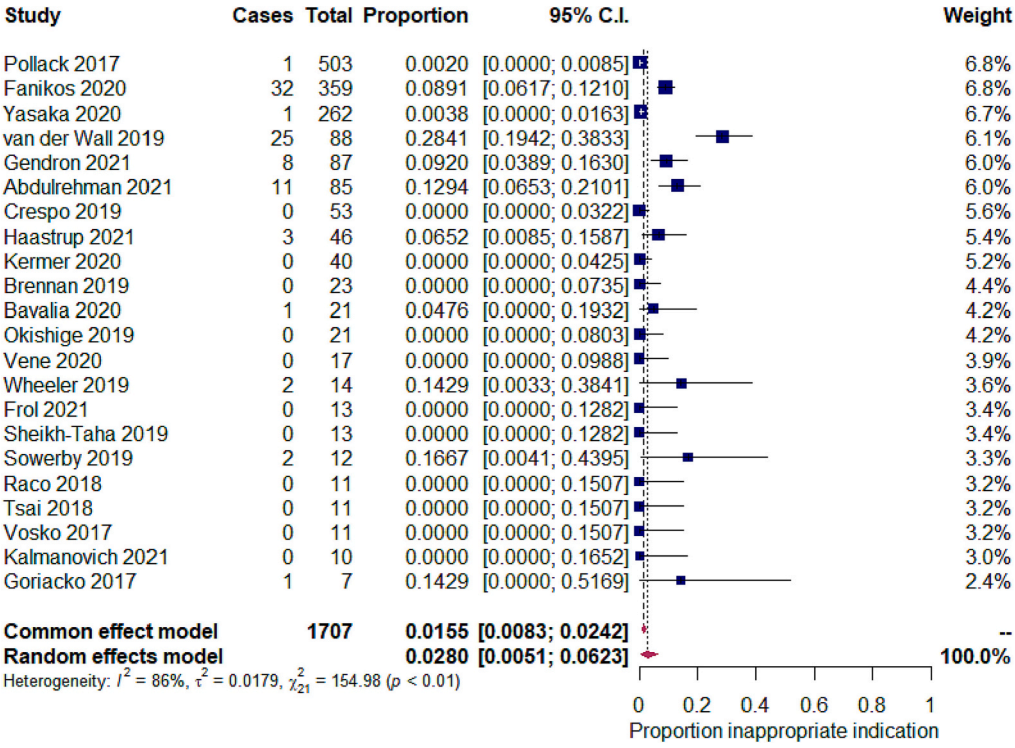

Fig. 6. Forest plot with pooled proportion of inappropriate indication idarucizumab.

[3,19,29,35,38].

According to the European Medicine Agency's (EMA) Summary of Product Characteristics (SmPC) and Food and Drug Administration (FDA)-approved Prescribing Information (PI), administration of a second 5 g dose of idarucizumab could be considered in the following situations: elevated coagulation parameters in the presence of a) recurrence of a clinically relevant bleeding, or b) in patients requiring a second emergency surgery or urgent procedure [1,2]. Additionally, when clotting times remain prolonged indicative for circulating dabigatran and potential re-bleeding is deemed life-threatening, a second administration could be considered in accordance with EMA SmPC [1]. Overall, 0.6 % (95%CI 0.0 % – 2.0 %, I^2: 54 %; 14 studies, n = 1777, Supplementary Fig. 3) of patients were administered a repeated dose of idarucizumab. In the majority of cases identified in this systematic review, a second dose of idarucizumab was administered in accordance with product labels (Table 2) [3,12,13,15,17,19,24,27,31–35,38].

Table 2
Incidence and rationales for a repeated idarucizumab administration.

Study	Incidence (n, %)	Rationale
Brennan et al., 2019 [12]	1 (4.3 %)	Ongoing cardiogenic shock due to pericardial effusion together with elevated dabigatran level (n = 1)[a]
Crespo et al., 2019 [13]	1 (1.9 %)	Life-threatening and uncontrolled bleeding after initial administration of idarucizumab for cardiac transplant surgery, despite aPTT within normal range[b]
Fanikos et al., 2020 [15]	6 (1.7 %)	Prolonged coagulation tests and: requirement of urgent procedure after initial administration of idarucizumab for uncontrolled bleeding (*n* = 1)[a], rebleeding after initial administration of idarucizumab for uncontrolled bleeding (*n* = 4)[a], prolonged bleeding after initial administration of idarucizumab for emergency surgery (n = 1)[a]
Gendron et al., 2020 [17]	4 (4.6 %)	Plasma dabigatran rebound and need for invasive procedure after initial administration of idarucizumab for bleeding (n = 1)[a], plasma dabigatran rebound after initial administration of idarucizumab for bleeding (n = 1)[b], plasma dabigatran rebound and need for invasive procedure after initial overdose without bleeding (n = 1[c])[a], bleeding transformation after mechanical thrombectomy (n = 1)[b]
Goriacko et al., 2017 [19]	0	N.A.
Oberladstätter et al., 2021 [24]	0	N.A.
Pollack et al., 2017 [3]	9 (1.8 %)	Residual anticoagulant activity and: recurrent bleeding after initial administration of idarucizumab for bleeding (n = 4)[a], new procedure after initial administration of idarucizumab for procedure (*n* = 2)[a], postoperative bleeding after initial administration of idarucizumab for procedure (*n* = 3)[a], second dose in error (n = 1)[b]
Sheikh-Taha et al., 2019 [27]	1 (7.7 %)	No clinical haemostasis and prolonged coagulation parameters after initial administration administration of idarucizumab for genitourinary bleeding (n = 1)[a]
Stone et al., 2022 [31]	13 (4.0 %)	Ongoing elevated coagulation parameters together with ongoing bleeding (n = 3)[a], ongoing elevated coagulation parameters without bleeding or need for procedure (*n* = 5)[b], recurrent bleeding after re-initiation of dabigatran during admission (n = 1)[a], unclear indication (*n* = 4)[b]
Tsai et al., 2018 [32]	0	N.A.
van der Wall et al., 2019 [33]	0	N.A.
Vene et al., 2020 [34]	1 (5.9 %)	Dabigatran rebound levels together with ongoing bleeding (n = 1)[a]
Vosko et al., 2017 [35]	0	N.A.
Yasaka et al., 2020 [38]	0	N.A.

Abbreviations: n: number, N.A.: not applicable.
[a] Appropriate use according to product labels 1, 2.
[b] Inappropriate use according to product labels 1, 2.
[c] This patient received a third idarucizumab administration.

3.4. Efficacy and safety

Varying definitions were used by the included studies for the assessment of haemostatic efficacy and periprocedural haemostasis (Supplementary Table 2). Haemostatic effectiveness was commonly defined as “controlled bleeding”, “adequate haemostasis”, “bleeding cessation”, “no hematoma enlargement”, or “effective reversal”. Further specifying criteria were often not available. Five studies evaluated haemostatic efficacy according to the ISTH criteria [45]. Good haemostatic effectiveness, as assessed by the ISTH criteria, was achieved in 77.7 % of patients after administration of idarucizumab (95%CI 66.7 % – 87.2 %, I^2 46%, 5 studies, *n* = 152, Fig. 7) [11,17,20,27,33]. The other studies, using varying definitions, reported effectiveness percentages ranging between 67.2 % and 100 % (assessed in 11 studies, Supplementary Table 2) [3,12,19,24–26,32,34–36,38]. Two studies focusing on patients with intracranial hemorrhage reported that hematoma growth with clinical deterioration occurred in 11.1 % (*n* = 3/27), and 38.5 % (*n* = 5/13) of patients needed surgical evacuation despite idarucizumab administration [16,22]. Adequate peri-procedural haemostasis was defined as “completion of procedure without major or excessive bleeding”, and was achieved in 98.8 % of cases (95%CI 88.7 % – 100 %, I^2 74%; 10 studies, *n* = 331, Fig. 8) [3,11,19,20,27,32,34–36,38]. Two studies categorized peri-procedural haemostasis into normal (72.4 % - 93.4 %), mildly abnormal (5.1–6.9 %), moderately abnormal (1.5–10.3 %) and severely abnormal (5.7 %) as assessed by the surgeon (Supplementary Table 2) [3,38].

The occurrence of rebleeding or new-onset bleeding after idarucizumab administration was evaluated in three studies with 5.5 % (95%CI 1.6 % – 11.4 %, I^2 67%; 3 studies, *n* = 463, Supplementary Fig. 4) of patients experiencing a (re)bleeding within 30 days [20,31,33]. Van der Wall et al. reported that all (n = 4, 4.5 %) (re) bleeding events occurred in patients who were initially prescribed idarucizumab in the context of bleeding and these events were at the same anatomical location as the index bleeding [33]. In the majority of cases, anticoagulant treatment was already re-initiated prior to (re) bleeding [20,33]. Two studies in patients undergoing cardiac transplant surgery, reported that re-thoracotomy due to bleeding complications was needed in 0 % to 7.5 % of patients [13,21].

All-cause mortality at any follow-up duration was evaluated in 23 studies including 1934 patients. The overall incidence was 13.6 % (95% CI 9.6 % – 17.9 %, I^2 69%, Fig. 9) [3,10–14,17,19–21,23–28,31–36,38]. The pooled incidence of all-cause mortality during index hospitalization was 10.8 % (95%CI 5.1 % – 17.9 %, I^2 64%, 11 studies, *n* = 535, Supplementary Fig. 5) [10,12–14,16,19,22,24,27,28,35]. The following in-hospital causes of death were reported: bleeding, ischemic stroke, cardiogenic shock, aspiration, respiratory failure, cancer, sepsis, progression of brain injury, renal failure, primary cardiac transplant graft failure and cardiac arrest (Supplementary Table 2).

The pooled incidence of thromboembolic events at any follow-up duration was 2.0 % (95%CI 0.8 % – 3.4 %, I^2 44%; 18 studies, *n* = 1822, Fig. 10) [3,10–12,17,20,21,24–28,31,33–36,38]. The following thrombotic events were reported: ischemic stroke (incidence: 1.1 % - 36.4 %), venous thrombo-embolism (pulmonary embolism (PE) and/or deep vein thrombosis (DVT)) (incidence 0.4 % - 18.2 %), PE (incidence 0.4 % - 3.5 %), DVT (incidence 0.3 % - 18.2 %), myocardial infarction (1.2 % - 1.5 %), catheter related thrombosis (1.1 %), arterial thrombosis (0.6 % - 1.5 %), and systemic embolism (0.4 %). Lastly, hypersensitivity or anaphylactic reactions were reported in 0.6 % to 1.1 % of patients [3,17]. The phase 3 RE-VERSE AD trial and a Japanese post-marketing surveillance study reported various serious adverse events (*n* = 117, 23.3 %) and adverse drug reactions (*n* = 18, 6.9 %) [3,38].

3.5. Re-initiation of antithrombotic therapy

Overall, any form of antithrombotic therapy was restarted in 58.7 % (95%CI 46.2 % – 70.7 %, I^2 91%, 14 studies, *n* = 1132, Supplementary Fig. 6) of patients [3,12,16,17,19,20,23,25,26,32–35,38]. Of these patients, 16.2 % - 100 % resumed dabigatran therapy. Other prescribed antithrombotic agents were: vitamin K antagonists (3.0 % – 20.0 %), apixaban (1.7 % – 50.0 %), rivaroxaban (2.0 % – 33.3 %), therapeutic or prophylactic (low-molecular-weight) heparin (5.0 % – 18.2 %), antiplatelet therapy (4.0 % – 33.3 %), or edoxaban (11.3 %) (**Supplementary Table 2**).

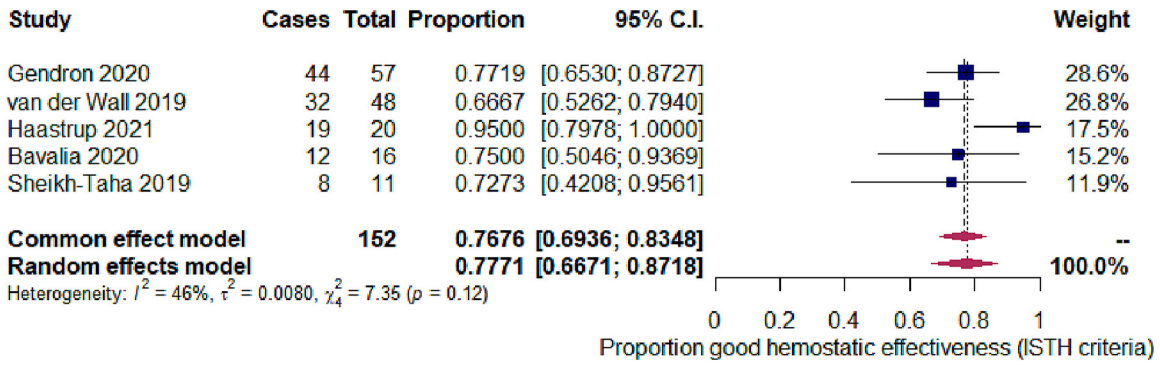

Fig. 7. Forest plot with pooled proportion of good hemostatic effectiveness (ISTH criteria).

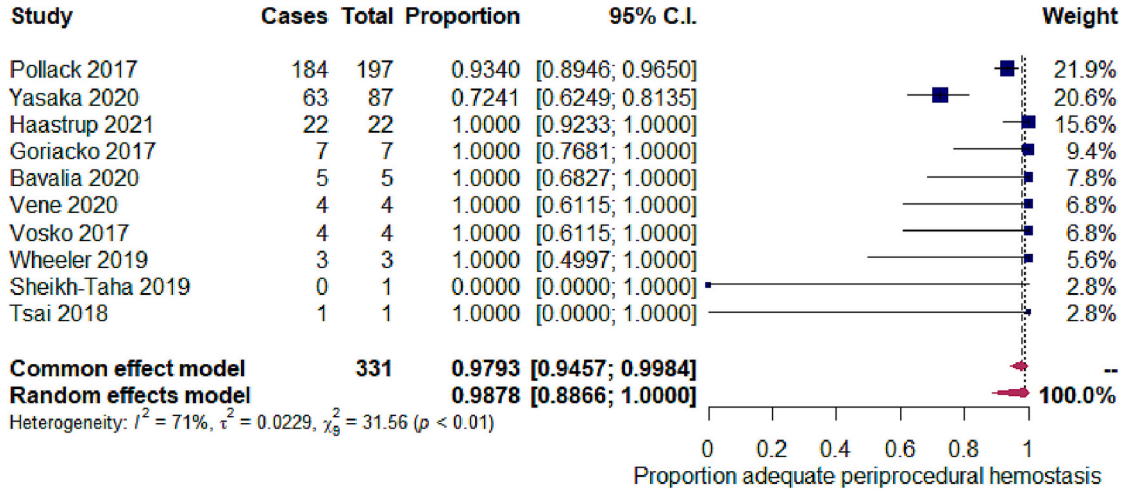

Fig. 8. Forest plot with pooled proportion of adequate peri-procedural haemostasis.

4. Discussion

We provide an overview on the published literature on the use and outcomes of idarucizumab by reporting on 3602 patients included in 30 studies. Idarucizumab was mainly prescribed in the context of bleeding. Good hemostatic efficacy and peri-operative haemostasis were reported to be achieved in respectively 77.7 % and 98.8 % of patients. Consequently, a repeated idarucizumab dosage was rarely administered. Lastly, the incidence of thrombotic complications was low in contrast to the incidence of overall all-cause mortality. The results of this systematic review are thus in line with the findings from the RE-VERSE-AD study with regard to both the safety and efficacy of idarucizumab [3]. All in all, eight years after the first approval in 2015, the best available evidence shows that idarucizumab has a favorable efficacy and safety profile in the anticoagulant reversal of dabigatran in studies and daily practice.

The GARFIELD-AF trial, the largest prospective registry in patients with newly diagnosed atrial fibrillation to date, reported that 26.2 % (n = 163/622) of patients experiencing a major bleeding died. Notably, only a quarter of patients presenting with major bleeding used a DOAC at the time of bleeding, and this study was largely performed in an era in which targeted DOAC reversal agents were not yet approved (recruitment of patients between 2010 and 2016) [46]. The considerably lower mortality rate observed in our study may indicate that the application of effective DOAC antidotes has improved the outcomes of bleeding complications. However, such conclusions cannot be drawn from our meta-analysis. The main reason for this is the complete lack of randomized controlled trials with idarucizumab, which are unlikely to ever be performed. Of note, the observed mortality rate in our study was still considerable at 13.6 %. However, there is no indication that these deaths were directly related to the administration of idarucizumab. It is reasonable to hypothesize that the mortality rate is foremost attributable to the underlying disease state for which idarucizumab was indicated, either a life-threatening bleeding or an urgent invasive procedure, in combination with the overall health condition. The well-known mechanism of action, the immediate effect on dabigatran activity, the low rate of thrombotic complications and the reported good hemostatic efficacy are additional arguments why application of idarucizumab is reasonable within the indication as stated in the product label.

Guideline non-adherence was observed in a small yet relevant proportion of idarucizumab prescriptions. Indications were reported to be inappropriate (2.8 %), patients received a non-recommended idarucizumab dosage (2.3 %) and laboratory analyses indicative of circulating dabigatran, either via coagulation tests such as APTT or dabigatran-specific assays, were not routinely performed and often unavailable at the moment of administration. This is likely the result of the acute medical care setting, in which prompt decisions are commonly required despite incomplete information. Even so, inappropriate prescribing could be a significant source of drug expenditure, is a potential threat to patient safety and should be avoided [30].

We found that any form of antithrombotic therapy was restarted in 58.7 % of patients, which may seem a low proportion. However, as some studies only evaluated re-initiation during hospitalization, the overall percentage in our study could be an underestimation. It is of great importance that re-initiation of anticoagulant therapy during hospitalization and after discharge is monitored. The risk of (re)bleeding versus thromboembolic events should be carefully weighted, keeping in mind that restarting anticoagulant therapy as soon as deemed safe may lead to

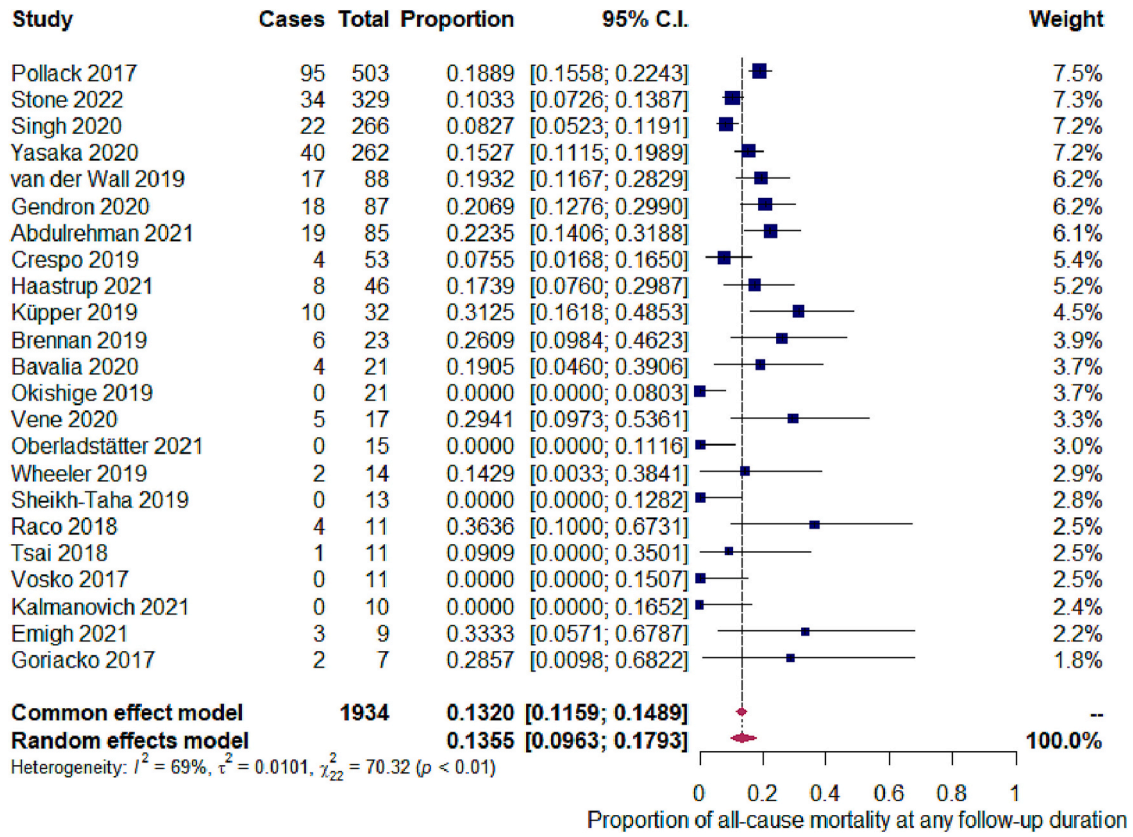

Fig. 9. Forest plot with pooled proportion of all-cause mortality at any follow-up duration.

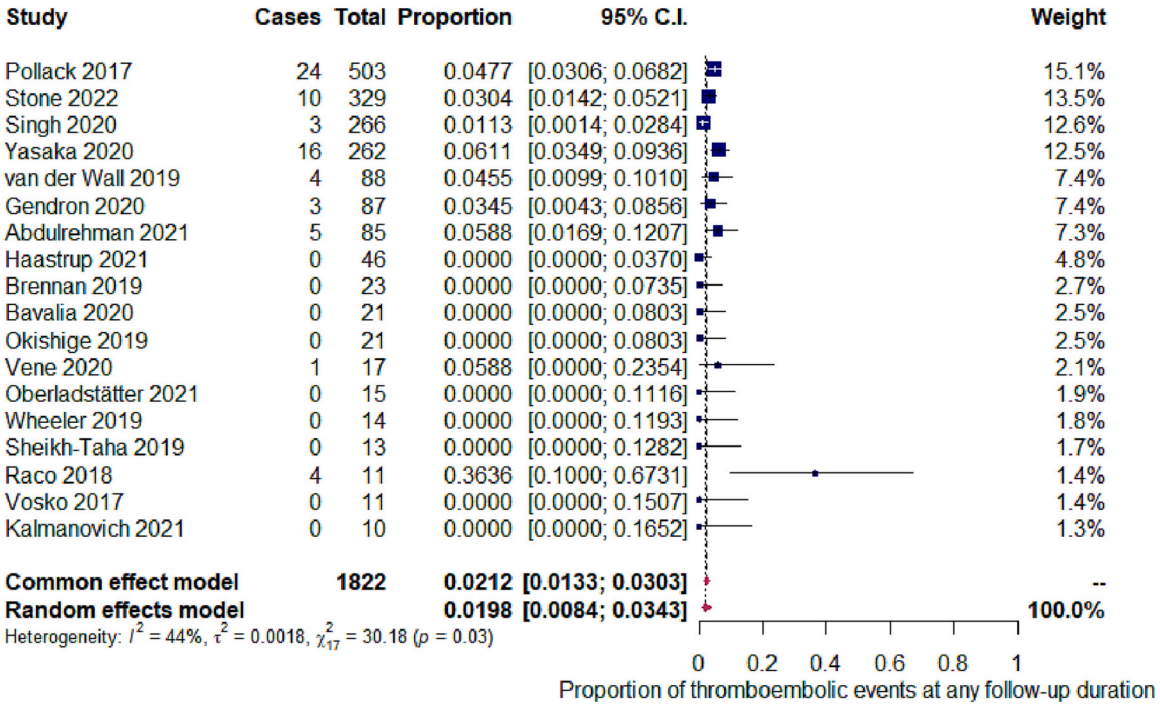

Fig. 10. Forest plot with pooled proportion of thromboembolic events at any follow-up duration.

better short- and long-term outcomes [47]. The immediate but also long-term management of major bleeding in patients on anticoagulant therapy is complex and involves multiple disciplines. In addition to appropriate action to achieve local haemostasis, procedures to allow for careful counseling of individual patients regarding the optimal timing of reinitiating anticoagulants and adequate control of modifiable risk factors for bleeding should be in place [48].

This systematic review and meta-analysis has several limitations.

First, the majority of included studies had a retrospective study design, small sample size, applied heterogeneous selection criteria and outcome definitions and the risk of bias was high for the vast majority of studies. Due to the observational study designs, the decision to administer idarucizumab was individually made for each patient. Therefore, it is reasonable to hypothesize that the more severe cases were more likely to receive reversal therapy. Second, when interpreting the results regarding prescription indications, the following should be taken into consideration. Both urgent and elective procedures were included in the pooled estimate of idarucizumab prescriptions for procedures, as insufficient detailed information was provided to study these separately. Also, three studies explicitly reported the number of patients who were initially prescribed idarucizumab for both a bleeding and urgent procedure indication [30,32,38]. As these patients most likely had to undergo these interventions in order to achieve hemorrhage control, we analyzed these patients as having an idarucizumab indication for bleeding. We assessed the prescription indications of other cohort studies and case-series in a similar manner, where possible. Nonetheless, in the study by Yasaka et al. some patients who required an emergency surgery due to a major bleeding were classified as having an idarucizumab indication for an invasive procedure [38]. We cannot rule out that this 'misclassification' has occurred in more studies. Third, it was not always clear whether the effectiveness of the treatment was attributable to idarucizumab. We were unable to ascertain whether patients underwent (invasive) hemostatic procedures in addition to idarucizumab administration and if so, whether these patients were included in the reported incidence of hemostatic efficacy by the individual studies. For that reason, we only pooled the results of included studies using the ISTH criteria in the analysis of hemostatic efficacy.

5. Conclusion

This systematic review and meta-analysis shows that idarucizumab was mainly prescribed in the setting of bleeding. While limited by the nature and quality of included studies, the hemostatic effectiveness was reported to be good, especially perioperatively, and the incidence of thromboembolic events was low, supporting the use of idarucizumab to reverse dabigatran effect in daily practice. Patients with dabigatran-associated bleeding or requiring an urgent medical procedure nonetheless face a high mortality risk, mostly reflecting their underlying disease state. Awareness should be raised to improve appropriate prescribing of idarucizumab and to carefully monitor the re-initiation of anticoagulant therapy.

CRediT authorship contribution statement

S.H. and F.K. conceptualised and designed the study and drafted the protocol. S.H., F.K. and E.M. performed the study selection, quality assessment and data extraction. S.H. performed the statistical analyses. S.H. and F.K. drafted the initial version of the manuscript, which was reviewed and edited by all authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.05.020.

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