# Supplemental Online Content

Chaudhary R, Singh A, Chaudhary R, et al. Evaluation of direct oral anticoagulant reversal agents in intracranial hemorrhage: a systematic review and meta-analysis. *JAMA Netw Open.* 2022;5(11):e2240145. doi:10.1001/jamanetworkopen.2022.40145



This supplemental material has been provided by the authors to give readers additional information about their work.

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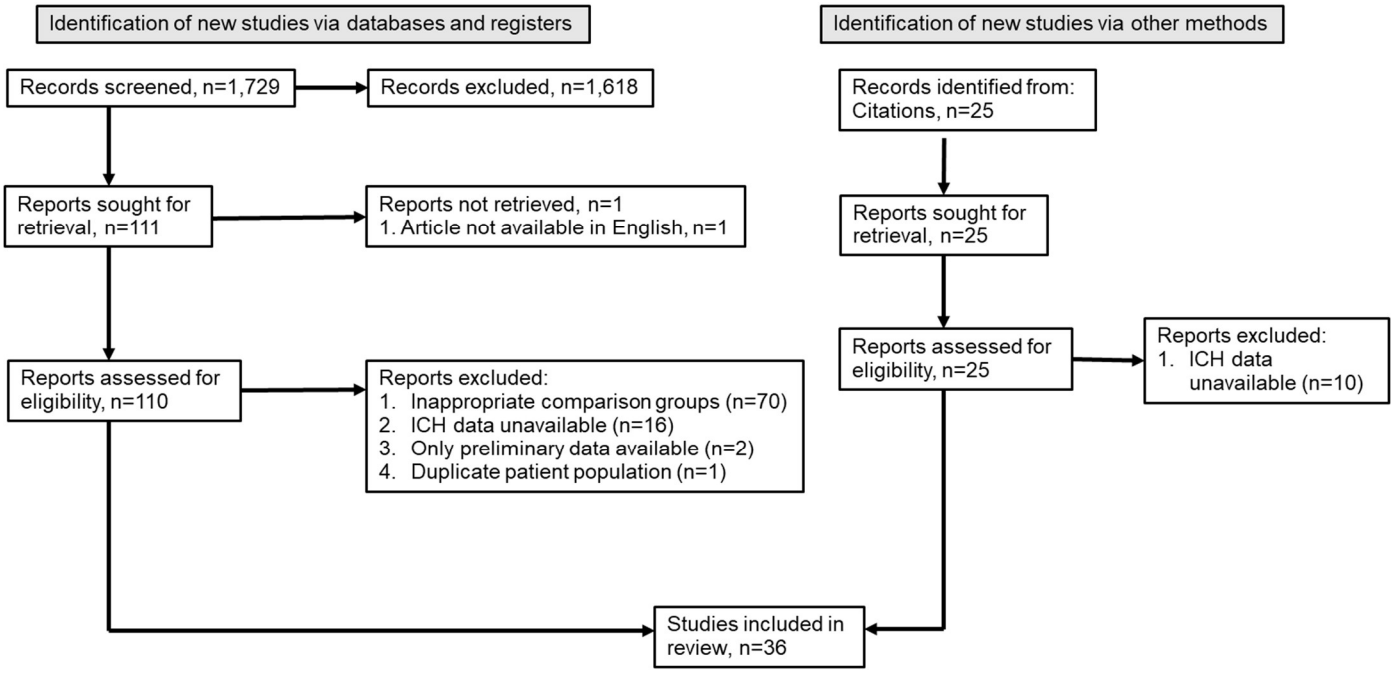
## eAppendix 1. Process of Study Selection for Clinical Trials

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**eAppendix 2. Search Strategy**

("DOAC"[All Fields] OR (("direct"[All Fields] OR "directed"[All Fields] OR "directing"[All Fields] OR "direction"[All Fields] OR "directional"[All Fields] OR "directions"[All Fields] OR "directivities"[All Fields] OR "directivity"[All Fields] OR "directs"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields])) OR ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields]) OR ("apixaban"[Supplementary Concept] OR "apixaban"[All Fields] OR "apixaban s"[All Fields]) OR ("betrixaban"[Supplementary Concept] OR "betrixaban"[All Fields]) OR ("dabigatran"[MeSH Terms] OR "dabigatran"[All Fields] OR "dabigatran s"[All Fields]) OR (("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields])) OR ("n 4 oleylcytosine arabinoside"[Supplementary Concept] OR "n 4 oleylcytosine arabinoside"[All Fields] OR "noac"[All Fields]) OR ("edoxaban"[Supplementary Concept] OR "edoxaban"[All Fields])) AND ((("DOAC"[All Fields] OR (("direct"[All Fields] OR "directed"[All Fields] OR "directing"[All Fields] OR "direction"[All Fields] OR "directional"[All Fields] OR

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"directions"[All Fields] OR "directivities"[All Fields] OR "directivity"[All Fields] OR "directs"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields])) OR ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields]) OR ("apixaban"[Supplementary Concept] OR "apixaban"[All Fields] OR "apixaban s"[All Fields]) OR ("betrixaban"[Supplementary Concept] OR "betrixaban"[All Fields]) OR ("dabigatran"[MeSH Terms] OR "dabigatran"[All Fields] OR "dabigatran s"[All Fields]) OR (("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields])) OR ("n 4 oleylcytosine arabinoside"[Supplementary Concept] OR "n 4 oleylcytosine arabinoside"[All Fields] OR "noac"[All Fields]) OR ("edoxaban"[Supplementary Concept] OR "edoxaban"[All Fields])) AND ("reversal"[All Fields] OR "reversals"[All Fields] OR "reverse"[All Fields] OR "reversed"[All Fields] OR "reversely"[All Fields] OR "reverses"[All Fields] OR "reversibilities"[All Fields] OR "reversibility"[All Fields] OR "reversible"[All Fields] OR "reversing"[All Fields] OR "reversion"[All Fields] OR "reversions"[All Fields])) OR ("prt064445"[Supplementary Concept] OR "prt064445"[All Fields] OR "andexanet alfa"[All

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Fields]) OR ("idarucizumab"[Supplementary Concept] OR "idarucizumab"[All Fields]) OR ("factor ix"[MeSH Terms] OR ("factor"[All Fields] AND "ix"[All Fields]) OR "factor ix"[All Fields] OR ("prothrombin"[All Fields] AND "complex"[All Fields] AND "concentrate"[All Fields]) OR "prothrombin complex concentrate"[All Fields]))

*Translations*

1. direct: "direct"[All Fields] OR "directed"[All Fields] OR "directing"[All Fields] OR "direction"[All Fields] OR "directional"[All Fields] OR "directions"[All Fields] OR "directivities"[All Fields] OR "directivity"[All Fields] OR "directs"[All Fields]
2. oral: "mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]
3. anticoagulants: "anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields]
4. rivaroxaban: "rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields] OR "rivaroxaban's"[All Fields]
1. apixaban: "apixaban"[Supplementary Concept] OR "apixaban"[All Fields] OR "apixaban's"[All Fields]
2. betrixaban: "betrixaban"[Supplementary Concept] OR "betrixaban"[All Fields]
3. dabigatran: "dabigatran"[MeSH Terms] OR "dabigatran"[All Fields] OR "dabigatran's"[All Fields]

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4. novel: "novel"[All Fields] OR "novel's"[All Fields] OR "novels"[All Fields]

5. oral: "mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]

1. anticoagulant: "anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields]

2. reversal: "reversal"[All Fields] OR "reversals"[All Fields] OR "reverse"[All Fields] OR "reversed"[All Fields] OR "reversely"[All Fields] OR "reverses"[All Fields] OR "reversibilities"[All Fields] OR "reversibility"[All Fields] OR "reversible"[All Fields] OR "reversing"[All Fields] OR "reversion"[All Fields] OR "reversions"[All Fields]

3. andexanet alfa: "PRT064445"[Supplementary Concept] OR "PRT064445"[All Fields] OR "andexanet alfa"[All Fields]

4. idarucizumab: "idarucizumab"[Supplementary Concept] OR "idarucizumab"[All Fields]

5. Prothrombin complex concentrate: "factor ix"[MeSH Terms] OR ("factor"[All Fields] AND "ix"[All Fields]) OR "factor ix"[All Fields] OR ("prothrombin"[All Fields] AND "complex"[All Fields] AND "concentrate"[All Fields]) OR "prothrombin complex concentrate"[All Fields]

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## eAppendix 3. Baseline Characteristics of Included Studies

| Name of Study | Study design | Total patients | Age (Mean) | Men (%) | Indication for Anticoagulation | | |
|---|---|---|---|---|---|---|---|
| | | | | | Atrial Fibrillation (%) | Venous Thromboembolism (%) | Others (%) |
| **Andexanet Alfa** | | | | | | | |
| Connolly et al,13 2019 | Prospective | 171 | - | - | - | - | - |
| Stevens et al,46 2019 | Retrospective | 6 | 69 | - | - | - | - |
| Culbreth et al,49 2019 | Prospective | 14 | 82 | - | 71% | - | - |
| Brown et al,47 2020 | Retrospective | 13 | 75 | 46.2% | 46.2% | 53.8% | 0% |
| Barra et al,35 2020 | Retrospective | 18 | 83 | 55.6% | 94.4% | 11.1% | 0% |
| Coleman et al,36 2020 | Retrospective | 67 | - | - | - | - | - |
| Giovino et al,48 2020 | Retrospective | 39 | 81 | 61.5% | 94.9% | 18% | 2.6% |
| Ammar et al,37 2021 | Retrospective | 28 | 78 | 61% | 75% | 21% | 4% |
| Stevens et al,39 2021 | Retrospective | 32 | 69 | 25% | 34% | 16% | 50% |
| Demchuk et al,50 2021 | Sub-analysis of ANNEXA-4 | 227 | 79 | 52% | 85% | 13% | 2% |
| Sobolewski et al,51 2021 | Retrospective | 7 | 75 | 86% | - | - | - |
| Pham et al,40 2021 | Retrospective | 47 | 77 | 66% | 83% | 13% | 4% |
| Parsels et al,41 2022 | Retrospective | 26 | 83 | 39% | 77% | 23% | 0% |
| Milioglou et al,42 2022 | Retrospective | 23 | 76 | 57% | 87% | 13% | 0% |
| Benz et al,52 2022 | Prospective | 36 | - | - | - | - | - |
| Vestal et al,44 2022 | Retrospective | 21 | 73 | 71% | 67% | 33% | 0% |
| **Idarucizumab** | | | | | | | |
| Pollack et al,12 2017 | Prospective | 98 | - | - | - | - | - |
| Sheikh-Taha et al,52 2019 | Retrospective | 6 | 80 | 83.3% | 100% | 0% | 0% |
| Singh et al,54 2020 | Retrospective | 112 | 76 | 57.1% | - | - | - |
| Kermer et al,55 2020 | Retrospective | 40 | 77 | 70% | 100% | 0% | 0% |
| Yasaka et al,56 2020 | Retrospective | 84 | - | - | - | - | - |
| **4F-PCC** | | | | | | | |
| Grandhi et al,24 2015 | Retrospective | 18 | 79.7 | 55.6% | 88.9% | 5.6% | 1.7% |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Majeed et al,25 2017 | Prospective | 59 | 75 | - | - | - | - |
| Gerner et al,8 2018 | Retrospective | 146 | 77.4 | 52.7% | - | - | - |
| Schulman et al,26 2018 | Prospective | 36 | 76.9 | - | - | - | - |
| Tao et al,27 2018 | Retrospective | 16 | 74 | - | - | - | - |
| Sheikh-Taha et al,28 2018 | Retrospective | 21 | 73.8 | - | - | - | - |
| Smith et al,29 2019 | Retrospective | 18 | 74 | - | - | - | - |
| Berger et al,30 2020 | Retrospective | 22 | 79.5 | 50% | 77.2% | 27.3% | 18.2% |
| Zheng et al,31 2020 | Retrospective | 13 | 68.3 | - | - | - | - |
| Korobey et al,32 2020 | Retrospective | 59 | 78.5 | 60% | 83.1% | 27.1% | 0% |
| Castillo et al,33 2020 | Retrospective | 67 | 77.3 | 56.7% | 77.6% | 10.5% | 9% |
| Lipari et al,34 2020 | Retrospective | 85 | 77 | - | - | - | - |
| Barra et al,35 2020 | Retrospective | 11 | 71 | 81.8% | 72.7% | 27.3% | 0% |
| Coleman et al,36 2020 | Retrospective | 170 | 70.1 | - | - | - | - |
| Ammar et al,37 2021 | Retrospective | 16 | 80 | 69% | 81% | 19% | 0% |
| Smythe et al,38 2021 | Retrospective | 29 | - | - | - | - | |
| Stevens et al,39 2021 | Retrospective | 32 | - | 34.4% | 43.8% | 6.3% | 50% |
| Pasciolla et al,45 2021 | Retrospective | 44 | 78 | 64% | 71% | 25% | |
| Pham et al,40 2021 | Retrospective | 62 | 81 | 51.6% | 77.4% | 16.1% | 6.5% |
| Parsels et al,41 2022 | Retrospective | 26 | 77 | 57.7% | 76.9% | 23.1% | 0% |
| Milioglou et al,42 2022 | Retrospective | 22 | 77 | 63.6% | 90.9% | 9.1% | 0% |
| Dev et al,43 2022 | Retrospective | 20 | - | - | - | - | - |
| Vestal et al,44 2022 | Retrospective | 35 | 74.5 | 40% | 71.4% | 25.7% | 2.9% |

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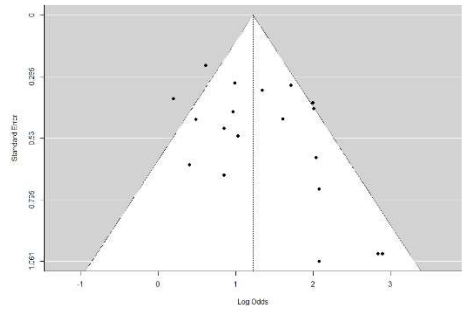
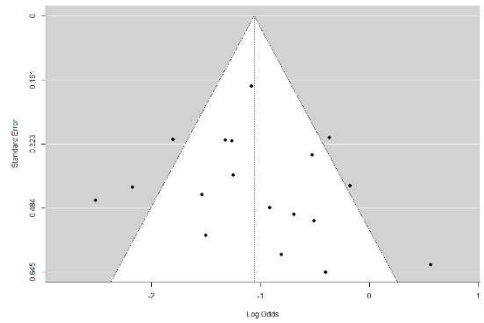
**eAppendix 4.** Funnel Plots for Primary Outcome of Anticoagulation Reversal and Primary Safety Outcomes for 4F-PCC, Andexanet Alfa (AA), and Idarucizumab

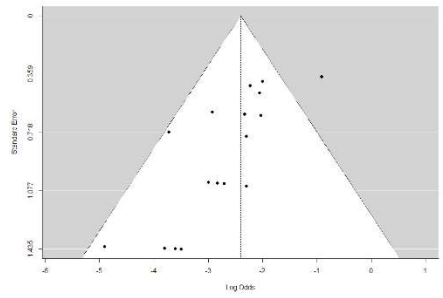
1a. 4-FPCC anticoagulation reversal




1b. 4-FPCC all-cause mortality




1c. 4F-PCC thromboembolic events




2a. AA anticoagulation reversal

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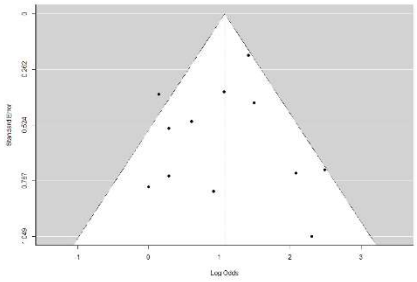
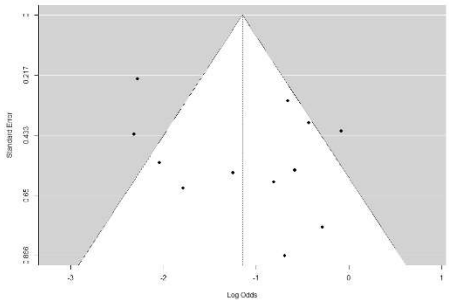
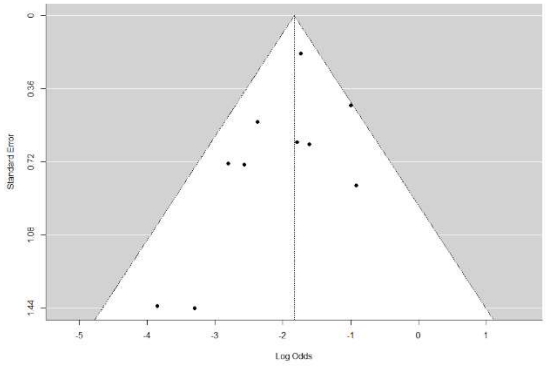



2b. AA all-cause mortality




2c. AA thromboembolic events




3a. Idarucizumab anticoagulation reversal

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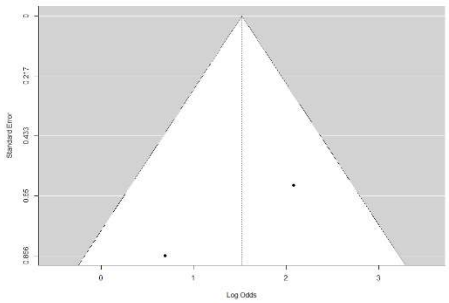
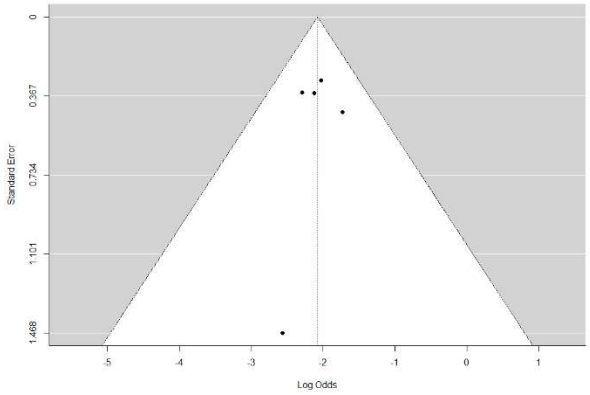
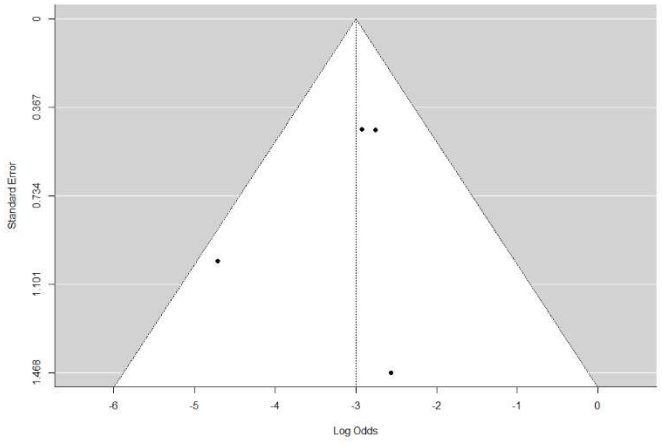



3b. Idarucizumab all-cause mortality




3c. Idarucizumab thromboembolic events




4a. 4F-PCC vs. andexanet alfa anticoagulation reversal

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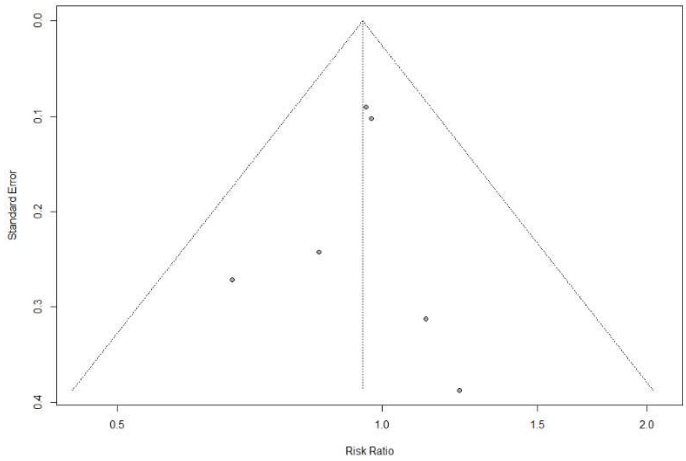
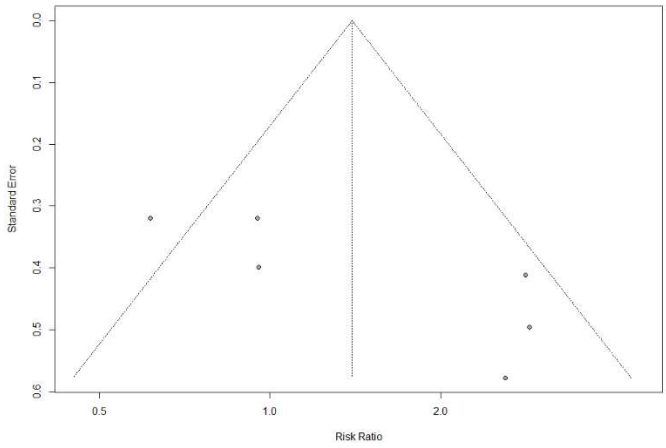
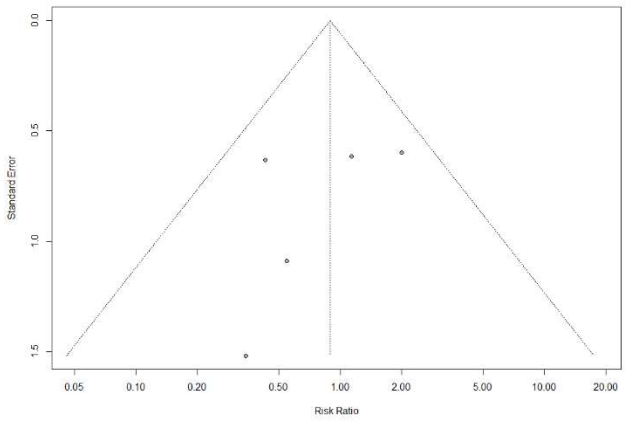



4b. 4F-PCC vs. andexanet alfa all-cause mortality




4c. 4F-PCC vs. andexanet alfa thromboembolic outcomes

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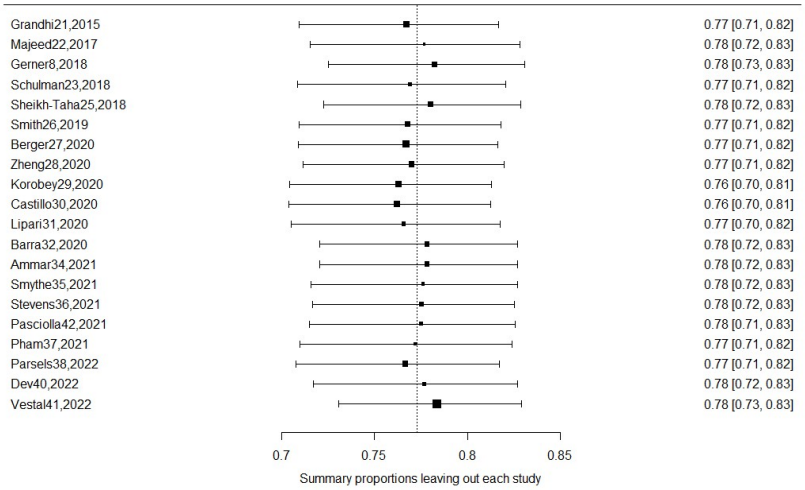
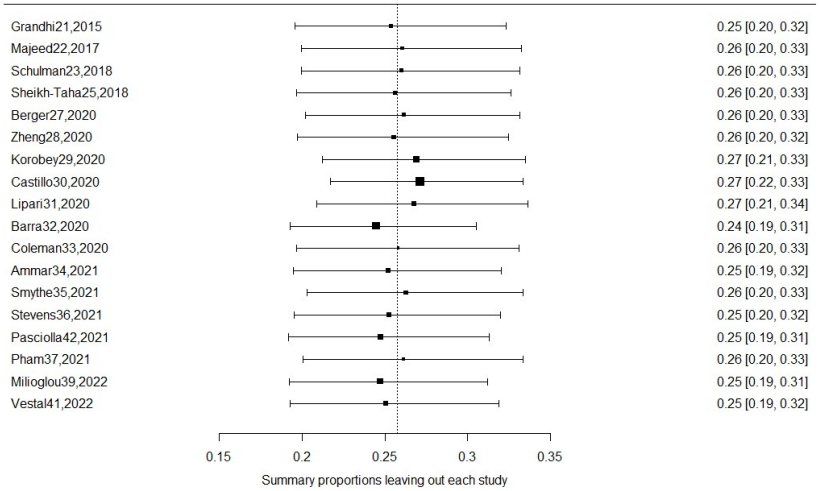
**eAppendix 5. Sensitivity Analysis for Primary Outcome of Anticoagulation Reversal and Primary Safety Outcomes for 4F-PCC, Andexanet Alfa (AA), and Idarucizumab**

1a. 4-FPCC anticoagulation reversal




1b. 4-FPCC all-cause mortality




1c. 4F-PCC thromboembolic events

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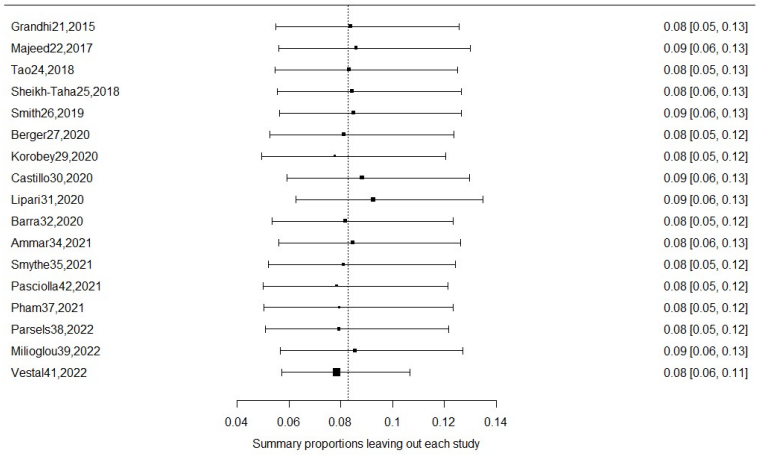
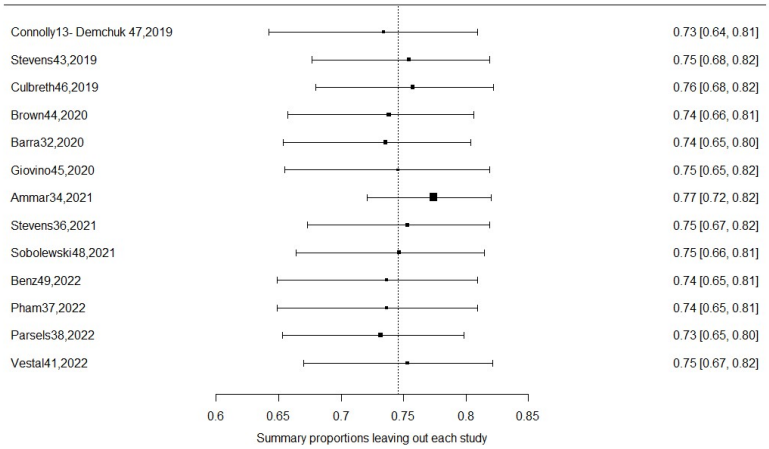
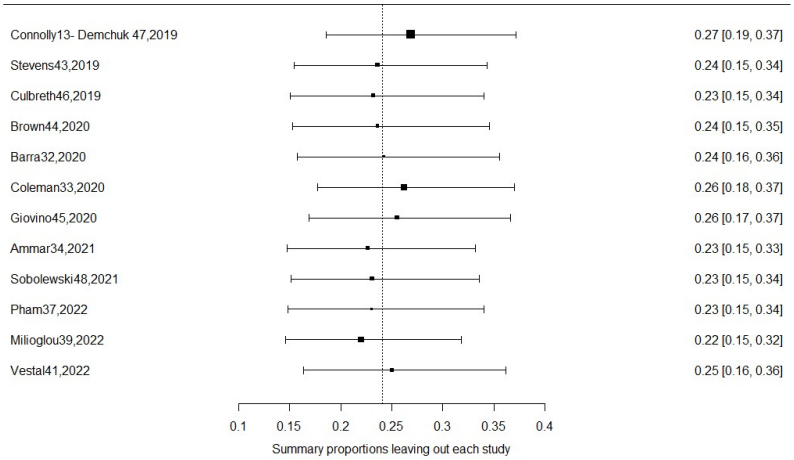



2a. AA anticoagulation reversal




2b. AA all-cause mortality

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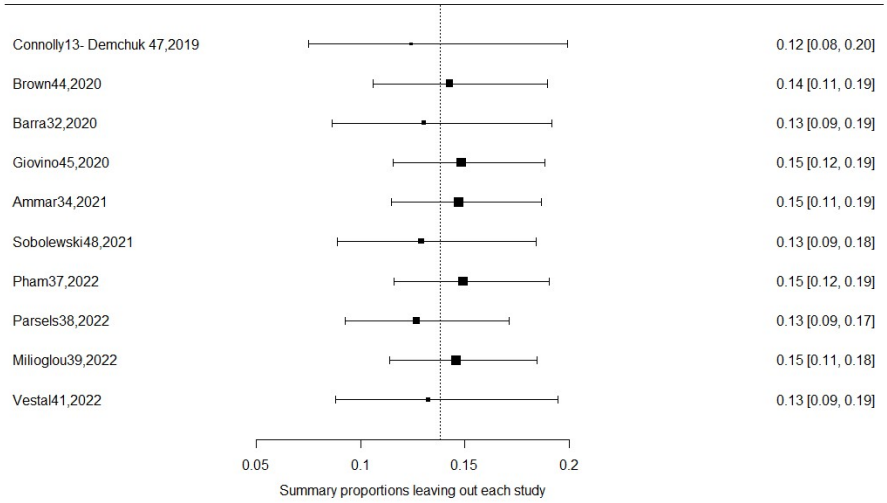
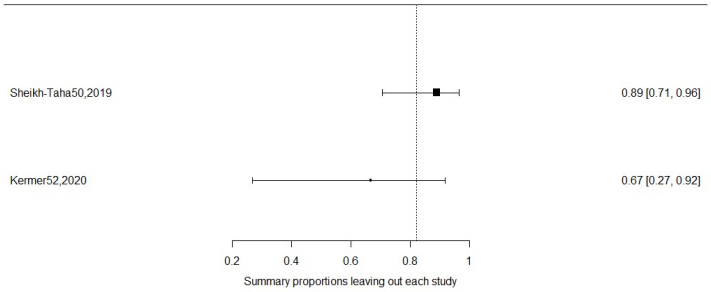
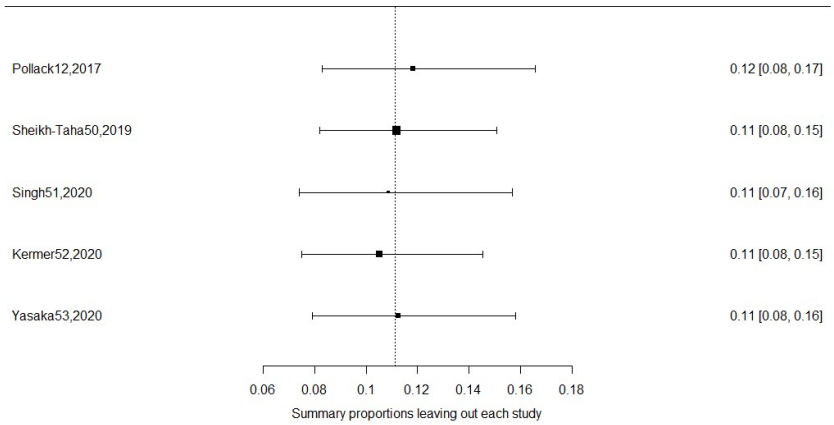
2c. AA thromboembolic events




3a. Idarucizumab anticoagulation reversal




3b. Idarucizumab all-cause mortality

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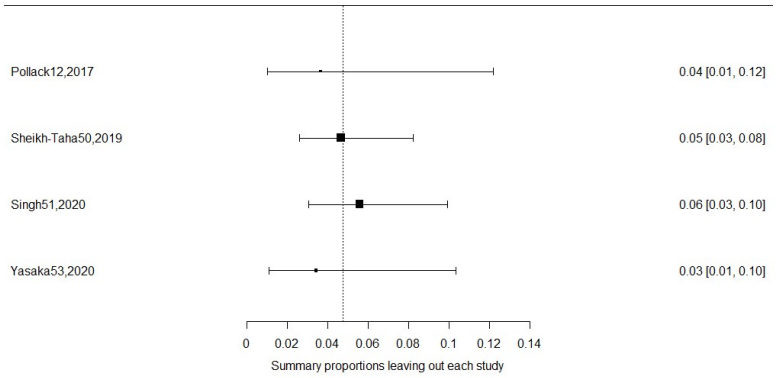
3c. Idarucizumab thromboembolic events

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## eAppendix 6. Definitions of Successful Anticoagulation Reversal in Included Studies

## Included in the Meta-analysis

| Study name | Hemostasis definition on brain imaging |
|---|---|
| **Andexanet alfa** | |
| Connolly et al,13 2019 **(ANNEXA-4)** + Demchuk et al,50 2021 | **Intracerebral hematoma**:<br>Excellent: ≤20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1- and **12-hour** post infusion time points<br>Good: >20% but ≤35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point<br><br>**Subarachnoid hemorrhage:**<br>Excellent: ≤20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1- and 12-hour post infusion time points<br>Good: >20% but <35% increase in maximum thickness using the most dense area on the follow-up at +12h vs baseline<br><br>**Subdural hematoma:**<br>Excellent: ≤20% increase in maximum thickness at both the 1- and 12-hour post infusion assessments compared to baseline<br>Good: >20% but < 35% increase in maximum thickness at +12h compared to baseline |
| Stevens et al,46 2019 | **Intracerebral hematoma**:<br>Excellent: ≤20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1- and **12-hour** post infusion time points<br>Good: >20% but ≤35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point<br><br>**Subarachnoid hemorrhage:**<br>Excellent: ≤20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1- and 12-hour post infusion time points<br>Good: >20% but <35% increase in maximum thickness using the most dense area on the follow-up at +12h vs baseline<br><br>**Subdural hematoma:**<br>Excellent: ≤20% increase in maximum thickness at both the 1- and 12-hour post infusion assessments compared to baseline<br>Good: >20% but < 35% increase in maximum thickness at +12h compared to baseline<br><br>Hemostatic outcomes after 12 hours of AA administration |
| Culbreth et al,49 2019 | Repeat CT scan -categorized as stable or worsening – no further details provided |
| Brown et al,47 2020 | **Expansion**: >20% increase from pre-treatment hematoma volume or diameter; For IPH, volume was determined by the ABC/2 method<br>- Clinical efficacy was defined as lack of hematoma expansion |
| Barra et al,35 2020 | **Excellent hemostasis** was defined as ≤ 20% increase in intracerebral hematoma volume, subarachnoid hemorrhage (SAH) thickness, or subdural hematoma (SDH) thickness. |

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| | |
|---|---|
| | **Good hemostasis** was defined as > 20% but ≤ 35% increase in intracerebral hematoma volume, SAH thickness, or SDH thickness. Poor hemostasis was defined as > 35% increase in intracerebral hematoma volume, SAH thickness, or SDH thickness.<br><br>- Repeat imaging within 24-hours of antithrombotic reversal |
| Coleman et al,36 2020 | Only mortality data available, no data available to evaluate ICH hemostasis |
| Giovino et al,48 2020 | Hemostatic efficacy on repeat head computed tomography (CT) after administration of andexanet alfa. The definition for hemostatic efficacy was adapted from the ANNEXA-4 trial[13], where an increase in hematoma expansion from baseline CT of ≤ 35% was defined as excellent or good and > 35% was considered poor efficacy |
| Ammar et al,37 2021 | Stable head computed tomography (CT) scan at 6 and 24 h post-administration of AA or 4F-PCC, defined for IPH as no significant increase in volume (less than 6 mL or 33% of baseline volume) Stability was defined as a similar amount of blood from one scan to the next. For intraparenchymal hemorrhages, the volume of the hematoma was calculated using the ABC/2 volume estimation method. In IPH, a similar amount of blood was defined as a volume growth of less than 6 mL or 33% from baseline CT and adjudicated by the three experienced independent providers. |
| Stevens et al,39 2021 | Difference in the achievement of excellent or good hemostasis within 12 h of andexanet alfa administration as compared to 4F-PCC. Hemostasis was defined based on the ANNEXA-4 study[13] definitions and classified as excellent, good, or poor. Excellent and good hemostasis were combined as "effective" hemostasis<br>Hematoma volume was calculated using the ABC/2 volume estimation method |
| Sobolewski et al,51 2021 | Hematoma expansion on imaging – mean time between imaging was 12.2 hours (5:15 – 22:40) – no further data available |
| Benz et al,52 2022 | Same definition as ANNEXA-4 trial[13] |
| Pham et al,40 2021 | Excellent and Good as per ANNEXA- 4[13, 72]<br>CT scans 12-hr apart |
| Parsels et al,41 2022 | Excellent or good hemostasis based on ANNEXA-4 study[13, 72] |
| Milioglou et al,42 2022 | Brain imaging on presentation and repeat imaging within the first 24-or 48-h were assessed. Hemostasis effectiveness was evaluated by two physicians who reviewed separately all CT and/or MRI results before and after intervention (PCC or andexanet). Differences between brain hemorrhage volume estimates between the two physicians were resolved by discussion. No further information provided. |
| Vestal et al,44 2022 | Hemostatic efficacy was determined by radiologists' interpretations of the diagnostic and first subsequent head scans. If radiologist's report stated an increase in hematoma volume, hemostatic efficacy was labeled as "No". If no progression was noted by the interpreting radiologist, hemostatic efficacy was labeled as "Yes". In terms of imaging, it was the standard institutional clinical practice to obtain a repeat scan six hours after the initial scan to assess progression of the hematoma. |
| **Idarucizumab** | |
| Pollack et al,12 2017 | Maximum percentage reversal of the anticoagulant effect of dabigatran, determined at any point from the end of the first idarucizumab infusion until 4 hours after the end of the second infusion, with the percentage reversal assessed on the basis of the diluted thrombin time or the ecarin clotting time.<br><br>Complete reversal was defined as a decrease in the diluted thrombin time or ecarin clotting time to a normal level.<br><br>Brain imaging studies to evaluate for bleeding cessation were not mandated. |
| Sheikh-Taha et al,52 2019 | Efficacy of idarucizumab using the International Society of Thrombosis and Hemostasis Scientific and Standardization Subcommittee (ISTH/SSC) criteria[72] |
| Singh et al,54 2020 | Hemostasis not measured |

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| Kermer et al,55 2020 | Information on hematoma growth with clinical deterioration (indicated by increase in NIHSS) with follow-up CT scan and comparison of hematoma volume at discretion of the attending physician. No further information provided |
| Yasaka et al,56 2020 | ICH data unavailable for effective hemostasis. |
| **4-F PCC** | |
| Grandhi et al,24 2015 | Progression of ICH was identified through review of subsequent head CTs and confirmed by radiology reports noting increased size of ICH on follow-up scans. No further information provided. |
| Majeed et al,25 2017 | - Effectiveness assessment as per ISTH criteria[72]<br>- For ICH, follow-up CT within 24 hours, when available, was compared with the initial CT when available.<br>- Effective hemostasis is achieved when:<br>a. The hematoma volume is stable, or increased by <35% as compared with baseline volume as assessed by a CT scan within 12 h (time window of 6–24 h after the index CT)<br>b. No deterioration of the Extended Glasgow Outcome Scale (GOS-E) as assessed at 24 h in comparison with that at presentation.<br>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.<br>Annotation of effective hemostasis with good clinical outcome when:<br>d. No neurologic deterioration/dysfunction is present at discharge (at discharge can be replaced by 'at day = 30', whenever applicable) as assessed with any validated scoring system (e.g. GOS-E) as compared with that at presentation.<br><br>All of the above criteria had to be met for the therapy to be considered effective. |
| Gerner et al,8 2018 | Hematoma enlargement defined as a relative parenchymal volume increase of >33% from initial to follow-up imaging. |
| Schulman et al,26 2018 | **Good**: ≤20% increase in hematoma volume compared with baseline on repeat CT scan performed and/or any neurological improvement noted over the following 12 h or—if the patient was progressively deteriorating until the treatment with FEIBA—even a stabilization of the condition<br>**Moderate**: >20%, but ≤35% increase in hematoma volume compared with baseline on a repeat CT scan performed and/or minimal deterioration of neurological condition<br>**Poor/none**: >35% increase in hematoma volume compared with baseline on repeat CT scan performed at the 24-h time point and/or clear deterioration of the condition or death. |
| Tao et al,27 2018 | Efficacy data for ICH not separated |
| Sheikh-Taha et al,28 2018 | International Society of Thrombosis and Hemostasis Scientific and Standardization Subcommittee (ISTH/SSC) criteria[72] |
| Smith et al,29 2019 | **Excellent**: ≤20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3- and 24-hour time points.<br>**Good:** >20%, but ≤35% increase in hematoma volume compared to baseline on a repeat CT scan performed at the 24-hour time point<br>**Poor/none**: >35% increase in hematoma volume compared to baseline on repeat CT scan performed at the 24 hour time point |
| Berger et al,30 2020 | Hemostatic effectiveness within 24 hours of 4F-PCC administration. Hemostatic effectiveness was achieved if the first neuroimaging result within 24 hours of 4F-PCC administration showed no change or an improvement in hematoma volume |
| Zheng et al,31 2020 | Re-evaluated by head CT within 8 hours of 4F-PCC administration – stable size. No other information was provided. |
| Korobey et al,32 2020 | ANNEXA-4 criteria[13] |
| Castillo et al,33 2020 | ANNEXA-4 criteria[13] |
| Lipari et al,34 2020 | ANNEXA-4 criteria[13] |

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| Smythe et al,[38] 2021 | ANNEXA-4 criteria[13] |
| Pasciolla et al,[45] 2021 | ANNEXA-4 criteria[13]<br>Excellent and good included in outcomes. Repeat CT head in 12 hours to assess hemostatic outcomes |
| Dev et al,[43] 2022 | ANNEXA-4 criteria[13] |

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