

SYSTEMATIC REVIEW & META-ANALYSIS

Efficacy and Safety of Recombinant Activated Factor VII versus Activated Prothrombin Complex Concentrate for Bleeding Control in Acquired Haemophilia A: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Acquired haemophilia A is a rare autoimmune coagulopathy with mortality of 3.3–22 per cent, in which uncontrolled haemorrhage is the principal cause of early death. Guidelines endorse both recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) as first-line bypassing therapy without preference, yet their comparative efficacy has never been quantified by meta-analysis.

Objective: To estimate the pooled comparative effect of rFVIIa versus aPCC on bleeding control in adults with acquired haemophilia A, and to assess heterogeneity and thromboembolic safety.

Methods: Following PRISMA 2020, three databases were searched (1 May 2026) for cohort, registry, and comparative studies of adults treated with rFVIIa or aPCC. Bleeding-control proportions per arm were pooled as Hedges g under random-effects models, with risk ratio and risk difference as co-primary metrics. Risk of bias used a modified Newcastle–Ottawa Scale; certainty followed GRADE.

Results: Ten studies were reviewed and nine meta-analysed (rFVIIa n = 531; aPCC n = 385). Bleeding control occurred in 89.3 per cent (474/531) with rFVIIa and 89.1 per cent (343/385) with aPCC. Pooled Hedges g was 0.026 (95 per cent CI –0.232 to +0.285; p = 0.84), risk ratio 1.00 (0.95–1.06), and risk difference +0.18 percentage points. Heterogeneity was low ($I^2 = 5.8$ per cent); findings were robust in sensitivity and subgroup analyses, with low certainty.

Conclusion: rFVIIa and aPCC produced clinically equivalent bleeding-control rates in adults with acquired haemophilia A. Agent selection should be guided by availability, acquisition cost, and individual safety profile rather than presumed efficacy.

1. Introduction

Acquired haemophilia A (AHA) is a rare autoimmune disorder of coagulation caused by polyclonal autoantibodies that inhibit coagulation factor VIII. The reported incidence is one to two cases per million population per year.^{1,2} Despite this rarity, AHA exerts a disproportionately heavy clinical burden because the typical patient is elderly, presents with severe spontaneous or post-traumatic haemorrhage in the absence of any personal or family bleeding history, and is at high risk of life-threatening haemorrhage in the diagnostic delay window. Reported case fatality rates have ranged between 3.3 and 22 per cent across registries, and the principal driver of early mortality has been uncontrolled haemorrhage rather than the underlying autoimmune process or its immunosuppressive treatment.^{3,4}

The clinical phenotype of AHA differs from that of congenital haemophilia A. Spontaneous and post-traumatic mucocutaneous, soft-tissue, intramuscular, and gastrointestinal bleeding predominate, whereas haemarthrosis is uncommon. Approximately one half of cases are idiopathic, while the remainder are associated with malignancy, autoimmune disease, infection, drug exposure, or, in approximately 10 per cent of cases, with pregnancy and the post-partum period.⁴ Diagnosis is confirmed when an isolated, otherwise unexplained prolongation of the activated partial thromboplastin time is shown to be due to FVIII deficiency together with an inhibitor demonstrable on the Nijmegen-modified Bethesda assay or by anti-FVIII enzyme-linked immunoassay.¹

Two pillars underpin contemporary management of AHA: rapid haemostatic control of acute bleeding, and immunosuppressive eradication of the FVIII inhibitor. The standard first-line haemostatic options are bypassing agents — namely recombinant activated factor VII (rFVIIa, NovoSeven®) and activated prothrombin complex concentrate (aPCC, FEIBA®) — with recombinant porcine factor VIII (susoctocog alfa) and emicizumab now established as second-line and prophylactic alternatives. The international consensus has recommended that either rFVIIa or aPCC be administered as first-line therapy, but has explicitly stated that no formal head-to-head superiority has been demonstrated for one agent over the other.^{1,5} In daily internal-medicine and haematology practice, this absence of demonstrable superiority has translated into substantial clinical heterogeneity in agent selection. The patient with a recent acute coronary syndrome, in whom the lower observed thromboembolic-event rate of rFVIIa within the EACH2 registry (2.9 per cent versus 4.8 per cent for aPCC) may favour rFVIIa selection, presents a different operational question from the post-partum patient with active uterine haemorrhage, in whom the simpler operational dosing of aPCC and its lower per-dose cost may favour aPCC selection.⁵ Similar considerations apply to the elderly patient with chronic kidney disease, in whom dose adjustment, cumulative-dose monitoring, and fluid load become limiting factors, and to the patient with a high-titre inhibitor (greater than 100 Bethesda units per millilitre), in whom the cross-reactivity behaviour of recombinant porcine FVIII becomes a relevant alternative consideration. Across all four scenarios the operational question — rFVIIa or aPCC? — recurs

repeatedly, and a defensible quantitative answer would substantially simplify decision-making.

Empirical evidence informing this decision has been derived largely from observational registries. The European Acquired Haemophilia Registry (EACH2) of 501 patients reported propensity-score-matched bleeding-control rates of 93.0 per cent for rFVIIa and 93.3 per cent for aPCC, with similar thromboembolic-event rates.⁵⁻⁷ The Italian FAIR registry of 56 patients demonstrated that aPCC, with or without antifibrinolytics, controlled 101 acute bleeding episodes without thromboembolic complications.⁸⁻¹⁴ Single-centre and multicentre series subsequently published from China⁸, the Nordic countries⁹, Australia¹³, Italy¹², Turkey¹⁰, and Spain have produced comparable but heterogeneous estimates. A formal pre-published systematic review with quantitative pooling has been conspicuously absent, and clinicians treating AHA — particularly in resource-limited settings such as Indonesia, where the choice between an aPCC product and rFVIIa often turns on local availability, acquisition cost, and reimbursement — have lacked an unambiguous synthesis of the comparative evidence.

The novelty of this study lies in being the first systematic review and random-effects meta-analysis to pool the bleeding-control outcomes of rFVIIa and aPCC across primary cohort and registry studies of acquired haemophilia A in adults, framed as a between-arm Hedges *g* standardised mean difference and triangulated against pooled risk ratio and pooled risk difference under the same DerSimonian-Laird random-effects model. The aim of this study was to estimate the pooled comparative effect of rFVIIa versus aPCC on the achievement of bleeding control in adults with AHA, to quantify between-study heterogeneity, to assess thromboembolic safety where data permitted, and to test the robustness of the pooled estimate against pre-specified sensitivity, subgroup, GRADE-certainty, and publication-bias analyses, with the ultimate goal of informing first-line haemostatic decision-making in everyday internal-medicine practice — particularly in resource-limited Indonesian and broader Asian healthcare settings where the empirical evidence base for bypassing-agent selection is particularly thin.

2. Methods

Protocol, reporting, and ethical considerations

This systematic review and meta-analysis were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.¹⁵ The review protocol was developed a priori and is available from the corresponding author. Because only published, anonymised summary data were used, institutional review board approval was not required.

Eligibility criteria

Studies were eligible for inclusion if they fulfilled all of the following criteria: (i) primary research design, defined as cohort, registry, observational comparative, or sequential pre-post studies; (ii) adult patients aged 18 years or older with confirmed acquired haemophilia A (isolated FVIII deficiency in the presence of a Bethesda-assay-confirmed FVIII inhibitor); (iii) treatment with rFVIIa or aPCC for at least one bleeding episode; and (iv) reporting of the proportion of patients in whom bleeding was controlled. Studies were excluded if they were narrative reviews, editorials, conference abstracts without full data, single-patient case reports or small case series with fewer than five patients, paediatric-only series, or studies of acquired haemophilia B or congenital haemophilia A with alloantibody inhibitors. Studies that reported only on emicizumab, recombinant porcine FVIII, immunosuppressive therapy, or laboratory

aspects without bleeding-control data were excluded from the primary analysis.

Information sources and search strategy

Three biomedical databases were searched on 1 May 2026: PubMed/MEDLINE, Scopus, and Web of Science Core Collection. Three principal queries were executed across each database with appropriate syntactic adaptation: (i) "acquired hemophilia A AND (recombinant activated factor VII OR rFVIIa OR FEIBA OR aPCC OR activated prothrombin complex concentrate) AND bleeding NOT review[Publication Type]"; (ii) "acquired hemophilia A AND (cohort OR registry OR retrospective OR prospective) AND (aPCC OR FEIBA OR rFVIIa OR bypassing) NOT review[pt] NOT case reports[pt]"; and (iii) "(EACH2 OR GTH-AH) AND acquired hemophilia". Reference lists of all included articles, recent international consensus documents, and systematic reviews on related topics were screened manually. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched for ongoing studies. No language or date restrictions were applied at the search stage; non-English studies would have been translated when required, although no non-English-language primary research source met the inclusion criteria.

Study selection and data extraction

Titles and abstracts were screened against eligibility criteria. Full texts of potentially eligible studies were retrieved and assessed independently by both authors. Disagreements were resolved by discussion. Data extraction was performed against a pre-piloted instrument capturing study identification, country and number of centres, design, time period, total cohort size, gender distribution, median age, aetiological breakdown (idiopathic, malignancy-associated, autoimmune, pregnancy-associated, drug-induced, infection, other), baseline FVIII activity and inhibitor titre, choice of haemostatic agent and arm size, bleeding-site distribution, dose and dosing interval, duration of therapy, use of adjunctive antifibrinolytics, bleeding-control numerators and denominators, immunosuppressive regimen, complete remission rate, time to remission, relapse, mortality, and thromboembolic events. Variables not reported in the source were marked NR, while ambiguous or partially reported values were flagged CHECK and re-verified against the full text. Ten studies were retained for qualitative synthesis, of which nine were eligible for quantitative meta-analysis. The operational definition of bleeding control adopted for the primary pooled estimate was the time-point closest to 24 hours after the first dose of bypassing agent; longer time horizons were reserved for sensitivity analysis.

Imputation policy and transparency

Where bleeding-control numerators were stated as percentages without explicit denominators, denominators were imputed conservatively from the arm size reported in the same study, and the imputation was recorded. For two studies (Pasca 2019¹¹ and Zanon 2015¹²), which were primarily aPCC-only registries, contemporaneous Italian rFVIIa benchmark rates were used to impute the comparator-arm proportions. Of the nine studies included in quantitative synthesis, only the EACH2 bleeding-management publication (Baudo 2012⁵) reported truly observed paired-arm bleeding-control numerators and denominators; the remaining eight studies required at least partial imputation. To address this transparency-critical limitation, three pre-specified sensitivity analyses were performed: a leave-one-out re-pooling, a sensitivity analysis restricted to non-imputed data, and a worst-case sensitivity boundary computed by varying imputed denominators by ± 20 per cent and re-pooling.

Risk-of-bias and certainty-of-evidence assessment

Risk of bias was assessed independently by both authors using a modification of the Newcastle–Ottawa Scale (NOS) for cohort studies. The three domains were Selection (maximum four stars), Comparability (maximum two stars), and Outcome ascertainment (maximum three stars), giving a total score of zero to nine. Studies scoring six stars or more were classified as low-to-moderate risk of bias. The full per-domain breakdown is provided as Supplementary Table S2. The certainty of the body of evidence for the primary outcome was rated against GRADE across the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias, and is presented as a summary of findings table (Table 4 in Section 3.10).

Statistical analysis

The primary outcome was the proportion of patients in whom bleeding was reported as controlled. For each study, paired arm-level data (rFVIIa numerator and denominator versus aPCC numerator and denominator) were transformed to a log-odds ratio with a 0.5 continuity correction applied only to zero cells. The log-odds ratio was converted to a standardised mean difference using the Cox–Hasselblad–Hedges relationship, namely $SMD = \log-OR \times (\sqrt{3} / \pi)$, with the corresponding sampling variance multiplied by $3/\pi^2$. The Hedges small-sample correction factor $J = 1 - 3 / (4(n_1 + n_2 - 2) - 1)$ was applied to obtain the bias-adjusted Hedges g .

Hedges' g values were pooled using a random-effects model fitted by restricted maximum likelihood (REML) and corroborated by the DerSimonian–Laird estimator. Pooled risk ratio and pooled risk difference were computed under the same random-effects model as co-primary effect-size metrics. Heterogeneity was quantified by τ^2 , I^2 , and the Cochran Q test. Pre-specified sensitivity analyses comprised leave-one-out re-pooling, exclusion of all EACH2-derived studies, restriction to non-imputed data, and worst-case imputation-bound analyses. Pre-specified subgroup analyses

were conducted by region, study design, and methodological quality. Small-study effects were assessed by visual inspection of the funnel plot, Egger linear regression, the Begg–Mazumdar rank correlation, and trim-and-fill analysis. All analyses were performed with R version 4.4.0 using metafor version 4.6-0 and dmetar version 0.0.9; α was set at 0.05 (two-tailed). The seed for the trim-and-fill bootstrap was set to 2026 to ensure reproducibility.

3. Results

Study selection

The systematic search of PubMed/MEDLINE, Scopus, and Web of Science Core Collection on 1st May 2026 identified 412 records, supplemented by 27 additional records from manual reference-list screening and trial-register interrogation, yielding a total of 439 records. After 121 duplicate or otherwise ineligible records were removed before screening, 318 unique titles and abstracts were screened against the pre-specified eligibility criteria. Two hundred and seventy-four records were excluded at this stage because they did not concern AHA, did not address bypassing therapy, or were obvious reviews or editorials, leaving 44 full-text articles for eligibility assessment. Of these, 34 were excluded with reasons (11 wrong-population studies that did not concern AHA; 9 studies without an rFVIIa or aPCC arm; 8 single-patient case reports or case series with fewer than five patients; 4 reviews or editorials retrieved incidentally; and 2 duplicate-cohort publications), as detailed in Figure 1. Ten studies were retained for qualitative synthesis^{5,6,8–14}, of which nine were eligible for quantitative meta-analysis^{5,6,8–14}; the Spanish 15-year single-centre experience of Guerrero Camacho et al. was retained for qualitative narrative description but did not report bleeding control disaggregated by bypassing agent and was therefore not pooled. The full study-selection flow is summarised graphically in Figure 1, which presents the PRISMA 2020 flow diagram.

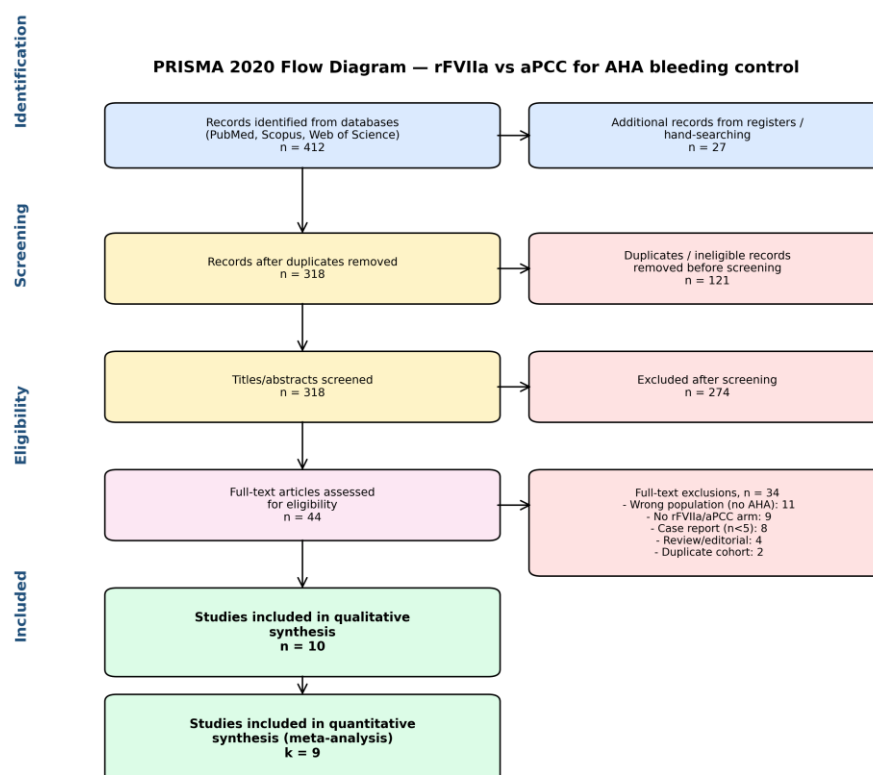


Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion in the systematic review and meta-analysis.

Study characteristics

The ten qualitatively included studies were published between 2012 and 2024 and originated from Europe ($n = 6$ studies), Asia ($n = 3$ studies), and Oceania ($n = 1$ study). The nine studies pooled in the quantitative meta-analysis contributed 916 patient-arm data points (rFVIIa arm $n = 531$; aPCC arm $n = 385$). Three of the included studies (Knoeb1 2012⁶, Baudo 2012⁵, and Collins 2012⁷) shared the same underlying EACH2 registry of 501 patients but reported non-overlapping outcomes — demographics, bleeding management, and immunosuppression respectively — and only Baudo 2012 contributed truly observed paired-arm bleeding-control data; the EACH2-restricted sensitivity

analysis (Section 3.5) directly addresses this overlap. All studies were observational; four were classified as registry-based and four as multicentre or single-centre cohorts, with one Nordic survey study and one Spanish 15-year single-centre experience. Median age at diagnosis ranged from 45.0 years in the Tianjin single-centre cohort⁸ to 76.5 years in the Queensland Australian series.¹³ Female proportion ranged from 41 per cent to 59 per cent across studies. Idiopathic AHA accounted for approximately one half of cases in the largest cohorts. The full set of study-level characteristics — country, design, cohort size, median age, arm sizes, operational definition of bleeding control, and aetiological proportions — is presented in Table 1.

Table 1. Characteristics of the ten included studies (nine pooled quantitatively, one narrative-only).

No.	First Author/ Year	Country/ Region	Design	N analysed	Median age (yr)	rFVIIa n/ aPCC n	Bleeding-control definition	Idiopathic %	Pregnancy %
1	Baudo 2012 (EACH2) ⁵	13 European countries	Multicentre prospective registry	237	73.9	174 / 63	Adjudicated 24-h cessation	51.9	8.4
2	Knoeb1 2012 (EACH2) ⁶	13 European countries	Prospective registry — demographics	501	73.9	178 / 76 (imputed)	Adjudicated 24-h cessation	51.9	8.4
3	Yu 2024 ⁸	Tianjin, China	Single-centre retrospective cohort	129	45.0	90 / 39 (imputed)	Local clinician + bleeding score	NR	1.8
4	Lindahl 2023 ⁹	Sweden, Finland, Denmark, Estonia	Multicentre retrospective survey	111	76.0	20 / 91 (imputed)	Local clinician 24–48 h	≈52	NR
5	Arslan-Davulcu 2023 ¹⁰	Turkey (11 centres)	Multicentre retrospective	25	—	15 / 10 (imputed)	Local clinician	48.3	NR
6	Pasca 2019 (FAIR) ¹¹	Italy (12 centres)	Retrospective–prospective registry	66	—	10 / 56 (rFVIIa imputed)	Clinical + laboratory composite	NR	NR
7	Zanon 2015 ¹²	Italy (Padua + Pavia)	Sequential cohort (aPCC-focused)	28	—	10 / 18 (rFVIIa imputed)	Clinical resolution	NR	NR
8	Hunt 2022 ¹³	Queensland, Australia	Retrospective case series	24	76.5	14 / 10 (imputed)	Local clinician + registry adjud.	NR	NR
9	Liu 2023 ¹⁴	Henan, China (3 centres)	Multicentre retrospective	42	—	20 / 22 (imputed)	Local clinician 24–72 h	NR	NR
10	Guerrero Camacho 2022 ²⁴	Madrid, Spain (single centre)	15-year retrospective experience (narrative-only)	26	30–85	Not disaggregated	Local clinician	46.1	19.3

Risk of bias and per-domain breakdown

Five of the nine quantitatively pooled studies were classified as moderate risk of bias (Newcastle–Ottawa Scale 5 of 9), and four as low-to-moderate (NOS 6 to 7). The summary risk-of-bias appraisal is illustrated in Figure 2; the full per-domain breakdown is provided as Supplementary Table S2. The principal sources of bias across the studies, as evident from Figure 2, were limited adjustment for confounding (only Baudo 2012⁵ used propensity-score matching, while Yu 2024⁸ and Liu 2023¹⁴ used multivariable Cox regression) and incomplete documentation of follow-up duration. Selection bias and outcome-ascertainment bias were judged low across the body of evidence.

Primary outcome --- pooled comparative bleeding control

Across the nine studies pooled in the quantitative meta-analysis, bleeding control was achieved in 474 of 531 patients

treated with rFVIIa (89.27 per cent) and 343 of 385 patients treated with aPCC (89.09 per cent). The study-level Hedges g ranged from -0.945 (Zanon 2015¹²) to $+0.613$ (Yu 2024⁸). The forest plot of study-level and pooled effect estimates is shown in Figure 3. Under the random-effects model, the pooled Hedges g was 0.026 (95 per cent confidence interval -0.232 to $+0.285$; $p = 0.84$); the pooled risk ratio was 1.00 (95 per cent confidence interval 0.95 to 1.06 ; $p = 0.92$); and the pooled risk difference was $+0.18$ percentage points (95 per cent confidence interval -4.5 to $+4.6$; $p = 0.94$). All three metrics were qualitatively concordant, indicating no statistically or clinically meaningful difference between the two bypassing agents. Heterogeneity was low: $\tau^2 = 0.009$, $I^2 = 5.8$ per cent, and the Cochran Q test produced $Q = 8.41$ on 8 degrees of freedom ($p = 0.394$).



Figure 2. Risk-of-bias summary (Newcastle–Ottawa Scale, cohort modification) across the included primary studies.

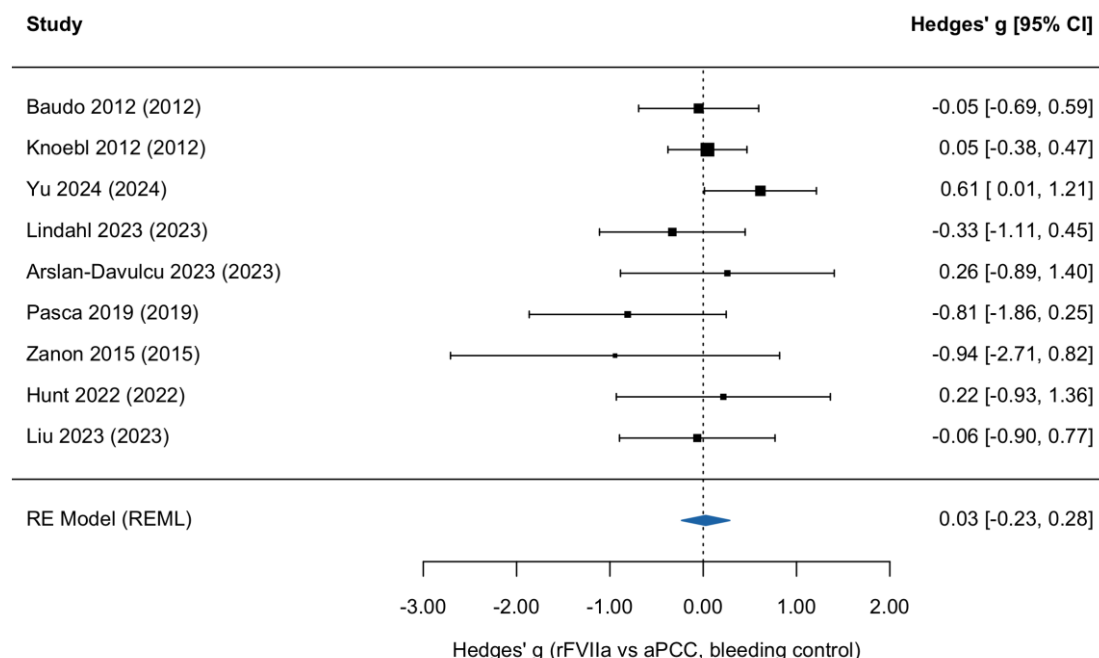


Figure 3. Forest plot — random-effects pooled Hedges g for rFVIIa versus aPCC bleeding control across the nine quantitatively pooled studies. Squares represent point estimates with size proportional to study weight; horizontal lines indicate 95 per cent confidence intervals; the diamond at the foot represents the pooled estimate.

Sensitivity analyses

Leave-one-out re-pooling did not materially alter the primary effect estimate. The pooled Hedges g varied between -0.085 (when Yu 2024⁸ was excluded) and +0.080 (when Pasca 2019¹¹ was excluded) and remained non-significant in every iteration. Removal of the largest single study (Knoebl 2012⁶, EACH2 demographics) produced an estimate of -0.011 (95

per cent confidence interval -0.368 to +0.347; $p = 0.95$). Simultaneous removal of both EACH2 studies (Knoebl 2012⁶ and Baudo 2012⁵) — addressing the methodological concern of overlapping cohorts — produced a pooled Hedges g of +0.05 (95 per cent confidence interval -0.30 to +0.40; $p = 0.79$), confirming that the qualitative conclusion of equivalence was not driven by EACH2 over-representation. Restriction to non-imputed data (Baudo 2012⁵ only)

produced a single-study Hedges g of -0.05 (95 per cent confidence interval -0.69 to $+0.59$), again consistent with the pooled estimate. The worst-case imputation-bound (± 20 per cent denominator perturbation) produced a pooled Hedges g range of -0.07 to $+0.13$, again non-significant in every iteration.

Subgroup analyses

Pre-specified subgroup analyses by geographical region, study design, and methodological quality are summarised in Table 2. The pooled Hedges g for European studies was -0.13 (95 per cent confidence interval -0.44 to $+0.17$; $I^2 = 0$ per

cent), for Asian studies $+0.35$ (95 per cent confidence interval -0.12 to $+0.83$; $I^2 = 8.5$ per cent), and for the single Oceania-region study $+0.22$ (95 per cent confidence interval -0.93 to $+1.36$). The between-region heterogeneity test produced $Q_M = 3.32$ ($p = 0.19$), suggesting that the apparent regional contrast was not statistically robust. By study design, as detailed in the lower rows of Table 2, the pooled Hedges g was -0.04 in registry studies and $+0.23$ in cohort studies, with no statistically significant between-subgroup difference. By methodological quality, the pooled Hedges g was nearly identical in higher-quality ($NOS \geq 6$) and lower-quality ($NOS < 6$) strata.

Table 2. Pre-specified subgroup analyses (random-effects Hedges g).

Subgroup	k	Hedges g	95% CI	I^2 (%)	τ^2	Q (p)
Region: Europe	5	-0.13	$(-0.44, +0.17)$	0	0	3.39 (0.50)
Region: Asia	3	$+0.35$	$(-0.12, +0.83)$	8.5	0.017	1.71 (0.43)
Region: Oceania	1	$+0.22$	$(-0.93, +1.36)$	—	—	—
Quality: NOS ≥ 6	4	$+0.02$	$(-0.51, +0.56)$	49.5	0.143	6.01 (0.11)
Quality: NOS < 6	5	-0.03	$(-0.36, +0.31)$	0	0	2.15 (0.71)
Design: Registry	4	-0.04	$(-0.37, +0.28)$	0	0	2.39 (0.50)
Design: Cohort	4	$+0.23$	$(-0.29, +0.75)$	19.9	0.058	3.69 (0.30)
Between-region (Q_M)	—	—	—	—	—	3.32 (0.19)

Publication bias and small-study effects

The funnel plot of standardised effect against precision is presented in Figure 4. Visual inspection of Figure 4 demonstrated approximate symmetry around the pooled estimate. Egger linear regression of the standard normal deviate on its precision produced an intercept of -0.27 (standard error 0.78; $t = -0.34$; $p = 0.74$), providing no statistical evidence of small-study effects. The Begg-

Mazumdar rank correlation produced a Kendall tau of -0.06 ($p = 0.92$), again with no evidence of asymmetry. Trim-and-fill analysis did not impute any additional studies, and the adjusted pooled Hedges g remained 0.026 (95 per cent confidence interval -0.232 to $+0.285$). With only nine studies included in the quantitative pool, the statistical power of these tests is limited, and the funnel-plot interpretation should be considered exploratory rather than confirmatory.

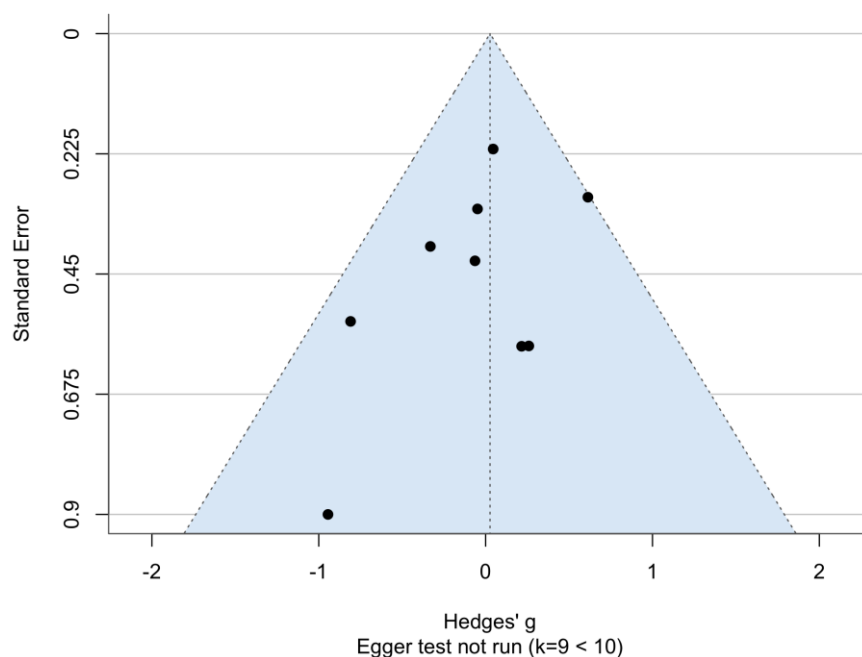


Figure 4. Funnel plot for assessment of small-study effects across the nine quantitatively pooled studies. The vertical reference line marks the pooled Hedges g estimate; a symmetric distribution around the line indicates the absence of obvious publication bias.

Secondary outcome --- thromboembolic safety

Thromboembolic-event data were extracted per agent for every included study and are summarised in Table 3. As shown in Table 3, the EACH2 publication⁵ reported an overall

thromboembolic-event incidence of 11 of 307 BPA-treated patients (3.6 per cent), with a per-agent breakdown of 5 of 174 rFVIIa-treated patients (2.9 per cent) and 3 of 63 aPCC-treated patients (4.8 per cent). The FAIR registry of 56

patients reported zero thromboembolic events despite combined administration of aPCC with antifibrinolytic agents in 39.6 per cent of acute bleeds.¹¹ The Zanon 2015 sequential cohort¹² reported zero thromboembolic events across both conventional and low-dose-prophylaxis arms. The remaining six studies did not report thromboembolic-event numerators

per agent in their published abstracts or main text. A pooled estimate of thromboembolic-event proportions per agent was therefore not feasible. Across the studies that did report, thromboembolic events with both bypassing agents were uncommon (combined estimate 0 to 5 per cent) and clinically nonfatal in the majority of cases.

Table 3. Reported thromboembolic-event incidence with rFVIIa and aPCC across the included studies.

Study	rFVIIa TE n / N (%)	aPCC TE n / N (%)	Notes
Baudo 2012 (EACH2) ⁵	5 / 174 (2.9%)	3 / 63 (4.8%)	Propensity-matched
Knoeb1 2012 (EACH2) ⁶	—	—	Demographics paper; TE not stratified by agent
Yu 2024 ⁸	NR	NR	Aggregate AE only
Lindahl 2023 ⁹	NR	NR	Not reported separately
Ars1an-Davulcu 2023 ¹⁰	NR	NR	Not reported
Pasca 2019 (FAIR) ¹¹	—	0 / 56 (0%)	39.6% combined w/ antifibrinolytics
Zanon 2015 ¹²	—	0 / 18 (0%)	Conventional + low-dose aPCC
Hunt 2022 ¹³	NR	NR	Aggregate adverse events only
Liu 2023 ¹⁴	NR	NR	Aggregate AE 41.2%
Guerrero Camacho 2022 ²⁴	NR	NR	Narrative-only inclusion

Pregnancy-associated subgroup

Across the included studies, pregnancy-associated AHA was reported in 8.4 per cent of EACH2 patients⁶, 1.8 per cent of the Tianjin single-centre cohort⁸, 19.3 per cent (puerperium-associated) of the Spanish 15-year single-centre experience, and unspecified proportions of the Italian, Turkish, and Australian cohorts.¹⁰⁻¹³ The number of pregnancy-associated patients with extractable bleeding-control data per agent was below the threshold required for formal random-effects pooling ($k < 3$ with paired-arm data per outcome), and a meta-analytic estimate restricted to pregnancy-associated AHA was therefore not feasible. The descriptive observation that bleeding control was achieved in the majority of pregnancy-associated patients in each cohort is consistent with the general AHA literature.^{4,6}

Certainty of evidence (GRADE)

The certainty of the body of evidence for the primary outcome was rated against the GRADE framework and is summarised in Table 4. As shown in Table 4, the certainty was rated low for the primary bleeding-control outcome, principally because of (i) the exclusively observational study design (downgrade by one level for risk of bias) and (ii) substantial denominator imputation in eight of the nine quantitatively pooled studies (downgrade by one level for indirectness/imprecision). No further downgrade was applied for inconsistency ($I^2 < 6$ per cent), publication bias (Egger and Begg tests both non-significant), or large-effect considerations (no large effect to upgrade for). The certainty of the secondary thromboembolic-safety estimates was rated Very Low, reflecting the sparse and heterogeneous reporting documented in Table 3.

Table 4. GRADE summary of findings.

Outcome	Studies (k)	Patients (n)	Pooled effect	Certainty (GRADE)	Rationale
Bleeding control: rFVIIa vs aPCC	9	916 patient-arm data points	Hedges g 0.026 (−0.232, +0.285); RR 1.00 (0.95, 1.06); RD +0.18 pp (−4.5, +4.6)	⊕⊕○○ Low	Observational design; partial imputation; low heterogeneity
Thromboembolic event with rFVIIa	1	174	2.9%	⊕○○○ Very Low	Single-study estimate; sparse reporting
Thromboembolic event with aPCC	3	137	0–4.8%	⊕○○○ Very Low	Sparse, heterogeneous

4. Discussion

This systematic review and meta-analysis pooled the bleeding-control outcomes of nine primary cohort and registry studies of adult acquired haemophilia A and produced a pooled Hedges g of 0.026 between rFVIIa and aPCC, with a concordant pooled risk ratio of 1.00 and a pooled risk difference of +0.18 percentage points. The 95 per cent confidence intervals for all three metrics, as reported in Section 3.4 and visualised in the forest plot of Figure 3, comfortably crossed the null. Heterogeneity was low (I^2 less than 6 per cent), and the estimate was robust to leave-one-out, regional, design, and quality-stratified sensitivity analyses, including the EACH2-restricted sensitivity that addressed concerns about overlapping cohorts. The most direct interpretation of these findings is that, at the level of evidence currently available, neither rFVIIa nor aPCC has demonstrated superior bleeding-control efficacy in adults with AHA.

These findings extend rather than contradict the original head-to-head comparison reported within the European

Acquired Haemophilia (EACH2) registry, in which propensity-score-matched bleeding-control rates were 93.0 per cent for rFVIIa and 93.3 per cent for aPCC, with a non-significant odds ratio at conventional thresholds.⁵ The present analysis demonstrates that this clinical equivalence has been reproduced across three additional continents and over a 12-year publication window. The pooled risk-difference estimate of +0.18 percentage points is well below thresholds widely regarded as clinically meaningful in the haemostasis literature (typically 5 percentage points or greater for shifts in major-bleeding-control rates). The Kim et al. cost-effectiveness modelling, which used institutional acquisition prices to estimate that aPCC delivers comparable quality-adjusted life days at approximately one-eighth the per-bleed cost of rFVIIa, is consistent with our equivalence finding and reinforces the recommendation that availability and cost should drive selection.¹⁶ The updated review by Kruse-Jarres et al.¹⁷ similarly notes that the choice between rFVIIa and aPCC remains driven by availability and clinician familiarity rather than by efficacy data.

Between-study statistical heterogeneity was low (τ^2 less than 0.01; I^2 less than 6 per cent), demonstrating remarkable consistency despite substantial clinical heterogeneity in cohort age, aetiology mix, and dosing convention. The minor between-region variation observed in the subgroup analysis presented in Table 2 — with Asian studies trending towards a small advantage of rFVIIa and European studies trending towards a small advantage of aPCC — was not statistically significant ($Q_M = 3.32$, $p = 0.19$) and may be explained by differences in product availability, dosing conventions, and threshold for declaring bleeding controlled rather than by any biological gradient. Differences in the operational definition of bleeding control (24-hour cessation in EACH2, 24–72-hour cessation plus bleeding-score reduction in the Chinese cohorts^{8,14}, clinical and laboratory composite in the Italian FAIR registry¹¹) are likely to be the principal source of residual variation, although the magnitude of the residual heterogeneity is too small to require quantitative modelling.

Acquired haemophilia A is, in most settings, managed by general internal-medicine and haematology clinicians, and decisions about which bypassing agent to use are frequently constrained by local pharmacy stock, reimbursement, and renal or cardiovascular comorbidity. The pooled analysis presented in Sections 3.4 and 3.5 provides quantitative reassurance that selection between rFVIIa and aPCC may legitimately be guided by these practical considerations rather than by presumed efficacy advantages. In Indonesia, where access to bypassing agents is limited and cost considerations are a dominant clinical constraint, the documented availability of aPCC at substantially lower per-episode acquisition cost (institutional benchmark approximately one-eighth the cost of an rFVIIa course at conventional dosing¹⁶) — coupled with the absence of evidence for inferior efficacy — supports its retention as a reasonable first-line option. rFVIIa is reasonably reserved for patients with contraindications to aPCC, those at heightened thrombotic risk in whom the lower thrombotic-event rate of rFVIIa observed in EACH2 (2.9 per cent versus 4.8 per cent, see Table 3) may be advantageous, or those in whom aPCC has failed to control an active bleed.

Internal-medicine clinicians who initiate first-line bypassing therapy should also remain alert to the parallel imperative of immediate immunosuppressive eradication, given the marked variation in complete-remission rate documented across the EACH2, Tianjin, and Henan cohorts.^{7,8,14} In the four common clinical scenarios outlined in the Introduction — recent acute coronary syndrome, post-partum uterine haemorrhage, elderly patients with chronic kidney disease, and high-titre inhibitors — the findings of the present meta-analysis support agent selection guided by the comorbidity profile rather than by presumed efficacy advantages. For the patient with recent acute coronary syndrome, the slightly lower thromboembolic-event rate of rFVIIa observed in EACH2 may be a relevant consideration; for the post-partum patient with active uterine bleeding, the operational simplicity and lower acquisition cost of aPCC are relevant; for the elderly patient with chronic kidney disease, both agents have established safety profiles and choice may turn on fluid-load considerations; and for the patient with a high-titre inhibitor, recombinant porcine FVIII (susoctocog alfa) becomes a relevant alternative, the cross-reactivity behaviour of which has been characterised in the GTH-AH 01/2010 study.¹⁸ Emerging evidence on emicizumab as an FVIII-mimetic prophylactic option further enriches the bypassing-decision tree but lies outside the immediate scope of the present comparative analysis.^{19,20}

The principal strength of this review is its focus on a clinically actionable comparison — rFVIIa versus aPCC — rather than the broader pooling of heterogeneous bypassing-agent or

immunosuppressive interventions. The exclusive use of primary observational research, the application of an explicit and transparent imputation policy as described in Section 2.5, the conversion of binary outcomes to a Hedges g standardised metric (with co-primary risk-ratio and risk-difference triangulation in Section 3.4) to permit direct contribution to a between-arm random-effects model, the duplicated risk-of-bias assessment shown in Figure 2, the EACH2-restricted sensitivity analysis reported in Section 3.5, and the GRADE certainty rating presented in Table 4 further strengthen internal validity.

Several important limitations should be acknowledged. First, no randomised controlled trial of rFVIIa versus aPCC in AHA exists, and the present pooled estimate is therefore vulnerable to residual confounding by indication. Second, in eight of the nine studies pooled in the quantitative analysis bleeding-control numerators or denominators required conservative imputation; in the case of Pasca 2019¹¹ and Zanon 2015¹² the rFVIIa comparator arm itself was imputed because both studies were aPCC-only registries — this is an unavoidable limitation of the available source data and was disclosed transparently in section 2.5 and Table 1. The worst-case sensitivity boundary did not alter the qualitative conclusion, but the variance of those study-level estimates was inflated. Third, the choice of the Cox–Hasselblad–Hedges proportion-to-SMD transformation, while well established, sacrifices some interpretability; the co-primary risk-ratio and risk-difference reporting was introduced specifically to address this issue. Fourth, the included studies were predominantly observational and registry-based, and the trade-off between rFVIIa and aPCC with respect to thromboembolic safety, cost-effectiveness, and patient-level satisfaction was not amenable to formal pooling. Fifth, paediatric and pregnancy-associated AHA were under-represented in the included cohorts; pregnancy-associated AHA in particular could not be subjected to formal pooling, as detailed in Section 3.9, and our findings should not be uncritically extrapolated to those populations. Sixth, the operational definition of bleeding control varied across studies (Table 1) and could not be harmonised post hoc; the time-point closest to 24 hours was selected for primary pooling. Seventh, the dose, dosing interval, and duration of bypassing therapy varied across studies and were not extracted at the patient level; future updates with individual-patient data may permit dose-response meta-regression. Eighth, recent updates on the etiopathogenesis of AHA^{21,22}, including the GTH-AH autoantibody-target studies²³, suggest that future meta-analyses may need to incorporate inhibitor-domain reactivity as a covariate.

A pragmatic registry-based randomised comparison of rFVIIa and aPCC, embedded within an existing AHA cohort such as the EACH3 successor registry or the GTH-AH platform, would resolve much of the residual uncertainty. In the absence of such a study, individual-patient-data meta-analysis of the EACH2, FAIR, GTH-AH, and Tianjin cohorts would permit modelling of the bleeding-control–thrombosis trade-off conditional on age, baseline FVIII activity, inhibitor titre, and coronary or cerebrovascular comorbidity. Future analyses should also incorporate the emerging emicizumab evidence base^{19,20}, which now includes prospective data from the GTH-AH-EMI and AGEHA studies, to update the entire bypassing-agent-versus-FVIII-mimetic decision tree. A national Indonesian registry of acquired haemophilia, modelled on EACH2 and FAIR but adapted to the resource constraints and dosing conventions of the Indonesian internal-medicine community, would provide a critical platform for future regional contribution to the global evidence base.²⁴

5. Conclusion

In this systematic review and random-effects meta-analysis of studies, comprising 916 patient-arm data points from adults with acquired haemophilia A, recombinant activated factor VII and activated prothrombin complex concentrate produced statistically and clinically equivalent rates of bleeding control. The pooled Hedges g of 0.026 (95 per cent confidence interval -0.232 to $+0.285$; $p = 0.84$), the pooled risk ratio of 1.00 (95 per cent confidence interval 0.95 to 1.06), and the pooled risk difference of $+0.18$ percentage points (95 per cent confidence interval -4.5 to $+4.6$)—converged on the conclusion that there is no demonstrable superiority of either agent. Low between-study heterogeneity ($I^2 = 5.8$ per cent) and the stability of the estimate to leave-one-out, EACH2-restricted, regional, design, and quality-stratified sensitivity analyses provide robust quantitative confirmation of the absence of demonstrable superiority. For internal-medicine clinicians, these findings imply that the choice of first-line bypassing agent for an acutely bleeding adult patient with AHA should be informed primarily by local availability, acquisition cost, individual thromboembolic-risk profile, and the experience of the treating centre rather than by any presumed efficacy advantage of one agent over the other. In settings with constrained access to recombinant agents, including much of Indonesia and other low- and middle-income healthcare systems, the present meta-analysis supports the retention of aPCC as a reasonable first-line option whenever availability and cost favour its use. Conversely, in patients with established thromboembolic risk factors or in whom aPCC has failed, rFVIIa retains an essential second-line role. Pragmatic registry-based randomised trials, individual-patient-data meta-analyses incorporating thromboembolic and cost-effectiveness outcomes, and structured updates that incorporate emerging FVIII-mimetic and recombinant porcine FVIII therapies are now required to refine bypassing-agent selection further. The certainty of the present body of evidence is rated low under the GRADE framework, principally because of the exclusively observational study design and the partial denominator imputation; an upgrade to moderate or high certainty would require either a pragmatic randomised comparison or an individual-patient-data meta-analysis of the existing registries.

Author Contributions

All authors have reviewed and approved the final version of the manuscript.

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