BMJ Open

Systematic Review and Quality Evaluation of Case Series Describing Four-Factor Prothrombin Complex Concentrate in Oral Factor Xa Inhibitor-Associated Bleeding

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040499
Article Type:	Original research
Date Submitted by the Author:	14-May-2020
Complete List of Authors:	Costa, Olivia; University of Connecticut School of Pharmacy, Pharmacy Practice; Hartford Hospital, Evidence-Based Practice Center Baker, William; University of Connecticut School of Pharmacy, Pharmacy Practice; Hartford Hospital, Evidence-Based Practice Center Roman-Morillo, Yuani; University of Connecticut School of Pharmacy, Pharmacy Practice; Hartford Hospital, Evidence-Based Practice Center McNeil-Posey, Kelly; Portola Pharmaceuticals Inc, Health Economics and Outcomes Research Lovelace, Belinda; Portola Pharmaceuticals Inc, Health Economics and Outcomes Research White, Michael; University of Connecticut School of Pharmacy, Pharmacy Practice; Hartford Hospital, Evidence-Based Practice Center Coleman, Craig; University of Connecticut School of Pharmacy, Department of Pharmacy Practice; University of Connecticut School of Pharmacy, Pharmacy Practice
Keywords:	Anticoagulation < HAEMATOLOGY, HAEMATOLOGY, NEUROLOGY, CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Systematic Review and Quality Evaluation of Case Series Describing Four-Factor Prothrombin Complex Concentrate in Oral Factor Xa Inhibitor-Associated Bleeding

Olivia S. Costa[1,2]; William L. Baker[1,2]; Yuani Roman-Morillo[1,2]; Kelly McNeil-Posey[3], Belinda Lovelace[3], C. Michael White[1,2]; Craig I. Coleman[1,2]

[1] Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, CT, USA

[2] Evidence-Based Practice Center, Hartford Hospital, Hartford, CT, USA

[3] Health Economics and Outcomes Research, Portola Pharmaceuticals, San Francisco, CA, USA

Corresponding Author:

Craig I. Coleman, PharmD

Professor of Pharmacy Practice

University of Connecticut

School of Pharmacy

69 North Eagleville Road, Unit 3092

Storrs, CT 06269, USA

860-972-2096

860-545-2277 (fax)

craig.coleman@hhchealth.org

ABSTRACT

INTRODUCTION As oral factor Xa inhibitor (oFXaI) use has increased, so has publication of case series describing related bleeding managed with 4-factor prothrombin complex concentrate (4F-PCC).

OBJECTIVE This review aimed to identify case series describing 4F-PCC management of oFXaI-related bleeding and appraise their methodological and reporting quality.

DESIGN We searched Medline and Embase (01/01/2011–11/08/2019) to identify series of ≥10-patients with oFXaI-related major bleeding given off-label 4F-PCC. Case series' were evaluated using a validated tool adapted for this topic. The tool addressed patient selection, bleed/outcome ascertainment, causal/temporal association, and reporting.

RESULTS We identified 11 case series. None had ≥100-patients (range=13-84), three were prospective, two detailed appropriate inclusion criteria, and three noted consecutive inclusion. While nine series provided clear/appropriate methods for diagnosis of intracranial hemorrhage (ICH); none did so for extracranial bleeds and it was not clear whether bleeding was adjudicated in any. Hemostatic effectiveness, thrombosis, and mortality were together evaluated in nine series, but only four used validated methods to evaluate/diagnosis hemostasis in ICH, five in gastrointestinal bleeds, four in other bleeds and one in thrombosis. Independent adjudication of hemostasis (n=1) and thrombosis (n=2) was infrequent. Thirty-day follow-up for mortality and thrombosis was noted in five and six series. Anticoagulation measurement/levels in at least some patients were conveyed in three series. Few series provided data on anticoagulant agent/dose (n=2), time from anticoagulant (n=4), time-to-reversal (n=5), baseline (n=5) or change (n=0) in neurologic function.

CONCLUSIONS Although many case series describe off-label use of 4F-PCC for oFXaI-related bleeding, methodological flaws and/or poor reporting necessitates caution in interpretation.

Keywords: Anticoagulation; Cardiology; Haematology; Neurology

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study compiles all available literature meeting inclusion criteria regarding the off-label use of use of 4-factor prothrombin complex concentrate to manage oral factor Xa related major bleeding.
- This study brings attention to the methodology and reporting flaws of this literature which gives perspective when considering effectiveness and safety.
- The disease-specific tool utilized in this study is derived from a previously validated tool, however our disease-specific tool has not been peer reviewed.

INTRODUCTION

Randomized controlled trials have demonstrated oral factor Xa inhibitors (oFXaIs) to be at least noninferior to warfarin for preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) [1-3] and reducing recurrent thrombosis in patients with venous thromboembolism (VTE) [4-6]. Moreover, data suggest that oFXaIs have a similar or reduced risk of overall major bleeding compared to warfarin, with a reduction in fatal bleeding including intracranial hemorrhage (ICH) [1-6]. Consequently, the proportion of NVAF and acute VTE patients treated with oFXaIs has increased in lieu of warfarin [7-8].

Despite the short duration of pharmacologic action (anticoagulation effect) of oFXaIs (apixaban, edoxaban and rivaroxaban), reversal agents are often needed to manage patients with severe or life-threatening bleeds [9-10]. In May 2018, the United States (US) Food and Drug Administration (FDA) approved coagulation factor Xa (recombinant), inactivated –zhzo (USAN: andexanet alfa), the first specific reversal agent to manage oFXaI-related bleeding [11]. Shortly after, in April 2019 the European Medicines Agency (EMA) also approved andexanet alfa for this indication [12]. Prior to regulatory approval of andexanet alfa, various non-specific reversal agents were supported by guidelines [13-15] as an off-label approach to manage oFXaI-related severe or life-threatening bleeds, most notably, four-factor prothrombin complex concentrate (4F-PCC). Evidence, primarily in the form of small case series, has suggested that 4F-PCC are safe and efficacious in the management of oFXaI bleeding, but variation in reporting, sample size, bleed definition and severity, hemostasis endpoint definitions and hospital practices, including various types and doses of 4F-PCC, make it difficult to assess their generalizability. While all case series have innate limitations, there may still be substantial variation in their clinical usefulness based upon the quality of methods used and extent of reporting of methods and results. Therefore, we sought to systematically identify existing case series describing 4F-PCC use for the reversal of oFXaIs-related bleeding and to evaluate their methodological and reporting quality.

METHODS

Preparation of this report was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

Search Strategy

We performed a bibliographic literature search of Medline and EMBASE from January 1, 2011 (year of first oFXaI availability) through November 8, 2019. Our search strategy is available in **Appendix 1**. Bibliographic searches were augmented with backwards citation tracking and review of conference proceedings of major cardiology, neurology and thrombosis and hemostasis meetings over the past two years (the latter were searched to identify case series available only in abstract form for inclusion into a pre-specified sensitivity analysis only).

Study Selection

Two investigators screened citations and assessed eligible reports for inclusion with disagreements reconciled through discussion or by a third investigator. To be included in this review, case series had to describe the use of 4F-PCC in ≥10 patients for management of major, severe or life-threatening bleeding while taking an oFXaI. Reports describing the use of andexanet alfa, 3-factor PCC, activated PCC, unspecified PCC or recombinant factor VIIa as the primary reversal agent were excluded; as were those assessing the reversal of dabigatran or warfarin, reversal of non-bleeding surgical patients, non-major bleeds or healthy volunteers.

Data Abstraction

Two investigators independently extracted all data with disagreements resolved by discussion or a third investigator. The following data were sought from each study: first author's last name; year of publication; journal and its impact factor; specific inclusion and exclusion criteria; enrollment timeframe; number of patients included and outcomes reported on; renal function at presentation; location of bleed; method of diagnosis/ascertainment of bleeding and any thrombotic events; measurement of neurologic function; anticoagulant characteristics (agent, dose, indication, time last taken, drug concentration level, anti-factor Xa activity level); reversal agent information (agent, dose, time to administration); concomitant methods of achieving hemostasis utilized (surgeries or procedures, transfusions, additional reversal agents or medications); reporting of hemostatic effectiveness, thrombotic events and mortality; definition of hemostatic effectiveness applied; adjudication of bleeding events, hemostatic effectiveness and/or thrombotic events; duration of follow-up for hemostatic effectiveness, change in neurologic status, thrombotic events and mortality; and description of treatment site(s) (i.e., geographic region/country, comprehensive stroke center, level one trauma center).

Methodological and Reporting Quality Assessment

We performed critical appraisal of the methodological and reporting quality of each included case series. We modified a tool originally developed by Murad and colleagues [17] for use in our disease/indication-specific literature review. Our tool uses exploratory questions/items to assess a case series' methodological and reporting quality in respect to its selection, exposure and outcome (i.e., alternative causes, dose-response, and sufficient duration of follow-up) and whether cases were reported with sufficient detail to allow for generalizability to patients in other practices. We included questions evaluating the domains of selection (n=5 items), ascertainment (n=12 items), causal and temporal association (n=6 items) and reporting (n=15 items). Items for the selection, ascertainment, causal and temporal association domains were answered/assessed as "yes", "no", "unclear" (or "not applicable"). Items for reporting were assessed as "yes" or "no". The specific criteria used to assess each item are provided in **Appendix 2.** Evaluation of methodological and reporting quality was performed by two investigators with all disagreements resolved by discussion or a third investigator.

Descriptive statistics were used to summarize assessment of each item, with the proportion of case series assessed as "yes" (+), "no" (-) and "unclear" (?) divided by the number of applicable case series (excluded studies deemed not applicable). Continuous data (e.g., journal impact factor and sample size) were reported as medians with 25%, 75% ranges.

Case series available as abstracts only would likely accentuate/inflate the number of "unclear" or "no" designations due to their limited word count and the lack of detailed peer review; therefore, abstracts were not included in our primary analysis. We did perform sensitivity analysis whereby both full-text and abstract-only case series were included.

RESULTS

Literature Search

The literature search identified 464 non-duplicate citations with four additional citations identified through other sources, resulting in 468 total citations (**Figure 1**). After title and abstract review, 436 citations were excluded, leaving 32 for full-text review. Upon the full-text review, 11 case series met inclusion criteria for this systematic review without exclusions [18-28]. An additional 7 case series available as abstracts only were included in the sensitivity analysis only [29-35].

Characteristics of Case Series

The impact factor of journals in which case series were published ranged from 0.0420 to 16.562 (median, 2.873) (**Table 1**). The number of patients in identified case series ranged from 13 to 84 (median, 33) (**Table 2**). Most studies included apixaban (n=10) and/or rivaroxaban (n=10). Atrial fibrillation was the most common indication for anticoagulation across all 11 case series. ICH was included in all case series, with 8 series including GI and 7 other types of extracranial bleeds.

Methodological and Reporting Quality

Selection

Two of identified case series specified all three key inclusion criteria (specific notation of a major bleed, anticoagulant(s) used and time since last anticoagulant dose) (**Figure 2a, Figure 3a**). Five case series did not provide timing since the last anticoagulant dose and four did not provide data regarding both time since last anticoagulant dose and the specific anticoagulant(s) used (**Figure 4**). Three case series noted they enrolled consecutive patients. Nine case series had no patients lost to follow-up, with the remaining reporting anywhere from 6 to 8% of patients lost to follow-up. Three case series described prospective collection of data.

Ascertainment of Qualifying Bleeding Event

The methods utilized for ascertainment of ICH diagnosis were specified and deemed appropriate in nine case series, though the diagnosis of gastrointestinal (n=8) or other extracranial bleeds (n=7) were not described in any case series **(Figure 2b)**. Further, no case series noted the use of an independent committee or process for adjudication of the diagnosis of the qualifying bleed.

Ascertainment of Outcomes

Nine case series assessed each of the three pre-specified key outcomes including hemostatic effectiveness, mortality and thrombosis (**Figure 2c**). Of those that assessed hemostatic effectiveness, four (ICH) to five (gastrointestinal bleeds) reported the use of a validated set of diagnostic criteria (i.e. those of the International Society on Thrombosis and Haemostasis or previous used in trials by Sarode and colleagues) [36-37]. A single case series reported the use of an accepted clinical definition/diagnostic criteria for thrombotic events; approximately 1 in 5 explicitly reported diagnoses were based solely on clinical judgment. Neurologic function was ascertained using a validated tool two

case series involving ICHs. For hemostatic effectiveness adjudication, one case series described using an independent party (and one explicitly stated not adjudicating events). Two case series explicitly noted they adjudicated thrombotic events, while the remainder did not make their methodology clear.

Causal and Temporal Associations

The duration of follow-up for hemostatic effectiveness was defined as between 3-24 hours for ICH and 36-60 hours for extracranial bleeds in five case series (**Figure 2d and Figure 3a**). Follow-up was ≥30-days for mortality and thrombotic events in five and six case series, respectively; ≤30 days in five case series each. For neurologic changes, follow-up duration was within 12-36 hours in three series and unclear in the remainder. Six case series clearly stated that no other reversal agent(s) were used prior to the 4F-PCC. Anticoagulant levels or anti-factor Xa activity levels were measured in three case series (all using a calibrated machine), not measured in two case series and unclear in the remaining six.

Reporting of Characteristics at Presentation

A summary of reporting of characteristics at presentation across all case series is depicted in **Figure 2e** and **Figure 3b**. Two case series provided both the anticoagulant used and the dose. All but one case series provided information regarding the reversal agent and dose. Time since last anticoagulant dose to presentation and time to administering the reversal agent from diagnosis was reported in four and five case series, respectively. Use of concomitant antiplatelets and renal function at presentation was reported in ten and six case series. Neurologic function at presentation was reported in five case series. A description (i.e. comprehensive stroke center, level I trauma center, etc.) and geographical region of the investigation site was reported in seven case series.

Reporting of Outcomes

The reporting of outcomes across all case series is depicted in **Figure 2f.** Most case series provided data on hemostatic effectiveness (n=10), thromboembolic events (n=11) and mortality (n=10). Other measures to manage bleeds including surgeries and/or procedures, transfusions, and other hemostatic medications were reported in seven, eight and six of case series, respectively. Change in neurologic function was not reported as an outcome in any case series.

Sensitivity Analysis

The addition of abstracts to full-text series resulted in a decreased median sample size of 31 (**eTable 1**). No case series available as an abstract only adequately reported inclusion criteria (**eFigure 1a, eFigure 2a**), detailed how thrombotic events were ascertained (**e Figure 1b**) or reported on anticoagulant agent and dose, time since last anticoagulant dose to arrival and renal function at presentation (**eFigure 1c, eFigure 2b**). The remainder of assessed quality items were generally similar between the sensitivity and primary analyses (**eFigure 1d, eFigure 1e, eFigure 1f**).

DISCUSSION

Our systematic review identified 11 modestly sized full-text case series published in journals of varying impact factor (and an additional 7 abstracts presented at international/national conferences). Using an adapted version of a tool [17] specifically designed to assesses methodological and reporting quality of case series, we identified the presence of several common methodological flaws and reporting deficiencies that limit these case series' internal and external validity and consequently necessitate clinicians/readers to use caution when interpreting their results.

One key methodological concern noted in the identified case series were unclear definitions, and lack of adjudication of, the index bleed (especially extracranial), hemostatic effectiveness and thrombosis. Despite accepted definitions of hemostasis that have been endorsed by the International Society of Thrombosis and Hemostasis or previously utilized in clinical trials [36,37], valid ascertainment of hemostatic effectiveness was only performed in 40% of case series including ICH, 63% including GI bleeds and 57% of other bleeds. Frequently, investigators relied on clinical judgment to assess hemostatic effectiveness. Similarly, only a single case series clearly described the requirement for a validated measure (i.e., ultrasound) to objectively confirm the diagnosis of a thrombotic event [25, 38]. Fewer than one-quarter of case series performed (independent or secondary) adjudication of outcomes [39]. More frequent use of a prospective study design (only 27.3% of identified case series reported being prospective) would allow for many of these concerns to be addressed.

Another common methodological flaw was case series' failure to impose and/or describe a maximum time since last anticoagulation dose (part of inclusion in 18%, reported in 36%) and/or the need for sufficiently elevated anticoagulation activity/levels for inclusion (measured in 27%). Guidelines state that a reversal agent should only be considered when a patient is expected to have clinically relevant levels of anticoagulant [13]. Given the relatively short half-life (8-15 hours for apixaban; 7-13 hours for

rivaroxaban) and duration of pharmacologic activity seen with oFXaIs, it is estimated that <25% of the drug would be present 14 hours after the last dose and <10% after 24-hours in most patients [40,41]. Inclusion of patients presenting with bleeds more than a day after the last dose or without verification of anticoagulation activity in case series could result in an overestimation of 4F-PCCs effectiveness.

Identified case series often failed to follow patients for sufficient duration of time to assess important outcomes including mortality (which can be seen as early as 48-72 hours after presentation in 20% of patients with ICH, but up to 40% by 30-days [42]) and thrombosis (which occurs in up to 14% of 4F-PCC users at 30-days) [25]. Moreover, the factor II in 4F-PCC has a half-life of ~60 hours [43] and requires ~12 days to fully clear from the body post-infusion [41]. Only 40% and 54.5% of case series follow patients for ≥30 days for mortality and thrombotic events, respectively. Due to the short duration of follow-up used in these case series, the risk of mortality and thrombotic events could have been underestimated.

Insufficient reporting was also present in identified case series. Few of the included case series provided detailed data on anticoagulant agents used, dosage, time from last anticoagulant administration, time from presentation for bleeding to 4F-PCC administration or baseline neurologic function (in ICH patients). Beyond the methodological concerns noted above, incomplete or lack of reporting of such detail makes it more difficult for clinicians to understand how these case series apply to their patients (generalizability) and how they might change their clinical practice.

Many of the case series limitations discussed above are known challenges when performing a study with this design [17,44]. While case series are often mistakenly interpreted as reporting on treatment efficacy, that is not their objective. Rather, case series are typically descriptive and intended to be hypothesis generating only. Even conscientious Investigators are limited by the data available to them (contained within their electronic health record), particularly when data is collected retrospectively. The flaws discussed previously and the inherent limitations of case series may explain much of the substantial variance in hemostatic effectiveness (ranging from 65% [30] to 94% [22]) reported with 4FPCC in identified series [18-35], and further underscores the importance of reporting quality metrics for case series when evaluating medical literature.

Based primarily on case series such as those identified in our review (as well as clinical opinion), guidelines and position statements have been published detailing the role of 4F-PCC as a reversal agent in the management of oFXaI-related bleeding [13-15]. European Stroke Organisation recommends

andexanet alfa first line and with second line option of 4F-PCC use if andexanet alfa not available for managing oFXaI-related ICH, but the strength of evidence supporting this recommendation is graded as "very low" [13]. Updates to AHA/ACC/HRS atrial fibrillation guidelines also provide guidance on oFXaI reversal, making a class IIa/B (moderate) recommendation for andexanet alfa use in life-threatening bleeding, without mentioning 4F-PCC [45]. Position statements from both the North American Anticoagulation Forum and the Emergency Medicine Cardiac Research and Education Group recommends 4F-PCC use as an alternative to andexanet alfa when it is unavailable (no strengths of recommendation provided) [14,15]. Although these recommendations may mention the use of 4F-PCC in oFXaI-related bleeding, clinicians should understand the strength of these recommendations is low based on the poor quality of evidence available.

We believe the tool we adapted for use in this systematic review provides a comprehensive framework that clinicians and other peer-reviewers can use to aid when critically appraising and developing case series of reversal agents (e.g., 4F-PCC) for oFXaIs-associated bleeding. It is important to note, however, that our tool has some limitations. Although we based our disease-specific tool on a previously validated generic case series assessment [17], ours has not undergone extensive peer evaluation and its reliability/validity is unclear. In its present form, our tool uses 38 items to assess methodological and reporting quality. We acknowledge that the number of items and time needed to appraise a case series may be burdensome to clinicians (and limit its use). Lastly, it is often difficult to assess the true methodological quality of a case series because of incomplete or unclear reporting. "Unclear" designations for items does not imply proper or improper use of methods (i.e., a case series may have used valid methods, but simply did not describe it in their report). For the abovementioned reason, case series published as abstracts only were excluded from our base analysis as they are more likely to have incomplete reporting due to strictly imposed word/character limits and the lack of back-and-forth peer-review.

CONCLUSION

Although many case series describing 4F-PCC for managing oFXaI-related bleeding have been published, the presence of common methodological flaws and/or poor reporting necessitates caution in interpretation. Major flaws of case series identified included unclear definitions, and lack of adjudication of, the index bleeding, effectiveness and thrombosis, failure to validly ascertain effectiveness in many cases and overall under-reporting of relevant clinical or methodological information. The tool adapted for this systematic review may be useful to clinicians and peer-reviewers

who need to critically appraise case series of reversal agents for oFXaIs-associated bleeding. To best support patients with oFXaI-related bleeds, it is crucial to assess the safety and efficacy of reversal agents using rigorous frameworks and across larger samples with enhanced generalizability.

ETHNICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Collected data is available upon request.

COMPETING INTEREST

O.S.C , Y.R., and C.M.W. have no competing interest to disclose.

B.L. and K.M. are employees of Portola Pharmaceuticals.

W.L.B has received consultancy fees from Bayer Inc.

C.I.C has received grant funding and consultancy fees from Janssen Scientific Affairs LLC and Bayer Inc.

FUNDING

Funding provided by Portola Pharmaceuticals.

AUTHORS CONTRIBUTIONS

C. I.C, and B.L. conceptualized and designed the study. Y.R and O.S.C. collected data. The manuscript was primary written by O.S.C. and C.I.C.; all remaining authors aided and/or contributed to revisions. All authors substantially contributed to this project, read and approved the manuscript and assume responsibility for the contents of the manuscript

ACKNOWLEDGEMENTS

None.

ABBREVIATIONS

EMA: European Medicines Agency

FDA: Food and Drug Administration

GI: gastrointestinal

ICH: intracranial hemorrhage

NVAF: nonvalvular atrial fibrillation

oFXaIs: oral factor Xa inhibitors

PCC: prothrombin complex concentrate

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

US: United States

VTE: venous thromboembolism

4F-PCC: Four factor prothrombin complex concentrate

REFERENCES

1. Giugliano RP, Ruff CT, Braunwald E. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369:2093-2104.
2. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-992.
3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365: 883-891.
4. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for treatment of acute venous thromboembolism. N Engl J Med. 2013;369: 799-808.
5. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J. 2013;11:1-10.
6. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361:2342-2352.
7. Steinberg BA, Gao H, Shrader P, et al. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: Results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. Am Heart J. 2017;194:132-140.
8. Zhu J, Alexander GC, Nazarian S, et al. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. Pharmacotherapy. 2018;38:907-920.
9. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330-1393.
10. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med. 2019;380:1326-1335.
11. Heo Y. Andexanet alfa: first global approval. Drugs. 2018;78:1049-1055.
12. Euopean Medicines Agency, andexanet alfa. https://www.ema.europa.eu (Last accessed on January 6, 2020).
13. Christensen H, Cordonnier C, Korv J, et al. European stroke organization guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. Euro Stroke J. 2019;0: 1-13.
14. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. Am J Hematol. 2019;94:697-708.

15. Gibler WB, Racadio JM, Hirsch AL, et al. Management of severe bleeding in patients treated with oral anticoagulants. Crit Pathw Cardiol 2019;13:143-166.
16. Liberati A, Altman DG, Tetzalaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. PLOS Med. 2009;6:1-28.
17. Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Medicine 2018;23:60-63.
18. Allison TA, Lin PJ, Gass JA, et al. Evaluation of the use of low-dose 4-factor prothrombin complex concentrate in the reversal of direct oral anticoagulants in bleeding patients. J Intensive Care Med. 2018; epub /doi.org/10.1177/0885066618800657.
19. Arachchillage D, Alavian S, Griffin J, et al. Efficacy and safety of prothrombin complex concentrate in patients treated with rivaroxaban or apixaban compared to warfarin presenting with major bleeding. Br J Haematol. 2019;184:808-816.
20. Dybdahl D, Walleser G, Spalding MC, et al. Four-factor prothrombin complex concentrate for the reversal of factor Xa inhibitors for traumatic intracranial hemorrhage. Am J Emerg Med. 2018;0: 1-5.
21. Frontera JA, Bhatt P, Lalchan R, et al. Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage. J Thromb Haemost. 2019; 1-11. https://doi.org/10.1007/s11239-019-01973-z.
22. Grandhi R, Newman WC, Zhang X, et al. Administration of 4-factor prothrombin complex concentrate as an antidote for intracranial bleeding in patients taking direct factor Xa inhibitors. World Neurosurg. 2015;84:1956-1961.
23. Harrison SK, Garrett JS, Kohman KN, et al. Comparison of outcome sin patients with intracranial hemorrhage on factor Xa inhibitors versus vitamin K antagonists treated with 4-factor prothrombin complex concentrate. Proc (Bayl Univ Med Cent). 2017;31:153-156.
24. Majeed A, Agron A, Holmstrom M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood. 2017;130:1706-1712.
25. Schenk B, Goerke S, Beer R. Four-factor prothrombin complex concentrate improves thrombin generation and prothrombin time in patients with bleeding complications related to rivaroxaban: a single-center pilot trial. Thromb J. 2018:16;1-10.
26. Schulman S, Gross PL, Ritchie B, et al. Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: a prospective cohort study. Thromb Haemost. 2018;118:842-851.

27. Sheikh-Taha M. Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate. Intern Emerg Med. 2019;14:265-269.
28. Smith MN, Deloney L, Carter C. Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. J Thromb Thrombolys. 2019;48:250-255.
29. Deloney L, Tatum C, Weant K, et al. Evaluation of 4F-PCC in the management of major bleeding associated with oral factor Xa inhibitors. Crit Care Med. 2019;47:417.
30. Dobesh P, Borsch M, Marth K, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate for the management of direct Xa inhibitor-induced major bleeding. ISTH Academy. https://academy.isth.org/isth/2019/melbourne/264679/paul.dobesh.efficacy.and.safety.of.a.4-factor.prothrombin.complex.concentrate.html. Accessed on January 6, 2020.
31. Fan BE, Gallardo CA, Tay HM. Reversal of anticoagulation in patients on rivaroxaban or apixaban (DOAC) with major bleeding episodes (MBE) with 4 factor prothrombin complex concentrates (PCC): A multicenter retrospective study. Res Pract Thromb Haemost. 2019; abstract PB1476.
32. Kaplan J, Procopio G, Perez JM, et al. Four-factor prothrombin complex concentrate for factor Xa inhibitor associated hemorrhage. Crit Care Med. 2018;46:259.
33. Nguyen K, Hurley M, Wdowlarz K, et al. Andexanet alfa versus four-factor prothrombin complex concentrate (4F-PCC) for the reversal of intracranial hemorrhage (ICH associated with rivaroxaban and apixaban: A retrospective comparative study. Neurocritical Care Society Conference 2019.
34. Silinskie K, Hite M. Safety of 4-factor PCC for reversal of FXa inhibitors versus warfarin in neurocritical care patients. Crit Care Med. 2018;47:110.
35. Zheng Y, Tormey CA. The use of 4F-PCC to correct direct oral anticoagulant (DOAC)-induced coagulopathy. Transfusion. 2018; 58:82A-83A.
36. Khorsand N, Majeed A, Sarode R, et al. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. J Thromb Haemost. 2016; 14: 211-214.
37. Sarode R, Milling TJ, Reffai MA et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonist presenting with major bleeding. Circulation. 2013; 10: 1234-1243.
38. Lim W, Gal GL, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. Blood Adv. 2018; 2: 3226-3256.

39. Kahan, BC, Feagan B, Jairath V. A comparison of approaches for adjudicating outcomes in clinical trials. Trials. 2017; 18:266-280.
40. Mekaj YH, Mekaj AY, Duci SB, et al. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Mang. 2015;11:967-977.
41. Ito S. Pharmacokinetics 101. Paediatr Child Health. 2011;16:535-536.
42. Aguilar MI, Brott TG. Update in intracerebral hemorrhage. Neurohospitalist. 2011; 1:148-159.
43. Kcentra package insert. Kankakee, IL: CSL Behring LLC; October 2018.
44. Kooistra B, Dijkman B, Einhorn TA Bhandari M. How to design a good case series. J Bone Joint Surg Am. 2009;91:S21-6.
45. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2019; 140 e125-e151.

Figure 1. Summary of case series search and selection
PCC: prothrombin complex concentrate, oFXaI: oral factor Xa inhibitor, 3F: 3-factor

Figure 2a. Percentage of full-text case series that received a "yes", "no", or "unclear" for selection quality items
Number of case series with each assessment is labeled within the bar
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2b. Percentage of full-text case series that received a "yes", "no" or "unclear" for bleeding event ascertainment items
Number of case series with each assessment is labeled within the bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2c. Percentage of full-text case series that received a "yes", "no", or "unclear" for outcomes ascertainment items
Number of case series with each assessment is labeled within the bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2d. Percentage of full-text case series that received a "yes", "no", or "unclear" for causal and temporal association items
Number of studies with each assessment is labeled within bar
Note that "not applicable" designations are not incorporated
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2e. Percentage of full-text case series that received a "yes" or "no" for reporting of characteristics at presentation items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2f. Percentage of full-text case series that received a "yes" or "no" for reporting of outcomes
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

Figure 3a. Individual full-text case series assessment of selection, ascertainment, casual and temporal association items
GI: gastrointestinal, ICH: intracranial hemorrhage, NA: not applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 3b. Individual full-text case series assessment for reporting items
Refer to Appendix 2 for specific definitions used to assess quality

Figure 4. Key inclusion criteria components in full-text case series
Figure expands on the findings of Figure 2a, S1

Table 1. Full-text case series and journal impact factor

Case Series	Journal	Journal Impact Factor
Arachchillage 2019	*British Journal of Haematology*	5.206
Dybdahl 2019	*American Journal of Emergency Medicine*	1.651
Frontera 2019	*Journal of Thrombosis and Thrombolysis*	2.941
Allison 2018	*Journal of Intensive Care Medicine*	2.873
Harrison 2018	*Baylor University Medical Center Proceedings*	0.420
Schenk 2018	*Thrombosis Journal*	1.830
Schulman 2018	*Thrombosis Haemostasis*	4.733
Sheikh-Taha 2018	*Internal and Emergency Medicine*	2.335
Smith 2019	*Journal of Thrombosis and Thrombolysis*	2.941
Majeed 2017	*Blood*	16.562
Grandhi 2015	*World Neurosurgery*	1.723

Table 2. Full-text case series, number of patients, anticoagulant and indication for anticoagulation

Case Series	N	Anticoagulant, n (%)			Indication, n (%)			Bleed Location, n (%)		
		A	Ed	R	AF	DVT/PE	Other	ICH	GI	Other
Arachchillage 2019	80	40 (50)	0 (0)	40 (50)	68 (85)	13 (16)	0 (0)	46 (88)	24 (30)	10 (13)
Dybdahl 2019	35	17 (49)	0 (0)	18 (51)	31 (89)	5 (14)	0 (0)	35 (100)	0 (0)	0 (0)
Frontera 2019	46	31 (67)	0 (0)	15 (33)	44 (96)	3 (7)	NR	35 (78) *	11 (24)	0 (0)
Smith 2019	31	17 (55)	0 (0)	14 (45)	28 (90)	3 (10)	NR	18 (58)	1 (3)	12 (39)
Allison 2018	33	6 (18.	0 (0)	27 (82)	24 (73)	6 (18)	3 (9)	30 (91)	1 (3)	2 (6)
Harrison 2018	14	NR	NR	NR	12 (86)	3 (21)	2 (14)	14 (100)	0 (0)	0 (0)
Schenk 2018	13	0 (0)	0 (0)	13 (100)	NR	NR	NR	10 (77)	1 (8)	2 (15)
Schulman 2018	66	29 (44)	0 (0)	37 (56)	56 (85)	10 (15)	1 (2)	36 (55)	16 (24)	15 (21)
Sheikh-Taha 2018	29	13 (45)	0 (0)	16 (55)	23 (79)	5 (17)	1 (3)	21 (72)	4 (14)	4 (14)
Majeed 2017	84	39 (46)	0 (0)	45 (54)	67 (80)	21 (25)	21 (25)	59 (70)	13 (16)	12 (14)
Grandhi 2015	18	2 (11)	0 (0)	16 (89)	16 (89)	1 (6)	3 (17)	18 (100)	0 (0)	0 (0)

A: apixaban; AF: atrial fibrillation, DVT: deep vein thromboembolism, Ed: edoxaban, En: enoxaparin, GI: gastrointestinal, ICH: intracranial hemorrhage, NR: not recorded, PE: pulmonary embolism, R: rivaroxaban

*Study pooled intracranial hemorrhage and intraspinal bleed

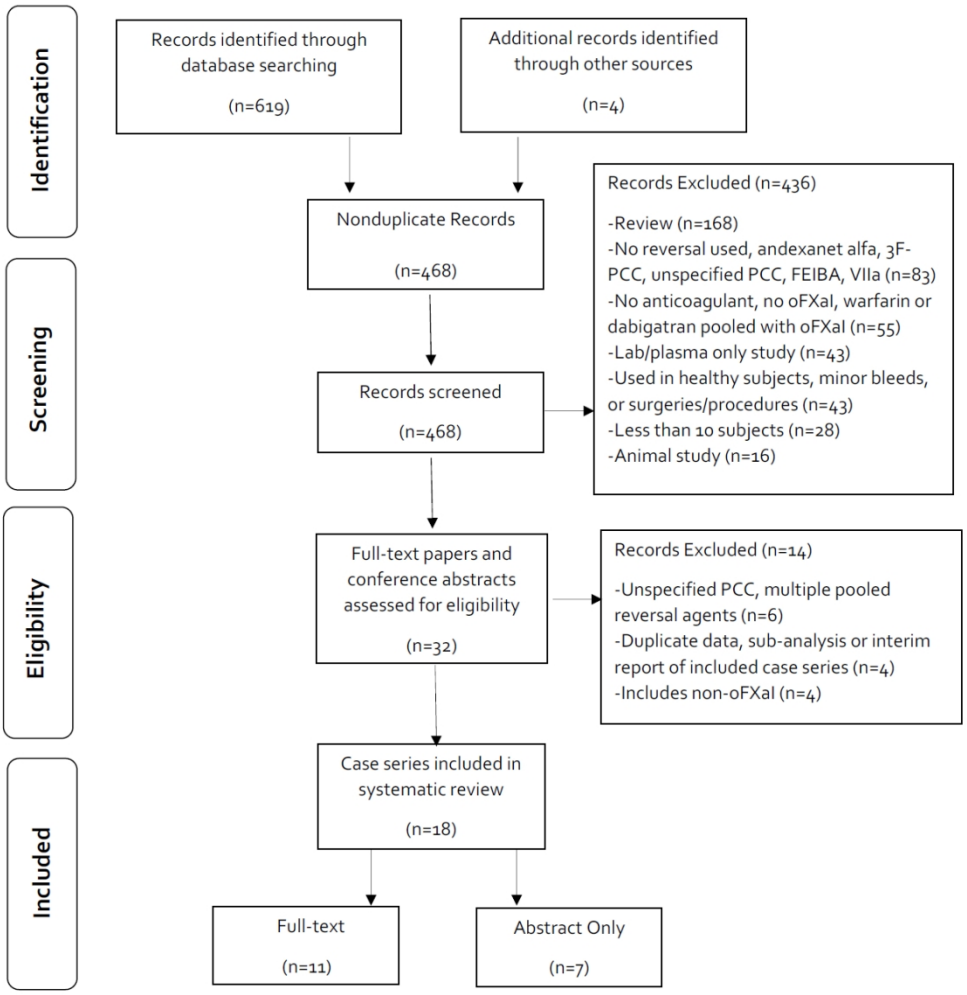


Figure 1. Summary of case series search and selection
PCC: prothrombin complex concentrate, oFXaI: oral factor Xa inhibitor, 3F: 3-factor

340x366mm (96 x 96 DPI)

Figure 2a. Percentage of full-text case series that received a "yes", "no", or "unclear" for selection quality items
Number of case series with each assessment is labeled within the bar
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2b. Percentage of full-text case series that received a "yes", "no" or "unclear" for bleeding event ascertainment items
Number of case series with each assessment is labeled within the bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2c. Percentage of full-text case series that received a "yes", "no", or "unclear" for outcomes ascertainment items
Number of case series with each assessment is labeled within the bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2d. Percentage of full-text case series that received a "yes", "no", or "unclear" for causal and temporal association items
Number of studies with each assessment is labeled within bar
Note that "not applicable" designations are not incorporated
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2e. Percentage of full-text case series that received a "yes" or "no" for reporting of characteristics at presentation items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

Figure 2f. Percentage of full-text case series that received a "yes" or "no" for reporting of outcomes
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

810x600mm (96 x 96 DPI)

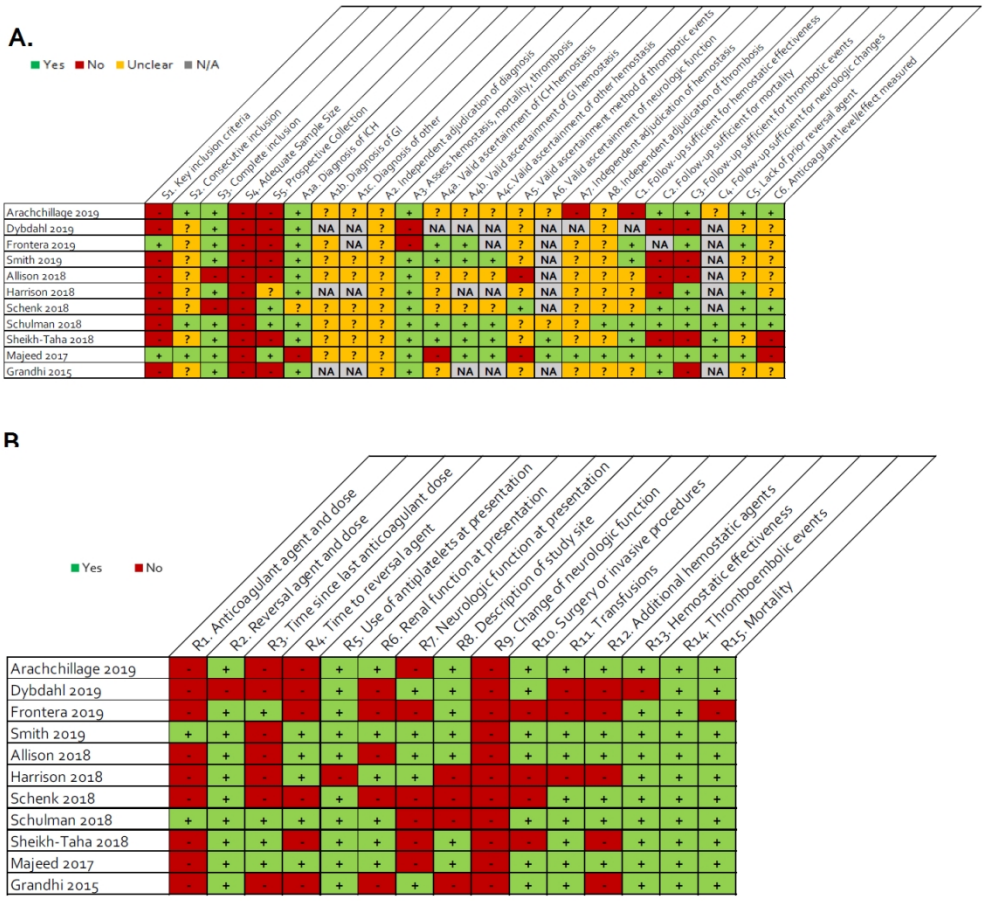


Figure 3a. Individual full-text case series assessment of selection, ascertainment, casual and temporal association items
GI: gastrointestinal, ICH: intracranial hemorrhage, NA: not applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 3b. Individual full-text case series assessment for reporting items
Refer to Appendix 2 for specific definitions used to assess quality

379x347mm (96 x 96 DPI)

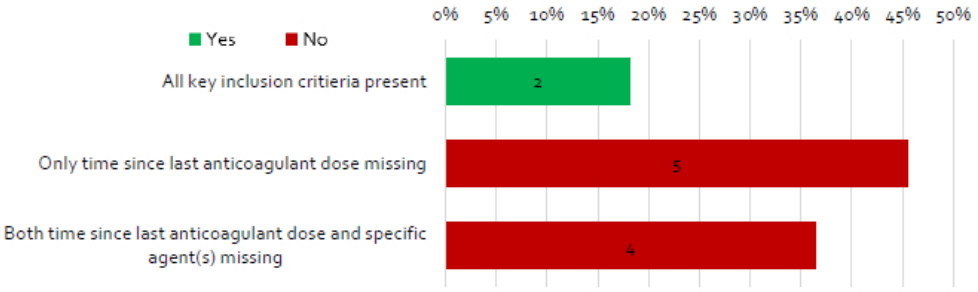


Figure 4. Key inclusion criteria components in full-text case series
Figure expands on the findings of Figure 2a, S1

178x54mm (96 x 96 DPI)

Systematic Review and Quality Evaluation of Case Series Describing Four-Factor Prothrombin Complex Concentrate in Oral Factor Xa Inhibitor-Associated Bleeding

SUPPLEMENTAL MATERIALS

1. Appendix 1. Literature Identification
2. Appendix 2. Methodological and Reporting Quality Tool and Definitions
3. Appendix 3. eFigures and eTables

APPENDIX 1. Literature Identification

Medline and Embase Search Strategy

1. NOAC OR "New oral anticoagulants" OR "Novel oral anticoagulants" OR "Non vitamin K antagonist" OR DOAC OR "Direct oral anticoagulants" OR "Direct-acting oral anticoagulants" OR "Factor Xa inhibitor" OR "factor-specific oral anticoagulants" OR Rivaroxaban OR Apixaban OR Edoxaban OR Betrixaban
2. OR PCC OR "Prothrombin complex concentrate"
3. 1 and 2
4. Limit 3 to humans
5. Limit 4 to dates 1/1/2011 to 11/8/2019
6. Remove duplicates

Conference Proceedings Searched

1. American Heart Association
2. American College of Cardiology
3. European Society of Cardiology
4. American Academy of Neurology
5. International Stroke Conference
6. European Stroke Organisation Conference
7. International Society on Thrombosis and Haemostasis
8. American Society of Hematology

Appendix 2. Methodological and Reporting Quality Tool and Definitions*

*adapted from Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018;23:60-63

SELECTION

S1. Are key criteria for inclusion into the case series provided?

- Yes: Detailed inclusion of major bleeds, specific qualifying anticoagulants and maximum time from last exposure of the anticoagulant allowed for inclusion
- No: At least one of the above-mentioned inclusion criteria was not described

S2. Was there consecutive enrollment of patients meeting inclusion criteria?

- Yes: Explicitly states consecutive inclusion of patients OR describes inclusion of all patients within a given time frame
- No: Nonconsecutive patients (convenience sample) were used
- Unclear: Unable to determine whether consecutive eligible patients were included

S3. Did the case series have complete follow-up of patients?

- Yes: Number of included patients matched the number of patients with outcome data reported (all outcomes have 100% follow-up)
- No: The number of patients/cases with outcomes reported was less than the total number of included patients/cases (at least one outcome with incomplete follow-up)
- Unclear: Unable to determine if of patient/case follow-up was complete for all outcomes

S4. Was there an adequate sample size?

- Yes: Number of included patients was ≥ 100
- No: Number of included patients was < 100
- Unclear: Number of included patients was not provided

S5. Was data collection prospective in nature?

- Yes: Methods explicitly state data was collected prospectively
- No: Methods explicitly state data was collected retrospectively
- Unclear: Methods did not clearly state if data collection was done retrospectively or prospectively

ASCERTAINMENT OF BLEEDING EVENT

A1. Was there clear ascertainment of the qualifying bleed diagnosis?

a. **Was there clear ascertainment of intracranial hemorrhage?**
   - Yes: Clearly describes or references an accepted (or closely adapted) set of diagnostic criteria for intracranial hemorrhage (e.g. CT, MRI, etc.)
   - No: Intracranial hemorrhage diagnosis was based upon non-accepted methods or clinician suspicion only
   - Unclear: Did not explicitly describe to diagnose ICH
   - N/A: Intracranial hemorrhages were not included in the case series

b. **Was there clear ascertainment of gastrointestinal bleeding?**
   - Yes: Clearly describes or references an accepted (or closely adapted) set of diagnostic criteria (e.g. barium-contrast swallow, colonoscopy, endoscopy, esophagogastroduodenoscopy, etc)
   - No: GI bleed diagnosis was based upon non-accepted methods or clinician suspicion only
   - Unclear: Did not explicitly describe to diagnose of gastrointestinal bleeding
   - N/A: Gastrointestinal bleeds were not included in the case series

c. **Was there clear ascertainment of other bleed type diagnosis?**
   - Yes: Clearly describes or references an accepted (or closely adapted) set of diagnostic criteria that was specific for the type of bleeding reported
   - No: Bleed diagnosis was based upon non-accepted methods or clinician suspicion only
   - Unclear: Did not explicitly describe the diagnosis of "other" bleeds
   - N/A: Other bleed types were not included in the case series

A2. Was there central, independent (or similar) adjudication of the qualifying bleeding event for inclusion into the case series?
   - Yes: Explicitly states central, blinded or independent (or similar terminology) reviewer(s)/committee assessed the qualifying bleeding event
   - No: Statement that a central, blinded or independent reviewer(s)/committee was not used
   - Unclear: No statement regarding the adjudication of the qualifying bleeding event

ASCERTAINMENT OF OUTCOME

A3. Did the case series assess hemostatic effectiveness, mortality and thrombotic events?

- Yes: Hemostatic effectiveness, mortality, and thromboembolism were all assessed
- No: At least one of the above outcomes was not assessed

A4. Was there clear and valid ascertainment of achieving hemostatic effectiveness?

a. Was there clear and valid ascertainment for intracranial hemorrhage?

- Yes: Clearly describes or references an accepted (or closely adapted) definition of hemostatic effectiveness was utilized by the case series (i.e. definition by the International Society on thrombosis and Haemostasis or Sarode et al.)
- No: A non-accepted definition was utilized (i.e. bleeding cessation, no repeat bleed)
- Unclear: Description/definition of hemostatic effectiveness was not provided (i.e. scale without quantitative cut-offs, qualitative description of stable vs. worsening, etc.)
- N/A: No intracranial hemostatic effectiveness outcome was reported in the case series

b. Was there clear and valid ascertainment for gastrointestinal bleeding?

- Yes: Clearly describes or references an accepted (or closely adapted) definition of hemostatic effectiveness was utilized by the case series
- No: A non-accepted definition was utilized (i.e. bleeding cessation, no repeat bleed)
- Unclear: Description/definition of hemostatic effectiveness was not provided (i.e. scale without quantitative cut-offs, qualitative description of stable vs. worsening, etc.)
- N/A: No extracranial hemostatic effectiveness outcome was reported in the case series

c. Was there clear and valid ascertainment for other bleeding?

- Yes: Clearly describes or references an accepted (or closely adapted) definition of hemostatic effectiveness was utilized by the case series
- No: A non-accepted definition was utilized
- Unclear: Description/definition of hemostatic effectiveness was not provided
- N/A: No extracranial hemostatic effectiveness outcome was reported in the case series

A5. Was there clear and valid ascertainment for diagnosis of thrombotic events?

- Yes: Clearly describes or references an accepted (or closely adapted) definition for thrombotic events including VTE, MI and stroke
- No: A non-accepted (e.g., investigator developed or clinician judgement only) definition was utilized
- Unclear: Description/definition of VTE, MI and stroke were not provided
- N/A: Thrombotic events were not reported as outcome

A6. Was there clear and valid ascertainment of neurologic function change?

- Yes: Neurologic function change was assessed using an accepted measure (e.g. Glasgow Coma Score, National Institutes of Health Stroke Scale); For studies using ISTH to assess ICH effectiveness, it is assumed appropriate ascertainment was used based on efficacy criteria
- No: A non-accepted (e.g., investigator developed or clinician judgement only) definition was utilized for ascertainment of neurologic function change
- Unclear: Description/definition of neurologic function change was not clear
- N/A: No assessment of neurologic function change was done in the case series

A7. Was there central, blinded, independent (or similar) adjudication of hemostatic effectiveness?

- Yes: Explicitly states central, blinded or independent (or similar terminology) reviewer(s)/committee assessed hemostatic effectiveness
- No: Statement that a central, blinded or independent reviewer(s)/committee was not used
- Unclear: No statement regarding the adjudication of hemostatic effectiveness
- N/A: Hemostatic effectiveness was not reported as an outcome

A8. Was there central, blinded, independent (or similar) adjudication of thrombotic events?

- Yes: Explicitly states central, blinded or independent (or similar terminology) reviewer(s)/committee assessed thrombotic events
- No: Statement that a central, blinded or independent reviewer(s)/committee was not used
- Unclear: No statement regarding the adjudication of thrombotic events
- N/A: Thrombotic events were not reported as an outcome

CASUAL & TEMPORAL ASSOCIATIONS

C1. Was the duration of follow-up for hemostatic effectiveness sufficient?

- Yes: Re-evaluation within 3-24 hours for ICH, within 36-60 hours for extracranial bleeds
- No: Re-evaluation outside 3-24 hours for ICH, outside 36-60 hours for extracranial bleeds
- Unclear: Timing of hemostatic effectiveness evaluation was not clearly defined
- N/A: Hemostatic effectiveness was an outcome

C2. Was the duration of follow-up for mortality sufficient?

- Yes: Follow-up was a minimum of 30-days
- No: Follow-up was less than 30-days (including in-hospital follow-up with reported mean or median length-of-stay less than 30-days)
- Unclear: Duration of follow-up not provided
- N/A: Mortality was not reported as an outcome

C3. Was the duration of follow-up thrombotic events sufficient?

- Yes: Follow-up was a minimum of 30-days
- No: Follow-up was less than 30-days (including in-hospital follow-up with reported mean or median length-of-stay less than 30-days)
- Unclear: Duration of follow-up not provided
- N/A: Thrombotic events were not reported as an outcome

C4. Was the duration of follow-up for change in neurologic function change sufficient?

- Yes: Re-evaluation at 24 hours (12-36 hour window)
- No: Re-evaluation outside the 12-36 hour window
- Unclear: Timing of change in neurologic function was not clearly defined
- N/A: Change in neurologic function was not as an outcome

C5. Was there lack of prior administration of an alternative reversal agent?

- Yes: No prior alternative reversal agents (e.g., andexanet alfa, 4F-PCC, 3F-PCC, FEIBA, recombinant VIIa) were administered
- No: At least one alternative/different reversal agent (e.g., andexanet alfa, 4F-PCC, 3F-PCC, FEIBA, recombinant VIIa) was previously administered after the index reversal agent
- Unclear: Unable to determine if a different reversal agent was previously administered

C6. Was the anticoagulation effect (e.g., drug level or anti–Factor Xa activity) measured?

- Yes: Anticoagulation levels/activity were measured

- No: Anticoagulation levels/activity were not measured
- Unclear: Anticoagulation levels/activity were not reported

REPORTING OF CHARACTERISTICS AT PRESENTATION

R1. Was the anticoagulant agent(s) utilized and dose reported?

- Yes: The specific type anticoagulant(s) and corresponding dose is reported as either at the individual patient level or in aggregate
- No: The specific anticoagulant(s) used by included patients/cases and/or corresponding doses of anticoagulant(s) were not reported

R2. Was the index reversal agent and dose reported?

- Yes: The reversal agent and corresponding dose is reported as either an aggregate for all patients or on a case-by-case basis
- No: The specific reversal agent used and/or dose is not reported

R3. Was the actual time since last anticoagulant dose reported?

- Yes: The time of the last anticoagulation dose since a defined time point (i.e. hospitalization, bleed diagnosis, reversal agent administration) was reported
- No: The time of the last anticoagulant dose was not reported or only a time window was provided (e.g. within x hours).

R4. Was the actual time to reversal agent reported?

- Yes: The time to reversal agent from a defined time point (i.e. hospitalization, bleed diagnosis, anticoagulant dose) was reported
- No: The time to reversal agent was not reported

R5. Was the use of antiplatelets at presentation reported?

- Yes: The use (or lack thereof) of antiplatelets (e.g., aspirin, P2Y12, cilostazol, etc.) was reported
- No: Antiplatelet use was not reported

R6. Was a measure of renal function at presentation reported?

- Yes: Serum creatinine, creatinine clearance or eGFR were provided
- No: Serum creatinine, creatinine clearance or eGFR were not provided

R7. Was neurologic function at presentation reported?

- Yes: Neurologic function at presentation was reported
- No: Neurologic function at presentation was not reported
- N/A: Intracranial hemorrhages were not included in the case series

R8. Was a description and geographical information of the investigation site reported?

- Yes: A description (i.e. comprehensive stroke center, level I trauma center, etc.) and geographical information of the investigation site was reported
- No: Description and/or geographic location of site was not reported

REPORTING OF OUTCOMES

R9. Was a change in neurologic function reported?

- Yes: Change of neurologic function was reported
- No: Change of neurologic function was not reported
- N/A: Intracranial hemorrhages were not included in the case series

R10. Were concomitant surgeries or procedures to manage bleeding reported?

- Yes: Surgeries or invasive procedures (e.g., craniotomy, burr hole, gastroscopy, evacuation, fasciotomy, embolization) were reported
- No: Surgeries or invasive procedures were not reported

R11. Was the use of blood transfusions reported?

- Yes: The utilization (or lack thereof) of red blood cells, platelets, fresh frozen plasma, cryoprecipitate was described
- No: The utilization (or lack thereof) of red blood cells, platelets, fresh frozen plasma, cryoprecipitate was not described

R12. Was the use of additional hemostatic agent described?

- Yes: The use (or lack thereof) of tranexamic acid, other reversal agents (e.g., aPCC, FEIBA), or repeat of initial reversal agent was described
- No: Did not report the use of any hemostatic agents

R13. Was the hemostatic effectiveness reported?

- Yes: The hemostatic effectiveness was reported
- No: The hemostatic effectiveness was reported

R14. Were thromboembolic events reported?

- Yes: Thromboembolic events were reported
- No: Thromboembolic events were not reported

R15. Was mortality reported?

- Yes: Mortality was reported
- No: Mortality was not reported

Rating of Hemostatic Efficacy

Sarode R, Milling TJ, Reffai MA et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonist presenting with major bleeding. Circulation 2013;10:1234-1243

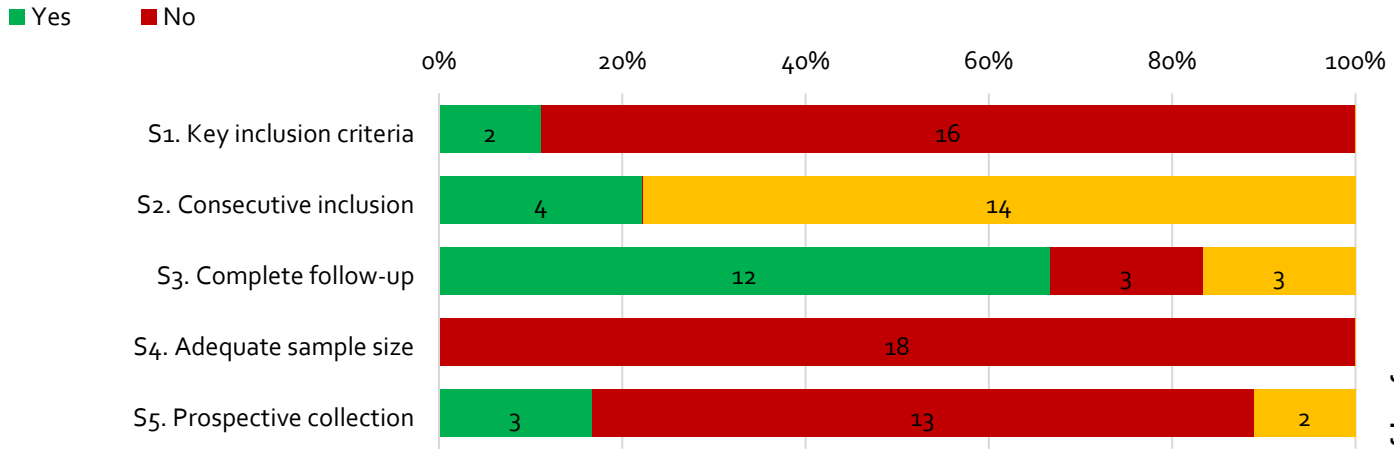
	Visible Bleeding	**Non-Visible Bleeding**
Excellent (effective)	Cessation of bleeding ≤1 hour after the end of infusion and no additional coagulation intervention required	1. Musculoskeletal bleeding: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 24-hour period 2. ICH: ≤20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3- and 24-hour time point 3. Non-visible bleeding that is not described above (e.g. GI bleeding): ≤10% decrease in both Hb/Hct† at 24 hours‡ compared to baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])
Good (effective)	Cessation of bleeding >1 and ≤4 hours after end of infusion and no additional coagulation intervention required	1. Musculoskeletal bleeding: Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after the end of infusion; and the condition has not deteriorated during the 24-hour period 2. ICH: >20%, but ≤35% increase in hematoma volume compared to baseline on a repeat CT scan performed at the 24-hour time point 3. Non-visible bleeding that is not described above: >10 to ≤20% decrease in both Hb/Hct† at 24 hours‡ compared with baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])
Poor (non-effective)	Cessation of bleeding >4 hours after end of the infusion, and/or additional coagulation intervention required (e.g. plasma, whole blood cell pack, or coagulation factor products)	1. Musculoskeletal bleeding: no improvement by 4 hours after the end of infusion and/or the condition has deteriorated during the 24-hour period 2. ICH: >35% increase in hematoma volume compared to baseline on repeat CT scan performed at the 24 hour time point 3. Non-visible bleeding that is not listed above: >20% decrease in both Hb/Hct at 24 hours‡ compared to baseline (initial correction of decrease in hemoglobin with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])

Rating of Hemostatic Efficacy

Khorsand N, Majeed A, Sarode R, et al. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. J Thromb Haemost 2016;14:211-214

	Effective Hemostasis
Non-visible Bleeding	a. The hemoglobin level is stable at 48 h after initial treatment with packed red cells and hemostatic agent (a reduction of ≤ 10% of the initial hemoglobin level is considered to be a stable level) b. By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products c. Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis
Visible Bleeding	a. There is cessation of visible bleeding within 4 h after the end of the administration of the hemostatic agent b. By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products c. Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis
Musculoskeletal Bleeding	a. Pain is reduced and swelling is improved within 24 h b. Fasciotomy is either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis c. By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products
Intracranial Bleeding	a. The hematoma volume is stable, or increased by <35% as compared with baseline volume), as assessed by a computed tomography (CT) scan within 12 h (time window of 6–24 h after the index CT) b. No deterioration of the Extended Glasgow Outcome Scale (or any validated scoring system) as assessed at 24 h in comparison with that at presentation. c. By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products. All of the above criteria have to be met for the therapy to be considered effective.

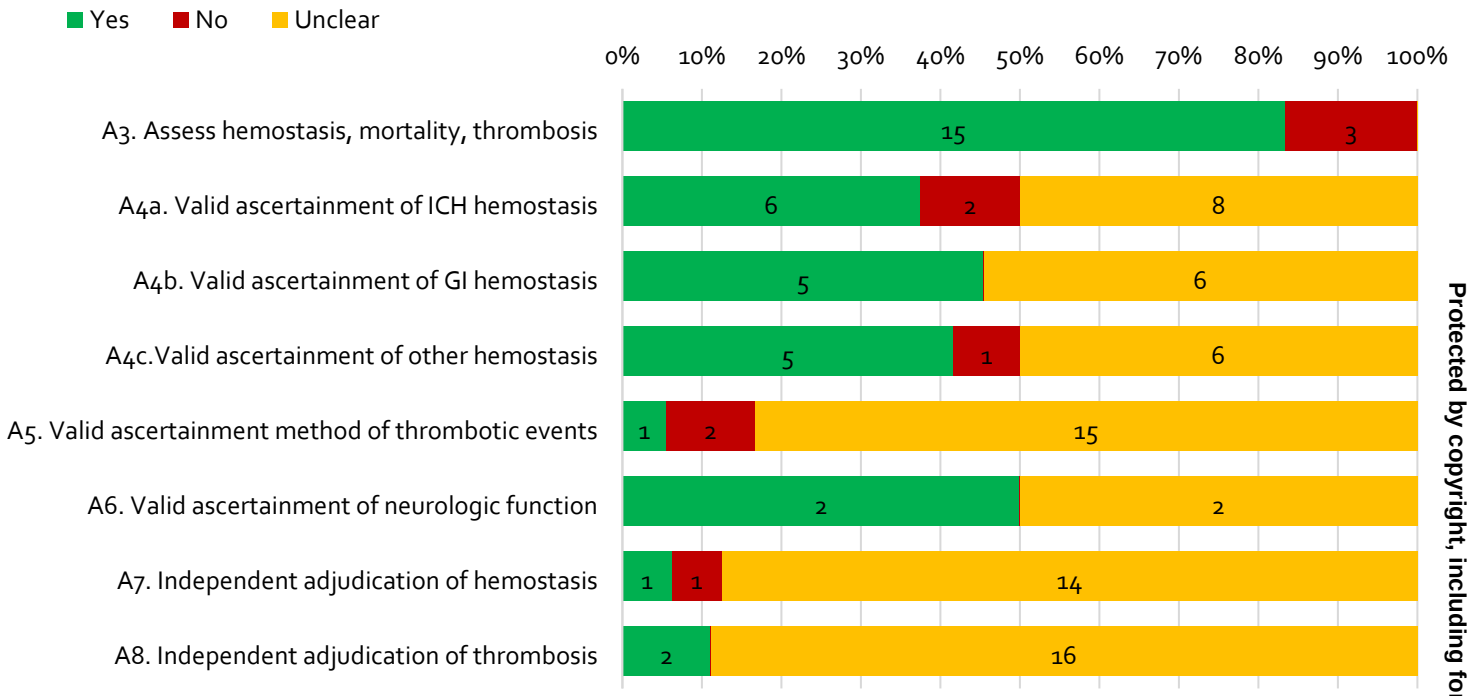
Appendix 3. Supplementary eFigures and eTables



eFigure 1a. Percentage of full-text and abstract only case series that received a "yes", "no", or "unclear" for selection quality items

Number of studies with each assessment is labeled within bar

Refer to Appendix 2 for specific definitions used to assess quality



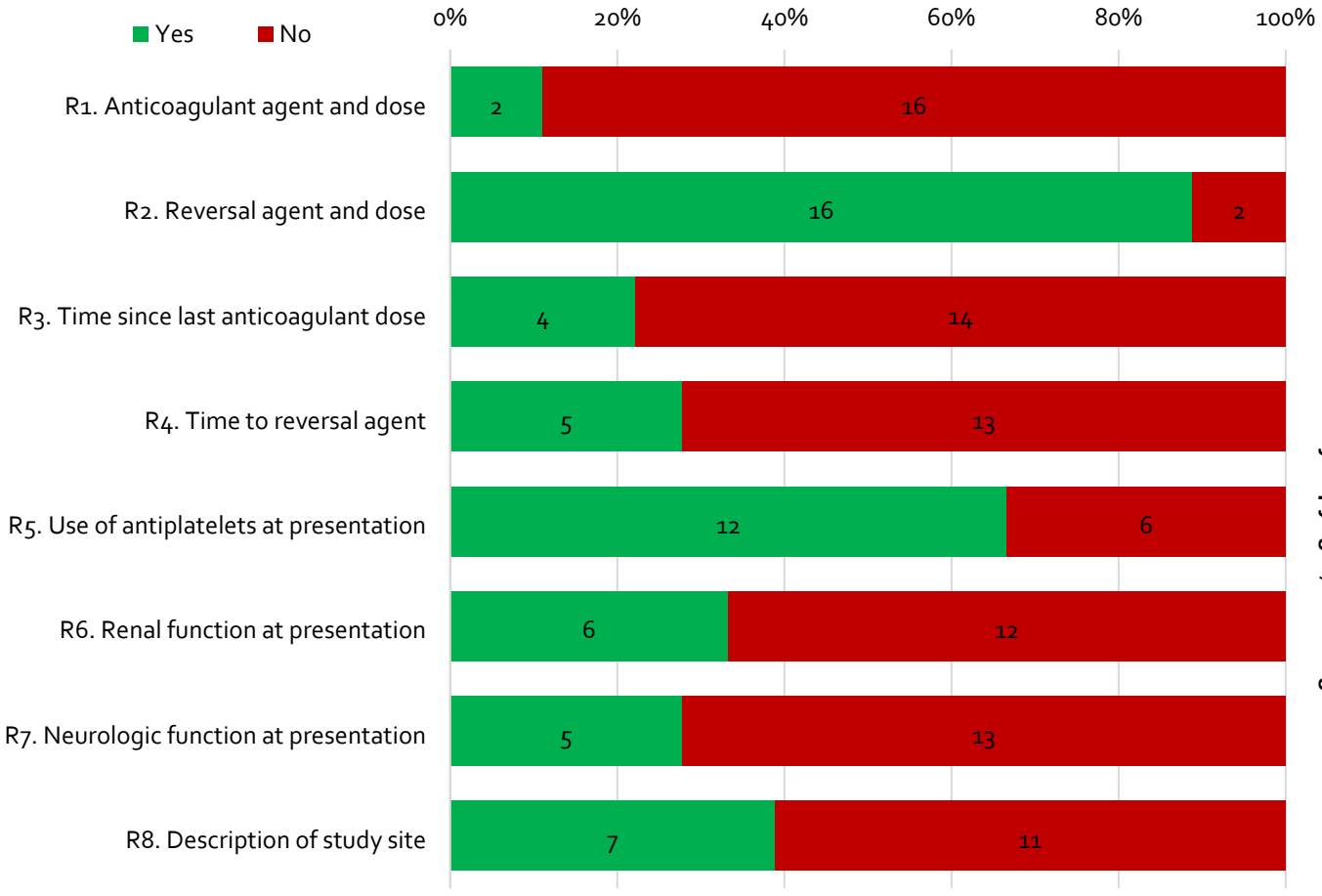
eFigure 1b. Percentage of full-text and abstract only case series that received a "yes", "no", or "unclear" for outcomes ascertainment items

Number of studies with each assessment is labeled within bar

GI: gastrointestinal, ICH: intracranial hemorrhage

Note that "not applicable" designations are not incorporated.

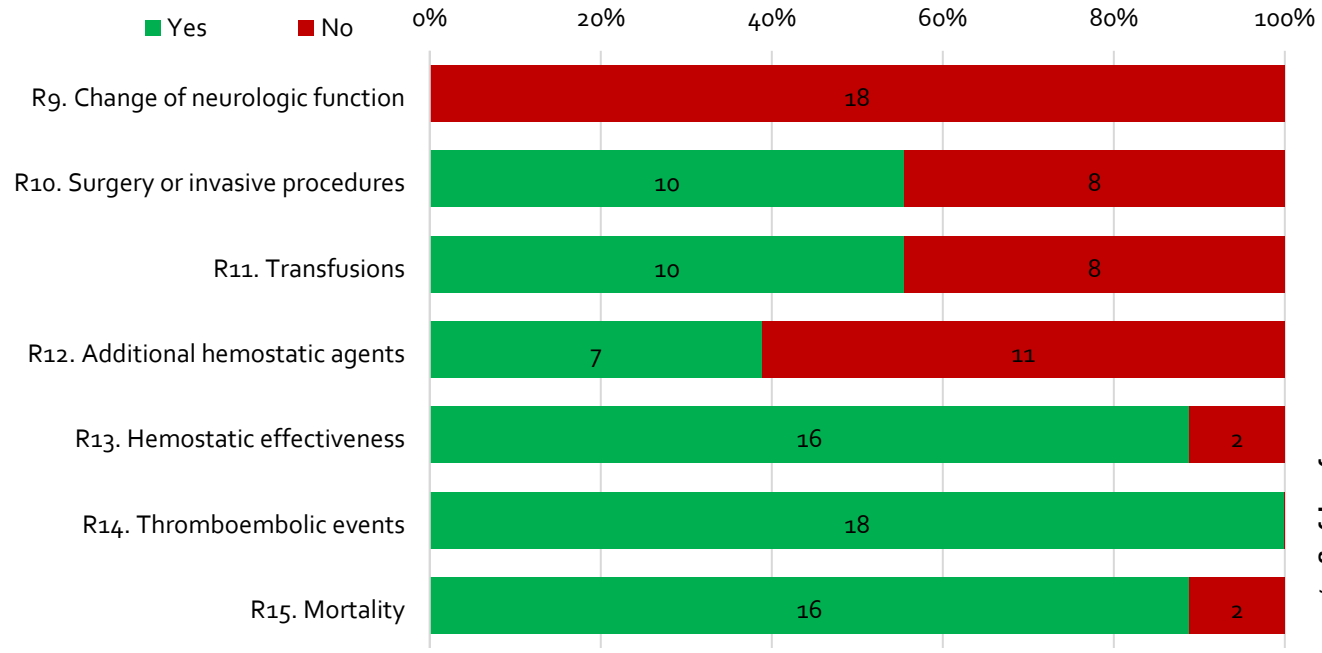
Refer to Appendix 2 for specific definitions used to assess quality



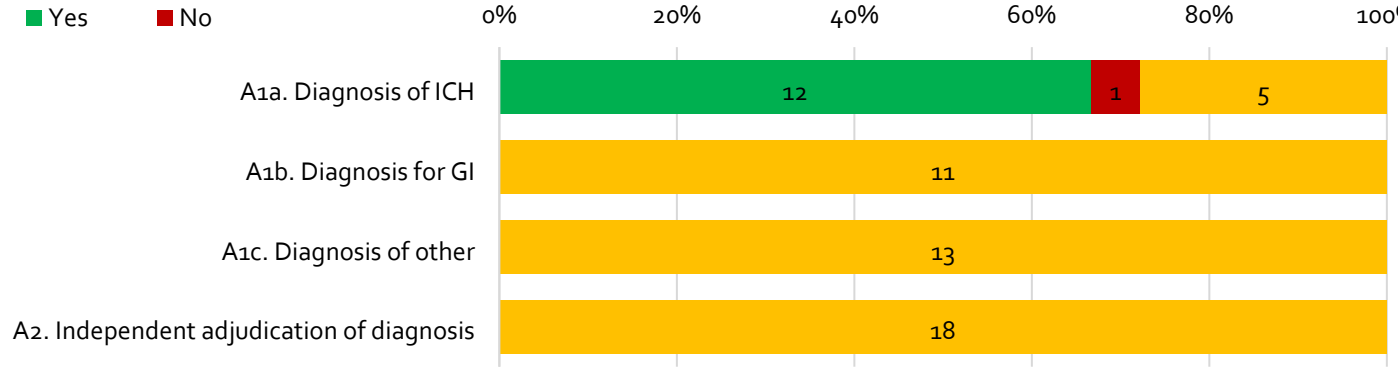
eFigure 1c. Percentage of full-text case series that received a "yes" or "no" for reporting of characteristics at presentation items

Number of studies with each assessment is labeled within bar

Refer to Appendix 2 for specific definitions used to assess quality

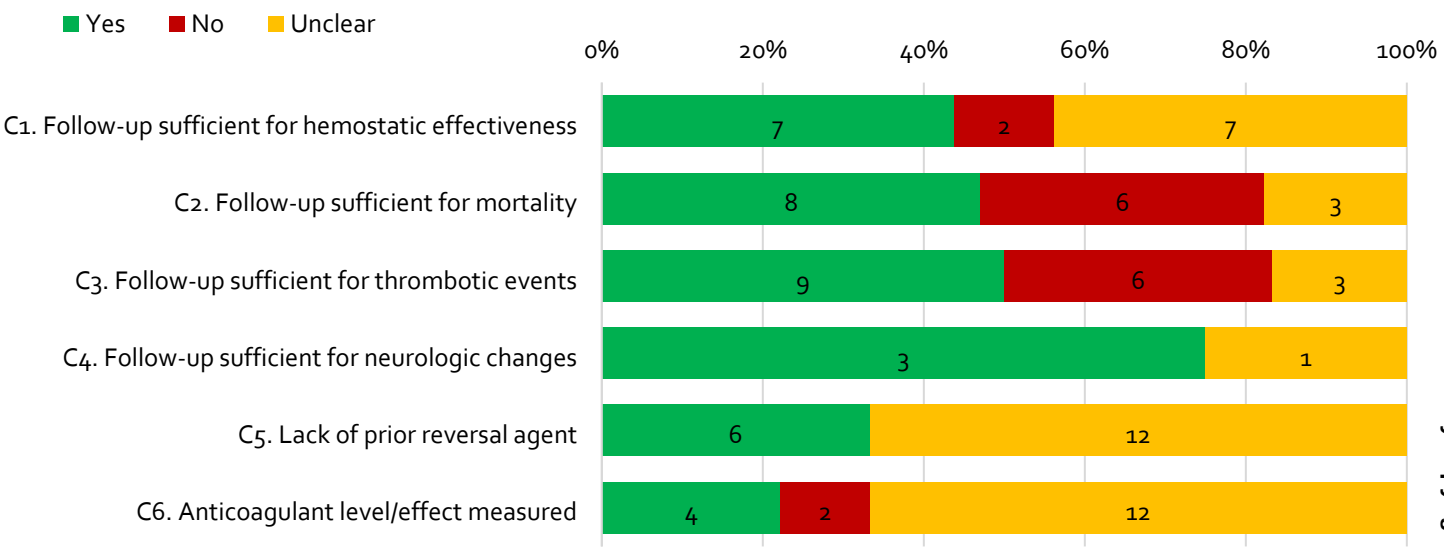


eFigure 1d. Percentage of full-text case series that received a "yes" or "no" for reporting of outcomes items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

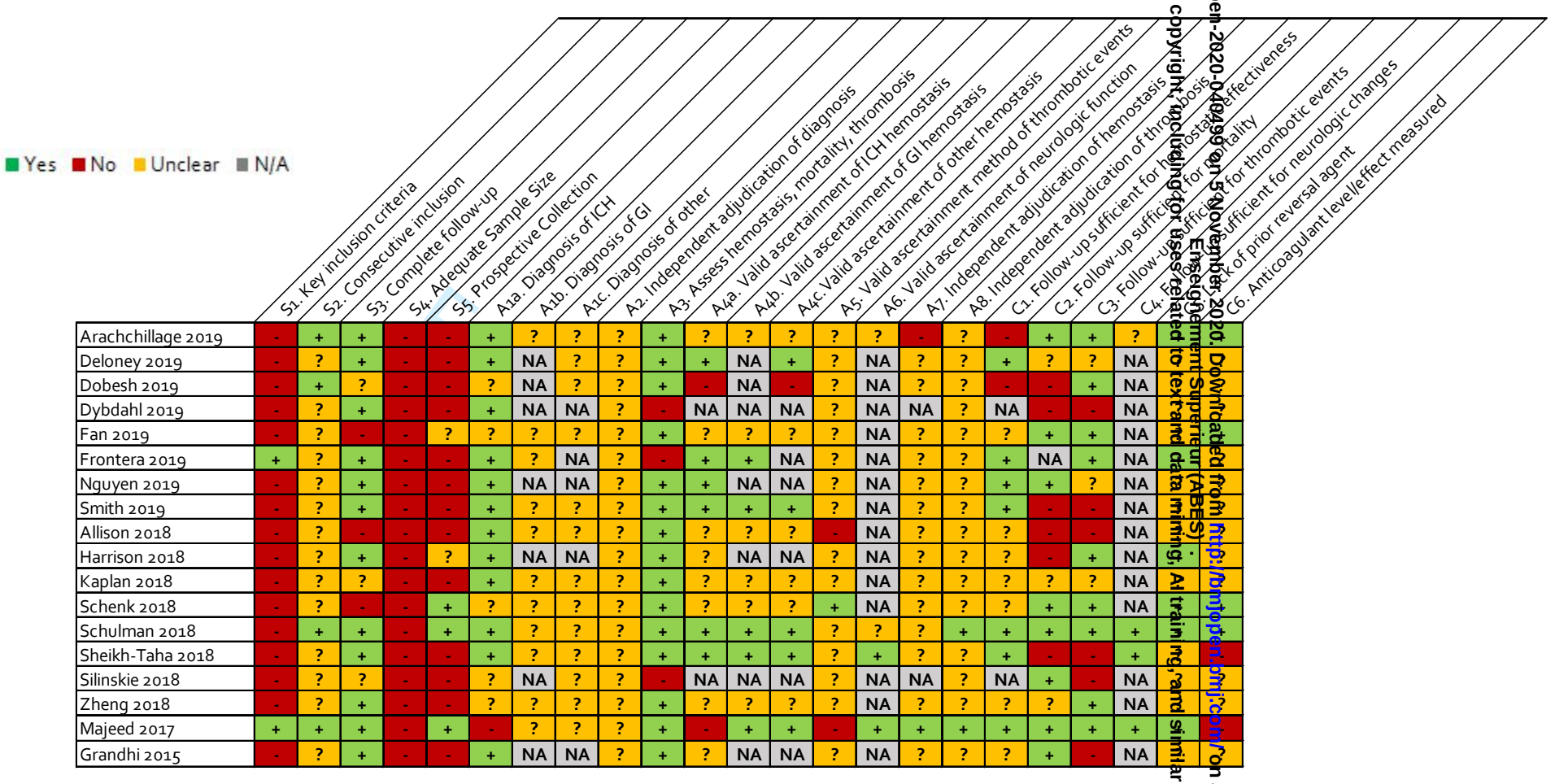


eFigure 1e. Percentage of full-text and abstract only case series that received a "yes", "no" or "unclear" for bleeding event ascertainment items

Number of studies with each assessment is labeled within bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Note that "not applicable" designations are not incorporated.
Refer to Appendix 2 for specific definitions used to assess quality

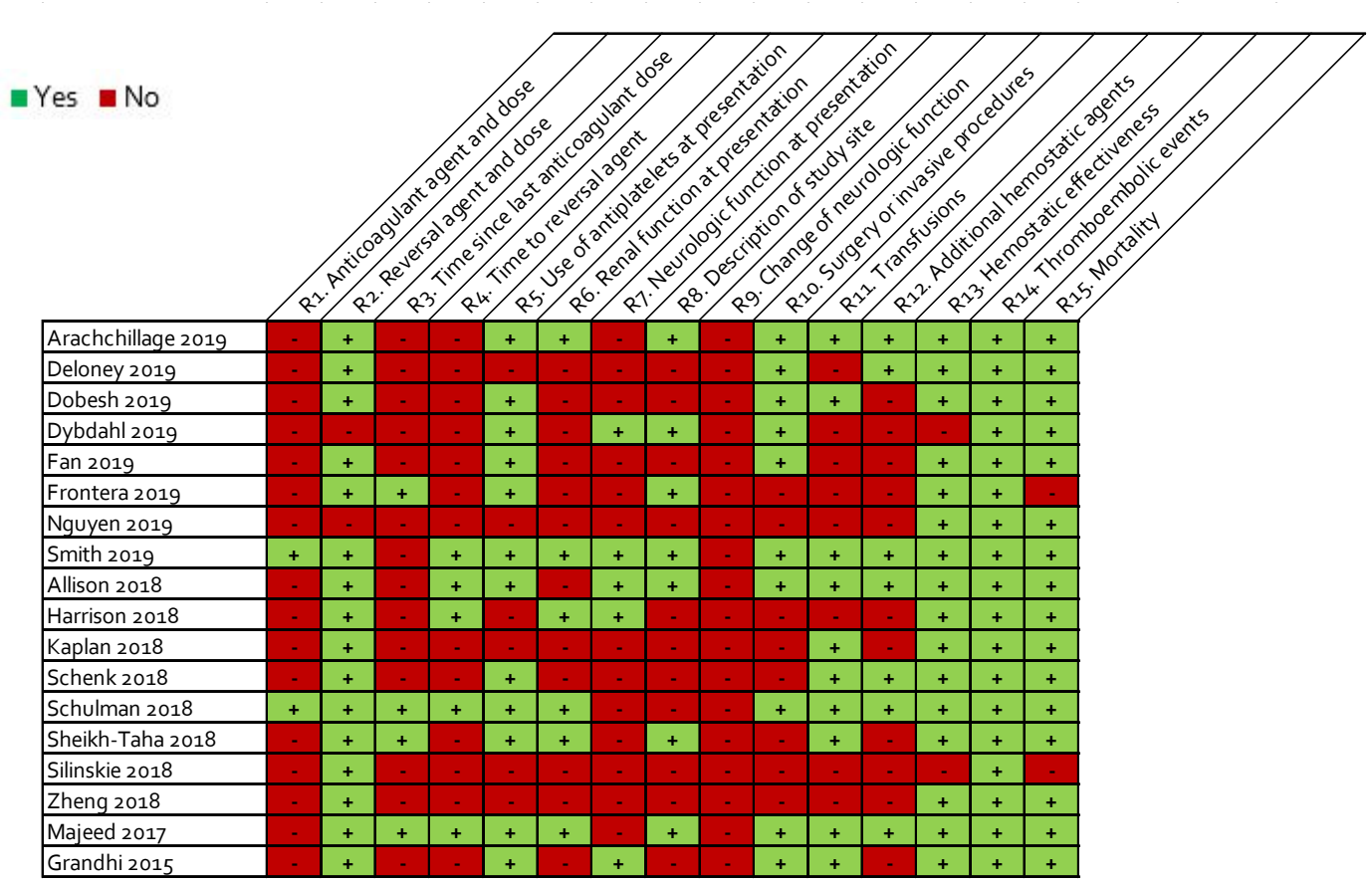


eFigure 1f. Percentage of full-text and abstract only case series that received a "yes", "no" or "unclear" for causal and temporal association items
Number of studies with each assessment is labeled within bar
Note that a "not applicable" designation is not incorporated.
Refer to Appendix 2 for specific definitions used to assess quality



Arachchillage 2019	-	+	+	-	-	+	?	?	?	+	?	?	?	?	?	-	?	-	+	+	?
Deloney 2019	-	?	+	-	-	+	NA	?	?	+	+	NA	+	?	NA	?	?	+	?	?	NA
Dobesh 2019	-	+	?	-	-	?	NA	?	?	+	-	NA	-	?	NA	?	?	-	-	+	NA
Dybdahl 2019	-	?	+	-	-	+	NA	NA	?	-	NA	NA	NA	?	NA	NA	?	NA	-	-	NA
Fan 2019	-	?	-	-	?	?	?	?	?	+	?	?	?	?	NA	?	?	?	+	+	NA
Frontera 2019	+	?	+	-	-	+	?	NA	?	-	+	+	NA	?	NA	?	?	+	NA	+	NA
Nguyen 2019	-	?	+	-	-	+	NA	NA	?	+	+	NA	NA	?	NA	?	?	+	+	?	NA
Smith 2019	-	?	+	-	-	+	?	?	?	+	+	+	+	?	NA	?	?	+	-	-	NA
Allison 2018	-	?	-	-	-	+	?	?	?	+	?	?	?	-	NA	?	?	?	-	-	NA
Harrison 2018	-	?	+	-	?	+	NA	NA	?	+	?	NA	NA	?	NA	?	?	?	-	+	NA
Kaplan 2018	-	?	?	-	-	+	?	?	?	+	?	?	?	?	NA	?	?	?	?	?	NA
Schenk 2018	-	?	-	-	+	?	?	?	?	+	?	?	?	+	NA	?	?	?	+	+	NA
Schulman 2018	-	+	+	-	+	+	?	?	?	+	+	+	+	?	?	?	+	+	+	+	+
Sheikh-Taha 2018	-	?	+	-	-	+	?	?	?	+	+	+	+	?	+	?	?	+	-	-	+
Silinskie 2018	-	?	?	-	-	?	NA	?	?	-	NA	NA	NA	?	NA	NA	?	NA	+	-	NA
Zheng 2018	-	?	+	-	-	?	?	?	?	+	?	?	?	?	NA	?	?	?	?	+	NA
Majeed 2017	+	+	+	-	+	-	?	?	?	+	-	+	+	-	+	+	+	+	+	+	+
Grandhi 2015	-	?	+	-	-	+	NA	NA	?	+	?	NA	NA	?	NA	?	?	?	+	-	NA

eFigure 2a. Individual full-text and abstract only case series assessment of selection, ascertainment, causal and temporal association items
GI: gastrointestinal, ICH: intracranial hemorrhage, 4F-PCC: 4-factor prothrombin complex concentrate
Refer to Appendix 2 for specific definitions used to assess quality



eFigure 2b. Individual full-text and abstract only case series assessment for reporting items
Refer to Appendix 2 for specific definitions used to assess quality

eTable 1. Full-text and abstract only case series, number of patients, anticoagulant, and indication for anticoagulation

Case Series	N	Anticoagulant, n (%)			Indication, n (%)			Bleed Location, n (%)		
		A	Ed	R	AF	DVT/PE	Other	ICH	GI	Other
Arachchillage 2019	80	40 (50)	0 (0)	40 (50)	68 (85)	13 (16)	0 (0)	46 (58)	24 (30)	10 (13)
Deloney 2019	31	17 (55)	0 (0)	14 (45)	28 (90)	NR	3 (9.7)	18 (58)	NR	13 (42)
Dobesh 2019	52	34 (65)	0 (0)	18 (35)	33 (63)	19 (37)	0 (0)	24 (67)	NR	17 (33)
Dybdahl 2019	35	17 (49)	0 (0)	18 (51)	31 (89)	5 (14)	0 (0)	35 (100)	0 (0)	0 (0)
Fan 2019	76	NR	0 (0)	NR	70 (92)	NR	6 (7.9)	54 (71)	17 (22)	5 (7)
Frontera 2019	46	31 (67)	0 (0)	15 (33)	44 (96)	3 (7)	NR	35 (76)	11 (24)	0 (0)
Nguyen 2019	14	NR	0 (0)	NR	NR	NR	NR	14 (100)	0 (0)	0 (0)
Smith 2019	31	17 (55)	0 (0)	14 (45)	28 (90)	3 (10)	NR	18 (58)	1 (3)	12 (39)
Allison 2018	33	6 (18.2)	0 (0)	27 (82)	24 (73)	6 (18)	3 (9)	30 (91)	1 (3)	2 (6)
Harrison 2018	14	NR	NR	NR	12 (86)	3 (21)	2 (14)	14 (100)	0 (0)	0 (0)
Kaplan 2018	22	14 (64)	0 (0)	8 (36)	13 (59)	NR	9 (41)	12 (55)	7 (32)	4 (18)
Schenk 2018	13	0 (0)	0 (0)	13 (100)	NR	NR	NR	10 (77)	1 (8)	2 (15)
Schulman 2018	66	29 (44)	0 (0)	37 (56)	56 (85)	10 (15)	1 (2)	36 (55)	16 (24)	15 (21)
Sheikh-Taha 2018	29	13 (45)	0 (0)	16 (55)	23 (79)	5 (17)	1 (3)	21 (72)	4 (14)	4 (14)
Silinskie 2018	23	NR	NR	NR	NR	NR	NR	12 (52.2)	NR	11 (48)
Zheng 2018	25	NR	NR	NR	NR	NR	NR	13 (52)	8 (32)	4 (16)
Majeed 2017	84	39 (46)	0 (0)	45 (54)	67 (80)	21 (25)	21 (25)	59 (70)	13 (16)	12 (14)
Grandhi 2015	18	2 (11)	0 (0)	16 (89)	16 (89)	1 (6)	3 (17)	18 (100)	0 (0)	0 (0)

A: apixaban; AF: atrial fibrillation, DVT: deep vein thromboembolism, Ed: edoxaban, En: enoxaparin, GI: gastrointestinal, ICH: intracranial hemorrhage, NR: not recorded, PE: pulmonary embolism, R: rivaroxaban

*Study pooled intracranial hemorrhage and intraspinal bleed

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

Quality Evaluation of Case Series Describing Four-Factor Prothrombin Complex Concentrate in Oral Factor Xa Inhibitor-Associated Bleeding: A Systematic Review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040499.R1
Article Type:	Original research
Date Submitted by the Author:	05-Oct-2020
Complete List of Authors:	Costa, Olivia; University of Connecticut School of Pharmacy, Pharmacy Practice; Hartford Hospital, Evidence-Based Practice Center Baker, William; University of Connecticut School of Pharmacy, Pharmacy Practice; Hartford Hospital, Evidence-Based Practice Center Roman-Morillo, Yuani; University of Connecticut School of Pharmacy, Pharmacy Practice; Hartford Hospital, Evidence-Based Practice Center McNeil-Posey, Kelly; Portola Pharmaceuticals Inc, Health Economics and Outcomes Research Lovelace, Belinda; Portola Pharmaceuticals Inc, Health Economics and Outcomes Research White, Michael; University of Connecticut School of Pharmacy, Pharmacy Practice; Hartford Hospital, Evidence-Based Practice Center Coleman, Craig; University of Connecticut School of Pharmacy, Department of Pharmacy Practice; University of Connecticut School of Pharmacy, Pharmacy Practice
Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Evidence based practice, Cardiovascular medicine, Neurology, Pharmacology and therapeutics, Qualitative research
Keywords:	Anticoagulation < HAEMATOLOGY, HAEMATOLOGY, NEUROLOGY, CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Quality Evaluation of Case Series Describing Four-Factor Prothrombin Complex Concentrate in Oral Factor Xa Inhibitor-Associated Bleeding: A Systematic Review

Olivia S. Costa[1,2]; William L. Baker[1,2]; Yuani Roman-Morillo[1,2]; Kelly McNeil-Posey[3], Belinda Lovelace[3], C. Michael White[1,2]; Craig I. Coleman[1,2]

[1] Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, CT, USA

[2] Evidence-Based Practice Center, Hartford Hospital, Hartford, CT, USA

[3] Health Economics and Outcomes Research, Portola Pharmaceuticals, San Francisco, CA, USA

Corresponding Author:

Craig I. Coleman, PharmD

Professor of Pharmacy Practice

University of Connecticut

School of Pharmacy

69 North Eagleville Road, Unit 3092

Storrs, CT 06269, USA

860-972-2096

860-545-2277 (fax)

craig.coleman@hhchealth.org

ABSTRACT

INTRODUCTION As oral factor Xa (oFXa) inhibitor use has increased, so has publication of case series describing related bleeding managed with 4-factor prothrombin complex concentrate (4F-PCC).

OBJECTIVE This review aimed to identify case series describing 4F-PCC management of oFXa inhibitor-related bleeding and appraise their methodological and reporting quality.

DESIGN We searched Medline and Embase (01/01/2011–5/31/2020) to identify series of ≥10-patients with oFXa inhibitor-related major bleeding given off-label 4F-PCC. Case series' were evaluated using a validated tool adapted for this topic. The tool addressed patient selection, bleed/outcome ascertainment, causal/temporal association, and reporting.

RESULTS We identified 14 case series. None had ≥100-patients (range=13-84), three were prospective, two detailed appropriate inclusion criteria, and four noted consecutive inclusion. While twelve series provided clear/appropriate methods for diagnosis of intracranial hemorrhage (ICH); none did so for extracranial bleeds and it was not clear whether bleeding was adjudicated in any. Hemostatic effectiveness, thrombosis, and mortality were together evaluated in twelve series, but only seven used validated methods to evaluate/diagnosis hemostasis in ICH, six in gastrointestinal bleeds, five in other bleeds and three in thrombosis. Independent adjudication of hemostasis (n=1) and thrombosis (n=2) was infrequent. Thirty-day follow-up for mortality and thrombosis was noted in five and seven series. Anticoagulation measurement/levels in at least some patients were conveyed in three series. Few series provided data on anticoagulant agent/dose (n=4), time from anticoagulant (n=4), time-to-reversal (n=7), baseline (n=7) or change (n=0) in neurologic function**.**

CONCLUSIONS Although many case series describe off-label use of 4F-PCC for oFXa inhibitor-related bleeding, methodological flaws and/or poor reporting necessitates caution in interpretation.

Keywords: Anticoagulation; Cardiology; Haematology; Neurology

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study compiles all available literature meeting inclusion criteria regarding the off-label use of use of 4-factor prothrombin complex concentrate to manage oral factor Xa related major bleeding.
- This study brings attention to the methodology and reporting flaws of this literature which gives perspective when considering effectiveness and safety.
- The disease-specific tool utilized in this study is derived from a previously validated tool, however our disease-specific tool has not been peer reviewed.

INTRODUCTION

Randomized controlled trials have demonstrated oral factor Xa (oFXa) inhibitors to be at least noninferior to warfarin for preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) [1-3] and reducing recurrent thrombosis in patients with venous thromboembolism (VTE) [4-6]. Moreover, data suggest that oFXa inhibitors have a similar or reduced risk of overall major bleeding compared to warfarin, with a reduction in fatal bleeding including intracranial hemorrhage (ICH) [1-6]. Consequently, the proportion of NVAF and acute VTE patients treated with oFXa inhibitors has increased in lieu of warfarin [7-8].

Despite the short duration of pharmacologic action (anticoagulation effect) of oFXa inhibitors (apixaban, edoxaban and rivaroxaban), reversal agents are often needed to manage patients with severe or life-threatening bleeds [9-10]. In May 2018, the United States (US) Food and Drug Administration (FDA) approved coagulation factor Xa (recombinant), inactivated –zhzo (USAN: andexanet alfa), the first specific reversal agent to manage oFXa inhibitor-related bleeding [11]. Shortly after, in April 2019 the European Medicines Agency (EMA) also approved andexanet alfa for this indication [12]. Prior to regulatory approval of andexanet alfa, various non-specific reversal agents were supported by guidelines [13-15] as an off-label approach to manage oFXa inhibitor-related severe or life-threatening bleeds, most notably, four-factor prothrombin complex concentrate (4F-PCC). Evidence, primarily in the form of small case series, has suggested that 4F-PCC are safe and efficacious in the management of oFXa inhibitor bleeding, but variation in reporting, sample size, bleed definition and severity, hemostasis endpoint definitions and hospital practices, including various types and doses of 4F-PCC, make it difficult to assess their generalizability. While all case series have innate limitations, there may still be substantial variation in their clinical usefulness based upon the quality of methods used and extent of reporting of methods and results. Therefore, we sought to systematically identify existing case series describing 4F-PCC use for the reversal of oFXa inhibitor-related bleeding and to evaluate their methodological and reporting quality.

METHODS

Preparation of this report was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

Search Strategy

We performed a bibliographic literature search of Medline and EMBASE from January 1, 2011 (year of first oFXa inhibitor availability) through May 31st, 2020. Our search strategy is available in **Appendix 1**. Bibliographic searches were augmented with backwards citation tracking and review of conference

proceedings of major cardiology, neurology and thrombosis and hemostasis meetings over the past two years (the latter were searched to identify case series available only in abstract form for inclusion into a pre-specified sensitivity analysis only).

Study Selection

Two investigators screened citations and assessed eligible reports for inclusion with disagreements reconciled through discussion or by a third investigator. To be included in this review, case series had to describe the use of 4F-PCC in ≥10 patients for management of major, severe or life-threatening bleeding while taking an oFXa inhibitor. Reports describing the use of andexanet alfa, 3-factor PCC, activated PCC, unspecified PCC or recombinant factor VIIa as the primary reversal agent were excluded; as were those assessing the reversal of dabigatran or warfarin, reversal of non-bleeding surgical patients, non-major bleeds or healthy volunteers.

Data Abstraction

Two investigators independently extracted all data with disagreements resolved by discussion or a third investigator. The following data were sought from each study: first author's last name; year of publication; journal and its impact factor; specific inclusion and exclusion criteria; enrollment timeframe; number of patients included and outcomes reported on; renal function at presentation; location of bleed; method of diagnosis/ascertainment of bleeding and any thrombotic events; measurement of neurologic function; anticoagulant characteristics (agent, dose, indication, time last taken, drug concentration level, anti-factor Xa activity level); reversal agent information (agent, dose, time to administration); concomitant methods of achieving hemostasis utilized (surgeries or procedures, transfusions, additional reversal agents or medications); reporting of hemostatic effectiveness, thrombotic events and mortality; definition of hemostatic effectiveness applied; adjudication of bleeding events, hemostatic effectiveness and/or thrombotic events; duration of follow-up for hemostatic effectiveness, change in neurologic status, thrombotic events and mortality; and description of treatment site(s) (i.e., geographic region/country, comprehensive stroke center, level one trauma center).

Methodological and Reporting Quality Assessment

We performed critical appraisal of the methodological and reporting quality of each included case series. We modified a tool originally developed by Murad and colleagues [17] for use in our disease/indication-specific literature review. Our tool uses exploratory questions/items to assess a case series' methodological and reporting quality in respect to its selection, exposure and outcome (i.e., alternative causes, dose-response, and sufficient duration of follow-up) and whether cases were reported with

sufficient detail to allow for generalizability to patients in other practices. We included questions evaluating the domains of selection (n=5 items), ascertainment (n=12 items), causal and temporal association (n=6 items) and reporting (n=15 items). Items for the selection, ascertainment, causal and temporal association domains were answered/assessed as "yes", "no", "unclear" (or "not applicable"). Items for reporting were assessed as "yes" or "no". The specific criteria used to assess each item are provided in **Appendix 2.** Evaluation of methodological and reporting quality was performed by two investigators with all disagreements resolved by discussion or a third investigator.

Descriptive statistics were used to summarize assessment of each item, with the proportion of case series assessed as "yes" (+), "no" (-) and "unclear" (?) divided by the number of applicable case series (excluded studies deemed not applicable). Continuous data (e.g., journal impact factor and sample size) were reported as medians with 25%, 75% ranges.

Case series available as abstracts only would likely accentuate/inflate the number of "unclear" or "no" designations due to their limited word count and the lack of detailed peer review; therefore, abstracts were not included in our primary analysis. We did perform sensitivity analysis whereby both full-text and abstract-only case series were included.

Patient and Public Involvement

No patient involvement.

RESULTS

Literature Search

The literature search identified 500 non-duplicate citations with four additional citations identified through other sources, resulting in 504 total citations (**Figure 1**). After title and abstract review, 464 citations were excluded, leaving 40 for full-text review. Upon the full-text review, 14 case series met inclusion criteria for this systematic review without exclusions [18-31]. An additional 9 case series available as abstracts only were included in the sensitivity analysis only [32-40].

Characteristics of Case Series

The impact factor of journals in which case series were published ranged from 0.0420 to 16.562 (median, 2.873) (e**Table 1**). The number of patients in identified case series ranged from 13 to 84 (median, 32) (**Table 1**). Most studies included apixaban (n=13) and/or rivaroxaban (n=13). Atrial fibrillation was the most common indication for anticoagulation across all 14 case series. ICH was included in all case series, with 9 series including GI and 8 other types of extracranial bleeds.

Methodological and Reporting Quality

Selection

Two of identified case series specified all three key inclusion criteria (specific notation of a major bleed, anticoagulant(s) used and time since last anticoagulant dose) (**Figure 2, Figure 3**). Eight case series did not provide timing since the last anticoagulant dose and four did not provide data regarding both time since last anticoagulant dose and the specific anticoagulant(s) used (**Figure 4**). Four case series noted they enrolled consecutive patients. Ten case series had no patients lost to follow-up, with the remaining reporting anywhere from 6 to 9.7% of patients lost to follow-up. Three case series described prospective collection of data.

Ascertainment of Qualifying Bleeding Event

The methods utilized for ascertainment of ICH diagnosis were specified and deemed appropriate in twelve case series, though the diagnosis of gastrointestinal (n=9) or other extracranial bleeds (n=8) were not described in any case series **(Figure 5)**. Further, no case series noted the use of an independent committee or process for adjudication of the diagnosis of the qualifying bleed.

Ascertainment of Outcomes

Twelve case series assessed each of the three pre-specified key outcomes including hemostatic effectiveness, mortality and thrombosis (**Figure 6**). Of those that assessed hemostatic effectiveness, five (other bleeds) to seven (ICH) reported the use of a validated set of diagnostic criteria (i.e. those of the International Society on Thrombosis and Haemostasis or previous used in trials by Sarode and colleagues) [41-42]. Three case series described and reported thrombotic events utilizing an accepted clinical definition/diagnostic criteria. Neurologic function was ascertained using a validated tool four case series involving ICHs. For hemostatic effectiveness adjudication, one case series described using an independent party (and one explicitly stated not adjudicating events). Two case series explicitly noted they adjudicated thrombotic events, while the remainder did not make their methodology clear.

Causal and Temporal Associations

The duration of follow-up for hemostatic effectiveness was defined as between 3-24 hours for ICH and 36-60 hours for extracranial bleeds in eight case series (**Figure 7 and Figure 3**). Follow-up was ≥30-days for mortality and thrombotic events in five and seven case series, respectively; ≤30 days in six and seven case series, respectively. For neurologic changes, follow-up duration was within 12-36 hours in three series and unclear in the remainder. Seven case series clearly stated that no other reversal agent(s) were used prior to the 4F-PCC. Anticoagulant levels or anti-factor Xa activity levels were measured in three case series (all using a calibrated machine), not measured in two case series and unclear in the remaining nine.

Reporting of Characteristics at Presentation

A summary of reporting of characteristics at presentation across all case series is depicted in **Figure 8** and **Figure 9**. Four case series provided both the anticoagulant used and the dose. All but one case series provided information regarding the reversal agent and dose. Time since last anticoagulant dose to presentation and time to administering the reversal agent from diagnosis was reported in four and seven case series, respectively. Use of concomitant antiplatelets and renal function at presentation was reported in thirteen and nine case series. Neurologic function at presentation was reported in seven case series. A description (i.e. comprehensive stroke center, level I trauma center, etc.) and geographical region of the investigation site was reported in seven case series.

Reporting of Outcomes

The reporting of outcomes across all case series is depicted in **Figure 10.** Most case series provided data on hemostatic effectiveness (n=13), thromboembolic events (n=14) and mortality (n=13). Other measures to manage bleeds including surgeries and/or procedures, transfusions, and other hemostatic medications were reported in nine, eleven and nine of case series, respectively. Change in neurologic function was not reported as an outcome in any case series.

Sensitivity Analysis

The addition of abstracts to full-text series resulted in a decreased median sample size of 31 (**eTable 2**). No case series available as an abstract only adequately reported inclusion criteria (**eFigure 1a, eFigure 2a**), detailed how thrombotic events were ascertained (**e Figure 1b**) or reported on anticoagulant agent and dose, time since last anticoagulant dose to arrival and renal function at presentation (**eFigure 1c, eFigure 2b**). The remainder of assessed quality items were generally similar between the sensitivity and primary analyses (**eFigure 1d, eFigure 1e, eFigure 1f**).

DISCUSSION

Our systematic review identified 14 modestly sized full-text case series published in journals of varying impact factor (and an additional 9 abstracts presented at international/national conferences). Using an adapted version of a tool [17] specifically designed to assesses methodological and reporting quality of case series, we identified the presence of several common methodological flaws and reporting deficiencies that limit these case series' internal and external validity and consequently necessitate clinicians/readers to use caution when interpreting their results.

One key methodological concern noted in the identified case series were unclear definitions, and lack of adjudication of, the index bleed (especially extracranial), hemostatic effectiveness and thrombosis. Despite accepted definitions of hemostasis that have been endorsed by the International Society of Thrombosis and Hemostasis or previously utilized in clinical trials [41-42], valid ascertainment of hemostatic effectiveness was only performed in 54% of case series including ICH, 74% including GI bleeds and 63% of other bleeds. Frequently, investigators relied on clinical judgment to assess hemostatic effectiveness. Similarly, only three case series clearly described and utilized the requirement for a validated measure (i.e., ultrasound) to objectively confirm and report the diagnosis of a thrombotic event [20, 27 28, 43]. Less than one-quarter of case series performed (independent or secondary) adjudication of outcomes [44]. More frequent use of a prospective study design (only 21% of identified case series reported being prospective) would allow for many of these concerns to be addressed.

Another common methodological flaw was case series' failure to impose and/or describe a maximum time since last anticoagulation dose (part of inclusion in 14%, reported in 29%) and/or the need for sufficiently elevated anticoagulation activity/levels for inclusion (measured in 21%). Guidelines state that a reversal agent should only be considered when a patient is expected to have clinically relevant levels of anticoagulant [13]. Given the relatively short half-life (8-15 hours for apixaban; 7-13 hours for rivaroxaban) and duration of pharmacologic activity seen with oFXa inhibitors, it is estimated that <25%

of the drug would be present 14 hours after the last dose and <10% after 24-hours in most patients [45-46]. Inclusion of patients presenting with bleeds more than a day after the last dose or without verification of anticoagulation activity in case series could result in an overestimation of 4F-PCCs effectiveness.

Identified case series often failed to follow patients for sufficient duration of time to assess important outcomes including mortality (which can be seen as early as 48-72 hours after presentation in 20% of patients with ICH, but up to 40% by 30-days [47]) and thrombosis (which occurs in up to 15% of 4F-PCC users at 30-days) [28]. Moreover, the factor II in 4F-PCC has a half-life of ~60 hours [48] and requires ~12 days to fully clear from the body post-infusion [46]. Only 36% and 50% of case series follow patients for ≥30 days for mortality and thrombotic events, respectively. Due to the short duration of follow-up used in these case series, the risk of mortality and thrombotic events could have been underestimated.

Insufficient reporting was also present in identified case series. Few of the included case series provided detailed data on anticoagulant agents used, dosage, time from last anticoagulant administration, time from presentation for bleeding to 4F-PCC administration or baseline neurologic function (in ICH patients). The dose of 4F-PCC was reported in the majority of case series; however, the dosage was inconsistent between studies ranging from 25 to 50 U/kg. Beyond the methodological concerns noted above, incomplete or lack of reporting of such detail makes it more difficult for clinicians to understand how these case series apply to their patients (generalizability) and how they might change their clinical practice.

Many of the case series limitations discussed above are known challenges when performing a study with this design [17,49]. While case series are often mistakenly interpreted as reporting on treatment efficacy, that is not their objective. Rather, case series are typically descriptive and intended to be hypothesis generating only. Even conscientious Investigators are limited by the data available to them (contained within their electronic health record), particularly when data is collected retrospectively. The flaws discussed previously and the inherent limitations of case series may explain much of the substantial variance in hemostatic effectiveness (ranging from 60% [20] to 94% [23]) reported with 4FPCC in identified series [18-40], and further underscores the importance of reporting quality metrics for case series when evaluating medical literature.

Based primarily on case series such as those identified in our review (as well as clinical opinion), guidelines and position statements have been published detailing the role of 4F-PCC as a reversal agent in the management of oFXa inhibitor-related bleeding [13-15]. European Stroke Organisation recommends andexanet alfa first line and with second line option of 4F-PCC use if andexanet alfa not available for

managing oFXa inhibitor-related ICH, but the strength of evidence supporting this recommendation is graded as "very low" [13]. Updates to AHA/ACC/HRS atrial fibrillation guidelines also provide guidance on oFXa inhibitor reversal, making a class IIa/B (moderate) recommendation for andexanet alfa use in life-threatening bleeding, without mentioning 4F-PCC [50]. Position statements from both the North American Anticoagulation Forum and the Emergency Medicine Cardiac Research and Education Group recommends 4F-PCC use as an alternative to andexanet alfa when it is unavailable (no strengths of recommendation provided) [14,15]. Although these recommendations may mention the use of 4F-PCC in oFXa inhibitor-related bleeding, clinicians should understand the strength of these recommendations is low based on the poor quality of evidence available.

We believe the tool we adapted for use in this systematic review provides a comprehensive framework that clinicians and other peer-reviewers can use to aid when critically appraising and developing case series of reversal agents (e.g., 4F-PCC) for oFXa inhibitor-associated bleeding. This tool may be especially useful in the absence of study designs with greater internal validity in order to evaluate the relative quality amongst case series. It is important to note, however, that our tool has some limitations. Although we based our disease-specific tool on a previously validated generic case series assessment [17], ours has not undergone extensive peer evaluation and its reliability/validity is unclear. In its present form, our tool uses 38 items to assess methodological and reporting quality. We acknowledge that the number of items and time needed to appraise a case series may be burdensome to clinicians (and limit its use). Lastly, it is often difficult to assess the true methodological quality of a case series because of incomplete or unclear reporting. "Unclear" designations for items does not imply proper or improper use of methods (i.e., a case series may have used valid methods, but simply did not describe it in their report). For the abovementioned reason, case series published as abstracts only were excluded from our base analysis as they are more likely to have incomplete reporting due to strictly imposed word/character limits and the lack of back-and-forth peer-review.

CONCLUSION

Although many case series describing 4F-PCC for managing oFXa inhibitor-related bleeding have been published, the presence of common methodological flaws and/or poor reporting necessitates caution in interpretation. Any data from these case series, are at best, hypothesis generating for future prospective, controlled studies. Major flaws of case series identified included unclear definitions, and lack of adjudication of, the index bleeding, effectiveness and thrombosis, failure to validly ascertain effectiveness in many cases and overall under-reporting of relevant clinical or methodological information. The tool adapted for this systematic review may be useful to clinicians and peer-reviewers who need to critically

appraise case series of reversal agents for oFXa inhibitor-associated bleeding. To best support patients with oFXa inhibitor-related bleeds, it is crucial to assess the safety and efficacy of reversal agents using rigorous frameworks and across larger samples with enhanced generalizability.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data are available upon reasonable request.

COMPETING INTEREST

O.S.C., Y.R., and C.M.W. have no competing interest to disclose.

B.L. and K.M. are employees of Portola Pharmaceuticals.

W.L.B has received consultancy fees from Bayer Inc.

C.I.C has received grant funding and consultancy fees from Janssen Scientific Affairs LLC and Bayer Inc.

FUNDING

Funding provided by Portola Pharmaceuticals.

AUTHORS CONTRIBUTIONS

C. I.C, and B.L. conceptualized and designed the study. Y.R and O.S.C. collected data. The manuscript was primary written by O.S.C. and C.I.C.; all remaining authors including W.L.B., M.W., and K.M. aided and/or contributed to revisions. All authors substantially contributed to this project, read and approved the manuscript and assume responsibility for the contents of the manuscript

ACKNOWLEDGEMENTS

None.

ABBREVIATIONS

EMA: European Medicines Agency

FDA: Food and Drug Administration

GI: gastrointestinal

ICH: intracranial hemorrhage

NVAF: nonvalvular atrial fibrillation

oFXa: oral factor Xa

PCC: prothrombin complex concentrate

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

US: United States

VTE: venous thromboembolism

4F-PCC: Four factor prothrombin complex concentrate

REFERENCES

1. Giugliano RP, Ruff CT, Braunwald E. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369:2093-2104.
2. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-992.
3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365: 883-891.
4. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for treatment of acute venous thromboembolism. N Engl J Med. 2013;369: 799-808.
5. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J. 2013;11:1-10.
6. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361:2342-2352.
7. Steinberg BA, Gao H, Shrader P, et al. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: Results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. Am Heart J. 2017;194:132-140.
8. Zhu J, Alexander GC, Nazarian S, et al. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. Pharmacotherapy. 2018;38:907-920.
9. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330-1393.
10. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med. 2019;380:1326-1335.
11. Heo Y. Andexanet alfa: first global approval. Drugs. 2018;78:1049-1055.
12. Euopean Medicines Agency, andexanet alfa. https://www.ema.europa.eu (Last accessed on January 6, 2020).
13. Christensen H, Cordonnier C, Korv J, et al. European stroke organization guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. Euro Stroke J. 2019;0: 1-13.
14. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. Am J Hematol. 2019;94:697-708.
15. Gibler WB, Racadio JM, Hirsch AL, et al. Management of severe bleeding in patients treated with oral anticoagulants. Crit Pathw Cardiol 2019;13:143-166.

16. Liberati A, Altman DG, Tetzalaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. PLOS Med. 2009;6:1-28.
17. Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Medicine 2018;23:60-63.
18. Allison TA, Lin PJ, Gass JA, et al. Evaluation of the use of low-dose 4-factor prothrombin complex concentrate in the reversal of direct oral anticoagulants in bleeding patients. J Intensive Care Med. 2018; epub /doi.org/10.1177/0885066618800657.
19. Arachchillage D, Alavian S, Griffin J, et al. Efficacy and safety of prothrombin complex concentrate in patients treated with rivaroxaban or apixaban compared to warfarin presenting with major bleeding. Br J Haematol. 2019;184:808-816.
20. Barra ME, Das AS, Hayed BD, et al. Evaluation of andexanet alfa and four-factor prothrombin complex concentrate (4F-PCC) for reversal of rivaroxaban- and apixaban-associated intracranial hemorrhage. J Thromb Haemost. 2020; 00: 1-11.
21. Dybdahl D, Walleser G, Spalding MC, et al. Four-factor prothrombin complex concentrate for the reversal of factor Xa inhibitors for traumatic intracranial hemorrhage. Am J Emerg Med. 2018;0: 1-5.
22. Frontera JA, Bhatt P, Lalchan R, et al. Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage. J Thromb Haemost. 2019; 1-11. https://doi.org/10.1007/s11239-019-01973-z.
23. Grandhi R, Newman WC, Zhang X, et al. Administration of 4-factor prothrombin complex concentrate as an antidote for intracranial bleeding in patients taking direct factor Xa inhibitors. World Neurosurg. 2015;84:1956-1961.
24. Harrison SK, Garrett JS, Kohman KN, et al. Comparison of outcome sin patients with intracranial hemorrhage on factor Xa inhibitors versus vitamin K antagonists treated with 4-factor prothrombin complex concentrate. Proc (Bayl Univ Med Cent). 2017;31:153-156.
25. Korobey MJ, Sadaka F, Javed M, et al. Efficacy of 4-factor prothrombin complex concentrates in factor Xa inhibitor-associated intracranial bleeding. Neurocrit Care. 2020; https://doi: 10.1007/s12028-020-00968-6.
26. Majeed A, Agron A, Holmstrom M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood. 2017;130:1706-1712.
27. Reynolds TR, Gilbert BW, Hall KM, et al. Utilization of 4-factor prothrombin complex concentrate for reversal of oral factor xa inhibitor-associated acute major bleeding: A case series. J Pharm Pract. 2020; https:// doi: 10.1177/0897190020907012.

28. Schenk B, Goerke S, Beer R. Four-factor prothrombin complex concentrate improves thrombin generation and prothrombin time in patients with bleeding complications related to rivaroxaban: a single-center pilot trial. Thromb J. 2018:16;1-10.
29. Schulman S, Gross PL, Ritchie B, et al. Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: a prospective cohort study. Thromb Haemost. 2018;118:842-851.
30. Sheikh-Taha M. Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate. Intern Emerg Med. 2019;14:265-269.
31. Smith MN, Deloney L, Carter C. Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. J Thromb Thrombolys. 2019;48:250-255.
32. Coleman CI, Danese S, Ulloa J, et al. Real-world management of oral factor Xa inhibitor bleeding-related hospitalization with andexanet alfa or 4 factor prothrombin complex concentrate. J Am Coll Cardiol.2020; 75: 11.
33. Deloney L, Tatum C, Weant K, et al. Evaluation of 4F-PCC in the management of major bleeding associated with oral factor Xa inhibitors. Crit Care Med. 2019;47:417.
34. Dobesh P, Borsch M, Marth K, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate for the management of direct Xa inhibitor-induced major bleeding. ISTH Academy. https://academy.isth.org/isth/2019/melbourne/264679/paul.dobesh.efficacy.and.safety.of.a.4-factor.prothrombin.complex.concentrate.html. Accessed on January 6, 2020.
35. Fan BE, Gallardo CA, Tay HM. Reversal of anticoagulation in patients on rivaroxaban or apixaban (DOAC) with major bleeding episodes (MBE) with 4 factor prothrombin complex concentrates (PCC): A multicenter retrospective study. Res Pract Thromb Haemost. 2019; abstract PB1476.
36. Goad N. Sanchez P, Levesque M, et al. Outcomes from the PITCH study: 4-factor PCC in intracranial Xa inhibitor coagulopathy hemorrhages. Crit Care Med. 2020; 48: 1.
37. Kaplan J, Procopio G, Perez JM, et al. Four-factor prothrombin complex concentrate for factor Xa inhibitor associated hemorrhage. Crit Care Med. 2018;46:259.
38. Nguyen K, Hurley M, Wdowlarz K, et al. Andexanet alfa versus four-factor prothrombin complex concentrate (4F-PCC) for the reversal of intracranial hemorrhage (ICH associated with rivaroxaban and apixaban: A retrospective comparative study. Neurocritical Care Society Conference 2019.
39. Silinskie K, Hite M. Safety of 4-factor PCC for reversal of FXa inhibitors versus warfarin in neurocritical care patients. Crit Care Med. 2018;47:110.
40. Zheng Y, Tormey CA. The use of 4F-PCC to correct direct oral anticoagulant (DOAC)-induced coagulopathy. Transfusion. 2018; 58:82A-83A.

41. Khorsand N, Majeed A, Sarode R, et al. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. J Thromb Haemost. 2016; 14: 211-214.
42. Sarode R, Milling TJ, Reffai MA et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonist presenting with major bleeding. Circulation. 2013; 10: 1234-1243.
43. Lim W, Gal GL, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. Blood Adv. 2018; 2: 3226-3256.
44. Kahan, BC, Feagan B, Jairath V. A comparison of approaches for adjudicating outcomes in clinical trials. Trials. 2017; 18:266-280.
45. Mekaj YH, Mekaj AY, Duci SB, et al. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Mang. 2015;11:967-977.
46. Ito S. Pharmacokinetics 101. Paediatr Child Health. 2011;16:535-536.
47. Aguilar MI, Brott TG. Update in intracerebral hemorrhage. Neurohospitalist. 2011; 1:148-159.
48. Kcentra package insert. Kankakee, IL: CSL Behring LLC; October 2018.
49. Kooistra B, Dijkman B, Einhorn TA Bhandari M. How to design a good case series. J Bone Joint Surg Am. 2009;91:S21-6.
50. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2019; 140 e125-e151.

Figure 1. Summary of case series search and selection
PCC: prothrombin complex concentrate, oFXa: oral factor Xa, 3F: 3-factor

Figure 2. Percentage of full-text case series that received a "yes", "no", or "unclear" for selection quality items
Number of case series with each assessment is labeled within the bar
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 3. Individual full-text case series assessment of selection, ascertainment, casual and temporal association items
GI: gastrointestinal, ICH: intracranial hemorrhage, NA: not applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 4. Key inclusion criteria components in full-text case series
Figure expands on the findings of Figure 2, S1

Figure 5. Percentage of full-text case series that received a "yes", "no" or "unclear" for bleeding event ascertainment items
Number of case series with each assessment is labeled within the bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 6. Percentage of full-text case series that received a "yes", "no", or "unclear" for outcomes ascertainment items
Number of case series with each assessment is labeled within the bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

Figure 7. Percentage of full-text case series that received a "yes", "no", or "unclear" for causal and temporal association items
Number of studies with each assessment is labeled within bar
Note that "not applicable" designations are not incorporated
Refer to Appendix 2 for specific definitions used to assess quality

Figure 8 Percentage of full-text case series that received a "yes" or "no" for reporting of characteristics at presentation items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

Figure 9. Individual full-text case series assessment for reporting items
Refer to Appendix 2 for specific definitions used to assess quality

Figure 10. Percentage of full-text case series that received a "yes" or "no" for reporting of outcomes
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

Table 1. Full-text case series, number of patients, anticoagulant and indication for anticoagulation

Case Series	N	Anticoagulant, n (%)			Indication, n (%)			Bleed Location, n (%)		
		A	Ed	R	AF	DVT/PE	Other	ICH	GI	Other
Barra 2020	11	3 (27)	0 (0)	8 (73)	8 (73)	3 (27)	NR	11 (100)	0 (0)	0 (0)
Korobey 2020	59	40 (68)	0 (0)	19 (32)	49 (83)	16 (27)	NR	59 (100)	0 (0)	0 (0)
Reynolds 2020	31	14 (45)	0 (0)	17 (55)	22 (71)	6 (19)	3 (10)	17 (55)	7 (23)	7 (23)
Arachchillage 2019	80	40 (50)	0 (0)	40 (50)	68 (85)	13 (16)	0 (0)	46 (58)	24 (30)	10 (13)
Dybdahl 2019	35	17 (49)	0 (0)	18 (51)	31 (89)	5 (14)	0 (0)	35 (100)	0 (0)	0 (0)
Frontera 2019	46	31 (67)	0 (0)	15 (33)	44 (96)	3 (7)	NR	35 (76)	11 (24)	0 (0)
Smith 2019	31	17 (55)	0 (0)	14 (45)	28 (90)	3 (10)	NR	18 (58)	1 (3)	12 (39)
Allison 2018	33	6 (18.	0 (0)	27 (82)	24 (73)	6 (18)	3 (9)	30 (91)	1 (3)	2 (6)
Harrison 2018	14	NR	NR	NR	12 (86)	3 (21)	2 (14)	14 (100)	0 (0)	0 (0)
Schenk 2018	13	0 (0)	0 (0)	13 (100)	NR	NR	NR	10 (77)	1 (8)	2 (15)
Schulman 2018	66	29 (44)	0 (0)	37 (56)	56 (85)	10 (15)	1 (2)	36 (55)	16 (24)	15 (21)
Sheikh-Taha 2018	29	13 (45)	0 (0)	16 (55)	23 (79)	5 (17)	1 (3)	21 (72)	4 (14)	4 (14)
Majeed 2017	84	39 (46)	0 (0)	45 (54)	67 (80)	21 (25)	21 (25)	59 (70)	13 (16)	12 (14)
Grandhi 2015	18	2 (11)	0 (0)	16 (89)	16 (89)	1 (6)	3 (17)	18 (100)	0 (0)	0 (0)

A: apixaban; AF: atrial fibrillation, DVT: deep vein thromboembolism, Ed: edoxaban, GI: gastrointestinal, ICH: intracranial hemorrhage, NR: not recorded, PE: pulmonary embolism, R: rivaroxaban

*Study pooled intracranial hemorrhage and intraspinal bleed

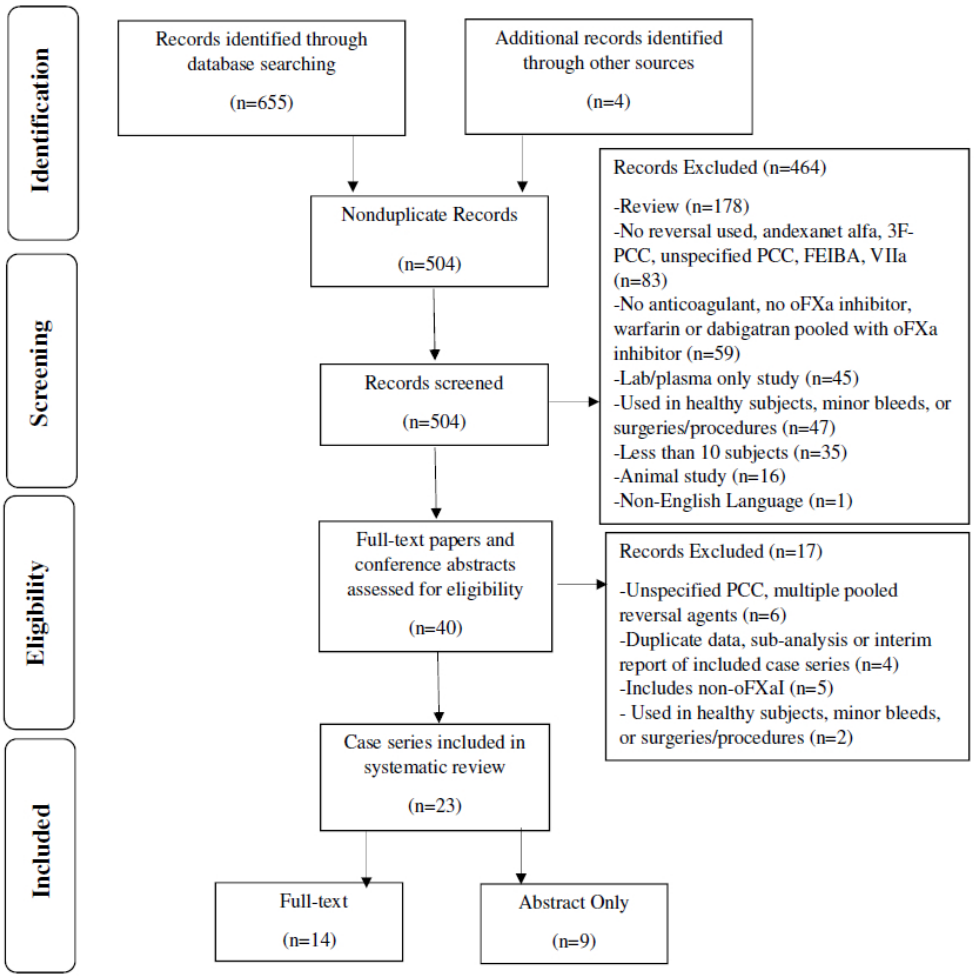


Figure 1. Summary of case series search and selection
PCC: prothrombin complex concentrate, oFXa: oral factor Xa, 3F: 3-factor

72x71mm (300 x 300 DPI)

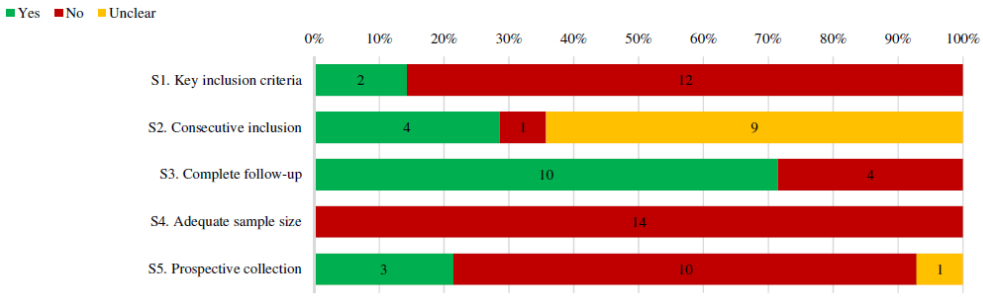


Figure 2. Percentage of full-text case series that received a "yes", "no", or "unclear" for selection quality items
Number of case series with each assessment is labeled within the bar
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

85x26mm (300 x 300 DPI)

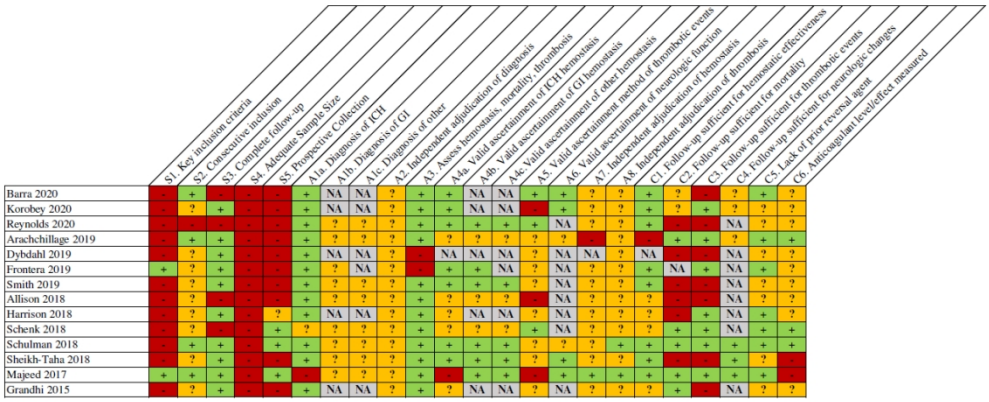


Figure 3. Individual full-text case series assessment of selection, ascertainment, casual and temporal association items
GI: gastrointestinal, ICH: intracranial hemorrhage, NA: not applicable
Refer to Appendix 2 for specific definitions used to assess quality

112x45mm (300 x 300 DPI)

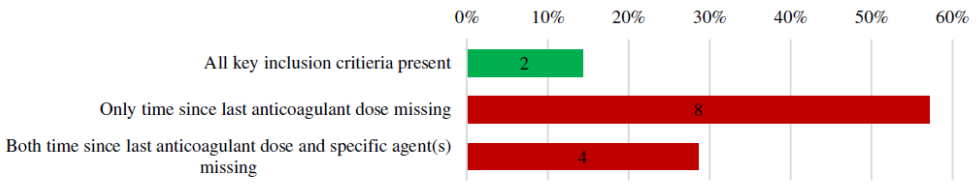


Figure 4. Key inclusion criteria components in full-text case series
Figure expands on the findings of Figure 2, S1

87x17mm (300 x 300 DPI)

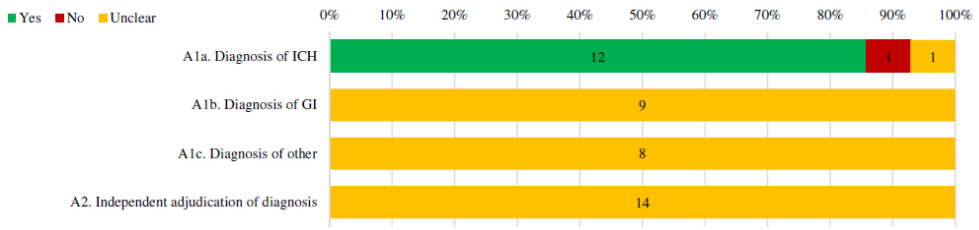


Figure 5. Percentage of full-text case series that received a "yes", "no" or "unclear" for bleeding event ascertainment items
Number of case series with each assessment is labeled within the bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

85x21mm (300 x 300 DPI)

Figure 6. Percentage of full-text case series that received a "yes", "no", or "unclear" for outcomes ascertainment items
Number of case series with each assessment is labeled within the bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Percentages are based on case series in which the item's assessment was deemed applicable
Refer to Appendix 2 for specific definitions used to assess quality

87x37mm (300 x 300 DPI)

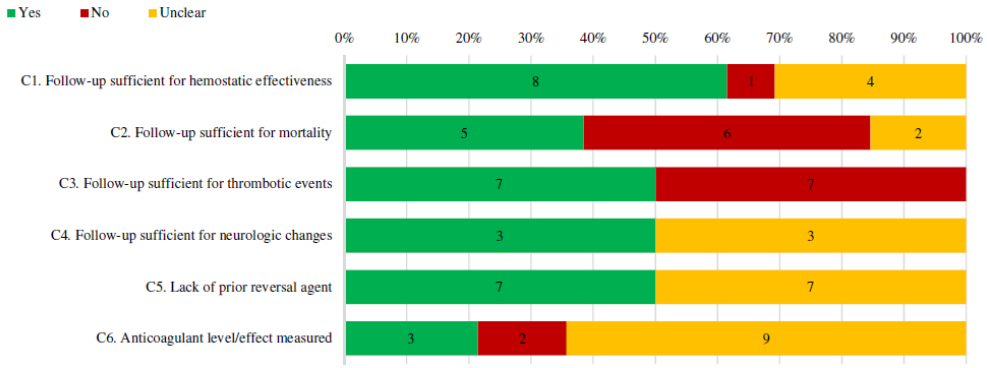


Figure 7. Percentage of full-text case series that received a "yes", "no", or "unclear" for causal and temporal association items
Number of studies with each assessment is labeled within bar
Note that "not applicable" designations are not incorporated
Refer to Appendix 2 for specific definitions used to assess quality

83x30mm (300 x 300 DPI)

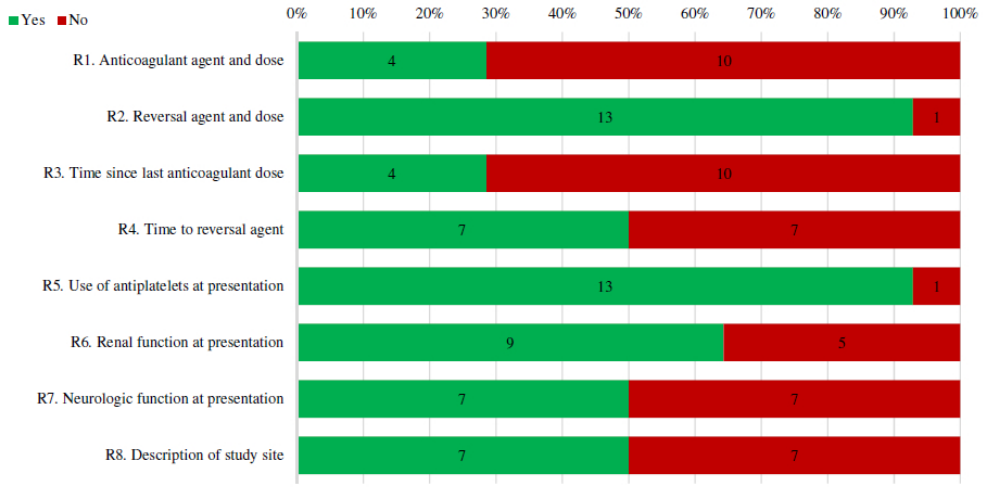


Figure 8 Percentage of full-text case series that received a "yes" or "no" for reporting of characteristics at presentation items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

77x38mm (300 x 300 DPI)

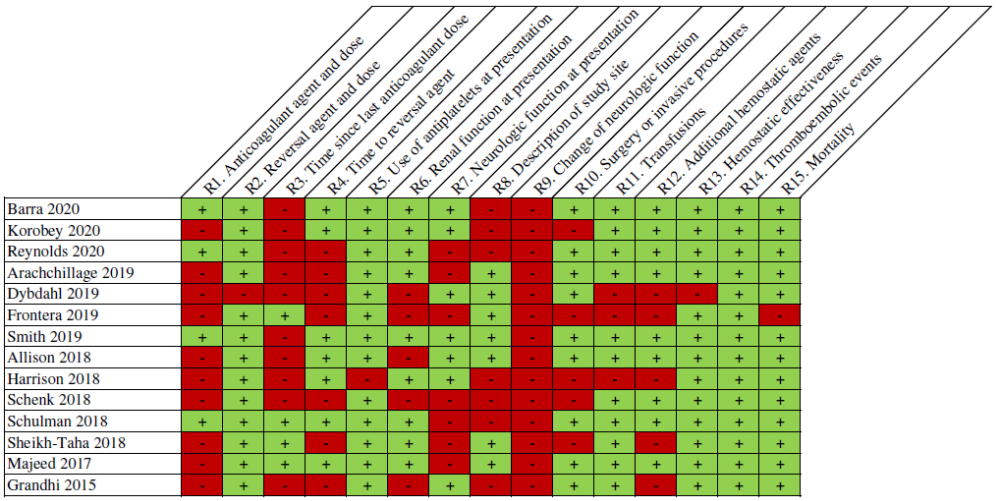


Figure 9. Individual full-text case series assessment for reporting items
Refer to Appendix 2 for specific definitions used to assess quality

86x43mm (300 x 300 DPI)

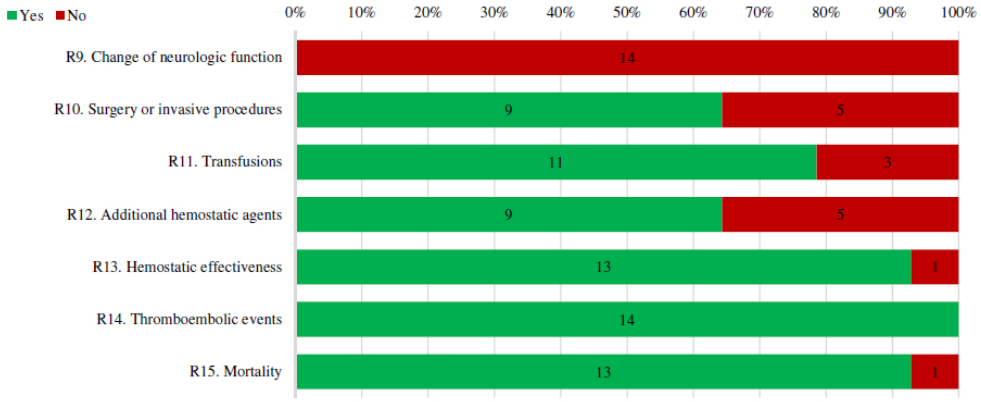


Figure 10. Percentage of full-text case series that received a "yes" or "no" for reporting of outcomes
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality

77x32mm (300 x 300 DPI)

Quality Evaluation of Case Series Describing Four-Factor Prothrombin Complex Concentrate in Oral Factor Xa Inhibitor-Associated Bleeding: A Systematic Review

SUPPLEMENTAL MATERIALS

1. Appendix 1. Literature Identification
2. Appendix 2. Methodological and Reporting Quality Tool and Definitions
3. Appendix 3. eFigures and eTables

APPENDIX 1. Literature Identification

Medline and Embase Search Strategy

1. NOAC OR "New oral anticoagulants" OR "Novel oral anticoagulants" OR "Non vitamin K antagonist" OR DOAC OR "Direct oral anticoagulants" OR "Direct-acting oral anticoagulants" OR "Factor Xa inhibitor" OR "factor-specific oral anticoagulants" OR Rivaroxaban OR Apixaban OR Edoxaban OR Betrixaban
2. OR PCC OR "Prothrombin complex concentrate"
3. 1 and 2
4. Limit 3 to humans
5. Limit 4 to dates 1/1/2011 to 11/8/2019
6. Remove duplicates

Conference Proceedings Searched

1. American Heart Association
2. American College of Cardiology
3. European Society of Cardiology
4. American Academy of Neurology
5. International Stroke Conference
6. European Stroke Organisation Conference
7. International Society on Thrombosis and Haemostasis
8. American Society of Hematology

Appendix 2. Methodological and Reporting Quality Tool and Definitions*

***adapted from Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018;23:60-63

SELECTION

S1. Are key criteria for inclusion into the case series provided?

- Yes: Detailed inclusion of major bleeds, specific qualifying anticoagulants and maximum time from last exposure of the anticoagulant allowed for inclusion
- No: At least one of the above-mentioned inclusion criteria was not described

S2. Was there consecutive enrollment of patients meeting inclusion criteria?

- Yes: Explicitly states consecutive inclusion of patients OR describes inclusion of all patients within a given time frame
- No: Nonconsecutive patients (convenience sample) were used
- Unclear: Unable to determine whether consecutive eligible patients were included

S3. Did the case series have complete follow-up of patients?

- Yes: Number of included patients matched the number of patients with outcome data reported (all outcomes have 100% follow-up)
- No: The number of patients/cases with outcomes reported was less than the total number of included patients/cases (at least one outcome with incomplete follow-up)
- Unclear: Unable to determine if of patient/case follow-up was complete for all outcomes

S4. Was there an adequate sample size?

- Yes: Number of included patients was ≥ 100
- No: Number of included patients was < 100
- Unclear: Number of included patients was not provided

S5. Was data collection prospective in nature?

- Yes: Methods explicitly state data was collected prospectively
- No: Methods explicitly state data was collected retrospectively
- Unclear: Methods did not clearly state if data collection was done retrospectively or prospectively

ASCERTAINMENT OF BLEEDING EVENT

A1. Was there clear ascertainment of the qualifying bleed diagnosis?

a. Was there clear ascertainment of intracranial hemorrhage?

- Yes: Clearly describes or references an accepted (or closely adapted) set of diagnostic criteria for intracranial hemorrhage (e.g. CT, MRI, etc.)
- No: Intracranial hemorrhage diagnosis was based upon non-accepted methods or clinician suspicion only
- Unclear: Did not explicitly describe to diagnose ICH
- N/A: Intracranial hemorrhages were not included in the case series

b. Was there clear ascertainment of gastrointestinal bleeding?

- Yes: Clearly describes or references an accepted (or closely adapted) set of diagnostic criteria (e.g. barium-contrast swallow, colonoscopy, endoscopy, esophagogastroduodenoscopy, etc)
- No: GI bleed diagnosis was based upon non-accepted methods or clinician suspicion only
- Unclear: Did not explicitly describe to diagnose of gastrointestinal bleeding
- N/A: Gastrointestinal bleeds were not included in the case series

c. Was there clear ascertainment of other bleed type diagnosis?

- Yes: Clearly describes or references an accepted (or closely adapted) set of diagnostic criteria that was specific for the type of bleeding reported
- No: Bleed diagnosis was based upon non-accepted methods or clinician suspicion only
- Unclear: Did not explicitly describe the diagnosis of "other" bleeds
- N/A: Other bleed types were not included in the case series

A2. Was there central, independent (or similar) adjudication of the qualifying bleeding event for inclusion into the case series?

- Yes: Explicitly states central, blinded or independent (or similar terminology) reviewer(s)/committee assessed the qualifying bleeding event
- No: Statement that a central, blinded or independent reviewer(s)/committee was not used
- Unclear: No statement regarding the adjudication of the qualifying bleeding event

ASCERTAINMENT OF OUTCOME

A3. Did the case series assess hemostatic effectiveness, mortality and thrombotic events?

- Yes: Hemostatic effectiveness, mortality, and thromboembolism were all assessed
- No: At least one of the above outcomes was not assessed

A4. Was there clear and valid ascertainment of achieving hemostatic effectiveness?

a. Was there clear and valid ascertainment for intracranial hemorrhage?

- Yes: Clearly describes or references an accepted (or closely adapted) definition of hemostatic effectiveness was utilized by the case series (i.e. definition by the International Society on thrombosis and Haemostasis or Sarode et al.)
- No: A non-accepted definition was utilized (i.e. bleeding cessation, no repeat bleed)
- Unclear: Description/definition of hemostatic effectiveness was not provided (i.e. scale without quantitative cut-offs, qualitative description of stable vs. worsening, etc.)
- N/A: No intracranial hemostatic effectiveness outcome was reported in the case series

b. Was there clear and valid ascertainment for gastrointestinal bleeding?

- Yes: Clearly describes or references an accepted (or closely adapted) definition of hemostatic effectiveness was utilized by the case series
- No: A non-accepted definition was utilized (i.e. bleeding cessation, no repeat bleed)
- Unclear: Description/definition of hemostatic effectiveness was not provided (i.e. scale without quantitative cut-offs, qualitative description of stable vs. worsening, etc.)
- N/A: No extracranial hemostatic effectiveness outcome was reported in the case series

c. Was there clear and valid ascertainment for other bleeding?

- Yes: Clearly describes or references an accepted (or closely adapted) definition of hemostatic effectiveness was utilized by the case series
- No: A non-accepted definition was utilized
- Unclear: Description/definition of hemostatic effectiveness was not provided
- N/A: No extracranial hemostatic effectiveness outcome was reported in the case series

A5. Was there clear and valid ascertainment for diagnosis of thrombotic events?

- Yes: Clearly describes or references an accepted (or closely adapted) definition for screening and reported thrombotic events including VTE, MI and stroke
- No: A non-accepted (e.g., investigator developed or clinician judgement only) definition was utilized
- Unclear: Description/definition of VTE, MI and stroke were not provided
- N/A: Thrombotic events were not reported as outcome

A6. Was there clear and valid ascertainment of neurologic function change?

- Yes: Neurologic function change was assessed using an accepted measure (e.g. Glasgow Coma Score, National Institutes of Health Stroke Scale); For studies using ISTH to assess ICH effectiveness, it is assumed appropriate ascertainment was used based on efficacy criteria
- No: A non-accepted (e.g., investigator developed or clinician judgement only) definition was utilized for ascertainment of neurologic function change
- Unclear: Description/definition of neurologic function change was not clear
- N/A: No assessment of neurologic function change was done in the case series

A7. Was there central, blinded, independent (or similar) adjudication of hemostatic effectiveness?

- Yes: Explicitly states central, blinded or independent (or similar terminology) reviewer(s)/committee assessed hemostatic effectiveness
- No: Statement that a central, blinded or independent reviewer(s)/committee was not used
- Unclear: No statement regarding the adjudication of hemostatic effectiveness
- N/A: Hemostatic effectiveness was not reported as an outcome

A8. Was there central, blinded, independent (or similar) adjudication of thrombotic events?

- Yes: Explicitly states central, blinded or independent (or similar terminology) reviewer(s)/committee assessed thrombotic events
- No: Statement that a central, blinded or independent reviewer(s)/committee was not used
- Unclear: No statement regarding the adjudication of thrombotic events
- N/A: Thrombotic events were not reported as an outcome

CASUAL & TEMPORAL ASSOCIATIONS

C1. Was the duration of follow-up for hemostatic effectiveness sufficient?

- Yes: Re-evaluation within 3-24 hours for ICH, within 36-60 hours for extracranial bleeds
- No: Re-evaluation outside 3-24 hours for ICH, outside 36-60 hours for extracranial bleeds
- Unclear: Timing of hemostatic effectiveness evaluation was not clearly defined
- N/A: Hemostatic effectiveness was an outcome

C2. Was the duration of follow-up for mortality sufficient?

- Yes: Follow-up was a minimum of 30-days
- No: Follow-up was less than 30-days (including in-hospital follow-up with reported mean or median length-of-stay less than 30-days)
- Unclear: Duration of follow-up not provided
- N/A: Mortality was not reported as an outcome

C3. Was the duration of follow-up thrombotic events sufficient?

- Yes: Follow-up was a minimum of 30-days
- No: Follow-up was less than 30-days (including in-hospital follow-up with reported mean or median length-of-stay less than 30-days)
- Unclear: Duration of follow-up not provided
- N/A: Thrombotic events were not reported as an outcome

C4. Was the duration of follow-up for change in neurologic function change sufficient?

- Yes: Re-evaluation at 24 hours (12-36 hour window)
- No: Re-evaluation outside the 12-36 hour window
- Unclear: Timing of change in neurologic function was not clearly defined
- N/A: Change in neurologic function was not as an outcome

C5. Was there lack of prior administration of an alternative reversal agent?

- Yes: No prior alternative reversal agents (e.g., andexanet alfa, 4F-PCC, 3F-PCC, FEIBA, recombinant VIIa) were administered
- No: At least one alternative/different reversal agent (e.g., andexanet alfa, 4F-PCC, 3F-PCC, FEIBA, recombinant VIIa) was previously administered after the index reversal agent
- Unclear: Unable to determine if a different reversal agent was previously administered

C6. Was the anticoagulation effect (e.g., drug level or anti–Factor Xa activity) measured?

- Yes: Anticoagulation levels/activity were measured
- No: Anticoagulation levels/activity were not measured
- Unclear: Anticoagulation levels/activity were not reported

REPORTING OF CHARACTERISTICS AT PRESENTATION

R1. Was the anticoagulant agent(s) utilized and dose reported?

- Yes: The specific type anticoagulant(s) and corresponding dose is reported as either at the individual patient level or in aggregate
- No: The specific anticoagulant(s) used by included patients/cases and/or corresponding doses of anticoagulant(s) were not reported

R2. Was the index reversal agent and dose reported?

- Yes: The reversal agent and corresponding dose is reported as either an aggregate for all patients or on a case-by-case basis
- No: The specific reversal agent used and/or dose is not reported

R3. Was the actual time since last anticoagulant dose reported?

- Yes: The time of the last anticoagulation dose since a defined time point (i.e. hospitalization, bleed diagnosis, reversal agent administration) was reported
- No: The time of the last anticoagulant dose was not reported or only a time window was provided (e.g. within x hours).

R4. Was the actual time to reversal agent reported?

- Yes: The time to reversal agent from a defined time point (i.e. hospitalization, bleed diagnosis, anticoagulant dose) was reported
- No: The time to reversal agent was not reported

R5. Was the use of antiplatelets at presentation reported?

- Yes: The use (or lack thereof) of antiplatelets (e.g., aspirin, P2Y12, cilostazol, etc.) was reported
- No: Antiplatelet use was not reported

R6. Was a measure of renal function at presentation reported?

- Yes: Serum creatinine, creatinine clearance or eGFR were provided
- No: Serum creatinine, creatinine clearance or eGFR were not provided

R7. Was neurologic function at presentation reported?

- Yes: Neurologic function at presentation was reported
- No: Neurologic function at presentation was not reported
- N/A: Intracranial hemorrhages were not included in the case series

R8. Was a description and geographical information of the investigation site reported?

- Yes: A description (i.e. comprehensive stroke center, level I trauma center, etc.) and geographical information of the investigation site was reported
- No: Description and/or geographic location of site was not reported

REPORTING OF OUTCOMES

R9. Was a change in neurologic function reported?

- Yes: Change of neurologic function was reported
- No: Change of neurologic function was not reported
- N/A: Intracranial hemorrhages were not included in the case series

R10. Were concomitant surgeries or procedures to manage bleeding reported?

- Yes: Surgeries or invasive procedures (e.g., craniotomy, burr hole, gastroscopy, evacuation, fasciotomy, embolization) were reported
- No: Surgeries or invasive procedures were not reported

R11. Was the use of blood transfusions reported?

- Yes: The utilization (or lack thereof) of red blood cells, platelets, fresh frozen plasma, cryoprecipitate was described
- No: The utilization (or lack thereof) of red blood cells, platelets, fresh frozen plasma, cryoprecipitate was not described

R12. Was the use of additional hemostatic agent described?

- Yes: The use (or lack thereof) of tranexamic acid, other reversal agents (e.g., aPCC, FEIBA), or repeat of initial reversal agent was described
- No: Did not report the use of any hemostatic agents

R13. Was the hemostatic effectiveness reported?

- Yes: The hemostatic effectiveness was reported
- No: The hemostatic effectiveness was reported

R14. Were thromboembolic events reported?

- Yes: Thromboembolic events were reported
- No: Thromboembolic events were not reported

R15. Was mortality reported?

- Yes: Mortality was reported
- No: Mortality was not reported

Rating of Hemostatic Efficacy

Sarode R, Milling TJ, Reffai MA et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonist presenting with major bleeding. Circulation 2013;10:1234-1243

	Visible Bleeding	**Non-Visible Bleeding**
Excellent (effective)	Cessation of bleeding ≤1 hour after the end of infusion and no additional coagulation intervention required	1. Musculoskeletal bleeding: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 24-hour period 2. ICH: ≤20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3- and 24-hour time point 3. Non-visible bleeding that is not described above (e.g. GI bleeding): ≤10% decrease in both Hb/Hct† at 24 hours‡ compared to baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])
Good (effective)	Cessation of bleeding >1 and ≤4 hours after end of infusion and no additional coagulation intervention required	1. Musculoskeletal bleeding: Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after the end of infusion; and the condition has not deteriorated during the 24-hour period 2. ICH: >20%, but ≤35% increase in hematoma volume compared to baseline on a repeat CT scan performed at the 24-hour time point 3. Non-visible bleeding that is not described above: >10 to ≤20% decrease in both Hb/Hct† at 24 hours‡ compared with baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])
Poor (non-effective)	Cessation of bleeding >4 hours after end of the infusion, and/or additional coagulation intervention required (e.g. plasma, whole blood cell pack, or coagulation factor products)	1. Musculoskeletal bleeding: no improvement by 4 hours after the end of infusion and/or the condition has deteriorated during the 24-hour period 2. ICH: >35% increase in hematoma volume compared to baseline on repeat CT scan performed at the 24 hour time point 3. Non-visible bleeding that is not listed above: >20% decrease in both Hb/Hct at 24 hours‡ compared to baseline (initial correction of decrease in hemoglobin with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])

Rating of Hemostatic Efficacy

Khorsand N, Majeed A, Sarode R, et al. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. J Thromb Haemost 2016;14:211-214

	Effective Hemostasis
Non-visible Bleeding	a. The hemoglobin level is stable at 48 h after initial treatment with packed red cells and hemostatic agent (a reduction of ≤ 10% of the initial hemoglobin level is considered to be a stable level) b. By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products c. Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis
Visible Bleeding	a. There is cessation of visible bleeding within 4 h after the end of the administration of the hemostatic agent b. By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products c. Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis
Musculoskeletal Bleeding	a. Pain is reduced and swelling is improved within 24 h b. Fasciotomy is either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis c. By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products
Intracranial Bleeding	a. The hematoma volume is stable, or increased by <35% as compared with baseline volume), as assessed by a computed tomography (CT) scan within 12 h (time window of 6–24 h after the index CT) b. No deterioration of the Extended Glasgow Outcome Scale (or any validated scoring system) as assessed at 24 h in comparison with that at presentation. c. By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products. All of the above criteria have to be met for the therapy to be considered effective.

Appendix 3. Supplementary eFigures and eTables

eTable 1. Full-text case series and journal impact factor

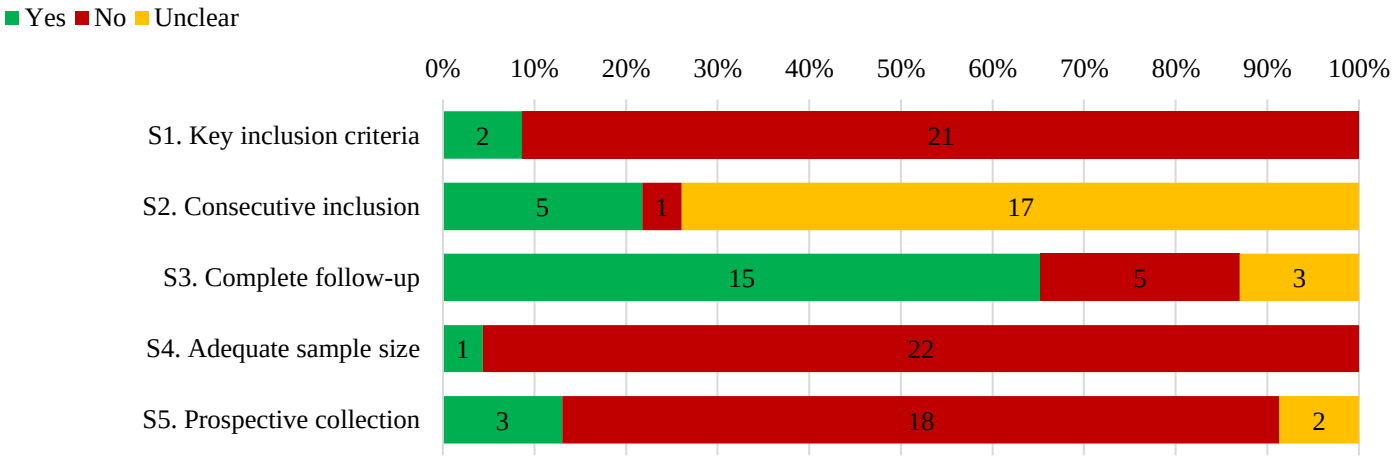
Case Series	Journal	Journal Impact Factor
Barra 2020	*Journal of Thrombosis and Haemostasis*	4.662
Korobey 2020	*Neurocritical Care*	2.790
Reynolds 2020	*Journal of Pharmacy Practice*	Not Available
Arachchillage 2019	*British Journal of Haematology*	5.206
Dybdahl 2019	*American Journal of Emergency Medicine*	1.651
Frontera 2019	*Journal of Thrombosis and Thrombolysis*	2.941
Allison 2018	*Journal of Intensive Care Medicine*	2.873
Harrison 2018	*Baylor University Medical Center Proceedings*	0.420
Schenk 2018	*Thrombosis Journal*	1.830
Schulman 2018	*Thrombosis Haemostasis*	4.733
Sheikh-Taha 2018	*Internal and Emergency Medicine*	2.335
Smith 2019	*Journal of Thrombosis and Thrombolysis*	2.941
Majeed 2017	*Blood*	16.562
Grandhi 2015	*World Neurosurgery*	1.723

eTable 2. Full-text and abstract only case series, number of patients, anticoagulant, and indication for anticoagulation

Case Series	N	Anticoagulant, n (%)			Indication, n (%)			Bleed Location, n (%)		
		A	Ed	R	AF	DVT/PE	Other	ICH	GI	Other
Barra 2020	11	3 (27)	0 (0)	8 (73)	8 (73)	3 (27)	NR	11 (100)	0 (0)	0 (0)
Coleman 2020	663	NR	NR	NR	NR	NR	NR	NR	NR	NR
Goad 2020	31	21 (68)	0 (0)	10 (32)	23 (74)	8 (26)	0 (0)	31 (100)	0 (0)	0 (0)
Korobey 2020	59	40 (68)	0 (0)	19 (32)	49 (83)	16 (27)	NR	59 (100)	0 (0)	0 (0)
Reynolds 2020	31	14 (45)	0 (0)	17 (55)	22 (71)	6 (19)	3 (10)	17 (55)	7 (23)	7 (23)
Arachchillage 2019	80	40 (50)	0 (0)	40 (50)	68 (85)	13 (16)	0 (0)	46 (58)	24 (30)	10 (13)
Deloney 2019	31	17 (55)	0 (0)	14 (45)	28 (90)	NR	3 (9.7)	18 (58)	0 (0)	13 (42)
Dobesh 2019	52	34 (65)	0 (0)	18 (35)	33 (63)	19 (37)	0 (0)	24 (67)	12 (33)	17 (33)
Dybdahl 2019	35	17 (49)	0 (0)	18 (51)	31 (89)	5 (14)	0 (0)	35 (100)	0 (0)	0 (0)
Fan 2019	76	NR	0 (0)	NR	70 (92)	NR	6 (7.9)	54 (71)	17 (22)	5 (7)
Frontera 2019	46	31 (67)	0 (0)	15 (33)	44 (96)	3 (7)	NR	35 (76) *	11 (24)	0 (0)
Nguyen 2019	14	NR	0 (0)	NR	NR	NR	NR	14 (100)	0 (0)	0 (0)
Smith 2019	31	17 (55)	0 (0)	14 (45)	28 (90)	3 (10)	NR	18 (58)	1 (3)	12 (39)
Allison 2018	33	6 (18.2)	0 (0)	27 (82)	24 (73)	6 (18)	3 (9)	30 (91)	1 (3)	2 (6)
Harrison 2018	14	NR	NR	NR	12 (86)	3 (21)	2 (14)	14 (100)	0 (0)	0 (0)
Kaplan 2018	22	14 (64)	0 (0)	8 (36)	13 (59)	NR	9 (41)	12 (55)	7 (32)	4 (18)
Schenk 2018	13	0 (0)	0 (0)	13 (100)	NR	NR	NR	10 (77)	1 (8)	2 (15)
Schulman 2018	66	29 (44)	0 (0)	37 (56)	56 (85)	10 (15)	1 (2)	36 (55)	16 (24)	15 (21)
Sheikh-Taha 2018	29	13 (45)	0 (0)	16 (55)	23 (79)	5 (17)	1 (3)	21 (72)	4 (14)	4 (14)
Silinskie 2018	23	NR	NR	NR	NR	NR	NR	12 (52.2)	NR	11 (48)
Zheng 2018	25	NR	NR	NR	NR	NR	NR	13 (52)	8 (32)	4 (16)
Majeed 2017	84	39 (46)	0 (0)	45 (54)	67 (80)	21 (25)	21 (25)	59 (70)	13 (16)	12 (14)
Grandhi 2015	18	2 (11)	0 (0)	16 (89)	16 (89)	1 (6)	3 (17)	18 (100)	0 (0)	0 (0)

A: apixaban; AF: atrial fibrillation, DVT: deep vein thromboembolism, Ed: edoxaban, GI: gastrointestinal, ICH: intracranial hemorrhage, NR: not recorded, PE: pulmonary embolism, R: rivaroxaban

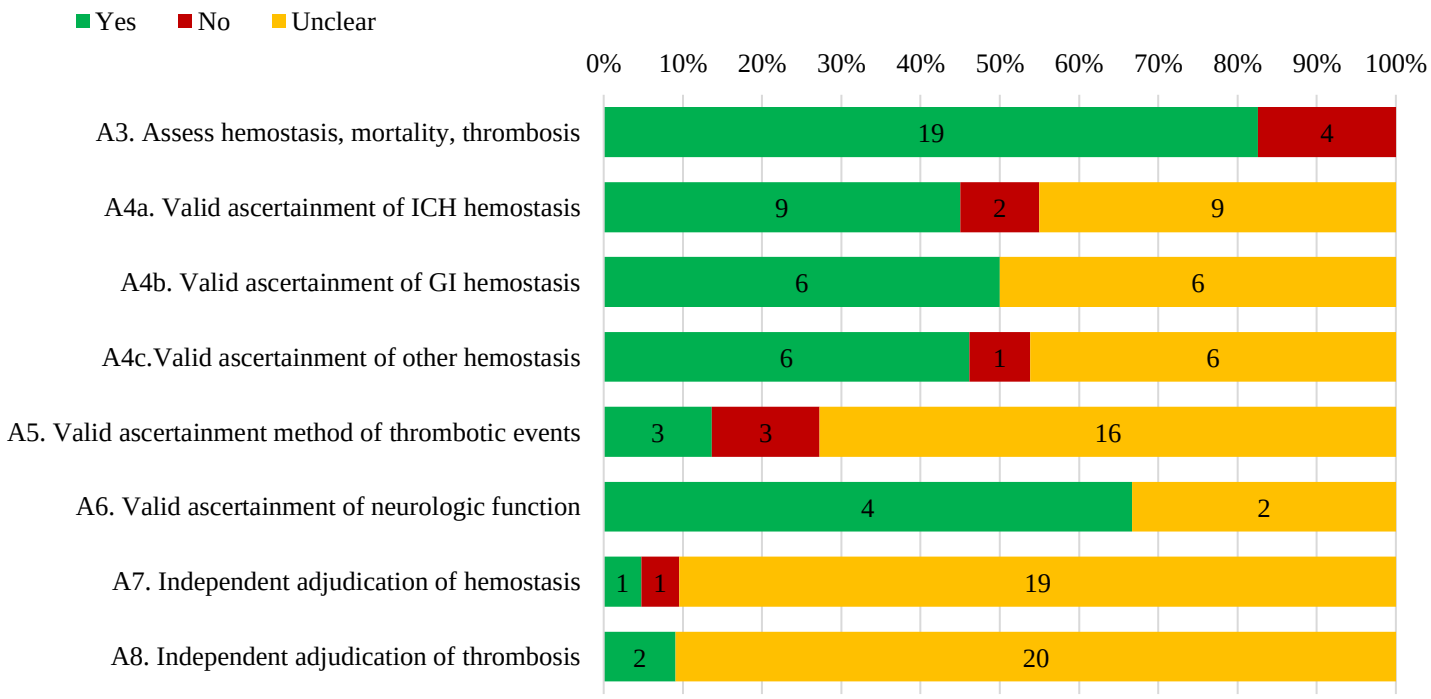
*Study pooled intracranial hemorrhage and intraspinal bleed



eFigure 1a. Percentage of full-text and abstract only case series that received a "yes", "no", or "unclear" for selection quality items

Number of studies with each assessment is labeled within bar

Refer to Appendix 2 for specific definitions used to assess quality



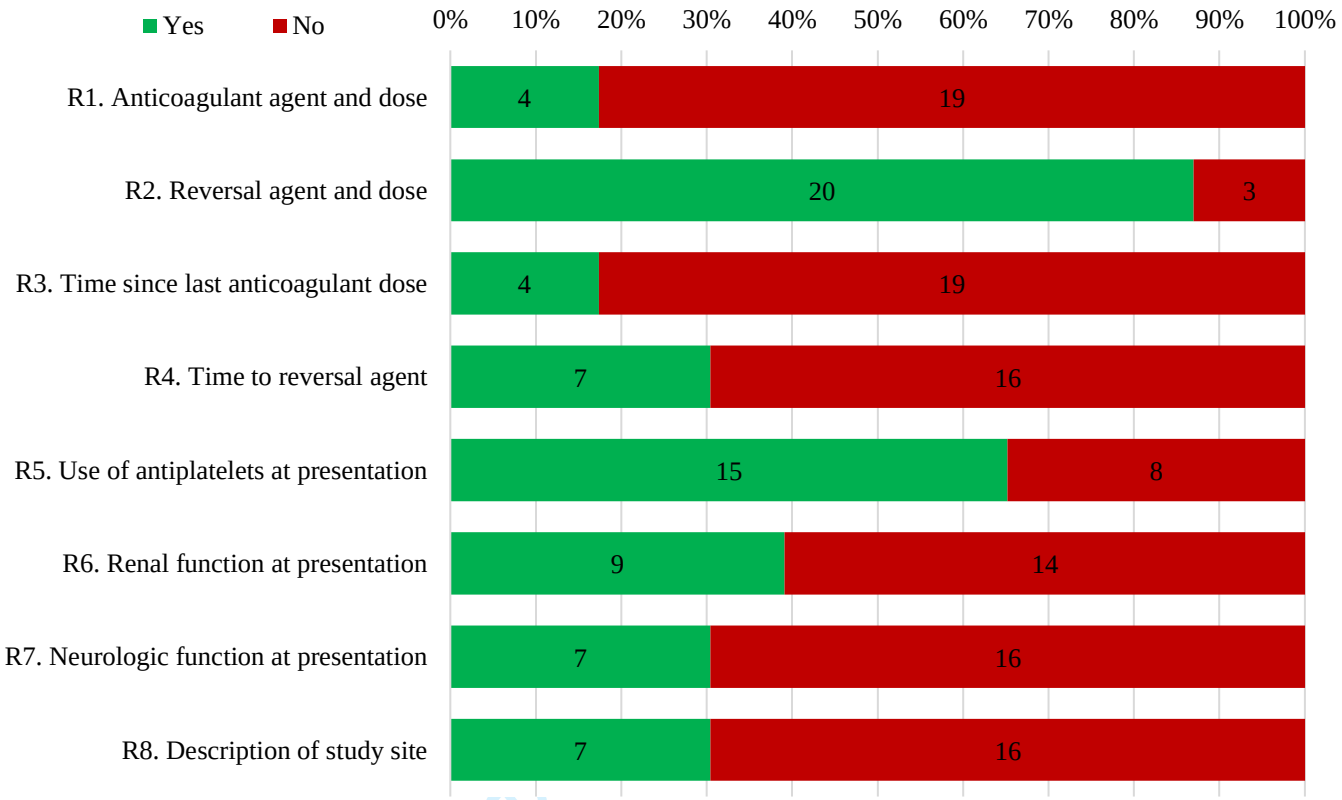
eFigure 1b. Percentage of full-text and abstract only case series that received a "yes", "no", or "unclear" for outcomes ascertainment items

Number of studies with each assessment is labeled within bar

GI: gastrointestinal, ICH: intracranial hemorrhage

Note that "not applicable" designations are not incorporated.

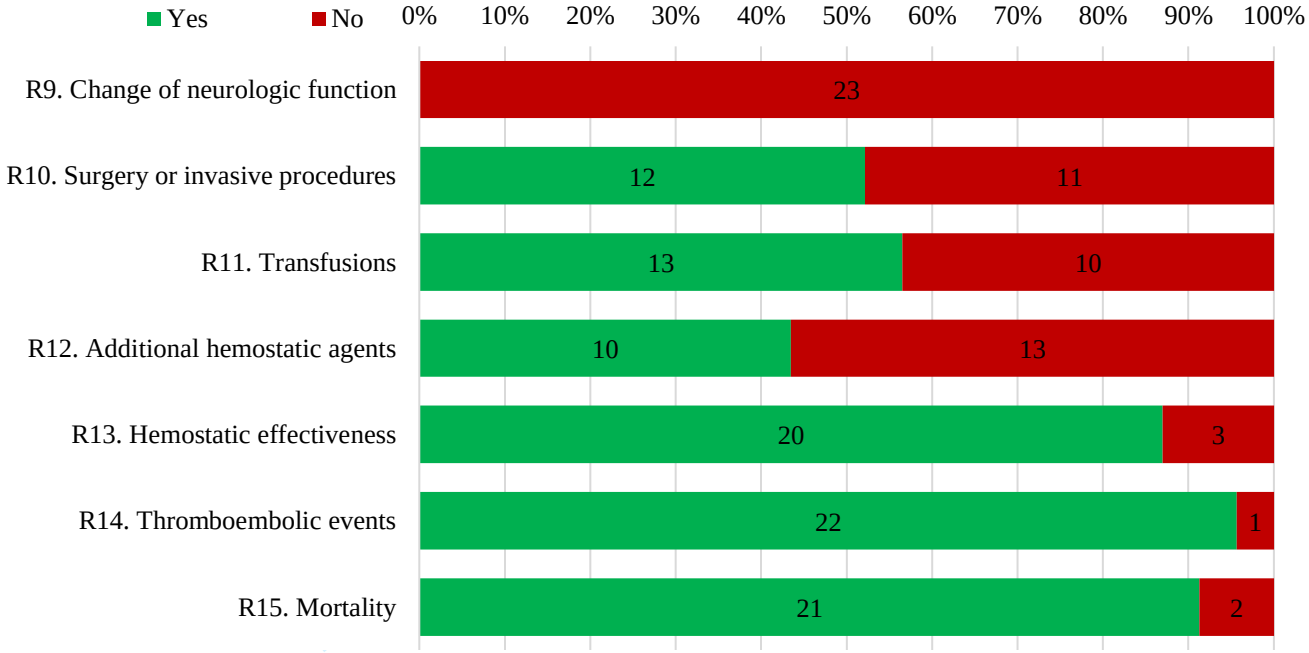
Refer to Appendix 2 for specific definitions used to assess quality



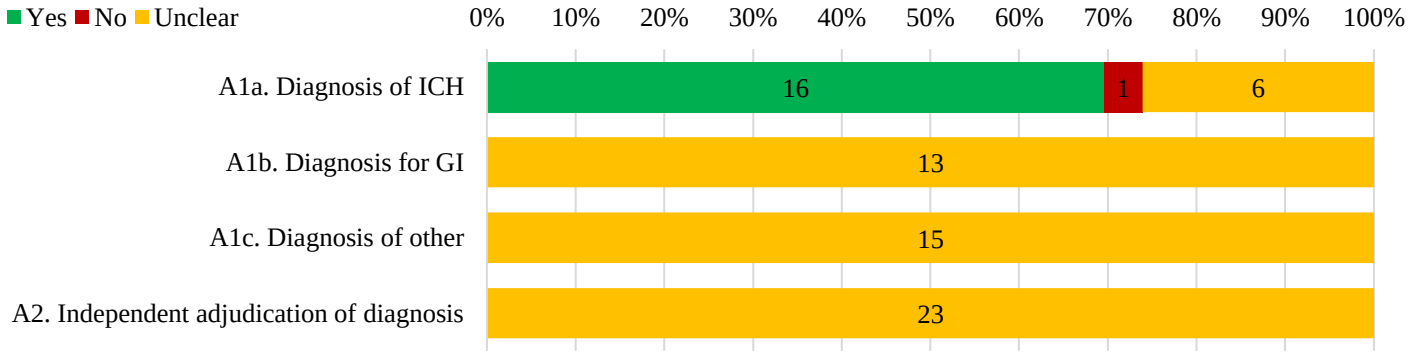
eFigure 1c. Percentage of full-text case series that received a "yes" or "no" for reporting of characteristics at presentation items

Number of studies with each assessment is labeled within bar

Refer to Appendix 2 for specific definitions used to assess quality

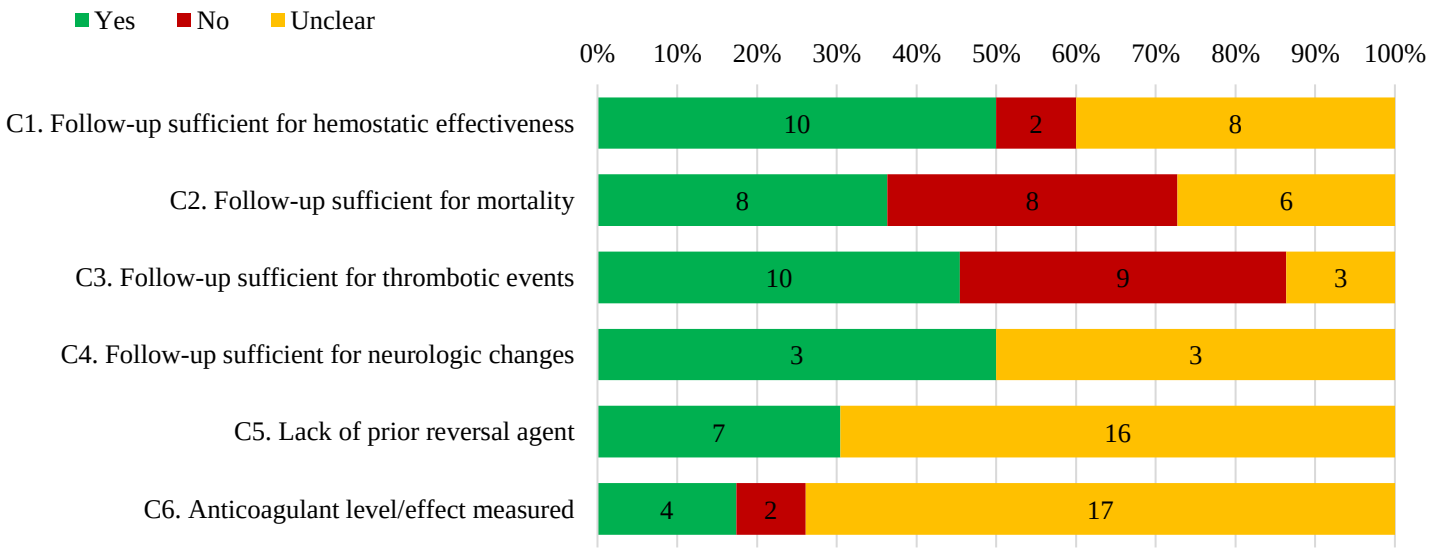


eFigure 1d. Percentage of full-text case series that received a "yes" or "no" for reporting of outcomes items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality



eFigure 1e. Percentage of full-text and abstract only case series that received a "yes", "no" or "unclear" for bleeding event ascertainment items

Number of studies with each assessment is labeled within bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Note that "not applicable" designations are not incorporated.
Refer to Appendix 2 for specific definitions used to assess quality

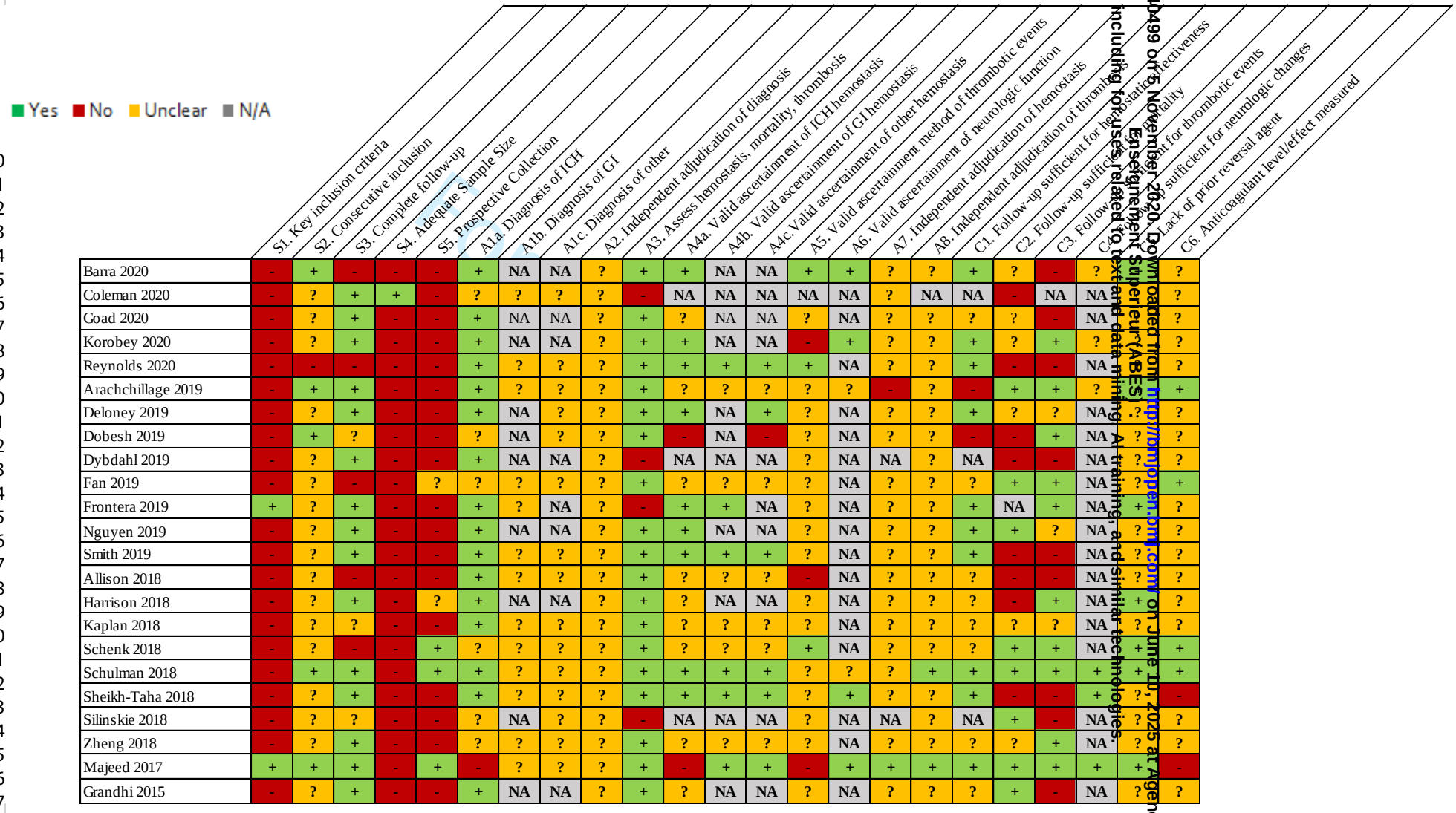


eFigure 1f. Percentage of full-text and abstract only case series that received a "yes", "no" or "unclear" for causal and temporal association items

Number of studies with each assessment is labeled within bar

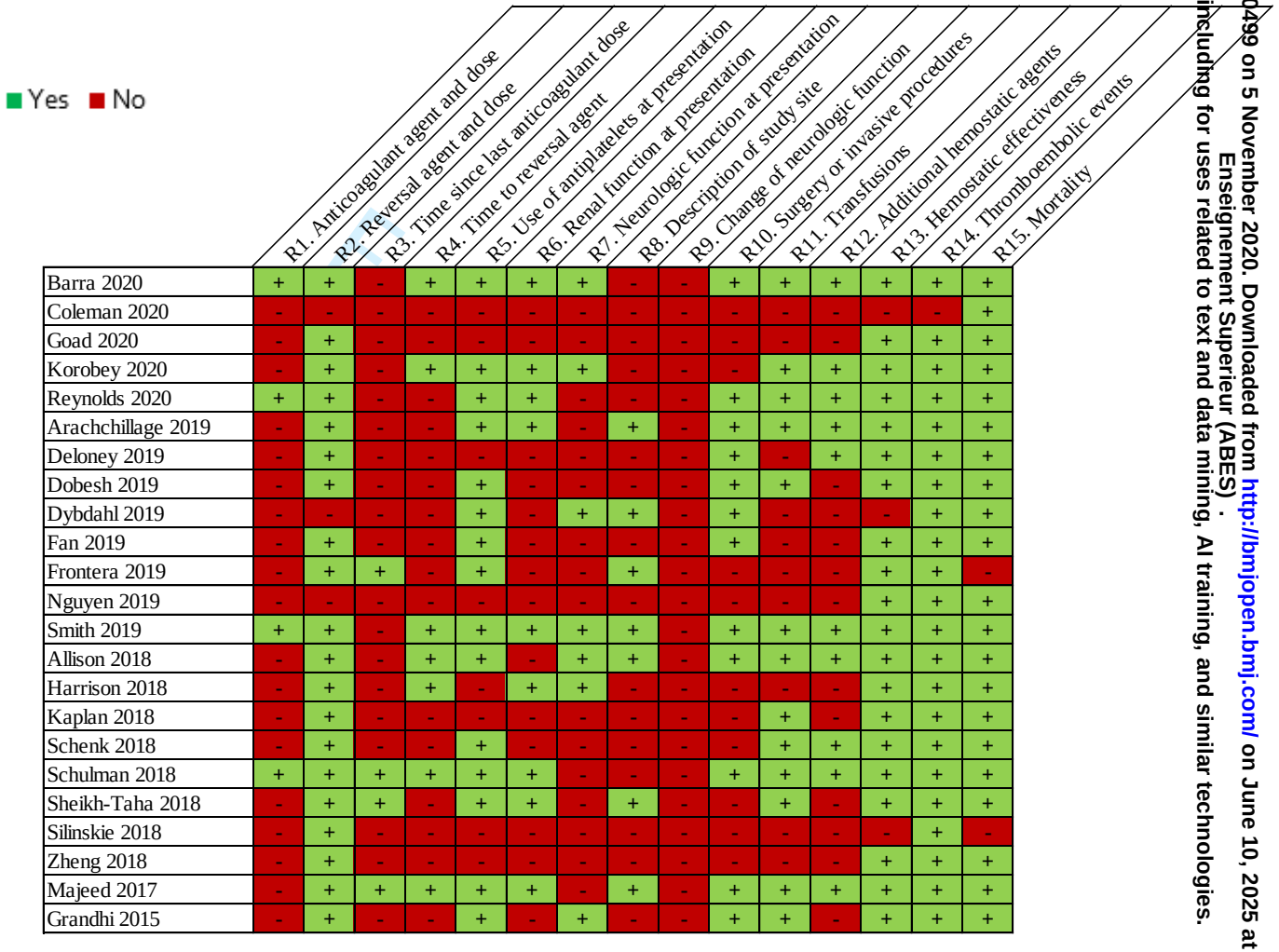
Note that a "not applicable" designation is not incorporated.

Refer to Appendix 2 for specific definitions used to assess quality



Barra 2020	-	+	-	-	-	+	NA	NA	?	+	+	NA	NA	+	+	?	?	+	?	-	?	NA	?
Coleman 2020	-	?	+	+	-	?	?	?	?	-	NA	NA	NA	NA	NA	?	NA	NA	-	NA	NA	NA	?
Goad 2020	-	?	+	-	-	+	NA	NA	?	+	?	NA	NA	?	NA	?	?	?	?	-	NA	NA	?
Korobey 2020	-	?	+	-	-	+	NA	NA	?	+	+	NA	NA	-	+	?	?	+	?	+	?	NA	?
Reynolds 2020	-	-	-	-	-	+	?	?	?	+	+	+	+	+	NA	?	?	+	-	-	NA	NA	?
Arachchillage 2019	-	+	+	-	-	+	?	?	?	+	?	?	?	?	?	-	?	-	+	+	?	NA	+
Deloney 2019	-	?	+	-	-	+	NA	?	?	+	+	NA	+	?	NA	?	?	+	?	?	NA	?	?
Dobesh 2019	-	+	?	-	-	?	NA	?	?	+	-	NA	-	?	NA	?	?	-	-	+	NA	?	?
Dybdahl 2019	-	?	+	-	-	+	NA	NA	?	-	NA	NA	NA	?	NA	NA	?	NA	-	-	NA	?	?
Fan 2019	-	?	-	-	?	?	?	?	?	+	?	?	?	?	NA	?	?	?	+	+	NA	?	+
Frontera 2019	+	?	+	-	-	+	?	NA	?	-	+	+	NA	?	NA	?	?	+	NA	+	NA	+	?
Nguyen 2019	-	?	+	-	-	+	NA	NA	?	+	+	NA	NA	?	NA	?	?	+	+	?	NA	?	?
Smith 2019	-	?	+	-	-	+	?	?	?	+	+	+	+	?	NA	?	?	+	-	-	NA	?	?
Allison 2018	-	?	-	-	-	+	?	?	?	+	?	?	?	-	NA	?	?	?	-	-	NA	?	?
Harrison 2018	-	?	+	-	?	+	NA	NA	?	+	?	NA	NA	?	NA	?	?	?	-	+	NA	+	?
Kaplan 2018	-	?	?	-	-	+	?	?	?	+	?	?	?	?	NA	?	?	?	?	?	NA	?	?
Schenk 2018	-	?	-	-	+	?	?	?	?	+	?	?	?	+	NA	?	?	?	+	+	NA	+	+
Schulman 2018	-	+	+	-	+	+	?	?	?	+	+	+	+	?	?	?	+	+	+	+	+	+	+
Sheikh-Taha 2018	-	?	+	-	-	+	?	?	?	+	+	+	+	?	+	?	?	+	-	-	+	?	-
Silinskie 2018	-	?	?	-	-	?	NA	?	?	-	NA	NA	NA	?	NA	NA	?	NA	+	-	NA	?	?
Zheng 2018	-	?	+	-	-	?	?	?	?	+	?	?	?	?	NA	?	?	?	?	+	NA	?	?
Majeed 2017	+	+	+	-	+	-	?	?	?	+	-	+	+	-	+	+	+	+	+	+	+	+	-
Grandhi 2015	-	?	+	-	-	+	NA	NA	?	+	?	NA	NA	?	NA	?	?	?	+	-	NA	?	?

eFigure 2a. Individual full-text and abstract only case series assessment of selection, ascertainment, causal and temporal association items
GI: gastrointestinal, ICH: intracranial hemorrhage, 4F-PCC: 4-factor prothrombin complex concentrate
Refer to Appendix 2 for specific definitions used to assess quality



Barra 2020	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+
Coleman 2020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Goad 2020	-	+	-	-	-	-	-	-	-	-	-	-	+	+	+
Korobey 2020	-	+	-	+	+	+	+	-	-	-	+	+	+	+	+
Reynolds 2020	+	+	-	-	+	+	-	-	-	+	+	+	+	+	+
Arachchillage 2019	-	+	-	-	+	+	-	+	-	+	+	+	+	+	+
Deloney 2019	-	+	-	-	-	-	-	-	-	+	-	+	+	+	+
Dobesh 2019	-	+	-	-	+	-	-	-	-	+	+	-	+	+	+
Dybdahl 2019	-	-	-	-	+	-	+	+	-	+	-	-	-	+	+
Fan 2019	-	+	-	-	+	-	-	-	-	+	-	-	+	+	+
Frontera 2019	-	+	+	-	+	-	-	+	-	-	-	-	+	+	-
Nguyen 2019	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+
Smith 2019	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+
Allison 2018	-	+	-	+	+	-	+	+	-	+	+	+	+	+	+
Harrison 2018	-	+	-	+	-	+	+	-	-	-	-	-	+	+	+
Kaplan 2018	-	+	-	-	-	-	-	-	-	-	+	-	+	+	+
Schenk 2018	-	+	-	-	+	-	-	-	-	-	+	+	+	+	+
Schulman 2018	+	+	+	+	+	+	-	-	-	+	+	+	+	+	+
Sheikh-Taha 2018	-	+	+	-	+	+	-	+	-	-	+	-	+	+	+
Silinskie 2018	-	+	-	-	-	-	-	-	-	-	-	-	-	+	-
Zheng 2018	-	+	-	-	-	-	-	-	-	-	-	-	+	+	+
Majeed 2017	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+
Grandhi 2015	-	+	-	-	+	-	+	-	-	+	+	-	+	+	+

eFigure 2b. Individual full-text and abstract only case series assessment for reporting items
Refer to Appendix 2 for specific definitions used to assess quality

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.