Thrombosis Research 162 (2018) 22–31

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Current evidence of oral anticoagulant reversal: A systematic review

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ARTICLE INFO

Keywords:
Oral anticoagulant
Reversal
Vitamin K antagonists
Direct oral anticoagulants

ABSTRACT

Introduction: Approximately 4–6% of patients treated with oral anticoagulants (OAC) will suffer from major hemorrhage or be in need of urgent surgery necessitating anticoagulant reversal therapy. Several new oral anticoagulants and reversal agents have been introduced that make it difficult for physicians to stay updated on the current evidence of reversal management. This study aims to review the recent literature on oral anticoagulation reversal therapy and to present the current evidence in an easily approachable manner.

Materials and methods: A systematic literature search was conducted using PubMed and EMBASE to identify the latest publications on both vitamin K antagonist (VKA) and direct oral anticoagulant (DOAC) reversal strategies. All studies on humans who received any acute reversal management of VKA treatment were included, except case studies. Since only two studies on acute reversal of DOAC treatment have been published, clinical trials on healthy volunteers were also included.

Results: Twenty-one studies with a total of 4783 VKA treated patients, and 12 studies with a total of 529 DOAC treated patients were included. Elevated INR values due to VKA treatment could be reversed (INR ≤ 1.5) in 63.1% (95% CI: 61.0–65.2) of study subjects after treatment with 4F-PCC, as compared with 12.2% (95% CI: 8.2–16.2) after treatment with fresh frozen plasma (FFP), ($p < 0.001$). Thromboembolism occurred in 1.6% (95% CI: 1.2–2.1) of VKA-patients treated with 4F-PCC, and in 4.5% (95% CI: 2.3–6.7) of FFP-treated patients. To date, reversal of laboratory parameters has been demonstrated for two reversal agents specific to DOACs: idarucizumab for dabigatran reversal and andexanet-alfa for factor Xa-inhibitor reversal.

Conclusions: This review supports the use of PCC for VKA reversal, specifically for 4F-PCC over FFP for laboratory reversal. There are no studies on clinical efficacy of non-specific agents for DOAC reversal and the evidence for laboratory reversal is not consistent.

1. Introduction

Millions of patients worldwide are treated with oral anticoagulation therapy (OAC), primarily for prevention of stroke in patients with atrial fibrillation (AF). Vitamin K antagonists (VKA), e.g. warfarin, is by far the most commonly used OAC agent and has long constituted the only alternative for OAC treatment [1]. However, in 2010 the activated thrombin (FIIa) inhibitor dabigatran was approved by the Food and Drug Administration, FDA, as an alternative to VKA, and since then an additional three non-vitamin K oral anticoagulants (DOACs) have been approved for use. These are all activated factor X (FXa)-inhibitors-apixaban, rivaroxaban, and edoxaban. Since their introduction on the market, the DOACs have steadily increased in popularity, For example in the United Stated, their use matched that of warfarin in 2014 [2]. Unlike VKA, the DOACs have a wide therapeutic range, predictable response effect and few food and drug interactions. The DOACs also have a more rapid onset (1–4 h) and a shorter half-life (7–12 h) than VKA. However, reversal of DOAC effect is naturally not nearly as well studied as with VKA. Around 2–4% of all OAC treated patients will suffer a major hemorrhage, and an additional 2% will need urgent invasive procedure that could require reversal of the anticoagulative effect [3]. Hence, there is a need for evidence-based reversal strategies, as well as precise tools to measure the effect of anticoagulants. Clinical outcomes in acute bleeding may be the most relevant measures of safety and efficacy of anticoagulant reversal strategies, but patients in need of acute reversal therapy are rare and with diverse disease profiles, which

Abbreviations: OAC, Oral anticoagulant; VKA, Vitamin K antagonist; DOAC, Direct oral anticoagulant; PCC, Prothrombin complex concentrate; 4F-PCC, Four factor PCC; 3F-PCC, Three factor PCC; aPCC, Activated PCC; FFP, Fresh frozen plasma; AF, Atrial fibrillation; TE, Thromboembolism; VTE, Venous thromboembolism; FIIa, Activated factor II; FXa, Activated factor X; rFVIIa, Recombinant activated factor VII; TTR, Time in therapeutic range; PT, Prothrombin time; INR, International Normalized Ratio; aPTT, Activated partial thromboplastin time; ECT, Ecarin clotting time; ETP, Endogenous thrombin potential; dTT, Diluted thrombin time; ICH, Intracranial hemorrhage; SBU, Statens beredning för medicinsk och social utvärdering (Swedish Agency for Health Technology Assessment and Assessment of Social Services); SEK, Swedish kronor

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https://doi.org/10.1016/j.thromres.2017.12.003
Received 9 August 2017; Received in revised form 7 November 2017; Accepted 5 December 2017
Available online 06 December 2017
0049-3848/

make clinical outcome difficult to standardize. Furthermore, a reduction of the bleeding (and thus the efficacy of the treatment) does not necessarily correlate with a beneficial clinical outcome. For these reasons, surrogate measurements in the form of laboratory values are often used to evaluate the result of a given treatment. International Normalized ratio (INR) is an established and standardized test that reflects the degree of the anticoagulative effect of VKA treatment. No equivalent is yet present for DOACs. Due to the many recent, and undergoing, developments of OAC and its reversal treatments, cause for uncertainty is likely to exist among the treating physicians, and the costs of these reversal agents demand a thorough evaluation of the advantage and effect to match its purpose and cost. This study aims to review the latest publications on oral anticoagulation reversal therapy, and to present the current evidence in an easily understandable manner, which hopefully will be of use to both the individual physician as well as the guideline decision makers.

2. Material and methods

2.1. Study identification

The report was prepared based on the PRISMA statement [4]. A systematic literature search was conducted in the PubMed and EMBASE electronical databases. The goal was to identify all published articles that presented outcome measures from real life patients treated with urgent reversal therapy reversal of oral anticoagulative treatment. Two separate searches were performed, one search targeting studies related to VKA-reversal, and one search targeting studies related to DOAC-reversal. For DOAC reversal treatment, only two published studies were identified. Therefore, the DOAC-search was expanded to also include clinical trials on healthy volunteers. The VKA search ranged from December 31st, 2005 to October 31st, 2016. The DOAC search ranged from December 31st, 2010 to October 31st, 2016. The searches were restricted to publications in the English language. The complete search strategy is presented in Supplementary Table 1. The search strategy was complemented by a manual search, where potentially interesting articles from reference lists of relevant publications were included.

2.2. Study selection

The aim of the search strategy was to identify studies including real life patients treated with acute reversal therapy. The following criteria were to be met for eligibility of a publication: availability of type (and preferably dose) of OAC therapy, availability of type (and preferably dose) of reversal agent and clinical and/or laboratory outcome measures used. Only human studies were considered, and for studies with multiple publications, only the latest publication was included. Case reports of individual patients were excluded.

2.3. Assessment of study validity

The randomized clinical trials (RCTs) were assessed with a quality assessment tool produced by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), which conforms to the recommendations in the PRISMA statement [4]. There is controversy regarding quality assessment of observational studies, especially studies without a control group, since these generally are regarded as being of low quality [5]. However, as the great majority of identified studies were of observational design, an assessment tool for the observational studies was constructed to systematically identify potential confounders and risks of bias (Supplementary Table 2). The tool was modified from the observational study assessment template of SBU [6], and the quality assessment tool for observational studies developed by the American national institute of health [7] All studies were classified as either at “High”, “Moderate” or “Low” risk of bias. The results are presented in Supplementary Table 3.

2.4. Data extraction

Information on study type, year of publication, study subjects (n and clinical context), OAC treatment, reversal agent and dose, time of follow up, laboratory and clinical outcomes, Thromboembolic events and rates of deaths was extracted. Reported partial or fully non-governmental funding of the studies and authors with ties to pharmaceutical companies were compiled in Supplementary Table 3.

2.5. Statistics

Rates of thromboembolic events, deaths and successfully reversed INR values from the VKA-studies were combined to mean values. Rates were classified based on type of reversal agent. Fisher's test was used to compare outcomes for the difference between FFP and PCCs rates of successfully reversed INR values, where sufficient data was considered available. Considering the DOAC studies, sufficient studies to make any comparisons of results were not found. Heterogeneity across cohorts was evaluated by calculation of Cochrane's Q and the I^2 statistic [8]. Calculations were performed with the Comprehensive Meta-Analysis software. Confidence intervals estimation for mean values and Fisher's tests were performed with software provided by McCallum Layton [9].

3. Results

3.1. Search results

The two searches on PubMed and EMBASE generated a total of 2044 citations. After screening the titles 1967 citations were excluded. The remaining 77 publications where read and screened, and finally 26 studies remained that were considered eligible. Reasons for exclusion were lack of original data ($n = 11$), inclusion criteria not met ($n = 23$), case reports ($n = 1$) and ongoing studies without results ($n = 13$). Another 7 publications were added after a manual search. In total 12 studies from the DOAC literature search and 21 studies from the VKA literature search were included in the review. Of the DOAC publications, 10 studies were randomized controlled studies on healthy volunteers, and 2 were interim analyses of ongoing trials in real clinical settings on patients with acute need of reversal therapy as described above. All of the VKA publications studied reversal in patients in real clinical situations. Seventeen of the VKA publications are observational (6 retrospective and 11 prospective), and 4 are randomized trials. A flow chart of the identification, selection and exclusion is shown in Fig. 1 and Fig. 2. Characteristics of the included studies are summarized in Table 1 and Table 2.

3.2. Risk of bias assessment

Of the twenty-one VKA studies, 4 were considered to have a high risk of bias, one was considered to have a low risk of bias and 16 were considered to have an average risk of bias. Six of the studies reported no conflict of interest, and 13 reported that at least one of the authors had ties to pharmaceutical companies. Nine of the studies were partly or completely funded by companies manufacturing PCC-products. Seven of the 12 DOAC studies were considered to have a low risk of bias, the remaining five were considered to have an average risk of bias. Only one study reported no conflict of interest, and all except one were partly or completely funded by companies producing DOAC, DOAC antidotes or PCC. A table of risk of bias and conflict of interests is presented in Supplementary Table 3.

3.3. Study subjects

A total of 4783 patients were included in the VKA review and 529 patients in the DOAC review. In the DOAC studies 136 patients were from clinical settings receiving reversal treatment for intracranial

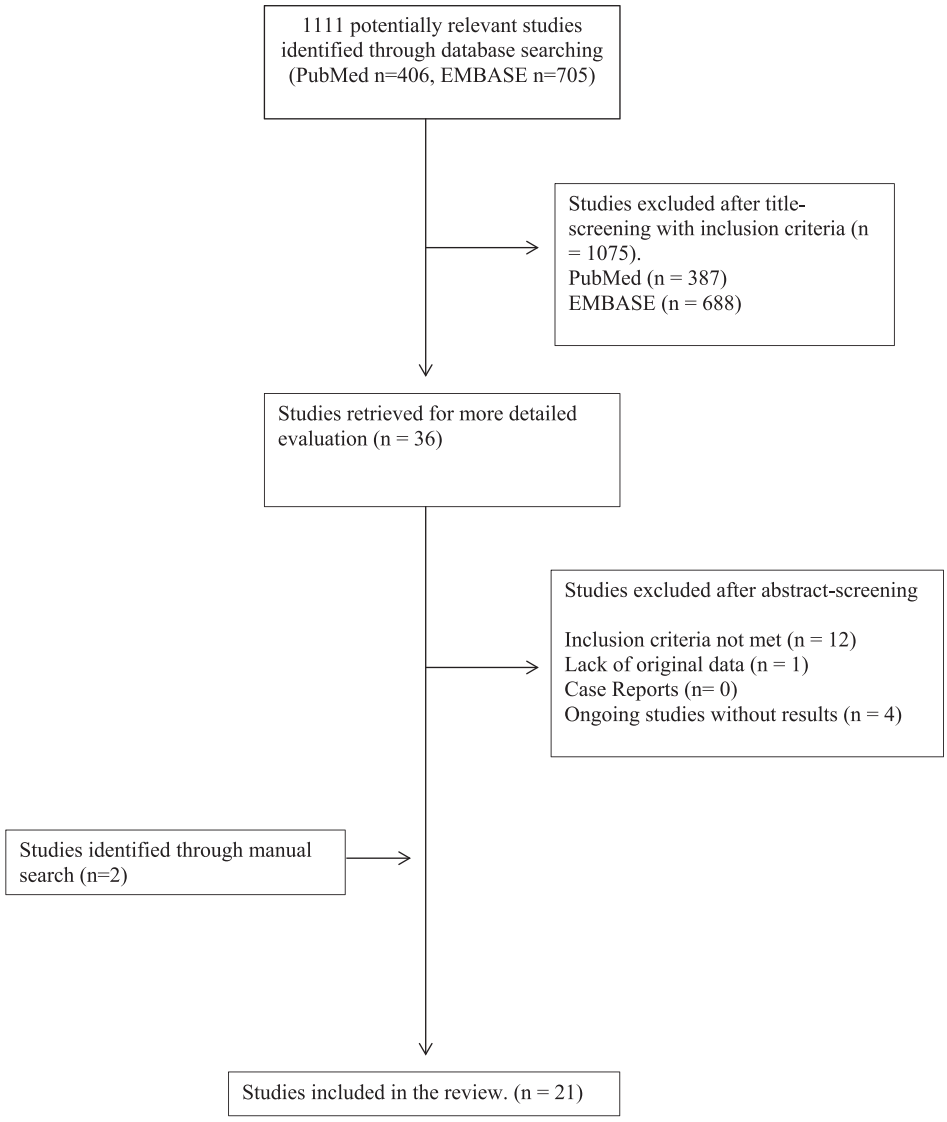

Fig. 1. Flowchart for study selection of VKA studies.

hemorrhage (ICH) (n = 20), other major bleeding (n = 77) or prior to urgent invasive intervention (n = 39). The remaining patients (n = 393) were healthy volunteers. In the VKA studies, reversal treatment was given for ICH (n = 2202), other major bleeding (n = 1642), prior to urgent invasive intervention (n = 596) or reasons classified as "other" (i.e. high INR) (n = 320). The size of the study population ranged from 30 to 825 patients in the VKA studies, and from 6 to 110 patients in the DOAC studies. Treatments for VKA reversal included 4F-PCC (n = 3649), 3F-PCC (n = 335), FFP (n = 799) and combinations of these or no treatment (n = 608). Follow up ranged from 0 to 90 days, with a mean of 31 days.

3.4. VKA reversal

An INR ≤ 1.5 was found in 63.1% (95% CI: 61.0–65.2) of cases after treatment with 4F-PCC (1298/2057), which was only achieved in 12.2% (95% CI: 8.18–16.22) when treated with FFP (31/255), $p < 0.001$. Some studies had endpoints lower than INR ≤ 1.5 [10–14], suggesting that additional patients may have achieved INR ≤ 1.5, but information on definite INR could not be obtained. Thromboembolic events were reported in 49 of 3009 cases of 4F-PCC administration (1.63%, 95% CI: 1.2–2.1). Ten studies [11,12,15–22] reported all thromboembolic events during follow up, while 5 studies [10,13,14,23,24] only reported those that were considered to be PCC-related. Death occurred in 20.0% (95% CI: 18.69–21.31) of the 4F-PCC treated patients (719/3594), and 29.6% (95% CI: 26.34–32.86) of the FFP treated patients (222/751). A subgroup analysis showed that death among ICH patients treated with 4F-PCC occurred in 33.3% (95% CI: 30.79–35.81) while death among patients treated with 4F-PCC for other reasons than ICH occurred in 12.9% (95% CI: 11.42–14.29). The results of the pooled data are presented in Supplementary Table 4.

3.5. Sensitivity analysis

Pooled data from the four randomized trials show achieved target INR values in 66.4% (95% CI: 60.3–72.1) of the patients. The pooled data from the observational studies presents achieved target INR values in 62.5% (95% CI: 60.2–64.8) of the patients.

3.6. DOAC reversal

Nine of twelve DOAC studies were RCTs. They were composed of 4 different OAC pharmaceuticals with a range of doses, and 6 different reversal agents with variable dosing. Two studies presented interim analyses from studies of patients in clinical settings in need of acute reversal therapy [25,26]. Pollack et al. [26] presented a study of

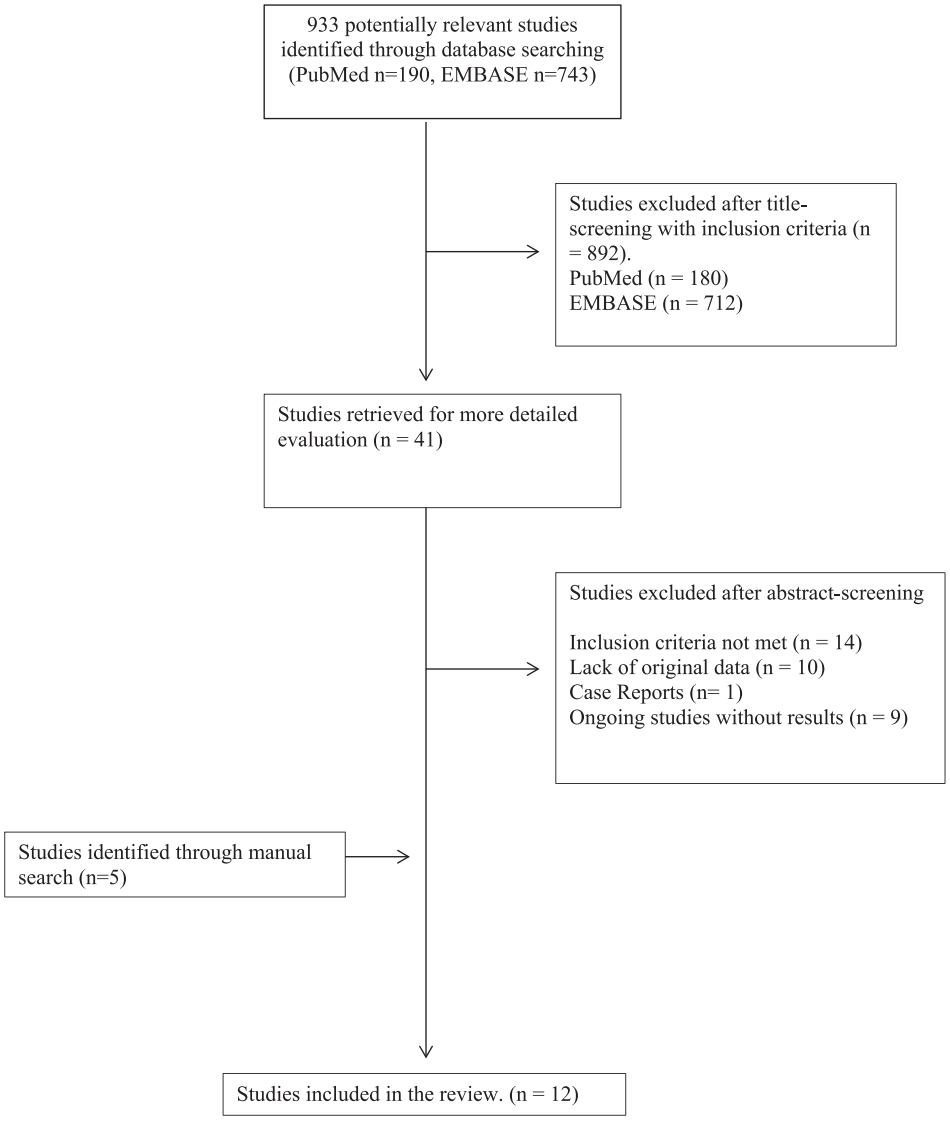

Fig. 2. Flowchart for study selection of DOAC studies.

idarucixumab for dabigatran reversal, which is an interim analysis of a phase 3 study estimated for final completion in April 2017. Ninety dabigatran treated patients with either major hemorrhage (n = 51) or in need of urgent surgery (n = 39) were given idarucizumab. The results of this study showed a complete and sustained reversal of dabigatran concentrations in 79% of the study population after two infusions of 2.5 g of idaricuzumab. Coagulopathy, estimated with dTT and ECT, was completely reversed in 88–98% of the patients within minutes after infusion. Intraoperative hemostasis was normalized in 92% in the group in need of invasive procedure, and the median time to cessation of bleeding was 11.4 h in the hemorrhage group. Connolly et al. presented a similar kind of interim analysis of a study of andexanet-alfa for reversal of factor Xa inhibitor activity. The relative decrease of factor Xa-activity were 89% for the rivaroxaban treated patients, and 95% for the apixaban treated patients after a bolus dose of andexanet-alfa. The hemostatic efficacy was rated excellent or good in 79% of the cases [25].

Ten of the twelve studies were clinical trials of healthy volunteers [27–36]. They studied the effect of non-specific reversal agents (aPCC, 3F-/4F-PCC, rFVIIa), on laboratory values (INR, aPTT, EDT, ECT). All four studies that presented results from rivaroxaban reversal with 4F-PCC showed improved INR values [27,28,31,33], but except from this, no correlating results could be seen throughout the studies.

4. Discussion

4.1. Efficacy and safety of VKA reversal

The results of this systematic review confirmed superiority of 4F-PCC as compared to FFP for reversal of INR to ≤ 1.5 (63.1% vs. 12.2%, $p < 0.001$). This finding is consistent with earlier systematic reviews on the subject [37]. However, we observed substantial differences in the achieved target INR values of included studies (35–100%). Nine of 15 studies reported achieved target INR in > 80% of the study population when using 4F-PCC. The reviewed studies are retrospective observational, prospective observational and randomized trials, and they differ both in target INR and in time frames for INR sampling.

This could in part explain the great heterogeneity in reported efficacy of the PCC-treatment.

Four of the 21 included studies were randomized trials [11,14,19,23]. The pooled data of the achieved target INR in these studies (66.5%, 95% CI 60.3–72.1) corresponds with the results from the observational studies (62.5%, 95% CI 60.2–64.8) indicating that the results of the observational studies are to be considered reliable.

A Cochrane review from 2015 was not able to prove superiority of PCC compared to FFP in terms of reducing mortality [38]. This review concluded that most studies on the subject are of high risk of bias, and that high-quality studies are urgently needed. However, the authors still

Table 1
Baseline characteristics of the VKA studies.

Author	Study type	Number and type of test subjects	Reversal agent	Dose	Follow up	Result			
						Lab	Deaths	TEs	Other clinical outcomes
				4F-PCC					
Altorjay et al. 2014 [10]	Prospective observation multicenter	61 patients S (n = 48) B (n = 13)	4F-PCC *Prothromplex Total®*	25, 35 or 50 IU/kg (1350–4200 IU)	15 days	100% INR < 1.3 within 30 min	0%	3.3%	"Excellent clinical response"
Appleby et al. 2016 [46]	Retrospective observational	15 patients ICH (n = 2) B (n = 8) S (n = 4) O (n = 1)	4F-PCC *Octaplex®*	25–50 IU/kg	–	86.7% INR < 1.5	–	–	–
Appleby et al. 2016 [46]	Prospective cohort	17 patients ICH (n = 8) B (n = 6) O (n = 3)	4F-PCC *Octaplex®*	25 IU/kg	–	88.2% INR < 1.5	–	–	–
Demeyere et al. 2010 [23]	Randomized prospective	18 patients S (n = 18)	4F-PCC *Cofact®*	800-1400 IU	0	35% INR < 1.5 15 min after surgery	0%	0%	0% "abnormal bleeding" post surgery
Desmettre et al. 2012 [16]	Prospective observational multicenter	256 patients ICH (n = 82) B (n = 92) S (n = 31) O (n = 51)	4F-PCC *Kaskadil®* *Octaplex®*	21.4–25 IU/kg	0	65% INR < 1.5	28%	0%	–
Desmettre et al. 2012 [15]	Prospective observational multicenter	825 patients ICH (n = 300) S (n = 139) B (n = 386)	4F-PCC *Octaplex®*	25.3 ± 9.8 IU/Kg	15 days	78.5% INR < 1.5	24.6%	0.5%	Bleeding controlled in 79.1%
Goldstein et al. 2015 [11]	Randomized open label multicenter	87 patients S (n = 86)	4F-PCC *Beriplex®* *Kcentra®* *Confidex®*	25, 35 or 50 IU/kg	45 days	55% INR < 1.3 after 30 min	3%	7%	90% "effective hemostasis"
Hickey et al. 2013 [17]	Retrospective cohort	165 patients ICH (n = 35) S (n = 37) B (n = 75) O (n = 18)	4F-PCC *Octaplex®*	1000-1500 IU	7 days	Median 5.7 h to normalized INR	9.1%	0.6%	–
Jones et al. 2015 [12]	Retrospective observational multicenter	64 patients ICH (n = 40) B (n = 11) O (n = 13)	4F-PCC *Kcentra®*	25-50 IU/kg	–	90.6% INR ≤ 1.4 within 24 min	28%	4.7%	–
Karaca et al. 2014 [18]	Prospective cohort	20 patients B (n = 20)	4F-PCC *Cofact®*	25-50 IU/kg	–	After 2 h mean INR 1.53	0%	5%	0% with active bleeding after administration
Kerebel et al. 2013 [19]	Prospective randomized open label multicenter	30 patients ICH (n = 30)	4F-PCC *Octaplex®*	40 IU/kg	30 days	100% INR ≤ 1.5 after 10 min	20%	6.7%	68% "Excellent clinical response"
Kerebel et al. 2013 [19]	Prospective randomized open label multicenter	29 patients ICH (n = 29)	4F-PCC *Octaplex®*	25 IU/kg	30 days	100% INR ≤ 1.5 after 10 min	13.8%	6.9%	68% "Excellent clinical response"
Khorsand et al. 2012 [20]	Prospective observation	139 patients B (n = 139)	4F-PCC *Cofact®*	"Variable dose" Median 1560 IU	14 days	INR ≤ 2.0 94.7%	26%	1.4%	88% "successful clinical outcome"
Khorsand et al. 2012 [20]	Prospective observation cohort	101 patients B (n = 101)	4F-PCC *Cofact®*	"Fixed dose" 1040 IU	14 days	INR ≤ 2.0 91.7%	14%	2%	96% "successful clinical outcome"
Laible et al. 2016 [47]	Retrospective observational	37 patients O (n = 37)	*Beriplex®* *Octaplex®* *PPSB-Human®*	Median 1000 IU	–	89.2% INR < 1.5	0%	5.4%	–
Majeed et al. 2012 [24]	Prospective cohort	160 patients S (n = 44) B (n = 57) ICH (n = 59)	4F-PCC *Prothromplex®* *Beriplex®* *Octaplex®*	Mean 24 IU/kg	7 days	57% INR < 1.5	11%	3.8%	91% "Good hemostatic effect"
Parry-Jones et al. 2015 [48]	Retrospective observational multinational	585 patients ICH (n = 585)	PCC (3F and 4F)	–	30 days	–	37.3%	–	–
Riess et al. 2007 [13]	Prospective open label No control or randomisation.	60 patients S (n = 57) B (n = 3)	4F-PCC *Octaplex®*	Median 41.1 IU/kg.	3 weeks	93% INR < 1.4 within 1 h	5%	0%	
Sarode et al. 2013 [14]	Prospective randomized open-label multicenter	98 patients B (n = 98)	4F-PCC	25, 35 or 50 IU/kg	30 days	62.2% INR ≤ 1.3 within 30 min	6%	2.0%	72.4% "effective hemostasis"

(*continued on next page*)

Table 1 (*continued*)

Author	Study type	Number and type of test subjects	Reversal agent	Dose	Follow up	Result			
						Lab	Deaths	TEs	Other clinical outcomes
Tazarourte et al. 2014 [21]	Prospective multicenter	822 patients ICH (n = 262) B (n = 371) O (n = 189)	4F-PCC *Kaskadil®* *Konakad®* *Octaplex®*	≥ 20 IU/kg	7 days	–	10%	1.2%	11% hemorrhagic recurrence
Voils et al. 2015 [40]	Retrospective single center	56 patients ICH (n = 34) B (n = 18)	4F-PCC *Kcentra®*	25, 35 or 50 IU/kg	–	84% INR ≤ 1.5 within 30 min	9%	7.1%	4F-PCC associated with lesser mortality than 3F-PCC.
Yanamadala et al. 2014 [49]	Prospective observation	5 patients ICH (n = 5)	4F-PCC *Kcentra®*	1500-2500 U	–	100% INR ≤ 1.5	–	–	–
				3F-PCC					
Frontera et al. 2014 [50]	Prospective observational	16 patients ICH (n = 16)	3F-PCC *Bebulin®*	Mean 48 IU/kg	3 months	87.5% INR < 1.4	44%	13%	0 worse or new ICH
Imberti et al. 2013 [51]	Prospective cohort	126 patients ICH (n = 72) B (n = 54)	3F-PCC	35–50 IU/kg	90 days	Mean INR 1.4 after 30 min ≤ 1.5 after 96 h	15%	0%	–
Jones et al. 2015 [12]	Retrospective observatinal multicenter	84 patients ICH (n = 80) B (n = 2) O (n = 2)	3F-PCC *Bebulin®*	30 IU/kg		85.7% INR ≤ 1.4 within 49 min	31%	0%	–
Voils et al. 2015 [40]	Retrospective single center	109 patients ICH (n = 65) B (n = 19) O (n = 6)	3F-PCC *Profilnine®*	25 IU/kg	–	80% INR ≤ 1.5 within 30 min	31%	2.8%	4F-PCC associated with lower mortality than 3F-PCC
				FFP					
Demeyere et al. 2010 [23]	Randomized prospective	20 patients S (n = 20)	FFP	2 × 400 ml	0	0% INR < 1.5 15 min after surgery 27% INR < 1.5 after 1 h	–	–	n = 2 "abnormal bleeding" post-surgery
Frontera et al. 2014 [50]	Prospective observational	25 patients ICH (n = 25)	FFP	Mean 12.5 ml/kg	3 months	84% INR < 1.4	60%	16%	n = 7 "worse or new ICH"
Goldstein et al. 2015 [11]	Randomized open label, multicenter	81 patients S (n = 76)	FFP	10, 12 or 15 ml/kg.	45 days	10% INR < 1.3 after 30 min	8%	9.2%	75% "effective hemostasis"
Hickey et al. 2013 [17]	Retrospective cohort	149 patients ICH (n = 44) S (n = 21) B (n = 69) O (n = 15)	FFP	–	7 day	Median 11.8 h to normalized INR	15%	2%	–
Karaca et al. 2014 [18]	Prospective cohort	20 patients B (n = 20)	FFP	Mean 5 units	–	INR 4.5 mean after 2 h	5%	–	n = 7 "active bleeding"
Parry-Jones et al. 2015 [48]	Retrospective multinational	377 patients ICH (n = 377)	FFP	–	30 days		46%	–	–
Sarode et al. 2013 [14]	Multicenter open-label randomized	104 patients ICH (n = 12) B (n = 92)	FFP	10,12 or 15 ml/kg	30 days	9.6% INR ≤ 1.3 within 30 min	5%	1.9%	65.4% "effective hemostasis"
Yanamadala et al. 2014 [49]	Prospective observation	28 patients ICH (n = 28)	FFP	–	–	256 min to INR < 1.6	–	–	–
				Other					
Frontera et al. 2014 [50]	Prospective observational	23 patients ICH (n = 23)	3F-PCC + FFP *Bebulin®*	Mean 47 IU/kg Mean 11.4 ml/kg	3 months	INR < 1.4 70%	9%	8.7%	4 worse or new ICH
Parry-Jones et al. 2015 [48]	Retrospective multinational	131 patients ICH (n = 131)	PCC + FFP	–	30 days	–	27.8%	–	–
Parry-Jones et al. 2015 [48]	Retrospective multinational	454 patients ICH (n = 454)	None	–	30 days	–	61.7%	–	–

S = need of/during surgery or invasive procedure; B = non intracranial major bleeding; O = other (e.g. minor bleeding or high INR); ICH = intracranial hemorrhage; TEs = thromboembolic events (arterial or venous).

emphasized that the included studies indicated that the possibility to reverse coagulopathy with PCC was equal to FFP. On the basis of this evidence, in addition to the practical shortcomings of FFP, such as need for thawing and AB0-match and longer infusion time, it seems reasonable that national guidelines from several European countries recommend FFP for VKA reversal only when PCC is not available [37].

A known complication of all non-specific reversal agents is the risk of thromboembolism. The rate of 4F-PCC associated thromboembolism in this review (1.63%, 95% KI 1.2–2.1) was however low and comparable to the findings of a meta-analysis from 2011 that compiled the thromboembolic event rates from 18 studies using 4F-PCC (1.8%, 95% CI 1.0–3.0) [39].

Only four publications that studied 3F-PCC could be identified, compared to 17 that studied 4F-PCC. Two of the reviewed studies compared efficacy and safety between 3F- and 4F-PCC and both reported fewer deaths and higher rates of reversed INR values when using 4F-PCC compared to 3F-PCC [12,40]. It is however important to emphasize that INR evaluates the extrinsic pathway of coagulation and

Table 2
Baseline characteristics of the DOAC studies.

Authors	Study type	Number and type of test subjects	Dose of DOAC	Reversal agent	Results				
					PT-INR	aPTT	ETP	ECT	Other
				Dabigatran					
Arellano-Rodrigo et al. 2015 [27]	Single blinded cross-sectional study	10 healthy volunteers	150 mg × 2	rFVIIa 270μg/kg *Novoseven®*	R	Partly R	–	–	
				aPCC 75 U/kg *FEIBA®*	R	Partly R	–	–	
				4F-PCC 50 IU/kg *Beriplex®*	Partly R	0	–	–	
Eerenberg et al. 2011 [31]	Randomized double blinded placebo controlled	12 healthy volunteers	150 mg × 2	4F-PCC 50 IU/kg *Cofact®*	–	0	0	0	
Glund et al. 2015 [32]	Randomized double blinded placebo controlled	47 healthy volunteers	220 mg × 2	Idarucizumab 1-5 g	–	R	–	R	TT Improved dTT R
Marlu et al. 2012 [34]	Randomized non blinded	10 healthy volunteers	150 mg single dose	4F-PCC 50 IU/kg *Beriplex®*	–	–	R	–	
				aPCC 80 U/kg *FEIBA®*	–	–	R	–	
				rFVII 120μg/kg *Novoseven®*	–	–	0	–	
Pollack et al. 2015 [26]	Prospective cohort	90 patients B (n = 51) S (n = 39)	110–150 mg × 2	Idarucizumab 5 g	–	–	–	R	Undbound plasma levels of dabigatran < 20 ng in 79%. dTT R Clinical outcomes described*
				Apixaban					
Cheung et al. 2015 [30]	Randomized double blinded placebo controlled	6 healthy volunteers	10 mg × 2	4F-PCC 37,5 IU/kg *Cofact®*	R	–	Improved	–	
				4F-PCC 25 IU/kg *Cofact®*	R	–	Improved	–	
Siegal et al. 2015 [35]	Randomized double blinded placebo controlled	48 healthy volunteers	5 mg × 2	Andexanet 400 mg	–	–	Improved	–	Anti-factor Xa-activity reduced by 94%
Connolly et al. 2016 [25]	Multicenter prospective open-label single-group	20 patients ICH (n = 12) B (n = 8)	5 mg daily dose	Andexanet alfa Bolus dose 400 mg Infusion 480 mg over 2 h	–	–	–	–	Anti-factor Xa-activity reduced by 93% after bolus dose with similar activity remaining during the infusion Clinical outcomes described**
				Edoxaban					
Brown et al. 2015 [29]	Randomized double blinded placebo controlled	24 healthy volunteers	60/180 mg single dose	3F-PCC 25 IU/kg *Bebulin®*	0	–	Improved	–	
				3F-PCC 50 IU/kg *Bebulin®*	0	–	Improved	–	
Zahir et al. 2015 [36]	Randomized double blinded placebo controlled	110 healthy volunteers	60 mg single dose	4F-PCC 50 IU/kg *Beriplex®*	Partly R	–	R	–	Bleeding time reversed Bleeding volume reversed
				4F-PCC 25 IU/kg *Beriplex®*	Partly R	–	Partly R	–	Bleeding time partly reversed Bleeding volume partly reversed
				4F-PCC 10 IU/kg *Beriplex®*	0	–	0	–	Bleeding time and bleeding volume no effect.
				Rivaroxaban					
Arellano-Rodrigo et al. 2015 [27]	Single blinded Cross-sectional study	10 healthy volunteers	20 mg × 1	rFVIIa 270 μg/kg *Novoseven®*	R	R	–	–	
				aPCC 75 U/kg *FEIBA®*	R	R	–	–	
				4F-PCC 50 IU/kg *Beriplex®*	Partly R	0	–	–	
Barco et al. 2016 [28]	Double blinded cross over placebo controlled	6 healthy volunteers	15 mg × 2	4F-PCC 37,5 IU/kg *Cofact®*	R	–	Improved	–	
				4F-PCC 25 IU/kg *Cofact®*	R	–	0	–	
Eerenberg et al. 2011 [31]	Randomized double blinded placebo controlled	12 healthy volunteers	20 mg × 2	4F-PCC 50 IU/kg *Cofact®*	R	–	R	–	
Levi et al. 2014 [33]	Parallel group study non blinded	35 healthy volunteers	20 mg × 2	4F-PCC 50 IU/kg *Beriplex®*	Improved	0	R	–	
					0	0	R		

(*continued on next page*)

Table 2 (*continued*)

Authors	Study type	Number and type of test subjects	Dose of DOAC	Reversal agent	Results				
					PT-INR	aPTT	ETP	ECT	Other
				3F-PCC 50 IU/kg *Profilnine®*					
Marlu et al. 2012 [34]	Randomized cross over non blinded	10 healthy volunteers	20 mg singeldos	4F-PCC 25 IU/kg *Kanokad®*	–	–	R	–	
				aPCC 80 U/kg *FEIBA®*	–	–	R	–	
				rFVII 120 μg/kg *Novoseven®*	–	–	0	–	
Siegal et al. 2015 [35]	Randomized double blinded placebo controlled	53 healthy volunteers	20 mg × 1	Andexanet 800 mg	–	–	Improved	–	Anti-factor Xa-activity reduced by 92%
Connolly et al. 2016 [25]	Multicenter prospective open-label single-group	26 patients ICH (n = 8) B (n = 18)	20 mg daily dose	Andexanet alfa Bolus dose 400/ 800 mg Infusion 480/ 960 mg over 2 h.	–	–	–	–	Anti-factor Xa-activity reduced by 89% after bolus dose with similar activity remaining during the infusion. Clinical outcomes described**

R = reversed; 0 = no effect; PT = prothrombin time; aPTT = activated partial thromboplastin time; ECT = ecarin clotting time; ETP = endogenous thrombin potential; dTT = diluted thrombin time; TT = thrombin time; TG = thrombin generation.

* Intraoperative hemostasis normalized in 92%. Median time to cessation of bleeding 11.4 h. Death occurred in 20%, and thromboembolic event in 6% during a 30 day follow up.

** "Excellent" or "good" clinical outcome in 79% of the combined group (both rivaroxaban and apixaban treated patients). Death occurred in 15%, and thromboembolic event in 18% during a 30 day follow up.

that FVII is the most important determinant of INR, which is present in 4F-PCC and not in 3F-PCC. Most guidelines today recommend 4F-PCC over 3F-PCC and is supported by the current evidence [41].

For VKA-reversal treated with 4F-PCC, this review showed a difference in the mortality rate for ICH (33.3%), compared to other reasons than ICH (12.9%). The mortality rate after ICH in anticoagulated patients (VKA-therapy) is 60% [42], exceeding the 40% observed in patients not taking OAC [43]. In the RE-LY trial, mortality was 38% and 36% in patients with ICH assigned to dabigatran and warfarin, respectively, with an extended mortality follow-up [44], illustrating that the risk of mortality is high in these circumstances.

The primary endpoint of most studies is based on target INR values after reversal treatment. However, the most relevant endpoint is the clinical outcome, and 12 of 21 studies included in this review presented data on clinical outcome. However, since there is no predefinition of improved or adverse clinical outcome of the reversal therapy, it is too complex for adequate comparison. A standardization of how to report outcome of different reversal strategies is recommended to assess the benefits and harms of the different treatment methods. Sarode et al. [14] in discussion with the Food and Drug Administration developed a hemostatic efficacy scale, that was used by a blinded adjudication committee, where the efficacy of hemostasis was rated as excellent, good or poor/none. Similar assessment for hemostatic efficacy was used in the study of andexanet alfa for factor Xa-inhibitor reversal [25]. This might lay ground for a wide spread tool for clinical outcome assessment.

Due to difficulties in quantifying objective clinical endpoints and effective hemostasis, laboratory measurements are used as surrogate endpoints in the efficacy of reversal strategies. Hence, the result of this review is primarily based on reversed surrogate endpoints that differentiates from clinical endpoints that are more beneficial to assess. This is an essential, and inevitable problem in this field for several reasons. Firstly, it is unethical to randomize patients that are severely ill to placebo when possible treatments are available. Secondly, OAC-related bleeding is relatively unusual and the diverseness among the affected patients is significant, which implies that a negative clinical outcome is not synonymous with failed reversal of the coagulopathy. All aspects taken in consideration, it is complicated to conclude the evidence for reversal strategy other than surrogate endpoints.

4.2. Efficacy and safety of DOAC reversal

It is important to recognize that the potential reversing agents/strategies, as described in this review, are in 9 of 12 studies evaluated with laboratory parameters in healthy volunteers rather than clinical outcome in bleeding patients. The results of this review show significant heterogeneity in studies of DOAC reversal. Except for a trend in PT reversal when administrating 4F-PCC to rivaroxaban treated subjects, no conformity of the results between the studies could be seen.

For optimal management, a standardized way to measure the anticoagulant effect is of great importance, and no equivalent of INR for VKA-treatment is yet present for DOACs. In theory INR should be elevated with both FXa- and FIIa-inhibition [45], but as this review shows, there is no well-documented consistency in terms of a linear relation between neither INR, ETP nor aPTT and the anticoagulative effect rendered by DOAC. However, some studies have showed improvement of coagulation parameters with non-specific reversal agents in healthy volunteers. These few studies have included small numbers of patients and are not fully consistent between the studies. Factor Xa-activity and unbound plasma levels of dabigatran are validated tests used in clinical trials, but these tests are not implemented in most clinical environments.

The antidote that has made most progress in the development process is idarucizumab for dabigatran reversal, which is already introduced in several countries. The capacity of idarucizumab to reverse the anticoagulative effects indefinitely with a single i.v bolus dose is very appealing. Similar approach does not apply andexanet alfa which requires a steady infusion to sustain the reversal therapy. If this should be of any clinical importance is however yet to be seen. It will be important to compare idarucizumab to andexanet-alfa to validate the overall safety of the different DOACs. The fact that the two studies used different tools for hemostatic efficacy makes it complex for comparison.

One can safely assume that specific antidotes for DOACs are in development. Until these antidotes are fully established in the clinical environment, the most qualified alternative is 4F-PCC, even though, as this review shows, evidence of beneficial clinical or laboratory outcomes is lacking.

4.3. Limitations

One of the main findings of this review is the significant heterogeneity of the reviewed publications. None of the analyzed outcomes were consistent with homogeneity to a degree that made it possible for meta-analyses to be made. Data pooling of non-randomized trials, and combination of results from observational studies is controversial and interpretation is complicated. The studies in this review differed to study type, size, inclusion and exclusion criteria, reversing agent and study population. The pooling of data has been made with no regards to the strength of each individual study. This could imply that pooling of data is inappropriate, and thus the combined results presented in this study should be interpreted with great caution. Calculations were made to present broad trends of the studies, and the main product of this systematic review is the data presented in Table 1 and Table 2. Eleven of the 12 DOAC studies and 9 of the 21 VKA studies were fully or partly funded by pharmaceutical companies that manufacture either PCC, DOAC or DOAC antidotes. Only 7 of the 33 publications declared that no authors had ties to pharmaceutical companies, which naturally is a limitation when assessing the current collective evidence.

5. Conclusion

Use of 4F-PCC is superior to FFP for reversal of VKA-associated INR elevation and the risk of thrombosis was low for both strategies. Reporting of clinical outcomes is however inconsistent, which complicates assessment of actual patient benefits of these treatments. There are no studies on clinical efficacy of non-specific agents for DOAC reversal and the evidence for laboratory reversal is not consistent. However, studies of specific antidotes for DOACs are underway with promising intermediate results. OAC reversal remains a topic with limited evidence, and this review also underscore the need for high quality non-sponsored randomized trials.

Funding sources

J. Gustav Smith was supported by the European Research Council (679242), Swedish Heart-Lung Foundation (20160134), the Wallenberg Center for Molecular Medicine in Lund, the Swedish Research Council (K2015-65X-22661-01-3), the Crafoord Foundation, governmental funding of clinical research within the Swedish National Health Service, Skåne University Hospital in Lund, and the Scania county.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2017.12.003.

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