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

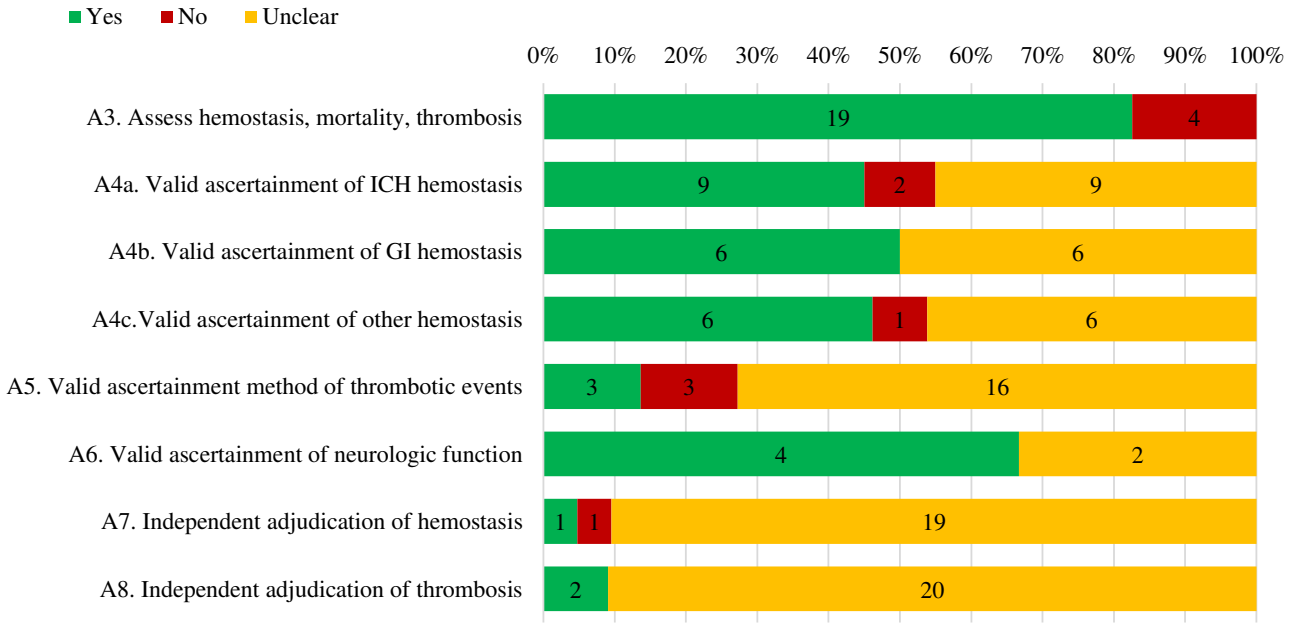
eTable 2. Full-text and abstract only case series, number of patients, anticoagulant, and indication for anticoagulation

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)	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)

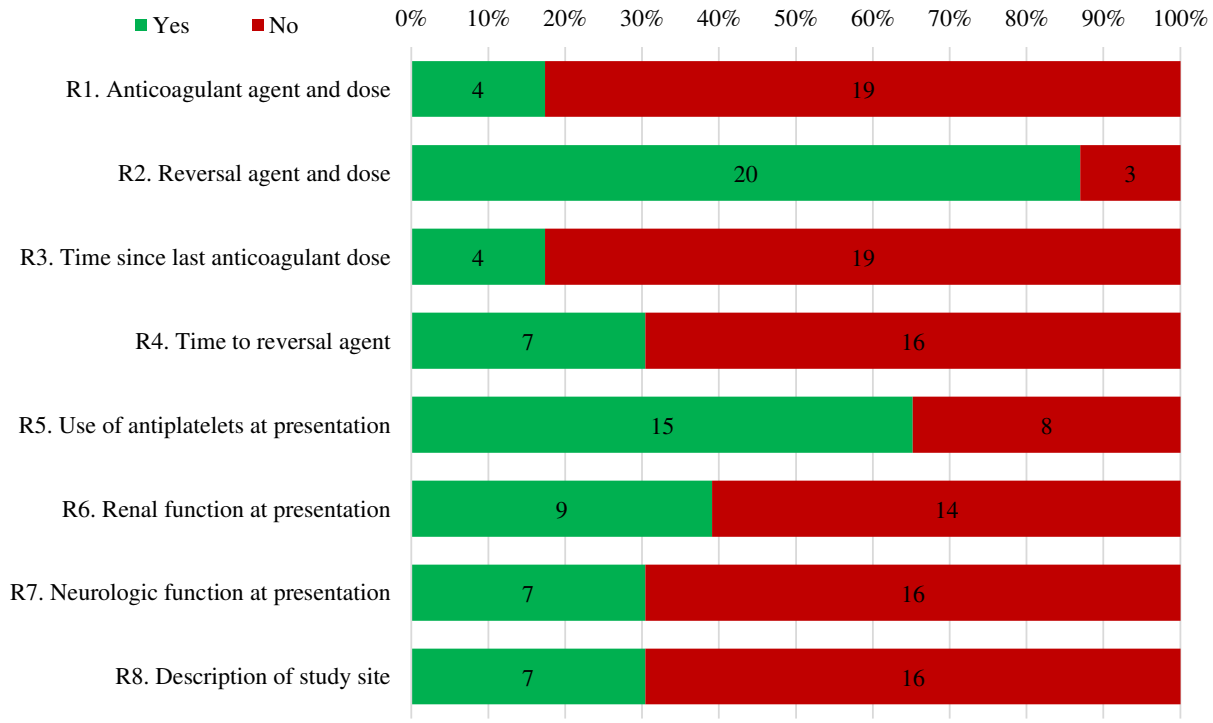
A: apixaban; AF: atrial fibrillation, DVT: deep vein thromboembolism, Ed: edoxaban, GI: gastrointestinal, ICH: intracranial hemorrhage, NR: not recorded, PE: pulmonary embolism, R: rivaroxaban

*Study pooled intracranial hemorrhage and intraspinal bleed

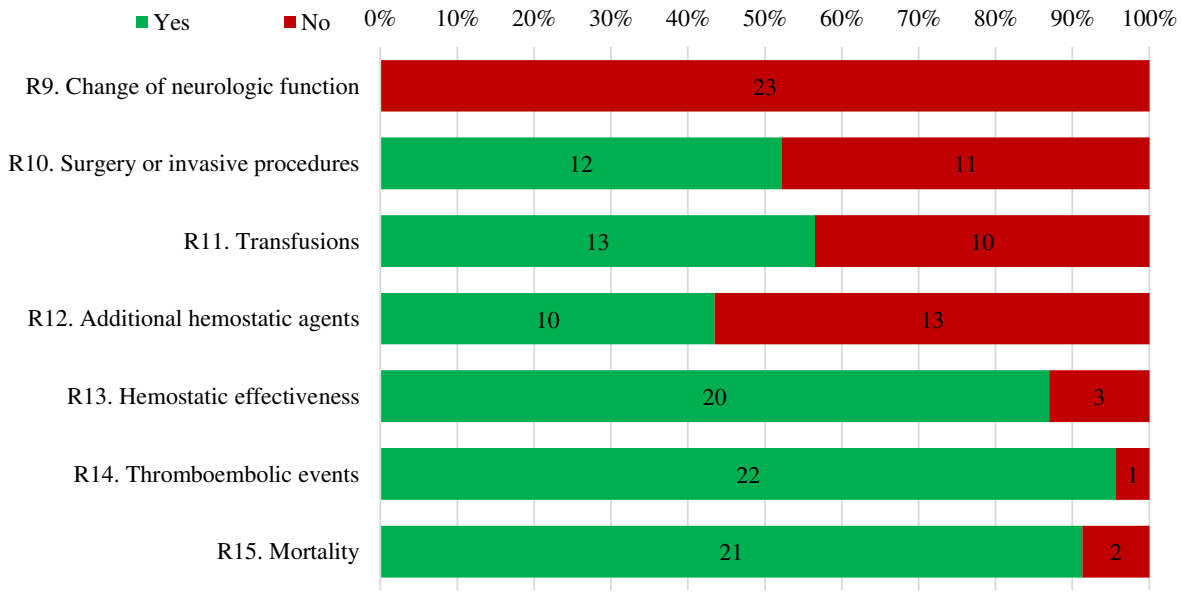
eFigure 1a. Percentage of full-text and abstract only case series that received a "yes", "no", or "unclear" for selection quality items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality



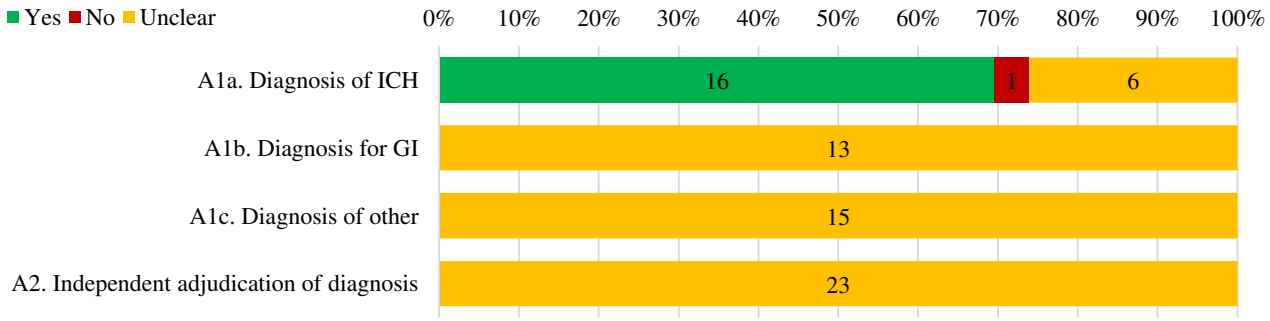
eFigure 1b. Percentage of full-text and abstract only case series that received a "yes", "no", or "unclear" for outcomes ascertainment items
Number of studies with each assessment is labeled within bar
GI: gastrointestinal, ICH: intracranial hemorrhage
Note that "not applicable" designations are not incorporated.
Refer to Appendix 2 for specific definitions used to assess quality



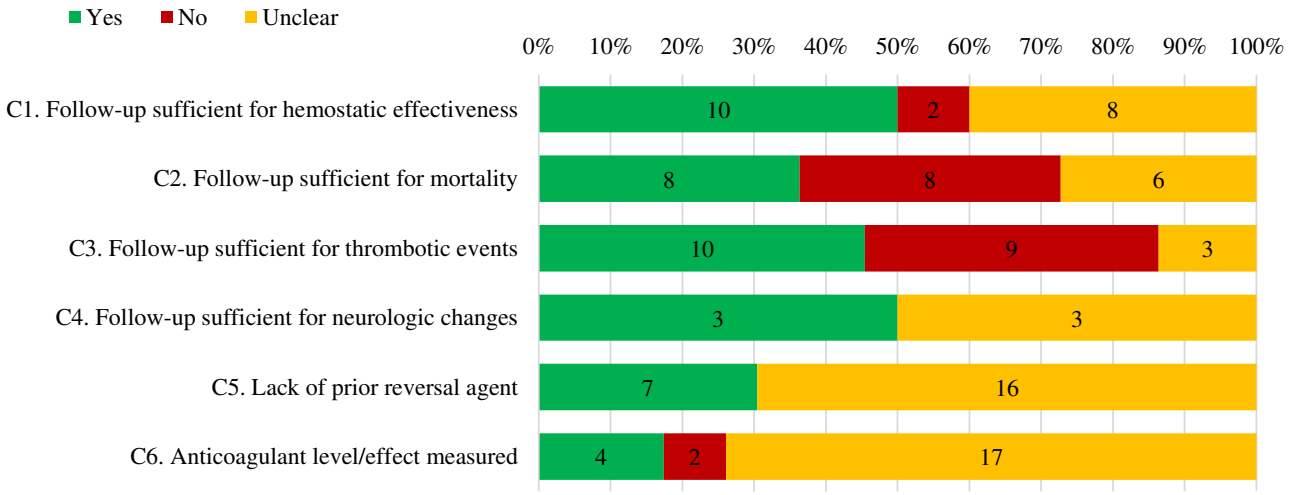
eFigure 1c. Percentage of full-text case series that received a "yes" or "no" for reporting of characteristics at presentation items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality



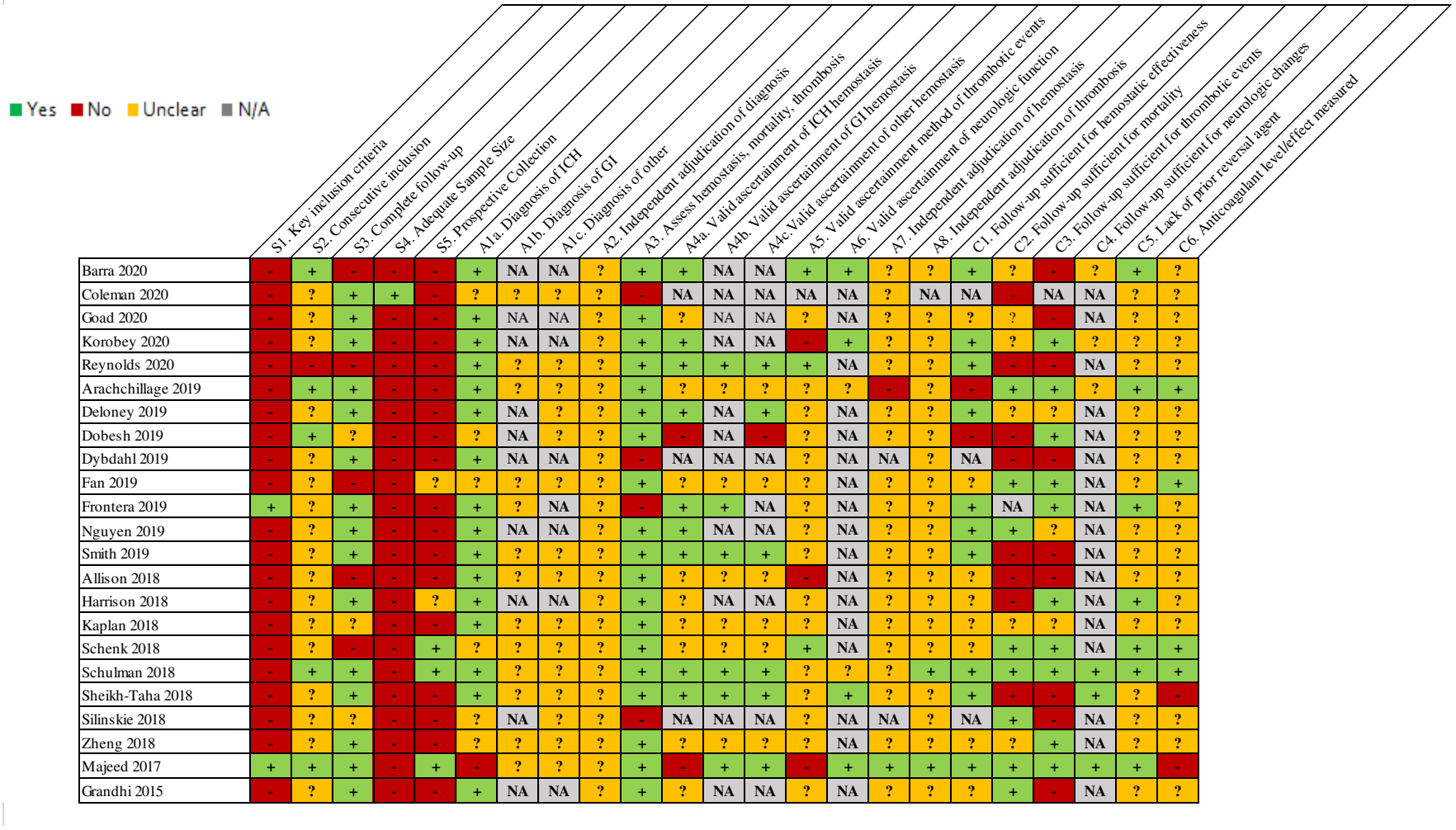
eFigure 1d. Percentage of full-text case series that received a "yes" or "no" for reporting of outcomes items
Number of studies with each assessment is labeled within bar
Refer to Appendix 2 for specific definitions used to assess quality



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

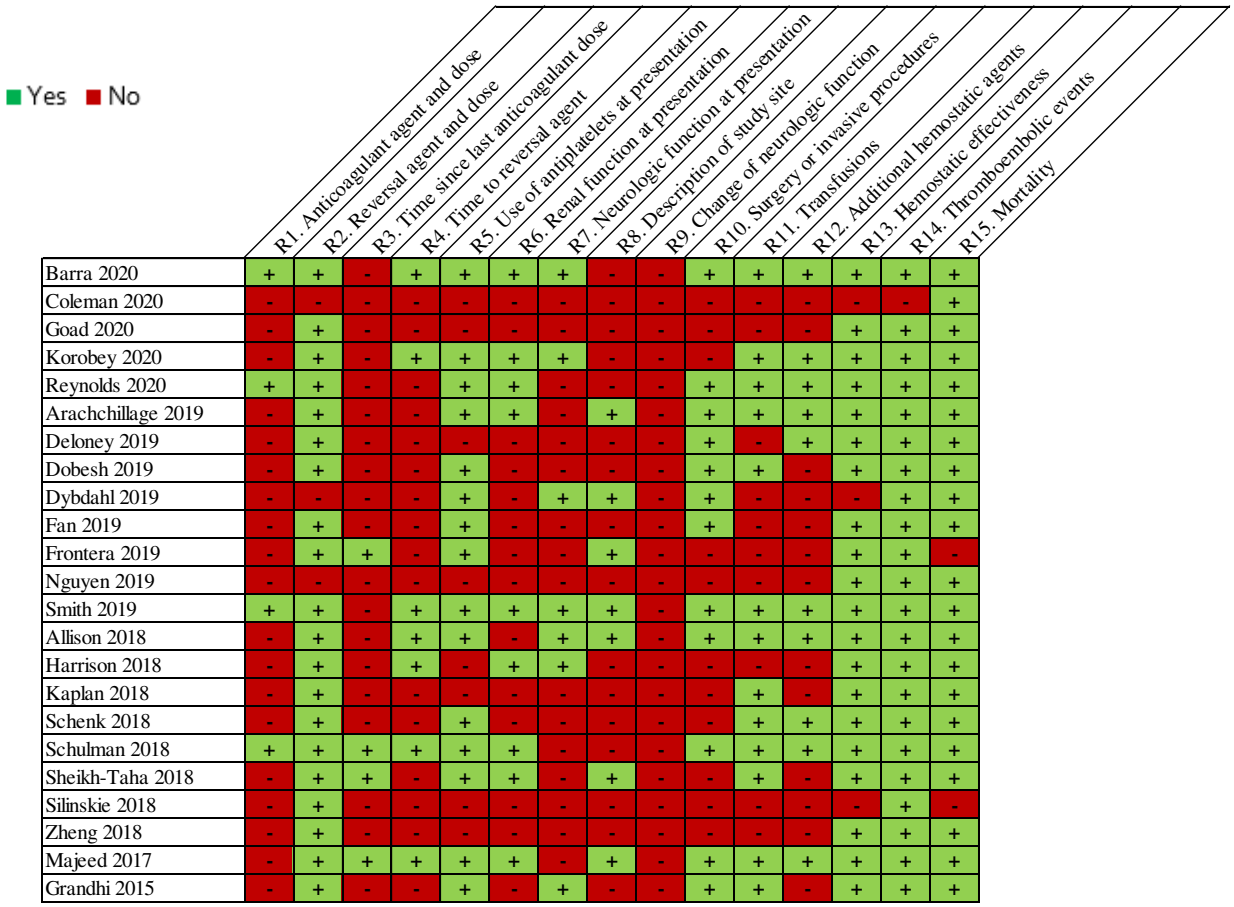


eFigure 1f. Percentage of full-text and abstract only case series that received a "yes", "no" or "unclear" for causal and temporal association items
Number of studies with each assessment is labeled within bar
Note that a "not applicable" designation is not incorporated.
Refer to Appendix 2 for specific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



	S1	S2	S3	S4	S5	A1a	A1b	A1c	A2	A3	A4a	A4b	A4c	A5	A6	A7	A8	C1	C2	C3	C4	C5	C6
Barra 2020	-	+	-	-	-	+	NA	NA	?	+	+	NA	NA	+	+	?	?	+	?	-	?	+	?
Coleman 2020	-	?	+	+	-	?	?	?	?	-	NA	NA	NA	NA	NA	?	NA	NA	-	NA	NA	?	?
Goad 2020	-	?	+	-	-	+	NA	NA	?	+	?	NA	NA	?	NA	?	?	?	?	-	NA	?	?
Korobey 2020	-	?	+	-	-	+	NA	NA	?	+	+	NA	NA	-	+	?	?	+	?	+	?	?	?
Reynolds 2020	-	-	-	-	-	+	?	?	?	+	+	+	+	+	NA	?	?	+	-	-	NA	?	?
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