

Treatment of Antithrombotic-Associated Intracranial Hemorrhage in Adults: A Focused Guideline Update from the Neurocritical Care Society and the Society of Critical Care Medicine

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Title Page

Treatment of Antithrombotic-Associated Intracranial Hemorrhage in Adults: A Focused Guideline Update from the Neurocritical Care Society and the Society of Critical Care Medicine

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Key Words: Evidence-based medicine; Grading of Recommendations Assessment, Development, and Evaluation criteria; GRADE criteria, guidelines; Anticoagulant Antiplatelet; Antithrombotic; Intracranial hemorrhage; Intracerebral hemorrhage; Intraparenchymal hemorrhage; ICH; Subarachnoid hemorrhage; SAH; Subdural hematoma; SDH; Reversal; Antidote; Factor Xa inhibitor; Apixaban; Rivaroxaban; Aspirin; Clopidogrel; Prothrombin complex concentrates; PCC; Platelets; DDAVP; Desmopressin; Viscoelastic hemostatic assays; Thromboelastography; Blood products; Traumatic brain injury

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Details Page

- 1) Confirm that manuscript complies with all instructions to authors
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- 2) Detailed description of individual author contributions
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- 3) Confirm that authorship requirements (see below) have been met and the final manuscript was approved by all authors
 - Authorship requirements have been met by all panel members. The manuscript in its entirety was reviewed by and approved in its final version by all writing panel members.
- 4) Confirm that this manuscript has not been published elsewhere and is not under consideration by another journal
 - This manuscript has not been submitted for publication elsewhere.
- 5) Confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate (see below). Retrospective studies require a statement regarding IRB approval.
 - No IRB approval was necessary for writing this guideline.
- 6) Disclose Conflicts of Interest for all authors:
 - a. Charlotte Cordonnier discloses the following:
 - i. Financial: Honoraria from Bayer (modest, \$500-50,000) for her role on a Steering Committee for a phase 3 trial for Factor XI inhibitors
 - ii. Intellectual:
 1. TIPITCH project Coordinator - Funded by the France 2030 - aims at transforming the prognosis of intracerebral hemorrhage with a special focus on bleeding associated with oral anticoagulants.
 2. Member of the writing committees for ESO ICH guidelines 2025 and AHA/ASA ICH guidelines (2022).
 - b. Adam Cuker discloses the following:
 - i. Financial:
 1. Honorarium from Pfizer (modest, \$500-50,000) for his role as a consultant.
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 - d. Joseph Burns discloses the following:

- i. Intellectual: serves as a member of the editorial board for *Neurology*.
- 7) Confirm the use of reporting checklist (see below), if appropriate
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Abstract

Background: Antithrombotic-associated intracranial hemorrhage (ICH) is a life-threatening condition, and rapid treatment in the setting of antithrombotic agents may limit hematoma expansion and improve outcomes. This focused update evaluated the available evidence after publication of the 2016 guidelines.

Methods: The Neurocritical Care Society, in conjunction with the Society of Critical Care Medicine, generated five questions to guide a systematic review and meta-analysis. Three of these questions update prior recommendations, while two are newly introduced. Each question followed a PICO (Population, Intervention, Comparator, Outcome) framework and focused on the management of acute ICH including spontaneous intraparenchymal hemorrhage (IPH) and traumatic ICH. The topics addressed were: 1) andexanet alfa versus 4-factor prothrombin complex concentrate (4F-PCC) for treatment of oral factor Xa inhibitor effects; 2) platelet transfusion versus no transfusion for treatment in the setting of antiplatelet agent use; 3) desmopressin versus no desmopressin for treatment in the setting of antiplatelet agent use; 4) treatment of anticoagulant effects versus no treatment in the setting of small IPH; and 5) use of viscoelastic hemostatic assays (VHAs) to treat coagulopathy in traumatic ICH. Recommendations were developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.

Results: The panel generated eight recommendations. For patients with acute ICH, the panel issued the following conditional recommendations: use 4F-PCC rather than

andexanet alfa for the treatment of the anticoagulant effects of factor Xa inhibitors, avoid platelet transfusion in non-neurosurgical patients with spontaneous IPH on antiplatelet agents, administer platelet transfusion in patients with spontaneous IPH on aspirin who are undergoing surgery, and use VHAs to guide treatment of coagulopathy in traumatic ICH. The panel was unable to issue recommendations regarding platelet transfusion for treatment of antiplatelet effects in traumatic ICH, use of desmopressin for treatment of antiplatelet effects, or treatment of anticoagulant effects in small IPH.

Conclusions: The guideline writing panel provided new conditional recommendations for the treatment of antithrombotic-associated acute ICH. These recommendations are intended for consideration along with the patient's clinical status and patient-specific factors.

Required Funding Statement: Funding for these guidelines was provided solely by the Neurocritical Care Society and the Society of Critical Care Medicine.

Introduction

The use of antithrombotic agents is critical in reducing thrombotic and embolic events across a wide spectrum of medical conditions. However, their use also increases the risk of intracranial hemorrhage (ICH). Compared to those with ICH not on antithrombotic medications, patients who take antithrombotic medications are at higher risk for hematoma expansion, poor functional outcomes and mortality.^{1,2} Despite this, the optimal treatment strategies for many antithrombotic agents remain uncertain, with available evidence often conflicting.

To address this, the Neurocritical Care Society (NCS) and the Society of Critical Care Medicine (SCCM) developed guidelines for reversal of antithrombotics in 2016.³ In 2022, these two professional societies embarked on the process of updating the guidelines using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. These guidelines are essential for all critical care professionals, as they provide evidence-based recommendations for treatment of antithrombotic effects in ICH, a clinical challenge with life-threatening implications.

The current guideline is a focused update of the 2016 guideline, with several updated recommendations from previous PICO questions as well as two new topics. Refer to Table 1 for both prior and updated recommendations; a comprehensive summary of prior recommendations not addressed in this focused update can be found in

Supplemental Table 1. As the number of PICO questions were limited for this update, several previous general recommendations and Good Practice Statements were not updated; however, they are still relevant for current practice. Prior to publication of the 2016 guideline, there was no formal guidance for the treatment of antithrombotic effects in the setting of acute ICH. The guideline was not only a scoping review of the management principles of acute ICH, but generated recommendations for practice based not only on common practice, but also very low quality or indirect evidence. As more attention has been paid to these questions in the intervening decade, the panel more strictly reviewed the evidence and found that some prior recommendations required new and potentially differing recommendations.³

For a comprehensive review of pharmacology and pharmacokinetic properties of antithrombotic agents and their treatments, please refer to the 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage, along with recommendations not reviewed in this guideline update in Supplemental Table 1.³

Methodology

This guideline was developed in accordance with Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.⁴

Panel Composition

The interdisciplinary guidelines task force was comprised of ten individuals from medical, nursing, advanced practice, and pharmacy disciplines with subspecialty experience in neurocritical care, trauma/neurosurgery and hematology. The panel consisted of six women and four men of diverse racial and ethnic backgrounds. In addition, a public member, identified through the Anticoagulation Forum, provided a patient and family perspective.

The Guidelines in Intensive Care Development and Evaluation (GUIDE) group appointed three clinician-methodologists (EBC, KH, EW), for methodological support. The panel applied the processes from the NCS Guidelines Committee and as described in the ACCM guidelines standard operating procedure manual to develop and publish evidence-based recommendations in alignment with the GRADE methodology. All panel members were required to comply with standard conflict of interest (COI) and commercial relationship disclosures, including review of any financial, intellectual, or other relationships that may be construed as a possible conflict of interest. We adhered to COI policies across all phases of guideline development, including task force selection and voting. Disclosures that were not directly related to the content of this article are listed in the Acknowledgments section. The chairs of the Neurocritical Care Society Guideline Committee that oversees the Guideline Panel were vetted of any potential COIs. All members of the Guideline Panel were determined to be free of COI.

Study Population

This guideline pertains to adult patients hospitalized with acute intracranial hemorrhage (ICH). In addition, where possible, we performed subgroup analyses based on mechanism (traumatic or spontaneous hemorrhage, and operative or nonoperative initial management).

The term intracranial hemorrhage (ICH) encompasses all bleeding within the cranium, which may be extra-axial (subdural, epidural, subarachnoid), intraventricular, or intraparenchymal (intracerebral). Intracranial hemorrhage is often erroneously interchanged for intracerebral hemorrhage, with both abbreviated as “ICH.”

Spontaneous intracerebral hemorrhage refers to non-traumatic parenchymal hematomas without a secondary cause such as aneurysm rupture or other underlying vascular abnormality, and are referred to in this guideline as intraparenchymal hemorrhage (IPH), for clarity. Traumatic ICH refers to intracranial hemorrhage occurring in the setting of traumatic brain injury.

Population, Intervention, Comparison, and Outcomes Generation

Five specific questions were addressed for this guideline following the population, intervention, comparison, and outcomes (PICO) format. The PICO topics and related outcomes are listed in Table 2. Specific PICOs were generated by the panel chairs based on several variables such as the availability of new published evidence which may change prior recommendations, and presence of significant gaps in the literature not addressed in the prior guideline and of interest to the critical care and neurocritical care community. For each PICO, specific outcomes were also identified. Panel

members independently rated each outcome in terms of its importance from patients' perspectives on a scale of 1 (least important) to 9 (most important).⁵ The outcomes categorized as "critical" based on aggregate panelist scores (indicating the highest level of importance) included the following: mortality, functional outcome, and thrombosis. Additional outcomes categorized as "important" included: hematoma expansion, hospital readmission, platelet transfusion reaction, blood transfusion reaction, desmopressin (DDAVP) adverse effects, intensive care unit (ICU) length of stay, hospital length of stay, and blood product usage. Table 2 presents the panel's outcome prioritization and additional details can be found in Supplemental Material 2.

Inclusion and Exclusion Criteria

We included studies that met the following criteria: randomized controlled trials (RCTs) or observational studies that addressed treatment of antithrombotic effects in acute ICH in the setting of pre-specified antithrombotic agents, the article included an adult population (aged > 18 years) hospitalized with ICH, and data were available on the primary outcomes of interest (Table 2). Articles were excluded if they involved a large proportion of patients receiving antithrombotics not relevant to the intervention of interest; were not published in English; were nonhuman studies; were case series with fewer than ten patients; or did not have a comparator group of interest. We excluded gray literature, including abstracts, conference proceedings, and non-peer-reviewed articles, as well as review articles and meta-analyses.

Search Strategy

A literature search was performed by an information specialist following Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S) guidance, using a peer-reviewed search strategy (Supplemental Material 1).⁶ The search strategy was reviewed according to the methods described by McGowan et al.⁷ Published literature was identified by searching the following bibliographic databases on January 25, 2024: MEDLINE (1946–) with all available records via Ovid; Embase (1974–) via Ovid; and, The Cochrane Library via Ovid. A gap literature search for PICO 1 was performed on April 5, 2025 to identify additional studies to inform the analysis as publication of a relevant large observational cohort study was anticipated.

See Supplemental Material 1 for further search details.

Systematic Review Process

For each PICO, the guideline methodologists and two reviewers screened titles and abstracts of all articles, independently and in duplicate, to identify potentially relevant articles. Then, the same group reviewed the full text of the articles to identify studies that met the inclusion criteria. We resolved disagreements by consensus or third-person adjudication. For each included article, we extracted article characteristics and relevant outcome data. We then assessed the risk of bias (ROB) of each study using the RoB-2 tool for randomized studies and the ROBINS-I tool for nonrandomized studies.^{8,9} When possible, adjusted analyses were completed for all individual outcomes for strengthened quality; however, when data was not available, unadjusted analyses were performed.

Heterogeneity as defined by the I^2 statistic, was also weighed in recommendations and contributed to the certainty of evidence. I^2 represents the proportion of observed variance in effect estimates across studies that is due to real differences (heterogeneity) rather than random error (sampling variability).

Statistical Analyses

For each PICO, we performed meta-analysis using DataParty (DataParty.ca) and RevMan, Version 5.4 (The Cochrane Collaboration, revman.cochrane.org), web-based platforms. For some outcomes that were reported as adjusted analyses, we used STATA (StataCorp 2025, College Station, TX). We performed meta-analyses using random-effects models and inverse variance weighting

GRADE Assessment

Finally, we evaluated the certainty of evidence using the GRADE methodology and generated evidence profiles using GRADEPro Guideline Development Tool (GDT) software (McMaster University and Evidence Prime Inc, 2025).^{4,10}

Development of Recommendation Statements

The panel applied the GRADE Evidence-to-Decision Framework for each PICO using GRADEPro GDT software (McMaster University and Evidence Prime Inc, 2025) to generate each recommendation. Final recommendations were based on consideration of the importance of the outcomes, the certainty in the evidence, the balance between the desirable and undesirable effects of the intervention, patient values, resource

requirements, equity considerations, and the acceptability and feasibility of the recommendation. While the writing panel heavily considered patient-centered endpoints rather than surrogate endpoints to inform recommendations, both types of outcomes were considered by the panel. Agreement by 80% or more of panel members was required for final recommendations.

Results

The panel generated recommendations which are summarized in Table 1.

Recommendations

PICO 1. In patients with intracranial hemorrhage on factor Xa inhibitors, should andexanet alfa, when compared to 4-factor prothrombin complex concentrate, be administered?

For patients with any type of intracranial hemorrhage on oral factor Xa inhibitors, we suggest 4-factor prothrombin complex concentrate over andexanet alfa for treatment of anticoagulant effects:

1. **Recommendation 1-1:** We suggest using 4-factor prothrombin complex concentrate rather than andexanet alfa in patients with factor Xa inhibitor-

associated spontaneous ICH (conditional recommendation; moderate certainty evidence).

2. **Recommendation 1-2:** We suggest using 4-factor prothrombin complex concentrate rather than andexanet alfa in patients with factor Xa inhibitor-associated traumatic ICH (conditional recommendation; very low certainty evidence).

Evidence Summary:

Factor Xa inhibitors (FXa-I) are associated with a lower bleeding risk than alternate systemic anticoagulants. They do not require routine laboratory monitoring of anticoagulant activity; therefore, their use in the management of atrial fibrillation and venous thromboembolism has increased dramatically since they were introduced to the market. However, intracranial hemorrhage remains a major complication associated with use of oral factor Xa-inhibitors.

Andexanet alfa is an inactive recombinant form of human factor Xa that binds FXa-I to restore thrombin generation. This agent was not FDA-approved when the 2016 NCS-SCCM antithrombotic reversal guideline was published. That guideline reviewed data from studies of healthy volunteers and animal models of hemorrhagic stroke, as well as the ANNEXA-4 trial. This trial included 352 patients treated with andexanet alfa for major bleeding associated with FXa-I use, without a comparator arm.^{11,12} The co-primary endpoints were hemostatic efficacy and anti-factor Xa activity levels. Among

249 evaluable patients, 204 (82%) achieved excellent or good hemostasis. Within 30 days, 49 (14%) patients died, and 34 (10%) experienced a thrombotic event. While the reduction in anti-factor Xa activity did not predict hemostatic efficacy in the total cohort, it was modestly predictive in patients with ICH.

The prior guidelines included good practice statements and recommendations for initial treatment, including discontinuation of oral FXa-I medications and administration of activated charcoal for those patients with low risk of aspiration and known ingestion within 2 hours of presentation to a medical facility. Suggestions for treatment included administration of 4-factor PCC (50 IU/kg) or activated PCC (50 units/kg) (conditional recommendations, low quality of evidence) in FXa-I-associated ICH that occurred within 3-5 half-lives of drug exposure or in patients with liver failure. Recombinant factor VIIa was not recommended due to risk of adverse thrombotic events.

Twenty-one studies informed our current recommendation, comprising 4,938 patients with intracranial hemorrhage, comparing andexanet alfa to some formulation of PCC: one randomized controlled trial,¹³ nineteen retrospective studies¹⁴⁻³² and one matched cohort study.³³ Regarding outcomes, 19 studies addressed mortality, 12 studies addressed functional outcome, 11 studies evaluated hemostatic efficacy, 15 addressed hematoma expansion and 15 assessed the risk of thrombosis. Recommendations were made based on studies reporting data adjusted for covariates where available. Studied populations were identified as traumatic or spontaneous, and mixed if it was both or not defined.

The highest quality data derived from the sole RCT did not demonstrate a significant mortality benefit with administration of andexanet alfa (Figure 1). Observational data, adjusted for covariates, also did not suggest a significant benefit of andexanet administration in either mortality or functional outcome in the total cohort of intracranial hemorrhage (Supplemental Figure 2 and Supplemental Figure 6). Andexanet alfa did demonstrate significant improvement in hemostatic efficacy (RR 1.09; 95% confidence interval (CI), 1.04 to 1.14) (Supplemental Figure 5). Data regarding hematoma expansion favored andexanet alfa; however, the effect was not significant when adjusted for covariates (Supplemental Figure 4). Importantly, the significant increase in the risk of thrombotic events (RR 1.35; 95% CI, 1.04 to 1.76), especially arterial thromboses, combined with the RCT, suggest that andexanet is probably associated with harm (Figure 3).

When defined as discharge to hospice, functional outcome favored treatment with PCC: 15/59 on andexanet versus 49/265 on PCC (adjusted RR 1.24; 95% CI, 0.91 to 1.70) (Supplemental Figure 8).²⁵ However, when functional outcome is evaluated as a continuous variable and not dichotomized, it may favor andexanet alfa (standardized mean difference, SMD -0.36; 95% CI, -0.127 to 0.54) (Supplemental Figure 9). Importantly, neither treatment significantly improved functional outcome assessment regardless of definition. It should be noted that these data were derived from three observational studies that used three different outcome scores, which significantly increases heterogeneity and decreases the estimated effects. In terms of hospital length

of stay, patients treated with PCC had relatively shorter hospital stays compared to those treated with andexanet alfa (mean difference (MD) 0.5; 95% CI, 0.08 to 0.91) based on 13 observational studies (Supplemental Figure 15). Similarly, regarding ICU length of stay, treatment with PCC was favored (MD 0.11; 95% CI, -0.17 to 0.39) (Supplemental Figure 16).

Spontaneous ICH

Regarding the subpopulation of spontaneous IPH, the highest quality data derives from the ANNEXA-I study, an international, multi-center, randomized clinical trial of andexanet alfa versus usual care.¹³ The study was stopped early after a pre-planned interim analysis for efficacy and the trial was not designed to detect differences in mortality and functional outcome due to insufficient power. Initial inclusion criteria permitted any type of intracranial hemorrhage; however, an amendment to the protocol in April 2020 limited enrollment to patients with spontaneous IPH to increase the homogeneity of the study population and to clarify eligible hematoma blood volume. Sixty-five (12%) of the total cohort had antecedent trauma. Eighty-eight percent of the total cohort and 91% of the efficacy cohort had a spontaneous IPH and thus, results of this trial are included in this subgroup analysis.

All 530 patients enrolled in the study comprised the safety population. Four hundred and fifty-two comprised the primary efficacy population.¹³ Two hundred and twenty-four were randomized to receive andexanet alfa and 228 to receive usual care, of which 195

(85.5%) were treated with some formulation of PCC (median dose 3000 IU, interquartile range 2000 to 3500 IU). The formulation of PCC administered was known in over half of the usual care patients: 110 (92.4%) patients were treated with 4-factor PCC, 4 (3.4%) with 3-factor PCC, and 5 (4.2%) with activated PCC.

In the ANNEXA-I trial, seventy-three of 263 (27.8%) patients receiving andexanet alfa died compared to sixty-eight of 267 (25.5%) in the usual care arm (RR 1.09; 95% CI, 0.82 to 1.45). The relative risk of mortality in ANNEXA-I was 1.09 (95% CI, 0.82 to 1.45). Additionally, mortality analysis of the observational studies limited to spontaneous IPH patients resulted in the evaluation of 1600 patients and demonstrated a relative risk of mortality of 0.91 (95% CI, 0.68 to 1.21) (Figure 2). Adjusted 30-day mortality is derived from one single observational study and trends in favor of andexanet alfa (RR 0.49; 95% CI, 0.24 to 1.0) although the certainty of evidence is very low (Supplemental Figure 2).

Poor functional outcome, defined as a modified Rankin Scale (mRS) score of 4-6 at 30 days following randomization, for spontaneous IPH was not significantly different between groups in ANNEXA-I: [177/246 (72.0%) versus 176/255 (69.0%) (RR 1.04; 95% CI, 0.93 to 1.17). Observational data finds an adjusted odds ratio for poor functional outcome of 0.91 (95% CI, 0.73 to 1.14) (Supplemental Figure 7).³³

In ANNEXA-I, 27/263 (10.3%) experienced thrombotic events in the andexanet arm compared to 15/267 (5.6%) in the PCC arm (RR 1.83, 95% CI 1.0 to 3.36). In the RCT,

thrombotic events were defined as strokes, transient ischemic attacks, myocardial infarctions, deep vein thromboses (DVTs), pulmonary embolism (PEs), and arterial systemic embolism. In the three observational studies, the RR for thrombosis in spontaneous IPH patients was 1.99, (95% CI, 1.15 to 3.45) (Figure 3).

The primary end point in the RCT was hemostatic efficacy, defined as a composite of:

- 1) expansion of hematoma volume by 35% or less at 12 hours after baseline CT scan;
- 2) an increase in the NIHSS of less than 7 points at 12 hours; and 3) no need for rescue therapy between 3 and 12 hours.

Hemostatic efficacy was achieved in 150 of 224 (67.0%) receiving andexanet alfa and in 121 of 228 (53.1%) receiving usual care [adjusted difference, 13.4%; 95% CI, 4.6 to 22.2; $p=0.003$]. One hundred and sixty-five patients of 215 (76.7%) in the andexanet arm experienced hematoma volume change of $\leq 35\%$ compared to 64.6% of the 212 patients in the control arm. Similarly, 188/214 (87.9%) patients treated with andexanet experienced an NIHSS score change of less than 7 points, compared to 181/218 (83.0%) in the usual care group. There was no significant difference in the receipt of rescue between groups. Very large hematoma expansion, defined as more than 12.5 mL or death in 12 hours after randomization, occurred less frequently [24/216 (11.1%)] in the andexanet group than in the usual care group [36/214 (16.8%)]. Andexanet outperformed usual care in the three components of the composite primary outcome, however its use was associated with the increased incidence of thrombosis, especially arterial events.

Taken together, there was no significant benefit in mortality or functional outcome, which were considered two critical patient-centered outcomes for review by the panel, after treatment with andexanet alfa for patients with spontaneous IPH. Additionally, 15% of patients in the usual care arm received no treatment at all. This could potentially bias the results in favor of andexanet. Although hemostatic efficacy was better with andexanet alfa, this was considered a surrogate outcome and not a patient-centered primary outcome. The significant increase in the relative risk of thrombosis with andexanet alfa reduces the potential benefits of treatment. Therefore we suggest the use of 4-factor PCC rather than andexanet alfa for the treatment of the anticoagulant effects of oral FXa-I in patients with spontaneous IPH.

Trauma Subgroup

Ten studies^{13-15,20,21,23,25,29-31} mention outcomes in patients with traumatic ICH and one²⁵ reported data adjusted for covariates. There are no high-quality data exclusively addressing the trauma subpopulation. Using data adjusted for covariates, the point estimate for the risk reduction of mortality was 1.34 (95% CI, 0.67 to 2.69) (Supplemental Figure 2). There were no differences in hematoma expansion in the one identified observational study (unadjusted RR 0.21; 95% CI, 0.03 to 1.43) (Supplemental Figure 3). In terms of thrombosis risk, two observational studies were identified and there was no difference between the groups (unadjusted RR 1.14; 95% CI, 0.63 to 2.04) (Figure 3).

Although the hematoma expansion and hemostatic efficacy data favor andexanet alfa, the quality of data are quite low and there was no mortality benefit to treatment with andexanet. The data did not suggest that there was a higher frequency of thrombotic events in the trauma population; however, given the high incidence of venous thromboembolism in trauma patients and the higher thrombotic risk with andexanet alfa overall, we suggest the use of 4-factor PCC rather than andexanet alfa for the treatment of the anticoagulant effects of oral FXa-I in patients with traumatic ICH. However, the level of evidence is considered very low. Future studies are warranted.

Limitations

It is important to note that, by the design of the PICO (Population– Intervention– Comparator–Outcome) analysis, only a head-to-head comparison was conducted between andexanet alfa and prothrombin complex concentrates. A comprehensive review of 4-factor PCC versus placebo was not performed. Unfortunately, many studies did not specify which formulation of PCC was used. These formulations can vary significantly in their factor content, and some contain significant amounts of heparin, adding further heterogeneity.³ Importantly, we were unable to address the question of optimal dosing of 4F-PCC in this update. When reported in included studies, the dose largely varied between 25-50 units/kg and was not always standardized (Supplemental Table 6). Additionally, studies have also assessed fixed dosing.³⁴ In the 2016 guideline, the recommended dose of 4F-PCC was 50 units/kg, however this was not

based on robust data. It should be acknowledged that 4F-PCC products do not carry a labeled indication for treatment of oral factor Xa inhibitor-associated bleeding.

Additionally, the "usual care" arms of non-randomized studies are likely subject to inherent bias. Patients enrolled in the treatment arms often receive care more timely and intensive management and may represent a population with greater clinical severity or need for intervention. In contrast, patients assigned to the usual care group may have been perceived as having a better prognoses (e.g., smaller hemorrhages) and therefore were less likely to receive active treatment. For example, in a substudy of ANNEXA-4 and RETRACE, patients in the usual care group were treated later and had significantly higher blood pressures than those in the andexanet alfa group.³³ These differences could bias the results in favor of andexanet alfa, particularly when assessing hemostatic efficacy. This pattern was observed in patients both with and without hematoma expansion.

Andexanet alfa may be prothrombotic via two distinct mechanisms: 1) reversal of factor Xa inhibitor anticoagulation, and 2) direct inhibition of tissue factor pathway inhibitor. It has been associated with an increased risk of thrombotic events, which are predominantly arterial in nature and most commonly manifest as acute ischemic strokes identified on neuroimaging. It remains unclear whether these infarcts are symptomatic; however, even small, asymptomatic strokes may negatively affect long-term functional outcomes.³⁵ Furthermore, a recent study not included in this pooled analysis provides additional evidence of increased arterial thrombotic events among patients treated with andexanet alfa.³⁶ These findings from ANNEXA-I in part resulted in the FDA's decision to decline AstraZeneca's application for full approval, with the manufacturer voluntarily

withdrawing their Biologics License Application and ceasing commercial sales in the United States as of December 22, 2025. Andexanet alfa remains available outside of the US.

Importantly, there are few recent cost analyses to inform cost effectiveness of andexanet as compared to 4-factor PCC. In the United States in 2021, the wholesale acquisition price was reduced by nearly fifty percent. Since becoming available, andexanet alfa has been eligible for New Technology Add-On Payments (NTAP) from the Centers for Medicare & Medicaid Services which allows additional reimbursement for hospitalized patients receiving new technologies. The most recent analysis by Keinath et al. published in 2023 evaluated the cost associated with andexanet alfa or PCC in deterioration-free discharges using local data and which factored in NTAP reimbursement. In ICH, cost per deterioration-free discharge for PCC was found to be \$4,970 compared to \$17,925 for andexanet; with recent changes in wholesaler pricing and NTAP, however, the cost for andexanet was re-calculated to be \$13,787, still representing a significant cost difference over PCC.¹⁸ This cost analysis data is specific to the United States and may not be applicable elsewhere.

Another limitation seen in the available studies for this PICO as well as others, pertains to the varying definitions of hematoma expansion and time points for outcome assessment. This increases heterogeneity among results and reduces confidence in the findings. Functional outcomes assessments at only the 30-day period in ANNEXA-I are also unlikely to be robust enough in this patient population, and extended assessments should be conducted in the future (Table 3).

Lastly, andexanet alfa has largely not been studied in the neurosurgical setting as it is not approved in this population due to its short half-life. Patients requiring neurosurgical intervention were excluded from the ANNEXA trials including ANNEXA-I except for minimally invasive procedures such as ventriculostomy placement; rescue therapy including neurosurgical intervention were rare. No recommendations can be made regarding treatment with andexanet alfa in patients requiring emergent neurosurgical intervention.

Good Practice Statement: Due to the prothrombotic risk, we advise against combining andexanet alfa and PCC unless the benefit clearly outweighs the risk.³⁷

Practical Tip: Assessing prior treatment is crucial when patients are transferred between centers where urgent administration of therapeutic treatments may not be well documented or properly communicated between the sending and receiving care teams.

PICO 2. In patients with intracranial hemorrhage on antiplatelet therapy, should platelet transfusion, when compared to no platelet transfusion, be administered?

Antiplatelet agents are prescribed for cardiovascular and cerebrovascular conditions for the prevention and treatment of disease and may be associated with an increased risk of ICH. While evidence noting the risk and outcomes of ICH in the setting of anticoagulants is well documented, evidence in the setting of antiplatelet use is less

clear. The impact of antiplatelet agent exposure on outcomes in patients with traumatic or spontaneous ICH remains unclear and often contradictory, including influence on hematoma expansion, need for surgery, and clinical outcomes.³⁸⁻⁴⁰ Additionally, the use of alternate or multiple antiplatelet agents by patients in studies makes the impact of specific antiplatelet agents on ICH outcomes difficult to elucidate, as well as interpretation of studies assessing treatment of the antithrombotic effects of these agents.

Available antiplatelet agents have differing mechanisms of action, half-lives and reversibility of platelet inhibition, including how effectively their effects can be reversed with platelet transfusion. For example, ticagrelor is a reversible inhibitor of adenosine diphosphate (ADP) and is not readily reversible with platelet transfusion, due to the inhibition of the newly administered platelets by the drug and metabolites.⁴¹ For irreversible platelet inhibitors including aspirin and clopidogrel, function is not restored until new platelets are synthesized, and effects may be more amenable to transfusion of platelets.

The meta-analyses conducted by the panel compared platelet transfusion to no platelet transfusion for the outcomes of mortality, functional outcome, thrombosis, hematoma expansion, hospital readmission, ICU length of stay, and additional adverse effects including transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO) and post-transfusion purpura. Three subgroups were evaluated: spontaneous intraparenchymal hemorrhage without neurosurgical

intervention; spontaneous intraparenchymal hemorrhage with neurosurgical management; and traumatic intracranial hemorrhage.

Recommendation 2-1: We suggest against administering platelet transfusions to patients with spontaneous intraparenchymal hemorrhage taking antiplatelet agents who do not require neurosurgical intervention. (Conditional recommendation, low certainty of evidence)

Evidence Summary:

Evidence for patients with spontaneous intraparenchymal hemorrhage managed without neurosurgical intervention is evaluated in one randomized controlled trial⁴² and four retrospective cohort studies.⁴³⁻⁴⁶ The current studies largely encompassed patients with intraparenchymal hemorrhage receiving aspirin, clopidogrel, and dipyridamole, alone or in combination. All studies compared platelet transfusion to no transfusion for improvement of platelet function. The panel's recommendation for this population remains unchanged compared to the 2016 guideline.

In our meta-analysis, there was no difference in mortality (pooled RR 1.16; 95% CI, 0.57 to 2.38) (Supplemental Figure 20) or adjusted survival rates (adjusted OR 0.62; 95% CI, 0.33 to 1.18) (Supplemental Figure 19). In the overall cohort, there was no difference in poor functional outcome defined as Modified Rankin Scale (mRS) 4-6 (RR 1.04; 95% CI, 0.79 to 1.36) (Supplemental Figure 21), although in the PATCH trial, assessment of

poor functional outcome favored the no platelet transfusion (control) group (adjusted OR 2.04; 95% CI, 1.12 to 3.73) (Figure 4). While definitions varied, the risk of hematoma expansion was unchanged with platelet transfusion (RR 1.25; 95% CI, 0.8 to 1.94) (Figure 5), although a difference was found when viewing as a continuous variable, with a pooled estimate favoring no platelet transfusion (mean difference 1.94; 95% CI, 0.45 to 3.42). Otherwise, there was no difference in other outcomes assessed including risk of arterial and venous thrombosis with a RR 1.89 (95% CI, 0.75 to 4.81) (Supplemental Figure 22).

Because a high quality randomized controlled trial was included in the analysis, the panel gave significant weight to its findings when formulating the recommendation, particularly with the observed association between-platelet transfusion with poor functional outcome. There was no identified impact on mortality, functional outcome or thrombosis, low likelihood of impact on hematoma expansion, and there was evidence of harm with platelet transfusion. Therefore, the panel voted to recommend against platelet transfusion for the treatment of antiplatelet effects in patients with spontaneous intraparenchymal hemorrhage who are not undergoing neurosurgical management.

Limitations of this data include lack of consistent dosing for platelet transfusion, and the treatment of multiple antiplatelet agents in included patients, and especially a low representation of patients receiving dual antiplatelet therapy. The PATCH trial protocol administered two platelet concentrates (10 donor units) to those taking ADP inhibitors, and one platelet concentrate (5 donor units) to all others.⁴² It remains unclear if this

dosing strategy is most effective, and dosing otherwise varied in the other included observational studies. Additionally, a major consideration is that this cohort largely evaluated intraparenchymal hemorrhage, with low representation of extra-axial hemorrhage. It is not clear if platelet transfusion would impact outcomes in other hemorrhage locations.

Recommendation 2-2: We suggest administering platelet transfusions to patients with spontaneous intraparenchymal hemorrhage who were on aspirin therapy who require neurosurgical intervention (Conditional recommendation, very low certainty evidence).

Evidence Summary:

Evidence for patients undergoing surgical management is evaluated in one randomized controlled trial.⁴⁷ Based on this study, patients on aspirin undergoing neurosurgical management who were administered platelet transfusion, as compared to no platelet transfusion, had lower mortality with a RR 0.46 (95% CI, 0.32 to 0.68), reduced postoperative hemorrhage rate (RR 0.4; 95% CI, 0.27 to 0.6) with reduced hematoma expansion based on hemorrhage volume (mean difference -20.89; 95% CI, -25.05 to -16.73), and increased favorable functional outcomes based on ADL score at 6 months (see Supplemental Figures 23-26). This recommendation is given with low certainty of evidence despite being an RCT due to several limitations. This single-center open-label study completed in China included five arms totaling 780 patients admitted with basal ganglia hemorrhage undergoing craniotomy for hematoma evacuation, of which 501 patients who were taking aspirin underwent assessment of aspirin responsiveness as

tested by photoelectric turbidimetry. A total of 244 “aspirin-sensitive” patients were randomized to receive either one or two doses of platelet transfusion perioperatively, and were compared to 122 aspirin-sensitive patients who did not receive transfusion. Outcomes did not seem to differ between patients receiving one pre-operative dose of platelets compared to those receiving one pre-operative dose plus a second dose 24 hours later, and the optimal dose of platelets in this population remains unclear.

Several factors limit the generalizability of this study, including its single-center design, the use of a less commonly available method for aspirin sensitivity testing, reliance on a potentially non-validated functional outcome measure (ADL score), and its focus on a narrowly defined neurosurgical intervention. There are no studies assessing other neurosurgical interventions or hematoma locations, or perioperative platelet transfusion in patients receiving other classes of antiplatelet agents (ie, P2Y12 inhibitors) such that it is unknown if this strategy is effective outside of the narrow spectrum of the current study parameters. Additionally, limiting to one unit of platelets seems reasonable as outcomes were not different from patients who received two units of platelets. Further studies are needed in patients requiring emergent neurosurgical intervention, including other types of procedures, clarification of the dose of platelets, and assessment in patients receiving other classes of antiplatelet agents.

Our recommendation to transfuse platelets in this population remains largely unchanged from the 2016 guideline with no new evidence, with one difference. As there are no included studies evaluating the effect of platelet transfusion in patients receiving P2Y12

inhibitors, we limit the application of this data to patients receiving pre-morbid aspirin only, which is an update from our 2016 recommendation. However, it may be reasonable to transfuse platelets in patients on antiplatelet agents other than aspirin prior to neurosurgical intervention. Additionally, ventriculostomy placement is not specifically addressed by Li et al. However common current practice dictates that patients on antithrombotic medications are managed in a similar fashion to neurosurgical intervention prior to ventriculostomy placement, and thus platelet transfusion in patients on antiplatelet agents may be reasonable.

Recommendation 2-3: We make no recommendation regarding administration of platelets for patients with traumatic intracranial hemorrhage who were on antiplatelet therapy.

Evidence Summary:

The panel reviewed evidence for patients with traumatic ICH as a separate subgroup from spontaneous ICH and neurosurgical intervention, aiming to generate a new recommendation. Traumatic brain injury encompasses a wide spectrum of injury patterns and hemorrhage locations which may have varying predispositions on the risk of hematoma expansion and affected patient outcomes. Evidence in traumatic intracranial hemorrhage was reviewed in 10 retrospective studies which generated very low certainty of evidence.⁴⁸⁻⁵⁷ All studies included cohorts of patients receiving antiplatelet therapy, including aspirin, P2Y12 inhibitors, and combination therapy, and included platelet transfusion and no transfusion groups. Most studies excluded patients

with major extracranial injury, and encompassed a range of intracranial hemorrhage locations, including subdural hematoma, intraparenchymal hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage, and epidural hematoma.

In the meta-analysis conducted by the panel, there was no difference in mortality following transfusion of two packs of platelets (adjusted OR 0.97; 95% CI, 0.76 to 1.22) (Figure 6), poor functional outcome (adjusted OR 0.69; 95% CI, 0.40 to 1.18) (Figure 7), or ICU length of stay (mean difference 1.07, 95% CI -0.39 to 2.53) (Supplemental Figure 30). In our analysis, hematoma expansion was found to be reduced with platelet transfusion in two studies with adjusted analyses following transfusion of two packs of platelets^{51,53} (adjusted OR 0.68; 95% CI, 0.54 to 0.88) (Figure 8), however no difference in unadjusted hematoma expansion from 8 studies (RR 1.06; 95% CI, 0.52 to 2.16) (Supplemental Figure 31). Only one study reported on adverse effects of platelet transfusion which showed no difference in the risk of thrombosis (RR 0.55; 95% CI, 0.1 to 2.91) (Supplemental Figure 32), however the true incidence of adverse effects is likely underreported in these retrospective studies.⁵⁶

Two studies limited their assessment to mild TBI.^{48,54} In both studies focusing on mild TBI, there was no difference in mortality, hematoma expansion, or functional outcome at discharge between groups receiving platelet transfusion as compared to no transfusion. In one study, which analyzed patients with severe TBI as a separate subgroup, there was no difference in outcomes among patients who received platelet transfusion as compared to no transfusion when compared to the overall cohort.⁵⁷ While these studies

do not suggest that severity of TBI influences outcomes following platelet transfusion, these studies are insufficient to draw conclusions about whether patients with mild versus moderate-severe injury may preferentially benefit from platelet transfusion for treatment of antiplatelet effects following TBI.

Two studies reported the effects of transfusion of two units of platelets rather than a single dose of apheresis platelets.^{53,56} Lokhandwala and colleagues assessed the effect of platelet transfusion as compared to no platelet transfusion in 343 patients with traumatic ICH on pre-injury antiplatelet therapy with aspirin (59%), clopidogrel (35%) and dual antiplatelet therapy (5%). In the overall cohort, patients who received platelet transfusion had lower rates of hemorrhage expansion ($p<0.01$) and decreased need for neurosurgical intervention ($p<0.01$), however no difference in discharge Glasgow Outcome Scale-Extended (GOS-E) or mortality. Interestingly, when comparing patients who received one pack of platelets ($n=145$) to those who received two packs ($n=108$), transfusion of two packs was associated with lower rates of progression of intracranial bleeding (adjusted OR 0.69; 95% CI, 0.4 to 0.8), neurosurgical intervention (adjusted OR 0.81; 95% CI, 0.3 to 0.9) and mortality (aOR 0.84; 95% CI, 0.5 to 0.9) in multivariate regression, leading the authors to conclude that two packs of platelets may improve these endpoints.⁵³ Conversely, Holland et al presented data on their center's experience with changing from a liberal platelet transfusion strategy to a restrictive strategy for patients receiving neurosurgical intervention. The previous practice was to transfuse two platelet packs for patients on pre-injury P2Y12 inhibitors or aspirin-dipyridamole, and one pack for patients on aspirin alone. The study found no difference between

transfusion strategies in regards to need for neurosurgical intervention, functional outcomes, mortality or hospital readmission. When they compared the protocols with respect to aspirin only (one platelet unit) use versus clopidogrel with or without aspirin (two platelet units), outcomes were similar for all of the aforementioned outcomes including need for operative management (aspirin only $p = 1.0$; clopidogrel $p = 0.55$) and hematoma expansion (aspirin only $p = 0.37$, clopidogrel $p = 0.068$).⁵⁶ It remains unclear what dose of platelet transfusion is necessary to improve outcomes and for which antiplatelet agents different doses may benefit; we note that the 2016 guideline suggested a single-donor apheresis unit of platelets with repeat dosing only following platelet testing, and this was not separately addressed in this current guideline for a forthright dosing recommendation (Supplemental Table 13).

Use of platelet function testing was reported in three studies.^{49,52,54} One study reported utilization of VerifyNow assays, however, it did not include patients with normal platelet function despite antiplatelet use. Therefore, it was not possible to compare the effect of these results on outcomes.⁵⁴ Agyabeng-Dadzie et al also reported using the VerifyNow Aspirin and P2Y12 assays but did not disclose these results for evaluation.⁵²

Conversely, Holzmacher et al utilized thromboelastography with platelet mapping (TEG-PM) in 66 patients with blunt TBI, 89.4% of whom were on aspirin, 50% on clopidogrel, 22.7% on dual antiplatelets, and 4.5% on other agents. The degree of platelet inhibition in the arachidonic acid (AA) pathway, but not the adenosine diphosphate (ADP) pathway, were significantly reduced after platelet transfusion with a mean of 1.2 units of platelets transfused. The change in inhibition for both AA and ADP were not associated

with changes in Marshall classification scores, signifying that improvement in platelet function did not predict hematoma expansion.⁴⁹ More high quality research is needed to define whether platelet transfusion and at what dose may improve PFAs and if use of PFAs in patients with TBI can lead to improved outcomes.

The interpretation of these studies in traumatic ICH is limited by several factors, including varied severity of injury and varied location of injury, varied antiplatelet agents including dual antiplatelet use, use of antiplatelet assays, and dose of platelets transfused. Transfusion practices also vary between centers, such that often the decision to administer platelets was at the discretion of the provider, which likely created significant selection bias.

Overall, due to the poor quality of evidence, the panel felt it could not make a recommendation for or against transfusion of platelets in patients with traumatic intracranial hemorrhage receiving antiplatelet agents, as compared to no transfusion.

Platelet transfusion carries well known risks of adverse effects. These risks include transfusion reactions such as anaphylaxis, transfusion-related acute lung injury and transfusion-associated circulatory overload, alloimmunization, infections, and post-transfusion purpura.⁵⁸ Some studies also noted worse outcomes following platelet transfusion with unknown mechanisms, particularly evidenced in the PATCH trial.⁴² In developing these recommendations, the panel considered both the known general risks of platelet transfusion and the need to conserve blood products, especially during

shortages or in resource-limited settings. It is also difficult to estimate the precise cost of platelet transfusion, given the many steps necessary for collection, processing, distributing, and administering transfusions. In one center in the United States in 2017, the total cost attributed to transfusion of one unit of platelets was reported to be \$1,359.99, which excluded collection and processing costs.⁵⁹ In another study published in 2018, the direct costs per transfusion was estimated to be \$3,723 to \$4,436.⁶⁰

The panel also acknowledges the lack of robust data for platelet transfusion for treatment of antiplatelet effects in extra-axial ICH outside of traumatic ICH. Only one retrospective study was identified in the population of aneurysmal subarachnoid hemorrhage.⁶¹ Additionally, overall there is a paucity of evidence in all ICH sub-populations regarding the efficacy of platelet transfusion in the setting of use of specific P2Y12 inhibitors and dual antiplatelet therapy, which require further study (Table 3).

PICO 3. In patients with intracranial hemorrhage on antiplatelet therapy, should desmopressin, when compared to no desmopressin, be administered?

Recommendation 3-1: We make no recommendation regarding use of desmopressin in patients with intracranial hemorrhage on antiplatelet therapy.

Summary of Evidence:

Desmopressin (also known as DDAVP) is a vasopressin analog that promotes hemostasis by inducing release of factor VIII and von Willebrand factor from endothelial

cells into the circulation. It may also enhance the procoagulant activity of platelets. It is used in a variety of inherited and acquired bleeding disorders for prevention and/or treatment of hemorrhage.⁶² Most relevant to antiplatelet agent-associated intracranial hemorrhage, a meta-analysis that included 10 randomized controlled trials showed that DDAVP, when compared to usual care, was associated with reduced bleeding in patients taking antiplatelet agents who underwent cardiac surgery.⁶³ Accordingly, as there is currently no proven treatment strategy for patients with antiplatelet-associated intracranial hemorrhage, DDAVP has been investigated for this purpose. Based on the suggestion of possible benefit and a low risk of adverse effects in two very small studies of patients with antiplatelet-associated intracranial hemorrhages of various types, the 2016 NCS/SCCM guideline suggested consideration of a single dose of DDAVP (0.4 mcg/kg IV) for ICH associated with aspirin/COX-1 inhibitors or ADP receptor inhibitors.³ We sought to reexamine this question in the context of new evidence published since the 2016 guideline.

A total of 10 studies were included in our analysis, including one phase 2 RCT and nine retrospective studies.^{54,57,64-71} Data were unfortunately insufficient to subgroup outcomes by hemorrhage subtype (spontaneous versus traumatic), and data are reviewed in aggregate. For the outcome of hematoma expansion, we identified one RCT trial and eight observational studies. The DASH trial, a phase 2, randomized, placebo-controlled, multicenter feasibility trial is the only RCT to examine this topic.⁶⁴ In 54 patients with primary intraparenchymal hemorrhage who were taking an oral antiplatelet drug (46% on aspirin alone and 43% on clopidogrel alone) and could be

randomized within 24 hours of symptom onset, a single 20 mcg intravenous dose of DDAVP had no effect on hematoma expansion (RR 0.92; 95% CI, 0.31 to 2.74). Despite its prospective, randomized, controlled nature, we deemed the quality of evidence from the DASH trial low as it was a feasibility trial in a very small, highly selected study population, and hematoma expansion was a secondary outcome. Importantly, the analysis of hematoma expansion outcomes did not control for potential confounding influences on hematoma expansion. The non-randomized studies included in the analysis^{54,65-71} had additional limitations beyond those inherent to their design, such as small sample sizes and substantial heterogeneity in ICH types and severity, DDAVP dosing, number and type of antiplatelet agents to which patients were exposed, and definitions of hematoma expansion. Overall, our meta-analysis showed no effect of DDAVP on hematoma expansion (RR 0.84; 95% CI, 0.48 to 1.49) (Supplemental Figure 36) including in the adjusted analysis for hematoma expansion (RR 0.66; 95% CI, 0.34 to 1.30) (Figure 9).

For the outcome of mortality/discharge to hospice, we identified one RCT and eight observational studies. Again, the DASH trial was the only RCT and, as with hematoma expansion, mortality was a secondary outcome on which no effect of DDAVP was demonstrated (RR 0.71, 95% CI 0.26 to 1.97). When the same eight observational studies from the hematoma expansion analysis were included in the meta-analysis, there was again no effect of DDAVP on mortality (RR 1.15; 95% CI, 0.92 to 1.44) (Supplemental Figure 34). Our meta-analysis of one RCT and two observational studies that assessed the effect of DDAVP on the likelihood of unfavorable functional

outcome in patients with spontaneous^{64,65} or traumatic⁵⁴ antiplatelet-associated intracranial hemorrhage again showed no effect of DDAVP (RR 1.5; 95% CI, 0.82 to 2.72) (Supplemental Figure 35). Finally, we identified three observational studies that examined the effect of DDAVP on length of stay in the ICU.^{57,66,69} Mean length of stay in the ICU was not significantly affected by treatment with DDAVP (mean difference 0.44 days higher with DDAVP; 95% CI, 0.26 fewer days to 1.14 more days) (Supplemental Figure 40).

Potential adverse effects of DDAVP administration mainly include thrombosis and hyponatremia-related seizures. The DASH trial along with one observational study reported on the outcome of seizures in patients with antiplatelet-associated intracranial hemorrhage who received DDAVP.^{64,66} There was no significant difference in the risk of seizures in patients treated with DDAVP compared to those who did not receive DDAVP (RR 0.74; 95% CI, 0.22 to 2.48) (Supplemental Figure 38). We identified one randomized controlled trial and six observational studies that reported on venous and arterial thromboembolic events.⁶⁶⁻⁷¹ There was no significant difference in the risk of thrombotic events between patients treated with DDAVP and those who did not receive it (RR 0.86; 95% CI, 0.59 to 1.23) (Supplemental Figure 39). Lastly, dosing was not assessed separately in this update, however in most included studies the dosage of IV desmopressin ranged between 0.3-0.4 mcg/kg (Supplemental Table 16)

For all of the outcomes we examined, the 95% confidence interval of the risk ratio (mean difference in the case of ICU LOS) was wide and crossed unity. Additionally, the

evidence was very low certainty. Key limitations in the evidence included a paucity of randomized controlled trials (only one randomized controlled feasibility trial including 54 patients was identified); inconsistent timing of DDAVP administration in relation to ICH onset or presentation; lack of adjustment for potential confounders in some observational studies; heterogeneous eligibility criteria, especially the inclusion of patients with intracranial hemorrhages of different etiologies, exposure to different antiplatelet agents, or both; inconsistent allowance of concomitant platelet transfusion; and inconsistent ascertainment and reporting of outcomes. For these reasons, the panel determined that the balance of effects favored neither the intervention (DDAVP) nor the comparator (no intervention) and that the evidence was too limited to make a recommendation for or against DDAVP in patients with intracranial hemorrhage associated with antiplatelet therapy. The panel emphasized the urgent need for sufficiently powered, well-designed RCTs that overcome the aforementioned shortcomings in the existing literature to address this question, particularly given the biological plausibility of DDAVP being a safe and effective treatment for a critical condition that currently has no proven treatment.

PICO 4. In patients with small spontaneous intraparenchymal hemorrhage on therapeutic anticoagulant therapy, should treatment of anticoagulant effects, when compared to no treatment, be administered?

Recommendation 4-1: We cannot make a recommendation regarding treatment of anticoagulant effects in patients with small intraparenchymal hemorrhage due to lack of evidence.

Evidence Summary:

In the setting of intraparenchymal hemorrhage (IPH), hematoma expansion (HE) is an important predictor of neurologic deterioration, poor functional outcome and mortality. Small IPH is a subjective term, however generally refers to hemorrhage volumes less than 5-10 mL, depending on IPH location. For every 1 mL increase in IPH size, there is a 5% increased risk of death or dependency.⁷² The pathophysiology of HE remains unclear. Coagulation status seems to influence acute IPH formation, but whether it has a direct causal effect is unknown. Previously identified predictors of HE include time from symptom onset to baseline imaging, IPH volume, and antiplatelet or anticoagulant use.⁷³ Approximately 20% of patients with IPH, or 33% of patients presenting within 6 hours of symptom onset, will have HE.⁷⁴ The relationship between time of IPH onset and risk of HE is non-linear - the highest expansion risk occurs within the first 3 hours and then the risk plateaus after 6 hours, though is expected to be prolonged in the setting of anticoagulant use.⁷³

Patients with underlying coagulopathy are at high risk of HE due to ongoing bleeding or potential for early rebleeding.⁷⁵ Patients with vitamin K antagonist-associated IPH can have a HE risk of > 50% in the first 6 hours following stroke onset. This expansion can also occur beyond 24 hours, and patients have a higher risk of death compared to

patients without coagulopathy. Patients taking direct oral anticoagulants also have an increased risk of HE, but the risk appears lower than that in vitamin K antagonist-associated IPH, and clinical outcomes may be less severe.⁷⁶

Therefore, in patients with small hemorrhage volumes on admission, some key factors that may influence the treatment decision include delay from symptom onset to imaging, location of ICH, type of oral anticoagulant and timing of last dose, severity of neurological deficit and indication for anticoagulation. Critical elements such as the anticoagulation level or the ultra-early hematoma growth [(baseline hemorrhage volume divided by onset-to-imaging time [mL/h]) which is an indirect indicator of the speed of bleeding] may further guide clinicians. The balance is delicate when considering risk of thrombosis versus prevention of HE leading to significant practice variability in the decision to reverse anticoagulant therapy in small IPH.⁷⁷ Future research evaluating treatment of small IPH volumes should consider key factors listed above to help provide more guidance to clinicians.

Due to the limited evidence available in the literature, we cannot make a recommendation for or against treatment of anticoagulant effects in small IPH.

PICO 5. In patients with traumatic intracranial hemorrhage, should the use of viscoelastic hemostatic assays (VHAs), when compared to no use of VHAs, be used to guide treatment of coagulopathy?

Recommendation 5-1: We suggest using VHA-guided management in patients with traumatic intracranial hemorrhage, when VHAs are available (conditional recommendation, very low quality evidence).

Summary of Evidence:

Viscoelastic hemostatic assays (VHA) are whole blood point-of-care tests that provide real time coagulation dynamics and have been used in the last sixty years, primarily driving perioperative solid organ transplantation transfusion management.⁷⁸

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have been used to guide trauma resuscitation.⁷⁹ While common coagulation tests have guided management of patients with isolated deficiencies and those treated with anticoagulant therapies, the limitations of these tests have prompted clinicians to utilize VHA more broadly to guide management. This PICO question aimed to identify evidence that may clarify impact of VHA guidance for this population and noted outcomes of interest including mortality, functional outcome, hemorrhagic expansion, and blood products administered. Other outcomes of interest included thrombosis, hospital readmission, ICU length of stay, and transfusion reaction, but none of these were reported in the literature. One member abstained from voting for this PICO as they were an author in one of the included studies.

Based on our meta-analysis, mortality may be favorably impacted by VHA-guided treatment (RR 0.59; 95% CI, 0.39 to 0.89), but this was limited to a non-stratified subgroup (severe TBI) of one RCT (Figure 10).⁸⁰ Functional outcome was not impacted

by VHA-guided treatment (RR 0.85; 95% CI, 0.64 to 1.12) (Supplemental Figure 43).^{81,82} Hospital length of stay among survivors was only reported in one observational study where there was no difference between standard care and VHA-guided treatment ($p = 0.28$).⁸² There was no impact of VHA-guided treatment on hematoma expansion (RR 0.9; 95% CI, 0.4 to 2.01) (Supplemental Figure 45).^{81,82} In the only study reporting overall blood product administration, there was no impact of VHA guidance on overall blood administration ($p = 0.94$).⁸² Kvint et al reported a reduction in platelet transfusion in their thromboelastography with platelet mapping (TEG-PM) group as compared to standard of care, however the pooled estimate showed no difference when combined with another study evaluating the use of ROTEM (RR 0.42; 95% CI, 0.07 to 2.56) (Supplemental Figure 46).^{81,82}

The included data has several limitations that must be acknowledged. The reduction in mortality with use of VHAs was largely driven by one RCT which included 396 trauma patients receiving major hemorrhage protocols, of which the severe TBI subgroup comprised 74 patients. The population in this study had low overall rates of coagulopathy which limited ability to evaluate responses to VHA-guided treatment (see Supplemental Table 17).⁸⁰ It is important to note that coagulopathy was defined in various ways in these studies, with differing inclusion or exclusion criteria based on pre-morbid anticoagulant or antiplatelet use. Hota et al assessed the use of TEG in patients for treatment of anticoagulant or antiplatelet effects, while Kvint assessed the use of TEG-PM in patients on antiplatelet agents (68-84% of patients on aspirin monotherapy, 19-22% of patients on dual antiplatelet therapy).^{81,83} Lastly, Rimaitis et al evaluated the use of ROTEM in patients with TBI undergoing craniotomy, excluding patients on pre-

morbidity and mortality.⁸² These heterogeneous study populations and mechanisms of coagulopathy make it difficult to appreciate the true place in therapy for VHA testing in the TBI population, and further studies are required to elucidate this. Finally, the VHA protocols varied between studies and often were not specified to elucidate treatment threshold and interventions; VHA protocols are often developed in a center-specific fashion in current practice. Additional research is required to define the optimal treatment protocols for the use of various blood products and medications based on specific VHA results to improve outcomes in TBI.

While VHA technology is not new, some limitations related to training and quality control processes may limit broader use. This may result in reduced equity for utilization in areas where the technology is not adopted. In more developed areas with organized trauma systems, this patient population is likely treated in trauma centers where the technology is more widely adopted. Different devices may offer advantages for use. ROTEM might be different than other devices. Additionally, newer VHA devices are more user friendly. Regardless, standardized training as well as accessibility of results for clinicians who can utilize the results for treatment decisions are necessary.

A limitation to this recommendation is the lack of a treatment nomogram or algorithm to guide therapy. However treatment nomograms are not standardized and often vary between centers. They may utilize different platforms or versions of the technology (TEG 6S, ROTEM, etc.). It should be noted that various guidelines make recommendations for the use of diagnostic technology without making specific recommendations for treatment thresholds. For example, the Surviving Sepsis

Guideline recommends using dynamic measures to guide fluid resuscitation, but does not provide or stipulate specific algorithms or treatment thresholds. Similarly, the Eastern Association for the Surgery of Trauma (EAST) practice management guideline for TEG and ROTEM in bleeding patients with coagulopathy does not provide static thresholds for treatment.⁸⁴

Despite very low quality evidence, the panel felt it was appropriate to make a recommendation for use of VHAs, when available, in the management of patients with traumatic ICH, particularly given that the recommendation is for use of a laboratory test rather than a medication or other therapeutic intervention, and potential for positive impact on mortality in the TBI subgroup of the included RCT.

Research Agenda

See Table 3 for suggested research priorities related to the treatment of antithrombotic medication effects in acute ICH.

Conclusions

A summary of recommendations is listed in Table 1. The care of patients with acute ICH and decisions for treatment in the setting of antithrombotic agent use can be highly complex and may be additionally guided by the patient's clinical status and patient-

specific factors. Overall the panel was unable to generate any strong recommendations indicating the need for additional high quality research in this practice area (Table 3).

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Glossary of Terms

- **Strong Recommendation:** A strong recommendation is made when the totality of anticipated desirable effects of one intervention (or nonintervention) outweigh those of the alternatives. A strong recommendation implies that most or all patients will be best served by the recommended course of action.
- **Conditional Recommendation:** Previously referred to as weak recommendations, are used when the desirable effects likely outweigh the undesirable effects (conditional recommendation for an intervention) or undesirable effects likely outweigh the desirable effects (conditional recommendation against). These recommendations imply that the panel believes most patients would want their care to align with the recommendation but many would not. Conditional recommendations are used when the certainty of evidence is low/very low, when

there is variability in the values and preferences of individuals or when the balance of desirable and undesirable effects is small.

- High Quality: A high-quality recommendation indicates high confidence that the true effect is close to what is found in the literature.
- Moderate Quality: A moderate-quality recommendation indicates moderate confidence in the true effect, but it might be different from what is found in the literature.
- Low Quality: A low-quality recommendation indicates that the true effects may be substantially different from what is found in the literature and subsequent research may change the effect.
- Very Low Quality: A very-low-quality recommendation indicates little confidence in the effect found in the literature and true effects may be considerably different.
- Good Practice Statement: Recommends a course of action when the benefits outweigh the harms but there is no evidence to support it, making a formal GRADE recommendation impossible.

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Figure Captions

Figure 1. PICO 1, Andexanet alfa versus PCC for factor Xa inhibitor-associated ICH. Meta-analysis of mortality (unadjusted), stratified by hemorrhage mechanism subtype and randomized versus non-randomized study design. PCC, prothrombin complex concentrate; RCT, randomized controlled trial; RR, relative risk.

Figure 2. PICO 1, Andexanet alfa versus PCC for factor Xa inhibitor-associated ICH. Meta-analysis of mortality (unadjusted) in observational studies in patients with spontaneous IPH. PCC, prothrombin complex concentrate; RR, relative risk.

Figure 3. PICO 1, Andexanet alfa versus PCC in factor Xa inhibitor-associated ICH. Meta-analysis of thrombosis (unadjusted), stratified by hemorrhage mechanism subtype and randomized versus non-randomized study design. PCC, prothrombin complex concentrate; RCT, randomized controlled trial; RR, relative risk.

Figure 4. PICO 2, Platelet transfusion versus no platelet transfusion in antiplatelet-associated spontaneous ICH with no neurosurgical intervention. Meta-analysis of poor functional outcome (adjusted). ICH, intracranial hemorrhage; Plt, platelet.

Figure 5. PICO 2, Platelet transfusion versus no platelet transfusion in antiplatelet-associated spontaneous ICH with no neurosurgical intervention. Meta-analysis of hematoma expansion (unadjusted), stratified by randomized versus nonrandomized

study design. ICH, intracranial hemorrhage; non-RCT, non-randomized controlled trial; Plt, platelet; RCT, randomized controlled trial; RR, relative risk.

Figure 6. PICO 2, Platelet transfusion versus no platelet transfusion in antiplatelet-associated traumatic ICH. Meta-analysis of mortality (adjusted) with transfusion of two packs of platelets. Adjusted analyses completed with STATA (StataCorp 2025, College Station, TX).

Figure 7. PICO 2, Platelet transfusion versus no platelet transfusion in antiplatelet-associated traumatic ICH. Meta-analysis of poor functional outcomes (adjusted). GOS, Glasgow Outcome Scale; ICH, intracranial hemorrhage; Plt, platelet.

Figure 8. PICO 2, Platelet transfusion versus no platelet transfusion in antiplatelet-associated traumatic ICH. Meta-analysis of hematoma expansion (adjusted) with transfusion of two packs of platelets. Adjusted analyses completed with STATA (StataCorp 2025, College Station, TX). OR, odds ratio.

Figure 9. PICO 3, DDAVP versus no DDAVP in antiplatelet-associated ICH. Meta-analysis of hematoma expansion (adjusted). DDAVP, desmopressin.

Figure 10. PICO 5, VHA use versus no VHA use in traumatic ICH. Meta-analysis of mortality (unadjusted) in patients with severe TBI stratified by randomized versus non-

randomized study design. RCT, randomized controlled trial; TBI, traumatic brain injury;
VHA, viscoelastic hemostatic assay.

Figure 1

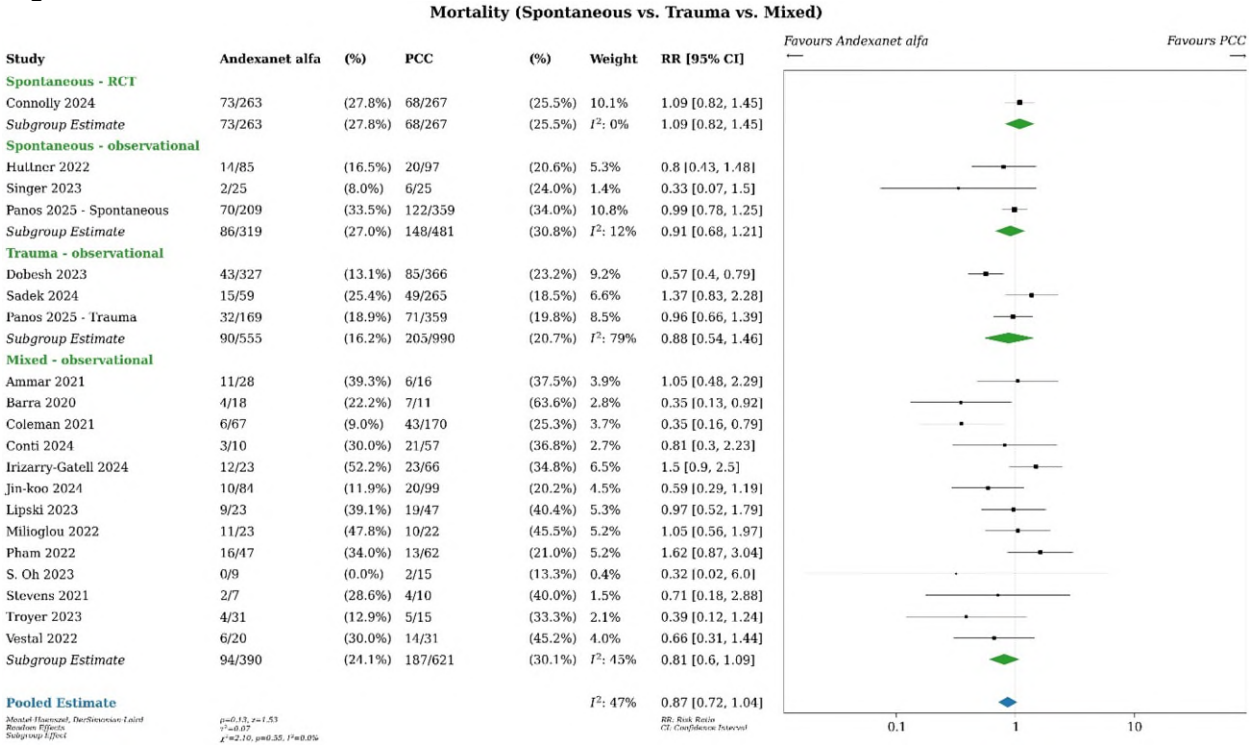


Figure 2

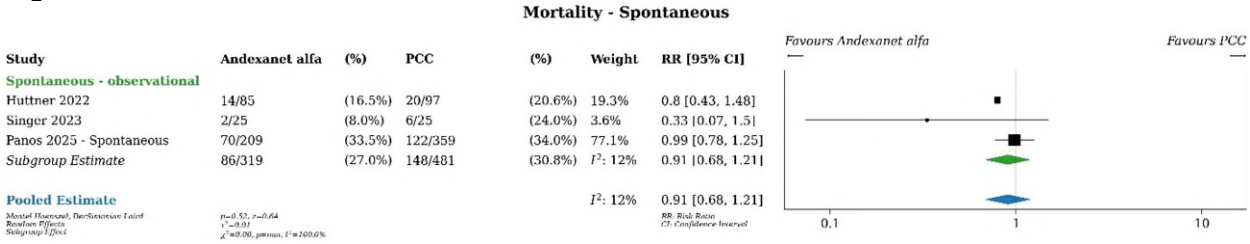


Figure 3

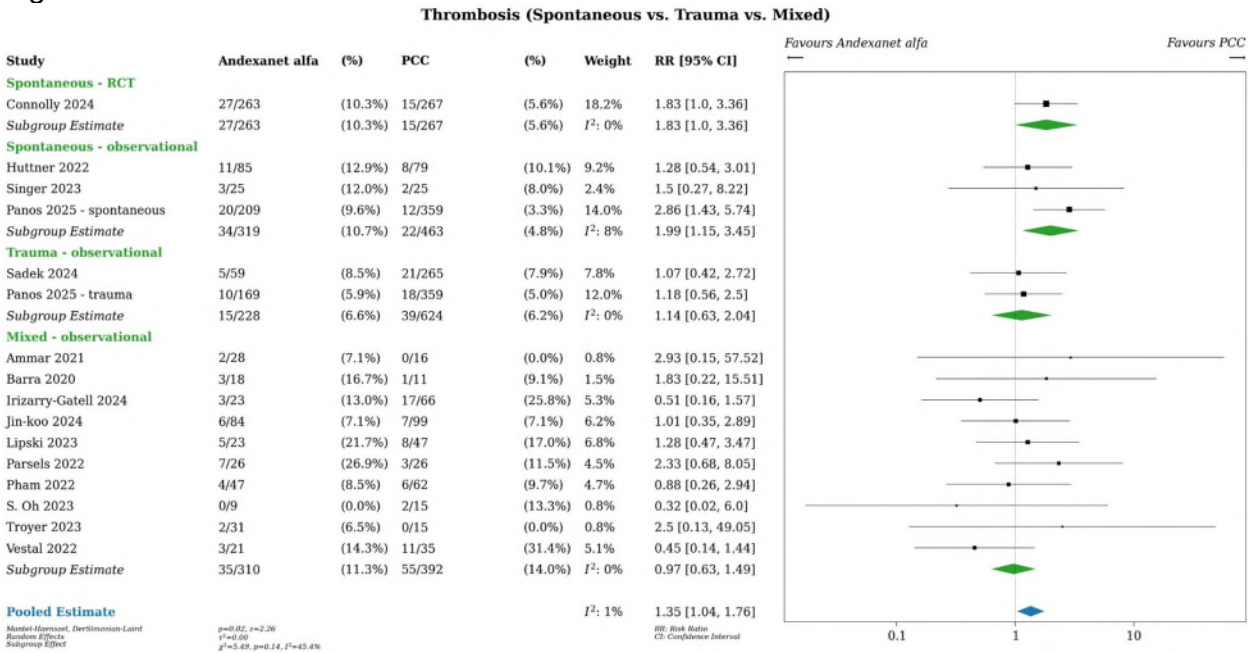


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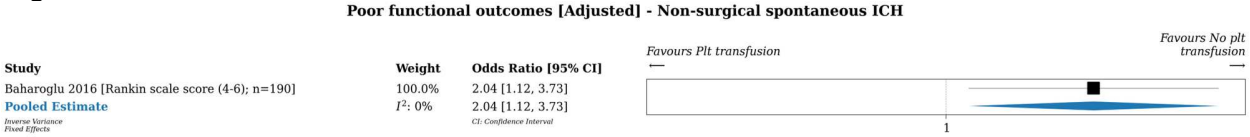


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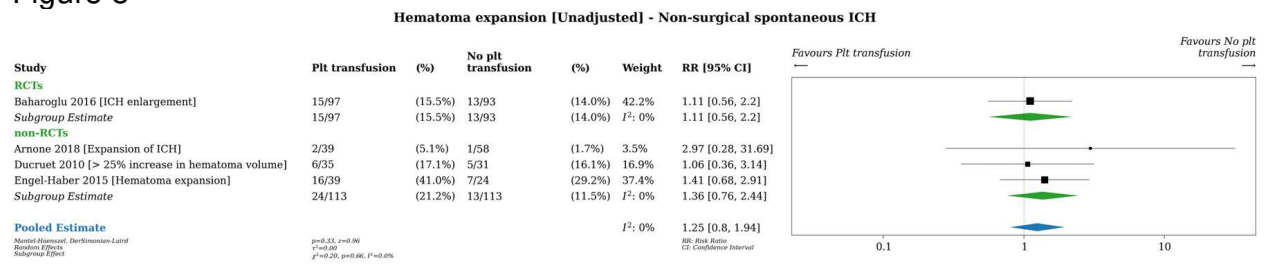
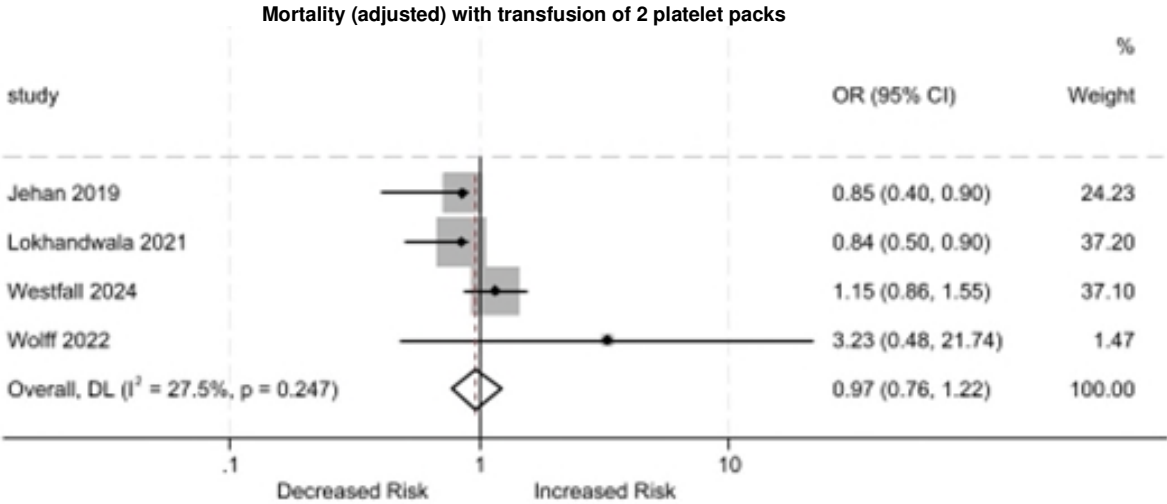


Figure 6



NOTE: Weights are from random-effects model

Figure 7

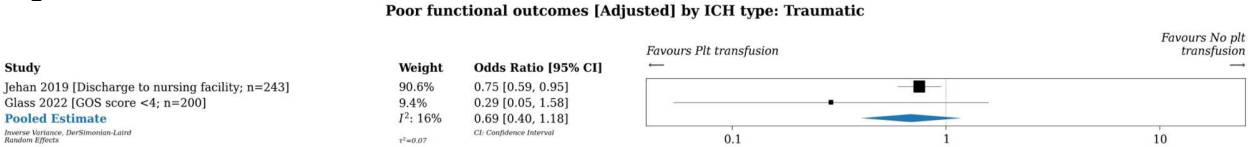


Figure 8

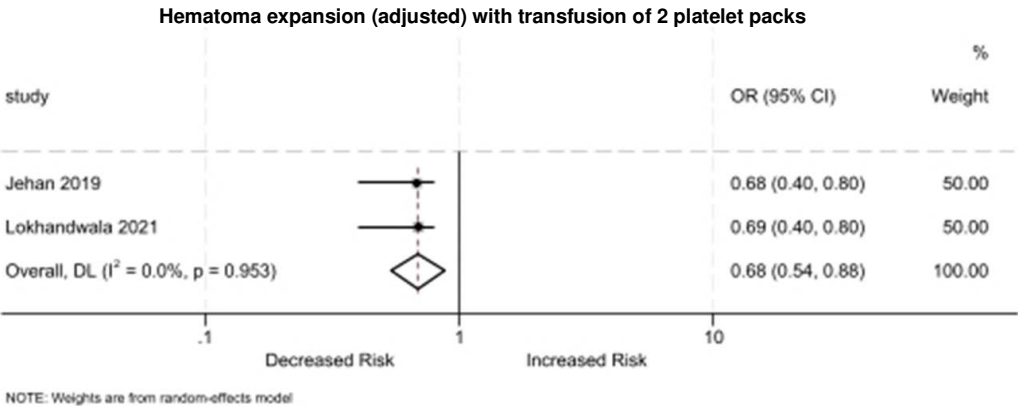


Figure 9

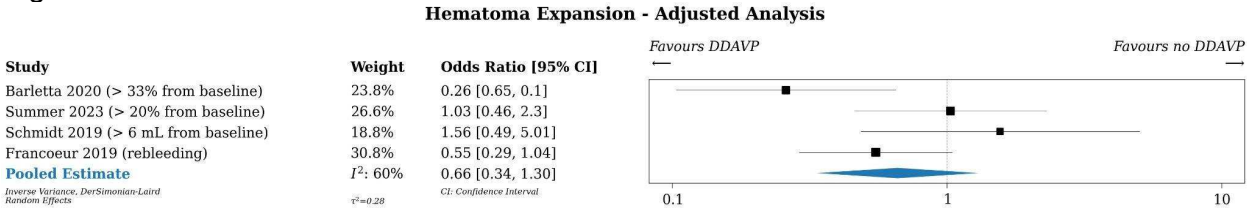


Figure 10

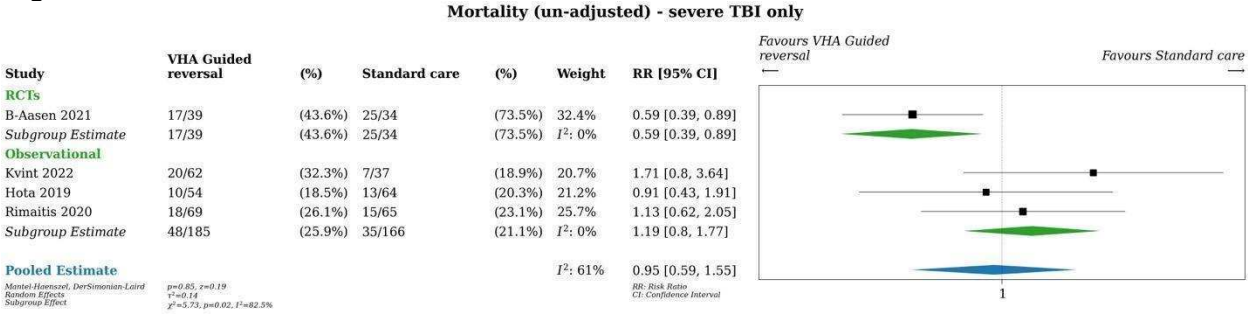


Table 1. Updated and Prior Recommendations

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	Recommendations from 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage	Current Recommendations
Direct Oral Factor Xa Inhibitors	<p><u>Prior Recommendations (Not reviewed or updated):</u></p> <ol style="list-style-type: none"> 1. We recommend discontinuing factor Xa inhibitors when intracranial hemorrhage is present or suspected. (Good Practice statement) 2. We recommend obtaining information on the time elapsed since the last dose of direct factor Xa inhibitor and possible medication interactions to assist in estimating the degree of anticoagulation exposure. (Good Practice statement) 3. We suggest that pharmacological reversal of oral factor Xa inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing. (Conditional recommendation, low-quality evidence) 4. We suggest administration of activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of 	<ol style="list-style-type: none"> 1. For patients with any type of intracranial hemorrhage on factor Xa inhibitors, we suggest 4-factor prothrombin complex concentrate over andexanet alfa for treatment of anticoagulant effects. <ol style="list-style-type: none"> 1-1. We suggest using 4-factor prothrombin complex concentrate rather than andexanet alfa in patients with factor Xa inhibitor-associated spontaneous ICH (conditional recommendation; moderate certainty evidence). 1-2. We suggest using 4-factor prothrombin

Table 1: Updated and Prior Recommendations		
	Recommendations from 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage	Current Recommendations
	<p>ingestion of an oral direct factor Xa inhibitor. (Conditional recommendation, very low-quality evidence)</p> <p><u>Revised Recommendations:</u></p> <p>5. We suggest administering a 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure. (Conditional recommendation, low-quality evidence)</p> <p>6. We suggest administering 4-factor PCC or activated PCC over rFVIIa because of the lower risk of adverse thrombotic events. (Conditional recommendation, low-quality evidence)</p>	<p>complex concentrate rather than andexanet alfa in patients with factor Xa inhibitor-associated traumatic ICH (conditional recommendation; very low certainty evidence).</p> <p>Good Practice Statement: Due to the prothrombotic risk, we advise against the combination of andexanet alfa and PCC</p>
Antiplatelet Agents – Platelet Transfusion	<p><u>Prior Recommendations (Not reviewed or updated):</u></p> <p>1. We recommend discontinuing antiplatelet agents when intracranial hemorrhage is present or suspected. (Good Practice statement)</p> <p>1. In candidates for platelet transfusion, we suggest an initial dose of one single-</p>	<p>2-1. We suggest against administering platelet transfusions to patients with spontaneous intraparenchymal hemorrhage taking antiplatelet agents who do not require neurosurgical</p>

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	Recommendations from 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage	Current Recommendations
	<p>donor apheresis unit of platelets. Platelet testing is suggested prior to repeat platelet transfusion, if available and repeat transfusion should be used only for those with persistently abnormal platelet function tests and/or ongoing bleeding. (Conditional recommendation, moderate quality evidence)</p> <p>2. In candidates for platelet transfusion, we suggest an initial dose of one single-donor apheresis unit of platelets. Platelet testing is suggested prior to repeat platelet transfusion, if available and repeat transfusion should be used only for those with persistently abnormal platelet function tests and/or ongoing bleeding. (Conditional recommendation, moderate quality evidence)</p> <p><u>Revised Recommendations:</u></p> <p>3. We suggest against platelet transfusion for patients with antiplatelet-associated intracranial hemorrhage who will not undergo a neurosurgical procedure, regardless of the type of platelet</p>	<p>intervention (conditional recommendation, very low certainty evidence).</p> <p>2-2. We suggest administering platelet transfusions to patients with spontaneous intraparenchymal hemorrhage who were on aspirin therapy who require neurosurgical intervention (conditional recommendation, very low certainty evidence).</p> <p>2-3. We make no recommendation regarding administration of platelets for patients with traumatic intracranial hemorrhage who were on antiplatelet therapy.</p>

Table 1: Updated and Prior Recommendations		
	Recommendations from 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage	Current Recommendations
	<p>inhibitor, platelet function testing, hemorrhage volume, or neurological exam. (Conditional recommendation, low-quality evidence)</p> <p>4. We suggest platelet transfusion for patients with aspirin- or ADP inhibitor-associated intracranial hemorrhage who will undergo a neurosurgical procedure. (Conditional recommendation, moderate quality of evidence)</p>	
Antiplatelet Agents – Desmopressin	<p><u>Revised Recommendations:</u></p> <p>1. We suggest consideration of a single dose of desmopressin (DDAVP) in intracranial hemorrhage (0.4 mcg/kg IV) associated with aspirin/COX-1 inhibitors or ADP receptor inhibitors. In patients deemed appropriate (e.g., those undergoing a neurosurgical procedure), DDAVP can be used in addition to platelet transfusion. (Conditional recommendation, low-quality evidence)</p>	<p>3-1. We make no recommendation regarding use of desmopressin in patients with intracranial hemorrhage on antiplatelet therapy.</p>
Small spontaneous	<p>Not reviewed.</p>	<p>4-1. We cannot make a recommendation regarding treatment of anticoagulant</p>

Table 1: Updated and Prior Recommendations		
	Recommendations from 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage	Current Recommendations
intraparenchymal hemorrhage		effects in patients with small intraparenchymal hemorrhage due to lack of evidence.
Use of viscoelastic hemostatic assays in traumatic ICH	Not reviewed.	5-1. We suggest using VHA-guided management in patients with traumatic intracranial hemorrhage, when VHAs are available (conditional recommendation, very low certainty evidence).

Table 2. PICO and related outcomes

PICO	Topic	Outcomes*
1	Adexanet alfa	Mortality, functional outcome, thrombosis , hemorrhage expansion, hospital readmission, ICU LOS
2	Desmopr essin	Mortality, functional outcome, thrombosis , hemorrhage expansion, hospital readmission, ICU LOS, (any) seizure , anaphylaxis, hyponatremia
3	Platelets	Mortality, functional outcome, thrombosis , hemorrhage expansion, hospital readmission, ICU LOS, transfusion reaction**
4	Small ICH	Mortality, functional outcome, thrombosis , hemorrhage expansion, hospital readmission, ICU LOS
5	VHAs	Mortality, functional outcome, thrombosis , hemorrhage expansion, hospital readmission, ICU LOS, blood products administered, transfusion reaction**

* Adverse effects outcomes bolded; **If specified, includes: **transfusion related acute lung injury (TRALI)**,
transfusion associated circulatory overload (TACO), **post-transfusion purpura** , **infection**, **alloimmunization**,
or any adverse reaction classified by study authors as “**transfusion reaction**.”

Table 3. Research Priorities in Treatment of Antithrombotic Effects of Factor Xa Inhibitors, Antiplatelet Agents, Small ICH and Use of VHAs in Acute ICH

PICO	Suggested Research Priorities
Factor Xa Inhibitors	<ul style="list-style-type: none"> • Robust assessment of long-term functional outcomes (minimum 90 days) • Multicenter RCT in patients with traumatic ICH to define role in TBI management in patients on factor Xa inhibitors • Define efficacy and safety of andexanet alfa in neurosurgical populations
Platelet Transfusion	<ul style="list-style-type: none"> • Global questions <ul style="list-style-type: none"> ○ Clarify optimal dosing of platelet transfusion based on specific antiplatelet agent(s), including dual antiplatelet therapy ○ Establish utility of platelet function assays (PFAs) to guide need for platelet transfusion • Spontaneous IPH without neurosurgical intervention <ul style="list-style-type: none"> ○ Define use of platelet transfusion in extra-axial ICH • Spontaneous IPH with surgery <ul style="list-style-type: none"> ○ Explore application in surgical interventions other than craniotomy

	<ul style="list-style-type: none"> • Traumatic ICH <ul style="list-style-type: none"> ◦ Determine influence of TBI severity on need for platelet transfusion (mild vs moderate-severe TBI)
Desmopressin	<ul style="list-style-type: none"> • Well-designed RCTs involving traumatic and spontaneous ICH, ICH of different sites, and different antiplatelet agents • Elucidate role of combining DDAVP with platelet transfusion in antiplatelet-associated ICH
Small ICH	<ul style="list-style-type: none"> • Identify robust predictors of hematoma expansion according to anatomical location, size, and hemostatic profiles
VHAs	<ul style="list-style-type: none"> • Sufficiently large RCT comparing VHA-guided management with standard care in traumatic ICH • Development and testing of therapeutic interventions based on VHAs that are specific for antithrombotic medication-associated ICH • Development of validated neuro-specific protocols for patient management based on VHA results

DDAVP, desmopressin; ICH, intracranial hemorrhage; IPH, intraparenchymal hemorrhage; RCT, randomized controlled trial; TBI, traumatic brain injury; VHA, viscoelastic hemostatic assay.

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