


# The Reversal of Bleeding Caused by New Oral Anticoagulants (NOACs): A Systematic Review and Meta-Analysis

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## Abstract

New oral anticoagulants (NOACs; ie, direct thrombin inhibitor [DTI] and factor Xa [FXa] inhibitors) were used as alternatives to warfarin. Specific antidotes (idarucizumab for dabigatran and andexanet alfa for FXa inhibitors) and hemostatic reversal agents were used for lowering bleeding, but their efficacies were still uncertain. The objectives of this study were to estimate and compare the efficacy of NOAC antidotes on bleeding reversal and death. Studies were identified from MEDLINE and Scopus databases until May 2018. Case reports/series and cohorts were selected if they assessed reversal or death rates. Data were independently extracted by 2 reviewers. Individual patient data and aggregated data of outcomes were extracted from case reports/series and cohorts. Binary regression was used to estimate outcome rates, risk ratio (RR) along with 95% confidence interval (CI). Interventions were NOACs and reversal agents (ie, DTI-specific, DTI-standard, FXa-specific, and FXa-standard). Among 220 patients of 93 case reports/series, reversal rates were 95.9%, 77.6%, and 71.5% for DTI-specific, FXa-standard, and DTI-standard. Pooled RRs for DTI-specific and FXa-standard versus DTI-standard, respectively, were 1.34 (CI: 1.13-1.60) and 1.09 (CI: 0.84-1.40). Death rate was 0.18 (CI: 0.06-0.57) times lower in DTI-specific versus DTI-standard. For pooling 10 subcohorts, pooled RRs were 1.08 (CI: 1.00-1.16), 1.29 (CI: 1.20-1.39), and 1.13 (CI: 1.01-1.25) for DTI-specific, FXa-specific, and FXa-standard versus DTI-standard. In conclusion, specific reversal agents might be useful for reversal of bleeding and lowering the risk of death than standard reversal agents. Our findings were based on case reports/series and selected cohorts, further comparative studies are thus needed.

## Keywords

NOAC, antidotes, reversal agents, bleeding reversal, stroke

## Introduction

Warfarin is a commonly used anticoagulant worldwide for the prevention of thrombotic events.<sup>1</sup> It is also used in nonvalvular atrial fibrillation (AF) for stroke prevention and the treatment of venous thromboembolism (VTE), for example, deep vein thrombosis and pulmonary embolism.<sup>2</sup> The advantages of warfarin include convenience (once daily dosing), ability for monitoring (international normalized ratio [INR]) and specific antidote (vitamin K) for bleeding events.

However, many challenges and precautions should be considered during warfarin treatment. Firstly, warfarin interacts with other medications (ie, antifungals, antibiotics, and lipid lowering agents), alcohol, and food (ie, green vegetables, ginkgo, garlic, etc). Secondly, it causes severe hemorrhage due to its narrow therapeutic range. Thirdly, it requires frequent

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INR monitoring for dose adjustment, so patients may have inadequate anticoagulation if INR is too low or from bleeding if the INR is too high. In addition, dose adjustments can complicate prescribing and cause medication errors and poor adherence. Finally, initiating warfarin requires the concurrent use of other parenteral anticoagulants (eg, enoxaparin) to achieve warfarin optimal level.

New oral anticoagulants (NOACs), direct thrombin inhibitor (DTI), and factor Xa (FXa) inhibitor have recently been developed. Four NOACs are currently prescribed (ie, dabigatran [Pradaxa<sup>®</sup>, Boehringer Ingelheim Pharmaceuticals Inc., Germany], rivaroxaban [Xarelto<sup>®</sup>, Janssen Pharmaceuticals Co., Belgium], apixaban [Eliquis<sup>®</sup>, Bristol-Myers Squibb Co., USA], and edoxaban [Lixiana<sup>®</sup>/Savaysa<sup>®</sup>, Daiichi Sankyo Co., Japan]) for the treatment of VTE<sup>3</sup> and prevention of stroke in patients with AF.<sup>2,4-6</sup> Betrixaban (Bevyxxa), another FXa inhibitor was recently approved in June 2017 for VTE prophylaxis. Factor Xa inhibitors are also indicated for thromboprophylaxis in orthopedic surgery.<sup>7-9</sup> Many advantages of these drugs are claimed over warfarin including less drug interactions, rapid onset of action without initial parenteral anticoagulation, fixed once or twice daily dose without the need for frequent monitoring or dose adjustment. These advantages can significantly simplify treatment and improve patients' adherence.<sup>10</sup>

Previous evidence showed that NOACs were noninferior, and even superior in some cases to warfarin in stroke prevention and systemic embolism.<sup>2,4-6,11</sup> with lower risk of major bleeding<sup>5</sup> including intracranial hemorrhage (ICH),<sup>2,4-6,12</sup> and similar risk of major gastrointestinal bleeding.<sup>2,4,5,10</sup>

Despite their short action, reversal agents are needed to reverse anticoagulation effects in major bleeding or critical care practice. Hemostatic agents have been used for this purpose due to the absence of specific antidotes. Preclinical studies were conducted to assess the efficacy of hemostatic agents including coagulation factor replacement<sup>13-18</sup> including prothrombin complex concentrate (PCC), activated PCC (aPCC; ie, FEIBA<sup>®</sup>, Shire US Inc., UK/USA; Cofact<sup>®</sup>, Sanquin, The Netherlands) and recombinant factor VIIa (rFVIIa, Novoseven<sup>®</sup>, Novo Nordisk, Denmark). Results only demonstrated the ability to normalize the prolonged prothrombin time (PT) caused by rivaroxaban but could not reverse the prolonged activated partial thromboplastin time caused by dabigatran.<sup>13</sup>

The United States Food and Drug Administration (US FDA) had approved idarucizumab (Praxbind<sup>®</sup>, Boehringer Ingelheim Pharmaceuticals Inc., Germany) in 2015 for the reversal of dabigatran. Idarucizumab is a monoclonal antibody fragment that binds free and thrombin-bound dabigatran and reverses its activity.<sup>19</sup> However, conventional hemostatic agents are still important because of less accessibility of idarucizumab due to its high cost. The FDA approval was based on preclinical studies in healthy volunteers and cohort studies, but good evidence of its efficacy is still limited.<sup>20-25</sup> Furthermore, idarucizumab is only specific to dabigatran, so the use of hemostatic agents is still crucial. Although there are specific antidotes for FXa inhibitors (ie, andexanet alfa and ciraparantag), clinical

use and data are still limited because andexanet alfa has just recently been approved by the US FDA in May 2018, whereas ciraparantag is still waiting for the FDA approval.<sup>26-28</sup> Therefore, conventional nonspecific hemostatic agents are still routinely prescribed.

A previous systematic review<sup>29</sup> compared the outcomes between PCC, aPCC, and rFVIIa for the reversal of NOACs in which data were mainly from animal studies with 2 healthy volunteers without bleeding studies,<sup>13,14</sup> but no definite conclusions were provided due to the lack of data in human studies. Another systematic review and meta-analysis<sup>30</sup> was later conducted addressing the efficacy and safety of reversal of NOACs including 8 volunteer studies. Coagulation parameters were pooled including PT and endogenous thrombin potential.

Other human studies have recently been published, but they were limited to serum samples or randomized crossover trials in healthy volunteers without underlying thrombotic risks or clinical bleeding.<sup>13,16-18,22,23,31</sup> There were a number of case reports, case series, and cohorts in which patients with NOAC-related bleeding were small subgroups of those cohorts. Additionally, the studies reported reversal agents for descriptive purposes rather than assessing treatment effectiveness.<sup>24,32-44</sup> Therefore, we conducted a systematic review and meta-analysis to explore all regimens used and their efficacy in reversing the effect of NOACs and mortality using data from these kinds of studies.

## Methods

The systematic review protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement<sup>45</sup> and registered at PROSPERO which is an international database of prospectively registered systematic reviews (registration number: CRD42016032983).

### Search Strategy and Selection Criteria

Studies published in English were identified from MEDLINE via PubMed and Scopus databases until May 3, 2018. Search terms were constructed mainly based only on interventions to yield more relevant studies including NOACs and antidotes as follows: NOAC (eg, direct oral anticoagulant), anticoagulant classes (ie, DTI and FXa inhibitor), and their product names. Antidotes included PCCs, activated PCCs, rFVIIa, and fresh frozen plasma (FFP), and idarucizumab (Online Appendix A).

### Eligibility Criteria

Studies were included if they were descriptive or comparative observational studies or experimental designs conducted in humans; patients experienced bleeding from NOACs for stroke prevention in AF or VTE treatment; used at least one of the following antidote/reversal agents: PCC, aPCC, rFVIIa, FFP, or specific antidotes (idarucizumab or andexanet alfa); and reported bleeding reversal or in-hospital death or death within

30 days. Studies were excluded if patients received NOACs for VTE prophylaxis in orthopedic surgery or if data were insufficient.

### Study Selection and Data Extraction

Selection of studies was done by 2 independent reviewers (S.U. and S.R.). Full texts were retrieved for review if a decision could not be made from the title and abstract. Studies were selected according to eligibility criteria. Disagreement of selections was resolved by consensus with a third party (A.T.).

Three reviewers (S.U., S.R., and T.A.) independently extracted data. For cohorts, aggregated data of treatments and outcomes were extracted. For case report/series, patients' characteristics, interventions, and outcome data for individual patients (IPD) were extracted. Any disagreement was resolved by discussion/consensus with a third party (A.T.).

### Interventions

New oral anticoagulants were classified as DTI (dabigatran) and FXa inhibitors (rivaroxaban, apixaban, and edoxaban). Reversal agents were also classified into standard (ie, PCC, aPCC, rFVIIa, and FFP) and specific groups (ie, idarucizumab for dabigatran, andexanet alfa for FXa inhibitors). Patients who received idarucizumab or andexanet alfa as monotherapy or combined with hemostatic agents were classified as specific group, otherwise were classified as standard reversal agent group. Combined NOACs and reversal agents were further classified as 4 treatment regimens of interest including dabigatran-idarucizumab (DTI-specific), dabigatran-standard reversal agents (DTI-standard), FXa inhibitors-andexanet alfa (FXa-specific), and FXa inhibitors-standard reversal agents (FXa-standard).

### Outcomes

The outcomes of interest were reversal of bleeding and deaths. Bleeding reversal was defined according to the original studies including bleeding cessation, no hematoma expansion by computerized tomography (CT), clinically stable, normalized coagulation parameters, and survived or discharged.

### Statistical Analysis

For cohort or subcohort studies, aggregated data were expanded to IPD data. For case reports/series, patients' characteristics were compared between interventions and/or outcomes using *t* test for continuous data and  $\chi^2$  or Fisher exact test where appropriate for categorical data. The reversal and death rates along with their 95% confidence intervals (CIs) were calculated by the type of interventions. Binary regression was applied to compare bleeding reversal between DTI-specific, DTI-standard, FXa-specific, and FXa-standard. A risk ratio (RR) along with its 95% CI was then estimated. All analyses were performed using STATA software version 14. Two-sided  $P < .05$  was considered statistically significant.

## Results

### Study Selection

A total of 1026 and 2253 relevant studies were respectively identified from MEDLINE and Scopus databases, 901 duplicate studies were removed leaving 2378 studies for screening titles/abstracts. Among them, 2275 studies were later excluded with provided reasons leaving 103 studies for eligibility. Among them, 74, 19, and 10 were case reports, case series, and subcohort studies, respectively (Figure 1).

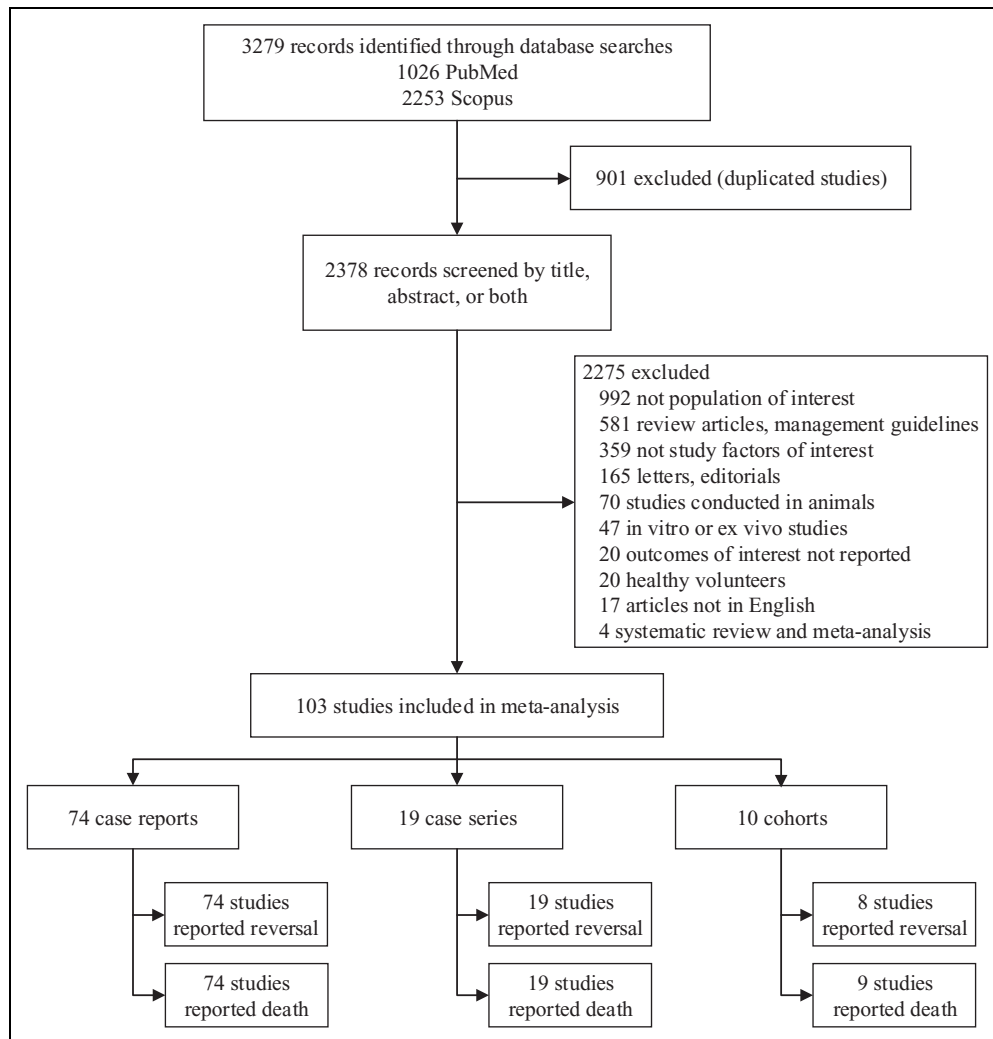
### Case Reports/Case Series

**Characteristics of included studies and participants.** Among 93 case reports/series, most studies were from the United States (54.8%). The number of included patients was 85 and 135 for case reports and series, respectively, with a total of 220 patients. The characteristics of these patients were summarized in Table 1. A total of 120 (61.9%) were male, and mean age was 77.3 years (standard deviation [SD] = 9.6). Among 152 patients with medical history, hypertension was the majority (50.7%), followed by coronary artery disease (20.4%), renal impairment (17.8%), diabetes (15.1%), and cerebrovascular disease (13.8%).

Mean serum creatinine (SCr) and creatinine clearance at admission were 1.2 mg/dL (SD = 0.3) and 47.6 mL/min (SD = 22.8), respectively. Of 90 patients with home medications, 40.0% took antiplatelet medications concomitantly. Most of the patients (146/220, [66.4%]) had spontaneous bleeding, 64 (29.1%) were trauma related, and 10 (4.6%) were bleeding from any medical procedure without receiving a reversal agent before the procedure. The most prevalent bleeding site was ICH (129/220 [58.6%]) followed by gastrointestinal bleeding (55/220 [25.0%]).

**Descriptions of NOACs.** Prevention of stroke in nonvalvular AF (85.5%) was the most common indication for NOACs. Dabigatran was the most commonly used in 136 (61.8%) of 220 patients, while rivaroxaban and apixaban were, respectively, used in 68 (30.9%) and 16 (7.3%) patients, and none used edoxaban or betrixaban. Doses per day could be calculated in 94/136, 31/68, and 9/16 patients who took dabigatran, rivaroxaban, and apixaban, respectively. The median time since last NOAC dose was 11.5 hours (range: 1-96 hours; Appendix B). As for NOACs' classes, 136 (61.8%) and 84 (38.2%) patients received the DTI (ie, dabigatran) and FXa inhibitors (ie, rivaroxaban and apixaban), respectively.

**Descriptions of reversal agents.** More patients received a single reversal agent than combined agents, that is, PCC was the most frequently used (30.9%), followed by idarucizumab (20.9%), FFP (13.2%), aPCC (12.7%), and rFVIIa (5.9%), whereas only 16.4% received combined agents with/without idarucizumab. Idarucizumab had a fixed dose of 5 g. Each reversal agent could not be analyzed individually due to the small number of observations. Therefore, reversal agents were recategorized into



**Figure 1.** Study flow from literature search.

standard and specific agents for further analysis. Patients who received idarucizumab (either alone or combined) were categorized as specific group (50/220, 22.7%) and those did not receive idarucizumab were categorized as standard reversal agent group (170/220, 77.3%). Additional treatments for bleeding were used, that is, packed red blood cells transfusion (67/204, 32.8%) with a median of 4 (range: 1, 32) units, hemodialysis (27/200, 13.5%).

Our interventions of interest were combinations of NOACs and reversal agents: 86 (39.1%), 50 (22.7%), and 84 (38.2%) were included for DTI-standard, DTI-specific, and FXa-standard groups, respectively. These intervention groups were used for the main analysis. None of patients received andexanet alfa; therefore, there were no data for FXa-specific intervention.

**Pooling of reversal outcome.** Reversal of bleeding was variously defined across studies: 86/220 (39.1%) bleeding cessation, 68 (30.9%) stable/no hematoma, 29 (13.2%) survived or discharged, 23 (10.5%) clinical stability, and 14 (6.4%)

normalization of coagulation parameters (Appendix C). Among 220 patients, 174 patients had bleeding reversal with a rate of 79.09% (95% CI: 71.58%-87.39%).

Characteristics of the included patients were compared between reversal groups (Appendix D). Although they were not significantly different between reversal and nonreversal groups, patients in the reversal group had a higher proportion of hypertension (52.8% vs 40.7%), diabetes (17.6% vs 3.7%), and use of concomitant antiplatelet (43.2% vs 25.0%), but lower creatinine clearance (46.4 vs 55.5 mL/min).

Indications for NOAC prescriptions were significantly different between reversal and nonreversal groups, that is, 87.9% versus 69.1% for AF, respectively. Types of NOACs were not much different between the groups except for rivaroxaban (29.3% vs 37.0%). However, the mean dosage of dabigatran (261.4 vs 285.9 mg/d,  $P = .027$ ) and apixaban (7.1 vs 10.0 mg/d,  $P = .030$ ) were significantly lower in reversal than the nonreversal groups, whereas rivaroxaban dosage was higher but not significant (19.2 vs 15.8 mg/d,  $P = .086$ ). The median time since last NOAC dosage was 12 hours for both 2 groups. Use of

**Table 1.** Characteristics of Included Participants From Case Reports/Case Series.<sup>a</sup>

Characteristics	n	n (%)
Number of patients, n (%)	220	
Case report		85 (38.64)
Case series		135 (61.36)
Sex, n (%)	194	
Male		120 (61.86)
Female		74 (38.14)
Age, years, mean (SD)	213	77.34 (9.55)
Medical history, n (%)		
Hypertension	152	77 (50.66)
Coronary artery disease	152	31 (20.39)
Renal impairment	152	27 (17.76)
Diabetes	152	23 (15.13)
Cerebrovascular disease	152	21 (13.82)
Renal function at baseline		
SCr, mg/dL, mean (SD)	11	1.20 (0.30)
CrCl, mL/min, mean (SD)	8	47.58 (22.79)
Renal function on admission		
SCr, mg/dL, median (range)	41	1.75 (0.74, 11.27)
CrCl, mL/min, median (range)	69	53 (14, 113)
Concomitant antiplatelet, n (%)	90	36 (40.00)
Cause of bleeding, n (%)	220	
Spontaneous		146 (66.36)
Trauma		64 (29.09)
Postprocedure		10 (4.55)
Site of bleeding, n (%)	220	
Intracranial		129 (58.64)
Gastrointestinal		55 (25.00)
Other		36 (16.36)

Abbreviations: SCr, serum creatinine; SD, standard deviation.

<sup>a</sup>n, total number of participants available for that data.

specific antidote was higher (17.5% vs 4.8%,  $P = .040$ ), or in other words, the use of standard reversal agents was lower in reversal than nonreversal groups (82.6% vs 95.2%). The total dosage for PCC, the most commonly used standard reversal agents, was higher in reversal than nonreversal groups (2476.4 vs 2154.0 units,  $P = .417$ ) but was not statistically significant.

Site of major organ bleeding was explored by the intervention groups, indicating the most prevalent site of major organ bleeding was ICH (58.6%) followed by the GI bleeding (25.0%) and other (16.4%; Appendix E). Bleeding site varied by the intervention groups, that is, ICH was the higher in FXa-standard (76.2%) and DTI-specific (60.0%) than DTI-standard groups (40.7%). Therefore, the site of bleeding was considered in further analyses.

A binary regression was applied by fitting the intervention groups (ie, DTI-standard, DTI-specific, and FXa-Standard) on reversal event with adjustment for site of major organ bleeding (Table 2). This indicated that the reversal rate was highest in DTI-specific, followed by FXa-standard, and DTI-standard, that is, 95.9%, 77.6%, and 71.5%, respectively. The estimated RRs were respectively 1.34 (95% CI: 1.13-1.60) and 1.09 (95% CI: 0.84-1.40) for DTI-specific and FXa-standard groups compared to DTI-standard group. This could be interpreted that patients who received DTI-specific and FXa-standard reversal

**Table 2.** Incidence and Risk Ratios Adjusted for Bleeding Sites in Case Reports/Case Series.

Treatment Regimen	IR/100	95% CI	RR	95% CI	P Value
<b>Reversal</b>					
FXa-standard	77.60	63.83-91.37	1.09	0.84-1.40	.526
DTI-specific	95.93	90.13-100	1.34	1.13-1.60	.001
DTI-standard	71.46	58.92-84.00	1		
<b>Death</b>					
FXa-standard	20.73	12.45-29.01	0.64	0.33-1.22	.174
DTI-specific	5.95	0-11.94	0.18	0.06-0.57	.003
DTI-standard	32.64	16.94-48.33	1		

Abbreviations: CI, confidence interval; DTI, direct thrombin inhibitor; FXa, factor Xa; IR, incidence rate; RR, risk ratio.

agents had approximately 34% and 9% higher chance of reversal than patients who received DTI-standard reversal agents, respectively.

**Pooling of death outcome.** A total of 48/220 patients died with a rate of 21.8% (95% CI: 15.70-30.32). Cerebrovascular disease was higher (18.2% vs 12.6%,  $P = .403$ ), but hypertension (33.3% vs 55.5%,  $P = .024$ ) and diabetes (6.1% vs 17.7%,  $P = .100$ ) were lower in those who died versus alive (Appendix F). In addition, median creatinine clearance was lower (35.6 vs 53.0 mL/min,  $P = .271$ ), and the use of concomitant antiplatelet was higher (52.9% vs 37.0%;  $P = .227$ ), as well as greater intracranial bleeding (65.9% vs 57.8%;  $P = .502$ ) in death than those who were alive but these were not significant.

Although NOAC types (dabigatran, rivaroxaban, and apixaban) were not much different between the groups, the mean dabigatran dosage (280.0 vs 262.0 mg/d,  $P = .085$ ) was higher in death than alive. However, the percentage of patients receiving a specific antidote was significantly lower in death than alive (4.6% vs 17.7%;  $P = .031$ ). In other words, standard reversal agents were prescribed more often in those who died (95.5% vs 82.3%), with mean total PCC dosage of 3017.8 versus 2179.3 units ( $P = .011$ ).

Death rate was lowest in the DTI-specific group (6.0%) followed by FXa-standard (20.7%) and DTI-standard was highest (32.6%). The RRs were respectively 0.18 (95% CI: 0.06-0.57) and 0.64 (95% CI: 0.33-1.22) for DTI-specific and FXa-standard versus DTI-standard (Table 2).

### Cohort Studies

Ten cohorts<sup>27,33,34,46-52</sup> met our inclusion criteria. Among them, 6 studies<sup>27,34,46-50</sup> were subcohorts, whereas 4 studies<sup>33,48,51,52</sup> were the whole cohorts of NOAC-related bleeding with a total of 559 patients (Table 3). Dabigatran was the most commonly used (321/559, 57.4%), while rivaroxaban and apixaban were used in 238 (42.6%) patients. Three hundred twenty-one (57.4%) and 238 (42.6%) patients were in DTI and FXa inhibitor groups. Idarucizumab was the most frequently used antidote in 301 (53.9%) patients, followed by PCC (26.8%), 4F-PCC (8.6%), and andexanet alfa (8.2%).

**Table 3.** Characteristics of Cohort Studies.

Author (year)	Setting	Study Population (n1/n2)	Type of NOAC	Type of Antidote	Outcome	Definition of Reversal
Bouget and Oger (2015) <sup>46</sup>	France	Patients with bleeding related to NOAC (6/54)	Rivaroxaban	4F-PCC	Death	
Smythe et al. (2015) <sup>47</sup>	United States	Patients with bleeding related to dabigatran or warfarin (3/105)	Dabigatran	4F-PCC	Death	
Sin et al. (2016) <sup>34</sup>	United States	Patients who received 4F-PCC (11/93)	Rivaroxaban, Apixaban, Dabigatran	4F-PCC	Reverse	INR < 1.5
Connolly et al. (2016) <sup>27</sup>	United States, United Kingdom, Canada	Patients with bleeding related to FXa and receive andexanet alfa (46/67)	Rivaroxaban, Apixaban	Andexanet alfa	Reverse	Excellent or good hemostasis efficacy
Pollack et al. (2017) <sup>49</sup>	38 countries	Patients with bleeding related to dabigatran and receive idarucizumab (301/503)	Dabigatran	Idarucizumab	Death, reverse	Stop bleeding in 24 hours
Schulman et al. (2017) <sup>33</sup>	Canada	Patients with bleeding related to dabigatran (14/14)	Dabigatran	aPCC	Death, reverse	Effectiveness assessment for major bleeding management
Majeed et al. (2017) <sup>48</sup>	Sweden	Patients with major bleeding related to rivaroxaban or apixaban with PCC (84/84)	Rivaroxaban, Apixaban	PCC	Death, reverse	Effectiveness assessment for bleeding management
Harrison et al. (2018) <sup>50</sup>	United States	Patients with intracranial hemorrhage related to FXa versus vitamin K treated with 4F-PCC (14/42)	FXa inhibitor	4F-PCC	Death, reverse	Hemorrhagic expansion
Schenk et al. (2018) <sup>51</sup>	Austria	Patients with bleeding complications related to rivaroxaban (13/13)	Rivaroxaban	4F-PCC	Death, reverse	Stop bleeding
Schulman et al. (2018) <sup>52</sup>	Canada	Patients with major bleeding related to FXa treated with PCC (66/66)	Rivaroxaban, Apixaban	PCC	Death, Reverse	Effectiveness assessment for major bleeding management

Abbreviations: aPCC, activated prothrombin complex concentrate; FXa, factor Xa; INR, international normalized ratio; PCC, prothrombin complex concentrate. <sup>a</sup>n1/n2: n1, number of patients included in our study, n2 number of patients in original cohort.

**Pooling of reversal outcome.** Eight of 10 cohorts reported bleeding reversal, 381/549 patients achieved bleeding reversal with an overall pooled reversal rate of 69.40% (95% CI: 65.36-73.23). Reversal rate was highest in FXa-specific, followed by FXa-standard, DTI-specific, and DTI-standard with pooled incidence rates of 80.43%, 75.57%, 67.44%, and 62.60%, respectively (Table 4). The incidence rate for each cohort study was presented in Appendix G. The estimated RRs for these 3 corresponding interventions versus DTI-standard were 1.29 (95% CI: 1.20-1.39), 1.13 (95% CI: 1.01-1.25), and 1.08 (95% CI: 1.00-1.16), respectively. This could be interpreted that patients who received FXa-specific, FXa-standard, and DTI-specific reversal agents had approximately 29%, 13%, and 8% higher bleeding reversal than patients who received DTI and standard reversal agents, respectively.

**Pooling of death outcome.** Nine cohorts reported death outcome (n = 548) with a pooled death rate of 13.14% (95% CI: 10.42-16.26). Pooled death rate was lowest in DTI-specific, followed by DTI-standard, FXa-specific, and FXa-standard with pooled death rates of 6.31%, 10.16%, 15.22%, and 21.76%,

**Table 4.** Incidence and Risk Ratios in Cohort Studies.

Treatment Regimen	N/n	IR/ 100	95% CI	RR	95% CI	P Value
<b>Reversal</b>						
FXa-specific	1/46	80.43	66.83-89.35	1.29	1.20-1.39	< .001
FXa-standard	5/186	75.57	64.46-86.68	1.13	1.01- 1.25	.030
DTI-specific	1/301	67.44	61.96-72.49	1.08	1.00-1.16	.042
DTI-standard	2/16	62.60	39.00-86.20	1		
<b>Death</b>						
FXa-specific	1/46	15.22	7.57-28.22	0.91	0.25-3.37	.891
FXa-standard	5/183	21.76	11.60-31.93	1.41	0.35-5.66	.628
DTI-specific	1/301	6.31	4.08-9.65	0.38	0.10-1.40	.145
DTI-standard	2/18	10.16	0.0-23.17	1		

Abbreviations: CI, confidence interval; DTI, direct thrombin inhibitor; FXa, factor Xa; IR, incidence rate; N/n, numbers of included studies/numbers of patients; NOAC, new oral anticoagulant; RR, risk ratio.

respectively (Table 4). The death rate was estimated for each cohort (Appendix G) with the pooled RRs of 0.38 (95% CI: 0.10-1.40), 0.91 (95% CI: 0.25-3.37), and 1.41 (95% CI: 0.35-5.66) for DTI-specific, FXa-specific, and FXa-standard versus

DTI-standard group. This could be interpreted that patients who received DTI-specific and FXa-specific antidotes were approximately 62% and 9% lower risk of death, respectively, while FXa-standard group had approximately 41% higher risk of death than those who received DTI-standard reversal agents.

## Discussion

We conducted a systematic review and meta-analysis to assess the efficacy of reversal agents for different NOACs using evidence from 93 case reports/series ( $n = 220$ ) and 10 cohorts ( $n = 559$ ). Evidence from case reports/series suggested that 95.93%, 77.60%, and 71.46% of patients in the DTI-specific, FXa-standard, and DTI-standard groups, respectively, could achieve bleeding reversal. The DTI-specific and FXa-standard were 34% and 9% more likely to achieve bleeding reversal compared with DTI-standard group, respectively. In addition, the mortality was lowest in the DTI-specific group followed by the FXa-standard and DTI-standard. Results from cohorts were slightly different from case reports/series, that is, FXa-specific achieved highest bleeding reversal followed by FXa-standard and DTI-specific with 29%, 13%, and 8% higher than DTI-standard, although magnitudes of reversal rates were lower than those estimated from case reports/series. However, DTI-specific yielded lowest death rate compared to the rest.

Indications for NOAC use were mainly stroke prevention in AF (85.45%), followed by the treatment of VTE, and either AF or VTE (not specified). Both classes of NOACs (ie, DTI and FXa inhibitors) were approved for these 2 indications, but FXa inhibitors were approved only for VTE prophylaxis. We therefore did not consider including NOACs for VTE prophylaxis. Our study mainly focused on reversal outcomes, originally defined by the included studies, which mainly considered clinical signs and symptoms in addition to CT scanning. Although death was ascertained, specific cause of death was reported only in small numbers. In addition, we were also interested in other relevant surrogate outcomes (eg, INR, PT, activated partial thromboplastin, and thrombin time), but these surrogate outcomes were not commonly reported.

Our findings from case reports/series indicated that idarucizumab was promising in bleeding reversal and lowering the risk of death compared to standard reversal agents. This result was in accordance with a systematic review of dabigatran reversal using idarucizumab.<sup>53</sup> A large prospective cohort also found that idarucizumab rapidly and safely reversed the anticoagulant effect of dabigatran.<sup>24,49</sup> These studies highlighted the need for specific antidotes of NOACs in clinical practice.

We were able to assess the efficacy of FXa-specific group from 1 subcohort, which had quite small sample size (46) compared to sample size of its original cohort (67). Our findings suggested that 80.43%, 75.57%, 67.44%, and 62.60% of patients in the FXa-specific, FXa-standard, DTI-specific, and DTI-standard could achieve bleeding reversal, respectively. Patients in DTI-specific group had the lowest mortality rate (6.31%) when compared to DTI-standard groups (10.16%), FXa-specific (15.22%), and FXa-standard (21.76%). Our

findings from cohort studies suggested that idarucizumab and andexanet alfa, NOAC-specific antidotes, were promising in bleeding reversal compared to standard reversal agents.

Idarucizumab might be the most effective for bleeding reversal and preventing death in patients taking dabigatran, whereas andexanet alfa might be the most effective for FXa inhibitors. Standard reversal agents for dabigatran and FXa inhibitors yielded lower efficacy in bleeding reversal than idarucizumab-dabigatran, but both were not much different. Therefore, where idarucizumab is not accessible, standard reversal agents might be the treatment of choice.

Physical approach using activated charcoal for reduction in anticoagulant absorption may be useful and had also been used in some cases.<sup>54,55</sup> Given limited evidence from only one study,<sup>56</sup> an activated charcoal was able to reduce apixaban exposure and facilitated its elimination when it was given up to 6 hours after apixaban overdose. A mechanical approach by dialysis might also be useful for clearance of serum level of dabigatran especially in cases with renal impairment.<sup>57-59</sup>

Dabigatran was the first-approved NOAC; therefore, there was evidence on dabigatran usage whereas evidence for other NOACs was limited. Although edoxaban and betrixaban had been approved by the US FDA since January 2015 and June 2017, respectively, they are still available in only some countries. Their data are still lack as for none of studies with edoxaban or betrixaban was identified by our search strategies. Thus, there is a big need for well-conducted studies evaluating the efficacy of specific antidotes.<sup>26,28</sup> Before prescribing NOACs in clinical practice, physicians should account for baseline patients' risks (eg, age, renal impairment, and site of bleeding [eg, ICH and GI bleeding])<sup>60,61</sup> and availability of specific antidote in their settings.

Our study had some strengths. First, we included studies in which patients had bleeding in the real-world settings rather than using animal models or coagulopathy induction in healthy volunteers. Second, we could access IPD from 93 case reports/series with 220 patients, allowing us to explore patients' characteristics and specific interventions which affected reversal and death outcomes. In addition, efficacy of interventions was assessed with adjustment for bleeding site.

However, there were some limitations. The best study design for assessing efficacy is randomized controlled trial or cohort. Although there were 10 cohorts which met our inclusion criteria, they were mainly small parts of original cohorts conducted for other purposes. In addition, these cohorts were only single-arm studies without comparing reversal or death with other interventions. Data were mainly from case reports/series in which interventions were not planned for direct comparisons. Therefore, selection bias might be present. Only patients who achieved bleeding reversal were selected and reported, whereas some other patients who failed to reverse might not have been reported. This hypothesis corresponded with results from pooling cohorts showing lower reversal rate in cohorts than case reports/series. Therefore, further comparative studies are needed to fill in the gap of knowledge. Publication bias is also likely because the patients represented here

are likely to be more severe or at the “interesting” end of the spectrum, who were needed to break the publication barrier. Although we had attempted to pool treatment effects using cohort studies, they were mostly only minor parts of other cohorts which mainly aimed to assess other interests, not reversal rates in NOAC’s antidotes.

## Conclusion

In summary, current evidence from case reports/series showed idarucizumab might be the most effective antidote for dabigatran-induced bleeding. Andexanet alfa is promising for bleeding reversal for FXa inhibitors. New oral anticoagulants should be used with caution considering the availability of specific antidote and patients’ risks. Further comparative studies particularly randomized controlled trials are needed.


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## Supplemental Material

Supplemental material for this article is available online.

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