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C. Michael White

Kimberly Snow Caroti

Youssef Bessada

Adrian V. Hernandez

William L. Baker

See next page for additional authors

Authors

C. Michael White, Kimberly Snow Caroti, Youssef Bessada, Adrian V. Hernandez, William L. Baker, Paul P. Dobesh, Heleen van Haalen, Kirsty Rhodes, and Craig I. Coleman

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REVIEW

Andexanet alfa versus PCC products for factor Xa inhibitor bleeding: A systematic review with meta-analysis

C. Michael White[1,2] | Kimberly Snow Caroti[1,2] | Youssef Bessada[1] | Adrian V. Hernandez[1,2,3] | William L. Baker[1,2] | Paul P. Dobesh[4] | Heleen van Haalen[5] | Kirsty Rhodes[6] | Craig I. Coleman[1,2]

[1]University of Connecticut School of Pharmacy, Storrs, Connecticut, USA

[2]Hartford Hospital Health Outcomes, Policy and Evidence Synthesis Group, Hartford, Connecticut, USA

[3]Unidad de Revisiones Sistemáticas y Meta-análisis (URSIGET), Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima, Peru

[4]University of Nebraska Medical Center College of Pharmacy, Omaha, Nebraska, USA

[5]Health Economics & Payer Evidence, AstraZeneca, Gothenburg, Sweden

[6]Medical and Payer Evidence, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK

Correspondence
C. Michael White, Pharmacy Practice, University of Connecticut School of Pharmacy, 69 North Eagleville Road, Storrs, CT 06269-3092, USA.
Email: charles.white@uconn.edu

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AstraZeneca Pharma UK

Abstract

Previous meta-analyses assessed andexanet alfa (AA) or prothrombin complex concentrate (PCC) products for the treatment of Factor Xa inhibitor (FXaI)-associated major bleeding. However, they did not include recent studies or assess the impact of the risk of bias. We conducted a systematic review with meta-analysis on the effectiveness of AA versus PCC products for FXaI-associated major bleeding, inclusive of the studies' risk of bias. PubMed and Embase were searched for comparative studies assessing major bleeding in patients using FXaI who received AA or PCC. We used the Methodological Index for NOn-Randomized Studies (MINORS) checklist and one question from the Joanna Briggs Institute (JBI) Critical Appraisal of Case Series tool to assess the risk of bias. Random-effects meta-analyses were performed to provide a pooled estimate for the effect of AA versus PCC products on hemostatic efficacy, in-hospital mortality, 30-day mortality, and thrombotic events. Low–moderate risk of bias studies were meta-analyzed separately, as well as combined with high risk of bias studies. Eighteen comparative evaluations of AA versus PCC were identified. Twenty-eight percent of the studies ($n = 5$) had low–moderate risk and 72% ($n = 13$) had a high risk of bias. Studies with low–moderate risk of bias suggested improvements in hemostatic efficacy [Odds Ratio (OR) 2.72 (95% Confidence Interval (CI): 1.15–6.44); one study], lower in-hospital mortality [OR 0.48 (95% CI: 0.38–0.61); three studies], and reduced 30-day mortality [OR 0.49 (95% CI: 0.30–0.80); two studies] when AA was used versus PCC products. When studies were included regardless of the risk of bias, pooled effects showed improvements in hemostatic efficacy [OR 1.36 (95% CI: 1.01–1.84); 12 studies] and reductions in 30-day mortality [OR 0.53 (95% CI: 0.37–0.76); six studies] for AA versus PCC. The difference in thrombotic events with AA versus PCC was not statistically significant in the low–moderate, high, or combined risk of bias groups. The evidence from low–moderate quality real-world studies suggests that AA is superior to PCC in enhancing hemostatic efficacy and reducing

in-hospital and 30-day mortality. When studies are assessed regardless of the risk of bias, the pooled hemostatic efficacy and 30-day mortality risk remain significantly better with AA versus PCC.

KEYWORDS
andexanet alpha, factor Xa inhibitor, major bleeding, prothrombin complex concentrate

1 | BACKGROUND

Factor Xa inhibitors (FXaIs) are commonly used to prevent coagulation in patients with atrial fibrillation and in patients with, and at risk for, venous thromboembolism.[1,2] FXaIs can infrequently induce or complicate severe bleeding with potentially catastrophic outcomes, creating a need for anticoagulation reversal agents that can rapidly reduce the extent of bleeding.[1,2] The most commonly used therapies for the treatment of FXaI-associated major bleeding in the United States are andexanet alfa and prothrombin complex concentrate (PCC) products.

Andexanet alfa is a modified recombinant Factor Xa protein that inactivates FXaI molecules in the plasma. In clinical trials evaluating apixaban 5 mg daily (ANNEXA-A trial) or rivaroxaban 20 mg daily (ANNEXA-R trial) versus placebo, anti-FXa activity was reduced by 92%–94% in the andexanet alfa groups versus 18%–21% in the placebo groups, respectively.[2] The single-arm ANNEXA-4 trial confirmed the efficacy and safety of andexanet alfa in patients with life-threatening or uncontrolled bleeding.[3,4] Based on this evidence, andexanet alfa was conditionally approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for adult patients treated with apixaban or rivaroxaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, with the stipulation that an additional randomized controlled trial be conducted (subsequently named ANNEXA-I).[5]

In contrast, PCC products do not affect anti-FXa activity but contain high concentrations of different clotting factors (procoagulant factors II, IX, and X [in 3-factor PCC], as well as factor VII [in 4-factor PCC]) and were developed and FDA approved to reverse coagulation factor deficiency induced by vitamin K antagonists (e.g., warfarin).[6] Hence, PCC products are not FDA or EMA approved for the treatment of FXaI-associated major bleeding.[6]

Both andexanet alfa and PCCs have been studied in patients with FXaI-associated major bleeding, but overwhelmingly in single-arm assessments.[1] Direct comparative evidence between both products was previously scarce, and in attempts to determine the relative benefit of one therapy versus the other, several previously published meta-analyses (MAs) have pooled the single-arm outcomes of andexanet alfa and PCC trials, allowing the reader to cross-compare event rates and interpret relative benefit.[1,7–10] However, cross comparing results from single arms of two different studies (i.e., a "naïve" indirect comparison) is highly discouraged by methodologists due to concerns about the inability to adjust for cross-study differences.[11] In one assessment of single-arm studies used in Phase II cancer trials, a 5% absolute shift in a historical control response rate amplified the false-positive error rates 2–4 times in statistical models versus what was ultimately found in direct comparative Phase III trials.[12] Changes in the proportion of patients enrolled from high- versus low-volume treatment centers, differences in patient selection effects, temporal drift in response rates over time, and random small-sample variation in historical controls all amplified the magnitude of inaccuracy.[11,12]

Studies that minimize imbalances in the distributions of effect modifiers and prognostic factors between treatment groups are superior alternatives to naïve indirect comparisons. These include randomized controlled trials (as the gold standard), comparative observational studies, and cross-trial treatment comparisons using population adjustment methods.[13] At the time when the previous systematic literature reviews were conducted, there were no published randomized controlled trials, but there were a few comparative observational studies and a few studies comparing the single-arm study data from ANNEXA-4 with data from different control groups using population-adjustment methods.[1] Only two MAs specifically pooled comparative studies of andexanet alfa versus PCC products, and additional comparative studies have since been published.[1,14] Previous MAs also did not systematically evaluate the risk of bias within each included study and the impact of including studies with high risk of bias on the results, nor was appropriate caution applied when interpreting the results.[1,7–10,14] The inclusion of studies at high risk of bias in a MA may distort the observed effect away from the true effect.

To overcome these limitations, we conducted a systematic review to better guide clinical decision-making by: (i) summarizing the body of evidence regarding effectiveness of andexanet alfa and PCC products, (ii) rigorously and consistently assessing the risk of bias in studies and MA comparatively assessing andexanet alfa and/or PCC products in the treatment of FXaI-associated major bleeding, (iii) assessing the comparative impact of andexanet alfa versus PCC products on in-hospital mortality, 30-day mortality, and hemostatic efficacy for the treatment of FXaI-associated major bleeding, and (iv) assessing the comparative impact of andexanet alfa versus PCC products on the aforementioned outcomes in studies with low to moderate versus high risk of bias.

2 | METHODS

2.1 | Search strategy

We conducted a systematic literature search of Medline and EMBASE from January 1, 2010 through September 1, 2023 looking for individual studies or MAs (Table S1). Search terms included

free-text and medical subject heading (MeSH) terms related to "factor Xa inhibitors," "hemorrhage," "reversal," "prothrombin complex concentrate," and "andexanet alfa." Bibliographic searches were augmented with backwards citation tracking of references from identified papers and newly published articles identified through other means. The citations that were found were de-duplicated and then independently assessed in duplicate by two investigators with expertise in both clinical thrombosis/hemostasis and evidence synthesis methods at the title and abstract phases and full text phases for predetermined inclusion criteria. Discrepancies were resolved through discussion. The search strategy and reporting were consistent with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines.[15]

2.2 | Inclusion criteria

To be included in this review, the studies had to meet a priori defined PICOS criteria as defined in Table 1. MAs had to be within a systematic review of the literature that comprises constituent studies meeting our PICOS criteria.

2.3 | Risk of bias assessment and scoring

2.3.1 | Comparative study risk of bias assessment

Commonly used tools for assessing the risk of bias are mostly for clinical trials or comparative observational studies, but not for single-arm studies with matched or adjusted control groups.[16] Given the nature of the patient population, the severity of the patients' clinical issues, and the methodological challenges that extend from these issues, a risk of bias tool that is appropriate to this literature base was needed. The basis for our risk of bias assessment were the Methodological Index for NOn-Randomized Studies (MINORS) criteria, which were supplemented with a criterion from the Joanna Briggs Institute (JBI) Critical Appraisal of Case Series Tool with 13 evaluable criteria.[17,18] Table S2A provides more detailed definitions of each item, which were tailored to the context of the treatment of major bleeding by a reversal or replenishment product. Table S2B provides the decision rules for rating a study as "high," "moderate," or "low" risk of bias.

To assess the level of agreement among assessors of differing levels of methodological or thrombosis expertise, we sent our risk of bias assessment tool to eight independent clinicians to score five different studies to assess the tool's reliability. The Fleiss Kappa statistic was utilized with levels of <0.2 representing slight agreement, 0.21–0.4 representing fair agreement, 0.41–0.6 representing moderate agreement, 0.61–0.8 representing substantial agreement, and 0.81–0.99 representing almost perfect agreement.[19,20] We first assessed the agreement between reviewers across the individual criteria per study using the Fleiss Kappa score and then averaged the Fleiss Kappa scores across the five studies. We then determined the agreement between reviewers for the overall assessment of bias according to Table S2B across the five studies using the Fleiss Kappa statistic.

2.3.2 | MA risk of bias assessment and scoring

The Risk of Bias in Systematic Reviews (ROBIS) tool was used to assess the risk of bias in MAs that met our inclusion criteria.[21] The ROBIS tool identifies concerns with the review process in four different domains, including study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. Based on the concerns identified, it allowed the judging of the risk of bias for the systematic review as a whole.

Each domain was ranked as a "low," "high," or "unclear" level of concern explored through the answering of targeted questions, which are answered as "Yes," "No," "Partially Yes," "Partially No," or "No Information," with "Yes" corresponding to the lowest risk of bias for that question.[21] Domains 1, 2, and 3 have five questions each while domain 4 has six questions for a total of 21 questions.[22]

2.4 | Comparative outcome assessment and data extraction

Given the inherent limitations of using single-arm studies, or MAs comprised of single-arm studies with only naïve indirect comparisons between groups, these studies were excluded. For all comparative studies, important study characteristics and patient characteristics were collected before collecting data on in-hospital mortality, 30-day mortality, and hemostatic efficacy. If hemostatic efficacy in a comparative study was reported at more than one time point, the latter time point was used in our analyses. If a comparative study did not have mortality data presented separately but did report the composite end point of mortality or hospice, that data was included in our analyses. As a post-hoc analysis, we also assessed thrombotic events.

Our primary assessment was to compare major outcomes in comparative studies of low or moderate risk of bias. In secondary analyses, we assessed the same end points but only included studies with high risk of bias and then pooled study results together regardless of methodological quality.

2.5 | Synthesis methods

We could not pool the results of all available studies together in our MA because several of the comparative studies with adjusted controls used portions of the andexanet alfa data from the Phase 3b/4 single-arm

TABLE 1 PICOS for individual study inclusion in the systematic review.

Category	Inclusion criteria	Exclusion criteria
Population (P)	• Patients with major bleeding from the use of FXa-inhibiting anticoagulants[a,b]	• Healthy volunteers • Sample size <10 patients • Inadequate population (<10 patients) receiving FXa inhibitors (apixaban, rivaroxaban, edoxaban, betrixaban, fondaparinux, or enoxaparin)
Intervention (I)	• Andexanet alfa • PCC • 4FPCC • aPCC-FEIBA	• Studies that are not assessing a reversal/replenishment agent to treat major bleeding • Idarucizumab
Comparators (C)	• Any comparator above or placebo	• None
Outcomes (O)	• Hemostatic effectiveness • Mortality	• Studies that do not report at least one of the outcomes of interest
Study design (S)	• RCTs – both parallel-group and crossover (double-blind, single-blind, and open-label) • Retrospective and prospective cohort studies • Single-arm trials with added control groups	• In vitro studies • Preclinical studies • Narrative reviews, comments, letters and editorials • Single-arm studies without the addition of control groups
Language	• English, Spanish, and Dutch	• Non-English, -Spanish, or -Dutch articles will be excluded

Abbreviations: 4F, four factor; aPCC-FEIBA, activated prothrombin complex concentrate-anti-inhibitor coagulant complex; FXa, factor ten activated; PCC, prothrombin complex concentrate; RCT, randomized controlled trial.

[a]In the case of a comingled population, at least 95% of the population must be on FXa inhibitors.

[b]Studies with populations receiving either factor Xa inhibitors or dabigatran or vitamin K antagonists could still be included if the subpopulation with factor Xa inhibitors is reported separately.

ANNEXA-4 study. That would have led to double-counting the same andexanet alfa-treated subjects in the pooled analysis, amplifying the weight of those studies relative to the others. To remedy this, only a single trial containing ANNEXA-4 data was allowed to be used in a pooled analysis. Therefore, if there were two ANNEXA-4 data-containing studies reporting on an end point, we would use the study with the lowest risk of bias. However, if the study selected showed a different direction of effect from any other ANNEXA-4 data-containing study, we would conduct a sensitivity analysis whereby the initial study was removed, and the study showing a differing direction of effect inserted. Each of the studies using ANNEXA-4 for their andexanet alfa data contained a unique control group using a PCC product, so there is value in assessing whether those results are consistent with the other ANNEXA-4 data containing studies. Similarly, if there was a study not using ANNEXA-4 data where data was published previously and then a newer analysis containing those initial patients in addition to newer patients were found, we would assess the risk of bias for both publications but only include the data from the newer publication to prevent duplication of data and overamplification of the results.

Data from individual studies included the unadjusted or adjusted odds ratios (OR) and corresponding 95% confidence intervals (CIs) for the effect of andexanet alfa versus a PCC product on the outcomes of interest using logarithmic transformation. If a constituent study adjusted the OR for baseline differences between the groups, we preferentially used adjusted OR data over unadjusted data. Between-study variance tau^2 was calculated with the Paule-Mandel method, which has shown improved performance over the commonly used DerSimonian and Laird procedure.[23] To reflect uncertainty in estimation of between-study variance, an adjustment to the 95% CI for the treatment effect proposed by Hartung and Knapp and by Sidik and Jonkman was used when five or more studies were meta-analyzed, given its enhanced performance in simulation evaluations and provides 95% CIs at least as wide as other traditional methods.[24] However, given concerns about applying the Hartung-Knapp adjustments to small data sets, we used the generic inverse variance method to estimate a random-effects model where two to four studies were available for pooling.[25–27] The random-effects model was chosen given the known or potential demographic or clinical differences between the studies included in our MAs. Forest plots of study results were produced to visually assess statistical heterogeneity, as determined by the lack of overlap in 95% CIs across studies. We used the I^2 statistic to quantify the proportion of variation in study results explained by statistical heterogeneity rather than

the sampling error within studies, where a value >50% was interpreted as high heterogeneity. Two a priori subgroups (low–moderate vs. high risk of bias) were assessed, where a p-value <0.10 indicated significant subgroup differences. Small study effects (i.e., publication bias) were evaluated only when 10 or more studies were available. Funnel plots and Egger's tests were conducted, with a $p<0.05$ in Egger's test indicating the presence of small study effects. Prediction intervals for the treatment effect in a single new study were added to the forest plots if there were two or more studies in the risk of bias subgroup under assessment. The prediction interval is based on a t-distribution with k-2 degrees of freedom, where k is the number of studies in the meta-analysis, so it is only calculable if there are three or more studies available. The *metagen* function from the *meta* package of R 4.2.0 was used for all analyses.

3 | RESULTS

3.1 | Articles included

A subset of 227 studies were assessed for eligibility. In total, 209 studies were excluded for the following reasons: not a comparative study or systematic review ($n=39$), <10 eligible patients evaluated ($n=23$), not assessing an FXaI ($n=49$), not assessing a reversal/replenishment agent ($n=14$), not reporting on an outcome of interest ($n=4$), and not a full-text study in humans ($n=80$). We identified 18 studies for the review that fit the inclusion criteria and two systematic reviews (Figure 1).[28–45] Study characteristics for the comparative studies and the systematic reviews are reported in Tables S3–S5.[28–45]

Three studies used ANNEXA-4 data for their andexanet alfa arms (Cohen 2022, Costa 2022, Huttner 2022) with adjusted control groups.[30,32,34] All three studies were included in our systematic review, and the risk of bias was assessed for each of these studies separately, but, as described above, only one study was used for each pooled analysis. Although Dobesh 2023 and Coleman 2021 were both assessed for risk of bias separately, we only used Dobesh 2023 outcome data in our pooled outcome assessments since the Dobesh 2023 dataset encompasses the entirety of Coleman 2021 as well as newer data.[31,33]

3.2 | Risk of bias in comparative studies

Figure 2 provides the aggregated ratings of risk of bias, tabulated and graphically, in comparative studies for individual criteria and overall using the rating schema in Table S2B. For the 18 studies comparing andexanet alfa versus 4F-PCC or PCC, 17% ($n=3$) of the studies had low risk, 11% ($n=2$) had moderate risk, and 72% ($n=13$) had a high risk of bias (Table S6).[28–45] The criteria where ≥50% of studies had a high risk of bias included Criteria 1, 4, 9, and 12.

3.2.1 | Agreement among raters for risk of bias determinations in individual studies

When the eight raters (three cardiovascular/thrombosis specialists, three generalists, and two methodologists) independently applied the adapted JBI and MINORs criteria to five studies using our written guidance, a substantial level of agreement with the risk of bias determinations was found. When evaluated by the level of agreement by individual criteria, the Fleiss Kappa statistic was 0.50, 0.84, 0.72, 0.32, and 0.81 for the five studies, respectively, for an average Fleiss Kappa statistic across the studies of 0.64 ± 0.23. When we compared the level of agreement solely based on the overall determination of the risk of bias in a study, the Fleiss Kappa statistic was 0.76, showing substantial agreement among raters. The main disagreements were where a rater chose a moderate risk of bias, while the majority of their colleagues chose either a high or low risk of bias rating.

3.3 | Risk of bias in MAs

Table 2 includes the risk of bias assessment of the two comparative MAs conducted to date (Shrestha 2021 and Chaudhury 2022) with rationales for the ratings.[1,14] The Shrestha 2021 MA included only three studies (Ammar 2021, Barra 2020, Coleman 2021).[14,28,29,31] The most recent systematic review by Chaudhury 2022 had eight studies (Ammar 2021, Barra 2020, Coleman 2021, Milioglou 2022, Pham 2022, Parsels 2022, Stevens 2021, Vestal 2022) and was limited only to patients with intracranial hemorrhage.[1,28,29,31,37,39,40,42,45] Both MAs were found to have a high overall risk of bias with domains 1 and 2 having an unclear risk of bias, domain 3 having a low risk of bias for Shrestha 2021 and a high risk of bias for Chaudhury 2022, and domain 4 having a high risk of bias for both MAs.[1,14]

3.4 | Outcome assessment of comparative studies with the different risks of bias and overall

Only six studies comparing andexanet alfa to a PCC product met the criteria for low to moderate risk of bias (Coleman 2021, Huttner 2022, Costa 2022, Cohen 2022, Sutton 2023, Dobesh 2023).[30–34,43] The remaining 12 comparative studies (Ammar 2021, Barra 2020, Keinaith 2023, Lipski 2022, Miliogou 2022, Oh 2023, Parsels 2022, Pham 2022, Schmidt 2022, Stevens 2021, Troyer 2023, Vestal 2022) had a high risk of bias.[28,29,35–42,44,45]

Twelve of the comparative studies assessed for hemostatic efficacy (Figure 3). The only low–moderate risk of bias study was Costa 2022, which found significantly better hemostatic efficacy for andexanet alfa versus PCC [OR 2.72 (95% CI: 1.15–6.44)].[32] No significant improvement in hemostatic efficacy was found in high risk of bias studies [OR 1.22 (95% CI: 0.94–1.60), $I^2=0\%$, $\tau^2=0$]. When studies were included in the meta-analysis for hemostatic efficacy regardless

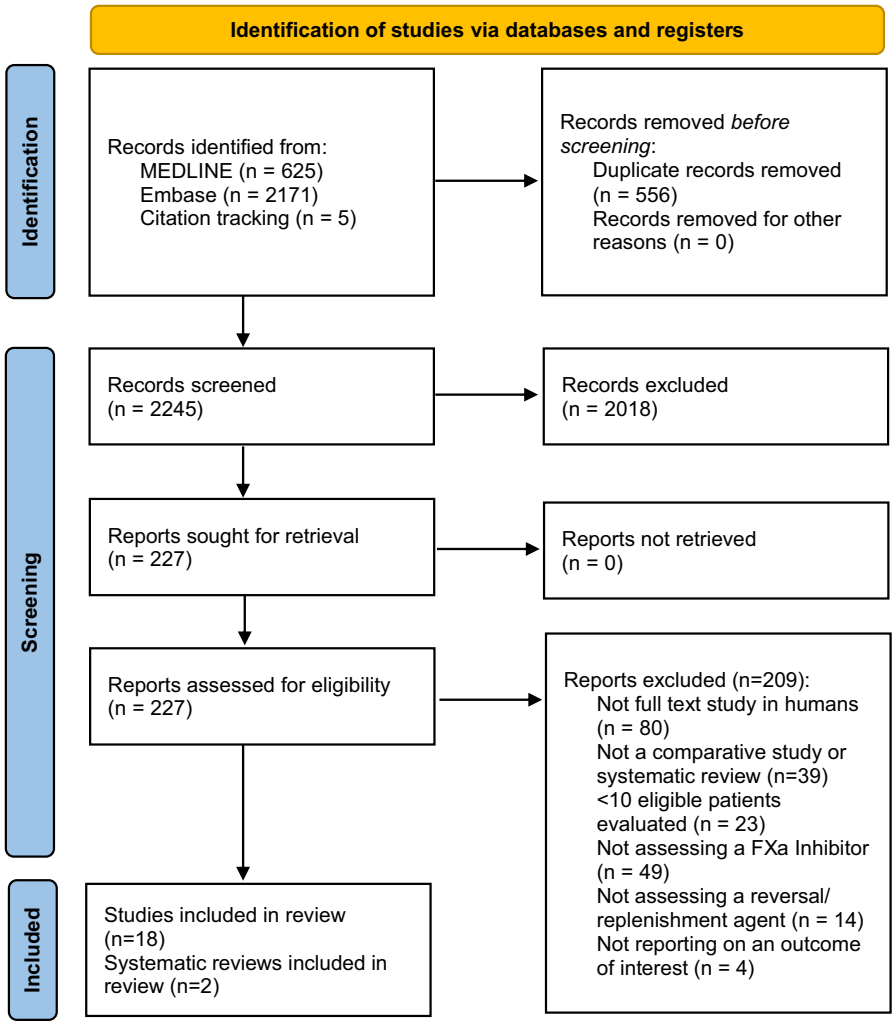

FIGURE 1 PRISMA diagram of included and excluded studies.

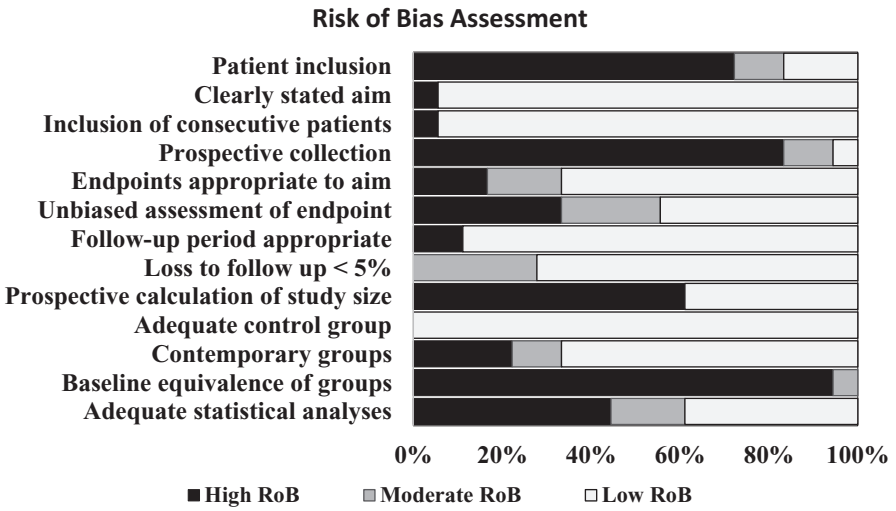

FIGURE 2 Aggregate ratings of risk of bias (RoB) in comparative studies.

of risk of bias, there was improved hemostatic efficacy with andexanet alfa benefit versus PCC [OR 1.36 (95% CI: 1.01–1.84), I^2=0%, τ^2=0]. There was no evidence of statistical heterogeneity or publication bias in these assessments of hemostatic efficacy (Figure S1). The hemostatic efficacy results in low–moderate risk of bias studies were significantly different from those in high risk of bias studies, as evidenced by a value of p=0.08, which was below our a priori p-value threshold of <0.10.

Twelve of the comparative studies assessed in-hospital mortality (Figure 4). Three low–moderate risk of bias studies showed evidence of lower in-hospital mortality for andexanet alfa versus PCC [OR 0.48 (95% CI: 0.38–0.61), I^2=0%, τ^2=0]. The direction of the

TABLE 2 Meta-analysis ROBIS findings for each criterion and overall findings.

Name of 1st author, year of publication[1,14]	1.1	1.2	1.3	1.4	1.5		Domain 1 RoB	Rationale for rating
Shrestha 2021[14]	Y	PY	PY	Y	PN		Unclear	Optimal effort to clearly specify review questions and objectives and to pre-specify detailed eligibility criteria. However, there was no justification for excluding unpublished studies (conference abstracts, ongoing studies)
Chaudhury 2022[1]	PY	PY	PY	Y	PN		Unclear	Optimal effort to clearly specify review questions, objectives, and pre-specify detailed eligibility criteria. However, there was no justification for excluding unpublished studies and non-English studies. No protocol available
	2.1	**2.2**	**2.3**	**2.4**	**2.5**		**Domain 2 RoB**	**Rationale for rating**
Shrestha 2021[14]	PN	PN	PN	PY	Y		Unclear	A limited effort has been made to identify published studies using a sensitive and appropriate search strategy in 5 engines, but no additional methods to identify other relevant reports. Steps were taken to minimize bias and errors when selecting studies for inclusion. Some eligible unpublished studies are likely to be missing from the review
Chaudhury 2022[1]	PN	PY	Y	N	Y		Unclear	A substantial effort has been made to identify published studies using a sensitive and appropriate search strategy, and steps have been taken to minimize bias and errors when selecting studies for inclusion. However, some eligible unpublished studies are likely to be missing from the review
	3.1	**3.2**	**3.3**	**3.4**	**3.5**		**Domain 3 RoB**	**Rationale for rating**
Shrestha 2021[14]	Y	PY	PY	PY	Y		Low	All study characteristics were extracted independently by two reviewers, and outcome data were available for synthesis. Selected studies were clearly labeled as cohorts or case series. The authors used JBI tools for assessing the RoB of cohorts and case series, which were pre-defined in the protocol
Chaudhury 2022[1]	Y	PN	PN	PN	PN		High	Some characteristics were extracted independently, and outcome data were available for synthesis. The authors described study designs as "prospective" and "retrospective," without actual designs. The risk of bias was evaluated with the NOS tool, and there were no independent assessments
	4.1	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**Domain 4 RoB**	**Rationale for rating**
Shrestha 2021[14]	PY	N	PY	N	PN	N	High	There was a brief description of the effect measures (MD, OR) for outcomes, no description of the methods for meta-analyses, and the selection of model was based on heterogeneity of effects. The synthesis was appropriate. There was no evaluation of small study effects, and a sensitivity analysis excluding one study with an "outlier" effect without explanation. The authors reported moderate-to-high quality included studies without explanations, and this information was not used in the synthesis

(Continues)

TABLE 2 (Continued)

Name of 1st author, year of publication[1,14]	1.1	1.2	1.3	1.4	1.5		Domain 1 RoB	Rationale for rating
Chaudhury 2022[1]	PY	NI	PN	N	PY	N	High	There was no description of methods for meta-analyses of proportions. The synthesis was appropriate. Heterogeneity was not addressed in synthesis, sensitivity analyses, or discussion. High risk of bias in all included studies
	Overall factor 1	**Overall factor 2**	**Overall factor 3**				**Total SR RoB assessment**	**Rationale for overall RoB rating**
Shrestha 2021[14]	N	PY	Y				High	One domain had a high risk of bias in the synthesis and findings, and two domains in study eligibility criteria and identification and selection of studies had an unclear risk of bias. These issues were not addressed in the discussion or limitations section. The review also considered the relevance of the identified studies to the review's research question. There is therefore a high risk of bias in this review
Chaudhury 2022[1]	N	PY	Y				High	The four domains identified a number of areas of concern with the review process that were not addressed by the authors. These included lack of clarity in inclusion criteria (unpublished studies, non-English language studies), possibility of missing studies, use of a non-validated quality assessment tool (NOS), insufficient details on study designs of included studies, absence of description of methods for meta-analysis of proportions, absence of addressing heterogeneity in synthesis or discussion, and high risk of bias in all included studies. There is therefore a high risk of bias in this review

Abbreviations: MD, mean difference; N, no; NI, no information; OR, odds ratio; PN, partially no; PY, partially yes; RoB, risk of bias; Y, yes.

pooled effect for the high risk of bias studies was toward reduced in-hospital mortality with andexanet alfa versus PCC, but this was lower in magnitude than that for the low–moderate studies, and the corresponding 95% CI was wide and crossed the null [OR 0.84 (95% CI: 0.42–1.68), $I^2=47\%$, $\tau^2=0.397$]. When studies were included in the meta-analysis for in-hospital mortality regardless of risk of bias, the direction of the pooled effect was toward andexanet alfa benefit versus PCC but this pooled effect was subject to uncertainty in estimation due to high heterogeneity between studies [OR 0.67 (95% CI: 0.40–1.10), $I^2=61\%$, $\tau^2=0.328$], but no statistical heterogeneity was found (Figure S1). The in-hospital results in the low–moderate risk of bias studies were significantly different from those in high risk of bias studies, as evidenced by a value of $p=0.08$, which was below our a priori p-value threshold of <0.10.

Six of the comparative studies assessed 30-day mortality (Figure 5). Two low–moderate risk of bias studies both showed significantly lower 30-day mortality for andexanet alfa versus PCC [OR 0.49 (95% CI: 0.30–0.80), $I^2=0\%$, $\tau^2=0$]. The direction of effect for the high risk of bias studies was toward andexanet alfa benefit versus PCC, and the magnitude of benefit for 30-day mortality was lower than that for the low–moderate risk of bias studies [OR 0.62 (95% CI: 0.31–1.25), $I^2=0\%$, $\tau^2=0$]. There was a significant reduction in 30-day mortality for andexanet alfa versus PCC when studies were included regardless of risk of bias [OR 0.53 (95% CI: 0.37–0.76), $I^2=0\%$, $\tau^2=0$]. No evidence of statistical heterogeneity was obtained in the assessments of 30-day mortality, and publication bias could not be adequately assessed given the smaller study number (Figure S1). No significant difference was found between the results in the low–moderate versus the high risk of bias studies ($p=0.43$).

In a post-hoc analysis, 11 studies assessed thrombotic events (Figure 6). One low–moderate risk of bias study showed a direction of effect toward an increase in thrombotic events with andexanet alfa versus PCC, but the CIs were very wide and did not achieve statistical significance [OR 4.85 (95% CI: 0.22–109.55)]. The high risk of bias studies [OR 1.40 (95% CI: 0.76–2.57), $I^2=0\%$, $\tau^2=0$] and the studies regardless of risk of bias [OR 1.45 (95% CI: 0.81–2.59), $I^2=0\%$, $\tau^2=0$] both showed a direction of effect toward an increase in thrombotic events with andexanet alfa versus PCC, but these findings were not statistically significant. Publication bias was not noted (Figure S1). No significant difference was found between the results in the low–moderate versus the high risk of bias studies ($p=0.44$).

3.5 | Outcome assessment from published MAs

The random-effects MA by Chaudhury 2022 reported almost identical hemostatic efficacy for 4F-PCC versus andexanet alfa [risk ratio 0.95 (95% CI: 0.85–1.06)] with no evidence of statistical heterogeneity ($I^2=0\%$).[1] For their mortality assessment, they used an amalgam of in-hospital and 30-day mortality with a fixed effect MA showing a direction of effect toward PCC having a higher risk, but this was imprecisely estimated [risk ratio 1.40 (95% CI: 0.68–2.86)] and high statistical heterogeneity was observed ($I^2=65\%$). Shrestha 2021 only reported comparative pooled data for andexanet alfa versus PCC on in-hospital mortality.[14] Using a random-effects model, they found that the direction of the pooled effect was toward andexanet alfa having a benefit, but the 95% CI crossed the null [OR 0.39 (95% CI: 0.14–1.06)] and there was moderate statistical heterogeneity ($I^2=49\%$). Neither MA analyzed studies with low or moderate risk of bias separately from those with higher risk of bias, but they only had one study in their analysis that was not high risk of bias, according to our criteria.[1,14]

4 | DISCUSSION

Fxals have been rapidly replacing warfarin since their introduction in 2012, thereby lowering the overall risk of major bleeding in patients requiring anticoagulant treatment for thromboembolism or stroke prevention.[46–48] However, Fxals carry a small risk of severe, potentially life-threatening bleeding, with 30-day mortality risks ranging from approximately 6%–40%, depending on bleed location.[1,2,49,50] These risks impose a substantial clinical burden, and a US patient survey indicated that more than 20% of patients with thromboembolism on an anticoagulant were extremely concerned about major bleeding.[51] Most patients strongly preferred an anticoagulant that was reversible, as this reduced their anxiety about the major bleeding risks.

Rapid reversal of the anticoagulant effects of Fxals can be achieved with andexanet alfa, which has been demonstrated to effectively reduce anti-Fxa activity within 2–5 min in clinical trials of normal volunteers.[2–4] Nevertheless, PCC products are commonly used off-label in this setting, despite not interacting with Fxals in the circulation but rather replenishing the plasma with clotting factors.[52–54]

In this literature review, we aimed to answer important research questions on the effectiveness of andexanet alfa versus PCC, including assessing the bias across previous literature reviews and MA as well as including more recent studies. We found that four of the previous MAs relied solely on assessing the results of single-arm studies, and only two of them specifically pooled comparative studies of andexanet alfa versus PCC products. Both the comparative systematic reviews were outdated and did not include the latest comparative studies in this emerging area of research, and none of the systematic reviews evaluated the impact of high risk of bias studies on their results. The high or unclear risk of bias ratings of these previous systematic reviews and their lack of contemporary published studies preclude their ability to inform current evidence-based decisions.

In our systematic review and MA of the available evidence, studies with low–moderate risk of bias showed evidence of improvements in hemostatic efficacy and reductions in in-hospital and 30-day mortality when andexanet alfa was used versus PCC products to treat Fxal-associated major bleeding. In a post-hoc analysis, we assessed the variable of "any mortality" where Costa 2022 provided in-hospital mortality data and Dobesh 2023 and Sutton 2023 provided 30-day mortality data and found a significant reduction in this composite

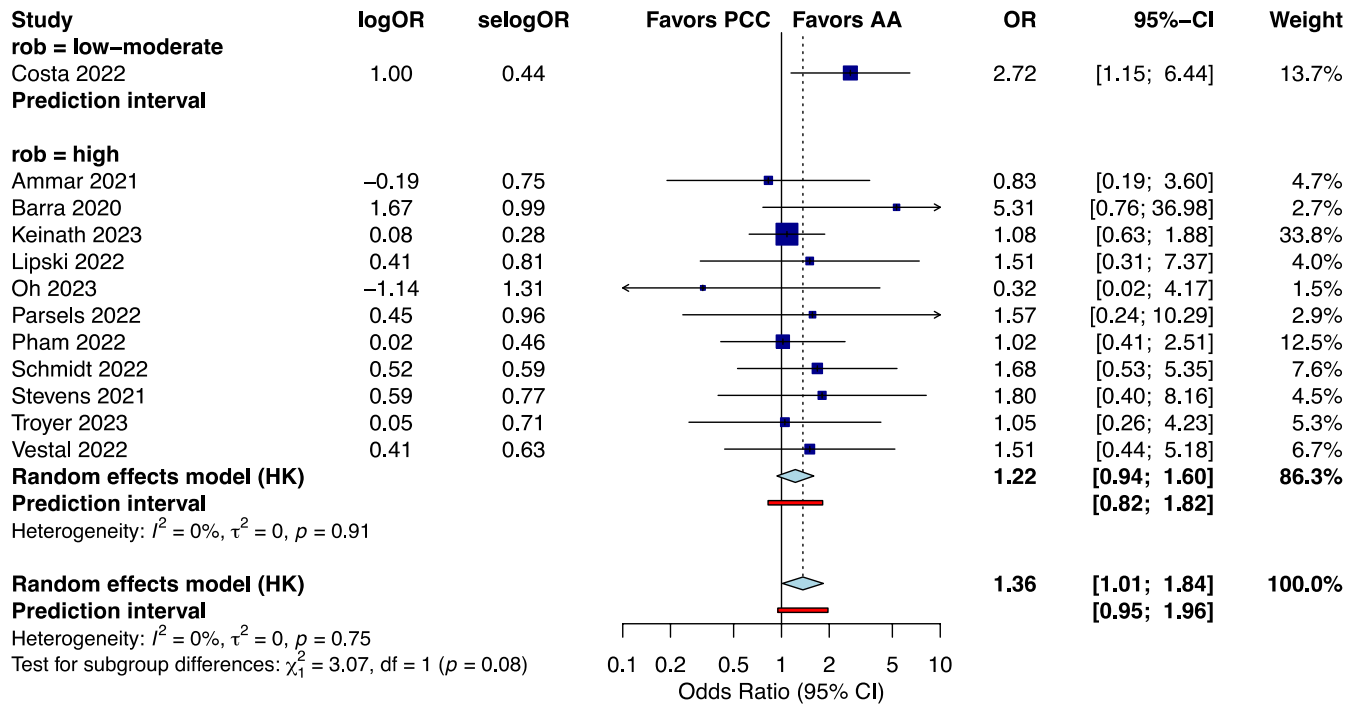

FIGURE 3 Pooled hemostatic efficacy for AA vs. PCC. (n = 12 studies). AA, andexanet alfa; HK, Hartung-Knapp Adjusted; log, logarithm; OR, odds ratio; PCC, prothrombin complex concentrate; RoB, risk of bias; se, standard error.

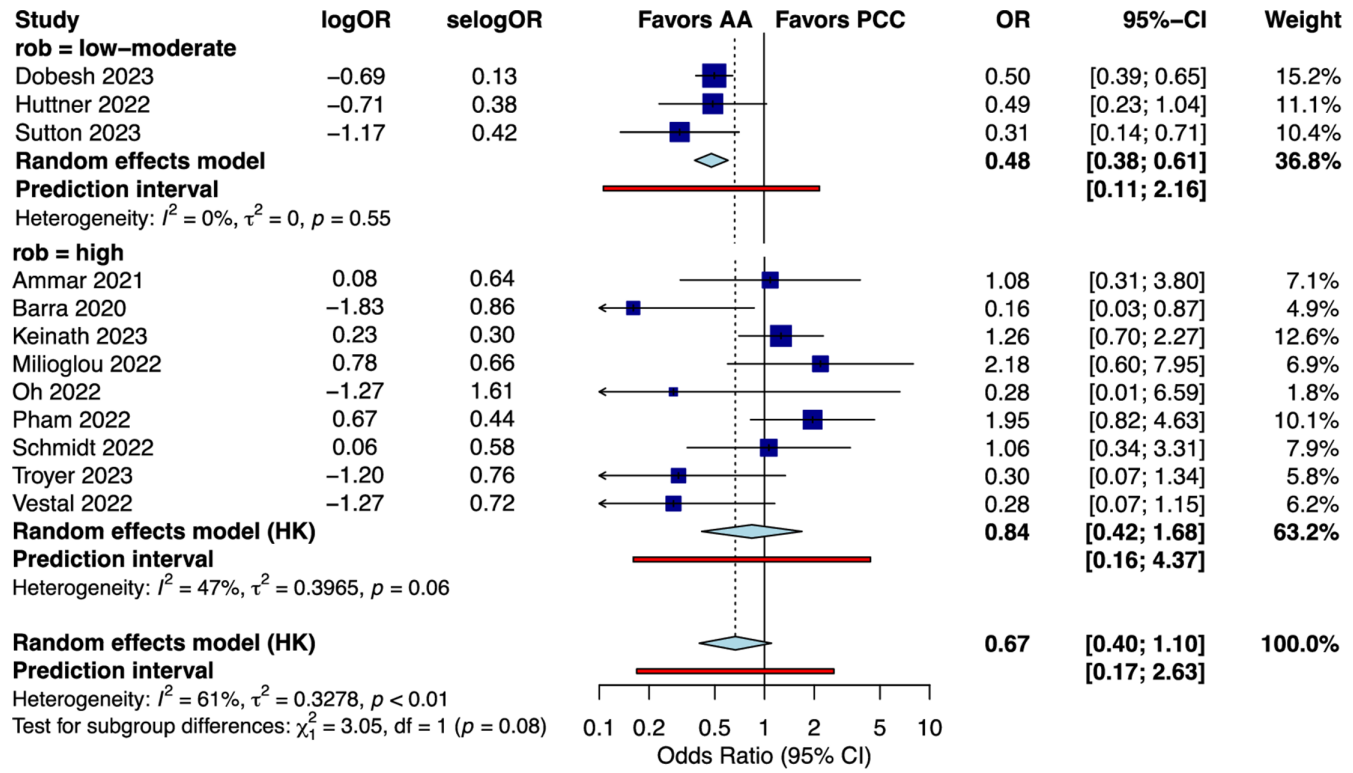

FIGURE 4 Pooled in-hospital mortality for AA vs. PCC. (n = 12 studies). AA, andexanet alfa; HK, Hartung-Knapp Adjusted; log, logarithm; OR, odds ratio; PCC, prothrombin complex concentrate; RoB, risk of bias; se, standard error.

mortality end point [OR 0.50 (95% CI: 0.39–0.64)] with no statistical heterogeneity (I^2 = 0%) as well.[32,33,43] In a second post-hoc analysis, we also assessed thrombotic events, and although the direction of effect was toward an increase with andexanet alfa therapy versus PCC therapy, this was not a statistically significant finding with extremely wide CIs.

The pooling of high risk of bias studies in our systematic review resulted in a consistent direction of effect toward benefit with andexanet alfa versus PCC for hemostatic efficacy, in-hospital mortality, and 30-day mortality, although no significant effects were found across these studies. The much wider 95% CIs for the high risk of bias versus the low–moderate risk of bias studies reflect the underlying methodological weaknesses that yielded the high risk of bias determinations in the first place. For the hemostatic efficacy and in-hospital mortality end points in particular, there were significant differences between the pooled results for low–moderate versus high risk of bias studies. The less assurance that the intervention and control groups are similar in myriad important ways, the greater the risk that confounders can drive differences in results between them. Pooling the low–moderate risk of bias studies together with those at high risk of bias showed that, on average, the odds of 30-day mortality are reduced by 47% with andexanet alfa versus PCC, and there are strong trends toward enhancing hemostatic efficacy and reducing in-hospital mortality.

The results on hemostatic efficacy are consistent with the newly released findings from the ANNEXA-I trial.[55] ANNEXA-I was a randomized, multi-center clinical trial comparing the efficacy and safety of andexanet alfa versus usual care (including 4-factor PCC in 87% of patients) in 530 adult patients receiving oral FXaIs with intracranial (mostly intracerebral) hemorrhage. The primary end point was the rate of excellent or good hemostasis. In ANNEXA-I, the percentages of patients with excellent or good hemostasis in the andexanet alfa and usual care groups were 63.9% versus 52.4%, respectively ($p = 0.0008$).[55] The trial was stopped early due to the achievement of a significant difference in hemostatic efficacy at a pre-planned interim analysis.[56] The study was not designed to assess mortality outcomes. In the ANNEXA-I trial, 30-day mortality rates were balanced between the treatment groups, although an increase in thrombotic events was observed in patients treated with andexanet alfa.[55] When viewed together, the strong internal validity of the ANNEXA-I trial for its primary end point and our pooled results from low–moderate risk of bias studies suggest that andexanet alfa is superior to usual care, including PCC, for improving hemostasis in patients with a FXaI-associated major bleed. The analytic framework for severe bleeding postulates that major bleeding is a driver of excess mortality, and enhancements in hemostasis may be expected to drive improvements in patient survival, as we found in our systematic review.[57] The differences between our 30-day mortality findings and those from ANNEXA-I could be related to chance, the higher average age in ANNEXA-I versus our constituent studies, the longer lag time from arrival to treatment in clinical trials, or the primary focus on intracerebral hemorrhage in ANNEXA-I versus our inclusion of several major bleeding sites, including gastrointestinal bleeds.[55] Future randomized controlled trials powered to assess 30-day mortality as a primary end point would be needed to definitively assess this issue. Finally, the ANNEXA-I trial found an increase in thrombotic events, a trend that was also observed in our analysis, although nonsignificant. This consistency in the direction of effect toward higher thrombotic events between the ANNEXA-I study and the real-world evidence supports each other and makes pharmacologic sense in a patient population with a high innate risk of thrombotic events treated with a rapid reversal agent. To mitigate this thrombotic risk, anticoagulation is advised to be restarted as soon as it is clinically reasonable.[58] Since ANNEXA-I was comprised predominantly of patients with intracerebral hemorrhage, there might have been more reticence to restart anticoagulation than in the

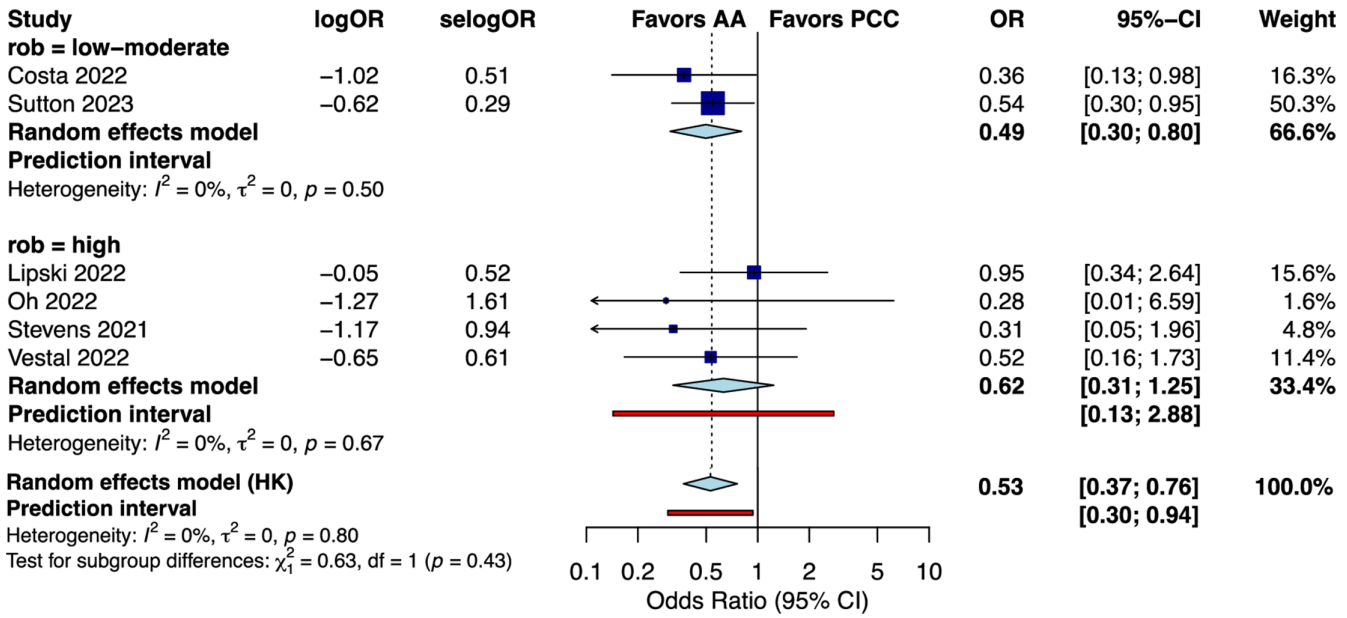

FIGURE 5 Pooled 30-day mortality for AA vs. PCC. ($n = 6$ studies). AA, andexanet alfa; HK, Hartung-Knapp Adjusted; log, logarithm; OR, odds ratio; PCC, prothrombin complex concentrate; RoB, risk of bias; se, standard error.

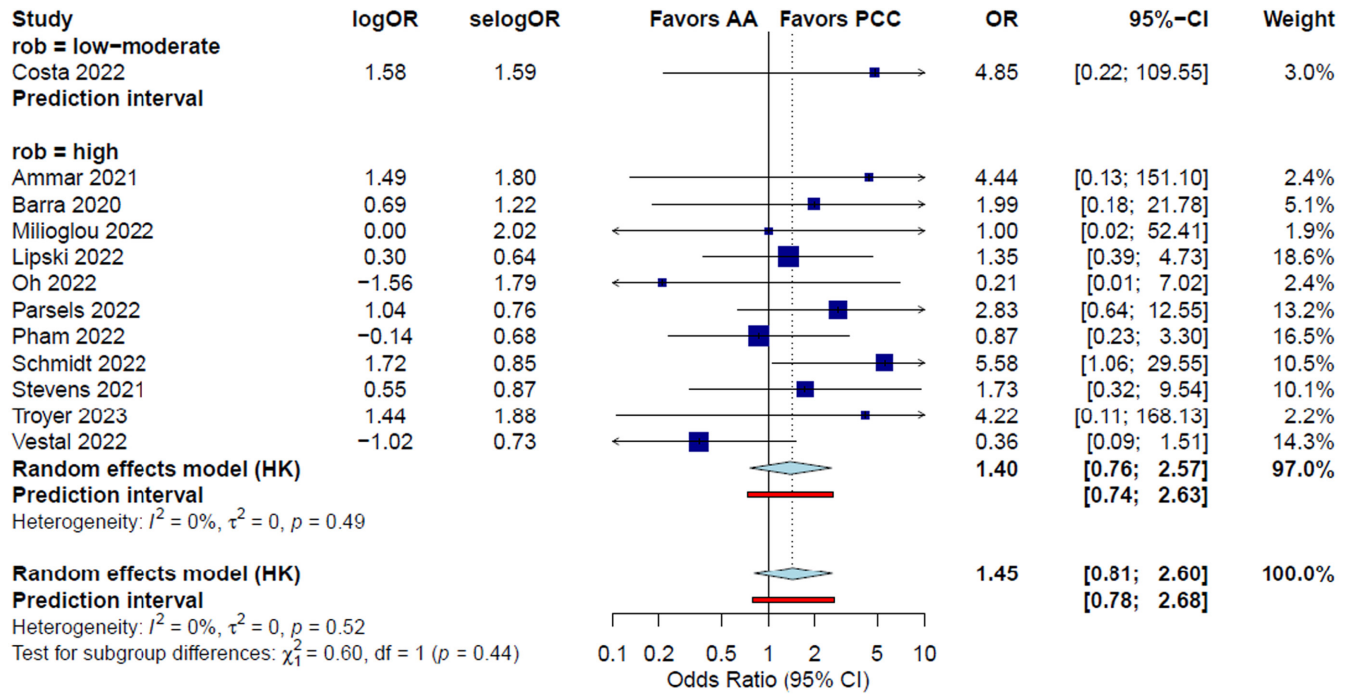

FIGURE 6 Pooled thrombotic events for AA vs. PCC. (n = 11 studies). AA, andexanet alfa; HK, Hartung-Knapp Adjusted; log, logarithm; OR, odds ratio; PCC, prothrombin complex concentrate; RoB, risk of bias; se, standard error.

mixed populations included in the various real-world evidence studies.

This systematic review has several strengths and limitations. For its strengths, it included the available studies published through September 1, 2023, avoided the use of single-arm studies in assessing outcomes, adapted criteria to assess risk of bias and generated guidance specific to this topic area that led to consistent assessments by different raters, evaluated the results of higher versus lower quality studies separately before evaluating them together, and avoided overamplifying the results of studies with overlapping patients in the pooled analyses. For its weaknesses, we pooled non-randomized studies. Even low–moderate risk of bias studies still have inherent limitations in internal validity compared with randomized controlled trials. Additionally, the lack of randomized controlled trials precluded the use of the commonly applied Cochrane risk of bias tool. Given these limitations, our systematic review cannot prove that andexanet alfa is superior to PCC for treating Fxal-associated major bleeding. However, it has increased confidence that the current best evidence available from low–moderate risk of bias real-world studies, supported by the outcomes of the only randomized controlled trial in patients with major bleeding, suggests that andexanet alfa is superior to PCC in improving hemostasis. However, achieving hemostasis is a subjective outcome as it is based on the judgment of the assessor. The use of standardized rating criteria, such as those from the International Society on Thrombosis and Hemostasis, can reduce subjectivity but cannot eliminate it.[3]

Investigators have previously developed cost-effectiveness models to estimate whether the additional benefits associated with andexanet alfa make up for its higher acquisition costs, with conflicting results.[59–61] Our systematic review with MA does not prove cost-effectiveness for andexanet alfa but does provide insight into which studies have greater methodological quality for incorporation into future models, contains contemporary studies not used in previous models, and pools the impact of therapy on important outcomes such as hemostatic efficacy and mortality.

5 | CONCLUSIONS

The available evidence from low–moderate risk of bias studies suggests that andexanet alfa is superior to PCC in enhancing hemostatic efficacy and reducing in-hospital and 30-day mortality. When studies are assessed regardless of the risk of bias, the pooled hemostatic efficacy and 30-day mortality risk remain significantly better with andexanet alfa versus PCC. The difference in thrombotic events was not significant in the real-world evidence base.

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CONFLICT OF INTEREST STATEMENT

Two of the study team members are employed by the company; and three of the other research team members (Drs. Dobesh, White, and Coleman) have received speaker fees for speaking about AstraZeneca products in the past.

DATA AVAILABILITY STATEMENT

We include our data extraction tables in the supplementary section of the paper.

ORCID

C. Michael White https://orcid.org/0000-0002-9367-4893
Kimberly Snow Caroti https://orcid.org/0000-0002-7081-7054
Youssef Bessada https://orcid.org/0000-0001-5999-9099
Adrian V. Hernandez https://orcid.org/0000-0002-9999-4003
William L. Baker https://orcid.org/0000-0003-2172-0931
Paul P. Dobesh https://orcid.org/0000-0002-2668-7168
Heleen van Haalen https://orcid.org/0000-0002-4001-0006
Kirsty Rhodes https://orcid.org/0000-0002-8568-4979
Craig I. Coleman https://orcid.org/0000-0003-4868-7158

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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